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ORIGINAL ARTICLE

On the reaction of phenacylmalononitrile with hydrazines: A new route to pyrazolo[3,4-c]pyridazine, isoxazolo[5,4-c]pyridazine and pyrimido[4,5-c]pyridazine

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Pyrazolo[3,4-c]pyridazine;
Pyrimido[4,5-c]pyridazine;
Phenylisoxazolo[5,4-c] pyridazin

Abstract The reaction of arylmalononitiles **1a,b** with hydrazine hydrate at room temperature has afforded 3-oxo-6-aryl-2,3,4,5-tetrahydropyridazine-4-carbonitrile **3a,b** as the sole isolable product. These 3-oxopyridazin-4-carbonitriles underwent aromatization to 3-oxo-6-phenylpyridazine-4-carbonitrile **4** on attempted coupling with benzene diazonium chloride. Compound **3a** reacted with hydrazine hydrate as well as urea to yield pyrazolo[3,4-c]pyridazine **5** and pyrimido[4,5-c]pyridazine **6**. On the other hand, amidoximes **7a,b** were isolated from reaction of **3a,b** with hydroxylamine hydrochloride. Amidoximes **7a** could be cyclized successfully into 5-phenylisoxazolo[5,4-c]pyridazin-3-amine **8** while **7b** could not be cyclized on our hand.

1. Introduction

Malononitrile and malononitrile derivatives are versatile reagents and their chemistry has been studied in the past (Freeman, 1969, 1980; Fatiadi, 1978) and still attracts considerable interest (Evdokimov et al., 2007; Ranu et al., 2007). In the past thirty years, we have reported several new approaches to a variety of polyfunctional heterocycles utilizing malononitrile or substituted malononitriles as precursors (Elnagdi and Abdoula, 1973; Elnagdi, 1974; Elnagdi et al., 1977, 1979; Ghozlan et al., 1986) and several of these products as been established to act as anti-profiler agents. Very recently we have reported on the utility of benzylmalononitrile as precursor to diaminopyrazoles, diaminoisoxazoles, thiazoles and condensed azoles (Al-Mousawi et al., 2008a,b). Also in the last few years, we were interested in developing the syntheses of polyfunctional pyrazolo[1,5-a]pyrimidines utilizing differently substituted aminopyrazoles as precursors (Anwar et al., 2006; Al-Mousawi et al., 2008a,b). Our contribution to this area has been recently reviewed (Anwar and Elnagdi, 2009). In a trial to synthesize 4-phenaylpyrazole-3,5-diamine **2** *via* reacting phenacylmalononitrile **1** with hydrazine hydrate; a mixture of products was obtained (Elnagdi et al., 1997). However, when **1** and hydrazine hydrate were stirred at room temperature the pyridazine **3a,b** was obtained as the sole product in more than 95% yield (Al-Mousawi et al., 2009). It was also noticed that **3a** reacts

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with hydrazine hydrate to yield the pyrazolo[3,4-c]pyridazine in 65% yield. This has prompted us to see if this reaction can be utilized as one of the bases for producing condensed pyridazines in connection to our interest in the chemistry of condensed pyridazines(Elnagdi et al., 2009) **5** especially in the light of repeated reported formation of **2** and its derivatives (Abdelrazek, 1989; Abdelrazek and Metwally, 2003).

2. Experimental

All melting points are uncorrected and were determined with Sanyo (Gallaenkamp) instrument. Infrared spectra were recorded in KBr and were determined on a Perkin–Elmer 2000 FT-IR system. ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker DPX at (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) spectrometer in DMSO-d_6 as solvent and TMS as internal standard; chemical shifts are reported in δ (ppm). Mass spectra were measured on VG Autospec Q MS 30 and MS 9 (AEI) spectrometers, with EI 70 EV. Elemental analyses were measured by means of LEOCHNS-932 Elemental Analyzer.

