Turkish Journal of Chemistry

Volume 37 | Number 2 Article 9

1-1-2013

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MEHDI RIMAZ

HOSSEIN MOUSAVI

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Turkish Journal of Chemistry

http://journals.tubitak.gov.tr/chem/

Research Article

Turk J Chem
(2013) 37: 252 – 261

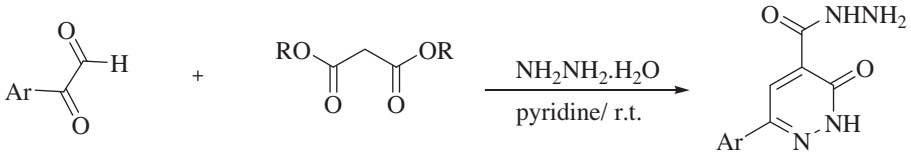
doi:10.3906/kim-1210-5

A one-pot strategy for regioselective synthesis of 6-aryl-3-oxo-2,3-dihydropyridazine-4-carbohydrazides

Mehdi RIMAZ,* Hossein MOUSAVI
Department of Chemistry, Payame Noor University, Tehran, Iran

Received: 04.10.2012 • **Accepted:** 29.01.2013 • **Published Online:** 17.04.2013 • **Printed:** 13.05.2013

Abstract: A simple and efficient method for the synthesis of 6-aryl-3-oxo-2,3-dihydropyridazine-4-carbohydrazide derivatives was developed. The synthesis was achieved via one-pot multicomponent reaction of arylglyoxals, dialkylmalonates, and hydrazine hydrate in pyridine at room temperature. This procedure features high regioselectivity, generally good to excellent yields, the use of easily available starting materials, and operational simplicity. This chemistry provides an efficient and promising synthetic strategy for diversity-oriented construction of the 6-arylpyridazinone skeleton.



11 examples

Ar = C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-$CH_3OC_6H_4$, 4-$NO_2C_6H_4$, 3,4$(CH_3O)_2C_6H_3$, 3,4$(OCH_2O)C_6H_3$, 4-OH-3-$CH_3OC_6H_3$, 3-BrC_6H_4, 3-$CH_3OC_6H_4$
R = CH_3, CH_2CH_3

Key words: Pyridazinone, arylglyoxal, dialkylmalonate, hydrazine, regioselective

1. Introduction

The growth of organic synthesis has been facilitated by the development of one-pot methods, since they generate less waste, minimize isolation of intermediates in multistep syntheses of complex molecular targets, and save time and minimize cost.[1] One-pot reactions can be classified roughly as tandem,[2a] domino,[2b] or cascade[2c] reactions. Of one-pot synthetic strategies, multicomponent reactions (MCRs), leading to interesting heterocyclic scaffolds, are particularly useful for combinatorial chemistry as powerful tools[3] because of their valuable features such as atom-economy, environmental friendliness, straightforward reaction design, and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical operation.[4] In addition, these reactions often give excellent chemo- and regioselectivities.[5,6] Therefore, a great deal of current interest is focused on the development of novel MCRs.[7]

The pyridazinone motif is an important pharmacophore and is known to exhibit promising biological properties such as antidepressant,[8] antithrombotic,[9] anticonvulsant,[10] cardiotonic,[11] antibacterial,[12] diuretics,[13]

*Correspondence: mrimaz@pnu.ac.ir

anti-HIV,[14] and anticancer.[15] Some pyridazinone derivatives like indolidan,[16] bemoradan,[17] primobendan,[18] levosimendan[19], minaprine[20], emorfazone[21], and azanrinone[22] have already appeared in the clinical market.

