A Novel Method for the High-Pressure-Promoted, Uncatalyzed Aza-Michael Reaction of Nitrogen Heterocycles with Enones in Water[1]

Md. Imam Uddin, Keiji Nakano, Yoshiyasu Ichikawa, Hiyoshizo Kotsuki*

Laboratory of Natural Product Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780-8520, Japan
Fax +81(888)448359; E-mail: kotsuki@kochi-u.ac.jp

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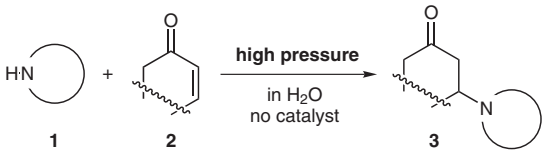
Abstract: A new green chemical method for the aza-Michael reaction of nitrogen heterocycles with enones in water as a solvent without the use of any catalysts under high-pressure conditions is described.

Key words: aza-Michael reaction, nitrogen heterocycles, enones, water, high-pressure reaction

The conjugate addition of nitrogen nucleophiles including NH-containing heterocycles to α,β-unsaturated ketones and esters is one of the most important carbon–nitrogen bond-forming reactions in organic synthesis and leads to a pharmacologically important family of β-amino carbonyl compounds.[2] The so-called aza-Michael reaction generally can be catalyzed or promoted by a variety of Brønsted[3] or Lewis acids containing Li, Cs and Mg,[4] B,[5] Al,[6] Sc, Ti and Hf,[7] Fe and Co,[8] Ni and Cu,[9] Zn,[10] Y,[11] Zr,[12] Ru, Rh and Pd,[13] In,[14] lanthanides (Ce, Sm, Yb),[15] Pt and Au,[16] and Bi.[17] In addition, inorganic solid supports,[18] fluorides,[19] organocatalysts[20] including asymmetric catalysts,[21] polymer-supported organobase,[22] and even enzymes[23] have also recently been developed for the same purpose. Despite this enormous progress, there have been only a few reports on the use of nitrogen heterocycles as Michael donors due to their low nucleophilicity. Moreover, the reported methods are often associated with some drawbacks, such as the polymerization of Michael acceptors, and the use of harmful organic solvents or expensive catalysts. Although some alternative procedures which might be feasible for environment-friendly transformations have also been reported,[24] conceptually new versions using noncatalytic and aqueous systems are rare.[25,26]

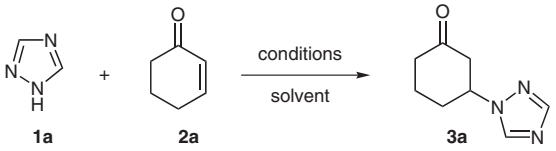
In our continuing efforts to demonstrate the outstanding value of high pressure in organic synthesis,[27,28] we have been interested in devising a new uncatalyzed and aqueous process for the aza-Michael reaction of nitrogen heterocycles with enones (Scheme 1).

To establish the optimal conditions for transformations of this type, we first examined the reaction of 1,2,4-triazole (**1a**, 1.1 equiv) with 2-cyclohexenone (**2a**) under various conditions including high pressure as well as microwave irradiation, and the results are summarized in Table 1.[29]



Scheme 1

Table 1 Aza-Michael Reaction of 1,2,4-Triazole (**1a**) with 2-Cyclohexenone (**2a**) under High-Pressure or Microwave Conditions[a]



Entry	Conditions	Solvent	Yield (%)[b]
1	0.1 MPa, 60 °C, 72 h	H_2O	71
2	0.2 GPa, 60 °C, 20 h	H_2O	95
3	0.4 GPa, 60 °C, 20 h	H_2O	98
4	**0.6 GPa, 60 °C, 20 h**	**H_2O**	**100**
5	MW, 100 °C, 30 min[c]	H_2O	76
6	0.6 GPa, 60 °C, 20 h	MeOH	67[d]
7	MW, 100 °C, 30 min[c]	MeOH	55
8	0.6 GPa, 60 °C, 20 h	MeCN	81
9	MW, 100 °C, 30 min[c]	MeCN	Trace
10	0.6 GPa, 60 °C, 20 h	CH_2Cl_2	90
11	MW, 100 °C, 30 min[c]	CH_2Cl_2	Trace
12	0.6 GPa, 60 °C, 20 h	no solvent[e]	94

