A Novel and Practical Method for the Synthesis of 3-Trifluoromethylated Pyrazoles

Xiao-Qing Tang and Chang-Ming Hu*

Shanghai Institute of Organic Chemistry, Academia Sinica, 345 Lingling Lu, Shanghai 200032, China

A new building block strategy for the synthesis of a series of 3-trifluoromethyl substituted pyrazoles **4** by a two-step sequence is described.

The development of new and efficient synthetic methodologies for the selective introduction of the trifluoromethyl group into organic molecules is currently of considerable interest because of their unique biological activities in medicine and agrochemicals.[1] The building block strategy for introducing a trifluoromethyl group into a molecule is now the subject of active investigation[2] and is thought to be superior to a selective introduction of such a group in the final step of the reaction sequence. However, high yielding regiospecific methods for the synthesis of trifluoromethyl substituted heteroaromatic compounds are quite limited. In the case of 3- or 5-trifluoromethyl substituted pyrazoles, 1,3-dipolar addition reaction of 2,2,2-trifluorodiazoethane with alkyne[3] needs a hazardous reagent. Cyclocondensations of trifluoromethyl substituted starting materials with hydrazine[4] or alkylhydrazines[5] involve a lengthy preparation of the starting materials.[6] Here we report some preliminary results on a new versatile route to the synthesis of 3-trifluoromethyl substituted pyrazoles starting from pentafluoroethyl iodide and alkynes.

Our regiocontrolled synthesis of 3-trifluoromethylated pyrazoles is based on a two-step sequence: (*i*) free radical reaction of pentafluoroethyl iodide with an alkyne to give a 1:1 adduct;[7] (*ii*) nucleophilic reaction of hydrazine monohydrate with the resultant 1:1 adduct to provide the corresponding pyrazole. Such a synthesis is illustrated with propynyl alcohol as an example. Similar results (see Table 1) were obtained using either 1- or 2-alkynes. Addition of a mixture of $Na_2S_2O_4$ (20 mmol) and $NaHCO_3$ (20 mmol) into a stirred solution of pentafluoroethyl iodide (20 mmol) and propynyl alcohol (20 mmol) in MeCN (20 ml) and water (20 ml) at 0 °C provided 2.78 g (92%) of the corresponding 5,5,5,4,4-pentafluoro-2-iodopent-2-en-1-ol **3a** (*E*, *Z*).† Treatment of the resultant 1:1 adduct (10 mmol, *E* + *Z*) with hydrazine monohydrate (40 mmol) in EtOH (15 ml) provided 1.59 g (96%) of 5-hydroxymethyl-3-trifluoromethyl pyrazole **4a**.† The formation of trifluoromethylated pyrazoles could go through a hydrazone intermediate formed by the nucleophilic addition of hydrazine monohydrate to the 1:1 adduct of pentafluoroethyl iodide with alkyne (see Scheme 1).

As shown in Table 1, this two-step methodology proved to be quite general for various alkynes, the substitution pattern at the skeletal C-4 and C-5 atoms of the pyrazole ring can be altered simply by choosing the appropriate alkyne as the starting material. With both non-functionalized alkynes and alkynes substituted with a number of functional groups, including diethylamino, hydroxy, carbon–carbon double bonds, PhS, OTHP and aromatic ring, the yields of the 3-trifluoromethylated pyrazoles are usually excellent. Therefore, this reaction can serve as a convenient route to CF_3-substituted pyrazole derivatives.

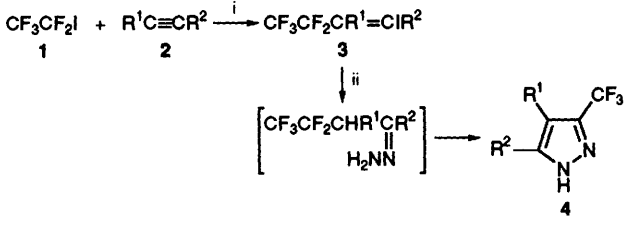
We thank the National Natural Science Foundation of China for the financial support.

Received, 11th November 1993; Com. 3/06769F

Footnote

† *Selected spectroscopic data for 3a*: ^{19}F NMR (neat TFA): δ 8.1 (s, 3F), 31.0 (m, 2F, *E* isomer), 35.0 (m, 2F, *Z* isomer); ^1H NMR (neat Me_4Si): δ 3.4 (w, 1H), 4.35 (s, 2H), 6.80 (t, J_{H-F} 15.0 Hz, 1H); IR ν/cm^{-1} (film): 3200, 1630, 1200–1100; MS (%): 302 (M^+, 6.50), 175 ($M^+ - I$, 6.42), 127 (I^+, 4.24), 69 (CF_3^+, 100.00), 55 ($M^+ - C_2F_5$-HI, 76.30).

