Highly efficient hydrazination of conjugated nitroalkenes *via* imidazole or DMAP mediated Morita–Baylis–Hillman reaction†‡

Mamta Dadwal,[a] Shaikh M. Mobin[b] and Irishi N. N. Namboothiri*[a]

Received 4th April 2006, Accepted 22nd May 2006
First published as an Advance Article on the web 31st May 2006
DOI: 10.1039/b604899d

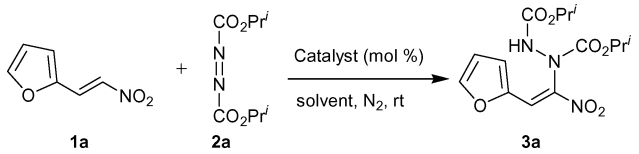
Novel α-hydrazino-α,β-unsaturated nitroalkenes, which exhibit dynamic phenomenon on the NMR time scale, were synthesized in excellent yields *via* imidazole or DMAP mediated Morita–Baylis–Hillman (MBH) type reaction of nitroalkenes with azodicarboxylates.

The coupling of the α-position of activated alkenes (vinyl anion equivalents) with various carbon electrophiles mediated by a tertiary amine or tertiary phosphine, popularly known as the Morita–Baylis–Hillman (MBH) reaction, has emerged as an important C–C bond forming reaction in organic synthesis.[1–4] It provides a simple, convenient and atom-economical methodology for the synthesis of densely functionalized molecules.[3] However, C-hetero atom bond formation *via* similar strategy has not received much attention.[5,6] For instance, C–N bond formation *via* the MBH reaction is equivalent to electrophilic amination of a vinyl anion.

Electrophilic amination of carbanion equivalents is, in fact, an important C–N bond forming strategy offering a convenient entry into natural/unnatural amino acids and other synthetically and biologically useful building blocks.[7] Commonly employed electrophiles for this purpose are azodicarboxylates,[8] azides,[8,9] oxaziridines[10] *etc.*[7] Among the handful of methods available in the literature for the synthesis of α-hydrazino-α,β-unsaturated compounds[5,11] which are potential precursors to bioactive compounds,[12] only two reports, to our knowledge, involve the electrophilic amination of vinyl anion equivalents with azodicarboxylate.[5] More importantly, there is no report, to our knowledge, on the MBH type coupling of the α-position of β-substituted activated alkenes with azodicarboxylate or any other electrophilic aminating agents mentioned above.[13] Furthermore, despite their well documented synthetic utility, especially as powerful Michael acceptors, conjugated nitroalkenes[14] have been scarcely employed as substrates in more than three decades of the MBH chemistry.[15–18]

The possible application of multifunctional MBH adducts arising from nitroalkenes as novel synthetic scaffolds and biologically active molecules[17] prompted us to pursue a fundamentally novel coupling of nitrovinyl anion with N-centered electrophiles. Thus, in this report, we describe our results on the successful MBH type reaction of β-substituted nitroalkenes with activated azo compounds, namely, azodicarboxylates leading to α-hydrazino-α,β-unsaturated nitro compounds in excellent yields.

Our initial optimization studies using 2-nitrovinyl furan (NVF) **1a** as the model substrate with diisopropyl azodicarboxylate (DIAD) **2a** as the electrophile in THF at room temperature in the presence of 10 mol% of various catalysts revealed the suitability of imidazole[19] and/or DMAP[20] as catalyst(s) of choice for further optimization (Scheme 1) (see ESI†).



Scheme 1

Subsequent optimization experiments suggested that stoichiometric amounts of imidazole or DMAP, would be beneficial to obtain the best yield of the MBH adduct **3a** in the shortest possible reaction time. In contrast to the excellent catalytic ability of imidazole in THF (4 h, 98%), DMAP, even in stoichiometric amounts provided only moderate yield of **3a** when THF was used as solvent (24 h, 43%). Since no conclusions could be drawn on the behavior of DMAP from the experiments in THF alone, other solvents were screened uniformly for both the catalysts. Thus, the most appropriate solvent for the imidazole catalyzed reaction was found to be THF and for the DMAP catalyzed reaction, it was acetonitrile. Finally, the optimum substrate–electrophile ratio (**1a** : **2a**) was determined to be 1 : 1.5 for the imidazole catalyzed reaction and 1 : 1.3 for the DMAP catalyzed reaction.

