Molecules **2008**, *13*, 3140-3148; DOI: 10.3390/molecules13123140

OPEN ACCESS

molecules

ISSN 1420-3049

www.mdpi.com/journal/molecules

Article

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

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Received: 5 September 2008; in revised form; 27 September 2008 / Accepted: 5 November 2008 / Published: 15 December 2008

Abstract: Heteroaromatization of ethyl 2-cyano-4-oxo-2-(2-oxo-2-arylethyl)-4-aryl-butanoates **3a,b** with ammonium acetate gave ethyl 2,6-diarylisonicotinates **4a,b**. Treatment of the latter with acetonitrile afforded novel β-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: β-Oxoalkanonitriles; 3-Pyrazolylamine; 3-Isoxazolylamine; Phenacyl bromide; Ethyl cyanoacetate.

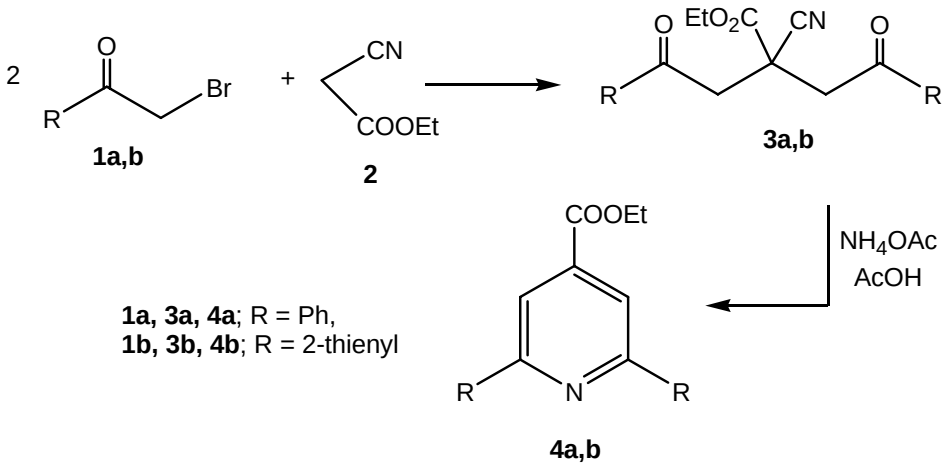
Introduction

β-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 azolylazines [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

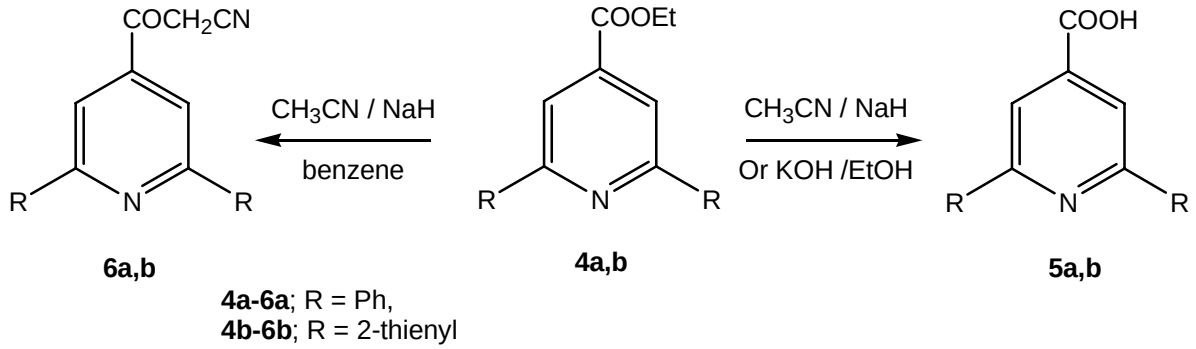
β-Oxoalkanonitriles are generally prepared *via*: i) acylation of active nitriles in the presence of suitable basic catalysts [16-18]; ii) reacting *α*-haloketones with cyanide ion [19], and iii) hydrolysis of *β*-enaminonitriles [7]. We decided to develop our synthesis *via* reaction of acetonitrile with ethyl 2,6-diarylisonicotinate. Although the parent ethyl 2,6-diphenylisonicotinate (**3a**) is a known compound, [20] the 2,6-diarylsubsubstituted 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).

