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# 2-TRIFLUOROMETHYLIMIDAZOLE, 2,4,5-TRIS(TRIFLUOROMETHYL)IMIDAZOLE AND RELATED COMPOUNDS †

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## SUMMARY

2-Trifluoromethylimidazole, prepared by the reaction of imidazole-2-carboxylic acid with sulphur tetrafluoride, afforded a silver salt which reacted with organohalides (bromomethane, ethyl bromoacetate, N,N-dimethyl-2-chloroethylamine, and chloroacetonitrile) to give the corresponding N-alkylated derivatives. 2-Trifluoromethylimidazole-4,5-dicarboxylic acid was obtained by oxidation of 2-trifluoromethylbenzimidazole, and on decarboxylation gave only traces of 2-trifluoromethylimidazole; the major product was 2-trifluoromethylimidazole-4-carboxylic acid. The di-acid and sulphur tetrafluoride gave 2,4,5-tris(trifluoromethyl)imidazole.

## INTRODUCTION

Though 2-trifluoromethylbenzimidazoles are well known [1,2], 2-trifluoromethylimidazole was first described only recently [3] made by a classical Bamberger reaction from trifluoroacetic anhydride. We now describe an efficient alternative synthesis of 2-trifluoromethylimidazole.

## RESULTS AND DISCUSSION

Two approaches (scheme 1) were explored. The first was successful and involved the reaction of imidazole-2-carboxylic acid with sulphur tetrafluoride. The second and less successful route required the decarboxylation of 2-trifluoromethylimidazole-4,5-dicarboxylic acid.

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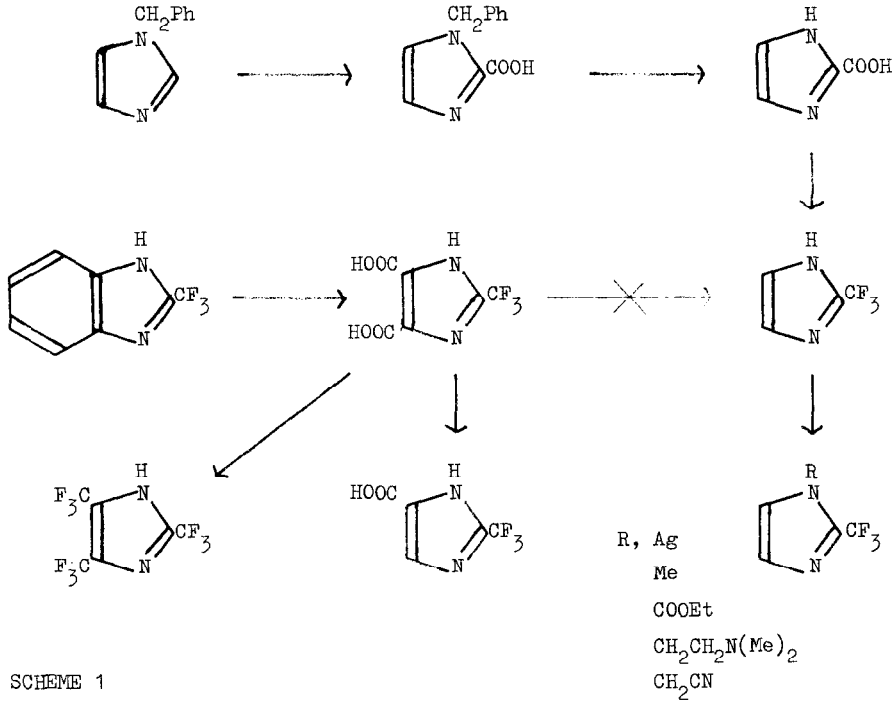


SCHEME 1

The synthesis of imidazole-2-carboxylic acid started with the preparation of 1-benzylimidazole [4] from imidazole. A choice of routes was then possible. The benzyl compound was converted either to the lithio derivative which was carbonated [5] or it was treated with formaldehyde and the derived 2-hydroxymethyl compound oxidised with potassium permanganate [6]. The former process gave the better yield. The protecting group was then removed easily to give the required acid [6].

