# Functionalization of pyridyl ketones using deprotolithiation-*in situ* zincation

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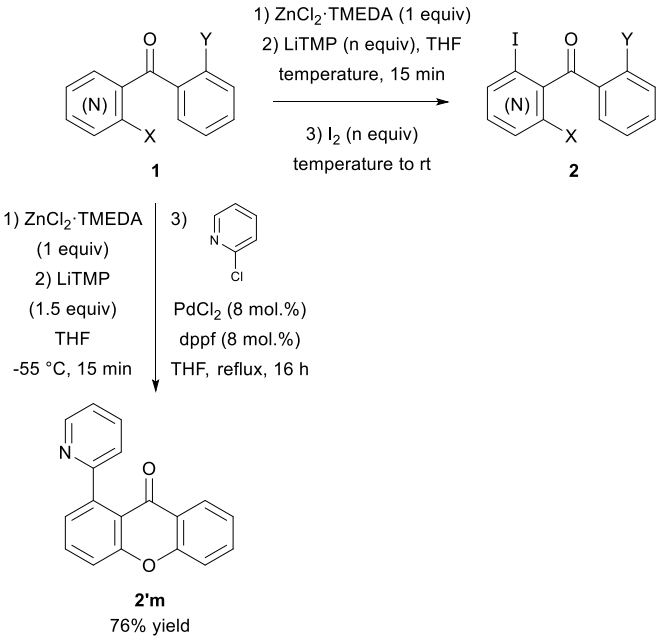
**The metallation of aryl ketones was achieved by using LiTMP in the presence of $ZnCl_2$·TMEDA, as evidenced by subsequent interception with iodine or by palladium-catalysed cross-coupling reaction. One of the synthesized iodo ketones has been further elaborated to reach derivatives of biological interest.**

Pyridines play a large part in biological processes (nicotine, niacin, NADP, vitamin $B_6$…), in pharmaceuticals and agrochemicals,[1] as well as in organic materials.[2] In addition, pyridyl ketones bearing a halogen at the position adjacent to the carbonyl function are key intermediates to access heterocyclic scaffolds of interest such as azafluorenones,[3] azaxanthones,[4] naphthyridones,[5] and thieno-,[6] pyrazolo-[7] and isoxazolo-pyridines.[8]

Even if deprotonative lithiation[9] has been largely used to regioselectively functionalize pyridines,[10] the method has never been extended to pyridyl ketones due to their low compatibility with organolithiums. Mixed lithium-nonalkali metal combinations have been developed to achieve chemoselective deprotometallation of aromatics.[11] In this context, the 1:1 mixture of homometallic amides LiTMP (TMP = 2,2,6,6-tetramethylpiperidino) and $Zn(TMP)_2$,[12] obtained by mixing in a 3:1 ratio LiTMP and $ZnCl_2$·TMEDA (TMEDA = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine) in THF (THF = tetrahydrofuran), was successfully employed with a large range of sensitive substrates.[13] Such a synergy, attributed to reversible deprotolithiation shifted by zinc-mediated transmetallation[12] (or 'trans-metal trapping'[14]), has since been extended to the use of LiTMP in the presence of $ZnCl_2$·2LiCl, $MgCl_2$ or CuCN·2LiCl.[15]

Herein, we report the efficiency of aryl ketones as directing groups for LiTMP-mediated deprotometallation of pyridines and other arenes in the presence of $ZnCl_2$·TMEDA as *in situ* trap (Scheme 1, Table 1).




**Scheme 1** Zincation of aryl ketones **1** using LiTMP in the presence of $ZnCl_2$·TMEDA followed by iodolysis or palladium-catalysed cross-coupling to afford ketones **2** and **2'**.