*2.1. General syntheses of compounds (**3a**,**b**)*

A mixture of compound **1a**,**b** (0.01 mol) and hydrazine hydrate (0.50 g, 0.01 mol) in ethanol (10 mL) was stirred for 1 h at room temperature (followed by TLC until completion using ethyl acetate-petroleum ether 1:1 as eluent). The reaction mixture was poured onto ice-water. The solid product formed was collected by filtration and crystallized from ethanol to give a white product.

*2.2. 3-Oxo-6-phenyl-2,3,4,5-tetrahydropyridazine-4-carbonitrile (**3a**)*

Yield 90%; mp 253–255 °C. Anal. Calcd for $C_{11}H_9N_3O$ (199.2): C, 66.32; H, 4.55; N, 21.09. Found: C, 66.54; H, 4.32; N, 21.30%. IR (KBr): ν_{max} = 3234 (NH), 2154 (CN), 1693 (CO); ^{1}H NMR (DMSO): δ, ppm = 3.27 (m, 1H), 3.59 (m, 1H), 4.50 (m, 1H), 7.45–7.79 (m, 5H, Ar–H), 11.49 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO): δ, ppm = 159.81, 148.66, 134.91, 129.91, 126.99 (2C), 125.75 (2C), 116.92, 29.90, 25.61; MS: *m*/*z* (%) 199 (M^+, 100), 170 (15), 155 (15), 140 (15), 115 (25), 103 (80), 77 (35).

*2.3. 6-(4-Chlorophenyl)-3-oxo-2,3,4,5-tetrahydropyridazine-4-carbonitrile (**3b**)*

Yield 92%; mp 224–225 °C. Anal. Calcd for $C_{11}H_8ClN_3O$ (233.66): C, 56.54; H, 3.45; N, 17.94. Found: C, 56.60; H, 3.65; N, 18.02%. IR (KBr): ν_{max} = 3227 (NH), 2257 (CN), 1675 (CO); ^{1}H NMR (DMSO): δ, ppm = 3.30 (m, 1H), 3.56 (m, 1H), 4.52 (m, 1H), 7.51 (d, 2H, *J* = 8, Ar–H), 7.79 (d, 2H, *J* = 8, Ar–H), 11.54 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO): δ, ppm = 159.77, 147.62, 134.51, 133.79, 128.92 (2C), 127.65 (2C), 116.84, 29.83, 25.50; MS: *m*/*z* (%) 234 (M^{+1}, 30), 233 (M^+, 100), 206 (10), 176 (10), 152 (10), 137 (55), 111 (10), 102 (15), 75 (15).

*2.4. Synthesis of 3-oxo-6-phenyl-2,3-dihydropyridazine-4-carbonitrile (**4**)*

Procedure 1: A mixture of **3a** (1.99 g, 0.01 mol) and *N*,*N*-dimethylformamide (DMF) (10 mL) was refluxed for 4 h (followed to completion by TLC using 1:1 ethyl acetate-petroleum ether as eluent). The mixture was cooled and then poured onto ice-water. The solid formed was collected by filtration and recrystallized from ethanol to give a yellow product in yield of 95%.

