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A simple, rapid and efficient protocol for the synthesis of methylthiomethyl esters under Swern oxidation conditions

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Abstract—A rapid, mild and high yielding method for the synthesis of methylthiomethyl esters is reported from the corresponding aliphatic, aromatic and unsaturated carboxylic acids under Swern oxidation conditions using dimethylsulfoxide, oxalyl chloride and triethylamine at low temperature.
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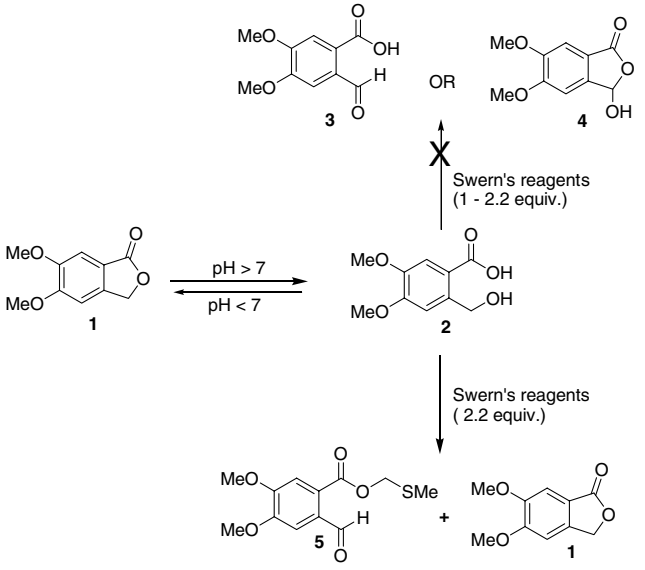
The methylthiomethyl (MTM) group is a useful carboxylic acid protecting group, which can be cleaved under neutral non-hydrolytic conditions.[1] This property of the MTM group has made it a suitable carboxyl protecting group in peptide synthesis.[2] MTM esters also show interesting chemistry under photochemical conditions involving electron transfer processes.[3] MTM esters have been utilised as easily absorbable pro-drugs of non-steroidal anti-inflammatory agents,[4] flavour additives for foods, especially dairy products[5] and are also present in essential oils.[6] The routine use of MTM protecting groups has been restricted primarily due to the lack of sufficiently mild and convenient methods which give consistently good yields.

Methylthiomethyl esters are usually prepared by the reaction of carboxylic acid salts with chloromethyl methyl sulfide.[7] Dimethylsulfoxide (DMSO) when activated by reagents such as *t*-butyl bromide,[8] *N*-chlorosuccinimide,[9] dicyclohexylcarbodiimide[10] and chlorine or sulfuryl chloride[11] reacts with carboxylate salts under various conditions to produce mainly MTM esters. Activation of dimethyl sulfide (DMS) or DMSO by various reagents occurs during the well-known Corey–Kim[12] and Swern oxidations.[13] Amongst the various reagents used to activate DMSO, oxalyl chloride appeared to be the best suited and most widely used in alcohol oxidations. Swern and co-workers[13] have shown that even with an excess of these reagents, oxidation of hydroxy acids gives keto acids only and no MTM ester formation has been observed.

In an ongoing project involving the synthesis of pharmaceutical intermediates, we required ring-substituted phthaldehydic acids/esters. We speculated that, these could easily be obtained by Swern oxidation of a suitably substituted benzyl alcohol. Lactone **1** on hydrolysis under controlled pH, gave substituted hydroxymethyl benzoic acid **2** (Scheme 1). When **2** was reacted under



Scheme 1.

