An Efficient Synthesis of α-Isothiocyanato-α,β-unsaturated Esters from Morita–Baylis–Hillman Adducts

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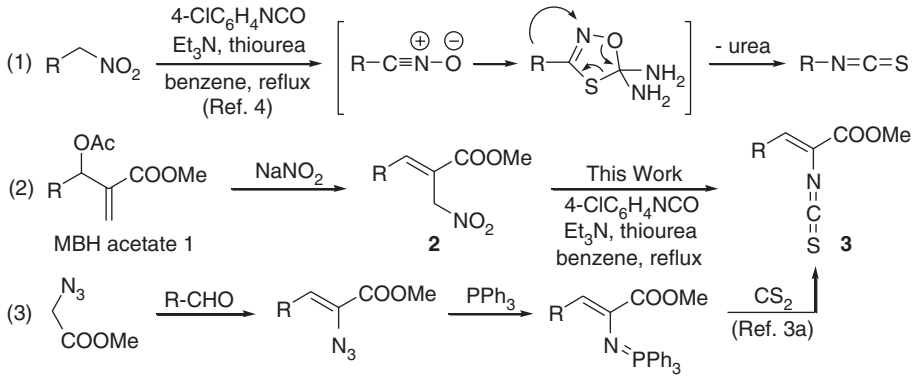
Isothiocyanates (ITCs) have been used extensively in organic synthesis, particularly for the synthesis of various heterocyclic compounds.[1a,b] Numerous ITCs including phenethyl ITC (PEITC) and sulforaphane showed interesting biological activities such as antitumor activity.[1c–f] Among ITCs, α-isothiocyanato-α,β-unsaturated ester derivatives, including paulomycins A and B and their analogues, have been known as antibiotics.[2] In addition, α-isothiocyanato-α,β-unsaturated esters have been used for the synthesis of many heterocyclic compounds such as 1,3-oxazolidine-2-thione,[3a] 2-alkylthio-4*H*-imidazol-4-ones,[3b,c] carbolines,[3d] pyrimido[4,5-*b*]indoles,[3d] and poly-substituted pyridines.[3e]

In the early 1990s, we reported an efficient synthesis of ITCs from primary nitroalkanes in a one-pot procedure (Eq. (1) in Scheme 1).[4] Dehydration of primary nitroalkane by Mukaiyama procedure[5] generates the corresponding nitrile oxide, and the following [3 + 2] cycloaddition to C=S double bond of thiourea afforded 5,5-diamino-1,4,2-oxathiazole intermediate.[4,6] The 1,4,2-oxathiazole was readily converted to ITC at room temperature in short time (<5 min.).[4,6,7]

Morita–Baylis–Hillman (MBH) adducts have been used for the synthesis of various cyclic and acyclic compounds.[8] During our continuous studies with MBH adducts, we reasoned out that α-isothiocyanato-α,β-unsaturated ester **3** could be synthesized from primary nitroalkane **2**, prepared from MBH acetate **1** and $NaNO_2$,[9] as shown in Eq. (2). The synthesis of **3** has been reported by sequential Knoevenagel condensation of aldehyde and methyl azidoacetate to form the azide derivative, a subsequent Staudinger reaction with PPh_3 to form iminophosphorane, and the *aza*-Wittig reaction with carbon disulfide (Eq. (3) in Scheme 1).[3,10] However, the yields of α-isothiocyanato-α,-β-unsaturated esters were low to moderate in most cases (49–78%).[3a,3c,10a]

