ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 12, pp. 1851–1855. © Pleiades Publishing, Inc., 2006.
Original Russian Text © L.G. Voskresenskii, T.N. Borisova, T.A. Vorob'eva, O.V. Grishachkina, L.N. Kulikova, A.I. Chernyshev, A.V. Varlamov, 2006, published in Zhurnal Organicheskoi Khimii, 2006, Vol. 42, No. 12, pp. 1860–1864.

# Transformations of 2-Trifluoroacetyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridines by the Action of Ethyl Propynoate. A Novel Synthesis of 2-Trifluoroacetyl-4,7,8,9-tetrahydro-1*H*-pyrrolo[2,3-*d*]azocines

**L. G. Voskresenskii, T. N. Borisova, T. A. Vorob'eva, O. V. Grishachkina, L. N. Kulikova, A. I. Chernyshev, and A. V. Varlamov**

*Russian University of Peoples' Friendship, ul. Miklukho-Maklaya 6, Moscow, 117198 Russia*
*e-mail: lvoskressensky@sci.pfu.edu.ru*

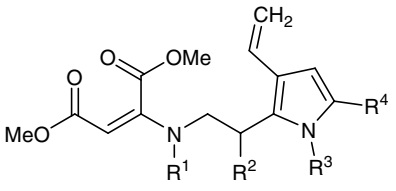
Received February 20, 2006

**Abstract**—2-Trifluoroacetyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridines reacted with ethyl propynoate in acetonitrile and methanol to give ethyl 2-trifluoroaceyl-4,7,8,9-tetrahydro-1*H*-pyrrolo[2,3-*d*]azocine-5-carboxylates. The reactions of 2-trifluoroacetyl-1-vinyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridines with ethyl propynoate in alcohols were accompanied by cleavage of the tetrahydropyridine fragment with formation of alkyl 3-{benzyl[2-(3-alkoxy-5-trifluoroacetyl-1-vinyl-1*H*-pyrrol-2-yl)ethyl]amino}acrylates.

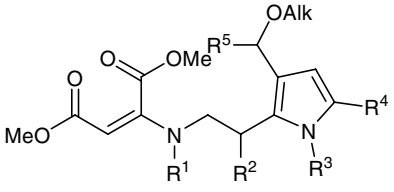
**DOI:** 10.1134/S1070428006120165

We recently showed for the first time that tandem transformations in reactions of 4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridines with dimethyl acetylenedicarboxylate in various solvents could give rise to 3-vinylpyrroles like **A** [1], 3-alkoxy(hydroxy)alkylpyrroles like **B** [2], and tetrahydropyrrolo[2,3-*d*]azocines like **C** [3]. Analogous tandem transformations of the tetrahydropyridine fragment were observed in the reactions of tetrahydro-γ- and β-carbolines (which may be regarded as benzo-fused analogs of tetrahydropyrrolopyridines) with dimethyl acetylenedicarboxylate and ethyl propynoate. γ-Carbolines reacted with dimethyl acetylenedicarboxylate and ethyl propynoate in alcohols to afford 3-alkoxymethylindoles like **B**, while β-carbolines reacted with ethyl propynoate in ethanol, yielding tetrahydroazocino[5,4-*b*]indoles **D** [4].

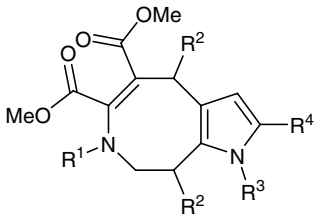
The present study was aimed at elucidating general relations holding in tandem transformations of fused tetrahydropyridines with activated alkynes. For this purpose, we examined reactions of 2-trifluoroacetyl-substituted 4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridines with ethyl propynoate in MeCN and MeOH.



