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# A Convenient Synthesis of 3,5-Diaryl-2-Pyrazoline-1-Carboxamides Through the Reactions of Chalcones with Semicarbazide in the Presence of Potassium Carbonate

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**Abstract:** Synthesis of 3,5-diaryl-2-pyrazoline-1-carboxamides have been achieved *via* the reactions of 1,3-diaryl-2-propen-1-ones with semicarbazide hydrochloride in the presence of potassium carbonate, a green and inexpensive catalyst. The reactions were performed at reflux in ethanol within short reaction times, good to excellent yields and easy-isolation/purification of the products.

**Keywords:** Pyrazoline, Semicarbazide, Chalcones, Potassium Carbonate

## Introduction

Semicarbazide and its derivatives are multifunctional nucleophiles. The reaction of these compounds with enones holds both theoreticalandpracticalinterestsincethisreaction is leading to pyrazoline which is an important class of nitrogen-containing five-membered heterocyclic compounds.[1] It is also worthy of mention that pyrazolinederivatives have been known to possess widespread pharmacological activities, such as anti-inflammatory,[2] anticonvulsant,[3,4]antimicrobial,[5,6]anticancer,[7] antiviral,[8] and hypotensive[9]activities.In addition, the pyrazole moiety is an active ingredient of several blockbuster drugs such as celecoxib (Celebrex),[10]sildenafil (Viagra),[11] and rimonabant (Acomplia).[12]

Therefore, the synthesis of pyrazolines has received significant attention. A Synthesis of pyrazoline-l-carboxamide derivatives have been reported using different synthetic procedures and catalyst systems.[2-5, 13-14]However, these procedures have been associated with use of toxic and expensive reagents, harsh reaction conditions, long reaction times andlow yields. Thus developing versatile approaches towards synthesis of 3,5-diaryl-2-pyrazoline-1-carboxamides still remains a significant interest

in organic synthesis.

As a continuation of our interest in the evolvement of efficient procedures for the synthesis of biologically active molecules,[15-17] herein, we describe the development of a powerfuland reliable reaction for the synthesis of3,5-diaryl-2-pyrazoline-1-carboxamides.

## Experimental

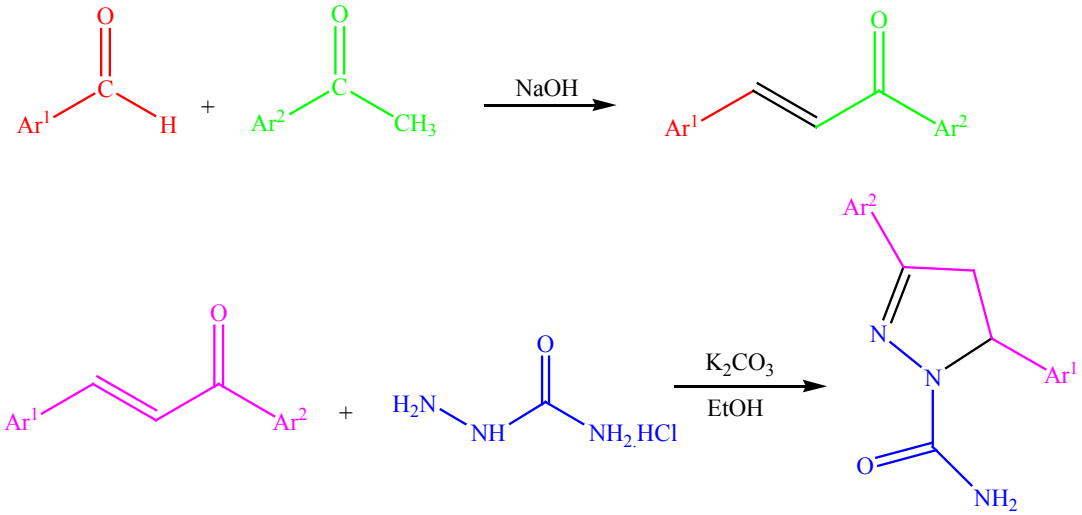
All chemicals were commercially available and used without further purification. However, the synthesis of 1,3-diaryl-2-propen-1-ones (chalcones) was performed through the cross-aldol condensation of arylaldehydes and acetophenones according to a modified reported method.[18] Melting points were measured by an electrothermal type 9100 melting point apparatus. The infrared (IR) spectra in KBr pellets were recorded on a Bruker Tensor 27 FT-IR spectrophotometer as KBr disks. NMR spectra were determined on a Bruker AC 400 MHz spectrometer as DMSO solutions.

