Regioselective substitution in α-bromo-β-butoxyvinyl trifluoromethyl ketone by N-nucleophiles

A. Yu. Rulev,[a] S. V. Fedorov,[a] V. G. Nenajdenko,[b]★ E. S. Balenkova,[b] and M. G. Voronkov[a]

[a]A. E. Favorsky Institute of Chemistry, Siberian Division of the Russian Academy of Sciences, 1 ul. Favorskogo, 664033 Irkutsk, Russian Federation. Fax: +7 (395 2) 39 6046. E-mail: rulev@irioch.irk.ru
[b]Department of Chemistry, M. V. Lomonosov Moscow State University, Leninskie Gory, 119899 Moscow, Russian Federation. Fax: +7 (095) 939 3181. E-mail: nen@acylium.chem.msu.ru

The reaction of α-bromo-β-butoxyvinyl trifluoromethyl ketone with N-nucleophiles proceeds regiospecifically to give amino enones of the push-pull type.

Key words: α,β-unsaturated trifluoromethyl ketones, N-nucleophiles, nucleophilic vinylic substitution.

Among organofluorine compounds, trifluoroacetylalkenes become increasingly attractive as valuable building blocks for the synthesis of various heterocycles and other organofluorine derivatives.[1—5] The chemistry of push-pull β-functionalized α,β-unsaturated trifluoromethyl ketones has been intensely developed in the last decades.

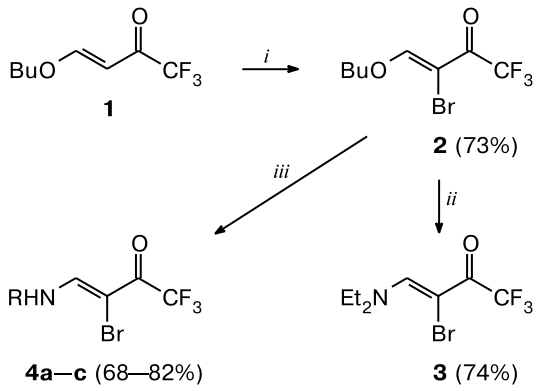
In continuation of our investigations into *gem*-carbonyl(amino)alkenes,[6,7] we studied the possibility of creating such systems with the trifluoroacetyl group as an acceptor.

Easily accessible β-butoxyvinyl trifluoromethyl ketone (**1**) reacts with Br_2 in $CHCl_3$ to give the corresponding dibromide; when treated with Et_3N in THF, the dibromide is smoothly converted into α-bromo-β-butoxyvinyl trifluoromethyl ketone (**2**).* Recently, it has been found that the reactions of methylamine and dimethylamine with β-ethoxy-α-halovinyl trifluoromethyl ketones afford the corresponding amino derivatives in which the alkoxy group is substituted.[8—10]

The reactions of bromo enone **2** with primary or secondary amines and 2-amino-2-methylpropanol proceed selectively, only the alkoxy group being the leaving group. Attempts to substitute the Br atom by increasing the amine/ketone ratio or the reaction temperature failed (Scheme 1).

The structures of amino enones **3** and **4a—c** were unambiguously proved by ^1H, ^{13}C, and ^{19}F NMR spectroscopy, IR spectroscopy, and mass spectrometry; their compositions were confirmed by elemental analysis. Unlike β-aminovinyl trifluoromethyl ketones,[11—13] enones **3** and **4a—c** form only one stereoisomer. Even β-amino enones **4a—c** containing the secondary amino group exist in the *Z*-form. A possible reason is the presence of the α-Br atom. Since vicinally substituted haloolefins retain their configurations in most nucleophilic substitution reactions,[14] one may conclude that the starting bromo ketone **2** also exists only as the *Z*-isomer.

Scheme 1



R = Me (**a**), Bn (**b**), $HOCH_2CMe_2$ (**c**)

i. 1) Br_2, $CHCl_3$ 2) Et_3N, THF; *ii*. Et_2NH, Et_2O; *iii*. RNH_2, THF or Et_2O.

It is known that the $^3J_{C-H}$ values are larger for the isomers in which the interacting nuclei are *trans*-arranged. For instance, the coupling constant $^3J_{C-H}$ of the C atom of the carbonyl group with the olefinic proton is in the interval from 0 to 6 Hz for the *cis*-arrangement and

* This study was carried out and prepared for publication independently from Ukrainian scientists (see Refs. 8—10).

