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A novel synthesis of 2-arylhydrazono-6-amino-4-arylbenzene-1,3-dicarbonitriles and their conversion into phthalazines

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A B S T R A C T

Compounds **1a**–**d** react with benzylidenemalononitrile **2** to yield dihydroaminopyridazines **3a**–**d** and, in contrast, compounds **1e**,**f** react with **2** under the same conditions to yield aminobenzenedicarbonitriles **8e**,**f** compound **8e** underwent intramolecular cyclization to phthalazine **9e**. Compound **10e** reacted with **2a** to yield **11e**.

1. Introduction

Recently, we reported that 2-oxo-2-arylhydrazonals **1a**,**b** reacted with α,β-unsaturated nitriles **2** to yield 1,4-dihydro-6-aminopyridazines **3a**,**b**.[1–3] We were interested to see if reactions of this type could be extended to provide a new general route to derivatives of **3**. Our work has revealed that, while a variety of substituted 2-oxoarylhydrazonals **1c**,**d** reacted similar to **1a**,**b** yielding **3c**,**d**; *p*- and *o*-nitro-substituted derivatives **1e**,**f** reacted differently yielding the title compounds which could be readily cyclised into phthalazines **9**.

Compounds **1a**–**d** reacted with **2** to yield the dihydropyridazines **3a**–**d** in good yields. Although the reaction may also yield **4**, structure **3** was established based on HMBC experiments which revealed that dihydropyridazine H-4 and the C=O function showed cross peaks (Scheme 1).

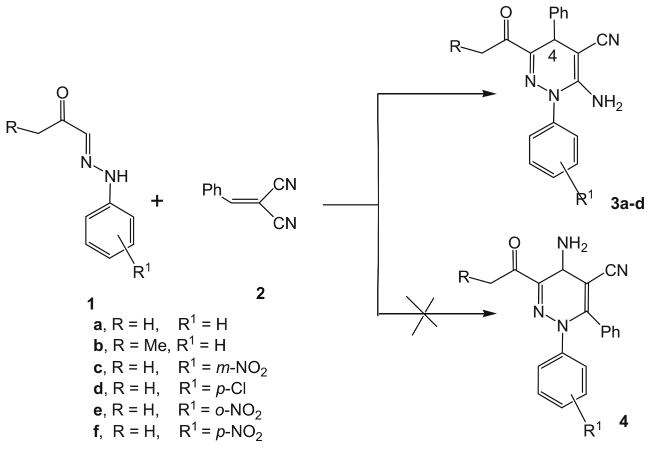
In contrast, compounds **1e**,**f** reacted with **2a** which exists in equilibrium with malononitrile and benzaldehyde in ethanolic solutions, to yield products that were identified as aminobenzenedicarbonitriles **8e**,**f**. These were assumed to form via initial condensation of malononitrile with the acetyl moiety of **1e**,**f** to yield intermediates **5e**,**f** that reacted further with **2** to yield products **8e**,**f** via intermediates **6e**,**f** and **7e**,**f** (Scheme 2). Compound **8e** was cyclized into the phthalazine **9e** in 80% yield on reflux in DMF in the presence of $ZnCl_2$ (Scheme 3).

To avoid potential participation of the carbonyl group, compound **1e** was reduced with sodium borohydride to give **10e**. This was reacted with *p*-methoxybenzylidenemalononitrile **2a** to give **11e** which is formed via condensation of phenyl hydrazine produced by hydrolysis of **10a** with aldehyde produced from hydrolysis of **2a**.

In conclusion, as a result of the strong electron-withdrawing nature of the nitro substituent, the hydrazone N lone pair reacts preferably at the aryl moiety rendering the hydrazone CH inactive toward electrophiles and a new mode of reaction is thus followed leading to novel benzenedicarbonitrile derivatives. We are now exploring the effect of substituents on the aryl moiety on the nature of the products.

2. General procedure for the synthesis of compounds 3c,d

A mixture of **1c**,**d** (0.01 mol) and benzylidenemalononitrile (1.54 g, 0.01 mol) in EtOH (10 mL) as a solvent was treated with 5 drops of piperidine and then refluxed for 2–4 h (monitored by TLC using a mixture of petroleum ether (bp 60–80):EtOAc 2:1). The reaction mixture was evaporated under reduced pressure.



