β-Enamino Esters in Heterocyclic Synthesis: Synthesis of Pyrazolone and Pyridinone Derivatives

Abdellatif Mohamed Salaheldin 1 and Mariam Abdullah Al-Sheikh 2,*

1 Department of Chemistry, Faculty of Science, Cairo University, Giza-12613, Egypt
2 Department of Chemistry, Girls College of Education, Jeddah, P. O. Box 138016, Jeddah 21323, Saudi Arabia

* Author to whom correspondence should be addressed; E-Mail: r1425@hotmail.com; Tel.: + 966 0505694706.

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Abstract: An efficient and convenient synthesis of pyrrolidinones and pyridinones utilizing enamino esters as starting material has been described. The structures of the compounds obtained were confirmed by spectral and elemental analyses.

Keywords: β-enamino esters; pyrazolone; pyridinone; phenylhydrazones

1. Introduction

β-Enamino esters are versatile intermediates for the synthesis of nitrogen containing compounds [1–8]. Also, they are important subunits present in some biologically important natural products as well as therapeutic agents [9–12]. Due to the importance of β-enamino ester derivatives as bioactive leads and versatile building blocks, their synthesis and applications have long been an active topic in organic synthesis [13–19].

As part of our ongoing studies on the synthesis of nitrogen-containing compounds and in conjunction of our interest in the chemistry of enamines [20–25], we report herein the synthesis of the starting enamino esters 2 and 3 and a study of their reactivity towards some selected nitrogen and carbon nucleophiles as well as benzenediazonium salts to synthesize the new pyrazolone, pyridinone and phenylhydrazone derivatives with the expectation that they would be of biological interest. In our
chemical reactivity studies described here, we principally employed the intermediates 2b and 3 due to their easy preparation and good yield of the subsequent reactions.

2. Results and Discussion

Reaction of ethyl phenyl acetate and ethyl p-nitrophenyl acetate 1a,b with N,N-dimethylformamide dimethyl acetal (DMFDMA) in DMF at 60 °C for 4h yielded the enamino esters 2a,b in good yields. On the other hand, the enamino ester 3 was prepared by reacting compound 1b with triethyl orthoformate and piperidine in DMF at reflux temperature for 24 h (Scheme 1). The structures of the enamino esters 2a,b and 3 were confirmed by mass spectrometry, ¹H- and ¹³C-NMR. For example, the ¹H-NMR spectrum of compound 3 showed two broad signals for the piperidinyl protons at δ = 1.48 (3 CH₂) and 3.01 (2 CH₂) ppm and singlet signal at δ = 7.63 ppm for the olefinic proton, besides the signals of ester and aromatic protons in their expected positions (see Experimental).

Scheme 1. Synthesis and reactivity of β-enamino esters.

The reaction of enamino esters 2b or 3 with aromatic amines in refluxing toluene and in the presence of p-toluenesulfonic acid (PTSA) afforded compounds 4a-c as the only reaction products. Attempts to convert compounds 4 into the corresponding pyrrolidinone derivatives 5 either by heating with chloroacetonitrile in triethylamine or in DMF/K₂CO₃ were unsuccessful (Scheme 1) [25,26].
Coupling compound 2b or 3 with benzenediazonioum chloride furnished the phenylhydrazone 8. It is believed that nitrogen lone pair resonance increases the nucleophilicity of C-2 and that the diazonium salts 6, which are initially formed, are hydrolyzed under the reaction conditions and then underwent a Japp-Klingmann type of cleavage to yield 8, which could not be obtained by direct coupling with benzenediazonioum chloride. Compound 8 failed to react with chloroacetonitrile in triethylamine or in DMF/K2CO3 to give the pyrazolone 9 (Scheme 1).

