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Synthesis of Indole and Biindolyl Triflones: Trifluoromethanesulfonylation of Indoles with Tf₂O/TTBP (2,4,6-tri-*tert*-butylpyridine) System

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A convenient synthesis of indole triflones is reported. *N*-Alkyl, aryl and *N*-H indole triflones were obtained in 82-96% yields by the Tf₂O/TTBP System. Biindolyl triflones were accessed in 51-81% yields for the first time by simple treatment of the resulting indole triflones with a base and without any use of organometallic chemistry. An environmentally friendly solvent, Solkane 365/227, can be substituted for this process without any loss of efficiency.

Aryl trifluoromethyl sulfones 1 (aryl triflones, ArSO₂CF₃) are frequently used as structural units in bioactive

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compounds,¹ chiral catalysts,² and functional materials (Figure 1).³ They are also important precursors in the organic synthesis of various trifluoromethylated compounds⁴ or aryl sulfones.⁵ The common methods for preparing aryl trifluors include the oxidation of aryl trifluoromethyl sulfides,⁶ trifluoromethylation of aryl sulfonyl fluorides or aryl sulfonates,⁷ thia-Fries rearrangement of

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aryl trifluoromethanesulfonates,⁸ and direct trifluoromethanesulfonylation of aromatic compounds.⁹



Figure 1. Aryl triflones 1 and indole triflones 2.

Recently, Taguchi and co-workers reported a unique regioselective synthesis of poly substituted aryl triflones through a self-promoting three-component reaction.¹⁰ A tremendous number of aryl triflones have been reported in the literature; however, no synthetic studies have been reported on indole triflones 2 except for two patents¹¹ despite their potential importance related to pharamaceuticals and agrochemicals. In this paper, we describe a general and high-yielding method for the synthesis of indole triflones 2 by Friedel-Crafts trifluoromethanesulfonylation of indoles with a triflic anhydride $(Tf_2O)/2,4$, 6-tri-tert-butylpyridine (TTBP) system. The use of a weak base, TTBP, is indispensable to reduce undesirable dimeric byproducts, while the complex mixture resulted from conventional Lewis acids-mediated Friedel-Crafts acvlation and sulfonylation.^{12,13} The reaction is guite insensitive to the choice of solvent and therefore an environmentally friendly solvent, Solkane 365/227, can be hypothetically substituted for CH₂Cl₂ and CH₃NO₂ without any loss of efficiency. Biindolyl triflones were also accessed for the first time by simple treatment of the resulting indole

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triflones with a base and without any use of organometallic chemistry.

First, trifluoromethanesulfonylation of indole 3a or 3b with Tf₂O in CH₂Cl₂ was attempted under a conventional Friedel–Crafts condition using AlCl₃; however, complex mixtures were obtained (Table 1, entries 1 and 2). In the absence of an additive, indole 3a was converted to dimer 4a in 63% yield, and indole triflone was not observed (entry 3).

Table 1. Optimization of Reaction Conditions



When the *N*-methyl indole **3b** was used as the substrate, indole triflone 2b was obtained in 20% yield along with the unwanted dimer 4b in 60% yield (Table 1, entry 4). Encouraged by this result, reaction conditions were screened to improve the yield of 2b. Since indole dimers are known to undergo thermal depolymerisation to give corresponding monomers,¹⁴ optimization of the reaction temperature might be a key for success (entries 5-7). The yield of **2b** was slightly increased to 24% at 40 °C in CH₂Cl₂. When the temperature was increased to 70 °C in CH₃NO₂, the desired 2b was obtained in 45% yield, while no dimer 4b was obtained. At a higher reaction temperature (100 °C in toluene), however, the yield of 2b was decreased to 35%. We next examined the use of additives. Since indole dimers are formed under dilute acid conditions,¹⁵ the addition of a base could prevent the formation of an indole dimer. By the addition of bases, such as NaHCO₃, KOBu^t, Et₃N or DBU, the reaction worsened or became more complex (entries 8-11). To our delight, trifluoromethanesulfonylation of **3b**

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proceeded nicely in CH_2Cl_2 in the presence of TTBP, delivering indole triflone **2b** in 82% yield, without any formation of the dimer **4b** (entry 12). The yield of triflone **2b** was further increased to 88% in CH_3NO_2 (entry 13).

Under the optimized reaction condition, Friedel-Crafts trifluoromethanesulfonylation of various indoles was examined to investigate the substrate generality (Table 2). The N-alkyl- and aryl-protected indoles 3b-f were smoothly converted into indole triflones in good to excellent yields (entries 1-5). The reactions with C-2 methyl and phenyl substituted indoles 3g and 3h also proceeded well to give 2-substituted indole triflones 2g and 2h in excellent yield, respectively (entries 6 and 7). Trifluoromethanesulfonylation of indole involves regioselectively at the 3-position^{12,13} and thus a complex mixture resulted by the reaction using C-3 methyl indole 3i as substrate (entry 8). The reaction proceeded well in 83-96% vields almost independently of the functional groups of the indole ring, including electron-withdrawing and electron-donating groups, and their substitution positions (entries 9-15).

