SYNTHETIC STUDIES ON TRIFLUOROACETYLINDOLES

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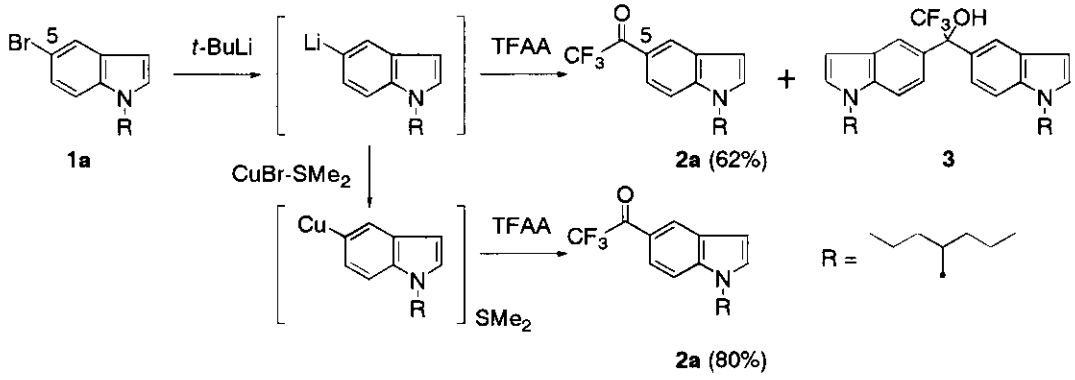
Abstract — Trifluoroacetylindoles were obtained regioselectively through the reaction of indolylorganometallic species, prepared by halogen-metal exchange or direct metalation of *N*-substituted or -nonsubstituted indoles, with TFAA in good yield.

Introduction of fluorine atoms in the biologically active molecules occasionally enhances activity and stability. A fluorine atom has roughly the same steric size as a hydrogen but very different electronic character.[1] In conjunction with our research for potent 5α-reductase inhibitors,[2] we focused on the synthesis of variety of trifluoroacetylindoles instead of acylindoles as the important intermediate to biologically active molecules.

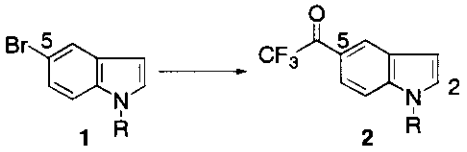
The primary method for preparation of these substrates involves introduction of trifluoroacetyl moiety into the position 5 of indole *via* halogen-metal exchange[3-8] because neither direct fluorination of 5-acetylindole using fluorinating reagent[9] nor Friedel-Crafts type acylation of indoline[10,11] afforded the desired 5-trifluoroacetylindole equivalent. In utilizing the halogen-metal exchange on the indole skeleton, it was critical to prevent reaction at the most reactive position 2,[7,12] since *N*-methylindole and several *N*-protected indoles were effectively converted to 2-lithio derivatives.[13,14] Scheme 1 shows the introduction of trifluoroacetyl group into the position 5 of indole derivative (**1a**) possessing 4-heptyl substituent at the nitrogen atom. Lithiation of compound (**1a**) with 2 equivalent of *t*-BuLi, followed by treatment with TFAA afforded the desired product (**2a**) in 62% yield. Although 2-trifluoroacetylindole was not detected in this reaction conditions, tertiary alcohol (**3**) was obtained as a byproduct possibly through the reaction of 5-lithioindole with compound (**2a**). To minimize the side reaction, we investigated reducing the nucleophilicity of 5-lithioindole by transmetalation. Recently, arylcopper reagents were reported to be useful in preparing aryl trifluoromethyl ketones.[15] Indol-5-ylcopper reagent, prepared *in situ* from lithio precursor and $CuBr{\cdot}SMe_2$, allowed reaction with TFAA to afford 5-trifluoroacetylindole (**2a**) in

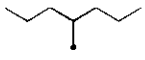
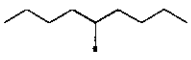
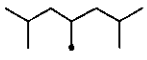
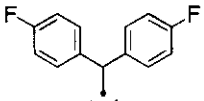
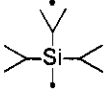
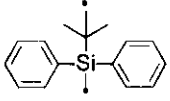
excellent yield. A product, formed by reaction at position 2 of indole was not detected under this reaction condition. This procedure was extended to other *N*-substituted indoles, and the results were summarized in Table 1.



