Current Chemistry Letters 1 (2012) 115–122

Contents lists available at Growing Science

Current Chemistry Letters

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# Regioselective one-pot, three component synthesis of ethyl 6-aryl-3-propylpyridazine-4-carboxylates in water

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**ARTICLE INFO**

*Article history*:
Received March 30, 2012
Received in Revised form
May 21, 2012
Accepted 14 June 2012
Available online
14 June 2012

*Keywords*:
*Pyridazine*
*Arylglyoxal*
*Hydrazine*
*Regioselective*

**ABSTRACT**

A regioselective synthesis of ethyl 6-aryl-3-propylpyridazine-4-carboxylates by one-pot three-component reaction of ethyl butyrylacetate with various arylglyoxals in the presence of hydrazine hydrate at room temperature in water was described.



## 1. Introduction

Chemical processes that allow assembly of several building blocks in a single operation are gaining increasing attention in the search for new efficient, diversity-oriented synthetic methodologies, and particularly those directed toward heterocyclic compounds. Such processes are highly desirable for the rapid generation of libraries of small drug-like molecules for high-throughput screaning.[1-6] The design of multicomponent syntheses often relies on the integration of multiple individual reactions to give a one-pot synthetic operation, a new concept with important economical and environmental issues.[7-10]

The chemistry and pharmacology of pyridazine derivatives have recently received considerable interest. This can be realized from the vast number of articles and patents published in the synthesis,

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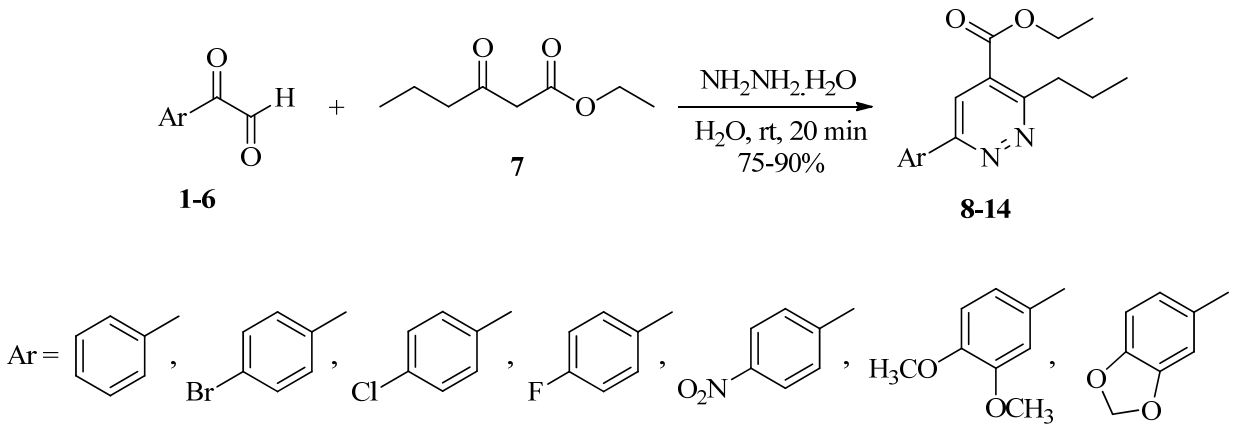
doi: 10.5267/j.ccl.2012.6.001

chemistry, and biological activities of pyridazines.[11-14] The pyridazines and their derivatives exhibit a broad range of biological activity, such as analgesic,[15] antibacterial,[16] anti-inflammatory,[11] antihypertensive[17] or antihistaminic[18] properties. The derivatives of pyridazines could also find application as ligands in metallic complexes which possess catalytic properties.[19,20] These compounds could also be used as semi-conductor materials and as materials with non-linear optical properties.[21] These pharmacological and technological properties of pyridazines encourage the development of methods for their synthesis and functionalization. In continuation of our interest in the synthesis of various pyridazine derivatives,[22-26] we decided to investigate the three-component reaction of arylglyoxals, ethyl butyrylacetate and hydrazine hydrate which is extended to the regioselective synthesis of ethyl 6-aryl-3-propylpyridazine-4-carboxylates as a new series of three substituted pyridazines.

## 2. Results and Discussion

Similar to our latest researches describing the synthesis of pyridazine derivatives,[22-26] firstly the arylglyoxals (**1-6)** were produced from the corresponding acetophenones via oxidation with $SeO_2$ in dioxane at reflux conditions.[27] Then the reaction of arylglyoxals **(1-6)** with ethyl butyrylacetate **(7)** in the presence of hydrazine hydrate at room temperature in water leds to form the ethyl 6-aryl-3-propylpyridazine-4-carboxylates **(8-14**) in good yields as shown in the Scheme **1**.

