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Three-component synthesis of tetrasubstituted pyrroles by condensation with amines and arylglyoxals

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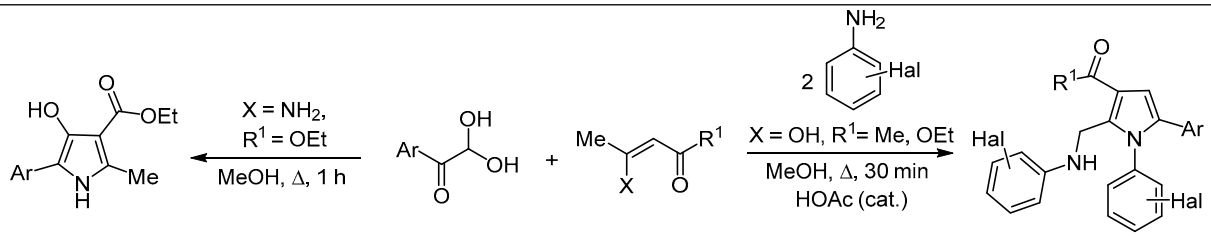


A one-pot three-component condensation for the synthesis of functionalized pyrroles from arylglyoxal hydrates, acetylacetone or acetoacetic ester, and halo-substituted anilines has been developed. The reaction of ethyl 3-aminocrotonate and arylglyoxal led to the respective ethyl 5-aryl-4-hydroxy-2-methyl-(1*H*)-pyrrole-3-carboxylates.

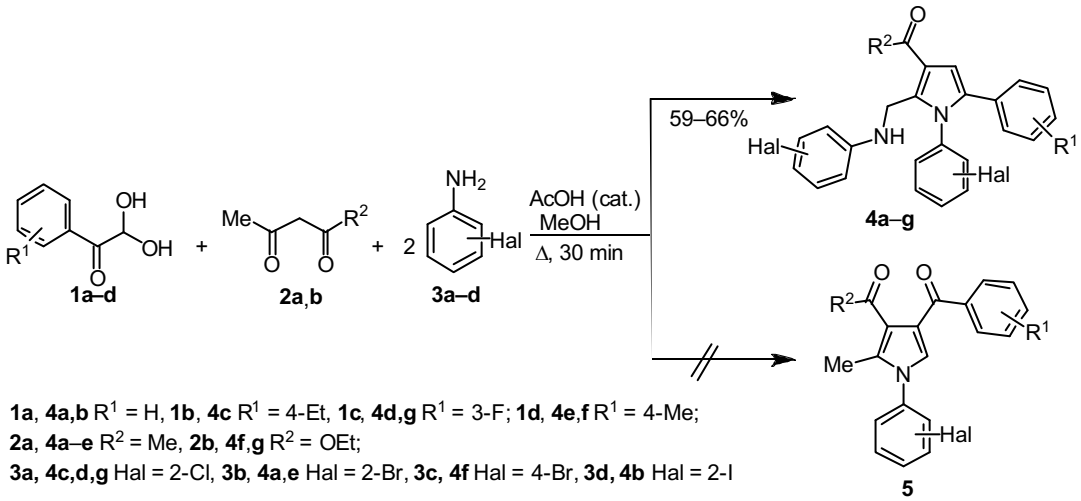
Keywords: acetoacetic ester, acetylacetone, anilines, arylglyoxals, ethyl 3-aminobuten-2-oate, pyrroles, multicomponent reactions.

The pyrrole ring is a part of many biologically important compounds, such as hemoglobin and chlorophyll, as well as medications (psychotropic, antiemetic, anticholinergic, antihistaminic, and antihypertensive agents).[1,2] Several classical methods of synthesis (Paal–Knorr, Knorr, Hantzsch[3–9]) and modern approaches to the formation of pyrrole ring (for example, cyclizations using α,β-unsaturated nitro compounds,[10] nitro compounds and isocyanoacetates (Barton–Zard synthesis),[11–13] and one-pot procedures involving aldehydes, β-dicarbonyl compounds, nitromethane, and aromatic amines[14]) have been described in the literature. Formation of 3-acetyl(alkoxycarbonyl)-1,4-diaryl-2-methylpyrrole derivatives was proposed by authors of the latter work. Only a few examples have been reported were pyrrole derivatives were synthesized using arylglyoxals,[15–20] and the ring closure always occurred by a Paal–Knorr type reaction.[21]

While continuing the study of the reactivity of arylglyoxal hydrates in condensation reactions involving β-dicarbonyl compounds and nucleophilic reagents,[22–25] we discovered a convenient method for the synthesis of tetrasubstituted pyrroles. Refluxing of arylglyoxal hydrates **1a**–**d**, acetylacetone (**2a**) or acetoacetic ester (**2b**), nitromethane, and substituted anilines **3a**–**d** in methanol with added catalytic amounts of acetic acid was found to result in precipitation of a mixture of pyrroles **4a**–**g** from the hot reaction mixture after 30 min (Scheme 1). Substituents in the aniline and arylglyoxal fragments practically did not affect the reaction duration and the yield of products. We should note that anilines with electron-withdrawing substituents (*p*-nitroaniline, *m*-nitroaniline) did not produce the target products and were isolated from the reaction mixture in unchanged form, as should be expected from the proposed reaction mechanism.

