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Solvent-free Brønsted acid-catalyzed Michael addition of nitrogen- and carbon-containing nucleophiles by ultrasound activation

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ABSTRACT

A new method has been developed for the Michael addition of nitrogen- and carbon-containing nucleophiles to cyclic enones. Using this conjugate addition reaction, a variety of different nucleophiles can react with a range of cyclic enones in the presence of *p*-toluenesulfonic acid under solvent-free ultrasound irradiation conditions affording the corresponding C–N or C–C adducts in good to excellent yields. Comparatively, performing the reaction under ultrasound irradiation gives higher yields, is more efficient and environmentally benign than performing it at high pressure.

Introduction

The conjugate addition of nitrogen- and carbon-containing nucleophiles to α,β-unsaturated carbonyl compounds (i.e., Michael reaction) is a powerful tool in organic synthesis for the construction of C—N and C—C bonds. Reactions of this type have been successfully applied to the preparation of pharmacologically important β-substituted carbonyl compounds.[1,2] In many cases, these reactions can be catalyzed or promoted under strongly basic conditions, Brønsted acid or Lewis acid catalysis. The application of these catalysts to these reactions may be less effective, however, when weakly nucleophilic systems such as amides or nitrogen-containing heterocycles are used as the nucleophiles.[3,4] During the course of the last decade, tremendous progress has been made toward the development of green versions of this important transformation using high reaction temperatures,[5] high pressures,[6] and UVA irradiation.[7] Although the use of a high pressure reaction represents an efficient green method, it can be difficult in practice to achieve sufficiently high compaction pressures. High-powered ultrasound (US) can be used to generate cavitations capable of inducing temperatures of several thousand degrees and pressures in excess of 1000 atm inside bubbles.[8,9] Our previous studies have shown that the use of an ultrasound method for sterically congested Passerini reactions generated results that were far superior to those that could be achieved using the high pressure method.[10] In this Letter, we wish to report the development of an efficient solvent-free ultrasound method for the functionalization of enones via a reaction with a variety of different Michael donors.

Results and discussion

The Michael addition between cyclohex-2-enone (**1a**) and benzamide (**2a**) was selected as a model reaction for the optimization of the reaction conditions. This reaction was initially investigated using a conventional procedure from the literature,[11] where a mixture of cyclohexenone **1a** (1.2 equiv) and benzamide (**2a**) in acetonitrile was heated for 24 h in the presence of *p*-TsOH (10 mol %). Unfortunately, this procedure only provided a trace amount of the desired product (Table 1, entry 1). When the reaction was performed under a pressure of 0.6 GPa over a reaction time of 10 h, the yield increased to 75% (Table 1, entry 3). To determine the effects of ultrasound irradiation on this reaction, a series of experiments were carried out using a sonic horn as an ultrasound source, with the other conditions same as those already described in the literature.[12] The reaction mixture was irradiated in acetonitrile at 20 kHz/675 W (pulse-on time, 1.2 s; pulse-off time, 1.5 s) for 2 h. Pleasingly, the use of ultrasound effectively enhanced the rate of the reaction. Although the yield for the reaction remained unchanged under the high pressure and ultrasound irradiation conditions, the reaction time was reduced significantly from 10 to 2 h. Solvent-free reactions have proven to be efficient and

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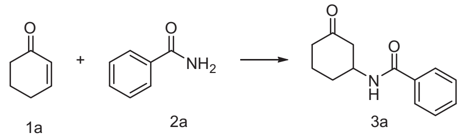
Table 1
Effect of ultrasound on Michael addition of 1,2,4-triazole **1a** with 2-cyclohexenone **2a**

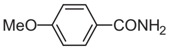
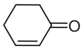
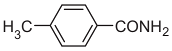
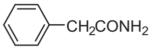
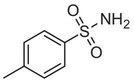
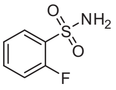


Entry	**1a**:**2a**	Cat. (mol %)	Temp. (°C)	Condition	Solvent	Time (h)	Yield (%)
1	1.2:1	10	70	0.1 MPa	MeCN	24	Trace
2	1.2:1	1	60	0.6 GPa	MeCN	10	40
3	1.2:1	10	60	0.6 GPa	MeCN	10	75
4	1.2:1	10	60	US	MeCN	2	73
5	1.2:1	10	60	US	No solvent	0.5	73
6	2:1	10	60	US	No solvent	0.5	96
7	2:1	1	60	US	No solvent	0.5	99
8	2:1	10	60	Stir	No solvent	24	48
9	2:1	10	25	US	No solvent	0.5	83
10	1.2:1	10	60	US	H_2O	2	Trace

environmentally friendly procedures for organic synthesis.[13–15] With this in mind, we turned our attention to investigating the possibility of a solvent-free ultrasound promoted approach. In the absence of a solvent, using the same temperature and ultrasonic power conditions, product **3a** was obtained in 30 min in 73% yield (Table 1, entry 5). The ultrasound-assisted solvent-free condition therefore provided a 4-fold acceleration in the rate of the reaction compared with the ultrasound-assisted solvent condition. The use of a slight excess of cyclohexenone (2.0 equiv) was then investigated because it is well known that a self-solidifying mixture can hinder the progress of the reaction. In this case, the product **3** was obtained in nearly quantitative yield following a reaction time of only 30 min (Table 1, entry 6). A similar result was also achieved when the amount of *p*-TsOH catalyst was reduced to only 1 mol % (Table 1, entry 7). In contrast, a yield of only 40% was achieved when the reaction was carried out in the presence of 1 mol % of the *p*-TsOH catalyst under high pressure conditions after 10 h (Table 1, entry 2). The temperature also plays a role in the reaction. For example, when the reaction was carried out at room temperature over a period of 30 min, the yield was reduced to 83% (Table 1, entry 9). It is noteworthy that the reaction mixture became more viscous at this lower temperature, and we believe that this may have negatively affect to the reaction. For comparison, we also examined the same reaction under traditional solvent-free conditions. In this case, the reaction was completed in 24 h under the solvent-free conditions (48% isolated yield; Table 1, entry 8).

With the optimized reaction conditions in hand, we proceeded to investigate the Michael addition of other Michael acceptors, including cyclohex-2-enone (**1a**) and cyclopent-2-enone (**1b**), with three different weak N-centered nucleophiles, including benzamide, 1-phenylurea, and *p*-toluenesulfonamide (*p*-TsNH$_2$) (Table 2). The results revealed that most of the Michael additions proceeded smoothly under the optimized reaction conditions, except for the addition reaction of the amide substrate **2a** to the acyclic enone **1c**, and the addition of the alkyl amide **2f** to cyclohex-2-enone

Table 2
Scope and limitations of the optimized protocol[a]

Entry	Amide	Cat. mol %	Enone	Time (min)	Product	Yield (%)
1	 MeO—CONH$_2$ **2b**	1	 **1a**	30	**3b**	95
2	 H$_3$C—CONH$_2$ **2c**	1	**1a**	60	**3c**	88
3	 CH$_2$CONH$_2$ **2d**	1	**1a**	30	**3d**	Trace
4	**2d**	10	**1a**	30	**3d**	61
5	$C_3H_7CONH_2$ **2e**	1	**1a**	60	**3e**	57
6	Me_3CCONH_2 **2f**	1	**1a**	30	**3f**	Trace
7	**2f**	10	**1a**	30	**3f**	Varied
8	 **2g**	1	**1a**	5	**3g**	90
9	 **2h**	1	**1a**	60	**3h**	55

(*continued on next page*)