Studies with $\beta$-Oxoalkanonitriles: Simple Novel Synthesis of 3-[2,6-Diaryl-4-pyridyl]-3-oxopropanenitriles

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Abstract: Heteroaromatization of ethyl 2-cyano-4-oxo-2-(2-oxo-2-arylethyl)-4-arylbutanoates $3a,b$ with ammonium acetate gave ethyl 2,6-diarylisonicotinates $4a,b$. Treatment of the latter with acetonitrile afforded novel $\beta$-oxoalkanonitriles $6a,b$. Reactions of $6a,b$ with phenyl hydrazine and hydroxylamine gave the corresponding pyridyl aminopyrazoles $8a,b$ and pyridyl aminoisoxazoles $10a,b$, respectively.

Keywords: $\beta$-Oxoalkanonitriles; 3-Pyrazolylamine; 3-Isoxazolylamine; Phenacyl bromide; Ethyl cyanoacetate.

Introduction

$\beta$-Oxoalkanonitriles are versatile reagents and their chemistry has received in the past [1] and continues to receive considerable attention [2-9]. In conjunction with our interest in utilizing oxoalkanonitriles to prepare azolyazines [10-13] a route to 3-(4-pyridyl)-3-oxopropanenitrile was needed. 4-Pyridyl derivatives possess many pharmacological activities [14], and they can also be used as $N$-donor ligands in complexation with metal ions with superior cytotoxicity towards bacteria [15].
Results and Discussion

β-Oxoalkanonitriles are generally prepared via: i) acylation of active nitriles in the presence of suitable basic catalysts [16-18]; ii) reacting α-haloketones with cyanide ion [19], and iii) hydrolysis of β-enaminonitriles [7]. We decided to develop our synthesis via reaction of acetonitrile with ethyl 2,6-diarylisonicotinate. Although the parent ethyl 2,6-diphenylisonicotinate (3a) is a known compound, [20] the 2,6-diarylsubstituted derivatives have not, to our knowledge, been previously reported. Consequently, a method for their synthesis was developed. Reaction of phenacyl bromide (1a) with ethyl cyanoacetate (2) afforded the dialkylated derivative 3a [21]. Similarly, 3b was obtained by reacting 1b with ethyl cyanoacetate. Refluxing 3a,b in acetic acid in the presence of ammonium acetate afforded the target pyridines 4a,b (Scheme 1).

Attempts to condense acetonitrile in an aqueous protic solvent with pyridines 4a,b under different conditions afforded only the carboxylic acid derivatives 5a,b [22]. However, the target β-oxoalkanonitriles 6a,b were obtained by reacting 4a,b with acetonitrile in dry benzene in the presence of sodium hydride (Scheme 2).

As would be expected, β-oxoalkanonitriles 6a,b reacted with phenyl hydrazine hydrochloride to yield the corresponding 5-aminopyrazoles 7a,b or 3-aminopyrazoles 8a,b. Despite literature reports...
[23,24], the δ value for the pyrazole ring H-4 for both isomers vary over the range between 5.3-6.1 ppm. To substantiate the regioselectivity of the reaction products, NOE difference experiments were performed, which showed that irradiation of the amino protons at δ 4.45 ppm did not enhance the aryl protons at δ 7.5 ppm and vice versa, irradiation of the o-aryl protons at δ 7.5 ppm did not enhance the amino protons. These results allowed us to conclude that the amino and aryl protons are not proximal (Scheme 3); that is, the compounds have the structures 8a,b. Moreover, the reaction of β-oxoalkanenitriles 6a,b with hydroxylamine hydrochloride in the presence of sodium acetate could yield 5-aminoisoxazoles 9a,b or the isomeric 3-aminoisoxazole structures 10a,b. 1H-NMR revealed a singlet signal at δ = 7.00 ppm correlated to the isoxazole ring H-4. It was reported that the H-4 of 3-aminoisoxazole appears at lower field (δ ~ 6.1 ppm) than that of 5-aminoisoxazole (δ ~ 5.5 ppm) [25, 26]. Moreover, 15N, 1H-heteronuclear multiple bond correlation (HMBC) of the product indicated that amino proton at δ 5.85 ppm has a cross peak at δ 350 ppm (3J coupling). These results indicated that structures 10a,b are the most probable for the reaction products (cf. Scheme 3). The reaction of 2-substituted-3-oxoalkanonitriles with hydroxylamine hydrochloride in presence of sodium acetate has been reported by Eltagdi et al. [27] to yield amidoximes that cyclised into 3-aminoisoxazoles. On the other hand formation of 5-aminoisoxazoles from the reaction of isonicotinylacetonitriles with hydroxylamine hydrochloride was reported in the patent literature [28, 29], although there is no mention of added base in those cases.

