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Mechanochemical Oxidative Mannich Reaction: Evaluation of Chemical and Mechanical Parameters for Mild and Chemo-Selective Coupling of *N*-Boc Tetrahydroquinolines and Ketones

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Abstract: A mechanochemical oxidative Mannich reaction of *N*-Boc tetrahydroquinolines and ketones has been successfully developed under solvent-free ball-milling conditions. The reaction affords desired coupling products in satisfied yields under mild and tractable oxidative system. Side reactions such as deprotection of Boc group have been prevented by carefully adjustment of the milling parameters, including milling frequency, time, milling ball filling degree, milling ball size and grinding auxiliary. Further examination of scope indicates the reaction system could also be applied to the *N*-Cbz, and *N*-aryl substrates affording the corresponding products in moderate to good yields.

High-speed ball-milling (HSBM) promoted mechanochemical organic synthesis has been attracted considerable attention due to its intriguing feature that such process could be carried out under the solvent-free or solvent-less environment.^[1] Comparing with conventional solvent-based systems, where temperature is the critical parameter for process control, the HSBM systems control become more complicated and require delicate adjustment towards series of parameters including milling frequency (ν), time (t), milling ball size (d_{MB}) and milling ball filling degree (Φ_{MB}), along with solid grinding auxiliary and stock's filling degree (Φ_{ST}).^[2] The combined evaluation of reaction parameters may enhance the reactions proceeding in chemo-selective, energy-saving and atom/substrate efficient manners, resulting in an efficient and environmental friendly synthesis.

Oxidative Mannich reaction, as one of the most powerful method for C-C bond construction, has been widely used in the fields of organic synthesis and medicinal chemistry.^[3] Inspired by the pioneering work of Murahashi^[4] and Li^[5], the oxidative coupling of amines have been mainly focused on *N*-aryl protected tetrahydroquinolines (THIQs),^[3e, 6] in which the *in-situ* generated imine or iminium species could be well stabilized. However, removal of those aromatic protecting groups (PGs) usually requires harsh conditions.^[7] Moreover, the *N*-acyl derived THIQs perform inferior reactivity,^[8] and require the

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participation of stronger oxidants.^[9] Very recently, carboxybenzyl (Cbz) protected THIQs have been coupled with series of pronucleophiles under both solvent and solvent-free heating (SFH) conditions.^[10] Despite the excellent performance of *N*-Cbz protected THIQs, *t*-butyloxycarbonyl (Boc) protected THIQs still work poorly under similar conditions resulting large amount of unexpected mixtures, which assumed to be brought by the harsh reaction conditions. Thus, realizing this type of reaction under mild conditions is still a challenge. As our continuously focusing on functionalization of THIQs^[11] the *N*-Boc THIQs were subjected under HSBM conditions to improve their performance by carefully examination of milling parameters. Thus, herein we would like to unveil our latest efforts on mechanochemical oxidative Mannich reaction of *t*-butyloxycarbonyl protected THIQs and ketones under ball milling conditions.



Scheme 1. Selection of model reaction.

At the beginning, the reaction of N-Boc THIQ (1a, 1 mmol) and acetophenone (2a, 1.2 mmol) as substrates were preliminary evaluated by using DDQ (1 equiv.) as oxidant, milling with four stainless-steel balls ($d_{MB} = 14$ mm) at 30 Hz (Scheme 1). Similar as solvent-based system, a complex of unexpected side products together with desired N-Boc 1-(2-oxo-2-phenylethyl)-tetrahydroguinoline 3aa (21%) were obtained. Also, deprotected THIQ was detected implicating the Boc group had been removed during the milling process, which might further lead to side reactions like oxidative polymerizations. In order to suppress the side reaction, reaction optimizations were started with the reagent system. As shown in Table 1, series of oxidants were tested, where DDQ remain the optimal choice for the reaction (Table 1, entry 1). Changing DDQ to its analogues as TCQ and BQ resulted in obvious erosion of yields (Table 1, entries 2, 3). Halide oxidants including NBS, NCS and lodine didn't give desired product during the grinding process (Table 1, entries 4-6). Persulfates, which was reported as a suitable oxidant for the similar reactions of N-Cbz THIQ, [10] were also tested which only gave low yield, even increasing the amount of Na₂S₂O₈ to 1.5 equiv. (Table 1, entries 7-9). Further testing on the usage of DDQ showed 1.0 equiv. was the optimum, in which adding DDQ in portions did not improve the performance (Table 1, entries 10-12). Considering the potential requirement