We envisaged that the reaction of 2a,b with o-phenylenediamine in refluxing toluene and in the presence of PTSA might afford the 2-phenylacrylate derivatives 10a,b or diazepene derivative 11 (Scheme 2). The identity of compounds 10 was supported by a correct element analysis and spectral data. Thus, IR spectrum of 10b relived a broad absorption bands at 3,448 (NH), 3,325 (NH2) cm\(^{-1}\), corresponding to NH and NH2 stretching, and 1,664 for C=O absorption. The \(^1\)H-NMR spectrum displayed the presence of broad signals at \(\delta = 3.65\) ppm and a doublet signal at \(\delta = 10.41\) ppm with \(J\) coupling = 12.6 Hz, (D2O exchanged for both signals), assignable to a NH2 group and the NH. A doublet signal at \(\delta = 7.45\) ppm with \(J\) coupling = 12.6 Hz, was assigned for H-3 (=CH), besides signals due to the ester group and aromatic protons in their expected positions. Additionally, its structure was fully confirmed by \(^{13}\)C-NMR, which was compatible with the suggested structure. Furthermore, in its mass spectrum, this product has the molecular ion \(m/z = 327\) (84%), also confirming its presumed structure. Analytical data are thus all in accordance with the proposed structure for compound 10b. Our efforts to synthesize the interesting diazepenes 11 via the intramoleculer condensation of compound 10 failed (Scheme 2) [27,28].

Scheme 2. Reaction of \(\beta\)-enamino ester with hydrazines, amine and active methylen group.

Next, we investigated the reaction of compounds 2a,b or 3 with acetylacetone in acetic acid in the presence of ammonium acetate that afforded the pyridinone 12. This find is similar to the reported synthesis of pyridines from the reaction of enaminones with acetylacetone under similar conditions [29]. On the other hand, when compounds 2b or 3 reacted with substituted hydrazines 13a,b in ethanol at reflux temperature for 3h they afforded the pyrazolone derivatives 14a-c [30]. Although pyrazolone
derivatives 14 can also exist as 14A or hydroxypyrroles 14B, the pyrazolone structure 14 is established based on the presence of carbonyl absorption band in IR spectra and also the 1H-NMR spectra that revealed pyrazolone H-5 and NH signals. Moreover, structure 14 was confirmed by the 13C-NMR spectra which allowed an unambiguous assignment in the 1H- and 13C-NMR spectra (see Experimental).

3. Experimental

3.1. General

The melting points were determined on a Stuart melting point apparatus. The IR spectra were recorded as KBr pellets using a FTIR Bruker-Vector 22 spectrophotometer. The 1H and 13C-NMR spectra were recorded in DMSO-d6 or CDCl3 as solvent, on a Varian Gemini 300 MHz NMR spectrometer using TMS as internal standard. Double resonance, HMQC and HMBC experiments were carried out for complete assignment of 1H and 13C peaks in the NMR spectra, whenever possible. Chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GCMS-QP-1000 EX mass spectrometer in EI (70 ev) mode. The elemental analyses were performed at the Micro analytical Center, Cairo University, Egypt.

3.2. Synthesis of ethyl 3-(dimethylamino)-2-arylacrylates 2a,b

To a solution of ethyl phenylacetate 1a or ethyl 4-nitrophenylacetate 1b (0.01 mol) in DMF (10 mL), DMFDMA (0.012 mol) was added. Then, the mixture was heated at 60 °C for 4 h. After cooling to r.t., the mixture was left standing overnight, then the resulting solid product was collected by filtration and washed with ethanol to give 2b. In case of compound 2a, brine (10 mL) was added to the reaction mixture. After extraction with CH2Cl2 (3 × 10 mL), the combined organic fractions were dried over MgSO4 and concentrated under vacuum to afford compound 2a as a brown oil.

Ethyl 3-(dimethylamino)-2-phenylacrylate (2a). Yield 86%, 1H-NMR (CDCl3): δ = 1.18 (t, 3H, J = 7.5 Hz, CH3), 2.65 (s, 6H, 2CH3), 4.10 (q, 2H, J = 7.5 Hz, CH2), 7.17–7.29 (m, 5H, Ar-H), 7.57 (s, 1H, CH-olfeinic-H-3), MS (EI, 70eV): m/z = 219 (M+); Anal. Calcd. for C13H17NO2 (219.13): C, 71.21; H, 7.81; N, 6.39. Found: C, 71.34; H, 7.69; N, 6.52.

