Regioselective synthesis of 1-aryl-4-bromo-5-trifluoromethylpyrazoles

V. G. Nenajdenko, A. L. Reznichenko, and E. S. Balenkova*

Department of Chemistry, M. V. Lomonosov Moscow State University,
1 Leninskie Gory, 119992 Moscow, Russian Federation.
Fax: +7 (495) 932 8846. E-mail: nen@acylium.chem.msu.ru

A novel regioselective route to 1-aryl-4-bromo-5-trifluoromethylpyrazoles involves reactions of arylhydrazines with 3-bromo-4-ethoxy-1,1,1-trifluorobut-3-en-2-one.

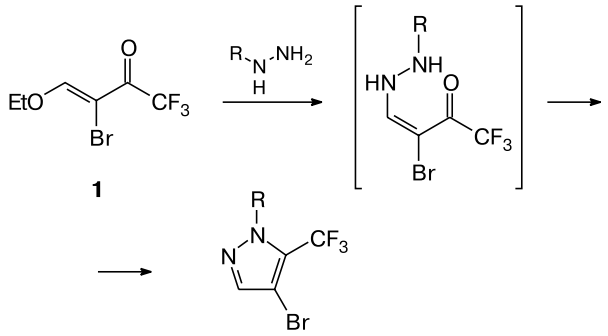
Key words: pyrazoles, arylhydrazines, heterocyclization, organofluorine compounds, enones.

The unique stereoelectronic and biological properties of the trifluoromethyl group make it topical to develop efficient methods for the synthesis of heterocyclic compounds containing this group. The most promising route to such compounds involves polyfunctional fluoro-containing building blocks, *e.g.*, α,β-unsaturated trifluoromethyl ketones, which have two electrophilic sites and thus can be employed for the synthesis of various CF_3-containing heterocyclic systems.[1]

Earlier,[2—5] α,β-unsaturated trifluoromethyl ketones have been used to obtain CF_3-containing pyrazoles. A topical problem in the chemistry of pyrazoles is the regioselective synthesis of *N*-substituted derivatives, which often form as a mixture of regioisomers. The present study is devoted to the synthesis of 1-aryl-4-bromo-5-trifluoromethylpyrazoles, which are promising intermediates for further functionalization due to the presence of the bromine atom. It has been recently demonstrated that 3-bromo-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**1**) acts as a 1,2-bielectrophile in the synthesis of trifluoroacetylimidazopyridine.[6] We assumed that enone **1** can also serve as a 1,3-bielectrophile in reactions with arylhydrazines.

It should be noted that enone **1** is a polyfunctional compound and its heterocyclization can theoretically yield two regioisomeric pyrazoles. However, we found that the reaction of enone **1** with phenylhydrazine gives the known 4-bromo-1-phenyl-5-trifluoromethylpyrazole (**2a**)[7] as the sole product in 65% yield (Scheme 1). We studied this reaction in various solvents (ethanol, methanol, acetonitrile, DMF, and acetic acid). The highest yield of the target product was achieved in acetic acid. According to GC-MS data for reaction mixtures, the solvent nature does not affect the reaction pathway: in all the cases, the alternative regioisomer was not formed. Under the optimized conditions, we carried out reactions of enone **1** with other arylhydrazines (see Scheme 1) and obtained the corresponding 1-aryl-4-bromo-5-trifluoromethylpyrazoles **2a**—**f** in satisfactory to good yields. The reaction of enone **1** with hydrazine hydrate afforded *N*-unsubstituted 4-bromo-3-trifluoromethylpyrazole (**2g**).

Scheme 1



2	R	Yield (%)	2	R	Yield (%)
a	Ph	65	**e**	3-$CF_3C_6H_4$	55
b	4-$MeOC_6H_4$	61	**f**	3,4-$(OCH_2CH_2O)C_6H_3$	63
c	4-MeC_6H_4	61	**g**	H	64
d	3-ClC_6H_4	52			

The regiochemistry of the heterocyclization observed conforms with data on the reactivities of CF_3-containing alkoxy enones.[1] The first step involves replacement (addition—elimination) of the ethoxy group; arylhydrazine is attached by its most nucleophilic terminal N atom. This is followed by closure of the target heterocycle (see Scheme 1).

In the conclusion, we developed a novel, simple and efficient method for the synthesis of 1-aryl-4-bromo-5-trifluoromethylpyrazoles. The combination of the Br atom and the CF_3 group makes these compounds promising for further transformations by means of cross-coupling,[8] nucleophilic substitution, and transmetalation, which open up routes to novel CF_3-containing heterocyclic systems.

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Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ with Me_4Si as the internal standard. GC-MS spectra were recorded on a Finnigan SSQ 7000 mass spectrometer connected to a Varian 3400 GC gas chromatograph. TLC analysis was carried out on Merck 60 F_{254} plates. Silica gel (63—200 mesh, Merck) was used for column chromatography. 3-Bromo-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**1**) was prepared according to a known procedure.[9]

1-Aryl-4-bromo-5-trifluoromethylpyrazoles 2a—g (general procedure). An arylhydrazine (1 mmol) was added to a stirred solution of enone **1** (1 mmol) in AcOH (5 mL). Stirring was continued at ~20 °C until the reaction was completed (12—24 h; TLC monitoring). Then the solvent was removed *in vacuo* and the product was isolated by column chromatography with hexane—CH_2Cl_2 as the eluent.