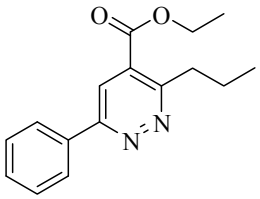
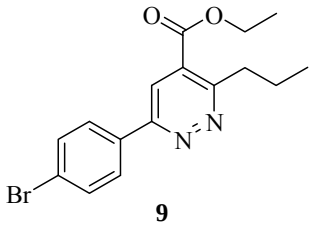
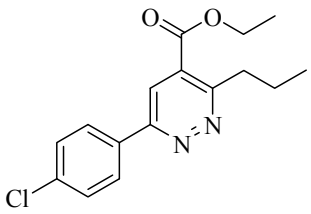
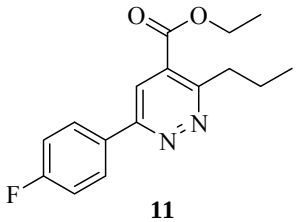
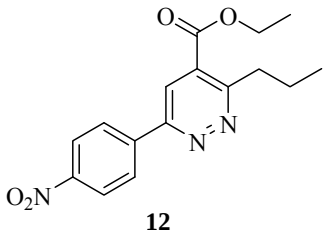
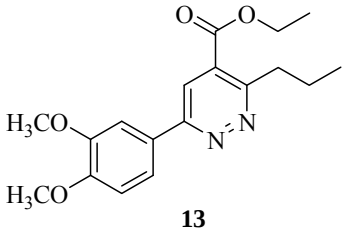
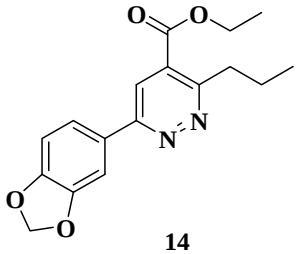