**Scheme 3.** Reactions of β-oxoalkanenitriles 6a,b with nitrogen nucleophiles.
Conclusions

A novel route for the synthesis of $\beta$-oxoalkanenitriles has been developed. The products from this synthesis were further reacted with nitrogen nucleophiles to give azoles. The features of the present method include the ready availability of the starting materials, mild reaction conditions, and the simplicity of the workup.

Experimental

General

Melting points were recorded on a Gallenkamp apparatus and are uncorrected. Infrared spectra (KBr) were determined on a Perkin-Elmer 2000 FT-IR system. $^1$H-NMR spectra were recorded on a Bruker DPX 600 MHz superconducting spectrometer using DMSO-d$_6$ as solvent and TMS as internal standard. Mass spectra were measured on MS 30 and MS 9 (AEI) spectrometers, operating at EI 70 ev. Elemental analyses were measured by means of LECO CHNS-932 Elemental Analyzer.

Synthesis of ethyl 2-cyano-4-oxo-2-(2-oxo-2-arylethyl)-4-arylbutanoates 3a,b

To a stirred solution of $\alpha$-haloketone (20 mmol) in ethanol (50 mL) containing ethyl cyanoacetate (10 mmol) was added potassium hydroxide solution (10 mmol, 0.56 g, dissolved in 20 mL H$_2$O). The mixture was stirred for 30 minutes and acidified. The solid precipitate was collected by filtration and recrystallized from hexane/EtOAc (3:1).

Ethyl 2-cyano-4-oxo-2-(2-oxo-2-phenylethyl)-4-phenylbutanoate (3a): Yield: 2.79 g (80%); mp 140 °C (lit. [21] mp 141 °C); IR $\nu$ = 2250, (CN), 1722 (CO, ester), 1689 (CO, benzoyl) cm$^{-1}$; $^1$H-NMR $\delta$ = 1.22 (t, 3H, CH$_3$), 3.95 (d, 2H, CH$_2$), 4.03 (d, 2H, CH$_2$), 4.19 (q, 2H, CH$_2$), 7.56-8.01 (m, 10H, Ar-H) ppm; MS, m/z (%) 349 (M$^+$, 20), 276 (30), 244 (50), 105 (100), 77 (80); Anal. Calcd. for C$_{21}$H$_{19}$NO$_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.44; H, 5.24; N, 4.05.

Ethyl 2-cyano-4-oxo-2-{(2-oxo-2-(2-thienyl)ethyl)}-4-(2-thienyl)butanoate (3b): Yield: 2.7 g (75%); mp 102 °C; IR $\nu$ = 2251, (CN), 1730 (CO, ester), 1668 (CO, thienoyl) cm$^{-1}$; $^1$H-NMR $\delta$ = 1.21 (t, 3H, CH$_3$), 3.84 (d, 2H, CH$_2$), 3.96 (d, 2H, CH$_2$), 4.17 (q, 2H, CH$_2$), 7.28-8.10 (m, 6H, Ar-H) ppm; MS, m/z (%) 361 (M$^+$, 55), 288 (70), 250 (60), 126 (80), 111 (100), 83 (30); Anal. Calcd. for C$_{17}$H$_{15}$NO$_4$S$_2$: C, 56.49; H, 4.18; N, 3.88; S, 17.74. Found: C, 56.40; H, 4.11; N, 3.95; S, 18.01.

Synthesis of ethyl 2,6-diarylisonicotinates 4a,b

A mixture of ethyl 2-cyano-4-oxo-2-(2-oxo-2-arylethyl)-4-arylbutanoate (10 mmol) and ammonium acetate (15 mmol) in glacial acetic acid (20 mL) was refluxed for 8 hours and poured into water. The solid precipitate was collected by filtration and purified by long column chromatography [eluent: hexane/EtOAc (3:1)].
**Ethyl 2,6-diphenylisonicotinate (4a):** Yield: 1.82 g (60%); mp 98 °C (lit. [20] mp 99 °C); IR ν = 1716 (CO, ester), 1561 (C=N), 1250 (C-O) cm⁻¹; ¹H-NMR δ = 1.39 (t, 3H, CH₃), 4.44 (q, 2H, CH₂), 7.52-8.27 (m, 12H, Ar-H) ppm; MS, m/z (%) 303 (M⁺, 90), 231 (100), 127 (50), 77 (20); Anal. Calcd. for C₂₀H₁₇NO₂: C, 79.19; H, 5.65; N, 4.62. Found: C, 78.96; H, 5.90; N, 4.66.

