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COMMUNICATION

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 SN_2 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).

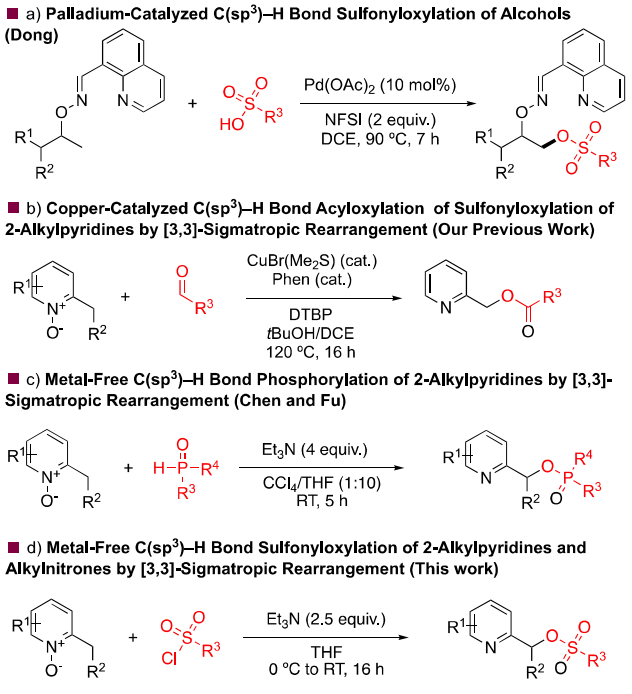

Figure 1. Previous C(sp^3)–H Bond Sulfonyloxylation and Functionation of 2-Alkyl Pyridines via [3,3]-Sigmatropic Rearrangements

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

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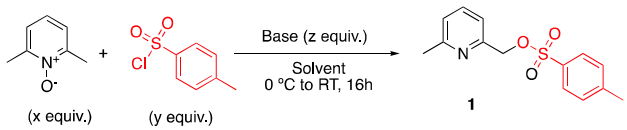
potassium carbamate (K_2CO_3) as base in acetonitrile (CH_3CN), although those reaction conditions have been employed by the Sledeski' group for the C(sp^3)–H bond sulfonyloxylation of 2-methylquinoline 1-oxide (Table 1, entry 1).[6] No reaction occurred in CH_2Cl_2 when K_2CO_3 and KOH were employed 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).

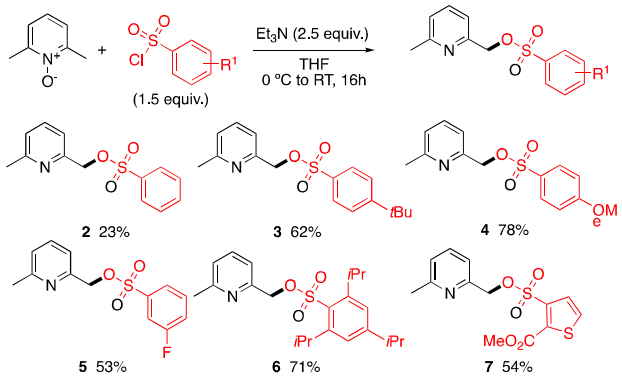
Table 1. Optimization of the Reaction Conditions



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)

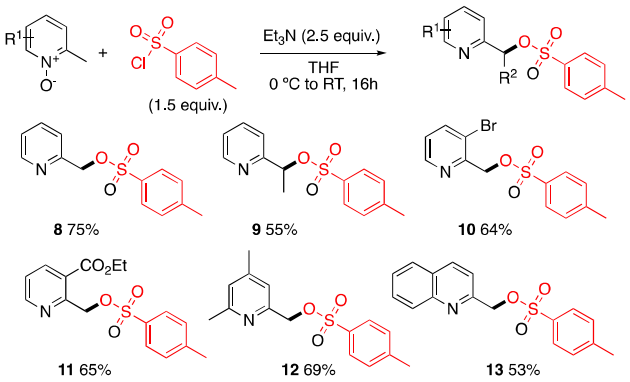
[a] Determined by GC-MS analysis using *n*-dodecane as internal standard, isolated yield is shown in parentheses

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). Phenylbenzenesulfonyl 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. 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. Interestingly, this reaction sequence for the α-tosyloxylation of

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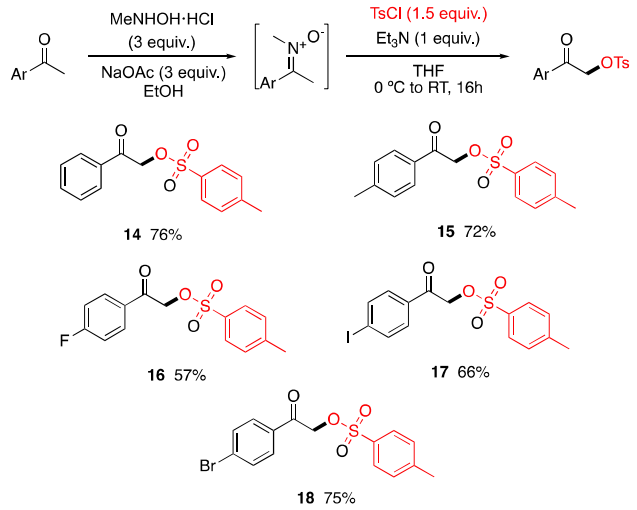
enolizable ketones tolerates halo substituents (e.g., X = F, Br, I) on the aryl group of the acetophenone derivatives allowing the formation of the tosylates **16**-**18** in high yields. Noteworthy, only a limited number of synthetic methods toward α-keto tosylates have been reported.[9] Most of them 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**.

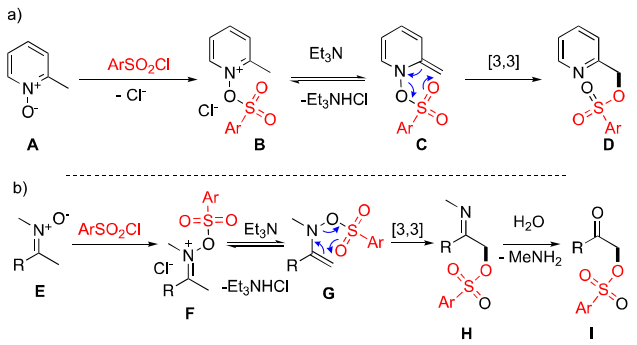
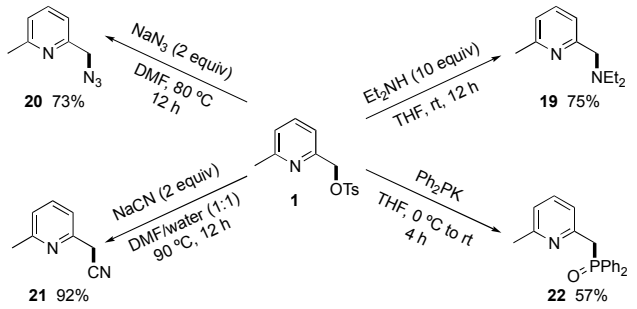


Figure 2. Proposed Mechanistic Pathways: a) for the Sulfonyloxylation of 2-Alkylpyridine 1-Oxides; b) for the Sulfonyloxylation of Nitrone Derivatives

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 SN_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,[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.

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Conflicts of interest

"There are no conflicts to declare".

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