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Base-Mediated C4-Selective C–H-Sulfonylation of Pyridine**

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The direct regioselective C–H-functionalization of simple, unfunctionalized pyridines is considered a long-standing challenge in heterocyclic chemistry. Herein, we report a novel one-pot protocol for the C4-selective sulfonylation of pyridines via triflic anhydride (Tf_2O) activation, base-mediated addition of a sulfinic acid salt, and subsequent elimination/re-aromatization. Contrary to previous approaches employing tailored blocking groups, positional selectivity can be controlled by using *N*-methylpiperidine as simple, readily available external base. This method offers a highly modular and streamlined access to C4-sulfonylated pyridines.

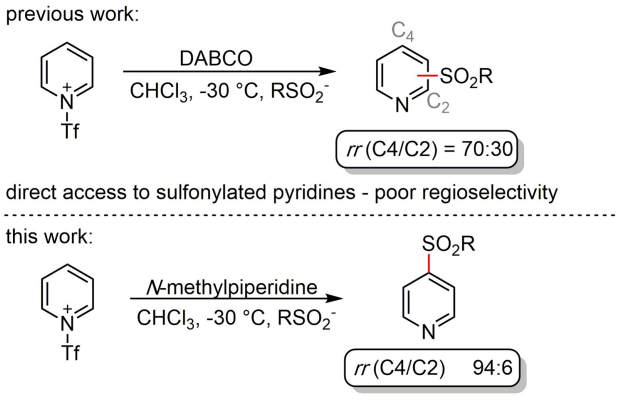
Introduction

The pyridine ring system is a ubiquitous heterocyclic motif in natural products and active pharmaceutical ingredients.[1] Owing to its relevance, there is a continuous interest in novel and effective methods for the preparation of this heteroaromatic scaffold. The direct C–H-functionalization of pyridines represents a particular attractive approach for the synthesis or late-stage modification of structural complex pyridine-based heterocycles.[2,3] Recently, we described a novel approach for the direct C–H-sulfonylation of pyridine and related *N*-heteroaromatics.[4] This process is based on activation of the pyridine ring with triflic anhydride (Tf_2O)[5,6] followed by a 1,4-diazabicyclo[2.2.2]octane (DABCO) mediated addition of a sulfinate salt and re-aromatization (Scheme 1a).

Although it enables a modular synthesis of *N*-heterocyclic sulfones and sulfonamides, this method sometimes suffers from the poor regioselectivity of the sulfinate addition. As a representative example, the C–H-sulfonylation of the parent pyridine delivers both the C2- and the C4-regiosiomer in a 30:70 ratio (Scheme 1a). An analogous formation of two or more regioisomers has been observed in many similar processes.[2,3,5] Therefore, a general method to address the poor regioselectivity in the C–H-functionalization of activated pyridinium salts would be highly desirable.[7] Herein, we report a novel method for the C4-selective C–H-sulfonylation of pyridines. Contrary to previous described procedures which exploit tailored C2-blocking groups,[7d] we were able to achieve a so far unprecedented base-induced C4-selective C–H-functionalization of pyridine (Scheme 1b).

Results and Discussion

During our initial investigations on the C–H-sulfonylation of *N*-heteroaromatics, we observed some unexpected results in the functionalization of pyridine **1** with sodium *para*-toluenesulfinate **2** (Table 1). Whereas the reaction with our previously reported conditions (base: DABCO; solvent: CH_2Cl_2) afforded the sulfonylated pyridine as 70:30 mixture of the C4- and C2-regiosiomer (**3a** and **3b**) (entry 1), we could observe a significant influence of both base and solvent on the reaction outcome. Replacement of CH_2Cl_2 with $CHCl_3$ led to a slight improvement in terms of regioselectivity (entry 2).[9] Addition of *N*-methylpiperidine instead of DABCO as base, furnished the sulfonylated pyridine **3** in 73% yield and a C4/C2-selectivity of 83:17 (entry 3). Combining $CHCl_3$ as solvent with *N*-methylpiperidine as base resulted in a highly regioselective functionalization of pyridine (entry 4).



Scheme 1. C4-selective sulfonylation of pyridine.