Sulphur tetrafluoride is the standard reagent [7] for converting carboxyl groups to trifluoromethyl groups and indeed 4,5-bis-(trifluoromethyl)imidazole [8] has been prepared from imidazole-4,5-dicarboxylic acid. Under similar conditions imidazole-2-carboxylic acid was converted to 2-trifluoromethylimidazole (61% yield). This offers an improvement over the earlier synthesis [3].

Under carefully controlled conditions certain benzimidazoles are oxidised to imidazole-4,5-dicarboxylic acids [9]. The reaction of 2-trifluoromethylbenzimidazole with hydrogen peroxide and sulphuric acid gave 2-trifluoromethylimidazole-4,5-dicarboxylic acid. This dicarboxylic acid was treated with sulphur tetrafluoride to give 2,4,5-tris(trifluoromethyl)imidazole.

Several imidazole dicarboxylic acids undergo decarboxylation when heated [9]. Usually this is a stepwise process proceeding through the monocarboxylic acid. Heating 2-trifluoromethylimidazole-4,5-dicarboxylic acid at 250°C gave 2-trifluoromethylimidazole-4-carboxylic acid as the major product. Traces of 2-trifluoromethylimidazole were also produced but since more drastic heating did not increase the yield significantly this method cannot be regarded as a suitable source of the imidazole.

2-Trifluoromethylimidazole is a white crystalline solid which is readily hydrolysed by aqueous sodium hydroxide to sodium imidazole-2-carboxylate [10]. N-Methylation of the imidazole with diazomethane was incomplete. However, a white silver salt was precipitated quantitatively when solutions of the imidazole and silver nitrate were mixed. Such silver salts are reactive in substitution reactions with organohalides [11]. The silver salt reacted with bromomethane, with ethyl bromoacetate, with N,N-dimethyl-2-chloroethylamine, and with chloroacetonitrile to give the corresponding N-alkyl derivatives (Scheme 1) in good yields. Thus by avoiding aqueous basic conditions this provides an attractive route for the synthesis of N-substituted 2-trifluoromethylimidazoles.

## EXPERIMENTAL

$^1H$ (60 MHz) and $^{19}F$ (56.4 MHz) n.m.r. spectra were measured with a Perkin Elmer R12B spectrometer. Samples were dissolved in [$^2H_6$] acetone, unless stated otherwise, with tetramethylsilane ($^1H$) and trichlorofluoromethane ($^{19}F$) as internal standards.

### Imidazole-2-carboxylic acid

This acid was obtained by the debenzylation [6] of 1-benzylimidazole-2-carboxylic acid m.p. 103-104°C (decomp.) prepared in 85% yield by the published method [5] except that the lithio derivative of benzylimidazole was generated rapidly at 0°C using methyl lithium in diethyl ether.

Preparation of 2-trifluoromethylimidazole

Imidazole-2-carboxylic acid (2.75g, 24.6 mmol), anhydrous hydrogen fluoride (10 $cm^3$) and sulphur tetrafluoride (47.5g, 440 mmol) were heated at 70°C in a stainless steel rocking autoclave (50 $cm^3$ capacity) for 48h. After cooling the reaction mixture was poured into a polythene beaker allowing the volatile products to evaporate. Diethyl ether (60 $cm^3$) was added and the ethereal solution was washed thoroughly with 10% sodium hydrogencarbonate solution, filtered, dried ($MgSO_4$) and evaporated to leave an off-white solid which was recrystallised from trichloromethane to give 2-trifluoromethylimidazole (2.02g, 15 mmol, 61%) m.p. 145-7°C (cited m.p. 145-6°C [3]). Analysis: Found: C, 35.0; H, 2.0; F, 42.2; N, 20.9. Calc. for $C_4H_3F_3N_2$ C, 35.3; H, 2.2; F, 41.9; N, 20.6%. m/e 136 ($M^+$), 117 ($M^+ - F$). $^1H$ n.m.r. $\tau$ - 2.05 (1H , s , - NH -) and 2.7 (2H , s , - CH = CH -). $^{19}F$ n.m.r. $\delta$ -62.5 (s , $CF_3$).

