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**LIQUID-ASSISTED MECHANOSYNTHESIS OF
trans-2,3-DIHYDROPYRROLES FROM CHALCONES AND
ENAMINONES**

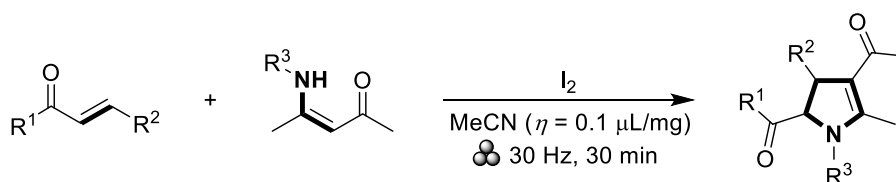
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Abstract – An efficient synthesis of a variety of *trans*-2,3-dihydropyrroles *via* iodine-promoted cyclization between chalcones and enaminones has been demonstrated under liquid-assisted grinding conditions. The present protocol provides a practical, fast and green alternative to traditional solvent-based methods due to its notable advantages such as significantly higher yield, much shorter reaction time, good functional group tolerance and mild reaction conditions.

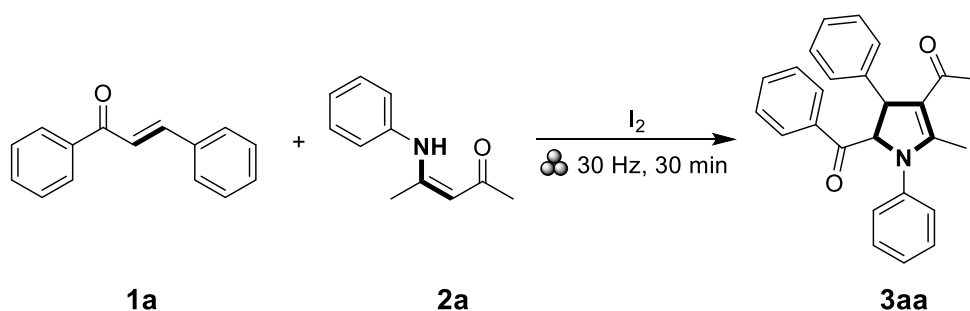
Polysubstituted 2,3-dihydropyrroles are prevalent frameworks in numerous bioactive natural products and pharmaceuticals, such as bohemamine,¹ NP25302,² sibiromycin,³ anthramycin,⁴ thienamycin,⁵ and so on. Furthermore, they are versatile synthetic intermediates in the construction of functionalized pyrroles⁶ and pyrrolidines.⁷ Due to their great importance in pharmaceutical and organic chemistry, the development of novel approaches for the efficient synthesis of 2,3-dihydropyrroles has thus become a fascinating objective. Cycloaddition reactions catalyzed by transition metal catalysts including Pd,⁸ Rh,⁹ Cu,¹⁰ Au¹¹ and Ni¹² are the generally used methods. Besides, some novel reactions are also reported.¹³ Although most of these methods are very powerful, they often involve complicated starting materials, expensive metal catalysts, limited substrate scope, harsh reaction conditions, etc. Recently, Gao and co-workers revealed a novel and effective iodine-promoted cyclization reaction of chalcones and enamines, and synthesized a variety of *trans*-2,3-dihydropyrrole derivatives.¹⁴ However, this reaction had the disadvantage of very poor compatibility with enaminones, long reaction time (8 h) and relatively high temperature (80 °C). To overcome this problem for more efficient construction of diverse 2,3-dihydropyrroles, an attractive alternative is to perform the reaction under ball-milling conditions.

Over the past few years, the ball-milling technique has acted as an attractive and outstanding tool to facilitate chemical reactions under solvent-free or solvent-less conditions.¹⁵ In many cases, reactions under ball-milling conditions lead to higher yields within shorter time, and even provide unexpected products compared to the analogous solution-based reactions.¹⁶ Thus, the ball-milling technique has been widely utilized in organic synthesis.¹⁷ In light of our continued interest in mechanochemical organic synthesis,¹⁸ and the aforementioned importance and synthetic limitations of 2,3-dihydropyrroles, herein we reported an efficient synthesis of polysubstituted 2,3-dihydropyrroles *via* iodine-promoted cyclization of chalcones and enaminones under liquid-assisted grinding (LAG) conditions (Scheme 1). To the best of our knowledge, this is the first attempted mechanosynthesis of 2,3-dihydropyrroles from chalcones and enaminones.



