Fused Systems Based on 2-Aminopyrimidines: Synthesis Combining Deprotolithiation-in situ Zincation with N -Arylation Reactions and Biological Properties

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Abstract: Various aromatic ketones were first functionalized next to the carbonyl function by deprotolithiation in the presence of a zinc salt followed by iodolysis. The outcome of the reactions was analyzed, and in particular their regioselectivity in the light of the calculated pK_a values. The various halogenated ketones were next involved in copper-catalyzed two-fold C-N bond formation in order to obtain fused systems based on 2-aminopyrimidines. Besides potential antibacterial effect, reached 2-aminobenzothiopyrano[4,3,2-*de*]quinazoline proved to inhibit PIM1 (IC_{50}: 0.61 µM) and CDK2/cyclin A (IC_{50}: 2.0 µM) kinases.

Introduction

Aromatic ketones halogenated next to the carbonyl function are important key intermediates in organic synthesis. They can be used to access various scaffolds for applications in the fields of medicinal[1] and material[2] chemistry. Combining C-N bond formation[3] with condensation reactions[4] can provide an access from such ketones to elaborated fused systems based on 2-aminopyrimidines, potentially endowed with various biological properties.[5] However, in spite of their interest, few efficient methods presently exist to selectively introduce a halogen onto an aroyl group next to the carbonyl. Unlike electrophilic halogenation, that in general requires the presence of additional directing substituents,[1b,1c,2] transition-metal-catalyzed C-H bond halogenation using *N*-halo succinimides as oxidants can regioselectively provide aromatic ketones halogenated next to the carbonyl. Indeed, rhodium(III)-catalyzed bromination or iodination can be performed in the presence of catalytic silver hexafluoroantimonate(V), and stoichiometric pivalic acid or copper acetate,[6] whereas palladium-catalyzed chlorination can be achieved in the presence of triflic acid and potassium persulfate.[7] The former has not been applied to diaryl ketones[6] and the latter showed a coordination-driven regioselectivity.[7] We developed an alternative way based on polar-reagent-mediated deprotonative metalation in order to access various iodinated aromatic ketones.

We recently communicated our preliminary studies centered on the functionalization of pyridyl ketones by deprotolithiation-in situ zincation.[8] We here detail our investigations in order to better understand the behavior of the ketone function as directing group. Because CH acidity concept helps understand deprotometalation outcomes, pK_a values in THF (THF = tetrahydrofuran) solution were calculated by means of quantum chemistry within the DFT framework using an approach elaborated earlier.[8,9]

Results and Discussion

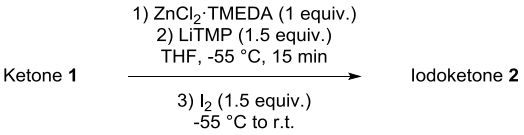
Deprotolithiation has been largely used to activate aromatic compounds and make them react with a large range of electrophiles.[10] Whereas heteroatom-containing groups can help when connected to the aromatic ring, either by acidification (electron-withdrawing effect),[10e] or by metal coordination,[11] they can also modify the reaction outcome by reacting with the base or the generated aromatic lithium species as is the case for ketone functions.[12]

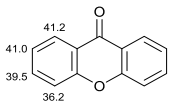
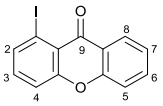
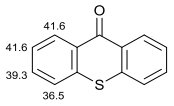
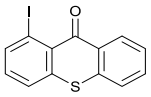
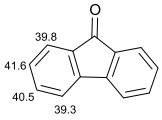
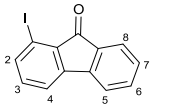
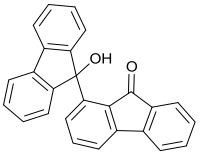
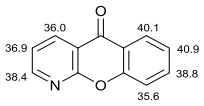
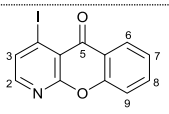
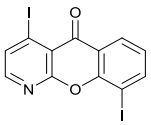
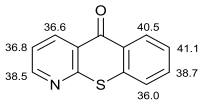
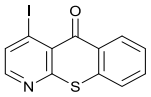
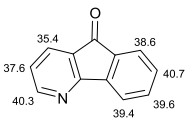
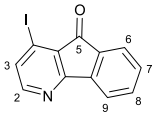
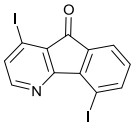
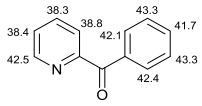
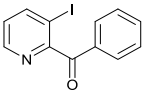
Because of their low compatibility with organolithiums, ketone-containing substrates have only been sporadically deprotometalated. Chromone and *N*-methyl quinolone could be deprotozincated using TMP-based zinc amides (TMP = 2,2,6,6-tetramethylpiperidino) either next to the carbonyl (3 position) or to the other heteroatom (2 position), respectively in the absence or presence of $MgCl_2$, resulting of the Lewis acid coordination by the ketone.[13] Pyronones[13a,14] were functionalized at C3 by using TMPZnCl·LiCl whereas thiochromone[13a] was attacked at C2 by the same reagent. Tropolones were deprotometalated next to the function upon treatment by TMPZnCl·LiCl.[15] Five-membered heteroaromatic aldehydes[16] were similarly functionalized using TMP-based zinc amides. In contrast, very few diaryl ketones were concerned: benzoyl behaved as tolerated group in the TMPMgCl·LiCl-mediated deprotonation of a polysubstituted diethyl 1,3-phenylenedicarboxylate,[17] whereas it only acted as directing group in the deprotometalation of benzophenone using a lithium-cadmium base.[18]

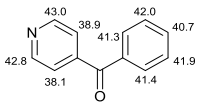
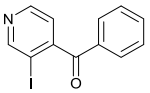
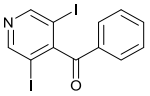
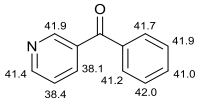
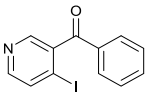
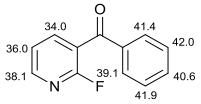
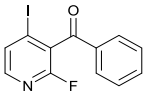
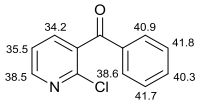
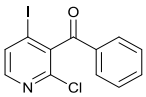
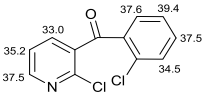
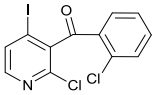
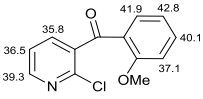
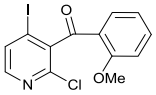
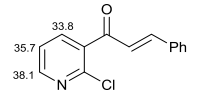
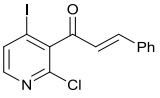
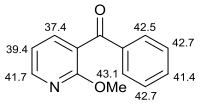
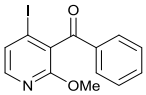
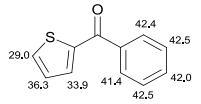
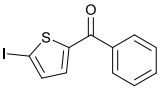
Ketones are compatible to some extent with hindered lithium amides such as LiTMP, as shown for example in the generation of lithium enolates. In contrast, these functions are attacked by organolithiums.[19] Thus, to tackle the compatibility issue between organolithiums and ketones, we planned LiTMP-mediated deprotometalation in the presence of a zinc-based in situ trap. Studies have shown that it is possible to employ species such as $Zn(TMP)_2$[20] and $ZnCl_2·2LiCl$[21] to intercept polar arylmetals. Within this study, we chose $ZnCl_2$·TMEDA[22] (TMEDA = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine) as in situ trap to attempt deprotolithiation followed by 'trans-metal trapping'[23] and iodolysis from various diaryl ketones (Table 1).

Xanthone dimethyl acetal can be dimetalated next to the pyran oxygen (4 and 5 positions) in tetrahydropyran at -13 °C upon treatment by butyllithium (3 equiv.) in the presence of potassium *tert*-butoxide (3 equiv.), a result evidenced by subsequent trapping with iodomethane.[24] Treatment of xanthone (**1a**) in THF containing $ZnCl_2$·TMEDA (1 equiv.) with LiTMP (1.5 equiv.) at -55 °C for 15 min and then iodine (1.5 equiv.) provided the 1-iodo derivative **2a** in 72% yield (entry 1). Thioxanthone (**1b**) was similarly converted to afford **2b** (entry 2). The calculated pK_a values of **1a**,**b** can help rationalize this regioselectivity change and explain the directing group properties of the ketone. Compared with those next to the ketone function (1 and 8 positions), CH acidities next to the pyran or thiopyran heteroatom (4 and 5 positions) are higher. The observed deprotonation at the 1 position (beyond thermodynamic acidity)[11] could result from (i) ketone coordination to lithium, with induced acidity increase, (ii) favored approach of the base, and/or (iii) stabilization. Indeed, when compared with esters and *N*,*N*-dialkylcarboxamides, the coordination ability of the ketone carbonyl group is known to be higher.[7]

Table 1. Substrates **1** and their calculated pK_a (THF) values, and iodinated aromatic ketones **2** obtained by deprotometalation-iodination.



Entry	Ketone **1**	Iodoketone **2**, Yield[a] (%)
1	 **1a**	 **2a**, 72%
2	 **1b**	 **2b**, 53% 80%[b]
3	 **1c**	 **2c**, 52%  **2c'**, 35%
4	 **1d**	 **2d**, 60%  **2d'**, 10%
5	 **1e**	 **2e**, 60%
6	 **1f**	 **2f**, 33%[c]  **2f'**, 20%[c]
7[b]	 **1g**	 **2g**, 50%[d]

8[b,e]		**1h**	 	**2h**, 45% **2h'**, 10%
9		**1i**		**2i**, 30% 37%[f]
10		**1j**		**2j**, 63%
11		**1k**		**2k**, 73%
12		**1l**		**2l**, 78%
13		**1m**		**2m**, 70%
14		**1n**		**2n**, 27%
15		**1o**		**2o**, 88%
16		**1p**		**2p**, 80%

[a] After purification by column chromatography. [b] Reaction carried out at -30 °C instead of -55 °C. [c] Other products also formed but could not be isolated or even identified. [d] A similar yield was obtained by using 2 equiv. of $ZnCl_2$·TMEDA. [e] Reaction carried out by using 2 equiv. (instead of 1.5 equiv.) of LiTMP. [f] By performing the reaction at -70 °C (instead of -55 °C).

