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Synthesis and spin trapping properties of 1,1-dimethyl-3-(trifluoromethyl)-1*H*-isoindole N-oxide

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ABSTRACT

We have achieved an efficient synthesis of 1,1-dimethyl-3-(trifluoromethyl)-1*H*-isoindole N-oxide (**2**) in 39% yield by seven steps from 2-bromobenzoic acid (**3**). This compound serves as a spin trap reagent, giving a strong and stable ESR signal of the radical adduct of **2** in the presence of *i*-amyloxy radical generated by UV photolysis of *i*-amyl nitrite.

Free radicals such as reactive oxygen species may be involved in a variety of biological processes which are associated with certain diseases, such as cancer, heart attack, and Alzheimer's disease and aging.[1] The investigation of free radicals in biological systems serves to elucidate diseases mechanisms. In decades, the effect of free radicals on biological systems has been revealed by ESR or ESR-CT technique using 5,5-dimethyl-1-pyrroline N-oxide (DMPO) as a spin trap reagent.[2] Several issues, however, complicate the use of DMPO derivatives: these include the formation of spurious ESR signals due to non-radical reactions such as hydrolysis, decomposition, self-condensation, and so on.[3] The development of better spin traps remains an attractive research area to expand the reliable investigation of free radicals as well as the detection of a slight amount of radical species.

In previous report, we described a new synthetic route of 1,1,3-trimethyl-1*H*-isoindole N-oxide (TMINO, **1**), giving **1** in nine steps and 28% yield from 2-chlorobenzoic acid (Fig. 1).[4,5] We now report the first synthesis of TMINO derivative bearing trifluoromethyl group, 1,1-dimethyl-3-(trifluoromethyl)-1*H*-isoindole N-oxide (3-TF-TMINO, **2**) and the evaluation of its spin trapping ability in the presence of *i*-amyloxy radical.

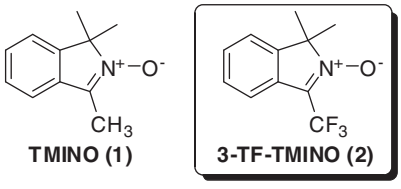
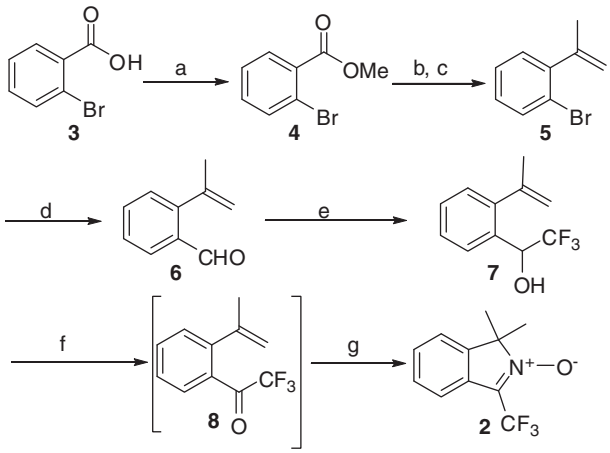


Figure 1.

The synthesis was summarized in Scheme 1. Esterification of 2-bromobenzoic acid (**3**) with MeOH in the presence of a catalytic amount of sulfuric acid gave ester **4** in 99% yield. The methylation of **4** with methylmagnesium iodide and subsequent dehydration under acidic conditions afforded a 82% yield of olefin **5**. After olefin **5** was converted into Grignard reagent, the treatment with DMF led to the corresponding aldehyde **6** in 74% yield after distillation. Pure alcohol **7** was obtained in 93% yield using trimethyl(trifluoromethyl)silane in the presence of a catalytic amount of tetrabutylammonium fluoride, followed by acid-catalyzed TMS deprotection.[6] Unfortunately, the next oxidation step gave complex mixture in the case of Jones reagent, PCC reagent, and sulfur trioxide pyridine complex reagent. Finally, Dess–Martin oxidation led to ketone **8**, which decomposed to complex mixture for one month.[7] Avoiding the decomposition of **8**, crude ketone **8** was immediately treated with four equivalents of hydroxylamine



Scheme 1. Reagents and conditions: (a) cat. H_2SO_4, MeOH, reflux, 99%; (b) MeMgI, Et_2O, rt; (c) 20% H_2SO_4–AcOH, 82% in two steps; (d) Mg THF, reflux, then, DMF, rt, 74%; (e) cat. TBAF, $TMSCF_3$ THF, rt, then, 3 N HCl, 93%; (f) Dess–Martin oxidation, CH_2Cl_2; (g) NH_2OH, AcONa, EtOH, 80 °C, 70% in two steps.

