Thermal ene reactions of methyl 3,3,3-trifluoro-2-R-sulfonyliminopropionates. Synthesis of γ,δ-unsaturated derivatives of α-amino α-trifluoromethylcarboxylic acids

N. M. Kobel'kova, S. N. Osipov, and A. F. Kolomiets*

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 119991 Moscow, Russian Federation. Fax: +7 (095) 135 5085. E-mail: osipov@ineos.ac.ru

Thermal ene reactions of methyl 3,3,3-trifluoro-2-methanesulfonyliminopropionate and methyl 2-benzenesulfonylimino-3,3,3-trifluoropropionate with terminal alkenes afford derivatives of γ,δ-unsaturated α-amino α-trifluoromethylcarboxylic acids in one step.

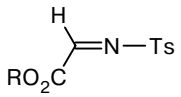
Key words: unsaturated α-amino acids, imino-ene reaction, methyl 3,3,3-trifluoro-2-R-sulfonyliminopropionates, terminal alkenes.

Unsaturated α-CF_3-α-amino acids, like their saturated analogs, are used in searching for new irreversible inhibitors of pyridoxal-phosphate—dependent enzymes[1] and in the syntheses of peptidomimetics.[2] Recently,[3] we have shown that these compounds can be used to prepare new promising biologically active substances. In the presence of ruthenium carbene complexes, unsaturated *N*-alkenyl-α-amino α-trifluoromethylcarboxylic acids are easily involved in the ring-closure metathesis of olefins to give dehydroderivatives of five-, six-, and seven-membered cyclic α-imino α-trifluoromethylcarboxylic acids in high yields.

At present, unsaturated α-amino α-trifluoromethylcarboxylic acids are mainly obtained by the reactions of methyl 2-acyliminotrifluoropropionates with alkenylmagnesium halides.[4,5] This method has three limitations, which include, first, accessibility of alkenyl halides for the synthesis of organometallic derivatives; second, the free-radical mechanism of the formation of Grignard reagents, which sometimes induces undesirable side processes; and third, the high reactivities of the Grignard reagents with respect to many functional groups, which precludes involvement of different functionalized alkenyl halides in the Grignard reactions.

In the last two decades, ene reactions of imines have become rather important in synthetic organic chemistry as an efficient way to the formation of C—C bonds. Intra- and intermolecular ene syntheses have successfully been used in the synthesis of various natural compounds,[6] including amino acids.[7] The latter are most often synthesized from glyoxylate tosylimines, whose thermal reactions with terminal olefins (even with such reactive ones as isobutylene) require temperatures above 110 °C.[8]

In the present communication, we report for the first time the results of the study of thermal ene reactions of α-CF_3-containing analogs of glyoxylate tosylimines **1**, namely, methyl 3,3,3-trifluoro-2-R-sulfonyliminopropionates **2** (R = Me and Ph),[9] as an alternative method for the synthesis of γ,δ-unsaturated α-amino-α-trifluoromethylcarboxylic acids.



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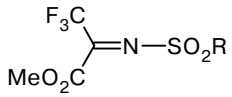
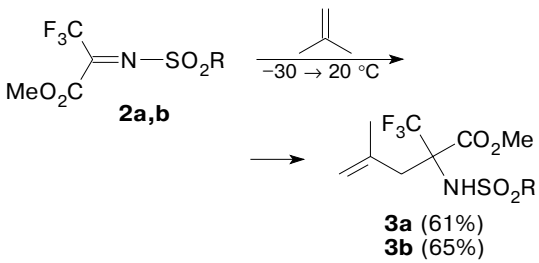


2a,b

R = Me (**a**), Ph (**b**)

Unlike glyoxylate imines, imines **2** react with isobutylene even at −30 °C; the reactions are completed upon warming the reaction mixtures to ~20 °C, giving derivatives of dehydroleucine **3** in good yields (Scheme 1).

Scheme 1



2a,b

3a (61%)
3b (65%)

2-Phenylpropene and methylidenecycloalkanes also react easily with imines **2** at 20 °C to give products (**4**—**8**) in preparative yields (Scheme 2).

