Tetrahedron Letters 55 (2014) 1002–1005

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Xiu-Jiang Du, Zhi-Peng Wang, Yan-Ling Hou, Cheng Zhang, Zheng-Ming Li, Wei-Guang Zhao *

State Key Laboratory of Elemento-Organic Chemistry, National Pesticide Engineering Research Center (Tianjin), Nankai University, Tianjin 300071, China

ARTICLE INFO

Article history:
Received 13 October 2013
Revised 5 December 2013
Accepted 17 December 2013
Available online 30 December 2013

Keywords:
Michael addition
Cyclic enones
Ultrasound
Solvent-free
p-Toluenesulfonic acid

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.

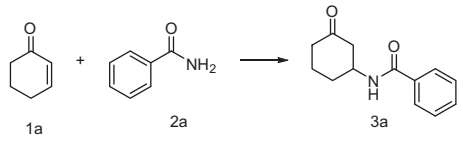
Results and discussion

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

* Corresponding author. Tel.: +86 2223498368; fax: +86 2223505948.
E-mail address: zwg@nankai.edu.cn (W.-G. Zhao).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.12.059

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

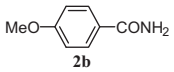
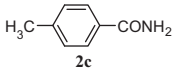
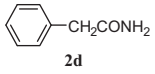
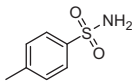
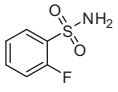


Entry	**1a**:**2a**	Cat. (mol %)	Temp. (°C)	Condition	Solvent	Time (h)	Yield (%)
1	1.2:1	10	70	0.1 MPa	MeCN	24	Trace
2	1.2:1	1	60	0.6 GPa	MeCN	10	40
3	1.2:1	10	60	0.6 GPa	MeCN	10	75
4	1.2:1	10	60	US	MeCN	2	73
5	1.2:1	10	60	US	No solvent	0.5	73
6	2:1	10	60	US	No solvent	0.5	96
7	2:1	1	60	US	No solvent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

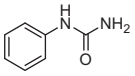
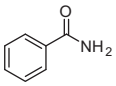
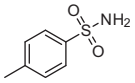
With the optimized reaction conditions in hand, we proceeded to investigate the Michael addition of other Michael acceptors, including cyclohex-2-enone (**1a**) and cyclopent-2-enone (**1b**), with three different weak N-centered nucleophiles, including benzamide, 1-phenylurea, and *p*-toluenesulfonamide (*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	 **2b**	1	 **1a**	30	**3b**	95
2	 **2c**	1	**1a**	60	**3c**	88
3	 **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

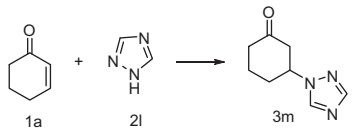
(*continued on next page*)

Table 2 (*continued*)

Entry	Amide	Cat. mol %	Enone	Time (min)	Product	Yield (%)
10	 **2i**	1	**1a**	30	**3i**	86
11	 **2j**	1	 **1b**	30	**3j**	78
12	 **2k**	1	**1b**	5	**3k**	78
13	**2a**	1	 **1c**	30	**3l**	NR
14	**2a**	10	**1c**	30	**3l**	Varied
15	 **2l**	1	**1a**	30	**3m**	99
16	 **2m**	1	**1a**	30	**3n**	99
17	**2l**	1	**1b**	30	**3o**	98
18	**2m**	1	**1b**	30	**3p**	71

[a] All the reactions were carried out using nucleophiles (1.0 mmol) and enones (2.0 mmol) at 60 °C under solvent-free ultrasound irradiation conditions.

