S. Afr. J. Chem., 2013, **66**, 179–182,
<http://journals.sabinet.co.za/sajchem/>.

A Simple Three-component Synthesis of 3-Amino-5-arylpyridazine-4-carbonitriles

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Received 26 December 2012, revised 1 May 2013, accepted 9 June 2013.

ABSTRACT

New 3-amino-5-arylpyridazine-4-carbonitriles have been synthesized by a one-pot three-component reaction of malononitrile with arylglyoxals in the presence of hydrazine hydrate at room temperature in water and ethanol.

KEYWORDS

Arylglyoxals, arylpyridazines, hydrazine hydrate, one-pot, malononitrile.

1. Introduction

In recent years, nitrogen-containing heterocyclic compounds have been indispensable structural units for both chemists and biochemists due to their biological and pharmaceutical properties. Among various heterocycles, pyridazines and their annulated derivatives continue to attract attention due to their wide range of interesting biological activities.[1]

The synthesis of pyridazine derivatives[2–5] and their pharmacological properties as analgesics,[6] insecticidals,[7] fungicidals,[8–9] cardiotonics,[10] and bacteriocides[11] have been reported, as well as the synthesis of pyridazine derivatives by reaction of hydrazine with 1,4-dicarbonyl compounds,[12] reaction of arylglyoxals[13] with β-ketoesters[14–15] and alkyl 2-cyanoacetates in presence hydrazine hydrate.[16]

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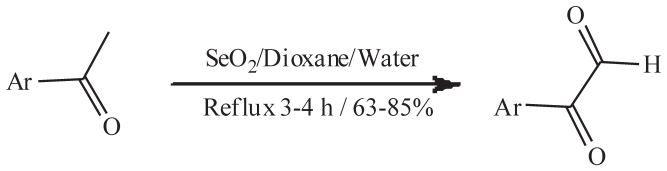
Therefore, continuing our interest in the synthesis of pyridazine derivatives, we decided to investigate the synthesis of 3-amino-5-arylpyridazine-4-carbonitriles as a new series of tri-substituted pyridazines by reaction of arylglyoxals, malononitrile and hydrazine hydrate.

2. Results and Discussion

Firstly, the arylglyoxals **2a–j** were prepared from the corresponding acetophenones **1a–j** *via* oxidation with SeO_2 in dioxane under reflux conditions (Scheme 1).[13]

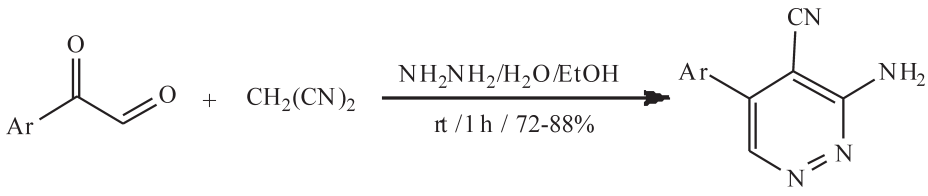
The desired pyridazines were prepared by adding arylglyoxals **2a–g** to hydrazine hydrate 80 % in water and ethanol (1:1) and stirred for 30 min at room temperature to form corresponding hydrazones. The malononitrile **3** was then added to the reaction mixture and stirred at room temperature (Scheme 2). All of the products obtained are listed at Table 1.



1a-j **2a-j**

a; Ar= C_6H_5 **b**; Ar= 4-BrC_6H_4 **c**; Ar= 4-ClC_6H_4 **d**; Ar= 4-FC_6H_4
e; Ar= 4-$NO_2C_6H_4$ **f**; Ar= 3-BrC_6H_4 **g**; Ar= 3-$MeOC_6H_4$ **h**; Ar= 4-$MeOC_6H_4$
i; Ar= 4-(OH)-3-(MeO)C_6H_3 **j**; Ar= 3,4-$(MeO)_2C_6H_3$