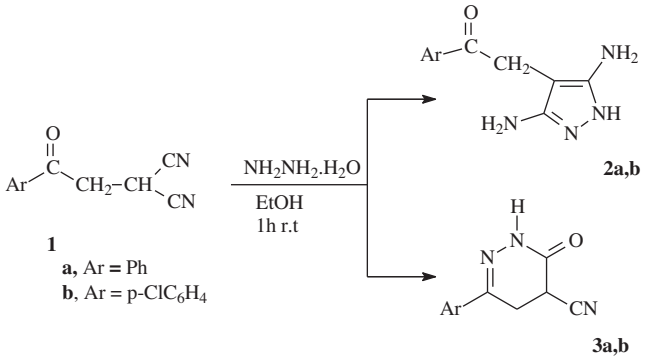
Procedure 2: A cold solution of phenyldiazonium chloride (0.01 mol) was prepared by adding a solution of sodium nitrite (0.7 g into 10 mL H_2O) to a cold solution of aniline hydrochloride (0.93 g, 0.01 mol of aniline in 5 mL concentrated HC1) with stirring at room temperature. The resulting solution of phenyldiazonium chloride was then added to a cold solution of compound **3a** (1.99 g, 0.01 mol) in ethanol (50 mL) containing sodium acetate (2 g). The reaction mixture was stirred for 1 h. The solid product formed was collected by filtration and crystallized from ethanol to give a yellow product, yield 70%; mp 295–297 °C. Anal. Calcd for $C_{11}H_7N_3O$ (197.2): C, 67.00; H, 3.58; N, 21.31. Found: C, 66.98; H, 3.92; N, 21.65%. IR (KBr): ν_{max} = 3217 (NH), 2233 (CN), 1664 (CO); ^{1}H NMR (DMSO): δ, ppm = 7.46–7.91 (m, 5H, Ar–H), 8.85 (s, 1H, CH), 14.04 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO): δ, ppm = 158.78, 148.35, 142.99, 138.34, 135.90, 130.34 (2C), 128.22 (2C), 119.26, 114.66. MS: *m*/*z* (%) 197 (M^+, 100), 169 (65), 140 (95), 114 (35), 102 (40), 77 (35), 63 (20).

*2.5. Synthesis of dihydro-1H-pyrazolo[3,4-c]pyridazin-3-ylamine (**5**)*

A mixture of compound **3a** (1.99 g, 0.01 mol) and hydrazine hydrate (0.50 g, 0.01 mol) in ethanol (10 mL) was refluxed for 5 h (followed by TLC until completion using ethyl acetate–petroleum ether 1:1 as eluent). The reaction mixture was cooled and poured onto ice-water. The solid product thus formed was collected by filtration and crystallized from *N*,*N*-dimethylformamide (DMF) to yield purple crystals; yield 70%; mp 288–290 °C. Anal. Calcd for $C_{11}H_{11}N_5$ (213.2): C, 61.96; H, 5.20; N, 32.84. Found: C, 61.77; H, 5.32; N, 32.65%. IR (KBr): ν_{max} = 3159, 3012 (NH_2), 3012 (NH), 2983 (NH); ^{1}H NMR (DMSO): δ, ppm = 3.57 (s, 2H, 4-H), 7.33–7.70 (m, 5H, Ar-H),10.11 (br. s, 1H, 7-H, D_2O exchangeable), the other NH signals are too broad to be localized; ^{13}C NMR (DMSO): δ, ppm = 154.1, 146.7, 138.0 (2C), 137.8 (2C), 128.3, 128.1, 124.7, 77.7, 21.3; MS: *m*/*z* (%) 214 (M^+, 100), 185 (35), 171 (15), 141 (15), 115 (25), 77 (35).

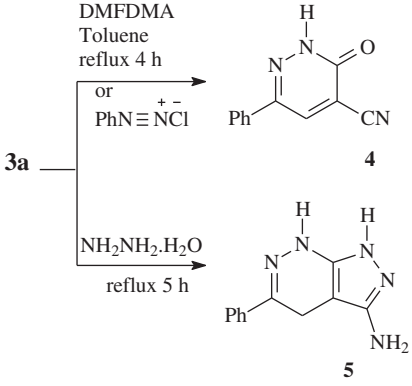
*2.6. Synthesis of 5-amino-3-phenylpyrimido[4,5-c]pyridazin-7(8H)-one (**6**)*

A mixture of compound **3a** (1.99 g, 0.01 mol) and urea (0.60 g, 0.01 mol) in ethanol (10 mL) was refluxed for 10 h (followed by TLC until completion using ethyl acetate-petroleum ether 1:1 as eluent). The reaction mixture was cooled and poured onto ice-water. The solid product thus formed was collected by filtration and crystallized from ethanol to give a yellow product; yield 82%; mp 278–280 °C. Anal. Calcd for



