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Remote Anionic Fries Rearrangement of Sulfonates: Regioselective Synthesis of Indole Triflones

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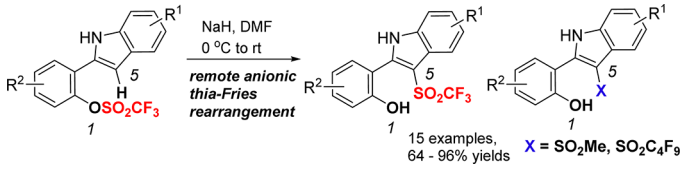
ABSTRACT



An unusual NaH-mediated remote anionic 1,5-thia-Fries rearrangement reaction was developed. This method provides an efficient approach for the regioselective synthesis of not only 2-(2-hydroxyphenyl)-3-indole triflones but also related 3-sulfonylindoles.

Over a time period of about 30 years, the anionic Fries rearrangement has been developed as a common synthetic concept in aromatic chemistry.[1,2] This rearrangement offers a mild and regioselective complement to a nonselective acid-catalyzed Fries rearrangement[3] and photo-Fries rearrangement.[4] Since the primary work of Lloyd-Jones,[5a] the anionic thia-Fries rearrangement, mainly involving a 1,3-sulfonyl migration reaction of aryl trifluoromethanesulfonate (triflate), has received much attention (Scheme 1a).[5]

This rearrangement affords aryl triflones which are an important class of compounds used as structural units in bioactive molecules,[6] chiral catalysts,[5c,d,7] and functional

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materials,[8] because of the unique properties of the SO_2CF_3 group.[9] We recently expanded the anionic *ortho*-Fries rearrangement to the synthesis of several types of heteroaryl triflones.[10] In these anionic thia-Fries rearrangement reactions, the carbanions are generated via directed *ortho* metalation (DoM).[11] It is highly desirable to develop new variations of anionic thia-Fries rearrangement under mild conditions. In continuation of our research on heterocyclic aryl triflones,[10,12] we were next interested in 2-hydroxyaryl-3-indole triflones **2** since 2-hydroxyaryl-3-indole is an important structural motif frequently encountered in biologically active molecules.[13] We herein report the regioselective synthesis of **2** by the first remote anionic thia-Fries rearrangement of **1** (Scheme 1b).[14] It should be noted that the anionic Fries rearrangement is induced by a *carbanion* generated via directed remote metalation (DreM),[15] while our rearrangement does not require powerful alkyllithium bases since it is induced by a *nitranion*.

2-(1*H*-Indol-2-yl)phenyl triflate **1a** was initially chosen as a test substrate for remote trifluoromethanesulfonyl (triflyl) rearrangement (Table 1). When **1a** was treated with LDA, the most commonly used base for remote anionic Fries rearrangement, the reaction was complex and the desired compound **2a** was obtained in 29% yield (Table 1, entry 1). The low yield was probably caused by the lower stability and better leaving ability of OSO_2CF_3 compared to other directed metalation groups (DMGs). Different bases were then screened, and NaH was proven to be the best base giving the desired compound in 87% yield (Table 1, entries 2–9). The solvent had a significant effect on yield. Only a 22% yield was obtained when the reaction was carried out in THF, while an 81% yield was achieved in DMSO (Table 1, entries 10 and 11). Decreasing the amount of base from 2.0 to 1.0 equiv caused a slight drop in yield (Table 1, entry 12). It is noteworthy that only the C(3)-Tf product was detected from crude ^{19}F NMR, while no N(1)-Tf product was found. The C(3)/N(1) chemo- or regioselectivity in this intramolecular rearrangement reaction is opposite to that in general sulfonylation reactions of indoles.[16]

Scheme 1. Anionic Thia-Fries Rearrangement

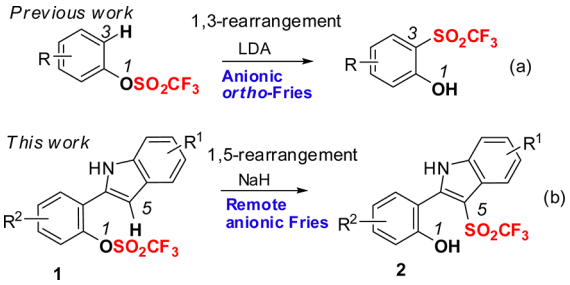
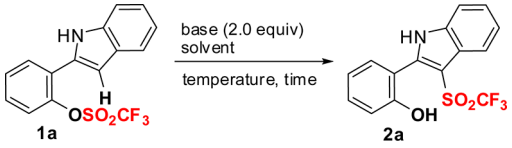


