Mechanically activated synthesis of 1,3,5-triaryl-2-pyrazolines by high speed ball milling[†]

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An efficient mechanically activated solvent-free synthesis of 1,3,5-triaryl-2-pyrazolines from chalcones and phenylhydrazines using high speed ball milling is described. This method has notable advantages in terms of good yield, short reaction time and neat conditions.

Pyrazoline derivatives have been found to possess a broad spectrum of biological activities¹ including antibacterial, antifungal, anti-inflammatory, antiamoebic, and antidepressant activity. Among various pyrazoline derivatives, 1,3,5-triaryl-2-pyrazolines seem to be the most frequently studied pyrazoline type compounds. A variety of methods have been reported for the preparation of this class of compounds. One of the most commonly used methods is the cyclization of chalcones with phenylhydrazines or phenylhydrazine hydrochlorides. Many of these procedures use AcOH,² HCl,³ Et₃N,⁴ C₅H₅N,⁵ Ba(OH)₂⁶ or NaOH⁷ as the reagent or catalyst, most of these require high temperature or long times to complete the reaction. Other methods, including using ultrasound irradiation and microwave-assisted synthesis, have been reported with various yields.⁸

In recent years solvent-free chemical synthesis has developed into a powerful methodology as it reduces the toxic waste produced and therefore becomes less harmful to the environment. Mechanically activated solvent-free reactions are reactions conducted by grinding or ball milling without solvent. High speed ball milling (HSBM) is an attractive mechanically activated method that has started to gain attention. It has often been used for milling minerals into fine particles and for the preparation and modification of inorganic solids.9 In the field of synthetic organic chemistry, it has also found many applications,10 such as Heck-type cross-couplings,11 asymmetric Aldol reactions,12 Baylis-Hillman reactions,13 reduction of esters,¹⁴ synthesis of fluoroaromatic compounds,¹⁵ protection of diamines, anthranilic acid, diols and polyols,16 and so on. However, the application of HSBM on the cyclization of chalcones with phenylhydrazines has not been reported. It is known that NaHSO₄ is an efficient reagent which can be used for different functional group transformations under heterogeneous conditions.¹⁷ The stability and cheapness, low toxicity, heterogeneous nature of the reactions, high yields of the products and short reaction times are the notable advantages which have attracted more attention of organic chemists. Herein, we wish to report an efficient method for the synthesis of 1,3,5-triaryl-2-pyrazolines in the presence of NaHSO₄·H₂O by HSBM.

Initial research was focused on the synthesis of 1,3,5triphenyl-2-pyrazoline from chalcone and phenylhydrazine. The HSBM experiments were conducted in a AGO-2 planetarycentrifugal mill (acceleration: 60 g; volume of one drum: 35 mL; diameter of stainless steel ball: 5 mm; weight of balls: 75 g). To prevent "overheating" of the reaction mixture, a milling cycle with a rotational speed of 1290 rpm for 5 min followed by a 5 min pause was specified. This cycle can be repeated until the reaction is completed. Different feed ratios of the reaction were tested to find the optimized conditions. As shown in Table 1, chalcone/phenylhydrazine/NaHSO₄· $H_2O = 1:2:0.2$ was determined to be the more suitable system to obtain the desired products with good yield (Table 1, Entry 2). When the amount of phenylhydrazine increased to three times that of chalcone, the yields did not improve significantly (Table 1, Entry 3). Higher yields could be obtained by employing more $NaHSO_4 \cdot H_2O$ (Table 1, Entries 4, 5), but more catalyst could not increase the yield obviously. While using the lower amounts of catalyst, longer reaction times were usually used, and only the relatively lower yields were obtained (Table 1, Entry 6). In addition, when silica gel or the catalyst was absent in this reaction, the yield declined sharply (Table 1, Entries 7, 8). It was supposed that the silica gel might act as the grinding-aid agent or absorbent in this reaction.