Ethyl 3-(dimethylamino)-2-(4-nitrophenyl)acrylate (2b). Orange crystals (85%), mp 127–129 ºC; IR (KBr) ν = 1,668 (C=O), 1,463, 1,376 (NO2) cm⁻¹; 1H NMR (CDCl3): δ = 1.20 (t, 3H, J = 7.5 Hz, CH3), 2.73 (s, 6H, 2CH3), 4.14 (q, 2H, J = 7.5 Hz, CH2), 7.32 (d, 2H, J = 9.0 Hz, H-2´,6´), 7.65 (s, 1H, CH-olfeinic- H-3), 8.14 (d, 2H, J = 9.0 Hz, H-3´,5´); 13C-NMR (CDCl3): δ = 14.46 (CH3), 43.64 (2CH3), 59.80 (CH2), 97.27 (C=CH,C-2), 122.36 (C-3´,5´), 132.39 (C-2´,6´), 144.45 (C-1´), 145.75 (C-4´), 150.50 (C=CH,C-3), 168.73 (CO). MS (EI, 70eV): m/z = 264 (M+). Anal.Calcd. for C13H16N2O4 (264.28) : C, 59.08; H, 6.10; N, 10.60. Found: C, 58.87; H, 6.21 ; N, 10.68.
3.3. Synthesis of ethyl 2-(4-nitrophenyl)-3-(piperidin-1-yl)acrylate (3)

A mixture of ethyl 4-nitrophenylacetate 1b (0.2 mol), triethylorthoformate (0.2 mol) and piperidine (0.2 mol) in DMF (30 mL) was refluxed for 24 h. The reaction mixture was then cooled to r. t. and poured into water. The solid product thus formed was collected by filtration and recrystallized from ethanol. m.p. 94–95 °C. Yield: 75%. IR (KBr) ν = 1,665 (C=O), 1,463, 1,377 (NO2) cm−1; 1H-NMR (CDCl3): δ = 1.19 (t, 3H, J = 7.5 Hz, CH3), 1.47–1.52 (m, 6H, 3CH2), 2.98–3.03 (m, 4H, 2CH2), 4.13 (q, 2H, J = 7.5 Hz, CH2), 7.33 (d, 2H, J = 9Hz, H-2′,6′), 7.63 (s, 1H, CH=oléfinic- H-3), 8.15 (d, 2H, J = 9 Hz, H-3′,5′); 13C-NMR (CDCl3): δ = 14.46 (CH3), 23.53 (2CH2), 25.62 (2CH2), 52.16 (CH2), 59.75 (OCH2), 96.15 (C=CH, C-2), 122.74 (C-3′,5′), 131.93 (C-2′,6′), 145.14 (C-1′), 145.80 (C-4′), 149.39 (C=CH,C-3), 168.89 (CO); MS (EI, 70 eV): m/z = 304 (M+); Anal. Calcd. for C16H20N2O4 (304.34) : C, 63.14; H, 6.62; N, 9.20. Found: C, 62.99; H, 6.80; N, 8.99.

3.4. General procedure for preparation of 3-arylamino-2-(4-nitrophenyl)acrylate derivatives 4a-c and 10a,b

Aromatic amines (0.01 mol) and p-toluenesulfonic acid (0.15 g) were added to a solution of enamino esters 2a,b or 3 (0.01 mol) in toluene (25 mL). The reaction mixture was refluxed for 7 h. After cooling to r.t., the precipitated solid product was collected by filtration and recrystallized from the proper solvents to afford 4a-c and 10a,b, respectively.

