Journal of Organometallic Chemistry, 423 (1992) 361–366
Elsevier Sequoia S.A., Lausanne
JOM 21835

Organostannyl mediated synthesis of 1-alkyl- and 1-sulfonyl-2-trifluoromethylbenzimidazole derivatives

N. Narayanan [1] and T.R. Balasubramanian *
Department of Chemistry, RKM Vivekananda College, Madras 600-004 (India)
(Received March 14, 1991)

Abstract

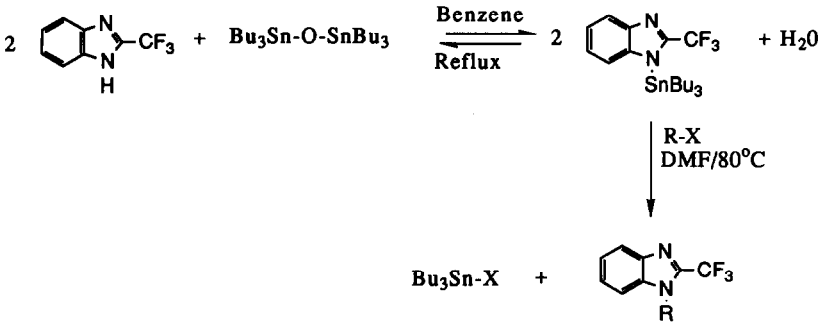
The synthesis and characteristics of a new series of 1-alkyl and 1-sulfonyl derivatives of 2-trifluoromethylbenzimidazole through an organostannyl intermediate is described.

Among the heterocyclic bases benzimidazole has received considerable attention because of its pivotal role in the metabolic processes. Owing to the structural similarity to purines, nucleosides of bezimidazole and some of its derivatives are important in many biological applications [1]. Numerous derivatives of benzimidazoles have been reported to have wide biological activity and find use as anthelmintics [2], herbicides and insecticides [3], biocides [4], fungicides [5], germicides, anticancer reagents and also as plant growth stimulators [6]. This has been realized especially with benzimidazoles substituted by such groups as trifluoromethyl, thiazolyl, phenyl and substituted phenyl and carbamates at the 2-position and alkyl, aryl sulfonyl and acyl derivatives at the 1-position. Some of these are known to exhibit high degrees of antiinflammatory, antimalarial and antineoplastic activity [6]. The increasing importance of commercial uses of these compounds in pharmaceutical industry is indicated by the large number of patents.

Notwithstanding their widespread applications and high medicinal value, the synthetic strategies for these compounds are confined only to a few general procedures. The search for a novel and an efficient methodology for the synthesis of benzimidazoles and related heterocyclic derivatives has resulted in the development of organometallic routes [7–9].

It was established in our laboratory that *N*-organostannyl heterocycles can be readily destannylated by electrophilic halogen leading to the formation of *N*-halo compounds [10] and by carbon electrophiles giving rise to *N*-alkyl products [11]. In the present work, we extend this synthetic strategy for the preparation of *N*-alkyl and sulfonyl derivatives of 2-trifluoromethylbenzimidazole.

[1] Present address: Dept. of Chemistry, Georgia State University, Atlanta, GA 30303, USA.



Scheme 1

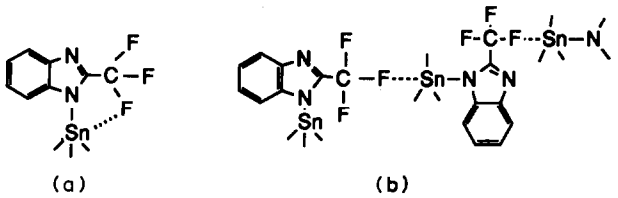
The general procedure involves the generation of *N*-stannylbenzimidazole followed by cleavage with an organic halide in a suitable solvent. Thus, in a typical experiment, treatment of 2-trifluoromethylbenzimidazole with bis(tri-n-butyltin oxide) [TBTO] in 2 : 1 ratio in refluxing benzene with azeotropic removal of water affords the *N*-(tri-n-butylstannyl)-2-trifluoromethylbenzimidazole in 100% yield, which in the subsequent step is treated with benzyl bromide in DMF heated to 80 °C to form the *N*-benzyl-2-trifluoromethylbenzimidazole in 92% yield (Scheme 1). The pure product is obtained by removing the tri-n-butyltin bromide by column chromatography. Neutral reaction conditions and the recyclability of the tin compound are the advantages of this method.

