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Solvent and catalyst free azo-Michael addition under high-speed vibration milling

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Under the high-speed vibration milling conditions, the solvent and catalyst-free azo-Michael addition of chalcone derivatives and amines was found to proceed efficiently in excellent yields at ambient temperature in short reaction time. In most cases, conventional side reactions were avoided and thus quantitative yields were achieved. The influences of the vibration frequency and reaction time on the azo-Michael addition were investigated.

azo-Michael addition, solvent and catalyst-free, HSVM, chalcone

1 Introduction

Environmental concerns about the solvent-based chemistry have stimulated renewed interest in the study of chemical reactions under solvent-free conditions [1–5]. Mechanochemistry is seldom attempted in organic synthesis. Even if attempted, mechanical processing of organic reactants is sometimes followed by additional treatment (usually heating) [6, 7], or occasionally it is carried out in the presence of a solvent [8]. During the past two decades, solvent-free organic synthesis has received considerable attention owing to growing worldwide concerns over chemical wastes and future resources. Recently the technique of 'high-speed vibration milling' (abbreviated as HSVM) has been successfully utilized in organic reactions [9–11]. Beginning with research largely from Wang's group in China, there have been many reports on fullerene and non-fullerene mechanochemical reactions under HSVM conditions [12–16]. In the course of their study on mechanical organic synthesis，they were inspired to perform Michael reaction [17, 18]. Michael reaction is one of the most efficient methods for carbon-carbon bond formation and has wide synthetic applications [19–22]. Generally, Michael additions are conducted in a suitable solvent in the presence of a strong base, such as NaOH, KOH, $Ba(OH)_2$, and NaOEt [23–25]. However, these drastic conditions often cause side reactions, such as bis-addition, auto-condensation, rearrangement and retro Michael additions, leading to low yields and difficulty in purification of the target product, and thus making it unsuitable for the synthesis of desired compounds [26, 27].

To avoid the aforementioned problems, solvent-free conditions are undoubtedly an important method to be considered [28]. From these points of view, our group has applied the HSVM technique to synthesize β-enamino ketones (esters) [29]. Herein, we report our study on the azo-Michael addition of chalcones with aliphatic amine or aromatic amines in the absence of a catalyst. In our present protocol, the azo-Michael addition reactions were found to proceed efficiently under solvent and catalyst-free conditions in very short reaction time under the HSVM conditions (Scheme 1).

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2 Experimental

The reagents were obtained from commercial sources. The ^{1}H NMR spectra were recorded at 500 MHz in $CDCl_3$ with a Bruker AM 500 spectrometer. The HSVM was achieved with Retsch MM301 (Retsch GmbH, Haan, Germany).

General procedure for the synthesis of compound 3

A mixture of compound **1** (1 mmol) and amine **2** (1 mmol) was vigorously shaken by HSVM for a designated time. The obtained product **3** was purified by column chromatography on silica gel with petroleum ether–EtOAc (3:1) as an eluent.

*3-(Benzylamino)-1,3-diphenylpropan-1-one (**3a**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.0 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.53–7.20 (m, 12H, ArH), 4.34 (dd, *J* = 9.0, 4.5 Hz, 1H), 3.65 (d, *J* =13.0 Hz, 1H), 3.58 (d, *J* = 13.0 Hz, 1H), 3.40–3.28 (m, 2H), 1.77 (bs, NH).

*3-(Benzylamino)-3-(3-bromophenyl)-1-phenylpropan-1-one (**3b**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01–7.18 (m, 14H, ArH), 4.31 (dd, *J* = 8.5, 4.5 Hz, 1H), 3.66–3.57 (m, 2H), 3.36–3.25 (m, 2H), 1.91(bs, NH).

*3-(Benzylamino)-3(3-nitrophenyl)-1-phenylpropan-1-one (**3c**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36–7.20 (m, 14H, ArH), 4.47 (dd, *J* = 8.5, 4.0 Hz, 1H), 3.67–3.58 (m, 2H), 3.39–3.31 (m, 2H), 1.77(bs, NH).

