UDC 547.97+535.37

THE INVESTIGATION OF CONVERSION OF BENZYLIDENEMALONONITRILES WITH ACETOACETANILIDE

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Received 08.06.2018

By the Michael addition reaction of *p*-methyl, *p*-nitro substituted benzylidenemalononitriles and thiophenylidenemalononitrile with acetoacetanilide pyridine derivatives were synthesized. Michael addition reaction was carried out for 2,6-dichlorobenzylidenemalononitrile with acetoacetanilide and (*E*)-2-amino-4-(2,6-dichlorophenyl)-5-(1-hydroxyethylidene)-6-oxo-1-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile that is corresponding derivative of pyridine was obtained. Unlike V, VI and VII in this reaction the main product of this reaction is mainly in enol-form. Also the Michael addition reaction of *p*-trifluorobenzylidenemalononitrile and 2-chloro-5-nitrobenzylidenemalononitrile with acetoacetanilide has been investigated.

Keywords: *p*-trifluorobenzylidenemalononitrile, 2-chloro-5-nitrobenzylidenemalononitrile, acetoacetanilide, NMR.

Introduction

Benzylidenemalononitriles been Knoevenagel adducts are very important synthones in synthesis of such functionally-substituted compounds as 4*H*-pyranes, substituted pyridines, pyrazoles etc. Pyridine ring demonstrates fungicidal and bacterial activity. 2-Amino-5-substituted pyridine derivatives were synthesized, their antimicrob properties against fitopatogen candidas, bacterias were investigated and conformation analysis was carried out [1, 2]. In other paper [3] various 3,6-diamino-1*H*-pyrazolo[3,4-*b*]pyridine derivatives were synthesized and their biological activity was presented. Also researches investigated several new 2-amino-3,4,5,6-tetrahydropyridine derivatives that can show muscarinic agonist activity in rats brain [4].

Authors carried out the reaction between α -cyano- and α -benzoylcinnamonitrile dervatives with acetoacetanilide for getting hexasubstituted pyridine derivatives. But from the reaction of α -carboxamide and α -thiocarboxamidocinnamonitrile derivatives with acetoasetanilide pyridines penta-substituted derivatives were synthesized [5].

In next work corresponding pyrane derivatives were obtained on the basis of benzylidenemalononitrile and benzylideneacetophenone [6]. In presented paper by three-component condensation of acetoacetanilide, benzaldehyde and malononitrile in water and at room temperature by using K_2CO_3 the 4*H*-pyranes were obtained [7]. By the same reaction, but by using of $MgVCO_3$ catalyst and ethanol as solvent the corresponding

pyridin derivatives were synthesized [8]. In some works in three-component condensation of acetoacetanilide with various aldehydes and malononitrile, three-ethylamine used as catalyst [9], but in [10] using of NaOH has been shown.

Results and discussions

In present work, by Michael addition reaction of *p*-methyl, *p*-nitro substituted benzylidenemalononitriles and thiophenylidenemalononitrile with acetoacetanilide in methanol, at 60–65°C and for 4–6 minutes the corresponding acetyl substituted pyridine derivatives were synthesized. The NMR investigations confirmed the presence of keto-enol tautomerism in reaction mixture. On the basis of 1H NMR spectra we assumed that the keto-form was dominant in reaction mixture (Figure 1).

As well at Michael addition reaction carried out for 2,6-dichlorobenzylidenemalononitrile with acetoacetanilide in methanol media, at 60–65°C temperature, for 4–6 minutes the corresponding substituted pyridine derivative – (*E*)-2-amino-4-(2,6-dichlorophenyl)-5-(1-hydroxyethylidene)-6-oxo-1-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile was obtained.

Unlike V, VI and VII, in this reaction product the dominant is enol-form. According to our investigation, the reason of domination of enol-form is connected with formation of intramolecular hydrogen bonds between hydrogen atom of hydroxyl group and chlorine atom of aromatic ring (Scheme 2, Figure 2).

Scheme 1. Reaction of *p*-methyl, *p*-nitro substituted benzylidenemalononitriles (I), (II) and thiophenylidenemalononitrile (III) with acetoacetanilide.

Fig. 1. ¹H NMR spectrum of 5-acetyl-2-amino-6-oxo-1-phenyl-4-[(4-(thiophen-2-yl)phenyl)]-1,4,5,6-tetrahydropyridine-3-carbonitrile (VII).

Scheme 2. Reaction of 2,6-dichlorobenzylidenemalononitrile (XI) with acetoacetanilide.

Fig. 2. ¹H NMR spectrum of (E)-2-amino-4-(2,6-dichlorophenyl)-5-(1-hydroxyethylidene)-6-oxo-1-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile (XII).

Scheme 3. Reaction of *p*-trifluorobenzylidenemalononitrile (XIII) with acetoacetanilide.