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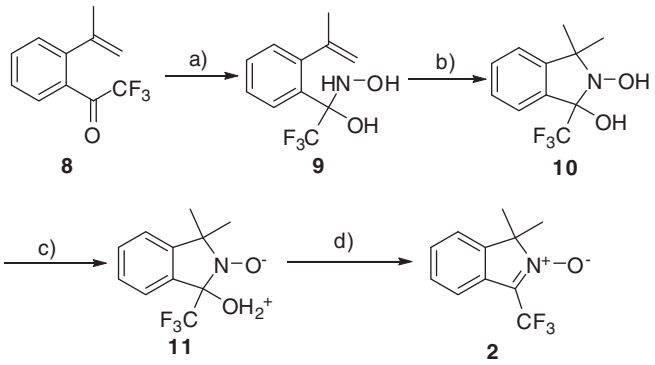
under basic conditions. Surprisingly, final 3-TF-TMINO (**2**) was isolated in 70% yield instead of the expected oxime.[8–10]

This transformation in the final step is thought to proceed through the pathway shown in Scheme 2. (a) *N,O*-Acetal **9** was formed by the reaction of **8** with hydroxylamine.[11] (b) *N,O*-Acetal **9** was transformed to isoindole **10** by reverse-Cope cyclization.[5,12] (c) The proton at the hydroxylamine was transferred to give the intermediate **11**. (d) The subsequent dehydration of **11** gave 3-TF-TMINO (**2**).



Scheme 2. Plausible reaction pathway for N-oxide **2** from ketone **8**.

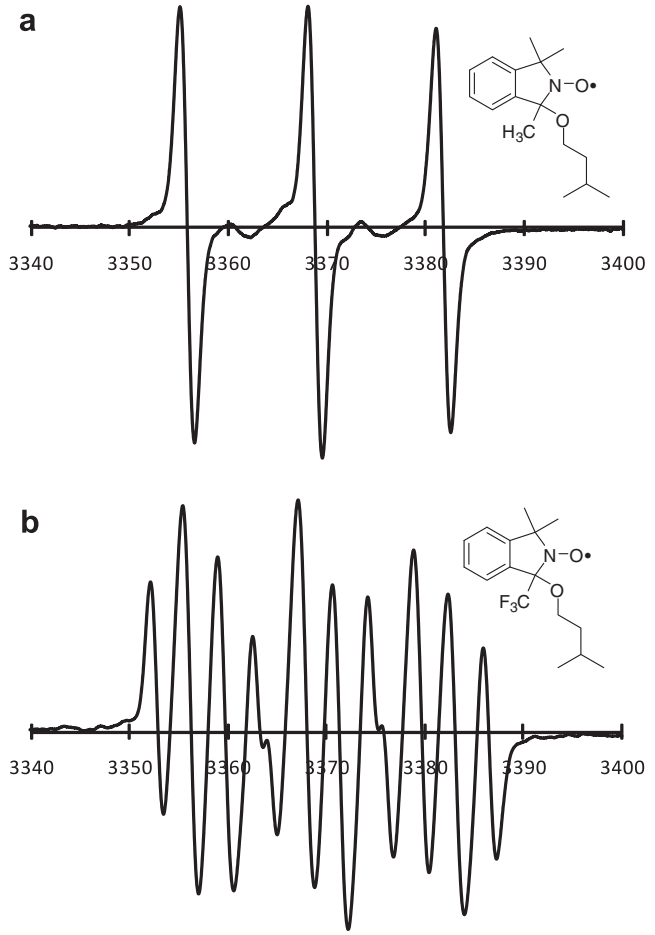


Figure 2. ESR spectra of spin adducts of **1** (a) and **2** (b) in the presence of *i*-amyloxy radical. Spectra obtained by UV photolysis of a solution of *i*-amyl nitrite (40 mM) in the presence of N-oxide (2.0 mM) in benzene. Spectrometer settings: microwave power = 4.00 mW at about 9.2 GHz, magnetic field modulation width = 1.0 G at 100 kHz, time constant = 0.30 s, sweep time = 40.0 s, center field = 3370.0 G, and sweep width = ±25.0 G, temperature = 25 °C.

Table 1
Relative ESR signal intensity of radical adduct[a]

Radical adduct	Time (min)						
	0	20	40	60	80	100	140
TMINO	1	0.85	0.67	0.47	0.28	0.12	0.02
3TF-TMINO	1	1	1	1	0.99	0.99	0.99

[a] The measurement conditions are the same as those in Figure 2. The relative intensity was the ratio of intensity for each minute to starting intensity of the *i*-amyloxy adducts of **1** or **2**.