Ethyl-2-(4-nitrophenyl)-3-(phenylamino)acrylate (4a). Colorless needles, 75% yield, mp 140–141 °C; IR (KBr) ν = 3,448 (NH), 1,664.9 (C=O), 1,460, 1,370 (NO2) cm−1; 1H-NMR (CDCl3): δ= 1.33 (t, 3H, J = 7.5 Hz, CH3), 4.29 (q, 2H, J = 7.5 Hz, CH2); 7.06-7.11 (m, 3H, H-4´´, 3´´,5´´); 7.33-7.38 (m, 2H, H-2´´, 6´´), 7.51 (d, 2H, J = 9.2 Hz, H-2´,6´), 7.55 (d, 1H, J = 12.8 Hz, H-3), 8.19 (d, 2H, J = 9Hz, H-3′,5′), 10.57 (d, 1H, J = 12.8 Hz, NH); 13C NMR (CDCl3): δ = 14.32 (CH3), 60.31 (CH2), 99.11 (C-2), 116.44 (C-3´´, 5´´), 124.73 (C-3´, 5´), 130.37 (C-2´, 6´), 135.60 (C-1´´), 146.54 (C-1´), 147.77 (C-4´), 148.26 (C-3), 157.01 (C-4´´), 170.75 (CO); MS (EI, 70eV): m/z = 312 (M+); Anal. Calcd. for C17H16N2O4 (312.32): C, 65.38; H, 5.16; N, 8.97. Found: C, 65.52; H, 5.04; N, 8.90 %.

Ethyl-3-(4-methoxyphenylamino)-2-(4-nitrophenyl) acrylate (4b). Colorless needles, 75% yield, mp 102–104 °C; IR (KBr) ν = 3,446 (NH), 1,665 (C=O), 1,469, 1,372 (NO2) cm−1; 1H-NMR (CDCl3): δ= 1.33 (t, 3H, J = 7.5 Hz, CH3), 3.81 (s, 3H, OCH3), 4.28 (q, 2H, J = 7.5 Hz, CH2); 6.88 (d, 2H, J = 9.0 Hz, H-3′,5′), 7.03 (d, 2H, J = 9.0 Hz, H-2′,6′), 7.43 (d, 1H, J = 12.9 Hz, H-3), 7.51 (d, 2H, J = 9 Hz, H-2′,6′), 8.18 (d, 2H, J = 9.0 Hz, H-3′,5′), 10.52 (d, 1H, J = 12.9 Hz, NH); 13C-NMR (CDCl3): δ = 14.35 (CH3), 55.54 (OCH3), 60.16 (CH2), 99.11 (C-2), 116.44 (C-3′´, 5′´), 118.80 (C-2′´, 6′´), 124.73 (C-3´´, 5´´), 130.37 (C-2´´, 6´´), 135.60 (C-1´´), 146.54 (C-1´), 147.77 (C-4´), 148.26 (C-3), 157.01 (C-4´´), 170.75 (CO); MS (EI, 70eV): m/z = 342 (M+); Anal. Calcd. for C18H18N2O5 (342.35): C, 63.15; H, 5.16; N, 8.97. Found: C, 62.99; H, 5.04; N, 8.81 %.

Ethyl-3-(4-chlorophenylamino)-2-(4-nitrophenyl) acrylate (4c). Yellow crystals, 82% yield, mp 119–120 °C; IR (KBr) ν = 3,447 (NH), 1,665 (C=O), 1,459, 1,371 (NO2) cm−1; 1H-NMR (DMSO-
Ethyl 3-(2-aminophenylamino)-2-phenylacrylate (10a). Colorless needles, 75% yield, mp 156–158 °C; IR (KBr) ν = 3,440 (NH), 3,317 (NH 2), 1,670 (C=O) cm -1; 1H-NMR (DMSO-d 6): δ = 1.37 (t, 3H, J = 7.5 Hz, CH 3), 3.80 (brs, 2H, NH 2), 4.27 (q, 2H, J = 7.5 Hz, CH 2); 6.90-6.96 (m, 2H, Ar-H), 6.98–7.06 (m, 2H, Ar-H), 7.14–7.22 (m, 5H, Ar-H), 7.42 (d, 1H, J = 12.6 Hz, H-3), 10.41 (d, 1H, J = 12.6 Hz, NH); MS (EI, 70 eV): m/z = 282 (M +); Anal. Calcd. for C 17H18N2O2 (282.34): C, 72.32; H, 6.43; N, 9.92;. Found: C, 72.26; H, 6.79; N, 10.22.