Scheme 1.

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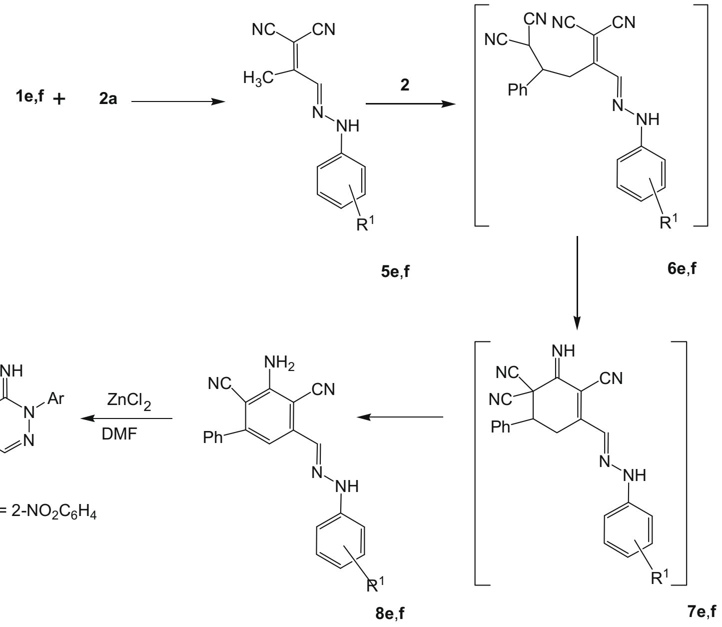
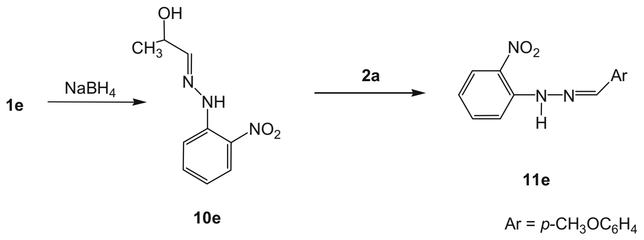


Scheme 2.



Scheme 3.

The solid product, so formed, was recrystallized from EtOH to give yellow crystals.

2.1. 6-Acetyl-3-amino-2-(3-nitrophenyl)-5-phenyl-2,5-dihydropyr-idazine-4-carbonitrile 3c

Yield 85%; mp 203–205 °C. Anal. Calcd for $C_{19}H_{15}N_5O_3$ (361.36): C, 63.15; H, 4.18; N, 19.18. Found: C, 63.21; H, 4.24; N, 19.00; IR (KBr, cm^{-1}): 3400, 3328 (NH_2), 2181 (CN), 1685 (CO); ^1H NMR (400 MHz, DMSO-d_6): δ, ppm = 2.36 (s, 3H, CH_3), 4.77 (s, 1H, CH), 6.37 (br, 2H, NH_2) D_2O exchangeable, 7.2–7.37 (m, 5H, Ar–H), 7.8–8.31 (m, 4H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ, ppm = 196.50 (CO), 150.93, 149.12, 145.76, 142.48, 141.96, 132.82, 131.75, 129.89 (2C), 128.22, 127.76 (2C), 123.09, 121.18, 121.13, 58.58, 37.17, 25.63. MS: *m/z* (%) 361 (M^+, 55), 318 (100), 272 (35), 245 (20), 195 (15), 155 (15), 128 (10).

2.2. 6-Acetyl-3-amino-2-(4-chlorophenyl)-5-phenyl-2,5-dihydro-pyridazine-4-carbonitrile 3d

Yield 80%; mp 206–208 °C. Anal. Calcd for $C_{19}H_{15}N_4OCl$ (350.81): C, 65.05; H, 4.31; N, 15.97. Found: C, 65.20; H, 4.33; N, 16.10; IR (KBr, cm^{-1}): 3422, 3339 (NH_2), 2211 (CN), 1665 (CO); ^1H NMR (400 MHz, DMSO-d_6): δ, ppm = 2.33 (s, 3H, CH_3), 4.75 (s, 1H, CH), 6.22 (br, 2H, NH_2) D_2O exchangeable, 7.17–7.70 (m, 9H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ, ppm = 196.19 (CO), 150.73, 144.68, 142.34, 139.53, 132.55, 129.90 (2C), 129.45 (2C), 128.08 (2C), 127.89, 127.35 (2C), 120.94, 57.33, 36.52, 25.14. MS: *m/z* (%) 350 (M^+, 40), 307 (100), 273 (100), 244 (20), 231 (20), 204 (15), 153 (30), 127 (25), 128 (10), 111 (50), 75 (20).