### General procedure for the synthesis 3,5-diaryl-2-pyrazoline-1-carboxamides

A solution of chalcone (1 mmol), semicarbazide hydrochloride (1.4 mmol) and potassium carbonate (0.1 g) in ethanol (5 ml) was boiled under reflux for a certain period of time as required to complete the reaction (Table 2). The progress of reactions was monitored by TLC (ethyl acetate/n-hexane). At completion, the reaction mixture was allowed to reach room temperature, poured into crushed ice. The solid mass which separated out was filtered, washed carefully with water and recrystallized from ethanol/chloroform (4:1) to afford pure products.

**3,5-diphenyl-2-pyrazoline-1-carboxamide (3a):** IR spectrum, ν, $cm^{-1}$: 3493, 3293, 3135, 1687, 1650, 1583, 1439, 1344, 1072, 762, 696; $^1$H NMR (400 MHz, DMSO-d6) spectrum, δ, ppm(*J*, Hz): 3.05 (1H, dd, *J*= 17.4, 4.8), 3.80 (1H, dd, *J*= 17.2, 12.4), 5.40 (1H, dd, *J*= 12.4, 4.8), 6.51 (2H, s), 7.16-7.18 (2H, m), 7.22-7.24 (1H, m), 7.29-7.33 (2H, m), 7.41-7.42 (3H, m), 7.77-7.78 (2H, m).

**5-(4′-methoxyphenyl)-3-phenyl-2-pyrazoline-1-carboxamide (3d):** IR spectrum, ν, $cm^{-1}$: 3490, 3293, 3130, 1690, 1653, 1564, 1345, 1210, 850 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-d6) spectrum, δ, ppm(*J*, Hz): 3.08 (1H, dd, *J*= 17.4, 5.4), 3.78 (1H, dd, *J*=17.4, 12.0),




**Scheme 1.**Synthesis of 3,5-diaryl-2-pyrazoline-1-carboxamides

3.85 (3H, s), 5.42 (1H, dd, 12.0, 5.3), 6.53 (2H, s), 7.16-7.80 (9H, m).

**3,5-diphenyl-2-pyrazoline-1-carbthioamide (3i):** IR spectrum, ν, $cm^{-1}$: 3416, 3266, 3142, 2925, 1584, 1565, 1456, 1352, 1072, 830, 780, 666 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-d6) spectrum, δ, ppm(*J*, Hz): 3.18 (1H, dd, 17.9, 5.5), 3.92 (1H, dd, 17.9, 12.9), 5.62 (1H, dd, 5.5, 12.9), 6.53 (2H, s), 7.24-7.90 (10H, m).

## Results and discussion

First, 1,3-diaryl-2-propen-1-ones (chalcones) have been synthesized through the cross-aldol condensation of arylaldehydes and acetophenones according to a modified reported method[18] (Scheme 1).

In an initial attempt, 1,3-diphenyl-2-propen-1-one **1** and semicarbazide hydrochloride**2** were chosen for the model reaction in the presence of various conditions. After preliminary screening,potassium carbonate ($K_2CO_3$) was selected as the best choice based on its higher efficiency, stability, and lower cost. In recent years, potassium carbonate has been considered as an efficient, inexpensive, and readily available catalyst for several organic transformations. [17,19-21]

To achieve suitable conditions for the above transformation, various solvents such as EtOH, MeCN, and $H_2O$ have been investigated (Table 1). After several attempts, it was found thatthe desired product 3,5-diphenyl-2- pyrazoline-1-carboxamide **3a** was isolated in 50 min with94% yield at reflux conditions in ethanol in the presence of 0.1 g of potassium carbonate as a catalystand a molar ratio of chalcone/ semicarbazide of1:1.4 (Table 1, entry 5). A very low yield of the product was only obtained in the absence of the catalyst, indicating that the catalyst was necessary to the reaction.

