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Chang-Sheng Wang, Pierre H. Dixneuf, Jean-François Soulé. Metal-free C(sp<sup>3</sup>)-H bond sulfonyloxylation of 2-alkylpyridines and alkylnitrones. *Organic & Biomolecular Chemistry*, 2018, 16 (27), pp.4954-4957. 10.1039/c8ob01075g. hal-01863970

**HAL Id: hal-01863970**

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Submitted on 3 Sep 2018

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# Metal-Free C(sp<sup>3</sup>)-H Bond Sulfonyloxylation of 2-Alkylpyridines and Alkyl Nitrones

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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-alkylpyridine 1-oxides with benzenesulfonyl chlorides. Moreover, alkyl nitrones also undergo [3,3]-sigmatropic rearrangement to give  $\alpha$ -tosylated ketones after hydrolysis. Substitution reactions with nucleophiles then lead to diverse useful functionalizations for the synthesis of pincer ligands.

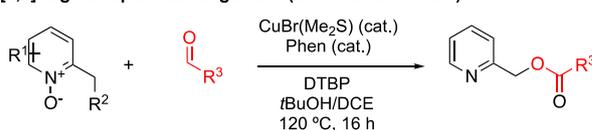
Alkyl sulfonates, such as alkyl tosylates, are typical substrates for S<sub>N</sub>2 reactions. Compared to alkyl halides, they often display higher thermal/light stability and resistance to radical-triggered side reactions. They are generally synthesized from alcohols by condensation reactions with benzenesulfonyl chlorides. A more straightforward access to these synthetically useful synthons would involve the direct transformation of inert C(sp<sup>3</sup>)-H bond into C-OSO<sub>2</sub>R bond.<sup>1</sup> In 2015, Dong and co-workers reported an elegant approach for the synthesis of  $\beta$ -sulfonyloxyated alcohols through a palladium-catalyzed regioselective C(sp<sup>3</sup>)-H bond functionalizations of masked alcohols bearing 8-formylquinoline-derived oxime as directing group (Figure 1a).<sup>2</sup> The reaction has employed *p*-toluenesulfonic acid as sulfonyloxylation 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,<sup>3</sup> are generally prepared from pyridin-2-ylmethanol derivatives. In 2017, our group has succeeded the C(sp<sup>3</sup>)-H bond benzyloxylation of 2-alkylpyridine derivatives through copper-catalyzed oxidative esterification of 2-alkylpyridine 1-oxides with aldehydes followed by [3,3]-sigmatropic rearrangement (Figure 1b).<sup>4</sup> The same year, Chen, Fu and co-workers reported metal-free conditions for the phosphorylation of 2-alkylpyridine and nitron derivatives via a similar [3,3]-sigmatropic rearrangement (Figure 1c).<sup>5</sup> 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).

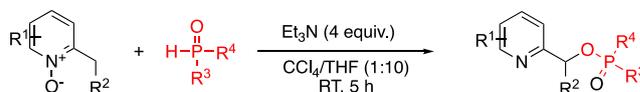
## a) Palladium-Catalyzed C(sp<sup>3</sup>)-H Bond Sulfonyloxylation of Alcohols (Dong)



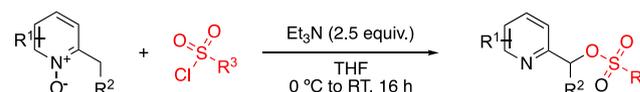
## b) Copper-Catalyzed C(sp<sup>3</sup>)-H Bond Acyloxylation of 2-Alkylpyridines by [3,3]-Sigmatropic Rearrangement (Our Previous Work)



## c) Metal-Free C(sp<sup>3</sup>)-H Bond Phosphorylation of 2-Alkylpyridines by [3,3]-Sigmatropic Rearrangement (Chen and Fu)



## d) Metal-Free C(sp<sup>3</sup>)-H Bond Sulfonyloxylation of 2-Alkylpyridines and Alkyl Nitrones by [3,3]-Sigmatropic Rearrangement (This work)



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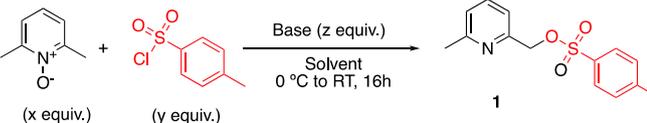
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Figure 1. Previous C(sp<sup>3</sup>)-H Bond Sulfonyloxylation and Functionalization of 2-Alkyl Pyridines via [3,3]-Sigmatropic Rearrangements

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

such as triethylamine (Et<sub>3</sub>N), 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<sub>3</sub>CN, 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).

