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An efficient Morita–Baylis–Hillman reaction for the synthesis of multifunctional 2-hydroxy-3-nitrobut-3-enoate derivatives

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ABSTRACT

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.

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 acrylamides[5] 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. Organic processes in aqueous medium have attracted a great deal of attention and have become one of the most exciting research areas.[12]

Namboothiri and co-workers reported the reaction of a variety of conjugated nitroalkenes with activated non-enolizable carbonyl compounds with DMAP (40 mol %) in CH_3CN or imidazole (100 mol %) in $CHCl_3$ 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 $CHCl_3$ 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**

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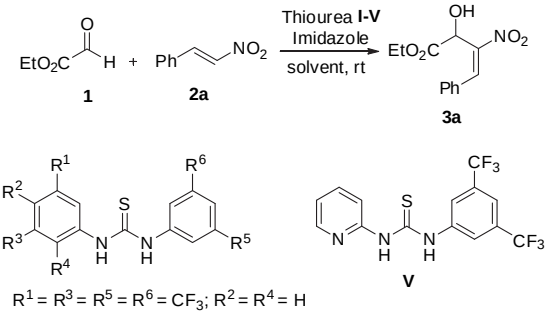
was obtained with 88% chemical yield within a 1 h reaction in the presence of thiourea **III** (Table 1, entry 8). It is interesting to note that thiourea **III** exhibited better activity than that of **I** (with four 3, 5-trifluoromethyl substituents on the phenyl rings). The hydroxy group in the phenyl 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[a]



I: $R^1 = R^3 = R^5 = R^6 = CF_3$; $R^2 = R^4 = H$
II: $R^1 = R^3 = R^4 = H$; $R^2 = OMe$; $R^5 = R^6 = CF_3$
III: $R^1 = R^2 = R^3 = H$ $R^4 = OH$, $R^5 = R^6 = CF_3$
IV: $R^1 = R^2 = R^3 = R^5 = R^6 = H$; $R^4 = OH$

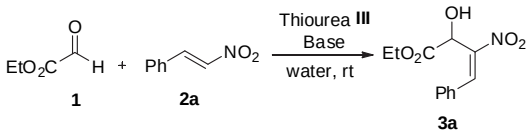
Entry	Thiourea (20 mol %)	Solvent	Time (h)	% Yield[b]
1	**I**	CH_3Cl_3	1	70
2	**I**	THF	3	80
3	**I**	Neat	0.5	65
4	**I**	Brine	2	60
5	**I**	H_2O	2	72
6	**I**	THF/H_2O	3	70
7	**II**	H_2O	4	—[c]
8	**III**	H_2O	1	88
9	**IV**	H_2O	2	80
10	**V**	H_2O	4	60

[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.[16] 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, ^{13}C NMR spectral data, and HRMS analyses and product **3a** was further confirmed by single crystal X-ray data analysis (Fig. 1).[17]

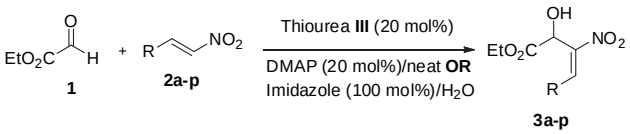
Table 2
Optimization of the MBH reaction



Entry	Base (mol %)	**III** (mol %)	Time (h)	% Yield[a]
1	*Imidazole (100 mol %)*	*20*	*1*	*88*
2	Imidazole (100 mol %)	10	4	80
3	Imidazole (50 mol %)	20	8	70
4	Imidazole (20 mol %)	20	12	68
5	DMAP (20 mol %)	20	1	75
6	DMAP (20 mol %)	20	0.5	70
7[b]	*DMAP (20 mol %)*	*20*	*0.5*	*92*
8[b]	DMAP (10 mol %)	20	0.5	80
9	DABCO (20 mol %)	20	5	—
10[b]	DABCO (20 mol %)	20	10	—

[a] Isolated yield.
[b] No other solvent was added.