[a] All reactions were carried out using **1a** (1.1 mmol) and **2a** (1.0 mmol) in solvent (ca. 3 mL).
[b] Isolated yield.
[c] At 120 W and 50 psi.
[d] Additionally, 24% of the corresponding dimethyl acetal of **3a** was isolated.
[e] The reaction was performed using **1a** (1.0 mmol) in **2a** (ca. 1.3 mL, 13 equiv).

Among the several solvents examined, water gave the best result, and when the reaction was conducted at 0.6 GPa and 60 °C for 20 hours, **3a** was isolated in nearly quantitative yield (entry 4, Table 1). At lower pressures, slightly reduced yields were obtained (entries 2 and 3, Table 1).

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Methanol, MeCN, and CH_2Cl_2 also gave **3a**, but in somewhat lower yields due to incomplete conversion (entries 6, 8, and 10, Table 1). When the reaction was conducted in MeOH, the desired adduct **3** (67%) was obtained along with a considerable amount (24%) of the corresponding dimethyl acetal derivative (entry 6, Table 1).[30] Consistent with the reported examples,[20b,c,24h] microwave irradiation facilitated the reaction in water and in MeOH (entries 5 and 7, Table 1), but a high-pressure environment is superior because of its cleanliness. For comparison, we also examined the same reaction at atmospheric pressure in water at 60 °C, but in this case the reaction was very slow, and after three days **3a** was obtained in 71% yield (entry 1, Table 1). The reaction under solvent-free conditions proved to be also useful in producing **3a** and the yield reached 94% (entry 12, Table 1).

With these results in hand, we performed experiments to clarify the generality of this method for other substrates. The results are summarized in Table 2.[31]

The efficiency of this synthetic procedure strongly depends on the reactivity of the Michael acceptors. Thus, the reaction of cyclic enones such as **2a**, **2b**, **2c**, and **2g** with nitrogen heterocycles such as **1a**, pyrazole (**1c**), benzotriazole (**1e**), and purine (**1g**) gave the corresponding adducts **3b**, **3c**, **3h**, **3l**, **3o**, **3q**, and **3r** in excellent yields (entries 1, 2, 6, 9, 12, 14, Table 2). In the last example, a mixture of the N9- and N7-alkylated regioisomers (**3q** and **3r**) was obtained in a ratio of around 1.4:1.[32] As represented by the reaction of **2f**, β-substitution of cyclic enones considerably reduced the reactivity, probably due to steric and electronic reasons (entry 5, Table 2).

On the other hand, acyclic enones **2d** and **2e** were less reactive, and rather drastic conditions were necessary to derive substantial amounts of the products (entries 3, 4, 10, Table 2). Interestingly, when the reaction of **1a** with **2d** was performed, the desired adduct **3d** and its regioisomer **3e** were obtained in respective yields of 36% and 29%,[33] accompanied by the unavoidable polymerization of **2d** (entry 3, Table 2).

Among several nitrogen heterocycles, a family of imidazole derivatives, that is, imidazole (**1b**), 2-methylimidazole (**1d**), and benzimidazole (**1f**), showed remarkably distinctive behavior in the present aza-Michael reactions (entries 7, 11, 13, Table 2). Thus, a significant amount of **3j**, which might be formed by the Morita–Baylis–Hillman-type dimerization of **2a**, was obtained as a byproduct, and this tendency was dramatically increased when **1d** was used as the donor molecule (up to 60% yield).[34]

In conclusion, we have developed a new efficient method for the aza-Michael reaction of a variety of nitrogen heterocycles to enones using an aqueous system under high pressure. Notably, this reaction can be performed under completely uncatalyzed and essentially neutral conditions, and should be useful for easily preparing β-amino ketone derivatives.[35] Further studies to extend the scope of this reaction are now in progress.

