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Three-Component Synthesis of New C^3-Substituted 5,6-Dihydropyrrolo[2,1-*a*]isoquinolines

A. R. Miftyakhova[a],*, M. B. Sidakov[a], T. N. Borisova[a], A. N. Fakhrutdinov[b], A. A. Titov[a], E. A. Sorokina[a], and A. V. Varlamov[a]

[a] *Peoples' Friendship University of Russia, Moscow, 117198 Russia*

[b] *Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, 119991 Russia*

**e-mail: almira244@gmail.com*

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Abstract—New C^3-substituted 5,6-dihydropyrrolo[2,1-*a*]isoquinolines have been synthesized via three-component domino reaction of 1-aroyl-3,4-dihydroisoquinolines, dimethyl acetylenedicarboxylate, and CH acids in anhydrous acetonitrile under microwave irradiation at 130°C.

Keywords: pyrrolo[2,1-*a*]isoquinolines, dimethyl acetylenedicarboxylate, domino reaction, CH acids, three-component synthesis

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INTRODUCTION

The pyrrolo[2,1-*a*]isoquinoline ring system is the main structural fragment of many natural compounds [1–3], including Lamellarin alkaloids [4]. Most natural pyrrolo[2,1-*a*]isoquinoline derivatives were found to exhibit various biological activities [5–10]. Chemists' interest in searching for new efficient methods of synthesis of analogs of that heterocyclic system constantly increases. In recent time, multicomponent and cascade reactions have been extensively used for the preparation of new substituted pyrrolo[2,1-*a*]isoquinolines starting from isoquinolines or their partially hydrogenated isoquinoline derivatives and alkenes or alkynes [11–20].

RESULTS AND DISCUSSION

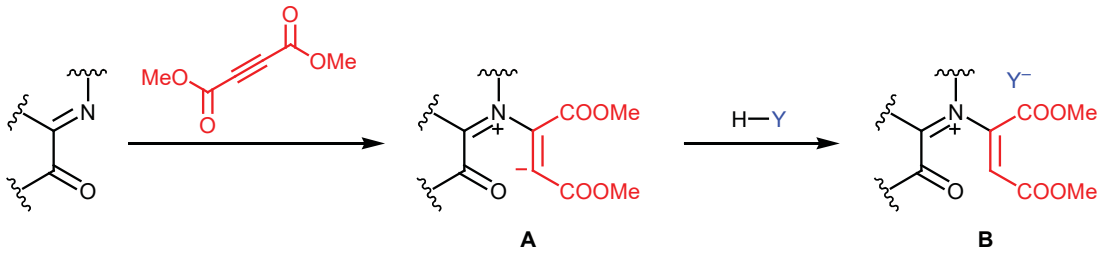
We have developed two three-component syntheses of 3-substituted pyrrolo[2,1-*a*]isoquinolines via domino reaction of 1-aroyl-3,4-dihydroisoquinolines containing an imino ketone fragment with electron-deficient terminal alkynes such as methyl propynoate and acetylacetylene. The third component was a CH acid (*N*,*N*′-dimethylbarbituric acid, dimedone, acetylacetone, ethyl acetoacetate, or malonic acid derivatives) [21] or an NH acid (cyclic amides or azoles) [22]. The goal of the present study was to find out how the use of dimethyl acetylenedicarboxylate (DMAD) in combination with CH or NH acids in three-component reactions with 1-aroyl-3,4-dihydroisoquinolines could change the transformation direction.

The possibility of a reaction to occur is determined by the charge on the anionic center of zwitterion **A** and its ability to abstract a proton from the third component to generate intermediate **B** (Scheme 1). In the reaction with DMAD, the charge on the anionic center in the corresponding intermediate **A** is lower than in those derived from methyl propynoate and acetylacetylene due to the presence of two electron-withdrawing ester groups, which could lead to a change in the reaction direction or inhibition of the process.

By studying the reactions of 1-aroyl-3,4-dihydroisoquinolines **1a**–**1c** with DMAD and CH acids we found that in the case of fairly strong CH acids, such as *N*,*N*′-dimethylbarbituric acid (**3a**), dimedone (**3b**), and acetylacetone (**3c**), under microwave irradiation at 130°C the products were pyrrolo[2,1-*a*]isoquinolines **4**–**6** which were obtained in moderate yields (Scheme 2).

1-Aroyl-3,4-dihydroisoquinolines **1a**–**1c** reacted with DMAD and strong CH acids in a more complicated fashion than with terminal alkynes. Pyrrolo-[2,1-*a*]isoquinolines **4**–**6** were formed as a result of three-component reaction followed by rearrangement

Scheme 1.

