The Baylis-Hillman reaction of substituted aminomethylbenzotriazoles

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Dedicated to Professor Csaba Szantay on the occasion of his 80th anniversary

Abstract
Aminomethylbenzotriazoles react as effective Baylis-Hillman electrophiles with ethyl acrylate in the presence of $TiCl_4$ at 20 ºC to afford the corresponding benzotriazolated adducts in 66-80% yield. These adducts are (i) readily transformed to the Baylis-Hillman olefins by sodium hydride and (ii) smoothly undergo substitution of Bt with thiols.

Keywords: Baylis-Hillman reaction, aminomethylbenzotriazoles, Baylis-Hillman olefins, substitution

Introduction

Carbon-carbon bond formation is the essence of organic synthesis and provides the foundation for generating more complicated organic compounds from simpler ones. Many classical carbon-carbon bond-forming reactions are well documented e.g. the aldol, Friedel-Crafts, Reformatsky and Grignard reactions. More recently the Baylis-Hillman reaction, which couples electron deficient alkenes with carbon electrophiles has demonstrated great synthetic utility in converting simple starting materials into densely functionalized products, capable of numerous transformations.[1,2]

The Baylis-Hillman reaction had a precedent when in 1968, Morita described tricyclohexylphosphine catalyzed reactions of an aldehyde with acrylic compounds.[3] In 1972, Anthony Baylis and Melville Hillman patented catalyzed reactions using similar tertiary amine.[4] In 1983, the reaction was rediscovered, and its scope was explored primarily by Drewes and Basavaiah.[5] Since then, alkyl vinyl ketones, acrylonitriles, vinyl sulfones, acrylamides, allenic esters, vinyl sulfonates, vinyl sulfoxides, vinyl phosphonates, and acroleins have been substituted

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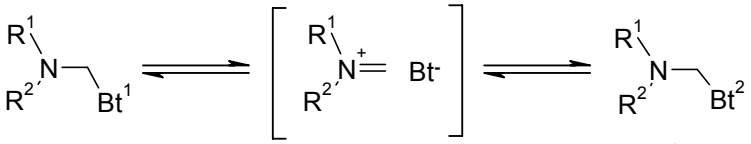
for the acrylate component. Imines, tosylimines, α-ketoesters or aldehydes and fluoroesters have also been used.[1]

Versatile functionality, i.e. hydroxyl (or amino), alkene, and electron-withdrawing groups, make Baylis-Hillman adducts valuable intermediates in Friedel–Crafts [6-8] and Heck reactions,[9,10] hydride addition,[11,12] hydrogenation,[13-16] aminohydroxylation,[17] radical[18,19] and photochemical reactions[20] and 1,3-dipolar cycloaddition.[21]

Numerous chemical and physical methods have been developed[22-27] to accelerate the Baylis-Hillman reaction, overcoming traditional slow reaction rates (weeks or months).[28] Among Lewis acids, $TiCl_4$ has been successfully utilized to promote the Baylis-Hillman reaction in the presence of Lewis base catalysts. Recent work has revealed that the combination of Lewis base such as phosphanes,[29] organic chalcogenides,[30-32] bisoxazolines[33,34], amines[35,36] and quaternary ammonium halides[37,38] with $TiCl_4$ can significantly improve the reaction rate. More interestingly, the combination of a Lewis base with the Lewis acid $TiCl_4$ gives the corresponding chlorinated Baylis-Hillman products.[35-38]

Aminomethylbenzotriazoles **1** are useful synthetic intermediates[39] in which the methylene carbon is highly electrophilic because of equilibrium with the benzotriazolide-iminium ion pair **2** (Scheme 1).[40] Our group has successfully applied this concept to carbon-carbon bond formation reactions in their reactions with Grignard[41,42] and Reformatsky[43] reagents to provide secondary and tertiary amines. Aminomethylbenzotriazoles have been also successfully used for the synthesis of functionalized amides and β-aminoalkyl nitriles.[44,45]



