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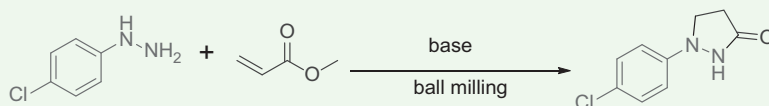
A solvent-free synthesis of 1-(4-chlorophenyl)pyrazolidin-3-one in a ball mill

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ABSTRACT

An easy, solvent-free method for the synthesis of 1-(4-chlorophenyl)pyrazolidin-3-one has been achieved by grinding 4-chlorophenyl hydrazine and methyl acrylate in the presence of base in a ball mill. A systematic investigation of the reaction has been made in order to study the various factors affecting the reaction.



Formation of 1-(4-chlorophenyl)pyrazolidin-3-one in ball mill

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1. Introduction

Ball milling is a mechanochemical technique which is primarily used in the grinding of minerals and the preparation and modification of inorganic solids (1,2). Nowadays, its use in synthetic organic chemistry is a strong emerging field of research, some recent examples of ball milling in organic synthesis include catalyzed C–C bond forming reactions (3,4) (metal-catalyzed C–C, C–N and C–F bond formation (5–12), organocatalyzed C–C bond formation (13–21), cycloaddition reaction (22)), synthesis of heterocycles (23), protecting group chemistry (24), redox processes (25–27), reactions with fullerenes (28) and bromination reactions (29). Often the described reactions take advantage of the fact that different and usually increased selectivities and reactivities have been found when working in a ball mill compared with conventional solution-phase reactions. Therefore, during the further exploration of the applications of ball mill in synthesis (11,21), we wondered whether it would be possible to develop an organic reaction in the ball mill for the formation of 1-(4-chlorophenyl)pyrazolidin-3-one, which is an important intermediate for the synthesis of strobilurin fungicide pyraclostrobin (Figure 1).

Compared with conventional solution-phase reaction (30) (Scheme 1), which requires strict condition to keep the reaction system absolutely anhydrous and to use a


relatively strong base, our attempts in the ball mill are under mild conditions using relatively weak base instead of sodium methylate, and the solvent-free method decreasing the amount of harmful organic reagents proved to be more environmental friendly (Scheme 2).

2. Results and discussion

To study the influence of the base in the ball mill, some commonly used bases were used (Table 1). A milling cycle consisting of a 5 min milling period at a rotational speed of 600 rpm, followed by a 4 min pause to avoid overheating, was used. What surprised us was that the common inorganic base potassium hydroxide and sodium hydroxide functioned well in this solvent-free process to give moderate yields (entries 1–2). However, the reaction exhibited the worse performance when the stronger base like sodium methylate and sodium ethylate was used (entries 3–4). Further, the organic base DABCO and triethylamine could not initiate the reaction well in these conditions (entries 5–6). On the other hand, the same reaction almost could not proceed in conventional solution-phase using potassium hydroxide as the base (entry 7). Therefore, potassium hydroxide was chosen as the base for the following optimization.

Once the base chosen, we turned to explore the effect of the base amount on the reaction (Table 2), and an

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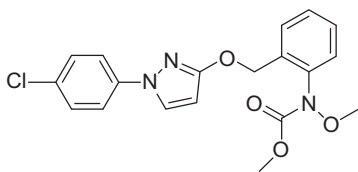


Figure 1. Strobilurin fungicide Pyraclostrobin.

increase of the reaction yield was observed if the base amount was changed from 1:1 to 2.5:1 (entries 1–4). The excessive base reducing the sufficient contact of the reactants may cause the yield erosion (entry 5).

Subsequently, the ratio of methyl acrylate (**2**) and 4-chlorophenyl-hydrazine (**1**) (Table 3) was optimized, the results clearly show an increase of yields from 44% to 63% by raising the ratio from 1:1 to 1.8:1, then it became constant if the ratio was further increased.

Having optimized the common reaction parameters, we proceeded now to investigating the influence of the ball milling conditions (Table 4), including the ball types, the frequency of milling and the milling time. Initially, $\Phi 10$ mm agate balls were chosen to evaluate the frequency and the milling time effects. The yield increased by raising frequency within the restriction speed of the apparatus (entries 1, 3 vs. 2, 4), and it tended to be constant if we continued to prolong the milling time (entries 3, 4). Next, some different types of balls were examined (Table 4, entries 5–9), the results reveal that different types of balls, including the ball materials, diameters and ball numbers, may significantly influence the final yield. Generally, the $\Phi 10$ mm balls were proved better than others (entries 5, 7 vs. 6, 8); agate ball as well as stainless steel ball gave better yields than zirconium oxide ball (entries 4, 7 vs. 5).