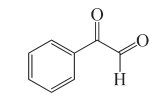
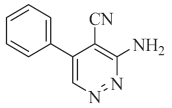
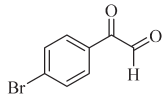
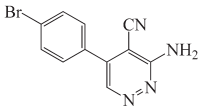
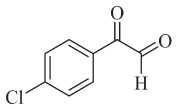
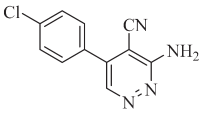
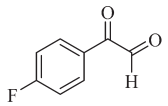
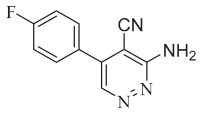
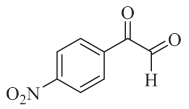
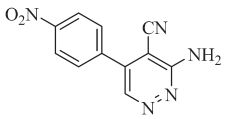
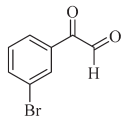
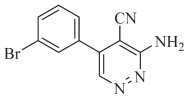
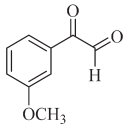
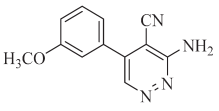
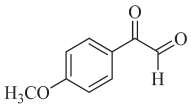
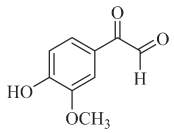
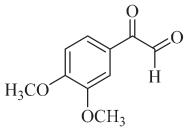
Scheme 1
Synthesis of arylglyoxals **2a–j**.



2a-g **3** **4a-g**

Scheme 2
Synthesis of 3-amino-5-arylpyridazine-4-carbonitrile.

Table 1 List of pyridazine products.

Entry	Arylglyoxal	Pyridazine	Yield /%
1	 **2a**	 **4a**	78
2	 **2b**	 **4b**	86
3	 **2c**	 **4c**	87
4	 **2d**	 **4d**	83
5	 **2e**	 **4e**	88
6	 **2f**	 **4f**	76
7	 **2g**	 **4g**	72
8	 **2h**	N.R	-
9	 **2i**	N.R	-
10	 **2j**	N.R	-

The mechanism of reaction is shown in Scheme 3. The alternative structure for the products described herein, namely the 3-amino-6-arylpyridazine-4-carbonitriles (**6**), was considered unlikely because this procedure involves adding the hydrazine to the arylglyoxal first, and then the malononitrile after 30 min, assuring the prior formation of the monohydrazone (**5**). To confirm this, the preparation of (**4c**) was carried out in two stages, with the isolation of the hydrazone (**5c**), which was then reacted with malononitrile, leading to the formation of the product (**4c**). The spectral data of **4c** prepared by the two-stage method was identical with that produced in the one-pot sequence.

Further evidence for the proposed mechanism comes from the fact that the reaction of arylglyoxals **2h–j** with hydrazine formed monohydrazone derivatives in 30 min at room temperature, but failed to cyclize to the corresponding pyridazines even under reflux conditions for 4 h. This may be due to the presence of electron-donating hydroxy and methoxy groups at the *p*-position of arylglyoxals **2h–j**, which deactivate the keto-carbonyl group of arylglyoxals by resonance effect.

Attempts to synthesize compound **6** by reaction of arylglyoxals with malononitrile followed by addition of hydrazine hydrate under different solvent systems and temperatures failed due to decomposition in the first step (Scheme 4).

2. Experimental

General Procedures

Melting points were determined on a Philip Harris apparatus (Model C4954718). Infrared spectra were recorded on a Thermonicolet (Nexus 670) Fourier-transform (FT)-infrared spectrometer, using KBr discs. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR measurements were recorded on a Bruker 300 spectrometer in [D_6]DMSO using TMS as the internal reference. Microanalyses were performed on a Leco Analyzer 932.