When a mixture of 2-phenylpropene and tosylimine **1** is kept at 20 °C for five days, no corresponding product of the ene reaction is formed.[10] Low-reactive linear terminal olefins react with imines **2** at 80—100 °C. Thus, the reactions of benzenesulfonylimine **2b** with 4-bromo-

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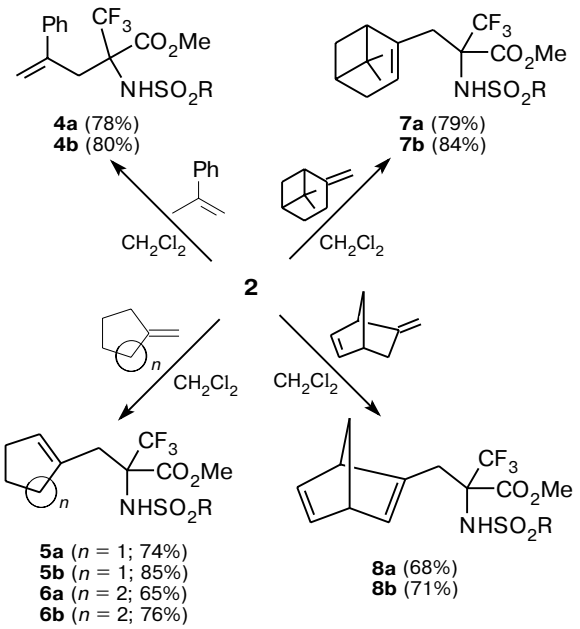
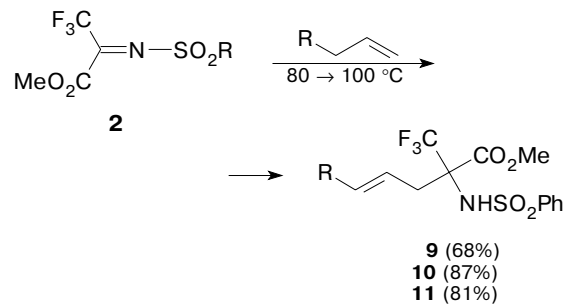
Scheme 2



but-1-ene, -hex-1-ene, and -oct-1-ene give the corresponding unsaturated derivatives **9**—**11** in preparative yields over 24 h, only the *E* isomers being formed (Scheme 3).

Scheme 3



R = CH_2Br (**9**), Pr (**10**), C_5H_9 (**11**)

Thus, our studies of the ene reactions of sulfonylimines **2** with terminal alkenes allow regarding these imines as the most reactive enophiles, the so-called "superenophiles". They are as reactive in the imino-ene reaction as, and sometimes more reactive than, such enophiles as hexafluoroacetone and methyl trifluoropyruvate in the keto-ene reaction.[11] Hence, we developed a preparative one-step method for the synthesis of previously unavailable derivatives of γ,δ-unsaturated α-amino α-trifluoromethylcarboxylic acids, which are promising for modification of biologically active peptides.

Experimental

^1H and ^{19}F NMR spectra were recorded on a Bruker WR-SY instrument (200 and 188 MHz, respectively). The chemical shifts (ppm) were referenced to HMDS as the internal standard and CF_3COOH as the external standard, respectively. The R_f values were determined using Merck TLC plates (60 F-254, 0.25 mm). The substances were purified by column chromatography on silica gel (Kieselgel 60, 0.063—0.200 mm) in mixtures of ethyl acetate with light petroleum.

Synthesis of compounds 3 (general procedure). Isobutylene (0.06 mol) was passed in a solution of imine **2** (0.02 mol) in 10 mL of CH_2Cl_2 at −30 °C. The reaction mixture was kept at −30 °C for 2 h and then warmed to ~20 °C. The solvent was removed *in vacuo*, and the residue was crystallized by trituration with hexane.

