A novel one-pot, three-component synthesis of alkyl 6-aryl-3-methylpyridazine-4-carboxylates in water

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Abstract

A series of new alkyl 6-aryl-3-methylpyridazine-4-carboxylates were efficiently synthesized by a three-component reaction of *β*-ketoesters with arylglyoxals in the presence of hydrazine hydrate in water at room temperature.

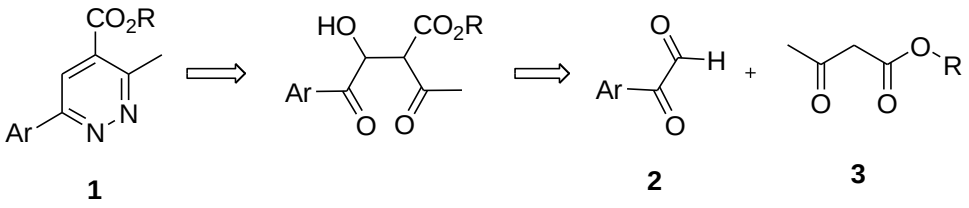
Keywords: Pyridazine, arylglyoxal, hydrazine, *β*-ketoester

Introduction

Polyfunctionalized heterocyclic compounds play important roles in the drug discovery process, and analysis of drugs in late development or on the market shows that 68% of them are heterocycles.[1] Therefore, it is not surprising that research on the synthesis of polyfunctionalized heterocyclic compounds has received special attention. Of these heterocycles, pyridazine derivatives which are a rarity in nature have been reported[2] to possess a wide range of biological activities, these include antiviral and anticancer,[3] antituberculosis,[4] antihypertensive,[5] anti-inflammatory,[6] and antimicrobial,[7] activities. Pyridazine derivatives have also been the subject of extensive research in the agrochemical areas.[8-11] Moreover, pyridazines are useful intermediates in the construction of several other heterocycles[12] and in physical organic chemistry[13] and recently have been explored as new R-helix mimetics.[14]

One of the most common approaches to pyridazine construction is its Paal-Knorr synthesis in which 1,4-dicarbonyl compounds are converted to pyridazine *via* acid-mediated dehydrative cyclization in the presence of hydrazine and subsequent oxidation.[15-17] In this reaction, the 1,4-dicarbonyl compounds provide the four carbons of the pyridazine with the possible substituents, whereas the hydrazine provides the nitrogen atoms. The main limitations to intensive use of this reaction are the strong reaction conditions required for cyclization and aromatization (use of boiling acetic acid for extended times) and the low availability of nonsymmetrically substituted 1, 4-dicarbonyl compounds. The classical approach to this class of products is the condensation

of enolates with phenacyl bromides,[18] thus limiting the preparation to pyridazines with aryl substituents. Alternative approaches need several steps of reactions with chromatographic separations to obtain the intermediates for cyclization. We have recently reported the novel synthesis of new 3-arylpyrimido[4, 5-c]pyridazine-5, 7(6*H*, 8*H*)-diones and their sulfur analogues as potential monoamine oxidase inhibitors.[19]Herein, we report one-pot synthesis of new alkyl 6-aryl-3-methylpyridazine-4-carboxylate **1** *via* reaction of *β*-ketoesters **3** with arylglyoxals **2** in the presence of excess hydrazine hydrate (Scheme 1). To the best of our knowledge, there are no reports in the literature for the formation of pyridazine derivatives *via* condensation of *β*-ketoesters with arylglyoxals in water.



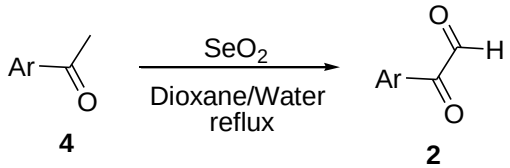
1 **2** **3**

Scheme 1. Retro synthesis of alkyl 6-aryl-3-methylpyridazine-4-carboxylate.

Currently, multicomponent reactions are being rapidly developed[20] because using a "one-pot" methodology makes the synthesis simpler and more environmentally friendly. Additionally, the prospect of extending one-pot reactions into combinatorial and solid-phase syntheses[21,22] promises manifold opportunities for developing novel lead structures of pharmaceuticals, catalysts and even novel molecule-based materials.