The oxidation of 2-trifluoromethylbenzimidazole

Hydrogen peroxide (13 $cm^3$, 28% W/V) was added slowly to a stirred solution of 2-trifluoromethylbenzimidazole [2] (2.3g, 13.4 mmol) in 14M sulphuric acid (33 $cm^3$) heated at 120°C. The mixture was cooled, poured into water (75 $cm^3$) and extracted with ether (3 x 50 $cm^3$). The ethereal solution was dried ($MgSO_4$) and evaporated to give a residue which on sublimation (170°C, 25 mmHg) afforded 2-trifluoromethylimidazole-4,5-dicarboxylic acid (nc) (2.28g, 10.2 mmol, 82%) m.p. 220 - 3°C (decomp.) Analysis: Found: C, 32.2; H, 1.5; F, 25.0; N, 12.2. $C_6H_3F_3N_2O_4$ requires C, 32.1; H, 1.3; F, 25.5; N, 12.5%. m/e 224 ($M^+$), 222 ($M^+ - 2H$), 207 ($M^+ - OH$), 205 ($M^+ - F$), 180 ($M^+ - CO_2$) and 136 ($M^+ - 2CO_2$). $\nu$ (-OH), 3600, 3500 and $\nu$ (-COOH) 1700 $cm^{-1}$ $^1H$ n.m.r. $\tau$ -0.65 (broad s , -OH , NH?), $^{19}F$ n.m.r. $\delta$ - 63.1 (s, $CF_3$).

2,4,5-Tris(trifluoromethyl)imidazole

2-Trifluoromethylimidazole-4,5-dicarboxylic acid (4.0g, 17.9 mmol), anhydrous hydrogen fluoride (10 $cm^3$) and sulphur tetrafluoride (38g, 352 mmol) were heated at 50°C for 18h in a stainless steel rocking autoclave (50 $cm^3$ capacity). After cooling the reaction mixture was poured into a polythene beaker allowing the volatile compounds to evaporate. Water

($20\ cm^3$) and ether ($100\ cm^3$) were added, the ethereal solution was filtered, dried ($MgSO_4$) and evaporated to leave a residue which was sublimed (120°C, 30 mmHg) to give 2,4,5-tris(trifluoromethyl)imidazole (nc) (2.7g, 9.78 mmol, 55%) m.p. 139-141°C. Analysis: Found: C, 26.7; H, 0.3; F, 63.2; N, 10.0. $C_6HF_9N_2$ requires C, 26.5; H, 0.4; F, 62.9; N, 10.3% m/e 272 ($M^+$), 253 ($M^+$ - F). $^1$H n.m.r.$\tau$ - 3.5 (broad s, -NH-), $^{19}$F n.m.r. $\delta$ - 59.7 (6F,s, $-CF_3$) and - 63.7 (3F,s, $-CF_3$).

The decarboxylation of 2-trifluoromethylimidazole-4,5-dicarboxylic acid

The dicarboxylic acid (0.75g) was heated at 250°C for 15 min; carbon dioxide was evolved. The brown residue (0.54g) was boiled with charcoal suspended in methanol and filtered. The filtrate was evaporated to leave a residue, a portion (0.17g) of which was sublimed at 130°C (30 mmHg) and a fraction was collected to give, after washing with hot trichloromethane, 2-trifluoromethylimidazole-4-carboxylic acid (nc) (0.10g) m.p. 264-5°C (decomp.). Analysis: Found: C, 33.9; H, 2.2; N, 15.4. $C_5H_3F_3N_2O_2$ requires C, 33.3; H, 1.7; N, 15.6%. $\nu$(-OH), 3200 and $\nu$(-COOH), 1685 $cm^{-1}$. $^1$H n.m.r.$\tau$ -0.55 (2H,s,-OH, -NH) and 2.05 (1H,s, = CH-), $^{19}$F n.m.r. (ca. 95% pure) $\delta$ - 63.3(s); also signals attributable to small amounts of the dicarboxylic acid and 2-trifluoromethylimidazole.