Pyridazinones are also agrochemically important heterocycles and they have been used as herbicides, such as norflurazon, and as insecticides, like pyridaben, for crop protection.[23] Furthermore, in drug discovery, pyridazinones were identified as selective COX-2 inhibitors (ABT-963[24] and CK−126[25]) and α_4 integrin receptor antagonists.[26] They are also cyclooxygenase-2 inhibitors, thereby acting as anti-inflammatory drugs,[27,28] and show strong affinity for α_1-adrenergic receptors.[29,30]

Substituted 5-hydroxypyridazin-3(2*H*)-ones have been characterized as potent inhibitors of the HCV RNA-dependent RNA polymerase (NS5B).[31−33] Most of the 6-aryl-3(2*H*)- pyridazinones are active in the cardiovascular system. For example, zardaverine and imazodan have been developed as phosphodiesterase type III inhibitors (PDE III) in the search for new antiplatelet or cardiotonic agents.[34] It is also observed that various pyridazinone derivatives possess antihypertensive activity due to vasorelaxant activity and the 6-aryl-3(2*H*)-pyridazinone residue is a pharmacophoric group for this activity.[35−37]

Because the pyridazinone scaffold exhibits such extensive bioactivity, the development of efficient synthetic protocols to construct a pyridazinone derivatives library for high-throughput biological screening has been very attractive to chemists. One of the major synthetic routes to pyridazinone formation is Paal–Knorr synthesis in which 1,4-keto-esters or 1,4-keto-acids condensed with hydrazine.[38−44] In the course of our ongoing project aimed at the synthesis of new pyridazine derivatives,[45] we report herein a novel strategy for direct regioselective synthesis of new 6-aryl-3-oxo-2,3-dihydropyridazine-4-carbohydrazide derivatives based on a 1-pot 3-component reaction of arylglyoxal, dialkylmalonate, and hydrazine in pyridine at room temperature.

2. Experimental

2.1. General procedure

All solvents used were freshly distilled and dried according to the methods described by Perrin and Armarego.[46] Melting points were determined on an Electrothermal 9200 apparatus and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker DRX-300 AVANCE spectrometer in [D_6]DMSO with tetramethylsilane as internal standard. Infrared spectra were recorded on a Thermonicolet (Nexus 670) FT-infrared spectrophotometer, measured as films or KBr disks. Microanalyses were performed on a Leco Analyzer 932.

2.2. General procedure for the synthesis of 6-aryl-3-oxo-2,3-dihydropyridazine-4-carbohydrazides

A mixture of dialkylmalonate (1 mmol) and arylglyoxal (1 mmol) in pyridine (1 mL) was stirred for 30 min at room temperature. Then hydrazine hydrate (3 mmol) was added and the stirring was continued for 30 min. Water (5 mL) was added to the reaction mixture and the resulting suspension was filtered. Recrystallization of the solid from methanol gave the title products in good to excellent yields.

3-Oxo-6-phenyl-2,3-dihydropyridazine-4-carbohydrazide (15): cream solid, mp 252 °C (dec). ^{1}H NMR (d_6-DMSO) δ (ppm) 13.89 (bs, 1H, NH), 10.46 (s, 1H, NH), 8.46 (s, 1H, Ar), 7.86 (d, J = 7.8 Hz, 2H, Ar), 7.52–7.40 (m, 3H, Ar), 4.89 (s, 2H, NH_2). ^{13}C NMR (d_6-DMSO) δ (ppm) 167.7, 160.5, 159.9, 145.5, 134.5, 131.0, 130.0, 129.5, 126.2. FT-IR (KBr) ν_{max} 3316, 3245, 3051, 2947, 2864, 1686, 1629, 1575, 1518, 1226, 913, 772, 605 cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_4O_2$, C 57.39, H 4.38, N 24.34; found, C 57.48, H 4.41, N 24.22.