A detailed study on the variation in the solvent for the cleavage of the N–Sn bond by R–X has been carried out. It was found that the polarity of the solvent has a significant influence on the reaction, which is reflected in the yield of the final product. The yield increases with increasing polarity of the medium, for a constant reaction time of 24 h (Table 1). DMF is found to be the ideal solvent at 80 °C for this reaction as revealed by the maximum yield of the 1-benzyl derivative. However, this trend is, quite interestingly, just opposite to that observed for the cleavage of the 1-stannyl derivatives of the simple benzimidazole and benzotriazole [11]. This may be attributed to the trifluoromethyl group at the 2-position. Since the tin atom has a great affinity towards fluorine, it is likely that the trifluoromethyl group might take part in weak bonding with the tin atom both intramolecularly, forming a

Table 1

Effect of various solvents on the reaction of benzyl bromide with 1-(tri-n-butylstannyl)-2-trifluoromethyl benzimidazole

Solvent	Isolated yield (%)
Petroleum ether (40–60 °C)	10
n-Hexane	18
Benzene	23
Acetonitile	60
THF	65
Acetone	71
DMF	92



(a) (b)

Fig. 1. Intra- (a) and intermolecular (b) bond formation between tin atom and trifluoromethyl group in *N*-(tri-n-butylstannyl)-2-trifluoromethylbenzimidazole.

five-membered ring structure (Fig. 1a) and intermolecularly (Fig. 1b), by which the cleavage of N–Sn bond is made more difficult in less polar solvent.

The infrared spectrum of *N*-stannyl-2-trifluoromethylbenzimidazole shows two peaks at 673 and 832 cm^{-1} characteristic of the N–Sn bond. As these are far lower than those expected for a typical N–Sn bond, it suggests that the compound may also exist in polymeric form. The polymeric nature, with penta coordinate tin moiety of the stannyl derivatives of imidazole and benzimidazole has been well established [12].

Benzyl bromide has been found to react faster than benzyl chloride, and *p*-nitrobenzyl chloride faster than benzyl chloride with *N*-stannyl-2-trifluoromethyl-benzimidazole (Table 2); similarly, the reactivities of the methylhalo acetates are in the order iodo > bromo > chloro. From this it is clear that the N–Sn bond, though weakly polarized, is more covalent in nature.

The absence of stannylating agent did not yield any product under identical conditions and the use of a free radical initiator did not alter the course of the reaction. Based on these observations a mechanism involving the formation of a four-membered, concerted transition state may be envisaged.

The various 1-substituted products obtained from the reaction of 1-stannyl-2-tri-fluoromethylbenzimidazole with different halides are given in Table 2. All of the compounds made were previously unreported in the literature. They were hence all

Table 2

Reaction of 1-(tri-n-butyl stannyl)-2-trifluoromethyl benzimidazole with alkyl and sulfonyl halides (solvent: DMF at 80 °C)

R–X	Time (h)	Yield (%)	M.p.	B.p (°C/mmHg)
Ethyl iodide	4.5	91	–	168–170/1.0
Butyl bromide	4.0	89	–	174–177/1.8
Allyl bromide	2.5	90	–	185–188/1.2
Propargyl bromide	2.0	89	105–106	–
Benzyl bromide	1.5	92	72– 73	–
Benzyl chloride	2.5	87	72– 73	–
p-Nitrobenzyl chloride	1.5	89	58– 59	–
Phenacyl bromide	1.0	88	140–141	–
Benzenesulfonyl chloride	2.0	88	86– 87	–
p-Toluenesulfonyl chloride	1.5	90	143–144	–
Methyl chloroacetate	3.5	91	88– 89	–
Methyl bromoacetate	2.5	90	88– 89	–
Methyl iodoacetate	1.5	90	88– 89	–

characterized by spectroscopic data and satisfactory elemental analyses. Studies on the biological activities of these compounds are in progress.

