Novel Synthetic Approaches to (Trifluoromethyl)triazoles

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Received 26 November 2009; revised 8 December 2009

Abstract: New synthetic procedures for the trifluoromethyl-substituted triazoles, 3-(trifluoromethyl)-4*H*-1,2,4-triazole and 4-(trifluoromethyl)-1*H*-1,2,3-triazole, have been elaborated. The target compounds were prepared from commercially available trifluoroacethydrazide (one step) and methyl propiolate (three steps), respectively.

Key words: fluorine, triazoles, trifluoromethyl group

Triazoles are an important class of organic compounds, playing an important role in modern medicinal chemistry.[1,2] Compounds with 1,2,3- and 1,2,4-triazole moieties are known to possess fungicidal, antimicrobial, anticonvulsant, antidepressant, antibacterial, anti-inflammatory, analgesic and antitumor activities.[1,2] Moreover, many compounds with the triazole core are market available (Figure 1).

The substitution of hydrogen for fluorine in organic compounds is widely used to modify the physical, chemical and biological characteristics of such compounds.[3] Taking into account the great potential of triazoles as valuable building blocks for drug design, fluorinated triazole derivatives are of enormous practical interest; however, although the chemistry of triazoles is quite well elaborated,[1,2] fluorine-containing triazoles have received much less attention so far.[4] Therefore, in the present work, we wish to report straightforward, practical procedures for the multigram preparation of the mono(trifluoromethyl)-substituted triazoles, 3-(trifluoromethyl)-4*H*-1,2,4-triazole (**1**) and 4-(trifluoromethyl)-1*H*-1,2,3-triazole (**2**) (Figure 2), starting from commercially available materials.

Despite the structural simplicity of 3-(trifluoromethyl)-4*H*-1,2,4-triazole (**1**), there is, to the best of our knowledge, only one synthetic approach to **1** reported in the literature to date.[5] According to that publication, the target compound was obtained in two steps from trifluoroacethydrazide and methyl 2,2,2-trichloroacetimidate, as shown in Scheme 1; however, despite much effort, we

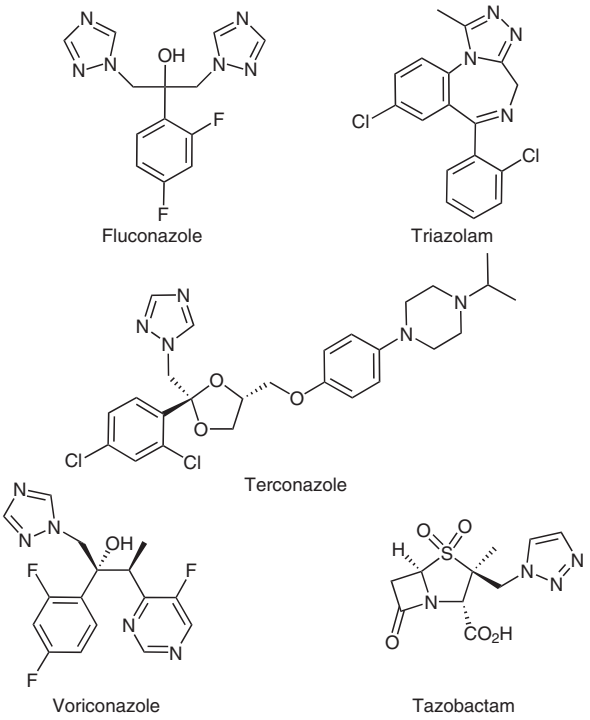


Figure 1 Some representative examples of the marketed triazole derivatives: Fluconazole (antifungal), Triazolam (sedative), Terconazole (antifungal), Voriconazole (antifungal), Tazobactam (used in combination with the antibiotic Piperacillin)

failed to reproduce this procedure. A complex mixture formed each time when we tried to obtain the intermediate **3**. Therefore, we elaborated an alternative procedure for **1**. Refluxing trifluoroacethydrazide with formamidine acetate in acetic acid for four hours afforded the target compound **1** in 25% yield after purification by flash column chromatography. Despite the relatively poor yield of 25%, the given procedure represents an easy and practical method to obtain **1** in one synthetic step from inexpensive, commercially available materials. Moreover, the reaction was easily scaled up for the preparation of 10 grams of **1** in a single batch.