The synthesized compounds **4** were obtained after purification as white crystals. The molecular structures of these compounds were established based on elemental analysis, IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, and mass spectrometry. The obtained results pointed to the presence of three aromatic rings and an acetyl group in the molecule. Besides that, ^{1}H NMR spectra indicated the presence of an ABX spin-spin coupling pattern, manifested as double doublets of methylene group protons and a broadened triplet at 4.7–5.0 ppm, which disappeared due to deuterium exchange. This gave evidence that the methylene group protons were non-equivalent and there were steric obstacles to free rotation, caused by bulky aromatic groups. The analysis of ^{1}H NMR signals in the aromatic region

Scheme 1



1a, **4a,b** R^1 = H, **1b**, **4c** R^1 = 4-Et, **1c**, **4d,g** R^1 = 3-F; **1d**, **4e**,**f** R^1 = 4-Me;
2a, **4a–e** R^2 = Me, **2b**, **4f**,**g** R^2 = OEt;
3a, 4c,d,g Hal = 2-Cl, **3b**, **4a**,**e** Hal = 2-Br, **3c, 4f** Hal = 4-Br, **3d, 4b** Hal = 2-I

allowed to reach a conclusion about the presence of two substituted aniline fragments and an aromatic ring from arylglyoxal in the molecules of compounds **4**, which did not match the structure of the expected 3-acetyl (ethoxycarbonyl)-4-aroyl-1-aryl-2-methylpyrroles **5** (by analogy to published data[14]) and provided evidence that nitromethane, which is a synthon containing one carbon atom, did not participate in the reaction. The structure of condensation products was proved conclusively by X-ray structural analysis in the case of compound **4b** (Fig. 1), identified as 3-acetyl-1-(2-iodophenyl)-2-{[(2-iodophenyl)-amino]methyl}-5-phenylpyrrole.

The N(1) atom in compound **4b** had a planar configuration (the sum of valence angles was 359.6(5)°), all parameters of pyrrole ring geometry matched the average values for tetrasubstituted pyrroles of analogous structure (according to the structural database data for 21 compounds[26]). The C(2)–C(24) bond (1.474(5) Å) was longer than the average value for carbonyl substituents at β-position (1.451 Å), while the C(24)–O(1) bond (1.209(5) Å) was shortened (1.222 Å), indicating a disrupted π-conjugation between the C(1)=C(2) and C(24)=O(1) bonds. The aryl substituent at the N(1) atom was rotated by 72.1(6)° relative to the pyrrole ring plane, preventing conjugation between the π-systems of rings; this was confirmed by lengthening of the N(1)–C(5) bond (1.437(4) Å) compared to the average value (1.371 Å).[27] The aryl substituent at the C(4) atom was rotated by 37.8(6)° relative to the pyrrole ring, allowing the possibility of conjugation (the C(4)–C(18) bond length (1.469(5) Å) matched the average value for conjugated systems (1.470 Å)). The N(2) atom had a flattened pyramidal configuration (the sum of valence angles was 352(3)°), probably caused by the shift in the H(2) atom position that enhanced the intramolecular N(2)–H(2)···O(1) hydrogen bond (H···O 2.32(4) Å, N–H···O 128(3)°). The N(2)–C(12) bond (1.379(4) Å) had an intermediate length between conjugated and non-conjugated bonds of similar type (1.353/1.419 Å), while the N(2)–C(11) bond (1.446(4) Å) was substantially shortened (1.469 Å).[27]

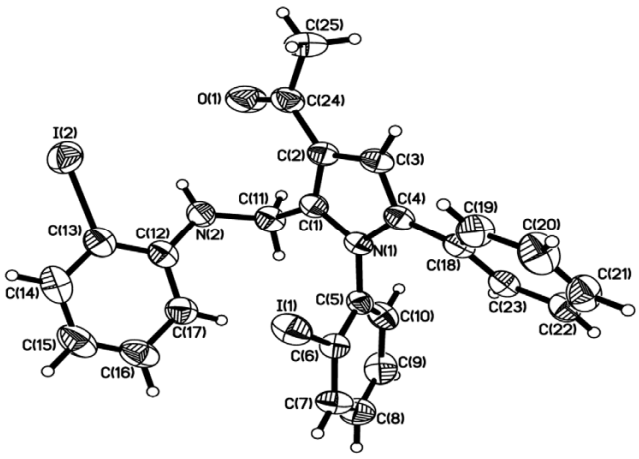


Figure 1. The molecular structure of compound **4b** with atoms represented by thermal vibration ellipsoids of 50% probability.

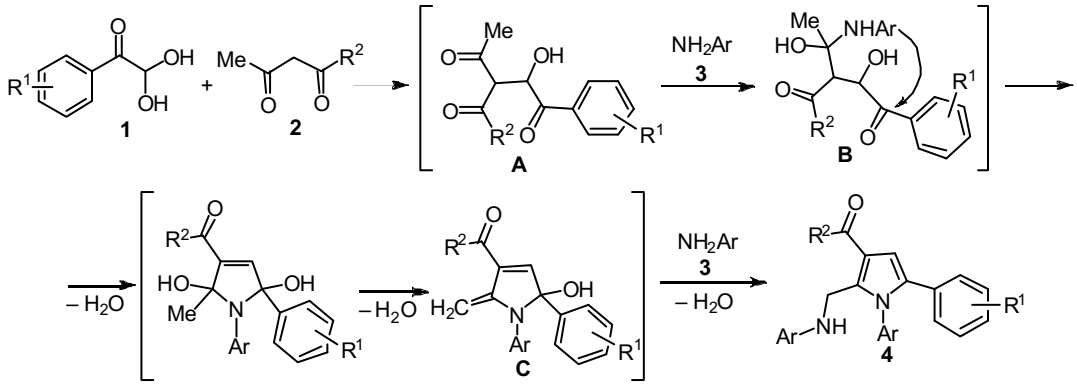
We should note that mass spectra of the synthesized compounds contained molecular ion peaks of relatively low intensity. For example, the strongest peak in the mass spectrum of compound **4b** had *m*/*z* 400, corresponding to the loss of 2-iodophenylimine radical.

Taking into account the unusual course of this reaction, including the need for 2 mol of aniline in the formation of products **4**, we performed the reaction with a double excess of substituted aniline, but the product yield increased insignificantly (by 10–15%).

The probable mechanism leading to the synthesis of the target compounds included the formation of hydroxy ketone **A**, which was converted to aminal **B** by the action of aromatic amine **3** (Scheme 2). The further cyclization by Paal–Knorr reaction led to the formation of pyrrole ring. The subsequent α-elimination of water and 1,4-addition of the second molecule of aniline **3** to the intermediate s-*trans*-diene **C** eventually led to the pyrrole **4**.

