ORGANIC LETTERS

2013
Vol. 15, No. 3
686–689

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

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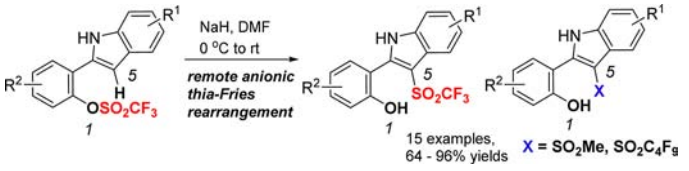
Received December 28, 2012

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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10.1021/ol3035559
Published on Web 01/23/2013

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

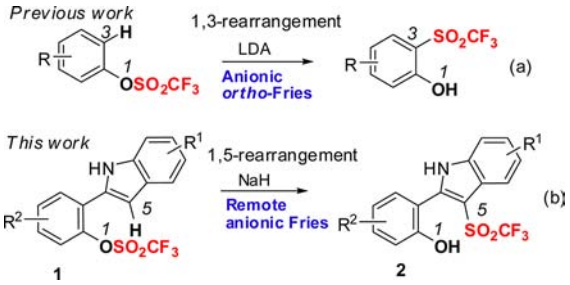
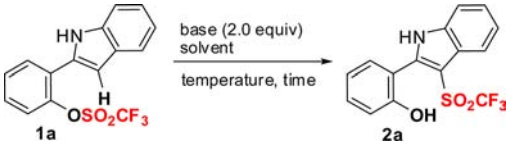


Table 1. Optimization of Reaction Conditions



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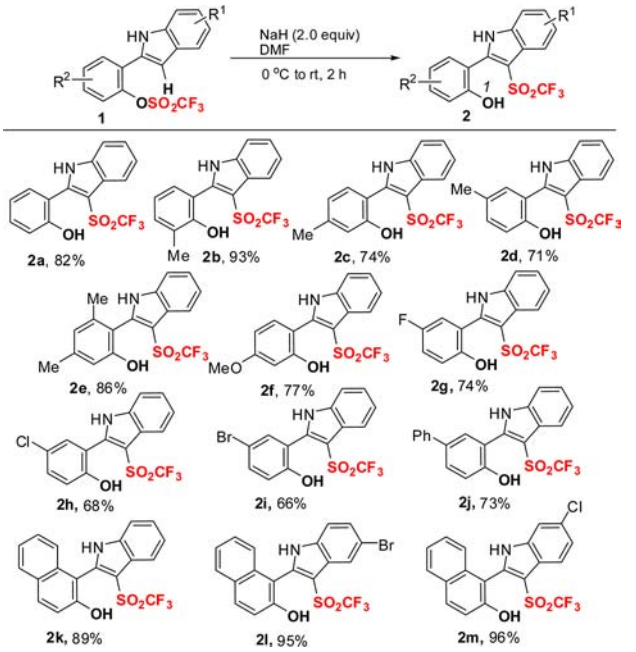
Scheme 2. NaH-Mediated Remote Anionic Rearrangement of Various Aryl Triflates[a]



[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).

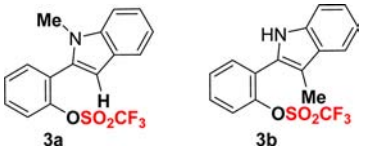
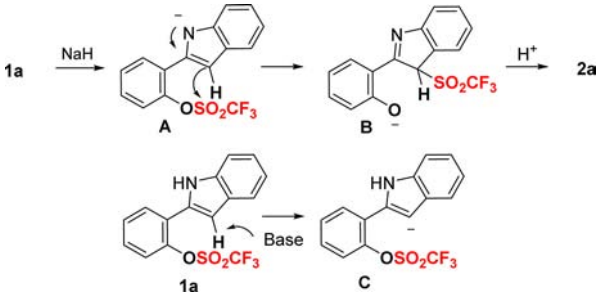


Figure 1. *N*-Methylindole **3a** and 3-methylindole **3b**.

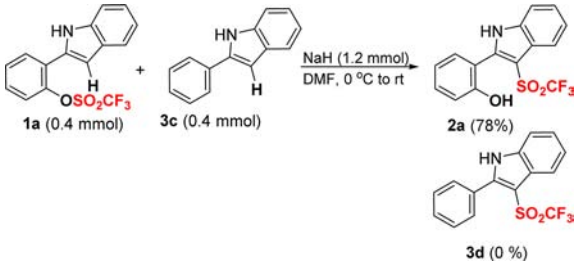
According to the above results, we proposed the following reaction mechanism (Scheme 3). Compound **1a** was treated with NaH giving intermediate **A**, which underwent intramolecular triflyl migration to produce intermediate **B**. Protonation and aromatic isomerization of intermediate **B** afforded 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

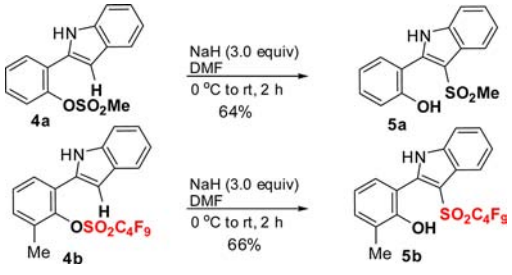


To further prove the reaction mechanism, a 1:1 mixture of compounds **1a** and **3c** was treated with NaH (Scheme 4). After analysis, one single peak was found from the crude ^{19}F NMR, and after column chromatography compound

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



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



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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.

Acknowledgment. This study was financially supported in part by the Platform for Drug Discovery, Informatics, and Structural Life Science from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We are grateful to Central Glass Co., Ltd. for the gift of triflic anhydride.

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.