6-(4-Chlorophenyl)-3-oxo-2,3-dihydropyridazine-4-carbohydrazide (16): pale yellow solid, mp 292 °C (dec). ^{1}H-NMR (d_6-DMSO) δ (ppm) 13.98 (bs, 1H, NH), 10.44 (s, 1H, NH), 8.47 (s, 1H, Ar), 7.91 (d, J = 8.1 Hz, 2H, Ar), 7.54 (d, J = 8.1 Hz, 2H, Ar), 4.89 (s, 2H, NH_2). ^{13}C NMR (d_6-DMSO) δ (ppm) 160.5, 159.8, 150.0, 144.5, 134.8, 133.4, 131.0, 129.8, 128.1. FT-IR (KBr) ν_{max} 3324, 3142, 3100, 3036, 2958, 2879, 1677, 1585, 1535, 1496, 1442, 1403, 1227, 1146, 1089, 1011, 965, 837, 760, 593 cm^{-1}. Anal. Calcd for $C_{11}H_9ClN_4O_2$, C 49.92, H 3.43, N 21.17; found, C 49.88, H 3.47, N 21.13.

6-(4-Bromophenyl)-3-oxo-2,3-dihydropyridazine-4-carbohydrazide (17): cream solid, mp 281 °C (dec). ^{1}H NMR (d_6-DMSO) δ (ppm) 13.95 (bs, 1H, NH), 10.44 (s, 1H, NH), 8.47 (s, 1H, Ar), 7.85 (d, J = 8.4 Hz, 2H, Ar), 7.68 (d, J = 8.4 Hz, 2H, Ar), 4.89 (s, 2H, NH_2). ^{13}C NMR (d_6-DMSO) δ (ppm) 160.5, 159.8, 144.6, 133.7, 132.4, 130.9, 129.5, 128.3, 123.5. FT-IR (KBr) ν_{max} 3322, 3141, 3096, 3039, 2955, 2876, 1666, 1582, 1542, 1495, 1399, 1227, 1074, 1007, 913, 835, 591 cm^{-1}. Anal. Calcd for $C_{11}H_9BrN_4O_2$, C 42.74, H 2.93, N 18.12; found, C 42.80, H 3.00, N 18.02.

6-(4-Fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carbohydrazide (18): yellow solid, mp 280 °C (dec). ^{1}H NMR (d_6-DMSO) δ (ppm) 13.97 (bs, 1H, NH), 10.46 (s, 1H, NH), 8.46 (s, 1H, Ar), 7.96–7.91 (m, 2H, Ar), 7.34–7.28 (m, 2H, Ar), 4.89 (s, 2H, NH_2). ^{13}C NMR (d_6-DMSO) δ (ppm) 165.0, 161.7, 160.4, 159.8, 144.8, 131.1, 129.5, 128.7, 128.6, 116.5, 116.2. FT-IR (KBr) ν_{max} 3482, 3317, 3246, 2945, 2883, 1680, 1641, 1582, 1511, 1234, 1161, 1026, 550 cm^{-1}. Anal. Calcd for $C_{11}H_9FN_4O_2$, C 53.23, H 3.65, N 22.57; found, C 53.28, H 3.71, N 22.61.

6-(4-Methoxyphenyl)-3-oxo-2,3-dihydropyridazine-4-carbohydrazide (19): yellow solid, mp 253 °C (dec). ^{1}H NMR (d_6-DMSO) δ (ppm) 13.80 (bs, 1H, NH), 10.46 (s, 1H, NH), 8.40 (s, 1H, Ar), 7.79 (d, J = 8.1 Hz, 2H, Ar), 7.00 (d, J = 7.50 Hz, 2H, Ar), 4.85 (s, 2H, NH_2), 3.76 (s, 3H, OCH_3). ^{13}C NMR (d_6-DMSO) δ (ppm) 160.8, 160.4, 160.0, 145.4, 130.8, 129.4, 127.7, 126.9, 114.8, 55.7. FT-IR (KBr) ν_{max} 3473, 3321, 3018, 2942, 2883, 1690, 1590, 1514, 1254, 1177, 916, 832, 566 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_4O_3$, C 55.38, H 4.65, N 21.53; found, C 55.35, H 4.69, N 21.44.