Results and Discussion

The arylglyoxals **2** were prepared from commercially available acetophenones **4** as shown in Scheme 2.[23]

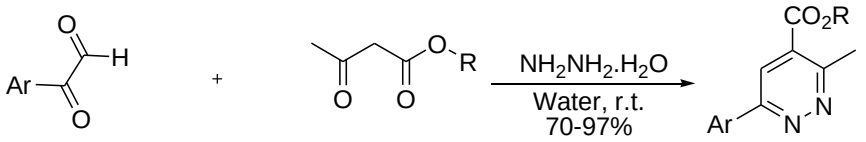


4 **2**

Scheme 2. Synthesis of arylglyoxals.

The reactions were performed by adding arylglyoxals **2** to the mixture of *β*-ketoesters **3** in water at room-temperature in the presence of excess amounts of hydrazine hydrate (Scheme 3). After 30-60 min, the mixture was solidified and isolated by filtering. The products were obtained

in good yields after recrystallization from ethanol (70-97%). Of these products only the synthesis of compound **14** has been reported by Attanasi and coworkers.[24]



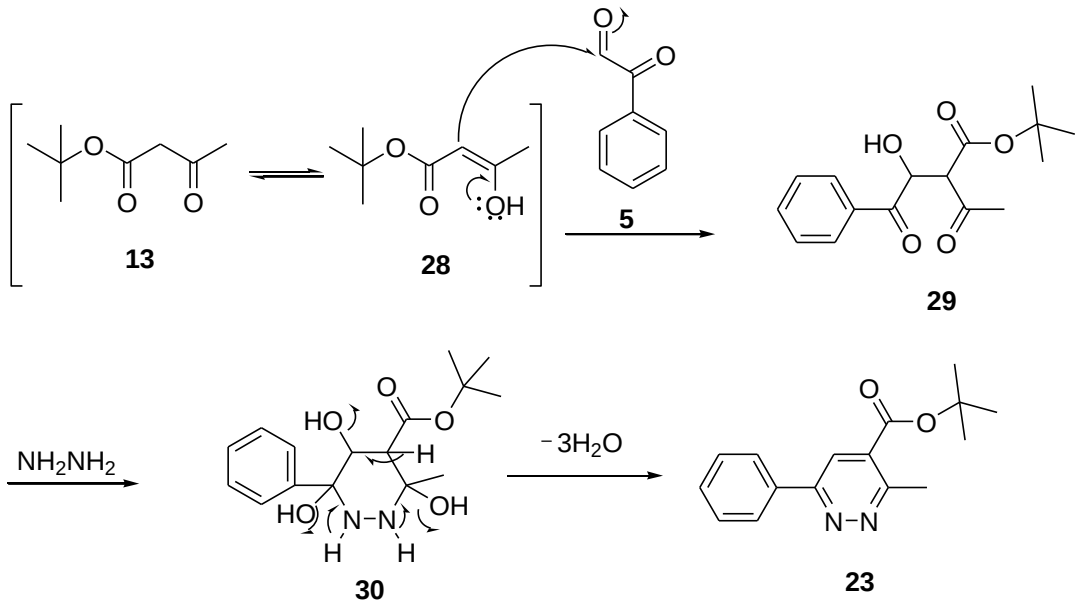
5, Ar= phenyl
6, Ar= 4-bromophenyl
7, Ar= 4-chlorophenyl
8, Ar= 4-fluorophenyl
9, Ar= 3,4-dimethoxyphenyl
10, Ar= 3,4-methylenedioxyphenyl

11, R= Me
12, R= Et
13, R= t-Bu

14, Ar= phenyl, R= Et
15, Ar= 4-bromophenyl, R= Et
16, Ar= 4-chlorophenyl, R= Et
17, Ar= 4-fluorophenyl, R= Et
18, Ar= 3,4-dimethoxyphenyl, R= Et
19, Ar= 3,4-methylenedioxyphenyl, R= Et
20, Ar= 4-bromophenyl, R= Me
21, Ar= 4-chlorophenyl, R= Me
22, Ar= 3,4-dimethoxyphenyl, R= Me
23, Ar= phenyl, R= *t*-Bu
24, Ar= 4-chlorophenyl, R= *t*-Bu
25, Ar= 4-fluorophenyl, R= *t*-Bu
26, Ar= 3,4-dimethoxyphenyl, R= *t*-Bu
27, Ar= 3,4-methylenedioxyphenyl, R= *t*-Bu

Scheme 3. Synthesis of alkyl 6-aryl-3-methylpyridazine-4-carboxylates.