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Entry	Oxidant (equiv.)	1a:2a	Yield (%) ^[b]
1	DDQ (1.0)	1:1.2	21
2	TCQ (1.0)	1:1.2	10
3	BQ (1.0)	1:1.2	trace (< 5%)
4	NBS (1.0)	1:1.2	n.d.
5	NCS (1.0)	1:1.2	n.d.
6	l ₂ (1.0)	1:1.2	n.d.
7	Oxone (1.0)	1:1.2	trace (< 5%)
8	Na ₂ S ₂ O ₈ (1.0)	1:1.2	10
9	Na ₂ S ₂ O ₈ (1.5)	1:1.2	11
10	DDQ (1.3)	1:1.2	12
11	DDQ (0.8)	1:1.2	13
12 ^[c]	DDQ (1.0)	1:1.2	20
13	DDQ (1.0)	1:1.5	25
14	DDQ (1.0)	1:2	34
15	DDQ (1.0)	1:2.5	42
16	DDQ (1.0)	1:3	43
17 ^[d]	DDQ (1.0)	1:3	trace (< 5%)
18 ^[e]	DDQ (1.0)	1:5	< 10%

Table 1. Optimization of reagent system of oxidative Mannich reaction.^[a]

[a] Reaction conditions: **1a** (1.0 mmol), **2a**, oxidant and Silica gel (0.45 g) were placed in a 50 mL stainless steel vessel with four stainless-steel ball ($d_{MB} = 14$ mm, $\Phi_{MB} = 0.115$). Ball milling conditions: 35 min at 30 Hz. [b] Isolated yields based on **1a**. [c] DDQ was added in 3 portions. [d] The reaction was proceeded in 4.0 mL CH₃CN at 80 °C for 24 h. [e] The reaction was proceeded without solvent by heating at 80 °C for 24 h.

of excessive usage of pro-nucleophiles in similar reactions,^[3d, 3e, 3e, 6] the usage of **2a** was then increased for further improvement (Table 1, entries 13-16). The results showed that the ratio of 1:2.5 was essential for a better transformation and further increasing of **2a** did not lead to a significant improvement. Comparative experiments indicated that the reaction carried out under solvent-based conditions and/or solvent-free heating conditions merely gave the product in very poor yields (Table 1, entries 17 and 18). Noteworthy, although the reaction may be catalyzed by iron, shifting the stainless-steel vessel and milling balls to the zirconium dioxide ones still gave similar results.

With optimal reagent system combination in hand, we then turned our focus on the evaluation of mechanical process for the reaction, wishing to restrain the process of deprotection during the milling. According to previous study,^[2] the milling frequency (v) usually plays an important role in mechanochemical process,



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Figure 1. Influence of milling time and frequency on the oxidative Mannich reaction: **1a** (1.0 mmol), **2a** (2.5 mmol), **DDQ** (1.0 mmol) and silica gel (0.45 g) were placed in a 50 mL stainless steel vessel with four stainless-steel balls ($d_{MB} = 14 \text{ mm}, \Phi_{MB} = 0.115$).

which regulates the energy input and therefore influences the heat generation during the grinding. Considering the interruption of the grinding process will lead to irreproducible results, the examination of frequency was performed with specified time, and was summarized in Figure 1. Obviously, changing frequency led to dramatically fluctuation of yields, and the best result came up at 20 Hz with 45 minutes' grinding. A stepwise increasing of the yield was found at 15 Hz with prolonging of the time. Similar trends were also observed at 20 Hz, where over long reaction time led to undesired deprotection of the substrate. However, compared with 20Hz, grinding at 25 Hz for 45 minutes resulted in obvious drop of product yield, which probably due to the heat accumulation. Further energy input led to a significant and unpredictable deprotection of both substrate and product, in which the inflection point appeared at 35 minutes.