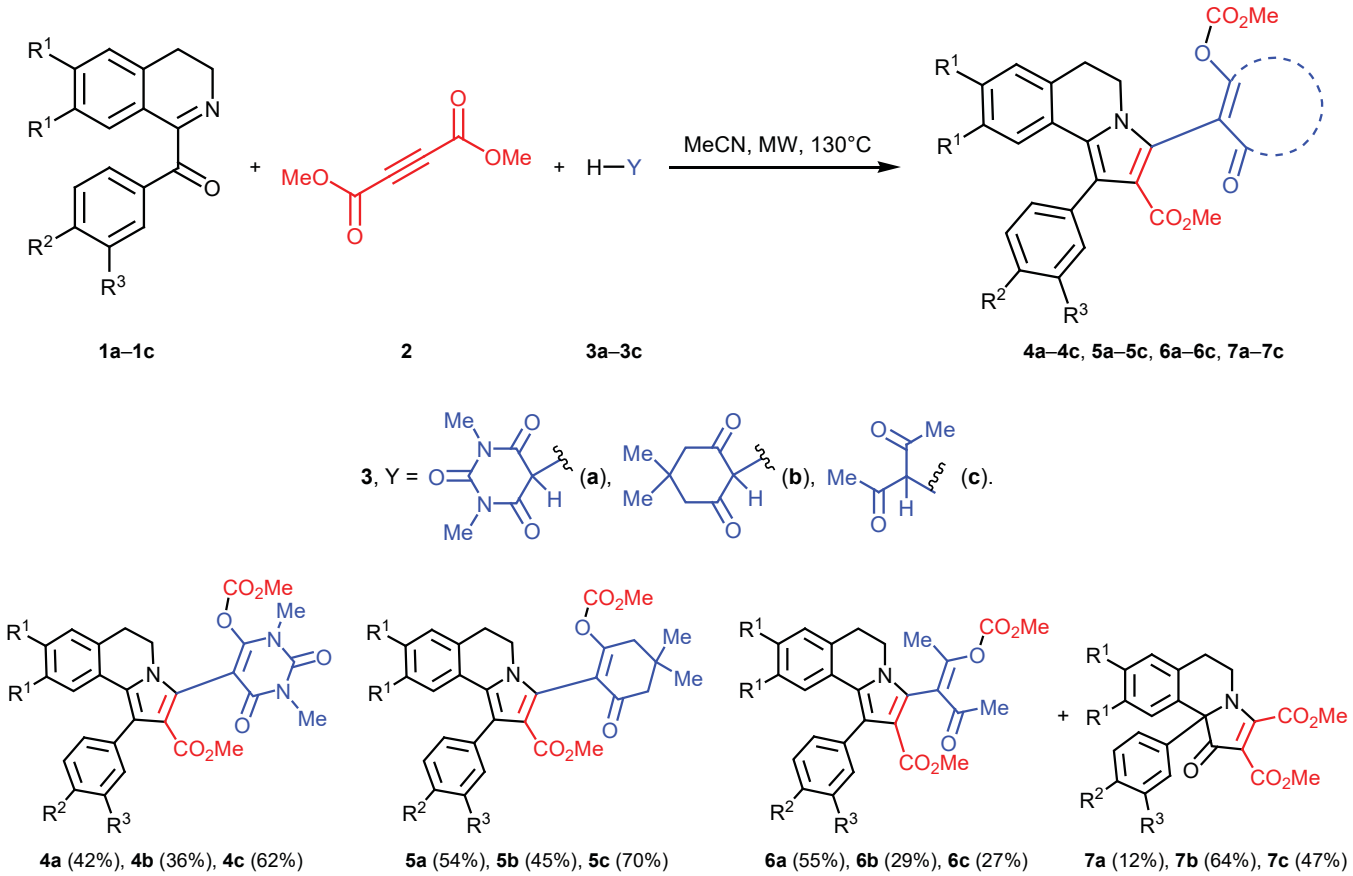


involving transfer of the methoxycarbonyl group. It should be noted that no such transformations were observed in the reaction with terminal alkynes [21]. The described process is driven by the aromatization of five-membered nitrogen-containing intermediate **F** (Scheme 3). The reactions with a weaker CH acid, acetylacetone (**3c**), were accompanied by the formation of pyrrolo[2,1-*a*]isoquinolines **7a**–**7c** in addition to the three-component condensation products. Compounds **7a**–**7c** are formed as a result of concurrent two-component reaction whose mechanism was described by us previously [23].

The structure of pyrroloisoquinolines **4**–**6** was confirmed by spectral data (see Experimental). The ^{1}H NMR spectra of **4**–**6** showed no singlet signals assignable to enolic proton or proton at the tertiary carbon atom of the CH acid moiety [21], whereas two singlets belonging to the ester methoxy groups were present. Further confirmation of the proposed structure of pyrrolo[2,1-*a*]isoquinolines **4**–**6** was obtained by studying two-dimensional NMR correlation spectra of **5b** and **6a** (Figs. 1, 2).

The key C–H interactions were most clearly seen in the correlation spectra of **6a**. The ^{1}H NMR spectrum of

Scheme 2.



1, **4**–**7**, R^1 = OMe, R^2 = R^3 = H (**a**); R^1 = OMe, R^2 = F, R^3 = H (**b**); R^1 = R^2 = R^3 = OEt (**c**).

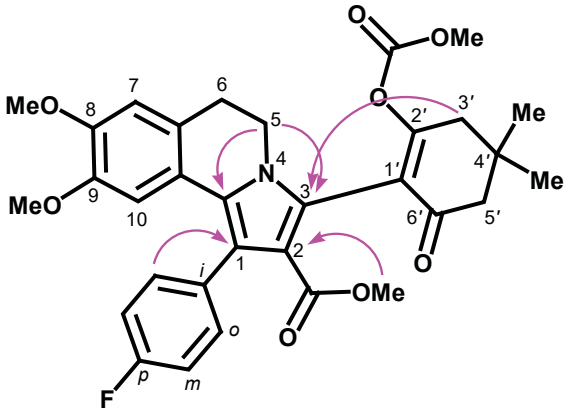


Fig. 1. Key $^{1}H–^{13}C$ HMBC correlations in molecule **5b**.

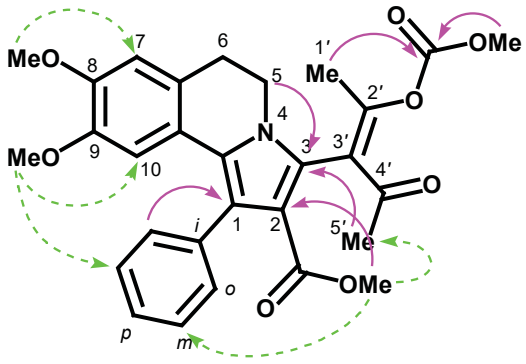


Fig. 2. Key NOE (dashed arrows) and $^{1}H–^{13}C$ HMBC correlations (solid arrows) in molecule **6a**.

6a showed signals of protons in the benzene ring, protons on C^{7} and C^{10}, two methylene groups, and six methyl groups. This means that the methyl groups in the acetylacetone moiety are nonequivalent, i.e., the acetylacetone residue lost its symmetry. The ^{13}C NMR spectrum of **6a** contained 27 signals, only one of which belonged to the carbonyl group of the CH acid residue. There were two more carbonyl carbon signals at δ_C 152.0 and 159.2 ppm, the first of which was assigned to the carbonate fragment. The substitution positions were determined by analysis of the $^{1}H–^{1}H$ NOE and $^{1}H–^{13}C$ HMBC correlations. To identify long-range spin–spin couplings, the $^{1}H–^{13}C$ HMBC spectrum optimized for a coupling constant of 2 Hz was recorded. Likewise, we examined the structure of compound **5b** which was also characterized by asymmetry of the dimedone residue.

The obtained results can be explained by the following scheme. Successive generation of zwitterion **A**, proton abstraction from CH acid (intermediate **B**), and addition of CH nucleophile produces zwitterion **C**. Next follow five-membered ring closure as a result of attack of the anionic center on the carbonyl group (intermediate **D**), proton transfer to the oxygen atom at C^{1}, and enolization with the formation of structure **E**. Further dehydration and migration of the methoxycarbonyl group through intermediate **F** lead to aromatization of the pyrrole ring and formation of final products **4**–**6** (Scheme 3).