1 **2** **3**

Scheme 1

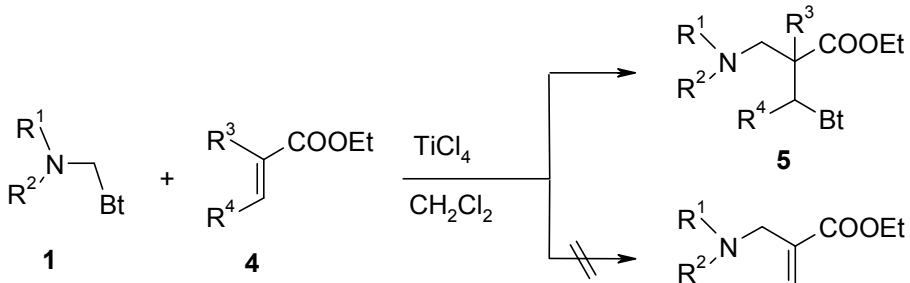
We found only a single report of the Baylis-Hillman reaction using an iminium salt prepared *in situ* as an electrophile.[46] The hygroscopicity, susceptibility to hydrolysis and the low stability of iminium salts with α-H atoms[47] hinder their isolation and encouraged coupling of electron deficient alkenes with the corresponding iminium salts bearing α-H. We report herein reactions of aminomethylbenzotriazoles **1** with ethyl acrylate and analogs.

Results and Discussion

Aminomethylbenzotriazoles **1** are easily prepared according to well-established condensations of benzotriazole, formaldehyde and a secondary amine.[48, 49]

Aminomethylbenzotriazoles **1** reacted with acrylates **4** in the presence of $TiCl_4$ (1.0 equiv) at 20 ºC for 16-20 h to give exclusively the benzotriazolated product **5** in 66-80% yield rather than **6** which is usually expected as the product of the Baylis-Hillman reaction (Table 1). Extension of the reaction time to 72 h gave the same yields, but less than 12 h resulted in the isolation of the compound **5** in lower yield. To our knowledge, this is the first Baylis-Hillman reaction using iminium salts with α-H atoms.

Table 1. Preparation of the Baylis-Hillman adducts **5**



1 **a** Morpholinyl; **b** Piperidinyl; **c** NCH_3CH_3; **d** Pyrrolidinyl

4a $R^3 = R^4 = H$; **4b** $R^3 = H$, $R^4 = CH_3$; **4c** $R^3 = CH_3$, $R^4 = H$

For designation of R^1, R^2 in **1** see Table 1

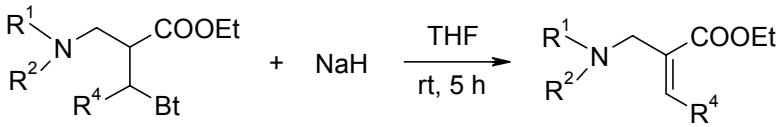
5	R^1	R^2	R^3	R^4	Yield (%)
a	$(CH_2)_2O(CH_2)_2$		H	H	69
b	$(CH_2)_4$		H	H	71
c	$(CH_2)_5$		H	H	73
d	$(CH_2)_2O(CH_2)_2$		H	CH_3	66
e	CH_3	CH_3	H	H	80
f	$(CH_2)_2O(CH_2)_2$		CH_3	H	80
g	CH_3	CH_3	CH_3	H	75
h	$(CH_2)_4$		CH_3	H	71
i	$(CH_2)_5$		CH_3	H	78

Conversion of compounds **5a-d** into the Baylis-Hillman olefin **7a-d** was accomplished in 65-71% yields by treatment of **5a-d** with sodium hydride in THF at room temperature for 5 h. With one equivalent of sodium carbonate at 20 ºC, **5a** gave **7a** in low yield; a complex mixture was obtained under reflux conditions.

Compounds **7** are synthetic precursors for quaternary ammonium amphiphilic methacrylates, widely applied industrially, e.g., in waste-water treatment.[50,51] Previous preparations of **7** from (i)

mono ethyl malonate, formaldehyde, and a secondary amine[52] or (ii) halomethyl acrylates and a secondary amine[53,54] have several drawbacks such as tedious procedure, multi-step synthesis, slow reaction rates (days or weeks), and low yields and selectivity.