Another trifluoromethyl-substituted triazole, compound **2**, has also been described in the literature, with three synthetic approaches to **2** known. In 1973, Crossman and coworkers reported the preparation of milligram quantities

SYNTHESIS 2010, No. 7, pp 1075–1077
Advanced online publication: 29.01.2010
DOI: 10.1055/s-0029-1218656; Art ID: Z25709SS

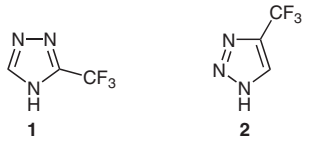
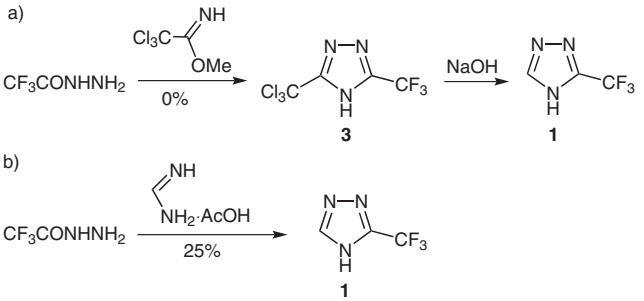


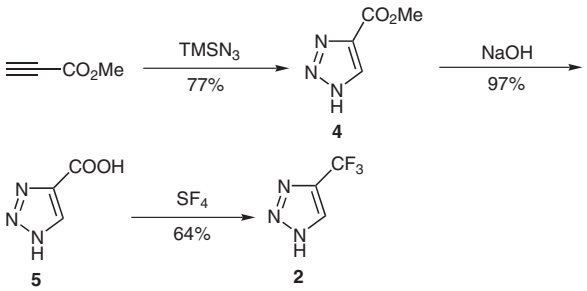
Figure 2 3-(Trifluoromethyl)-4*H*-1,2,4-triazole (**1**) and 4-(trifluoromethyl)-1*H*-1,2,3-triazole (**2**)



Scheme 1 Synthetic approaches to 3-(trifluoromethyl)-4*H*-1,2,4-triazole (**1**): a) original procedure described in the literature[5] (could not be reproduced); b) proposed approach to **1** (successfully performed)

of **2** by the reaction of trifluoroacetonitrile with (diazomethyl)trimethylsilane.[6] Subsequently, in 2007, Shreeve and co-workers obtained **2** from 3,3,3-trifluoropropyne and trimethylsilyl azide, however, still on a milligram scale.[7] In the same year, Bandera and co-workers proposed an alternative strategy to **2**.[8] Their procedure represents a practical way to obtain **2**; however, it commences from a rather exotic starting material ($C_2F_5CH_2SO_2Tol$) and requires the use of sodium mercury amalgam. Therefore, in order to easily prepare gram quantities of **2**, we turned our attention to the well-elaborated tetrafluoro-λ^4-sulfane technique.[9] The starting compound **4** was readily prepared from methyl propiolate and trimethylsilyl azide in 77% yield (Scheme 2). Thereafter, the methyl ester group in **4** was hydrolyzed under basic conditions to produce acid **5** in 97% yield. Finally, treatment of acid **5** with tetrafluoro-λ^4-sulfane in hydrogen fluoride smoothly afforded triazole **2** in 64% yield. Using this strategy, a scaled-up synthesis afforded 30 grams of **2** in one synthetic run.

In summary, we have developed simple and efficient procedures to prepare the mono(trifluoromethyl)-substituted triazoles **1** and **2**. 3-(Trifluoromethyl)-4*H*-1,2,4-triazole (**1**; 10 g) and 4-(trifluoromethyl)-1*H*-1,2,3-triazole (**2**; 30 g) were prepared in single synthetic runs starting from inexpensive, commercially available materials.



