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FIRST EXAMPLE OF THE SYNTHESIS OF PYRROLO[1,2-*d*][1,4]DIAZOCINE BY THE REACTION OF TETRAHYDRO-PYRROLO[1,2-*a*]PYRAZINES WITH ACTIVATED ALKYNES

L. G. Voskresensky[1], T. N. Borisova[1], T. M. Kamalitdinova[1], V. I. Terenin[2], A. A. Titov[1], and A. V. Varlamov[1]

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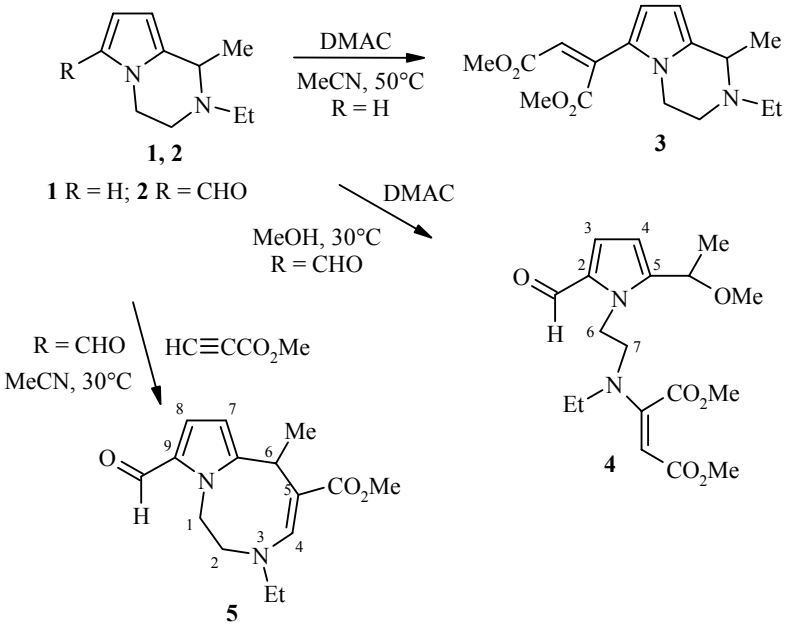
The tandem reaction of 4,5,7-trimethyl-4,5,6,7-tetrahydropyrrolo[3,2-*c*]pyridine and its 2-formyl derivative with dimethyl acetylenedicarboxylate (DMAC) and methyl propiolate in acetonitrile and THF gives a mixtures of the corresponding 2-[N-methoxycarbonyl(dimethoxycarbonyl)vinyl]aminoethyl-3-vinylpyrroles and 4,7,9-trimethyl-4,7,8,9-tetrahydro-5-methoxycarbonyl(5,6-dimethoxycarbonyl)pyrrolo[2,3-*d*]azocines, which are the products of the dissociation and expansion of the tetrahydropyridine ring. The reaction with alkynes



[1]Russian Peoples' Friendship University, Moscow 117198, Russia; e-mail: lvoskressensky@sci.pfu.edu.ru. [2]M. V. Lomonosov Moscow State University, Moscow 119992, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 793-795, May, 2008. Original article submitted February 26, 2008.

in methanol leads exclusively to clevage of the tetrahydropyridine fragment of the starting molecule to form a mixture of diastereomeric 3-methoxyethyl-2-[N-methoxycarbonyl(dimethoxycarbonyl)vinyl-N-methylamino]-ethylpyrroles [1,2].

2,3,5-Trimethyl-7-trifluoroacyl-1,2,3,4-tetrahydropyrrolo[1,2-*c*]pyrimidine, which has different fusion of the pyrrole and tetrahydropyridine fragments, reacts with the same alkynes in both acetonitrile and methanol to give only clevage of the tetrahydropyridine ring, leading to formation of substituted pyrroles [3]. Hence, it was of interest to study the behavior of tetrahydropyrrolo[1,2-*a*]pyrazine **1** and its 6-formyl derivative **2** under tandem reaction conditions. These pyrrolopyrazines differ from the two systems mentioned above in the fusion of the azole and azine fragments.

DMAC vinylates **1** in acetonitrile at reflux at the α-position of the pyrrole fragment to give 6-vinylpyrrolopyrazine **3**, which is a 1:1 mixture of *Z*- and *E*- isomers relative to the vinyl group as indicated by ^{1}H NMR spectroscopy. DMAC does not react with formyl derivative **2** in acetonitrile even upon prolonged heating at reflux. A reaction occurs in methanol at 30°C over a week to give 2-methoxyethylpyrrole **4**. The reaction of methyl propiolate with pyrrolopyrazine **2** in acetonitrile proceeds at 30°C over seven days to give a mixture, which yielded the first representative of a new heterocyclic system, namely, pyrrolo-[1,2-*d*][1,4]diazocine **5**. Considerable tar formation was noted in all the reactions of pyrrolopyrazines **1** and **2.**

The ^{1}H NMR spectra were taken on a Bruker WP-400 spectrometer (400 MHz) in $CDCl_3$ with TMS as the internal standard. The IR spectra were taken on a INFRALUM FT-801 Fourier transform spectrometer for KBr pellets. The mass spectra were taken on a Finnigan MAT 95 XL GC/MS with direct inlet of the sample into the ion source with 70 eV ionization energy.

