ORGANIC LETTERS

2011
Vol. 13, No. 18
4854–4857

Synthesis of Indole and Biindolyl Triflones: Trifluoromethanesulfonylation of Indoles with Tf_2O/TTBP (2,4,6-tri-*tert*-butylpyridine) System

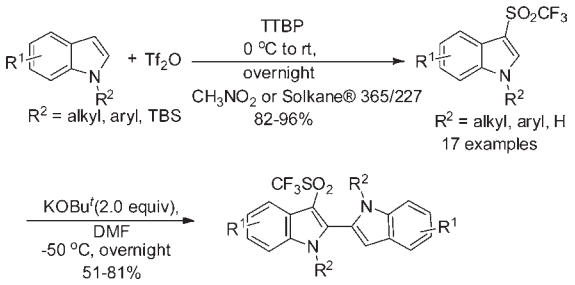
Xiu-Hua Xu, Guo-Kai Liu, Ayaka Azuma, Etsuko Tokunaga, and Norio Shibata*

Department of Frontier Materials, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya, 466-8555, Japan

nozshiba@nitech.ac.jp

Received July 17, 2011

ABSTRACT



A convenient synthesis of indole triflones is reported. *N*-Alkyl, aryl and *N*-H indole triflones were obtained in 82−96% yields by the Tf_2O/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, $ArSO_2CF_3$) are frequently used as structural units in bioactive compounds,[1] chiral catalysts,[2] and functional materials (Figure 1).[3] They are also important precursors in the organic synthesis of various trifluoromethylated compounds[4] or aryl sulfones.[5] The common methods for preparing aryl triflones include the oxidation of aryl trifluoromethyl sulfides,[6] trifluoromethylation of aryl sulfonyl fluorides or aryl sulfonates,[7] thia-Fries rearrangement of

(1) (a) Park, C.-M.; Bruncko, M.; Adickes, J.; Bauch, J.; Ding, H.; Kunzer, A.; Marsh, K. C.; Nimmer, P.; Shoemaker, A. R.; Song, X.; Tahir, S. K.; Tse, C.; Wang, X.; Wendt, M. D.; Yang, X.; Zhang, H.; Fesik, S. W.; Rosenberg, S. H.; Elmore, S. W. *J. Med. Chem.* **2008**, *51*, 6902–6915. (b) Brown, B. S.; Keddy, R.; Zheng, G. Z.; Schmidt, R. G.; Koenig, J. R.; McDonald, H. A.; Bianchi, B. R.; Honore, P.; Jarvis, M. F.; Surowy, C. S.; Polakowski, J. S.; Marsh, K. C.; Faltynek, C. R.; Lee, C.-H. *Bioorg. Med. Chem.* **2008**, *16*, 8516–8525. (c) Wang, G.; Zhang, H.; Zhou, J.; Ha, C.; Pei, D.; Ding, K. *Synthesis* **2008**, 2398–2404.

(2) (a) Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett.* **1988**, *29*, 2835–2838. (b) Mouhtady, O.; Gaspard-Iloughmane, H.; Laporterie, A.; Roux, C. L. *Tetrahedron Lett.* **2006**, *47*, 4125–4128. (c) Kargbo, R.; Takahashi, Y.; Bhor, S.; Cook, G. R.; Lloyd-Jones, G. C.; Shepperson, I. R. *J. Am. Chem. Soc.* **2007**, *129*, 3846–3847. (d) Barta, K.; Franciò, G.; Leitner, W.; Lloyd-Jones, G. C.; Shepperson, I. R. *Adv. Synth. Catal.* **2008**, *350*, 2013–2023.

(3) (a) Wolff, J. J.; Gredel, F.; Oeser, T.; Irngartinger, H.; Pritzkow, H. *Chem.—Eur. J.* **1999**, *5*, 29–38. (b) Matsui, M.; Suzuki, M.; Hayashi, M.; Funabiki, K.; Ishigure, Y.; Doke, Y.; Shiozaki, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 607–612. (c) Porrès, L.; Mongin, O.; Katan, C.; Charlot, M.; Pons, T.; Mertz, J.; Blanchard-Desce, M. *Org. Lett.* **2004**, *6*, 47–50. (d) Droumaguet, C. L.; Mongin, O.; Werts, M. H. V.; Blanchard-Desce, M. *Chem. Commun.* **2005**, 2802–2804. (e) Mongin, O.; Porrès, L.; Charlot, M.; Katan, C.; Blanchard-Desce, M. *Chem.—Eur. J.* **2007**, *13*, 1481–1498.