Methyl 4-methyl-2-methylsulfonylamino-2-trifluoromethylpent-4-enoate (3a). Yield 61%, m.p. 70—73 °C, R_f 0.26 (ethyl acetate : hexane, 1 : 3). ^1H NMR (acetone-d_6), δ: 7.01 (br.s, 1 H, NH); 4.97 (m, 1 H, $=CH_2$); 4.90 (m, 1 H, $=CH_2$); 3.81 (s, 3 H, OMe); 3.10 (s, 3 H, Me); 3.03, 2.79 (both d, AB system, 1 H each, CH_2, $^2J_{H,H}$ = 13.8 Hz); 1.80 (s, 3 H, Me). ^{19}F NMR (acetone-d_6), δ: 9.08 (s, CF_3). Found (%): C, 37.39; H, 4.62; N, 4.73. $C_9H_{14}F_3NO_4S$. Calculated (%): C, 37.37; H, 4.84; N, 4.84.

Methyl 4-methyl-2-phenylsulfonylamino-2-trifluoromethylpent-4-enoate (3b). Yield 65%, m.p. 75—78 °C, R_f 0.42 (ethyl acetate : hexane, 1 : 3). ^1H NMR (acetone-d_6), δ: 7.91 (m, 2 H, Ph); 7.61 (m, 3 H, Ph); 7.34 (s, 1 H, NH); 4.86 (m, 2 H, $=CH_2$); 3.75 (s, 3 H, OMe); 3.10 (s, 3 H, Me); 3.01, 2.70 (both d, AB system, 1 H each, CH_2, $^2J_{H,H}$ = 14.3 Hz); 1.70 (s, 3 H, Me). ^{19}F NMR (acetone-d_6), δ: 4.51 (s, CF_3). Found (%): C, 47.98; H, 4.72; N, 4.08. $C_{14}H_{16}F_3NO_4S$. Calculated (%): C, 47.86; H, 4.56; N, 3.98.

Synthesis of compounds 4—8 (general procedure). 2-Phenylpropene (or the corresponding methylidenecycloalkane) (14.4 mmol) was added to a solution of imine **2** (14.2 mmol) in 5 mL of CH_2Cl_2. The reaction mixture was kept at ~20 °C for 24 h, the solvent was removed *in vacuo*, and the product was purified by column chromatography in ethyl acetate : light petroleum (1 : 3).

Methyl 2-methylsulfonylamino-4-phenyl-2-trifluoromethylpent-4-enoate (4a). Yield 78%, pale yellow oil, R_f 0.35 (ethyl acetate : light petroleum, 1 : 3). ^1H NMR (acetone-d_6), δ: 7.39 (m, 5 H, Ph); 7.60 (s, 1 H, NH); 5.43 (m, 2 H, $=CH_2$); 3.45, 3.35 (both d, AB system, 1 H each, CH_2, $^2J_{H,H}$ = 14.3 Hz); 3.29 (s, 3 H, OMe); 2.97 (s, 3 H, Me). ^{19}F NMR (acetone-d_6), δ: 4.42 (s, CF_3). Found (%): C, 47.66; H, 4.41; N, 4.11. $C_{14}H_{16}F_3NO_4S$. Calculated (%): C, 47.86; H, 4.56; N, 3.98.

Methyl 4-phenyl-2-phenylsulfonylamino-2-trifluoromethylpent-4-enoate (4b). Yield 80%, m.p. 74—77 °C (from hexane), R_f 0.30 (ethyl acetate : light petroleum, 1 : 3). ^1H NMR ($CDCl_3$), δ: 7.61 (m, 10 H, 2 Ph); 5.82 (s, 1 H, NH); 5.51 (d, 2 H, $=CH_2$, $^2J_{H,H}$ = 25.62 Hz); 3.68, 3.37 (both d, AB system, 1 H each, CH_2, $^2J_{H,H}$ = 13.3 Hz); 3.27 (s, 3 H, OMe). ^{19}F NMR ($CDCl_3$), δ: 5.16 (s, CF_3). Found (%): C, 55.34; H, 4.50; N, 3.51. $C_{19}H_{18}F_3NO_4S$. Calculated (%): C, 55.20; H, 4.36; N, 3.39.

