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Synthesis of 2,3-dicyanopyrazine and ethyl 5-amino-4,6-dicyanobiphenyl-3-carboxylate derivatives from ethyl aroylpyruvates

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Abstract: Reactions of ethyl 4-aryl-2,4-dioxobutanoates **1a–c** at ambient temperature with diaminomaleonitrile in glacial acetic acid and with malononitrile in ethanol/H_2O (1:1) led to the formation of 5-(2-aryl-2-oxoethyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbontrile **2a–c** and ethyl 5-amino-4,6-dicyanobiphenyl-3-carboxylate derivatives **3a–c**, respectively.

Keywords: 5-amino-4,6-dicyanobiphenyl-3-carboxylate; 4-aryl-2,4-dioxobutanoate; diaminomaleonitrile; malononitrile; pyrazine-2,3-dicarbonitrile.

Introduction

Pyrazines are important flavor components in food [1], and show diverse biological activities [1–11]. Diaminomaleonitrile (DAMN), a tetramer of hydrogen cyanide and a weakly basic diamine with similar reactivity to *o*-phenylenediamine, is an important synthetic precursor to pyrazine-2,3-dicarbonitriles [12]. DAMN can be condensed with α-diketones [12], glyoxal, α-keto aldehydes, α-keto oximes [13], α-keto thioesters [14], α-keto esters [15–17] and 4-acylfuran-2,3-diones [16, 17] to provide pyrazine-2,3-dicarbonitriles in good yields. On the other hand, malononitrile is an important starting material for the preparation of 2,6-dicyanoanilines [18] biphenyl-3-carboxylates [19] and 3-cyano-2-pyridinones [20]. In this paper we report simple procedures for synthesis of 2,3-dicyanopyrazine **2a–c** and ethyl 4,6-dicyanobiphenyl-3-carboxylate derivatives **3a–c** by reaction of ethyl 4-aryl-2,4-dioxobutanoates **1a–c** with diaminomaleonitrile and malononitrile, respectively (Scheme 1).

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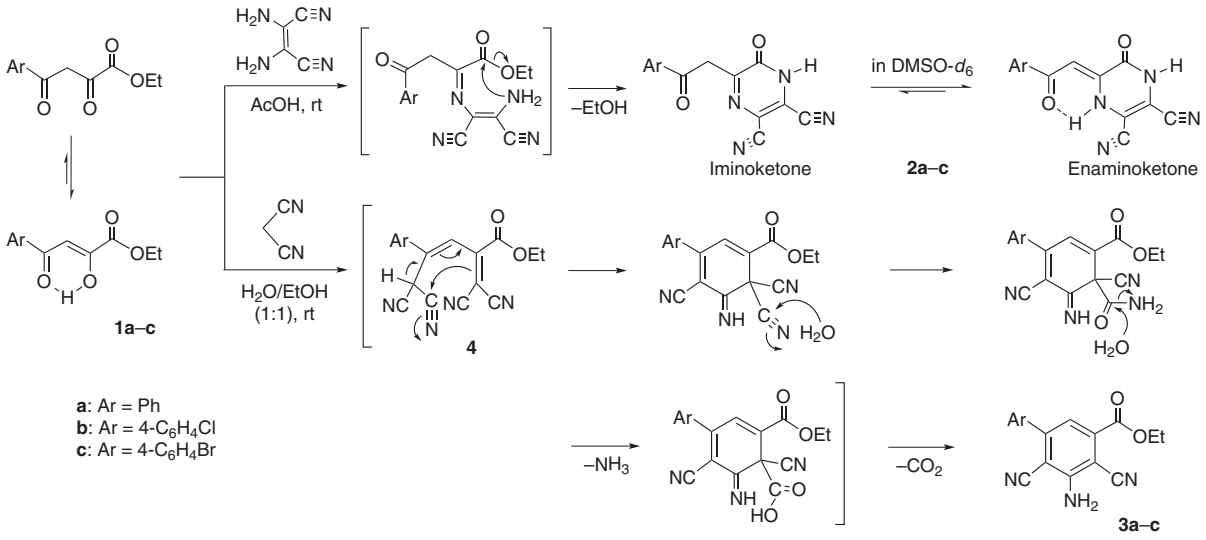
Results and discussion

