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# Convenient One-Pot Synthesis of β-Alkylthio Acid Derivatives from Thioacetates and the Corresponding α,β-Unsaturated Compounds

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### CONVENIENT ONE-POT SYNTHESIS OF β-ALKYLTHIO ACID DERIVATIVES FROM THIOACETATES AND THE CORRESPONDING α,β-UNSATURATED COMPOUNDS

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**ABSTRACT:** Various  $\beta$ -alkylthio acid derivatives were prepared conveniently from thioacetates and  $\alpha$ , $\beta$ -unsaturated compounds through borohydride exchange resin (BER)-Pd catalyzed transesterification of thioacetates to the corresponding thiols and Michael addition of the resulting thiols to  $\alpha$ , $\beta$ -unsaturated compounds.

Thiols are known to undergo Michael type addition reaction readily,<sup>1</sup> and  $\beta$ -alkylthio acid derivatives were reported to be prepared in high yields from corresponding  $\alpha$ , $\beta$ -unsaturated compounds and thiols in the presence of catalytic amounts of sodium methoxide, Triton B,<sup>2</sup> or quaternary ammonium fluoride catalyst.<sup>3</sup> However thiols are relatively labile under ambient atmosphere. Thus the process is highly desired in which protected thiols are directly utilized for the synthesis of  $\beta$ -alkylthio

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 $X = COOR, CONR_2, CN$ \*BER(1.0 eq) + Pd(OAc)<sub>2</sub>(0.05 eq), MeOH, 65 °C, 3 h

#### Scheme 1

acid derivatives. Recently lanthanide metal (Yb) mediated reaction of dialkyl disulfide with  $\alpha$ , $\beta$ -unsaturated ketones was reported to give Michael adducts readily, however yields were not always good.<sup>4</sup> Recently we have found that n-hexanethiol easily reacts with methyl crotonate to give the corresponding 1,4-addition product quantitatively in 3 h at 65 °C in the presence of borohydride exchange resin (BER) in methanol. This prompted us to test the possibility to perform these two reactions in one pot, since we already know that thioacetates are readily converted to the corresponding thiols by palladium catalyzed methanolysis of thioacetates.<sup>5</sup> We report herein a convenient one-pot synthesis of  $\beta$ -alkylthio acid derivatives from the corresponding thioacetates and  $\alpha$ , $\beta$ -unsaturated acid derivatives under essentially neutral conditions. The results are summarized in Scheme 1 and Table 1.

As shown in Scheme 1, BER-Pd(OAc)<sub>2</sub> was refluxed for 3 h in methanol to destroy the hydride to prevent the undesired reduction of  $\alpha$ ,  $\beta$ -unsaturated compounds. As shown in Table 1, acrylate, methacrylate, and crotonate reacted with a stoichiometric amount of thioacetates (1.05 eq) in methanol to give the corresponding  $\beta$ -alkylthio products quantitatively in 3 h at 65 °C in the presence of BER(1.0 eq)-Pd(0.05 eq) (entries 1-3). Michael addition to ethyl crotonate also proceeded quantitatively; however, a substantial amount of methyl  $\beta$ -(hexylthio)-

entry	substrate	product	time(h) yield(%) <sup>b</sup>	
1	methyl acrylate	methyl 3-(hexylthio)propionate	1	94
2	methyl 2-methyl-	methyl 3-(hexylthio)-2-methyl-	3	92
	acrylate	propionate		
3	methyl crotonate	methyl 3-(hexylthio)butyrate	2	93
4	ethyl crotonate	ethyl 3-(hexylthio)butyrate	3	95°
5	methyl cinnamate	methyl 3-(hexylthio)hydrocinnamate	3	93 <sup>d</sup>
6	methyl angelate	methyl 3-(hexylthio)-2-methyl-	24	(65) <sup>d</sup>
		butyrate		
7	acrylamide	3-(hexylthio)propionamide	1	94
8	crotonamide	3-(hexylthio)butyramide	3	94
9	N,N-dimethyl-	N,N-dimethyl-3-(hexylthio)-	2	95
	acrylamide	propionamide		
10	crotononitrile	3-(hexylthio)butyronitrile	2	93
11	cinnamonitrile	3-(hexylthio)hydrocinnamonitrile	1	94 <sup>d</sup>
12	methyl crotonate	methyl 3-(cyclohexylthio)butyrate	3	92
13	crotonamide	3-(cyclohexylthio)butyramide	6	94
14	crotononitrile	3-(cyclohexylthio)butyronitrile	3	97
15	methyl crotonate	methyl 3-(phenylthio)butyrate	6	90°
16	crotonamide	3-(phenylthio)butyramide	24	95°
17	crotononitrile	3-(phenylthio)butyronitrile	3	95°