The proposed mechanism involves the attack of enolate **28** onto the phenylglyoxal **5** as shown in Scheme 4, then *in situ* generated 3-hydroxy-1, 4-dicarbonyl compounds **29**, in the presence of NH_2NH_2, converts to **30** which then loses three H_2O molecules to afford product **23**.



Scheme 4. Plausible mechanism for reaction of *t*-butyl acetoacetate with phenylglyoxal in the presence of hydrazine.

Conclusions

We have reported a novel and efficient arylglyoxal-mediated synthesis of new alkyl 6-aryl-3-methylpyridazine-4-carboxylates from *β*-ketoesters and hydrazine in water. Considering the availability of the starting materials, the simple procedure at room temperature and the robust nature of this chemical process provides a very straightforward route to construct various trisubstituted pyridazines without using an acidic condition or metal catalysts.

Experimental Section

General. 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 $CDCl_3$ using TMS as the internal reference. Microanalyses were performed on a Leco Analyzer 932 in the Chemistry Department of Urmia University. All of the chemicals were purchased from Merck and Acros.

Sample procedure for pyridazine synthesis

To a mixture of *β*-ketoester (1 mmol) and arylglyoxal (1 mmol) in water (5 mL), was successively added hydrazine hydrate 100% (5 mmol) at room temperature; the resultant mixture was stirred for 30-60 min. After an appropriate time, the reaction mixture was solidified; the obtained solid was then filtered and washed with water (4×10 mL). The crude product was purified by recrystallization from ethanol.

Ethyl 3-methyl-6-phenylpyridazine-4-carboxylate (14). Yellow crystals, 95%, mp 100-102 ºC.[24] FT-IR (KBr) ν_{max}/ cm^{-1}: 3062, 2981, 2932, 1732, 1585, 1439, 1398, 1375, 1256, 1095, 774, 693. ^{1}H NMR δ 1.45 (t, *J*= 7.2 Hz, 3H), 3.01 (s, 3H), 4.46 (q, *J*= 7.2 Hz , 2H), 7.49-7.55 (m, 3H), 8.11(dd, J_1 =7.8 Hz, J_2 =1.8 Hz, 2H), 8.21 (s, 1H).^{13}C NMR δ 14.1, 21.9, 62.3, 123.6, 126.9, 128.6, 129.0, 130.1, 135.6, 157.0, 158.4, 165.3. Anal. Calcd for $C_{14}H_{14}N_2O_2$, C 69.41, H 5.82, N 11.56; found, 69.52, H 5.89, N 11.45.

Ethyl 6-(4-bromophenyl)-3-methylpyridazine-4-carboxylate (15). Pale brown crystals, 70%, mp 99-101 ºC. FT-IR (KBr) ν_{max}/ cm^{-1}: 3084, 2990, 2926, 1733, 1587, 1411, 1389, 1235, 1087, 1004, 843, 780. ^{1}H NMR δ 1.46 (t, *J*= 7.2 Hz, 3H), 3.02 (s, 3H), 4.48 (q, *J*= 7.2 Hz, 2H), 7.69 (d, *J*= 8.7 Hz, 2H), 8.01 (d, *J*= 8.7 Hz, 2H), 8.20 (s, 1H). ^{13}C NMR δ 14.2, 22.0, 62.4, 123.3, 124.9, 128.4, 128.7, 132.3, 134.5,157.3, 157.4, 165.1. Anal. Calcd for $C_{14}H_{13}BrN_2O_2$, C 52.36, H 4.08, N 8.72; found, C 52.46, H 4.17, N 8.58.

