Addition reactions of 1,1,1-trifluoro-4-trimethylstannylbut-3-yn-2-one and 1,1,1-trifluorobut-3-yn-2-one to some tetrahydropyridines. Synthesis of trifluoroacylated polysubstituted tetrahydroazocines

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A reaction of tetrahydropyridines, obtained by the Diels—Alder reaction from α,β-unsaturated *N*,*N*-dimethylhydrazones and methyl acrylate, with acetylenes activated with the trifluoroacetyl group has been studied and found to lead to polysubstituted trifluoroacylated tetrahydroazocines. No cyclobutene intermediates have been detected.

Key words: trifluoroacetylacetylenes, tetrahydropyridines, [2+2] cycloaddition, ring expansion, tetrahydroazocines.

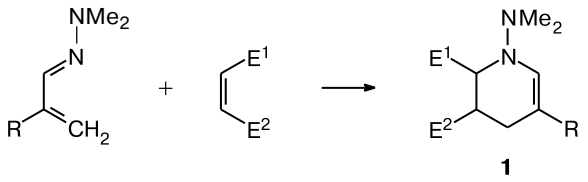
Cycloaddition of *N*,*N*-disubstituted enamines to electron-withdrawing acetylenes is known already for more than 40 years and serves as a general method for the synthesis of cyclobutenes.[1,2] The latter readily undergo thermal ring opening with the formation of 1,3-dienes,[2,3] with the arising long chain of conjugation involving the unshared pair of electrons on the nitrogen atom and π-electrons of the C=C and C=O bonds being a driving force of the process. In the case of enamines of cyclic ketones, this transformation is a standard method for the ring expansion by two carbon atoms.[4—6]

Tetrahydropyridines containing an activating nitrogen atom in the ring give this reaction as well, which depending on the reaction conditions and the nature of reagents leads to the corresponding [2+2]-cycloadducts or products of their thermal ring opening, *viz,*, substituted tetrahydroazocines.[7—9]

Despite that this transformation is one of the principal methods for the construction of eight-membered nitrogen-containing heterocycles, it is used relatively seldom because of two significant restrictions. The first is related to poor availability and often low stability of tetrahydropyridines, the second, to very narrow scope of the electron-withdrawing acetylenes used: thus, in all the transformations described only acetylenedicarboxylic and propiolic esters have been studied.

Earlier, we have developed a general method for the synthesis of α-substituted acroleine dimethylhydrazones,[10] then it was found[11] that they are active 1-azadienes in the Diels—Alder reaction and readily add acrylonitrile, methyl acrylate, and other dienophiles to form stable tetrahydropyridines **1** (Scheme 1).

Scheme 1



1

R = H, Alk, —$(CH_2)_nCH(OEt)_2$, —SAlk, —$SiMe_3$
E^1 = COOMe, CN, COMe; E^2 = COOMe, CN, H

Reaction of some of them (**1a—c**, Scheme 2) with activated acetylenes was studied in the present work. Recently synthesized[12] 1,1,1-trifluoro-4-trimethylstannylbut-3-yn-2-one (**2a**) and 1,1,1-trifluorobut-3-yn-2-one (**2b**) were used as acetylenes. It should be noted that in the literature, no cycloaddition reactions of trifluoroacetylacetylenes to enamines are described, and accomplishment of such transformation opens access to the earlier unknown trifluoroacylated polysubstituted tetrahydroazocines, having a character of macrocyclic trifluoromethyleneaminoketones, which are of great interest for biochemistry and medicine[13,14] and as new polyfunctional reagents.[15]

Initially, it was found that upon mixing acetylene **2a** with tetrahydropyridines **1a—c** in acetonitrile or tetrahydrofuran at 20 °C, the solution gradually acquires a yellowish orange color, however, according to the ^{1}H NMR spectroscopic data (CD_3CN, 4 h, 20 °C) no reaction takes place under such conditions and the coloring apparently is due to the equilibrium formation of unstable π-complexes. However, reflux of the reagents in the