Thus, after optimization of the reaction conditions (using four different reaction temperatures from -70 to -10 °C and different amounts of LiTMP from 1 to 3 equiv), treatment of 2-benzoylpyridine (**1a**) in THF containing $ZnCl_2$·TMEDA (1 equiv) with LiTMP (1.5 equiv) at -30 °C for 15 min and then iodine led to the 3-iodo derivative **2a** in 50% yield (entry 1). Similarly, 4-benzoylpyridine (**1b**) was converted to the 3-iodo derivative **2b** by using LiTMP (2 equiv); with this substrate benefiting from two free positions adjacent to the benzoyl group, a second deprotonation was observed to some extent, as evidenced by the competitive formation of the diiodo **2b'** (entry 2).

3-Benzoylpyridine (**1c**) is more prone to nucleophilic attack onto the ring than its 2- and 4-isomers.[16] As a consequence, deprotolithiation-zincation could only be evidenced by subsequent iodolysis at temperatures below -50 °C. Using LiTMP (1.5 equiv) at -55 or -70 °C for 15 min and then iodine provided the 4-iodo derivative **2c** in 30 or 37% yield, respectively (entry 3).

When present at pyridine 2-position, halogens are known to acidify the 4-position, as shown by p$K_a$ values calculated in THF.[13a] The 2-halogeno 3-benzoylpyridines **1d**-**h** were thus prepared.[17] Accordingly, when similarly reacted by using LiTMP at -55 °C, the iodo derivatives **2d**-**g** were isolated in improved yields, in line with the long range effects of fluorine and chlorine (entries 4-7). In contrast, the reaction from **1h** proved more complex, giving the iodide **2h** in a modest yield (entry 8).

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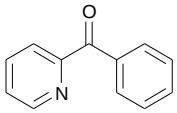
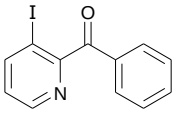
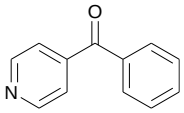
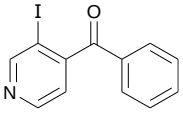
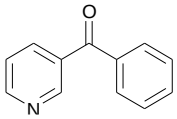
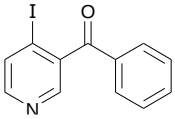
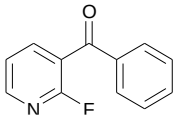
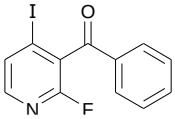
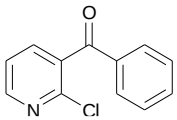
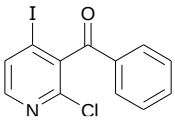
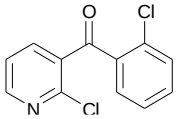
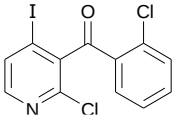
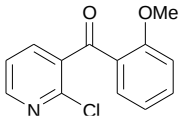
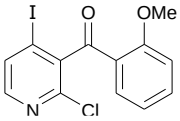
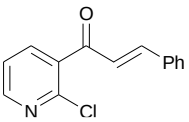
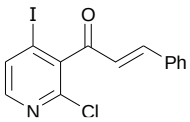
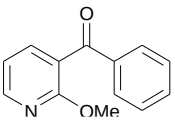
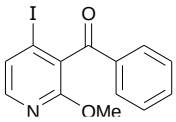
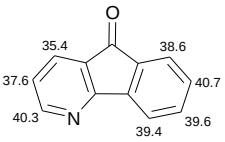
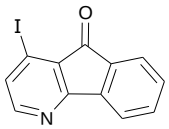
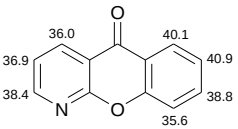
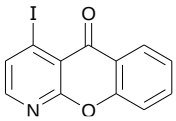
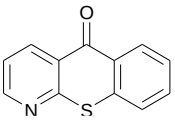
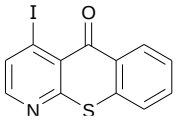
† Electronic supplementary information (ESI) available: General procedures, experimental procedures and compound characterizations, $^1$H and $^{13}$C NMR spectra of the new compounds, and X-ray crystallographic data. CCDC 1475309 (**2j'**), 1475009 (**2k'**) and 1475010 (**2n'**). For ESI and crystallographic data in CIF see DOI: 10.1039/x0xx00000x