6-(4-Nitrophenyl)-3-oxo-2,3-dihydropyridazine-4-carbohydrazide (20): yellow solid, mp 299 °C (dec). ^{1}H NMR (d_6-DMSO) δ (ppm) 13.61 (bs, 1H, NH), 10.51 (s, 1H, NH), 8.41 (s, 1H, Ar), 7.56 (d, J = 7.2 Hz, 2H, Ar), 6.61 (d, J = 8.1 Hz, 2H, Ar), 4.86 (s, 2H, NH_2). ^{13}C NMR (d_6-DMSO) δ (ppm) 160.2, 160.1, 150.8, 146.2, 130.5, 129.1, 127.2, 121.4, 114.2. FT-IR (KBr) ν_{max} 3377, 3292, 3206, 3049, 2958, 1683, 1589, 1517, 1428, 1387, 1297, 1180, 831, 594 cm^{-1}. Anal. Calcd for $C_{11}H_9N_5O_4$, C 48.00, H 3.30, N 25.45; found, C 48.06, H 3.35, N 25.49.

6-(3,4-Dimethoxyphenyl)-3-oxo-2,3-dihydropyridazine-4-carbohydrazide (21): yellow solid, mp 258 °C (dec). ^{1}H NMR (d_6-DMSO) δ (ppm) 13.81 (bs, 1H, NH), 10.49 (s, 1H, NH), 8.43 (s, 1H, Ar), 7.42–7.30 (m, 2H, Ar), 7.01 (d, J = 8.4 Hz, 1H, Ar), 4.87 (s, 2H, NH_2), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3). ^{13}C NMR (d_6-DMSO) δ (ppm) 160.3, 160.0, 150.8, 149.4, 145.4, 130.9, 129.2, 127.0, 119.2, 112.0, 108.9, 55.9, 55.8. FT-IR (KBr) ν_{max} 3429, 3319, 3251, 2996, 2938, 1681, 1639, 1585, 1518, 1465, 1381, 1266, 1137, 1021, 596 cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_4O_4$, C 53.79, H 4.86, N 19.30; found, C 53.82, H 4.93, N 19.22.

6-(3,4-Methylenedioxyphenyl)-3-oxo-2,3-dihydropyridazine-4-carbohydrazide (22): yellow solid, mp 285 °C (dec). ^{1}H NMR (d_6-DMSO) δ (ppm) 13.78 (bs, 1H, NH), 10.47 (s, 1H, NH), 8.39 (s, 1H, Ar), 7.38–7.32 (m, 2H, Ar), 6.98 (d, J = 8.7 Hz, 1H, Ar), 6.07 (s, 2H, CH_2), 4.87 (s, 2H, NH_2). ^{13}C NMR

(d_6-DMSO) δ (ppm) 160.4, 159.9, 149.0, 148.5, 145.3, 131.0, 129.3, 128.7, 120.8, 109.0, 106.2, 102.0. FT-IR (KBr) ν_{max} 3317, 3150, 3058, 2960, 2893, 1684, 1664, 1574, 1507, 1442, 1254, 1231, 1033, 929, 886, 805, 597 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_4O_4$, C 52.56, H 3.68, N 20.43; found, C 52.61, H 3.70, N 20.31.

