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One-pot three component α-aminoalkylation of conjugated nitroalkenes and nitrodienes

Kunjanpillai Rajesh, Pramod Shanbhag, Manjoji Raghavendra, Pallavi Bhardwaj, Irishi N. N. Namboothiri *

Department of Chemistry, Indian Institute of Technology, Bombay, Mumbai 400 076, India

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ABSTRACT

Nitroethylenes possessing aryl, heteroaryl, and alkyl substituents at the β-position as well as δ-substituted nitrobutadienes undergo facile aminoalkylation at the α-position upon treatment with formaldehyde and a secondary amine in the presence of imidazole and trifluoroacetic acid to afford α-aminoalkylated nitroalkenes and nitrodienes in good to excellent yield and stereoselectivity.

The C–C or C–N bond formation via coupling of an activated alkene with an electrophile, mediated normally by a Lewis base, has emerged as a highly atom-efficient strategy for the synthesis of small multi-functional molecules.[1–3] The enormous diversity in the components and conditions for this reaction, commonly known as Morita–Baylis–Hillman (MBH) reaction, has enthralled organic chemists in the last two decades.[3] The scope of this reaction in generating novel building blocks via inter- and intra-molecular reactions and asymmetric versions as well as applications in the synthesis of complex molecules is ever expanding.[3]

The reaction of an activated alkene with an imine or iminium electrophile under the MBH conditions (aza-MBH reaction) is particularly attractive as it generates synthetically and biologically relevant α-aminoalkylated activated alkenes.[4] The aminoalkylation relied primarily on activated imines such as sulfonylimines,[5] sulfinylimines,[6] phosphinoylimines,[7] and related species[8] which provided secondary amines with the activating group still attached to the products. Removal of such activating groups to liberate the amine requires an additional step which can be cumbersome.

An alternative means to generate α-aminoalkylated activated alkenes via MBH reaction is to employ iminium salts as electrophiles for which there are only two examples in the literature.[9,10] Azizi and Saidi reported the first MBH reaction of iminium salt as electrophile.[9] The salt which was generated in situ from benzaldehyde and *N*-trimethylsilyl pyrrolidine was reacted with methyl acrylate in the presence of DBU/$LiClO_4$ as the catalyst to afford the MBH adducts. More recently, Aggarwal and co-workers employed α-methoxypyrrolidine, a cyclic *N*,*O*-acetal and an iminium salt surrogate, as electrophile with a variety of activated alkenes in the presence of Me_2S/TMSOTf as the catalyst system.[10]

In recent years, we have reported the Morita–Baylis–Hillman reaction of conjugated nitroalkenes with various electrophiles such as formaldehyde and other carbonyl compounds, activated alkenes, imines, and azo compounds.[11] This strategy enabled us to synthesize a diverse array of potentially useful nitroethylenes replete with a range of functional groups.

We regarded the aminoalkylation of nitroalkenes using iminium salts generated in situ from aldehyde and amine as a simple and convenient method to synthesize 1,2-nitramines[12] which can be easily transformed to unsymmetrical 1,2-diamines which, besides being important synthetic intermediates, are prospective ligands and organocatalysts. 1,2-Nitramines are also immediate precursors to α-amino-oximes and α-amino-ketones.

Our preliminary optimization studies using β-furyl nitroethylene **1a** as the model substrate and formaldehyde–morpholine system **2–3a** as the electrophile revealed that DABCO, DMAP and imidazole were suitable catalysts for the desired transformation (Table 1, entries 1–6). Among these, imidazole provided the product in better yield in 24 h (entry 4) and after further optimization of the quantity of imidazole and solvent (Table 1, entries 7–14), it became apparent that stoichiometric amounts of imidazole in THF at room temperature offered satisfactory conditions for the α-aminoalkylation.[13]

