



Efficient Brønsted acid-catalyzed aza-Michael reaction of amides and ureas with α,β -unsaturated enones under high-pressure conditions[☆]

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ABSTRACT

A new strategy for the aza-Michael reaction of amides and ureas with α,β -unsaturated enones, which uses *p*-TsOH·H₂O as an efficient and inexpensive catalyst under high-pressure conditions, has been developed.

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The conjugate addition of nitrogen nucleophiles to α,β -unsaturated ketones/esters (aza-Michael reaction) is one of the most convenient and straightforward methods known for preparing a pharmacologically important family of β -amino carbonyl compounds and related derivatives.² In many cases, these reactions require the use of strongly basic conditions or acid catalysis to enhance either the nucleophilicity of nitrogen donor molecules or the electrophilicity of acceptor components.³

Despite this fundamental importance in organic synthesis, there have been only a few reports on the use of amides⁴ as Michael donors, in contrast to an abundance of carbamate analogs,⁵ probably due to the reduced nucleophilicity of amide nitrogen atoms. In 1994, Ahn and Lee reported that the combination of a stoichiometric amount of Si(OEt)₄ and a catalytic amount of CsF could overcome this difficulty.^{4a} Thereafter, Pd- and V-based catalyst systems were introduced.^{4c,d} Unfortunately, however, the use of Brønsted acid catalysts in these transformations is very limited,^{5d,e,i} even though they are non-metallic, economical, and environment-friendly.⁶ Moreover, no practical method for the aza-Michael reaction of ureas has been reported.⁷

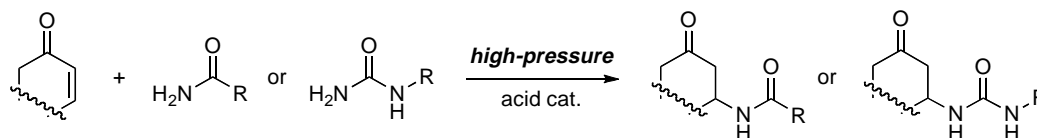
As a continuation of our extensive efforts to devise new methods for aza-Michael reactions using weakly reactive nitrogen nucleophiles,¹ we anticipated that the combination of Brønsted acid catalysis and a high-pressure technique^{8,9} should provide a

uniquely powerful tool to promote the aza-Michael reaction of amide- and urea-based nitrogen nucleophiles. We describe here the realization of this expectation (Scheme 1).

To establish the optimal conditions, we first examined the reaction of benzamide (**1a**) with 2-cyclohexen-1-one (**2a**, 1.2 equiv) using a variety of acid catalysts under various conditions, including high-pressure and microwave irradiation, and the results are summarized in Table 1.^{10,11}

Among several catalysts examined, *p*-toluenesulfonic acid (*p*-TsOH) gave the best result, and when the reaction was conducted in MeCN containing 10 mol % of *p*-TsOH·H₂O at 0.6 GPa and 60 °C for 10 h, the mono-coupling adduct **3a** was obtained in 75% yield (Table 1, entry 5).¹² At lower pressures or at lower loading of the catalyst, reduced yields were observed (Table 1, entries 1–4). The use of anhydrous *p*-TsOH as a catalyst or the application of microwave irradiation was less satisfactory for the present purpose (Table 1, entries 6 and 7).^{13,14}

2,4-Dinitrobenzenesulfonic acid and (+)-(*S*)-camphorsulfonic acid (CSA) were found to be less effective (Table 1, entries 8 and 9), and other acid catalysts such as *p*-nitrophenol and ethyl 3,4-dihydroxybenzoate were all useless (Table 1, entries 10 and 11). Finally, diphenyl phosphate showed a comparable catalytic activity, though this reagent is rather expensive (Table 1, entry 12). In these examples, no formation of the bis-aza-Michael adduct



Scheme 1.