*3-(Benzylamino)-1-phenyl-3-(4-(trifluoromethyl)-phenyl)-propan-1-one (**3d**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97–7.21 (m, 14H, ArH), 4.42 (dd, *J* = 8.5, 4.0 Hz, 1H), 3.67–3.58 (m, 2H), 3.42–3.30 (m, 2H).

*3-(Benzylamino)-3-(4-bromophenyl)-1-(4-methoxyphenyl)-propan-1-one (**3e**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91–7.23 (m, 13H, ArH), 4.40 (dd, *J* = 8.5, 4.0 Hz, 1H), 3.85 (s, 3H), 3.64–3.57 (m, 2H), 3.30–3.24 (m, 2H).

*3-(Benzylamino)-1-(4-methoxyphenyl)-3-(4-(trifluoromethyl)-phenyl)propan-1-one (**3f**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–6.87 (m, 13H, ArH), 4.29 (dd, *J* = 8.7, 4.1 Hz, 1H), 3.86 (s, 3H), 3.66–3.57 (m, 2H), 3.31–3.19(m, 2H).

*3-(Benzylamino)-1,3-bis(4-methoxyphenyl)propan-1-one (**3g**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–6.87 (m, 13H, ArH), 4.27 (dd, *J* = 8.6, 4.2 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.60 (m, 2H), 3.28 (d, *J* = 8.6 Hz, 1H), 3.24 (d, *J* = 4.2 Hz, 1H).

*3-(Benzylamino)-1-(4-methoxyphenyl)-3-(4-nitrophenyl) propan-1-one (**3h**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36–6.88 (m, 13H, ArH), 4.45 (dd, *J* = 8.5, 4.4 Hz, 1H), 3.86 (s, 3H), 3.62 (d, *J* = 1.5 Hz, 2H), 3.32 (d, *J* = 8.4 Hz, 1H), 3.27 (d, *J* = 4.5 Hz, 1H).

*3-(Benzylamino)-1-(4-methoxyphenyl)-3-phenylpropan-1-one (**3i**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92–6.86 (m, 14H, ArH), 4.33 (dd, *J* = 8.8, 4.1 Hz, 1H), 3.85 (s, 3H), 3.61 (m, 2H), 3.30 (d, *J* = 8.8 Hz, 1H), 3.26 (d, *J* = 4.1 Hz, 1H).

*3-(p-Toluidino)-1,3-diphenylpropan-1-one (**3j**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92–6.45 (m, 14H, ArH), 4.97 (dd, *J* = 7.6, 5.3 Hz, 1H), 4.43(s, 1H), 3.45 (dd, *J* = 28.2, 6.5 Hz, 2H), 2.17 (s, 3H).

*3-(p-Toluidino)-3-(3-nitrophenyl)-1-ph5enylpropan-1-one (**3k**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32–6.46 (m, 13H, ArH), 5.08 (t, *J* = 6.2 Hz, 1H), 4.54(s, 1H), 3.51 (d, *J* = 6.3 Hz, 2H), 2.18 (s, 3H).

*3-(4-Methoxyphenylamino)-1,3-diphenylpropan-1-one (**3l**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91–6.53 (m, 14H, ArH), 4.92 (dd, *J* = 7.7, 5.1 Hz, 1H), 4.29 (s, 1H), 3.68 (s, 3H), 3.46 (d, *J* = 5.1 Hz, 1H), 3.42 (d, *J* = 7.8 Hz, 1H).

*3-(3-Chlorophenylamino)-1,3-diphenylpropan-1-one (**3m**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30–6.41 (m, 14H, ArH), 5.08 (t, *J* = 6.0 Hz, 1H), 4.81 (s, 1H), 3.52 (d, *J* = 6.2 Hz, 2H).

*1-Phenyl-3-(piperidin-1-yl)-3-(4-(trifluoromethyl)-phenyl)-propan-1-one (**3n**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91–7.39 (m, 9H, ArH), 4.29 (dd, *J* = 7.7, 5.8 Hz, 1H), 3.61 (dd, *J* = 16.7, 5.7 Hz, 1H), 3.41 (dd, *J* = 16.7, 7.9 Hz, 1H), 2.84–2.27 (m, 4H), 1.52 (m, 4H), 1.36 (dd, *J* = 11.5, 5.7 Hz, 2H).