Experimental

All of the reported melting points were recorded on a Toshnival melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 298 spectrometer, either in chloroform or as a KBr pellet. Ultraviolet spectra were recorded on a Hitachi 260A UV–Visible double beam spectrometer. Proton NMR spectra were run on a Varian EM 390 or 360 instrument in $CDCl_3$ with TMS as the internal standard. Mass spectra were obtained with Finnigan GC/MS and MAT-CH7 instruments.

2-Trifluoromethylbenzimidazole was prepared from *ortho*-phenylene diamine and trifluoroacetic acid according to the literature procedure [13]. M.p.: 210–211 °C (Rep.: 210–210.5 °C). IR: 3060–2650 (broad), 1585, 1465, 1325, 1190, 1125, 738 cm^{-1}.

Preparation of 1-(tri-n-butylstannyl)-2-trifluoromethylbenzimidazole

2-Trifluoromethylbenzimidazole (0.93 g, 5 mmol) in 25 ml of dry benzene was placed in a 50 ml round bottom flask, attached to a Dean–Stark water separator and a reflux condenser. Bis(tri-n-butyl tin)oxide (1.49 g, 2.5 mmol), dissolved in 5 ml of dry benzene, was then transferred to the flask and the contents of the flask heated to reflux. Water formed during the reaction was completely removed in 3 hours. The refluxing was continued for an additional half hour and the reaction mixture then cooled to room temperature. The solvent was removed by Rotovap. A colorless solid (2.37 g, 100%) was obtained.

IR: ν, cm^{-1} (KBr): 2954, 2860, 1519, 1454, 1366, 1290, 1225, 1172, 1137, 979, 873, 832, 743, 673, 567 and 479; ^1H NMR ($CDCl_3$, δ ppm): 0.8–1.6 (m, 27 H); 7.30–7.75 (m, 4H, ArH). Elemental anlaysis: Found C, 50.32; H, 6.39; N, 5.84. (Calc.: C, 50.56; H, 6.53; N, 5.90).

Typical reaction for the formation of 1-benzyl derivatives from 1-stannyl-2-trifluoromethylbenzimidazole

The stannyl compound prepared above was dissolved in 15 ml of DMF in a round bottom flask with magnetic stirring under a nitrogen atmosphere. A freshly distilled solution of benzyl bromide (0.86 g; 5 mmol), dissolved in 5 ml of DMF was added and the contents were heated to 80 °C. After the completion of the reaction as revealed by TLC, the reaction mixture was cooled to room temperature and poured on to cold water with stirring. The floating oily material was then extracted with diethyl ether followed by three times washing with water. Removal of solvent after drying over anhydrous sodium sulfate afforded a gummy product, which was purified by column chromatography (hexane : ethyl acetate 7 : 3). The desired 1-benzyl-2-trifluoromethylbenzimidazole was obtained as the second fraction as a white solid, melting at 72 °C. Yield: 1.27 g (92%).

IR (KBr) ν, cm^{-1}: 3050, 3020, 1610, 1585, 1420, 1350, 1280, 1265, 1170, 1120, 745 and 690. UV λ_{max}, nm (log ϵ) (EtOH): 288(sh), 278 (3.72), 256 (3.91); ($CHCl_3$): 287(sh), 278 (3.64), 257 (3.82). ^1H NMR: ($CDCl_3$, δ ppm) 5.20 (s, 2H, CH_2); 6.93–7.20 (m, 9H, ArH). Mass spectrum: *m/e* (%relative intensity): 276 (15), 199

(100), 130 (35), 129 (30), 104 (25), 103 (45), 91 (25), 77 (92), 69 (90). Elemental analysis: Found C, 65.21, H, 3.98, N, 10.14. $C_{15}H_{11}F_3N_2$ calc.: C, 65.15; H, 3.96; N, 10.08.

Characterization of other 1-substituted derivatives

1-Ethyl-2-trifluoromethylbenzimidazole: IR (KBr): 3020, 2980, 1585, 1510, 1475, 1450, 1420, 1345, 1330, 1175, 1120, 740 cm^{-1}. ^1H NMR: 1.50 (t, 3H, CH_3), 4.10–4.40 (q, 2H, CH_2), 7.20–7.60 (m, 4H, ArH). n_D^{25}: 1.4920; UV: λ_{max}, nm (log ϵ) (EtOH): 279 (3.75), 258 (3.85); ($CHCl_3$): 289 (3.53), 280 (3.50), 274 (3.49), 263 (3.53). Mass spectrum: 214 (31, M^+), 199 (100). Elemental analysis: Found C, 55.94; H, 4.14; N, 13.01; $C_{10}H_9F_3N_2$ calc.: C, 56.07; H, 4.21; N, 11.57.