(4) (a) Prakash, G. K. S.; Hu., J.; Olah, G. A. *J. Org. Chem.* **2003**, *68*, 4457–4463. (b) Prakash, G. K. S.; Hu., J.; Olah, G. A. *Org. Lett.* **2003**, *5*, 3253–3256. (c) Zhao, Y.; Zhu, J.; Ni, C.; Hu, J. *Synthesis* **2010**, 1899–1904. (d) Prakash, G. K. S.; Wang, Y.; Mogi, R.; Hu, J.; Mathew, T.; Olah, G. A. *Org. Lett.* **2010**, *12*, 2932–2935.

(5) Steensma, R. W.; Galabi, S.; Tagat, J. R.; McCombie, S. W. *Tetrahedron Lett.* **2001**, *42*, 2281–2283.

(6) (a) Beaumont, A. J.; Clark, J. H. *J. Fluorine Chem.* **1991**, *52*, 295–300. (b) Chen, Q.-Y.; Duan, J.-X. *J. Chem. Soc., Chem. Commun.* **1993**, 918–919. (c) Su, W. *Tetrahedron Lett.* **1994**, *35*, 4955–4958. (d) González-Núñez, M. E.; Mello, R.; Royo, J.; Ríos, J. V.; Asensio, G. *J. Am. Chem. Soc.* **2002**, *124*, 9154–9163. (e) Liang, X.; Cheng, J.; Trudell, M. L. *J. Org. Chem.* **2003**, *68*, 5388–5391.

(7) (a) Kolomeitsev, A. A.; Movchun, V. N.; Kondratenko, N. V.; Yagupolski, Y. L. *Synthesis* **1990**, 1151–1152. (b) Movchun, V. N.; Kolomeitsev, A. A.; Yagupolski, Y. L. *J. Fluorine Chem.* **1995**, *70*, 255–257. (c) Singh, R. P.; Cao, G.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1999**, *64*, 2873–2876.

10.1021/ol201931x
Published on Web 08/17/2011

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

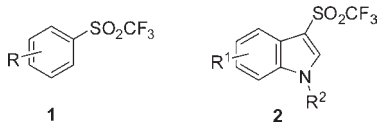
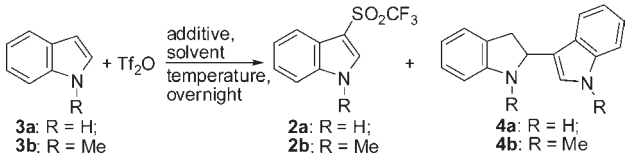


Figure 1. Aryl triflones **1** and indole triflones **2**.

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 patents[11] 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 acylation and sulfonylation.[12,13] The reaction is quite insensitive to the choice of solvent and therefore an environmentally friendly solvent, Solkane 365/227, can be hypothetically substituted for CH_2Cl_2 and CH_3NO_2 without any loss of efficiency. Biindolyl triflones were also accessed for the first time by simple treatment of the resulting indole triflones with a base and without any use of organometallic chemistry.

First, trifluoromethanesulfonylation of indole **3a** or **3b** with Tf_2O in CH_2Cl_2 was attempted under a conventional Friedel–Crafts condition using $AlCl_3$; 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