Ethyl-3-(2-aminophenylamino)-2-(4-nitrophenyl) acrylate (10b). Colorless needles, 75% yield, mp 186–188 °C; IR (KBr) ν = 3,448 (NH), 3,325 (NH 2), 1,664 (C=O) cm¯1; 1H-NMR (DMSO-d6): δ = 1.33 (t, 3H, J = 7.5 Hz, CH 3), 3.65 (brs, 2H, NH 2), 4.32 (q, 2H, J = 7.5 Hz, CH 2); 6.82-6.88 (m, 2H, Ar-H), 6.98–7.06 (m, 2H, Ar-H), 7.45 (d, 1H, J = 12.6 Hz, H-3), 7.50 (d, 2H, J = 9.0 Hz, H-2’,6’), 8.17 (d, 2H, J = 9.0 Hz, H-3’,5’), 10.36 (d, 1H, J = 12.6 Hz, NH); 13C-NMR (DMSO-d6): δ = 14.49 (CH 3), 59.77 (CH 2), 96.86 (C-2), 115.07 (C-3”), 121.29 (C-4”), 122.50 (C-3’, 5’), 122.74 (C-5”), 123.17 (C-6”), 132.06 (C-1”), 132.46 (C-2’, 6’), 136.04 (C-2”), 145.97 (C-4’), 149.40 (C-3), 169.70 (CO); MS (EI, 70 eV): m/z = 327 (M +); Anal. Calcd. for C 17H17N3O4 (327.33): C, 61.34; H, 4.83; N, 13.41. Found: C, 61.42; H, 4.88; N, 13.38 %.

3.5. General procedure for preparation of ethyl (4-nitrophenyl)phenylhydrazono acetate (8)

A solution of benzenediazonium chloride salt (10 mmol), prepared by adding sodium nitrite solution (0.7 g in 10 mL of H 2O) to a chilled solution of aniline hydrochloride (10 mmol of aniline in 5 mL of conc. HC1) with stirring, was added to a cold solution of ethyl 3-substituted-2-(4-nitrophenyl)acrylates 2b or 3 in ethanol (50 mL) containing sodium acetate (10 mmol). The reaction mixture was stirred for 1 h. The solid product formed was collected by filtration, washed well with water and recrystallized from ethanol. The title compound was obtained in 90% yield as yellow crystals, mp 145–146 °C, IR (KBr) ν = 3,220 (NH); 1,669 (C=O) cm−1; 1H-NMR (DMSO-d6): δ=1.16 (t, 3H, J = 7.5 Hz, CH 3), 4.25 (q, 2H, J = 7.5 Hz, CH 2); 7.11–7.25 (m, 3H, Ar-H), 7.30–7.40 (m, 4H, Ar-H); 7.62 (d, 2H, J = 8.5 Hz, Ar-H), 11.78 (bs, 1H, NH), MS (EI, 70eV): m/z = 313 (M+); Anal. Calcd. for C 16H15N3O4 (313.31): C, 61.34; H, 4.83; N, 13.41. Found: C, 61.42; H, 4.88; N, 13.38 %.

