Metal-free C(sp(3))-H bond sulfonyloxylation of 2-alkylpyridines and alkylnitrones

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Metal-Free C(sp^3)–H Bond Sulfonyloxylation of 2-Alkylpyridines and Alkylnitrones

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Pyridin-2-ylmethyl tosylate derivatives are obtained in high yields from 2-alkylpyridine 1-oxides *via* a [3,3]-sigmatropic rearrangement of the adduct between 2-alkylpridine 1-oxides with benzenesylfonyl chlorides. Moreover, alkylnitrones also undergo [3,3]-sigmatropic rearrangement to give α-tosylated ketones after hydrolysis. Substitution reactions with nucleophiles then lead to diverse useful functionalizations for the synthesis of pincer ligands.

Alkyl sulfonates, such as alkyl tosylates, are typical substrates for S_N2 reactions. Compared to alkyl halides, they often display higher thermal/light stability and resistance to radical-triggered side reactions. They are generally synthetized from alcohols by condensation reactions with benzenesulfonyl chlorides. A more straightforward access to these synthetically useful synthons would involve the direct transformation of inert C(sp^3)–H bond into C–OSO_2R bond.[1] In 2015, Dong and co-workers reported an elegant approach for the synthesis of β-sulfonyloxylated alcohols through a palladium-catalyzed regioselective C(sp^3)–H bond functionalizations of masked alcohols bearing 8-formylquinoline-derived oxime as directing group (Figure 1a).[2] The reaction has employed *p*-toluenesulfonic acid as sulfonyloxation agent and *N*-fluorobenzenesulfonimide (NFSI) as the oxidant. Pyridin-2-ylmethyl tosylate derivatives, which are important building blocks for the preparation of metal pincer complexes,[3] are generally prepared from pyridin-2-ylmethanol derivatives. In 2017, our group has succeeded the C(sp^3)–H bond benzoxylation of 2-alkylpyridine derivatives through copper-catalyzed oxidative esterification of 2-alkylpyridine 1-oxides with aldehydes followed by [3,3]-sigmatropic rearrangement (Figure 1b).[4] The same year, Chen, Fu and co-workers reported metal-free conditions for the phosphorylation of 2-alkylpyridine and nitrone derivatives *via* a similar [3,3]-sigmatropic rearrangement (Figure 1c).[5]

To the best of our knowledge, there is no example of [3,3]-sigmatropic rearrangement of 2-alkylpyridine 1-oxides with benzenesulfonyl chlorides, although it could provide an efficient synthetic method to pyridin-2-ylmethyl tosylate derivatives. We decided to tackle this challenge by investigating the reactivity of 2-alkylpyridine 1-oxides in the presence of benzenesulfonyl chlorides (Figure 1d).