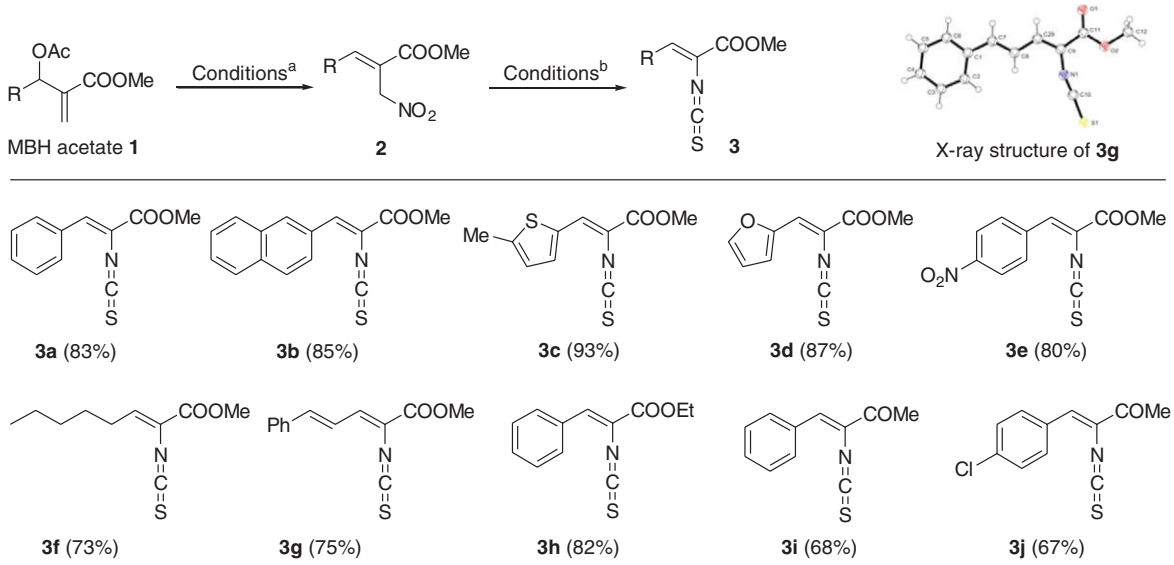
The required primary nitroalkanes **2a–2j** were prepared from MBH acetates and sodium nitrite according to the reported method.[9] The reaction of **2a** in the presence of *p*-chlorophenylisocyanate (2.0 equiv), thiourea (1.1 equiv), and a catalytic amount of Et_3N (5 mol%) in benzene (reflux) for 2 h afforded **3a** in good yield (83%). Similarly, the reactions of 2-naphthyl, 5-methyl-2-thienyl, 2-furyl, and 4-nitrophenyl derivatives **2b–2e** afforded the corresponding α-isothiocyanato-α,β-unsaturated esters **3b–3e** in good yields (80–93%). The alkyl derivative **3f** and styryl derivative **3g** were also synthesized in good yields (73 and 75%, respectively). In addition, ethyl ester **3h** and acetyl derivatives **3i** and **3j** were synthesized in good yields (67–82%).[11] The structure of **3g** was confirmed unequivocally by its crystal structure,[12] as also shown in Table 1.

In summary, a facile one-pot synthetic procedure of α-isothiocyanato-α,β-unsaturated esters has been developed



Scheme 1. Synthetic rationale of α-isothiocyanato-α,β-unsaturated esters.

Table 1. Synthesis of α-isothiocyanato-α,β-unsaturated esters.



[a]Primary nitroalkanes **2a-2j** were prepared from MBH acetates according to the reported method[9] ($NaNO_2$, DMF, room temperature) in moderate to good yields (53-84%).

[b]Conditions: **2a-2j** (1.0 mmol), 4-ClC_6H_4NCO (2.0 equiv.), thiourea (1.1 equiv.), Et_3N (5 mol%), benzene, reflux, 2 h.

starting from primary nitroalkanes that prepared from MBH adducts. The yields of products were higher than the reported one using expensive methyl azidoacetate. Further studies on the scope of reaction and biological activity of the ITCs are currently underway.

Experimental

Typical Procedure for the Synthesis of 3a. A stirred mixture of **2a** (221 mg, 1.0 mmol), 4-chlorophenylisocyanate (306 mg, 2.0 mmol), thiourea (84 mg, 1.1 mmol), and Et_3N (5 mg, 0.05 mmol) in benzene (4.0 mL) was heated to reflux for 2 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/Et_2O, 10:1) **3a** was isolated as a white solid, 182 mg (83%). Other compounds were synthesized similarly, and the spectroscopic data of **3a–3j** are as follows.

Compound 3a.[3e] 83%; white solid, mp 52–53 °C; IR (KBr) 2014, 1728, 1622, 1435, 1259 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.87 (s, 3H), 7.22 (s, 1H), 7.34–7.41 (m, 3H), 7.72–7.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 53.41, 119.32, 128.88, 130.19, 130.82, 131.81, 132.35, 144.16, 163.39; ESIMS *m/z* 220 [M^++H]. Anal. Calcd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14; N, 6.39. Found: C, 60.50; H, 4.27; N, 6.28.

