A R T I C L E   I N F O
Article history:
Received 2 August 2010
Received in revised form 13 October 2010
Accepted 22 October 2010
Available online 28 October 2010

Keywords:
Morita–Baylis–Hillman reaction
Nitroalkenes
Organocatalysis
Thiourea
Aqueous media

A B S T R A C T
An efficient thiourea promoted MBH reaction of various conjugated nitroalkenes with ethyl glyoxylate was developed. The desired multifunctional products, 2-hydroxy-3-nitro-4-aryl/alkylbut-3-enoate derivatives were obtained in good to high chemical yields (56–92%) with DMAP (20 mol %) under solvent-free conditions or imidazole (100 mol %) in the presence of water.

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1. Introduction
Morita–Baylis–Hillman (MBH),1 a tertiary amine catalyzed reaction, has emerged as one of the important C=C bond forming methods in organic synthesis to give densely functionalized products. Various activated alkenes, such as enals,2 enones,3 acrylates,4 and acrylamides5 have been successfully employed in MBH and related reactions, where reaction products have been extensively used for further applications.6 One of the major drawbacks of this reaction is the poor reaction rates, which limits the range of substrates tolerated.7 Several attempts for substantial rate acceleration of the MBH reaction that involved the addition of a co-catalyst and optimization of reaction conditions have been reported.8 In addition, it is only recently that nitroalkenes were found to be useful Michael acceptors for MBH reactions.9 The potential use of the adducts, includes chemical transformations, biological evaluations, and the complexity of the reaction sequence make this approach an interesting chemical process.6b,10,11 On the other hand, environmental concerns have stimulated a new concept of chemical reactions under solvent-free conditions or in aqueous media.12

Namboothiri and co-workers reported the reaction of a variety of conjugated nitroalkenes with ethyl glyoxylate with DMAP (40 mol %) in CH3CN or imidazole (100 mol %) in CHCl3 or THF to give the desired MBH adducts with decent to good chemical yields.13

In continuation to our research interest in organocatalysis,14 the thiourea promoted an efficient MBH reaction of a variety of nitroalkenes with ethyl glyoxylate was developed. The multifunctional 2-hydroxy-3-nitrobut-3-enoate derivatives were obtained with good to high chemical yields (56–92%) under the optimum conditions. Furthermore, we were able to successfully carry out the MBH reactions in an aqueous solvent system.3f,12b

2. Results and discussion

The ethyl glyoxylate 1 (in 50% toluene) and β-nitrostyrene 2a were chosen as model substrates. We suspected the presence of a thiourea component could synergistically activate the nitroalkenes and ethyl glyoxylate, subsequently enhancing the reactivity.15 Various thiourea promoters were studied. An initial screening using various solvents with thiourea catalysts I was carried out. The reaction proceeded smoothly in CHCl3 to afford the desired product with 70% yield when imidazole and thiourea I (20 mol %) was used (Table 1, entry 1). The chemical yield improved slightly when the reaction was carried out in THF over 3 h (Table 1, entry 2). However, the reactivity decreased under neat conditions, in brine, and in water (Table 1, entries 3–5). It is shown here that the use of a mixed solvent system failed to improve the chemical outcome (Table 1, entry 6). Next, we examined the reactions of various thiourea catalysts II–V in water (Table 1, entries 7–10). Fortunately, the desired product 3a
was obtained with 88% chemical yield within a 1 h reaction in the presence of thiourea III (Table 1, entry 8). It is interesting to note that the presence of thiourea III exhibited better activity than that of I (with four 3, 5-trifluoromethyl substituents on the phenyl rings). The hydroxy group in the phenyl group may contribute to this result.