1
a, Ar = Ph
b, Ar = p-ClC$_6$H$_4$

Scheme 1



Scheme 2

$C_{12}H_9N_5O$ (239.24): C, 56.89; H, 5.21; N, 24.12. Found: C, 59.84; H, 4.02; N, 29.15%. IR (KBr): ν_{max} = 3327, 3215 (NH_2), 3054 (NH), 1662 (CO); ^{1}H NMR (DMSO): δ, ppm = 7.44–7.90 (m, 7H, Ar–H, NH_2 D_2O exchangeable), 8.83 (s, 1H, CH), 13.91 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO): δ, ppm = 158.23, 157.07, 143.66, 138.43, 133.46, 129.85, 129.01 (2C), 125.85 (2C), 114.66, 114.24; MS: m/z (%) 239 (M^+, 90), 223 (60), 196 (25), 167 (15), 141 (10), 115 (45), 77 (15), 63 (10).

*2.7. General syntheses of compounds (**7a**,**b**)*

A mixture of **3a** (1.99 g, 0.01 mol), hydroxylamine hydrochloride (0.69 g, 0.01 mol), and sodium acetate (1.5 g) in AcOH (20 mL) was refluxed for 3 h (followed by TLC until completion using ethyl acetate–petroleum ether 1:1 as eluent). The reaction mixture was cooled and poured onto ice-water. The solid product thus formed, was collected by filtration and crystallized from EtOH to give a yellow product.

*2.8. N-Hydroxy-3-oxo-6-phenyl-2,3-dihydropyridazine-4-carboxamidine (**7a**)*

Yield 75%; mp 250–252 °C. Anal. Calcd for $C_{11}H_{10}N_4O_2$ (230.23): C, 57.39; H, 4.38; N, 24.34. Found: C, 57.51; H, 4.36; N, 24.33%. IR (KBr): ν_{max} = 3485 (OH), 3324, 3164 (NH_2), 3100 (NH), 1670 (CO); ^{1}H NMR (DMSO): δ, ppm = 6.34 (br, 2H, NH_2, D_2O exchangeable), 7.43–7.85 (m, 5H, Ar–H), 8.21 (s, 1H, CH), 10.09 (br, 1H, OH, D_2O exchangeable) 13.63 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO): δ, ppm = 160.03, 147.89, 144.59, 142.26, 134.53, 131.80, 130.65, 130.09 (2C), 129.12 (2C); MS: m/z (%) 230 (M^+, 100), 200 (65), 172 (25), 149 (40), 115 (45), 77 (45), 61 (80).

*2.9. 6-(4-Chloro-phenyl)-N-hydroxy-3-oxo-2,3-dihydropyridazine-4-carboxamidine (**7b**)*

Yield 83%; mp 233–235 °C. Anal. Calcd for $C_{11}H_9ClN_4O_2$ (264.67): C, 49.92; H, 3.43; N, 21.17. Found: C, 50.05; H, 3.68; N, 20.98%. IR (KBr): ν_{max} = 3473 (OH), 3316, 3182 (NH_2), 3098 (NH), 1675 (CO); ^{1}H NMR (DMSO): δ, ppm = 6.32 (br, 2H, NH_2, D_2O exchangeable), 7.55 (d, 2H, J = 8, Ar–H), 7.86 (d, 2H, J = 8, Ar–H), 8.20 (s, 1H, CH), 10.10 (br, 1H, OH, D_2O exchangeable) 13.66 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO): δ, ppm = 159.96, 147.83, 143.56, 134.16, 134.40, 130.73, 129.04 (2C), 127.55 (2C), 125.73; MS: m/z (%) 265 (M^{+1}, 40), 264 (M^+, 100), 233 (70), 206 (10), 176 (50), 152 (25), 137 (55), 111 (30), 102 (15), 75 (65).