*3-(3-Bromophenyl)-1-phenyl-3-(piperidin-1-yl)propan-1-one (**3o**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95–7.13 (m, 9H, ArH), 4.30–4.05 (m, 1H), 3.58 (dd, *J* = 16.6, 6.1 Hz, 1H), 3.35 (dd, *J* = 16.5, 7.5 Hz, 1H), 2.36 (m, 4H), 1.57–1.46 (m, 4H), 1.40–1.28 (m, 2H).

*1-(4-Methoxyphenyl)-3-phenyl-3-(piperidin-1-yl)propan-1-one (**3p**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92–6.90 (m, 9H, ArH), 4.20 (dd, *J* = 7.5, 6.1 Hz, 1H), 3.87 (s, 3H), 3.53 (dd, *J* = 16.1, 6.0 Hz, 1H), 3.35 (dd, *J* = 16.2, 7.5 Hz, 1H), 2.48–2.28 (m, 4H), 1.51 (m, 4H), 1.40–1.26 (m, 2H).

*3-(3-Nitrophenyl)-1-phenyl-3-(piperidin-1-yl)propan-1-one (**3q**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18–7.42 (m, 9H, ArH), 4.36 (dd, *J* = 8.1, 5.5 Hz, 1H), 3.64 (dd, *J* = 16.8, 5.5 Hz, 1H), 3.44 (dd, *J* = 16.8, 8.1 Hz, 1H), 2.39 (m, 4H), 1.58–1.47 (m, 4H), 1.37 (dd, *J* = 11.5, 5.8 Hz, 2H).

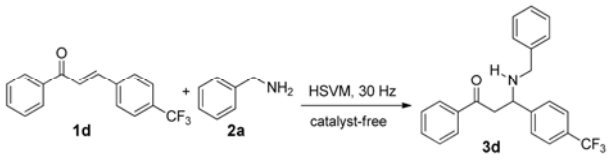
*1-(4-Methoxyphenyl)-3-(piperidin-1-yl)-3-(4-(trifluoromethyl)-phenyl)propan-1-one (**3r**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92–6.89 (m, 8H, ArH), 4.18 (dd, *J* = 7.3, 6.1 Hz, 1H), 3.87 (s, 3H), 3.51 (dd, *J* = 16.4, 5.9 Hz, 1H), 3.29 (dd, *J* = 16.4, 7.5 Hz, 1H), 2.40 (d, *J* = 5.1 Hz, 2H), 2.33 (d, *J* = 4.9 Hz, 2H), 1.58–1.46 (m, 4H), 1.40–1.29 (m, 2H).

3 Results and discussion

The azo-Michael reaction of chalcone and benzylamine was first examined and found to proceed efficiently in excellent yield under HSVM under solvent and catalyst-free conditions. All solvent-free reactions were performed using a high-speed vibration mill consisting of a capsule and a milling ball made of stainless steel [30]. The capsule containing the milling ball was fixed on a vibration arm of a homebuilt mill, and was vibrated vigorously at a maximum rate of 1800 rpm. The solvent-free mechanochemical reaction of chalcone **1** with benzylamine **2** under the HSVM conditions afforded essentially pure product **3** after washing the reaction mixture with water in most cases.

To explore this reaction system, we have carried out this azo-Michael reaction at different vibration frequency and reaction time. It was found that the vibration frequency of the applied vibration mill had a significant effect on this reaction (Table 1).



Scheme 1

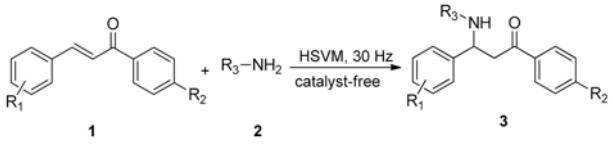
Table 1 Michael addition of benzylamine to chalcone **1** at different vibration frequency and reaction time under HSVM conditions

Entry	Vibration frequency (Hz)	Time (min)	Yield (%)[a)]
1	10	25	66
2	20	25	90
3	30	25	99
4	30	10	78
5	30	15	82
6	30	20	96
7	30	25	99

a) The yield of ^{1}H NMR.