Table 2. Preparation of the Baylis-Hillman olefin **7**

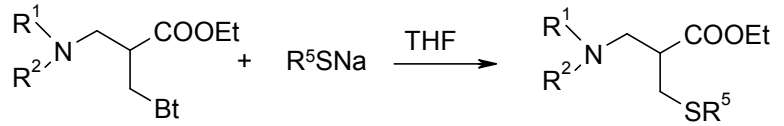


5a-d **7a-d**

7	R^1	R^2	R^4	Yield (%)
a	$(CH_2)_2O(CH_2)_2$	H	H	71
b	$(CH_2)_4$	H	H	67
c	$(CH_2)_5$	H	H	68
d	$(CH_2)_2O(CH_2)_2$	CH_3	H	65

Treatment of **5a-c** with 2 equiv. of thiols in THF at 20-50 ºC for the time indicated in Table 3, monitoring the reactions by TLC, afforded novel compound **8a-g** in 71-82% yield (Table 3). The use of less than 2 equiv. of sodium thiolate left some unreacted starting material.

Table 3. Reaction of compounds **5** with thiols



5a-c **8a-g**

8	R^1	R^2	R^5	Temp	Time (h)	Yield (%)
a	$(CH_2)_2O(CH_2)_2$	C_6H_5	RT	12	82
b	$(CH_2)_2O(CH_2)_2$	4-$CH_3C_6H_4$	RT	12	79
c	$(CH_2)_2O(CH_2)_2$	4-ClC_6H_4	reflux	6	81
d	$(CH_2)_2O(CH_2)_2$	C_2H_5	RT	24	79
e	$(CH_2)_2O(CH_2)_2$	4-$CH_3OC_6H_4$	RT	4	82
f	$(CH_2)_4$	C_6H_5	RT	12	71
g	$(CH_2)_5$	C_6H_5	RT	12	76

The structures of all compounds **5**, **7** and **8** were elucidated by ^1H, ^{13}C NMR spectroscopy and elemental analysis.

In summary we have developed a novel and general access to functionalized esters possessing an amino group at the β-position *via* the Baylis-Hillman reaction of ethyl acrylate and

ethyl butenoate utilizing an easily accessible *N*-(α-aminomethyl)benzotriazoles. The good yields of **5** demonstrate the convenience of *N*-(α-aminomethyl)benzotriazoles as imminium ion equivalents with α -H atoms generated *in situ*.

Experimental Section

General Procedures. Reagents were obtained form commercial suppliers and were used without further purification. All reactions were carried out under N_2 atmosphere. ^{1}H NMR (300 MHz) and ^{13}C (75 MHz) spectra were recorded on a 300 MHz NMR spectrometer in $CDCl_3$ using TMS as an internal standard. Column chromatography was performed on silica gel 200-425 mesh. THF was distilled from sodium-benzophenone ketyl and CH_2Cl_2 was distilled from CaH_2 prior to use.

General procedure for preparation of 5a-i

$TiCl_4$ (0.19 g, 1.0 mmol) was added to a solution of aminomethylbenzotriazole (1.0 mmol) and acrylate (2.0 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 ^{o}C. The resulting mixture was stirred at 0 ^{o}C for 30 min and room temperature for 16-20 h. The mixture was quenched by saturated $NaHCO_3$ (5 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by flash silica gel chromatography (eluent: diethyl ether/*n*-hexane = 2/1)

Ethyl (3-benzotriazol-1-yl)-2-(morpholin-4-ylmethyl)propionate (5a). Yield 0.22 g (69%); colorless oil; ^{1}H NMR δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.46-7.52 (m, 1H), 7.33-7.39 (m, 1H), 4.85-4.98 (m, 2H), 3.96-4.10 (m, 2H), 3.63 (t, *J* = 4.2 Hz, 4H), 3.35-3.44 (m, 1H), 2.69 (dd, *J* = 12.6, 6.9 Hz, 1H), 2.60 (dd, *J* = 12.6, 8.5 Hz, 1H), 2.34-2.50 (m, 4H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 172.5, 145.7, 133.4, 127.3, 123.9, 119.9, 109.5, 66.8, 61.2, 57.9, 53.6, 47.3, 44.0, 13.9; HRMS (ESI-TOF) : Calcd. for $C_{16}H_{22}N_4O_3$ $[M+H]^+$: 319.1771. Found: 319.1797