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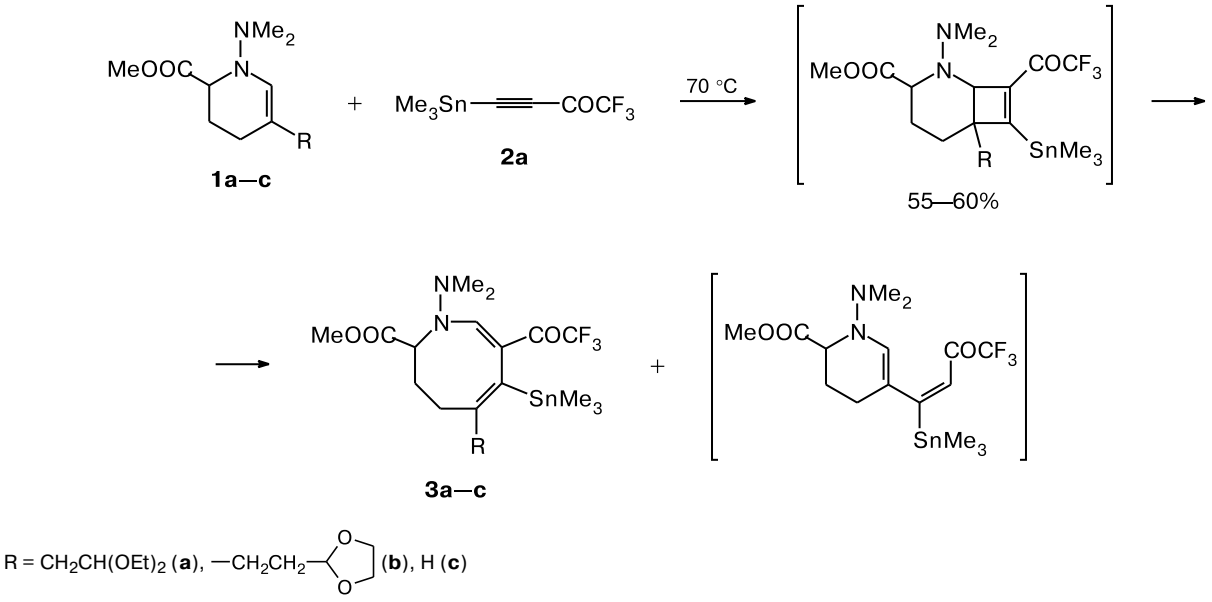
Scheme 2

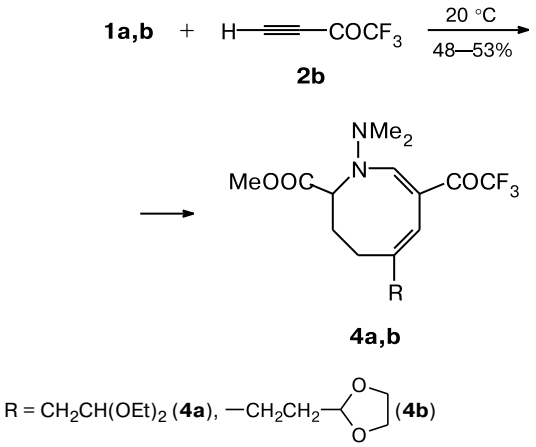


THF—acetonitrile = 2 : 1 mixture leads to the completion of the process after 6—8 h and directly yields tetrahydroazocines **3a—c** (Scheme 2). The latter are reddish orange crystalline compounds, easily isolated by crystallization. In the case of enamine **1c**, about 20% of the ene addition product was also detected in the reaction mixture, attempted isolation of which in the pure form failed. It is obvious that this product is formed in the competing proton transfer in the zwitterionic intermediate, which is possible only if R = H in the starting tetrahydropyridines **1**. Note that no intermediately formed [2+2] cycloadducts were found even in trace amounts.

It should be noted that in heterocycles **3**, there is present a chain of conjugation N—C=C—$COCF_3$ of the push-pull type, in which the unshared pair of electrons on the nitrogen atom in the ring is significantly redistributed to the oxygen atom of the carbonyl group (it is obvious that if the reverse polarity of addition occurs, the trifluoroacetyl and trimethylstannyl substituents would have exchanged their places, which would have lead for this effect to disappear). As a result, in the ^{1}H NMR spectra of azocines **3** the signals for the protons HC(2), HC(8), and $(CH_3)_2N$ are found in the lower fields by 0.5—0.6 ppm, for example, as compared to the protons HC(2), HC(6), and $(CH_3)_2N$ in compounds **1**, which have no trifluoroacetyl group in the chain of conjugation. The same effect causes the signal of the carbon atom N—C=C in the ^{13}C NMR spectra of azocines **3** to be downfield shifted by 30—40 ppm as compared with the same atom in tetrahydropyridines **1**.