We next demonstrated the spin-trapping experiment using **1** and **2**. When the solution of **1** with *i*-amyl nitrite was irradiated with UV light for 35 s at room temperature, a strong ESR signal exhibiting nitrogen hyperfine interactions a(N) of 13.2 G was observed along with a small unknown signal (Fig. 2a).[13] In contrast to the result of **1**, similar treatment of **2** gave only a single spectrum, consisting of three groups of 1:3:3:1 quarters (Fig. 2b). The ESR absorption profile was similar to those of radical adducts generated by the reaction of 2TF-DMPO with *n*-butyl nitrite, *i*-butyl nitrite, and *i*-amyl nitrite.[14] The hyperfine splitting constants (hfsc) obtained were a(N) = 11.7 and a(F) = 3.5 G. Furthermore, the *i*-amyloxy radical adduct of **2** had extremely long-half life compared to that of **1**; the relative ESR signal intensity of *i*-amyloxy radical adduct of **2** hardly decays within 140 min (Table 1). When stored at room temperature in the dark, the radical adduct of **2** had a half-life of three days.

In conclusion, we achieved the first synthesis of isoindole nitrone bearing trifluoromethyl group, 1,1-dimethyl-3-(trifluoromethyl)-1*H*-isoindole N-oxide (3-TF-TMINO, **2**), in an overall yield of 39% starting from readily available 2-bromobenzoic acid (**3**) in seven steps. Furthermore, **2** trapped *i*-amyloxy radical, giving only a stable radical adduct of **2**, efficiently. More detailed studies of the synthesis of functional spin trap reagents and their utilization are now in progress.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.161.

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6. Analytical and spectral data of alcohol **7**: IR (neat): ν_{max} = 3400, 2978, 1643, 1491, 1450, 1375, 1269, 1171, 1128, 1057, 914, 766 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, 1H, *J* = 7.8 Hz), 7.39–7.34 (m, 2H), 7.21–7.19 (m, 1H), 5.41 (q, 1H, *J* = 6.8 Hz), 5.30 (dq, 1H, *J* = 1.7, 1.5 Hz), 4.91–4.90 (m, 1H), 2.50 (br, 1H), 2.06 (dd, 3H, *J* = 1.5, 1.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 143.8, 130.8, 129.2, 128.2, 127.5, 127.2 (q, *J* = 2 Hz), 124.6 (q, *J* = 281 Hz), 116.6, 68.9 (q, *J* = 32 Hz), 25.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ −77.3 (d, *J* = 6.8 Hz); HRMS (ESI) calcd for $C_{11}H_{10}F_3O_1$: 215.06837 [M−H]$^-$; found: 215.06860.

7. Analytical and spectral data of ketone **8**: IR (neat): ν_{max} = 1726, 1191, 1148, 934, 768 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, 1H, *J* = 7.8 Hz), 7.57 (dd, 1H, *J* = 7.5, 7.4 Hz), 7.41 (dd, 1H, *J* = 7.8, 7.4 Hz), 7.38 (d, 1H, *J* = 7.5 Hz), 5.19 (dq, 1H, *J* = 1.5, 1.5 Hz), 4.82–4.81 (m, 1H), 2.11 (dd, 3H, *J* = 1.5, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.6 (q, *J* = 35 Hz), 145.4, 144.8, 132.9, 131.0, 129.0 (q, *J* = 2 Hz), 128.8, 127.3, 117.0, 116.0 (q, *J* = 291 Hz), 23.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −72.8; Anal. Calcd for $C_{11}H_9F_3O$: C, 61.68; H, 4.24. Found: C, 61.68; H, 4.18.
8. Analytical and spectral data of 3-TF-TMINO (**2**): mp 71.6–73.1 °C; IR (neat): ν_{max} = 3398, 1535, 1479, 1200, 1149, 974, 763, 663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.58–7.55 (m, 1H), 7.44–7.40 (m, 2H), 7.31–7.28 (m, 1H), 1.60 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 130.9 (q, *J* = 35 Hz), 129.0, 128.8, 128.3, 120.9, 120.1 (q, *J* = 2 Hz), 120.0 (q, *J* = 271 Hz), 80.3, 24.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −65.7; HRMS (ESI) calcd for $C_{11}H_{11}F_3N_1O_1$: 230.07927 $[M+H]^+$; found: 230.08007.
9. Neither remarkable by-product nor decomposed product of **8** was observed in this reaction.
10. The purified **2** was successfully stored under nitrogen at room temperature, with little or no decomposition, for a period of at least six months.
11. In the reaction of α,α,α-trifluoroacetophenone with hydroxylamine, the corresponding *N,O*-acetal intermediate was observed, see: Ritchie, C. D. *J. Am. Chem. Soc.* **1984**, *106*, 7187.
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13. Generally, *i*-amyl nitrite disproportionates by UV photolysis to *i*-amyloxy radical and nitric oxide radical (·NO). The two kinds of radical adducts of **1** were observed in the presence of nitric oxide radical (·NO), see: Ref. 4b.
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