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Regioselective Synthesis of Heteroaryl Triflones by LDA (Lithium Diisopropylamide)-Mediated Anionic Thia-Fries Rearrangement

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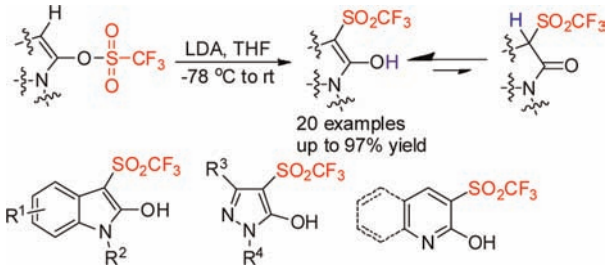
ABSTRACT



Novel heteroaryl triflones including oxindole, pyrazolone, pyridine, and quinoline derivatives have been regioselectively synthesized by LDA-mediated thia-Fries rearrangement for the first time. These reactions are also the first examples of the application of anionic thia-Fries rearrangement in heteroaromatic compounds.

The anionic *ortho*-Fries rearrangement is a 1,3-acyl migration reaction of aryl esters to *ortho*-substituted hydroxy aryl ketones through *ortho*-metalation mediated with either alkyl lithium or by halogen−metal exchange.[1,2] This rearrangement offers a mild and regioselective complement to nonselective acid-catalyzed Fries rearrangement[3] and photo-Fries rearrangement,[4] and it has been widely used in the synthesis of natural products and pharmaceuticals.[5] Several homologous anionic versions of the *ortho*-Fries rearrangement have also been developed.[6−8] All of these rearrangements of carboxylates have become useful methodologies for the synthesis of polysubstituted aromatics, whereas the analogous change of aryl sulfonates into phenolic sulfones, the "thia-Fries rearrangement",

(1) (a) For the first example of an aryl ester-derived anionic Fries rearrangement, see: Miller, J. A. *J. Org. Chem.* **1987**, *52*, 322–323. (b) For the first example of an aryl carbamate-derived anionic Fries rearrangement, see: Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935–1937. (c) For the first example of an aryl phosphate ester-derived anionic Fries rearrangement, see: Melvin, L. S. *Tetrahedron Lett.* **1981**, *22*, 3375–3376.

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(3) (a) Fries, K.; Finck, G. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 4271–4284. (b) For a recent review, see: Sartori, G.; Maggi, R. *Chem. Rev.* **2011**, *111*, PR181–PR214.

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(5) For recent applications, see: (a) Macklin, T. K.; Panteleev, J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2008**, *47*, 2097–2101. (b) Ding, F.; Zhang, Y.-D.; Qu, B.; Li, G.-S.; Farina, V.; Lu, B. Z.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 1067–1070. (c) Assimomytis, N.; Sariyannis, Y.; Stavropoulos, G.; Tsoungas, P. G.; Varvounis, G.; Cordopatis, P. *Synlett* **2009**, 2777–2782. (d) Miller, R. E.; Rantanen, T.; Ogilvie, K. A.; Groth, U.; Snieckus, V. *Org. Lett.* **2010**, *12*, 2198–2201. (e) Wessels, M.; Mahajan, V.; Boßhammer, S.; Raabe, G.; Gais, H.-J. *Eur. J. Org. Chem.* **2011**, 2431–2449. (f) Jeong, Y.-C.; Moloney, M. G. *J. Org. Chem.* **2011**, *76*, 1342–1354. (g) Chang, C.-W.; Chein, R.-J. *J. Org. Chem.* **2011**, *76*, 4154–4157.

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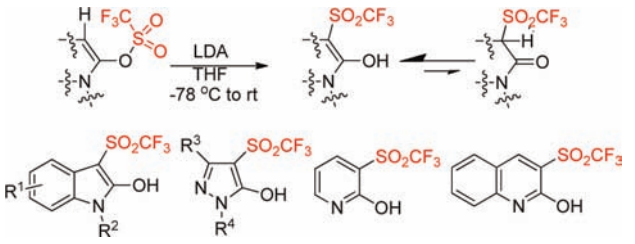
has received much less attention,[9] despite their potential utility to produce useful organosulfur compounds. The first anionic thia-Fries rearrangement of aryl triflate was reported by Lloyd-Jones in 2003.[10a] After that, more studies have been devoted to the synthetic potential of this reaction,[10b–h] probably because its product aryl triflones are frequently used as structural units in bioactive compounds,[11] chiral catalysts,[10c,d] and functional materials.[12] However, no attention has been paid to use this method for preparing heteroaryl triflones, which are potentially important heteroaromatic compounds because of the unique properties of the SO_2CF_3 group.[13] The synthesis of heteroaryl triflones still remains challenging, with synthesis often suffering from poor regioselectivity and low yields due to oxidative degradation. Our group has recently developed two methods for preparation of heteroaryl triflones, including modified Friedel–Crafts sulfonylation for indole triflones[14a] and cyclization of SO_2CF_3-containing building blocks for isoxazole triflones.[14b] In continuation of our research on fluorinated heterocycles,[15] we herein report the efficient synthesis of previously unknown heteroaryl triflones including oxindole, pyrazolone, pyridine, and quinoline derivatives by lithium diisopropylamide (LDA)-mediated thia-Fries rearrangement (Scheme 1). All of these heteroaryl triflones are synthesized for the first time, and their characterization reveals that they exist as enol tautomers rather than as amido forms.