The reactions of ethyl aroylpyruvates **1a–c** with diaminomaleonitrile in glacial acetic acid at room temperature for 12 h gave the pyrazine-2,3-dicarbonitriles **2a–c** in moderate to good yields. On the other hand, treatment of compounds **1a–c** with malononitrile under the neutral conditions in ethanol/H_2O at room temperature for 3 h afforded the corresponding ethyl 5-amino-4,6-dicyanobiphenyl-3-carboxylates **3a–c** in good to high yields (Scheme 1). The structures of products **2a–c** and **3a–c** were deduced from their elemental analyses, IR, ^{1}H NMR, ^{13}C NMR and mass spectra. In particular, analysis of ^{1}H NMR and ^{13}C NMR spectra revealed that compounds **2a–c** exist in two tautomeric forms of iminoketone and enaminoketone in DMSO-d_6 solution. For example, the ^{1}H NMR spectrum of **2a** shows four broad singlets at δ 4.64, 6.76, 10.49 and 13.62 for CH_2, =CH, amidic NH and enaminic NH protons and multiplet signals integrated for 10 protons of two aromatic rings at δ 7.49–8.02. The ^{13}C NMR spectrum of **2a** shows carbon signals of CH_2, =CH, four C≡N, amide C=O and ketone C=O at δ 43.5, 91.4, 111.3, 112.1, 113.3, 114.6, 176.9 and 195.0, respectively. The IR absorptions of NH, C≡N, amide C=O and ketone C=O groups are seen at 3442, 2224, 1711, 1697 and 1624 cm^{-1}, respectively. The ratios of iminoketone tautomer to enaminoketone tautomer for compounds **2a–c** from the proton integration values of CH_2 and =CH signals are 0.48:0.52, 0.33:0.67 and 0.33:0.67, respectively. Thus, for halogen-substituted compounds **2b,c** the enaminoketone form becomes two-fold predominant. In the IR and ^{13}C NMR spectra of products **3a–c** the absorptions of ketone carbonyl groups are absent. The ^{1}H NMR spectra of **3a–c** are also consistent with the given structures.

These results show that DAMN undergoes cyclization by nucleophilic attack on the hydroxy ester fragment (C-1 and C-2) of compound **1** to produce pyrazine-2,3-dicarbonitrile derivatives **2** (Scheme 1) [21]. Nucleophilic attacks of



Scheme 1 Synthesis of pyrazines **2a–c** and ethyl biphenyl-3-carboxylates **3a–c**.

two equivalents of $CH_2(CN)_2$ occur at carbonyl groups (C-2 and C-4) of the ethyl aroylpyruvate **1**, followed by cyclization of the intermediate product **4** and then hydrolysis of the nitrile function to obtain the corresponding 5-amino-4,6-dicyanobiphenyl-3-carboxylate **3** (Scheme 1) [19].

Conclusion

Convenient synthetic routes to 5-(2-aryl-2-oxoethyl)-6-oxo-1,6-dihydropyrazine-2,3-dicarbontriles **2a–c** and ethyl 5-amino-4,6-dicyanobiphenyl-3-carboxylates **3a–c** starting from ethyl 4-aryl-2,4-dioxobutanoates **1a–c** are described.