Ethyl (3-benzotriazol-1-yl)-2-(pyrrolidin-1-ylmethyl)propionate (5b). Yield 0.214 g (71%); yellow oil; ^{1}H NMR δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.44-7.51 (m, 1H), 7.33-7.39 (m, 1H), 4.99 (dd, *J* = 14.0, 5.4 Hz, 1H), 4.90 (dd, *J* = 14.0, 8.3 Hz, 1H), 3.95-4.08 (m, 2H), 3.30-3.40 (m, 1H), 2.79 (dd, *J* = 11.2, 6.8 Hz, 1H), 2.73 (dd, *J* = 11.2, 5.6 Hz, 1H), 2.40-2.56 (m, 4H), 1.72-1.81 (m, 4H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 172.8, 145.7, 133.4, 127.2, 123.8, 119.8, 109.7, 61.1, 55.2, 54.1, 47.3, 46.1, 23.6, 13.9 Anal. Calcd. for $C_{16}H_{22}$ N_4O_2: C, 63.55; H, 7.33; N, 18.53. Found: C, 63.66; H, 7.38; N, 18.26.

Ethyl (3-benzotriazol-1-yl)-2-(piperidin-1-ylmethyl)propionate (5c). Yield 0.23 g (73%); pale yellow oil; ^{1}H NMR δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.45-7.51 (m, 1H), 7.32-7.39 (m, 1H), 4.96 (dd, *J* = 15.0, 5.4 Hz, 1H), 4.88 (dd, *J* = 15.0, 8.1 Hz, 1H), 3.95-4.10 (m, 2H), 3.33-3.43 (m, 1H), 2.63 (dd, *J* = 12.0, 6.5 Hz, 1H), 2.55 (dd, *J* = 12.0, 8.7 Hz, 1H), 2.30-

2.48 (m, 4H), 1.48-1.59 (m, 4H), 1.36-1.46 (m, 2H), 1.08 (t, *J* = 7.1 Hz, 3H); 13C NMR δ 172.8, 145.5, 133.3, 127.1, 123.7, 119.6, 109.7, 60.9, 58.1, 54.5, 47.4, 44.3, 25.8, 24.1, 13.8 Anal. Calcd. for $C_{17}H_{24}N_4O_2$: C, 64.53; H, 7.65; N, 17.71. Found: C, 64.19; H, 7.68; N, 18.09

Ethyl (3-benzotriazol-1-yl)-3-methyl-2-(morpholin-4-ylmethyl)propionate (5d). Yield 0.218 g(66%); colorless oil; ^{1}H NMR δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.47-7.54 (m, 1H), 7.36-7.43 (m, 1H), 5.10-5.22 (m, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.50-3.58 (m, 1H), 3.37-3.46 (m, 4H), 2,55 (dd, *J* = 15 9.2 Hz, 1H), 2.22-2.32 (m, 2H), 2.01-2.12 (m, 3H), 1.73 (d, *J* = 6.9 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 172.6, 145.9, 132.8, 127.3, 124.0, 120.1, 109.3, 66.6, 61.0, 58.4, 55.5, 53.4, 49.3, 19.4, 14.2 Anal. Calcd. for $C_{17}H_{24}N_4O_{23}$: C, 61.43; H, 7.28; N, 16.85. Found: C, 61.79; H, 7.49; N, 16.22.