Table 3
Effects of solvent on the ultrasound-promoted Michael addition[a]



Entry	Ratio	Cat. mol %	Solvent	Condition	Time (h)	Yield (%)
1	1.1:1	—	H_2O	0.1 Mpa	72	71
2	1.1:1	—	H_2O	0.6 GPa	20	100
3	1.1:1	—	H_2O	US	1	59
4	1:3	—	—	US	1.5	78
5	1:3	10	—	US	0.5	99

[a] All the reactions were carried out using **1a** (2.0 mmol) and **2l** (1.0 mmol) at 60 °C.

(**1a**). Cyclohex-2-enone (**1a**) reacted with 4-methoxybenzamide, 4-methylbenzamide, 4-methylbenzenesulfonamide, 1,2,4-triazole, imidazole, and 1-phenylurea in the presence of *p*-TsOH (10 mol %) over 5 to 60 min to give the corresponding adducts in yields of 95%, 88%, 90%, and 86%, respectively (Table 2, entries 1, 2, 8, and 10). The addition reactions of cyclopent-2-enone with benzamide and 4-methylbenzenesulfonamide proceeded smoothly to give the corresponding adducts in the same yield of 78% (Table 2, entries 11 and 12). In contrast, the addition reactions of cyclopent-2-enone only gave complex mixtures of products when they were conducted under high pressure conditions. The use of aliphatic amides and aromatic amides bearing electron-withdrawing substituents on the phenyl rings led to reduction in the yield of the reaction (Table 2, entries 3, 5, and 9), whereas the rate of the reaction was increased significantly by increasing the amount of catalyst (Table 2, entries 3 and 4). The application of the optimized reaction conditions to the acyclic enone 1-acetyl-1-cyclohexene

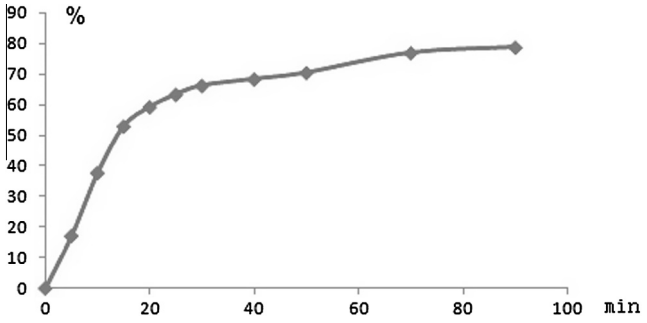


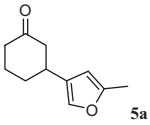
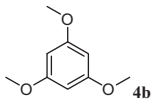
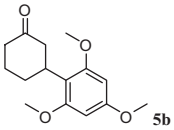
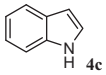
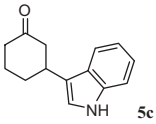
Figure 1. Dependence of the NMR yield on the reaction.

(**1c**) and benzamide gave a complex mixture of products (Table 2, entries 14 and 7).

The Michael addition of nitrogen-containing heterocycles such as 1,2,4-triazole and imidazole to cyclohex-2-enone (**1a**) and cyclopent-2-enone was also investigated, with the corresponding adducts being isolated in near quantitative yields (Table 2, entries 15–17).

According to a procedure described in the literature,[6] when the Michael addition was conducted in water at a pressure of 0.6 GPa and a temperature of 60 °C over a period of 20 h in the absence of a catalyst, the desired adduct **3** was obtained in quantitative yield. For comparison, we also examined the same reaction in water under ultrasound irradiation conditions at 60 °C. In this particular case, however, the reaction was very slow, and provided the desired product 3-(1*H*-1,2,4-triazol-1-yl)cyclohexanone in a yield of only 59% following a reaction time of 60 min (Table 3, entry 3). When the same reaction was conducted under solvent-free ultrasound irradiation conditions in the absence of catalyst at 60 °C, the reaction was also very slow, and provided the desired product 3-(1*H*-1,2,4-triazol-1-yl)cyclohexanone in a yield of 78% following

Table 4
Ultrasound-promoted Friedel–Crafts-type additions of (Hetero) aromatics to **1a**[a]