 Table 1. Synthesis of β-Alkylthio Acid Derivatives from Thioacetates and

 α,β-Unsaturated Compounds<sup>a</sup>

<sup>a</sup>Substrates and of thioacetates (1.05 eq) were refluxed in methanol in the presence of pre-refluxed BER(1.0 eq)-Pd(0.05 eq). <sup>b</sup>Isolated yields. GC yields were in parenthesis. <sup>c</sup>Before the addition of substrates and thioacetates, methanol was replaced with ethanol. <sup>d</sup>2.0 eq of thioacetate was used. <sup>c</sup>1.0 eq of triethylamine hydrochloride was added together with substrates. butyrate was also formed via transesterification. This was prevented by replacing methanol with ethanol before the addition of ethyl crotonate (entry 4). The reaction of methyl cinnamate proceeded 90% in 6 h and the reaction did not proceed further. This was proved to be an equilibrium, since the product, methyl 3-(hexylthio)hydrocinnamate, underwent the reverse reaction (elimination) at the same reaction conditions. We could improve the yield by increasing the amount (2.0 eq) of thioacetates (entry 5). However, in the case of methyl angelate, a more hindered ester, the reaction proceeded very slowly under standard conditions, and gave low yield (50 %) of the desied product in 24 h. The yield was improved only slightly (65%) by increasing the amount (2.0 eq) of thioacetates. We found that a substantial amount (0.9 eq) of n-hexanethiol was transformed to the corresponding disulfide (entry 6). Acrylamide, crotonamide, N,N-dimethylacrylamide, and crotononitrile were all reacted readily to give quantitative yields of addition products (entries 7-10), and cinnamonitrile behaved similarly as methyl cinnamate (entry 11). Cyclohexyl thioacetates also reacted smoothly (entries 12-14). Finally the reaction with phenyl thioacetates did not proceed satisfactorily. Thus in the reaction of methyl crotonate with phenyl thioacetate, only 65% yield of the product was obtained in 6 h, and the reaction did not proceed further under the standard conditions. However, the problem was solved by the addition of an equimolar triethylamine hydrochloride (entries 15-17). Apparently some of benzenethiol was transferred to benzenethiolate which is inert to methyl crotonate under the standard conditions.6

In conclusion, this one-pot synthesis is a good synthetic method of  $\beta$ -alkylthio acid derivatives from thioacetates and  $\alpha$ , $\beta$ -unsaturated acid derivatives, since it utilizes a protected form of thiols (thioacetates), proceeds in almost neutral conditions, and gives excellent yields in most cases.

#### **Experimental Section**

#### **General Procedure**

The reaction of methyl crotonate is representative. The methanol solution (50 mL) of Pd(OAc)<sub>2</sub> (0.112 g, 0.5 mmol) was added to BER (3.33 g, 10 mmol), and the mixture was stirred under reflux. After 3 h, methyl crotonate (1.0 g, 10 mmol) and hexyl thioacetate (1.68 g, 10.5 mmol) were added and the mixture was refluxed for 2 h. Complete reaction was confirmed by GLPC. After the resin was removed by filtration, methanol was evaporated under reduced pressure. Short column separation of the excess hexanethiol (0.05 mmol) gave the pure methyl 3-(hexylthio)butyrate (2.03 g, 93%): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.88 (t, 3 H, *J* = 6.6),  $\delta$  1.32 - 1.41 (m, 6 H),  $\delta$  1.51 - 1.65 (m, 2 H),  $\delta$  2.44 (dd, 1 H, *J* = 15.4, 8.2),  $\delta$  2.54 (t, 2 H, *J* = 7.5),  $\delta$  2.64 (dd, 1 H, *J* = 15.4, 6.2),  $\delta$  3.11 - 3.28 (m, 1 H),  $\delta$  3.70 (s, 3 H); MS m/z (relative intensity) (EI, 70 eV) 218 (M<sup>+</sup>, 18) 187 (3) 145 (15) 133 (33) 117 (48) 101 (73) 87 (39) 83 (36) 75 (24) 57 (100) 55 (41).