Table 3
Substrate scope for MBH reaction[a]



entry	R (**2**)	**3a**–**p**	DMAP[b]		Imidazole[c]	
			Time (h)	Yield[d]	Time (h)	Yield[d]
1	C_6H_5 (**2a**)	**3a**	0.5	92	1.0	88
2	2-$CF_3C_6H_4$ (**2b**)	**3b**	0.5	57	1.5	86
3	3-$CF_3C_6H_4$ (**2c**)	**3c**	0.5	73	1.0	80
4	3-ClC_6H_4 (**2d**)	**3d**	0.5	88	1.5	75
5	4-ClC_6H_4 (**2e**)	**3e**	0.5	85	1.5	82
6	2-BrC_6H_4 (**2f**)	**3f**	0.5	88	1.5	74
7	3-BrC_6H_4 (**2g**)	**3g**	1.5	75	1.5	75
8	4-BrC_6H_4 (**2h**)	**3h**	1.5	70	2.0	75
9	4-MeC_6H_4 (**2i**)	**3i**	0.5	88	3.0	81
10	2-$MeOC_6H_4$ (**2j**)	**3j**	0.5	75	12.0	78
11	3-$MeOC_6H_4$ (**2k**)	**3k**	0.5	85	4.0	75
12	4-$MeOC_6H_4$ (**2l**)	**3l**	0.5	84	12.0	77
13	2-Thienyl (**2m**)	**3m**	0.5	87	1.5	84
14	2-Furyl (**2n**)	**3n**	0.5	86	1.5	82
15	$C_6H_5CH_2CH_2$ (**2o**)	**3o**	0.5	56	8.0	35
16	$(CH_3)_2CHCH_2$ (**2p**)	**3p**	0.5	83	8.0	47

[a] All the reactions were carried out with ethyl glyoxylate **1** (in 50% toluene, 0.6–1.0 mmol) and nitroolefins **2a**–**p** (0.2 mmol) in the presence of catalyst **III** (20 mol %).
[b] DMAP (20 mol %) used with ethyl glyoxylate (5 equiv) under solvent-free condition at ambient temperature.
[c] Ethyl glyoxylate (3 equiv) used with imidazole (100 mol %) in water at ambient temperature.
[d] Isolated yields.

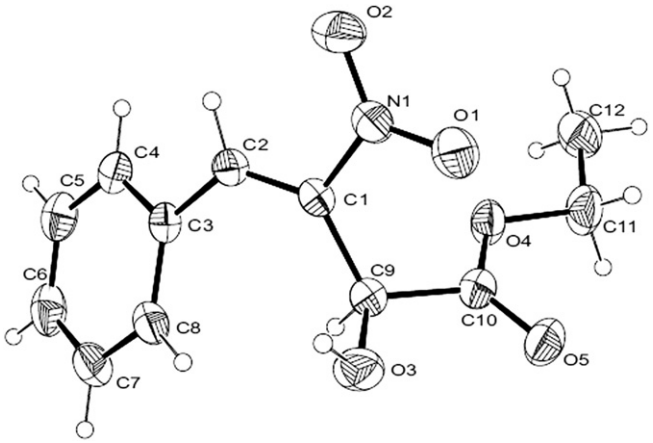


Fig. 1. ORTEP diagram of **3a** at 50% probability level.

3. Conclusions

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 (in 50% 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. Experimental

4.1. General information

Infrared spectra were obtained using a Perkin Elmer Spectrum RX spectrometer with thin films of products coated on NaCl plates. Only absorption frequencies higher than 1000 cm^{-1} were reported. ^1H and ^{13}C NMR spectra were measured on the Bruker Avance 400 MHz instruments, and spectral data are reported in parts per million relative to tetramethylsilane (TMS, δ=0.0) using $CDCl_3$ as solvent for ^1H NMR and relative to the central $CDCl_3$ resonance (δ=77.0) for ^{13}C NMR. HRMS analysis was accomplished at the Academia Sinica, Scientific Instrument Center (EI and ESI). All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on Merck precoated TLC plates (silica gel 60 F_{254}). The products were purified by flash column chromatography silica gel 60 (Merck, 230–400 mesh) using the indicated eluent.