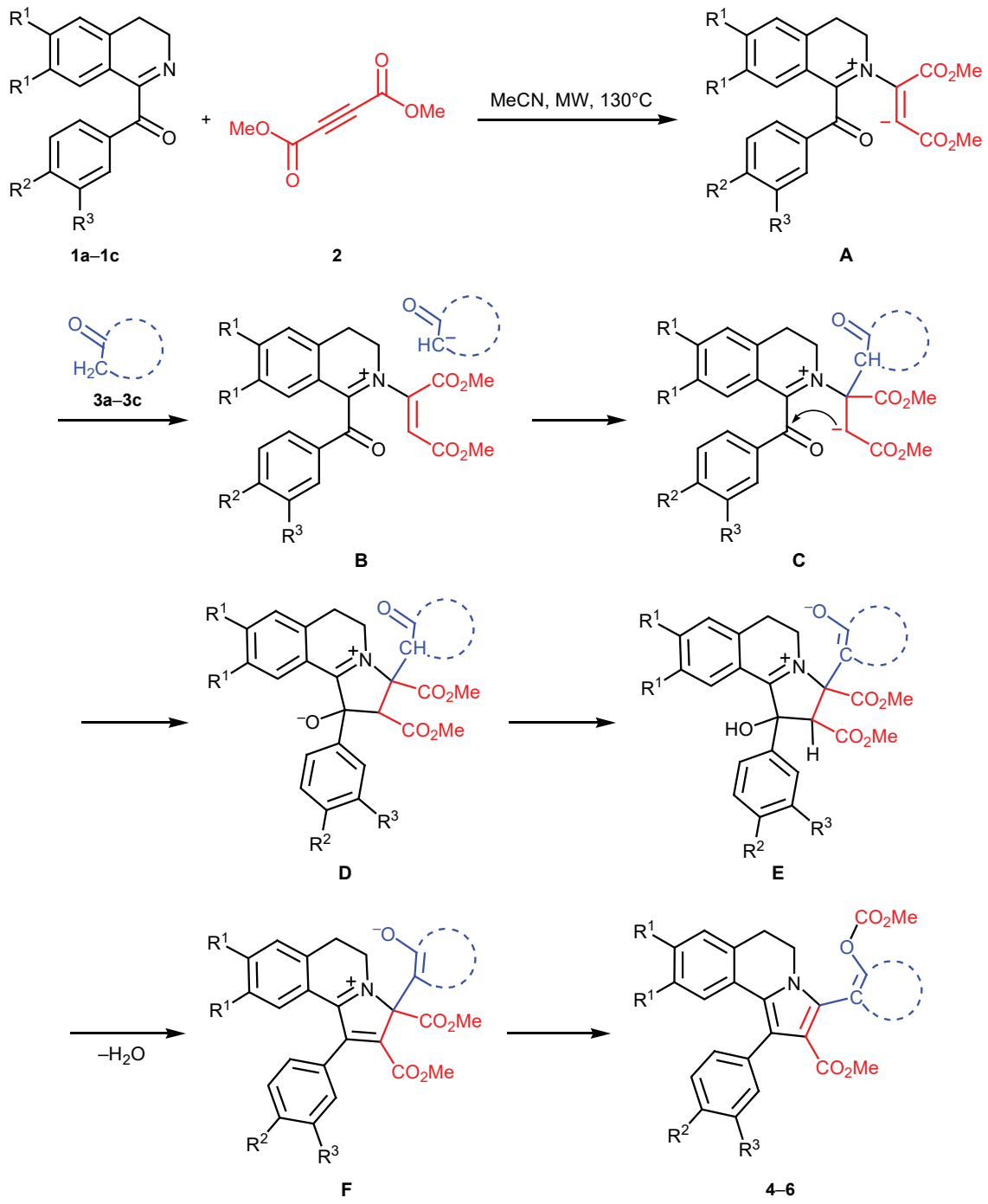
The reactions of drotaveraldine (**1c**) with dimethyl acetylenedicarboxylate (**2**) and weak CH acids, such as malononitrile (**3d**), ethyl cyanoacetate (**3e**), and ethyl acetoacetate (**3f**), resulted in the formation of the two-component condensation product, previously described [23] 1-oxopyrrolo[2,1-*a*]isoquinoline **7c** (63–77%; Scheme 4). As might be expected, zwitterion **A** derived from **1c** and DMAD (Scheme 3) is incapable of deprotonating weak CH acids, in contrast to the reactions with terminal alkynes [21].

No three-component condensation products were formed in the reaction of **1c** with dimethyl acetylenedicarboxylate **2** and strong NH acids (succinimide, phthalimide, 1,3-benzoxazol-2-one). In all cases, the reaction mixtures contained 1-oxopyrrolo[2,1-*a*]isoquinoline **7c** which was detected by HPLC. Presumably, the reactions with NH acids involve generation of intermediates **A**–**D**, but no aromatization of the pyrrole ring occurs due to the lack of possibility for the migration of methoxycarbonyl to the NH acid residue.

EXPERIMENTAL

Initial compounds **1a**–**1c** were synthesized as described previously [24]. Commercially available reagents from Alfa Aesar were used. The melting points were measured in open capillary tubes on a Stuart SMP 30 melting point apparatus. Microwave-assisted reactions were carried out in an Anton Paar Monowave 300 microwave reactor. Sorbfil STKh-1Å plates (particle size 5–17 μm) were used for thin-layer chromatography, visualization was done by treatment with a solution of potassium permanganate. Column chromatography was performed on Silicagel 60 (0.060–0.200 mm; Acros Organics). The ^{1}H and ^{13}C NMR spectra were recorded on a Jeol JNM ECA spectrometer with Fourier transform at 600 and 151 MHz, respectively; the chemical shifts were measured relative to the residual proton and carbon signals of the solvent ($CHCl_3$, δ 7.26 ppm; $CDCl_3$, δ_C 77.16 ppm). The high-resolution mass spectra were obtained on a Bruker maXis QTOF instrument (tandem quadrupole/time-of-flight mass analyzer) equipped with an electrospray ionization source (positive ioniza-