Scheme 1. Synthesis of Heteroaryl Triflones by LDA-Mediated Regioselective Thia-Fries Rearrangement



Indolyl triflate **1a** was initially chosen as the test substrate. Several types of bases (1.50 equiv) were screened (Table 1). No reaction happened when **1a** was treated with DMAP (Table 1, entry 1). When *n*-BuLi or LDA was used as the base, the reaction was complete after 2 h (Table 1, entries 2 and 3). Some starting material was not converted under the condition of phosphazene P_4-*t*-Bu after 24 h (Table 1, entry 4). Among these three bases, LDA was proven to be the best, giving the product **2a** in good yield with much less byproduct. To our delight, when the amount of LDA was decreased from 1.50 to 1.10 equiv, almost single product was obtained (Table 1, entry 5). Thus it was concluded that not only LDA but also its amount were important to this rearrangement.[16] Interestingly, characterization of **2a** conducted by ^{13}C NMR and DEPT-45 analysis reveals all quaternary ^{13}C signals, which is in accord with the structure of enol tautomer **2a** but is not consistent with another structural tautomer, the amido form, which is theoretically possible.

Under the optimized reaction condition, the scope of this rearrangement was first investigated with a variety of

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(16) A high quality of LDA was also necessary for this rearrangement. The LDA used in our lab was purchased from Aldrich. For mechanisic studies of LDA-mediated Fries rearrangement, see ref 10e and the following references: (a) Singh, K. J.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 13753–12760. (b) Ma, Y.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 14818–14825. (c) Riggs, J. C.; Singh, K. J.; Ma, Y.; Collum, D. B. *J. Am. Chem. Soc.* **2008**, *130*, 13709–13717.

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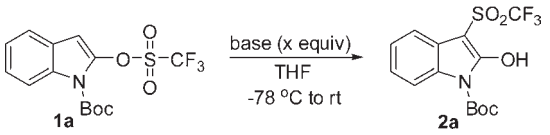
Table 1. Optimization of Reaction Condition



1a 2a

entry	base	equiv	yield (%)
1[a]	DMAP	1.50	NR
2	*n*-BuLi	1.50	trace[b]
3	LDA	1.50	75[b]
4	P_4-*t*-Bu	1.50	48[b]
5	LDA	1.10	96[c]

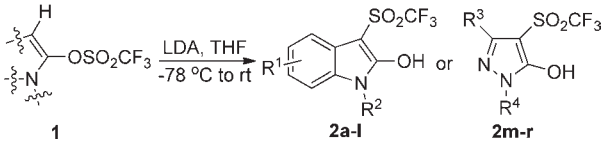
[a] Reaction was carried out from 0 °C to rt. [b] Determined by ^{19}F NMR. [c] Isolated yields by silica gel column chromatography.

oxindole derivatives, which constitute an important structural motif in the library of natural products and biologically active drugs.[17] The results were summarized in Table 2, entries 1−12. Different substituents on nitrogen were screened. A range of *N*-acylated, *N*-alkylated, and *N*-arylated oxindole derivatives were converted to their corresponding oxindole triflones **2a**−**j** in moderate to good yields (Table 2, entries 1−3, 4−6, and 7−10). It was noteworthy that different substituents on the *N*-phenyl ring, such as methyl, methoxy, and chloride, were tolerated in this reaction (Table 2, entries 8−10). Oxindole substrates **1k** and **1l** carrying an electron-donating or -withdrawing group on different positions of the oxindole ring could also undergo the rearrangement to afford the desired compounds **2k** and **2l** in good yields (Table 2, entries 11 and 12). We next examined the rearrangement of pyrazolone derivatives, another type of important heteroaromatic compound,[18] to explore the reaction scope (Table 2, entries 13−18). To our delight, the rearrangement is general and proceeded well to afford pyrazolone triflones in moderate to good yields. The pyrazolone derivatives **1m**−**p** bearing C-3 alkyl or aryl groups (Me, *n*-Pr, *t*-Bu, or Ph) can be converted to triflones **2m**−**p** in good yields (Table 2, entries 13−16). The same reactions were also carried out with pyrazolone derivatives **1q** and **1r**, which contain *N*1-substistuted phenyl groups (Table 2, entries 17 and 18). The pyrazolone triflones also exist as enol tautomers characterized by ^1H and ^{13}C NMR and DEPT-45 analysis.