The presence of a methoxy group at 2-position of 3-benzoylpyridine also had a positive impact on the course of the reaction since involving **1i** in the sequence furnished the iodo derivative **2i** in 88% yield (entry 9). Whereas this group does not acidify remote pyridine 4-position,[13b] it acts by making the pyridine ring less sensitive towards competitive nucleophilic attack. Indeed, based on the $^1$H NMR chemical shifts in $CDCl_3$ of **1c** (8.12 and 8.82 ppm for H4 and H6, respectively) and **1i** (7.72 and 8.32 ppm for H4 and H6, respectively), one can predict as shown by Handy and Zhang[18] that the partial positive charges at C4 and C6 will be reduced for **1i**.

**Table 1** Substrates **1a-l**, calculated p$K_a$(THF) values for **1j** and **1k**, conditions used for the deprotolithiation-zincation, and iodinated aryl ketones **2a-l** obtained.

| Entry | Substrate/n/temperature | Product/yield[a] (%) |
|---|---|---|
| 1 |  **1a**: 1.5 equiv, -30 °C |  **2a**: 50% |
| 2 |  **1b**: 2 equiv, -30 °C |  **2b**: 45%[b] |
| 3 |  **1c**: 1.5 equiv, -55 °C<br>**1c**: 1.5 equiv, -70 °C |  **2c**: 30%<br>**2c**: 37% |
| 4 |  **1d**: 1.5 equiv, -55 °C |  **2d**: 63% |
| 5 |  **1e**: 1.5 equiv, -55 °C |  **2e**: 73% |
| 6 |  **1f**: 1.5 equiv, -55 °C |  **2f**: 78% |
| 7 |  **1g**: 1.5 equiv, -55 °C |  **2g**: 70% |
| 8 |  **1h**: 1.5 equiv, -55 °C |  **2h**: 27% |
| 9 |  **1i**: 1.5 equiv, -55 °C |  **2i**: 88% |
| 10 |  **1j**: 1.5 equiv, -55 °C |  **2j**: 33%[c] |
| 11 |  **1k**: 1.5 equiv, -55 °C |  **2k**: 60%[d] |
| 12 |  **1l**: 1.5 equiv, -55 °C |  **2l**: 60% |

[a] Yield after purification by column chromatography. [b] 4-Benzoyl-3,5-diiodopyridine (**2b'**) was also obtained in 10% yield. [c] 1,5-Diiodo-4-azafluorenone (**2j'**) was also obtained in 20% yield. [d] 1,6-Diiodo-4-azaxanthone (**2k'**) was also obtained in 10% yield.

The behaviour of the ketones **1j-l**, possessing reduced flexibility on carbonyl direction, was similarly examined. 4-azafluorenone (**1j**) was converted to the 1-iodo derivative **2j** in a moderate yield, similar to that obtained from 3-benzoylpyridine (**1c**). In the case of **1j**, the phenyl ring was also attacked to a lesser extent at a position facing the pyridine nitrogen to afford the diiodide **2j'** (entry 10, Figure 1). In contrast with the reaction from **1j**, the sequence using 4-azaxanthone (**1k**) and 4-azathioxanthone (**1l**) provided the iodides **2k** and **2l** in higher 60% yields (entries 11 and 12).