Table 1 Effect of reaction condition on synthesis of 1,3,5-triphenyl-2-
pyrazoline"

| Ph | $P_{h} + P_{h} NH_{2}$ | $\frac{\text{NaHS O4} \cdot \text{H}_2\text{O}}{\text{HSB M}} \xrightarrow{\text{Ph}}_{\text{Ph}}$ | Ph N | |
|-------|-------------------------------------|--|------------------------|--|
| Entry | Chalcone/phenylhydraz NaHSO₄·H₂O | zine/ Time (min) | Yield (%) ^b | |
| 1 | 1:1:0.2 | 5 | 76 | |
| 2 | 1:2:0.2 | 5 | 93 | |
| 3 | 1:3:0.2 | 5 | 94 | |
| 4 | 1:2:0.3 | 5 | 95 | |
| 5 | 1:2:0.5 | 5 | 96 | |
| 6 | 1:2:0.05 | 15 | 67 | |
| 7 | 1:2:0 | 15 | 10 | |
| 8 | $1:2:0.2^{c}$ | 15 | 40 | |

^{*a*} For a typical experimental procedure, see ref. 18. ^{*b*} Based on chalcone. ^{*c*} Not using silica gel.

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| Entry | Phenylhydrazine (new + recovered) (g) | Time (min) | Recovered phenylhydrazine (g)/ recovered yield (%) | Yield (%) ^b |
|-------|--|------------|---|------------------------|
| 1 | 2.2 + 0 | 5 | 1.05/95.5 | 95 |
| 2 | 1.15 + 1.05 | 5 | 1.00/91.1 | 93 |
| 3 | 1.2 + 1.00 | 5 | 0.94/85.5 | 91 |

 Table 2
 The recovery and reuse of the phenylhydrazine^a

Table 3 Synthesis of 1,3,5-triaryl-2-pyrazolines catalyzed by NaHSO₄·H₂O under HSBM conditions^a

| | $Ar_{2} \xrightarrow{Ar_{1}} + Ar_{3} \xrightarrow{NH_{2}} \frac{NaHS O4 \cdot H_{2}O}{HSBM} \xrightarrow{Ar_{1}} \xrightarrow{N} \xrightarrow{N} Ar_{2}$ | | | | | | | |
|-------|---|--|-----------------------------------|---------|------------|------------------------|--|--|
| | | 1 | 2 | 3 | | | | |
| Entry | Ar_1 | Ar_2 | Ar ₃ | Product | Time (min) | Yield (%) ^b | | |
| 1 | C ₆ H ₅ | C_6H_5 | C ₆ H ₅ | 3a | 5 | 87 ^c | | |
| 2 | C ₆ H ₅ | C ₆ H ₅ | 4-ClC ₆ H ₄ | 3b | 5 | 91 | | |
| 3 | $4-ClC_6H_4$ | C ₆ H ₅ | C ₆ H ₅ | 3c | 5 | 92 | | |
| 4 | $4-ClC_6H_4$ | C ₆ H ₅ | 4-ClC ₆ H ₄ | 3d | 5 | 90 | | |
| 5 | C ₆ H ₅ | $4-ClC_6H_4$ | C ₆ H ₅ | 3e | 5 | 90 | | |
| 6 | C ₆ H ₅ | $4-ClC_6H_4$ | 4-ClC ₆ H ₄ | 3f | 15 | 89 | | |
| 7 | 4-ClC ₆ H ₄ | 4-ClC ₆ H ₄ | C ₆ H ₅ | 3g | 5 | 92 | | |
| 8 | 4-ClC ₆ H ₄ | 4-ClC ₆ H ₄ | 4-ClC ₆ H ₄ | 3h | 5 | 91 | | |
| 9 | 4-CH ₃ OC ₆ H ₄ | 4-ClC ₆ H ₄ | C ₆ H ₅ | 3i | 5 | 90 | | |
| 10 | C ₄ H ₅ | 4-CH ₂ OC ₄ H ₄ | C ₄ H ₅ | 3i | 5 | 92 | | |
| 11 | 4-CH ₂ OC ₄ H ₄ | 4-CH ₂ OC ₆ H ₄ | C ₄ H ₅ | 3k | 5 | 93 | | |
| 12 | $3-O_2NC_6H_4$ | C ₆ H ₅ | C ₆ H ₅ | 31 | 15 | 85 | | |
| 13 | C_6H_5 | $4-O_2NC_6H_4$ | C_6H_5 | 3m | 15 | 82 | | |

^a Substrate 1 (10 mmol), substrate 2 (20 mmol) and NaHSO₄·H₂O (2 mmol) in silica gel (10 g) was used. ^b Based on chalcone. ^c Yield after four cycles.