Reaction of Pyrrolopyrazines 1 and 2 with Activated Alkynes (General Method). DMAC (6.0 mmol) or methyl propiolate was added to a solution of pyrrolopyrazine **1** or **2** (2.4 mmol) in methanol or acetonitrile (20 ml). The reaction was carried out either at 50° or 30°C. The reaction course was monitored by thin-layer chromatography. The solvent was distilled off. Azocine **5** was isolated by crystallization of the residue from hexane–ethyl acetate. Esters **3** and **4** were isolated from the reaction mixtures by chromatography on an alumina column using 1:10-1:3 ethyl acetate as the eluent.

Dimethyl 2-(2-ethyl-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-6-yl)but-2-enedioate (3) was obtained in 36% yield as a yellow oil, R_f 0.15 (Alufol, 1:3 ethyl acetate–hexane). IR spectrum, ν, cm^{-1}: 1735 (CO). Ratio 1:1. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.08 (3H, t, *J* = 7.2, C<u>H</u>$_3$CH$_2$); 1.12 (3H, t, *J* = 7.2, C<u>H</u>$_3$CH$_2$); 1.39 (3H, d, *J* = 6.7, 1-CH$_3$); 1.42 (3H, d, *J* = 6.7, 1-CH$_3$); 2.52 (1H, m, C<u>H</u>$_2$CH$_3$); 2.70 (1H, m, CH$_2$); 2.88 (1H, m, C<u>H</u>$_2$CH$_3$); 3.16 (1H, m, CH$_2$); 3.66 (3H, s, OCH$_3$); 3.70 (1H, m, C<u>H</u>–H$_3$); 3.73 (3H, s, OCH$_3$); 3.75 (1H, m, CH$_2$); 3.80 (3H, s, OCH$_3$); 3.96 (3H, s, OCH$_3$); 4.05 (1H, m, CH$_2$); 5.85 (1H, s, –CH=); 5.92 (1H, d, *J* = 3.7, H-8); 5.97 (1H, d, *J* = 4.1, H-8); 6.25 (1H, d, *J* = 3.7, H-7); 6.41 (1H, d, *J* = 4.1, H-7); 6.86 (1H, s, CH=). Found, %: C 62.48; H 7.30; N 9.25. M$^+$ 306. $C_{16}H_{22}N_2O_4$. Calculated, %: C 62.75; H 7.19; N 9.15. M 306.

Dimethyl 2-(ethyl{2-[2-formyl-5-(1-methoxyethyl)-1H-pyrrol-1-yl]ethyl}amino)but-2-enedioate (4) was obtained in 47% yield as a yellow oil. R_f 0.82 (Silufol, 20:1 2-propanol–ammonia). IR spectrum, ν, cm^{-1}: 1737 (CO), 1655 (CHO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10 (3H, t, *J* = 7.0, C<u>H</u>$_3$CH$_2$N); 1.54 (3H, d, *J* = 6.5, C<u>H</u>$_3$CH); 3.04-3.13 (1H, m, 7-CH$_2$); 3.15-3.22 (1H, m, 7-CH$_2$); 3.30 (3H, m, OCH$_3$); 3.39-3.48 (2H, m, N–C<u>H</u>$_2$CH$_3$); 3.65 (3H, s, OCH$_3$); 3.95 (3H, s, OCH$_3$); 4.41-4.52 (2H, m, 6-CH$_2$); 4.59 (1H, q, *J* = 6.5, C<u>H</u>-OCH$_3$); 4.84 (1H, br. s, <u>H</u>C=C); 6.23 (1H, d, *J* = 4.1, H-4); 6.93 (1H, d, *J* = 4.1, H-3); 9.49 (1H, s, CHO). Found, %: C 59.18; H 6.92; N 7.80. M$^+$ 366. $C_{18}H_{26}N_2O_6$. Calculated, %: C 59.02; H 7.10; N 7.65. M 366.

Methyl 3-ethyl-9-formyl-6-methyl-1,2,3,6-tetrahydropyrrolo[1,2-*d*][1,4]diazocine-5-carboxylate (5) was obtained in 11% yield; mp 104-106°C, R_f 0.73 (Silufol, ethyl acetate). IR spectrum, ν, cm^{-1}: 1716 (CO), 1656 (CHO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10 (3H, t, *J* = 7.0, C<u>H</u>$_3$CH$_2$); 1.53 (3H, d, *J* = 7.4, 6-CH$_3$); 3.17-3.29 (2H, m, N–C<u>H</u>$_2$CH$_3$); 3.68 (3H, s, OCH$_3$); 3.74 (1H, dt, *J* = 4.5, *J* = 15.6, 2-CH$_2$); 3.84 (1H, ddd, *J* = 4.5, *J* = 11.4, *J* = 15.4, 1-CH$_2$); 4.44 (1H, dt, *J* = 4.5, *J* = 15.6, 2-CH$_2$); 4.68 (1H, q, *J* = 7.4, H-6); 5.34-5.42 (1H, m, 1-CH$_2$); 6.05 (1H, d, *J* = 4.0, H-7); 6.85 (1H, d, *J* = 4.0, H-8); 7.52 (1H, s, H-4); 9.36 (1H, s, CHO).

Found, %: C 65.11; H 7.31; N 10.20. M^+ 276. $C_{15}H_{20}N_2O_3$. Calculated, %: C 65.22; H 7.25; N 10.14. M 276.

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