 Table 2. Friedel-Crafts Trifluoromethanesulfonylation of Various Indoles

R ¹	$\mathbf{X}_{\mathbf{N}}^{\mathbf{N}}$	+ Tf ₂ O (1.1 equiv)	TTBP (1.2 equiv), CH ₃ NO ₂ 0 °C to rt, overnight	R ¹	SO ₂ CF ₃
entry	3	\mathbb{R}^1	\mathbb{R}^2	2	yield $(\%)^a$
1	3b	Н	Me	2b	88
2	3c	Н	Et	2c	94
3	3d	Н	Bn	2d	86
4	3e	Н	Ph	2e	85
5	3f	Н	$4-MeOC_6H_4$	2f	86
6	3g	2-Me	Me	$2\mathbf{g}$	91
7	3h	2-Ph	Me	2h	88
8	3i	3-Me	Me	_	Complex
9	3j	4-Me	Me	2j	92
10	3k	5-Me	Bn	$2\mathbf{k}$	91
11	31	5-OMe	Bn	21	84
12	3m	5-F	Me	2m	84
13	3n	5-Cl	Bn	2n	87
14	30	5-Br	Bn	2o	83
15	3p	7-Me	Me	$2\mathbf{p}$	96
^a Iso	olated yi	eld by silica-g	el column chromato	ography.	

The *N*-substitution of indoles **3** is important for this transformation. When the trifluoromethanesulfonylation of indole **3a** was attempted, trace of desired **2a** was obtained along with other several byproducts. Fortunately, the preparation of *N*-H indole triflone was accomplished by an unexpected reaction. When using *N*-TBS indole **3q** as a substrate, *N*-H indole triflone **2a** was obtained in 81% yield. The *N*-TBS moiety was removed spontaneously presumably due to its instability (Scheme 1).

After several attempts, the yield of *N*-H indole triflone **2a** was further improved to 92%. For other *N*-TBS indole



derivatives **3r** and **3s**, the trifluoromethanesulfonylated products **5b** and **5c** were also obtained in good to excellent yields (Scheme 2).

Scheme 2. Friedel-Crafts Trifluoromethanesulfonylation of *N*-TBS Indoles



We were next interested in 2,2'-biindolyl triflones **6**. Biindolyls are frequently encountered as structural motifs in pharmaceuticals and functional materials,¹⁶ hence their triflones were focused on. 2,2'-Biindolyls are generally obtained by a metal-mediated coupling reaction.¹⁷ We found the 2,2'-biindolyl triflones to be easily synthesized by a simple base treatment without any help of an organometallic coupling reaction. Namely, indole triflones **2** were treated with KOBu' in DMF at -50 °C to afford the targeted, previously unknown 2,2'-biindolyl triflones **6a**–**d** in moderate to good yields. The significant electron withdrawing power of the SO₂CF₃ group¹⁸ realized a successive deprotonation-addition–elimination pathway to dimerize the indoles at low temperature (Scheme 3).

Interestingly, treatment of biindolyl triflone **6a** with LiAlH₄ gave a symmetric 2,2'-biindolyl **7**,^{17b} which was previously synthesized via a metal-mediated coupling reaction (Scheme 4). These results indicate that this method provides not only the first synthesis of biindolyl triflones

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but also a rare example of the preparation of 2,2'-biindolyls without using a metal-mediated coupling reaction.¹⁷





Finally, the reaction was carried out in Solkane 365/227. We recently reported that Solkane 365/227, a blend solvent with 93/7 mixture of Solkane 365mfc (1,1,1,3,3-pentafluorobutane) and Solkane 227 (1,1,1,2,3,3,3-heptafluoropropane) developed by Solvay Fluor GmbH, can be used as an environmentally benign alternative solvent for several types of organic reactions.¹⁹ As shown in Table 3, with Solkane 365/227 as the reaction medium, for various substrates with different N-protecting groups and different substitutions at different positions of the indole ring, good to excellent vields were obtained (entries 1-5). The results were comparable to those when CH₃NO₂ was used as the solvent, although a slightly longer reaction time was required. What is more, under a scale-up condition, **3b** (10.0 mmol) in Solkane 365/ 227, the yield of **2b** was still high (up to 88%) and TTBP was recovered in 95% yield (entry 6).

Table 3. Friedel-Crafts Trifluoromethanesulfonylation of Various Indoles in Solkane 365/227, an Alternative Environmentally Benign Solvent

R ¹	3^{R^2}	+ Tf ₂ O (1.1 equi	TTBP (1 <u>Solkane</u> v) 0 °C	.2 equiv) ® 365/227 ► to rt ►	2	SO ₂ CF ₃ N R ²
entry	3	\mathbb{R}^1	\mathbb{R}^2	time (h)	2	yield (%) ^a
1	3b	Н	Me	15	2b	89
2	3d	Н	Bn	24	2d	78
3	3g	2-Me	Me	15	$2\mathbf{g}$	88
4	31	5-OMe	Bn	24	21	82
5^b	3q	Н	TBS	24	2a	81
6^c	3b	Н	Me	15	2b	88

^{*a*} Isolated yield by silica-gel column chromatography. ^{*b*} Tf_2O (2.4 equiv) and TTBP (2.2 equiv) were added. ^{*c*} **3b** (10.0 mmol) was used.

In conclusion, we primarily developed a convenient synthesis of indole triflones by trifluoromethanesulfonylation of indoles with the $Tf_2O/TTBP$ system. Both *N*-alkyl, aryl substituted and nonsubstituted indole triflones were nicely accessed in good to excellent yields. The reactions also preceded efficiently in an environmentally friendly solvent, Solkane 365/227. The biindolyl triflones were synthesized for the first time by the base-mediated dimerization of indole triflones via a successive deprotonation-addition–elimination pathway. The SO₂CF₃ substitution is a key for this dimerization process. The application of indole triflones and trifluoromethanesulfonylation of other heteroaromatics is currently in progress.

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Supporting Information Available. Experimental procedures, spectra data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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