The authors of a publication[14] considered in four-component condensation of aldehydes, anilines, acetylacetone, and nitromethane the formation of an enamino-ketone intermediate with the participation of aniline and β-diketone, which reacted with an α,β-unsaturated nitro compound, formed by the condensation of aromatic aldehyde with nitromethane. We decided to test the possibility of analogous three-component condensation

Scheme 2



occurring between arylglyoxals **1**, enaminocrotonate **6**, and nitromethane. However, only pyrroles **7** were isolated in all cases as products of two-component condensation between glyoxal hydrates **1** and aminoester **6** (Scheme 3), isolated examples of which have been already described in the literature.[15,16,20] Similarly to the reaction that we described above, nitromethane did not participate in this reaction.

The structures of previously undescribed compounds **7b**–**d**,**f**–**j** were established by spectral methods, and compound **7f** was also characterized by X-ray structural analysis (Fig. 2). Similarly to structure **4b**, the nitrogen atom in pyrrole ring was planar (the sum of valence angles was 360(1)°). Its geometry, however, was substantially different from the parameters of *N*-substituted ring systems. The asymmetry of N–C bond lengths in structure **7f**, characteristic for β-carbonyl-substituted pyrroles (results from structural database,[26] averaged for 139 structures), was quite pronounced (N(1)–C(4) 1.345(2) Å with the mean value of 1.357 Å, N(1)–C(1) 1.398(2) Å with the mean value of 1.377 Å). Taking into account the shortening of C(1)–C(2) bond to 1.377 Å (1.382 Å) and lengthening of C(2)–O(3) bond to 1.355(2) Å (the average value for enols is 1.333 Å),[27] these data suggest some disruption of conjugation in the HN(1)–C(1)=C(2)–O(3)H chain, while favoring conjugation in the HN(1)–C(4)=C(3)–C(6)=O(2) chain. Remarkably, the C(1)–C(9) bond (1.441(2) Å) at the same time was markedly shortened even compared to typical conjugated systems (1.470 Å),[27] indicating the presence of π-conjugation with aryl substituent, which was confirmed by the coplanar ring orientation (the angle between ring planes was 10.0(3)°). The hydroxy group O(3)–H(3) formed intramolecular hydrogen bonds – a classical O(3)–H(3)···O(2) hydrogen bond (H···O 1.85(2) Å, O–H···O 148(2)°) and a non-classical C(14)–H(14)···O(3) hydrogen bond (H···O 2.31(2) Å, C–H···O 129(2)°), which stabilized the planar molecular configuration. The molecules in crystal structure formed chains along the crystallographic direction (100) linked by paired intermolecular hydrogen bonds N(1)–H(1)···O(5)' (0.5+*x*, –0.5–*y*, 1–*z*; H···O 2.17 Å, N–H···O 175°) and C(10)–H(10)···O(5)' (0.5+*x*, –0.5–*y*, 1–*z*; H···O 2.40 Å, C–H···O 161°).

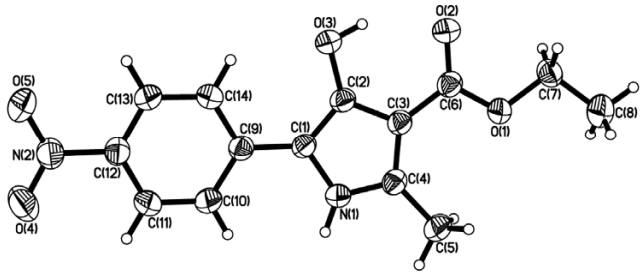
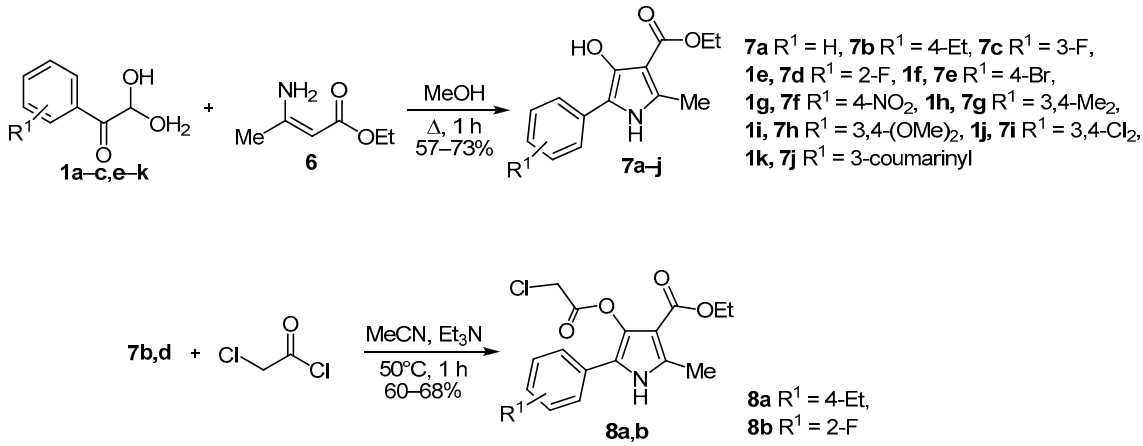


Figure 2. The molecular structure of compound **7f** with atoms represented by thermal vibration ellipsoids of 50% probability.

Scheme 3



The presence of hydroxy group at position 3 of pyrrole ring was additionally confirmed by an acylation reaction, when the treatment of pyrroles **7b**,**d** with chloroacetyl chloride in acetonitrile in the presence of triethylamine gave the esters **8a**,**b** (Scheme 3).

Thus, we have demonstrated that a three-component reaction involving arylglyoxals, acetylacetone or acetoacetic ester, and halo-substituted anilines in 1:1:2 ratio offers a convenient method for the synthesis of 3-acetyl-(ethoxycarbonyl)-1,2-diaryl-5-(arylaminomethyl)pyrroles. The condensation of ethyl β-aminocrotonate, hydrates of arylglyoxals, and nitromethane was found to proceed without participation of the latter, and led to the formation of ethyl 5-aryl-4-hydroxy-2-methyl-1*H*-pyrrole-3-carboxylates.