Scheme 1. Mechanochemical synthesis of 2,3-dihydropyrroles from chalcones and enaminones

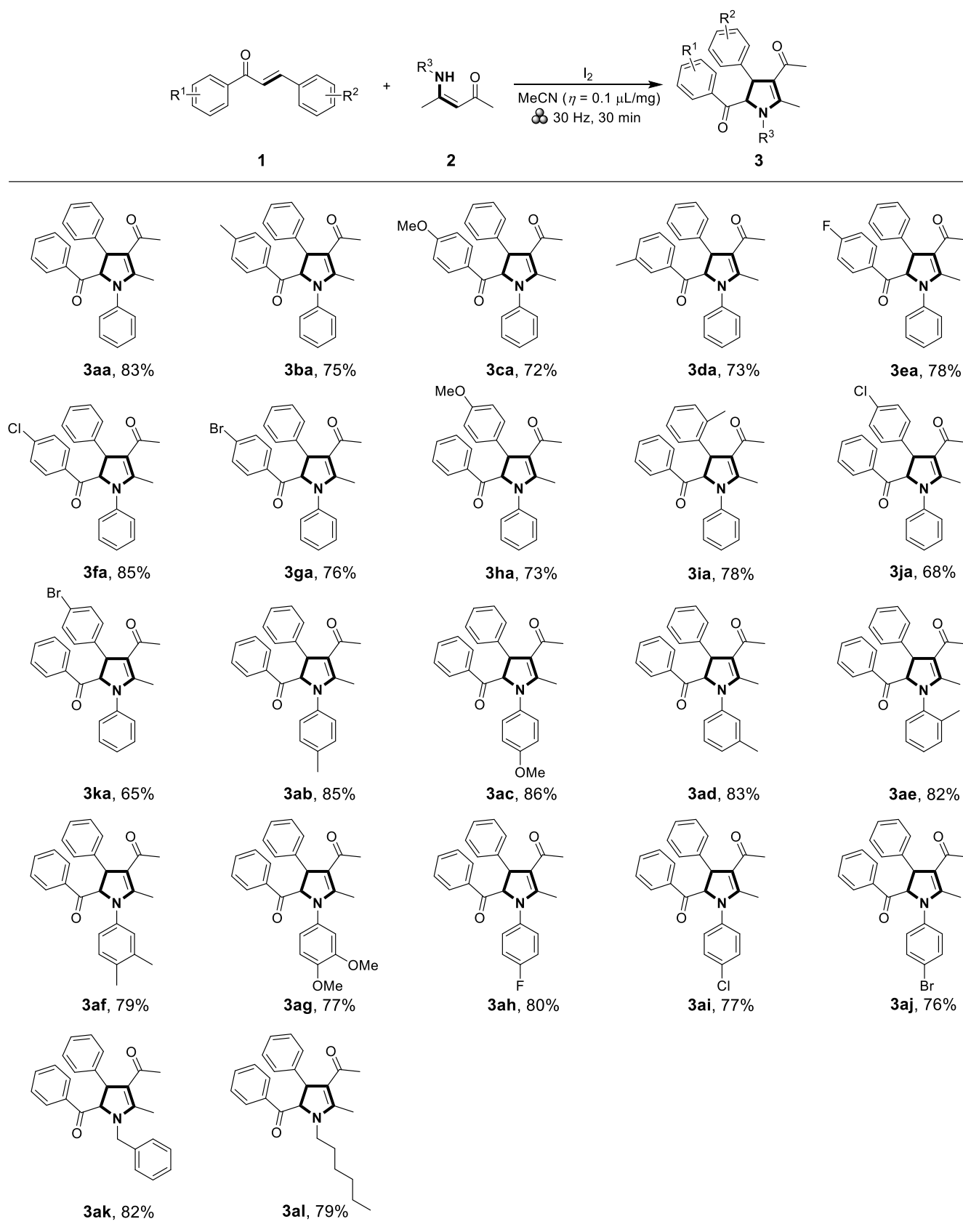
Initially, we chose chalcone (**1a**) and 4-(phenylamino)pent-3-en-2-one (**2a**) as the model substrates to screen the optimal reaction conditions. At first, a mixture of **1a** (0.5 mmol), **2a** (0.5 mmol) and I₂ (0.5 mmol) together with a stainless steel ball (7 mm in diameter) was introduced into a stainless steel jar (5 mL). The reaction vessel and another identical empty vessel were closed and fixed on the vibration arms of a ball milling apparatus (Retsch MM400 mixer mill, Retsch GmbH, Haan, Germany) and were vibrated vigorously at a rate of 1800 rounds per minute (30 Hz) at room temperature for 30 min. After general workup, the desired product, *i.e.*, 1-(5-benzoyl-2-methyl-1,4-diphenyl-4,5-dihydro-1*H*-pyrrol-3-yl)ethanone **3aa**, was isolated in a poor 26% yield (Table 1, entry 1). It can be found that the dihydropyrrole **3aa** is in the *trans* form according to the coupling constant ($J = 3.3$ Hz) of the two protons.¹⁹ To enhance the reaction efficiency, the usage amounts of **1a** and I₂ were successively adjusted (Table 1, entries 2-6). The results demonstrated that 1.5 equiv. of **2a** with 2 equiv. of I₂ were optimal to afford the desired product **3aa** in 68% yield (Table 1, entry 5). In the liquid-phase reaction,¹⁴ K₂CO₃ was found as a good base to enhance the product yield. Unfortunately, product **3aa** was obtained in a significantly decreased yield when 1 equiv. of K₂CO₃ was added to this ball-milling reaction (Table 1, entry 7). Considering that the LAG protocol is a power tool to promote mechanochemical reactions,²⁰ thus several liquids were added to the reaction system (Table 1, entries 8-13) to further increase the yield. It was found that the addition of 49 μL of EtOH and tetrahydrofuran (THF) were detrimental to the reaction (Table 1, entries 8 and 9), while MeCN, toluene, 1,2-dichloroethane (DCE) and dimethyl