Meanwhile, the recovery and reuse of the phenylhydrazine was investigated. Chalcone (2.1 g, 10 mmol), phenylhydrazine (2.2 g, 20 mmol), NaHSO₄·H₂O (0.28 g, 2 mmol) and silica gel (10 g, 200–300 mesh) were reacted under similar conditions. After completion, the product of 1,3,5-triaryl-2-pyrazoline was firstly obtained by column chromatography (petroleum ether:EtOAc = 5:1), then the phenylhydrazine was attained (petroleum ether:EtOAc = 3:1). The recovered phenylhydrazine together with the new phenylhydrazine was used in the next reaction. The results are summarized in Table 2. It was found that the excess phenylhydrazine can be recovered and reused without obvious effect on the yield.

On the basis of the above results, to extend the scope and generality of this method, several structurally diverse chalcones and phenylhydrazines were cyclized to give 1,3,5-triaryl-2-pyrazolines by HSBM. The results are listed in Table 3. It could be seen that the reactions proceeded well with all the substrates, but substrates with electron-donating groups were generally more reactive than those with electron-withdrawing groups.

In a typical experiment, after the reaction was completed, NaHSO₄·H₂O with silica gel was collected and dried to be regenerated. The reusability of the catalyst was examined and resulted in 92, 92, 90 and 87% yield over four recycles (Table 3, Entries 1).

Next, we attempted to prepare other types of 2-pyrazolines under the above optimum conditions. When α , β -unsaturated ketone (10 mmol), phenylhydrazine or thiosemicarbazide (20 mmol), NaHSO₄·H₂O (2 mmol) and silica gel (10 g) were used, the corresponding 2-pyrazolines (**3n**, **3o**, **3p**) were obtained in 80%, 76% and 62% yield, respectively (Scheme 1). However, when chalcone was examined with acyl hydrazides such as benzoylhydrazide and acethydrazide, we only got the corresponding hydrazones but not the target products, although the reaction time was extended to 25 min. This may be attributed



Scheme 1

to the strong electron-donating effect of acyl groups in acyl hydrazides. Preparation of 1-acyl-2-pyrazolines using other catalysts by HSBM is now under investigation.

In conclusion, we have developed an efficient and comparatively green strategy for the synthesis of 1,3,5-triaryl-2pyrazoline by HSBM. Good yield, short reaction times and neat conditions are the notable advantages of this method. Besides, catalyst recovery and reusability is another feature of this procedure. We believe that this method has provided a better scope of the synthesis of 1,3,5-triaryl-2-pyrazolines and will be a more practical alternative to the existing methods for other organic reactions.

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- 18 Typical procedure: the following components were added to the reaction vessels: chalcone (2.1 g, 10 mmol), phenylhydrazine (2.2 g, 20 mmol), NaHSO₄·H₂O (0.28 g, 2 mmol), silica gel (10 g, 200–300 mesh). Then, stainless steel balls were added and the vessel was closed with lid and gasket. The ball mill was then run at a milling cycle with a rotational speed of 1290 rpm for 5 min followed by a 5 min pause. During the pause, a mixture example was taken out and dissolved in dichloromethane to monitor the progress of the reaction using TLC. This cycle was repeated until the reaction was completed. All the reaction mixture was washed off the vessel using EtOAc (20 ml) and then was filtered. The filtrate was dried (MgSO₄) and evaporated. The crude product was purified by column chromatography to provide 1,3,5-triphenyl-2-pyrazoline.