By Michael addition reaction of *p*-trifluorobenzylidenemalononitrile with acetoacetanilide under the same conditions, 2-amino-6-oxo-1-phenyl-4-(4-(trifluoromethyl)phenyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile was synthesized. The investigations proved the elimination of acetyl-group (Scheme 3).

By Michael addition reaction of 2-chloro-

5-nitrobenzylidenemalononitrile and acetoacetanilide in the same conditions for 15 min at room temperature two reaction products were obtained: 5-acetyl-2-amino-4-(2-chloro-5-nitrophenyl)-6-oxo-1-phenyl-1,6-dihydropyridine-3-carbonitrile (XVI) and 5-acetyl-2-amino-4-(2-chloro-5-nitrophenyl)-6-oxo-1-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile (XVII, Scheme 4).

Scheme 4. Reaction of 2-chloro-5-nitrobenzylidenemalononitrile (XV) with acetoacetanilide.

Experimental part. General remarks

All commercially available chemicals were obtained from Merck and Fluka (sigmaaldrich) companies and used without further purification. Melting points were measured on Stuart SMP30 apparatus without correction. ¹H and ¹³C NMR spectra were recorded on Bruker Avance 300-MHz spectrometer at 300 and 75 MHz, respectively. X-ray analyses were performed on Bruker APEX X-ray equipment. Thin-layer chromatography (TLC) on commercial aluminum-backed plates of silica gel (60 F254) was used to monitor the progress of reactions.

General experimental procedure

5-Acetyl-2-amino-6-oxo-1-phenyl-4-(*p*-tolyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (V). 4-Methylbenzylidenemalononitrile (4.56 mmol) and acetoacetanilide (4.6 mmol) stirred in 35 ml of methyl alcohol. 3–4 drops of pyridine added to obtained reaction mixture and stirred 2–3 min. Then reaction mixture was heated at 60–65°C for 4–6 min and held at room temperature. The progress of the reaction was monitored by TLC (EtOAc/*n*-hexane, 3:1). Crystals were precipitated after evaporation of solvent, filtered by paper, re-crystallized from ethanol-water mixture and obtained in pure form

(yield – 1.25 g, 79.62%).

White powder; m.p.208°C; ¹H NMR (300 MHz, DMSO-*d*₆): 2.28 (s, 3H, CH₃-Ar); 2.30 (s, 3H, CH₃); 4.04 (d, 1H, CH, ³*J*_{H-H} = 4.5); 4.23 (d, 1H, CH, ³*J*_{H-H} = 4.5); 5.87 (s, 2H, NH₂); 7.17–7.53 (m, 9H, 9Ar-H). ¹³C NMR (75 MHz, DMSO-*d*₆): 21.04 (CH₃-Ar), 28.95 (CH₃), 38.41 (CH-Ar), 57.85 (=C_{quat}), 63.25 (CH), 121.03 (CN), 127.41 (2CH_{arom}), 129.42 (CH_{arom}), 129.61 (2CH_{arom}), 129.94 (2CH_{arom}), 130.31 (2CH_{arom}), 135.09 (C_{ar}), 137.13 (C_{ar}), 137.53 (C_{ar}), 154.63 (=C_{quat}), 167.16 (N-C=O), 203.13 (C=O).

5-Acetyl-2-amino-4-(4-nitrophenyl)-6-oxo-1-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile (VI) was synthesized by the same methods. Crystals were filtered by the paper and recrystallized from ethanol–water mixture. Yield – 1.18 g, 69%.

White powder with; m.p.259°C; ¹H NMR (300 MHz, DMSO-*d*₆): 2.34 (s, 3H, CH₃); 4.12 (d, 1H, CH, ³*J*_{H-H} = 4.2); 4.32 (d, 1H, CH, ³*J*_{H-H} = 4.2); 5.96 (s, 2H, NH₂); 7.20–7.51 (m, 9H, 9Ar-H). ¹³C NMR (75 MHz, DMSO-*d*₆): 28.95 (CH₃), 43.29 (CH-Ar), 57.72 (=C_{quat}), 63.20 (CH), 121.09 (CN), 127.85 (2CH_{arom}), 128.11 (CH_{arom}), 129.02 (2CH_{arom}), 129.39 (2CH_{arom}), 130.09 (2CH_{arom}), 135.13 (C_{ar}), 140.79 (C_{ar}),

154.72 ($=C_{\text{quat}}$), 165.34 (C_{ar}), 167.08 ($N-C=O$), 202.96 ($C=O$).

5-Acetyl-2-amino-6-oxo-1-phenyl-4-(thiophen-2-yl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (VII) was synthesized by the same methods. Crystals were filtered by the paper and recrystallized from ethanol–water mixture. Yield – 1.34 g, 87.01%.