Ethyl 6-(4-chlorophenyl)-3-methylpyridazine-4-carboxylate (16). Brown crystals, 85%, mp 102-103ºC. FT-IR (KBr) ν_{max}/ cm^{-1}: 3071, 2980, 2935, 1727, 1593, 1415, 1394, 1240, 1088, 1006, 839. ^{1}H NMR δ 1.46 (t, *J*= 7.2 Hz, 3H), 3.02 (s, 3H), 4.48 (q, *J*= 7.2 Hz, 2H), 7.51 (d, *J*= 8.7 Hz, 2H), 8.08 (d, *J*= 8.7 Hz, 2H), 8.19 (s, 1H). ^{13}C NMR δ 14.2, 21.9, 62.4, 123.3, 128.1,

128.7, 129.3, 134.0, 136.5, 157.2, 157.3, 165.1. Anal. Calcd for $C_{14}H_{13}ClN_2O_2$, C 60.77, H 4.74, N 10.12; found, C 60.85, H 4.70, N 10.20.

Ethyl 6-(4-fluorophenyl)-3-methylpyridazine-4-carboxylate (17). Pale yellow crystals, 88%, mp 78-79 ºC. FT-IR (KBr) ν_{max}/ cm^{-1}: 3067, 2995, 1729, 1600, 1508, 1393, 1248, 1159, 1087, 852, 550. ^{1}H NMR δ 1.47 (t, *J*= 7.2 Hz, 3H), 3.02 (s, 3H), 4.48 (q, *J*= 7.2 Hz, 2H), 7.21-7.27 (m, 2H), 8.11-8.16 (m, 2H), 8.19 (s, 1H). ^{13}C NMR δ 14.2, 21.9, 62.3, 116.0, 116.3, 123.3, 128.7, 128.8, 128.9, 131.7, 157.0, 157.4, 162.6, 165.2, 165.9. Anal. Calcd for $C_{14}H_{13}FN_2O_2$, C 64.61, H 5.03, N 10.76; found, C 64.57, H 5.12, N 10.85.

Ethyl 6-(3, 4-dimethoxyphenyl)-3-methylpyridazine-4-carboxylate (18). Yellow crystals, 92%, mp 137-138 ºC. FT-IR (KBr) ν_{max}/ cm^{-1}: 3057, 2994, 2930, 2833, 1733, 1592, 1519, 1401, 1326, 1260, 1209, 1177, 1095, 1023, 869, 780. ^{1}H NMR δ 1.47 (t, *J*= 7.2 Hz, 3H), 3.00 (s, 3H), 3.97 (s, 3H), 4.01 (s, 3H), 4.48 (q, *J*= 7.2 Hz, 2H), 7.01 (d, *J*= 8.4 Hz, 1H), 7.57 (dd, J_1 8.4 Hz, J_2 2.1 Hz, 1H), 7.92 (d, *J*= 2.1 Hz, 1H), 8.19 (s, 1H). ^{13}C NMR δ 14.2, 21.9, 56.0, 56.1, 62.3, 109.7, 111.1, 119.5, 123.1, 128.3, 128.7, 149.6, 151.1, 156.4, 157.8, 165.5. Anal. Calcd for $C_{16}H_{18}N_2O_4$, C 63.56, H 6.00, N 9.27; found, C 63.65, H 6.10, N 9.15.

Ethyl 6-(1, 3-benzodioxol-5-yl)-3-methylpyridazine-4-carboxylate (19). Brown crystals, 80%, mp 115-116˚C. FT-IR (KBr) ν_{max}/ cm^{-1}: 2982, 2899, 1726, 1607, 1598, 1503, 1487, 1445, 1251, 1105, 1036, 926, 808. ^{1}H NMR δ 1.46 (t, *J*= 7.2 Hz, 3H), 2.99 (s, 3H), 4.47 (q, *J*= 7.2 Hz, 2H), 6.06 (s, 2H), 6.96 (d, *J*= 7.8 Hz, 1H), 7.58 (dd, J_1= 7.8 Hz, J_2= 2.1 Hz, 1H), 7.70 (d, *J*= 2.1 Hz, 1H), 8.13 (s, 1H). ^{13}C NMR δ 14.1, 21.8, 62.2, 101.5, 107.2, 107.9, 108.7, 121.2, 123.2, 123.6, 124.0, 140.3, 156.5, 157.7, 164.9. Anal. Calcd for $C_{15}H_{14}N_2O_4$, C 62.93, H 4.93, N 9.79; found, C 62.98, H 4.90, N 9.67.