1-n-Butyl-2-trifluoromethylbenzimidazole: IR (KBr): 2930, 2860, 1585, 1510, 1470, 1460, 1410, 1360, 1330, 1260, 1170, 1125, 745 cm^{-1}. ^1H NMR: 0.95–1.33 (t, 3H, CH_3); 2.0–2.7 (m, 4H, $-CH_2-CH_2$); 4.10 (t, 2H, CH_2): 7.10–7.50 (m, 4H, ArH). n_D^{25}: 1.4975. UV (EtOH): 286(sh), 278 (3.83), 255 (3.79); ($CHCl_3$) 287 (3.39), 279 (3.60), 258 (3.75). Mass spectrum: 242 (21, M^+), 199 (100). Elemental analysis: Found C, 59.02; H, 5.27; N, 11.42; $C_{12}H_{13}F_3N_2$ calc.: C, 59.50; H, 5.37; N, 11.57.

1-Allyl-2-trifluoromethylbenzimidazole: IR (KBr): 3060, 2940, 1520, 1465, 1420, 1330, 1270, 1250, 1190–1170(b), 1120, 1090, 980, 745 cm^{-1}. ^1H NMR: 4.65 (m, 2H, $N-CH_2$); 5.18 (m, 1H); 5.80 and 6.05 (m, 2H, vinylic H); 7.15–7.80 (m, 4H, ArH). n_D^{25}: 1.5085. UV (EtOH): 280 (3.84), 252 (3.88); ($CHCl_3$): 289 (3.49), 281 (3.41). Mass spectrum: 226 (27, M^+), 185 (100), 166 (85). Elemental analysis: Found C, 59.11; H, 4.05; N, 12.50; $C_{11}H_9F_3N_2$ calc.: C, 58.41; H, 3.98; N, 12.39.

1-Propargyl-2-trifluoromethylbenzimidazole: IR (KBr): 3300, 2940, 2120, 1580, 1510, 1460, 1345, 1170–1120(b), 980, 740 cm^{-1}. ^1H NMR: 2.30 (s, 1H, C≡C-H), 4.73 (s, 2H, $-CH_2-$); 7.15–7.60 (m, 4H, ArH). UV (EtOH): 286 (3.62), 278 (3.76), 252 (3.93); ($CHCl_3$): 288 (3.51), 280 (3.63), 2.56 (3.81). Mass spectrum: 224 (20, M^+), 185 (100), 166 (90), 147 (65), 39 (50). Elemental analysis: Found C, 58.59; H, 3.02; N, 12.38; $C_{11}H_7F_3N_2$ calc.: C, 58.92; H, 3.13; N, 12.44.

1-Phenacyl-2-trifluoromethylbenzimidazole: IR (KBr): 3050, 2970, 1685, 1590, 1460, 1230, 1135, 980, 740 cm^{-1}. ^1H NMR: 5.80 (s, 2H, $-CH_2-N-$), 6.76–7.70 (m, 9H, ArH). UV (EtOH): 286(sh), 278 (3.72), 250 (4.13); ($CHCl_3$): 287(sh), 279 (3.87) 260 (4.04). Mass spectrum: 304 (15, M^+), 285 (90), 199 (100), 105 (67). Elemental analysis: Found C, 63.10; H, 3.59; N, 9.16; $C_{16}H_{11}F_3N_2O$; calc.: C, 63.16; H, 3.62; N, 9.21.

1-Benzenesulfonyl-2-trifluoromethylbenzimidazole: IR (KBr): 3070, 1905, 1585, 1445, 1170, 840, 760 cm^{-1}. ^1H NMR: 7.13–7.53 (m, 9H, ArH); UV(EtOH): 275 (3.84), 268 (3.8), 249 (3.87); ($CHCl_3$): 276 (3.68), 269 (3.69), 258 (3.71); Mass spectrum: 326 (25, M^+), 185 (100), 77 (79). Elemental analysis: Found C, 50.98; H, 2.80; N, 8.53; $C_{14}H_9F_3N_2O_2S$ calc.: C, 51.53; H, 2.76; N, 8.59.