White powder; m.p.227°C; 1H NMR (300 MHz, DMSO-*d*6): 2.35 (s, 3H, CH_3); 4.13 (d, 1H, CH, $^3J_{H-H} = 2.7$); 4.56 (d, 1H, CH, $^3J_{H-H} = 2.7$); 6.02 (s, 2H, NH_2); 6.99–7.54 (m, 8H, 5Ar-H+3CH_{thioph}). ^{13}C NMR (75 MHz, DMSO-*d*6): 28.71 (CH_3), 34.60 (CH-Ar), 59.07 ($=C_{\text{quat}}$), 63.86 (CH), 120.80 (CN), 125.46 (CH_{arom}), 125.51 (CH_{thioph}), 128.12 (CH_{thioph}), 129.54 (CH_{thioph}), 130.09 (4 CH_{arom}), 135.06 (C_{ar}), 145.91 (C_{thioph}), 154.64 ($=C_{\text{quat}}$), 166.67 ($N-C=O$), 202.21 ($C=O$).

(E)-2-Amino-4-(2,6-dichlorophenyl)-5-(1-hydroxyethylidene)-6-oxo-1-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile (XII) was synthesized by the same methods. Crystals were filtered by the paper and recrystallized from ethanol–water mixture. Yield: 1.45 g, 79.23%.

White powder; m.p.265°C; 1H NMR (300 MHz, DMSO-*d*6): 1.77 (s, 3H, CH_3); 5.49 (s, 3H, NH_2 +CH-Ar); 7.18–7.57 (m, 9H, 9Ar-H); 14.49 (s, 1H, OH_{enol}). ^{13}C NMR (75 MHz, DMSO-*d*6): 19.66 (CH_3), 35.85 (CH-Ar), 55.80 ($=C_{\text{quat}}$), 96.44 ($=C_{\text{quat}}$), 120.10 (CN), 129.06 (CH_{arom}), 129.78 (CH_{arom}), 130.01 (2 CH_{arom}), 130.10 (2 CH_{arom}), 131.36 (CH_{arom}), 134.14 (CH_{arom}), 134.96 (C_{ar}), 135.21 (2 C_{ar}), 137.96 (C_{ar}), 151.97 ($=C_{\text{quat}}$), 169.53 ($=C_{\text{quat}}-O$), 176.43 ($N-C=O$).

2-Amino-6-oxo-1-phenyl-4-(4-(trifluoromethyl)phenyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (XIV) was synthesized by the same methods. Crystals were filtered by the paper and recrystallized from ethanol–water mixture. Yield: 1.41 g, 86.50%.

White powder; m.p.223°C; 1H NMR (300 MHz, DMSO-*d*6): 2.82 (dd, 1H, CH_2 , $^3J_{H-H} = 10.5$); 3.22 (dd, 1H, CH_2 , $^3J_{H-H} = 9$); 4.07 (t, 1H, CH, $^3J_{H-H} = 5.7$); 5.93 (s, 2H, NH_2); 7.23–7.80 (m, 9H, 9Ar-H). ^{13}C NMR (75 MHz, DMSO-*d*6): 36.29 (CH-Ar), 40.13 (CH_2), 58.59 ($=C_{\text{quat}}$), 121.26 (CN), 126.14 (CH_{arom}), 126.19 (CH_{arom}), 126.24 (CH_{arom}), 126.28 (CH_{arom}), 128.04 (CH_{arom}),

128.32 (C_{ar}), 128.47 (C_{ar}), 129.35 (CH_{arom}), 129.83 (CH_{arom}), 129.94 (CH_{arom}), 135.44 (C_{ar}), 147.59 ($=C_{\text{quat}}$), 155.42 (CF_3), 168.88 ($N-C=O$).

5-Acetyl-2-amino-4-(2-chloro-5-nitrophenyl)-6-oxo-1-phenyl-1,6-dihydropyridine-3-carbonitrile (XVI). 2-Chloro-5-nitrobenzylidene-malononitrile (4.56 mmol) and acetoacetanilide (4.6 mmol) were stirred in 35 ml of methanol. Then 3–4 drops of piperidine were added to reaction mixture and stirred again for 2–3 min. The progress of the reaction was monitored by TLC (EtOAc/n-hexane, 3:1). Crystals were precipitated after evaporation of solvent, filtered by paper, recrystallized from ethanol–water mixture and obtained in pure form (yield – 0.7 g, 37.63%).