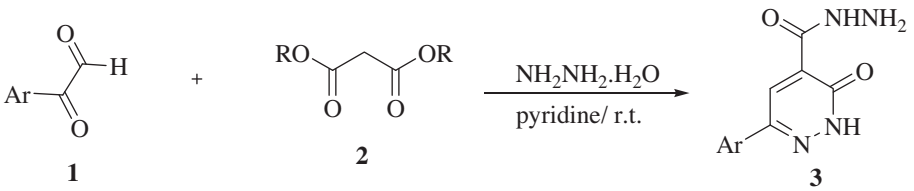
6-(4-Hydroxy-3-methoxyphenyl)-3-oxo-2,3-dihydropyridazine-4-carbohydrazide (23): yellow solid, mp 280 °C (dec). ^{1}H NMR (d_6-DMSO) δ (ppm) 11.37 (bs, 1H, NH), 10.50 (s, 1H, NH), 8.42 (s, 1H, Ar), 7.38 (s, 1H, Ar), 7.30 (d, J = 7.50 Hz, 1H, Ar), 6.87 (d, J = 7.20 Hz, 1H, Ar), 4.87 (s, 2H, NH_2), 3.82 (s, 3H, OCH_3), 3.36 (bs, 1H, OH). ^{13}C NMR (d_6-DMSO) δ (ppm) 160.4, 160.1, 148.7, 148.5, 145.7, 130.9, 129.2, 125.7, 119.6, 116.1, 109.6, 56.0. FT-IR (KBr) ν_{max} 3474, 3237, 2966, 1678, 1592, 1519, 1453, 1422, 1269, 1223, 1114, 1023, 795, 587 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_4O_4$, C 52.17, H 4.38, N 20.28; found, C 52.15, H 4.40, N 20.35.

6-(3-Bromophenyl)-3-oxo-2,3-dihydropyridazine-4-carbohydrazide (24): brown solid, mp 272 °C (dec). ^{1}H NMR (d_6-DMSO) δ (ppm) 13.21 (bs, 1H, NH), 9.63 (s, 1H, NH), 8.21 (s, 1H, Ar), 7.69–7.23 (m, 4H, Ar), 3.75 (s, 2H, NH_2). ^{13}C NMR (d_6-DMSO) δ (ppm) 163.3, 154.7, 140.7, 131.3, 130.9, 129.4, 128.1, 127.3, 121.5, 119.0, 115.3. FT-IR (KBr) ν_{max} 3436, 2924, 1654, 1506, 1422, 1253, 1224, 1102, 1033, 786 cm^{-1}. Anal. Calcd for $C_{11}H_9BrN_4O_2$, C 42.74, H 2.93, N 18.12; found, C 42.77, H 2.98, N 18.08.

6-(3-Methoxyphenyl)-3-oxo-2,3-dihydropyridazine-4-carbohydrazide (25): yellow solid, mp 281 °C (dec). ^{1}H NMR (d_6-DMSO) δ (ppm) 13.91 (bs, 1H, NH), 10.45 (s, 1H, NH), 8.45 (s, 1H, Ar), 7.44–7.36 (m, 3H, Ar), 7.01 (dd, J_1 = 7.20 Hz, J_2 = 1.80 Hz, 1H, Ar), 4.89 (s, 2H, NH_2), 3.80 (s, 3H, OCH_3). ^{13}C NMR (d_6-DMSO) δ (ppm) 160.5, 160.1, 159.9, 145.3, 135.9, 131.2, 130.7, 129.4, 118.7, 115.9, 111.1, 55.6. FT-IR (KBr) ν_{max} 3354, 3252, 3151, 3061, 2838, 1689, 1655, 1580, 1517, 1490, 1431, 1375, 1271, 1218, 1037, 924, 712, 603 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_4O_3$, C 55.38, H 4.65, N 21.53; found, C 55.33, H 4.70, N 21.49.

3. Results and discussion

During our research on the synthesis of new pyridazine derivatives,[45] we found that some 1,3-dicarbonyl compounds did not react with the carbonyl groups of the arylglyoxals and were recovered. We speculated that this phenomenon was due to the low activity of 1,3-dicarbonyl compounds, resulting in their failure to form the corresponding enolate anion under neutral conditions such as water or ethanol. Dialkylmalonates **2** are weakly acidic 1,3-dicarbonyl compounds and hence do not react with the arylglyoxals **1** in water or ethanol under neutral conditions. Moreover, attempts to react the dialkylemalonates with the arylglyoxals in the presence of catalytic amounts of pyridine in water or ethanol in both room temperature and heating conditions failed. However, when pyridine was used as the solvent, the reaction proceeded smoothly to afford the substituted pyridazinone derivatives **3** (Scheme 1).