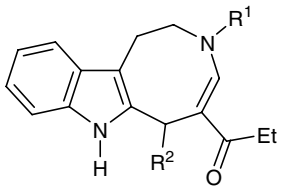

**A**




**B**

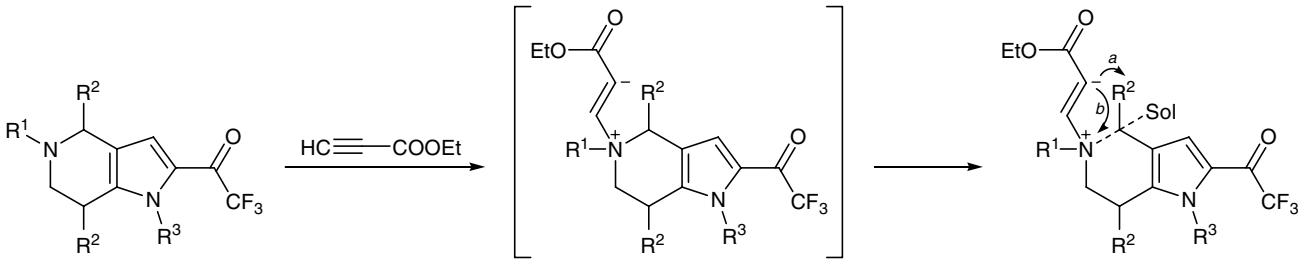



**C**



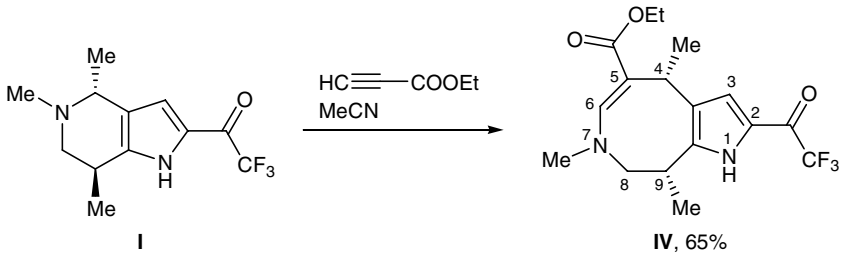

**D**

**Scheme 1.**



**I**, $R^1 = R^2 = Me$, $R^3 = H$; **II**, $R^1 = PhCH_2$, $R^2 = R^3 = H$; **III**, $R^1 = PhCH_2$, $R^2 = H$, $R^3 = CH_2{=}CH$.

**Scheme 2.**



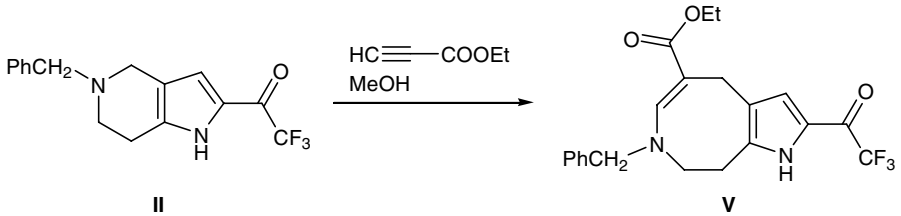
4,5,7-Trimethyl-2-trifluoroacetyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine (**I**), 5-benzyl-2-trifluoroacetyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine (**II**), and 5-benzyl-2-trifluoroacetyl-1-vinyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine (**III**) were synthesized by trifluoroacetylation of the corresponding tetrahydropyrrolo[3,2-*c*]pyridines which were prepared in turn by heterocyclization of piperidin-4-one oximes with acetylene according to Trofimov [5].

The reaction of tetrahydropyrrolopyridines **I**–**III** with ethyl propynoate, as well as with dimethyl acetylenedicarboxylate, begins with formation of zwitterion **E** as a result of addition of the tertiary $sp^3$-hybridized nitrogen atom at the triple bond (Scheme 1). Further transformation pathways of this intermediate depend on the reactivity of the anionic center, effects of the substituents at the pyrrole nitrogen atom and in the tetrahydropyridine fragment, and polarity and nucleophilicity of the solvent. In all cases, ethyl propynoate turned out to be more reactive than dimethyl acetylenedicarboxylate. The reason is that the negative charge in intermediate zwitterion **E** is less delocalized; therefore, the anionic center is more reactive than in the corresponding intermediate derived from dimethyl acetylenedicarboxylate, where two methoxycarbonyl groups are involved in charge delocalization.