White powder; m.p.209°C; 1H NMR (300 MHz, DMSO-*d*6): 2.29 (s, 3H, CH_3); 7.33–8.27 (m, 10H, 8Ar-H+ NH_2). ^{13}C NMR (75 MHz, DMSO-*d*6): 31.50 (CH_3), 75.34 ($=C_{\text{quat}}$), 115.05 ($=C_{\text{quat}}$), 115.91 (CN), 123.97 (CH_{arom}), 124.91 (CH_{arom}), 128.75 (CH_{arom}), 130.43 (CH_{arom}), 130.97 (CH_{arom}), 131.06 (3 CH_{arom}), 134.42 (C_{ar}), 138.51 (C_{ar}), 139.27 (C_{ar}), 146.62 ($=C_{\text{quat}}$), 153.23 (NO_2-C_{ar}), 156.89 ($=C_{\text{quat}}$), 160.71 ($N-C=O$), 196.81 ($C=O$).

5-Acetyl-2-amino-4-(2-chloro-5-nitrophenyl)-6-oxo-1-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile (XVII) was synthesized by the same methods. Crystals were filtered by the paper and recrystallized from ethanol–water mixture. Yield: 1 g, 53.76%.

White powder with m.p.224°C; 1H NMR (300 MHz, DMSO-*d*6): 2.41 (CH_3), 4.14 (d, 1H, CH, $^3J_{H-H} = 3.6$); 4.23 (d, 1H, CH, $^3J_{H-H} = 3.6$); 6.35 (s, 2H, NH_2); 7.26–7.63 (m, 8H, 8Ar-H). ^{13}C NMR (75 MHz, DMSO-*d*6): 28.98 (CH_3), 36.43 (CH-Ar), 55.24 ($=C_{\text{quat}}$), 60.72 (CH), 120.33 (CN), 123.26 (CH_{arom}), 124.90 (CH_{arom}), 129.50 (CH_{arom}), 129.81 (CH_{arom}), 129.91 (CH_{arom}), 130.23 (CH_{arom}), 132.36 (2 CH_{arom}), 134.83 (C_{ar}), 139.54 (C_{ar}), 140.23 (C_{ar}), 147.38 (NO_2-C_{ar}), 155.84 ($=C_{\text{quat}}$), 166.26 ($N-C=O$), 201.63 ($C=O$).

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BƏZİ BENZİLİDENMALONONİTRİLLƏRİN ASETOASETANİLİD İLƏ ÇEVRİLMƏSİNİN TƏDQIQI

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p-Metil-, *p*-nitroəvəzli benzilidenmalononitrillərin və tiofenilidenmalononitrilin asetoasetanilidlə Mixael birləşmə reaksiyasından uyğun əvəzlənmiş piridin törəmələri sintez edilmişdir. 2,6-Dixlorbenzilidenmalononitrilin asetoasetanilidlə Mixael birləşmə reaksiyası aparılmış və uyğun əvəzlənmiş piridin törəməsi olan (*E*)-2-amin-4-(2,6-dixlorfenil)-5-(1-hidroksiethyliden)-6-okso-1-fenil-1,4,5,6-tetrahidropiridin-3-karbonitril birləşməsi alınmışdır. V, VI və VII birləşmələrindən fərqli olaraq bu reaksiyada enol formasında olan reaksiya məhsulunun üstünlük təşkil etdiyi müəyyən edilmişdir. Həmçinin *p*-triflüorbenzilidenmalononitril və 2-xlor-5-nitrobenzilidenmalononitrilin asetoasetanilidlə Mixael birləşmə reaksiyası tədqiq edilmişdir.

Keywords: *p*-triflüorbenzilidenmalononitril, 2-xlor-5-nitrobenzilidenmalononitril, asetoasetanilid, NMR.

ИССЛЕДОВАНИЕ ПРЕВРАЩЕНИЙ НЕКОТОРЫХ БЕНЗИЛИДЕНМАЛОНОНИТРИЛОВ С АЦЕТОАЦЕТАНИЛИДОМ

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Реакцией присоединения Михаеля *n*-метил-, *n*-нитрозамещенных бензилиденмалононитрилов и тиофенилиденмалононитрила с ацетоацетанилидом синтезированы замещенные пиридиновые производные. Реакция присоединения Михаеля была также проведена между 2,6-дихлорбензилиденмалононитрилом и ацетоацетанилидом с получением соответствующего пиридинового производного (*E*)-2-амино-4-(2,6-дихлорофенил)-5-(1-гидроксиэтилиден)-6-оксо-1-фенил-1,4,5,6-тетрагидропиридин-3-карбонитрила. В отличие от соединений V, VI и VII, в данной реакции продукты находятся преимущественно в енольной форме. Кроме того, была изучена реакция присоединения Михаеля *n*-трифторбензилиденмалононитрила и 2-хлор-5-нитробензилиденмалононитрила с ацетоацетанилидом.

Ключевые слова: *n*-трифторбензилиденмалононитрил, 2-хлор-5-нитробензилиденмалононитрил, ацетоацетанилид, ЯМР.