Our further attempts to improve the yield via dual activation employing LiCl or a Brønsted acid such as acetic acid as co-catalyst showed only marginal improvement in the yield (Table 1, entries 15 and 16). However, remarkable rate acceleration and enhancement in the yield was observed when TFA (10 mol %) was used as the co-catalyst (Table 1, entry 17, 7 h, 82% yield)[14] though the reaction in water alone (entry 18) and under microwave irradiation conditions (entry 19) did not proceed well. Therefore, the conditions described in Table 1, entry 17 were applied to aminoalkylation of other β-heteroaryl and β-aryl nitroethylenes **1b–j** (Table 2). Thus, 3-furyl and 2-thienyl nitroethylenes, **1b** and **1c**, were subjected to α-aminomethylation to afford the MBH adducts **4b** and **4c** in 65% and 71% yields, respectively (Table 2, entries 2 and 3). As for the reactivity of β-aryl nitroethylenes, no appreciable

* Corresponding author. Tel.: +91 22 2576 7196; fax: +91 22 2576 7152.
E-mail address: irishi@iitb.ac.in (I.N.N. Namboothiri).

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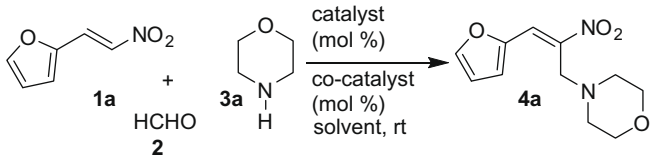
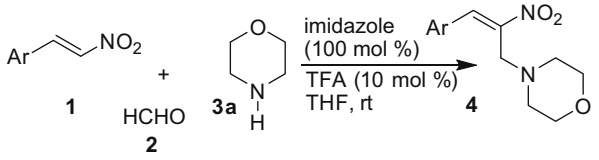
Table 1
α-Aminoalkylation of nitroalkene **1a** with formaldehyde **2**[a] and morpholine **3a**: catalyst and solvent screening



Entry	Catalyst (mol %), solvent	Time	% Yield[b]
1	DABCO (100), THF	24 h	58
2	DBU (100), THF	48 h	—[c]
3	DMAP (100), THF	48 h	40
4	Imidazole (100), THF	24 h	60
5	Me_3N (100), THF	96 h	23
6	Ph_3P (100), THF	60 h	27
7	Imidazole (10), THF	48 h	30
8	Imidazole (20), THF	48 h	42
9	Imidazole (50), THF	36 h	55
10	Imidazole (200), THF	24 h	56
11	Imidazole (100), CH_3CN	24 h	50
12	Imidazole (100), methanol	24 h	30
13	Imidazole (100), DMF	48 h	17
14	Imidazole (100), acetone	24 h	56
15	Imidazole (100), LiCl (10), THF	36 h	66
16	Imidazole (100), AcOH (10), THF	36 h	65
17	Imidazole (100), TFA (10), THF	7 h	82
18	Imidazole (100), TFA (10), water	24 h	—[d]
19	Imidazole (100), TFA (10), MW	1–2 min	—[e]

[a] 38% aqueous.
[b] Isolated yield after purification by silica gel column chromatography.
[c] No reaction.
[d] Traces.
[e] Nitroalkene polymerized.

Table 2
α-Aminoalkylation of nitroalkenes **1** with formaldehyde **2**[a] and morpholine **3a**



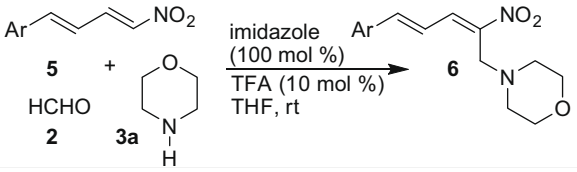
Entry	**1**, Ar	Time (h)	% Yield[b,c]
1	**1a**, 2-Furyl	7	82
2	**1b**, 3-Furyl	12	65
3	**1c**, 2-Thienyl	10	71
4	**1d**, Ph	7	65
5	**1e**, 4-MeO–Ph	10	68
6	**1f**, 3,4-$(MeO)_2$Ph	10	95
7	**1g**, 3,4-OCH_2O–Ph	10	72
8	**1h**, 4-Cl–Ph	10	65
9	**1i**, 4-F–Ph	12	68
10	**1j**, 2-NO_2–Ph	6	68

[a] 38% aqueous.
[b] Isolated yield after purification by silica gel column chromatography.
[c] 10–20% of nitroalkene **1** polymerized.

substituent effect[15] was observed except in the case of **1f** (Table 2, entry 6, 95% yield). Parent β-nitrostyrene **1d** (entry 4), nitrostyrenes with electron donating (**1e** and **1g**, entries 5 and 7), weakly electron withdrawing (**1h–i**, entries 8 and 9) and strongly electron withdrawing substituents (**1j**, entry 10) at the para position underwent aminoalkylation in comparable yield (65–72%, Table 2) over 6–12 h.