4.2. General experimental procedure

DMAP catalyzed MBH reaction: DMAP (4.9 mg, 0.04 mmol) was added to a stirred solution of ethyl glyoxylate **1** (50% in toluene, 0.2 mL, 1.0 mmol), corresponding nitroolefins **2a**–**p** (0.20 mmol), and thiourea **III** (15.3 mg, 0.04 mmol) under neat conditions at ambient temperature. The mixture was stirred until the starting material disappeared completely by inspection of TLC by UV lamp (254 nm). To the mixture were added ethyl acetate (10 mL) and water (0.5 mL). The layers were separated and the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluting with hexanes/ethyl acetate=4:1) to give the desired pure adducts, 2-hydroxy-3-nitrobut-3-enoates **3a**–**p**.

Imidazole mediated MBH reaction: Imidazole (13.7 mg, 0.20 mmol) was added to a stirred solution of ethyl glyoxylate **1** (50% in toluene, 0.12 mL, 0.6 mmol), corresponding nitroolefins **2a**–**p** (0.20 mmol), and thiourea **III** (15.3 mg, 0.04 mmol) in water (0.2 mL) at ambient temperature. The reaction mixture was stirred until the starting material disappeared completely by inspection of TLC by UV lamp (254 nm). The mixture was extracted with ethyl acetate (10 mL×2). The layers were separated and the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluting with hexanes/ethyl acetate=4:1) to give the desired pure products **3a**–**p**.

*4.2.1. Ethyl 2-hydroxy-3-nitro-4-phenylbut-3(E)-enoate (**3a**).* IR (ν/cm^{-1}): 3491, 3070, 2982, 1749, 1650, 1532, 1447, 1336, 1296, 1255, 1222, 1104, 1012; ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.60–7.54 (m, 2H), 7.53–7.47 (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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 252 (M^++1, 11%), 234 (15), 187 (17), 178 (100), 160 (20), 131 (9), 116 (38), 107 (27), 79 (6); HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{12}H_{13}NO_5Na$ 274.0691, found 274.0685. Crystal data for **3a** at 296 K: $C_{12}H_{13}NO_5$, M 251.23, monoclinic, $P21/n$, a=10.7256(3) Å, b=7.6027(2) Å, c=15.2187(5) Å, V=1240.39(6) $Å^3$, Z=4, λ=0.71073 Å, D_c=1.345 g/cm^3, μ=0.0446 mm^{-1}, 2181 reflections, 163 parameters, R=0.0619, R_w=0.0916 for all data.

*4.2.2. Ethyl 2-hydroxy-3-nitro-4-(2-trifluoromethylphenyl) but-3(E)-enoate (**3b**).* IR (ν/cm^{-1}): 3491, 3070, 2989, 2915, 1753, 1665, 1580, 1535, 1451, 1347, 1318, 1263, 1226, 1171, 1119, 1060, 1034, 1019; ^1H NMR (400 MHz, $CDCl_3$): δ 8.49 (d, J=2.0 Hz, 1H), 7.83–7.79 (m, 1H), 7.72–7.65 (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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 319 (M^+, 27%), 302 (11), 256 (6), 246 (54), 212 (55), 184 (100), 132 (15); HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{12}F_3NO_5Na$ 342.0565, found 342.0573.

*4.2.3. Ethyl 2-hydroxy-3-nitro-4-(3-trifluoromethylphenyl) but-3(E)-enoate (**3c**).* IR (ν/cm^{-1}): 3483, 3077, 2989, 2915, 1749, 1657, 1613, 1535, 1443, 1329, 1207, 1167, 1126, 1078, 1016; ^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.87–7.82 (m, 1H), 7.80–7.73 (m, 2H), 7.69–7.61 (m, 1H), 5.13 (d, J=5.6 Hz, 1H), 4.39–4.26 (m, 2H), 3.73 (d, J=5.8 Hz, 1H), 1.29 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 149.1, 137.1, 132.7, 131.8 (q, J=32 Hz), 131.7, 129.9, 127.5 (q, J=3 Hz), 126.4 (q, J=4 Hz), 123.5 (q, J=271 Hz), 65.7, 63.2, 13.9 ppm; LRMS (EI) m/z 319 (M^+, 25%), 301 (7), 256 (13), 246 (60), 230 (8), 184 (100), 175 (15), 131 (7); HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{12}F_3NO_5Na$ 342.0565, found 342.0560.