4-Bromo-1-phenyl-5-trifluoromethyl-1*H*-pyrazole (2a). A yellow oil, R_f 0.42 (hexane—CH_2Cl_2 (1 : 2)). ^{1}H NMR, δ: 7.39—7.43 (m, 2 H); 7.46—7.50 (m, 3 H); 7.70 (s, 1 H). ^{13}C NMR, δ: 96.8; 119.4 (q, $J_{C,F}$ = 270 Hz); 125.9; 129.1; 129.7; 130.1 (q, $J_{C,F}$ = 30 Hz); 139.4; 141.7. The ^{1}H NMR spectrum agrees with the known data.[4]

4-Bromo-1-(4-methoxyphenyl)-5-trifluoromethyl-1*H*-pyrazole (2b). White crystals, m.p. 55 °C, R_f 0.42 (hexane—CH_2Cl_2 (1 : 2)). Found (%): C, 41.01; H, 2.39. $C_{11}H_8BrF_3N_2O$. Calculated (%): C, 41.15; H, 2.51. ^{1}H NMR, δ: 3.84 (s, 3 H); 6.96, 7.32 (both d, 2 H each, J = 9.0 Hz); 7.66 (s, 1 H). ^{13}C NMR, δ: 55.5; 96.4; 119.4 (q, $J_{C,F}$ = 270 Hz); 127.3; 130.2 (q, $J_{C,F}$ = 30 Hz); 132.2; 141.4; 160.4.

4-Bromo-1-(4-methylphenyl)-5-trifluoromethyl-1*H*-pyrazole (2c). White crystals, m.p. 64 °C, R_f 0.42 (hexane—CH_2Cl_2 (1 : 2)). Found (%): C, 43.17; H, 2.57. $C_{11}H_8BrF_3N_2$. Calculated (%): C, 43.30; H, 2.64. ^{1}H NMR, δ: 2.42 (s, 3 H); 7.24—7.30 (m, 4 H); 7.68 (s, 1 H). ^{13}C NMR, δ: 21.2; 96.6; 119.4 (q, $J_{C,F}$ = 270 Hz); 125.7; 129.6; 130.2 (q, $J_{C,F}$ = 30 Hz); 136.9; 140.0; 141.5.

4-Bromo-1-(3-chlorophenyl)-5-trifluoromethyl-1*H*-pyrazole (2d). A yellow oil, R_f 0.42 (hexane—CH_2Cl_2 (1 : 2)). Found (%): C, 36.68; H, 1.42. $C_{10}H_5BrClF_3N_2$. Calculated (%): C, 36.90; H, 1.55. ^{1}H NMR, δ: 7.31—7.49 (m, 4 H); 7.71 (s, 1 H). ^{13}C NMR, δ: 97.5; 119.3 (q, $J_{C,F}$ = 270 Hz); 124.1; 126.3; 130.06; 130.11; 130.2 (q, $J_{C,F}$ = 30 Hz); 134.9; 140.2; 142.2.

4-Bromo-5-trifluoromethyl-1-[3-(trifluoromethyl)phenyl]-1*H*-pyrazole (2e). A yellow oil, R_f 0.42 (hexane—CH_2Cl_2 (1 : 2)). Found (%): C, 36.49; H, 1.30. $C_{11}H_5BrF_6N_2$. Calculated (%): C, 36.79; H, 1.40. ^{1}H NMR, δ: 7.64—7.68 (m, 2 H); 7.75—7.79 (m, 3 H). ^{13}C NMR, δ: 97.8; 119.3, 123.2 (both q, $J_{C,F}$ = 270 Hz); 126.5; 129.1; 129.9; 130.3 (q, $J_{C,F}$ = 38 Hz); 131.9 (q, $J_{C,F}$ = 33 Hz); 139.7; 142.4.

1-(1,4-Benzodioxan-6-yl)-4-bromo-5-trifluoromethyl-1*H*-pyrazole (2f). White crystals, m.p. 73 °C, R_f 0.42 (hexane—CH_2Cl_2 (1 : 2)). Found (%): C, 41.37; H, 2.17. $C_{12}H_8BrF_3N_2O_2$. Calculated (%): C, 41.29; H, 2.31. ^{1}H NMR, δ: 4.27 (s, 4 H); 6.85—6.94 (m, 3 H); 7.64 (s, 1 H). ^{13}C NMR, δ: 64.15; 64.24; 96.4; 115.4; 117.3; 119.1; 119.3 (q, $J_{C,F}$ = 270 Hz); 130.1 (q, $J_{C,F}$ = 37 Hz); 132.5; 141.3; 143.3; 144.8.

4-Bromo-3-trifluoromethylpyrazole (2g). Hydrazine hydrate (2.5 mL, 5 mmol) was added dropwise to a stirred solution of enone **1** (5 mmol) in ethanol (20 mL). The reaction mixture was refluxed for 30 min, cooled, and concentrated *in vacuo*. The residue was purified by column chromatography with CH_2Cl_2 as the eluent to give pyrazole **2g** as yellow crystals, m.p. 108 °C (*cf.* Ref. 10: m.p. 112 °C), R_f 0.2 (CH_2Cl_2). Found (%): C, 21.97; H, 1.06. $C_4H_2BrF_3N_2$. Calculated (%): C, 22.35; H, 0.94. ^{1}H NMR, δ: 7.73 (s, 1 H); 13.14 (br.s, 1 H). ^{13}C NMR, δ: 92.2; 120.8 (q, $J_{C,F}$ = 270 Hz); 132.1; 140.6 (q, $J_{C,F}$ = 36 Hz).

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