Experimental

The reagents were purchased from Merck and used without purification. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Infrared spectra were measured using KBr disks on a Thermo Nicolet 8700 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300 AVANCE instrument at 300 MHz or 500 MHz and 75 MHz or 125 MHz, respectively, using TMS as internal standard and DMSO-d_6 or $CDCl_3$ as solvent. Thin-layer chromatography was performed on Silufol-UV 254 plates. Mass spectra were obtained on an Agilent HP 5973 mass spectrometer operating at ionization potential of 70 eV. Ethyl 4-aryl-2,4-dioxobutanoates **1a-c** were prepared from diethyl oxalate (10 mmol) and 4′-substituted acetophenone (10 mmol) in the presence of sodium ethoxide (10 mmol) in ethanol (30 mL) as previously reported [22].

General procedure for the synthesis of pyrazine-2,3-dicarbonitriles 2a–c

To a stirred solution of diaminomaleonitrile (1.0 mmol) in glacial acetic acid (10 mL) was added compound **1a–c** (1.0 mmol) at room temperature and the mixture was then stirred for 12 h. The progress of the reaction was monitored by TLC (eluent AcOEt/hexane, 1:1). After removal of the solvent, the residue was crystallized from acetonitrile for **2a**, 2-propanol for **2c** and washed with chloroform for **2b**.

6-Oxo-5-(2-oxo-2-phenylethyl)-1,6-dihydropyrazine-2,3-dicarbonitrile (2a) Brown crystals; yield 0.18 g (68%); mp 242–244°C (ref. [16] mp 243°C); IR: ν 3442 (NH), 3064 (CH, aromatic), 2896 (CH, aliphatic), 2224 (C≡N), 1711 (C=O, amide), 1697, 1624 (C=O, ketone), 1597 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 4.64 (2H, s, CH_2), 6.76 (1H, s, =CH), 7.49–7.71 (6H, m, 2Ph), 7.94 (2H, d, ^3J = 7.1 Hz, $2CH_{ortho}$ of Ph), 8.02 (2H, d, ^3J = 7.4 Hz, $2CH_{ortho}$ of Ph), 10.49 (2H, br s, 2NH, amide), 13.62 (1H, br s, NH, enamine); ^{13}C NMR (DMSO-d_6): δ 43.5 (CH_2), 91.4 (=CH), 111.3, 112.1, 113.3, 114.6 (4C≡N), 120.1, 126.7, 128.4, 128.7, 128.9, 129.0, 132.3, 133.9 (12C, 2Ph), 134.9, 135.9, 151.0, 151.5, 155.2, 159.2 (6C=N), 176.9 (2C=O, amide), 195.0 (2 C=O); EI-MS: *m/z* (%) 264 (M^+, 99), 235 (50), 186 (34), 159 (20), 131 (24), 105 (100), 77 (99), 51 (44). Anal. Calcd for $C_{14}H_8N_4O_2$ (264.24): C, 63.64; H, 3.05; N, 21.20. Found: C, 63.89; H, 3.34; N, 20.92.

5-[2-(4-Chlorophenyl)-2-oxoethyl]-6-oxo-1,6-dihydropyrazine-2,3-dicarbontrile (2b) Yellow powder; yield 0.15 g (50%); mp 262–264°C; IR: ν 3434 (NH), 3082 (CH, aromatic), 2914 (CH, aliphatic), 2236, 2223 (C≡N), 1700 (C=O, amide), 1624 (C=O, ketone), 1590 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 4.62 (2H, s, CH_2), 6.70 (1H, s, =CH), 7.56 (2H, d, ^3J = 8.5 Hz, $2CH_{ortho}$ of Ph-Cl), 7.62 (2H, d, ^3J = 8.5 Hz, $2CH_{ortho}$ of Ph-Cl), 7.95 (2H, d, ^3J = 8.5 Hz, $2CH_{meta}$ of Ph-Cl), 8.03 (2H, d, ^3J = 8.5 Hz, $2CH_{meta}$ of Ph-Cl), 13.81 (1H, br s, NH, enamine), amidic NH protons signals are missing; ^{13}C NMR (DMSO-d_6): δ 43.5 (CH_2), 92.6 (=CH), 112.7, 113.4, 113.7, 114.8 (4C≡N), 119.0, 128.4, 128.9, 129.0, 129.1, 130.2, 134.1 (11C, 2Ph), 134.7, 136.5 (2C=N), 138.7 (C_{ipso} of Ph-Cl), 150.9, 151.4,