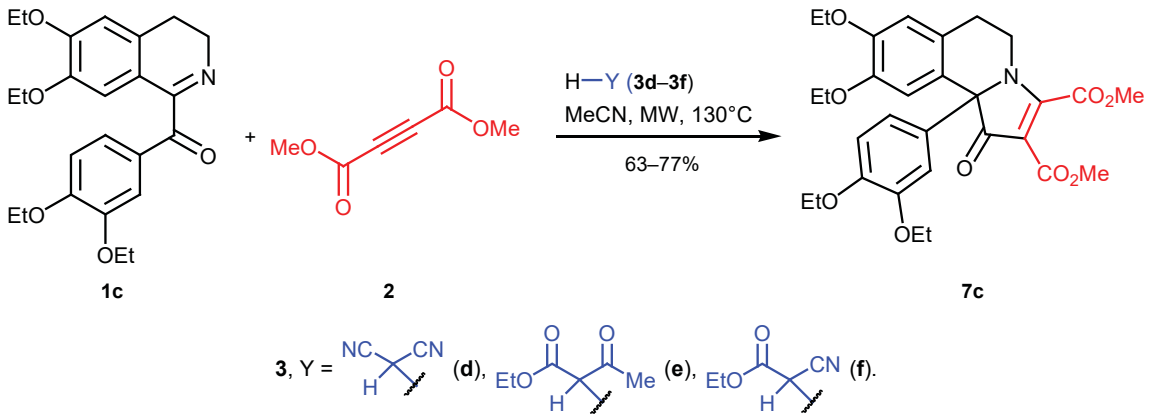
Scheme 3.



tion mode); a.m.u. range 50–3000; external calibration was performed using a low-concentration tuning mix (Agilent Technologies); samples were injected with a 500-μL Hamilton RN 1750 syringe; grounded spraying needle, capillary voltage 4500 V, end plate displacement BH: –500 V; injection flow rate was maintained at 3 μL/min using a syringe pump; nebulizer gas nitrogen (1.0 bar); drying gas flow rate 4.0 L/min at 200°C; the data were processed using Bruker Data Analysis 4.0 software. The IR spectra were recorded in KBr on an InfraLUM FT 801 spectrometer.

Compounds 4–7 (*general procedure*). CH Acid **3a**–**3f** was added to a solution of 1-aroyl-3,4-dihydroisoquinoline **1a**–**1c** and dimethyl acetylenedicarboxylate (**2**) in 5 mL of anhydrous acetonitrile. The mixture was heated in a hermetically closed vessel in a micro-

Scheme 4.



wave reactor at 130°C for 20–60 min. The progress of reactions was monitored by TLC using ethyl acetate–hexane (1:1) as eluent. After completion of the reaction, the mixture was cooled, and the solvent was evaporated. Compounds **4a**–**4c** and **5a**–**5c** were isolated by recrystallization of the residue from ethyl acetate–hexane. Compounds **6a**–**6c** and **7a**–**7c** were isolated by column chromatography using ethyl acetate–hexane (gradient elution, 1:10 to 1:3) or by crystallization of the residue from ethyl acetate–hexane.

Methyl 8,9-dimethoxy-3-{6-[(methoxycarbonyl)-oxy]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropy-rimidin-5-yl}-1-phenyl-5,6-dihydropyrrolo[2,1-*a*]-isoquinoline-2-carboxylate (4a) was synthesized from 0.51 mmol of **1a**, 0.51 mmol of **2**, and 0.66 mmol of **3a**. Yield 0.123 g (42%), white crystals, mp 184–186°C. IR spectrum, ν, cm^{-1}: 1793, 1715, 1680 (C=O). ^1H NMR spectrum, δ, ppm: 2.96 t (2H, 6-H, J = 6.5 Hz), 3.26 s (3H, 9-OCH_3), 3.45 s (3H, NCH_3), 3.47 s (3H, 2-CO_2CH_3), 3.48 s (3H, NCH_3), 3.74 s (3H, OCO_2CH_3), 3.83 s (3H, 8-OCH_3), 3.87–3.93 m (2H, 5-H), 6.33 s (1H, 10-H), 6.66 s (1H, 7-H), 7.27–7.32 m (1H, H_{arom}), 7.33–7.42 m (4H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 29.0, 29.1, 30.5, 42.6, 50.8, 55.1, 56.0, 57.0, 95.6, 108.0, 111.0, 114.0, 121.5, 121.7, 123.9, 125.1, 126.9, 128.1 (2C), 128.2, 131.0 (2C), 137.0, 147.4, 147.5, 150.2, 150.7, 153.5, 161.8, 164.8. Mass spectrum: *m*/*z*: 575.1909 $[M]^+$. $C_{30}H_{29}N_3O_9$. Calculated: *M* 575.1898.

Methyl 1-(4-fluorophenyl)-8,9-dimethoxy-3-{6-[(methoxycarbonyl)oxy]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl}-5,6-dihydro-pyrrolo[2,1-*a*]isoquinoline-2-carboxylate (4b) was synthesized from 0.48 mmol of **1b**, 0.48 mmol of **2**, and 0.62 mmol of **3a**. Yield 0.102 g (36%), white crystals, mp 191–192°C. IR spectrum, ν, cm^{-1}: 1794, 1715, 1677 (C=O). ^1H NMR spectrum, δ, ppm: 2.96 t (2H, 6-H, J = 6.3 Hz), 3.34 s (3H, 9-OCH_3), 3.45 s (3H, NCH_3), 3.47 s (3H, 2-CO_2CH_3), 3.49 s (3H, NCH_3), 3.74 s (3H, OCO_2CH_3), 3.85 s (3H, 8-OCH_3), 3.87–3.91 m (2H, 5-H), 6.33 s (1H, 10-H), 6.67 s (1H, 7-H), 7.00–7.13 m (2H, H_{arom}), 7.34 d (2H, H_{arom}, J = 5.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 29.0, 29.1, 30.5, 42.6, 50.8, 55.2, 56.0, 57.0, 95.6, 107.9, 111.1, 115.1 d (2C, J = 21.2 Hz), 120.4, 121.3, 124.0, 125.3, 128.4, 132.7 d (2C, J = 8.0 Hz), 132.8 d (J = 3.3 Hz), 147.5, 147.7, 147.7, 150.2, 150.7, 153.5, 161.7, 162.1 d (J = 245.4 Hz), 164.7. Mass spectrum: *m*/*z* 594.1891 $[M + H]^+$. $C_{30}H_{28}FN_3O_9$. Calculated: $[M + H]^+$ 594.1882.