Table 2 High-Pressure-Promoted Aza-Michael Reaction of Heterocycles **1** with Enones **2** in Water[a]

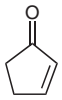
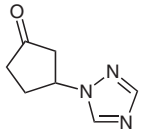
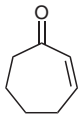
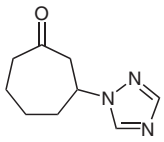
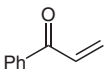
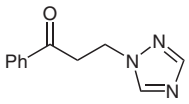
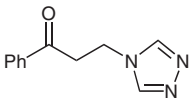
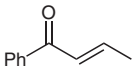
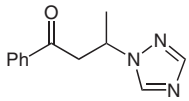
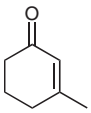
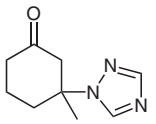
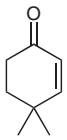
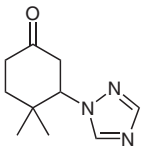
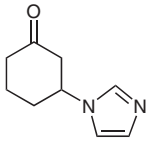
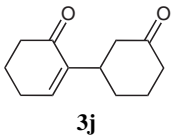
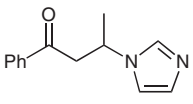
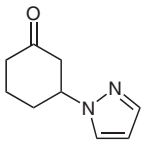
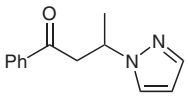
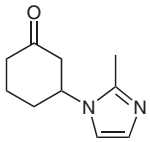
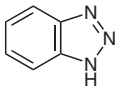
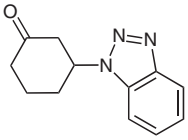
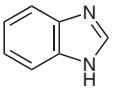
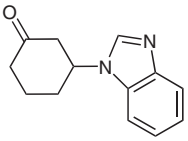
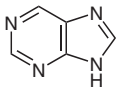
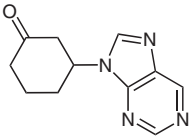
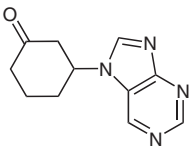
Entry	Heterocycle	Enone	Product(s)	Yield (%)[b]
1	 **1a**	 **2b**	 **3b**	99
2		 **2c**	 **3c**	99
3[c]		 **2d**	 **3d**	36 (11) 29
			 **3e**	
4[d]		 **2e**	 **3f**	73 (12)
5[e]		 **2f**	 **3g**	76 (16)
6		 **2g**	 **3h**	92
7[d]	 **1b**	**2a**	 **3i**	76 10
			 **3j**	
8[d]		**2e**	 **3k**	63 (18)

Table 2 High-Pressure-Promoted Aza-Michael Reaction of Heterocycles **1** with Enones **2** in Water[a] (continued)

Entry	Heterocycle	Enone	Product(s)	Yield (%)[b]
9	 **1c**	**2a**	 **3l**	99
10[d]		**2e**	 **3m**	71 (12)
11	 **1d**	**2a**	 **3n** **3j**	11 60
12	 **1e**	**2a**	 **3o**	96
13[f]	 **1f**	**2a**	 **3p** **3j**	73 10
14	 **1g**	**2a**	 **3q**  **3r**	51 36

[a] Unless otherwise noted, all reactions were performed at 0.6 GPa and 60 °C for 20 h in H_2O (3 mL) using **1** (1.1 mmol) and **2** (1.0 mmol).
[b] Isolated yield. Yields in parentheses are recovery of **2**.
[c] At 0.8 GPa, r.t., 60 h.
[d] At 0.8 GPa, 80 °C, 40 h.
[e] At 0.8 GPa, 80 °C, 60 h.
[f] At 0.6 GPa, 60 °C, 36 h.