Scheme 1. Synthetic pathway for preparation of compounds **4a,b**.



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*-oxo-alkanonitriles **6a,b** were obtained by reacting **4a,b** with acetonitrile in dry benzene in the presence of sodium hydride (Scheme 2).

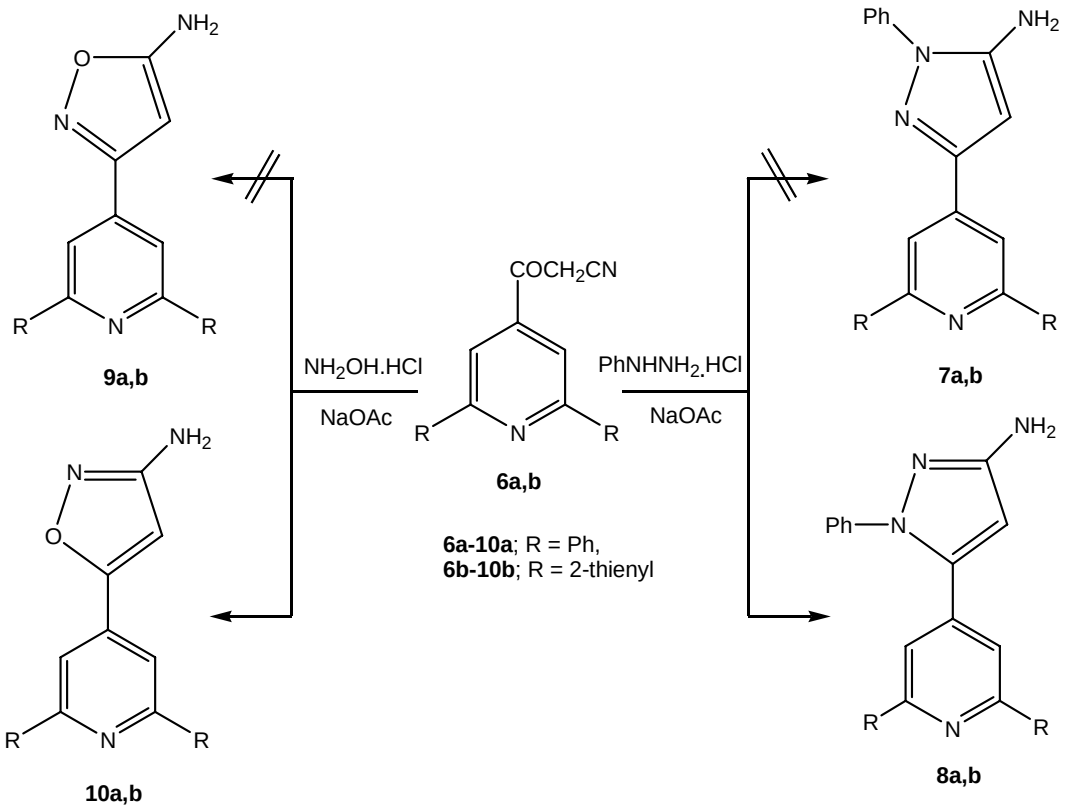
Scheme 2. Synthetic pathway for preparation of compounds **5a,b** and **6a,b**.



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-oxoalkanonitriles **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**. ^{1}H-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, ^{15}N, 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 Elnagdi *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-oxoalkanonitriles **6a,b** with nitrogen nucleophiles.