Methyl 1-(3,4-diethoxyphenyl)-8,9-diethoxy-3-{6-[(methoxycarbonyl)oxy]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl}-5,6-dihydro-pyrrolo[2,1-*a*]isoquinoline-2-carboxylate (4c) was synthesized from 0.36 mmol of **1c**, 0.36 mmol of **2**, and 0.47 mmol of **3a**. Yield 0.156 g (62%), white crystals, mp 182–183°C. IR spectrum, ν, cm^{-1}: 1795, 1715, 1676 (C=O). ^1H NMR spectrum, δ, ppm: 1.16 t (3H, $OCH_2C\mathbf{H}_3$, J = 6.8 Hz), 1.39–1.44 m (6H, $OCH_2C\mathbf{H}_3$), 1.47 t (3H, $OCH_2C\mathbf{H}_3$, J = 6.8 Hz), 2.93 t (2H, 6-H, J = 6.3 Hz), 3.44 s (3H, NCH_3), 3.46 s (3H, 2-CO_2CH_3), 3.48 s (3H, NCH_3), 3.55 q (2H, $OC\mathbf{H}_2CH_3$, J = 6.8 Hz), 3.74 s (3H, OCO_2CH_3), 3.88 t (2H, 5-H, J = 6.3 Hz), 4.01–4.07 m (4H, $OC\mathbf{H}_2CH_3$), 4.12 q (2H, $OC\mathbf{H}_2CH_3$, J = 6.8 Hz), 6.47 s (1H, 10-H), 6.66 s (1H, 7-H), 6.73–6.95 m (3H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 14.7, 14.9, 15.0, 15.1, 29.0 (2C), 30.4, 42.6, 50.8, 57.0, 63.8, 64.6, 64.7 (2C), 64.8, 95.8, 109.6, 113.1, 113.5, 114.2, 121.3, 121.7, 123.7, 125.0, 128.3, 129.7, 147.1, 147.2, 147.7, 147.8, 148.6, 150.2, 150.8, 153.4, 161.8, 164.9. Mass spectrum:

m/*z* 692.2821 $[M + H]^+$. $C_{36}H_{41}N_3O_{11}$. Calculated: $[M + H]^+$ 692.2814.

Methyl 8,9-dimethoxy-3-{2-[(methoxycarbonyl)oxy]-4,4-dimethyl-6-oxocyclohex-1-en-1-yl}-1-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carboxylate (5a) was synthesized from 0.51 mmol of **1a**, 1.02 mmol of **2**, and 0.51 mmol of **3b**. Yield 0.154 g (54%), white crystals, mp 158–159°C. IR spectrum, ν, cm^{-1}: 1761, 1697 (C=O). ^1H NMR spectrum, δ, ppm: 1.23 s (3H, 4′-CH_3), 1.27 s (3H, 4′-CH_3), 2.46–2.59 m (2H, 5′-H), 2.63–2.77 m (2H, 3′-H), 2.92 t (2H, 6-H, *J* = 6.5 Hz), 3.24 s (3H, 9-OCH_3), 3.49 s (3H, 2-CO_2CH_3), 3.72 s (3H, OCO_2CH_3), 3.73–3.80 m (2H, 5-H), 3.82 s (3H, 8-OCH_3), 6.33 s (1H, 10-H), 6.63 s (1H, 7-H), 7.26–7.31 m (1H, H_{arom}), 7.33–7.41 m (4H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 28.2, 28.5, 29.1, 32.6, 42.6, 42.7, 50.7, 51.3, 55.1, 55.9, 56.0, 107.9, 110.9, 113.8, 120.8, 121.7, 122.0, 124.6, 125.7, 126.8, 127.6, 128.2 (2C), 131.0 (2C), 137.0, 147.3, 147.4, 151.7, 164.8, 165.8, 197.4. Mass spectrum: *m*/*z* 560.2273 $[M + H]^+$. $C_{32}H_{33}NO_8$. Calculated: $[M + H]^+$ 560.2279.

Methyl 1-(4-fluorophenyl)-8,9-dimethoxy-3-{2-[(methoxycarbonyl)oxy]-4,4-dimethyl-6-oxocyclohex-1-en-1-yl}-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carboxylate (5b) was synthesized from 0.48 mmol of **1b**, 0.96 mmol of **2**, and 0.48 mmol of **3b**. Yield 0.124 g (45%), white crystals, mp 187–188°C. IR spectrum, ν, cm^{-1}: 1760, 1697 (C=O). ^1H NMR spectrum, δ, ppm: 1.24 s (3H, 4′-CH_3), 1.28 s (3H, 4′-CH_3), 2.47–2.60 m (2H, 5′-H), 2.67–2.76 m (2H, 3′-H), 2.89–2.95 m (2H, 6-H), 3.33 s (3H, 9-OCH_3), 3.51 s (3H, 2-CO_2CH_3), 3.70–3.77 m (4H, 5-H, OCO_2CH_3), 3.77–3.82 m (1H, 5-H), 3.84 s (3H, 8-OCH_3), 6.34 s (1H, 10-H), 6.65 s (1H, 7-H), 7.09 t (2H, H_{arom}, *J* = 8.5 Hz), 7.29–7.44 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 28.2 (4′-CH_3), 28.5 (4′-CH_3), 29.1 (C^6), 32.7 ($C^{4'}$), 42.6 ($C^{3'}$), 42.7 (C^5), 50.8 (2-COO**C**H_3), 51.2 ($C^{5'}$), 55.2 (9-OCH_3), 55.9 (OCO_2**C**H_3), 56.0 (8-OCH_3), 107.7 (C^{10}), 111.0 (C^7), 113.9 (C^2), 115.0 d (2C, C^m, *J* = 21.2 Hz), 120.7 (C^1), 120.8 ($C^{1'}$), 121.5 (C^{10a}), 124.8 (C^{6a}), 126.0 (C^3), 127.8 (C^{1a}), 132.6 d (2C, C^o, *J* = 7.6 Hz), 132.8 d (C^i, *J* = 3.3 Hz), 147.5 (C^8), 147.5 (C^9), 151.6 (OCOO), 162.1 d (C^p, *J* = 245.2 Hz), 164.7 (2-COO), 165.9 ($C^{2'}$), 197.3 ($C^{6'}$). Mass spectrum: *m*/*z* 578.2164 $[M + H]^+$. $C_{32}H_{32}FNO_8$. Calculated: $[M + H]^+$ 578.2185.