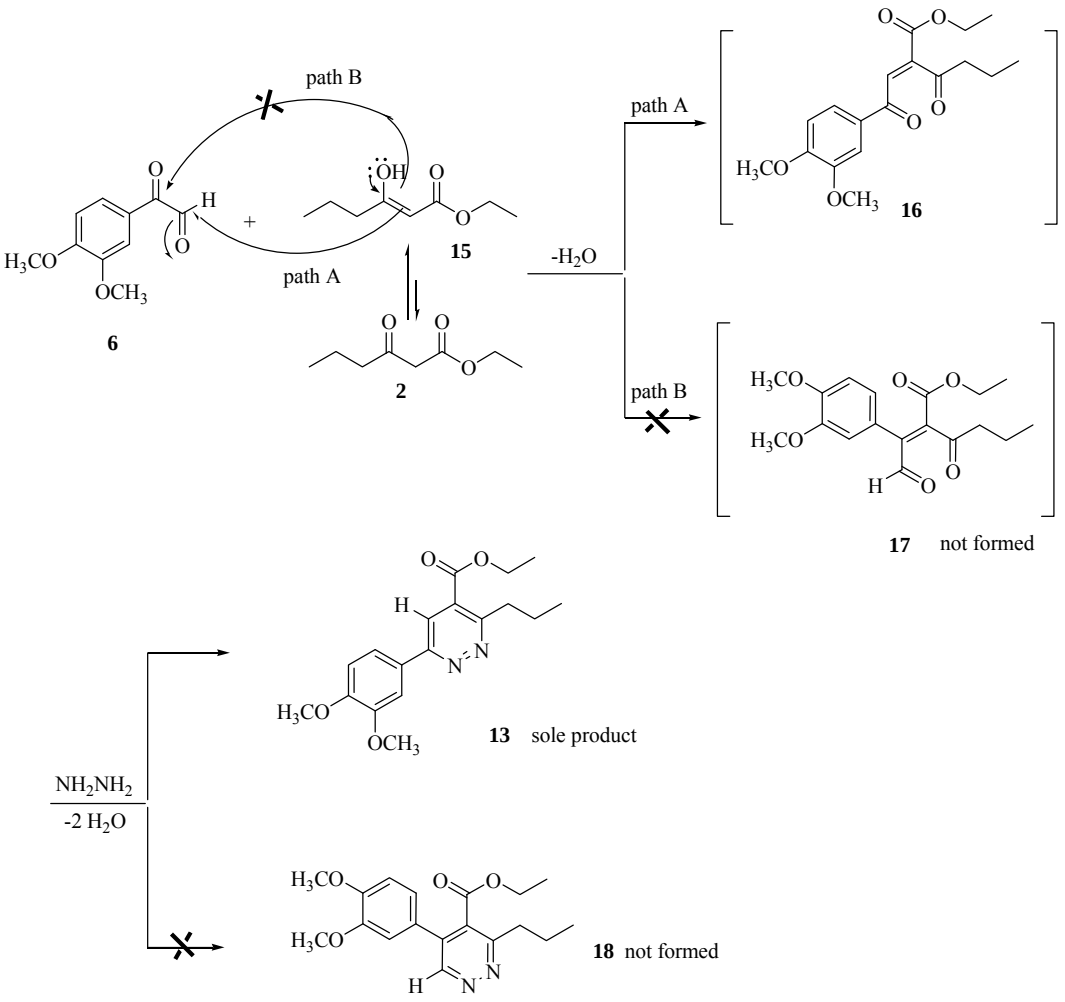

**Scheme 1:** Synthesis of ethyl 6-aryl-3-propylpyridazine-4-carboxylates

All of the obtained products were listed at the Table 1. Formation of the 6-aryl substituted pyridazines as sole products proves this fact that the outlined strategy acts regioselectively and there is no evidence for production of 5-aryl substituted isomers. The mechanism of the regioselective synthesis of the products was shown in Scheme **2**.

Owing to the high reactivity of the external carbonyl in comparison with internal carbonyl in an arylglyoxal system, the reaction was run through the nucleophilic attack of enol **(15**) to the aldehyde carbonyl of arylglyoxal **(6**) leading to form the intermediate **(16)** as a sole product. The subsequent condensation of hydrazine with the carbonyl groups of the intermediate (**16**) gives the final product **(13**).

**Table 1.** List of pyridazine products.

| Entry | Pyridazine | Yield (%) |
|---|---|---|
| **1** |  **8** | 75 |
| **2** |  **9** | 88 |
| **3** |  **10** | 84 |
| **4** |  **11** | 81 |
| **5** |  **12** | 90 |
| **6** |  **13** | 80 |
| **7** |  **14** | 79 |




**Scheme 3:** Suggested mechanism for regioselective synthesis of ethyl 6-(3,4-dimethoxyphenyl)-3-propylpyridazine-4-carboxylate

## 3. Conclusions

We have synthesized some new three substituted pyridazines via one-pot three component reaction of arylglyoxals, ethyl butyrylacetate and hydrazine hydrate in water at room temperature. The simple operation, the high regioselectivity and the convenient reaction condition of this procedure makes it a valuable route to prepare new substituted pyridazines.

## Acknowledgements

The authors express their thanks to the research council of Urmia University for financial support.

## Experimental

*General Procedures*

Elemental analyses for C, H and N were performed using Heraeus Leco analyzer 932. NMR spectra were recorded on a Bruker Avance spectrometer operating at 300 MHz for $^{1}H$ nuclei and 75.5 MHz for $^{13}C$ nuclei with tetramethylsilane as internal standard. Mass spectra were recorded using a Varian

Matt 311 spectrometer operating at nominal accelerating voltage of 70 eV. Thin layer chromatography (TLC) was run on silica percolated aluminium plates (Merck Kieselgel F254). Melting points were determined on a Kofler hot-stage apparatus.

*Sample procedure for pyridazine synthesis*.
To a mixture of ethyl butyrylacetate (1 mmol) and arylglyoxal[27] (1 mmol) in water (5 mL), was successively added hydrazine hydrate (5 mmol) at room temperature; the resultant mixture was stirred for 20-35 min during which time a precipitate was formed. The precipitate was then filtered and washed with excess water. The crude product was purified by recrystallization from ethanol.

**Ethyl 6-phenyl-3-propylpyridazine-4-carboxylate (8):** yellow crystals, 75%, mp 50-51 ºC.
FT-IR (KBr) $\nu_{max}$: 3064, 2958, 2868, 1725, 1648, 1582, 1451, 1394, 1240, 1093, 755, 690 $cm^{-1}$. $^1$H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.27 (s, 1H, Ar), 8.10-8.16 (m, 2H, Ar), 7.50-7.58 (m, 3H, Ar), 4.49 (q, J 7.2 Hz, 2H, $CH_2$), 3.41 (t, J 7.2 Hz, 2H, $CH_2$), 1.87 (sex, J 7.2 Hz, 2H, $CH_2$), 1.47 (t, J 7.2 Hz, 3H, $CH_3$), 1.08 (t, J 7.2 Hz, 3H, $CH_3$). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ (ppm): 164.07, 160.38, 158.79, 134.02, 132.67, 131.18, 129.32, 127.19, 126.73, 62.96, 34.82, 23.48, 14.13, 14.05. Anal. Calcd for $C_{16}H_{18}N_2O_2$, C 71.09, H 6.71, N 10.36; Found: C, 71.13; H, 6.66; N, 10.50. Mass spectrum m/z (%): 270 ([$M^+$], 18), 242 (100), 241 (82), 213 (36), 197 (37), 170 (88).