methyl 3-(hexylthio)propionate: <sup>1</sup>H NMR (CDCl<sub>2</sub>)  $\delta$  0.88 (t, 3 H, J = 6.8),  $\delta$ 1.27 - 1.38 (m, 6 H),  $\delta$  1.52 - 1.61 (m, 2 H),  $\delta$  2.52 (t, 2 H, J = 7.4),  $\delta$  2.60 (t, 2 H, J = 7.2),  $\delta$  2.78 (t, 2 H, J = 7.2),  $\delta$  3.69 (s, 3 H); MS m/z (relative intensity) (EI, 70 eV) 204 (M<sup>+</sup>, 48) 173 (11) 145 (9) 133 (16) 120 (50) 117 (100) 89 (24) 88 (64) 87 (56) 83 (48) 60 (48) 55 (88) 45 (89).

methyl 3-(hexylthio)-2-methylpropionate: <sup>1</sup>H NMR(CDCl<sub>3</sub>)  $\delta$  0.89 (t, 3 H, J = 6.5),  $\delta$  1.25 (d, 3 H, J = 6.8),  $\delta$  1.25 - 1.40 (m, 5 H),  $\delta$  1.53 - 1.64 (m, 3 H),  $\delta$  2.51 (t, 2 H, J = 7.5),  $\delta$  2.55 - 2.85 (m, 3 H),  $\delta$  3.70 (s, 3 H); MS m/z (relative intensity) (EI, 70 eV) 218 (M<sup>+</sup>, 33) 187 (6) 158 (20) 147 (8) 134 (25) 131 (41) 117 (80) 101 (77) 87 (55) 83 (81) 61 (96) 55 (100) 47 (20).

ethyl 3-(hexylthio)butyrate: <sup>1</sup>H NMR(CDCl<sub>3</sub>)  $\delta$  0.89 (t, 3 H, J = 6.4),  $\delta$  1.20 -1.49 (m, 9 H),  $\delta$  1.51 - 1.62 (m, 5 H),  $\delta$  2.47 (dd, 1 H, J = 15.3, 8.3),  $\delta$  2.55 (t, 2 H, J = 7.3),  $\delta$  2.63 (dd, 1 H, J = 15.3, 6.1),  $\delta$  3.11 - 3.30 (m, 1 H),  $\delta$  4.16 (q, 2 H, J = 7.2); MS m/z (relative intensity) (EI, 70 eV) 232 (M<sup>+</sup>, 32) 187 (8) 159 (3) 147 (46) 145 (32) 117 (74) 116 (69) 115 (27) 101 (100) 88 (40) 59 (44) 55 (51) 45 (32).

methyl 3-(hexylthio)hydrocinnamate: <sup>1</sup>H NMR(CDCl<sub>3</sub>)  $\delta$  0.86 (t, 3 H, J = 6.8),  $\delta$  1.23 - 1.31 (m, 6 H),  $\delta$  1.45 - 1.57 (m, 2 H),  $\delta$  2.32 (t, 2 H, J = 7.3),  $\delta$  2.85 -2.89 (m, 2 H),  $\delta$  3.62 (s, 3 H),  $\delta$  4.27 (dd, 1 H, J =7.7, 7.7),  $\delta$  7.27 - 7.34 (m, 5 H); MS m/z (relative intensity) (EI, 70 eV) 280 (M<sup>+</sup>, 2) 207 (2) 163 (10) 121 (100) 117 (10) 104 (18) 91 (13) 77 (11) 59 (17) 55 (10).

**3-(hexylthio)propionamide:** <sup>1</sup>H NMR(CDCl<sub>3</sub>)  $\delta$  0.88 (t, 3 H, J = 6.6),  $\delta$  1.29 - 1.41 (m, 6 H),  $\delta$  1.51 - 1.61 (m, 2 H),  $\delta$  2.45 - 2.58 (m, 4 H),  $\delta$ 2.81 (t, 2 H, J = 7.1),  $\delta$  5.75 - 5.85 (br d, 2 H); MS m/z (relative intensity) (EI, 70 eV) 189 (M<sup>+</sup>, 8) 117 (10) 104 (11) 87 (7) 73 (100) 72 (43) 61 (26) 55 (25).