Afterwards, our investigation was focus on the combined effects of the milling ball filling degree (Φ_{MB}) and the size of the milling balls, which has strong influences not only on the occurrence of the collision and friction event, but also the trajectories of the balls affecting the yield and the amount of heat dissipation.^[2a, 12] The experiments were then carried out at 20 Hz. to test whether further improvement of vield could achieve or not. The grinding balls ranging from 6 mm to 14 mm were tested with different filling degrees. As shown in Figure 2, large ball systems $(\mathbf{d}_{MB} > 10 \text{ mm})$ and small ball system $(\mathbf{d}_{MB} < 10 \text{ mm})$ showed different trends, while larger ball system gave better yields than the smaller ones at the same filling degree when $\Phi_{MB} < 0.15$. A maximum product yield was observed at 20 Hz grinding with four balls of 1.4 cm diameter (Φ_{MB} = 0.115). Besides, two grinding balls also gave the similar result (57.9%) as the reaction grinding at 30 Hz ($\Phi_{MB} = 0.057$).^[13] Further increasing of Φ_{MB} led to sharp decrease of product yield for both large size and small size balls after the inflection point of Φ_{MB} \approx 0.10 and 0.20 respectively, implicating the energy input and heat accumulation was overabundant. This observation was in accord with the results found by Stolle^[14] and Takacs.^[15] On the other hand, the reaction with small ball system required relative higher Φ_{MB} to get a maximum product yield, which may due to the inner friction of ball-ball interaction for energy transfer. Nevertheless, overfull milling balls were also detrimental to the product yield since ball movement would be hindered and therefore the energy input



Figure 2. Influence of the milling ball filling degree with different size of the milling balls on the oxidative Mannich reaction: **1a** (1.0 mmol), **2a** (2.5 mmol), DDQ (1.0 mmol) and silica gel (0.45 g) were placed in a 50 mL stainless steel vessel milling for 45 min at 20 Hz. Isolated yield based on **1a**, average of three times. (rhombuses: d = 14 mm, squares: d = 12 mm, triangles: d = 10 mm, skew crossings: d = 6 mm)

Table 2. Influence of grinding auxiliary on the oxidative Mannich reaction.^[a]

Entry	Grinding auxiliary	Weight (g)	Yield (%) ^[b]
1	Silica gel	0.25	29
2 ^[c]	Silica gel	0.45	58
3	Silica gel	1.50	37
4	quartz sand	1.00	18
5 ^[c]	quartz sand	1.65	25
6	NaCl	0.80	27
7 ^[c]	NaCl	1.30	35
8	γ -Al ₂ O ₃ (neutral)	0.60	13
9 ^[c]	γ -Al ₂ O ₃ (neutral)	1.00	24
10 ^[c]	α -Al ₂ O ₃ (base)	1.00	35
11	_	_	10

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2.5 mmol), DDQ (1.0 equiv.) and grinding auxiliary were placed in a 50 mL stainless steel vessel with four stainless-steel ball (d_{MB} = 14 mm, Φ_{MB} = 0.115). Ball milling conditions: 45 min at 20 Hz. [b] Isolated yields based on **1a**. [c] Bulk volume of the grinding auxiliaries was kept as constant.

was reduced,^[16] while the heat accumulation increased dramatically through inner frictions.

Further optimization of the mechanochemistry system was paid to the solid grinding auxiliaries, which provided microenvironment for the transformation. Different kinds of solid auxiliaries were examined and the results were shown in Table 2.



Table 3. Substrate scope of oxidative Mannich reaction. $^{\left[a,b\right] }$

DDQ (1.0 equiv.)

 $\begin{array}{c} 3ah, PG = Boc, 61\%\\ 3bh, PG = Cbz, 79\%\\ 3ch, PG = Ph, 80\% \end{array}$ [a] Reaction conditions unless specified otherwise: **1** (1.0 mmol), **2** (2.5 mmol), DDQ (1.0 mmol) and Silica gel (0.45 g) were placed in a 50 mL stainless steel vessel with four stainless-steel balls (**d**_{MB} = 14 mm, **Φ**_{MB} = 0.115). Ball milling conditions: 45 min at 20 Hz. [b] Yield based on **1a**. [c] Two stainless-steel balls (**d**_{MB} = 14 mm, **Φ**_{MB} = 0.057) were used. Ball milling conditions: 60 min at 30 Hz. [d] Milling vessels were placed under the atmosphere of N₂ gas when adding the substrates.

Accordingly, 450 mg of silica gel remained the optimal choice for the screening (Table 2, entry 2). Decreasing the amount of silica gel resulted in flake form of the mixture, which could not give sufficient mixing of the reactants (Table 2, entry 1). While, the drop of yield using excessive silica gel (1.5 g) may be explained for the low dispersion concentration of **2a** (Table 2, entry 3). Low loading of quartz sand, NaCl, and γ -Al₂O₃ led to a slurry mixture with low product yields, which could be improved by increasing their usage until the mixture became powdery (Table 2 entries 4-9). Besides, it seemed the reaction favored basic α -Al₂O₃ than γ -Al₂O₃ due to its possible assistance for the enolation of **2a**. Noteworthy, different degrees of THIQ was recovered from all

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the cases tested implicating the acidity of silica gel may not be the main cause for the deprotection of Boc group.