As the grinding bowl volume is fixed in the ball mill vessel, too much or little raw material may affect the

Table 1. Screening of bases for the formation of 1-(4-chlorophenyl)pyrazolidin-3-one^a.

Entry	Base	Yield (%) ^b
1	KOH	49
2	NaOH	40
3	MeONa	8
4	EtONa	7
5	DABCO	8
6	Et ₃ N	11
7	KOH ^c	trace

^aReactions were carried out with **1** (0.4 g, 2.8 mmol), **2** (0.3 g, 3.4 mmol, 1.2 mol equiv.) and the base (5.6 mmol, 2.0 mol equiv.); ball milling method: 600 rpm, 12 cycles \times (5 min. rotation + 4 min. pause), $\Phi 10$ mm agate ball (6 balls).

^bIsolated yield.

^cReaction in ethanol.

Table 2. Influence of potassium hydroxide/4-chlorophenyl hydrazine (**1**) ratio^a.

Entry	KOH/(1)	Yield (%) ^b
1	1:1	32
2	1.5:1	43
3	2:1	49
4	2.5:1	50
5	3:1	46

^aReactions were carried out with **1** (0.4 g, 2.8 mmol), **2** (0.3 g, 3.4 mmol, 1.2 mol equiv.) and potassium hydroxide; ball milling method: 600 rpm, 12 cycles \times (5 min. rotation + 4 min. pause), $\Phi 10$ mm agate ball (6 balls).

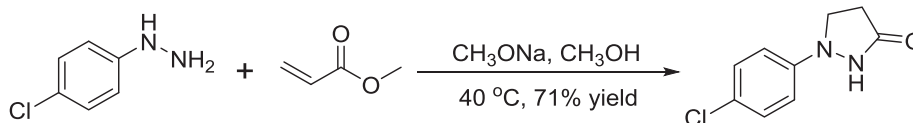
^bIsolated yield.

Table 3. Influence of methyl acrylate (**2**)/4-chlorophenyl hydrazine (**1**) ratio^a.

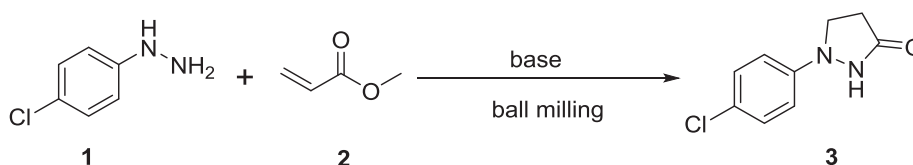
Entry	(2)/(1)	Yield (%) ^b
1	1:1	44
2	1.2:1	49
3	1.4:1	52
4	1.6:1	57
5	1.8:1	63
6	2:1	63

^aReactions were carried out with **1** (0.4 g, 2.8 mmol), **2** and potassium hydroxide (0.4 g, 7.0 mmol, 2.5 mol equiv.); ball milling method: 600 rpm, 12 cycles \times (5 min. rotation + 4 min. pause), $\Phi 10$ mm agate ball (6 balls).

^bIsolated yield.



Scheme 1. Formation of 1-(4-chlorophenyl)pyrazolidin-3-one in conventional solution-phase.



Scheme 2. Formation of 1-(4-chlorophenyl)pyrazolidin-3-one in ball mill.

Table 4. Optimization of the milling conditions for the formation of 1-(4-chlorophenyl)pyrazolidin-3-one^a.

Entry	Ball type	Ball number	Frequency (r/min)	Cycles ^b	Yield (%) ^c
1	Φ10 mm agate	6	400	8	45
2	Φ10 mm agate	6	400	12	50
3	Φ10 mm agate	6	600	8	64
4	Φ10 mm agate	6	600	12	65
5	Φ10 mm zirconium oxide	6	600	12	45
6	Φ5 mm zirconium oxide	30	600	12	34
7	Φ10 mm stainless steel	6	600	12	65
8	Φ5 mm stainless steel	30	600	12	55
9	Φ3 mm stainless steel	80	600	12	60

^aReactions were carried out with **1** (0.4 g, 2.8 mmol), **2** (0.4 g, 5.0 mmol, 1.8 mol equiv.), and potassium hydroxide (0.4 g, 7.0 mmol, 2.5 mol equiv.).