entry	**3**	additive	solvent	temperature	yield (**2**/**4**, %)[a]
1	**3a**	$AlCl_3$	CH_2Cl_2	0 °C to rt	complex
2	**3b**	$AlCl_3$	CH_2Cl_2	0 °C to rt	complex
3	**3a**	–	CH_2Cl_2	0 °C to rt	0/63
4	**3b**	–	CH_2Cl_2	0 °C to rt	20/60
5	**3b**	–	CH_2Cl_2	0 to 40 °C	24/48
6	**3b**	–	CH_3NO_2	0 to 70 °C	45/0
7	**3b**	–	toluene	0 to 100 °C	35/0
8	**3b**	$NaHCO_3$	CH_3CN	0 °C to rt	7/68
9	**3b**	$KOBu^t$	CH_3CN	0 °C to rt	complex
10	**3b**	Et_3N	CH_2Cl_2	0 °C to rt	complex
11	**3b**	DBU	CH_2Cl_2	0 °C to rt	complex
12	**3b**	TTBP	CH_2Cl_2	0 °C to rt	82/0
13	**3b**	TTBP	CH_3NO_2	0 °C to rt	88/0

[a] Isolated yield by silica-gel column chromatography.

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 CH_2Cl_2. When the temperature was increased to 70 °C in CH_3NO_2, 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 $NaHCO_3$, $KOBu^t$, Et_3N or DBU, the reaction worsened or became more complex (entries 8–11). To our delight, trifluoromethanesulfonylation of **3b**

(8) (a) Charmant, J. P.; Dyke, A. M.; Lloyd-Jones, G. C. *Chem. Commun.* **2003**, 380–381. (b) Zhao, Z.; Messinger, J.; Schön, U.; Wartchow, R.; Butenschön, H. *Chem. Commun.* **2006**, 3007–3009. (c) Crevatin, L. K.; Bonesi, S. M.; Erra-Balselle, R. *Helv. Chim. Acta* **2006**, *89*, 1147–1157. (d) Dyke, A. M.; Gill, D. M.; Harvey, J. N.; Hester, A. J.; Lloyd-Jones, G. C.; Muñoz, M. P.; Shepperson, I. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 5067–5070. (e) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Org. Lett.* **2010**, *12*, 1956–1959.

(9) (a) Hendrickson, J. B.; Bair, K. W. *J. Org. Chem.* **1977**, *42*, 3875–3878. (b) Creary, X. *J. Org. Chem.* **1980**, *45*, 2727–2729. (c) Magnier, E.; Blazejewski, J.-C.; Tordeux, M.; Wakselman, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1279. (d) Macé, Y.; Raymondeau, B.; Pradet, C.; Blazejewski, J.-C.; Magnier, E. *Eur. J. Org. Chem.* **2009**, 1390.

(10) Yanai, H.; Fujita, M.; Taguchi, T. *Chem. Commun.* **2011**, *47*, 7245–7247.

(11) (a) Gange, D. M. EP 697172, 1996. (b) Kumamoto, K.; Miyazaki, H. WO 2009028727, 2009.

(12) (a) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451–5457. (b) Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H. *Org. Lett.* **2000**, *2*, 1485–1487. (c) Ottoni, O.; Neder, A. D. V. F.; Dias, A. K. B.; Cruz, R. P. A.; Aquino, L. B. *Org. Lett.* **2001**, *3*, 1005–1007. (d) Yeung, K.-S.; Farkas, M. E.; Qiu, Z.; Yang, Z. *Tetrahedron Lett.* **2002**, *43*, 5793–5795. (e) Katritzky, A. R.; Suzuki, K.; Singh, S. K.; He, H.-Y. *J. Org. Chem.* **2003**, *68*, 5720–5723. (f) Yeung, K.-S.; Qiu, Z.; Farkas, M. E.; Xue, Q.; Regueiro-Ren, A.; Yang, Z.; Bender, J. A.; Good, A. C.; Kadow, J. F. *Tetrahedron Lett.* **2008**, *49*, 6250–6253. (g) Taylor, J. E.; Jones, M. D.; Williams, J. M. J.; Bull, S. D. *Org. Lett.* **2010**, *12*, 5740–5743. (h) Guchhait, S. K.; Kashyap, M.; Kamble, H. *J. Org. Chem.* **2011**, *76*, 4753–4758.

(13) (a) Yadav, J. S.; Reddy, B. V. S.; Krishna, A. D.; Swamy, T. *Tetrahedron Lett.* **2003**, *44*, 6055–6058. (b) Singh, D. U.; Singh, P. R.; Samant, S. D. *Tetrahedron Lett.* **2004**, *45*, 9079–9082. (c) Hosseini-Sarvari, M. *Lett. Org. Chem.* **2008**, *5*, 425–428. (d) Boroujeni, K. P. *J. Sulfur Chem.* **2010**, *31*, 197–203.