Table 1. Optimization of the reaction conditions^a


Entry	Molar ratio (1a / 2a /I ₂)	Liquid ^b	Time (min)	Yield (%) ^c
1	1:1:1	–	30	26
2	1:1.5:1	–	30	34
3	1:2:1	–	30	34
4	1:1.5:1.5	–	30	49
5	1:1.5:2	–	30	68
6	1:1.5:2.5	–	30	66
7 ^d	1:1.5:2	–	30	19
8	1:1.5:2	EtOH	30	51
9	1:1.5:2	THF	30	65
10	1:1.5:2	MeCN	30	83
11	1:1.5:2	toluene	30	80
12	1:1.5:2	DCE	30	76
13	1:1.5:2	DMSO	30	75
14	1:1.5:2	MeCN	60	83
15 ^{e,f}	1:1.5:2	–	120	26
16 ^{e,g}	1:1.5:2	–	120	23
17 ^{e,h}	1:1.5:2	–	120	27
18 ^{e,i}	1:1.5:2	–	120	trace

^a The reactions were carried out in a Retsch MM400 mixer mill with 0.5 mmol of **1a**. ^b The amount of liquid was 49 μL ($\eta = 0.1 \mu\text{L}/\text{mg}$). ^c Isolated yields based on **1a**. ^d 1 equiv. of K_2CO_3 was used. ^e The reaction was performed in an organic solvent (3 mL) at 80 °C. ^f MeCN was used as the solvent. ^g DCE was used as the solvent. ^h DMSO was used as the solvent. ⁱ Toluene was used as the solvent.

sulfoxide (DMSO) could facilitate the reaction in different degrees (Table 1, entries 10-13). Among them, MeCN exhibited the highest efficiency to deliver product **3aa** in 83% yield (Table 1, entry 10). Subsequently, the reaction time was also examined. As the reaction time was extended to 60 min, product **3aa** was obtained in the same yield of 83% (Table 1, entry 14).

Table 2. Liquid-assisted mechanochemistry of 2,3-dihydropyrroles **3** from chalcones **1** and enaminones **2**

^a The reactions were performed with **1** (0.5 mmol), **2** (0.75 mmol), I₂ (1.0 mmol) and MeCN (49 μL, η = 0.1 μL/mg) in a Retsch MM400 mixer mill. ^b Isolated yields based on **1**.

In order to compare this mechanochemical reaction with its liquid-phase counterpart, the reaction was also performed in several organic solvents including MeCN, toluene, DCE and DMSO, which as the LAG agents could facilitate the cyclization to some extent. It was found that all the employed solvents gave product **3aa** only in very poor yields (Table 1, entries 15-17) or even in a trace amount (Table 1, entry 18). From these results, it can be seen that the LAG protocol has obvious advantages, including significantly higher yield, shorter reaction time and convenient reaction operation. Therefore, the optimal reaction conditions were determined as follows: **1a** with 1.5 equiv. of **2a** and 2 equiv. of I₂ in the presence of MeCN (49 μ L) under ball-milling conditions for 30 min (Table 1, entry 10). It should be pointed out that a three-component reaction of chalcone with pentane-2,4-dione and aniline was also investigated under the optimal reaction conditions. However, the desired product **3aa** was obtained in a poor yield of 32%, along with significant amounts of unreacted chalcone and byproducts.

