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Hydroxyalkylation of Conjugated Nitroalkenes with Activated Nonenolizable Carbonyl Compounds

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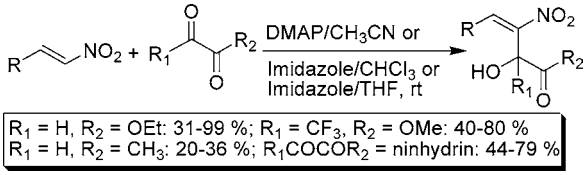
ABSTRACT



The Morita–Baylis–Hillman reaction of a variety of conjugated nitroalkenes with activated nonenolizable carbonyl compounds such as glyoxylate, trifluoropyruvate, pyruvaldehyde, and ninhydrin in the presence of 40–100 mol % of DMAP in acetonitrile or 100 mol % of imidazole in $CHCl_3$ or THF provided the adducts in decent to good yields. In most cases, the reactions catalyzed by DMAP in acetonitrile were faster and provided the desired MBH adducts in higher yields as compared to the imidazole catalyzed reactions.

Baylis and Hillman, in their patent,[1] have reported the synthesis of α-hydroxyethyl nitroethylene via the reaction between nitroethylene and acetaldehyde under the catalytic influence of DABCO. This was part of their DABCO-catalyzed reactions of various activated alkenes with aldehydes.[1,2] Their reactions of acrylates, acrylonitrile, acrylamides, and vinyl ketones with aldehydes have received further attention and, with the inclusion of many other activated alkenes and electrophiles, have blossomed into a highly efficient, multicomponent, and atom-economical methodology.[2−4] However, there were no further reports in the literature by the same authors or others on such reactions of nitroalkenes until we recently reported the imidazole mediated hydroxymethylation of a variety of β-substituted conjugated nitroalkenes using formaldehyde.[5,6] This is despite the well-documented synthetic utility of nitroalkenes, especially, as excellent Michael acceptors.[7]

Conjugated nitroalkenes are also distinguished by their biological properties.[8] Among various biological properties, the anticancer activity of nitroalkenes[9,10] and their novel

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(1) Hillman, M. E. D.; Baylis, A. B. U.S. Patent US 3743669, 1973.

(2) (a) Baylis, A. B.; Hillman, M. E. D. Ger. Offen. DE 2155113, 1972; *Chem. Abstr.* **1972**, *77*, 434174. (b) Prior to Baylis and Hillman, Morita et al. had reported similar reactions catalyzed by tertiary phosphine, see: Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.

(3) For a recent review: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. See also: (b) Kataoka, T.; Kinoshita, H. *Eur. J. Org. Chem.* **2005**, 45.

(4) For recent mechanistic studies: (a) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1706. (b) Santos, L. S.; Pavam, C. H.; Almeida, W. P.; Coelho, F.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 4330. (c) Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980. (d) Buskens, P.; Klankermayer, J.; Leitner, W. *J. Am. Chem. Soc.* **2005**, *127*, 16762.

(5) Rastogi, N.; Namboothiri, I. N. N.; Cojocaru, M. *Tetrahedron Lett.* **2004**, *45*, 4745.

(6) Ballini et al. also reported a reaction between aliphatic nitroalkenes and ethyl-2-bromomethylacrylate under the DBU-catalyzed conditions: Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D.; Mignini, E.; Palmieri, A. *Tetrahedron* **2004**, *60*, 4995. However, this reaction apparently involves an overall allylic displacement of bromide and the product is not a conjugated nitroalkene.

(7) (a) For a recent review: Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (b) For a recent article: Namboothiri, I. N. N.; Ganesh, M.; Mobin, S. M.; Cojocaru, M. *J. Org. Chem.* **2005**, *70*, 2235. (c) The first step in the Morita−Baylis−Hillman (MBH) reaction is the Michael-type addition of the nucleophilic catalyst.