^b1 cycle = 5 min. rotation + 4 min. Pause.

^cIsolated yield.

milling process, therefore, an investigation to search for the optimized milling capacity was then performed. As shown in Table 5, the highest yield reached 68% when 4-chlorophenyl hydrazine (**1**) amount was 0.2 g (entry 2). Actually, the yield dropped if the reactant amount is increased probably for the inefficient mixing.

In addition, we also investigated the reaction by adding grinding aids such as alumina and silica powder, but no evidence showed a positive influence in this reaction.

Eager to improve the yield of this reaction, we continued to explore other efficient bases. In recent years, the crown ether complex cation ionic liquids (CECILs) have been applied in various reactions, such as Michael addition, Henry reaction, Knoevenagel condensation and Heck reaction, with excellent results (31). Moreover, the complexes of ionic liquids with poly(ethylene glycol)s (PEG-ILs) were also reported (32). According to these pioneering works, a series of novel poly(ethylene glycol) complex cation ionic liquids (PEG-CILs) were synthesized and applied in this reaction (Table 6). To our delight, better results were obtained by [15-Crown-5Na⁺][OH⁻], [18-Crown-6K⁺][OH⁻] and [PEG400 K⁺][OH⁻] (entries 1, 2, 4), and the yield could be maintained even reducing the

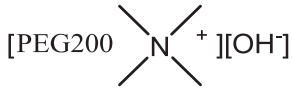
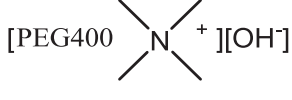
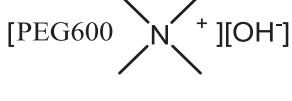

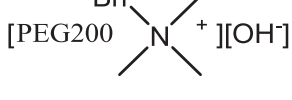
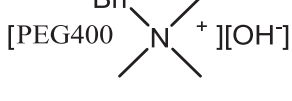
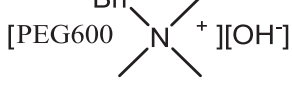
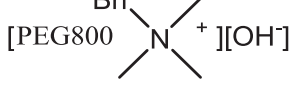
Table 5. Influence of the reactant amount^a.

Entry	Amount of (1) (g)	Yield (%) ^b
1	0.15	62
2	0.2	68
3	0.4	65
4	0.6	57
5	0.8	52

^aReactions were carried out with **1**, **2** (1.8 mol equiv.) and potassium hydroxide (2.5 mol equiv.); ball milling method: 600 rpm, 12 cycles × (5 min. rotation + 4 min. pause), Φ10 mm stainless steel ball (6 balls).

^bIsolated yield.

Table 6. Influence of different types of PEG-CILs^a.

Entry	Base	Yield (%) ^b
1	[15-Crown-5Na ⁺][OH ⁻]	70
2	[18-Crown-6K ⁺][OH ⁻]	73
3	[PEG200 K ⁺][OH ⁻]	50
4	[PEG400 K ⁺][OH ⁻]	71
5	[PEG600 K ⁺][OH ⁻]	51
6	[PEG200  ⁺][OH ⁻]	38
7	[PEG400  ⁺][OH ⁻]	62
8	[PEG600  ⁺][OH ⁻]	58
9	 ⁺][OH ⁻]	31
10	[PEG200  ⁺][OH ⁻]	60
11	[PEG400  ⁺][OH ⁻]	78(57 ^c)
12	[PEG600  ⁺][OH ⁻]	61
13	[PEG800  ⁺][OH ⁻]	55

^aReactions were carried out with **1** (0.2 g, 1.4 mmol), **2** (0.2 g, 2.5 mmol, 1.8 mol equiv.) and base (1.4 mmol, 1.0 mol equiv.); ball milling method: 600 rpm, 12 cycles × (5 min. rotation + 4 min. pause), Φ10 mm stainless steel ball (6 balls).

^bIsolated yield.