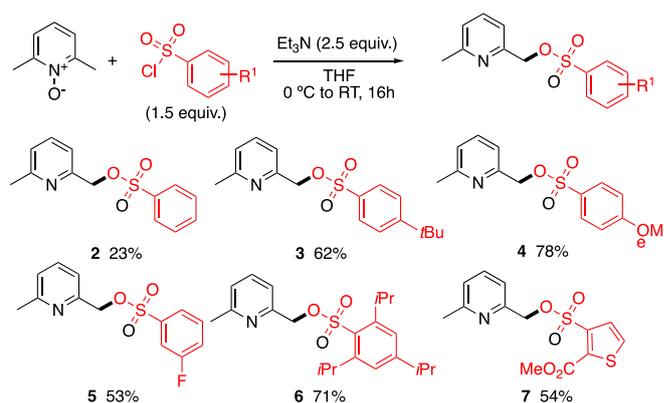
**Table 1.** Optimization of the Reaction Conditions



Entry	x / y	Base (z equiv.)	Solvent	Yield in <b>1</b> (%)
1	1:1.1	K <sub>2</sub> CO <sub>3</sub> (2)	CH <sub>3</sub> CN	0
2	1:1.1	K <sub>2</sub> CO <sub>3</sub> (2)	CH <sub>2</sub> Cl <sub>2</sub>	0
3	1:1.1	KOH (2)	CH <sub>2</sub> Cl <sub>2</sub>	0
4	1:1.1	Et <sub>3</sub> N (2)	CH <sub>2</sub> Cl <sub>2</sub>	12
5	1:1.1	Et <sub>3</sub> N (2)	CH <sub>3</sub> CN	0
6	1:1.1	Et <sub>3</sub> N (2)	DCE	0
7	1:1.1	Et <sub>3</sub> N (2)	EtOH	0
8	1:1.1	Et <sub>3</sub> N (2)	THF	72
9	1:1.5	Et <sub>3</sub> N (2)	THF	82
10	1:1.5	Et <sub>3</sub> N (2.5)	THF	87 (81)

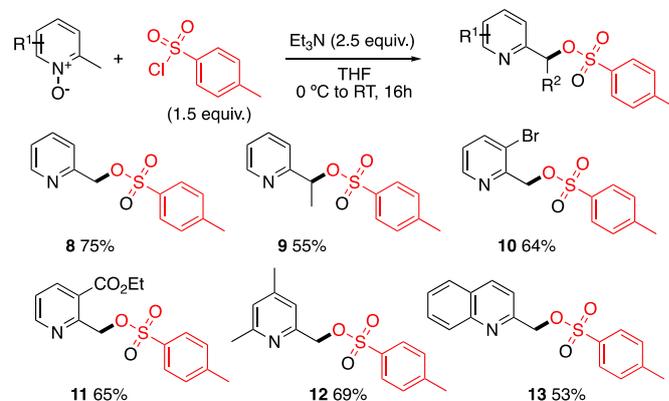
[a] Determined by GC-MS analysis using *n*-dodecane as internal standard, isolated yield is shown in parentheses

With the best conditions in hands, namely 2.5 equivalents of Et<sub>3</sub>N 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<sub>2</sub> CN or CF<sub>3</sub>, 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.<sup>7</sup>



**Scheme 1.** Scope of Benzenesulfonyl Chloride in C(sp<sup>3</sup>)-H Bond Sulfonyloxylation of 2,6-Dimethylpyridine 1-Oxide

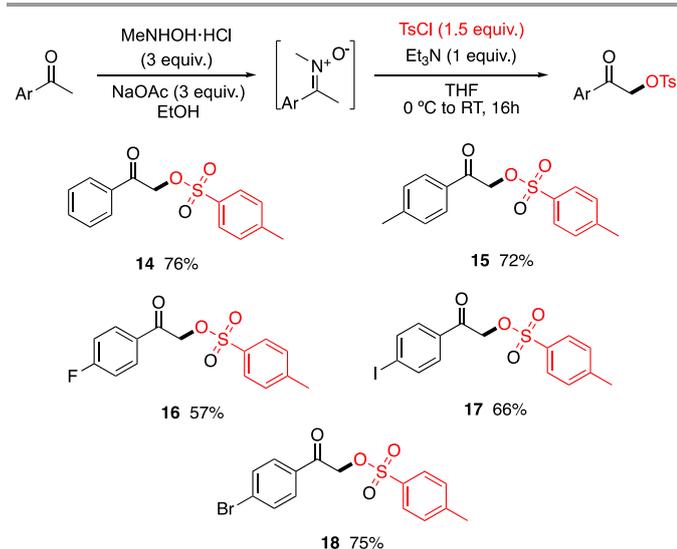
Next, we investigated the reactivity of a set of 2-alkylpyridine 1-oxides in the presence of tosyl chloride (Scheme 2). 2-Methyl pyridine 1-oxide underwent selectively C(sp<sup>3</sup>)-H bond tosyloxylation to afford **8** in 75% yields, without the formation of C(sp<sup>2</sup>)-H tosyloxylated product.<sup>8</sup> 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