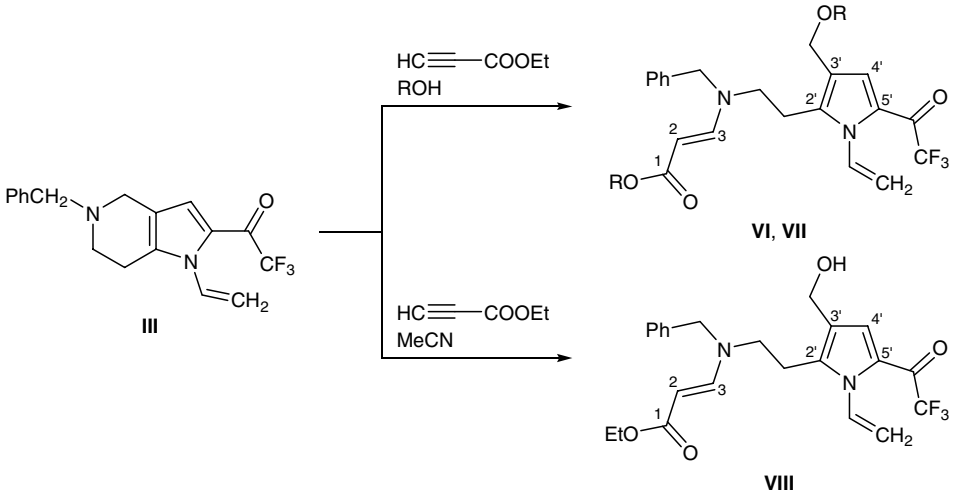
The reaction of tetrahydropyrrolopyridine **I** with ethyl propynoate in acetonitrile gave ethyl 4,7,9-trimethyl-2-trifluoroacetyl-4,7,8,9-tetrahydro-1*H*-pyrrolo[2,3-*d*]azocine (**IV**) in 65% yield (Scheme 2). Unlike the reaction with dimethyl acetylenedicarboxylate, no 3-vinylpyrrole derivatives were detected in the reaction mixture. By analogy with the data of [2], the methyl groups on $C^4$ and $C^9$ in molecule **IV** were assigned *cis* configuration. Ethyl 3-phenylpropynoate failed to react with tetrahydropyrrolopyridine **I**.

Compounds **II** and **III** reacted with ethyl propynoate in different ways. In the reaction of ethyl propynoate with tetrahydropyrrolopyridine **II** having no substituent on the pyrrole nitrogen atom (methanol, 20°C) we obtained 78% of pyrroloazocine **V** (Scheme 3); when the reaction was carried out in acetonitrile, the

**Scheme 3.**



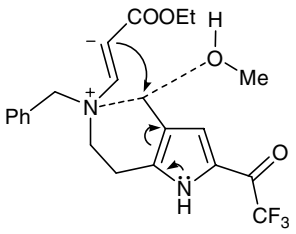
**Scheme 4.**




**VI**, R = Me; **VII**, R = Et.

yield of **V** was only 30%. The reaction of N-vinyl-substituted tetrahydropyrrolopyridine **III** with ethyl propynoate in methanol or ethanol involved cleavage of the tetrahydropyridine ring, and the products were substituted *N*-vinylpyrroles **VI** and **VII**, respectively (Scheme 4). The reaction in methanol was accompanied by transesterification. Compound **III** reacted with ethyl propynoate in acetonitrile in a complicated mode, leading to a mixture of products. By chromatography we isolated 7.5% of 3-hydroxymethylpyrrole **VIII**. Presumably, compound **VIII** is formed due to participation of water (which is present in commercial acetonitrile) in the tandem cleavage. When the reaction was carried out in anhydrous acetonitrile, we failed to isolate pyrrole **VIII** from the resulting multicomponent mixture.

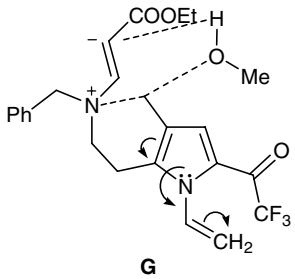
The different behaviors of NH- and N-vinyl-substituted tetrahydropyrrolo[3,2-*c*]pyridines in the reaction with ethyl propynoate are likely to result from different aromaticities of the pyrrole fragments in these compounds and their abilities to stabilize "push–pull" transition state. The electron-withdrawing trifluoroacetyl group in NH-pyrroles enhances the aromaticity via delocalization of the nitrogen lone electron pair




**F**

over the pyrrole ring. Therefore, the latter better stabilizes the positive charge in transition state **F**, and nucleophilic assistance of methanol is sufficient for the N–C$^4$ bond to be broken.