It is known that monosubstituted acetylene **2b** is much more active in the Diels—Alder processes[16] than derivative **2a** and already at 20 °C can be slowly involved into the ene reaction with isobutylene and methylenecyclohexane (see Ref. 12). High electrophilic activity of **2b** allowed us to suggest that its addition to tetrahydropyridines **1a—c** would proceed under milder conditions as compared to **2a** and isolation of the [2+2] cycloaddition products would be possible. In fact, we found that this reaction rapidly comes to completion already at 20 °C (in the concentrated solutions, a noticeable exothermicity is observed), however, enamine **1c** yields a complex unseparable mixture of products. Addition to derivatives **1a,b** leads to the corresponding tetrahydroazocines **4a,b** in good yields (Scheme 3), and, as in the preceding series of transformations, no cyclobutene intermediates were isolated or detected spectroscopically

Scheme 3



either. Apparently, their instability even under mild conditions can be explained by the high energy of conjugation of powerful electron-withdrawing trifluoroacetyl group with the π-electron system of the dieneamine.

Apparently, this method opens wide possibilities for the synthesis of trifluoroacylated polysubstituted tetrahydroazocines from cycloadducts **1** formed not only from acrylic acid derivatives, but maleic, fumaric, and other dienophiles as well. Probably, hydrogenolysis of the N—N bond is also very promising, as well as various cross-coupling reactions at the C—$SnMe_3$ bond in heterocycles **3a—c**.

Experimental

Tetrahydropyridines **1a—c** were obtained by cycloaddition of methyl acrylate to the corresponding α,β-unsaturated dimethylhydrazones,[11] 1,1,1-trifluoro-4-trimethylstannylbut-3-yn-2-one (**2a**), and 1,1,1-trifluorobut-3-yn-2-one (**2b**) were synthesized according to the known procedures.[12,16] Synthesis of azocines **3a—c** was carried out under argon. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer (400 MHz (^1H) and 100 MHz (^{13}C)) in $CDCl_3$. IR spectra were recorded on a Bruker IFS 25 spectrometer in Nujol.

Synthesis of tetrahydroazocines (3a—c) (general procedure). A solution of tetrahydropyridine **1a—c** (0.002 mol) and acetylene **2a** (0.57 g, 0.002 mol) in a mixture of anhydrous tetrahydrofuran (6 mL) and acetonitrile (3 mL) was refluxed for 6—8 h under argon. The solvent was evaporated *in vacuo*, the residue was diluted with cold hexane (10 mL) and the mixture was kept for 12 h at 0 °C. A crystalline precipitate was washed on the filter with cold hexane and recrystallized from hexane—toluene (4 : 1).

Methyl 5-(2,2-diethoxyethyl)-7-(trifluoroacetyl)-1-(dimethylamino)-6-(trimethylstannyl)-1,2,3,4-tetrahydroazocine-2-carboxylate (3a). The yield was 0.64 g (55%), orange crystals, m.p. 89—90 °C. Found (%): C, 45.41; H, 6.54; N, 4.60. $C_{22}H_{37}F_3N_2O_5Sn$. Calculated (%): C, 45.15; H, 6.37; N, 4.79. IR, ν/cm^{-1}: 1665, 1628, 1596 (C=O, C=C); 1270 (CF_3). ^1H NMR, δ: 0.21 (s, 9 H, Me_3Sn); 1.18 (t, 6 H, C<u>H</u>$_3$CH$_2$O, J = 7.2 Hz); 1.96—2.30 (m, 4 H, —CH_2CH_2—); 2.43 (d, 2 H, C<u>H</u>$_2$CH(OEt)$_2$, J = 5.6 Hz); 2.69 (s, 6 H, Me_2N); 3.51, 3.66 (both m, 4 H, 2 CH$_3$C<u>H</u>$_2$O); 3.75 (s, 3 H, MeO); 4.33 (dd, 1 H, N—CH—CO, J = 8.2 Hz, J = 3.6 Hz); 4.45 (t, 1 H, C<u>H</u>(OEt)$_2$, J = 5. Hz); 6.49 (s, 1 H, H—C=C). ^{13}C NMR, δ: –7.2 (Me_3Sn); 14.9 (2 C<u>H</u>$_3$CH$_2$O); 26.5, 28.4, 35.0 (—CH_2CH_2—, C<u>H</u>$_2$CH(OEt)$_2$); 44.9 (Me_2N); 59.8, 59.9 (2 CH$_3$C<u>H</u>$_2$O); 61.9 (MeO); 64.4 (N—C<u>H</u>—CO); 102.4 (C<u>H</u>(OEt)$_2$); 112.7 (N—C=C); 116.1 (q, CF_3, $J_{C,F}$ = 290 Hz); 124.6 (Sn—C=C); 128.7 (Sn—C=C); 165.7 (N—C=C); 170.3 (q, C=O, $J_{C,F}$ = 38 Hz); 177.6 (COO).