Methyl 3-(cyclopent-1-enyl)-2-methylsulfonylamino-2-trifluoromethylpropionate (5a). Yield 74%, m.p. 42—45 °C (from hexane), R_f 0.46 (ethyl acetate : light petroleum, 1 : 3). ^1H NMR ($CDCl_3$), δ: 5.77 (s, 1 H, NH); 5.63 (s, 1 H, =CH); 3.88 (s, 3 H, OMe); 3.31 (d, AB system, 1 H, CH_2, $^2J_{H,H}$ = 14.2 Hz); 3.11 (s, 3 H, Me); 2.90 (d, AB system, 1 H, CH_2); 2.30 (m, 4 H, 2 CH_2); 1.86 (m, 2 H, CH_2). ^{19}F NMR ($CDCl_3$), δ: 3.95 (s, CF_3). Found (%): C, 41.98; H, 4.92; N, 4.28. $C_{11}H_{16}F_3NO_4S$. Calculated (%): C, 41.90; H, 5.08; N, 4.44.

Methyl 3-(cyclopent-1-enyl)-2-phenylsulfonylamino-2-trifluoromethylpropionate (5b). Yield 85%, m.p. 88—90 °C (from hexane), R_f 0.54 (ethyl acetate : light petroleum, 1 : 3). ^1H NMR ($CDCl_3$), δ: 7.87 (m, 2 H, Ph); 7.51 (m, 3 H, Ph); 5.90 (s, 1 H,

NH); 5.57 (s, 1 H, =CH); 3.84 (s, 3 H, OMe); 3.42, 2.89 (both d, AB system, 1 H each, CH_2, $^2J_{H,H}$ = 14.3 Hz); 2.28 (m, 4 H, 2 CH_2); 1.81 (m, 2 H, CH_2). ^{19}F NMR ($CDCl_3$), δ: 4.04 (s, CF_3). Found (%): C, 51.07; H, 4.70; N, 3.68. $C_{16}H_{18}F_3NO_4S$. Calculated (%): C, 50.93; H, 4.77; N, 3.71.

Methyl 3-(cyclohex-1-enyl)-2-methylsulfonylamino-2-trifluoromethylpropionate (6a). Yield 65%, m.p. 42—45 °C (from hexane), R_f 0.46 (ethyl acetate : light petroleum, 1 : 3). ^1H NMR ($CDCl_3$), δ: 5.59 (s, 1 H, =CH); 5.37 (s, 1 H, NH); 3.80 (s, 3 H, OMe); 3.09 (s, 3 H, Me); 3.00, 2.62 (both d, AB system, 1 H each, CH_2, $^2J_{H,H}$ = 14.4 Hz); 1.96 (m, 3 H, CH_2); 1.87 (m, 1 H, CH_2); 1.50 (m, 4 H, CH_2). ^{19}F NMR ($CDCl_3$), δ: 5.66 (s, CF_3). Found (%): C, 43.57; H, 5.38; N, 4.38. $C_{12}H_{18}F_3NO_4S$. Calculated (%): C, 43.77; H, 5.47; N, 4.25.

Methyl 3-(cyclohex-1-enyl)-2-phenylsulfonylamino-2-trifluoromethylpropionate (6b). Yield 76%, m.p. 83—86 °C (from hexane), R_f 0.46 (ethyl acetate : light petroleum, 1 : 3). ^1H NMR ($CDCl_3$), δ: 7.77 (m, 2 H, Ph); 7.46 (m, 3 H, Ph); 5.69 (s, 1 H, =CH); 5.51 (s, 1 H, NH); 3.75 (s, 3 H, OMe); 3.10, 2.60 (both d, AB system, 1 H each, CH_2, $^2J_{H,H}$ = 14.2 Hz); 1.90 (m, 4 H, 2 CH_2); 1.49 (m, 4 H, 2 CH_2). ^{19}F NMR ($CDCl_3$), δ: 5.54 (s, CF_3). Found (%): C, 52.34; H, 5.32; N, 3.68. $C_{17}H_{20}F_3NO_4S$. Calculated (%): C, 52.17; H, 5.12; N, 3.58.