Experimental

IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer in KBr pellets. ^{1}H NMR spectra were acquired on a Varian Mercury VX-200 spectrometer (200 MHz), ^{13}C NMR spectra – on a Bruker AM-400 spectrometer (100 MHz) in DMSO-d_6 solution, the internal standard was TMS. Mass spectra were recorded on a Hewlett-Packard LC/MSD 1100 instrument (EI, 70 eV). Elemental analysis was performed on a Eurovector EA 3000 Elemental Analyzer. Melting points were determined on a Kofler bench. The reaction progress and purity of the obtained compounds were controlled by TLC on Silufol UV-254 plates with 1:1 toluene–EtOAc and 10:1 $CHCl_3$–2-PrOH mobile phases, visualization with iodine vapor.

Synthesis of compounds 4a–g (General method). A mixture of acetylacetone (**2a**) (0.10 ml, 1.0 mmol) or acetoacetic ester (**2b**) (0.15 ml, 1.1 mmol), arylglyoxal hydrate **1a–d** (1.0 mmol), substituted aniline **3a–d** (2.0 mmol), and AcOH (5–7 drops) in MeOH (10 ml) was refluxed for 30 min. The reaction mixture was cooled, the precipitate was filtered off, washed with warm water, cold MeOH, and recrystallized from MeOH.

1-[1-(2-Bromophenyl)-2-{[(2-bromophenyl)amino]-methyl}-5-phenyl-1*H*-pyrrol-3-yl]ethanone (4a). Yield 0.34 g (65%), white powder, mp 148–149°C. IR spectrum, ν, cm^{-1}: 640, 1016, 1244, 1482, 1630, 1668, 2924, 3063, 3366. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.51 (3H, s, CH_3); 4.25 (1H, dd, J_{AB} = 14.4, J_{AX} = 7.0) and 4.45 (1H, dd, J_{AB} = 14.4, J_{BX} = 5.0, CH_2); 4.94 (1H, t, J_{BX} = 5.0, NH); 6.32 (1H, d, *J* = 7.8, H Ar); 6.47 (1H, t, *J* = 8.0, H Ar); 6.99–7.55 (11H, m, H-4, H Ar); 7.72 (1H, d, *J* = 7.8, H Ar). Mass spectrum, *m*/*z* (I_{rel}, %): 526 (10), 524 [M]$^+$ (19), 522 (9), 354 (100), 230 (49), 157 (8), 77 (15). Found, %: C 57.20; H 3.77; N 5.45. $C_{25}H_{20}Br_2N_2O$. Calculated, %: C 57.28; H 3.85; N 5.34.

1-(1-(2-Iodophenyl)-2-{[(2-iodophenyl)amino]methyl}-5-phenyl-1*H*-pyrrol-3-yl)ethanone (4b). Yield 0.39 g (63%), white powder, mp 153–154°C. IR spectrum, ν, cm^{-1}: 680, 1027, 1244, 1478, 1632, 1660, 2982, 3075, 3370. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.51 (3H, s, CH_3); 4.14 (1H, dd, J_{AB} = 14.0, J_{AX} = 7.0) and 4.47 (1H, dd, J_{AB} = 14.0, J_{BX} = 5.4, CH_2); 4.77 (1H, t, J_{BX} = 5.4, NH); 6.22 (1H, d, *J* = 8.0, H Ar); 6.33 (1H, t, *J* = 8.0, H Ar); 6.96–7.27 (8H, m, H-4, H Ar); 6.46–7.55 (3H, m, H Ar); 7.92 (1H, d, *J* = 8.0, H Ar). ^{13}C NMR spectrum, δ, ppm: 29.3 ($CO\underline{C}H_3$); 39.7 (NCH_2); 85.6; 86.2; 88.3; 101.2; 110.0; 111.4; 118.9; 123.0; 127.4; 128.3 (2C); 129.2; 129.4 (2C); 130.8; 131.3; 134.0; 135.9; 138.9; 139.6; 139.8; 146.6; 194.7 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 400 [M–(2-IC_6H_4NH)]$^+$ (100), 230 (26). Found, %: C 48.52; H 3.29; N 4.55. $C_{25}H_{20}I_2N_2O$. Calculated, %: C 48.57; H 3.26; N 4.53.

1-[1-(2-Chlorophenyl)-2-{[(2-chlorophenyl)amino]methyl}-5-(4-ethylphenyl)-1*H*-pyrrol-3-yl]ethanone (4c). Yield 0.28 g (61%), white powder, mp 143–144°C. IR spectrum, ν, cm^{-1}: 636, 790, 1030, 1244, 1478, 1630, 1662, 2970, 3069, 3362. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.07 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.52 (3H, s, CH_3); 2.70 (2H, q, *J* = 7.0, $C\underline{H}_2CH_2$); 4.30 (1H, dd, J_{AB} = 14.4, J_{AX} = 7.2) and 4.46 (1H, dd, J_{AB} = 14.4, J_{BX} = 5.2, CH_2); 5.02 (1H, t, J_{BX} = 5.2, NH); 6.33 (1H, d, *J* = 8.2, H Ar); 6.52 (1H, t, *J* = 8.8, H Ar); 6.90–7.17 (7H, m, H-4, H Ar); 7.41–7.58 (4H, m, H Ar). Found, %: C 70.11; H 5.30; N 6.11. $C_{27}H_{24}Cl_2N_2O$. Calculated, %: C 69.98; H 5.22; N 6.05.

1-[1-(2-Chlorophenyl)-2-{[(2-chlorophenyl)amino]methyl}-5-(3-fluorophenyl)-1*H*-pyrrol-3-yl]ethanone (4d). Yield 0.30 g (66%), white powder, mp 149–150°C. IR spectrum, ν, cm^{-1}: 638, 785, 1058, 1246, 1476, 1628, 1670, 2920, 3054, 3362. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.51 (3H, s, CH_3); 4.32 (1H, dd, J_{AB} = 14.6, J_{AX} = 7.0) and 4.46 (1H, dd, J_{AB} = 14.4, J_{BX} = 5.4, CH_2); 4.98 (1H, t, J_{BX} = 5.4, NH); 6.34 (1H, d, *J* = 8.2, H Ar); 6.52 (1H, t, *J* = 8.8, H Ar); 6.85–7.24 (6H, m, H-4, H Ar); 7.47–7.68 (4H, m, H Ar). Found, %: C 66.04; H 3.92; N 6.15. $C_{25}H_{19}Cl_2FN_2O$. Calculated, %: C 66.24; H 4.22; N 6.18.