**Table 1.** Optimizing the reaction conditions for the synthesis of **3a**

| Entry | Catalyst ($K_2CO_3$)(g) | Conditions* | Time(min) | Yield (%) |
|---|---|---|---|---|
| 1 | - | Ethanol, r.t. | 300 | 0 |
| 2 | - | Ethanol, reflux | 300 | trace |
| 3 | 0.05 | Ethanol, r.t. | 180 | 50 |
| 4 | 0.05 | Ethanol, reflux | 90 | 70 |
| 5 | 0.1 | Ethanol, reflux | 50 | 94 |
| 6 | 0.1 | $H_2O$, reflux | 180 | 50 |
| 7 | 0.1 | MeCN, reflux | 180 | 70 |

* 1,3-diphenyl-2-propen-1-one (1 mmol) and semicarbazide hydrochloride (1.4 mmol)

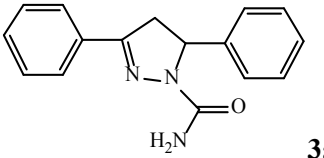
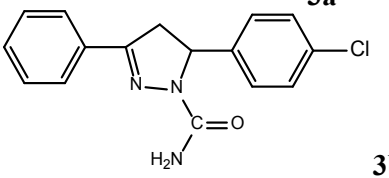
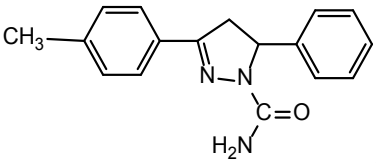
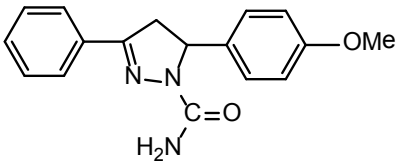
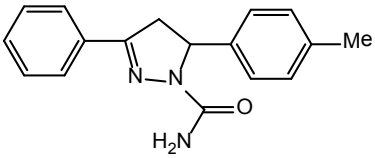
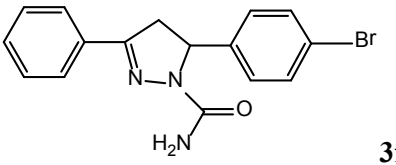
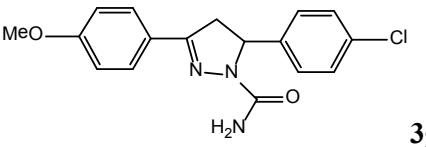
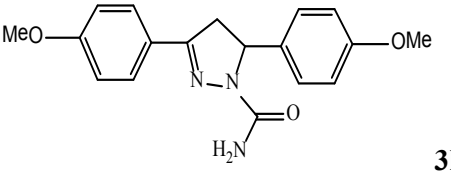
With this optimized procedure in hand, the scope of this reactionwas examined by using other1,3-diaryl-2-propen-1-ones and semicarbazide in the presence of 0.1g of potassium carbonate to afford the corresponding3,5-diaryl-2-pyrazoline-1-carboxamides. The results are summarized in Table2.

