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Metal-Free C(sp³)–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 SN₂ reactions. Compared to alkyl halides, they often display higher thermal/light stability and resistance to radicaltriggered side reactions. They are generally synthetized from alcohols by condensation reactions with benzenesulfonyl A more straightforward access to these chlorides. synthetically useful synthons would involve the direct transformation of inert C(sp³)–H bond into C–OSO₂R 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(sp³)–H bond functionalizations of masked alcohols bearing 8formylquinoline-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-2ylmethanol derivatives. In 2017, our group has succeeded the C(sp³)–H bond benzoxylation of 2-alkylpyridine derivatives through copper-catalyzed oxidative esterification of 2alkylpyridine 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).

a) Palladium-Catalyzed C(sp³)–H Bond Sulfonyloxylation of Alcohols



■ b) Copper-Catalyzed C(sp³)-H Bond Acyloxylation of 2-Alkylpyridines by [3,3]-Sigmatropic Rearrangement (Our Previous Work)



■ c) Metal-Free C(sp³)–H Bond Phosphorylation of 2-Alkylpyridines by [3,3]-Sigmatropic Rearrangement (Chen and Fu)

■ d) Metal-Free C(sp³)–H Bond Sulfonyloxylation of 2-Alkylpyridines and Alkylnitrones by [3,3]-Sigmatropic Rearrangement (This work)

$$\begin{array}{c} R^{1} \underbrace{\downarrow}_{N^{+}} \\ O \\ O \\ O \\ \end{array} + \begin{array}{c} O \\ R^{2} \end{array} + \begin{array}{c} O \\ C \\ C \\ \end{array} \xrightarrow{O} \\ R^{3} \end{array} \xrightarrow{Et_{3}N(2.5 \text{ equiv.})} \\ THF \\ O \\ C \\ C \\ THF \\ O \\ C \\ C \\ THF \\ O \\ C \\ C \\ THF \\ R^{2} \\ O \\ R^{3} \end{array} \xrightarrow{O} \\ \begin{array}{c} O \\ S \\ R^{3} \\ R^{2} \\ O \\ R^{3} \end{array}$$

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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 (K₂CO₃) as base in acetonitrile (CH₃CN), 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 CH₂Cl₂ when K₂CO₃ and KOH were employed as base, whereas in the presence of 2 equivalents of organic base such as triethylamine (Et₃N), 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 CH₃CN, 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

	-			
(x equiv.) (y equiv.) (y equiv.)				
Entry	x / y	Base (z equiv.)	Solvent	Yield in 1 (%)
1	1:1.1	K ₂ CO ₃ (2)	CH₃CN	0
2	1:1.1	K ₂ CO ₃ (2)	CH_2CI_2	0
3	1:1.1	KOH (2)	CH_2CI_2	0
4	1:1.1	Et₃N (2)	CH_2CI_2	12
5	1:1.1	Et₃N (2)	CH₃CN	0
6	1:1.1	Et₃N (2)	DCE	0
7	1:1.1	Et₃N (2)	EtOH	0
8	1:1.1	Et₃N (2)	THF	72
9	1:1.5	Et ₃ N (2)	THF	82
10	1:1.5	Et₃N (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 Et₃N 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-2yl)methyl benzenesulfonate 2 is isolated in only 23% yield. When benzenesulfonyl chloride is substituted by an electrondonating group such as tBu 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 NO₂ 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. Heteroarylsulfonly chloride such as methyl 3-(chlorosulfonyl)thiophene-2-carboxylate can be also employed under this reaction conditions with 2,6-dimethylpyridine 1oxide 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 Benzenesulfonly 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 1oxide 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 1methylhydroxylamine hydrochloride, in the presence of tosyl chloride (Scheme 3). We are pleased to find that using only 1 equivalent of Et₃N, 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 2methyl 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 Then, the intermediate **C** spontaneous Et₃NHCl salt. 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.



Finally, we performed leaving group-based strategy to latestage diversification of tosyloxylated pyridine **1** (Scheme 4). The C(sp³)–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.



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(sp³)–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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