1-[1-(2–Bromophenyl)-2-{[(2-bromophenyl)amino]methyl}-5-(4-methylphenyl)-1*H*-pyrrol-3-yl]ethanone (4e). Yield 0.35 g (65%), white powder, mp 155–156°C. IR spectrum, ν, cm^{-1}: 648, 1020, 1249, 1480, 1628, 1666, 2926, 3060, 3368. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.17 (3H, s, CH_3); 2.51 (3H, s, CH_3); 4.26 (1H, dd, J_{AB} = 14.2, J_{AX} = 7.0) and 4.47 (1H, dd, J_{AB} = 14.2, J_{BX} = 5.2, CH_2); 4.92 (1H, t, J_{BX} = 5.2, NH); 6.30 (1H, d, *J* = 8.2, H Ar); 6.46 (1H, t, *J* = 8.8, H Ar); 6.93–6.97 (5H, m, H-4, H Ar); 7.28–7.52 (4H, m, H Ar); 7.71 (1H, d, *J* = 7.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 20.7 (CH_3); 28.8 ($CO\underline{C}H_3$); 38.0 (NCH_2); 89.6; 109.0; 110.6; 111.6; 117.9 (2C); 122.7; 123.3; 127.9 (2C); 128.5; 128.9 (2C); 131.4 (2C); 132.3; 133.5; 134.4; 135.8; 136.2; 136.8; 144.1; 195.2 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 540 (5), 538 (10), 536 [M]$^+$ (5), 368 (100), 244 (68), 155 (8), 91 (16). Found, %: C 58.09; H 3.97; N 5.15. $C_{26}H_{22}Br_2N_2O$. Calculated, %: C 58.01; H 4.12; N 5.20.

Ethyl 1-(4-bromophenyl)-2-{[(4-bromophenyl)amino]-methyl}-5-(4-methylphenyl)-1*H*-pyrrole-3-carboxylate (4f). Yield 0.33 g (60%), white powder, mp 130–132°C (MeOH). IR spectrum, ν, cm^{-1}: 650, 797, 997, 1051, 1219, 1252, 1466, 1597, 1698, 2977, 3366. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.17 (3H, t, *J* = 7.0, CH_3); 2.19 (3H, s, CH_3); 4.18–4.26 (4H, m, $2CH_2$); 4.82 (1H, t, *J* = 5.2, NH); 6.40 (2H, d, *J* = 8.0, H Ar); 6.66 (1H, s, H-4); 6.91–7.24 (8H, m, H Ar); 7.56 (2H, d, *J* = 7.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 14.7 ($OCH_2\underline{C}H_3$); 21.0 ($ArCH_3$); 38.1 (NCH_2); 59.8 ($O\underline{C}H_2CH_3$); 106.9; 108.6; 110.0 (2C); 114.3; 122.3; 127.4;

128.5 (2C); 128.9; 129.4; 130.8 (2C); 131.6 (2C); 132.5 (2C); 135.0 (2C); 136.7; 137.1; 147.9; 164.3 (C=O). Found, %: C 57.09; H 4.23; N 4.95. $C_{27}H_{24}Br_2N_2O_2$. Calculated, %: C 57.06; H 4.26; N 4.93.

Ethyl 1-(2-Chlorophenyl)-2-{[(2-chlorophenyl)amino]-methyl}-5-(3-fluorophenyl)-1*H*-pyrrole-3-carboxylate (4g). Yield 0.28 g (59%), white powder, mp 96–98°C. IR spectrum, ν, cm^{-1}: 790, 825, 949, 1069, 1069, 1245, 1493, 1695, 2977, 3361. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.26 (3H, t, *J* = 7.0, $CO_2CH_2C\underline{H}_3$); 4.26 (2H, q, *J* = 7.0, $CO_2C\underline{H}_2CH_3$); 4.32 (1H, dd, J_{AB} = 14.6, J_{AX} = 7.0) and 4.46 (1H, dd, J_{AB} = 14.4, J_{BX} = 5.6, CH_2); 4.79 (1H, t, J_{BX} = 5.6, NH); 6.47–6.57 (2H, m, H Ar); 6.68 (1H, s, H-4); 6.83–7.23 (6H, m, H Ar); 7.47–7.67 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 14.7 ($OCH_2\underline{C}H_3$); 37.8 (NCH_2); 60.2 ($O\underline{C}H_2CH_3$); 110.9; 111.7; 114.4; 114.6; 114.8; 114.9; 117.7; 118.5; 124.2; 128.3; 128.7; 129.3; 130.6; 130.8; 131.7; 132.7; 133.8; 134.8; 137.8; 143.4; 160.9; 163.3; 164.5 (C=O). Found, %: C 64.69; H 4.33; N 5.85. $C_{26}H_{21}Cl_2FN_2O_2$. Calculated, %: C 64.61; H 4.38; N 5.80.

Synthesis of compounds 7a–j (General method). A mixture of ethyl 3-amino-2-butenoate (**6**) (0.3 g, 1 mmol) and arylglyoxal hydrate **1a–c**,**e–k** (1 mmol) in MeOH (10 ml) was refluxed for 1 h. The precipitate that formed after cooling was filtered off, washed on filter with MeOH, and recrystallized from MeOH.

Ethyl 4-hydroxy-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate (7a). Yield 0.16 g (65%), cream-colored crystals, mp 157–158°C (mp 159–161°C (EtOH)[15]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 7.0, $CO_2CH_2C\underline{H}_3$); 2.39 (3H, s, CH_3); 4.25 (2H, q, *J* = 7.0, $CO_2C\underline{H}_2CH_3$); 7.04–7.31 (3H, m, H Ar); 7.67 (2H, d, *J* = 7.6, H-2,6 Ar); 8.26 (1H, s, OH); 11.18 (1H, s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 245 $[M]^+$ (94), 199 (90), 159 (32), 128 (40), 104 (50), 67 (100). Found, %: C 68.40; H 6.07; N 5.65. $C_{14}H_{15}NO_3$. Calculated, %: C 68.56; H 6.16; N 5.71.