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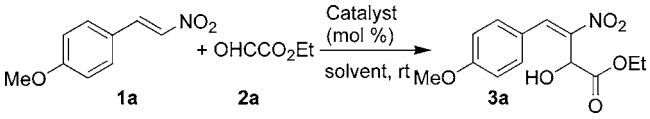
Scheme 1



MBH adducts with other activated alkenes such as MVK and acrylate by targeting microtubules/tubulins[10] has highlighted the enormous potential of nitroalkene derivatives as bioactive molecules.[9,10] This, together with the possibility of transforming the MBH adducts of nitroalkenes to amino alcohols, unusual amino acids, etc., prompted us to further explore the reactivity of nitroalkenes with other electrophiles, viz. various carbonyl compounds.

Since our attempts to carry out the hydroxyalkylation of nitroalkenes using simple aliphatic or aromatic aldehydes in the presence of various catalysts provided unsatisfactory results, we envisioned that suitably activated carbonyl compounds would be reactive as electrophiles in the MBH reaction of nitroalkenes. Our literature survey showed that activated aldehydes such as glyoxylates[11] and α-amido aldehydes[12] and activated ketones such as 1,2-diketones,[13] 1,2,3-triketones,[13] keto esters,[15] keto amides,[16] and halo ketones[17] have been used as electrophiles in the MBH reaction of activated alkenes such as vinyl ketones, acrylates, and acrylonitrile.[3]

The experimental conditions suitable for the MBH reaction of nitroalkenes with various activated carbonyl compounds were established using *p*-methoxynitrostyrene **1a** and ethyl glyoxylate **2a** as model substrate and electrophile, respectively (Scheme 1, see the Supporting Information).

Under the optimized conditions, i.e., 40 mol % of DMAP in acetonitrile or 100 mol % of imidazole in $CHCl_3$, various aromatic nitroalkenes **1a**−**i** and heteroaromatic nitroalkenes **1j**−**m** were reacted with ethyl glyoxylate **2a (**Figure 1, Table 1). Remarkably, under the DMAP-catalyzed conditions, all of the reactions were complete in less than 30 min providing good to excellent yields of the MBH adducts **3a**−**m (**Table 1, entries 1a−13a). In general, the yields were in the 80−100% range for aromatic nitroalkenes **1a**−**d** (Table 1, entries

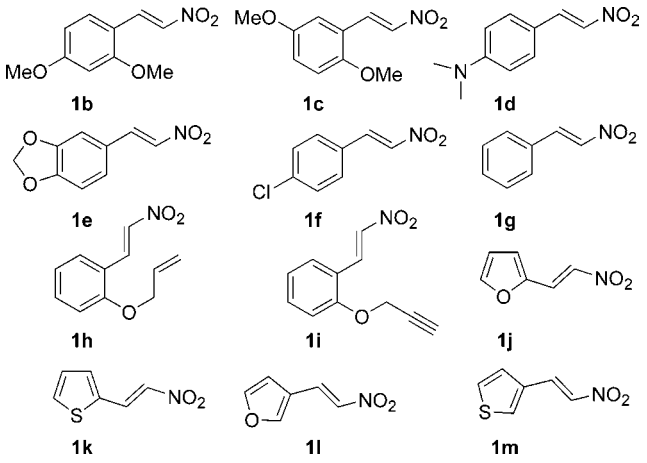
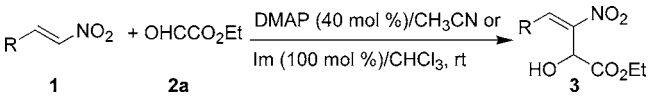


Figure 1.

Table 1. MBH Reaction of Nitroalkenes **1** with Ethyl Glyoxylate **2a**[a] in the Presence of DMAP or Imidazole



		DMAP (a)		imidazole (b)	
entry	**1**	time (min)	yield of **3**[b] (%)	time (h)	yield of **3**[b] (%)
1	**1a**	10	81	2.75	73
2	**1b**	5	95	13	80
3	**1c**	5	99	7	78
4	**1d**	20	98	24	83
5	**1e**	15	65	10	50
6	**1f**	15	45	24	38
7	**1g**	30	33	5	31
8	**1h**	20	69	2	62
9	**1i**	15	52	2	52
10	**1j**	5	63	7	67
11	**1k**	5	64	6	68
12	**1l**	10	60	6	60
13	**1m**	20	60	6	68

[a] 4 equiv as a 50% solution in toluene for both DMAP- and imidazole-catalyzed reactions (see the Supporting Information). [b] Isolated yield after column chromatography.