3. General procedure for the synthesis of compounds 8e,f

A mixture of **1e**,**f** (0.01 mol) and benzylidenemalononitrile (3.08 g, 0.02 mol) in EtOH (10 mL) was treated with 5 drops of piperidine and then refluxed for 2–4 h (monitored by TLC using a mixture of petroleum ether (bp 60–80):EtOAc 2:1). The reaction mixture was evaporated under reduced pressure. The solid product, so formed, was recrystallized from EtOH to give yellow crystals.

3.1. 2-(2-Nitrophenyl)hydrazine-6-amino-4-arylbenzene-1,3-dicarbonitrile 8e

Yield 75%; mp 297–298 °C. Anal. Calcd for $C_{21}H_{14}N_6O_2$ (382.38): C, 65.96; H, 3.69; N, 21.98. Found: C, 65.79; H, 3.67; N, 21.77; IR (KBr, cm^{-1}): 3462, 3369 (NH_2), 3273 (NH), 2225 (CN), 2211 (CN); ^1H NMR (400 MHz, DMSO-d_6): δ, ppm = 6.84 (br, 2H, NH_2) D_2O exchangeable, 7.02–8.13 (m, 10H, Ar–H, CH), 8.72 (s, 1H, CH), 11.65 (br, 1H, NH) D_2O exchangeable; ^{13}C NMR (125 MHz, $CDCl_3$): δ, ppm = 154.20, 149.78, 141.87, 140.16, 139.62, 137.62, 136.30, 132.20, 129.49, 128.82 (2C), 128.51 (2C), 125.70, 119.86, 116.74, 116.12, 115.48, 115.37, 94.66, 92.19. MS: *m/z* (%) 382 (M^+, 40), 336 (100), 320 (20), 308 (10), 256 (10), 247 (15), 219 (10), 191 (30), 164 (15), 129 (25), 83 (15), 73 (40).

3.2. 2-(4-Nitrophenyl)hydrazine-6-amino-4-arylbenzene-1,3-dicarbonitrile 8f

Yield 65%; mp 299–300 °C. Anal. Calcd for $C_{21}H_{14}N_6O_2$ (382.38): C, 65.96; H, 3.69; N, 21.98. Found: C, 65.80; H, 3.82; N, 21.83; IR (KBr, cm^{-1}): 3456, 3355 (NH_2), 3230 (NH), 2221 (CN), 2204 (CN); ^1H NMR (400 MHz, DMSO-d_6): δ, ppm = 6.66 (br, 2H, NH_2) D_2O exchangeable, 7.23–7.98 (m, 8H, Ar–H, CH), 8.22 (d, 2H, Ar–H), 8.85 (s, 1H, CH), 11.77 (br, 1H, NH) D_2O exchangeable; ^{13}C NMR (125 MHz, $CDCl_3$): δ, ppm = 161.81, 154.44, 150.50, 146.52, 145.95, 139.83, 137.76, 132.94, 130.60, 128.92 (2C), 127.31 (2C), 127.06 (2C), 124.05 (2C), 116.75, 108.51, 105.49, 94.53. MS: *m/z* (%) 382 (M^+, 60), 336 (100), 320 (55), 256 (35), 247 (65), 191 (30), 164 (15), 129 (25), 83 (15), 73 (50).