From xanthone (**1a**) to fluorenone (**1c**), changes were noticed. Thus, whereas the iodide **2a** was isolated in 72% yield (together with recovered starting material), the 1-iodo derivative **2c** was obtained in 52% yield due to the competitive formation of the keto-alcohol **2c'** (entry 3). The latter had previously been isolated in 63% yield by reacting fluorenone (**1c**) with the base prepared in situ from $ZnCl_2$·TMEDA and LiTMP in a 1:3 ratio, and supposed to be LiTMP-$Zn(TMP)_2$,[20] with $Zn(TMP)_2$ acting as in situ trap.[25] Because arylzincs hardly react with ketones,[26] **2c'** would rather result from an addition of the generated 1-lithiofluorenone onto starting **1c**. At first sight, this is surprising since fluorenone (**1c**) benefits from a more favorable CH acidity at its 1 position than xanthone (**1a**). That such a competitive reaction does not take place from **1a** is in favor of an impact of the ketone carbonyl orientation on the stabilization of the lithio compound before its interception by 'trans-metal trapping'. This is also in accordance with data previously recorded with *N*,*N*-dialkylcarboxamides as deprotolithiation directing groups. Indeed, from studies performed on benzamides, Beak and co-workers suggest a correlation between the reaction efficiency and the distance from the directing group oxygen to the ortho hydrogen, as well as an optimal distance to accommodate the base effectively in the transition structure.[27]

By switching from symmetrical xanthone (**1a**) to the dissymmetrical azaxanthone **1d**, one moves from two different potential deprotometalation sites to four. Nevertheless, from the two CH sites next to the carbonyl group, the pyridine 4 position is clearly the more acidified, and it is logically attacked to give the 4-iodo derivative **2d** in 60% yield (entry 4). The corresponding thio analog **2e** was obtained in 60% yield by reacting the azathioxanthone **1e** under the same conditions (entry 5). In the case of **1d**, the diiodide **2d'** resulting from a two-fold deprotonation at the 4 and 9 positions was also isolated (entry 4); that such a diiodo derivative is not formed from **1e** might result from a lower propensity of sulfur to coordinate lithium, when compared with oxygen.

Due to its strong ability to coordinate lithium, the pyridine nitrogen is a good candidate to compete with the ketone oxygen in coordinating metals. Thus, it is not surprising that the azafluorenone **1f** is also attacked at its 9 position (to afford **2f'** in 20% yield) in addition to the 4 one giving **2f** in 33% yield (entry 6). The second functionalization at the 9 position might happen after a first deprotolithiation-'trans-metal trapping' at the 4 position, as previously observed from other heterocycles.[9a,28]

Because of their π-deficiency, benzoylpyridines are more sensitive toward nucleophiles than simpler aryl ketones; not only the function, but also the pyridine ring (and in particular when the ketone function activates its 2 and 4 positions toward nucleophilic attack) can be subjected to the addition of organolithiums. From 2-benzoylpyridine (**1g**), optimization of the reaction conditions was carried out in THF containing $ZnCl_2$·TMEDA (1 equiv.) by using four different reaction temperatures, between -70 and -10 °C, and four different amounts of LiTMP, between 1 and 3 equiv. The best results were observed when 1.5 equiv. of LiTMP were employed at -30 °C for 15 min before interception with iodine to furnish the 3-iodo derivative **2g** in 50% yield (entry 7). The reaction from 4-benzoylpyridine (**1h**) was performed as for its 2-isomer, but using 2 equiv. of LiTMP; under these conditions, the 3-iodo derivative **2h** was isolated in 45% yield (entry 8).

Among the three different benzoylpyridines used **1g**-**i**, 3-benzoylpyridine (**1i**) is by far the more sensitive due to its free 4 position next to the ketone function.[29] To limit side nucleophilic attacks, the reaction has to be conducted at lower temperatures. Under the conditions used to make **1a**-**f** react (reaction at -50 °C), the product **2i** resulting from a metalation at the 4 position was isolated from a complex mixture in 30% yield. At -70 °C, the result was slightly improved, with **2i** obtained in 37% yield (entry 9). Diiodides were suspected as side products in the course of the reactions coming from **1g**-**i**; unambiguously, such

a derivative (**2h'**) was obtained in 10% yield from **1h** (entry 8).

The pyridine regioselective deprotonation of **1g**-**i** is in accordance with higher calculated pK_a values for the phenyl ring. If the pyridine pK_a values might help understand regioselective deprotometalation next to the ketone in the case of **1h** and **1i**, things are different for **1g**. Indeed, for the latter, the most acidic sites are rather the 4 and 5 positions whereas the reaction takes place at the 3 position flanked by the function (entries 7-9). It is thus of importance to take into account possible coordination of the present heteroatoms onto metals in order to have a better idea of the pK_a values within premetalation complexes or transition structures. To this purpose, we calculated the CH acidities of the 1:1 complexes between **1g**-**i** and LiTMP (Figure 1). As it was proved earlier for methoxypyridines,[28e] coordination by nitrogen was predicted to be slightly more effective than by oxygen (with the corresponding isomeric complexes being by 0.9 kcal mol^{-1} more stable for **1h** and 1.1 kcal mol^{-1} for **1i**; in the case of **1g**, both atoms take part in the complexation). The metal coordination by the ring nitrogen lone pair drastically increases the pyridine CH acidity. Thus, in the case of **1g**·LiTMP, metal chelation strongly increases the acidity at the 3 position, adjacent to the ketone function. Similar coordination by the ketone oxygen can also operate to increase acidity, favor the approach of the base and stabilize the arylmetal species.

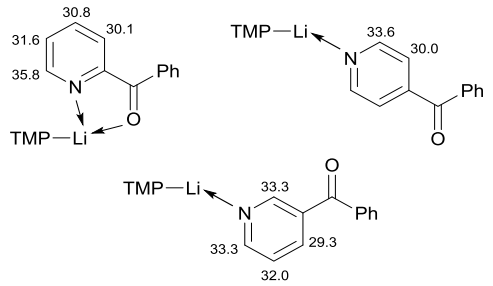


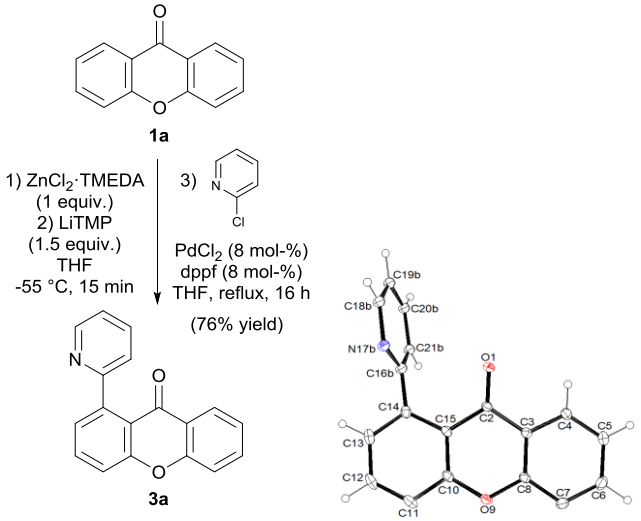
Figure 1. Selected calculated pK_a values of the complexes between **1g**·LiTMP (top, left), **1h**·LiTMP (top, right) and **1i**·LiTMP (bottom).

To identify which metal, between lithium and zinc, is involved in such coordinations, we first compared spectral data of 3-benzoylpyridine (**1i**), $ZnCl_2$·TMEDA, TMEDA and 3-benzoylpyridine (**1i**) in the presence of $ZnCl_2$·TMEDA. The IR, ^{1}H and ^{13}C NMR spectra recorded in d^8-THF showed no significant difference between 3-benzoylpyridine (**1i**) with and without $ZnCl_2$·TMEDA on the one hand, and between $ZnCl_2$·TMEDA in the presence or not of **1i** on the other hand (e.g. ~1 cm^{-1} for the C=O IR absorption band; ≤ 0.1 ppm for ^{13}C NMR chemical shifts). Because the chelating TMEDA is not displaced by addition of 3-benzoylpyridine (**1i**), and TMPZnCl·LiCl not capable of deprotonation at such low temperatures,[16b,16c,30] we can suggest that $ZnCl_2$·TMEDA only operates after deprotolithiation and intercepts the generated aryllithium.

On this basis, the scope of our approach will be determined by the efficiency of the in situ traps employed, and by the stability of the transient lithiated arylketones involved. When present at pyridine 2 position,[31] halogens are known to acidify the 4 position, and thus to stabilize a 4-lithio derivative. This long-range effect, well-known for bromine,[32] also exists for chlorine[33] and fluorine.[28e,34] As a consequence, the deprotolithiation-transmetalation-iodolysis sequence carried out on the 2-halogenated 3-benzoylpyridines **1j**-**m** offered more satisfactory yields (63-78%, entries 10-13) than from reference 3-benzoylpyridine (**1i**) (30%, entry 9). Nevertheless, in spite of the presence of a stabilizing chloro group, the reaction from **1n** proved more complex, only affording **2n** in a modest 27% yield (entry 14). Unlike halogens, methoxy is not a suitable group to acidify long-range positions.[28e] If the yield to convert **1o** into **2o** was found higher (88% against 30% from **1i** under similar reaction conditions, entry 15), it might rather be related to the higher propensity of methoxy to make the pyridine ring less prone to nucleophilic attacks.[8]

In all the above examples, functionalization takes place at a position adjacent to the ketone function. It was thus of interest to attempt the reaction on a substrate benefiting from a more activated site. To this purpose, we chose 2-benzoylthiophene (**1p**) for which the most acidic site is next to sulfur. When submitted to LiTMP in the presence of $ZnCl_2$·TMEDA as before, the iodide **2p** logically resulting from proton abstraction at the thiophene 5 position was isolated in 80% yield (entry 16).

Until now, we used iodine to evidence the formation of deprotometalated species, the resulting iodoketones being of high relevance to perform further functionalization. It is also of interest to combine deprotometalation with Negishi-type cross-coupling[35] in order to directly connect aryl groups. In the presence of catalytic amounts of palladium(II) chloride and 1,1'-diphenylphosphinoferrocene (dppf), and under THF reflux, the deprotozincated product coming from xanthone (**1a**) was coupled with 2-chloropyridine to afford the derivative **3a** in 76% yield (Scheme 1). The products **2d**, **2f**, **2g**, **2h**, **2h'**, **2i**, **2j**, **2k**, **2l**, **2m**, **2o**, **2p** and **3a** were identified unambiguously by X-ray diffraction (see Supporting information).