*4.2.4. Ethyl 4-(3-chlorophenyl)-2-hydroxy-3-nitrobut-3(E)-enoate (**3d**).* IR (ν/cm^{-1}): 3469, 2989, 2915, 2856, 1749, 1653, 1565, 1528, 1473, 1340, 1259, 1108, 1016; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.58–7.54 (m, 1H), 7.50–7.40 (m, 3H), 5.17 (d, J=4.4 Hz, 1H), 4.38–4.24 (m, 2H), 3.72 (d, J=5.2 Hz, 1H), 1.28 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 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 285 (M^+, 42%), 267 (59), 222 (25), 214 (32), 212 (100), 194 (39), 150 (76), 141 (22), 84 (13); HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{12}H_{12}ClNO_5Na$ 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, $CDCl_3$): δ 8.27 (s, 1H), 7.57–7.43 (m, 4H), 5.16 (d, J=4.0 Hz, 1H), 4.39–4.20

(m, 2H), 3.72 (d, J=5.2 Hz, 1H), 1.27 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 148.1, 137.9, 137.5, 131.1, 129.6, 129.2, 65.8, 63.1, 13.9 ppm; LRMS (EI) m/z 286 (M^++1, 16%), 268 (26), 222 (16), 214 (31), 212 (100), 194 (6), 152 (13), 150 (57), 141 (32), 131 (11); HRMS (EI) m/z: $[M]^+$ calcd for $C_{12}H_{12}ClNO_5$ 285.0404, found 285.0410.

*4.2.6. Ethyl 4-(2-bromophenyl)-2-hydroxy-3-nitrobut-3(E)-enoate (**3f**).* IR (ν/cm^{-1}): 3469, 2989, 2915, 2849, 1749, 1653, 1532, 1465, 1436, 1347, 1263, 1229, 1104, 1027; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.75–7.67 (m, 1H), 7.62–7.55 (m, 1H), 7.48–7.39 (m, 1H), 7.39–7.31 (m, 1H), 5.07 (d, J=6.0 Hz, 1H), 4.39–4.20 (m, 2H), 3.67 (d, J=6.0 Hz, 1H), 1.28 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 148.7, 138.2, 133.3, 132.0, 131.8, 130.5, 127.9, 124.8, 65.9, 63.1, 13.9 ppm; LRMS (EI) m/z 329 (M^++1, 2%), 311 (17), 256 (69), 250 (84), 238 (10), 194 (27), 177 (80), 159 (100), 132 (29), 102 (10); HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{12}H_{12}BrNO_5Na$ 351.9797, found 351.9794.

*4.2.7. Ethyl 4-(3-bromophenyl)-2-hydroxy-3-nitrobut-3(E)-enoate (**3g**).* IR (ν/cm^{-1}): 3454, 2989, 2915, 2849, 1749, 1650, 1561, 1528, 1473, 1340, 1259, 1229, 1108, 1071, 1016; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.76–7.70 (m, 1H), 7.66–7.60 (m, 1H), 7.54–7.47 (m, 1H), 7.41–7.33 (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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 148.7, 137.2, 133.8, 132.8, 132.4, 130.7, 128.1, 123.2, 65.7, 63.1, 14.0 ppm; LRMS (EI) m/z 329 (M^++1, 14%), 311 (36), 266 (19), 256 (100), 238 (37), 196 (43), 194 (47), 160 (64), 132 (30), 84 (11); HRMS (EI) m/z: $[M]^+$ calcd for $C_{12}H_{12}BrNO_5$ 328.9899, found 328.9908.

*4.2.8. Ethyl 4-(4-bromophenyl)-2-hydroxy-3-nitrobut-3(E)-enoate (**3h**).* IR (ν/cm^{-1}): 3476, 2989, 2915, 2849, 1749, 1650, 1587, 1532, 1488, 1403, 1336, 1303, 1259, 1233, 1100, 1071, 1012; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 148.1, 137.9, 132.5, 131.2, 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 (EI) m/z: $[M]^+$ calcd for $C_{12}H_{12}BrNO_5$ 328.9899, found 328.9896.