Compound 3b. 85%; white solid, mp 100–101 °C; IR (KBr) 2039, 1721, 1617, 1428, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.96 (s, 3H), 7.44 (s, 1H), 7.51–7.57 (m, 2H), 7.84–7.90 (m, 3H), 7.97 (dd, *J* = 8.0 and 1.5 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 53.44, 119.29, 126.07, 126.78, 127.74, 127.82, 128.56, 128.91, 129.92, 131.44, 131.92, 132.99, 134.21, 144.26, 163.48; ESIMS *m/z* 270 [M^++H]. Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12; N, 5.20. Found: C, 66.71; H, 4.01; N, 5.26.

Compound 3c. 93%; pale yellow solid, mp 92–93 °C; IR (KBr) 2032, 1718, 1597, 1434, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 2.56 (d, *J* = 0.6 Hz, 3H), 3.90 (s, 3H), 6.77–6.78 (m, 1H), 7.22 (dd, *J* = 3.6 and 0.6 Hz, 1H), 7.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 15.83, 53.14, 115.19, 126.16, 126.21, 134.22, 134.45, 144.50, 147.25, 163.38; ESIMS *m/z* 240 [M^++H]. Anal. Calcd for $C_{10}H_9NO_2S_2$: C, 50.19; H, 3.79; N, 5.85. Found: C, 50.30; H, 3.94; N, 5.82.

Compound 3d. 87%; white solid, mp 65–66 °C; IR (KBr) 2018, 1726, 1619, 1471, 1435, 1274 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.90 (s, 3H), 6.57 (dd, *J* = 3.6 and 1.8 Hz, 1H), 7.11 (d, *J* = 3.6 Hz, 1H), 7.25 (s, 1H), 7.58 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 53.28, 112.90, 116.04, 116.67, 120.21, 142.59, 145.44, 149.05, 163.01; ESIMS *m/z* 210 [M^++H]. Anal. Calcd for $C_9H_7NO_3S$: C, 51.67; H, 3.37; N, 6.69. Found: C, 51.85; H, 3.20; N, 6.56.

Compound 3e. 80%; white solid, mp 133–134 °C; IR (KBr) 2027, 1724, 1515, 1347, 1274 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.98 (s, 3H), 7.28 (s, 1H), 7.98 (d, *J* = 9.0 Hz, 2H), 8.29 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 53.79, 123.34, 123.99, 127.77, 130.65, 138.39, 146.63, 148.10, 162.68; ESIMS *m/z* 265 [M^++H]. Anal. Calcd for $C_{11}H_8N_2O_4S$: C, 50.00; H, 3.05; N, 10.60. Found: C, 50.23; H, 3.18; N, 10.43.

Compound 3f. 73%; colorless oil; IR (film) 2032, 1735, 1637, 1437, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ

0.91 (t, J = 7.0 Hz, 3H), 1.31–1.36 (m, 4H), 1.44–1.50 (m, 2H), 2.34 (q, J = 7.5 Hz, 2H), 3.86 (s, 3H), 6.65 (t, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.90, 22.35, 27.79, 28.77, 31.37, 53.02, 122.95, 139.66, 142.58, 162.40; ESIMS *m/z* 214 [M^++H]. Anal. Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57. Found: C, 56.20; H, 7.22; N, 6.54.

Compound 3g. 75%; pale yellow solid, mp 110–111 °C; IR (KBr) 2064, 1719, 1606, 1427, 1277 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.89 (s, 3H), 6.95–7.00 (m, 1H), 7.14–7.20 (m, 2H), 7.33–7.40 (m, 3H), 7.51–7.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 53.12, 119.97, 122.17, 127.64, 128.91, 129.75, 134.11, 135.65, 142.03, 143.71, 162.96; ESIMS *m/z* 246 [M^++H]. Anal. Calcd for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71. Found: C, 63.71; H, 4.77; N, 5.56.