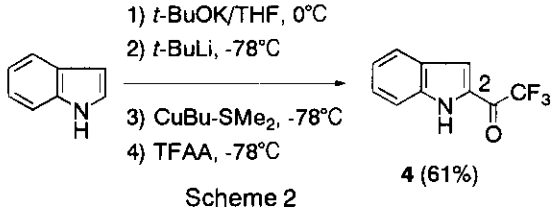
Scheme 1

Table 1. Synthesis of 5-Trifluoroacetylindoles

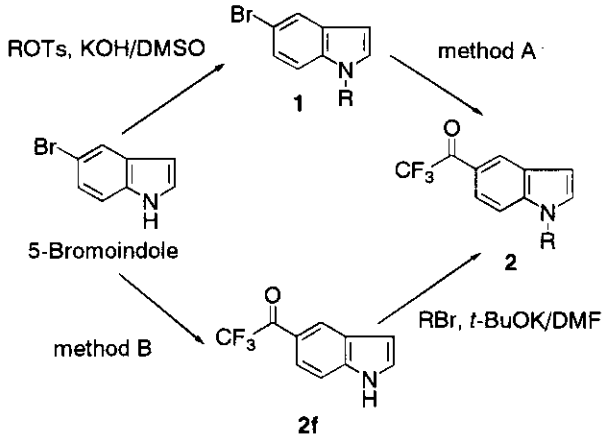


entry	R	method [a]	2 (yield, %)
1		A	**2a** (80)
2		A	**2b** (82)
3		A	**2c** (65)
4		A	**2d** (10)
5		A	**2e** (62)
6		A	– [b]
7	H	B	**2f** (58)

[a] A; *t*-BuLi (2 eq), $CuBr{\cdot}SMe_2$ (2 eq), TFAA (1.05 eq).
B; KH (1 eq), *t*-BuLi (2 eq),[7] TFAA (1.05 eq).
[b] The desired product was not obtained.



Scheme 2



Scheme 3

Branched alkyl substituent at the nitrogen of indole resulted to give 5-trifluoroacetylindoles in good yield

(entries 1 – 3), whereas 4,4'-difluorobenzhydryl gave the complex mixture containing the desired product (**2d**) in poor yield (entry 4). We also extended this procedure for compounds protected by silyl groups at the nitrogen of indole.[13] Triisopropylsilyl (TIPS) was an excellent protecting group in this reaction (entry 5), whereas *tert*-butyldiphenylsilyl (TBDPS) was not suitable (entry 6). 2-Trifluoroacetylindole was detected from the complex mixture in case of TBDPS. These results indicate that reaction at C-2 of indole was prevented by the bulky substituents at the nitrogen. Benzhydryl and TBDPS groups were insufficient to block the reaction at this position, possibly due to the planar structure of benzene ring or unfavorable interaction between the benzene ring and the indol-2-yl copper species. TIPS was removed with tetrabutylammonium fluoride to give 5-trifluoroacetylindole (**2f**) in moderate yield.

On the other hand, an anion on the nitrogen effectively blocks lithiation at C-2 of indole as previously reported.[12,16] Reaction of 5-bromoindole with potassium hydride in THF at 0°C gave the homogeneous solution of potassium salt, which upon treatment with *t*-BuLi, and then TFAA at -78°C, afforded 5-trifluoroacetylindole (**2f**) in 58 % yield (entry 7). In this case, tertiary alcohol and C-2 substituted compounds were not detected. Deprotonation of the indole NH before halogen-metal exchange with potassium hydride proceeded efficiently to give the desired product, whereas *t*-BuOK failed to block the lithiation at C-2 of indole and the resultant mixture gave the mixture of 2- and 5-trifluoroacetylindoles in low yield. This result indicated that the production of *t*-BuOH by the NH deprotonation with *t*-BuOK might quench the deprotonated and lithiated indole. But the latter condition could be effectively utilized to prepare 2-trifluoroacetylindole (**4**) from nonprotected indole. (see Scheme 2)