Scheme 2 Synthesis of 4-(trifluoromethyl)-1*H*-1,2,3-triazole (**2**)

Chemicals were purchased from Aldrich and Enamine Ltd. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 499.9, 124.9 and 470.3 MHz, respectively). Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standard. Mass spectra were recorded on an Agilent 1100 LC/MSD SL instrument by chemical ionization (CI).

3-(Trifluoromethyl)-4*H*-1,2,4-triazole (1)

To a stirred soln of trifluoroacethydrazide (40.0 g, 313 mmol) in anhyd MeOH (200 mL), formamidine acetate (32.5 g, 313 mmol) was added. The mixture was stirred at r.t. for 5 h. The solvent was evaporated under reduced pressure and AcOH (200 mL) was added to the residue. The resulting soln was heated at reflux for 4 h. The solvent was evaporated and EtOAc (200 mL) was added. The formed precipitate was removed by filtration and the mother liquor was concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc; R_f = 0.6). The obtained oil was redissolved in $CHCl_3$ (200 mL) and decanted from the insoluble material. Evaporation of the solvent produced the oil, which was further purified by flash column chromatography ($CHCl_3$–MeOH, 9:1; R_f = 0.4) to give **1** (10.7 g, 78 mmol, 25%) as a white solid.

Mp 80–81 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 13.70 (br s, NH), 8.55 (s, CH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 152.91 (q, $^2J_{C,F}$ = 37.7 Hz, C), 146.32 (s, CH), 120.15 (q, $^1J_{C,F}$ = 269.0 Hz, CF_3).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.05 (s, CF_3).

MS: *m*/*z* = 137 [M$^+$].

Methyl 1*H*-1,2,3-Triazole-4-carboxylate (4)

A mixture of methyl propiolate (39.8 g, 474 mmol) and $TMSN_3$ (109.0 g, 948 mmol) in MeCN (500 mL) was heated at reflux for 72 h. The reaction mixture was cooled to r.t. and MeOH (200 mL) was added. The formed suspension was concentrated under reduced pressure and the obtained residue was recrystallized (MeOH) to produce **4** (46.3 g, 365 mmol, 77%) as a white solid. Spectroscopic and analytical data were in accordance to those previously reported.[10]

1*H*-1,2,3-Triazole-4-carboxylic Acid (5)

A soln of methyl ester **4** (46.0 g, 362 mmol) and NaOH (31.9 g, 800 mmol) in H_2O (500 mL) was heated at reflux for 3 h. The soln was cooled to r.t. and washed with CH_2Cl_2 (2 × 100 mL). The aqueous phase was acidified with aq HCl to pH 2, and then extracted with EtOAc (2 × 150 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to produce **5** (39.6 g, 351 mmol, 97%) as a white solid.

Mp 260–261 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.70 (br s, NH), 8.20 (br s, CH).

^{13}C NMR (125 MHz, D_2O): δ = 164.35 (s, COOH), 138.15 (s, C), 131.12 (s, CH).

MS: *m*/*z* = 114 [M + 1]$^+$.

4-(Trifluoromethyl)-1*H*-1,2,3-triazole (2)

A mixture of acid **5** (39.0 g, 345 mmol), anhyd HF (50 mL) and SF_4 (46.5 g, 430 mmol) in a 500-mL autoclave was heated at 120 °C (oil bath temperature) for 16 h. The reaction mixture was cooled to 0 °C and the autoclave was then opened. The residue was put on a Teflon plate; after the residual HF had been removed by heating at 30 °C for 1–2 h (CAUTION! This procedure must be carried out in a fume

hood!), the product was dissolved in CH_2Cl_2 (300 mL) to remove all insoluble materials. The solution was evaporated under vacuum and the thus-formed tarry residue was purified by double sublimation (20 mmHg, ~80–90 °C) to give **2** (30.3 g, 221 mmol, 64%) as a white solid.

Mp 79–80 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.95–8.20 (2 × br s, NH + CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.21 (br s), 124.15 (br s), 121.71 (q, $^1J_{C,F}$ = 267.7 Hz, CF_3).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –61.55 (s, CF_3).

MS: *m*/*z* = 137 [M^+].

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