

EXPEDIENT PREPARATIONS OF 2-TRIFLUOROMETHYLINDOLE AND ITS *N*-METHYL DERIVATIVE

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Abstract - Procedures have been developed which provide direct regiocontrolled syntheses of 2-trifluoromethylindole and 1-methyl-2-trifluoromethylindole from readily available starting materials in moderate yields.

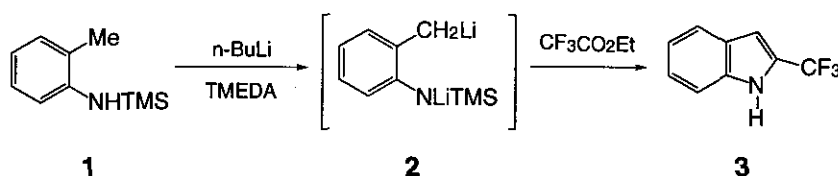
Heterocyclic compounds containing trifluoromethyl substituents have important applications in medicinal and agricultural chemistry.¹ Despite the variety of trifluoromethylated heterocycles that are available, references in the literature for 2-trifluoromethylindole or its derivatives are sparse, presumably due to the lack of reasonable approaches to these compounds.²⁻⁴ In this paper we describe practical methods for the preparation of the parent 2-trifluoromethylindole and its *N*-methylated derivative.

Three syntheses of 2-trifluoromethylindole have been reported. One of these methods utilizes 2-trifluoromethylquinoline as a starting material for a four-step synthesis, affording the desired indole in less than 30% isolated yield.² More direct syntheses involve the reaction of indole^{3a} or 2-trimethylsilylindole^{3b} with trifluoromethyl radical. Both of these radical additions afford a 2:1 mixture of the 2- and 3-trifluoromethylated indoles respectively, with 2-trifluoromethylindole isolated in *ca.* 30% yield. A recent paper has described the preparation of 2-trifluoromethylindoles through an acid-catalyzed cyclization of trifluoromethylacetamides containing ortho-methoxymethyl substitution.^{3c} This method is applicable to the preparation of a variety of 2-trifluoromethylindoles containing electron donating groups at the 5- and 6-positions and has been used to prepare the parent ring system as well.

During the course of our studies, we have found that application of the Smith procedure for the preparation of indoles⁵ provides an efficient entry to 2-trifluoromethylindole as outlined in Scheme 1. Thus, reaction of the dianion of *N*-trimethylsilyl-*o*-toluidine (1)

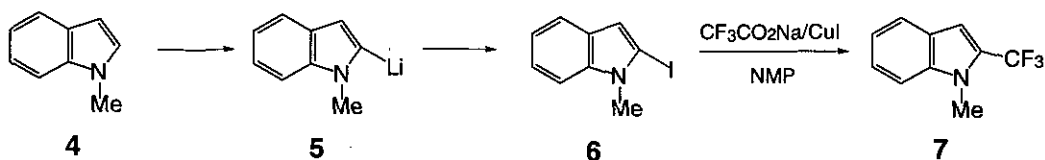
with ethyl trifluoroacetate affords 2-trifluoromethylindole (**3**) in 47% isolated yield. The reaction is highly dependent on both the nature of the solvent system and electrophile. Addition of TMEDA is necessary for the effective conversion of **1** to the dianion (**2**). In its absence, insoluble material precipitates resulting in low yields of **3**. These problems persisted when cyclohexane or ether is utilized as the reaction solvent without TMEDA. Additionally, other CF_3 -containing electrophiles have been examined in the reaction sequence. For example, none of **3** was obtained when trifluoroacetic anhydride was employed in the reaction sequence, while the use of other trifluoroacetic acid esters (TMS; 2,2,2-trifluoroethyl) offered no significant advantage.

Scheme 1



With these results in hand, we turned our attention to the preparation of the *N*-methylated-2-trifluoromethyl derivative. Several methods have been reported for the trifluoromethylation of aryl and heterocyclic halides. Among the reagents reported to effect this transformation are $\text{CF}_3\text{I}/\text{Cu}$ under pressure,⁶ Burton's reagent ($\text{CF}_2\text{Br}_2/\text{Cu}$),⁷ and sodium trifluoroacetate/ CuI .⁸ We have found that the latter method is readily applicable to the preparation of **7**. 1-Methyl-2-iodoindole (**6**), which was prepared by iodination of 1-methyl-2-lithioindole (**5**) in accordance to a literature procedure,⁹ smoothly undergoes trifluoromethylation upon heating at 160°C with 10 equivalents of sodium trifluoroacetate and a single equivalent of CuI in *N*-methylpyrrolidinone to afford the desired product (**7**)

Scheme 2



in 65% isolated yield. In view of the somewhat unstable nature of **6**, it may be advantageous to use the crude product in the reaction sequence since the major impurity, 1-methylindole (**4**), does not interfere with the trifluoromethylation and is easily separable from the product during chromatography. Additionally, impurities arising from aryl cross-coupling are not observed.⁹ While attempts to directly trifluoromethylate were unsuccessful, these procedures provide direct regiocontrolled syntheses of 2-trifluoromethylindole and 1-methyl-2-trifluoromethylindole from readily available starting materials.