1-(4-Toluenesulfonyl)-2-trifluoromethylbenzimidazole: IR (KBr): 1585, 1440, 1335, 1175, 1010, 840, 745 cm^{-1}. ^1H NMR: 2.62 (s, 3H, CH_3), 6.93–7.66 (m, 8H, ArH). UV (EtOH): 283 (3.54), 275 (3.64), 245 (3.83); ($CHCl_3$): 284 (3.61), 276 (3.70), 253 (3.82). Mass spectrum: 340 (19, M^+), 185 (100), 91 (68). Elemental analysis: Found C, 52.78; H, 3.19; N, 8.24; $C_{15}H_{11}F_3N_2O_2S$ calc.: C, 52.94; H, 3.24; N, 8.17.

1-(4-Nitrobenzyl)-2-trifluoromethylbenzimidazole: IR (KBr): 3050, 1590, 1460, 1170, 980, 730 cm^{-1}. ^1H NMR: 4.47 (s, 2H, $-CH_2-$), 7.06–7.90 (m, ArH). UV (EtOH): 285 (3.81), 260 (4.25); ($CHCl_3$): 290 (3.78), 264 (3.74). Mass spectrum: 321

(19, M^+), 199 (100), 136 (58). Elemental analysis: Found C, 56.10; H, 3.12; N, 13.13; $C_{15}H_{10}F_3N_3O_2$ calc.: C, 56.07; H, 3.11; N, 13.08.

1-(Carbomethoxymethyl)-2-trifluoromethylbenzimidazole: IR (KBr): 3056, 1766, 1472, 1284, 1119, 896, 743 cm^{-1}. ^1H NMR: 3.78 (s, 3H, CH_3), 5.04 (s, 2H, $-CH_2-$), 7.33–7.92 (m, 4H, ArH). UV (EtOH): 274 (3.59), 252 (3.67); ($CHCl_3$): 277 (3.60), 257 (3.70). Mass spectrum: 258 (M^+, 29), 199 (100), 185 (79). Elemental analysis: Found C, 51.04; H, 3.44; N, 10.69; $C_{11}H_9F_3N_2O_2$ calc.: C, 51.16; H, 3.49; N, 10.85.

Acknowledgements

We gratefully thank Dr. S. Chandrasekar, IIT, Kanpur, India, for his help in obtaining the elemental analysis data and CSIR, New Delhi, India for financial support.

References

1 L.B. Townsend and G.R. Revanker, Chem. Rev., 70 (1970) 389.
2 Chem. Abstr., 58 (1963) 2456d; 59 (1963) 11504c.
3 Chem. Abstr., 70 (1969) 96797j.
4 Chem. Abstr., 77 (1972) 48473y.
5 Chem. Abstr., 79 (1973) 115589x.
6 P.N. Preston, Chemistry of Heterocyclic Compounds, Vol. 40, John Wiley and Sons, London, 1980, chap 1 and 10.
7 J.C. Pommier and D. Lucas, J. Organomet. Chem., 57 (1973) 139.
8 R. Gassend, J.C. Maire and J.C. Pommier, J. Organomet. Chem., 133 (1977) 169; E.C. Taylor, Y. Maki and A. McKillop, J. Org. Chem., 34 (1969) 1170.
9 J.J. Zuckerman, Organotin Compounds: New Chemistry and Applications, Adv. Chem. Ser. No. 157, American Chemical Society, Washington, DC, 1976, pp. 82–112.
10 R. Soundararajan, S. Krishnamurthy, V.S. Srinivasan and T.R. Balasubramanian, J. Organomet. Chem., 255 (1983) 295.
11 R. Soundararajan and T.R. Balasubramanian, Tetrahedron Lett., (1984) 5555.
12 W.P. Neumann, Organic Chemistry of Tin, Intersciene, New York, 1970.
13 W.T. Smith, Jr. and E.C. Steinle, Jr., J. Am. Chem. Soc., 75 (1953) 1292.