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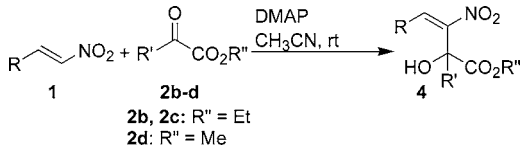
(17) Reference 15g.

1a−4a) and 33−69% range for nitroalkenes **1e**−**i** (Table 1, entries 5a−9a). The heteroaromatic nitroalkenes **1j**−**m** also provided the MBH adducts in good yields (Table 1, entries 10a−13a). In contrast to the DMAP-catalyzed reactions, the imidazole-catalyzed reactions required up to 24 h for completion and the yields were less impressive (Table 1, entries 1b−13b). Further comparison of the DMAP- and the imidazole-catalyzed reactions shows that for nitroalkenes **1a**−**d** DMAP is clearly the catalyst of choice (Table 1, entries 1−4). On the other hand, the performance of both of the catalysts is comparable in terms of the % yield of the MBH adducts **3** for nitroalkenes **1e**−**m** (Table 1, entries 5−13). But, nevertheless, Table 1 demonstrates the power of DMAP and imidazole in catalyzing the MBH reaction of a variety of nitroalkenes with glyoxylate **2a**.

The performance of an activated carbonyl compound such as glyoxylate **2a** as an excellent electrophile in the MBH reaction of nitroalkenes **1** prompted us to screen several other easily available electrophiles, and the results are summarized in Tables 2−4. The optimized conditions successfully

Table 2. MBH Reaction of Nitroalkenes **1** with Activated Carbonyl Compounds **2b**−**d**[a] in the Presence of DMAP[b]



				DMAP	
entry	**1**	**2** (R′)	**4**	time	yield of **4**[c] (%)
1	**1a**	**2b** (Me)	**4a**	7 d	none[d]
2	**1a**	**2c** (Ph)	**4b**	7 d	none[d]
3	**1a**	**2d** (CF_3)	**4c**	2 d	40[d]
				3 h	70[e]
4	**1c**	**2d** (CF_3)	**4d**	3.5 h	71[e]
5	**1d**	**2d** (CF_3)	**4e**	10 h	80[e]
6	**1l**	**2d** (CF_3)	**4f**	30 min	40[e]

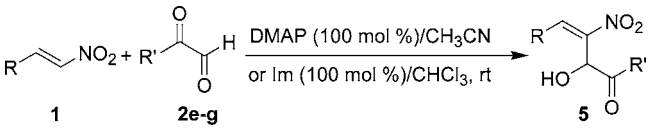
[a] 4 equiv (see the Supporting Information). [b] There was no reaction when imidazole (100 mol % in $CHCl_3$) was used as the catalyst. [c] Isolated yield after column chromatography. [d] 40 mol % of DMAP was used. [e] 100 mol % of DMAP was used.

employed for the reaction between nitroalkenes **1a**−**m** and glyoxylate **2a** were used in these reactions as well with minor modifications in some cases.

Table 2 reveals that pyruvate **2b** and phenyl glyoxylate **2c** are not suitable electrophiles for the MBH reaction of nitroalkenes (entries 1 and 2). However, by stark contrast, trifluoropyruvate **2d**[18] reacted with a variety of nitroalkenes under the DMAP-catalyzed conditions and provided the MBH adducts **4** in high yields (Table 2, entries 3−6). To obtain high yields of the novel quaternary trifluoromethylated compounds in shorter reaction times, 100 mol % of DMAP was necessary (Table 2, entry 3).

(18) For synthetic and other applications of trifluoropyruvate, see: Takikawa, G.; Katagiri, T.; Uneyama, K. *J. Org. Chem.* **2005**, *70*, 8811 and references therein.