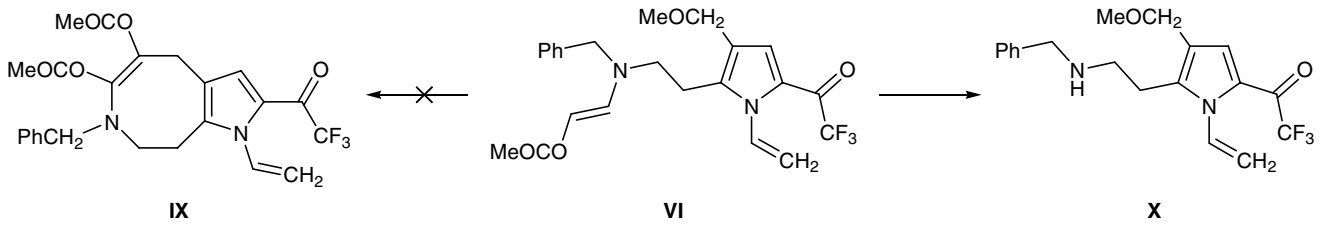
The lone electron pair on the nitrogen atom in *N*-vinylpyrroles is partially delocalized over the *N*-vinyl group, which makes the pyrrole fragment less aromatic. Reduction of the electron density on the pyrrole ring leads to weaker stabilization of the positive charge in transition state **G**. Therefore, dissociation of the N–C$^4$ bond is likely to follow a bimolecular mechanism, resulting in the formation of 3-alkoxy(hydroxy)-alkyl-substituted pyrroles.




**G**

We made an attempt to effect cyclization of methoxymethyl-substituted *N*-vinylpyrrole **VI** to pyrroloazocine **IX** in acetonitrile at 20°C using boron trifluoride–diethyl ether complex as catalyst. We recently reported on an analogous cyclization of dimethyl 2-{*N*-R-2-[3-(1-alkoxyalkyl)-1*H*-pyrrol-2-yl]ethylamino}maleates **B** into the corresponding pyrroloazocines **C** by the action of trimethylsilyl trifluoromethanesulfonate [6]. However, no cyclization of pyrrole **VI** occurred under the given conditions, but

**Scheme 5.**




devinylation of the enamine fragment led to the formation of *N*-vinylpyrrole **X** in 17% yield (Scheme 5). The reaction was accompanied by polymerization of pyrroles **VI** and **X** at the *N*-vinyl group.

The structure of compounds **IV**–**VIII** and **X** was confirmed by the $^1$H NMR, IR, and mass spectra. All these compounds showed in the IR spectra an absorption band at 1650–1669 cm$^{-1}$ due to stretching vibrations of the carbonyl group in the trifluoroacetyl substituent; stretching vibrations of the ester carbonyl group in the spectra of **IV**–**VIII** appeared in the region 1700–1720 cm$^{-1}$. The IR spectra of azocines **IV** and **V** and pyrroles **VIII** and **X** also contained broad bands in the region 3300–3500 cm$^{-1}$ due to vibrations of associated NH and OH groups. In the $^1$H NMR spectra of azocines **IV** and **V**, a singlet at δ 7.45–7.56 ppm (6-H) was present. The 2-H and 3-H protons in the acrylate fragment of vinylpyrroles **VI**–**VIII** resonated as two doublets at δ 5.21–5.50 and 7.35–7.75 ppm, respectively. The corresponding coupling constant $^3J_{2,3}$ = 13.1–14.0 Hz indicates *trans* orientation of these protons. Protons in the *N*-vinyl group of pyrroles **VI**–**VIII**, and **X** gave rise to three doublets of doublets with characteristic vicinal ($^3J$ = 15.7–15.8, 8.4 Hz) and geminal coupling constants ($^2J$ = 0.6–0.7 Hz).

## EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrometer from samples prepared as KBr pellets or thin films (liquids). The mass spectra (electron impact, 70 eV) were obtained on a Finnigan MAT Incos 50 instrument with direct sample admission into the ion source. The $^1$H NMR spectra were measured from 2% solutions in $CDCl_3$ on a Bruker WH-400 spectrometer (400 MHz) using tetramethylsilane as internal reference. Thin-layer chromatography was performed on Silufol and Alufol plates (development with iodine vapor), and aluminum oxide (Brockmann activity grade II) was used for column chromatography.