*4.2.9. Ethyl 2-hydroxy-4-(4-methylphenyl)-3-nitrobut-3(E)-enoate (**3i**).* IR (ν/cm^{-1}): 3491, 2982, 2915, 2849, 1749, 1650, 1609, 1524, 1329, 1292, 1259, 1229, 1185, 1104, 1071, 1019; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.51–7.44 (m, 2H), 7.33–7.27 (m, 2H), 5.25 (d, J=6.0 Hz, 1H), 4.37–4.20 (m, 2H), 3.70 (d, J=6.0 Hz, 1H), 2.42 (s, 3H), 1.26 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 147.1, 141.9, 139.5, 130.0, 128.0, 66.0, 62.9, 29.7, 21.5, 13.9 ppm; LRMS (EI) m/z 265 (M^+, 6%), 247 (8), 230 (4), 202 (7), 201 (32), 192 (100), 174 (5), 131 (6), 130 (19), 121 (35), 93 (6); HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}NO_5$ 265.0950, found 265.0955.

*4.2.10. Ethyl 2-hydroxy-4-(2-methoxyphenyl)-3-nitrobut-3(E)-enoate (**3j**).* IR (ν/cm^{-1}): 3454, 2982, 2915, 2841, 1746, 1650, 1598, 1524, 1491, 1462, 1440, 1336, 1296, 1255, 1163, 1108, 1019; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 1H), 7.57–7.52 (m, 1H), 7.51–7.44 (m, 1H), 7.07–7.01 (m, 1H), 7.00–6.95 (m, 1H), 5.23 (d, J=4.8 Hz, 1H), 4.37–4.21 (m, 2H), 3.91 (s, 3H), 3.69 (d, J=5.7 Hz, 1H), 1.27 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 158.6, 147.2, 135.9, 133.0, 130.2, 120.9, 120.0, 110.9, 66.2, 62.8, 55.7, 13.9 ppm; LRMS (EI) m/z 281 (M^+, 38%), 264 (6), 209 (14), 208 (100), 190 (7), 146 (10), 137 (21), 133 (7); HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}NO_6$ 281.0899, found 281.0893.

*4.2.11. Ethyl 2-hydroxy-4-(3-methoxyphenyl)-3-nitrobut-3(E)-enoate (**3k**).* IR (ν/cm^{-1}): 3439, 2915, 2841, 1749, 1646, 1528, 1491, 1465, 1432, 1340, 1300, 1266, 1163, 1108; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.43–7.36 (m, 1H), 7.17–7.12 (m, 1H), 7.12–7.08 (m, 1H), 7.07–7.01 (m, 1H), 5.27 (d, J=5.7 Hz, 1H), 4.37–4.21 (m, 2H), 3.85 (s, 3H), 3.70 (d, J=6.0 Hz, 1H), 1.27 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 160.0, 148.0, 139.2, 132.1, 130.3, 122.1, 116.9, 114.8, 65.9, 63.0, 55.4, 14.0 ppm; LRMS (EI) m/z 281 (M^+, 36%), 263 (43), 218 (9), 208 (100), 190 (68), 162 (38), 146 (30), 137 (11), 109 (17); HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}NO_6$ 281.0899, found 281.0893.

*4.2.12. Ethyl 2-hydroxy-4-(4-methoxyphenyl)-3-nitrobut-3(E)-enoate (**3l**).* IR (ν/cm^{-1}): 3461, 2982, 2915, 2841, 1749, 1646, 1606, 1524, 1510, 1462, 1329, 1307, 1263, 1178, 1104, 1071, 1023; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.61–7.52 (m, 2H), 7.05–6.97 (m, 2H), 5.26 (d, J=5.7 Hz, 1H), 4.37–4.19 (m, 2H), 3.87 (s, 3H), 3.73 (d, J=6.0 Hz, 1H), 1.25 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 162.2, 145.9, 139.5, 132.2, 123.1, 114.8, 66.0, 62.9, 55.5, 13.9 ppm; LRMS (EI) m/z 281 (M^+, 23%), 208 (100), 146 (5), 137 (18); HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{15}NO_6$ 281.0899, found 281.0898.