Methyl 1-(3,4-diethoxyphenyl)-8,9-diethoxy-3-{2-[(methoxycarbonyl)oxy]-4,4-dimethyl-6-oxocyclohex-1-en-1-yl}-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carboxylate (5c) was synthesized from 0.36 mmol of **1c**, 0.73 mmol of **2**, and 0.36 mmol of **3b**. Yield 0.169 g (70%), white crystals, mp 148–149°C. IR spectrum, ν, cm^{-1}: 1762, 1691 (C=O). ^1H NMR spectrum, δ, ppm: 1.16 t (3H, OCH_2C**H**$_3$, *J* = 7.0 Hz), 1.23 s (3H, 4′-CH_3), 1.27 s (3H, 4′-CH_3), 1.37–1.42 m (6H, OCH_2C**H**$_3$), 1.45 t (3H, OCH_2C**H**$_3$, *J* = 7.0 Hz), 2.45–2.60 m (2H, 5′-H), 2.66–2.76 m (2H, 3′-H), 2.89 t (2H, 6-H, *J* = 6.4 Hz), 3.49 s (3H, 2-CO_2CH_3), 3.54 q (2H, O**C**H_2CH_3, *J* = 7.0 Hz), 3.68–3.81 m (5H, 5-H, OCO_2CH_3), 4.04 q (4H, O**C**H_2CH_3, *J* = 7.0 Hz), 4.11 q (2H, O**C**H_2CH_3, *J* = 7.0 Hz), 6.47 s (1H, 10-H), 6.64 s (1H, 7-H), 6.84–6.96 m (3H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 14.6, 14.9, 14.9, 15.0, 28.3, 28.4, 29.1, 32.6, 42.5, 42.7, 50.7, 51.2, 55.8, 63.7, 64.5, 64.7 (2C), 109.4, 113.0, 113.4, 114.0, 116.4, 120.9, 121.6, 121.9, 123.1, 124.4, 125.8, 127.7, 129.6, 146.9, 147.1, 147.6, 148.5, 151.7, 164.9, 165.6, 197.4. Mass spectrum: *m*/*z* 675.3042 $[M]^+$. $C_{38}H_{45}NO_{10}$. Calculated: *M* 675.3038.

Methyl 8,9-dimethoxy-3-{(2*E*)-2-[(methoxycarbonyl)oxy]-4-oxopent-2-en-3-yl}-1-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carboxylate (6a) was synthesized from 0.51 mmol of **1a**, 0.76 mmol of **2**, and 0.76 mmol of **3c**. Yield 0.145 g (55%), white crystals, mp 133–134°C. IR spectrum, ν, cm^{-1}: 1752, 1719, 1696 (C=O). ^1H NMR spectrum, δ, ppm: 2.14 s (3H, 5′-H), 2.51 s (3H, 1′-H), 2.91–3.02 m (2H, 6-H), 3.28 s (3H, 9-OCH_3), 3.55 s (3H, 2-CO_2CH_3), 3.71 s (3H, OCO_2CH_3), 3.79–3.84 m (1H, 5-H), 3.84 s (3H, 8-OCH_3), 3.94–4.02 m (1H, 5-H), 6.40 s (1H, 10-H), 6.68 s (1H, 7-H), 7.30–7.34 m (1H, H_{arom}), 7.36–7.43 m (4H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 19.1 ($C^{1'}$), 29.2 (C^6), 30.3 ($C^{5'}$), 42.4 (C^5), 50.9 (2-CO_2**C**H_3), 55.2 (9-OCH_3), 55.7 (OCO_2**C**H_3), 56.1 (8-OCH_3), 107.9 (C^{10}), 111.0 (C^7), 114.0 (C^2), 121.5 (C^{10a}), 121.7 ($C^{3'}$), 122.2 (C^1), 124.6 (C^{6a}), 127.1 (C^p), 127.4 (C^{1a}), 128.3 (2C, C^m), 129.4 (C^3), 130.9 (2C, C^o), 136.4 (C^i), 147.56 (C^8), 147.63 (C^9), 152.0 (OCOO), 159.2 ($C^{2'}$), 164.8 (2-COO), 198.3 ($C^{4'}$). Mass spectrum: *m*/*z* 519.1887 $[M]^+$. $C_{29}H_{29}NO_8$. Calculated: *M* 519.1888.

Methyl 1-(4-fluorophenyl)-8,9-dimethoxy-3-{(2*E*)-2-[(methoxycarbonyl)oxy]-4-oxopent-2-en-3-yl}-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carboxylate (6b) was synthesized from 0.48 mmol of **1b**, 0.72 mmol of **2**, and 0.72 mmol of **3c**. Yield 0.075 g (29%), white crystals, mp 154–155°C. IR spectrum, ν, cm^{-1}: 1754, 1715, 1697 (C=O). ^1H NMR spectrum, δ,

ppm: 2.13 s (3H, 5′-H), 2.51 s (3H, 1′-H), 2.89–3.03 m (2H, 6-H), 3.35 s (3H, 9-OCH_3), 3.56 s (3H, 2-CO_2CH_3), 3.71 s (3H, OCO_2CH_3), 3.79–3.84 m (1H, 5-H), 3.85 s (3H, 8-OCH_3), 3.95–4.00 m (1H, 5-H), 6.40 s (1H, 10-H), 6.69 s (1H, 7-H), 7.09–7.13 m (2H, H_{arom}), 7.33–7.38 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 19.1, 29.2, 30.3, 42.4, 50.9, 55.2, 55.7, 56.1, 107.8, 111.1, 114.0, 115.2 d (2C, J = 21.0 Hz), 120.9, 121.3, 121.7, 124.8, 127.6, 129.6, 132.3 d (J = 3.2 Hz), 132.6 d (2C, J = 7.4 Hz), 147.7, 147.7, 152.0, 159.3, 162.2 d (J = 245.7 Hz), 164.7, 198.2. Mass spectrum: m/z 537.1805 $[M]^+$. $C_{29}H_{28}FNO_8$. Calculated: M 537.1793.