**Ethyl 4,7,9-trimethyl-2-trifluoroacetyl-4,7,8,9-tetrahydro-1*H*-pyrrolo[2,3-*d*]azocine-5-carboxylate (IV).** A solution of 0.2 g (0.77 mmol) of pyrrolopyridine **I** and 0.08 g (0.82 mmol) of ethyl propynoate in 10 ml of acetonitrile was kept for 20 h at 25–35°C (TLC, Silufol, ethanol). The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography using ethyl acetate–hexane (1:20) as eluent. Yield 0.18 g (65%), colorless crystals, mp 208–210°C (from hexane–ethyl acetate), $R_f$ 0.61 (Alufol, ethyl acetate–hexane, 1:2). $^1$H NMR spectrum, δ, ppm: 1.28 t (3H, C**H**$_3$CH$_2$, $J$ = 7.0 Hz), 1.30 d (3H, 9-CH$_3$, $J$ = 7.0 Hz), 1.51 d (3H, 4-CH$_3$, $J$ = 7.3 Hz), 2.98 s (3H, NCH$_3$), 3.12 d.d (1H, 8-H, $J$ = 15.3, 5.2 Hz), 3.25 m (1H, 9-H), 3.97 d.d (1H, 8-H, $J$ = 15.3, 12.8 Hz), 4.18 q (2H, CH$_3$C**H**$_2$O, $J$ = 7.0 Hz), 4.55 q (2H, 4-H, $J$ = 7.3 Hz), 6.99 q (1H, 3-H, $J$ = 2.4 Hz), 7.45 s (1H, 6-H), 9.93 br.s (1H, NH). Mass spectrum, *m*/*z* ($I_{rel}$, %): 358 (9.2) $[M]^+$, 343 (7.1), 313 (5.0), 285 (6.2), 230 (8.1), 203 (19.0), 156 (100), 134 (30.5), 110 (21.0), 91 (10.2), 84 (9.1), 82 (10.0), 71 (9.9), 57 (9.3), 56 (8.1), 55 (9.5), 44 (73.0), 42 (45.2), 41 (18.3). Found, %: C 57.12; H 5.63; N 7.70. $C_{17}H_{21}F_3N_2O_3$. Calculated, %: C 56.98; H 5.87; N 7.82. $M$ 358.36.

**Ethyl 7-benzyl-2-trifluoroacetyl-4,5,8,9-tetrahydro-1*H*-pyrrolo[2,3-*d*]azocin-5-carboxylate (V).** A solution of 0.23 g (0.75 mmol) of pyrrolopyridine **II** and 0.08 g (0.82 mmol) of ethyl propynoate in 5 ml of methanol was kept for 5 days at 25–30°C (TLC, Silufol, ethyl acetate). The solvent was distilled off under reduced pressure, and the residue was recrystallized from ethyl acetate–hexane. Yield 0.24 g (78%), colorless crystals, mp 164–165°C (from hexane–ethyl acetate), $R_f$ 0.86 (Silufol, ethyl acetate). $^1$H NMR spectrum, δ, ppm: 1.29 t (3H, C**H**$_3$CH$_2$, $J$ = 7.3 Hz), 2.87 t (2H, 9-H, $J$ = 5.8 Hz), 3.81 s (2H, 4-H), 3.90 t (2H, 8-H, $J$ = 5.8 Hz), 4.18 q (2H, OC**H**$_2$CH$_3$, $J$ = 7.3 Hz), 4.35 s (2H, C**H**$_2$Ph,), 6.99 q (1H, 3-H, $J$ = 2.4 Hz), 7.20–7.35 m (5H, Ph), 7.56 s (1H, 6-H), 9.04 br.s (1H, NH). Mass spectrum, *m*/*z* ($I_{rel}$, %): 406 (100) $[M]^+$, 377 (10.5), 361 (10.2), 333 (36.0), 315 (25.4), 218 (20.3), 189 (10.7), 91 (80.2), 65 (10.1). Found, %: C 61.43; H 4.50; N 6.89. $C_{21}H_{21}F_3N_2O_3$. Calculated, %: C 61.22; H 4.85; N 7.14. $M$ 406.40.