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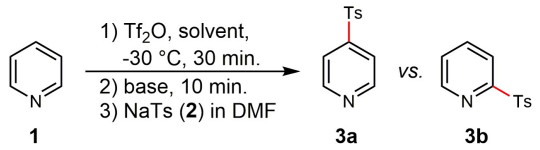
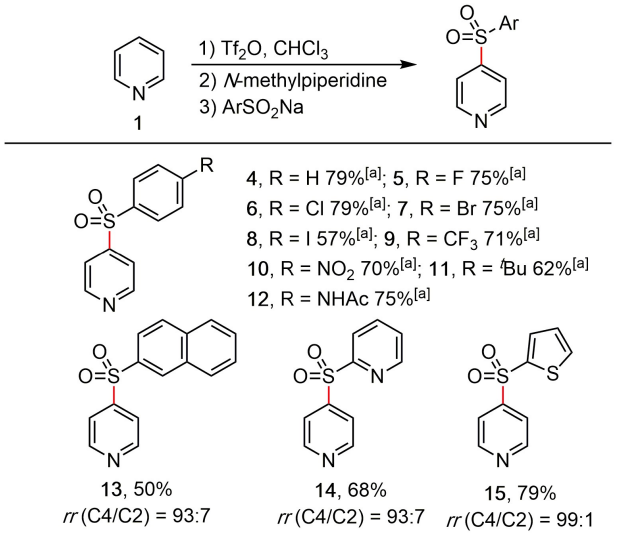
Table 1. Influence of base and solvent on the regioselective sulfonylation of pyridine.



1 3a 3b

Entry	Base	Solvent	Yield[a]	*rr* (C4/C2)[b]
1	DABCO	CH_2Cl_2	87[c]	70:30
2	DABCO	$CHCl_3$	83	78:22
3	*N*-methylpiperidine	CH_2Cl_2	73[c]	83:17
4	*N*-methylpiperidine	$CHCl_3$	79[c]	94:6
5	*N*-methylpyrrolidine	CH_2Cl_2	61	48:52
6	*N*-methylpyrrolidine	$CHCl_3$	75	70:30
7	*N*-methylmorpholine	CH_2Cl_2	<5	nd
8	*N*-methylmorpholine	$CHCl_3$	<5	nd
9	1,2,2,6,6-pentamethyl-piperidine	CH_2Cl_2	9	95:5
10	1,2,2,6,6-pentamethyl-piperidine	$CHCl_3$	<5	nd
11	*N,N'*-dimethylpiperazine	CH_2Cl_2	43	95:5
12	*N,N'*-dimethylpiperazine	$CHCl_3$	27	96:5

[a] Yield in [%] determined by GC with *n*-dodecane as internal standard. [b] Regioisomeric ratio (*rr*) in [%] determined by ^{1}H NMR of the crude mixture. [c] Isolated yield.



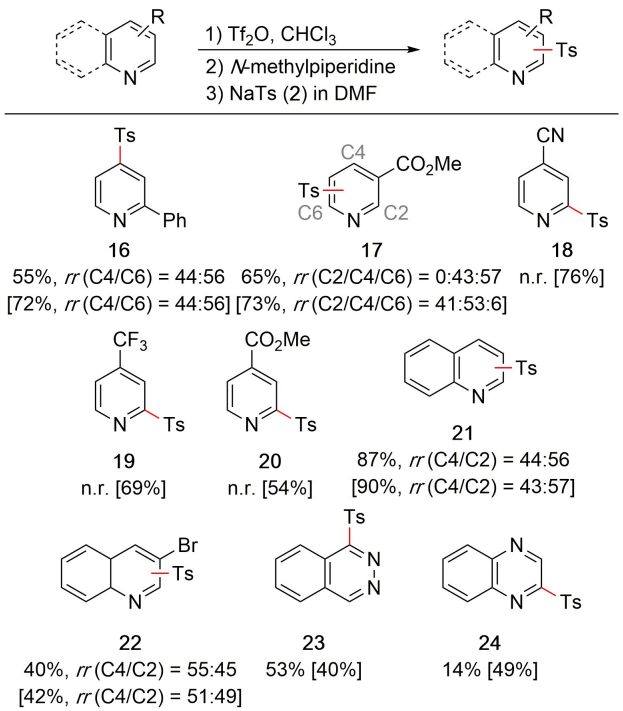
Scheme 2. C4-selective sulfonylation of pyridine, [a] if not specified otherwise a regioisomeric ratio (C4/C2) ≥ 95:5 was determined by ^{1}H NMR of the crude reaction mixture.

Interestingly, this effect could not be observed with structurally similar amine bases. *N*-methylpyrrolidine afforded the desired sulfonylated pyridine with significantly decreased regioselectivity both in CH_2Cl_2 and $CHCl_3$ (entries 5 and 6). Reactions with *N*-methylmorpholine or pentamethyl piperidine as base resulted in a very low overall yield (< 10%) (entries 7–10). Only the use *N,N*-dimethylpyridazine led to an regioselective formation of C4-sulfonylated pyridine in moderate yields (entries 11 and 12).