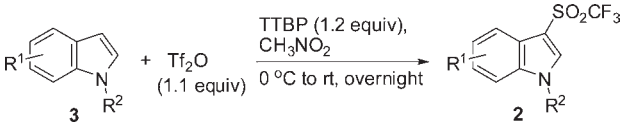
(14) (a) Hinman, R. L.; Shull, E. R. *J. Org. Chem.* **1961**, *26*, 2339–2342. (b) Yu, H.; Yu, Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 2929–2933.

(15) (a) Smith, G. F. *Adv. Heterocycl. Chem.* **1963**, *2*, 300–309. (b) Wu, Y. H.; Lobeck, W. G., Jr.; Ryan, R. P.; Gomoll, A. W. *J. Med. Chem.* **1972**, *15*, 529–534.

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% yields 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



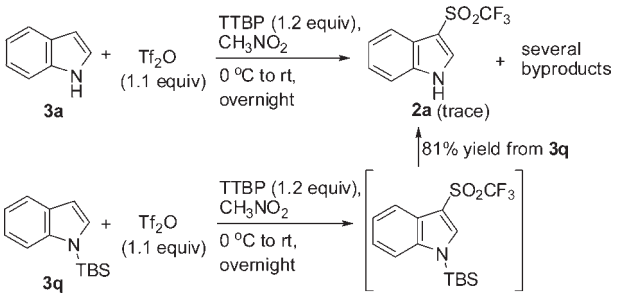
entry	**3**	R^1	R^2	**2**	yield (%)[a]
1	**3b**	H	Me	**2b**	88
2	**3c**	H	Et	**2c**	94
3	**3d**	H	Bn	**2d**	86
4	**3e**	H	Ph	**2e**	85
5	**3f**	H	4-$MeOC_6H_4$	**2f**	86
6	**3g**	2-Me	Me	**2g**	91
7	**3h**	2-Ph	Me	**2h**	88
8	**3i**	3-Me	Me	—	Complex
9	**3j**	4-Me	Me	**2j**	92
10	**3k**	5-Me	Bn	**2k**	91
11	**3l**	5-OMe	Bn	**2l**	84
12	**3m**	5-F	Me	**2m**	84
13	**3n**	5-Cl	Bn	**2n**	87
14	**3o**	5-Br	Bn	**2o**	83
15	**3p**	7-Me	Me	**2p**	96

[a] Isolated yield by silica-gel column chromatography.

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).

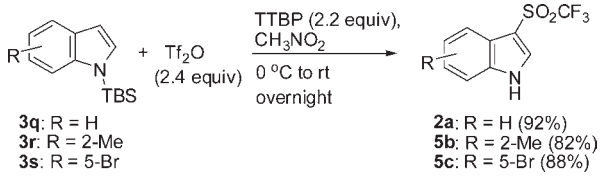
After several attempts, the yield of *N*-H indole triflone **2a** was further improved to 92%. For other *N*-TBS indole

Scheme 1. Preparation of *N*-H Indole Triflone



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 $KOBu^t$ 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 SO_2CF_3 group[18] realized a successive deprotonation-addition–elimination pathway to dimerize the indoles at low temperature (Scheme 3).

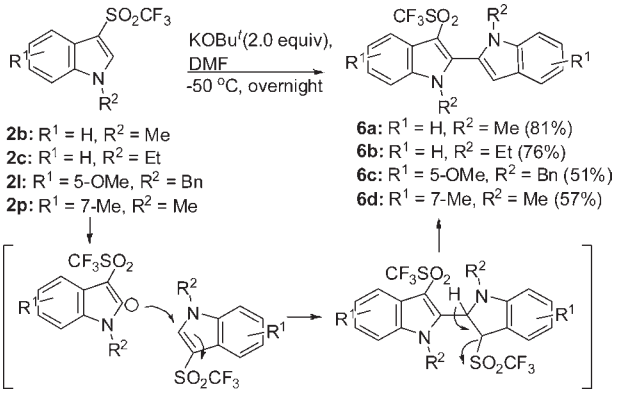
Interestingly, treatment of biindolyl triflone **6a** with $LiAlH_4$ gave a symmetric 2,2′-biindolyl **7**,[17b] which was previously synthesized via a metal-mediated coupling reaction (Scheme 4). These results indicate that this method provides not only the first synthesis of biindolyl triflones