Entry	Reactant	Cat. mol %	Product	Time (min)	Yield (%)
1	 **4a**	1	 **5a**	30	48
2	 **4b**	10	 **5b**	30	95
3	**4b**	1	**5b**	30	59
4	 **4c**	1	 **5c**	30	56
5	**4c**	10	**5c**	30	83

[a] All reactions were carried out using **1a** (1.0 mmol) and **4a** (1.2 mmol), **4b** and **4c** (2.0 mmol) at 60 °C under solvent-free ultrasound irradiation conditions.

a reaction time of 90 min (Table 3, entry 4). The influence of reaction time was studied in greater detail under the solvent-free ultrasound irradiation conditions in the absence of a catalyst (Fig. 1). ^{1}H NMR spectroscopy was used to monitor the progress of the reaction. Following a reaction time of 20 min, the reaction had almost reached its maximum yield of approximately 60%. Following an additional 20 min, the yield was found to have increased only slightly. In contrast, when the same reaction was conducted under solvent-free ultrasound irradiation conditions in the presence of a catalyst at 60 °C over a time period of 30 min, the adduct was obtain in 99% yield (Table 3, entry 5).

In view of the preliminary success regarding the development of a ultrasound-promoted catalytic conjugate addition to cyclic enones, we proceeded to investigate the Friedel–Crafts alkylation reaction of electron-rich (hetero) arenes, such as indoles, furans, and 1,3,5-trimethoxybenzene to enones, because this would represent a powerful C–C bond-forming methodology capable of providing access to biologically active templates, such as indole alkaloids. Pleasingly, all of the desired conjugate addition reactions proceeded to completion in 30 min in the presence of *p*-TsOH under solvent-free ultrasound irradiation conditions (Table 4).

In conclusion, we have developed a simple, convenient and efficient protocol for the Michael reaction of nitrogen- and carbon-containing nucleophiles under solvent-free ultrasound irradiation conditions. This approach works especially well with cyclic enones, providing the desired products in excellent yields. We have also presented promising preliminary results concerning the reaction with electron-rich (hetero) arenes.

Acknowledgements

We are grateful for the financial support for this work from the National Natural Science Foundation of China (21172124), the National Basic Research Science Foundation of China (2010CB126105), and the National Key Technologies R&D Program (2011BAE06B05).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.059.

References and notes

1. Comelles, J.; Moreno-Mañas, M.; Vallribera, A. *Arkivoc* **2005**, *9*, 207.
2. Guo, H. C.; Ma, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354.
3. Takasu, K.; Nishida, N.; Ihara, M. *Synlett* **2004**, 1844.
4. Uddin, M. I.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Synlett* **2008**, 1402.
5. Zaderenko, P.; López, M. C.; Ballesteros, P. *J. Org. Chem.* **1996**, *61*, 6825.
6. Uddin, M. I.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Synlett* **2008**, 1402.
7. Moran, J.; Dornan, P.; Beauchemin, A. M. *Org. Lett.* **2007**, *9*, 3893.
8. Mason, T. J. *Chem. Soc. Rev.* **1997**, *26*, 443.
9. Cravotto, G.; Cintas, P. *Chem. Soc. Rev.* **2006**, *35*, 180.
10. Cui, C.; Zhu, C.; Du, X.-J.; Wang, Z.-P.; Li, Z.-M.; Zhao, W.-G. *Green Chem.* **2012**, *14*, 3157.
11. Azad, S.; Kobayashi, T.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Tetrahedron Lett.* **2009**, *50*, 48.
12. Jenner, G. *Tetrahedron Lett.* **2002**, *43*, 1235.
13. Nagendrappa, G. *Resonance* **2002**, *7*, 59.
14. Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025.
15. Tanaka, K. *Solvent-Free Organic Synthesis*; Vch Verlagsgesellschaft Mbh, 2003.