With the optimized reaction conditions in hand, the scope and generality of this reaction were then examined. Firstly, a variety of chalcones were investigated under the ball-milling conditions (Table 2). Chalcones with either electron-donating or electron-withdrawing groups on the phenyl ring adjacent to the carbonyl group reacted smoothly to afford products **3ba–ga** in 72–85% yields. Chalcones with diverse groups on the phenyl ring adjacent to the C=C bond were also investigated, and the results demonstrated that chalcones bearing electron-withdrawing groups in R² exhibited a slightly lower efficiency (**3ja** and **3ka**). To further explore the substrate scope, a series of amines were investigated under the standard reaction conditions. Anilines with diverse substituents delivered products **3ab–aj** in good yields of 76–86%. Furthermore, alkylamines such as benzylamine and *n*-hexylamine were also compatible under the ball-milling conditions, affording products **3ak** and **3al** in 82% and 79% yields, respectively.

In summary, we have successfully developed a facile mechanochemical protocol for highly efficient and environmentally friendly synthesis of various 2,3-dihydropyrroles *via* I₂-promoted cyclization of chalcones and enaminones under liquid-assisted grinding conditions. The present mechanochemical protocol has the advantages of significant improved product yield and obvious shortened reaction time. These merits together with the mild reaction conditions and broad substrate scope make the present method a potential and practical alternative to the efficient and green synthesis of polysubstituted 2,3-dihydropyrroles.

EXPERIMENTAL

NMR spectra were recorded on a 400 MHz NMR spectrometer (400 MHz for ¹H NMR; 100 MHz for ¹³C NMR) or 500 MHz NMR spectrometer (500 MHz for ¹H NMR; 125 MHz for ¹³C NMR). ¹H NMR chemical shifts were determined relative to internal TMS at δ 0.0 ppm. ¹³C NMR chemical shifts were

determined relative to CDCl_3 at δ 77.16 ppm. Data for ^1H NMR and ^{13}C NMR are reported as follows: chemical shift (δ , ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet). High-resolution mass spectra (HRMS) were measured with ESI-TOF in a positive mode. Ball-milling reactions were performed in a MM400 mixer mill (Retsch GmbH, Haan, Germany) at room temperature. All solvents were obtained from SCRC (Sinopharm Chemical Reagent Co., Ltd. China) in AR grade and used without further purification.

Starting Materials. Chalcones **1**¹⁴ and enaminones **2**²¹ were prepared according to previously reported procedures. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of Products 3.

1-(trans-2-Methyl-5-(4-methylbenzoyl)-1,4-diphenyl-4,5-dihydro-1H-pyrrol-3-yl)ethanone (3ba). A mixture of chalcone **1b** (111.1 mg, 0.5 mmol), enaminone **2a** (131.4 mg, 0.75 mmol), I_2 (253.8 mg, 1.0 mmol) and MeCN (49 μL , $\eta = 0.1 \mu\text{L}/\text{mg}$) together with a stainless ball (7 mm in diameter) was introduced into a stainless steel jar (5 mL). The reaction vessel along with another identical empty vessel was closed and fixed on the vibration arms of a Retsch MM400 mixer mill, and was vibrated vigorously at a rate of 1800 rounds per minute (30 Hz) at room temperature for 30 min. After completion of the reaction, the resulting mixture was extracted with EtOAc, and the combined solution was evaporated to remove the solvent in vacuo. The residue was separated by flash column chromatography on silica gel with EtOAc/petroleum ether as the eluent to afford 2,3-dihydropyrrole **3ba** (148.4 mg, 75%); a yellow solid; mp 129–131 °C; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.78 (d, $J = 8.2$ Hz, 2H), 7.39 (t, $J = 7.3$ Hz, 2H), 7.35–7.30 (m, 3H), 7.30–7.23 (m, 4H), 7.23–7.14 (m, 3H), 5.35 (d, $J = 3.2$ Hz, 1H), 4.11 (d, $J = 3.2$ Hz, 1H), 2.51 (s, 3H), 2.43 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 193.70, 193.08, 160.23, 145.15, 143.70, 140.13, 131.17, 129.72 (2C), 129.45 (2C), 129.37 (2C), 129.26 (2C), 127.63, 127.45 (2C), 126.56, 126.24 (2C), 114.21, 77.75, 51.74, 29.30, 21.88, 15.35; HRMS (ESI-TOF) m/z calcd for $\text{C}_{27}\text{H}_{26}\text{NO}_2$ [$\text{M} + \text{H}$]⁺ 396.1964, found 396.1966.

Characterization data of other synthesized 2,3-dihydropyrroles and copies of NMR spectra for all products are available in the Supporting Information.

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SUPPORTING INFORMATION

Supplementary (IR, ^1H NMR, ^{13}C NMR, and MS) data associated with this article can be found, in the online version, at URL: <https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27046/102/1>.

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