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 10, pp. 2164—2166, October, 2003.

from 9 to 14 Hz for the *trans*-arrangement.[15—17] The vicinal constant $^3J_{C-H}$ ranges from <1 to 3.3 Hz for amino enones **3** and **4a—c** and the starting bromo ketone **2**. Additional studies of a structural analog, namely, 4-(4-ethoxyanilino)-1,1,1-trifluorobut-3-en-2-one, which exists in DMSO-d_6 as a mixture of *E*- and *Z*-isomers (2 : 1),[13] showed that $^3J_{C-H}$ = 3.6 Hz for the *E*-isomer and 9.6 Hz for the *Z*-isomer. Thus, these data confirm the *Z* configuration of amino bromo enones **3** and **4**.

Hence, the reactions of α-bromo β-butoxy enone **2** with N-nucleophiles involve only the alkoxy group.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 instrument (400.13 and 100.6 MHz, respectively); ^{19}F NMR spectra were recorded on a JEOL FX-90Q spectrometer (84.25 MHz) in $CDCl_3$. IR spectra were recorded on a Specord 75IR spectrophotometer (thin film or KBr pellets). GC-MS analysis was performed on a Hewlett-Packard HP 5971A instrument (70 eV, HP-5890 chromatograph, column Ultra-2 (5% phenylmethylsilicone)). Silica gel 60 (Merck, particle size 0.040—0.063 mm, 230—240 mesh) was used for column chromatography. The course of reactions was monitored and the purity of the products was checked by TLC on Silufol UV-254 plates. 4-Butoxy-1,1,1-trifluorobut-3-en-2-one (**1**) was prepared from butyl vinyl ether according to a known procedure.[18]

3-Bromo-4-butoxy-1,1,1-trifluorobut-3-en-2-one (2). A solution of Br_2 (1.6 g, 10 mmol) in $CHCl_3$ (5 mL) was slowly added at 5 °C to a solution of 4-butoxy-1,1,1-trifluorobut-3-en-2-one (**1**) (2.0 g, 10 mmol) in $CHCl_3$ (10 mL). The reaction mixture was allowed to warm slowly to ~20 °C and then stirred at this temperature for 3 h. The solvent was removed *in vacuo*, a solution of Et_3N (1.0 g, 10 mmol) in THF (25 mL) was added at 10 °C, and the reaction mixture was left for 12 h. The resulting $Et_3N \cdot HBr$ was filtered off, and the filtrate was concentrated. Vacuum distillation gave bromo enone **2**. The total yield over two steps was 2.0 g (73%), b.p. 86—87 °C (1 Torr). Found (%): C, 35.23; H, 4.08; Br, 28.74; F, 20.47. $C_8H_{10}BrF_3O_2$. Calculated (%): C, 34.93; H, 3.66; Br, 29.05; F, 20.72. ^{1}H NMR, δ: 0.93 (t, 3 H, J = 7.5 Hz); 1.43, 1.75 (both q, 2 H each, J = 7.5 Hz); 4.31 (t, 2 H, J = 7.5 Hz); 7.94 (s, 1 H). ^{13}C NMR, δ: 13.61 (CH_3); 18.77, 31.78 (CH_2); 77.74 (OCH_2); 99.25 (=CBr); 116.05 (q, CF_3, J = 290.8 Hz); 165.13 (CH=); 174.30 (q, C=O, J = 35.4 Hz). ^{19}F NMR, δ: –70.10. IR, ν/cm^{-1}: 1606 (C=C); 1695 (C=O). MS, m/z (I_{rel} (%)): 276, 274 $[M]^+$ (11), 151, 149 (20), 41 (100).

Reactions of 3-bromo-4-butoxy-1,1,1-trifluorobut-3-en-2-one (2) with N-nucleophiles (general procedure). A solution of an N-nucleophile (1.1—2.1 mmol) in Et_2O or THF (3—5 mL) was added to a solution of enone **2** (1—2 mmol) in Et_2O or THF (5—10 mL). The reaction mixture was left at ~20 °C for 24 h. The solvent was removed *in vacuo*, and the residue was chromatographed on SiO_2 with hexane—Et_2O (1 : 5) as the eluent to give enones **3** and **4b,c**.