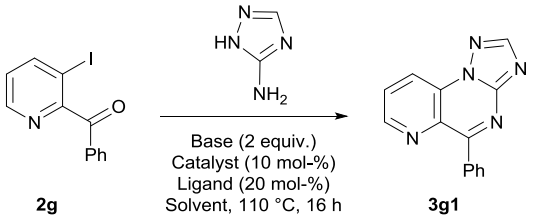


Scheme 1. Zincation of xanthone (**1a**) using LiTMP in the presence of $ZnCl_2$·TMEDA followed by palladium-catalyzed cross-coupling to afford **3a**; ORTEP diagram (30% probability) of compound **3a**.

Pyridopyrimidine is a core present in compounds of medicinal importance for their anticancer, CNS, fungicidal, antiviral, anti-inflammatory, antimicrobial and antibacterial properties.[36] To access such compounds, efficient synthetic methods are required. The two-fold functionalization of the bifunctional substrates **2** combining C-N bond formation[3] from the iodide with imine formation[4] from the ketone appears as an attracting way to reach original fused systems based on pyrido[2,3-*e*]pyrimidines.

To this end, we first considered the reaction between 2-benzoyl-3-iodopyridine (**2g**) and 3-amino-1,2,4-triazole (Table 2). Our attempt to obtain the 1,3,4,6,9b-pentaazacyclopenta[*a*]naphthalene **3g1** by simply heating the two coupling partners in the presence of a base (cesium carbonate) in DMF at 110 °C, as reported from 2-fluoro, 2-chloro and 2-bromo aryl ketones,[37] completely failed (entry 1). The starting materials were also recovered upon treatment by cesium carbonate and catalytic copper(I) oxide in DMSO at 110 °C (entry 2), which are suitable conditions for coupling iodopyridines.[38] Only traces of the expected product **3g1** were detected by using potassium carbonate and catalytic copper(I) iodide in either ethylene glycol (entry 3), or DMF containing ethylenediamine as ligand (entry 4), which are appropriate conditions for reacting 2-bromobenzaldehydes and 2-bromoaryl ketones with 3-aminopyrazoles.[4b] Finally, by keeping copper(I) iodide,[4b] employing potassium triphosphate as base,[39] and DMSO as solvent (no need of ligand),[38] led to **3g1**, which was isolated in 54% yield (entry 5; Figure 2, left).

Table 2. Optimization of the conversion of 2-benzoyl-3-iodopyridine (**2g**) into 5-phenyl-1,3,4,6,9b-pentaazacyclopenta[*a*]naphthalene (**3g1**).

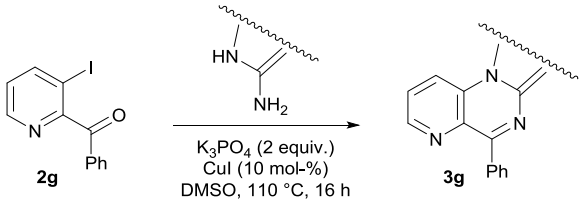


2g **3g1**

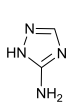
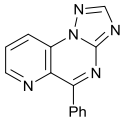
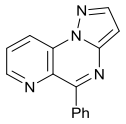
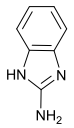
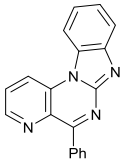
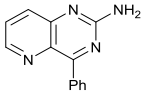
Entry	Base	Catalyst	Ligand	Solvent	Yield[a]
1	Cs_2CO_3	-	-	DMF	-
2	Cs_2CO_3	Cu_2O	-	DMSO	-
3	K_2CO_3	CuI	-	$(CH_2OH)_2$	traces
4	K_2CO_3	CuI	$(CH_2NH_2)_2$	DMF	traces
5	K_3PO_4	CuI	-	DMSO	54%

These conditions in hand, we attempted the reactions between 2-benzoyl-3-iodopyridine (**2g**) and other diamines (Table 3). Besides 3-amino-1,2,4-triazole (entry 1), we chose for this purpose commercial 3-aminopyrazole (entry 2), 2-aminobenzimidazole (entry 3) and guanidine (entry 4). Whereas the 4,6,7,11b-tetraazabenzo[*c*]fluorene **3g3** was obtained in a 50% yield (entry 3; Figure 2, right) similar to **3g1** (entry 1), the 1,4,6,9b-tetraaza-cyclopenta[*a*]naphthalene **3g2** (entry 2) and 2-aminopyrido[3,2-*d*]pyrimidine **4g** (entry 4) were isolated in only 18% and 30% yield, respectively. For the latter, not only starting materials, but also deiodinated **1g**, were recovered.

Table 3. Conversion of the iodoketone **2g** into fused systems based on pyrido[2,3-*e*]pyrimidines.



2g **3g**

Entry	Diamine	Product **3g**, Yield[a]
1		 **3g1**, 54%
2		 **3g2**, 18%
3		 **3g3**, 50%
4		 **4g**, 30%

[a] After purification by column chromatography.

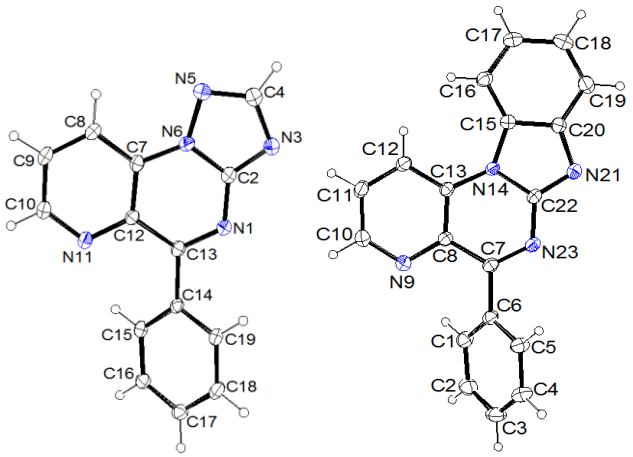


Figure 2. ORTEP diagrams (30% probability) of compounds **3g1** and **3g3**.

The importance of that 2-aminopyrimidine motif in various biologically active scaffolds[5] prompted us to identify the reasons behind this failure. Optimization of the amounts employed in the reaction between 2-benzoyl-3-iodopyridine (**2g**) and guanidine was thus performed. It was noticed that increasing the amounts of both guanidine (to 2 equiv. of the hydrochloride) and base (to 4 equiv.) could lead to **4g** in an improved 77% yield (Table 4, entry 1, Figure 3). Albeit in a somewhat lower yield of 61%, the 2-aminopyrido[3,4-*d*]pyrimidine **4h** was similarly formed from 4-benzoyl-3-iodopyridine (**2h**) (entry 2).

In order to access the 2-aminopyrido[4,3-*d*]pyrimidines **4i** and **4o**, for which the pyridine nitrogen is at the 6 position, we respectively involved in the reaction the 3-benzoyl-4-iodopyridines **2i** and **2o**. In spite of the known higher reactivity of 4-iodopyridines (higher partial positive charge on the carbon bearing the halogen) over 3-iodopyridines in copper-catalyzed C-N bond formation,[40] similar yields of 68% and 65% were remarked from **2i** and **2o** (entries 3 and 4, Figure 3).

To synthesize the isomer possessing the pyridine nitrogen at the 8 position, the 2-aminopyrido[2,3-*d*]pyrimidine **4j**, we rather reacted 3-benzoyl-2-fluoropyridine, easily prepared[41] from 2-fluoropyridine, with guanidine in the presence of potassium carbonate in dimethylacetamide at 135 °C[42] (entry 5, Figure 3).

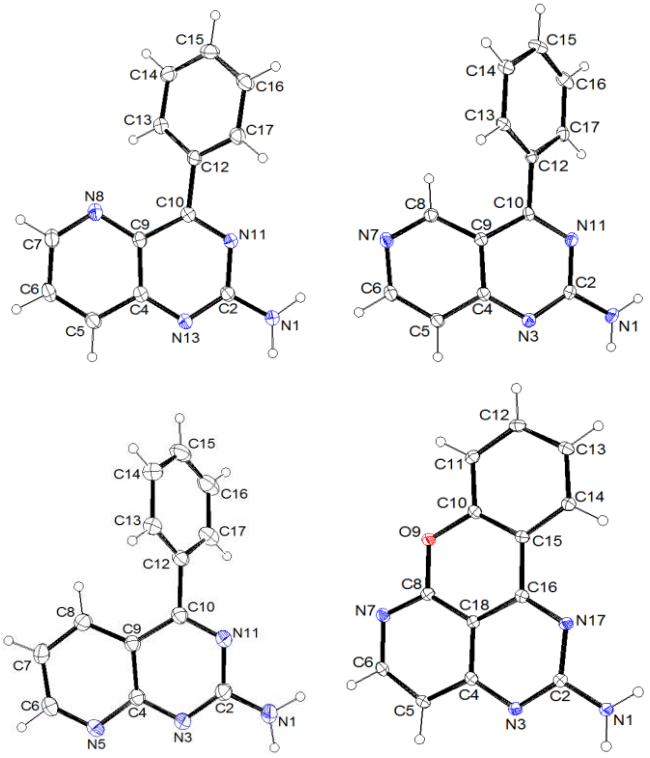
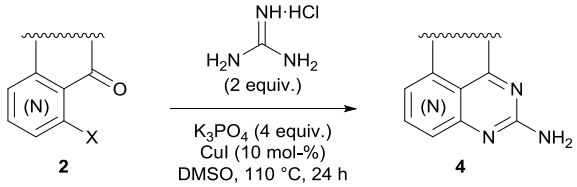


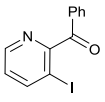
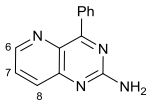
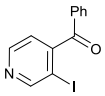
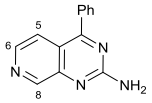
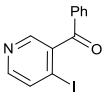
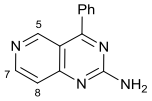
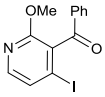
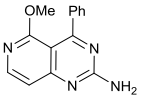
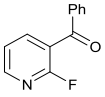
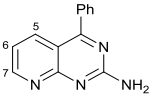
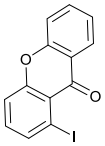
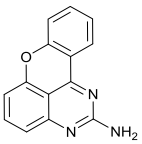
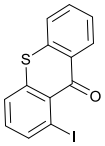
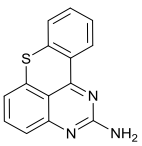
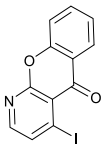
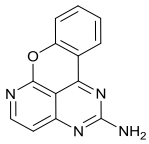
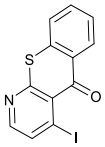
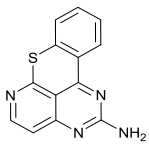
Figure 3. ORTEP diagrams (30% probability) of compounds **4g**, **4i**, **4j** and **4d**.