Table 1. Optimization of Reaction Conditions



entry	base	solvent	temperature	time	yield (%)[a]
1	LDA	THF	−78 °C to rt	2 h	29
2	*n*-BuLi	THF	−78 °C to rt	2 h	23
3	NaHMDS	THF	−78 °C to rt	2 h	75
4	DBU	THF	0 °C to rt	overnight	trace
5	K_2CO_3	DMF	0 °C to rt	overnight	50
6	*t*-BuOK	DMF	0 °C to rt	2 h	78
7	NaOMe	DMF	0 °C to rt	overnight	18
8	NaH	DMF	0 °C to rt	2 h	87
9	LiH	DMF	0 °C to rt	2 h	58
10	NaH	THF	0 °C to rt	4 h	22
11	NaH	DMSO	0 °C to rt	2 h	81
12[b]	NaH	DMF	0 °C to rt	2 h	80

[a] Yield was determined by ^{19}F NMR using trifluoromethoxybenzene as an internal standard. [b] NaH (1.0 equiv) was added.

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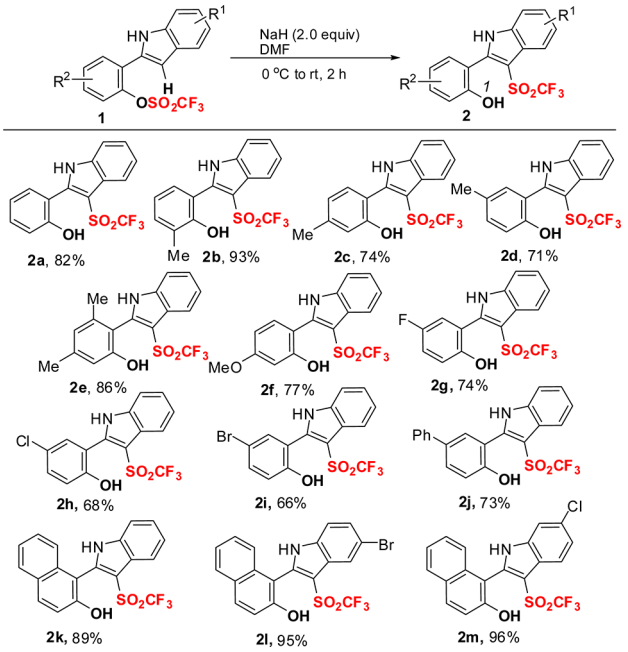
Scheme 2. NaH-Mediated Remote Anionic Rearrangement of Various Aryl Triflates[a]



[a] All reported reaction yields are isolated yields by silica-gel column chromatography.

Under optimized reaction conditions, the scope of the triflyl rearrangement of various 2-(1*H*-indol-2-yl)phenyl triflates **1a**–**m** was investigated (Scheme 2). Since the present method does not require strong alkyllithium bases, a variety of functional groups, including Cl and Br, are well tolerated. All the phenyl triflates **1b**–**j** bearing either electron-donating or -withdrawing substituents in different positions underwent remote triflyl rearrangement giving desired products **2b**–**j** in moderate to excellent yields. Notably, the rearrangement of 1-(1*H*-indol-2-yl)naphthalen-2-yl triflates **1k**–**m** also proceeded efficiently, giving the desired products **2k**–**m** in excellent yields. When *N*-methylindole derivative **3a** and 3-methylindole derivative **3b** were treated under the same optimized reaction conditions, no rearrangement was observed (Figure 1).