Subsequent to the above aminoalkylation of β-aryl and β-heteroaryl nitroethylenes **1**, we turned our attention to the reactivity of nitrodienes **5** (Table 3). Although nitrodiene can be easily prepared by condensing an α,β-unsaturated aldehyde with nitromethane,[16] the reactivity of nitrodiene in Michael addition and MBH

Table 3
α-Aminoalkylation of nitrodienes **5** with formaldehyde **2**[a] and morpholine **3a**



Entry	**5**, Ar	Time (h)	% Yield[b,c]
1	**5a**, 2-Furyl	15	71
2	**5b**, Ph	20	68
3	**5c**, 2-MeO–Ph	20	76
4	**5d**, 2-NO_2–Ph	24	63

[a] 38% aqueous.
[b] Isolated yield after purification by silica gel column chromatography.
[c] 10–20% of nitrodiene **5** polymerized.

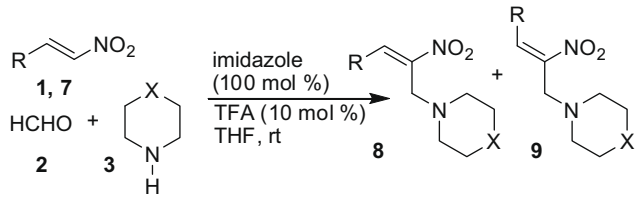
reaction was scarcely investigated.[17,18] Thus imidazole-catalyzed reaction of δ-heteroaryl and δ-aryl nitrodienes **5** afforded the α-aminoalkylated products **6** in good to high yield. As in the case of β-aryl and β-heteroaryl nitroethylenes **1**, nitrodienes **5** did not exhibit any appreciable effect of the nature of the aryl group. While δ-furyl nitrodiene **5a** and δ-phenyl nitrodiene **5b** underwent the one-pot three component aminoalkylation in good yield (Table 3, entries 1 and 2), the yield was marginally higher (76%) for **5c** with an electron donating substituent and lower (63%) for **5d** with an electron withdrawing substituent on the aromatic ring (Table 3, entries 3 and 4).

Having successfully generated the α-aminoalkylated products of aromatic and heteroaromatic nitroalkenes **1** and nitrodienes **5** using the iminium electrophile generated in situ from formaldehyde **2** and morpholine **3a**, we investigated further scope of this reaction using other amines such as piperidine **3b** and thiomorpholine **3c** (Table 4). We also employed a β-alkyl nitroethylene **7** for the first time in this aminoalkylation.

Although the yield is low (48%) and the product is prone to undergo decomposition, the MBH adduct of β-furyl nitroethylene **1a** with formaldehyde–piperidine system **2–3b** was isolated as a single *E*-stereoisomer (Table 4, entry 1). This is consistent with the product stereochemistry of all the MBH adducts of β-aryl and β-heteroaryl nitroethylenes **4** reported in Table 1. By contrast, the reaction of β-alkyl nitroethylene **7** with formaldehyde–morpholine 2–**3a** and formaldehyde–thiomorpholine **2–3c** provided the aminoalkylated products in good to excellent yield, but as a mixture of *E* and *Z* isomers (**8** + **9**) in ~ 9:1 ratio (Table 4, entries 2 and 3).

