

Communications

CeCl₃·7H₂O-NaI-SiO₂ Catalyzed Aza-Michael Addition of *N*-Heterocycles to Enones under Solvent Free Conditions

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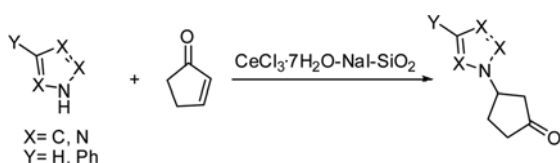
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The aza-Michael addition reaction promoted by Lewis acids and bases draws attention since it is one of the most important carbon-nitrogen bond forming reactions in organic synthesis. It is known that β -amino carbonyl compounds¹ can be obtained by the conjugate addition of aliphatic and aromatic amines to α,β -unsaturated carbonyl compounds. Numerous catalysts of the Lewis acids such as Yb(OTf)₃,^{2a} InCl₃,^{2b} Cu(OTf)₂,^{2c} Bi(OTf)₃,^{2d} FeCl₃·7H₂O/Co(OAc)₂,^{2e} SmI₂,^{2f} (NH₄)₂Ce(NO₃)₆,^{2g} and SiCl₄^{2h} had been developed for the aza-Michael reaction in the past years. As for the aza-Michael reaction, the conjugate addition of pyrazoles,³ imidazoles⁴ and triazoles⁵ has been reported. But in contrast, the conjugate addition reactions of pyrroles and indoles result in C-alkylation in the presence of Lewis acids. Marcantoni *et al.*⁶ reported that solvent free CeCl₃·7H₂O-NaI-SiO₂ system among the Lewis acids catalyzed the alkylation of several substituted indoles with α,β -unsaturated ketones giving C-alkylation in good yields. This method is more efficient, high-yielding, eco-friendly, and oxygen and moisture safe under the solvent free conditions. We applied this solvent free aza-Michael reaction to the reactions of cyclopentenone with pyrazoles, imidazoles, triazoles and purine.^{7a} Compared to the high-pressure-promoted reaction reported in the literature,^{5a} solvent free CeCl₃·7H₂O-NaI-SiO₂ system is much easier to handle. Although the *N*-heterocycles containing a cyclopentanone ring are seldom known, they are required for our drug design.

Under the system of CeCl₃·7H₂O-NaI-SiO₂, the addition of azoles with two and more nitrogen atoms to cyclic enones occurred but at the nitrogen centers instead of carbon centers. We have examined the reactions with cyclic and



Scheme 1. Aza-Michael addition of azoles to α,β -unsaturated ketones in CeCl₃·7H₂O-NaI-SiO₂ system.

Table 1. CeCl₃·7H₂O-NaI-SiO₂ Catalyzed Michael Reaction of Enones with Azoles

Entry	Amine	Enone	Product	Isolated yield (%)
1				87
2				91
3				33
4				62
5				65
6				92
7				78
8				<i>trans</i> :51 <i>cis</i> :17
9				97
10				52

acyclic α,β -unsaturated ketone substrates in the presence of this solvent free system at room temperature for 18 h. These results are shown in Table 1. Substrates **1b**,⁸ **1c**,⁹ **1e**¹⁰ and **1g**¹¹ were prepared by known procedure. The reaction of **1b**, **1f**, and **1h** with cyclic enone gave **3ba**, **3fa**, and **3ha** in higher yield (entries 2, 6, and 9). The reaction of **1a**, **1d**, **1e**, and **1g** with cyclic enone provided the corresponding *N*-heterocycles in moderate yields (entries 1, 4, 5, and 7). For imidazole **1c** and purine **1l**, yields were low (entry 3 and 10). In the case of entry 8, CeCl₃·7H₂O-NaI-SiO₂ system catalyzed Michael reaction of 1,2,3-triazole with 1-acetyl 1-cyclopentene provided an isomeric mixture of *trans* (51%) and *cis* triazole (17%). The stereochemistry of those isomers was identified according to the previous paper,^{7b} in which we described that 1,3-dipolar one pot reaction of organic azides and phenylacetylene with acetyl cyclopentene yields 1,2,3-triazoles, same as aza-Michael reaction products. And the identification of the triazoles was performed on the previous basis of documentation by X-ray crystallography.

In conclusion, we have found that solvent free CeCl₃·7H₂O-NaI-SiO₂ system efficiently catalyzed aza-Michael addition of pyrazoles, imidazole, triazoles and purine with α,β -unsaturated ketone in moderate yields by a one-pot procedure.

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12. **Typical procedure:** To a mixture of CeCl₃·7H₂O (100 mg, 0.27 mmol) and NaI (41 mg, 0.27 mmol) in CH₃CN (6 mL) was added SiO₂ (414 mg, 70-230 mesh, Merck). The mixture was stirred for overnight at room temperature and the solvent was removed in vacuo. The freshly prepared resulting mixture was added to pyrazole (100 mg, 0.694 mmol) and 2-cyclopentene-1-one (87 μ L, 1.04 mmol). After being stirred for overnight, CH₂Cl₂ was added and this suspension was passed through a short pad of Celite. The filtrate was concentrated under reduced pressure to give crude product which was purified by flash column chromatography (SiO₂, hexane: ethyl acetate = 2:1) to provide pure product. **3aa:** ¹H NMR (300 MHz, CDCl₃) δ 7.78 (s, 1H), 7.53 (s, 1H), 7.44 (d, *J* = 2.1 Hz, 1H), 6.26 (t, *J* = 2.0 Hz, 1H), 4.95 (pent, *J* = 6.4 Hz, 1H), 2.83 (dd, *J* = 18.4, 6.6 Hz, 1H), 2.94 (dd, *J* = 18.6, 7.6 Hz, 1H), 2.65-2.25 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 215.2, 139.8, 128.0, 105.7, 58.7, 44.9, 36.9, 30.4. MS (*m/z*, relative int): 150 (M⁺, 17), 122 (63), 94 (100), 68 (67), 54 (92), 52 (50).