156.6, 159.5 (4C=N), 173.3 (2C=O, amide), 194.2 (2C=O); EI-MS: *m/z* (%) 300 ($M^{+}+2$, 9), 298 (M^{+}, 27), 269 (11), 186 (16), 139 (100), 111 (51), 75 (31), 43 (28). Anal. Calcd for $C_{14}H_7ClN_4O_2$ (298.68): C, 56.30; H, 2.36; N, 18.76. Found: C, 56.58; H, 2.58; N, 18.49.

5-[2-(4-Bromophenyl)-2-oxoethyl]-6-oxo-1,6-dihydropyrazine-2,3-dicarbontrile (2c) Yellow powder; yield 0.15 g (44%); mp 270–272°C; IR: ν 3439 (NH), 3080 (CH, aromatic), 2911 (CH, aliphatic), 2235, 2224 (C≡N), 1701 (C=O, amide), 1624 (C=O, ketone), 1588 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.62 (2H, s, CH_2), 6.71 (1H, s, =CH), 7.70 (2H, d, $^3J=8.5$ Hz, $2CH_{meta}$ of Ph-Br), 7.77 (2H, d, $^3J=8.4$ Hz, $2CH_{meta}$ of Ph-Br), 7.87 (2H, d, $^3J=8.5$ Hz, $2CH_{ortho}$ of Ph-Br), 7.95 (2H, d, $^3J=8.4$ Hz, $2CH_{ortho}$ of Ph-Br), 13.80 (1H, br s, NH, enamine); ^{13}C NMR (DMSO-d_6): δ 43.4 (CH_2), 91.7 (=CH), 112.2, 113.2, 113.3, 114.6 (4C≡N), 119.9, 125.9, 128.0, 128.6, 128.7, 130.3, 131.9, 132.1 (12C, 2Ph), 134.1, 134.9, 150.8, 151.3, 155.5, 159.1 (6C=N), 175.0 (2C=O, amide), 194.3 (2C=O); EI-MS: *m/z* (%) 344 ($M^{+}+2$, 43), 342 (M^{+}, 44), 315 (14), 183 (100), 157 (50), 131 (16), 104 (13), 76 (30), 50 (11). Anal. Calcd for $C_{14}H_7BrN_4O_2$ (343.13): C, 49.00; H, 2.06; N, 16.33. Found: C, 49.28; H, 2.31; N, 16.05.

General procedure for the synthesis of ethyl 5-amino-4,6-dicyanobiphenyl-3-carboxylates 3a–c

To a stirred solution of malononitrile (1.0 mmol) in EtOH/H_2O (1:1, 10 mL) was added compound **1a–c** (1.0 mmol) at room temperature and the mixture was then stirred for 3 h. The progress of the reaction was monitored by TLC (eluent AcOEt/hexane, 1:1). The resulting solid was filtered, washed with EtOH/H_2O (1:1) and then crystallized from ethanol.