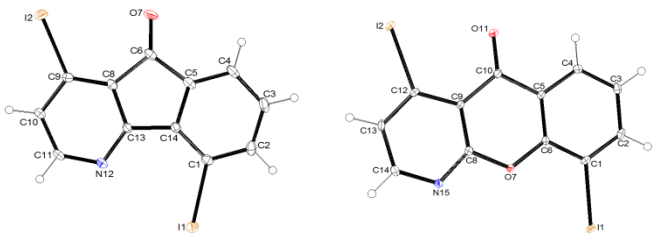
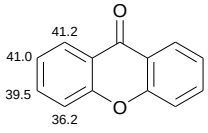
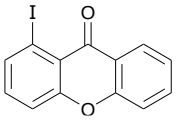
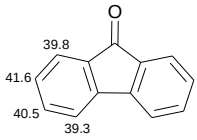
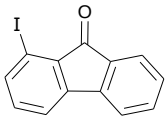
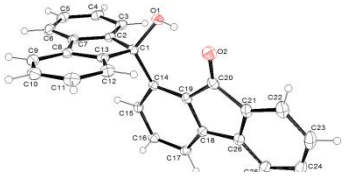
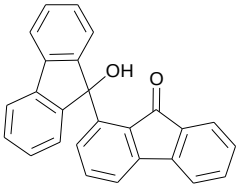


**Figure 1** ORTEP diagrams (30% probability) of compounds **2j'** and **2k'**.

In order to evaluate the scope of the method, we chose other aromatic substrates.[19] When compared with its 4-aza analogue **1k**, xanthone (**1m**) similarly led to the 1-iodo **2m** in 72% yield. On the contrary, as previously noted between **1j**

and **1k**, the reaction from **1n** was less efficient than from **1m**. Indeed, 1-iodofluorenone (**2n**) was obtained in 52% yield, but together with the ketone **2n'** (35% yield) resulting from an addition of the metallated product to **1n** (Scheme 1, Table 2). As organozincs hardly react with ketones, the product **2n'** could rather result from an addition of 1-lithiofluorenone to **1n** more rapid than its trapping by the zinc species. These results suggest that the carbonyl direction in the metallated derivative coming from **1n** is less prone to stabilize a 1-lithio compound than that from **1m**.

**Table 2** Substrates **1m** and **1n** and their calculated p$K_a$(THF) values, conditions used for the deprotolithiation-zincation, iodinated aryl ketones **2m** and **2n** obtained, and ORTEP diagram (30% probability) of compound **2n'**.

| Entry | Substrate/n/temperature | Product/yield[a] (%) |
|---|---|---|
| 1 |   **1m**: 1.5 equiv, -55 °C |   **2m**: 72% |
| 2 |   **1n**: 1.5 equiv, -55 °C |   **2n**: 52% |
| |  |   **2n'**: 35% |

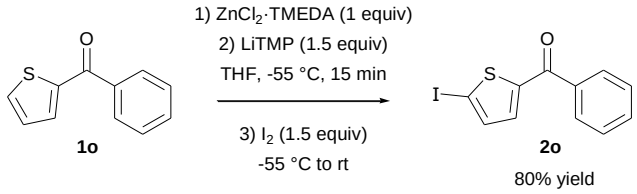
[a] Yield after purification by column chromatography.

Interestingly, the deprotolithiation-*in situ* zincation could be combined with a subsequent Negishi cross-coupling reaction.[20] Thus, using catalytic amounts of $PdCl_2$ as palladium source and 1,1'-diphenylphosphinoferrocene (dppf) as ligand with 2-chloropyridine[12a] allowed **2'm** to be formed from 9-xanthone (**1m**) in 76% yield (Scheme 1).

CH acidities are in general useful data to better understand deprotometallation outcomes, in particular regarding regioselectivity issues. We thus calculated selected p$K_a$ values in THF solution by means of quantum chemistry at the DFT B3LYP level of theory.[13] After geometry optimization and calculation of the vibrational frequencies by using the 6-31G(d) basis set, the single point energies were obtained using the 6-311+G(d,p) basis set. The solvent influence was treated through the polarized continuum model (PCM) with the default parameters for THF. Finally, the p$K_a$ values were reached from the Gibbs energy of the homodesmic reaction between the studied and probe heterocycles.