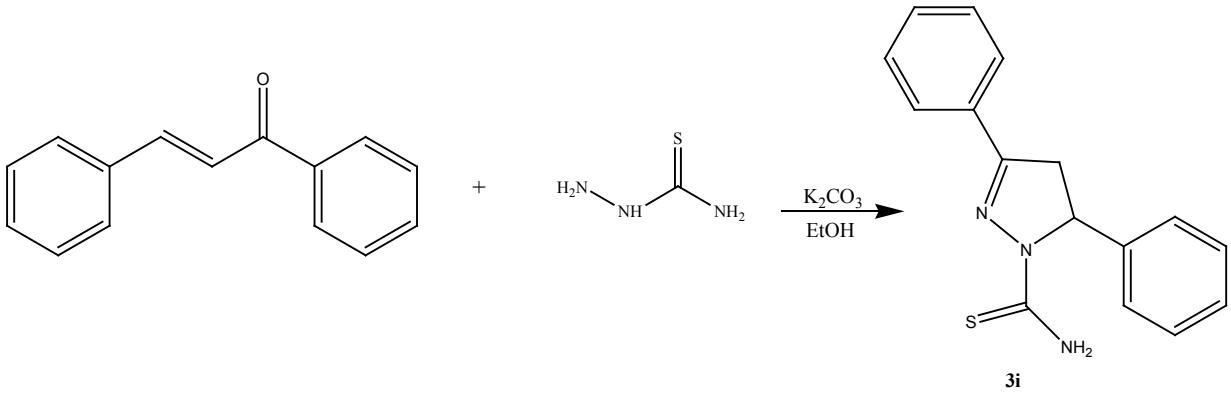
The data of Table 2 show that generally both electron-rich and electron-deficient substituents afforded their corresponding products in high to excellent yields. The products are known and their structures were characterized by comparing physical and spectral data with those of authentic samples.[2-5]

It is worthwhile to point out that all the products were purified by a simple process of crystallization and filtration; no chromatography was involved.

In addition, under the same condition, the reaction of 1,3-diphenyl-2-propen-1-one with thiosemicarbazide using potassium carbonate has been carried out. The desired product 3,5-diphenyl-2-pyrazoline-1-carbothioamide

**Table 2.** Synthesis of 3,5-diaryl-2-pyrazoline-1-carboxamidesusing $K_2CO_3$ in ethanol under reflux conditions

| Entry | $Ar^1$ | $Ar^2$ | product | Time, min | Yield, % | m.p.,C[2-5] |
|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | $C_6H_5$ |  **3a** | 50 | 94 | 194-196 |
| 2 | 4-$ClC_6H_4$ | $C_6H_5$ |  **3b** | 30 | 96 | 216-218 |
| 3 | $C_6H_5$ | 4-$CH_3C_6H_4$ |  **3c** | 60 | 88 | 183-184 |
| 4 | 4-$CH_3OC_6H_4$ | $C_6H_5$ |  **3d** | 45 | 55 | 188-190 |
| 5 | 4-$CH_3C_6H_4$ | $C_6H_5$ |  **3e** | 30 | 85 | 180-183 |
| 6 | 4-$BrC_6H_4$ | $C_6H_5$ |  **3f** | 40 | 50 | 175-178 |
| 7 | 4-$ClC_6H_4$ | 4-$CH_3OC_6H_4$ |  **3g** | 50 | 88 | 210-211 |
| 8 | 4-$CH_3OC_6H_4$ | 4-$CH_3OC_6H_4$ |  **3h** | 30 | 75 | 186-188 |




**3i**

**Scheme 2**. The reaction of 1,3-diphenyl-2-propen-1-one with thiosemicarbazide

has been obtained at 50 min with 90% yield in ethanol under reflux conditions (Scheme 2)

## Conclusions

In conclusion, we have successfully developed an efficient protocol to the synthesis 3,5-diaryl-2-pyrazoline-1-carboxamides through the cyclocondensation reaction of 1,3-diaryl-2-propen-1-ones with semicarbazide in the presence of potassium carbonate in ethanol under reflux conditions. The catalyst is readily available and inexpensive and can conveniently be handled and removed from the reaction mixture. We believe that this procedure is convenient, economic, and a user-friendly process for the synthesis of 3,5-diaryl-2-pyrazoline-1-carboxamide derivatives of biological and medicinal importance.

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