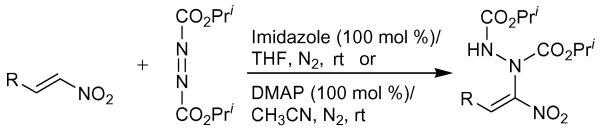
Having established the optimum experimental conditions for obtaining the best yields of the MBH adduct **3a**, *i.e.* one equiv. of imidazole in THF or DMAP in acetonitrile with 1 : 1.3 to 1 : 1.5 ratio of substrate to electrophile under N_2 at room temperature, we reacted a variety of aromatic and heteroaromatic nitroalkenes **1b–m** and an aliphatic nitroalkene **1n** with DIAD **2a** (Table 1). We were delighted to note the formation of the desired MBH adducts **3b–m** in impressive yields, especially under the imidazole catalyzed conditions (Table 1, Entries 1–13), although aliphatic nitroalkene **1n** did not provide satisfactory results (Entry 14). Surprisingly, the nature of aromatic ring in **1a–m** did not appreciably influence the reactivity in terms of the % yield. Parent nitrostyrene **1g** which is highly prone to polymerization and its analogues **1k** and **1m** with strongly electron withdrawing and electron donating substituents, respectively, reacted remarkably well providing the adducts **3g**, **3k**

[a]*Department of Chemistry, Indian Institute of Technology, Bombay, Mumbai, 400 076, India. E-mail: irishi@iitb.ac.in; Fax: +91 22 2576 7152; Tel: +91 22 2576 7196*
[b]*National Single Crystal X-ray Diffraction Facility, Indian Institute of Technology, Bombay, Mumbai, 400 076, India*

† Electronic Supplementary Information (ESI) available: Experimental procedures, full characterization data, copies of ^{1}H and ^{13}C NMR spectra for all the new compounds, complete set of variable temperature NMR spectra for **3f** and ^{1}H–^{1}H NOESY spectrum for **3a**. See DOI: 10.1039/b604899d

‡ Dedicated to Professor B. Shivarama Holla on the occasion of his 60th birthday.

Table 1 The MBH reaction of nitroalkenes **1** with DIAD **2a**[a] in the presence of 100 mol% imidazole in THF or 100 mol% DMAP in acetonitrile at room temperature



1 **2a** **3**

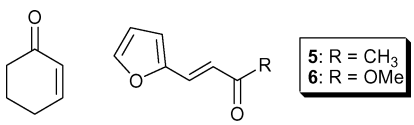
			Imidazole (a)		DMAP (b)	
Entry	**1**	R	Time/h	Yield (%)[b]	Time/h	Yield (%)[b]
1	**1a**	2-Furyl	4	98	$3\frac{1}{4}$	85
2	**1b**	2-Thienyl	$4\frac{1}{4}$	94	$\frac{3}{4}$	86
3	**1c**	3-Furyl	$2\frac{3}{4}$	100	$1\frac{1}{2}$	87
4	**1d**	3-Thienyl	2	98	$\frac{3}{4}$	83
5	**1e**	(4-Cl)Ph	$\frac{3}{4}$	93	$\frac{1}{2}$	70
6	**1f**	(4-OMe)Ph	4	98	2	84
7	**1g**	Ph	$\frac{3}{4}$	83	$\frac{1}{2}$	78
8	**1h**	3,4-(OCH_2O)Ph	2	92	2	82
9	**1i**	3,4-($OMe)_2$Ph	6	99	2	81
10	**1j**	(4-CF_3)Ph	$\frac{1}{2}$	93	$\frac{1}{4}$	43[d]
11	**1k**	(4-NO_2)Ph	$\frac{1}{2}$	84	$\frac{1}{4}$	68
12	**1l**	(3-OMe,4-OH)Ph	6	97	2	79
13	**1m**	(4-NMe_2)Ph	24	86[c]	8	46[e]
14	**1n**	*n*-C_6H_{13}	48	[f]	1	[g]

[a] 1.5 equiv. for imidazole catalyzed reaction and 1.3 equiv. for DMAP catalysed reaction. [b] Isolated yield of **3** after column chromatography. [c] 11% of **1m** was recovered. [d] Complete consumption of **1j** was observed. [e] 35% of **1m** was recovered, there was no further progress after 8 h. [f] Complex mixture. [g] **1n** polymerized.

and **3m**, respectively, in well over 80% yield under the imidazole catalyzed conditions (Table 1, Entries 7a, 11a and 13a). The reaction times were indeed less for parent nitrostyrene **1g** and its analogs with electron withdrawing groups at the *para* position **1e**, **1j** and **1k** (Table 1, Entries 7, 5, 10 and 11). In general, the reaction time exceeded 6 h only for nitrostyrene with a strongly electron donating group at the *para* position, *i.e.* **1m** (Table 1, Entry 13).