5-Trifluoroacetylindoles (**2**) were obtained by two different routes as shown in Scheme 3. Branched alkyls, good protecting group to prevent the reaction at C-2 of indole, were initially substituted at the nitrogen of 5-bromoindole, and then the trifluoroacetyl moiety was introduced to give **2a-c**. Alternatively, 5-bromoindole was directly converted to 5-trifluoroacetylindole (**2f**), which was alkylated to afford **2d** by the standard method using *t*-BuOK and 4,4'-difluorobenzhydryl bromide.

In summary, 5-trifluoroacetylindoles were prepared by the improved halogen-metal exchange strategy from 5-bromoindole. Indolylcopper reagents from *N*-protected indole and indolyllithium reagents with anion on the indole nitrogen were useful intermediates for trifluoroacetylindoles.

EXPERIMENTAL

Melting points were determined with a Büchi-510 melting point apparatus and are uncorrected. IR spectra were recorded on a Jasco IR-810 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM GX-270 or EX-270 (270 MHz) spectrometer with Me_4Si as internal standard. Elemental analyses were performed by the analytical department of our laboratories.

Method A. 2,2,2-Trifluoro-1-[1-(propyl)butylindol-5-yl]-1-ethanone (2a) To a solution of 5-bromo-1-(1-propyl)butylindole (**1a**) (2.0 g, 6.80 mmol) in 20 mL of THF, *t*-BuLi (1.7 M solution in pentane; 8.0 mL, 13.6 mmol) was added at -78°C and the resulting mixture was stirred at the same temperature for 10 min. After $CuBr{\cdot}SMe_2$ (2.79 g, 13.6 mmol) was added at one portion, the reaction mixture was stirred for 1 h between -70 and -40°C. TFAA (0.96 mL, 6.80 mmol) was added at -78°C, and the resulting reaction mixture was stirred for 30 min. After saturated aqueous NH_4Cl solution was added, the reaction mixture was filtered through celite. The filtrate was extracted with ether. The extract was washed with brine, dried with $MgSO_4$ and evaporated *in vacuo*. The yellow oil was chromatographed on silica gel eluting with hexane-AcOEt (7:1) to afford **2a** (1.70 g, 80%) as a pale yellow oil: ^{1}H NMR($CDCl_3$) δ 0.76-0.99 (m, 6H), 1.00-1.36 (m, 4H), 1.65-2.00 (m, 4H), 4.30-4.40 (m, 1H), 6.72 (d, 1H, J = 3.3 Hz), 7.25 (d, 1H, J = 3.3 Hz), 7.43 (d, 1H, J = 8.9 Hz), 7.94 (dd, 1H, J = 0.9 Hz and 8.9 Hz), 8.42 (d, 1H, J = 0.9 Hz); MS(EI) : m/z = 311 (M^+).

2,2,2-Trifluoro-1,1-bis[1-(1-propyl)butylindole-5-yl]-1-ethanol (3) To a solution of 5-bromo-1-(1-propyl)butylindole (**1a**) (0.2 g, 0.68 mmol) in 4.0 mL of THF, *t*-BuLi (1.7 M solution in pentane; 0.8 mL, 1.36 mmol) was added at -78°C and the resulting mixture was stirred at the same temperature for 10 min. TFAA (0.1 mL, 0.75 mmol) was added at -78°C and the resulting reaction mixture was stirred for 30 min. After saturated aqueous NH_4Cl solution was added, the reaction mixture was filtered through celite. The filtrate was extracted with ether. The extract was washed with brine, dried with $MgSO_4$ and evaporated *in vacuo*. The yellow oil was chromatographed on silica gel eluting with hexane-AcOEt (5:1) to afford **2a** (0.13 g, 62%) as a pale yellow oil and the byproduct (**3**) (0.03g, 8.4%) as an yellow oil: ^{1}H NMR($CDCl_3$) δ 0.81-0.90 (m, 12H), 1.07-1.28 (m, 8H), 1.58 (br, 1H), 1.78-1.91 (m, 8H), 4.25-4.40 (m, 2H), 6.54 (d, 2H, J = 3.3 Hz), 7.16 (d, 2H, J =3.3 Hz), 7.32 (br, 4H), 7.85 (br, 1H); MS(EI) : m/z = 527 (M^+), 508 (M^+–OH), 457 (M^+–CF_3).