Methyl 6-(4-bromophenyl)-3-methylpyridazine-4-carboxylate (20). Beige crystals, 84%, mp 88-90 ºC. FT-IR (KBr) ν_{max}/ cm^{-1}: 3087, 2953, 1732, 1586, 1485, 1432, 1390, 1241, 1090, 1070, 1004, 827. ^{1}H NMR δ 3.03 (s, 3H), 4.02 (s, 3H), 7.68 (d, *J*= 8.4 Hz, 2H), 8.02 (d, *J*= 8.4 Hz, 2H), 8.22 (s, 1H). ^{13}C NMR δ 21.9, 53.0, 123.4, 128.3, 129.4, 131.3, 132.0, 132.1, 132.3, 157.4, 165.5. Anal. Calcd for $C_{13}H_{11}BrN_2O_2$, C 50.84, H 3.61, N 9.12; found, C 50.96, H 3.67, N 8.97.

Methyl 6-(4-chlorophenyl)-3-methylpyridazine-4-carboxylate (21). Yellow crystals, 75%, mp 118-120 ºC. FT-IR (KBr) ν_{max}/ cm^{-1}: 3086, 2955, 1732, 1592, 1490, 1432, 1391, 1241, 1091, 1007, 832, 780. ^{1}H NMR δ 3.03 (s, 3H), 4.02 (s, 3H), 7.52 (d, *J*= 8.7 Hz, 2H), 8.08 (d, *J*= 8.7 Hz, 2H), 8.22 (s, 1H). ^{13}C NMR δ 21.9, 53.0, 123.4, 127.4, 128.1, 129.0, 129.2, 129.3, 136.6, 157.3, 165.5. Anal. Calcd for $C_{13}H_{11}ClN_2O_2$, C 59.44, H 4.22, N 10.66; found, C 59.55, H 4.29, N 10.56.

Methyl 6-(3,4-dimethoxyphenyl)-3-methylpyridazine-4-carboxylate(22). Orange crystals, 88%, mp 128-130 ºC. FT-IR (KBr) ν_{max}/ cm^{-1}: 3076, 2932, 2844, 1738, 1585, 1515, 1437, 1367, 1264, 1092, 1017, 848, 768. ^{1}H NMR δ 2.99 (s, 3H), 3.96 (s, 3H), 4.01 (s, 3H), 4.02 (s, 3H), 6.99 (d, *J*= 8.4 Hz, 1H), 7.56 (dd, J_1= 8.4 Hz J_2= 2.1 Hz, 1H), 7.90 (d, *J*= 1.8 Hz, 1H), 8.20 (s, 1H). ^{13}C NMR δ 21.9, 52.9, 56.0, 56.1, 109.6, 111.1, 119.5, 123.1, 128.2, 128.3, 149.6, 151.0, 156.4, 157.8, 165.8. Anal. Calcd for $C_{15}H_{16}N_2O_4$, C 62.49, H 5.59, N 9.72; found, C 62.61, H 5.66, N 9.63.

***tert*-Butyl 3-methyl-6-phenylpyridazine-4-carboxylate (23).** Yellow crystals, 97%, mp 98-100 ºC. FT-IR (KBr) ν_{max}/ cm^{-1}: 3058, 2997, 2974, 1706, 1617, 1398, 1363, 1273, 1159, 1134, 846, 772, 688. ^{1}H NMR δ 1.66 (s, 9H), 2.99 (s, 3H), 7.51-7.58 (m, 3H), 8.11 (dd, J_1= 7.5 Hz J_2= 1.5 Hz, 2H), 8.14 (s, 1H). ^{13}C NMR δ 22.0, 28.4, 83.7, 123.5, 126.9, 127.9, 129.0, 130.0, 135.8, 156.6, 158.4, 164.6. Anal. Calcd for $C_{16}H_{18}N_2O_2$, C 71.09, H 6.71, N 10.36; found, C 71.18, H 6.76, N 10.45.