Table 3. MBH Reaction of Nitroalkenes **1** with Activated Carbonyl Compounds **2e**−**g**[a] in the Presence of DMAP or Imidazole

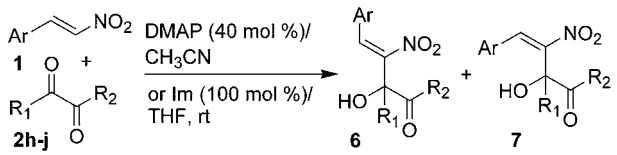


				DMAP (a)		imidazole (b)	
entry	**1**	**2** (R′)	**5**	time (d)	yield of **5**[b] (%)	time (d)	yield of **5**[b] (%)
1	**1a**	**2e** (H)	**5a**	7	none	7	none
2	**1a**	**2f** (CH_3)	**5b**	2	26 (50)	2	20 (52)
3	**1b**	**2f** (CH_3)	**5c**	2	32 (50)	2	30 (35)
4	**1c**	**2f** (CH_3)	**5d**	2	30 (40)	2	28 (30)
5	**1j**	**2f** (CH_3)	**5e**	2	33 (40)	2	25 (45)
6	**1l**	**2f** (CH_3)	**5f**	2	35 (25)	2	36 (35)
7	**1a**	**2g** (Ph)	**5g**	7	none	7	none

[a] 4 equiv for both DMAP and imidazole-catalyzed reactions (see the Supporting Information). [b] Isolated yield after column chromatography, amount of recovered **1** in parentheses.

While there was no reaction when glyoxal and phenylglyoxal were used as electrophiles (Table 3, entries 1 and 7), we were pleased to isolate the desired MBH adducts **5b**−**f** when pyruvaldehyde **2f** was used as the electrophile (entries

Table 4. MBH Reaction of Nitroalkenes **1** with Activated Carbonyl Compounds **2h**−**j**[a] in the Presence of DMAP or Imidazole[b]



				DMAP[c] (a)		imidazole (b)	
entry	**1**	**2**	**6/7**	time	yield of **6** + **7**[d] (%)	time	yield of **6** + **7**[d] (%)
1	**1a**	**2h**	**6/7a**	3 d	none	3 d	none
2	**1a**	**2i**	**6/7b**	3 d	none	3 d	none
3	**1a**	**2j**	**6/7c**	30 min	55[e]	24 h	61[e]
4	**1g**	**2j**	**6/7d**	45 min	44[f]	24 h	53[f]
5	**1j**	**2j**	**6/7e**	20 min	79[g]	5 h	74[g]
6	**1k**	**2j**	**6/7f**	15 min	73[g]	6 h	71[g]
7	**1l**	**2j**	**6/7g**	30 min	68[h]	5 h	70[h]

[a] 4 equiv for both DMAP and imidazole-catalyzed reactions (see the Supporting Information). [b] Due to the poor solubility of ninhydrin **2j** in $CHCl_3$, it was replaced by THF for all the reactions in this table. [c] The reaction goes to completion in all cases; increasing the amount of DMAP to 100 mol % did not have any positive effect. [d] Isolated yield of **6** and/or **7** after column chromatography; complete consumption of nitroalkene **1** was observed in the case of entries 3−7. [e] **6c**/**7c** = 56:44 (**6c**: 31% and **7c**: 24%, method a) and 65:35 (**6c**: 40% and **7c**: 21%, method b) (inseparable mixture). [f] **6d**/**7d** = 64:36 (**6d**: 28% and **7d**: 16%, method a) and 72:28 (**6d**: 38% and **7d**: 15%, method b) (inseparable mixture). [g] Single isomers. [h] **6g**/**7g** = 59:41 (**6g**: 40% and **7g**: 28%, method a) and 74:26 (**6g**: 52% and **7g**: 18%, method b) (separated by silica gel column chromatography; see the Supporting Information).