As shown in Table 1, higher vibration frequency of the vibration mill accelerated the reaction process significantly. It is easy to understand that the faster milling vibration gives the higher energy, and therefore the local pressure is applied to the reaction system. Furthermore, it was found that the decrease of the reaction time resulted in lower yields. The result indicated that the azo-Michael addition was obtained in good yield in the absence of any catalyst under HSVM conditions.

From the above results, the reaction conditions of the vibration frequency (30 Hz), reaction time (25 min) and raw material mole ratio (1:1) were selected for investigating the addition reaction of different amines **2** and chalcone or substitutional chalcone **1** (Scheme 2).



Scheme 2

This protocol does not require use of any base as catalysts and any organic solvent during the reaction process and HSVM alone is enough to promote the reaction efficiently. The yield of the azo-Michael addition is summarized in Table 2.

As shown in Table 2, the azo-Michael addition reactions generally gave products **3** in remarkably high yields. The electron-withdrawing and electron-donating of chalcone **1** could participate in the reaction of benzyl amine and chalcone. This protocol can be extended to the azo-Michael addition of other amines such as secondary amine piperidine to chalcones with good yield in almost all cases. It is easy to understand that the lower reactivity of phenylamine gave the lower yield of this azo-Michael addition (entry 11, 12, 13). Compared with existing methods, the main advantages of the present procedure are milder conditions, higher yield, shorter reaction time and occurrence of no side reactions. For example, compound **3a** was previously prepared in 64% yield which was catalyzed by natural phosphate in MeOH at room temperature for 24 h [31], whereas under our solvent-free HSVM conditions, it was obtained in 98.1% yield at room temperature for 25 min. The reasons for the efficiency of the current solvent-free procedure may be an enhanced second-order reaction rate resulting from ultimately high concentrations of reactants with no use of a solvent. Furthermore, in the HSVM technique, the high mechanical energy caused by local high pressure, friction, shear strain, etc. can significantly reinforce the reaction [13].

4 Conclusion

In summary, a powerful method was described for azo-Michael addition of chalcones with amines in quantitative

Table 2 azo-Michael addition of different amines to chalcone under HSVM conditions

Entry	R_1	R_2	**2**	Product **3**	Yield (%)[a]
1	H	H	benzyl amine	**3a** [31]	98
2	*m*-Br	H	benzyl amine	**3b**	99
3	*m*-NO_2	H	benzyl amine	**3c**	98
4	*p*-CF_3	H	benzyl amine	**3d**	99
5	*p*-Br	–OCH_3	benzyl amine	**3e**	90
6	*p*-CF_3	–OCH_3	benzyl amine	**3f**	82
7	*p*-OCH_3	–OCH_3	benzyl amine	**3g**	88
8	*p*-NO_2	–OCH_3	benzyl amine	**3h**	90
9	H	–OCH_3	benzyl amine	**3i**	94
10	H	–H	*p*-Me-aniline	**3j** [32]	83
11	*m*-NO_2	–H	*p*-Me-aniline	**3k**	59
12	H	–H	*p*-MeO-aniline	**3l** [32]	52
13	H	–H	*m*-Cl-aniline	**3m** [33]	47
14	*p*-CF_3	–H	piperidine	**3n**	91
15	*m*-Br	–H	piperidine	**3o**	91
16	H	–OCH_3	piperidine	**3p**	89
17	*m*-NO_2	–H	piperidine	**3q**	90
18	*p*-CF_3	–OCH_3	piperidine	**3r**	90

a) Isolated yield based on chalcone **1**.

yields in most cases. All these mechanochemical reactions were conducted under the catalyst-free and the HSVM conditions. The advantages of a mild condition, high yield, and short reaction time together with a straightforward and easy work-up procedure make the present method convenient, effective and environmentally friendly, which could be a very efficient alternative to the classic methodology.

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