Ar = C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-$CH_3OC_6H_4$, 4-$NO_2C_6H_4$, 3,4$(CH_3O)_2C_6H_3$, 3,4$(OCH_2O)C_6H_3$, 4-OH-3-$CH_3OC_6H_3$, 3-BrC_6H_4, 3-$CH_3OC_6H_4$
R = CH_3, CH_2CH_3

Scheme 1. Synthesis of 6-aryl-3-oxo-2,3-dihydropyridazine-4-carbohydrazides.

Table. List of new pyridazinones synthesized.

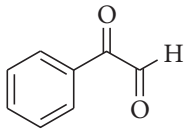
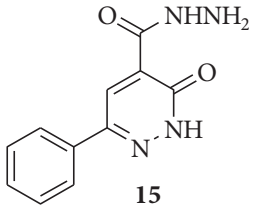
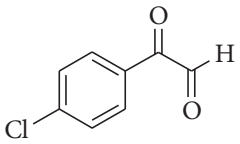
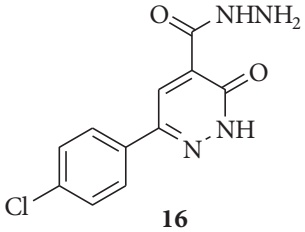
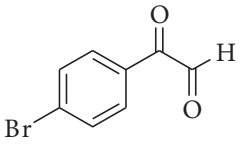
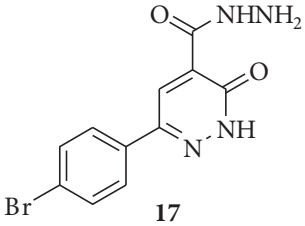
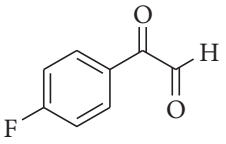
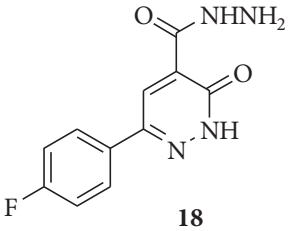
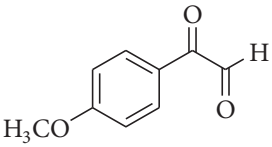
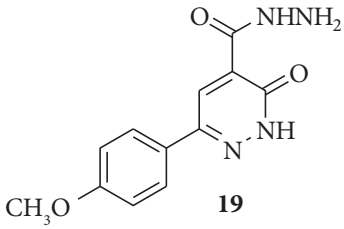
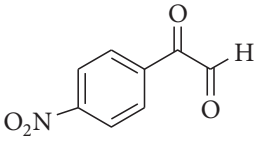
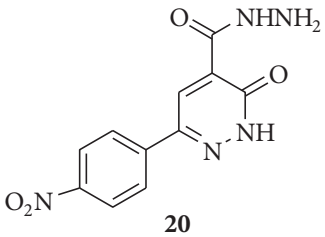
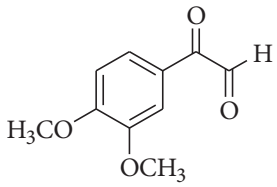
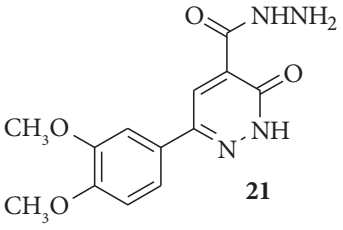
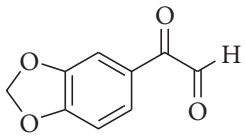
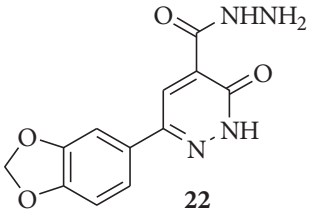
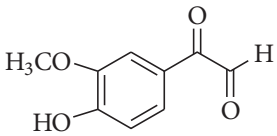
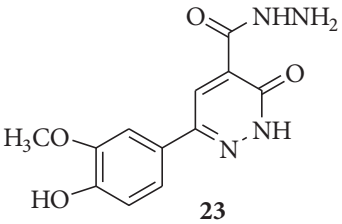
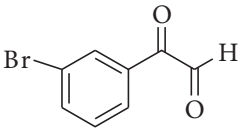
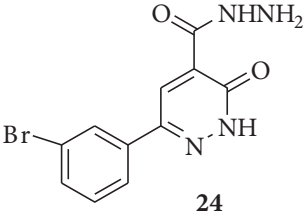
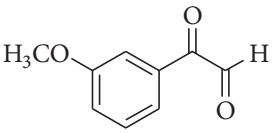
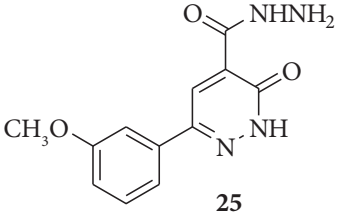
Entry	Arylglyoxal	Pyridazinone	Average yield (%)
1	 **4**	 **15**	96
2	 **5**	 **16**	82
3	 **6**	 **17**	78
4	 **7**	 **18**	90
5	 **8**	 **19**	81
6	 **9**	 **20**	**89**

