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Interaction of 1,2-Diaminoimidazoles with Ethoxymythelene-Containing Compounds

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Abstract: Interaction of 1, 2-diaminoimidazole with ethoxymethylene-containing derivatives has been studied. It is determined that the interaction malondinitrile, cyanoacetic ester, acetylacetone leads to linearly linked products: 2-[[(2-amino-4-phenyl-1H-imidazole-1-yl)amino] methylene] propanedinitrile, ethyl ester 2-[(2-emino-4-phenyl-1H-imidazole-1-yl)amino]-2-cyano-2-propanoic acid and 2-[[(2-amino-4-phenyl-1H-imodazole-1-yl)amino] methylene]-2,4-pentanedoine. An exception is the reaction of ethoxymethylene ester, in the result of which 7-amino-2-methyl-5-phenyl-imidazol [1, 5-b] pyridine-3-carboxylic acid ethyl ester is regioselectively formed. The products are obtained regardless of reaction condition. The structures of resulting compound are confirmed by NMR ^{1}H and mass spectroscopy. Further cyclization of linear intermediates with acetic acid, triethylamine, dimethylformamide and dioxane has led to asphaltization that implies difficulties of further individualize derived substances.

Key words: 1, 2-diamino-4-phenylimidazole, ethoxymethylenemalondinitrile, ethoxymythelenecyanoacetic ester, ethoxymethyleneacetylacetone, ethoxylacetoacetic ester, imidazopyridazines.

1. Introduction

Imidazole ring is a significant five-membered aromatic heterocycle presented in a great number of natural and synthetic substances. A unique structural feature allows it easily links with various enzymes and receptors in the biological systems [1]. That is exactly why developments of design and simplification of synthesis new heterocyclic structures on the imidazole basis, which would have directed action, have rapidly grown in medical chemistry [1-3]. Among the majority of condensed systems based on imidazole, special attention is paid to imidazopyridazine. These compounds have proven to be good anti-viral, anti-epileptic and anti-cancer drugs [2-12]. Imidazo[1,2-*b*]pyridazine and imodazo[1,5-*b*]pyridazine have a special place among possible variants of the system existence. What is more, the last-named is marginally studied.

A large amount of literature data reflect a various ways of this system design [6-11]. However many from this methods involve several steps including using hard-to-get reagents. This is way methods when using imidazoles derivatives are the most promising, in particular, 1, 2-diaminoimidazoles unsubstituted on carbon in the fifth position.

Previously it was described interaction ethoxymethylene-containing compounds with 4-substituted 2-amino-1-benzaliden (isopropylidene) of aminoimidazoles leading to imidazo[1,2-a]pyrimidines formation. The reaction was performed in acetonitrile with acid or basis catalyst [12]. However this reaction was not extended to 1,2-diaminoimidazoles unsubstituted on carbon in the fifth position.

The article is concerned with studying of 4-phenyl-1,2-diaminoimidazole interaction with ethoxymethylene derivatives with the aim of imidazo[1,5-b]pyridazine systems formation.

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2. Experimental

2.1 Characterization

NMR (Nuclear Magnetic Resonance) Spectra of all new compounds were registered on Bruker DRX, 500 ^{1}H spectrometer at 500 MHz and in DMSO-d6, internal standard is TMS. Mass-spectra recorder on FINNIGAN MAT. INCOS 50 spectrometer (EI ionization, 70 eV). Elemental analyses was performed on Carlo Erba NA 1500.

Melting points was determined on Stuart SMP30. Identity of the reagents and synthesized compounds, quality of reaction mass were controlled out by TLC on Merck TLC Silica gel 60 F_{254} plate; eluents: methanol, chlorophorm and its mixture in the different rations. Chromatograms were developed in the UV light and iodine vapour.