Ethyl 5-(4-ethylphenyl)-4-hydroxy-2-methyl-1*H*-pyrrole-3-carboxylate (7b). Yield 0.20 g (73%), beige crystals, mp 143–144°C. IR spectrum, ν, cm^{-1}: 700, 832, 1099, 1262, 1483, 1606, 1688, 2971, 3381, 3450. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, t, *J* = 6.8, $CH_2C\underline{H}_3$); 1.27 (3H, t, *J* = 7.2, $CO_2CH_2C\underline{H}_3$); 2.39 (3H, s, CH_3); 2.52 (2H, q, *J* = 6.8, $C\underline{H}_2CH_3$); 4.23 (2H, q, *J* = 7.2, $CO_2C\underline{H}_2CH_3$); 7.16 (2H, d, *J* = 8.2, H-2,6 H Ar); 7.59 (2H, d, *J* = 8.0, H-3,5 H Ar); 8.18 (1H, s, OH); 11.20 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 13.7 (2-CH_3); 14.7 ($OCH_2\underline{C}H_3$); 16.0 ($CH_2\underline{C}H_3$); 28.3 ($\underline{C}H_2CH_3$); 59.7 ($O\underline{C}H_2CH_3$); 100.9; 111.1; 123.2 (2C); 128.2 (2C); 129.8; 131.4; 139.9; 142.9 (C); 167.1 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 273 $[M]^+$ (87), 227 (100), 212 (15), 132 (16), 67 (13). Found, %: C 70.39; H 7.09; N 5.17. $C_{16}H_{19}NO_3$. Calculated, %: C 70.31; H 7.01; N 5.12.

Ethyl 5-(3-fluorophenyl)-4-hydroxy-2-methyl-1*H*-pyrrole-3-carboxylate (7c). Yield 0.15 g (57%), cream-colored crystals, mp 132–134°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 7.0, $CO_2CH_2C\underline{H}_3$); 2.40 (3H, s, CH_3); 4.25 (2H, q, *J* = 7.0, $CO_2C\underline{H}_2CH_3$); 7.30–7.70 (4H, m, H Ar); 8.42 (1H, s, OH); 11.30 (1H, s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 263 $[M]^+$ (53), 218 (24), 217 (77), 161 (100), 146 (7); 122 (11), 67 (80). Found, %: C 63.92; H 5.27; N 5.27. $C_{14}H_{14}FNO_3$. Calculated, %: C 63.87; H 5.36; N 5.32.

Ethyl 5-(2-fluorophenyl)-4-hydroxy-2-methyl-1*H*-pyrrole-3-carboxylate (7d). Yield 0.15 g (57%), cream-colored crystals, mp 110–111°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (3H, t, *J* = 7.0, $CO_2CH_2C\underline{H}_3$); 2.40 (3H, s, CH_3); 4.24 (2H, q, *J* = 7.0, $CO_2C\underline{H}_2CH_3$); 7.16–7.25 (3H, m, H Ar); 7.66–7.75 (1H, m, H Ar); 8.19 (1H, s, OH); 10.96 (1H, s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 263 $[M]^+$ (23), 218 (19), 217 (100), 122 (18). 84 (5). Found, %: C 63.92; H 5.27; N 5.27. $C_{14}H_{14}FNO_3$. Calculated, %: C 63.87; H 5.36; N 5.32.

Ethyl 5-(4-bromophenyl)-4-hydroxy-2-methyl-1*H*-pyrrole-3-carboxylate (7e). Yield 0.20 g (62%), beige crystals, mp 144–146°C (mp 145°C (decomp., EtOH)[15]). IR spectrum, ν, cm^{-1}: 825, 889, 1076, 1164, 1336, 1491, 1606, 1689, 2981, 3382, 3458. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 7.2, $CO_2CH_2C\underline{H}_3$); 2.36 (3H, s, CH_3); 4.23 (2H, q, *J* = 7.2, $CO_2C\underline{H}_2CH_3$); 7.50 (2H, d, *J* = 8.0, H-2,6, H Ar); 7.63 (2H, d, *J* = 8.0, H-3,5, H Ar); 8.37 (1H, s, OH); 11.26 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 13.8 (2-$\underline{C}H_3$); 14.7 ($OCH_2\underline{C}H_3$); 59.2 ($O\underline{C}H_2CH_3$); 101.0; 111.4; 123.6; 128.5 (2C); 132.0 (2C); 132.4; 134.0; 145.3; 167.8 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 323 $[M]^+$ (40), 279 (37), 277 (100), 182 (43), 115 (7). Found, %: C 52.03; H 4.29; N 4.37. $C_{14}H_{14}BrNO_3$. Calculated, %: C 51.87; H 4.35; N 4.32.

Ethyl 4-hydroxy-2-methyl-5-(4-nitrophenyl)-1*H*-pyrrole-3-carboxylate (7f). Yield 0.18 g (60%), light-orange crystals, mp 176°C . ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.29 (3H, t, *J* = 7.0, $CO_2CH_2C\underline{H}_3$); 2.43 (3H, s, CH_3); 4.25 (2H, q, *J* = 7.0, $CO_2C\underline{H}_2CH_3$); 7.87 (2H, d, *J* = 8.0, H-2,6 H Ar); 8.20 (2H, d, *J* = 8.0, H-3,5 H Ar); 8.84 (1H, s, OH); 11.53 (1H, s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 290 $[M]^+$ (40), 245 (18), 244 (100), 214 (10), 198 (12), 149 (15), 67 (32). Found, %: C 58.02; H 4.92; N 9.57. $C_{14}H_{14}N_2O_5$. Calculated, %: C 57.93; H 4.86; N 9.65.