Although the yields of MBH adducts **3a–m** from DMAP catalyzed reactions were less impressive (Table 1, Entries 1b–13b) as compared to that from the imidazole catalyzed reactions (Entries 1a–13a), complete conversion of **1** was observed in satisfactory reaction time except in the case of **1m** (Entry 13).

Finally, Table 2 shows that diethyl azodicarboxylate (DEAD) **2b** is equally effective as an electrophilic aminating agent for our β-substituted nitroalkenes (for *e.g.* for **1a** and **1f**, Entries 1 and 2). On the other hand, diamide **2c** was found to be an ineffective electrophile under our optimized conditions (Table 2, Entry 3). Entries 4–6 (Table 2) show that while β-substituted cyclic enone **4** reacts with **2a**, acyclic enone **5** and acrylate **6** are unreactive.



4 **5, 6**

The (*E*) geometry of MBH adducts **3** and **7** was determined by analysis of the ^1H–^1H NOESY spectrum of a representative compound **3a** (see ESI†). The positive NOE interaction between the furyl protons and the Me protons of the *i*-Pr group taken together with the absence of any NOE interaction between the styrenic proton and the Me protons of the *i*-Pr group were the basis for this assignment. Subsequently, the single crystal X-ray analysis of a representative system **3a** (Fig. 1)[21] unambiguously established the structure and (*E*) geometry of the double bond in **3** and **7**. In particular, a dihedral angle of close to 180° between C_4 and N_1 and partial double bond character for the C-N bonds of the hydrazino dicarboxylate moiety were apparent from the X-ray data (see ESI†).

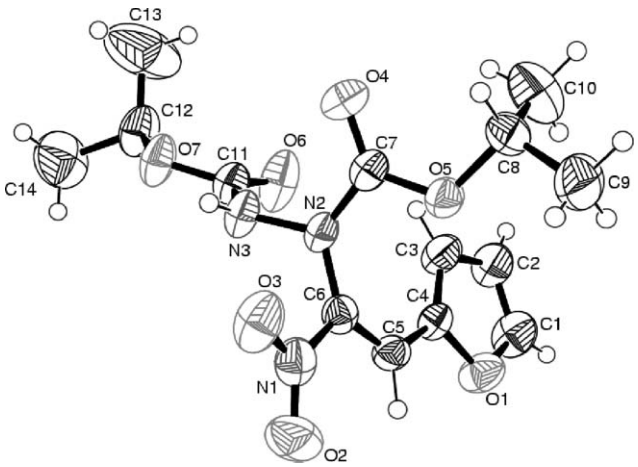
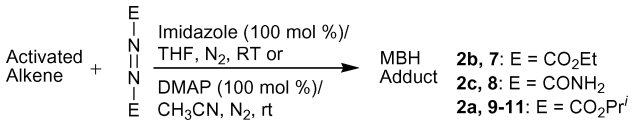


Fig. 1 ORTEP diagram of **3a**.

Interestingly, all the MBH adducts **3a–m**, **7a** and **7f** exhibited dynamic phenomenon on NMR time scale. For instance, ^1H NMR spectra recorded for **3f** in the temperature range −40 to +55 °C (233–328 K) showed broad resonances at room temperature for the Me group, the styrenic proton and the aromatic protons *meta* to OMe, sharp averaged signals at elevated temperature

Table 2 The MBH reaction of activated alkenes **1**, **4–6** with azo compounds **2a–c**[a] in the presence of 100 mol% imidazole in THF or 100 mol% DMAP in acetonitrile at room temperature



				Imidazole (a)		DMAP (b)	
Entry	**1**	**2**	**7–11**	Time/h	Yield (%)[b]	Time/h	Yield (%)[b]
1	**1a**	**2b**	**7a**	$3\frac{1}{2}$	95	2	75
2	**1f**	**2b**	**7f**	$2\frac{1}{4}$	94	$2\frac{1}{4}$	87
3	**1f**	**2c**	**8**	24	NR[c]	24	NR[c]
4	**4**	**2a**	**9**	72	52	120	38[d]
5	**5**	**2a**	**10**	168	NR[c]	72	NR[c]
6	**6**	**2a**	**11**	168	NR[c]	168	NR[c]