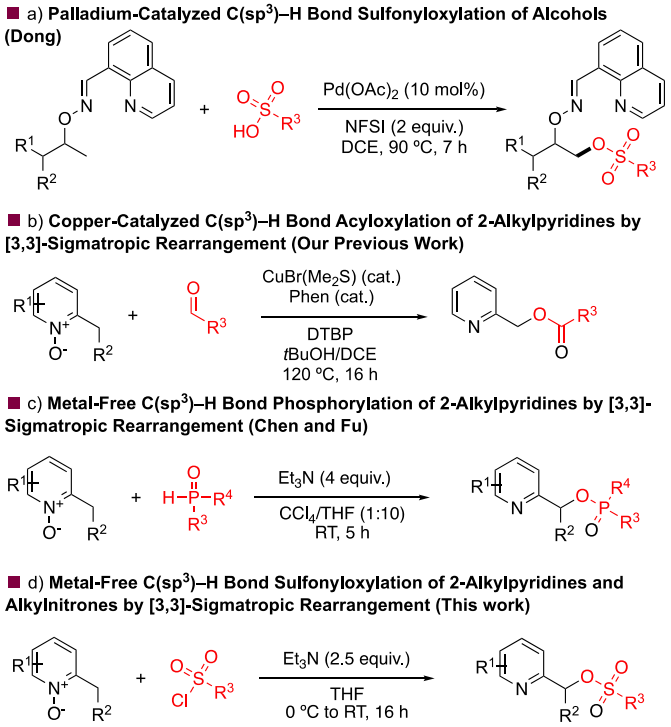

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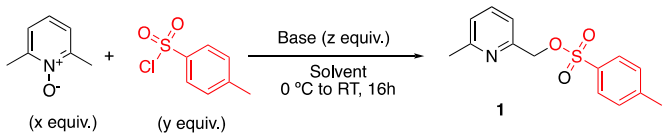
Figure 1. Previous C(sp^3)–H Bond Sulfonyloxylation and Functionation of 2-Alkyl Pyridines via [3,3]-Sigmatropic Rearrangements

We selected 2,6-dimethylpyridine 1-oxide and tosyl chloride as model substrates to study the formal C(sp^3)–H bond sulfonyloxylation through a [3,3]-rearrangement. Surprisingly, the expected product **1** was not formed in the presence of potassium carbamate (K_2CO_3) as base in acetonitrile (CH_3CN), although those reaction conditions have been employed by the Sledeski' group for the C(sp^3)–H bond sulfonyloxylation of 2-methylquinoline 1-oxide (Table 1, entry 1).[6] No reaction occurred in CH_2Cl_2 when K_2CO_3 and KOH were employed as base, whereas in the presence of 2 equivalents of organic base

such as triethylamine (Et_3N), the sulfonyloxylated product **1** was obtained in 12% yield (Table 1, entries 2-4). Then, we investigated the influence of nature of other solvents. The reaction is not operative in CH_3CN, dichloroethane (DCE) and ethanol (Table 1, entries 4-7). However, in THF the desired product **1** was obtained in a high yield of 72% (Table 1, entry 8). The use of 1.5 equivalents of tosyl chloride allowed to improve the yield of the sulfonyloxylated product **1** to 82% yield and even better (87%) using 2.5 equivalents of base (Table 1, entries 9 and 10).

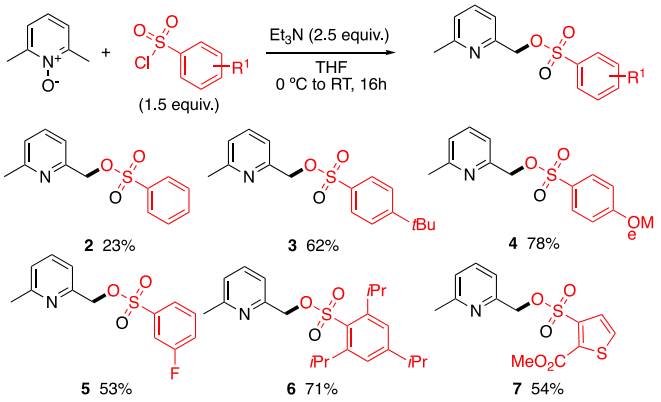
Table 1. Optimization of the Reaction Conditions



Entry	x / y	Base (z equiv.)	Solvent	Yield in **1** (%)
1	1:1.1	K_2CO_3 (2)	CH_3CN	0
2	1:1.1	K_2CO_3 (2)	CH_2Cl_2	0
3	1:1.1	KOH (2)	CH_2Cl_2	0
4	1:1.1	Et_3N (2)	CH_2Cl_2	12
5	1:1.1	Et_3N (2)	CH_3CN	0
6	1:1.1	Et_3N (2)	DCE	0
7	1:1.1	Et_3N (2)	EtOH	0
8	1:1.1	Et_3N (2)	THF	72
9	1:1.5	Et_3N (2)	THF	82
10	1:1.5	Et_3N (2.5)	THF	87 (81)