**3-(hexylthio)butyramide:** <sup>1</sup>H NMR(CDCl<sub>3</sub>)  $\delta$  0.89 (t, 3 H, J = 6.9),  $\delta$  1.23 - 1.37 (m, 8 H),  $\delta$  1.53 - 1.73 (m, 3 H),  $\delta$  2.30 - 2.57 (m, 2 H),  $\delta$  2.57 (t, 2 H, J = 7.2),  $\delta$  3.12 - 3.30 (m, 1 H),  $\delta$  5.80 - 5.93 (br d, 2 H); MS m/z (relative intensity) (EI, 70 eV) 203 (M<sup>+</sup>, 33) 118 (29) 101 (33) 87 (100) 86 (29) 72 (33) 59 (48) 55 (26).

N,N-dimethyl-3-(hexylthio)propionamide: <sup>1</sup>H NMR(CDCl<sub>3</sub>)  $\delta$  0.88 (t, 3 H, J = 6.5),  $\delta$  1.24 - 1.38 (m, 6 H),  $\delta$  1.52 - 1.63 (m, 2 H),  $\delta$  2.54 (t, 2 H, J = 7.3),  $\delta$  2.59 (t, 2 H, J = 7.8),  $\delta$  2.82 (t, 2 H, J = 7.8),  $\delta$  2.98 (s, 6 H); MS m/z (relative intensity) (EI, 70 eV) 217 (M<sup>+</sup>, 4) 132 (17) 101 (100) 100 (32) 87 (4) 72 (72) 62 (8) 58 (11) 55 (17) 45 (60).

**3-(hexylthio)butyronitrile:** <sup>1</sup>H NMR(CDCl<sub>3</sub>)  $\delta$  0.93 (t, 3 H, J = 6.6),  $\delta$  1.31 - 1.70 (m, 8 H),  $\delta$  1.46 (d, 3 H, J = 6.8),  $\delta$ 2.49 - 2.77 (m, 2 H),  $\delta$  2.64 (t, 2 H, J = 7.0),  $\delta$  3.04 - 3.15 (m, 1 H); MS m/z (relative intensity) (EI, 70 eV) 185 (M<sup>+</sup>, 18)

#### β-ALKYLTHIO ACID DERIVATIVES

145 (24) 117 (83) 102 (17) 84 (16) 83 (42) 75 (47) 69 (32) 68 (20) 61 (37) 60 (19) 56 (100) 55 (82).

**3-(hexylthio)hydrocinnamonitrile:** <sup>1</sup>H NMR(CDCl<sub>3</sub>)  $\delta$  0.86 (t, 3 H, J = 6.9),  $\delta$ 1.21 - 1.33 (m, 6 H),  $\delta$  1.49 - 1.60 (m, 2 H),  $\delta$  2.41 (t, 2 H, J = 7.2),  $\delta$  2.86 - 2.90 (m, 2 H),  $\delta$  4.09 (dd, 1 H, J = 7.8, 6.9),  $\delta$  7.34 - 7.41 (m, 5 H); MS m/z (relative intensity) (EI, 70 eV) 247 (M<sup>+</sup>, 4) 207 (24) 130 (100) 117 (47) 103 (22) 91 (23) 77 (21) 55 (24).

methyl 3-(cyclohexylthio)butyrate: <sup>1</sup>H NMR(CDCl<sub>3</sub>)  $\delta$  1.24 - 1.33 (m, 5 H),  $\delta$ 1.31 (d, 3 H, J = 6.6),  $\delta$  1.58 - 1.67 (m, 1 H),  $\delta$  1.70 - 1.83 (m, 2 H),  $\delta$  1.88 - 2.06 (m, 2 H),  $\delta$  2.44 (dd, 1 H, J = 15.5, 8.3),  $\delta$  2.60 - 2.69 (m, 1 H), 2.62 (dd, 1 H, J = 15.5, 6.1),  $\delta$  3.19 - 3.36 (m, 1 H),  $\delta$  3.69 (s, 3 H); MS m/z (relative intensity) (EI, 70 eV) 216 (M<sup>+</sup>, 22) 185 (3) 143 (8) 133 (19) 115 (100) 114 (85) 103 (35) 101 (37) 81 (52) 59 (78) 55 (89).