2.2 General Method for the Synthesis of 2-[[(2-Amino-4-Phenyl-1H-Imidazole-1-yl)Amino] Methylene] Propanedinitrile ***6***

The mixture of 0.87 g (5 mmol) diaminoimidazole 1, 0.67 g (5 mmol) ethoxymethylenemalondinitrile **2**, 5 mL of isopropyl alcohol and 1-2 drops of acetic acid was refluxed for 1-2 h. The resulted precipitate was filtrated and recrystallized from mixture of 2-PrOH-DMFA, 2:1. A yellow powdery compound **6** was obtained.

Yield 70 %. mp 193-194 °C. MS (EI, 70 ev), *m/z,* %: 250 [M^+]. NMR ^{1}H (500 MHz, DMSO-d6): δ = 6.05 (2H, s, NH_2); 7.34 (1H, t, J = 7.4, p-H Ph); 7.45 (2H, d, J = 7.8, m-H Ph); 7.66 (1H, s, CH-imidaz); 7.71 (2H, d, J-7.7, o-H Ph); 8.45 (1H, s, CH); 12.64 (1H, s, NH). Analysis: cal. for $C_{13}H_{10}N_6$: C 62.39; H 4.03; N 33.58. Found, %: C 62.03; H 4.05; N 33.52.

2.3 General Method for the Synthesis of Ethyl Ester 2-[(2-Amino-4-Phenyl-1H-Imidazole-1-yl)Amino]-2-Cyano-2-Propanoic Acid ***7****.*

The mixture of 0.87 g (5 mmol) diaminoimidazole **1**, 0.91 g (5 mmol) ethoxymethylenecyaneacetic ester **3**, 5 mL of isopropyl alcohol and 1-2 drops of acetic acid was refluxed for 1-2 h. The resulted precipitate was filtrated and recrystallized from mixture of 2-PrOH-DMFA, 2:1. A light yellow powdery compound **7** was obtained.

Yield 85 %. mp 218-219 °C. MS (EI, 70 ev), *m/z,* %: 297 [M^+]. NMR ^{1}H (500 MHz, DMSO-d6): δ = 1.29 (3H, t, J = 7.1, CH_3); 4.27 (2H, q, J = 7.1, CH_2); 6.16 (1H, s, NH_2); 7.20 (1H, t, J =7 .4, p-H Ph); 7.34 (2H, t, J = 7.8, m-H Ph); 7.54 (1H, d, J = 7.6, o-H Ph); 8.37 (1H, d, J = 13.2, CH); 11.2 (1H, d, J = 13.3, NH). Analysis: cal. for $C_{15}H_{15}N_5O_2$: C 60.60; H 5.09; N 23.55. Found, %: C 61.00; H 5.06; N 23.59.

2.4 General Method for the Synthesis of 2-[[(2-Amino-4-Phenyl-1H-Imodazole-1-yl)Amino] Methylene]-2,4-Pentanedoine ***8****.*

The mixture of 0.87 g (5 mmol) diaminoimidazole **1**, 0.84 g (5 mmol) ethoxymethyleneacetylacetone **4**, 5 mL of isopropyl alcohol and 1-2 drops of acetic acid was refluxed for 1-2 h. The resulted precipitate was filtrated and recrystallized from mixture of 2-PrOH-DMFA, 2:1. A yellow powdery compound **8** was obtained.

Yield 65 %. mp 196-197 °C. MS (EI, 70 ev), *m/z,* %: 284 [M^+]. NMR ^{1}H (500 MHz, DMSO-d6): δ = 2.38 (3H, s, CH_3); 2.43 (3H, s, CH_3); 6.17 (2H, s, NH_2); 7.20 (1H, t, J = 7.3, p-H Ph); 7.35 (2H, t, J = 7.8, m-H Ph); 7.55 (1H, s, CH imidaz); 7.78 (2H, d, J = 7.0, o-H Ph); 8.61 (1H, d, J = 12.5, CH); 12.74 (1H, d, J = 12.5, NH). Analysis: cal. for $C_{15}H_{16}N_4O_2$: C 63.37; H 5.67; N 19.71. Found, %: C 62.97; H 5.64; N 19.67.