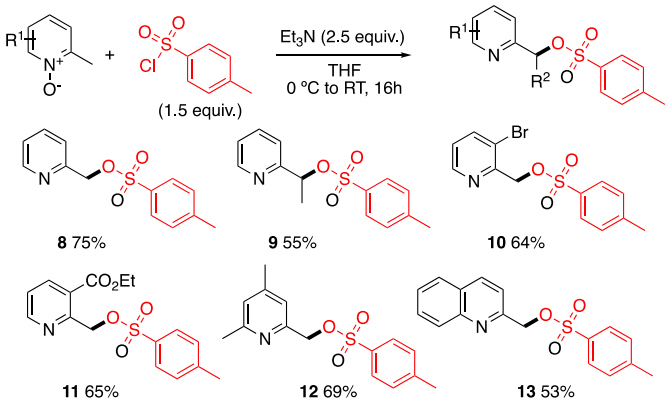
[a] Determined by GC-MS analysis using *n*-dodecane as internal standard, isolated yield is shown in parentheses

With the best conditions in hands, namely 2.5 equivalents of Et_3N as base in THF at room temperature, we turn our attention to the scope of the reaction. First, we examined the reactivity of other substituted benzenesulfonyl chlorides with 2,6-dimethylpyridine 1-oxide (Scheme 1). Benzenesulfonyl chloride displays a low reactivity, as the (6-methylpyridin-2-yl)methyl benzenesulfonate **2** is isolated in only 23% yield. When benzenesulfonyl chloride is substituted by an electron-donating group such as *t*Bu or OMe at the *para*-position, the sulfonyloxylated products **3** and **4** are obtained in 62% and 78% yield, respectively. However, when the benzenesulfonyl chloride bears an electron-poor substituent at the *para* position such as NO_2 CN or CF3, the desired product has not been isolated due to its instability. Benzenesulfonyl chlorides bearing an electron-withdrawing group at *meta* position such F displayed good reactivity, allowing the formation of desired product **5** in 53% yield. The reaction is not sensitive to the steric hindrance, as from 2,4,6-triisopropylbenzenesulfonyl chloride, the sulfonyloxylated products **6** is isolated in an excellent yield. Heteroarylsulfonyl chloride such as methyl 3-(chlorosulfonyl)thiophene-2-carboxylate can be also employed under this reaction conditions with 2,6-dimethylpyridine 1-oxide to prepare the sulfonyl bridged bis-heterocycle **7** in 54% yield. Similar bridged structures exhibit important biological activities and are pharmaceutical drug precursors.[7]



Scheme 1. Scope of Benzenesulfonyl Chloride in C(sp^3)–H Bond Sulfonyloxylation of 2,6-Dimethylpyridine 1-Oxide

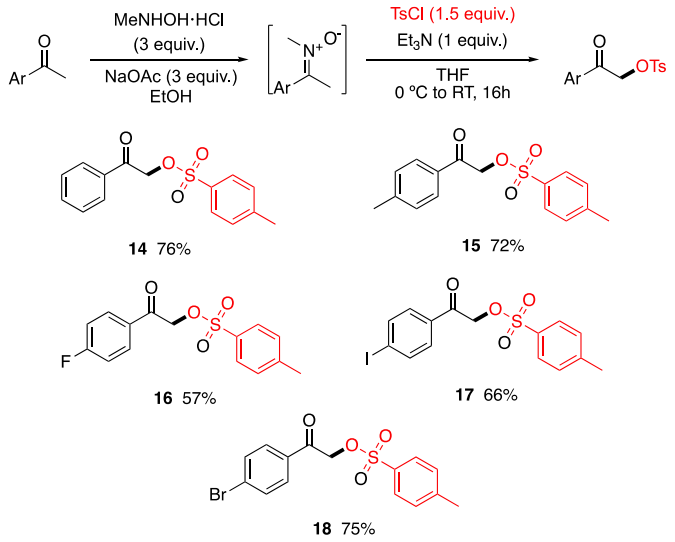
Next, we investigated the reactivity of a set of 2-alkylpyridine 1-oxides in the presence of tosyl chloride (Scheme 2). 2-Methyl pyridine 1-oxide underwent selectively C(sp^3)–H bond tosyloxylation to afford **8** in 75% yields, without the formation of C(sp^2)–H tosyloxylated product.[8] This reaction is successful for the formation of tertiary carbons, as from 2-ethylpyridine 1-oxide the tosyloxylated product **9** is obtained in 55% yield. The reaction tolerated a bromo or an ester substituent on the 2-methylpyridine 1-oxide partner allowing the formation of **10** and **11** in good yield, respectively. We also succeeded in the desymmetrization of one methyl group of 2,4,6-collidine 1-oxide with the formation of mono-tosyloxylated product **12** in 69% yield. Finally, 2-methylquinoline 1-oxide nicely reacted under these reaction conditions to deliver **13** in good yield.