For **4a**: Mp 115–116 °C; ^{19}F NMR (CD_3COCD_3–TFA): δ −15.2 (s); ^1H NMR (CD_3COCD_3–Me_4Si): δ 6.50 (s, 1H), 4.69 (s, 2H); ^{13}C NMR (CD_3COCD_3): δ 55.7 (s), 102.2 (s, C_4), 122.9 (q, J_{C-F} 265.9 Hz, CF_3), 143.1 (q, J_{C-F} 37.1 Hz, C_3), 146.4 (s, C_5); IR ν/cm^{-1} (KCl): 3200,



Scheme 1 *Reactions and conditions*: i, $Na_2S_2O_4$–$NaHCO_3$, MeCN, H_2O, 0 °C; ii, $NH_2NH_2·H_2O$, EtOH, reflux

Table 1 Preparation of CF_3-substituted pyrazoles **4**

Entry	Alkenes **3** R^1	Alkenes **3** R^2	Reaction time[a]/h	Product **4**	Yield (%)[b]
1	H	CH_2OH **a**	3	**a**	96
2	H	$C(OH)Me_2$ **b**	8	**b**	95
3	CH_2OH	CH_2OH **c**	5	**c**	92
4	H	$CH(OH)Pr^i$ **d**	6	**d**	92
5	H	CH(OH)CH=CHMe (*E*) **e**	8	**e**	85
6	H	n-C_6H_{13} **f**	20	**f**	84
7	H	Ph **g**	12	**g**	94
8	H	CH(OH)Ph **h**	10	**h**	93
9	H	$CH(OH)C_6H_4Cl$-*o* **i**	10	**i**	95
10	H	CH(OH)CH=CHPh (*E*) **j**	10	**j**	88
11	H	$CH_2CH(OH)Ph$ **k**	18	**k**	94
12	H	CH_2NEt_2 **l**	5	**l**	88
13	H	CH_2SPh **m**	6	**m**	92
14	H	CH_2OTHP **n**	8	**n**	95

[a] NH_2NH_2–H_2O (5–6 equiv.) was used. [b] Isolated yield of the second step. Satisfactory spectral and microanalytical data were obtained for all new compounds.

2910, 1490, 1350, 1200–1100; MS (%): 166 (M^+, 100), 165 ($M^+ - 1$, 35.29), 149 ($M^+ - OH$, 18.37), 69 (CF_3^+, 26.12).

Satisfactory elemental analyses were obtained for **3a** and **4a**.

References

1 R. Filler and Y. Kobayashi, *Biomedicinal Aspects of Fluorine Chemistry*, Kodansha, Tokyo, 1982; M. Hudlicky, *Chemistry of Organic Fluorine Compounds*, Ellis Horwood, New York, 1976.

2 N. Ishikawa, *Synthesis and Utilization of Organofluorine Compounds*, CMC: Tokyo, 1987; K. Uneyama, *J. Synth. Org. Chem. Jpn.*, 1991, **49**, 612, and references cited therein.

3 R. Fields and J. P. Tomlinson, *J. Fluorine Chem.*, 1979, **13**, 147; J. H. Atherton and F. Fields, *J. Chem. Soc. C*, 1968, 1507.

4 R. J. Linderman and K. S. Kirollos, *Tetrahedron Lett.*, 1989, **30**, 2049; Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, T. Kobuchi and T. Nishigaki, *Synthesis*, 1986, 340; E. Okada, R. Masuda and M. Hojo, *Heterocycles*, 1992, **34**, 791.

5 C. Hamper, M. L. Kurtzweil and J. P. Beck, *J. Org. Chem.*, 1992, **57**, 5680; J. R. Beck and F. L. Wright, *J. Heterocycl. Chem.*, 1987, **24**, 739.

6 B. C. Hamper, *Org. Synth.*, 1991, **70**, 246; Y. Huang, Y. Shen, Y. Xin, G. Fu and Y. Xu, *Sci. Sin., Ser. B*, 1982, **25**, 557.

7 W. Y. Huang, L. Lu and Y. F. Zhang, *Chin. J. Chem.*, 1990, 351.