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Formamide as an efficient nitrogen nucleophile for the Michael addition to nitroalkenes

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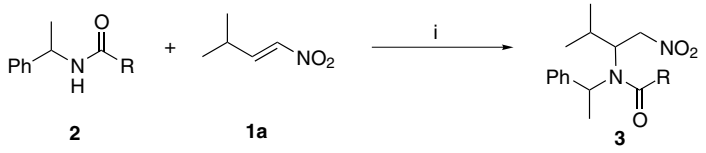
Abstract—Secondary acyclic formamide serves as an efficient nucleophile to nitroalkenes to give corresponding Michael adducts in good yields. The nitro group in the adducts was useful for further heterocyclic synthesis.

The Michael addition is one of the most useful reactions in organic synthesis.[1] Nitroalkenes are known as one of the most active alkenes for the reaction and used frequently in construction of carbon backbones.[2] A wide range of carbon- and heteroatom-centered nucleophiles underwent the addition reaction to give adducts in good yields. Although amines serve as a good nucleophile and the adducts, β-nitroamines, are regarded as a useful building block for the preparation of polyamino compounds or nitrogen heterocycles,[3] their labile property under acidic and basic conditions sometimes arises serious limitation for their use in the synthetic field. On the other hand, *N*-(β-nitro)amides are much stable and easy for handling so that it should be much useful for organic synthesis.[4] There are two ways to prepare these compounds, one is the imino-Henry reaction, and another is the Michael addition of amides to nitroalkenes. The former approach is now interesting to many organic chemists,[5] while there have been a few reports on the latter reaction so far[6] due to the low reactivity of amides.[7] Especially, development of conjugate addition of acyclic amides has been highly desired because the adducts would be promising reagents for heterocyclic synthesis. To improve the drawback, we have launched our investigation, and found that formamide acts as a good nucleophile to give the adducts in good yields. In this letter, we disclose the Michael addition of formamides and some heterocyclic synthesis using the adducts.

First of all, we examined a variety of amides for the Michael addition to nitroalkene **1a** under basic conditions (Scheme 1). The results are summarized in Table 1.

Treatment of *N*-Boc-amide **2a** with *t*-BuOK in the presence of 18-crown-6 did not form the corresponding adducts (entry 1). The starting amide **2a** was recovered quantitatively. Methyl carbamate **2b** or acetamide **2c** did not undergo the addition either. In contrast to these results, exposure of **2d** to **1a** under the same conditions gave desired Michael adduct **3d** in 48% yield (entry 4).



2 1a 3

Scheme 1. Reagents and conditions: (i) *t*-BuOK, 18-crown-6, THF, −50 °C, 2–4 h.

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Table 1. Nucleophilic addition of amides **2** to nitroalkene **1a**

Entry	Amide	R	Products	Yield[a] (%)	Diastereomeric ratio
1	**2a**	O–*t*-Bu	**3a**	0	—
2	**2b**	OMe	**3b**	0	—
3	**2c**	Me	**3c**	0	—
4	**2d**	H	**3d**	48	1:1

[a] Isolated yield.

The adduct contained two diastereomers, whose ratio seemed close to 1:1, so that almost no asymmetric induction from phenylethyl side chain was observed.

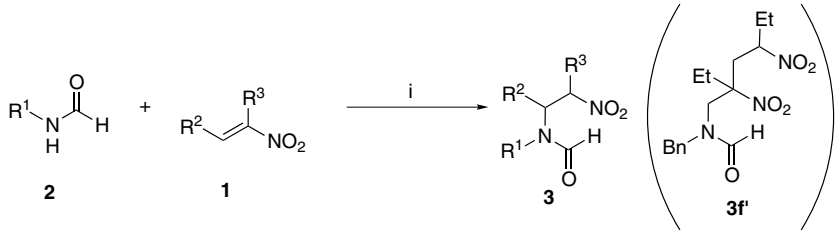
Since formamide successfully worked as a nucleophile in the Michael addition to nitroalkenes, a variety of nitroalkenes and formamides were examined for the conjugate addition reaction (Scheme 2). The results are summarized in Table 2.

For example, *N*-benzylformamide in the presence of a base attacked nitroalkene to give adduct **3e** in 80% yield (entry 1). β-Unsubstituted nitroalkene was very reactive toward the Michael addition so bis-adduct **3f′** was also observed in the reaction mixture (entry 2). The other formamide underwent the smooth addition to give the corresponding β-nitroamide **3** in good yields (entries 3–8). The addition to α,β-disubstituted nitroalkene resulted in the formation of two diastereomers in about 1:1 ratio (entry 7).[8]