2.5 General Method for the Synthesis of Ethyl Ester 7-Amino-2-Methyl-5-Phenylmidazo[1,5-b]Pyridazine-3-Carbonic Acid ***10****.*

The mixture of 0.87 g (5 mmol) diaminoimidazole **1**, 0.99 g (5 mmol) ethoxymethyleneacetylacetone **4**, 5 mL of isopropyl alcohol and 1-2 drops of acetic acid was refluxed for 1-2 h. The resulted precipitate was filtrated and recrystallized from mixture of

2-PrOH-DMFA, 2:1. A red powdery compound **10** was obtained.

Yield 95 %. mp 179-180 °C. MS (EI, 70 ev), *m/z,* %: 296 [M^+]. NMR ^{1}H (500 MHz, DMSO-d6): δ = 1.30 (3H, t, J = 7.1, $CH_2\underline{CH_3}$); 2.45 (3H, s, CH_3); 4.25 (2H, q, J = 7.1, $\underline{CH_2}CH_3$); 6.56 (2H, s, NH_2); 7.37-7.45 (3H, m, H Ph); 7.54 (2H, dt, J = 6.8, J=1.6, o-H Ph); 8.24 (1H, s, CH-piridaz). Analysis: cal. for $C_{16}H_{16}N_4O_2$: C 64.85; H 5.44; N 18.91. Found, %: C 65.12; H 5.41; N 18.95.

3. Results and Discussion

3.1 Synthesis and Characterization

As a polynucleophilic agent (1,3-C,N and 1,4-N,N) diaminoimidazole can form six- and seven-membered systems in the reaction with dielectrophilic agents. The determinative factor in the reaction direction are electrophile nature and conditions in which synthesis was performed [12-16].

The heterocyclization reaction of diaminoimidazole **1** with ethoxymethylene derivatives **2-5** was performed by refluxing in isopropyl alcohol in the presence of catalytic amount of acetic acid for 1-2 h (Fig. 1). Yellow linearly linked products were isolated in the result of **2-4** reaction. According to NMR ^{1}H spectroscopy they were assigned the structures of **6-8**. Attempts to perform this interaction with others solvent, such as acetonitrile, acetic acid, dimethylformaide, dioxane, as well as cyclization of intermediates; led to hard separable uncrystallizable mixtures.

However, in the case of ethoxymethyleneacetoacetic ester a crystalline bright red substance was isolated to which it were assigned