Preparation of the silver salt of 2-trifluoromethylimidazole

2-Trifluoromethylimidazole (2.0g, 14.7 mmol) in ethanol ($10\ cm^3$) was added slowly to silver nitrate (5g) in water ($50\ cm^3$); the pH was maintained at 7 by dropwise addition of 0.1M sodium hydroxide solution. The white precipitate was filtered, washed with water, ethanol and ether, and dried in vacuo to give the silver salt of 2-trifluoromethylimidazole (nc) (3.4g, 14 mmol, 95%) Analysis: Found: C, 19.7; H, 0.6; N, 11.7. $C_4H_2AgF_3N_2$ requires C, 19.7; H, 0.8; N, 11.5%.

Reactions of the silver salt of 2-trifluoromethylimidazole

(a) With bromomethane

The silver salt (0.25g, 1.0 mmol) and bromomethane ($5\ cm^3$) were shaken at 18°C for 60h. in a sealed glass Carius tube. The tube was vented and the residue mixed with ether ($10\ cm^3$). The ethereal solution was filtered and evaporated to leave an oil which was

further purified by g.l.c. [Pye Series 104, Column 9.1m x 6mm, silicone SE30 - Supasorb AW-HMDS 60-80 (1:19), 135°C, $N_2$ 6ℓh$^{-1}$] to give after distillation in vacuo from $P_2O_5$ a colourless liquid, 1-methyl-2-trifluoromethylimidazole (lit [10] solid, only $^{19}F$ n.m.r. data given) (.09g, 0.6 mmol, 60%) Analysis: Found: C, 39.7; H, 3.0; N, 18.8. $C_5H_5F_3N_2$ requires C, 40.0; H, 3.3; N, 18.7%. $^1H$ n.m.r. $\tau$ 2.7 (1H,s, = CH-), 3.0 (1H,s, = CH-) and 6.1 (3H,s, $-CH_3$), $^{19}F$ n.m.r. $\delta$ - 61.3 (s).

(b) With ethyl bromoacetate

The silver salt (0.75g , 3.1 mmol) and ethyl bromoacetate (5 cm$^3$) were heated under reflux for 2h. The yellow precipitate (AgBr) was removed by filtration and washed with acetone. The filtrate and acetone washings were distilled to leave a residue which after separation by g.l.c. [as above, 170°C, $N_2$ 6ℓh$^{-1}$] afforded a colourless liquid, 1-(ethoxycarbonyl)-2-trifluoromethyl-imidazole (nc) (0.35g, 1.5 mmol, 48%). Analysis: Found: C, 42.9; H, 4.1; F, 25.6; N, 12.5. $C_8H_9F_3N_2O_2$ requires C, 43.2; H, 4.1; F, 25.7; N, 12.6%. $\nu$(=CH-), 3015, $\nu(-CH_3)$, 2995 and $\nu$(-COOR) 1750 cm$^{-1}$. $^1H$ n.m.r. $\tau$ 2.6 (1H,s, = CH-), 2.9 (1H,s, = CH- ), 4.9 (2H,s, $-CH_2N<$), 5.8 (2H, q, $-CH_2-$, J 7Hz) and 8.8 (3H, t, $-CH_3$, J 7Hz), $^{19}F$ n.m.r. $\delta$ -60.5 (s).

