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RAPID TRIFLUOROMETHYLATION OF INDOLE DERIVATIVES

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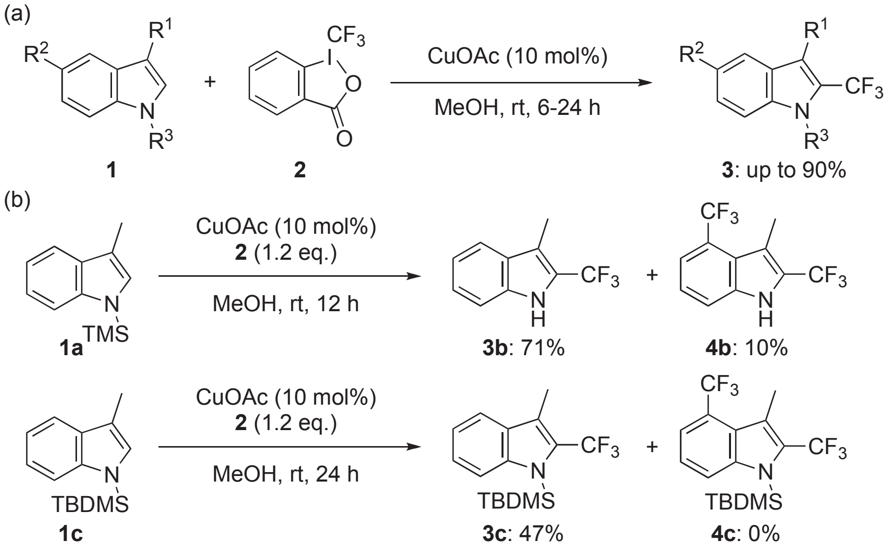
Dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday.

Abstract – Rapid trifluoromethylation of indole derivatives was achieved using trimethylsilyltriflate as the catalyst. Good to high yields were observed within only 5 min at room temperature. This reaction system is able to provide not only the mono-trifluoromethylated products, but also the di-trifluoromethylated derivatives, because of its high reaction efficiency.

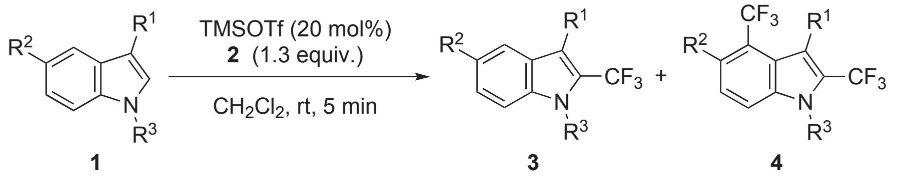
Indole frameworks have often been found in many natural products and bioactive compounds. Therefore, transformation of indole derivatives is of great interest in organic chemistry and many functionalizations of indoles have been investigated for a long time.[1] On the other hand, the trifluoromethyl group has increasingly attracted attention in the pharmaceutical and agrochemical fields. This is because the presence of the trifluoromethyl group often brings about unique properties to molecules, such as improved metabolic stability and hydrophobicity.[2] Accordingly, trifluoromethylated indole derivatives would be an intriguing target.[3,4] The direct indole trifluoromethylation reaction, in particular the catalytic version, has recently been developed.[5] In 2010, we reported the copper-catalyzed direct trifluoromethylation of indole derivatives using Togni reagent **2**[6] (Scheme 1a).[7] The *C2*-trifluoromethylated compounds were selectively obtained, and it was found that the *N*-protecting group affected the reactivity and selectivity for this reaction. In the course of this study, we encountered curious results (Scheme 1b). The desilylated di-trifluoromethylated product **4b** was obtained in 10% yield when *N*-TMS-3-methylindole **1a** was used as a substrate, while the reaction of *N*-TBDMS-3-methylindole **1c** provided only the 2-trifluoromethylated product **3c** in 47% yield with the di-trifluoromethylated product **4c** not being detected. In the latter case, the TBDMS group remained intact on the nitrogen of the indole ring. Based on these results, we hypothesized that the silyl cation would be a good activator for trifluoromethylation using Togni reagent **2**. In this communication, we disclose the rapid trifluoromethylation of indole derivatives using trimethylsilyltriflate (TMSOTf) under mild conditions.

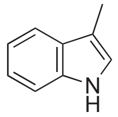
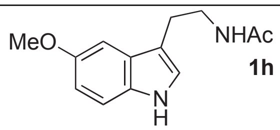
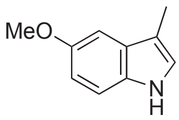
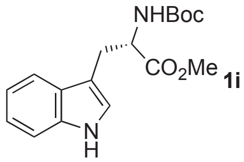
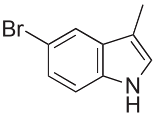
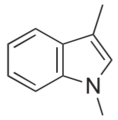
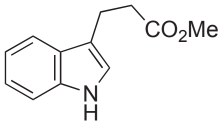
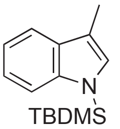
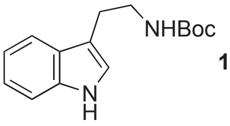
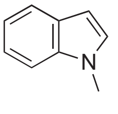