Finally, the reaction of nitrodienes **5** with formaldehyde–piperidine **2–3b** and formaldehyde–thiomorpholine **2–3c** systems was

Table 4
α-Aminoalkylation of nitroalkenes with formaldehyde **2**[a] and various secondary amines **3a–c**



Entry	**1**/**7**, R	**3**, X	Time (h)	% Yield[b] (**8** + **9**)	Ratio (**8**:**9**)
1	**1a**, 2-Furyl	**3b**, CH_2	5	**8a** + **9a**, 48[c]	100:0
2	**7**, Cy	**3a**, O	24	**8b** + **9b**, 83	93:07
3	**7**, Cy	**3c**, S	24	**8c** + **9c**, 62	89:11

[a] 38% aqueous.
[b] Isolated yield after purification by silica gel column chromatography.
[c] Partially decomposed during purification.

investigated (Table 5). These results further confirmed the generality of our methodology for the facile α-aminoalkylation of activated alkenes and dienes. As is discernible from Table 5, the reaction of nitrodienes **5a–c** with formaldehyde–piperidine system 2–**3b** proceeded satisfactorily to afford the MBH adducts **10a–c** in good yields (54–63%, Table 5, entries 1–3). Similar reaction of nitrodienes **5a–c** with formaldehyde–thiomorpholine system **2–3c** provided the MBH adducts **10d–f** in good to high yield (59–72%, Table 5, entries 4–6).

The structures of all the aminoalkylated products were confirmed by their IR, ^{1}H and ^{13}C NMR as well as mass spectral characteristics. The geometry of the nitroethylenic double bond was found to be *E* in all the products which were formed as single isomers. In the case of mixtures (Table 4, entries 2 and 3, Table 5, entry 6), *E* geometry was assigned for the nitroethylenic double bond in the major products. These assignments are based on the deshielding effect experienced by the proton β to nitro group in *E* isomers by 1.2–1.4 ppm in the ^{1}H NMR spectrum (Tables S1–S2, see Supplementary data). This was further confirmed by ^{1}H–^{1}H 2D NOESY experiment with a representative adduct **4j**. A medium NOE between the allylic CH_2 and one of the aromatic protons, presumably, the one ortho to the nitroethylenic moiety was observed for **4j** (see Supplementary data). In the case of α-aminoalkylated nitrodienes **6** and **10**, both the double bonds were assigned *E* configuration based on the coupling characteristics of the three protons in the dienic moiety. In general, the proton β to nitro group coupled with the γ-proton with a *J* value of ~10.5–12.0 Hz and the γ-proton coupled with the δ-proton with a *J* value of ~15.0–16.0 Hz suggesting that both the double bonds have *E* configuration. Further confirmation of this assignment was obtained from ^{1}H–^{1}H 2D COSY and NOESY experiments with a representative adduct **6c** (Fig. 1). A strong NOE between H^a and H^c and a medium NOE between H^b and the allylic methylene were indicative of the *EE* geometry of the two double bonds in **6c** (see also Supplementary data).

The catalytic role of imidazole and TFA involving a dual activation mechanism is depicted in Scheme 1. While imidazole functions as the nucleophilic Lewis base which adds to nitroalkene in a Michael fashion, TFA could act as Brønsted acid by (a) activating the nitroalkene for conjugate addition and stabilizing the nitronate via hydrogen bonding (**I** to **II**) and (b) facilitating the formation of iminium by activating the aldehyde (**2** + **3** to **III**) and (c) activating the iminium **III** towards addition of nitronate **II** by stabilizing the counter ion (Scheme 1). It is important to note that stoichiometric amount of imidazole is required to obtain high yield of the product. This suggests that high concentration of the nitronate **II** arising from conjugate addition of imidazole to nitroalkenes is necessary for the success of the reaction.[19]

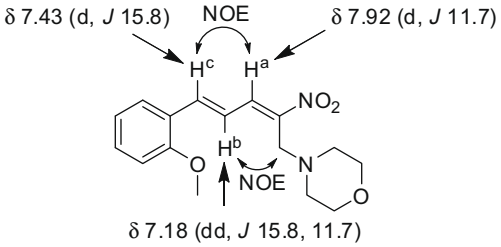
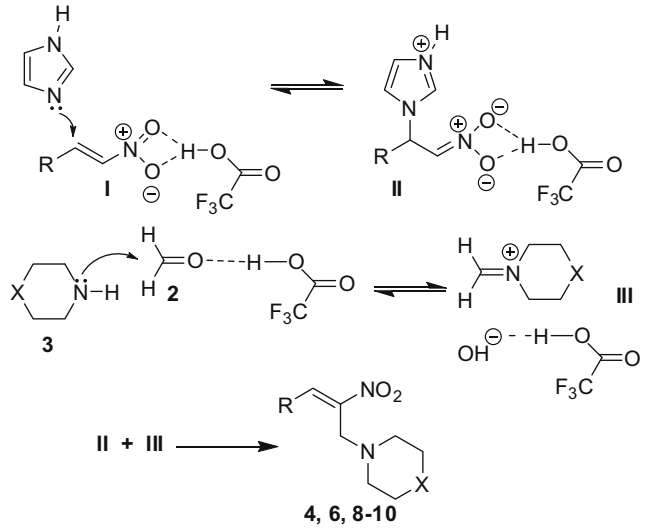