Scheme 2. Scope of 2-Alkylpyridine 1-Oxides in Tosyloxylation with Tosyl Chlorides

Next, we investigated the reactivity of nitrones, derived from the *in-situ* condensation of acetophenones with 1-methylhydroxylamine hydrochloride, in the presence of tosyl chloride (Scheme 3). We are pleased to find that using only 1 equivalent of Et_3N, the nitrone reacts with tosyl chloride followed by [3,3] sigmatropic rearrangement and then by *in situ* hydrolysis to yield α-keto tosylate **14** in 76% yield. The use of 2 equivalent of base lead to lower yield in **14** due to the formation of degradation products. Interestingly, this reaction sequence for the α-tosyloxylation of enolizable ketones tolerates halo substituents (e.g., X = F, Br, I) on the aryl group

of the acetophenone derivatives allowing the formation of the tosylates **16**-**18** in high yields. Noteworthy, only a limited number of synthetic methods toward α-keto tosylates have been reported.[9] Most of them employed a two-step procedure or required the use of stoichiometric amount of a strong oxidant. In contrast, our method based on [3,3]-rearrangement of nitrone-tosylate adducts has some advantages, as it takes place under mild reaction conditions, with user-friendly procedure and the reactants are available at an affordable cost.



Scheme 3. [3,3] Rearrangement Reaction of Nitrone with Tosyl or Benzenesulfonyl Chlorides

Based on the previous Boekelheide rearrangements between 2-alkyl 1-oxide pyridine and acyl chloride,[10] we proposed a mechanistic pathway (Figure 2). The reaction is expected to start with a nucleophilic addition–elimination between 2-methyl pyridine 1-oxide **A** and arylsulfonyl chloride to give the formation of positively charged intermediate **B** associated to the chloride anion. Et_3N deprotonates the acidic C(sp^3)–H bond of **B**, giving neutral intermediate **C** with the formation of Et_3NHCl salt. Then, the intermediate **C** spontaneous undergoes [3,3]-rearrangement leading to the formation of sulfonyloxylated pyridine **D**. The driving force of this [3,3]-rearrangement is the rearomatization of the pyridine unit. We proposed a similar pathway with nitrone (Figure 2b). The addition–elimination of 2-methyl nitrone **E** to arylsulfonyl chloride affords **F**, which undergoes deprotonation of its acidic C(sp^3)–H bond followed [3,3]-rearrangement to afford the imine **H**. In the presence of water the imine **H** is hydrolyzed to the sulfonyloxylated ketone **I**.

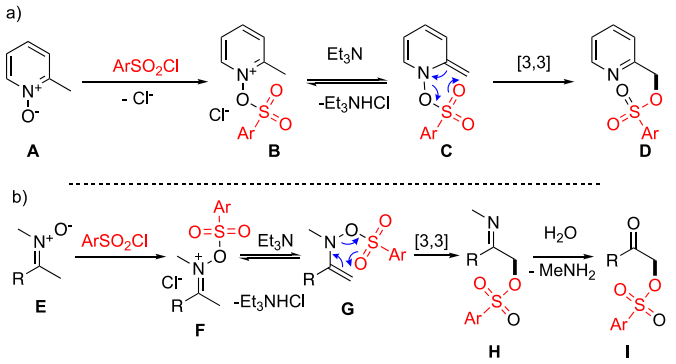
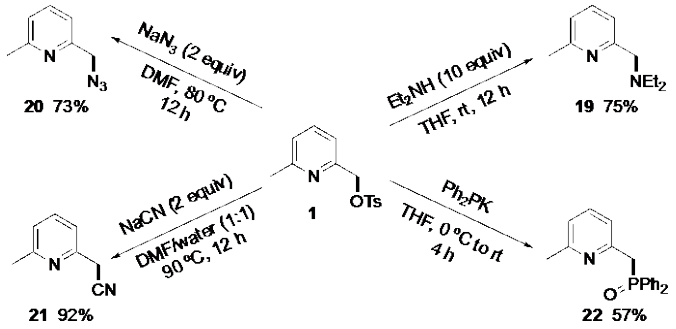