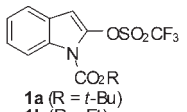
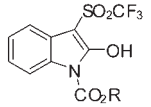
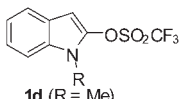
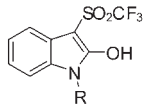
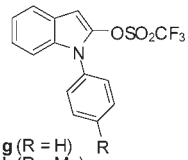
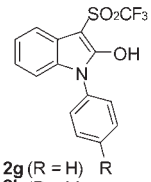
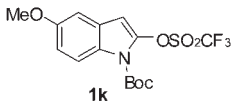
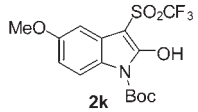
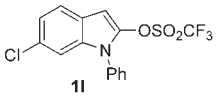
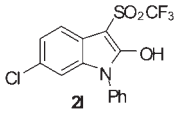
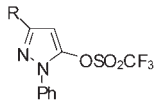
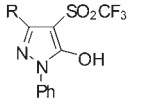
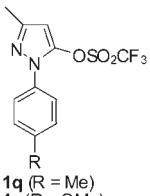
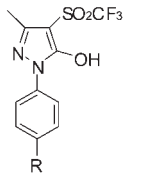
Finally, this rearrangement was applied to pyridyl and quinolyl triflates **3a** and **3b** (Scheme 2). Although the reactions were a bit more complex compared to those of oxindole and pyrazolone derivatives, the desired pyridine triflone **4a** and quinoline triflone **4b** were separated in moderate yields, respectively.

(18) For selected examples, see: (a) Kimata, A.; Nakagawa, H.; Ohyama, R.; Fukuuchi, T.; Ohta, S.; Suzuki, T.; Miyata, N. *J. Med. Chem.* **2007**, *50*, 5053–5056. (b) Uramaru, N.; Shigematsu, H.; Toda, A.; Eyanagi, R.; Kitamura, S.; Ohta, S. *J. Med. Chem.* **2010**, *53*, 8727–8733. (c) Chen, T.; Benmohamed, R.; Kim, J.; Smith, K.; Amante, D.; Morimoto, R. I.; Kirsch, D. R.; Ferrante, R. J.; Silverman, R. B. *J. Med. Chem.* **2012**, *55*, 515–527.

Table 2. LDA-Mediated Regioselective Thia-Fries Rearrangement of Various Oxindole and Pyrazolone Derivatives



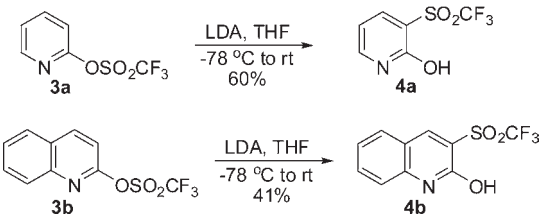
1 2a-l 2m-r

entry	triflate	product	yield (%)[a]
1			97 (**2a**)
2			76 (**2b**)
3	**1a** (R = *t*-Bu) **1b** (R = Et) **1c** (R = Me)	**2a** (R = *t*-Bu) **2b** (R = Et) **2c** (R = Me)	63 (**2c**)
4			74 (**2d**)
5			59 (**2e**)
6	**1d** (R = Me) **1e** (R = Et) **1f** (R = *i*-Pr)	**2d** (R = Me) **2e** (R = Et) **2f** (R = *i*-Pr)	68 (**2f**)
7			89 (**2g**)
8			93 (**2h**)
9			54 (**2i**)
10	**1g** (R = H) **1h** (R = Me) **1i** (R = OMe) **1j** (R = Cl)	**2g** (R = H) **2h** (R = Me **2i** (R = OMe) **2j** (R = Cl)	82 (**2j**)
11	 **1k**	 **2k**	80
12	 **1l**	 **2l**	91
13			84 (**2m**)
14			87 (**2n**)
15	**1m** (R = Me) **1n** (R = *n*-Pr) **1o** (R = *t*-Bu)	**2m** (R = Me) **2n** (R = *n*-Pr) **2o** (R = *t*-Bu)	87 (**2o**)
16	**1p** (R = Ph)	**2p** (R = Ph)	72 (**2p**)
17			72 (**2q**)
18			76 (**2r**)
	1q (R = Me) **1r** (R = OMe)	**2q** (R = Me) **2r** (R = OMe)	

[a] Isolated yields by silica gel column chromatography.

In conclusion, the anionic thia-Fires rearrangement was applied for the first time in the regioselective synthesis of heteroaromatic triflones including oxindole, pyrazolone, pyridine, and quinoline triflones in moderate to good

Scheme 2. LDA-Mediated Regioselective Thia-Fries Rearrangement of Pyridyl and Quinolyl Triflates



yields. Their characterization reveals that they exist as enol tautomers rather than as amido forms. It should be noted that all yields are higher than for the rearrangement of phenyl and naphthyl triflates, according to the Lloyd-Jones's report (30−80%).[10a] All of these novel heteroaryl triflones are attractive as building blocks for the synthesis of novel biologically active compounds as well as functional materials. These applications will be reported in the future.

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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 at http://pubs.acs.org.

The authors declare no competing financial interest.