3-Bromo-4-diethylamino-1,1,1-trifluorobut-3-en-2-one (3). The yield was 74%; colorless oil. Found (%): C, 35.45; H 4.39; Br, 28.90; F, 20.41; N, 5.53. $C_8H_{11}BrF_3NO$. Calculated (%): C, 35.06; H 4.05; Br, 29.15; F, 20.79; N, 5.11. ^{1}H NMR, δ: 1.26 (t, 6 H, J = 7.1 Hz); 3.25—3.95 (br.s, 4 H); 7.68 (s, 1 H). ^{13}C NMR, δ: 14.80 (CH_3); 42.90 (NCH_2); 85.51 (=CBr); 117.45 (q, CF_3, J = 291.6 Hz); 150.74 (CH=); 172.69 (q, C=O, J = 30.8 Hz). ^{19}F NMR, δ: –67.21. IR, ν/cm^{-1}: 1595 (C=C); 1668 (C=O). MS, m/z (I_{rel} (%)): 275, 273 $[M]^+$ (45), 194 (100).

4-Benzylamino-3-bromo-1,1,1-trifluorobut-3-en-2-one (4b). The yield was 68%, m.p. 94 °C. Found (%): C, 42.54; H, 3.04; Br, 26.28; F, 18.44; N, 4.51. $C_{11}H_9BrF_3NO$. Calculated (%): C, 42.88; H, 2.94; Br, 25.93; F, 18.50; N, 4.55. ^{1}H NMR, δ: 4.62 (AB system, 2 H); 6.38 (br.s, 1 H); 7.25—7.45 (m, 5 H); 7.80 (d, 1 H, J = 13.7 Hz). ^{13}C NMR, δ: 52.69 (NCH_2); 92.41 (=CBr); 117.03 (q, CF_3, J = 291.5 Hz); 127.66, 128.82, 129.38, 135.71 (C_6H_5); 151.68 (q, CH=, J = 4.8 Hz); 171.34 (q, C=O, J = 32.7 Hz). ^{19}F NMR, δ: –68.54. IR, ν/cm^{-1}: 1580 (br.s, C=C, C=O); 3437 (NH). MS, m/z (I_{rel} (%)): 309, 307 $[M]^+$ (12), 228 (13), 91 (100).

3-Bromo-4-[(2-hydroxy-1,1-dimethyl)ethylamino]-1,1,1-trifluorobut-3-en-2-one (4c). The yield was 79%. Found (%): C, 33.31; H, 3.59; Br, 27.53; F, 19.25; N, 4.85. $C_8H_{11}BrF_3NO_2$. Calculated (%): C, 33.12; H, 3.82; Br, 27.55; F, 19.65; N, 4.83. ^{1}H NMR, δ: 1.32 (s, 6 H); 3.52 (s, 2 H); 3.58, 6.55 (both br.s, 1 H each); 7.94 (d, 1 H, J = 14.5 Hz). ^{13}C NMR, δ: 24.56 (CH_3); 57.69 (NCH_2); 69.86 (OCH_2); 92.27 (=CBr); 117.28 (q, CF_3, J = 291.5 Hz); 149.29 (CH=); 171.27 (q, C=O, J = 33.1 Hz). ^{19}F NMR, δ: –68.25. IR, ν/cm^{-1}: 1594 (br.s, C=C, C=O); 3243 (OH); 3464 (NH). MS, m/z (I_{rel} (%)): 291, 189 $[M^+]$ (12), 260, 258 (100), 150, 148 (33).