Ethyl (3-benzotriazol-1-yl)-2-(*N*,*N*-dimethylaminomethyl)propionate (5e). Yield 0.22 g (80%); colorless oil; ^{1}H NMR δ (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.46-7.52 (m, 1H), 7.33-7.39 (m, 1H), 4.94 (dd, *J* = 14.2, 5.4 Hz, 1H), 4.87 (dd, *J* = 14.2, 8.3 Hz, 1H), 3.96-4.06 (m, 2H), 3.29-3.38 (m, 1H), 2.64 (dd, *J* = 12.5, 6.8 Hz, 1H), 2.54 (dd, *J* = 12.5, 8.3 Hz, 1H), 2.27 (s, 6H), 1.04 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 172.7, 145.7, 133.3, 127.3, 123.8, 119.8, 109.6, 61.1, 58.8, 47.3, 45.6, 45.1, 13.8; HRMS (ESI-TOF) : Calcd. for $C_{14}H_{20}N_4O_2$ $[M+H]^+$: 277.1665. Found 277.1689.

Ethyl (3-benzotriazol-1-yl)-2-methyl-2-(morphlinylmethyl)propionate (5f). Yield 0.264 g (80%); pale yellow oil; ^{1}H NMR δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.45-7.52 (m, 1H), 7.33-7.39 (m, 1H), 4.91 (s, 2H), 4.12 (dd, *J* = 7.2, 2.7 Hz. 1H), 4.07 (dd, *J* = 7.2, 2.4 Hz, 1H), 3.69 (t, *J* = 4.7 Hz, 4H), 2.71 (d, *J* = 13.8 Hz, 1H, A part of AB system), 2.65 (d, *J* = 13.8 Hz, 1H, B part of AB system), 2.54 (t, *J* = 4.7 Hz, 4H), 1.22 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 175.0, 145.4, 134.1, 127.2, 123.9, 119.8, 110.1, 67.1, 63.5, 61.2, 55.1, 51.6, 48.7, 20.3, 13.9 Anal. Calcd. for $C_{17}H_{24}N_4O_3$: C, 61.43; H, 7.28; N, 16.85. Found: C, 61.13; H, 7.33; N, 17.26

Ethyl (3-benzotriazol-1-yl)-2-(*N*,*N*-dimethylaminomethyl)-2-methylpropionate (5g). Yield 0.218 g (75%); pale yellow oil; 1H NMR δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.44-7.50 (m, 1H), 7.32-7.38 (m, 1H), 4.93 (d, *J* = 14.3 Hz, 1H, A part of AB system), 4.86 (d, *J* = 14.3 Hz, 1H, B part of AB system), 4.14 (dd, *J* = 7.2, 1.5 Hz, 1H), 4.09 (dd, *J* = 7.2, 1.5 Hz, 1H), 2.64 (d, *J* = 13.5 Hz, 1H, A part of AB system), 2.58 (d, *J* = 13.5 Hz, 1H, B part of AB system), 2.27 (s, 6H), 1.22 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H) ; ^{13}C NMR δ 175.1, 145.4, 134.2, 127.1, 123.7, 119.7, 110.4, 64.9, 61.2, 51.8, 48.7, 47.3, 20.3, 13.9 Anal. Calcd. for $C_{15}H_{22}N_4O_2$: C, 62.05; H, 7.64; N, 19.30. Found: C, 62.39; H, 7.86; N, 18.92

Ethyl (3-benzotriazol-1-yl)-2-methyl-2-(pyrrodin-1-ylmethyl)propionate (5h). Yield 0.224 g (71%); pale yellow oil; 1H NMR δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.43-7.48 (m, 1H), 7.31-7.37 (m, 1H), 4.95 (d, *J* = 14.4 Hz, 1H, A part of AB system), 4.91 (d, *J* = 14.4 Hz, 1H, B part of AB system), 4.16 (dd, *J* = 7.2, 2.4 Hz, 1H), 4.11 (dd, *J* = 7.2, 2.1 Hz, 1H), 2.75 (d, *J* = 13.2 Hz, 1H, A part of AB system), 2.67 (d, *J* = 13.2 Hz, 1H, B part of AB system), 2.50-2.59 (m, 2H), 2.43-2.49 (m, 2H), 1.70-1.79 (m, 4H), 1.27 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 175.4, 145.4, 134.2, 126.9, 123.6, 119.6, 110.5, 61.5, 61.1, 55.3, 51.6, 48.6, 23.9, 20.8,