3.6. Synthesis of 5-acetyl-6-methyl-3-(4-nitrophenyl)pyridin-2(1H)-one (12)

To a mixture of enamino ester 2b or 3 (4 mmol) and the acetylacetone (4 mmol) in acetic acid (10 mL), ammonium acetate (6 mmol) was added, then the reaction mixture was refluxed for 6 h. After cooling to r.t., the precipitated solid product was collected by filtration and recrystallized from...
DMF/EtOH (1:3) to give compound 12 as brown crystals, yield (70%), mp 260–262 °C; IR (KBr) ν = 3,225 (NH); 1,680 (C=O); 1,660 (C=O), 1,374 (NO₂) cm⁻¹; ¹H-NMR (DMSO-d₆): δ = 2.21 (s, 3H, CH₃), 2.65 (s, 3H, CH₃), 7.28 (d, 2H, J = 8.8 Hz, Ar-H), 7.79–7.88 (m, 3H, 3H, Ar-H), 8.01 (s, 1H, NH); MS (EI, 70 eV): m/z = 272 (M⁺); Anal. Calcd. for C₁₄H₁₂N₂O₄ (272.26): C, 61.76; H, 4.44; N, 10.29. Found: C, 61.81; H, 4.32; N, 10.35 %.

3.7. General procedure for preparation of 4-aryl pyrazolo-3-one (14)

A mixture of enamino esters 2a,b or 3 (0.01 mol) and substituted hydrazine hydrochlorides 13a,b (0.01 mol) in ethanol (25 mL) was refluxed for 3h. After cooling to r.t., the reaction mixture was poured into cold water. The resulting solid was collected by filtration and washed with ethanol.

4-Phenyl-1,2-dihydropyrazol-3-one (14a). Orange crystals, 80% yield, mp 199–200 °C; IR (KBr) ν = 3,430 (NH), 1,666 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆): δ = 7.06 (t, 1H, J = 8.2 Hz, H-4´), 7.29 (t, 2H, J = 8.2 Hz, H-3’, 5’), 7.66 (d, 2H, J = 8.2 Hz, H-2’, 6’), 7.88 (s, 1H, H-5), 11.06 (bs, 1H, NH), 11.14 (br s, 1H, NH); ¹³C-NMR (DMSO-d₆): δ = 104.68 (C-4), 124.03 (C-3´, 5´), 124.86 (C-2´, 6´), 129.33 (C-5), 141.0 (C-1´), 145.47 (C-4´), 146.11 (C-5), 156.33 (C-4´), 168.45 (CO); MS (EI, 70 eV): m/z = 160 (M⁺); Anal. Calcd. for C₉H₇N₂O (160.17): C,67.49; H,5.03; N,17.49. Found:C,67.52; H,4.98; N, 17.60.

4-(4-Nitrophenyl)-1, 2-dihydropyrazol-3-one (14b). Yellow crystals, 85% yield, mp 170–172 °C from dilute ethanol; IR (KBr) ν = 3,500 (NH), 1,670 (C=O), 1,468, 1,380 (NO₂) cm⁻¹; ¹H-NMR (CDCl₃): δ = 3.84 (s, 3H, OCH₃), 6.90 (d, 2H, J = 9.0 Hz, Ar-H), 7.10 (d, 2H, J = 9.0 Hz, Ar-H), 7.45 (s, 1H, H-5), 7.59 (d, 2H, J = 9.0 Hz, Ar-H), 8.15 (d, 2H, J = 9.0 Hz, Ar-H), 8.90 (s, 1H, NH); ¹³C-NMR (CDCl₃): δ = 55.57 (OCH₃), 100.01 (C-4), 115.04 (C-3´, 5´), 117.82 (C-2´, 6´), 123.33 (C-3´, 5´), 129.17 (C-2´, 6´), 133.62 (C-1´), 145.40 (C-1´), 145.47 (C-4´), 146.11 (C-5), 156.33 (C-4´), 168.45 (CO); MS (EI, 70 eV): m/z = 311 (M⁺); Anal. Calcd. for C₁₆H₁₃N₃O₄ (311.29): C, 61.73; H, 4.21; N, 13.50. Found: C, 61.94; H, 3.95; N, 13.88 %.

4. Conclusions

β-Enamino esters could be easily obtained by reaction of ethyl phenylacetate derivatives with DMF DMA or with triethylorthoformate and piperidine in the presence of DMF. β-enamino esters are versatile intermediates for the synthesis of pyrrolidinones and pyridinones.

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*Sample Availability:* Samples of all the compounds are available from the authors.

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