In spite of the widespread biological properties of quinazolines, the derived tetracyclic benzopyrano-[5b] and benzothiopyrano[4,3,2-*de*]quinazolines[43] (for which a 1,3-diazine ring is fused to a xanthene) have very rarely been synthesized. By applying the optimized method, we could convert the iodides **2a** and **2b** into the corresponding 2-amino derivatives **4a** and **4b** in high yields (entries 6 and 7).

Table 4. Conversion of the iodoketones **2** into fused systems based on 2-aminopyrimidines.



2 **4**

Entry	Halogenoketone **2**		Product **4**, Yield[a]
1		**2g**	 **4g**, 77%
2		**2h**	 **4h**, 61%
3		**2i**	 **4i**, 68%
4		**2o**	 **4o**, 65%
5[b]		**1j**	 **4j**, 94%
6		**2a**	 **4a**, 86%
7		**2b**	 **4b**, 84%
8		**2d**	 **4d**, 83%
9		**2e**	 **4e**, 88%

[a] After purification by column chromatography. [b] Reaction performed without CuI in the presence of K_2CO_3 instead of K_3PO_4, and using dimethylacetamide as solvent at 135 °C.

The 7-oxa-1,3,6-triazabenz[*de*]anthracene skeleton has been reported once only[44] whereas the 7-thia analog has never been described. We could prepare for the first time 2-amino derivatives, the tetracycles **4d** and **4e** (entries 8 and 9, Figure 3), which are potential candidates for biological studies.

All the pyrimidine-containing products were evaluated for their biological properties. They were first screened for their antimicrobial activity against bacteria and for their antifungal activity (Table 5). An effect on the microbial growth of strains of bacteria was noticed in the case of **4g**, **4h**, **4i**, **4o**, **4j**, **4a**, **4b**, **4d** and **4e**, and a fairly broad spectrum of activity was precisely observed in the case of **4j** and **4b**, highlighting their potential antibacterial effect.

Table 5. Antimicrobial and antifungal activity of the compounds **3g1**, **3g2**, **3g3**, **4g**, **4h**, **4i**, **4o**, **4j**, **4a**, **4b**, **4d** and **4e**.[a]

Compound	Amount (µg dissolved in DMSO)	*Escherichia coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Enterococcus faecium*	*Listeria monocytogenes*	*Candida dubliniensis*
3g1[b]	250	±	±	0	±	0	0
3g2[b]	200	0	0	0	0	±	0
3g3[b]	200	0	0	0	0	0	0
4g[c]	250	-	-	±	13	24	19
4h[c]	250	-	-	-	8	27	-
4i[c]	250	-	-	±	12	20	17
4o[c]	250	10	±	±	13	32	23
4j[b]	250	10	17	±	8	-	13
4a[c]	250	-	-	±	10	16	±
4b[c]	250	15	17	±	13	17	17
4d[c]	250	-	-	±	10	-	-
4e[c]	250	-	-	±	12	-	-
DMSO		0	0	0	0	0	0
Reference compound		28 Ceftazidime (30 µg)	28	18 Vancomycin (30 µg)	24	30 Ampicillin (25 µg)	10 Nystatin (416 UI)

[a] The diameters of zones of inhibition are given in mm. [b] 10 µL/well. [c] 50 µL/well.

As evidenced in Table 6, all the compounds showed an antioxidant activity around 50%. The hemolytic activity was tested for the compounds **4g**, **4h**, **4i**, **4o**, **4j**, **4a**, **4b**, **4d** and **4e** (250 µg) that showed an antimicrobial activity. Small hemolytic activities below 15% were recorded (data not shown). The absence or low toxicity on the human red blood cells, observed for products that have demonstrated an antimicrobial effect, highlights the value of their specific and selective antibacterial and antifungal effects and equally emphasizes a possible therapeutic interest of their application.

Table 6. Antioxidant activity of the compounds.

Compound	RSA (%)[a] at t = 0 min	RSA (%)[a] at t = 30 min
4g	42	46
4h	43	47
4i	43	49
4o	45	48
4j	48	51
4a	44	45
4b	44	49
4d	44	47
4e	45	46

[a] Percentage of the Radical Scavenger Activity.

Still in order to study the bioactivity of the synthesized compounds, we evaluated their bioactivity against a short panel of disease-related serine/threonine protein kinases: three human cyclin-dependent kinases (CDK2/Cyclin A, CDK5/p25 and CDK9/Cyclin T), human proto-oncogene PIM1, glycogen-synthase kinase-3 (native GSK-3 purified from porcine brain), receptor-interacting protein 3 (RIPK3), human mitotic kinases Haspin and Aurora B, and leishmania casein kinase 1 (*Lm*CK1 from *Leishmania major*).

Whereas none of the derivatives was shown to inhibit significantly CDK5/p25, CDK9/Cyclin T, GSK-3 and RIPK3, positive results were noticed with CDK2/Cyclin A, PIM1, *Lm*CK1, Haspin and Aurora B (Table 7). These first results were then verified by testing the dose-dependent effect of the small chemical compounds against a selected panel of kinases (Table 8).

The inhibition reported for **4b** on PIM1 is interesting. Indeed, Horiuchi *et al.* showed that PIM1 kinase inhibition should be explored for developing targeted therapy against triple-negative breast tumors with elevated MYC expression.[45] Moreover, despite the structural similarities between the three CDKs tested, **4b** was shown to be selective for CDK2/Cyclin A.

Table 7. Inhibitory activities of synthesized compounds against a short panel of five disease-related protein kinases. The table displays the remaining activities detected after treatment with 10 µM of the tested compounds. Results are expressed in % of maximal activity, i.e. measured in the absence of inhibitor. ATP concentration used in the kinase assays was 15 µmol/L (values are means, n = 2). Kinases are from human origin unless specified: *Lm*, *Leishmania major*.

Compound	CDK2/Cyclin A	PIM1	Haspin	Aurora B	*Lm*CK1
3g1	78	82	103	109	56
3g2	57	87	117	49	61
3g3	82	81	102	70	65
4g	83	104	107	98	111
4h	67	92	99	60	65
4i	65	95	98	80	61
4o	76	74	115	106	47
4j	78	85	102	64	58
4a	70	49	65	51	**40**
4b	**41**	**32**	59	**40**	55
4d	54	86	73	**15**	**22**
4e	59	77	**41**	45	**37**

Table 8. Dose-dependent effect of the tested synthesized compounds on the kinase activities. The IC_{50} values are reported in µM. Compounds showing less than 50% inhibition at 10 µM were considered as inactive (values are means, n = 3).

Compound	CDK2/Cyclin A	PIM1	Haspin	Aurora B	*Lm*CK1
3g1	>10	>10	>10	>10	>10
3g2	>10	>10	>10	>10	>10
3g3	>10	>10	>10	>10	>10
4g	>10	>10	>10	>10	>10
4h	>10	>10	>10	>10	>10
4i	>10	>10	>10	>10	>10
4o	>10	>10	>10	>10	**4.5**
4j	>10	>10	>10	>10	>10
4a	>10	>10	>10	>10	**6.5**
4b	**2.0**	**0.61**	>10	>10	>10
4d	>10	>10	>10	**1.9**	**1.8**
4e	>10	>10	>10	>10	**1.0**

Conclusions

We showed that the carbonyl group of aromatic ketones can be efficiently employed to induce deprotolithiation at an adjacent site. The reaction can be carried out by using a hindered non-nucleophilic lithium amide in the presence of a zinc salt that acts as in situ trap. The usefulness of aromatic ketones halogenated next to the carbonyl function was demonstrated by the synthesis of promising fused systems based on 2-aminopyrimidines.

Experimental Section

All the reactions were performed under an argon atmosphere. THF was distilled over sodium/benzophenone. Column chromatography separations were achieved on silica gel (40-63 µm). Melting points were measured on a Kofler apparatus. IR spectra were taken on a Perkin-Elmer Spectrum 100 spectrometer. ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III spectrometer at 300 MHz and 75 MHz, respectively. ^{1}H chemical shifts (δ) are given in ppm relative to the solvent residual peak, ^{13}C chemical shifts are relative to the central peak of the solvent signal,[46] and coupling constants (*J*) are given in Hz.

1-Azaxanthone (**1d**),[47] 1-azathioxanthone (**1e**),[48] 1-azafluorenone (**1f**),[49] 3-benzoyl-2-fluoropyridine (**1j**),[41] 3-benzoyl-2-chloropyridine (**1k**),[41] 2-chloro-3-(2-chlorobenzoyl)pyridine (**1l**),[8] 2-chloro-3-(2-methoxybenzoyl)pyridine (**1m**),[8] 2-chloro-3-cinnamoylpyridine (**1n**),[8] 3-benzoyl-2-methoxypyridine (**1o**),[41] and $ZnCl_2$·TMEDA[22] were prepared as described previously.

General procedure 1 for the synthesis of the aryl iodides 2. To a stirred mixture of the required ketone (1.0 mmol) and $ZnCl_2$·TMEDA (0.26 g, 1.0 mmol) in THF (3 mL) at -30 °C was added dropwise a solution of LiTMP (prepared by adding BuLi (about 1.6 M hexanes solution, 1.5 mmol) to a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.5 mmol) in THF (3 mL) and stirring for 5 min) cooled at -30 °C. After 15 min at -30 °C, a solution of I_2 (0.38 g, 1.5 mmol) in THF (5 mL) was introduced, and the mixture was stirred overnight before addition of an aqueous saturated solution of $Na_2S_2O_3$ (5 mL) and extraction with AcOEt (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (the eluent is given in the product description).

General procedure 2 for the synthesis of the aryl iodides 2. To a stirred mixture of the required ketone (1.0 mmol) and $ZnCl_2$·TMEDA (0.26 g, 1.0 mmol) in THF (3 mL) at -55 °C was added dropwise a solution of LiTMP (prepared by adding BuLi (about 1.6 M hexanes solution, 1.5 mmol) to a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.5 mmol) in THF (3 mL) and stirring for 5 min) cooled at -55 °C. After 15 min at -55 °C, a solution of I_2 (0.38 g, 1.5 mmol) in THF (5 mL) was introduced, and the mixture was stirred overnight before addition of an aqueous saturated solution of $Na_2S_2O_3$ (5 mL) and extraction with AcOEt (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (the eluent is given in the product description).