2,2,2-Trifluoro-1-[1-tri(1-methyl)ethylsilylindol-5-yl]-1-ethanone (2e) By the same procedure described above, 5-bromo-1-tri(1-methyl)ethylsilylindole (**1e**) (1.0 g, 2.84 mmol) was converted into **2e** (0.65 g, 62%) as an yellow oil: ^{1}H NMR($CDCl_3$) δ 1.15 (d, 18H, J = 7.5 Hz), 1.68-1.76 (m, 3H), 6.79 (d, 1H, J = 3.3 Hz), 7.36 (d, 1H, J = 3.3 Hz), 7.58 (d, 1H, J = 8.9 Hz), 7.91 (d, 1H, J = 8.9 Hz), 8.42 (s, 1H).

Method B. 2,2,2-Trifluoro-1-(indol-5-yl)-1-ethanone (2f) To a suspension of potassium hydride (1.02 g, 25.5 mmol) in 50 mL of THF, a solution of 5-bromoindole (5.0 g, 25.5 mmol) in 25 mL of THF was added dropwise. The mixture was stirred at 0°C for 15 min and then *t*-BuLi (1.7 M solution in pentane; 30 mL, 51.0 mmol) was added through canula. After being stirred at -78°C for 10 min, TFAA (7.2 mL, 51.0 mmol) was added dropwise and resulting mixture was stirred for 30 min at the same temperature. After saturated aqueous NH_4Cl solution was added, the reaction mixture was extracted with ether. The

organic layer was washed with brine, dried with $MgSO_4$ and evaporated *in vacuo*. The yellow oil was chromatographed on silica gel eluting with hexane-AcOEt (2:1) to afford crystalline product (**2f**) (3.18 g, 58%), which was recrystalized from hexane-AcOEt to give pure **2f** (3.10 g, 57%) as a pale brown powder: mp 86-89°C (hexane-AcOEt); ^{1}H NMR($CDCl_3$) δ 6.74 (br, 1H), 7.34 (br, 1H), 7.49 (d, 1H, J = 8.6 Hz), 7.96 (d, 1H, J = 8.6 Hz), 8.46 (s, 1H), 8.50 (br, 1H); Anal. Calcd for $C_{10}H_6NOF_3$: C, 56.35; H, 2.84; N, 6.57. Found: C, 56.28; H, 3.09; N, 6.31.

2,2,2-Trifluoro-1-[1-di(4-fluorophenyl)methylindol-5-yl]-1-ethanone (2d). To a stirred solution of 2,2,2-trifluoro-1-(indol-5-yl)-1-ethanone (**2f**) (3.0 g, 14.1 mmol) in 30 mL of DMF a portion of *t*-BuOK (1.90 g, 16.9 mmol) was added at 0°C and the resulting mixture was stirred at the same temperature for 10 min. 4,4'-Difluorobenzhydryl bromide (5.20 g, 18.3 mmol) in 16 mL of DMF was added to the reaction mixture and the mixture was stirred for 1 h. After saturated aqueous NH_4Cl solution was added, the reaction mixture was extracted with ether. The organic layer was washed with brine, dried with $MgSO_4$, and evaporated *in vacuo*. The brown oil was chromatographed on silica gel eluting hexane-AcOEt (7:1) to afford **2d** (1.35 g, 32%) as a brown oil: ^{1}H NMR($CDCl_3$) δ 6.68 (d, 1H, J = 3.5 Hz), 6.83 (s, 1H), 6.90-7.18 (m, 10H), 7.27 (d, 1H, J = 8.8 Hz), 8.44 (br, 1H).