3-Bromo-1,1,1-trifluoro-4-methylaminobut-3-en-2-one (4a). A suspension of $MeNH_2 \cdot HCl$ (270 mg, 4 mmol), enone **2** (550 mg, 2 mmol), and K_2CO_3 (280 mg, 2 mmol) in THF (10 mL) was stirred at ~20 °C for 24 h. The precipitate was filtered off, the filtrate was concentrated *in vacuo*, and the residue was chromatographed on SiO_2 with hexane—Et_2O (1 : 5) as the eluent to give enone **4a**. The yield of compound **4a** was 380 mg (82%), m.p. 103 °C (*cf.* Ref. 8). Found (%): C, 25.97; H, 2.18; Br, 34.45; F, 24.02; N, 6.14. $C_5H_5BrF_3NO$. Calculated (%): C, 25.89; H, 2.17; Br, 34.44; F, 24.57; N, 6.04. ^{1}H NMR, δ: 3.21 (d, 3 H, J = 5.0 Hz); 6.20 (br.s, 1 H), 7.69 (d, 1 H, J = 4.0 Hz). ^{13}C NMR, δ: 35.59 (NCH_3); 91.92 (=CBr); 117.18 (q, CF_3, J = 291.4 Hz); 153.32 (q, CH=, J = 4.7 Hz); 171.05 (q, C=O, J = 34.1 Hz). ^{19}F NMR, δ: –67.35. IR, ν/cm^{-1}: 1580 (C=C), 1650 (C=O), 3250 (NH). MS, m/z (I_{rel} (%)): 233, 231 $[M]^+$ (37), 164, 162 (100), 69 (55).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 02-03-32547).

References

1. V. G. Nenajdenko, A. V. Sanin, and E. S. Balenkova, *Usp. Khim.*, 1999, **68**, 483 [*Russ. Chem. Rev.*, 1999, **68**, 437 (Engl. Transl.)].
2. J.-P. Bégué and D. Bonnet-Delpon, *Tetrahedron*, 1991, **47**, 3207.
3. R. J. Linderman, E. A. Jamois, and S. D. Tennyson, *J. Org. Chem.*, 1994, **59**, 957.

4. R. J. Andrew and J. M. Mellor, *Tetrahedron*, 2000, **56**, 7261.
5. K. Funabiki, A. Isomura, Y. Yamagushi, W. Hashimoto, K. Matsunaga, K. Shibata, and M. Matsui, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2578.
6. A. Yu. Rulev, *Usp. Khim.*, 2002, **71**, 225 [*Russ. Chem. Rev.*, 2002, **71**, 195 (Engl. Transl.)].
7. A. Yu. Rulev, D. Sc. (Chem.) Thesis, A. E. Favorsky Institute of Chemistry, Siberian Division of the Russian Academy of Sciences, Irkutsk, 2002, 299 pp.
8. I. I. Gerus, L. M. Kacharova, and S. I. Vdovenko, *Synthesis*, 2001, 431.
9. L. M. Kacharova, A. D. Kacharov, and I. I. Gerus, *J. Fluor. Chem.*, 2001, **111**, 29.
10. L. M. Kacharova, I. I. Gerus, and A. D. Kacharov, *J. Fluor. Chem.*, 2002, **117**, 193.
11. I. I. Gerus, M. G. Gorbunova, S. I. Vdovenko, Yu. L. Yagupol´skii, and V. P. Kukhar´, *Zh. Org. Khim.*, 1990, **26**, 1877 [*J. Org. Chem. USSR*, 1990, **26** (Engl. Transl.)].
12. S. V. Pazenok, I. I. Gerus, E. A. Chaika, and L. M. Yagupol´skii, *Zh. Org. Khim.*, 1989, **25**, 379 [*J. Org. Chem. USSR*, 1989, **25** (Engl. Transl.)].
13. A. L. Krasovskii, V. G. Nenajdenko, and E. S. Balenkova, *Izv. Akad. Nauk, Ser. Khim.*, 2001, 1329 [*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 1395].
14. Z. Rappoport, *Adv. Phys. Org. Chem.*, 1969, **7**, 1.
15. P. E. Hansen, *Progress in NMR Spectroscopy*, 1981, **14**, 175.
16. J. L. Chiara and A. Gomez-Sanchez, *NMR Spectra*, in *The Chemistry of Enamines*, Ed. Z. Rappoport, J. Wiley and Sons, 1994, Ch. 5, 279.
17. J. Wójcik, W. Domalewski, K. Kamieńska-Trela, L. Stefaniak, S. I. Vdovenko, I. I. Gerus, and M. G. Gorbunova, *Magn. Res. Chem.*, 1993, **31**, 808.
18. M. Hojo, R. Masuda, Y. Kokuryo, H. Shioda, and S. Matsuo, *Chem. Lett.*, 1976, **3**, 499.

Received April 17, 2003;
in revised form September 24, 2003