Table. Continued.

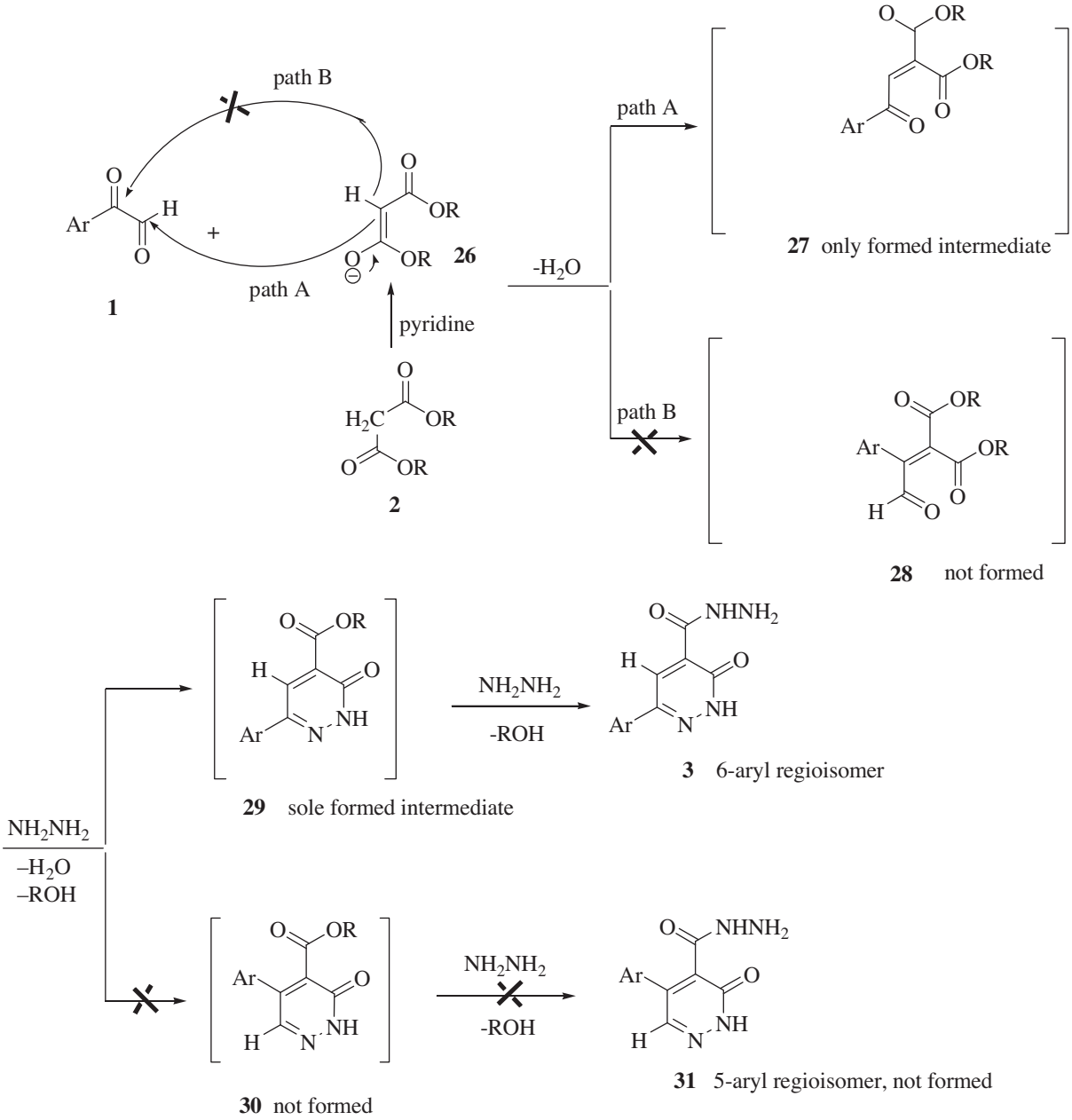
Entry	Arylglyoxal	Pyridazinone	Average yield (%)
7	 **10**	 **21**	93
8	 **11**	 **22**	92
9	 **12**	 **23**	78
10	 **13**	 **24**	73
11	 **14**	 **25**	93