13.9 Anal. Calcd. for $C_{17}H_{24}N_4O_2$: C, 64.53; H, 7.65; N, 17.71. Found: C, 64.84; H, 7.65; N, 17.23

Ethyl (3-benzotriazol-1-yl)-2-methyl-2-(piperidin-1-ylmethyl)propionate (5i). Yield 0.257 g (78%); pale yellow oil; 1H NMR δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.44-7.50 (m, 1H), 7.32-7.37(m, 1H), 4.94 (d, *J* = 14.3 Hz, 1H, A part of AB system), 4.84 (d, *J* = 14.3 Hz, 1H, B part of AB system), 4.09 (q, *J* = 7.2 Hz, 2H), 2.65 (d, *J* = 13.8 Hz, 1H, A part of AB system), 2.56 (d, *J* = 13.8 Hz, 1H, B part of AB system), 2.38-2.50 (m, 4H), 1.50-1.59 (m, 4H), 1.40-1.43 (m, 2H), 1.21 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); 13C NMR δ 175.2, 145.4, 134.1, 127.0, 123.7, 119.7, 110.4, 64.1, 61.0, 56.2, 51.9, 48.9, 26.3, 23.9, 20.0, 13.9 Anal. Calcd. for $C_{18}H_{26}N_4O_2$: C, 65.43; H, 7.93; N, 16.96. Found: C, 65.04; H, 8.01; N, 16.76

General procedure for preparation of compound 7a-d

Compound **5** (1.0 mmol) dissolved in THF (1 mL) was added dropwise to a suspension of sodium hydride (0.024 g, 1 mmol, 60% dispersed in mineral oil) in anhydrous THF (5 mL) and the mixture was stirred at room temperature for 5 h. The resulting mixture was quenched by saturated NaCl solution, extracted with diethyl ether (2 x 15 mL). The organic phase was dried over anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The residue was purified by flash silica gel chromatography (eluent: *n*-hexane/diethyl ether = 2/1).

Ethyl 2-(morphlinomethyl)acrylate (7a).[52-54] Yield 0.140 g (71%); yellow oil; ^{1}H NMR δ 6.27 (d, *J* = 0.6 Hz, 1H), 5.76 (d, *J* = 1.5 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.70 (t, *J* = 4.7 Hz, 4H), 3.20 (s, 2H), 2.47 (t, *J* = 4.7 Hz, 4H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 166.8, 136.8, 126.5, 67.0, 60.7, 58.8, 53.5, 14.1.

Ethyl 2-(pyrolidin-1-ylmethyl)acrylate (7b).[52-54] Yield 0.123 g (67%); yellow oil; ^{1}H NMR δ6.27 (s, 1H), 5.78 (d, *J* = 1.5 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.34 (s, 2H), 2.50-2.57 (m, 4H), 1.74-1.81 (m, 4H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 166.9, 138.2, 126.1, 60.6, 56.1, 54.1, 23.5, 14.2.

Ethyl 2-(piperdin-1-ylmethyl)acrylate (7c). [52-54] Yield 0.134 g (68%); yellow oil; ^{1}H NMR δ (m, 1H), 5.75 (d, *J* = 1.8 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.17 (s, 2H), 2.36-2.43 (m, 4H), 1.53-1.61 (m, 4H), 1.38-1.46 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 167.1, 137.4, 126.1, 60.5, 58.9, 54.5, 26.0, 24.3, 14.2.

Ethyl 2-(morpholinomethyl)but-2-enoate (7d). Yield 0.138 g (65%); yellow oil; ^{1}H NMR δ 7.02 (q, *J* = 7.2 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.67 (t, *J* = 4.7 Hz, 4H), 3.25 (s, 2H), 2.44 (t, *J* = 4.7 Hz, 4H), 1.89 (d, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 167.7, 141.0, 129.7, 67.0, 60.4, 53.3, 53.0, 14.7, 14.2. Anal. Calcd. for C11H19NO3: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.24; H, 9.35; N, 6.58.