General Procedure for Synthesis of 3-Amino-5-arylpyridazine-4-carbonitriles

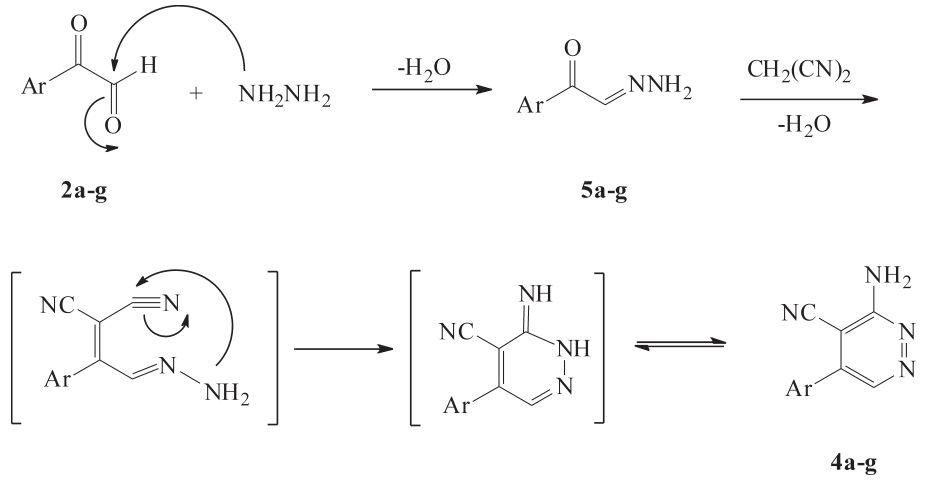
A mixture of arylglyoxal (1 mmol) and hydrazine hydrate 80 % (4 mmol) in water and ethanol (1:1) (3 mL) was stirred at room temperature for 30 min. Then malononitrile (1 mmol) was added to the reaction mixture and was stirred for a further 30 min at room temperature. The product was then collected as a white precipitate, washed with hot water (2 × 5 ml) and purified by recrystallization from ethanol.

3-Amino-5-phenylpyridazine-4-carbonitrile (4a)

White solid, 78 %, mp 247 °C (dec.). ^{1}H-NMR (300 MHz) δ (ppm) 8.75 (s, 1H, Ar), 7.65–7.57 (m, 5H, Ar), 7.39 (bs, 2H, exchanged by D_2O addition, NH_2). ^{13}C-NMR δ (ppm) 159.37, 142.17, 141.96, 133.47, 130.98, 129.53, 129.09, 114.96, 93.62. FT-IR ν_{max} 3437, 3300, 3105, 2219, 1641, 1562, 1498, 1474, 1441, 1162, 764 cm^{-1}. Mass spectrum *m/z* (%): 196 ([M$^+$], 70), 168 (24), 140 (68), 127 (17), 114 (44), 102 (100), 87 (25), 76 (88), 74 (48), 66 (61), 63 (74), 51 (96), 50 (80). Anal. Calc. for $C_{11}H_8N_4$: C, 67.34; H, 4.11; N, 28.55. Found: C, 67.45; H, 4.01; N, 28.12.

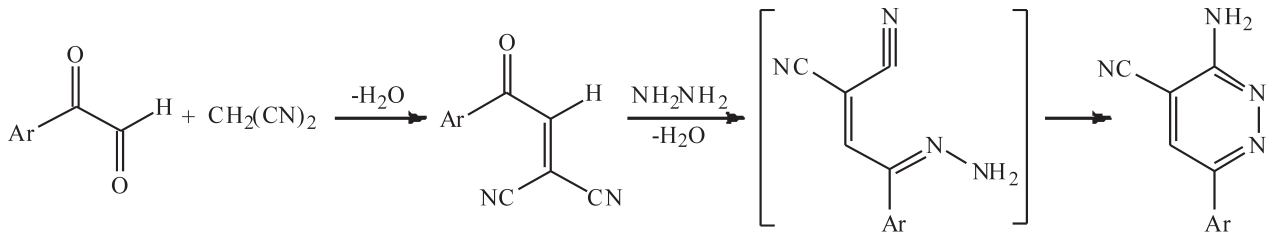
3-Amino-5-(4-bromophenyl)pyridazine-4-carbonitrile (4b)