**Ethyl 2,6-di(2-thienyl)isonicotinate (4b):** Yield: 1.89 g (60%); mp 113 °C; IR ν = 1714 (CO, ester), 1565 (C=N), 1250 (C-O) cm⁻¹; ¹H-NMR δ = 1.39 (t, 3H, CH₃), 4.42 (q, 2H, CH₂), 7.20-8.10 (m, 8H, Ar-H) ppm; MS, m/z (%) 315 (M⁺, 100), 243 (20), 133 (25), 89 (15); Anal. Calcd. for C₁₆H₁₃NO₂S₂: C, 60.93; H, 4.15; N, 4.44; S, 20.33. Found: C, 60.63; H, 4.45; N, 4.74; S, 20.58.

**Synthesis of 2,6-diarylisonicotinic acids 5a,b**

A solution of ethyl 2,6-diarylisonicotinate (10 mmol) in ethanol (20 mL) was treated with potassium hydroxide solution (15 mmol in 10 mL water) and refluxed for 4 hours. The reaction mixture was poured into ice/HCl. The solid precipitate was collected by filtration and recrystallized from ethanol.

**2,6-Diphenylisonicotinic acid (5a):** Yield: 1.92 g (70%); mp 265 °C (lit. [22] mp 263 °C); IR ν = 3500-2600 (br, OH acid), 1698 (CO, acid), 1555 (C=N), 1279 (C-O) cm⁻¹; ¹H-NMR δ = 7.49-8.26 (m, 12H, Ar-H), 13.98 (COOH) ppm; MS, m/z (%) 275 (M⁺, 100), 231 (40), 127 (10), 77 (10); Anal. Calcd. for C₁₈H₁₃NO₂: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.38; H, 4.68; N, 5.01.

**2,6-Di(2-thienyl)isonicotinic acid (5b):** Yield: 1.72 g (60%); mp 251 °C; IR ν = 3500-2500 (br, OH acid), 1700 (CO, acid), 1561 (C=N), 1271 (C-O) cm⁻¹; ¹H-NMR δ = 7.31-8.21 (m, 8H, Ar-H), 13.86 (COOH) ppm; MS, m/z (%) 287 (M⁺, 100), 242 (40), 83 (10); Anal. Calcd. for C₁₄H₉NO₂S₂: C, 58.52; H, 3.16; N, 4.87; S, 22.32. Found: C, 58.33; H, 3.11; N, 4.64; S, 22.51.

**Synthesis of β-oxoalkanonitriles 6a,b**

A mixture of ethyl 2,6-diarylisonicotinate (1 mmol), dry acetonitrile (2 mmol), and sodium hydride (20 mmol) in dry benzene (20 mL) was refluxed for 4 hours and poured into water, extracted by ethyl acetate. The solvent was evaporated under vacuum and the residue was purified by long column chromatography [eluent: hexane/EtOAc (3:1)].

**3-(2,6-Diphenyl-4-pyridyl)-3-oxopropanenitrile (6a):** Yield: 0.149 g (50%); mp 180 °C; IR ν = 2217 (CN), 1710 (CO), 1594 (C=N) cm⁻¹; ¹H-NMR δ = 4.98 (s, 2H, CH₂), 7.36-8.30 (m, 12H, Ar-H) ppm; MS, m/z (%) 298 (M⁺, 100), 270 (15), 127 (65), 77 (70); Anal. Calcd. for C₂₀H₁₄N₂O: C, 80.52; H, 4.73; N, 9.39. Found: C, 80.38; H, 4.61; N, 9.08.

**3-(2,6-Di(2-thienyl)-4-pyridyl)-3-oxopropanenitrile (6b):** This compound was obtained in 0.155 g (50%), mp 192 °C; IR (KBr) ν = 2214 (CN), 1703 (CO), 1592 (C=N) cm⁻¹; ¹H NMR (DMSO-d₆) δ = 4.41 (s, 2H, CH₂), 7.02-8.10 (m, 8H, Ar-H) ppm; MS, m/z (%) 310 (M⁺, 100), 282 (35), 139 (20), 83
Reactions of $\beta$-oxoalkanenitriles with nitrogen nucleophiles

A mixture of $\beta$-oxoalkanenitriles (1 mmol) in dioxane (20 mL) in presence of anhydrous sodium acetate (2 mmol) and hydroxylamine hydrochloride or phenylhydrazine hydrochloride (1 mmol) was refluxed for 4 hours. After pouring into water, the solid precipitate was collected by filtration and recrystallized from hexane/ethyl acetate mixture (3:1).