General procedure for the synthesis of compound 8a-g

Sodium hydride (0.055 g, 2.3 mmol, 60% dispersed in mineral oil) was added to solution of thiol (2.2 mmol) in anhydrous THF (5 mL) at room temperature, and the reaction mixture was stirred for 1 h. Compound **5** (1.0 mmol) dissolved in THF (1 mL) was added dropwise at room

temperature, the reaction mixture was stirred at room temperature or under reflux for the time indicated in Table 3. The resulting mixture was quenched by saturated NaCl solution, extracted with diethyl ether (2 x 15 mL). The organic phase was dried over anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The residue was purified by flash silica gel chromatography (eluent: *n*-hexane/diethyl ether = 2/1).

Ethyl 2-(morpholin-4-ylmethyl)-3-phenylthiopropionate (8a). Yield 0.253 g (82%); colorless oil; ^{1}H NMR δ 7.37-7.41 (m, 2H), 7.25-7.32 (m, 2H), 7.16-7.23 (m, 1H), 4.16 (dd, *J* = 7.2, 1.2 Hz, 1H), 4.11 (dd, *J* = 7.2, 1.2 Hz, 1H), 3.64 (t, *J* = 4.7 Hz, 4H), 3.16 (d, *J* = 6.6 Hz, 2H), 2.83 (qn, *J* = 7.2 Hz, 1H), 2.63 (dd, *J* = 12.3, 7.2 Hz, 1H), 2.52, (dd, *J* = 12.3, 7.2 Hz, 1H), 2.32-2.45 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 173.5, 135.7, 130.0, 128.9, 126.4, 66.9, 60.7, 59.7, 53.6, 43.8, 33.9, 14.2. Anal. Calcd. for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49; N, 4.53. Found: C, 62.40; H, 7.49; N, 4.68.

Ethyl 3-(4-methylphenylthio)-2-(morpholin-4-ylmethyl)propionate (8b). Yield 0.255 g (79%); yellow oil; ^{1}H NMR δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 4.16 (dd, *J* = 9.0, 0.9 Hz, 1H), 4.11 (dd, *J* = 9.0, 0.9 Hz, 1H), 3.63 (t, *J* = 4.8 Hz, 4H), 3.10 (d, *J* = 6.6 Hz, 2H), 2.81 (qn, *J* = 4.2 Hz, 1H), 2.61, (dd, *J* = 12.0, 7.8 Hz, 1H), 2.50 (dd, *J* = 12.0, 7.2 Hz, 1H), 2.34-2.44 (m, 4H), 2.32 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 173.6, 136.6, 131.8, 130.8, 129.7, 66.9, 60.6, 59.7, 53.6, 43.7, 34.6, 21.0, 14.2. Anal. Calcd. for $C_{17}H_{25}NO_3S$: C, 63.13; H, 7.79; N, 4.33. Found: C, 63.28; H, 7.86; N, 4.41.

Ethyl 3-(4-chlorophenylthio)-2-(morpholin-4-ylmethyl)propionate (8c). Yield 0.278 g (81%); colorless oil; ^{1}H NMR δ 7.29-7.34 (m, 2H), 7.23-7.28 (m, 2H), 4.16 (dd, *J* = 7.1, 1.8 Hz, 1H), 4.11 (dd, *J* = 7.1, 1.7 Hz, 1H), 3.64 (t, *J* = 4.7 Hz, 4H), 3.14 (d, *J* = 6.6 Hz, 2H), 2.81 (qn, *J* = 7.2 Hz, 1H), 2.62 (dd, *J* = 12.3, 7.5 Hz, 1H), 2.50 (dd, *J* = 12.3, 7.5 Hz, 1H), 2.33-2.46 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 173.3, 134.2, 132.5, 131.3, 129.0, 66.9, 60.8, 59.7, 53.6, 43.7, 34.1, 14.2. Anal. Calcd. for $C_{16}H_{22}ClNO_3S$: C, 55.88; H, 6.45; N, 4.07. Found: C, 56.28; H, 6.66; N, 4.28.