Ethyl 5-(3,4-dimethylphenyl)-4-hydroxy-2-methyl-1*H*-pyrrole-3-carboxylate (7g). Yield 0.19 g (70%), light cream-colored crystals, mp 152°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (3H, t, *J* = 7.0, $CO_2CH_2C\underline{H}_3$); 2.16 (3H, s, CH_3 Ar); 2.20 (3H, s, CH_3 Ar); 2.38 (3H, s, CH_3); 4.23 (2H, q, *J* = 7.0, $CO_2C\underline{H}_2CH_3$); 7.07 (1H, d, *J* = 8.2, H Ar); 7.40–7.47 (2H, m, H Ar); 8.16 (1H, s, OH); 11.10 (1H, s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 273 $[M]^+$ (10), 228 (23), 227 (100), 171 (28), 132 (23), 77 (8). Found, %: C 70.62; H 7.07; N 5.15. $C_{16}H_{19}NO_3$. Calculated, %: C 70.31; H 7.01; N 5.12.

Ethyl 5-(3,4-dimethoxyphenyl)-4-hydroxy-2-methyl-1*H*-pyrrole-3-carboxylate (7h). Yield 0.21 g (69%), cream-colored crystals, mp 157–158°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (3H, t, *J* = 7.2, $CO_2CH_2C\underline{H}_3$); 2.40 (3H, s, CH_3); 3.72 (3H, s, OCH_3); 3.76 (3H, s, OCH_3); 4.24 (2H, q, *J* = 7.3, $CO_2C\underline{H}_2CH_3$); 6.92 (1H, d, *J* = 8.2, H-6 Ar); 7.20–7.30 (2H, m, H Ar); 8.13 (1H, s, OH); 11.08 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 13.7 (2-CH_3); 14.8 ($OCH_2\underline{C}H_3$); 56.0 (2OCH_3); 59.6 ($O\underline{C}H_2CH_3$); 100.9;

107.7; 111.1; 112.7; 115.7; 125.5; 131.5; 142.1; 146.3; 149.2; 166.9 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 305 $[M]^+$ (30), 260 (19), 259 (100), 244 (13), 203 (6). Found, %: C 62.74; H 6.38; N 4.65. $C_{16}H_{19}NO_5$. Calculated, %: C 62.94; H 6.27; N 4.59.

Ethyl 5-(3,4-Dichlorophenyl)-4-hydroxy-2-methyl-1*H*-pyrrole-3-carboxylate (7i). Yield 0.22 g (70%), white crystals, mp 144–146°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (3H, t, *J* = 7.0, $CO_2CH_2C\underline{H}_3$); 2.38 (3H, s, CH_3); 4.23 (2H, q, *J* = 7.0, $CO_2C\underline{H}_2CH_3$); 7.56 (1H, d, *J* = 7.8, H Ar); 7.65 (1H, d, *J* = 7.8, H Ar); 7.89 (1H, s, H Ar); 8.51 (1H, s, OH); 11.30 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 13.8 (2-CH_3); 14.7 ($OCH_2\underline{C}H_3$); 59.8 ($O\underline{C}H_2CH_3$); 101.3; 109.2; 122.8; 123.9; 125.8; 131.0; 131.7; 132.8; 133.8; 145.0; 168.5 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 269 (40), 269 (18), 267 $[M–C_2H_5OH]^+$ (100), 232 (8), 172 (25). Found, %: C 53.74; H 4.28; N 4.55. $C_{14}H_{13}Cl_2NO_3$. Calculated, %: C 53.52; H 4.17; N 4.46.

Ethyl 4-hydroxy-2-methyl-5-(2-oxo-2*H*-chromen-3-yl)-1*H*-pyrrole-3-carboxylate (7j). Yield 0.19 g (60%), light-yellow powder, mp 204–205°C (decomp.). IR spectrum, ν, cm^{-1}: 750, 985, 1138, 1287, 1473, 1610, 1666, 1704, 2981, 3329, 3400. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (3H, t, *J* = 7.0, $CO_2CH_2C\underline{H}_3$); 2.43 (3H, s, CH_3); 4.24 (2H, q, *J* = 7.0, $CO_2C\underline{H}_2CH_3$); 7.31 (1H, t, *J* = 7.6, H Ar); 7.38 (1H, d, *J* = 7.8, H Ar); 7.48 (1H, t, *J* = 7.6, H Ar); 7.66 (1H, d, *J* = 7.8, H Ar); 8.22 (1H, s, CH); 8.83 (1H, s, OH); 10.97 (1H, s, NH). Found, %: C 65.24; H 4.70; N 4.50. $C_{17}H_{15}NO_5$. Calculated, %: C 65.17; H 4.83; N 4.47.

Ethyl 4-(2-chloroacetoxy)-5-(4-ethylphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (8a). Chloroacetyl chloride (0.24 ml, 3 mmol) and Et_3N (0.40 ml, 3 mmol) were added to a solution of compound **7b** (0.27 g, 1 mmol) in acetonitrile (5 ml). The mixture was stirred at 50°C for approximately 1 h (TLC control), then the solvent was evaporated to dryness on a vacuum evaporator, and the obtained precipitate was recrystallized from methanol. Yield 0.21 g (60%), light-beige crystals, mp 140°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.13–1.19 (6H, m, $CO_2CH_2C\underline{H}_3$, $CH_2C\underline{H}_3$); 2.47 (3H, s, CH_3); 2.56 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 4.10 (2H, q, *J* = 7.2, $CO_2C\underline{H}_2CH_3$); 4.65 (2H, s, CH_2); 7.22 (2H, d, *J* = 7.0, H-3,5 H Ar); 7.42 (2H, d, *J* = 7.0, H-2,6 H Ar); 11.59 (1H, s, NH). Found, %: C 61.60; H 5.76; N 4.09. $C_{18}H_{20}ClNO_4$. Calculated, %: C 61.80; H 5.76; N 4.00.

Ethyl 4-(2-chloroacetoxy)-5-(2-fluorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (8b) was obtained analogously. Yield 0.23 g (68%), light-beige crystals, mp 118–119°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.21 (3H, t, *J* = 7.2, $CO_2CH_2C\underline{H}_3$); 2.47 (3H, s, CH_3); 4.11 (2H, q, *J* = 7.2, $CO_2C\underline{H}_2CH_3$); 4.60 (2H, s, CH_2); 7.23–7.39 (4H, m, Ar); 11.69 (1H, s, NH). Found, %: C 56.82; H 4.37; N 4.18. $C_{16}H_{15}ClFNO_4$. Calculated, %: C 56.56; H 4.45; N 4.12.