**Ethyl 6-(4-bromophenyl)-3-propylpyridazine-4-carboxylate (9):** yellow crystals, 88%, mp 66-68 ºC.
FT-IR (KBr) $\nu_{max}$: 3070, 2959, 2935, 2872, 1706, 1597, 1505, 1404, 1388, 1223, 1156, 851, 574 $cm^{-1}$. $^1$H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.25 (s, 1H, Ar), 8.02 (d, J 8.1 Hz, 2H, Ar), 7.68 (d, J 8.1 Hz, 2H, Ar), 4.49 (q, J 7.2 Hz, 2H, $CH_2$), 3.41 (t, J 7.2 Hz, 2H, $CH_2$), 1.86 (sex, J 7.2 Hz, 2H, $CH_2$), 1.46 (t, J 7.2 Hz, 3H, $CH_3$), 1.07 (t, J 7.2 Hz, 3H, $CH_3$). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ (ppm): 164.71, 160.63, 157.41, 133.78, 132.43, 130.01, 128.49, 125.46, 124.84, 62.74, 35.76, 23.30, 14.17, 14.09. Anal. Calcd for $C_{16}H_{17}BrN_2O_2$, C 55.03, H 4.91, N 8.02; Found: C, 55.05; H, 4.99; N, 8.11.

**Ethyl 6-(4-chlorophenyl)-3-propylpyridazine-4-carboxylate (10):** yellow crystals, 84%, mp 69-70 ºC.
FT-IR (KBr) $\nu_{max}$: 3068, 2963, 2931, 2871, 1734, 1594, 1414, 1385, 1238, 1095, 1010, 850, 756 $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.16 (s, 1H, Ar), 8.07 (d, J 8.4 Hz, 2H, Ar), 7.51 (d, J 8.4 Hz, 2H, Ar), 4.47 (q, J 7.2 Hz, 2H, $CH_2$), 3.35 (t, J 7.2, 2H, $CH_2$), 1.85 (sex, J 7.2 Hz, 2H, $CH_2$), 1.45, (t, J 7.2 Hz, 3H, $CH_3$), 1.05 (t, J 7.2 Hz, 3H, $CH_3$). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ (ppm): 165.24, 160.50, 157.06, 136.63, 133.90, 129.34, 129.15, 128.15, 123.72, 62.48, 36.25, 23.15, 14.16, 14.08. Anal. Calcd for $C_{16}H_{17}ClN_2O_2$, C 63.05, H 5.62, N 9.19; Found: C, 63.00; H, 5.56; N, 9.20. Mass spectrum m/z (%): 306 ([$M^+$+2], 3), 304 ([$M^+$], 10), 276 (100), 247 (42), 231 (40), 206 (32), 204 (89), 152 (19), 139 (46), 75 (20).

**Ethyl 6-(4-fluorophenyl)-3-propylpyridazine-4-carboxylate (11):** pale yellow crystals, 81%, mp 42-43 ºC.
FT-IR (KBr) $\nu_{max}$: 3055, 2963, 2873, 1716, 1602, 1509, 1389, 1254, 1163, 1094, 845, 757, 552 $cm^{-1}$. $^1$H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.16 (s, 1H, Ar), 8.08-8.15 (m, 2H, Ar), 7.18-7.27 (m, 2H, Ar), 4.48 (q, J 7.2 Hz, 2H, $CH_2$), 3.36 (t, J 7.2, 2H, $CH_2$), 1.86 (sex, J 7.2 Hz, 2H, $CH_2$), 1.47 (t, J 7.2 Hz, 3H, $CH_3$), 1.08 (t, J 7.2 Hz, 3H, $CH_3$). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ (ppm): 165.92, 165.30, 162.60, 160.21, 157.15, 131.60, 128.92, 128.81, 123.68, 116.30, 116.01, 62.44, 36.21, 23.14, 14.14, 14.07. Anal. Calcd for $C_{16}H_{17}FN_2O_2$, C, 66.65, H 5.94, N 9.72; Found: C, 65.72; H, 5.90; N, 9.85. Mass spectrum m/z (%): 288 ([$M^+$], 38), 260 (100), 231 (37), 215 (45), 188 (90), 157 (13), 120 (29).

