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. 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 to possess a wide range of biological activities, these include antiviral and anticancer, antituberculosis, antihypertensive, anti-inflammatory, and antimicrobial activities. Pyridazine derivatives have also been the subject of extensive research in the agrochemical areas. Moreover, pyridazines are useful intermediates in the construction of several other heterocycles and in physical organic chemistry and recently have been explored as new R-helix mimetics. 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. 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, 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(6H, 8H)-diones and their sulfur analogues as potential monoamine oxidase inhibitors. 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.

![Scheme 1. Retro synthesis of alkyl 6-aryl-3-methylpyridazine-4-carboxylate.](image)

Currently, multicomponent reactions are being rapidly developed 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 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.

![Scheme 2. Synthesis of arylglyoxals.](image)

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.\(^{24}\)

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. 1H (300 MHz) and 13C (75.5 MHz) nmr measurements were recorded on a Bruker 300 spectrometer in CDCl3 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 (4x10 mL). The crude product was purified by recrystallization from ethanol.

Ethyl 3-methyl-6-phenylpyridazine-4-carboxylate (14). Yellow crystals, 95%, mp 100-102°C.24 FT-IR (KBr) νmax/cm⁻¹: 3062, 2981, 2932, 1732, 1585, 1439, 1398, 1375, 1256, 1095, 774, 693. 1H 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, J1 = 7.8 Hz, J2 = 1.8 Hz, 2H), 8.21 (s, 1H). 13C 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 C14H14N2O2, C 69.41, H 5.82, N 11.56; found, C 69.52, H 5.89, N 11.45.

Ethyl 6-(4-bromophenyl)-3-methylpyridazine-4-carboxylate (15). Pale brown crystals, 70%, mp 99-101°C. FT-IR (KBr) νmax/cm⁻¹: 3084, 2990, 2926, 1733, 1587, 1411, 1389, 1235, 1087, 1004, 843, 780. 1H 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). 13C 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 C14H13BrN2O2, 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 102-103°C. FT-IR (KBr) νmax/cm⁻¹: 3071, 2980, 2935, 1727, 1593, 1415, 1394, 1240, 1088, 1006, 839. 1H 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). 13C NMR δ 14.2, 21.9, 62.4, 123.3, 128.1,

**Ethyl 6-(4-fluorophenyl)-3-methylpyridazine-4-carboxylate (17).** Pale yellow crystals, 88%, mp 78-79 °C. FT-IR (KBr) v_{max} / cm\(^{-1}\): 3067, 2995, 1729, 1600, 1508, 1393, 1248, 1159, 1087, 852, 550. \(^1\)H NMR \(\delta 1.47\) (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 \(\delta 14.2\), 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_{2}O_{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 °C. FT-IR (KBr) v_{max} / cm\(^{-1}\): 3057, 2994, 2930, 2833, 1733, 1592, 1519, 1401, 1326, 1260, 1209, 1177, 1095, 1023, 869, 780. \(^1\)H NMR \(\delta 1.47\) (t, \(J = 7.2\) Hz, 3H), 1.87 (d, \(J = 7.2\) Hz, 3H), 3.02 (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), 7.75 (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 \(\delta 14.2\), 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_{2}O_{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) v_{max} / cm\(^{-1}\): 2982, 2899, 1726, 1607, 1598, 1503, 1487, 1445, 1251, 1105, 1036, 926, 808. \(^1\)H NMR \(\delta 1.46\) (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 \(\delta 14.1\), 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_{2}O_{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 °C. FT-IR (KBr) v_{max} / cm\(^{-1}\): 3087, 2953, 1732, 1586, 1485, 1432, 1390, 1241, 1090, 1070, 1004, 827. \(^1\)H NMR \(\delta 3.03\) (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 \(\delta 21.9\), 53.0, 123.4, 128.3, 129.4, 131.3, 132.0, 132.1, 132.3, 157.4, 165.5. Anal. Calcd for C_{11}H_{11}BrN_{2}O_{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 °C. FT-IR (KBr) v_{max} / cm\(^{-1}\): 3086, 2955, 1732, 1592, 1490, 1432, 1391, 1241, 1091, 1007, 832, 780. \(^1\)H NMR \(\delta 3.03\) (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 \(\delta 21.9\), 53.0, 123.4, 127.4, 128.1, 129.0, 129.2, 129.3, 136.6, 157.3, 165.5. Anal. Calcd for C_{15}H_{11}ClN_{2}O_{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 °C. FT-IR (KBr) v_{max} / cm\(^{-1}\): 3076, 2932, 2844, 1738, 1585, 1515, 1437, 1367, 1264, 1092, 1017, 848, 768. \(^1\)H NMR \(\delta 2.99\) (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 \(\delta 21.9\), 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_{2}O_{4}, C 62.49, H 5.59, N 9.72; found, C 62.61, H 5.66, N 9.63.
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**tert-Butyl 3-methyl-6-phenylpyridazine-4-carboxylate (23).** Yellow crystals, 97%, mp 98-100 °C. FT-IR (KBr) ν max/cm⁻¹: 3058, 2977, 2974, 1706, 1617, 1398, 1363, 1273, 1159, 1134, 846, 772, 688. ¹H NMR δ 1.66 (s, 9H), 2.99 (s, 3H), 7.51-7.58 (m, 3H), 8.11 (dd, J₁ = 7.5 Hz J₂ = 1.5 Hz, 2H), 8.14 (s, 1H). ¹³C 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 C₁₈H₁₈N₂O₂, 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 °C. FT-IR (KBr) ν max/cm⁻¹: 3064, 2980, 1722, 1595, 1491, 1393, 1258, 1166, 1098, 839, 819. ¹H 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). ¹³C 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 C₁₈H₁₇ClN₂O₂, 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 °C. FT-IR (KBr) ν max/cm⁻¹: 3063, 2984, 2933, 1720, 1601, 1508, 1393, 1369, 1270, 1158, 1094, 844, 783, 551. ¹H 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). ¹³C 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 C₁₈H₁₇FClN₂O₂, 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 °C. FT-IR (KBr) ν max/cm⁻¹: 3057, 2976, 2935, 2836, 1719, 1591, 1520, 1463, 1401, 1371, 1262, 1157, 1094, 1019, 872, 813, 782. ¹H 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, J₁ = 8.4 Hz J₂ = 2.1 Hz, 1H), 7.89 (d, J = 2.1 Hz, 1H), 8.14 (s, 1H). ¹³C 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 C₁₈H₂₂N₂O₄, 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: 2973, 2911, 1728, 1602, 1491, 1445, 1405, 1369, 1246, 1152, 1035, 930, 812. ¹H 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, J₁ = 8.1 Hz, J₂ = 1.5 Hz, 1H), 7.68 (d, J₁ = 1.5 Hz, 1H), 8.03 (s, 1H). ¹³C 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 C₁₇H₁₈N₂O₄, C 64.96, H 5.77, N 8.91; found, C 65.00, H 5.83, N 8.78.

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References and Notes