Table 1  
Thiourea catalysts screening for MBH reaction of ethyl glyoxylate 1 with β-nitrostyrene 2a in the presence of imidazole

| Entry | Thiourea (20 mol%) | Solvent | Time (h) | % Yield
<table>
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<tr>
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<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>CHCl₃</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>THF</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>Neat</td>
<td>0.5</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>Brine</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>II</td>
<td>H₂O</td>
<td>2</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>II</td>
<td>H₂O₂</td>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>II</td>
<td>H₂O₈</td>
<td>4</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>III</td>
<td>H₂O</td>
<td>1</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>III</td>
<td>H₂O₂</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>V</td>
<td>H₂O₈</td>
<td>4</td>
<td>60</td>
</tr>
</tbody>
</table>

a Unless otherwise specified, the reaction was carried out with ethyl glyoxylate 1 (in 50% toluene, 0.6 mmol), β-nitrostyrene 2a (0.2 mmol), imidazole (0.2 mmol), and thiourea catalysts I–V (20 mol%) in 0.2 mL of solvent indicated at ambient temperature.

b Isolated yield.

c Unseparable mixtures were observed.

To further optimize the reaction conditions, screening of bases (imidazole, DMAP and DABCO) was carried out. As expected, the reactivity decreased, when low amounts of either imidazole or thiourea III were used in water (Table 2, entries 1–4). We then studied the effect of DMAP in the MBH reaction. The desired product was obtained with comparable chemical yields when DMAP (20 mol%) was used under similar reaction conditions (Table 2, entries 5 and 6). The chemical yield was significantly improved to a satisfactory 92% when the reaction was carried out using ethyl glyoxylate and β-nitrostyrene under solvent-free condition (Table 2, entry 7). By contrast, the reactions failed to proceed when DABCO was employed as the nucleophile (Table 2, entries 9 and 10). After optimizing conditions, the best reaction condition was realized using ethyl glyoxylate 1 (3.0 equiv), nitroalkenes (1.0 equiv), and thiourea catalyst III (20 mol%) in the presence of DMAP (20 mol%) under solvent-free condition or imidazole (100 mol%) in water at ambient temperature.

To test the general utility of the optimized reaction conditions, we examined the reaction with a variety of nitroalkenes and ethyl glyoxylate. The results are tabulated in Table 3. The use of electron withdrawing substituted nitroalkenes gave the desired adducts with good to high chemical yields (Table 3, entries 2–8). For all the substrates studied, no significant differences in reactivity were observed when the nucleophilic species DMAP and imidazole were used for the reaction. Most of the reactions were completed in 2 h at ambient temperature under optimized reaction conditions. On the other hand, for electron-donating group of nitroalkenes, the reactions also proceeded smoothly to afford the MBH adducts with good to high chemical yields (Table 3, entries 9–12). However, the presence of a methoxy substituent at ortho and para position, resulted in a decrease in reactivity in the presence of imidazole (Table 3, entries 10 and 12). Hetero-aromatic nitroalkenes were also suitable substrates for the MBH reaction, where high chemical yields were obtained (Table 3, entries 13 and 14). The reactivity decreased when aliphatic nitroalkenes were used, giving moderate chemical yields (Table 3, entries 15 and 16). The structures of 2-hydroxy-3-nitrobut-3-enoate derivatives 3a–p were fully characterized using IR, 1H, 13C NMR spectral data, and HRMS analyses and product 3a was further confirmed by single crystal X-ray data analysis (Fig. 1).
4.1. General information

In summary, an efficient thiourea promoted Morita–Baylis–Hillman reaction was developed for the synthesis of multifunctional 2-hydroxy-3-nitrobut-3-enoate derivatives. Treatment of a variety of nitroalkenes (aromatic, hetero-aromatic, and aliphatic) and ethyl glyoxylate (50% in toluene) with DMAP or imidazole to give the desired adducts with good to high chemical yields. The reaction proceeded smoothly, when DMAP (20 mol%) under solvent-free condition or imidazole (100 mol%) in the presence of water with thiourea III (20 mol%) as a co-catalyst. The synthetic applications of the MBH adducts were studied in our laboratory.