5-(2,6-Diphenyl-4-pyridyl)-1-phenyl-1H-3-pyrazolylamine ($8a$): Yield: 0.194 g (50%); mp 210 °C; IR $\nu$ = 3424, 3280 (NH$_2$), 1602 (C=N) cm$^{-1}$; $^1$H-NMR $\delta$ = 4.45 (s, 2H, NH$_2$), 6.93 (s, 1H, pyrazole-H), 7.34-8.30 (m, 17H, Ar-H) ppm; $^{13}$C-NMR $\delta$ = 97.3, 117.8, 118.1, 126.3, 127.1, 127.9, 128.3, 129.1, 130.2, 138.6, 139.3, 144.3, 153.7, 161.5 (Ar-Cs); MS, m/z (%) 388 (M$^+$, 100), 284 (5), 230 (10), 77 (15); Anal. Calcd. for C$_{26}$H$_{20}$N$_4$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.17; H, 5.49; N, 14.51.

5-[2,6-Di(2-thienyl)-4-pyridyl]-1-phenyl-1H-3-pyrazolylamine ($8b$): Yield: 0.20 g (50%); mp 235 °C; IR $\nu$ = 3410, 3271 (NH$_2$), 1601 (C=N) cm$^{-1}$; $^1$H-NMR $\delta$ = 4.43 (s, 2H, NH$_2$), 6.93 (s, 1H, pyrazole-H), 7.20-8.30 (m, 13H, Ar-H) ppm; $^{13}$C-NMR $\delta$ = 96.8, 117.1, 118.4, 125.7, 126.3, 126.9, 127.1, 128.3, 129.4, 130.2, 134.1, 144.5, 152.7, 161.1 (Ar-Cs); MS, m/z (%) 400 (M$^+$, 40), 296 (100), 241 (40), 77 (15); Anal. Calcd. for C$_{22}$H$_{16}$N$_4$S$_2$: C, 65.97; H, 4.03; N, 13.99; S, 16.01. Found: C, 66.13; H, 4.15; N, 13.81; S, 15.91.

5-(2,6-Diphenyl-4-pyridyl)-3-isoxazolylamine ($10a$): Yield: 0.188 g (60%); mp 179 °C; IR $\nu$ = 3349, 3297 (NH$_2$), 1640 (C=N) cm$^{-1}$; $^1$H-NMR $\delta$ = 5.85 (s, 2H, NH$_2$), 7.00 (s, 1H, isoxazole-H), 7.48-8.29 (m, 12H, Ar-H) ppm; $^{13}$C-NMR $\delta$ = 98.3, 124.2, 126.1, 127.3, 128.4, 136.5, 142.6, 148.3, 162.8, 167.2 (Ar-Cs); MS, m/z (%) 314 (M$^{++}$+1, 35), 313 (M$^+$, 30), 275 (100), 127 (25), 77 (15); Anal. Calcd. for C$_{20}$H$_{15}$N$_3$O: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.82; H, 5.05; N, 13.68.

5-[2,6-Di(2-thienyl)-4-pyridyl]-3-isoxazolylamine ($10b$): Yield: 0.195 g (60%); mp 192 °C; IR $\nu$ = 3342, 3291 (NH$_2$), 1645 (C=N) cm$^{-1}$; $^1$H-NMR $\delta$ = 5.85 (s, 2H, NH$_2$), 7.21 (s, 1H, isoxazole-H), 7.22-8.10 (m, 8H, Ar-H) ppm; $^{13}$C-NMR $\delta$ = 98.8, 125.4, 126.8, 127.5, 128.4, 138.5, 142.2, 149.1, 163.8, 168.1 (Ar-Cs); MS, m/z (%) 325 (M$^+$, 100), 287 (35), 133 (25), 83 (15); Anal. Calcd. for C$_{16}$H$_{11}$N$_3$O$_2$: C, 59.06; H, 3.41; N, 12.91; S, 19.71. Found: C, 59.13; H, 3.34; N, 12.81; S, 19.51.

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