***tert*-Butyl 6-(4-chlorophenyl)-3-methylpyridazine-4-carboxylate (24).** Beige crystals, 78%, mp 82-83 ºC. FT-IR (KBr) ν_{max}/ cm^{-1}: 3064, 2980, 1722, 1595, 1491, 1393, 1258, 1166, 1098, 839, 819. ^{1}H NMR δ 1.65 (s, 9H), 2.99 (s, 3H), 7.51 (d, *J*= 8.7 Hz, 2H), 8.06 (d, *J*= 8.7 Hz, 2H), 8.10 (s, 1H). ^{13}C NMR δ 22.0, 28.1, 83.9, 123.2, 128.1, 129.3, 130.4, 134.1, 136.4, 156.9, 157.3, 164.5. Anal. Calcd for $C_{16}H_{17}ClN_2O_2$, C 63.05, H 5.62, N 9.19; found, C 63.16, H 5.68, N 9.10.

***tert*-Butyl 6-(4-fluorophenyl)-3-methylpyridazine-4-carboxylate (25).** Pale brown crystals, 82%, mp 61-63 ºC. FT-IR (KBr) ν_{max}/ cm^{-1}: 3063, 2984, 2933, 1720, 1601, 1508, 1393, 1369, 1270, 1158, 1094, 844, 783, 551. ^{1}H NMR δ 1.65 (s, 9H), 2.98 (s, 3H), 7.19-7.25 (m, 2H), 8.09 (s, 1H), 8.10-8.13 (m, 2H). ^{13}C NMR δ 21.9, 28.1, 83.8, 115.9, 116.2, 123.1, 128.7, 128.9, 130.4, 156.6, 157.4, 162.5, 164.5, 165.8. Anal. Calcd for $C_{16}H_{17}FN_2O_2$, C 66.65, H 5.94, N 9.72; found, C 66.77, H 6.01, N 9.60.

***tert*-Butyl 6-(3, 4-dimethoxyphenyl)-3-methylpyridazine-4-carboxylate (26).** Yellow crystals, 90%, mp 88-90 ºC. FT-IR (KBr) ν_{max}/ cm^{-1}: 3057, 2976, 2935, 2836, 1719, 1591, 1520, 1463, 1401, 1371, 1262, 1157, 1094, 1019, 872, 813, 782. ^{1}H NMR δ 1.65 (s, 9H), 2.98 (s, 3H), 3.96 (s, 3H), 4.00 (s, 3H), 6.99 (d, 1H, *J*= 8.4 Hz), 7.55 (dd, J_1= 8.4 Hz J_2= 2.1 Hz, 1H), 7.89 (d, *J*= 2.1 Hz, 1H), 8.14 (s, 1H). ^{13}C NMR δ 21.6, 28.1, 56.0, 56.1, 84.0, 109.7, 111.1, 119.6, 123.6, 128.0, 130.9, 149.7, 151.2, 156.0, 157.9, 164.4. Anal. Calcd for $C_{18}H_{22}N_2O_4$, C 65.44, H 6.71, N 8.48; found, C 65.53, H 6.78, N 8.45.

***tert*-butyl 6-(1, 3-benzodioxol-5-yl)-3-methylpyridazine-4-carboxylate (27).** Beige crystals, 84%, mp 102-103˚C. FT-IR (KBr) ν_{max}/ cm^{-1}: 2974, 2911, 1728, 1602, 1491, 1445, 1405, 1369, 1246, 1152, 1035, 930, 812. ^{1}H NMR δ 1.64 (s, 9H), 2.95 (s, 3H), 6.05 (s, 2H), 6.95 (d, *J*= 8.1 Hz, 1H), 7.56 (dd, J_1= 8.1 Hz, J_2= 1.5 Hz, 1H), 7.68 (d, *J*= 1.5 Hz, 1H), 8.03 (s, 1H). ^{13}C NMR δ 21.9, 28.1, 83.7, 101.5, 107.1, 107.9, 108.6, 121.2, 123.0, 130.3, 148.5, 149.4, 156.2, 157.8, 164.6. Anal. Calcd for $C_{17}H_{18}N_2O_4$, C 64.96, H 5.77, N 8.91; found, C 65.00, H 5.83, N 8.78.

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