Compound 3h.[3a,b] 82%; colorless oil; IR (film) 2015, 1724, 1623, 1259 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.42 (t, J = 7.5 Hz, 3H), 4.40 (q, J = 7.5 Hz, 2H), 7.29 (s, 1H), 7.41–7.47 (m, 3H), 7.81–7.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.26, 62.86, 119.59, 128.85, 130.17, 130.73, 131.42, 132.41, 144.46, 162.86; ESIMS *m/z* 234 [M^++H]. Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.95; H, 4.59; N, 6.12.

Compound 3i. 68%; pale yellow solid, mp 72–73 °C; IR (KBr) 2053, 1667, 1447, 1244 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.53 (s, 3H), 7.11 (s, 1H), 7.43–7.47 (m, 3H), 7.85–7.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 25.44, 128.59, 128.93, 130.31, 131.04, 131.72, 132.34, 146.94, 191.48; ESIMS *m/z* 204 [M^++H]. Anal. Calcd for $C_{11}H_9NOS$: C, 65.00; H, 4.46; N, 6.89. Found: C, 65.29; H, 4.28; N, 6.96.

Compound 3j. 67%; white solid, mp 90–91 °C; IR (KBr) 1987, 1686, 1490, 1275 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.53 (s, 3H), 7.05 (s, 1H), 7.43 (d, J = 8.5 Hz, 2H), 7.81 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.44, 129.19, 129.25, 129.98, 130.87, 131.45, 136.90, 147.74, 191.27; ESIMS *m/z* 238 [M^++H], 240 [M^++H + 2]. Anal. Calcd for $C_{11}H_8ClNOS$: C, 55.58; H, 3.39; N, 5.89. Found: C, 55.83; H, 3.48; N, 5.81.

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Supporting Information. Additional supporting information is available in the online version of this article.