4.2. General experimental procedure

4.2.1. Ethyl 2-hydroxy-3-nitro-4-phenylbut-3(E)-enoate (3a). IR (ν/cm⁻¹): 3483, 3077, 2989, 2915, 1749, 1657, 1613, 1543, 1437, 1318, 1263, 1226, 1171, 1119, 1060, 1034, 1019; ¹H NMR (400 MHz, CDCl₃): δ 7.40 (m, 3H), 5.18 (d, J = 7.2 Hz, 3H), 4.24 (m, 2H), 3.65 (s, 1H), 1.26 (t, J = 7.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 170.2, 148.7, 137.4, 135.3, 132.5, 130.9, 130.5, 129.5, 127.7, 65.7, 63.1, 13.9 ppm; LRMS (EI) m/z: [M+Na⁺]⁺ calc for C₁₃H₁₂F₃NO₅Na 283.0450, found 283.0453.

4.2.2. Ethyl 2-hydroxy-3-nitro-4-(2-trifluoromethylphenyl)but-3(E)-enoate (3b). IR (ν/cm⁻¹): 3482, 3097, 2989, 2915, 1749, 1657, 1613, 1543, 1437, 1318, 1263, 1226, 1171, 1119, 1060, 1034, 1019; ¹H NMR (400 MHz, CDCl₃): δ 7.60 (m, 2H), 7.53 (m, 2H), 7.47 (m, 3H), 5.24 (d, J = 5.5 Hz, 1H), 4.39–4.21 (m, 2H), 3.70 (d, J = 5.9 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 170.5, 147.9, 139.2, 131.0, 130.9, 129.8, 129.2, 65.9, 63.0, 13.9 ppm; LRMS (EI) m/z: [M+Na⁺]⁺ calc for C₁₃H₁₃F₃NO₅Na 274.0685, found 274.0685.

4.2.3. Ethyl 2-hydroxy-3-nitro-4-(3-trifluoromethylphenyl)but-3(E)-enoate (3c). IR (ν/cm⁻¹): 3491, 3070, 2989, 2915, 1753, 1665, 1580, 1535, 1437, 1318, 1263, 1226, 1171, 1119, 1060, 1034, 1019; ¹H NMR (400 MHz, CDCl₃): δ 7.30–7.70 (m, 1H), 7.65–7.58 (m, 2H), 4.95 (s, 1H), 4.35–4.19 (m, 2H), 3.65 (s, 1H), 1.26 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 170.1, 149.6, 135.8, 132.4, 130.4, 129.5 (q, J = 31 Hz), 129.4, 129.2, 126.6 (q, J = 5 Hz), 123.5 (q, J = 272 Hz), 65.9, 63.1, 13.8 ppm; LRMS (EI) m/z: [M+Na⁺]⁺ calc for C₁₃H₁₁F₃NO₅Na 342.0656, found 342.0657.

4.2.4. Ethyl 4-(3-chlorophenyl)-2-hydroxy-3-nitrobut-3(E)-enoate (3d). IR (ν/cm⁻¹): 3464, 3099, 2989, 2915, 2856, 1749, 1653, 1655, 1528, 1473, 1340, 1259, 1108, 1016; ¹H NMR (400 MHz, CDCl₃): δ 8.24 (s, 1H), 7.58–7.54 (m, 1H), 7.50–7.40 (m, 3H), 5.17 (d, J = 4.4 Hz, 4H), 4.38–4.24 (m, 2H), 3.72 (d, J = 5.2 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 170.2, 148.7, 137.4, 135.3, 132.5, 130.9, 130.5, 129.5, 127.7, 65.7, 63.1, 13.9 ppm; LRMS (EI) m/z: 283 (M⁺, 42%), 267 (59), 222 (25), 214 (32), 212 (100), 194 (39), 150 (76), 141 (22), 84 (13); HRMS (ESI) m/z: [M+Na⁺]⁺ calc for C₁₃H₁₁Cl₂NO₅Na 308.0302, found 308.0305.