3.3. Synthesis of 5-amino-4-imino-3-(2-nitrophenyl)-7-phenyl-3,4-dihydrophthalazine-6-carbonitrile 9e

A mixture of **8e** (3.82 g, 0.01 mol) and zinc chloride (0.5 g) in DMF (10 mL) was refluxed for 4–6 h (monitored by TLC using a mixture of petroleum ether (bp 60–80):EtOAc 2:1). The reaction mixture was evaporated under reduced pressure. The solid product, so formed, was recrystallized from EtOH to give a dark yellow product, yield 80%; mp 240–242 °C. Anal. Calcd for $C_{21}H_{14}N_6O_2$ (382.38): C, 65.96; H, 3.69; N, 21.98. Found: C, 66.19; H, 3.80; N, 22.06; IR (KBr, cm^{-1}): 3468, 3371 (NH_2), 3328 (NH), 2202 (CN); ^1H NMR (400 MHz, DMSO-d_6): δ, ppm = 6.89 (br, 2H, NH_2) D_2O exchangeable, 7.13 (s, 1H, CH), 7.34–8.29 (m, 10H, Ar–H, CH), 10.51 (br, 1H, NH) D_2O exchangeable; MS: *m/z* (%) 382 (M^+, 35), 346 (50), 337 (100), 320 (10), 308 (10), 280 (10), 247 (25), 219 (10), 192 (30), 164 (25), 154 (25), 102 (15), 92 (10), 65 (20).

3.4. Synthesis of 1-(2-(2-nitrophenyl)hydrazono)propan-2-ol 10e

A solution of **1e** (2.07 g, 0.01 mol) in isopropanol (5 mL) was cooled to 0 °C. Sodium borohydride (0.756 g, 0.02 mol) was added and the reaction mixture was stirred (monitored by TLC using ethyl acetate:petroleum ether 1:2, until completion). The reaction was carefully quenched with ice-H_2O and 1 M HCl solution, and then the reaction mixture was extracted with CH_2Cl_2, filtered, and concentrated. The crude product was recrystallized from petroleum ether (60–80) to give a red product; yield 85%; mp 102–104 °C. Anal. Calcd for $C_9H_{11}N_3O_3$ (209.20): C, 51.67; H, 5.30; N, 20.09. Found: C, 51.48; H, 5.33; N, 19.88; IR (KBr, cm^{-1}): 3391 (OH), 3306 (NH); ^1H NMR (400 MHz, DMSO-d_6): δ, ppm = 1.46 (d, 3H, *J* = 8, CH_3), 2.67 (d, 1H, *J* = 8, OH), 4.60 (m, 1H, CH), 6.89–8.20 (m, 5H, Ar–H, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ, ppm = 145.30, 141.66, 131.07, 136.18, 125.88, 118.37, 115.75, 67.13, 21.24. MS: *m/z* (%) 209 (M^+, 100), 191 (30), 166 (20), 148 (25), 138 (100), 119 (25), 106 (40), 91 (60), 77 (95), 69 (80), 65 (70).

3.5. Synthesis of 1-(4-methoxybenzylidene)-2-(2-nitrophenyl)hydrazine 11e

A mixture of **10e** (2.09 g, 0.01 mol) and 4-methoxybenzylidene malononitrile (1.84 g, 0.01 mol) in EtOH (10 mL) was treated with 5 drops of piperidine, and then refluxed for 2–4 h (monitored by TLC using a 2:1 mixture of petroleum ether:EtOAc). The reaction mixture was evaporated under reduced pressure. The solid product, so formed, was recrystallized from EtOH to give a red product; yield 80%; mp 210–212 °C. Anal. Calcd for $C_{14}H_{13}N_3O_3$ (271.28): C, 61.99; H, 4.83; N, 15.49. Found: C, 62.12; H, 4.61; N, 15.68; IR (KBr, cm^{-1}): 3295 (NH); ^1H NMR (400 MHz, DMSO-d_6): δ, ppm = 3.81 (s, 3H, CH_3), 6.87–8.12 (m, 8H, Ar–H), 8.44 (s, 1H, CH), 11.13 (br, 1H, NH) D_2O exchangeable; ^{13}C NMR (125 MHz, $CDCl_3$): δ, ppm = 160.54, 145.22, 141.51, 136.36, 130.34, 128.40 (2C), 127.07, 125.03, 117.83, 115.91, 114.35 (2C), 55.27. MS: *m/z* (%) 271 (M^+, 100), 209 (20), 181 (20), 152 (25), 137 (50), 107 (15), 91 (20), 77 (50).

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