General procedure 3 for the synthesis of the aryl iodides 2. To a stirred mixture of the required ketone (1.0 mmol) and $ZnCl_2$·TMEDA (0.26 g, 1.0 mmol) in THF (3 mL) at -30 °C was added dropwise a solution of LiTMP (prepared by adding BuLi (about 1.6 M hexanes solution, 2.0 mmol) to a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.33 mL, 2.0 mmol) in THF (3 mL) and stirring for 5 min) cooled at -30 °C. After 15 min at -30 °C, a solution of I_2 (0.51 g, 2.0 mmol) in THF (5 mL), and the mixture was stirred overnight before addition of an aqueous saturated solution of $Na_2S_2O_3$ (5 mL) and extraction with AcOEt (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by

chromatography over silica gel (the eluent is given in the product description).

General procedure 4 for the synthesis of the fused systems based on pyrido[2,3-e]pyrimidines 3g. A mixture of CuI (20 mg, 0.10 mmol), the required amine (1.2 mmol), K_3PO_4 (0.44 g, 2.0 mmol), 2-benzoyl-3-iodopyridine (**2g**, 0.31 g, 1.0 mmol) and DMSO (1.4 mL) was degased and heated under argon and stirring at 110 °C for 16 h. After filtration over celite (washing using AcOEt) and removal of the solvents, the crude product is purified by chromatography over silica gel (the eluent is given in the product description).

General procedure 5 for the synthesis of the fused systems based on 2-aminopyrimidines 4. A mixture of CuI (20 mg, 0.10 mmol), guanidine hydrochloride (0.19 g, 2.0 mmol), K_3PO_4 (0.88 g, 4.0 mmol), the required halogenopyridine (1.0 mmol) and DMSO (0.5 mL) was degased and heated under argon at 110 °C for 24 h. After filtration over celite (washing using AcOEt) and removal of the solvents, the crude product is purified by chromatography over silica gel (the eluent is given in the product description).

*1-Iodo-9-xanthone (**2a**).* The general procedure 2 using 9-xanthone (**1a**, 0.20 g) gave **2a** (eluent: heptane-CH_2Cl_2 100:0 to 80:20) in 72% yield (0.23 g) as a pale yellow powder: mp 176 °C (lit.[24] 172-173.5 °C); IR (ATR): 663, 752, 777, 849, 903, 931, 1108, 1147, 1161, 1234, 1255, 1297, 1328, 1346, 1421, 1443, 1466, 1554, 1590, 1612, 1661, 3065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (dd, 1H, *J* = 8.4 and 7.8 Hz), 7.36 (ddd, 1H, *J* = 8.1, 7.2 and 0.9 Hz), 7.41 (dm, 1H, *J* = 9.0 Hz), 7.48 (dd, 1H, *J* = 8.4 and 1.2 Hz), 7.70 (ddd, 1H, *J* = 8.7, 7.2 and 1.8 Hz), 8.00 (dd, 1H, *J* = 7.6 and 1.1 Hz), 8.31 (ddd, 1H, *J* = 8.1, 1.8 and 0.5 Hz); ^{13}C NMR ($CDCl_3$) δ 91.3 (C), 117.7 (CH), 119.1 (CH), 120.1 (C), 121.3 (C), 124.3 (CH), 127.3 (CH), 134.7 (CH), 135.0 (CH), 138.6 (CH), 154.9 (C), 156.8 (C), 175.4 (C). These data are similar to those reported previously.[24]

*1-Iodo-9-thioxanthone (**2b**).*[25,50] The general procedure 2 using 9-thioxanthone (**1b**, 0.22 g) gave **2b** (eluent: heptane-CH_2Cl_2 100:0 to 80:20) in 53% yield (0.18 g) as a greenish powder: mp 156-158 °C; IR (ATR): 664, 711, 745, 777, 923, 1080, 1159, 1241, 1300, 1425, 1537, 1573, 1589, 1641, 3062 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10 (t, 1H, *J* = 7.8 Hz), 7.41-7.47 (m, 2H), 7.52-7.60 (m, 2H), 8.14 (dd, 1H, *J* = 7.5 and 1.2 Hz), 8.47 (dm, 1H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 94.8 (C), 125.5 (CH), 126.7 (CH), 126.8 (CH), 127.7 (C), 129.6 (C), 130.2 (CH), 131.8 (CH), 132.3 (CH), 135.0 (C), 138.7 (C), 141.8 (CH), 179.5 (C).

*1-Iodo-9-fluorenone (**2c**).* The general procedure 2 using 9-fluorenone (**1c**, 0.18 g) gave **2c** (eluent: heptane-AcOEt 90:10) in 52% yield (0.16 g) as a yellow powder: mp 148 °C (lit.[51] 147-148.5 °C); IR (ATR): 733, 747, 784, 792, 918, 1056, 1085, 1126, 1149, 1186, 1257, 1281, 1295, 1437, 1563, 1588, 1606, 1715, 3048 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15 (dd, 1H, *J* = 8.1 and 7.5 Hz), 7.33 (ddd, 1H, *J* = 10.2, 7.5 and 4.8 Hz), 7.49-7.56 (m, 3H), 7.68-7.74 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 91.6 (C), 120.1 (CH), 120.2 (CH), 124.7 (CH), 129.8 (CH), 134.0 (C), 134.1 (C), 135.0 (CH), 135.1 (CH), 140.6 (CH), 142.0 (C), 147.2 (C), 191.8 (C). *9'-Hydroxy-1,9'-bi-9-fluorenone (**2c'**)* was also isolated in 35% yield (0.13 g) as a yellow powder: mp 222-224 °C (lit.[52] 222-224 °C); IR (ATR): 686, 728, 753, 771, 803, 909, 958, 1066, 1102, 1139, 1195, 1265, 1284, 1427, 1451, 1469, 1572, 1592, 1607, 1683, 2245, 3060, 3302 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.47 (dd, 1H, *J* = 8.1 and 0.9 Hz), 7.11 (dd, 1H, *J* = 8.1 and 7.5 Hz), 7.28 (td, 2H, *J* = 7.5 and 0.9 Hz), 7.33-7.42 (m, 4H), 7.47-7.57 (m, 4H), 7.70 (d, 2H, *J* = 7.2 Hz), 7.78 (d, 1H, *J* = 7.2 Hz), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 85.5 (C), 119.9 (CH), 120.3 (2CH), 120.3 (CH), 124.7 (2CH), 125.3 (CH), 128.4 (CH), 128.4 (2CH), 129.2 (2CH), 129.6 (CH), 132.1 (C), 133.4 (C), 135.5 (CH), 136.0 (CH), 139.9 (2C), 144.3 (C), 146.8 (C), 148.8 (C), 149.5 (2C), 198.2 (C).

*4-Iodo-5*H*-benzopyrano[2,3-*b*]pyridin-5-one (**2d**).*[8] The general procedure 2 using 1-azaxanthone (**1d**, 0.20 g) gave **2d** (eluent: CH_2Cl_2-heptane 80:20) in 60% yield (0.19 g) as a yellow powder: mp 190-192 °C; IR (ATR): 728, 742, 761, 835, 922, 1085, 1115, 1183, 1219, 1248, 1274, 1318, 1346, 1367, 1443, 1464, 1537, 1557, 1612, 1659, 1724, 1978, 2925 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (ddd, 1H, *J* = 8.1, 6.9 and 1.1 Hz), 7.52 (dq, 1H, *J* = 8.4 and 0.6 Hz), 7.74 (ddd, 1H, *J* = 8.7, 6.9 and 1.5 Hz), 8.01 (d, 1H, *J* = 5.1 Hz), 8.17 (d, 1H, *J* = 4.8 Hz), 8.26 (ddd, 1H, *J* = 8.1, 1.8 and 0.6 Hz); ^{13}C NMR ($CDCl_3$) δ 106.6 (C), 116.0 (C), 118.3 (CH), 121.0 (C), 125.1 (CH), 127.2 (CH), 135.6 (CH), 135.8 (CH), 152.3 (CH), 154.3 (C), 160.2 (C), 176.1 (C). *4,9-Diiodo-5*H*-benzopyrano[2,3-*b*]pyridin-5-one (**2d'**)*[8] was also isolated in 10% yield (45 mg) as a yellow powder: mp 262-264 °C; IR (ATR): 734, 768, 920, 1019, 1101, 1266, 1369, 1428, 1444, 1538, 1655, 1722, 2924 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (t, 1H, *J* = 7.8 Hz), 8.07 (d, 1H, *J* = 4.8 Hz), 8.21-8.25 (m, 2H), 8.29 (dd, 1H, *J* = 7.2 and 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 85.2 (C), 106.9 (C), 115.7 (C), 121.8 (C), 126.5 (CH), 127.7 (CH), 136.1 (CH), 145.6 (CH), 152.7 (CH), 153.5 (C), 160.2 (C), 175.9 (C).

*4-Iodo-5*H*-benzothiopyrano[2,3-*b*]pyridin-5-one (**2e**).*[8] The general procedure 2 using 1-azathioxanthone (**1e**, 0.21 g) gave **2e** (eluent: CH_2Cl_2) in 60% yield (0.20 g) as a yellow powder: mp 184-186 °C; IR (ATR): 697, 724, 802, 922, 1079, 1166, 1232, 1301, 1319, 1348, 1412, 1433, 1521, 1542, 1588, 1643, 1945, 2234, 2929, 3087 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51 (ddd, 1H, *J* = 8.4, 6.9 and 1.2 Hz), 7.57 (ddd, 1H, *J* = 8.1, 1.5 and 0.6 Hz), 7.66 (ddd, 1H, *J* = 8.4, 6.9 and 1.5 Hz), 8.11 (d, 1H, *J* = 4.8 Hz), 8.17 (d, 1H, *J* = 5.1 Hz), 8.52 (ddd, 1H, *J* = 8.1, 1.5 and 0.6 Hz); ^{13}C NMR ($CDCl_3$) δ 107.4 (C), 125.3 (C), 125.9 (CH), 127.1 (CH), 128.9 (C), 130.4 (CH), 133.0 (CH), 135.2 (C), 136.8 (CH), 151.0 (CH), 159.7 (C), 179.8 (C).