**Methyl 3-{benzyl[2-(3-methoxymethyl-5-trifluoroacetyl-1-vinyl-1*H*-pyrrol-2-yl)ethyl]amino}acrylate (VI) and ethyl 3-{benzyl[2-(3-ethoxymethyl-5-trifluoroacetyl-1-vinyl-1*H*-pyrrol-2-yl)ethyl]amino}acrylate (VII)** (*general procedure*)**.** A solution of 0.2 g (0.60 mmol) of vinylpyrrole **III** and 0.08 g (0.82 mmol) of ethyl propynoate in 5 ml of methanol or ethanol was kept for 3 days at 25–30°C (TLC, Alufol, ethyl acetate–hexane, 1:1). The solvent was distilled off under reduced pressure, and the residue was subjected to column chromatography using ethyl acetate–hexane (1:1) as eluent.

Compound **VI**. Yield 0.17 g (63%), yellow oily substance, $R_f$ 0.58 (Alufol, ethyl acetate–hexane, 1:1). $^1$H NMR spectrum, δ, ppm: 2.90–3.31 m (4H, $CH_2CH_2$), 3.38 s (3H, C**H**$_3$OCH$_2$), 3.67 s (3H, $CH_3OCO$), 4.25 s (2H, C**H**$_2$Ph), 4.26 s (2H, $CH_2O$), 4.95 d.d (1H, $CH_2$=, $J$ = 15.7, 0.6 Hz), 5.18 d.d (1H, $CH_2$=, $J$ = 8.4, 0.6 Hz), 5.42 d.d (1H, CH=, $J$ = 15.7, 8.4 Hz), 5.50 d (1H, 2-H, $J$ = 13.1 Hz), 7.17 br.s (1H, 4'-H), 7.26–7.33 m (5H, Ph), 7.55 d (1H, 3-H, $J$ = 13.1 Hz). Found, %: C 61.00; H 5.70; N 6.45. $C_{23}H_{25}F_3N_2O_4$. Calculated, %: C 61.33; H 5.56; N 6.22. $M$ 450.45.

Compound **VII**. Yield 0.12 g (42%), yellow oily substance, $R_f$ 0.60 (Alufol, ethyl acetate–hexane, 1:2). $^1$H NMR spectrum, δ, ppm: 1.20 t (3H, C**H**$_3$CH$_2$, $J$ = 7.0 Hz), 1.28 t (3H, C**H**$_3$CH$_2$, $J$ = 7.0 Hz), 3.25–3.60 m (4H, $CH_2CH_2$), 4.25 s (2H, C**H**$_2$Ph), 4.26 s (2H, C**H**$_2$OEt), 4.10 q (2H, $CH_2O$, $J$ = 7.0 Hz), 4.15 q (2H, $CH_2O$, $J$ = 7.0 Hz), 5.30 d (1H, 2-H, $J$ = 13.1 Hz), 5.37 d.d (1H, $CH_2$=, $J$ = 8.4, 0.6 Hz), 5.70 d.d (1H, $CH_2$=, $J$ = 15.7, 0.6 Hz), 6.85 d.d (1H, CH=, $J$ = 15.7, 8.4 Hz), 7.21 br.s (1H, 4'-H), 7.26–7.33 m (5H, Ph), 7.35 d (1H, 3-H, $J$ = 13.1 Hz). Found, %: C 62.83; H 6.39; N 6.00. $C_{25}H_{29}F_3N_2O_4$. Calculated, %: C 62.76; H 6.07; N 5.86. $M$ 478.30.