Methyl 7-(trifluoroacetyl)-1-(dimethylamino)-6-(trimethylstannyl)-5-[2-(1,3-dioxolan-2-yl)ethyl]-1,2,3,4-tetrahydroazocine-2-carboxylate (3b). The yield was 0.68 g (60%), orange crystals, m.p. 125—126 °C. Found (%): C, 44.54; H, 5.90; N, 4.86. $C_{21}H_{33}F_3N_2O_5Sn$. Calculated (%): C, 44.31; H, 5.84; N, 4.92. IR, ν/cm^{-1}: 1667, 1628, 1595 (C=O, C=C); 1270 (CF_3). ^1H NMR, δ: 0.24 (s, 9 H, Me_3Sn); 1.77—1.90 (m, 4 H, —CH_2CH_2—); 1.94—2.28 (m, 4 H, —CH_2CH_2—); 2.70 (s, 6 H, Me_2N); 3.73 (s, 3 H, MeO); 3.84, 3.96 (both m, 4 H, —OCH_2CH_2O—); 4.28 (dd, 1 H, N—CH—CO, J = 8.2 Hz J = 3.4 Hz); 4.80 (t, 1 H, O—CH—O, J = 5.1 Hz); 6.55 (s, 1 H, H—C=C). ^{13}C NMR, δ: –8.0 (Me_3Sn); 22.5, 26.9, 29.0, 36.2 (4 CH_2); 44.1 (Me_2N); 62.0 (MeO); 63.9 (N—<u>CH</u>—CO); 66.7 (—OCH_2CH_2O—); 104.7 (O—CH—O);, 110.8 (N—C=<u>C</u>); 117.0 (q, CF_3, $J_{C,F}$ = 290 Hz); 123.6 (Sn—C=<u>C</u>); 127.2 (Sn—<u>C</u>=C); 164.4 (N—<u>C</u>=C); 172.3 (q, C=O, $J_{C,F}$ = 38 Hz); 175.5 (COO).

Methyl 7-(trifluoroacetyl)-1-(dimethylamino)-6-(trimethylstannyl)-1,2,3,4-tetrahydroazocine-2-carboxylate (3c). The yield was 0.50 g (54%), orange crystals, m.p. 72—73 °C. Found (%): C, 41.19; H, 5.30; N, 5.77. $C_{16}H_{25}F_3N_2O_3Sn$. Calculated (%): C, 40.97; H, 5.37; N, 5.97. IR, ν/cm^{-1}: 1671, 1629, 1599 (C=O, C=C); 1274 (CF_3). ^1H NMR, δ: 0.19 (s, 9 H, Me_3Sn); 1.94—2.27 (m, 4 H, —CH_2CH_2—); 2.66 (s, 6 H, Me_2N); 3.71 (s, 3 H, MeO); 4.34 (dd, 1 H, N—CH—CO, J = 8.0 Hz, J = 3.5 Hz); 5.38 (m, 1 H, CH=C—Sn); 6.59 (s, 1 H, N—CH=C). ^{13}C NMR, δ: –6.5 (Me_3Sn); 24.6, 29.9 (—CH_2CH_2—); 46.4 (Me_2N); 61.8 (MeO); 63.6 (N—<u>C</u>H—CO); 112.7 (N—C=<u>C</u>); 117.4 (q, CF_3, $J_{C,F}$ = 290 Hz); 120.1 (Sn—C=<u>C</u>); 127.2 (Sn—<u>C</u>=C); 167.3 (N—<u>C</u>=C); 171.1 (q, C=O, $J_{C,F}$ = 38 Hz); 173.8 (COO).

Synthesis of tetrahydroazocines (4a,b) (general procedure). A solution of acetylene **2b** (0.25 g, 0.002 mol) in tetrahydrofuran (2 mL) was added dropwise to a stirred solution of tetrahydropyridine **1a,b** (0.002 mol) in anhydrous tetrahydrofuran (10 mL) at 0 °C, the stirring was continued for another 4 h at 20 °C. The solvent was evaporated *in vacuo*, the residue was subjected to column chromatography (silica gel, ethyl acetate—hexane (1 : 1)).