*4-Iodo-5*H*-indeno[1,2-*b*]pyridin-5-one (**2f**).*[8] The general procedure 2 using 1-azafluorenone (**1f**, 0.18 g) gave **2f** (eluent: heptane-AcOEt 80:20) in 33% yield (0.10 g) as a yellow powder: mp 184 °C; IR (ATR): 669, 749, 805, 915, 1042, 1171, 1265, 1341, 1379, 1442, 1550, 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47 (td, 1H, *J* = 7.2 and 1.2 Hz), 7.61-7.67 (m, 2H), 7.76 (ddd, 1H, *J* = 7.2, 1.2 and 0.6 Hz), 7.87 (dt, 1H, *J* = 7.5 and 0.9 Hz), 8.14 (d, 1H, *J* = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 102.4 (C), 121.3 (CH), 124.5 (CH), 129.4 (C), 131.7 (CH), 134.6 (CH), 135.0 (C), 135.7 (CH), 141.3 (C), 152.7 (CH), 166.2 (C), 190.1 (C). *4,9-Diiodo-5*H*-indeno[1,2-*b*]pyridin-5-one (**2f'**)*[8] was also isolated in 20% yield (87 mg) as a yellowish powder: mp 244 °C; IR (ATR): 659, 693, 761, 783, 824, 924, 1054, 1102, 1164, 1266, 1338, 1369, 1454, 1543, 1556, 1713, 2854, 2924 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (dd, 1H, *J* = 7.8 and 7.2 Hz), 7.70 (d, 1H, *J* = 5.4 Hz) 7.76 (dd, 1H, *J* = 7.5 and 1.1 Hz), 8.07 (dd, 1H, *J* = 7.8 and 2.0 Hz), 8.30 (d, 1H, *J* = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 86.8 (C), 102.3 (C), 124.1 (CH), 129.6 (C), 132.2 (CH), 134.8 (CH), 137.1 (C), 141.4 (C), 147.5 (CH), 151.8 (CH), 165.8 (C), 188.7 (C).

*2-Benzoyl-3-iodopyridine (**2g**).*[8] The general procedure 1 using 2-benzoylpyridine (**1g**, 0.18 g) gave **2g** (eluent: heptane-AcOEt 80:20) in 50% yield (0.15 g) as a yellow powder: mp 98-100 °C; IR (ATR): 666, 702, 739, 795, 939, 1011, 1064, 1165, 1287, 1316, 1416, 1450, 1595, 1674, 3056 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16 (dd, 1H, *J* = 8.1 and 4.8 Hz), 7.44-7.50 (m, 2H), 7.61 (tt, 1H, *J* = 7.4 and 1.4 Hz), 7.81-7.86 (m, 2H), 8.26 (dd, 1H, *J* = 8.1 and 1.2 Hz), 8.63 (dd, 1H, *J* = 4.5 and 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 89.8 (C), 125.6 (CH), 128.8 (2CH), 130.6 (2CH), 134.1 (CH), 134.8 (C), 147.3 (CH), 148.1 (CH), 159.2 (C), 194.3 (C).

*4-Benzoyl-3-iodopyridine (**2h**).*[8] The general procedure 3 using 4-benzoylpyridine (**1h**, 0.18 g) gave **2h** (eluent: heptane-AcOEt 80:20) in 45% yield (0.14 g) as a yellow powder: mp 92-94 °C; IR (ATR): 683, 701, 728, 835, 938, 1011, 1082, 1175, 1262, 1281, 1316, 1394, 1448, 1580, 1595, 1669, 3058 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.19 (dd, 1H, *J* = 4.8 and 0.6

Hz), 7.41-7.48 (m, 2H), 7.61 (tt, 1H, *J* = 7.4 and 1.4 Hz), 7.72-7.76 (m, 2H), 8.61 (d, 1H, *J* = 4.8 Hz), 8.97 (d, 1H, *J* = 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 91.0 (C), 122.3 (CH), 128.9 (2CH), 130.2 (2CH), 134.0 (C), 134.4 (CH), 148.6 (CH), 151.3 (C), 157.7 (CH), 194.7 (C). *4-Benzoyl-3,5-diiodopyridine (**2h'**)*[8] was also isolated in 10% yield (43.5 mg) as a yellowish powder: mp 148 °C; IR (ATR): 683, 704, 728, 796, 934, 1037, 1174, 1202, 1270, 1314, 1389, 1450, 1499, 1580, 1595, 1672, 3059 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52 (td, 2H, *J* = 7.7 and 0.9 Hz), 7.68 (tt, 1H, *J* = 7.5 and 1.7 Hz), 7.79-7.83 (m, 2H), 8.91 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 90.7 (2C), 129.5 (2CH), 130.2 (2CH), 132.3 (C), 135.0 (CH), 155.4 (C), 156.3 (2CH), 194.8 (C).

*3-Benzoyl-4-iodopyridine (**2i**)*.[8] The general procedure 2 using 3-benzoylpyridine (**1i**, 0.18 g), but performed at -70 °C instead of -55 °C, gave **2i** (eluent: heptane-AcOEt 80:20) in 37% yield (0.11 g) as a yellow powder: mp 136-138 °C; IR (ATR): 656, 705, 731, 918, 938, 1156, 1259, 1290, 1317, 1393, 1449, 1538, 1558, 1580, 1667, 2928, 3063 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.46-7.53 (m, 2H), 7.65 (tt, 1H, *J* = 7.4 and 2.7 Hz), 7.78-7.84 (m, 2H), 7.91 (d, 1H, *J* = 5.4 Hz), 8.31 (d, 1H, *J* = 5.4 Hz), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 104.4 (C), 129.0 (2CH), 130.5 (2CH), 134.4 (CH), 134.9 (CH), 135.4 (C), 140.5 (C), 148.2 (CH), 150.7 (CH), 195.1 (C).

*3-Benzoyl-2-fluoro-4-iodopyridine (**2j**)*.[8] The general procedure 2 using 3-benzoyl-2-fluoropyridine (**1j**, 0.20 g) gave **2j** (eluent: heptane-AcOEt 80:20) in 63% yield (0.21 g) as a yellowish powder: mp 144 °C; IR (ATR): 660, 684, 827, 877, 926, 1171, 1230, 1271, 1316, 1391, 1442, 1449, 1539, 1574, 1669, 3084 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.46-7.53 (m, 2H), 7.65 (tt, 1H, *J* = 7.4 and 1.4 Hz), 7.75 (dd, 1H, *J* = 5.4 and 1.1 Hz), 7.79-7.83 (m, 2H), 7.97 (dd, 1H, *J* = 5.1 and 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 107.3 (d, C, *J* = 3.6 Hz), 127.9 (d, C, *J* = 36 Hz), 129.2 (2CH), 129.9 (2CH), 132.3 (d, CH, *J* = 4.5 Hz), 134.8 (C), 134.8 (CH), 148.4 (d, CH, *J* = 15 Hz), 158.8 (d, C, *J* = 241 Hz), 191.6 (d, C, *J* = 3.5 Hz).

*3-Benzoyl-2-chloro-4-iodopyridine (**2k**)*.[53] The general procedure 2 using 3-benzoyl-2-chloropyridine (**1k**, 0.22 g) gave **2k** (eluent: heptane-AcOEt 80:20) in 73% yield (0.25 g) as a yellow powder: mp 130-132 °C; IR (ATR): 657, 684, 725, 799, 827, 923, 1162, 1195, 1217, 1266, 1313, 1360, 1428, 1449, 1528, 1547, 1581, 1595, 1668, 2927, 3062 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.47-7.54 (m, 2H), 7.65 (tt, 1H, *J* = 7.4 and 1.4 Hz), 7.79-7.84 (m, 3H), 8.11 (d, 1H, *J* = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 105.3 (C), 129.3 (2CH), 129.9 (2CH), 133.2 (CH), 134.0 (C), 134.8 (CH), 140.0 (C), 146.9 (C), 149.8 (CH), 193.1 (C).

*2-Chloro-3-(2-chlorobenzoyl)-4-iodopyridine (**2l**)*.[8] The general procedure 2 using 2-chloro-3-(2-chlorobenzoyl)pyridine (**1l**, 0.25 g) gave **2l** (eluent: heptane-AcOEt 80:20) in 78% yield (0.29 g) as a yellowish powder: mp 112-114 °C; IR (ATR): 682, 732, 745, 761, 789, 829, 923, 1054, 1162, 1196, 1214, 1252, 1282, 1359, 1429, 1466, 1529, 1546, 1586, 1667, 1683, 3066 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38 (ddd, 1H, *J* = 7.8, 6.6 and 1.8 Hz), 7.47-7.56 (m, 2H), 7.78 (d, 1H, *J* = 5.1 Hz), 7.80 (ddd, 1H, *J* = 8.1, 1.8 and 0.6 Hz), 8.07 (d, 1H, *J* = 5.1 Hz); ^{13}C NMR ($CDCl_3$) δ 105.4 (C), 127.3 (CH), 132.0 (CH), 132.9 (CH), 133.2 (C), 133.5 (CH), 134.5 (CH), 134.7 (C), 140.8 (C), 146.9 (C), 149.7 (CH), 191.4 (C).

*2-Chloro-4-iodo-3-(2-methoxybenzoyl)pyridine (**2m**)*.[8] The general procedure 2 using 2-chloro-3-(2-methoxybenzoyl)pyridine (**1m**, 0.25 g) gave **2m** (eluent: heptane-AcOEt 70:30) in 70% yield (0.26 g) as a yellow powder: mp 162-164 °C; IR (ATR): 693, 712, 747, 786, 835, 925, 1014, 1045, 1090, 1114, 1160, 1177, 1199, 1215, 1251, 1294, 1366, 1434, 1465, 1482, 1532, 1550, 1575, 1595, 1651, 1940, 2840, 2944 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.62 (s, 3H), 6.95 (dd, 1H, *J* = 8.4 and 0.9 Hz), 7.11 (ddd, 1H, *J* = 8.1, 7.2 and 0.9 Hz), 7.60 (ddd, 1H, *J* = 9.0, 7.2 and 0.9 Hz), 7.74 (d, 1H, *J* = 5.1 Hz), 8.01 (d, 1H, *J* = 5.4 Hz), 8.06 (dd, 1H, *J* = 7.8 and 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 56.0 (CH_3), 103.6 (C), 112.3 (CH), 121.3 (CH), 123.7 (C), 132.1 (CH), 132.8 (CH), 136.4 (CH), 143.5 (C), 145.9 (C), 148.3 (CH), 160.2 (C), 191.3 (C).