White solid, 86 %, mp 290 °C (dec.). ^{1}H-NMR (300 MHz) δ (ppm) 8.72 (s, 1H, Ar), 7.77 (d, *J* 8.4 Hz, 2H, Ar), 7.64 (d, *J* 8.4 Hz, 2H, Ar), 7.37 (bs, 2H, exchanged by D_2O addition, NH_2). ^{13}C-NMR δ (ppm) 159.29, 141.64, 141.19, 132.65, 132.54, 131.21, 124.80, 114.78, 93.64. FT-IR ν_{max} 3442, 3296, 3089, 2214, 1645, 1589, 1559, 1494, 1475, 1403, 1389, 1098, 1073, 1008, 925, 818 cm^{-1}. Mass spectrum *m/z* (%): 276 ([M$^+$+2], 28), 274 ([M$^+$], 29), 196 (35), 180 (28),



2a-g **5a-g** **4a-g**

Scheme 3
Mechanism for the synthesis of 3-amino-5-arylpyridazine-4-carbonitriles.



2a-g **6**

Scheme 4
Attempted synthesis of 3-amino-6-arylpyridazine-4-carbonitriles.

140 (100), 113 (37), 102 (88), 87 (27), 75 (95), 66 (57), 50 (80). Anal. Calc. for $C_{11}H_7BrN_4$: C, 48.02; H, 2.56; N, 20.37. Found: C, 48.12; H, 2.48; N, 20.29.

3-Amino-5-(4-chlorophenyl)pyridazine-4-carbonitrile (4c)

White solid, 87 %, mp 290 °C (dec.). ^{1}H-NMR (300 MHz) δ (ppm) 8.75 (s, 1H, Ar), 7.73 (d, *J* 8.4 Hz, 2H, Ar), 7.66 (d, *J* 8.4 Hz, 2H, Ar), 7.43 (bs, 2H, exchanged by D_2O, NH_2). ^{13}C-NMR δ (ppm) 159.30, 141.71, 141.07, 139.99, 132.33, 131.04, 129.60, 114.80, 96.60. FT-IR ν_{max} 3450, 3300, 3091, 2220, 1646, 1594, 1560, 1496, 1475, 1096, 829 cm^{-1}. Mass spectrum *m/z* (%): 232 ([M$^+$+2], 34), 230 ([M$^+$], 100), 202 (20), 174 (12), 140 (20), 136 (34), 101 (40), 75 (43), 66 (23), 51 (23). Anal. Calc. for $C_{11}H_7ClN_4$: C, 57.28; H, 3.06; N, 24.29. Found: C, 57.31; H, 3.01; N, 24.33.

3-Amino-5-(4-fluorophenyl)pyridazine-4-carbonitrile (4d)

White solid, 83 %, mp 260 °C (dec.). ^{1}H-NMR (300 MHz) δ (ppm) 8.71 (s, 1H, Ar), 7.78–7.70 (m, 2H, Ar), 7.38 (t, *J* 8.4 Hz, 2H, Ar), 7.40 (bs, 2H, exchanged by D_2O addition, NH_2). ^{13}C-NMR δ (ppm) 165.50, 159.31, 141.90, 141.22, 131.74, 131.62, 116.78, 116.48, 114.91. FT-IR ν_{max} 3467, 3291, 3091, 2220, 1643, 1604, 1564, 1511, 1478, 1235, 1162, 1099, 833 cm^{-1}. Mass spectrum *m/z* (%): 214 ([M$^+$], 50), 158 (26), 120 (100), 107 (40), 101 (60), 75 (40), 66 (48), 57 (10). Anal. Calc. for $C_{11}H_7FN_4$: C, 61.68; H, 3.29; N, 26.16. Found: C, 61.59; H, 3.14; N, 26.02.