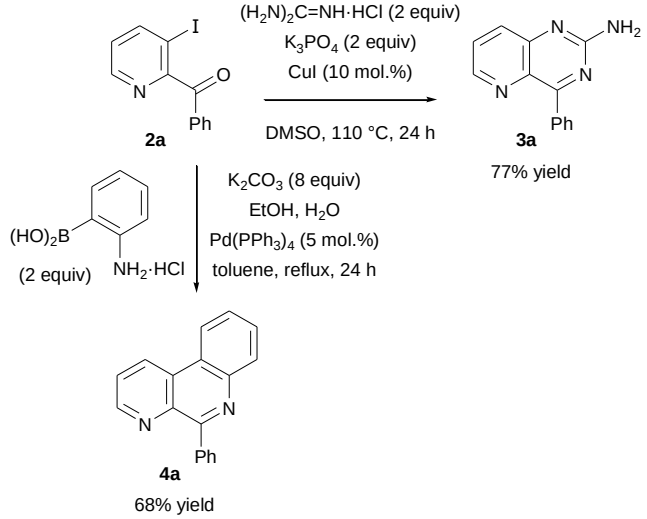
That both sets of CH acidity values for **1m** and **1n** are rather similar (Table 2) supports the role of the carbonyl direction on the course of the reaction through coordination. Analogously, the difference observed between the p$K_a$ values of **1j** and **1k** is not significant enough to allow for a rationalization of the distinct yields noted, rather suggesting a more efficient stabilization of the metallated compound by the carbonyl group in the case of **1k** at the origin of the higher yield. Besides, the formation of dimetallated products from **1j** and **1k**, as demonstrated by isolation of **2j'** and **2k'** (Figure 1), could be favoured for the former by a nitrogen assistance and, for the latter, by a relatively low p$K_a$ value (35.6) at the 6-position (Table 1).

Finally, when 2-benzoylthiophene (**1o**) was submitted to LiTMP in the presence of $ZnCl_2$·TMEDA as before, the reaction took place next to sulphur to afford after iodolysis the iodo derivative **2o** in 80% yield (Scheme 2).




**Scheme 2** Zincation of phenyl 2-thienyl ketone (**1o**) using LiTMP in the presence of $ZnCl_2$·TMEDA followed by iodolysis to afford the iodinated 2-thienyl ketone **2o**.

To move towards nitrogen-containing derivatives of biological interest, 2-benzoyl-3-iodopyridine (**2a**) was involved in further reactions (Scheme 3). A catalyst-base system was first optimized to perform guanidine copper-catalysed *N*-arylation.[21] Upon treatment with $K_3PO_4$ as base and CuI as catalyst source in the presence of DMSO, the iodide **2a** was converted to the pyrido[3,2-*d*]pyrimidine **3a** in 77% yield. Besides, cyclizing Suzuki coupling[22] was performed from the ketone **2a** and 2-aminophenylboronic acid under palladium catalysis to provide 5-phenylbenzo[*f*][1,7]naphthyridine (**4a**)[23] in 68% yield.




**Scheme 3** Conversion of 2-benzoyl-3-iodopyridine (**2a**) to derivatives of biological interest.

In summary, we have reported a short and simple access to iodinated aryl ketones. Additionally, transition metal-mediated reactions occurring with cyclization led to elaborated scaffolds. Applications towards the synthesis of libraries of compounds for biological evaluation are currently under investigation in our laboratory.

We thank the Ministère de l'Enseignement supérieur et de la Recherche scientifique Algérien (M. H.), the Centre national de la recherche scientifique and the Institut Universitaire de France (F. M.). We acknowledge FEDER founds (D8 VENTURE Bruker AXS diffractometer) and Thermo Fisher (generous gift of 2,2,6,6-tetramethylpiperidine). This research has been partly performed as part of the CNRS PICS project "Bimetallic synergy for the functionalization of heteroaromatics".

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