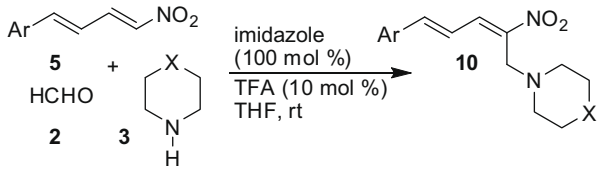
Figure 1. Structural assignment of **6c**.



Scheme 1.

In conclusion, conjugated nitroalkenes and nitrodienes have been aminoalkylated at the α-position via a one-pot multi-component, room temperature and atom economical reaction using formaldehyde and a secondary amine in the presence of a nucleophilic Lewis base Brønsted acid catalyst system, viz. imidazole and TFA.[20] The products, isolated in good to excellent yield, are prospective synthetic intermediates and precursors to unsymmetrical diamine ligands and organocatalysts. Our future work will be directed towards expanding the scope of this reaction, including the asymmetric version, and exploring the applications of the novel α-aminoalkylated nitroalkenes.

Table 5
α-Aminoalkylation of nitrodienes **5** with formaldehyde **2**[a] and piperidine **3b**/thiomorpholine **3c**



Entry	5	X	Time (h)	% Yield[b,c]
1	**5a**, 2-Furyl	**3b**, CH_2	6	**10a**, 54[d]
2	**5b**, Ph	**3b**, CH_2	24	**10b**, 63
3	**5c**, 2-MeO–Ph	**3b**, CH_2	16	**10c**, 57
4	**5a**, 2-Furyl	**3c**, S	20	**10d**, 59
5	**5b**, Ph	**3c**, S	24	**10e**, 71
6	**5c**, 2-MeO–Ph	**3c**, S	24	**10f**, 72[e]

[a] 38% aqueous
[b] Isolated yield after purification by silica gel column chromatography.
[c] ~15–20% of nitroalkene polymerized.
[d] Decomposed during purification.
[e] MBH adduct **10f** and its 2*Z* isomer were isolated as an inseparable mixture in 93:7 ratio.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.015.

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18. For aza-MBH reaction of sulfonylimines with conjugated dienes activated by other electron withdrawing groups such as sulfonyl, carboxylate and ketone: Sorbetti, J. M.; Clary, K. N.; Rankic, D. A.; Wulff, J. E.; Parvez, M.; Back, T. G. *J. Org. Chem.* **2007**, *72*, 3326.
19. For a detailed discussion on the superior role of imidazole in catalyzing the MBH reaction of nitroalkenes, see Ref. 11d. In this context, the term 'catalyst' is used to indicate that imidazole can in principle be recovered and recycled.
20. *General procedure for the α-aminoalkylation of nitroalkenes and nitrodienes*: To a stirred solution of nitroalkene or nitrodiene (1 mmol) and imidazole (1 mmol) in THF (2 mL) was added morpholine or piperidine or thiomorpholine (4 mmol) followed by 38% aqueous formaldehyde (4 mL, excess) and TFA (8 μL, 10 mol %). The reaction mixture was stirred at rt until the completion of the reaction (see Tables 1–5). Then THF was removed in vacuo, the aqueous layer was diluted with water (10 mL), extracted with EtOAc (3 × 10 mL) and the combined organic layer was concentrated in vacuo. The residue was purified by silica gel column chromatography to afford pure aminoalkylated nitroalkene or nitrodiene.