References

1. For general reviews on isothiocyanates, see: (a) A. K. Mukerjee, R. Ashare, *Chem. Rev.* **1991**, *91*, 1; (b) K. G. Bedane, G. S. Singh, *Arkivoc* **2015**, *vi*, 206; (c) J. R. Mays, R. L. Weller Roska, S. Sarfaraz, H. Mukhtar, S. R. Rajski, *ChemBioChem* **2008**, *9*, 729; (d) X. Wu, Q.-h. Zhou, K. Xu, *Acta Pharmacol. Sin.* **2009**, *30*, 501; (e) A. T. Dinkova-Kostova, R. V. Kostov, *Trends Mol. Med.* **2012**, *18*, 337; (f) S. S. Hecht, *Drug Metab. Rev.* **2000**, *32*, 395.
2. For biological activity of α-isothiocyanato-α,β-unsaturated esters, such as Paulomycins A and B, see:(a) P. F. Wiley, S. A. Mizsak, L. Baczynskyj, A. D. Argoudelis, D. J. Duchamp, W. Watt, *J. Org. Chem.* **1986**, *51*, 2493; (b) A. D. Argoudelis, L. Baczynskyj, S. A. Mizsak, F. B. Shilliday, P. A. Spinelli, J. DeZwaan, *J. Antibiot.* **1987**, *XL*, 419.
3. For synthetic usefulness of α-isothiocyanato-α,β-unsaturated esters, see:(a) K. Kobayashi, K. Ezaki, H. Hashimoto, *Helv. Chim. Acta* **2013**, *96*, 431; (b) Y. Sun, L.-P. Gao, M.-W. Ding, *Synth. Commun.* **2006**, *36*, 1185; (c) F.-L. Yang, Z.-J. Liu, X.-B. Huang, M.-W. Ding, *J. Heterocycl. Chem.* **2004**, *41*, 77; (d) P. Molina, P. M. Fresneda, *J. Chem. Soc., Perkin Trans. 1* **1988**, 1819; (e) J. Barluenga, M. Ferrero, E. Pelaez-Arango, F. Lopez-Ortiz, F. Palacios, *J. Chem. Soc., Chem. Commun.* **1994**, 865.
4. J. N. Kim, J. H. Song, E. K. Ryu, *Synth. Commun.* **1994**, *24*, 1101.
5. T. Mukaiyama, T. Hoshino, *J. Am. Chem. Soc.* **1960**, *82*, 5339.
6. For synthesis of isothiocyanates from nitrile oxides, see: (a) J. N. Kim, E. K. Ryu, *Tetrahedron Lett.* **1993**, *34*, 8283; (b) J. N. Kim, K. S. Jung, H. J. Lee, J. S. Son, *Tetrahedron Lett.* **1997**, *38*, 1597; (c) K. S. Jung, H. J. Lee, H. N. Song, J. N. Kim, *Synth. Commun.* **1998**, *28*, 1879.
7. For the formation and fragmentation of 1,4,2-oxathiazoles, see:(a) R. J. O'Reilly, L. Radom, *Org. Lett.* **2009**, *11*, 1325; (b) Y. W. Lim, R. J. Hewitt, B. A. Burkett, *Eur. J. Org. Chem.* **2015**, 4840; (c) B. A. Burkett, P. Fu, R. J. Hewitt, S. L. Ng, J. D. W. Toh, *Eur. J. Org. Chem.* **2014**, 1053; (d) R. J. Hewitt, M. J. H. Ong, Y. W. Lim, B. A. Burkett, *Eur. J. Org. Chem.* **2015**, 6687.
8. For general reviews on MBH reaction, see: (a) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811; (b) D. Basavaiah, B. S. Reddy, S. S. Badsara, *Chem. Rev.* **2010**, *110*, 5447; (c) V. Singh, S. Batra, *Tetrahedron* **2008**, *64*, 4511; (d) J. N. Kim, K. Y. Lee, *Curr. Org. Chem.* **2002**, *6*, 627; (e) K. Y. Lee, S. Gowrisankar, J. N. Kim, *Bull. Korean Chem. Soc.* **2005**, *26*, 1481; (f) S. Gowrisankar, H. S. Lee, S. H. Kim, K. Y. Lee, J. N. Kim, *Tetrahedron* **2009**, *65*, 8769; (g) M. Shi, F.-J. Wang, M.-X. Zhao, Y. Wei, *The Chemistry of the Morita–Baylis–Hillman Reaction*, RSC Publishing, Cambridge, **2011**.
9. For synthesis of primary nitroalkanes of MBH adducts, see: (a) W. P. Hong, K.-J. Lee, *Synthesis* **2005**, 33; (b) S.-H. Ji, W. P. Hong, S. H. Ko, K.-J. Lee, *J. Heterocycl. Chem.* **2006**, *43*, 799; (c) S.-R. Sheng, S.-Y. Lin, Q. Wang, X.-L. Liu, M. Lin, *Synth. Commun.* **2007**, *37*, 1011; (d) H. J. Kim, E. M. Jeong, K.-J. Lee, *J. Heterocycl. Chem.* **2011**, *48*, 965; (e) S. U. Dighe, S. Mukhopadhyay, S. Kolle, S. Kanojiya, S. Batra, *Angew. Chem. Int. Ed.* **2015**, *54*, 10926.
10. For reported synthesis, see:(a) P. Molina, A. Arques, P. M. Fresneda, M. V. Vinader, M. C. Foces-Foces, F. H. Cano, *Chem. Ber.* **1989**, *122*, 307; (b) P. Molina, P. M. Fresneda, P. Alarcon, *Tetrahedron Lett.* **1988**, *29*, 379.

11. An introduction of nitro group at the primary position of MBH acetate derived from acrylonitrile failed, unfortunately. To the best of our knowledge, there is no report on the synthesis of primary nitro compound of MBH adduct of acrylonitrile.
12. Crystal data of compound **3g**: solvent of crystal growth (hexane + CH_2Cl_2); empirical formula $C_{13}H_{11}NO_2S$, Fw = 245.3, crystal dimensions $0.12 \times 0.21 \times 0.10$ mm^3, Monoclinic, space group $P2_1/n$, a = 5.7385(3) Å, b = 15.0987(9) Å, c = 14.3355(8) Å, $\alpha = 90^\circ$, $\beta = 90.759(4)^o$, $\gamma = 90^\circ$, V = 1241.97 Å^3, Z = 4, D_{calcd} = 1.312 mg/m^3, F_{000} = 512.0, MoK (λ = 0.71073 Å), R_1 = 0.0481, wR_2 = 0.1514, GOF = 1.062 ($I > 2$ (I)). The X-ray data have been deposited in CCDC with number 1424661.