Methyl 3-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)-2-methylsulfonylamino-2-trifluoromethylpropionate (7a). Yield 79%, m.p. 98—100 °C (from hexane), R_f 0.42 (ethyl acetate : light petroleum, 1 : 3). ^1H NMR ($CDCl_3$), δ: 5.47 (s, 1 H, =CH); 5.30 (s, 1 H, NH); 3.23 (s, 3 H, OMe); 3.06 (s, 3 H, Me); 2.95, 2.68 (both d, AB system, 1 H each, CH_2, $^2J_{H,H}$ = 14.4 Hz); 2.31 (m, 1 H, CH_2); 2.20 (m, 2 H, CH_2); 1.88 (m, 2 H, CH_2); 1.20 (s, 3 H, Me); 1.05 (m, 1 H, CH_2); 0.76 (s, 3 H, Me). ^{19}F NMR ($CDCl_3$), δ: 5.66 (s, CF_3). Found (%): C, 48.91; H, 5.83; N, 3.77. $C_{15}H_{22}F_3NO_4S$. Calculated (%): C, 48.78; H, 5.96; N, 3.79.

Methyl 3-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)-2-phenylsulfonylamino-2-trifluoromethylpropionate (7b). Yield 84%, m.p. 94—96 °C (from hexane), R_f 0.36 (ethyl acetate : light petroleum, 1 : 5). ^1H NMR ($CDCl_3$), δ: 7.78 (m, 2 H, Ph); 7.42 (m, 3 H, Ph); 5.63 (s, 1 H, =CH); 5.41 (s, 1 H, NH); 3.75 (s, 3 H, OMe); 3.06, 2.67 (both d, AB system, 1 H each, CH_2, $^2J_{H,H}$ = 12.5 Hz); 2.33 (m, 1 H, CH_2); 2.17 (m, 2 H, CH_2); 2.00 (m, 2 H, CH_2); 1.19 (s, 3 H, Me); 1.03 (m, 1 H, CH_2); 0.77 (s, 3 H, Me). ^{19}F NMR ($CDCl_3$), δ: 5.79 (s, CF_3). Found (%): C, 55.72; H, 5.63; N, 3.18. $C_{20}H_{24}F_3NO_4S$. Calculated (%): C, 55.68; H, 5.57; N, 3.25.

Methyl 3-(bicyclo[2.2.1]hepta-2,5-dien-2-yl)-2-methylsulfonylamino-2-trifluoromethylpropionate (8a). Yield 68%, oil, R_f 0.50 (ethyl acetate : light petroleum, 1 : 4). ^1H NMR ($CDCl_3$), δ: 6.72 (m, 2 H, 2 =CH); 6.52 (s, 1 H, =CH); 5.37 (s, 1 H, NH); 3.84 (s, 3 H, OMe); 3.53 (br.s, 1 H, CH); 3.43 (d, AB system, 1 H, CH_2, $^2J_{H,H}$ = 14.5 Hz); 3.39 (br.s, 1 H, CH); 3.09 (s, 3 H, Me); 2.95 (d, AB system, 1 H, CH_2); 1.96 (m, 2 H, CH_2). ^{19}F NMR ($CDCl_3$), δ: 5.10 (s, CF_3). Found (%): C, 45.89; H, 4.59; N, 4.25. $C_{13}H_{16}F_3NO_4S$. Calculated (%): C, 46.02; H, 4.72; N, 4.13.

Methyl 3-(bicyclo[2.2.1]hepta-2,5-dien-2-yl)-2-phenylsulfonylamino-2-trifluoromethylpropionate (8b). Yield 71%, oil, R_f 0.38 (ethyl acetate : light petroleum, 1 : 5). ^1H NMR ($CDCl_3$), δ: 7.80 (m, 2 H, Ph); 7.41 (m, 3 H, Ph); 6.68 (m, 2 H, 2 =CH); 6.42 (s, 1 H, =CH); 5.67 (s, 1 H, NH); 3.73 (s, 3 H, OMe); 3.45 (d, AB system, 1 H, CH_2, $^2J_{H,H}$ = 15.6 Hz); 3.44 (br.s, 1 H, CH); 3.37 (br.s, 1 H, CH); 2.89 (d, AB system, 1 H, CH_2); 1.93 (m, 1 H, CH_2); 1.88 (m, 1 H, CH_2). ^{19}F NMR ($CDCl_3$), δ: 5.37 (s, CF_3). Found (%): C, 53.90; H, 4.61; N, 3.58. $C_{18}H_{18}F_3NO_4S$. Calculated (%): C, 53.86; H, 4.49; N, 3.49.