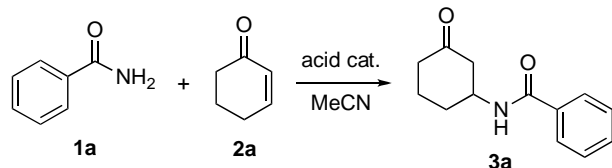
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Table 1

Aza-Michael reaction of benzamide (**1a**) with 2-cyclohexen-1-one (**2a**) under various conditions^a



Entry	Acid cat. ^b	Conditions	Yield ^c (%)
1	<i>p</i> -TsOH·H ₂ O	1 atm, 70 °C, 24 h	Trace
2	<i>p</i> -TsOH·H ₂ O	0.2 GPa, 40 °C, 10 h	40
3	<i>p</i> -TsOH·H ₂ O (1 mol %)	0.6 GPa, 60 °C, 10 h	40
4	<i>p</i> -TsOH·H ₂ O (5 mol %)	0.6 GPa, 60 °C, 10 h	65
5	<i>p</i>-TsOH·H₂O	0.6 GPa, 60 °C, 10 h	75
6	<i>p</i> -TsOH (anhyd)	0.6 GPa, 60 °C, 10 h	52
7	<i>p</i> -TsOH·H ₂ O	MW, 100 °C, 35 min ^d	20
8	2,4-(NO ₂) ₂ C ₆ H ₃ SO ₃ H	0.6 GPa, 60 °C, 10 h	68
9	(+)-CSA	0.6 GPa, 60 °C, 10 h	67
10	<i>p</i> -NO ₂ C ₆ H ₄ OH	0.6 GPa, 60 °C, 10 h	NR
11	3,4-(OH) ₂ C ₆ H ₃ CO ₂ Et	0.6 GPa, 60 °C, 10 h	NR
12	(C ₆ H ₅ O) ₂ P(O)OH	0.6 GPa, 60 °C, 10 h	73

^a All the reactions were carried out using **1a** (1.0 mmol) and **2a** (1.2 mmol) in MeCN (ca. 1.5 mL).

^b Unless otherwise noted, 10 mol % of the acid catalyst was used.

^c Isolated yield.

^d At 100 W and 150 psi.

was observed, probably due to the severe steric and electronic hindrance for the second addition.¹⁵

With these results in hand, we then sought to clarify the general scope of this method with various combinations of substrates, and the results are summarized in Table 2.^{10,11}

Cyclic enones, such as **2b** and 2-cyclohepten-1-one (**2c**), reacted with **1a** to give the corresponding adducts **3b** and **3c** in respective yields of 51% and 68% (Table 2, entries 1 and 2). On the other hand, 2-cyclopenten-1-one (**2d**) gave a complex mixture of products, and 1-acetyl-1-cyclohexene (**2e**) gave **3e** in 36% yield with some decomposition (Table 2, entries 3 and 4). Acyclic enones, such as **2f–h**, underwent conjugate addition with **1a** at elevated pressures to give the desired adducts **3f–h** after longer reaction times (20–78%), which clearly suggested that these enone systems were less reactive (Table 2, entries 5–7).

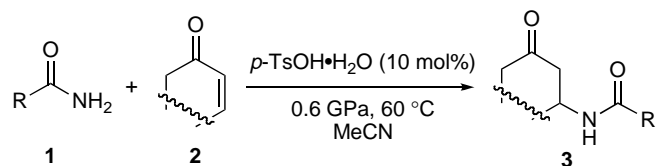
We also examined the use of other aromatic and aliphatic amides as donor molecules in the aza-Michael reaction toward **2a**. Thus, the reactions of *p*-methoxy- and *p*-methylbenzamide (**1b** and **1c**) with **2a** proceeded smoothly to give the corresponding adducts **3i** and **3j** in respective yields of 80% and 72% (Table 2, entries 8 and 9). The present method was also effective for the reaction using aliphatic amides such as **1d–f**, and the respective adducts **3k–m** were obtained in moderate to good yields (43–74%) (Table 2, entries 10–12). The lower reactivity of **1f** might be ascribed to the bulkiness of a pivaloyl function.