Methyl 5-(2,2-diethoxyethyl)-7-(trifluoroacetyl)-1-(dimethylamino)-1,2,3,4-tetrahydroazocine-2-carboxylate (4a). The yield was 0.42 g (50%), R_f 0.55, orange crystals, m.p. 38—39 °C. Found (%): C, 54.19; H, 7.08; F, 13.43; N, 6.60. $C_{19}H_{29}F_3N_2O_5$. Calculated (%): C, 54.02; H, 6.92; F, 13.49; N, 6.63. IR, ν/cm^{-1}: 1664, 1621, 1597 (C=O, C=C); 1270 (CF_3). ^1H NMR, δ: 1.12 (t, 6 H, C<u>H</u>$_3$CH$_2$O, J = 7.1 Hz); 1.99—2.32 (m, 4 H, —CH_2CH_2—); 2.42 (d, 2 H, C<u>H</u>$_2$CH(OEt)$_2$, J = 5.6 Hz); 2.75 (s, 6 H, Me_2N); 3.55, 3.65 (both m, 4 H, 2 CH$_3$C<u>H</u>$_2$O); 3.77 (s, 3 H, MeO); 4.35 (dd, 1 H, N—CH—CO, J = 8.6 Hz, J = 3.3 Hz); 4.49 (t, 1 H, C<u>H</u>(OEt)$_2$, J = 5.6 Hz); 5.70 (s, 1 H, H—C=C); 6.58 (s, 1 H, N—CH=C). ^{13}C NMR, δ: 15.9 (2 C<u>H</u>$_3$CH$_2$O); 25.0, 28.1, 38.8 (—CH_2CH_2—, C<u>H</u>$_2$CH(OEt)$_2$); 46.6 (Me_2N); 60.7, 60.8 (2 CH$_3$C<u>H</u>$_2$O); 62.7 (MeO); 65.0 (N—C<u>H</u>—CO); 104.4 (C<u>H</u>(OEt)$_2$); 114.0 (N—C=<u>C</u>); 116.8 (q, CF_3, $J_{C,F}$ = 290 Hz); 121.5, 132.4 (C=C); 168.0 (N—<u>C</u>=C); 171.6 (q, C=O, $J_{C,F}$ = 38 Hz); 176.2 (COO).

Methyl 7-(trifluoroacetyl)-1-(dimethylamino)-5-[2-(1,3-dioxolan-2-yl)ethyl]-1,2,3,4-tetrahydroazocine-2-carboxylate (4b). The yield was 0.47 g (58%), R_f 0.45, orange crystals, m.p. 61—62 °C. Found (%): C, 53.36; H, 6.28; F, 13.90; N, 6.60. $C_{18}H_{25}F_3N_2O_5$. Calculated (%): C, 53.20; H, 6.20; F, 14.03; N, 6.44. IR, ν/cm^{-1}: 1662, 1620, 1600 (C=O, C=C); 1270 (CF_3). ^1H NMR, δ: 1.80—1.96 (m, 4 H, —CH_2CH_2—); 2.02—2.30 (m, 4 H, —CH_2CH_2—); 2.67 (s, 6 H, Me_2N); 3.70 (s, 3 H, MeO); 3.84, 3.94 (both m, 4 H, —OCH_2CH_2O—); 4.33 (dd, 1 H, N—CH—CO, J = 8.6 Hz, J = 3.3 Hz); 4.82 (t, 1 H, O—CH—O, J = 5.1 Hz); 5.57 (s, 1 H, H—C=C); 6.64 (s, 1 H, N—CH=C). ^{13}C NMR, δ: 23.1, 27.5, 29.5, 39.2 (4 CH_2); 46.2 (Me_2N); 62.3 (MeO); 64.6 (N—<u>C</u>H—CO); 68.0 (—OCH_2CH_2O—); 105.3 (O—CH—O); 111.8 (N—C=<u>C</u>); 117.0 (q, CF_3, $J_{C,F}$ = 290 Hz); 125.2, 133.2 (C=C); 166.7 (N—<u>C</u>=C); 171.4 (q, C=O, $J_{C,F}$ = 38 Hz); 175.0 (COO).

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