(16) For excellent reviews see: (a) Pindur, U.; Kim, Y. S.; Mehrabani, F. *Curr. Med. Chem.* **1999**, *6*, 29–69. (b) Bergman, J.; Janosik, T.; Wahlstroem, N. *Adv. Heterocycl. Chem.* **2001**, *80*, 1–71. (c) d'Ischia, M.; Napolitano, A.; Pezzella, A.; Meredith, P.; Sarna, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 3914–3921.

(17) (a) Bergman, J.; Eklund, N. *Tetrahedron* **1980**, *36*, 1439–1443. (b) Pindur, U.; Kim, M.-H. *Tetrahedron* **1989**, *45*, 6427–6438. (c) Hudkins, R. L.; Diebold, J. L.; Marsh, F. D. *J. Org. Chem.* **1995**, *60*, 6218–6220. (d) Merlic, C. A.; McInnes, D, M. *Tetrahedron Lett.* **1997**, *38*, 7661–7664.

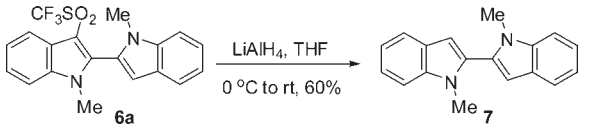
(18) (a) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195. (b) Goumont, R.; Faucher, N.; Moutiers, G.; Tordeux, M.; Wakselman, C. *Synthesis* **1997**, 691–695. (c) Goumont, R.; Kizilian, E.; Buncel, E.; Terrier, F. *Org. Biomol. Chem.* **2003**, *1*, 1741–1748.

Scheme 3. Base-mediated Synthesis of Biindolyl Triflones



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

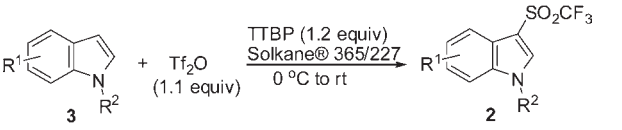
Scheme 4. Transformation of 2,2′-Biindolyl Triflone **6a** to Biindolyl **7**



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 yields were obtained (entries 1−5). The results were comparable to those when CH_3NO_2 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).

(19) (a) Kusuda, A.; Kawai, H.; Nakamura, S.; Shibata, N. *Green Chem.* **2009**, *11*, 1733–1735. (b) Xu, X.-H.; Kusuda, A.; Tokunaga, E.; Shibata, N. *Green Chem.* **2011**, *13*, 46–50. (c) Kusuda, A.; Xu, X.-H.; Wang, X.; Tokunaga, E.; Shibata, N. *Green Chem.* **2011**, *13*, 843–846.

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



entry	**3**	R^1	R^2	time (h)	**2**	yield (%)[a]
1	**3b**	H	Me	15	**2b**	89
2	**3d**	H	Bn	24	**2d**	78
3	**3g**	2-Me	Me	15	**2g**	88
4	**3l**	5-OMe	Bn	24	**2l**	82
5[b]	**3q**	H	TBS	24	**2a**	81
6[c]	**3b**	H	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 SO_2CF_3 substitution is a key for this dimerization process. The application of indole triflones and trifluoromethanesulfonylation of other heteroaromatics is currently in progress.

Acknowledgment. This study was financially supported in part by Grants-in-Aid for Scientific Research (21390030, 22106515, Project No. 2105: Organic Synthesis Based on Reaction Integration). We are grateful to Central Glass Co., Ltd. for the gift of triflic anhydride. We thank Dr. Max Braun and Mr. Yoshitaka Toyofuku, Solvay Fluor GmbH for the generous gift of Solkane 365/227. We also thank the Asahi Glass Foundation.

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.