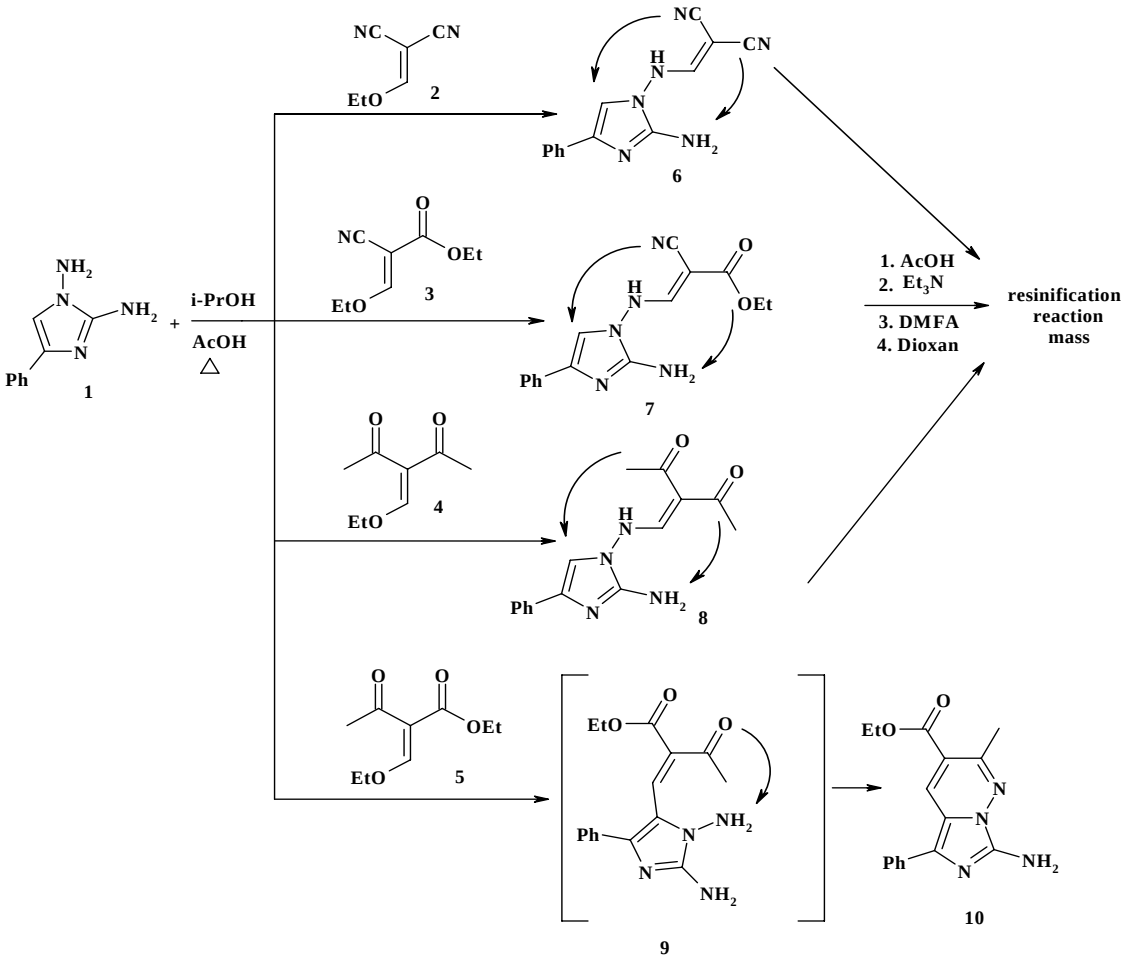

Fig. 1 The reaction of 1,2-diaminoimidazole with ethoxymethylene derivatives.

structure of ethyl 7-amino-2-methyl-5-phenyl-imidazol[1,5-b] pyridazine-3-carboxylic acid 10 by NMR ^{1}H spectra and literature data.

At NMR ^{1}H spectra analysis of 6-8 structures it was noted formation of new NH proton doublets at 11.2-12.8 ppm and methylene fragment proton at 8.4-8.6 ppm. An extant singlet of imidazole cycle proton at C-5 (7.2 ppm) and doublet signals NH_2 (6.2 ppm) group allows to affirm about liner structures ofthe compounds.

NMR ^{1}H spectrum analysis of 10 shows that there are no imidazole cycle and amino group of hydrazine moiety protons signals. Instead, proton signal of pyridazine cycle at 8.25 was formed. The presence in the spectrum 10 two protons singlet of amino group allows to unambiguously stating six-membered system formation.

4. Conclusions

Thus, interaction of 1,2-diamino-4-phenylimidazole with oxymethyleneacetylacetone, methoxymethylene cyanoacetic ester and ethoxymethylenemalonodinitrile leads to formation of 2-[[(2-amino-4-phenyl-1H-imidazole-1-yl)amino]methylene]-2,4-pentanedione, ethyl ester of 2 -[(2-amino-4-phenyl-1H-imidazol-1-yl) amino] -2-cyano-2-propanoic acid, 2-[[(2-amino-4-phenyl-1H-imidazol-1-yl) amino] methylene]propanedinitrile respectively. The present compounds are not then cyclized. Ethyl ester of 7-amino-2-methyl-5-phenylimidazo[1,5-b]pyridazine-3-carbonic acid is regioselectively isolated when using methoxymethyleneacetoacetic ester.

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