4.2.5. Ethyl 4-(3-chlorophenyl)-2-hydroxy-3-nitrobut-3(E)-enoate (3e). IR (ν/cm⁻¹): 3454, 2989, 2923, 2841, 1749, 1653, 1591, 1528, 1491, 1340, 1255, 1229, 1093, 1012; ¹H NMR (400 MHz, CDCl₃): δ 8.27 (s, 1H), 7.57–7.43 (m, 4H), 5.16 (d, J = 4.0 Hz, 1H), 4.39–4.20
3.67 (d, J = 5.6 Hz, 1H), 7.40 (m, 1H), 7.02 (m, 1H), 6.66 (m, 1H), 4.37 – 4.20 (m, 2H), 3.73 (d, J = 5.6 Hz, 1H), 1.27 (t, J = 7.0 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ 170.2, 148.1, 139.7, 132.5, 129.7, 125.9, 65.8, 63.1, 13.9 ppm; LRMS (EI) m/z 329 (M+ - 1, 8%), 267 (5), 258 (100), 232 (32), 194 (33), 187 (23), 131 (8); HRMS (El) m/z: [M]+ calc for C12H12BrNO5 328.9899, found 328.9890.

3.6.2. Ethyl 4-(2-bromophenyl)-2-hydroxy-3-nitrobut-3(E)-enoate (3g). IR (cm^-1): 3476, 2989, 2915, 2849, 2749, 1749, 1650, 1587, 1532, 1488, 1403, 1336, 1303, 1259, 1233, 1100, 1071, 1012; 1H NMR (400 MHz, CDCl3): δ 8.24 (s, 1H), 7.67 – 7.60 (m, 2H), 7.48 – 7.40 (m, 2H), 5.15 (d, J = 5.6 Hz, 1H), 4.39 – 4.20 (m, 2H), 3.73 (d, J = 5.6 Hz, 1H), 1.27 (t, J = 7.0 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ 170.1, 148.7, 137.2, 133.8, 132.4, 130.7, 128.1, 123.2, 65.7, 63.1, 14.0 ppm; LRMS (El) m/z 329 (M+ - 1, 14%), 316 (36), 266 (19), 256 (100), 238 (37), 196 (43), 194 (47), 160 (64), 132 (30), 84 (11); HRMS (El) m/z: [M]+ calc for C12H12BrNO5 328.9899, found 328.9890.

3.6.7. Ethyl 4-(3-bromophenyl)-2-hydroxy-3-nitrobut-3(E)-enoate (3h). IR (cm^-1): 3476, 2989, 2915, 2849, 2749, 1749, 1650, 1587, 1532, 1488, 1403, 1336, 1303, 1259, 1233, 1100, 1071, 1012; 1H NMR (400 MHz, CDCl3): δ 8.23 (s, 1H), 7.75 – 7.70 (m, 1H), 7.66 – 7.60 (m, 1H), 7.54 – 7.47 (m, 1H), 7.45 – 7.33 (m, 1H), 5.16 (d, J = 5.6 Hz, 1H), 4.39 – 4.24 (m, 2H), 3.72 (d, J = 5.6 Hz, 1H), 1.29 (t, J = 7.0 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ 170.1, 148.7, 137.2, 133.8, 132.4, 130.7, 128.1, 123.2, 65.7, 63.1, 13.9 ppm; LRMS (El) m/z 329 (M+ - 1, 8%), 267 (5), 258 (100), 232 (32), 194 (33), 187 (23), 131 (8); HRMS (El) m/z: [M]+ calc for C12H12BrNO5 328.9899, found 328.9890.

Acknowledgements

We thank the National Science Council of the Republic of China [NSC 99-2113-M-003-002-MY3] and NSC 99-2119-M-003-001-
References and notes


16. The reaction of nitroalkenes with some activated carbonyl compounds, such as pyruvate, phenyl glyoxylate, and diethyl ketomalonate was studied. Unfortunately, the reactions proceeded to give either low chemical yields or led to complex products under the optimum reaction conditions.

17. Detailed X-ray crystallographic data is available from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK for product 3a (CCDC No. 795732).