Using these novel conditions, we investigated the C–H-sulfonylation of pyridine with different sodium sulfinates (Scheme 2). Various aryl sulfinates containing different electron-withdrawing or -donating substituents, such as halogen atoms, a nitro or an amide group could be successfully attached to the heterocyclic ring (**4**–**13**). Good yields and uniformly high regioselectivities were obtained in all cases. To our delight heterocyclic sulfone residues (**14** and **15**) could be attached with a similar efficiency.

Next, we (re)investigated the C–H-sulfonylation of substituted pyridines and some other *N*-heteroaromatics with a particular focus on the observed differences in regioselectivity (Scheme 3). Therefore, reactions with 2-phenyl pyridine and nicotinic acid methyl ester as model substrates for C2- and C3-subsituted pyridines were examined. Interestingly, no changes in regioselectivity were observed for the C–H-sulfonylation of 2-phenyl pyridine using the novel conditions. In contrast, a distinct shift from the C2- to the C6-position occurred in the functionalization of nicotinic acid methyl ester. Strikingly, the C–H-sulfonylation of various 4-substituted pyridines (**18**–**20**) failed completely with our modified conditions.

On the other hand, the *N*-methylpiperidine-mediated C–H-sulfonylation of quinoline and 3-bromoquinolines proceeded with yields and selectivities in the same range as the initial version with DABCO. Direct functionalization of phtalazine and quinoxaline afforded the sulfonylated heterocycles **23** and **24** in 53% and 14% (vs. 40% and 49% with DABCO). These results show a quite distinct effect of the heterocyclic scaffold itself on the outcome of the reaction. However, the choice of base offers a useful handle to steer positioning of the sulfonyl substituent towards a specific position, in particular in the parent pyridine.



Scheme 3. Sulfonylation of substituted pyridines and other aza-heterocycles, yield and regioisomeric ratio in brackets refer to our previous method (CH_2Cl_2/DABCO).[4]

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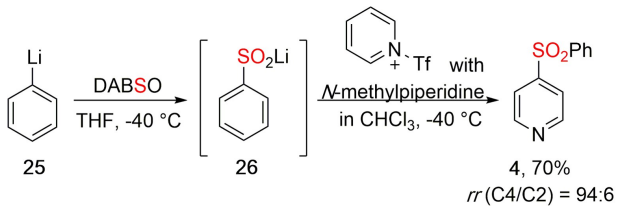
Therefore, our modified process opens an interesting opportunity to functionalize pyridine itself at an early stage.[3,7]

Next, we investigated a possible extension of our method for a modular installation of the sulfonyl residue onto pyridine. At first, we examined the direct incorporation of sulfur dioxide into the final sulfone product (Scheme 4).[8]

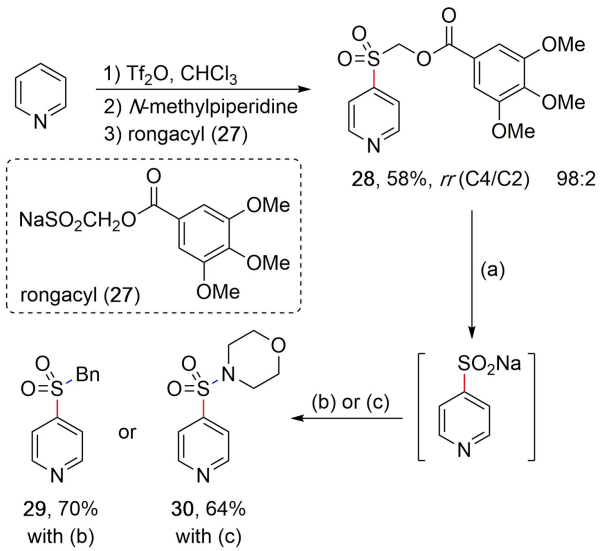
Therefore, a solution of phenyl lithium sulfinate **26** was prepared by the reaction of phenyl lithium **25** with the sulfur dioxide surrogate 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO).[10] Direct addition of the obtained crude sulfinate to the activated pyridinium triflate furnished the C4-sulfonylated pyridine **4** in 70% yield and a high regioselectivity.

In parallel, we examined the controlled installation of a masked sulfinate functionality using rongacyl (**27**), a readily available reagent, which offers both high flexibility for further modifications and good tolerance towards our reaction conditions (Scheme 5).[4,11] To our delight, the incorporation of **27** proceeded efficiently and with high C4-selectivity. Using a base-mediated cleavage-electrophilic trapping sequence, the masked sulfinate **28** could be converted into sulfone **29** and sulfonamide **30** in 70% and 64% yield.