3-Amino-5-(4-nitrophenyl)pyridazine-4-carbonitrile (4e)

Yellow solid, 88 %, mp 279 °C (dec.). ^{1}H-NMR (300 MHz) δ (ppm) 8.79 (s, 1H, Ar), 8.41 (d, *J* 8.7 Hz, 2H, Ar), 7.98 (d, *J* 8.7 Hz, 2H, Ar), 7.54 (s, 2H, exchanged by D_2O addition, NH_2). ^{13}C-NMR δ (ppm) 159.24, 148.99, 141.33, 140.33, 139.88, 130.81, 124.45, 114.52, 93.86. FT-IR ν_{max} 3446, 3425, 3311, 3112, 2218, 1656, 1603, 1568, 1526, 1501, 1480, 1359, 1320, 1105, 855 cm^{-1}. Mass spectrum *m/z* (%): 241 ([M$^+$], 4), 140 (17), 115 (15), 104 (15), 99 (24), 89 (80), 83 (22), 75 (46), 68 (26), 63 (100), 51 (60). Anal. Calc. for $C_{11}H_7N_5O_2$: C, 54.77; H, 2.93; N, 29.03;. Found: C, 54.69; H, 2.98; N, 29.10.

3-Amino-5-(3-bromophenyl)pyridazine-4-carbonitrile (4f)

White solid, 76 %, mp 208 °C (dec.). ^{1}H-NMR (300 MHz) δ (ppm) 8.76 (s 1H, Ar), 7.92 (s, 1H, Ar), 7.78 (d, *J* 7.8 Hz, 1H, Ar), 7.7 (d, *J* 7.8 Hz, 1H, Ar), 7.53 (t, *J* 7.8 Hz, 1H, Ar), 7.43 (bs, 2H, exchanged by D_2O addition, NH_2). ^{13}C-NMR δ (ppm) 159.26, 141.68, 140.68, 135.805, 133.65, 131.64, 131.58, 128.31, 122.58, 114.71, 93.85. FT-IR ν_{max} 3464, 3309, 3164, 2219, 1637, 1559, 1492, 1407, 1321, 1154, 1113, 1093, 939, 881, 774, 709, 693 cm^{-1}. Mass spectrum *m/z* (%): 276 ([M$^+$+2], 87), 274 ([M$^+$], 72), 180 (30), 167 (22), 140 (100), 113 (24), 101 (54), 75 (35), 66 (21), 55 (18). Anal. Calc. for $C_{11}H_7BrN_4$: C, 48.02; H, 2.56; N, 20.37. Found: C, 48.16; H, 2.52; N, 20.21.

3-Amino-5-(3-methoxyphenyl)pyridazine-4-carbonitrile (4g)

White solid, 72 %, mp 190 °C. ^{1}H-NMR (300 MHz) δ (ppm) 8.7 (s, 1H, Ar), 7.49 (t, *J* 7.8 Hz, 1H, Ar), 7.37 (bs, 2H, exchanged by D_2O addition, NH_2), 7.27–7.23 (m, 2H, Ar), 7.14 (bd, J 8.1 Hz, 1H, Ar), 3.82 (s, 3H, OCH_3). ^{13}C-NMR δ (ppm) 159.92, 159.35, 149.43, 141.96, 134.73, 130.78, 121.22, 116.72, 114.92, 114.42, 93.74, 55.82. FT-IR ν_{max} 3463, 3265, 3109, 2215, 1623, 1558, 1463, 1325, 1249, 1104, 1037, 856, 780, 695 cm^{-1}. Mass spectrum *m/z* (%): 226 ([M$^+$], 100), 183 (18), 155 (91), 140 (25), 132 (35), 128 (49), 102 (65), 91 (55), 77 (31), 63 (43), 57 (38). Anal. Calc. for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.76. Found: C, 63.67; H, 4.49; N, 24.83.

3. Conclusions

The procedure outlined provides a straightforward route to various 3-amino-5-arylpyridazine-4-carbonitriles with possible pharmaceutical applications.

Acknowledgements

We thank the University of Urmia for the financial support.

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