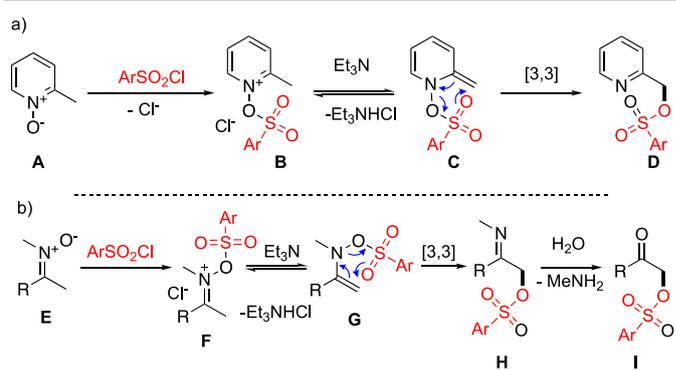
Next, we investigated the reactivity of nitrones, derived from the *in-situ* condensation of acetophenones with 1-methylhydroxylamine hydrochloride, in the presence of tosyl chloride (Scheme 3). We are pleased to find that using only 1 equivalent of Et<sub>3</sub>N, the nitron reacts with tosyl chloride followed by [3,3] sigmatropic rearrangement and then by *in situ* hydrolysis to yield  $\alpha$ -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  $\alpha$ -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  $\alpha$ -keto tosylates have been reported.<sup>9</sup> 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 nitron-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.



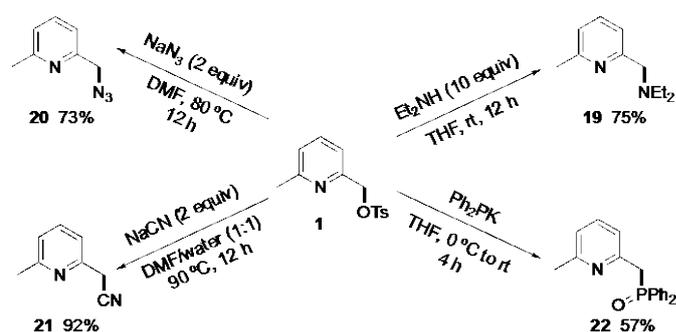
**Scheme 3.** [3,3] Rearrangement Reaction of Nitron with Tosyl or Benzenesulfonyl Chlorides

Based on the previous Boekelheide rearrangements between 2-alkyl 1-oxide pyridine and acyl chloride,<sup>10</sup> 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<sub>3</sub>N deprotonates the acidic C(sp<sup>3</sup>)–H bond of **B**, giving neutral intermediate **C** with the formation of Et<sub>3</sub>NHCl 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 nitron (Figure 2b). The addition–elimination of 2-methyl nitron **E** to arylsulfonyl chloride affords **F**, which undergoes deprotonation of its acidic C(sp<sup>3</sup>)–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 Nitron Derivatives

Finally, we performed leaving group-based strategy to late-stage diversification of tosylated pyridine **1** (Scheme 4). The C(sp<sup>3</sup>)–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<sub>N</sub>2 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,<sup>11</sup> which are very useful catalysts for the activation of small molecules.



**Scheme 4.** Diversification of Tosylated 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<sup>3</sup>)–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  $\alpha$ -keto sulfonated are also obtained by a [3,3] rearrangement of sulfonated nitron intermediate. Both rearrangements operate under very mild conditions in the presence of only triethylamine and did not required the use of oxidant.

## Acknowledgements

C.-S.W. acknowledges the China Scholarship Council (CSC) for a PhD grant.

## Conflicts of interest

"There are no conflicts to declare".

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TOC: Direct transformation of inert C(sp<sup>3</sup>)-H bond of 2-alkylpyridines and nitron into C-OSO<sub>2</sub>R bond has been described.