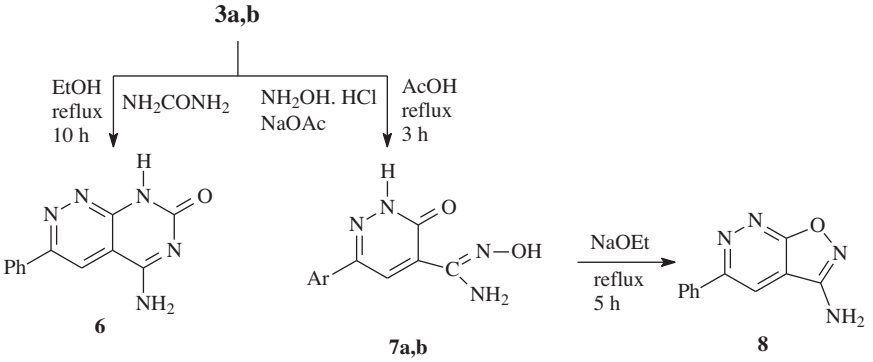
*2.10. Synthesis of 5-phenylisoxazolo[5,4-c]pyridazin-3-amine (**8**)*

A mixture of **7a** (2.30 g, 0.01 mol) and EtOH/EtONa (20 mL) was refluxed for 5 h (followed to completion by TLC using 1:1 ethyl acetate-petroleum ether as eluent). The mixture was cooled and then poured onto ice-water. The solid formed was collected by filtration and recrystallized from ethanol to give a yellow product; yield 70%; mp 289–290 °C. Anal. Calcd for $C_{11}H_8N_4O$ (212.21): C, 62.26; H, 3.80; N, 26.40. Found: C, 62.15; H, 3.39; N, 26.31%. IR (KBr): ν_{max} = 3355, 3151 (NH_2) ^{1}H NMR (DMSO): δ, ppm = 7.39 (br, 2H, NH_2, D_2O exchangeable), 7.47–7.90 (m, 5H, Ar–H), 8.52 (s, 1H, CH); ^{13}C NMR (DMSO): δ, ppm = 173.56, 150.14, 143.04, 135.33, 128.55 (2C), 127.65, 126.71 (2C), 124.27, 114.43; MS: m/z (%) 212 (M^+, 100), 197 (10), 172 (25), 142 (5), 130 (15), 115 (45), 104 (15), 77 (15), 63 (10).

3. Results and discussion

Mixing **1a,b** with hydrazine hydrate has afforded **3a,b** as the sole products in 90–92% yields. Trials to adopt the reported reaction conditions to obtained **2a,b** as reported in the literature failed (Abdelrazek, 1989). In fact we believe that compound **2a,b** has never been formed since such a electron rich highly substituted pyrazole derivative is difficult to form. Formation of **3a,b** in an exothermic reaction as has been noticed by us is thermally preferred and has a less energy demanding route (Scheme 1).

Attempted coupling of **3a** with benzenediazonium chloride has led to aromatization and isolation of compound **4** only. Compound **4** was also formed upon leaving **3a** solutions in acetic acid in the presence of sodium acetate to stand at room temperature for two hours. Compounds **3a** readily reacted with hydrazine hydrate to yield the pyrazolo[3,4-c]pyridazines **5** (Scheme 2).



Scheme 3

Likewise reacting **3a** with urea afforded **6**. In contrast to this; the reaction of **3a,b** with hydroxylamine hydrochloride afforded only amidoximes **7a,b**. Refluxing **7a** in EtOH/EtONa afforded the isoxzole[4,5-c]pyridazine **8**, while **7b** could not likewise be cyclized (Scheme 3).

In conclusion, we could make it clear that the reaction of **1a,b** with hydrazine hydrate affords only **3a,b** as sole isolable product despite repeated reports describing the formation of **2a,b**. The pyridazines **3a,b** could prove valuable precursors for condensed pyridazines thus opening an easy efficient route for the synthesis of the latter derivatives.

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