[a] 1.5 equiv. for imidazole catalyzed reaction and 1.3 equiv. for DMAP catalysed reaction. [b] Isolated yield of **7–11** after column chromatography. [c] No reaction. [d] 28% of **4** was recovered.

and sharp but multiple signals at low temperature (Fig. 2a–c). Even at +55 °C, the *i*-propyl Me of one of the ester groups, was broad (Fig. 2c). This is attributable to the anisotropy of the carbonyl group which arises from restricted rotation about the C–N bond(s) of the hydrazino dicarboxylate moiety which has partial double bond character. The dynamic phenomenon due to a possible tautomerism involving the $NHCO_2Pr^i$ group was ruled out as the product arising from N-allylation of **3a** also exhibited similar phenomenon. An independent phenomenon involving atropisomerism about the C_α–N bond due to the presence of a β-substituent[22] also appeared unlikely because similar broadening of peaks was observed in β-unsubstituted products, *e.g.* arising from MVK and **2a**.[23]

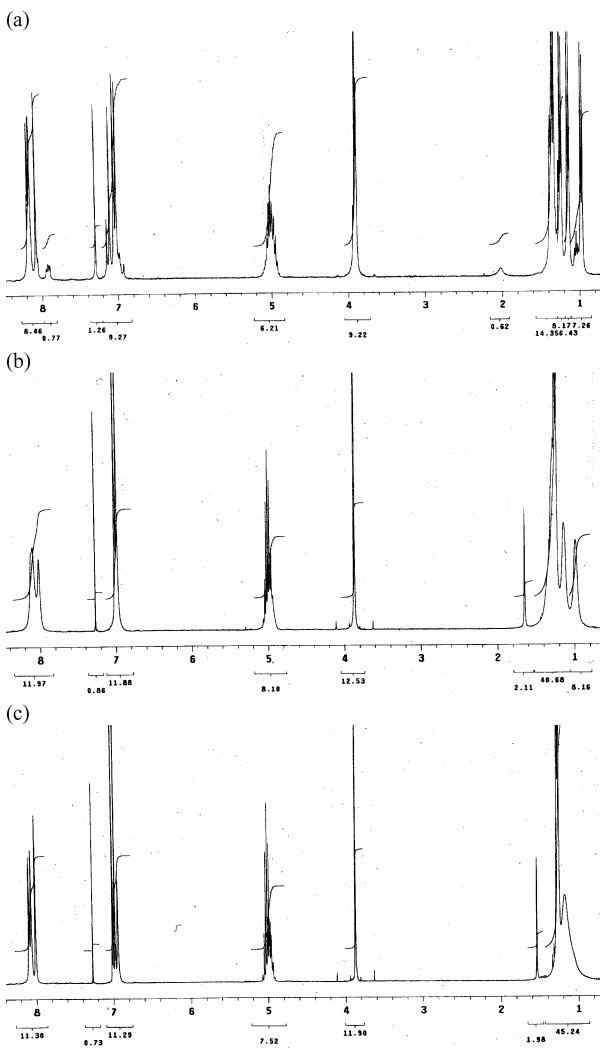


Fig. 2 ^{1}H NMR Spectra of **3f** recorded at (a) 223 K, (b) 293 K and (c) 328 K.

In conclusion, novel β-substituted α-hydrazinonitroalkenes have been synthesized in excellent yields in a very simple, one-pot, atom economical fashion from readily available β-substituted conjugated nitroalkenes and azodicarboxylates in short reaction times.[24] It is for the first time, to our knowledge, β-substituted activated alkenes have been transformed to their α-hydrazino derivatives under the MBH conditions. Our studies also establish the fact that nitroalkenes, whose reactivity as MBH substrates remained obscure until recently, are, in fact, amenable for the synthesis of novel embellished molecules with interesting properties. Future efforts will be focused on the application of other N-centered electrophiles in the MBH reaction of nitroalkenes as well as on the synthetic and biological applications of these nitrogen rich multifunctional molecules.

We thank DST India for funding and SAIF, IIT Bombay, for selected NMR data. MD thanks CSIR, India, for a research fellowship.

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