Figure 2. Proposed Mechanistic Pathways: a) for the Sulfonyloxylation of 2-Alkylpyridine 1-Oxides; b) for the Sulfonyloxylation of Nitrone Derivatives

Finally, we performed leaving group-based strategy to late-stage diversification of tosyloxylated pyridine **1** (Scheme 4). The C(sp^3)–H tosyloxylation of 2,6-dimethylpyridine 1-oxide has been performed on gram scale to afford **1** in a similar yield (73%, 2 g), which serves as a common intermediate for the diversification. The subsequent S_N2 reactions rapidly prepared a variety of pyridines derivatives through forming C–C, C–N, and C–P bonds. In particular, **19** and **22** are important intermediates for the preparation of PNN Milstein-type pincer ligands,[11] which are very useful catalysts for the activation of small molecules.



Scheme 4. Diversification of Tosyloxylated Pyridine **1** *via* Leaving Group Strategy

Conclusions

In summary, the present study provides a convenient and efficient approach for the diverse functionalization of alkyl pyridines and aryl alkyl ketones through the direct replacement of an C(sp^3)–H bond with a good leaving group (OTs). The formation of sulfonyloxylated pyridines is based on [3,3] rearrangement of sulfonated pyridinium intermediate, whereas the α-keto sulfonated are also obtained by a [3,3] rearrangement of sulfonated nitrone intermediate. Both rearrangements operate under very mild conditions in the presence of only triethylamine and did not required the use of oxidant.

Acknowledgements

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Conflicts of interest

"There are no conflicts to declare".