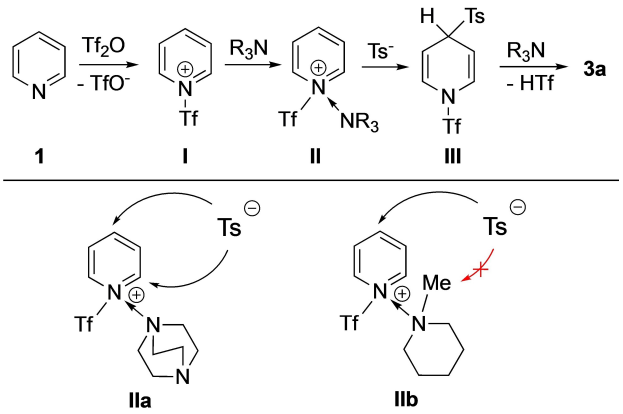
Based on our initial report,[4] we assume the following tentative reaction mechanism (Scheme 6). Treatment of



Scheme 4. Direct incorporation of SO_2 with DABSO, regioisomeric ratio (C4/C2) = 94:6 was determined by ^{1}H NMR of the crude mixture.



Scheme 5. Preparation of masked sulfinate **28** and further modification, reaction conditions (a): aqueous NaOH (1 M), TBAB, DMSO, ambient temperature; (b): benzyl bromide, 50 °C; (c) morpholine, NBS in THF, 0 °C.



Scheme 6. Tentative reaction mechanism.

pyridine (**1**) with Tf_2O affords the pyridinium salt **I**. Addition of the amine base (R_3N) to the activated pyridinium salt affords a charge transfer complex **II**. This complex displays a decreased reactivity of the Tf-group, thereby inhibiting a direct triflation (and subsequent decomposition) of the sulfinate **2**. Addition of the sulfinate **2** to **II** leads to the dihydropyridine intermediate **III**. Base-mediated elimination of HTf furnishes the final product **3**. We assume that the lower steric demand of the DABCO leads to competing addition at the C2- and C4-position of complex **IIa**. In contrast, the sterically more demanding *N*-methylpiperidine complex blocks addition of the sulfinate to the C2-position of **IIb** more efficiently. We assume, that the use of $CHCl_3$ leads to a stronger (and thereby shorter) N–N-bond in **II**. This fact could explain the generally higher regioselectivities in $CHCl_3$. However, additional mechanistic investigations are necessary to provide a more conclusive mechanistic rationale.

Conclusion

In summary, we have developed a novel, base-mediated highly regioselective C–H-sulfonylation of pyridine. This method gives a fast and efficient access to C4-functionalized pyridines. We could further demonstrate an extension towards a modular construction of sulfonylated pyridines using either the sulfur dioxide surrogate DABSO or a masked SO_2^{2-} equivalent as key building blocks. To the best of our knowledge, this is the first example for a regioselective functionalization of pyridines via the corresponding activated pyridinium salts controlled by an external base. It offers a streamlined access to C4-sulfonylated pyridines in a rapid and inexpensive fashion. Currently, we are examining the mechanism of this intriguing transformation in more detail, with the aim to extend the scope of this method both to other *N*-heteroaromatics and other types of nucleophiles.[12]

Experimental Section

A dried and nitrogen flushed 25 mL-Schlenk tube, equipped with a rubber septum and a magnetic stirring bar, was charged with pyridine (40 μL, 0.50 mmol, 1.0 equiv.) and dry $CHCl_3$ (5.0 mL). After cooling to −30 °C a solution of Tf_2O (100 μL, 0.55 mmol, 1.1 equiv.) in dry $CHCl_3$ (2.0 mL) was added dropwise over 10 min. resulting in a colourless suspension. After complete addition the suspension was stirred for another 30 min. at −30 °C. *N*-methylpiperidine (194 μL, 1.60 mmol, 3.2 equiv.) was added, whereupon a reddish solution was formed, which immediately turned into a suspension. After 10 min. a solution of the corresponding sodium sulfinate salt in DMF (6.5 ml, 0.1 M) was added. (The solution of the sulfinate salt was prepared at ambient temperature under sonication, which remained a solution during addition.) The resulting solution was stirred at −30 °C for another 2 h and slowly warmed to ambient temperature overnight. Then the reaction mixture was diluted with CH_2Cl_2 (5 mL) and transferred in a separation funnel. Aqueous saturated $NaHCO_3$ (15 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3× 15 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. Purification of the crude product by flash column chromatography (*n*-hexane/EtOAc) furnishing the desired sulfone.

Experimental details and characterization data for new compounds see Supporting Information (PDF).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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