Scheme 1. Copper-catalyzed trifluoromethylation of indole derivatives

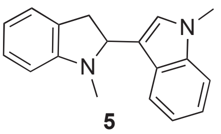
Based on our hypothesis, TMSOTf, which is a representative source of a silyl cation species was used as a catalyst in CH_2Cl_2 at room temperature. We initially examined the reaction with 3-methylindole **1b**. To our surprise, the rate of this reaction was remarkably fast. Compound **3b** was obtained in 71% yield within only 5 min, together with the di-trifluoromethylated product **4b** in 7% yield (Table 1, entry 1).[8] This remarkable result prompted us to examine the trifluoromethylation of other indole derivatives. The electron donating group at the 5-position accelerated the di-trifluoromethylation and the desired products **3d** and **4d** were obtained in 60% and 19% yields, respectively at 0 °C (entry 2). Various functional groups, such as aryl bromide, methyl ester, ether, carbamate and amide moieties, were tolerated in this reaction (entries 3-7).[9] Trifluoromethylated products of the tryptophan derivative **3i** and **4i** were afforded in 48% and 4% yields, respectively (entry 7). It is noteworthy that the enantiopurity of the derivatives was conserved under this reaction condition. We next examined 1-substituted indole derivatives. *N*-Methyl-3-methylindole **1j** was transformed to produce the desired products in high yield (entry 8). Analogous to the copper-catalyzed system, the *N*-TBDMS group was intact in this reaction system (entry 9). The reaction with **1k** bearing no substituent at the 3-position provided the 2-trifluoromethylated product **3k**, albeit in 26% yield (entry 10). In this case, dimer **5** was generated as the main product in 47% yield.[10] Unfortunately, we could not isolate **4k** and a complex mixture of mono- and di-trifluoromethylated indoles, with yet to be identified structures was obtained.

Table 1. Trifluoromethylation of indole derivatives using TMSOTf[a]



entry	substrate	product [%][b]	entry	substrate	product [%][b]
1	 **1b**	**3b**; 71%, **4b**; 7%	6	 **1h**	**3h**; 63%, **4h**; 10%
2[c]	 **1d**	**3d**; 60%, **4d**; 19%	7	 **1i**	**3i**; 48%, **4i**; 4%
3	 **1e**	**3e**; 67%, **4e**; 9%	8	 **1j**	**3j**; 75%, **4j**; 9%
4	 **1f**	**3f**; 59%, **4f**; 5%	9	 **1c**	**3c**; 55%, **4c**; 0%
5	 **1g**	**3g**; 68%, **4g**; 8%	10	 **1k**	**3k**; 26%, **4k**; ND[d]

[a] The reactions were carried out with TMSOTf (20 mol%) and Togni reagent **2** (1.3 equiv.) in CH_2Cl_2 on a 0.5 mmol scale. [b] Isolated yield. [c] The reaction was carried out at 0 °C for 15 min on a 0.2 mmol scale. [d] Not determined.



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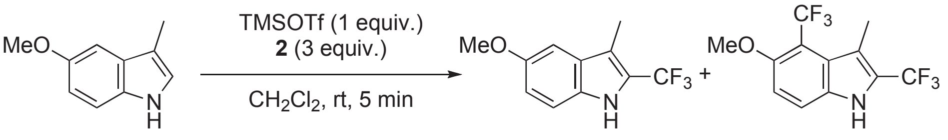
Inspired by these results, we investigated the reaction using an excess amount of Togni reagent **2** to obtain a higher amount of the di-trifluoromethylated product (Scheme 2). The di-trifluoromethylated compound **4d** was produced under the described conditions in 42% yield, together with **3d** in 35% yield.



Scheme 2. Trifluoromethylation using an excess amount of Togni reagent **2**

In summary, we achieved the rapid trifluoromethylation of indole derivatives using TMSOTf as a catalyst. This reaction was operated under very mild conditions and the desired trifluoromethylated products were obtained in high yield within 5 minutes. In addition, a reasonable amount of the di-trifluoromethylated product could be obtained when an excess amount of Togni reagent was used. This reaction system provides a quick method for the synthesis of trifluoromethylated indole derivatives.

ACKNOWLEDGEMENTS

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8. Typical experimental procedure for trifluoromethylation of indole derivatives; 3-Methylindole **1b** (65.6 mg, 0.5 mmol) and Togni reagent **2** (205.4 mg, 1.3 equiv.) were added to a Schlenk tube, which was flame-dried under vacuum. The tube was evacuated and back-filled with nitrogen. Dichloromethane (5 mL) and TMSOTf (18 μL, 20 mol%) were added to the tube and the reaction mixture was stirred for 5 min. After quenching the reaction mixture with saturated aqueous $NaHCO_3$ solution (5 mL), the organic layer was dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2; hexane/EtOAc 9:1) to give **3b** (70.2 mg, 71%, $R_f = 0.5$; hexane/EtOAc = 4/1) and **4b** (9.8 mg, 7%, $R_f = 0.35$; hexane/EtOAc = 4/1).
9. The reaction of substrates bearing an electron withdrawing group on the five-membered ring proceeded in low efficiency, which was consistent with the reaction using CuOAc.
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