*4.2.13. Ethyl 2-hydroxy-3-nitro-4-(thiophen-2-yl)but-3(E)-enoate (**3m**).* IR (ν/cm^{-1}): 3432, 2989, 2915, 2841, 1749, 1635, 1521, 1418, 1307, 1252, 1218, 1159, 1100, 1053, 1016; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.74–7.70 (m, 1H), 7.60–7.56 (m, 1H), 7.24–7.20 (m, 1H), 5.57 (d, J=5.3 Hz, 1H), 4.38–4.22 (m, 2H), 3.72 (d, J=5.9 Hz, 1H), 1.26 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 144.7, 136.0, 133.4, 132.9, 131.8, 128.7, 66.2, 63.0, 13.9 ppm; LRMS (EI) m/z 257 (M^+, 12%), 240 (24), 194 (11), 184 (100), 168 (7), 138 (16), 122 (19), 113 (31); HRMS (EI) m/z: $[M]^+$ calcd for $C_{10}H_{11}NO_5S$ 257.0358, found 257.0362.

*4.2.14. Ethyl 4-(furan-2-yl)-2-hydroxy-3-nitrobut-3(E)-enoate (**3n**).* IR (ν/cm^{-1}): 3476, 3063, 2989, 2915, 2849, 1746, 1650, 1517, 1469, 1322, 1303, 1229, 1097, 1060, 1023; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.70 (m, 1H), 7.05–7.02 (m, 1H), 6.66–6.62 (m, 1H), 6.00 (s, 1H), 4.37–4.20 (m, 2H), 3.66 (s, 1H), 1.25 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 147.9, 146.4, 143.8, 124.2, 122.9, 113.4, 66.3, 62.7, 14.0 ppm; LRMS (EI) m/z 241 (M^+, 11%), 178 (6), 168 (100), 105 (20), 97 (14), 83 (6); HRMS (EI) m/z: $[M]^+$ calcd for $C_{10}H_{11}NO_6$ 241.0586, found 241.0582.

*4.2.15. Ethyl 2-hydroxy-3-nitro-6-phenylhex-3(E)-enoate (**3o**).* IR (ν/cm^{-1}): 3410, 2923, 2849, 1735, 1646, 1554, 1454, 1370, 1159, 1108, 1056, 1023; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.16 (m, 6H), 5.07 (d, J=4.4 Hz, 1H), 4.34–4.17 (m, 2H), 3.47 (d, J=5.2 Hz, 1H), 2.89 (t, J=7.4 Hz, 2H), 2.77–2.68 (m, 2H), 1.25 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 148.8, 140.7, 139.4, 128.8, 128.3, 126.7, 65.2, 62.9, 34.4, 29.6, 14.0 ppm; LRMS (EI) m/z 280 (M^++1, 2%), 244 (6), 188 (16), 155 (44), 125 (55), 91 (100), 55 (5); HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{14}H_{17}NO_5Na$ 302.1004, found 302.0999.

*4.2.16. Ethyl 2-hydroxy-6-methyl-3-nitrohept-3(E)-enoate (**3p**).* IR (ν/cm^{-1}): 3432, 2967, 2915, 2856, 1746, 1642, 1561, 1528, 1465, 1370, 1347, 1270, 1222, 1104, 1064, 1019; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (t, J=8.2 Hz, 1H), 5.09 (d, J=6.0 Hz, 1H), 4.36–4.21 (m, 2H), 3.52 (d, J=6.3 Hz, 1H), 2.33–2.27 (m, 2H), 1.92 (septet, J=6.6 Hz, 1H), 1.26 (t, J=7.1 Hz, 3H); 1.02 (d, J=3.0 Hz, 3H); 1.00 (d, J=3.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 148.9, 141.2, 65.2, 62.9, 36.8, 28.4, 22.4, 22.3, 14.0 ppm; LRMS (EI) m/z 232 (M^++1, 17%), 168 (10), 167 (12), 158 (99), 140 (51), 129 (42), 112 (27), 98 (45), 96 (60), 71 (36), 70 (100), 67 (75); HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{10}H_{17}NO_5Na$ 254.1004, found 254.1010.

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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).