**3-(cyclohexylthio)butyramide:** <sup>1</sup>H NMR(CDCl<sub>3</sub>)  $\delta$  1.21 - 1.49 (m, 5 H),  $\delta$  1.34 (d, 3 H, J = 7.0),  $\delta$  1.51 - 2.02 (m, 5 H),  $\delta$  2.36 (dd, 1 H, J = 14.8, 6.8),  $\delta$  2.50 (dd, 1 H, J = 14.8, 6.8),  $\delta$  2.70 - 2.78 (m, 1 H),  $\delta$  3.24 - 3.48 (m, 1H), 5.38 - 6.00 (br d, 2 H); MS m/z (relative intensity) (EI, 70 eV) 201 (M<sup>+</sup>, 13) 114 (12) 101 (24) 87 (100) 86 (46) 81 (37) 67 (26) 59 (42) 55 (54).

**3-(cyclohexylthio)butyronitrile:** <sup>1</sup>H NMR(CDCl<sub>3</sub>)  $\delta$  1.25 - 1.39 (m, 4 H),  $\delta$  1.42 (d, 3 H, J = 6.8),  $\delta$  1.56 - 1.64 (m, 2 H),  $\delta$  1.72 - 1.85 (m, 2 H),  $\delta$  1.88 - 2.45 (m, 2 H),  $\delta$  2.51 (dd, 1 H, J = 16.8, 7.8),  $\delta$  2.66 - 2.84 (m, 1 H),  $\delta$  2.68 (dd, 1 H, J = 16.8, 5.4),  $\delta$  3.05 - 3.22 (m, 1 H); MS m/z (relative intensity) (EI, 70 eV) 183 (M<sup>+</sup>, 30) 115 (5) 83 (90) 82 (62) 81 (16) 67 (70) 61 (29) 60 (21) 55 (100) 54 (24).

methyl 3-(phenylthio)butyrate: <sup>1</sup>H NMR(CDCl<sub>3</sub>)  $\delta$  1.34 (d, 3 H, J = 6.6),  $\delta$  2.44 (dd, 1 H, J = 15.8, 8.5),  $\delta$  2.66 (dd, 1 H, J = 15.8, 6.0),  $\delta$  3.55 - 3.74 (m, 1 H),  $\delta$  3.67 (s, 3 H),  $\delta$  7.27 - 7.47 (m, 5 H); MS m/z (relative intensity) (EI, 70 eV) 210 (M<sup>+</sup>, 42) 179 (3) 150 (5) 137 (29) 110 (100) 109 (34) 101 (21) 59 (99).

**3-(phenylthio)butyramide:** <sup>1</sup>H NMR(CDCl<sub>3</sub>)  $\delta$  1.40 (d, 3 H, J = 6.8),  $\delta$  2.35 (dd, 1 H, J = 15.0, 8.0),  $\delta$  2.59 (dd, 1 H, J = 15.0, 5.8),  $\delta$  3.62 - 3.79 (m, 1 H),  $\delta$  5.48 -5.70 (br d, 2 H),  $\delta$  7.30 - 7.50 (m, 5 H); MS m/z (relative intensity) (EI, 70 eV) 195 (M<sup>+</sup>, 45) 150 (9) 137 (18) 110 (84) 109 (37) 86 (100) 77 (13) 65 (20). **3-(phenylthio)butyronitrile:** <sup>1</sup>H NMR(CDCl<sub>3</sub>)  $\delta$  1.48 (d, 3 H, J = 11.4),  $\delta$  2.45 (dd, 1 H, J = 16.8, 7.8),  $\delta$  2.63 (dd, 1 H, J = 16.8, 5.0),  $\delta$  3.35 - 4.01 (m, 1 H),  $\delta$ 7.27 - 7.50 (m, 5 H); MS m/z (relative intensity) (EI, 70 eV) 177 (M<sup>+</sup>, 61) 137 (100) 135 (19) 110 (33) 109 (49) 77 (15) 65 (30) 51 (19).

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