Ethyl 3-ethylthio-2-(morpholin-4-ylmethyl)propionate (8d). Yield 0.206 g (79%); colorless oil; ^{1}H NMR δ 4.21 (dd, *J* = 7.2, 1.2 Hz, 1H), 4.17 (dd, *J* = 7.2, 1.2 Hz, 1H), 3.66 (t, *J* = 4.7 Hz, 4H), 2.78-2.87 (m, 1H), 2.74 (dd, *J* = 6.9, 3.3 Hz, 2H), 2.55-2.68 (m, 2H), 2.45-2.53 (m, 4H), 2.37-2.44 (m, 2H), 1.21-1.31 (m, 6H); ^{13}C NMR δ 173.9, 66.9, 60.5, 60.0, 53.6, 44.2, 31.5, 26.4, 14.6, 14.3. Anal. Calcd. for $C_{12}H_{23}NO_3S$: C, 55.14; H, 8.87; N, 5.36. Found: C, 55.10; H, 9.24; N, 5.16.

Ethyl 3-(4-methoxyphenylthio)-2-(morpholin-4-ylmethyl)propionate (8e). Yield 0.278 g (82%); yellow oil; ^{1}H NMR δ 7.36-7.41 (m, 2H), 6.82-6.86 (m, 2H), 4.16 (dd, *J* = 6.0, 1.2 Hz, 1H), 4.11 (dd, *J* = 6.0, 0.9 Hz, 1H), 3.80 (s, 3H), 3.62 (t, *J* = 4.7 Hz, 4H), 3.00-3.09 (m, 2H), 2.73-2.83 (m, 1H), 2.60 (dd, *J* = 12.0, 8.1 Hz, 1H), 2.48 (dd, *J* = 12.0, 6.9 Hz, 1H), 2.28-2.44 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 173.7, 159.2, 133.9, 125.6, 114.5, 66.9, 60.6, 59.7, 55.3, 53.6, 43.8, 36.0, 14.3. Anal. Calcd. for $C_{17}H_{25}NO_4S$: C, 60.15; H, 7.42; N, 4.13. Found: C, 60.43; H, 7.66; N, 4.27.

Ethyl 3-phenylthio-2-(pyrrolidin-1-ylmethyl)propionate (8f). Yield 0.208 g (71%); yellow oil; ^{1}H NMR δ 7.36-7.41 (m, 2H), 7.26-7.30 (m, 2H), 7.16-7.22 (m, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.11-3.24 (m, 2H), 2.77-2.86 (m, 1H), 2.64-2.75 (m, 2H), 2.40-2.48 (m, 4H), 1.68-1.76 (m, 4H), 1.24 (t, *J* = 7.2 Hz, 3H); 13C NMR δ 173.8, 135.9, 123.0, 128.8, 126.3, 60.6, 57.3, 54.1, 45.8, 34.2, 23.6, 14.2 Anal. Calcd. for $C_{16}H_{23}NO_2S$: C, 65.49; H, 7.90; N, 4.77. Found: C, 65.47; H, 8.04; N, 5.05.

Ethyl 3-phenylthio-2-(piperidin-1-ylmethyl)propionate (8g). Yield 0.233 g (76%); yellow oil; ^{1}H NMR δ 7.35-7.41 (m, 2H), 7.24-7.32 (m, 2H), 7.15-7.21 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.22 (dd, *J* = 13.2, 4.8 Hz, 1H, A part of AB system), 3.13 (dd, *J* = 13.2, 8.7 Hz, 1H, B part of AB system), 2.80-2.89 (m, 1H), 2.57 (dd, *J* = 12.4, 7.2 Hz, 1H, A part of AB system), 2.47 (dd, *J* = 12.4, 7.7 Hz, 1H, B part of AB system), 2.27-2.37 (m, 4H), 1.46-1.56 (m, 4H), 1.35-1.43 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); 13C NMR δ 173.9, 136.0, 129.6, 128.8, 126.1, 60.5, 60.2, 54.7, 44.2, 33.8, 26.0, 24.3, 14.2 Anal. Calcd. for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.73; H, 8.41; N, 4.44.

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