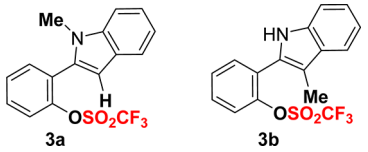
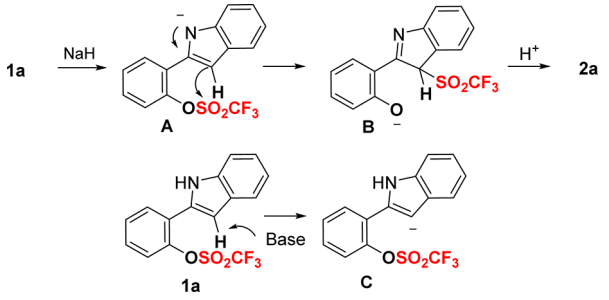


Figure 1. *N*-Methylindole **3a** and 3-methylindole **3b**.

(16) For selected examples, see: (a) Liu, W.; Lim, H. J.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2012**, *134*, 5496–5499. (b) Rueeger, H.; Lueoend, R.; Rogel, O.; Rondeau, J.-M.; Möbitz, H.; Machauer, R.; Jacobson, L.; Staufenbiel, M.; Desrayaud, S.; Neumann, U. *J. Med. Chem.* **2012**, *55*, 3364–3386. (c) Blessley, G.; Holden, P.; Walker, M.; Brown, J. M.; Gouverneur, V. *Org. Lett.* **2012**, *14*, 2754–2757.

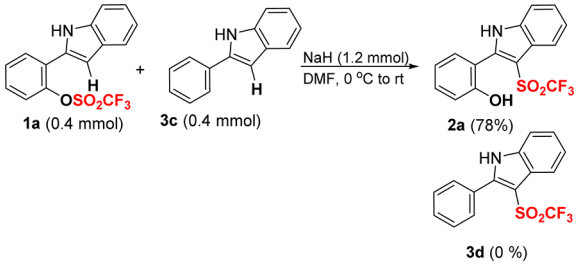
According to the above results, we proposed the following reaction mechanism (Scheme 3). Compound **1a** was treated with NaH giving intermediate **A**, which underwent intramolecular triflyl migration to produce intermediate **B**. Protonation and aromatic isomerization of intermediate **B** afforded the final product **2a**. Accordingly the direct generation of carbanion **C** from **1a** is not a feasible process. Hence, the present remote anionic thia-Fries rearrangement induced by *nitranion* is fundamentally different from the conventional thia-Fries rearrangement which generates a carbanion directly by strong alkyllithiums.

Scheme 3. Plausible Reaction Mechanism

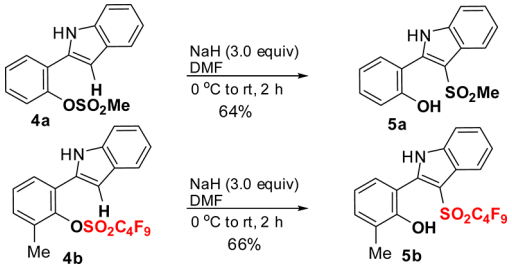


To further prove the reaction mechanism, a 1:1 mixture of compounds **1a** and **3c** was treated with NaH (Scheme 4). After analysis, one single peak was found from the crude ^{19}F NMR, and after column chromatography compound

Scheme 4. Crossover Experiment between **1a** and **3c**



Scheme 5. Reaction of **4a** and **4b** under Optimized Reaction Conditions



2a was obtained in good yield. Compound **1a** was triflylated but not compound **3c**, which could demonstrate that triflyl migration is an intramolecular process.

Finally, this rearrangement reaction was applied on methanesulfonate **4a** and perfluorobutanesulfonate **4b** (Scheme 5). To our delight, the migration process proceeded well and the desired compounds **5a** and **5b** were obtained in moderate yields.

In conclusion, we developed a novel remote anionic thia-Fries rearrangement reaction. To the best of our knowledge, this is the first example of remote anionic thia-Fries rearrangement. It provides an efficient method for the synthesis of not only biologically attractive 3-indole triflones but also various 2-(2-hydroxyphenyl)-3-sulfonyl-1*H*-indoles. Bromo- and chloro-substituted substrates are well accepted under these conditions, since the reaction does not require strong alkyllithium bases.

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Supporting Information Available. Experimental procedures, full characterization of new products, and copies of NMR spectra. This material is available free of charge via the Internet http://pubs.acs.org.

The authors declare no competing financial interest.