*2-Chloro-3-cinnamoyl-4-iodopyridine (**2n**)*.[8] The general procedure 2 using 2-chloro-3-cinnamoylpyridine (**1n**, 0.24 g) gave **2n** (eluent: heptane-AcOEt 80:20) in 27% yield (0.10 g) as a yellow powder: mp 118-120 °C; IR (ATR): 680, 700, 733, 748, 765, 975, 1037, 1110, 1138, 1198, 1269, 1330, 1363, 1429, 1449, 1528, 1548, 1575, 1595, 1619, 1649, 2925, 3063 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.95 (d, 1H, *J* = 16 Hz), 7.32 (d, 1H, *J* = 16 Hz), 7.38-7.49 (m, 3H), 7.55-7.59 (m, 2H), 7.80 (d, 1H, *J* = 5.1 Hz), 8.10 (d, 1H, *J* = 5.1 Hz); ^{13}C NMR ($CDCl_3$) δ 105.5 (C), 124.9 (CH), 129.0 (2CH), 129.3 (2CH), 131.7 (CH), 133.4 (CH), 134.0 (C), 140.2 (C), 146.9 (C), 148.5 (CH), 149.8 (CH), 193.2 (C).

*3-Benzoyl-4-iodo-2-methoxypyridine (**2o**)*.[8] The general procedure 2 using 3-benzoyl-2-methoxypyridine (**1o**, 0.21 g) gave **2o** (eluent: heptane-AcOEt 80:20) in 88% yield (0.30 g) as a yellow powder: mp 144-146 °C; IR (ATR): 660, 685, 707, 730, 803, 847, 926, 1015, 1234, 1274, 1301, 1313, 1372, 1455, 1552, 1668, 2948 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 7.39 (d, 1H, *J* = 5.4 Hz), 7.45 (tt, 2H, *J* = 7.5 and 1.7 Hz), 7.59 (tt, 1H, *J* = 7.4 and 1.4 Hz), 7.78-7.83 (m, 2H), 7.86 (d, 1H, *J* = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 54.2 (CH_3), 104.9 (C), 127.0 (CH), 128.6 (C), 128.9 (2CH), 129.7 (2CH), 134.1 (CH), 135.1 (C), 147.5 (CH), 160.5 (C), 194.5 (C).

*2-Benzoyl-5-iodothiophene (**2p**)*. The general procedure 2 using 2-benzoylthiophene (**1p**, 0.19 g) gave **2p** (eluent: heptane-AcOEt 80:20) in 80% yield (0.25 g) as a whitish powder: mp 129-131 °C (lit.[54] 132-133 °C); IR (ATR): 685, 696, 714, 783, 812, 857, 927, 952, 1066, 1138, 1213, 1297, 1316, 1378, 1405, 1443, 1516, 1575, 1595, 1613, 3054, 3228 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.27 (d, 1H, *J* = 3.9 Hz), 7.33 (d, 1H, *J* = 3.9 Hz), 7.46-7.53 (m, 2H), 7.57-7.63 (m, 1H), 7.80-7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 86.0 (C), 128.6 (2CH), 129.1 (2CH), 132.6 (CH), 135.7 (CH), 137.6 (C), 138.1 (CH), 149.5 (C), 186.7 (C). These data are as described previously.[54]

*1-(2-Pyridyl)-9-xanthone (**3a**)*.[8] To a stirred mixture of 9-xanthone (**1a**, 0.19 g, 1.0 mmol) and $ZnCl_2$·TMEDA (0.25 g, 1.0 mmol) in THF (3 mL) at -55 °C was added dropwise a solution of LiTMP (prepared by adding BuLi (about 1.6 M hexanes solution, 1.5 mmol) to a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.5 mmol) in THF (3 mL) and stirring for 5 min) cooled at -55 °C. After 15 min at -55 °C, 2-chloropyridine (0.55 g, 4.8 mmol), palladium(II) chloride (14 mg, 80 µmol) and 1,1'-diphenylphosphinoferrocene (44 mg, 80 µmol) were added to the reaction mixture, and the latter was heated at THF reflux for 16 h. After addition of water (0.5 mL) and EtOAc (50 mL), and drying over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure. The coupled product was isolated by purification by chromatography over silica gel (eluent: heptane-AcOEt 60:40 to 50:50) to afford **3a** in 76% yield (0.21 g) as a light grey powder: mp 183-184 °C; IR (ATR): 631, 672, 725, 750, 760, 786, 925, 1235, 1301, 1333, 1349, 1431, 1463, 1488, 1569, 1589, 1599, 1615, 1652, 2962, 3065 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28-7.35 (m, 3H), 7.40 (d, 1H, *J* = 7.8 Hz), 7.48 (d, 1H, *J* = 8.4 Hz), 7.58 (dd, 1H, *J* = 8.4 and 0.7 Hz), 7.69 (td, 1H, *J* = 7.8 and 1.5 Hz), 7.74 (t, 1H, *J* = 7.9 Hz), 7.77 (td, 1H, *J* = 7.7 and 1.7 Hz), 8.16 (dd, 1H, *J* = 8.0 and 1.4 Hz), 8.69 (d, 1H, *J* = 4.6 Hz); ^{13}C NMR ($CDCl_3$) δ 117.7 (CH), 118.7 (CH), 119.6 (C), 122.2 (CH), 122.7 (C), 123.7 (CH), 124.0 (CH), 126.5 (CH), 127.0 (CH), 133.9 (CH), 134.8 (CH), 135.6 (CH), 142.7 (C), 148.9 (CH), 155.6 (C), 157.1 (C), 159.9 (C), 176.9 (C).

*5-Phenyl-1,3,4,6,9b-pentaazacyclopenta[a]naphthalene (**3g1**)*. The general procedure 4 using 3-amino-1,2,4-triazole (0.10 g) gave **3g1** (eluent: heptane-AcOEt 50:50) in 54% yield (0.13 g) as a yellow powder:

mp 198 °C; IR (ATR): 681, 827, 1306, 1355, 1451, 1547, 1598, 3059 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52-7.56 (m, 3H), 7.88 (dd, 1H, *J* = 8.6 and 4.4 Hz), 8.28-8.32 (m, 2H), 8.51 (m, 1H), 8.80 (dd, 1H, *J* = 8.6 and 1.7 Hz), 9.03 (dd, 1H, *J* = 4.4 and 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 123.8 (CH), 128.0 (CH), 128.2 (2CH), 131.1 (CH), 131.7 (2CH), 133.4 (C), 134.3 (C), 135.7 (C), 148.9 (CH), 152.3 (C), 155.4 (CH), 164.5 (C).

*5-Phenyl-1,4,6,9b-tetraaza-cyclopenta[a]naphthalene (**3g2**).* The general procedure 4 using 3-aminopyrazole (0.10 g) gave **3g2** (eluent: heptane-AcOEt 50:50) in 18% yield (44 mg) as a yellow powder: mp 180 °C; IR (ATR): 690, 742, 795, 811, 909, 1297, 1350, 1396, 1439, 1450, 1526, 1549, 1596, 3061 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.88 (d, 1H, *J* = 2.1 Hz), 7.53-7.59 (m, 3H), 7.79 (dd, 1H, *J* = 8.6 and 1.4 Hz), 8.14-8.18 (m, 3H), 8.86 (dd, 1H, *J* = 8.6 and 1.7 Hz), 8.92 (dd, 1H, *J* = 4.4 and 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 100.6 (CH), 123.3 (CH), 127.3 (CH), 128.3 (2CH), 130.2 (CH), 131.0 (2CH), 134.0 (C), 134.2 (C), 136.7 (C), 144.3 (CH), 145.1 (C), 147.6 (CH), 159.0 (C).

*5-Phenyl-4,6,7,11b-tetraazabenzo[c]fluorene (**3g3**).* The general procedure 4 using 2-aminobenzimidazole (0.16 g) gave **3g3** (eluent: CH_2Cl_2-AcOEt 80:20) in 50% yield (0.15 g) as a yellow powder: mp 175 °C; IR (ATR): 684, 736, 1194, 1351, 1390, 1448, 1538, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41-7.52 (m, 2H), 7.53-7.59 (m, 3H), 7.83 (dd, 1H, *J* = 8.7 and 1.5 Hz), 8.00 (dd, 1H, *J* = 8.1 and 1.5 Hz), 8.11 (dd, 1H, *J* = 8.4 and 1.2 Hz), 8.34-8.38 (m, 2H), 8.75 (dd, 1H, *J* = 8.6 and 1.4 Hz), 8.89 (dd, 1H, *J* = 4.2 and 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 113.2 (CH), 121.5 (CH), 122.6 (CH), 123.7 (CH), 125.2 (CH), 127.1 (CH), 128.1 (2CH), 129.4 (C), 130.9 (CH), 131.7 (2CH), 134.4 (C), 135.1 (C), 136.2 (C), 144.7 (C), 146.1 (CH), 149.0 (C), 164.1 (C).

*2-Amino-4-phenylpyrido[2,3-*d*]pyrimidine (**4j**).* The general procedure 5, but without CuI, using 3-benzoyl-2-fluoropyridine (**1j**, 0.20 g) gave **4j** (eluent: AcOEt-MeOH-NEt_3 96:2:2) in 94% yield (0.21 g) as a yellowish powder: mp 192-194 °C; IR (ATR): 709, 730, 769, 786, 952, 1127, 1185, 1205, 1260, 1339, 1372, 1412, 1447, 1468, 1548, 1566, 1595, 1621, 2219, 3166, 3283, 3403 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.15 (br s, 2H), 7.13 (dd, 1H, *J* = 8.1 and 4.4 Hz), 7.52-7.56 (m, 3H), 7.64-7.68 (m, 2H), 8.13 (dd, 1H, *J* = 8.1 and 2.1 Hz), 8.94 (dd, 1H, *J* = 4.2 and 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ 112.8 (C), 118.7 (CH), 128.8 (2CH), 129.6 (2CH), 130.4 (CH), 136.3 (C), 136.8 (CH), 157.5 (CH), 161.1 (C), 162.1 (C), 172.3 (C).