Eleven 6-aryl-3-oxo-2,3-dihydropyridazine-4-carbohydrazide derivatives **3** were prepared from the reaction of the arylglyoxals **1** with dialkylmalonates **2** in the presence of excess hydrazine hydrate in pyridine at room temperature; yields with dimethyl or diethyl malonate were comparable. The pyridazinones obtained in this way are listed in the Table.

The products were a single isomer; only the 6-aryl regioisomers were obtained, presumably because of the high reactivity of the glyoxal's aldehyde carbonyl group toward the nucleophilic addition of the enolate anion.

As shown in Scheme 2, the proposed mechanism for the regioselective formation of the pyridazinones involves the initially regioselective Knoevenagel condensation reaction between the dialkyl malonate's enolate

anion **26** and the aldehyde carbonyl of arylglyoxals **1** (path A), leading to 1,4-dicarbonyl compound **27**. Reaction of hydrazine with compound **27** produces the pyridazinone **29** but the use of excess hydrazine hydrate allows the subsequent nucleophilic attack of hydrazine on the alkoxycarbonyl group of the intermediate **29** to afford the final product **3**. Attempts to produce the pyidazinones **29** by using stoichiometric amounts of hydrazine hydrate failed. Hence, this synthetic method is only applicable for the direct preparation of pyridazinone-4-carbohydrazide derivatives.



Scheme 2. Suggested mechanism for the regioselective formation of 6-aryl-3-oxo-2,3-dihydropyridazine-4-carbohydrazides.

In the ^{1}H NMR spectra, the deshielded CH group on the pyridazinone ring, which in all of these derivatives resonates as a sharp singlet at $\delta > 8.2$ ppm, can be reliable evidence for the formation of the pyridazinone framework.

4. Conclusions

We have reported a unique, potent, and entirely regioselective strategy for direct synthesis of 6-aryl-3-oxo-2,3-dihydropyridazine-4-carbohydrazides based on a 1-pot technique. In addition, the mild reaction conditions, easy workup, short reaction time, and the purity of the products are the advantages of this new method.

Acknowledgment

Financial support from the Research Council of Payame Noor University is gratefully acknowledged.

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