**Ethyl 3-{benzyl[2-(3-hydroxymethyl-5-trifluoroacetyl-1-vinyl-1*H*-pyrrol-2-yl)ethyl]amino}acrylate (VIII).** A solution of 0.2 g (0.60 mmol) of vinylpyrrole **III** and 0.09 g (0.92 mmol) of ethyl propynoate in 5 ml of acetonitrile was kept for 5 days at 30°C. The solvent was distilled under reduced pressure, and the residue was subjected to column chromatography. Elution with ethyl acetate–hexane (1:20) gave 0.10 g (50%) of initial vinylpyrrole **III** [colorless crystals, mp 68–71°C (from hexane); no depression of the melting point was observed on mixing with an authentic sample]. The subsequent elution with ethyl acetate–hexane (1:10) gave 0.03 g (7.4%) of pyrrole **VIII** as a yellow oily substance, $R_f$ 0.36 (Alufol, ethyl acetate–hexane, 1:3). $^1$H NMR spectrum, δ, ppm: 1.26 t (3H, $CH_3$, $J$ = 6.3 Hz), 2.89–3.46 m (4H, $CH_2CH_2$), 4.15 q (2H, $CH_2O$, $J$ = 6.3 Hz), 4.72 s (4H, PhC**H**$_2$, C**H**$_2$OH), 5.21 d (1H, 2-H, $J$ = 14.0 Hz), 5.42 d.d (1H, $CH_2$=, $J$ = 8.4, 0.7 Hz), 5.60 d.d (1H, $CH_2$=, $J$ = 15.8, 0.7 Hz), 6.55 d.d (1H, CH=, $J$ = 15.8, 8.4 Hz), 7.15 br.s (1H, 4'-H), 7.20–7.40 m (5H, Ph), 7.75 d (1H, 3-H, $J$ = 14.0 Hz). Found, %: C 61.05; H 5.84; N 6.54. $[M]^+$ 450. $C_{23}H_{25}F_3N_2O_4$. Calculated, %: C 61.33; H 5.56; N 6.22. $M$ 450.45.

**1-[2-(2-Benzylaminoethyl)-3-methoxymethyl-1-vinyl-1*H*-pyrrol-2-yl]-2,2,2-trifluoroethan-1-one (X).** A solution of 0.2 g (0.5 mmol) of pyrrole **VI** and a catalytic amount of boron trifluoride–diethyl ether complex in 5 ml of acetonitrile was kept for 3 weeks at 20°C (TLC, Alufol, ethyl acetate–hexane, 1:1). The solvent was distilled under reduced pressure, and the residue was subjected to column chromatography using ethyl acetate–hexane (1:10) as eluent. Yield 60 mg (7.5%), yellow oily substance, $R_f$ 0.4 (Alufol, ethyl acetate–hexane, 1:1). $^1$H NMR spectrum, δ, ppm: 2.95 t (2H, $CH_2$, $J$ = 7.4 Hz), 2.98 t (2H, $CH_2$, $J$ = 7.4 Hz), 3.30 s (3H, $OCH_3$), 4.25 s (2H, $CH_2O$), 4.28 s (2H, C**H**$_2$Ph), 5.25 d.d (1H, $CH_2$=, $J$ = 8.4, 0.7 Hz), 5.80 d.d (1H, $CH_2$=, $J$ = 15.7, 0.7 Hz), 7.00 d.d (1H, CH=, $J$ = 15.7, 8.4 Hz), 7.18 br.s (1H, 4'-H), 7.20–7.34 m (5H, Ph). Found, %: C 62.45; H 5.63; N 7.40. $[M]^+$ 366. $C_{19}H_{21}F_3N_2O_2$. Calculated, %: C 62.30; H 5.74; N 7.65. $M$ 366.38.

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 02-03-32941).

## REFERENCES

1. Varlamov, A.V., Borisova, T.N., Voskressensky, L.G., Nsabimana, B., and Chernyshev, A.I., *Heterocycl. Commun*., 2001, vol. 7, p. 461.
2. Borisova, T.N., Voskressensky, L.G., Soklakova, T.A., Kulikova, L.N., and Varlamov, A.V., *Mol. Diversity*, 2003, vol. 6, p. 202.
3. Varlamov, A.V., Borisova, T.N., Voskressensky, L.G., Soklakova, T.A., Kulikova, L.N., Chernyshev, A.I., and Alexandrov, G.G., *Tetrahedron Lett*., 2002, vol. 43, p. 6767.
4. Voskressensky, L.G., Borisova, T.N., Kulikova, L.N., Varlamov, A.V., Catto, M., Altomare, C., and Carotti, A., *Eur. J. Org. Chem*., 2004, p. 3128.
5. Borisova, T.N., Voskressensky, L.G., Soklakova, T.A., Nsabimana, B., and Varlamov, A.V., *Mendeleev Commun*., 2002, p. 162.
6. Voskressensky, L.G., Borisova, T.N., Soklakova, T.A., Kulikova, L.N., Borisov, R.S., and Varlamov, A.V., *Lett. Org. Chem*., 2005, vol. 2, p. 18.