We next examined the feasibility of the above acid-catalyzed aza-Michael reaction for primary ureas as novel nitrogen nucleophiles with α,β -unsaturated enones. Thus, various ureas **4** were treated with enones **2** in the presence of a catalytic amount of *p*-TsOH·H₂O under the standardized conditions (Table 3).^{10,11}

When a mixture of *N*-phenylurea (**4a**), 2-cyclohexen-1-one (**2a**, 1.2 equiv), and *p*-TsOH·H₂O (10 mol %) in MeCN was reacted at 0.6 GPa and 60 °C for 8 h, the corresponding adduct **5a** was obtained in 70% yield (Table 3, entry 1).¹⁶ Selective alkylation at the terminal NH₂ group of **4a** was unambiguously confirmed by ¹H NMR measurement.¹⁷ The generality of this method was further demonstrated by the reaction of **4a** with a variety of cyclic and acyclic α,β -unsaturated enones **2b–g** (56–93%), while **2d** was again an unfavorable substrate under these conditions (Table 3, entries

Table 2

High-pressure-promoted aza-Michael reaction of amides with enones^a



Entry	Amide	Enone	Yield 3^b (%)
1	1a	2b	51 (3b)
2	1a	2c	68 (3c)
3 ^c	1a	2d	Complex (3d)
4	1a	2e	36 (3e) ^d
5 ^e	1a	2f	78 (3f)
6 ^e	1a	2g	75 (3g)
7 ^e	1a	2h	20 (3h)
8 ^f	MeO-C ₆ H ₄ -CONH ₂ 1b	2a	80 (3i)
9 ^g	H ₃ C-C ₆ H ₄ -CONH ₂ 1c	2a	72 (3j)
10 ^g	C ₆ H ₅ -CH ₂ CONH ₂ 1d	2a	72 (3k)
11	C ₃ H ₇ CONH ₂ 1e	2a	74 (3l)
12 ^g	(CH ₃) ₃ C CONH ₂ 1f	2a	43 (3m)

^a Unless otherwise noted, all the reactions were performed at 0.6 GPa and 60 °C for 10 h in MeCN (1.5 mL) using **1** (1.0 mmol) and **2** (1.2 mmol) in the presence of *p*-TsOH·H₂O (0.1 mmol).

^b Isolated yield.

^c At 0.6 GPa, rt for 10 h.

^d Trans/cis = 4:1 by ¹H NMR.

^e At 0.8 GPa, 50 °C for 55 h.

^f At 0.8 GPa, rt for 55 h.

^g For 24 h.

Table 3
High-pressure-promoted aza-Michael reaction of ureas with enones^a

Entry	Urea	Enone	Yield 5 ^b (%)
1		2a	70 (5a)
2	4a	2b	59 (5b)
3	4a	2c	93 (5c)
4 ^c	4a	2d	Complex (5d)
5 ^d	4a	2e	56 (5e) ^e
6 ^f	4a	2f	74 (5f)
7 ^f	4b	2g	73 (5g)
8		2a	58 (5h)
9		2a	53 (5i)
10 ^d	$C_4H_9NHCONH_2$ 4d	2a	72 (5j)
11 ^f	$(C_2H_5)_2NCONH_2$ 4e	2a	86 (5k)
12 ^g		2a	60 (5l)

^a Unless otherwise noted, all the reactions were performed at 0.6 GPa and 60 °C for 8 h in MeCN (1.5 mL) using **4** (1.0 mmol) and **2** (1.2 mmol) in the presence of *p*-TsOH·H₂O (0.1 mmol).

^b Isolated yield.

^c At 0.6 GPa, rt for 10 h.

^d For 24 h.

^e Trans/cis = 4:1 by ¹H NMR.

^f At 0.8 GPa, 50 °C for 55 h.

^g At 0.6 GPa, rt for 55 h.

2–7). *p*-Tolylurea (**4b**) and mono-substituted aliphatic ureas, such as **4c** and **4d**, could also react with **2a** to afford the desired adducts **5h–j** in moderate to good yields (53–72%) (Table 3, entries 8–10). Efficient reactions were observed for *N,N*-dialkyl-substituted ureas, such as **4e** and **4f**, with **2a** after longer reaction times (Table 3, entries 11 and 12). These results clearly demonstrate the power of the present method, since it is the only method known for effectively preparing β-*N*-ureido-substituted ketone derivatives.