**Ethyl 6-(4-nitrophenyl)-3-propylpyridazine-4-carboxylate (12):** orange crystals, 90%, mp 118 ºC.
FT-IR (KBr) $\nu_{max}$: 3078, 2965, 2931, 2872, 1733, 1601, 1514, 1394, 1346, 1305, 1242, 1093, 1019, 857, 753, 694 $cm^{-1}$. $^1$H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.41 (d, J 8.7 Hz, 2H, Ar), 8.33 (d, J 8.7 Hz, 2H, Ar), 8.27 (s, 1H, Ar), 4.50 (q, J 7.2 Hz, 2H, $CH_2$), 3.40 (t, J 7.2 Hz, 2H, $CH_2$), 1.87 (sex, J 7.2

Hz, 2H, $CH_2$), 1.48 (t, J 7.2 Hz, 3H, $CH_3$), 1.08 (t, J 7.2, 3H, $CH_3$). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ (ppm): 164.83, 161.56, 156.14, 149.06, 141.26, 129.49, 127.84, 124.54, 124.30, 62.74, 36.21, 23.19, 14.15, 14.05. Anal. Calcd for $C_{16}H_{17}N_3O_4$, C 60.94, H 5.43, N 13.33; Found: C, 60.92; H, 5.39; N, 13.43. Mass spectrum m/z (%): 315 ([$M^+$], 7), 287 (93), 258 (59), 242 (44), 215 (100), 152 (27), 139 (28), 115 (19), 75 (18).

**Ethyl 6-(3,4-dimethoxyphenyl)-3-propylpyridazine-4-carboxylate (13):** yellow crystals, 80%, mp 64-65 ºC.
FT-IR (KBr) $\nu_{max}$: 3087, 2958, 2935, 2873, 2835, 1716, 1590, 1516, 1465, 1399, 1261, 1222, 1149, 1095, 1020, 872, 762 $cm^{-1}$. $^1$H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.26 (s, 1H, Ar), 7.93 (s, 1H, Ar), 7.57 (d, J 8.1 Hz, 1H, Ar), 7.01 (d, J 8.1 Hz, 1H, Ar), 4.50 (q, J 7.2 Hz, 2H, $CH_2$), 4.01 (s, 3H, $OCH_3$), 3.97 (s, 3H, $OCH_3$), 3.39 (t, J 7.2, 2H, $CH_2$), 1.87 (sex, J 7.2 Hz, 2H, $CH_2$), 1.47 (t, J 7.2 Hz, 3H, $CH_3$), 1.07 (t, J 7.2, 3H, CH3). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ (ppm): 163.57, 159.80, 158.27, 152.40, 150.01, 132.21, 127.72, 125.56, 120.55, 111.22, 109.88, 63.24, 56.37, 56.11, 34.22, 23.49, 14.14, 14.02. Anal. Calcd for $C_{18}H_{22}N_2O_4$, C 65.44, H 6.71, N 8.48; Found: C, 65.37; H, 6.68; N, 8.57. Mass spectrum m/z (%): 330 ([$M^+$], 26), 302 (100), 301 (55), 273 (24), 257 (25), 230 (82), 204 (24), 165 (32).

**Ethyl 6-(benzo[d][1,3]dioxol-5-yl)-3-propylpyridazine-4-carboxylate (14):** yellow crystals, 79%, mp 89-90 ºC.
FT-IR (KBr) $\nu_{max}$: 3083, 2961, 2928, 1725, 1499, 1446, 1402, 1254, 1036, 875 $cm^{-1}$. $^1$H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.20 (s, 1H, Ar), 7.71 (s, 1H, Ar), 7.62 (d, J 7.8 Hz, 1H, Ar), 6.96 (d, J 7.8 Hz, 1H, Ar), 6.08 (s, 2H, $CH_2$), 4.49 (q, J 7.2 Hz, 2H, $CH_2$), 3.40 (t, J 7.2, 2H, $CH_2$), 1.84 (sex, J 7.2 Hz, 2H, $CH_2$), 1.46 (t, J 7.2 Hz, 3H, $CH_3$), 1.07 (t, J 7.2, 3H, $CH_3$). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ (ppm): 164.86, 159.84, 158.17, 151.85, 149.02, 133.07, 131.53, 127.21, 122.14, 108.95, 107.28, 101.93, 63.11, 34.43, 23.48, 14.15, 14.06. Anal. Calcd for $C_{17}H_{18}N_2O_4$, C 64.96, H 5.77, N 8.91; Found: C, 64.90; H, 5.75; N, 8.86.

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