EXPERIMENTAL SECTION

Melting points were taken in open capillary tubes and are uncorrected. ¹H and ¹⁹F nmr spectra were recorded on a Varian Unity 300 spectrometer at 300 MHz and 282 MHz respectively. ¹H Chemical shifts were measured in ppm relative to TMS using CDCl₃ as the deuterium lock. ¹⁹F Chemical shifts were measured relative to CFC₃ as the external standard. Infrared spectra were recorded on a Perkin-Elmer Model 1420 spectrophotometer. High resolution mass spectra were obtained on a Finnigan Model MAT 95S at 70eV. *N*-Trimethylsilyl-*o*-toluidine (**1**)⁵ and 1-methyl-2-iodoindole (**6**)⁹ were prepared in accordance to literature procedures. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) and *N*-methylpyrrolidone (NMP) were distilled from CaH₂ and stored over activated 4Å molecular sieves. Sodium trifluoroacetate was dried in a vacuum oven at 120°C for 18 h prior to use. Copper (I) iodide was purchased from Fluka and used without purification. *n*-Butyllithium titre was determined by titration with diphenylacetic acid.

2-Trifluoromethylindole (3): TMEDA (3.3 ml, 22 mmol) was added to a solution of *n*-butyllithium in hexanes (8.8 ml, 22 mmol) at room temperature under N₂ and the resulting solution was stirred at room temperature for 30 min. *N*-Trimethylsilyl-*o*-toluidine (1.79 g, 10 mmol) was added and the mixture was heated under reflux for 6 h. The clear brown solution was cooled to -78°C and ethyl trifluoroacetate (1.4 ml, 12 mmol) was added and the mixture was stirred at -78°C for 15 min and was then allowed to warm to room temperature. Water was added and the mixture was extracted with ether. The

organics were washed with 1N HCl, saturated NaHCO₃ and dried over MgSO₄. The residue was chromatographed on silica gel (4:1 hexanes:ethyl acetate) to afford 0.81g (47%) of **3** as a light yellow solid, mp 104-106°C (lit, mp 102°C²; 107-108°C^{3a,b}).

1-Methyl-2-Trifluoromethylindole (7): A mixture of 1-methyl-2-iodoindole (4.40 g, 17.3 mmol), sodium trifluoroacetate (24.00 g, 176.5 mmol) and copper (I) iodide (17.10 g, 89.8 mmol) in *N*-methylpyrrolidone (100 ml) was heated at 160°C for 6 h. The reaction was cooled to room temperature, diluted with 100 ml of water and filtered through Celite[®] to remove copper salts. The filtrate was extracted with ether (3x100 ml), and the combined extracts were washed with water and dried over MgSO₄. The organics were concentrated and the residue was chromatographed on silica gel (4:1 hexanes:ethyl acetate) to afford 1.19 g (37%) of **7** as a pale yellow oil which solidified on standing, mp 28-32°C. *Anal.* Calcd for C₁₀H₈NF₃: C, 60.30; H, 4.05; N, 7.03; F, 28.62. Found: C, 59.97; H, 3.90; N, 7.02; F, 28.92. *Ir* (Nujol) 2920, 2850, 1555, 1470, 1415, 1375, 1360, 1320, 1260, 1235, 1180, 1160, 1145, 1115, 1050, 805, 755, 735 cm⁻¹; ¹H nmr (DMSO d₆): δ 3.79 (s, 3H, N-CH₃), 7.02 (s, 1H, 3-H), 7.15 (1H, dd, J = 7, 7 Hz, 5-H), 7.34 (1H, dd, J = 7, 7 Hz, 6-H), 7.55 (1H, d, J = 8 Hz, 7-H), 7.65 (1H, d, J = 8 Hz, 4-H); ¹⁹F nmr: δ -57.1. *Ms:* Calcd for C₁₀H₈F₃N: 199.0606. Found: 199.0609.

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