Synthesis of compounds 9—11 (general procedure). A mixture of benzenesulfonylimine **2b** (5.8 mmol) and an alkene (15.5 mmol) was heated in a sealed tube at 80 °C for 24 h (at 100 °C for **9b** and **9c**). The volatile components were removed *in vacuo*, and the product was purified by column chromatography.

Methyl (*E*)-6-bromo-2-phenylsulfonylamino-2-trifluoromethylhex-4-enoate (9). Yield 68%, oil, R_f 0.39 (ethyl acetate : light petroleum, 1 : 5). ^1H NMR (acetone-d_6): 7.93 (m, 2 H, Ph); 7.60 (m, 3 H, Ph); 7.51 (s, 1 H, NH); 5.81 (dt, 2 H, CH=CH, J_{trans} = 15.1 Hz, ^3J = 6.4 Hz); 3.99 (d, 2 H, $BrCH_2$, $^3J_{H,H}$ = 5.4 Hz); 3.74 (s, 3 H, OMe); 2.93 (m, 2 H, CH_2). ^{19}F NMR (acetone-d_6), δ: 5.61 (s, CF_3). Found (%): C, 39.15; H, 3.58; N, 3.42. $C_{14}H_{15}BrF_3NO_4S$. Calculated (%): C, 39.07; H, 3.49; N, 3.25.

Methyl 2-phenylsulfonylamino-(*E*)-2-trifluoromethyloct-4-enoate (10). Yield 87%, m.p. 44—45 °C (from hexane), R_f 0.29 (ethyl acetate : light petroleum, 1 : 5). ^1H NMR (acetone-d_6): 7.91 (m, 2 H, Ph); 7.61 (m, 3 H, Ph); 7.41 (s, 1 H, NH); 5.61 (dt, 1 H, =CH, J_{trans} = 16.1 Hz, ^3J = 5.8 Hz); 5.35 (dt, 1 H, =CH, ^3J = 5.8 Hz); 3.70 (s, 3 H, OMe); 2.86 (m, 2 H, CH_2); 1.90 (m, 2 H, CH_2); 1.31 (m, 2 H, CH_2); 0.84 (m, 3 H, Me). ^{19}F NMR (acetone-d_6), δ: 4.63 (s, CF_3). Found (%): C, 50.91; H, 4.98; N, 3.75. $C_{16}H_{20}F_3NO_4S$. Calculated (%): C, 50.65; H, 5.27; N, 3.69.

Methyl 2-phenylsulfonylamino-(*E*)-2-trifluoromethyldec-4-enoate (11). Yield 81%, oil, R_f 0.43 (ethyl acetate : light petroleum, 1 : 6). ^1H NMR (acetone-d_6): 7.91 (m, 2 H, Ph); 7.61 (m, 3 H, Ph); 7.40 (s, 1 H, NH); 5.61 (dt, 1 H, =CH, J_{trans} = 17.3 Hz, ^3J = 6.4 Hz); 5.35 (dt, 1 H, =CH, ^3J = 6.4 Hz); 3.72 (s, 3 H, OMe); 2.86 (m, 2 H, CH_2); 1.95 (m, 2 H, CH_2); 1.31 (m, 6 H, 3 × CH_2); 0.87 (m, 3 H, Me). ^{19}F NMR (acetone-d_6), δ: 4.64 (s, CF_3). Found (%): C, 53.18; H, 5.95; N, 3.34. $C_{18}H_{24}F_3NO_4S$. Calculated (%): C, 53.07; H, 5.89; N, 3.44.

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