^cBase: 0.5 mol equiv.

base from 2.5 to 1.0 mol equiv. However, the reaction gave relatively low yield when [PEG200 K⁺][OH⁻] or [PEG600 K⁺][OH⁻] was used (entries 3, 5), presumably because the chain length of PEG400 (most close to 18-crown-6) was more suitable to wrap around potassium cations. Tetrabutylammonium and benzyl trimethylammonium hydroxide were chosen to investigate whether PEG-CILs could further enhance the efficiency of the reaction. It was found that all the complexes (entries 6–8, 10–13), particularly PEG400 (entries 7, 11), gave much better yields than the comparative one (entry 9), and the desired product could be obtained in 78% yield when PEG400-benzyl trimethylammonium hydroxide complex

was used, but the yield was decreased when reducing the base loading from 1.0 to 0.5 equiv. (entry 11).

3. Experimental materials

3.1. General methods

Flash chromatography (FC) was carried out using silica gel (200–300 mesh). Monitoring of reactions was performed by TLC on silica gel precoated on glass plates, and spots were visualized with UV light at 254 nm. ^1H and ^{13}C NMR were recorded in CDCl_3 on Bruker AVANCE III (500 MHz for ^1H NMR and 126 MHz for ^{13}C NMR). TMS served as internal standard ($\delta = 0$ ppm) for ^1H NMR and CDCl_3 was used as internal standard ($\delta = 77.0$ ppm) for ^{13}C NMR; ^1H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz) and integration. IR were recorded on an EQUINOX 55. High-resolution electrospray ionization mass spectra (HR-ESI-MS) were recorded on an Agilent 6545 Q-TOF LCMS spectrometer equipped with an ESI source and controlled by using the MassHunter software. All experiments were carried out under air. Reactions in the ball mill were conducted using a Fritsch Planetary Micro Mill model “Pulverisette 7”. The milling instrument accommodates two grinding bowls (45 mL) which are made of stainless steel.

3.2. General procedure for the synthesis of 1-(4-Chlorophenyl)pyrazolidin-3-one

A clean, dry ball milling vessel was charged with 6 Φ 10 mm stainless steel balls, 4-chlorophenyl hydrazine (0.2 g), methyl acrylate (0.22 g, 1.8 mol equiv.) and KOH powder (0.2 g, 2.5 mol equiv.) were ball milled over periods of 12 cycles (1 cycle = 5 min. rotation + 4 min. pause). Afterwards, the vessel and the balls were rigorously washed with 30 ml water; adjust to a pH of 7 using 5% HCl. The aqueous phase was extracted three times with ethyl acetate, and the combined organic phase were dried over Na_2SO_4 , filtered off, and was concentrated to dryness under reduced pressure. The residue was purified via silica gel column chromatography. White solid; mp: 108.5–110.5 $^\circ\text{C}$; ^1H NMR (500 MHz, Chloroform- d) δ 8.96 (s, 1H, NH), 7.29 (m, part AA' of the AA'BB' system, $J = 9.0$ Hz, 3.0 Hz, 2H, H-2 and H-6, ClPh), 6.99 (m, part BB' of the AA'BB' system, $J = 9.0$ Hz, 3.0 Hz, 2H, H-3 and H-5, ClPh), 3.93 (t, $J = 8.0$ Hz, 2H, NCH_2), 2.60 (t, $J = 8.0$ Hz, 2H, COCH_2). ^{13}C NMR (126 MHz, Chloroform- d) δ 175.38, 149.93, 129.22, 127.77, 117.59, 55.34, 29.85. IR (film) 1685, 1594, 1497, 1465, 1276 cm^{-1} . HRMS (ESI) exact mass calculated for $\text{C}_9\text{H}_8\text{ClN}_2\text{O}$ ($[\text{M}-\text{H}]^-$) requires m/z 195.0331. Found m/z 195.0327.

3.3. Preparation of the PEG-CILs complexes

Potassium hydroxide or quaternary ammonium hydroxide (10 mmol), PEG (10 mmol) were added to methanol (30 mL), and the mixture stirred at room temperature overnight. The organic phase was concentrated to dryness under reduced pressure to give the PEG-CIL complexes.

4. Conclusions

In summary, a novel and convenient method for the synthesis of 1-(4-chlorophenyl)pyrazolidin-3-one in a ball mill has been developed. A series of poly(ethylene glycol) complex cation ionic liquids (PEG-CILs) were applied to afford the product with good yield. Simplicity of the reaction, solvent-free condition, fast reaction time and its potential application, led us to conclude that the ball mill procedure is a significantly improved version of the described reaction.

Disclosure statement

No potential conflict of interest was reported by the authors.

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