After the mechanochemical parameter optimization, we were pleased to obtain the desired coupling product of satisfied yield without significant deprotection under the optimal condition of 20 Hz in 45 minutes (d_{MB} = 14 mm, Φ_{MB} = 0.115). Encouraged by the result, continuous efforts were applied to extend the utility of this reaction system, especially the substrates with different protecting groups (Table 3). Firstly, the oxidative Mannich reaction of different aryl ketones 2a-e was examined. To our delight, N-Cbz, N-Ph and N-PMP protected THIQs also proceeded smoothly under this standard condition giving good to high yields, in which N-Cbz protected substrate performed better than N-aryl ones. Further expansion of aryl ketones showed the N-Boc THIQs could afford moderate yield in most cases, where propiophenone 2d and 3,4-dihydronaphthalen-1(2H)-one 2e gave higher yield of 60% within 45 minutes' grinding. Then, THIQ derivatives were subjected with acetone 2f. In this case. N-Boc THIQ could also give moderate vield after the milling process though the best yield was obtained by using N-phenyl substrate. Besides, when coupling with propanone 2g, N-Boc THIQ afforded inseparable mixtures, which probably due to the multiple-reaction site of the substrate as well as the steric factors. while N-Ph THIQ 1c could selectively give the coupling product at methyl position. Cyclic ketones 2h-j were also examined to give satisfied results, where N-Cbz and N-Ph substrates affording comparative yields to their solvent-free heating/stirring counterpart.^[3e, 10] Further attempt using 7-member ring substrate of tetrahydro-1H-benzo[c]azepine 1g failed in coupling, but afforded an oxidative ring-opening product as our previous reported (Scheme 2).^[11c] Furthermore, it is delight to find that under the above optimal condition, propionaldehyde could be tolerated in the coupling reaction, which give the desired amino aldehyde product in 56% yield (Scheme 3).



Scheme 2. Reaction of tetrahydro-1*H*-benzo[*c*]azepine and acetophenone.



Scheme 3. Reaction of *N*-boc THIQ and propionaldehyde.

In conclusion, a mild oxidative Mannich reaction of *N*-Boc THIQs and ketones has been developed by using HSBM techniques. To avoid the side reaction, carefully adjustment of milling parameters, including frequency, time, milling ball filling degree, and grinding auxiliary were conducted, which realized

the chemo-selective process without significant losing of *N*-Boc group. During the optimization, the deprotection was found to have correlation with the energy input and system temperature, which may due to overheat accumulation. Thus, through the optimization of HSBM system, the reaction could proceed successfully under mild oxidative conditions. Further examination showed the established reaction system could also be applied to the substrates as *N*-Cbz, and -aryl THIQs, affording moderate to high yields in short reaction time (no more than 60 minutes). The investigations of selective removing of Boc groups and cascade coupling-deprotection reaction by parameter controlling are under investigation in our lab.

Experimental Section

A mixture of the substrate *N*-acyl/aryl THIQs **1** (1.0 mmol, 1.0 equiv), ketone/aldehyde **2** (2.5 mmol, 2.5 equiv), DDQ (1.0 mmol, 227 mg, 1.0 equiv), and silica gel (0.45 g) was placed in a 50 mL screw-capped stainless-steel vessel, along with four stainless-steel balls (14 mm, $\Phi_{MB} = 0.115$) or two stainless-steel balls (14 mm, $\Phi_{MB} = 0.057$). Then, the vessel was placed in the mixer mill, and the contents were milled at 20 Hz or 30 Hz for 45 or 60 min. At the end of the experiment, all of the reaction mixtures were scratched of from the vessel and dissolved in ethyl acetate followed by concentrating in vacuo to give a residue, which was purified by column chromatography on silica gel (eluents: petroleum ether/ethyl acetate 20/1~6/1) to give the desired product.

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Keywords: oxidative mannich reaction• ball mill • mechanical parameters • cross coupling • chemoselectivity •

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High-speed ball-milling promoted mechanochemical oxidative Mannich reaction of N-Boc tetrahydroquinolines and ketones is developed to give desired products in satisfied yields under mild oxidative conditions, where chemoselective coupling can be realized by avoiding the side reactions through fine tuning of the milling parameters. The reaction is further applied to N-Cbz, and N-aryl substrates to afford good results.



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