The present Michael addition to cyclic nitroalkene took place in a stereoselective manner. For example, exposure of 1-nitrocyclohexene to amide anion followed by protonation at −50 °C resulted in the formation of adduct **4** in 72% yield (Scheme 3). This adduct contained almost single isomer. Treatment of the adduct in the presence of catalytic amounts of Et_3N induced efficient epimerization at α-carbon of the nitro group, giving *trans*-**4** selectively in quantitative yield. This epimerized product showed typical NMR pattern for *trans*-1,2-disubstituted cyclohexane, in which α-proton to the nitro group appeared as double triplet in relatively large coupling constant. The origin of stereoselectivity was explained in terms of kinetic protonation to nitronate intermediate.[9]

The nitro group in the adduct is potentially useful for further synthetic purpose. For example, the nitro group also served as a radical precursor by treatment with Bu_3SnH. Exposure of **3k**, which was 1:1 mixture of two diastereomers, to the standard radical conditions to remove aliphatic nitro group resulted in the smooth radical cyclization to give pyrrolidine **5** in good yields. Basic treatment of **5** and subsequent N-tosylation afforded tosylpyrrolidine **6** in 50% yield (see Scheme 4).[10]

In conclusion, formamides act as useful nitrogen nucleophiles for the Michael addition to nitroalkenes. The present method will provide a convenient method to prepare heterocyclic compounds through nitroalkene chemistry. Formamide is a protective group that is relatively easily removed by basic treatment so this would be an advantageous point from the synthetic point of view. As a variety of nitroalkenes as well as formamides are available, the present method will be applied to a wide range of synthesis. Further investigation on this issue is now underway in our laboratory.

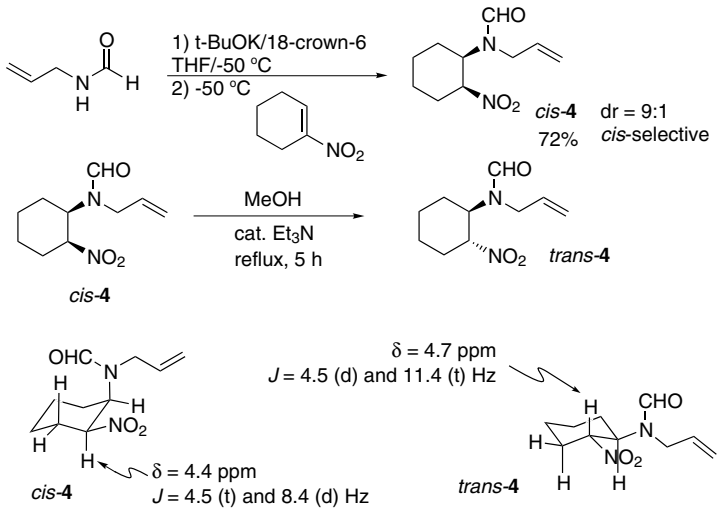


Scheme 2. Reagents and conditions: (i) *t*-BuOK, 18-crown-6, THF, −50 °C, 2–4 h.

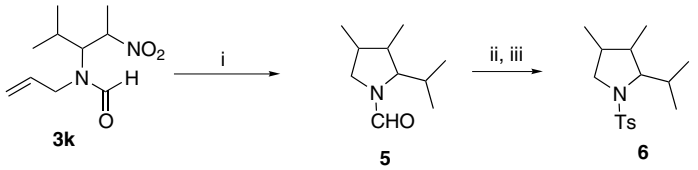
Table 2. The Michael addition of formamides **2** to nitroalkenes **1**

Entry	R^1	R^2	R^3	Products	Yield[a] (%)
1	$PhCH_2$	*i*-Pr	H	**3e**	80
2	$PhCH_2$	H	Et	**3f**	30[b]
3	3,4-$(MeO)_2C_6H_3CH_2CH_2$	*i*-Pr	H	**3g**	60
4	CH_2=$CHCH_2$–	*i*-Pr	H	**3h**	74
5	CH_2=$CHCH_2$–	Ph	H	**3i**	48
6	CH_2=$CHCH_2$–	Pr	H	**3j**	54[d]
7	CH_2=$CHCH_2$–	*i*-Pr	Me	**3k**	64[c]
8	CH_2=CH CH_2CH_2–	*i*-Pr	H	**3l**	73

[a] Isolated yield.
[b] Some amount of bis-adduct **3f′** was observed.
[c] Diastereomeric ratio was about 1:1.
[d] Without 18-crown-6.



Scheme 3.



Scheme 4. Reagents and conditions: (i) Bu_3SnH, AIBN, toluene, reflux, 3 h, 80%; (ii) NaOH, MeOH–H_2O, reflux; (iii) TsCl, DMAP, 50%.

References and notes

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10. Compound **6** contained two diastereomers in about 6:4 ratio, although the formation of four isomers was expected after the radical cyclization. So we assumed the radical cyclization should proceed in a stereoselective manner, that is, either 2,3-selective, 2,4-selective or 3,4-selective cyclization occurred. The investigation of the stereochemical course of the radical cyclization including determination of stereochemistry of **6** is now underway in our laboratory.