Ethyl 5-amino-4,6-dicyanobiphenyl-3-carboxylate (3a) Yellow cotton-like solid; yield 0.12 g (82%); mp 196–198°C; IR: ν 3459, 3330, 3235 (NH), 2973 (CH, aliphatic), 2229, 2214 (C≡N), 1739 (C=O, ester), 1643 (C=C), 1580 (NH), 1250 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.47 (3H, t, $^3J=7.2$ Hz, CH_3), 4.50 (2H, q, $^3J=7.2$ Hz, CH_2), 5.52 (2H, br s, NH_2), 7.51 (1H, s, CH), 7.53–7.62 (5H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 13.8 (CH_3), 62.3 (CH_2), 93.8 (C_4), 98.6 (C_6), 114.6, 115.3 (2C≡N), 118.2 (C_2), 128.4, 128.8, 129.7 (5C, Ph), 136.7 (C_{ipso} of Ph), 136.9 (C_3), 150.0 (C_1), 154.1 (C_5), 163.3 (C=O, ester); EI-MS: *m/z* (%) 291 (M^{+}, 100), 263 (50), 245 (36), 219 (34), 191 (51), 164 (44), 77 (9). Anal. Calcd for $C_{17}H_{13}N_3O_2$ (291.30): C, 70.09; H, 4.50; N, 14.42. Found: C, 70.27; H, 4.39; N, 14.65.

Ethyl 5-amino-4,6-dicyano-4′-chlorobiphenyl-3-carboxylate (3b) Yellow cotton-like solid; yield 0.14 g (86%); mp 212–214°C; IR: ν 3327, 3350, 3252 (NH), 2980 (CH, aliphatic), 2221 (C≡N), 1738 (C=O, ester), 1634 (C=C), 1579 (NH), 1257 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.45 (3H, t, $^3J=7.1$ Hz, CH_3), 4.48 (2H, q, $^3J=7.1$ Hz, CH_2), 5.57 (2H, br s, NH_2), 7.44 (1H, s, CH), 7.51 (4H, m, Ph-Cl); ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 63.0 (CH_2), 95.4 (C_4), 99.1 (C_6), 114.7, 115.1 (2C≡N), 120.0 (C_2), 129.4, 129.7 (4C, Ph), 135.0 (C_{ipso} of Ph-Cl), 136.5 (C_{para} of Ph-Cl), 136.6 (C_3), 148.8 (C_1), 153.2 (C_5), 163.2 (C=O, ester); EI-MS: *m/z* (%) 327 ($M^{+}+2$, 39), 325 (M^{+}, 100), 297 (52), 275 (30), 253 (28), 217 (53), 189 (23), 163 (12). Anal. Calcd for $C_{17}H_{12}ClN_3O_2$ (325.75): C, 62.68; H, 3.71; N, 12.90. Found: C, 62.92; H, 3.89; N, 12.58.

Ethyl 5-amino-4,6-dicyano-4′-bromobiphenyl-3-carboxylate (3c) Yellow cotton-like solid; yield 0.14 g (76%); mp 230–232°C; IR: ν 3428, 3350, 3251 (NH), 2979 (CH, aliphatic), 2220 (C≡N), 1737 (C=O, ester), 1634 (C=C), 1577 (NH), 1257 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.45 (3H, t, $^3J=7.1$ Hz, CH_3), 4.48 (2H, q, $^3J=7.1$ Hz, CH_2), 5.55 (2H, br s, NH_2), 7.44 (1H, s, CH), 7.45 (2H, d, $^3J=8.3$ Hz, $2CH_{meta}$ of Ph-Br), 7.67 (2H, d, $^3J=8.3$ Hz, $2CH_{ortho}$ of Ph-Br); ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 63.0 (CH_2), 95.5 (C_4), 99.1 (C_6), 114.7, 115.1 (2C≡N), 120.0 (C_2), 124.8 (C_{ipso} of Ph-Br), 130.0, 132.3 (4C, Ph), 135.5 (C_{para} of Ph-Br), 136.6 (C_3), 148.8 (C_1), 153.2 (C_5), 163.2 (C=O, ester); EI-MS: *m/z* (%) 371 ($M^{+}+2$, 99), 369 (M^{+}, 100), 341 (41), 326 (24), 297 (20), 217 (75), 189 (39), 163 (29). Anal. Calcd for $C_{17}H_{12}BrN_3O_2$ (370.20): C, 55.15; H, 3.27; N, 11.35. Found: C, 54.91; H, 3.08; N, 11.52.

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