Methyl 1-(3,4-diethoxyphenyl)-8,9-diethoxy-3-{(2*E*)-2-[(methoxycarbonyl)oxy]-4-oxopent-2-en-3-yl}-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carboxylate (6c) was synthesized from 0.36 mmol of **1c**, 0.55 mmol of **2**, and 0.55 mmol of **3c**. Yield 0.061 g (27%), white crystals, mp 156–157°C. IR spectrum, ν, cm^{-1}: 1755, 1715, 1696 (C=O). ^1H NMR spectrum, δ, ppm: 1.18 t (3H, $OCH_2C\mathbf{H}_3$, J = 6.9 Hz), 1.36–1.43 m (6H, $OCH_2C\mathbf{H}_3$), 1.47 t (3H, $OCH_2C\mathbf{H}_3$, J = 6.9 Hz), 2.13 s (3H, 5′-H), 2.51 s (3H, 1′-H), 2.84–3.03 m (2H, 6-H), 3.53–3.58 m (5H, $OC\mathbf{H}_2CH_3$, 2-CO_2CH_3), 3.71 s (3H, OCO_2CH_3), 3.76–3.87 m (1H, 5-H), 3.93–3.99 m (1H, 5-H), 4.06 q (4H, $OC\mathbf{H}_2CH_3$, J = 6.9 Hz), 4.13 q (2H, $OC\mathbf{H}_2CH_3$, J = 6.9 Hz), 6.54 s (1H, 10-H), 6.68 s (1H, 7-H), 6.85–6.94 m (3H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 14.6, 14.9, 14.9, 15.0, 19.0, 29.2, 30.3, 42.3, 50.8, 55.6, 63.8, 64.6, 64.7, 64.7, 109.4, 113.1, 113.5, 114.1, 116.4, 121.6, 121.7, 121.8, 123.1 (2C), 124.4, 127.4, 128.9, 129.3, 147.1, 147.3, 147.8, 152.0, 159.0, 164.8, 198.3. Mass spectrum: m/z 635.2728 $[M]^+$. $C_{35}H_{41}NO_{10}$. Calculated: M 635.2725.

Dimethyl 8,9-dimethoxy-1-oxo-10b-phenyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-2,3-dicarboxylate (7a). Yield 0.026 g (12%), white crystals, mp 175–179°C. IR spectrum, ν, cm^{-1}: 1745, 1698 (C=O). ^1H NMR spectrum, δ, ppm: 2.76–2.85 m (1H, 6-H), 3.07–3.17 m (1H, 5-H), 3.49–3.56 m (1H, 6-H), 3.66–3.72 m (1H, 5-H), 3.79 s (3H, 3-CO_2CH_3), 3.87 s (3H, 9-OCH_3), 3.88 s (3H, 8-OCH_3), 4.06 s (3H, 2-CO_2CH_3), 6.64 s (1H, 10-H), 7.04–7.10 m (2H, H_{arom}), 7.28–7.32 m (3H, H_{arom}), 7.47 s (1H, 7-H). ^{13}C NMR spectrum, δ_C, ppm: 29.8, 41.9, 51.7, 53.9, 56.0, 56.3, 75.5, 102.3, 110.2, 110.9, 123.6, 125.4, 127.8 (2C), 128.9, 129.0 (2C), 138.9, 148.1, 149.1, 161.8, 163.4, 169.2, 194.8. Mass spectrum (LCMS, ESI): m/z 438 $[M + H]^+$. $C_{24}H_{23}NO_7$. Calculated: M + H 438.

Dimethyl 10b-(4-fluorophenyl)-8,9-dimethoxy-1-oxo-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-2,3-dicarboxylate (7b). Yield 0.134 g (64%), white crystals, mp 155–158°C. IR spectrum, ν, cm^{-1}: 1738, 1697 (C=O). ^1H NMR spectrum, δ, ppm: 2.77–2.84 m (1H, 6-H), 3.08–3.17 m (1H, 5-H), 3.46–3.53 m (1H, 6-H), 3.67–3.72 m (1H, 5-H), 3.79 s (3H, 3-CO_2CH_3), 3.87 s (3H, 9-OCH_3), 3.88 s (3H, 8-OCH_3), 4.06 s (3H, 2-CO_2CH_3), 6.63 s (1H, 10-H), 6.99 t (2H, H_{arom}, J = 8.6 Hz), 7.03–7.07 m (2H, H_{arom}), 7.43 s (1H, 7-H). ^{13}C NMR spectrum, δ_C, ppm: 29.7, 41.9, 51.7, 53.9, 56.0, 56.2, 74.8, 102.3, 109.9, 110.9, 115.9 d (2C, J = 21.7 Hz), 123.3, 125.3, 129.8 d (2C, J = 8.6 Hz), 134.8 d (J = 3.6 Hz), 148.2, 149.2, 161.7, 162.9 d (J = 249.2 Hz), 163.2, 169.3, 194.7. Mass spectrum (LCMS, ESI): m/z 456 $[M + H]^+$. $C_{24}H_{22}FNO_7$. Calculated: M + H 456.

Dimethyl 10b-(3,4-diethoxyphenyl)-8,9-diethoxy-1-oxo-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-2,3-dicarboxylate (7c) was synthesized from 0.73 mmol of **3d**, **3e**, or **3f**, 0.36 mmol of **1c**, and 0.73 mmol of **2**. Yield 0.151 g (75%, from **3d**), 0.155 g (77%, from **3e**), 0.127 g (63%, from **3f**). The IR and ^1H and ^{13}C NMR spectral data were identical to those reported in [23].

CONCLUSIONS

Dimethyl acetylenedicarboxylate can be involved in three-component domino reactions with 1-aroyl-3,4-dihydroisoquinolines and strong CH acids. Unlike similar reactions with electron-deficient terminal alkynes, the transformation sequence includes migration of methoxycarbonyl group and participation of enolized CH acid. Weak CH and NH acids do not react as the third component, so that two-component condensation products are formed.