Conclusions

A novel route for the synthesis of β-oxoalkanonitriles 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 α-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_2O). 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 ^{o}C (lit. [21] mp 141 ^{o}C); IR υ = 2250, (CN), 1722 (CO, ester), 1689 (CO, benzoyl) cm^{-1}; ^{1}H-NMR δ = 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 ^{o}C; IR υ = 2251, (CN), 1730 (CO, ester), 1668 (CO, thienoyl) cm^{-1}; ^{1}H-NMR δ = 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 $C_{17}H_{15}NO_4S_2$: 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 ^{o}C (lit. [20] mp 99 ^{o}C); IR υ = 1716 (CO, ester), 1561 (C=N), 1250 (C-O) cm^{-1}; ^{1}H-NMR δ = 1.39 (t, 3H, CH_3), 4.44 (q, 2H, CH_2), 7.52-8.27 (m, 12H, Ar-H) ppm; MS, *m/z* (%) 303 (M^+, 90), 231 (100), 127 (50), 77 (20); Anal. Calcd. for $C_{20}H_{17}NO_2$: 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 ^{o}C; IR υ = 1714 (CO, ester), 1565 (C=N), 1250 (C-O) cm^{-1}; ^{1}H-NMR δ = 1.39 (t, 3H, CH_3), 4.42 (q, 2H, CH_2), 7.20-8.10 (m, 8H, Ar-H) ppm; MS, *m/z* (%) 315 (M^+, 100), 243 (20), 133 (25), 89 (15); Anal. Calcd. for $C_{16}H_{13}NO_2S_2$: 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 ^{o}C (lit. [22] mp 263 ^{o}C); IR υ = 3500-2600 (br, OH acid), 1698 (CO, acid), 1555 (C=N), 1279 (C-O) cm^{-1}; ^{1}H-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 $C_{18}H_{13}NO_2$: 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 ^{o}C; IR υ = 3500-2500 (br, OH acid), 1700 (CO, acid), 1561 (C=N), 1271 (C-O) cm^{-1}; ^{1}H-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 $C_{14}H_9NO_2S_2$: 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 ^{o}C; IR υ = 2217 (CN), 1710 (CO), 1594 (C=N) cm^{-1}; ^{1}H-NMR δ = 4.98 (s, 2H, CH_2), 7.36-8.30 (m, 12H, Ar-H) ppm; MS, *m/z* (%) 298 (M^+, 100), 270 (15), 127 (65), 77 (70); Anal. Calcd. for $C_{20}H_{14}N_2O$: 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 ^{o}C; IR (KBr) υ = 2214 (CN), 1703 (CO), 1592 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ = 4.41 (s, 2H, CH_2), 7.02-8.10 (m, 8H, Ar-H) ppm; MS, *m/z* (%) 310 (M^+, 100), 282 (35), 139 (20), 83

(15). *Anal*. Calcd. for $C_{16}H_{10}N_2OS_2$: C, 61.91; H, 3.25; N, 9.03; S, 20.66. Found: C, 61.86; H, 3.14; N, 9.11; S, 20.51.

Reactions of β-oxoalkanonitriles with nitrogen nucleophiles

A mixture of *β*-oxoalkanonitriles (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 ^oC; IR υ = 3424, 3280 (NH_2), 1602 (C=N) cm^{-1}; ^{1}H-NMR δ = 4.45 (s, 2H, NH_2), 6.93 (s, 1H, pyrazole-H), 7.34-8.30 (m, 17H, Ar-H) ppm; ^{13}C-NMR δ = 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 ^oC; IR υ = 3410, 3271 (NH_2), 1601 (C=N) cm^{-1}; ^{1}H-NMR δ = 4.43 (s, 2H, NH_2), 6.93 (s, 1H, pyrazole-H), 7.20-8.30 (m, 13H, Ar-H) ppm; ^{13}C-NMR δ = 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 $C_{22}H_{16}N_4S_2$: 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 ^oC; IR υ = 3349, 3297 (NH_2), 1640 (C=N) cm^{-1}; ^{1}H-NMR δ = 5.85 (s, 2H, NH_2), 7.00 (s, 1H, isoxazole-H), 7.48-8.29 (m, 12H, Ar-H) ppm; ^{13}C-NMR δ = 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 $C_{20}H_{15}N_3O$: 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 ^oC; IR υ = 3342, 3291 (NH_2), 1645 (C=N) cm^{-1}; ^{1}H-NMR δ = 5.85 (s, 2H, NH_2), 7.21 (s, 1H, isoxazole-H), 7.22-8.10 (m, 8H, Ar-H) ppm; ^{13}C-NMR δ = 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 $C_{16}H_{11}N_3OS_2$: 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.

Acknowledgements

Support for this work was received from the University of Kuwait through Research Grant SC04/06 and the use of the facilities of Analab/SAF through research grants GC01/01 and GS03/01 is gratefully acknowledged. The authors also express their gratitude and appreciation to the referees of this manuscript for their guidance and advice.

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Sample Availability: Not avaliable.