Notes and references

1. a) J. C. K. Chu and T. Rovis, *Angew. Chem. Int. Ed.*, 2018, **57**, 62-101; b) O. Baudoin, *Chem. Soc. Rev.*, 2011, **40**, 4902-4911; c) G. Qiu and J. Wu, *Org. Chem. Front.*, 2015, **2**, 169-178.
2. Y. Xu, G. Yan, Z. Ren and G. Dong, *Nat. Chem.*, 2015, **7**, 829.
3. a) T. Zhang and E. V. Anslyn, *Tetrahedron*, 2004, **60**, 11117-11124; b) N. C. Ackroyd and J. A. Katzenellenbogen, *Organometallics*, 2010, **29**, 3669-3671; c) C. Uttamapinant, A. Tangpeerachaikul, S. Grecian, S. Clarke, U. Singh, P. Slade, K. R. Gee and A. Y. Ting, *Angew. Chem. Int. Ed.*, 2012, **51**, 5852-5856, S5852/5851-S5852/5820; d) V. Bevilacqua, M. King, M. Chaumontet, M. Nothisen, S. Gabillet, D. Buisson, C. Puente, A. Wagner and F. Taran, *Angew. Chem. Int. Ed.*, 2014, **53**, 5872-5876; e) W. Li, J.-H. Xie, M.-L. Yuan and Q.-L. Zhou, *Green Chem.*, 2014, **16**, 4081-4085; f) H. J. Davis, M. T. Mihai and R. J. Phipps, *J. Am. Chem. Soc.*, 2016, **138**, 12759-12762.
4. C.-S. Wang, T. Roisnel, P. H. Dixneuf and J.-F. Soulé, *Org. Lett.*, 2017, **19**, 6720-6723.
5. Y. Yang, C. Qu, X. Chen, K. Sun, L. Qu, W. Bi, H. Hu, R. Li, C. Jing, D. Wei, S. Wei, Y. Sun, H. Liu and Y. Zhao, *Org. Lett.*, 2017, **19**, 5864-5867.
6. A. W. Sledeski, M. K. O'Brien and L. K. Truesdale, *Tetrahedron Lett.*, 1997, **38**, 1129-1132.
7. a) M. S. Sandhyavali, S. R. Brahmani Priyadarshini and D. R. Katta, *Res. J. Pharm., Biol. Chem. Sci.*, 2011, **2**, 373-381; b) A. K. Awasthi, L. Kumar, P. Tripathi, M. Golla, M. A. Aga, C. S. Reddy and P. Kumar, *ACS Omega*, 2017, **2**, 5460-5469; c) J. Guo, C. J. Sinclair, K. Selby and A. B. A. Boxall, *Environ. Toxicol. Chem.*, 2016, **35**, 1550-1559.
8. a) B. Du, P. Qian, Y. Wang, H. Mei, J. Han and Y. Pan, *Org. Lett.*, 2016, **18**, 4144-4147; b) Y. Su, X. Zhou, C. He, W. Zhang, X. Ling and X. Xiao, *J. Org. Chem.*, 2016, **81**, 4981-4987; c) W.-K. Fu, K. Sun, C. Qu, X.-L. Chen, L.-B. Qu, W.-Z. Bi and Y.-F. Zhao, *Asian J. Org. Chem.*, 2017, **6**, 492-495; d) L. Sumunnee, C. Buathongjan, C. Pimpasri and S. Yotphan, *Eur. J. Org. Chem.*, 2017, **2017**, 1025-1032.
9. a) S. Arava, J. N. Kumar, S. Maksymenko, M. A. Iron, K. N. Parida, P. Fristrup and A. M. Szpilman, *Angew. Chem. Int. Ed.*, 2017, **56**, 2599-2603; b) H. Kikui, K. Moriyama and H. Togo, *Synthesis*, 2013, **45**, 791-797; c) T. R. Lex, M. I. Swasy and D. C. Whitehead, *J. Org. Chem.*, 2015, **80**, 12234-12243; d) A. Yoshimura, S. C. Klasen, M. T. Shea, K. C. Nguyen, G. T. Rohde, A. Saito, P. S. Postnikov, M. S. Yusubov, V. N. Nemykin and V. V. Zhdankin, *Chem. Eur. J.*, 2017, **23**, 691-695; e) A. Tanaka, K. Moriyama and H. Togo, *Synlett*, 2011, **2011**, 1853-1858; f) T. Nabana and H. Togo, *J. Org. Chem.*, 2002, **67**, 4362-4365; g) W. Guo, O. Vallcorba, A. Vallribera, A. Shafir, R. Pleixats and J. Rius, *ChemCatChem*, 2014, **6**, 468-472; h) M. S. Khanna, C. P. Garg and R. P. Kapoor, *Tetrahedron Lett.*, 1992, **33**, 1495-1498.
10. a) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, 1954, **76**, 1286-1291; b) V. Boekelheide and W. L. Lehn, *J. Org. Chem.*, 1961, **26**, 428-430; c) J. F. Vozza, *J. Org. Chem.*, 1962, **27**, 3856-3860; d) C. Fontenas, E. Bejan, H. A. Haddou and G. G. A. Balavoine, *Synth. Commun.*, 1995, **25**, 629-633; e) S. Abbate, C. Bazzini, T. Caronna, F. Fontana, C. Gambarotti, F. Gangemi, G. Longhi, A. Mele, I. N. Sora and W. Panzeri, *Tetrahedron*, 2006, **62**, 139-148; f) C. Eidamshaus and H.-U. Reissig, *Eur. J. Org. Chem.*, 2011, **2011**, 6056-6069; g) T. Kawasuji, B. A. Johns, H. Yoshida, J. G. Weatherhead, T. Akiyama, T. Taishi, Y. Taoda, M. Mikamiyama-Iwata, H. Murai, R. Kiyama, M. Fuji, N. Tanimoto, T. Yoshinaga, T. Seki, M. Kobayashi, A. Sato, E. P. Garvey and T. Fujiwara, *J. Med. Chem.*, 2013, **56**, 1124-1135.
11. J. Zhang, G. Leitus, Y. Ben-David and D. Milstein, *J. Am. Chem. Soc.*, 2005, **127**, 10840-10841.

TOC: Direct transformation of inert C(sp^3)–H bond of 2-alkylpyridines and nitrone into C–OSO_2R bond has been described.