2−6). Although the yields are moderate (20−36%) and the reaction remained incomplete even after 2 days, to our knowledge, it is the first time pyruvaldehyde **2f** has been successfully used as an electrophile in the MBH reaction.[19]

Finally, cyclic activated carbonyl compounds **2h**−**j** were screened for the MBH reaction with various nitroalkenes **1** (Figure 2). Although β-dicarbonyl compounds **2h** and **2i** did

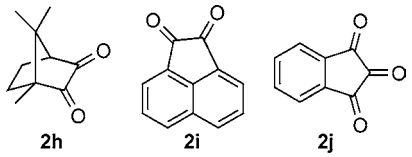


Figure 2.

not react under our experimental conditions (Table 4, entries 1 and 2), the tricarbonyl compound, ninhydrin **2j** provided good yields of the MBH adducts **6** and/or **7** with a variety of nitroalkenes **1a**, **1g,** and **1j**−**l**. While nitroalkenes **1a**, **1g**, and **1l** provided mixture of isomers (Table 4, entries 3, 4, and 7), **1j** and **1k** provided isomerically pure products (entries 5 and 6). In general, greater selectivity in favor of the (*Z*) isomer (vide infra) was observed when imidazole was used as the catalyst (Table 4, entries 3b, 4b, and 7b).

The structure and stereochemistry of the MBH adducts were confirmed by detailed analysis of NMR and X-ray data of representative systems. For instance, in the ^{1}H−^{1}H NOESY spectrum of **3d**, the positive NOE interaction between the aromatic protons ortho to the styrenic double bond (i.e., protons meta to the NMe_2 group) with the C−H of the CHOH group taken together with the absence of any NOE between the styrenic proton and the protons of the CHOH or the Et group confirmed the (*E*) configuration for **3d**. This was further unambiguously established by single-crystal X-ray diffraction analysis of **3d** (see the Supporting Information). By analogy, (*E*) configuration has been assigned to **3a**−**m**, **4c**−**f**, and **5b**−**f** (Tables 1−3, respectively).

(19) See ref 15e for the application of protected pyruvaldehyde (as dithiane) in a vinylalumination reaction.

In view of the formation of isomeric mixture of products **6** and **7** in the reaction of nitroalkenes **1** with ninhydrin **2j** (Table 4, entries 3, 4, and 7), structure and stereochemistry of **6** and **7** were independently determined. Thus, correlation of the IR, ^{1}H NMR, and ^{13}C NMR data showed different characteristics for the two sets of isomers. For instance, the major isomer **6g**, separated from **7g** by silica gel column chromatography, had similar spectral characteristics with those of **6e** and **6f** and the major isomers **6c** (of **6c** + **7c)** and **6d** (of **6d** + **7d**).[20] This assignment was further unambiguously established by single-crystal X-ray analysis of a representative system **6g** (see the Supporting Information).

In conclusion, conjugated nitroalkenes have been successfully hydroxyalkylated by treating with various activated carbonyl compounds such as glyoxylate, trifluoropyruvate, pyruvaldehyde, and ninhydrin. The reactions mediated by DMAP in acetonitrile or imidazole in $CHCl_3$ or THF provided the novel Morita−Baylis−Hillman adducts in high yields in majority of the cases. Synthetic and biological applications of these multifunctional adducts will be reported in due course.

Acknowledgment. This paper is dedicated to Prof. S. Chandrasekaran on the occasion of his 60th birthday. We thank DST (India) for financial support and SAIF (IIT Bombay) for selected NMR spectra. I.D. and M.D. thank CSIR (India) for research fellowships. I.N.N.N. thanks Prof. A. Vasella for helpful discussions.

Supporting Information Available: X-ray data for **3d** and **6g** (CIF), optimization tables, experimental procedures and full characterization data, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and a copy of the 2D-NOESY spectrum for **3d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The peaks for OH group in IR (cm^{-1}) appear at 3404 for **6g**, 3408 for **6e**, and 3403 for **6f**. On the other hand, the corresponding OH group in **7g** appears at 3370 cm^{-1}. Similarly, the styrenic proton in ^{1}H NMR of **6e**−**g** are shielded (at δ 8.10, 8.18, and 7.70, respectively) as compared to that in **7g** (at δ 8.50). Furthermore, the CHOH carbon in ^{13}C NMR appears at δ 76.5 in both **6e** and **6f** and at 76.6 in **6g**. However, in **7g** the corresponding carbon is deshielded by ~1 ppm, i.e., at δ 77.6. NOE experiments have not provided satisfactory results.