AUTHOR INFORMATION

A.R. Miftyakhova, ORCID: https://orcid.org/0000-0001-5453-2529

M.B. Sidakov, ORCID: https://orcid.org/0009-0000-0408-3948

T.N. Borisova, ORCID: https://orcid.org/0000-0003-4532-3762

A.N. Fakhrutdinov, ORCID: https://orcid.org/0009-0001-0502-5974

A.A. Titov, ORCID: https://orcid.org/0000-0001-8943-0362

E.A. Sorokina, ORCID: https://orcid.org/0000-0001-8867-7988

A.V. Varlamov, ORCID: https://orcid.org/0000-0003-2320-8747

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CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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REFERENCES

1. Xiang, L., Xing, D., Wang, W., Wang, R., Ding, Y., and Du, L., *Phytochemistry*, 2005, vol. 66, p. 2595. https://doi.org/10.1016/j.phytochem.2005.08.011
2. Ballot, C., Martoriati, A., Jendoubi, M., Buche, S., Formstecher, P., Mortier, L., Kluza, J., and Marchetti, P., *Mar. Drugs*, 2014, vol. 12, p. 779. https://doi.org/10.3390/md12020779
3. Reyes-Gutiérrez, P.E., Camacho, J.R., Ramírez-Apan, M.T., Osornio, Y.M., and Martínez, R., *Org. Biomol. Chem*., 2010, vol. 8, p. 4374. https://doi.org/10.1039/C004399K
4. Fukuda, T., Ishibashi, F., and Iwao, M., *Alkaloids*, 2020, vol. 83, p. 1. https://doi.org/10.1016/bs.alkal.2019.10.001
5. Nevskaya, A.A., Anikina, L.V., Purgatorio, R., Catto, M., Nicolotti, O., de Candia, M., Pisani, L., Borisova, T.N., Miftyakhova, A.R., Varlamov, A.V., Nevskaya, E.Y., Borisov, R.S., Voskressensky, L.G., and Altomare, C.D., *Molecules*, 2021, vol. 26, article no. 359. https://doi.org/10.3390/molecules26020359
6. Tangdenpaisal, K., Worayuthakarn, R., Karnkla, S., Ploypradith, P., Intachote, P., Sengsai, S., Saimanee, B., Ruchirawat, S., and Chittchang, M., *Chem. Asian J*., 2015, vol. 10, p. 925. https://doi.org/10.1002/asia.201403361
7. Reddy, M.V.R., Rao, M.R., Rhodes, D., Hansen, M.S.T., Rubins, K., Bushman, F.D., Venkateswarlu, Y., and Faulkner, D.J., *J. Med. Chem*., 1999, vol. 42, p. 1901. https://doi.org/10.1021/jm9806650
8. Su, B., Cai, C., Deng, M., Liang, D., Wang, L., and Wang, Q., *Bioorg. Med. Chem. Lett*., 2014, vol. 24, p. 2881. https://doi.org/10.1016/j.bmcl.2014.04.101
9. Fukuda, T., Ishibashi, F., and Iwao, M., *Heterocycles*, 2011, vol. 83, p. 491. https://doi.org/10.3987/REV-10-686
10. Maryanoff, B.E., Vaught, J.L., Shank, R.P., McComsey, D.F., Costanzo, M.J., and Nortey, S.O., *J. Med. Chem*., 1990, vol. 33, p. 2793. https://doi.org/10.1021/jm00172a018
11. Shang, Z.H., Zhang, X.J., Li, Y.M., Wu, R.X., Zhang, H.R., Qin, L.Y., Ni, X., Yan, Y., Wu, A.X., and Zhu, Y.P., *J. Org. Chem*., 2021, vol. 86, p. 15733. https://doi.org/10.1021/acs.joc.1c01682
12. Yue, Y., Sun, Y., Zhao, S., Yan, X., Li, R., Shi, Y., Zhuo, K., and Liu, J., *Chem. Asian J*., 2016, vol. 11, p. 3339. https://doi.org/10.1002/asia.201601233
13. Alizadeh, A. and Rostampoor, A., *ChemistrySelect*, 2021, vol. 6, p. 12960. https://doi.org/10.1002/slct.202103675
14. Tao, L., Xu, Z., Han, J., Deng, H., Shao, M., Chen, J., Zhang, H., and Cao, W., *Synthesis*, 2016, vol. 48, p. 4228. https://doi.org/10.1055/s-0035-1562624
15. Wu, F.S., Zhao, H.Y., Xu, Y.L., Hu, K., Pan, Y.M., and Ma, X.L., *J. Org. Chem*., 2017, vol. 82, p. 4289. https://doi.org/10.1021/acs.joc.7b00280
16. Ghosh, A., Kolle, S., Barak, D.S., Kant, R., and Batra, S., *ACS Omega*, 2019, vol. 24, p. 20854. https://doi.org/10.1021/acsomega.9b03546
17. Dumitrascu, F., Georgescu, E., Georgescu, F., Popa, M.M., and Dumitrescu, D., *Molecules*, 2013, vol. 18, p. 2635. https://doi.org/10.3390/molecules18032635
18. Zhou, W., Liu, H., Guo, Y., Gu, Y., Han, J., Chen, J., Deng, H., Shao, M., Zhang, H., and Cao, W., *J. Fluorine Chem*., 2019, vol. 222, p. 51. https://doi.org/10.1016/j.jfluchem.2019.04.015
19. Tang, E., Mao, D., Sun, Q., Liao, M., Li, Y., and Liu, S., *Heterocycles*, 2019, vol. 98, p. 1563. https://doi.org/10.3987/COM-19-14162
20. Wang, W., Sun, J., Hu, H., and Liu, Y., *Org. Biomol. Chem*., 2018, vol. 16, p. 1651. https://doi.org/10.1039/C7OB03048G

21. Miftyakhova, A.R., Borisova, T.N., Titov, A.A., Sidakov, M.B., Novikov, R.A., Efimov, I.V., Varlamov, A.V., and Voskressensky, L.G., *Chem. Biodiversity*, 2022, vol. 19, article ID e202100584. https://doi.org/10.1002/cbdv.202100584
22. Miftyakhova, A.R., Sidakov, M.B., Borisova, T.N., Ilyushenkova, V.V., Fakhrutdinov, A.N., Sorokina, E.A., Varlamov, A.V., and Voskressensky, L.G., *Tetrahedron Lett*., 2022, vol. 103, article ID 153991. https://doi.org/10.1016/j.tetlet.2022.153991
23. Voskressensky, L.G., Borisova, T.N., Matveeva, M.D., Khrustalev, V.N., Titov, A.A., Aksenov, A.V., Dyachenko, S.V., and Varlamov, A.V., *Tetrahedron Lett*., 2017, vol. 58, p. 877. https://doi.org/10.1016/j.tetlet.2017.01.061
24. Matveeva, M., Golovanov, A., Borisova, T., Titov, A., Varlamov, A., Shaabani, A., Obydennik, A., and Voskressensky, L., *Mol. Catal*. 2018, vol. 461, p. 67. https://doi.org/10.1016/j.mcat.2018.09.020