(c) With N,N-dimethyl-2-chloroethylamine

The silver salt (0.6g, 2.5 mmol) and benzene solution of N,N-dimethyl-2-chloroethylamine (from amine hydrochloride (5g) dissolved in 4M NaOH, extracted with benzene (20 cm$^3$), dried ($MgSO_4$) and filtered) were heated under reflux for 15h. The white precipitate (AgCl) was removed by filtration and washed with acetone. The filtrate and acetone washings were distilled to leave a residue which after separation by g.l.c. [as above] afforded a colourless liquid 1- (2-N,N-dimethyl aminoethyl)-2-trifluoromethyl-imidazole (nc) (0.36g, 1.7 mmol , 70%). Analysis: Found: C, 46.1; H, 5.9; N, 20.0. $C_8H_{12}F_3N_3$ requires C, 46.4; H, 5.8; N, 20.3%. $^1H$ n.m.r. $\tau$ 2.6 (1H,s, = CH- ), 3.0 (1H,s, = CH- ), 5.8 (2H, t, $-CH_2-$, 6Hz), 7.4 (2H, t, $-CH_2-$, J $6H_2$) and 7.8 (6H,s, $-CH_3$) $^{19}F$ n.m.r. $\delta$ - 60.4 (s).

(d) With chloroacetonitrile

The silver salt (0.30g, 1.2 mmol) and chloroacetonitrile (5 $cm^3$) were heated under reflux for 5h. The precipitate was removed by filtration and washed with acetone. The filtrate and acetone washings were distilled to leave a residue which after separation by g.l.c. [as above, 160°C, $N_2$ 6$\ell h^{-1}$] afforded a white solid, 1-(cyanomethyl)-2-trifluoromethylimidazole (nc) (0.07g, 0.4 mmol), 30%) m.p. 46-9°C, Analysis: Found: C, 41.3; H, 2.3; F, 32.5; N, 24.0. $C_6H_4F_3N_3$ requires C, 41.1; H, 2.3; F, 32.6; N, 24.0%. $^1H$ n.m.r. $\tau$ 2.4 (1H,s,=CH-), 2.8 (1H,s, =CH-) and 4.5 (2H,s, $-CH_2CN$), $^{19}F$ n.m.r. $\delta$ -60.6 (s).

Methylation of 2-trifluoromethylimidazole

An ethereal solution of diazomethane [from N-methyl-N-nitrosotoluene-4-sulphonamide (3.0g, 14 mmol)] was added to 2-trifluoromethylimidazole (0.5g , 3.7 mmol) in ether (30 $cm^3$). After 24h. at 18°C the reaction mixture was filtered and evaporated to leave a yellow oil (0.34g) which was shown by t.l.c. [MN - Silica Gel G/$UV_{254}$, trichloromethane-methanol (10:1)] to be a mixture (1:1) of 1-methyl-2-trifluoromethylimidazole and unreacted 2-trifluoromethylimidazole. The composition of this mixture was not changed by further treatment with diazomethane.

REFERENCES


1 W.T. Smith and E.C. Steinle, J.Amer-Chem. Soc., 75 (1953) 1292; E.S. Lane, Chem. and Ind. (1953) 798.

2 R. Belcher, A. Sykes and J.C. Tatlow, J. Chem. Soc., (1954) 4159.

3 H. Kimoto, K.L. Kirk and L.A. Cohen, J. Org. Chem., 43 (1978) 3403.

4 A.M. Roe, J. Chem. Soc., (1963) 2195.

5 D.A. Shirley and P.W. Alley, J. Amer. Chem. Soc., 79 (1957) 4922.

6 R.G. Jones, J. Amer. Chem. Soc., 71 (1949) 383.

7 G.A. Boswell, Jr., W.C. Ripka, R.M. Scribner and C.W. Tullock, Org. React. 21 (1974) 30.

8 M.S. Raasch, J. Org. Chem., 27 (1962) 1406.

9 G. Lehmann, G. Otterpohl and H. Schubert, Ger. (East) Patent (1970) 73768; Chem. Abs., 74 (1971) 76417.

10 H. Kimoto and L.A. Cohen, J. Org. Chem., 44 (1979) 2902.

11 H. Giesemann and G. Halschke, Chem. Ber., 92 (1959) 92; H. Giesemann, H. Lettau and H. Mannsfeldt, Chem. Ber. 93 (1960) 570.