*2-Amino-4-phenylpyrido[3,2-*d*]pyrimidine (**4g**).*[8] The general procedure 5 using 2-benzoyl-3-iodopyridine (**2g**, 0.31 g) gave **4g** (eluent: heptane-AcOEt-NEt_3 80:18:2) in 77% yield (0.17 g) as a yellowish powder: mp 140-142 °C; IR (ATR): 695, 739, 765, 804, 1124, 1231, 1344, 1376, 1422, 1458, 1548, 1583, 1601, 1628, 3060, 3171, 3313, 3477 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.67 (br s, 2H), 7.51-7.58 (m, 4H), 7.91 (dd, 1H, *J* = 8.7 and 1.7 Hz), 8.16-8.20 (m, 2H), 8.71 (dd, 1H, *J* = 3.9 and 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 127.9 (CH), 128.2 (2CH), 130.6 (CH), 131.2 (2CH), 133.8 (CH), 135.5 (C), 136.2 (C), 146.9 (CH), 149.5 (C), 159.9 (C), 169.4 (C).

*2-Amino-4-phenylpyrido[3,4-*d*]pyrimidine (**4h**).* The general procedure 5 using 4-benzoyl-3-iodopyridine (**2h**, 0.31 g) gave **4h** (eluent: heptane-AcOEt-NEt_3 70:28:2) in 61% yield (0.14 g) as a yellow powder: mp 242-244 °C; IR (ATR): 673, 704, 764, 779, 808, 1026, 1155, 1227, 1378, 1415, 1488, 1545, 1567, 1584, 1660, 3082, 3301 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.46 (br s, 2H), 7.57-7.60 (m, 3H), 7.66 (dd, 1H, *J* = 5.7 and 1.1 Hz), 7.72-7.77 (m, 2H), 8.39 (d, 1H, *J* = 5.7 Hz), 9.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 118.7 (CH), 121.1 (C), 129.0 (2CH), 129.6 (2CH), 130.7 (CH), 136.1 (C), 141.3 (CH), 147.9 (C), 151.7 (CH), 160.5 (C), 170.6 (C).

*2-Amino-4-phenylpyrido[4,3-*d*]pyrimidine (**4i**).* The general procedure 5 using 3-benzoyl-4-iodopyridine (**2i**, 0.31 g) gave **4i** (eluent: heptane-AcOEt-NEt_3 70:28:2) in 68% yield (0.15 g) as a yellowish powder: mp 112-114 °C; IR (ATR): 703, 765, 834, 952, 1030, 1042, 1179, 1272, 1356, 1384, 1413, 1442, 1456, 1507, 1548, 1602, 1637, 3167, 3309 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.03 (br s, 2H), 7.38 (dd, 1H, *J* = 6.0 and 0.9 Hz), 7.53-7.60 (m, 3H), 7.71-7.75 (m, 2H), 8.60 (d, 1H, *J* = 6.0 Hz), 9.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 115.2 (C), 119.0 (CH), 128.9 (2CH), 129.8 (2CH), 130.8 (CH), 135.7 (C), 150.8 (CH), 152.3 (CH), 156.7 (C), 161.7 (C), 172.1 (C).

*2-Amino-5-methoxy-4-phenylpyrido[4,3-*d*]pyrimidine (**4o**).* The general procedure 5 using 3-benzoyl-4-iodo-2-methoxypyridine (**2o**, 0.34 g) gave **4o** (eluent: heptane-AcOEt-NEt_3 80:18:2) in 65% yield (0.16 g) as a white powder: mp 146-148 °C; IR (ATR): 702, 837, 913, 980, 1104, 1131, 1290 1321, 1367, 1435, 1447, 1540, 1559, 1600, 1634, 2949, 3176, 3312 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69 (s, 3H), 5.89 (br s, 2H), 6.98 (d, 1H, *J* = 6.0 Hz) 7.40-7.50 (m, 5H), 8.13 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 53.4 (CH_3), 105.6 (C), 113.9 (CH), 127.6 (2CH), 128.3 (2CH), 129.1 (CH), 140.4 (C), 148.4 (CH), 160.3 (C), 161.3 (C), 161.7 (C), 171.1 (C).

*2-Aminobenzopyrano[4,3,2-*de*]quinazoline (**4a**).* The general procedure 5 using 1-iodoxanthone (**2a**, 0.32 g) gave **4a** (eluent: AcOEt-heptane-NEt_3 70:28:2) in 86% yield (0.20 g) as a yellow powder: mp 236-238 °C; IR (ATR): 717, 758, 816, 1053, 1072, 1249, 1259, 1324, 1348, 1435, 1453, 1490, 1561, 1596, 1615, 1640, 1667, 2854, 2924, 3173, 3302, 3481 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.21 (br s, 2H), 6.93 (dd, 1H, *J* = 8.1 and 0.8 Hz), 7.18 (dd, 1H, *J* = 8.4 and 0.8 Hz), 7.28-7.35 (m, 2H), 7.60 (ddd, 1H, *J* = 8.7, 7.2 and 1.8 Hz), 7.69 (dd, 1H, *J* = 8.4 and 8.1 Hz), 8.41 (ddd, 1H, *J* = 7.8, 1.8 and 0.6 Hz); ^{13}C NMR ($CDCl_3$) δ 105.9 (CH), 109.3 (C), 116.6 (CH), 117.7 (CH), 119.2 (C), 124.1 (CH), 125.0 (CH), 134.0 (CH), 135.4 (CH), 152.1 (C), 152.2 (C), 155.5 (C), 157.9 (C), 161.6 (C).

*2-Aminobenzothiopyrano[4,3,2-*de*]quinazoline (**4b**).* The general procedure 5 using 1-iodothioxanthone (**2b**, 0.34 g) gave **4b** (eluent: AcOEt-heptane-NEt_3 70:28:2) in 84% yield (0.21 g) as a yellow powder: mp 258-260 °C; IR (ATR): 714, 758, 772, 815, 986, 1081, 1205, 1237, 1268, 1336, 1417, 1437, 1466, 1476, 1549, 1561, 1602, 1639, 1666, 1733, 2853, 2923, 3167, 3324 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.13 (br s, 2H), 7.12 (dd, 1H, *J* = 7.5 and 0.9 Hz), 7.27 (dd, 1H, *J* = 8.6 and 0.9 Hz), 7.33-7.40 (m, 2H), 7.47 (td, 1H, *J* = 6.6 and 1.5 Hz), 7.55 (dd, 1H, *J* = 8.4 and 7.5 Hz), 8.80 (dd, 1H, *J* = 8.7 and 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 115.2 (C), 116.8 (CH), 120.7 (CH), 125.9 (CH), 126.5 (CH), 127.7 (C), 128.2 (CH), 131.8 (CH), 133.2 (C), 133.4 (CH), 136.0 (C), 154.4 (C), 160.2 (C), 160.7 (C).

*2-Amino-7-oxa-1,3,6-triazabenz[*de*]anthracene (**4d**).* The general procedure 5 using 4-iodo-1-azaxanthone (**2d**, 0.32 g) gave **4d** (eluent: AcOEt-heptane-NEt_3 80:18:2) in 83% yield (0.20 g) as a yellowish powder: mp > 264 °C; IR (ATR): 750, 837, 939, 1077, 1127, 1202, 1242, 1291, 1319, 1378, 1418, 1447, 1470, 1515, 1557, 1583, 1626, 1670, 3083, 3284 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 6.96 (d, 1H, *J* = 6.3 Hz), 7.45-7.51 (m, 3H), 7.60 (dd, 1H, *J* = 8.4 and 1.2 Hz), 7.79 (ddd, 1H, *J* = 8.7, 7.2 and 1.7 Hz), 6.24 (d, 1H, *J* = 6.0 Hz), 8.32 (dd, 1H, *J* = 8.0 and 1.7 Hz); ^{13}C NMR ($(CD_3)_2SO$) δ 102.8 (C), 112.9 (CH), 118.2 (CH), 118.3 (C), 124.1 (CH), 124.9 (CH), 134.6 (CH), 150.2 (CH), 154.5 (C), 158.1 (C), 158.2 (C), 158.3 (C), 164.1 (C).

*2-Amino-7-thia-1,3,6-triazabenz[*de*]anthracene (**4e**).* The general procedure 5 using 4-iodo-1-azathioxanthone (**2e**, 0.34 g) gave **4e** (eluent: AcOEt-heptane-NEt_3 70:28:2) in 88% yield (0.22 g) as a yellow powder: mp 264-266 °C; IR (ATR): 725, 763, 809, 834, 1009, 1038, 1081, 1156, 1181, 1235, 1260, 1314, 1373, 1451, 1538, 1595, 1662, 2851, 2922, 2959, 3111, 3293 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 7.00 (d, 1H, *J* = 6.0 Hz), 7.43 (br s, 2H), 7.56 (ddd, 1H, *J* = 8.1, 5.7 and 3.0 Hz), 7.68-7.71 (m, 2H), 8.31 (d, 1H, *J* = 6.0 Hz), 8.75 (dt, 1H, *J* = 8.1 and 1.1 Hz); ^{13}C NMR

($((CD_3)_2SO$) δ 111.2 (C), 114.6 (CH), 126.1 (C), 126.6 (CH), 127.0 (CH), 127.3 (CH), 132.5 (CH), 135.5 (C), 150.0 (CH), 157.3 (C), 157.5 (C), 160.3 (C), 162.9 (C).

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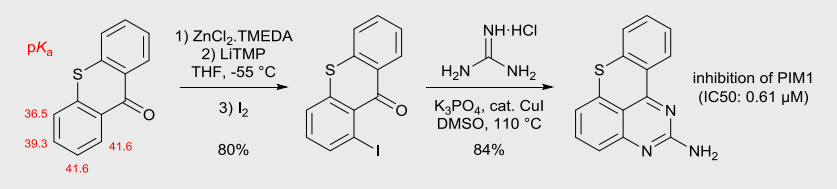
Key topic: Ketone functionalization



Aromatic ketones were functionalized by deprotolithiation in the presence of a zinc salt followed by iodolysis. The outcome of the reactions was analyzed in the light of the calculated pK_a values. The iodo derivatives were involved in copper-catalyzed two-fold C-N bond formation to afford fused systems based on 2-aminopyrimidines. Besides potential antibacterial effect, 2-aminobenzothiopyrano[4,3,2-*de*]quinazoline proved to inhibit PIM1 (IC_{50}: 0.61 μM) and CDK2/cyclin A (IC_{50}: 2.0 μM) kinases.

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Fused systems based on 2-aminopyrimidines: synthesis combining deprotolithiation-in situ zincation with *N*-arylation reactions and biological properties