X-ray structural analysis of pyrroles 4b and 7f. Crystals of compounds **4b** and **7f** (white and light-orange, respectively) were obtained by recrystallization from acetonitrile. X-ray structural study was performed on an Xcalibur-3 diffractometer (MoKα-radiation, CCD-detector, graphite monochromator, ω-scanning, *T* 298 K). The structures were solved directly and refined by F^2 with full matrix method of least squares in anisotropic approximation for non-hydrogen atoms, using the OLEX2[28] software with SHELXS and SHELXL[29] modules. The positions of all hydrogen atoms were revealed from differential synthesis of electron density and localized during further refinement, except for the H(2) atoms in compound **4b**, as well as H(1) and H(3) atoms in compound **7f**, the coordinates of which were refined independently. The length of the N(2)–H(2) bond in compound **4b** was constrained at 0.86(1) Å. The temperature parameters for hydrogen atoms were refined with the "rider" model with U_{iso} = 1.2U_{eq} (1.5U_{eq} for methyl groups), except for the H(1) and H(3) atoms in compound **7f**, which were refined isotropically. The crystallographic data, atomic coordinates, and geometry parameters for structures of compounds **4b** and **7f** were deposited at the Cambridge Crystallographic Data Center (deposits CCDC 1453290, CCDC 1453291, respectively).

References

1. Trofimov, B. A.; Mikhaleva, A. I.; Shmidt, E. Yu.; Sobenina, L. N. *New Pages in the Chemistry of Pyrrole* [in Russian]; Tolstikov, G. A., Ed.; Nauka: Novosibirsk, 2012.
2. *Pyrroles. The Synthesis*, *Reactivity and Physical Properties of Substituted Pyrroles*, *Part II*; Jones, R. A., Ed.; Wiley: New York, 1992.
3. Trofimov, B. A.; Sobenina, L. N.; Demenev, A. P.; Mikhaleva, A. I. *Chem. Rev*. **2004**, *104*, 2481.
4. Black, D. S. In *Science of Synthesis*; Thieme: Stuttgart, 2001, Chapt. 13, p. 441.
5. Liu, J.-H.; Yang, Q.-C.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem*. **2000**, *65*, 3587.
6. Zhang, X.; Sui, Z. *Tetrahedron Lett*. **2003**, *44*, 3071.
7. Azizian, J.; Karimi, A. R.; Arefrad, H.; Mohammadi, A. A.; Mohammadizadeh, M. R. *Mol. Diversity* **2003**, *6*, 223.
8. Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem*., *Int. Ed*. **2003**, *42*, 98.
9. Balme, G. *Angew. Chem*., *Int. Ed*. **2004**, *43*, 6238.
10. Ranu, B. C.; Dey, S. S. *Tetrahedron Lett*. **2003**, *44*, 2865.
11. Barton, D. H. R.; Zard, S. Z. *J. Chem. Soc*., *Chem. Commun*. **1985**, 1098.
12. Barton, D. H. R.; Kervagorel, J.; Zard, S. Z. *Tetrahedron* **1990**, *46*, 7587.
13. Boelle, J.; Shcneider, R.; Gerardin, P.; Loubinoux, B. *Synthesis* **1997**, 1451.
14. Li, B.-L.; Li, P.-H.; Fang, X.-N.; Li, Ch.-X.; Sun, J.-L.; Mo, L.-P.; Zhang, Z.-H. *Tetrahedron* **2013**, *69*, 7011.
15. Feliciano, A. S.; Caballero, E.; Pereira, J. A. P.; Puebla, P. *Tetrahedron* **1989**, *45*, 6553.
16. Caballero, E.; Puebla, P.; Domercq, M.; Medarde, M.; López, J.-L.; Feliciano, A. S. *Tetrahedron* **1994**, *50*, 7849.
17. Khalili, B.; Jajarmi, P.; Eftekhari-Sis, B.; Hashemi, M. M. *J. Org. Chem*. **2008**, *73*, 2090.
18. Eftekhari-Sis, B.; Zirak, M.; Akbari, A.; Hashemi, M. M. J. *Heterocycl. Chem*. **2010**, *47*, 463.
19. Yin, G.; Wang, Z.; Chen, A.; Gao, M.; Wu, A.; Pan, Y. *J. Org. Chem*. **2008**, *73*, 3377.
20. Bhat, S. I.; Trivedi, D. R. *Tetrahedron Lett*. **2013**, *54*, 5577.
21. Estevez, V.; Villacampa, M.; Menendez, *J. C. Chem. Soc. Rev.* **2014**, 43, 4633.

22. Gozalishvili, L. L.; Beryozkina, T. V.; Omelchenko, I. V.; Zubatyuk, R. I.; Shishkin, O. V.; Kolos, N. N. *Tetrahedron Lett*. **2008**, *64*, 8759.
23. Kolos, N. N.; Zamigaylo, L. L.; Chechina, N. V.; Omelchenko, I. V.; Shishkin, O. V.; Vashchenko, E. V. *Chem. Heterocycl. Compd*. **2012**, *48*, 1817. [*Khim. Geterotsikl. Soedin.* **2012**, 1941.]
24. Kolos, N. N.; Kibkalo, B. V.; Zamigaylo, L. L.; Omel'chenko, I. V.; Shishkin, O. V. *Russ. Chem. Bull.*, *Int. Ed.* **2015**, *64*, 1. [*Izv. Akad. Nauk*, *Ser. Khim*. **2015**, 864.]
25. Chechina, N. V.; Kravchuk, O. F.; Omelchenko, I. V.; Shishkin, O. V.; Kolos N. N. *ARKIVOC* **2015**, (vii), 77.
26. Groom, C. R.; Allen, F. H. *Angew. Chem.*, *Int. Ed. Engl*. **2014**, *53*, 662.
27. *Structure Correlation*, Bürgi, H-B.; Dunitz, J. D., Eds.; VCH: Weinheim, 1994, Vol. 2.
28. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Crystallogr*. **2009**, *42*, 339.
29. Sheldrick, G. M. *Acta Crystallogr.*, *Sect. A: Found. Crystallogr.* **2008**, *A64*, 112.