2,2,2-Trifluoro-1-(indol-2-yl)-1-ethanone (4). To a solution of indole (1.0 g, 8.54 mmol) in 20 mL of THF, *t*-BuOK (1.05 g, 9.39 mmol) was added at 0°C and resulting mixture was stirred for 15 min. *t*-BuLi (1.7 M solution in pentane; 6.5 mL, 11.1 mmol) was added dropwise to the reaction mixture at -78°C. After being stirred at -78°C for 10 min, $CuBr{\cdot}SMe_2$ (2.3 g, 11.1 mmol) was added at one portion and resulting mixture was stirred for 40 min. TFAA (1.45 mL, 10.2 mmol) was added dropwise at -78°C and resulting mixture was stirred for 1.5 h. After saturated aqueous NH_4Cl solution was added, the reaction mixture was filtered through celite. The filtrate was extracted with EtOAc. The extract was washed with brine, dried with $MgSO_4$ and evaporated *in vacuo*. The pale brown crystalline product was recrystallized from hexane-AcOEt to give pure product (**4**) (1.11 g, 61%) as a pale brown powder: mp 204-207°C(hexane-AcOEt); ^{1}H NMR($CDCl_3$) δ 7.26-7.32 (m, 2H), 7.45-7.48 (m, 1H), 8.02 (s, 1H), 8.33-8.36 (m, 1H), 11.30 (br, 1H); Anal. Calcd for $C_{10}H_6NOF_3{\cdot}0.25H_2O$: C, 55.18; H, 3.22; N, 6.44. Found: C, 55.16; H, 3.03; N, 6.18.

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REFERENCES

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1. R. D. Chambers, 'Fluorine in Organic Chemistry, 'John Wiley, New York, 1973.
2. H. Takami, H. Koshimura, N. Kishibayashi, A. Ishii, H. Nonaka, S. Aoyama, H. Kase, and T. Kumazawa, *J. Med. Chem.*, 1996, **39**, 5047.
3. W. S. DiMenna, *Tetrahedron Lett.*, 1980, **21**, 2129.
4. X. Creary, *J. Org. Chem.*, 1987, **52**, 5026.
5. S. Sibille, V. Ratovelomanana, and J. Périchon, *J. Chem. Soc., Chem. Commun.*, 1992, 283.
6. Y. Hatanaka, H. Nakayama, and Y. Kanaoka, *Heterocycles*, 1993, **35**, 997.
7. M. Amat, S. Hadida, S. Sathyanarayana, and J. Bosch, *J. Org. Chem.*, 1994, **59**, 10.
8. J. W. Guiles, *Synlett*, 1995, 165.
9. T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada, and K. Tomita, *J. Am. Chem. Soc.*, 1990, **112**, 8563.
10. H. A. Staab, G. Walther, and W. Rohr, *Chem. Ber.*, 1962, **95**, 2070.
11. T. Keumi, M. Shimada, M. Takahashi, and H. Kitajima, *Chem. Lett.*, 1990, 783.
12. M. P. Moyer, J. F. Shiurba, and H. Rapoport, *J. Org. Chem.*, 1986, **51**, 5106.
13. R. J. Sundberg and H. F. Russell, *J. Org. Chem.*, 1973, **38**, 3324.
14. I. Hasan, E. R. Marinelli, L-C. C. Lin, F. W. Fowler, and A. B. Levy, *J. Org. Chem.*, 1981, **46**, 157.
15. F. A. J. Kerdesky and A. Basha, *Tetrahedron Lett.*, 1991, **32**, 2003.
16. Y. Yang, A. R. Martin, D. L. Nelson, and J. Regan, *Heterocycles*, 1992, **34**, 1169.

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