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(29) **General Procedure**
A mixture of N-heterocycle (**1**, 1.1 mmol) and enone (**2**, 1.0 mmol) in distilled H_2O (ca. 3.0 mL) was placed in a Teflon reaction vessel, and the mixture was allowed to react at 0.6 GPa and 60 °C for 20 h. After the mixture was cooled and the pressure was released, the mixture was extracted with CH_2Cl_2. The extracts were dried, concentrated, and purified by silica gel column chromatography (elution with CH_2Cl_2–*i*-PrOH) to afford the pure adduct **3**.

(30) Acetalization of ketones under weakly acidic conditions (**1a**, pK_a = 14.75 in DMSO) in the absence of any dehydrating agents is quite unique, and we are currently performing experiments to explore the general scope of this reaction. See also: Kumamoto, K.; Ichikawa, Y.; Kotsuki, H. *Synlett* **2005**, 2254.

(31) All new compounds gave satisfactory analytical and spectral data.

(32) The higher reactivity of purine (**1g**) at the N9 position is well established. For example, see ref. 6.
Compound **3q**: mp 123–125 °C (hexane–CH_2Cl_2). FT-IR (KBr): ν = 1698, 1595, 1576, 1496, 1413 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.85 (1 H, dddd, *J* = 14.0, 12.0, 5.4, 3.6 Hz), 2.16–2.23 (1 H, m), 2.32–2.39 (1 H, m), 2.48–2.62 (3 H, m), 2.95 (1 H, ddt, *J* = 14.1, 4.9, 1.7 Hz), 3.26 (1 H, dd, *J* = 14.1, 11.7 Hz), 4.89 (1 H, tt, *J* = 11.5, 4.2 Hz), 8.13 (1 H, s), 8.98 (1 H, s), 9.17 (1 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 30.7, 40.5, 46.9, 54.4, 134.6, 143.2, 149.1, 150.9, 152.4, 206.3.
Compound **3r**: mp 143–144 °C (hexane–CH_2Cl_2). FT-IR (KBr): ν = 1708, 1606, 1559, 1488, 1412 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.83–1.96 (1 H, m), 2.17–2.26 (1 H, m), 2.37 (1 H, ddt, *J* = 14.6, 11.2, 3.6 Hz), 2.45–2.57 (2 H, m), 2.58–2.66 (1 H, m), 2.96 (1 H, ddd, *J* = 14.2, 11.0, 1.0 Hz), 3.03 (1 H, ddt, *J* = 14.2, 5.1, 1.7 Hz), 4.79 (1 H, ddt, *J* = 10.9, 5.1, 3.9 Hz), 8.33 (1 H, s), 9.04 (1 H, s), 9.18 (1 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 31.3, 40.4, 47.6, 55.7, 124.4, 140.0, 145.5, 153.7, 161.0, 205.3.

(33) Compound **3d**: mp 69–70 °C (hexane–CH_2Cl_2). FT-IR (KBr): ν = 1685, 1596, 1521, 1448 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.60 (2 H, t, *J* = 6.4 Hz), 4.65 (2 H, t, *J* = 6.4 Hz), 7.47 (2 H, m), 7.59 (1 H, tt, *J* = 7.3, 1.2 Hz), 7.91–7.95 (3 H, m), 8.23 (1 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.9, 44.0, 128.0 (2×), 128.7 (2×), 133.7, 136.0, 144.0, 152.0, 196.5.
Compound **3e**: mp 87–89 °C (hexane–CH_2Cl_2). FT-IR

(KBr): ν = 1687, 1538 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.50 (2 H, t, *J* = 6.1 Hz), 4.55 (2 H, t, *J* = 6.1 Hz), 7.50 (2 H, t, *J* = 7.8 Hz), 7.62 (1 H, m), 7.93 (2 H, m), 8.34 (2 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.2, 39.7, 128.0 (2×), 128.9 (2×), 134.2, 135.6, 143.2 (2×), 195.8.

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(35) α,β-Unsaturated esters were found to be mostly unreactive as Michael acceptors under the standard conditions (in H_2O, 0.6 GPa, 60 °C, 20 h), except for methyl acrylate (87% conversion yield).