In conclusion, we have developed a simple and expeditious method for the aza-Michael reaction of amides and ureas as weakly reactive nucleophiles by combining Brønsted acid catalysis and high-pressure conditions. This method should be valuable for deriving novel types of β-*N*-amide- and β-*N*-ureido-substituted carbonyl compounds, starting from readily available substrates.¹⁸ Further studies to extend the scope of this new method are now in progress in our laboratory.

Acknowledgments

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- For a related work on high-pressure-promoted aza-Michael reactions of amines, see: Rulev, A. Yu.; Yenil, N.; Pesquet, A.; Oulyadi, H.; Maddaluno, J. *Tetrahedron* **2006**, *62*, 5411 and references cited therein.
- All new compounds gave satisfactory spectral data.
- General procedure:** A mixture of amide **1** or urea **4** (1.0 mmol) and enone **2** (1.2 mmol) in MeCN (ca. 1.3 mL) containing 10 mol % *p*-TsOH·H₂O was placed in a Teflon reaction vessel (1.5 mL volume), and the mixture was allowed to react at 0.6 GPa at 60 °C for a certain period of time to complete the reaction. After the reaction mixture was cooled and the pressure was released, the mixture was evaporated in vacuo. The crude product was purified by silica gel column chromatography (elution with hexane/EtOAc) to afford the pure adduct **3** or **5**.
- Compound **3a**:^{4c,d} mp 128.0–128.5 °C (from hexane–CHCl₃); FTIR (KBr) ν 3323, 1713, 1633, 1530 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.78–1.90 (2H, m), 1.98–2.08 (1H, m), 2.17–2.24 (1H, m), 2.29–2.49 (3H, m), 2.82 (1H, dd, *J* = 13.9, 4.9 Hz), 4.47 (1H, m), 6.06 (1H, br), 7.44 (2H, t, *J* = 7.1 Hz), 7.49 (1H, m), 7.74 (2H, d, *J* = 7.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 22.2, 30.8, 41.0, 47.6, 49.0, 126.9 (×2), 128.6 (×2), 131.7, 134.3, 166.8, 208.7.
- The role of hydrated *p*-TsOH·H₂O is unclear at present.
- We recently found that microwave irradiation was effective for the homoconjugate addition of *N*-heteroaromatics: Uddin, Md. I.; Mimoto, A.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Tetrahedron Lett.* **2008**, *49*, 5867.
- We found that the reaction was quite sensitive to the steric environment for both donor and acceptor molecules. For example, no products were formed for the reaction of C₆H₅CONHMe with **2a** or **1a** with 3-methyl-2-cyclohexen-1-one.
- The same reaction under microwave irradiation (100 W, 150 psi, 100 °C, 35 min) produced **5a** in only 20% isolated yield.
- Compound **5a**: mp 179.0–181.5 °C (from AcOEt); FTIR (KBr) ν 3313, 1716, 1628, 1574 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.69–1.83 (2H, m), 1.89–2.00 (1H, m), 2.06–2.13 (1H, m), 2.22–2.32 (2H, m), 2.35–2.43 (1H, m), 2.73 (1H, dd, *J* = 14.2, 4.9 Hz), 4.23 (1H, m), 4.94 (1H, d, *J* = 7.3 Hz; exchangeable by D₂O), 6.60 (1H, br; exchangeable by D₂O), 7.10 (1H, m), 7.26–7.34 (4H, m); ¹³C NMR (100 MHz, CDCl₃) δ 22.1, 31.0, 41.1, 48.1, 49.4, 120.6 (×2), 123.7, 129.3 (×2), 138.5, 155.1, 210.0.
- Despite the extreme activity of the present method, however, no reaction was observed for **1a** with methyl acrylate, methyl cinnamate, or acrylonitrile under the standardized conditions.