Keywords: Swern oxidation; Carboxylic acids; Methylthiomethyl esters.
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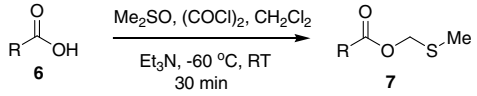
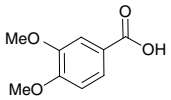
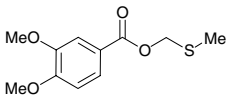
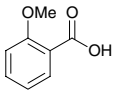
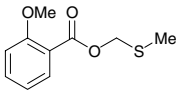
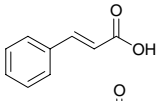
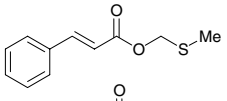
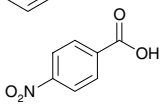
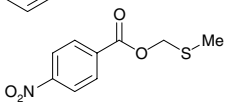
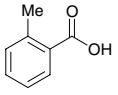
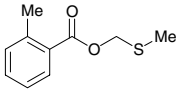
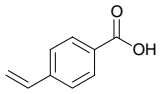
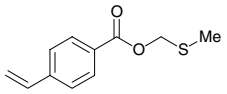
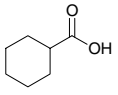
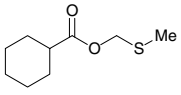
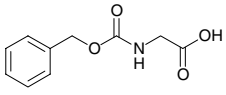
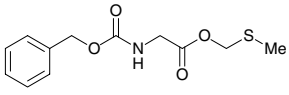
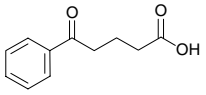
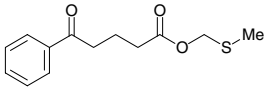
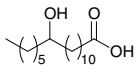
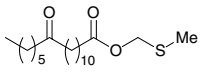
Swern conditions[13] with 1 equiv of reagents, we obtained only lactone **1** with no trace of aldehyde **3** or hydroxy lactone **4**. However, with 2 equiv of Swern reagent, two products were isolated, namely: lactone **1** (25%) and methylthiomethyl 2-formyl-4,5-dimethoxybenzoate[14] **5** (75%). We did not obtain 2-formyl-4,5-dimethoxybenzoic acid **3** or its cyclised product **4** under these conditions.

This indicated that MTM ester formation competes with alcohol oxidation. This was further confirmed by a competitive experiment. On subjecting a 1:1 mixture of benzoic acid and benzyl alcohol under Swern conditions using a quantity of reagents just sufficient to oxidise benzyl alcohol to benzaldehyde, a mixture of benzaldehyde (65%) and methylthiomethyl benzoate (35%) was formed as judged from the ^{1}H NMR spectrum of the crude reaction mixture. Although oxidation of the alcohol was marginally faster, the protocol appeared promising for preparing MTM esters of carboxylic acids at low temperature. In this Letter, we present the synthesis of MTM esters of carboxylic acids under mild conditions with high yields using Swern conditions.

Carboxylic acids with diverse structures were selected to determine the scope of the present MTM esterification protocol. The results are summarised in Table 1. Both aliphatic and aromatic carboxylic acids gave the corresponding MTM esters in near quantitative yields. Cinnamic acid[8] (Table 1, entry 3) gave the desired product without isomerisation of the double bond. The N-protected amino acid, *N*-*Z*-Gly also gave the corresponding

Table 1. Conversion of carboxylic acids **6** to MTM esters **7**



Entry	Acid **6**	MTM ester **7**	Yield[a] (%)
1			99 Ref. 16
2			99
3			97 Ref. 8
4			96 Ref. 15
5			97 Ref. 16
6			96
7			97 Ref. 5
8			95
9			95
10			80[b]

[a] Isolated yields. Spectral data for the products from entries 1, 3–5 and 7 are similar to those reported.[5,8,15,16]
[b] 2.2 equiv of reagents were used.

MTM ester (Table 1, entry 8) in very good yield. *p*-Nitrobenzoic acid[15] and an δ-keto acid (Table 1, entries 4 and 9) also gave the corresponding MTM esters in excellent yields. Contrary to Swern's observation,[13] 12-hydroxystearic acid, on treatment with 2 equiv of reagents, gave the corresponding keto methylthiomethyl ester in 80% yield (Table 1, entry 10) along with ~15–20% of a keto acid where only the hydroxy group had been oxidised. When this experiment was carried out according to the reported conditions by Swern[13] (at −10 °C), similar results to those above were obtained.

In summary, we report a very mild and effective protocol using Swern's reagent for the synthesis of MTM esters of aliphatic, aromatic, unsaturated carboxylic and N-protected amino acids.

In a typical procedure, DMSO (1.56 ml, 22 mmol) in dichloromethane (10 ml) was added dropwise to a stirred solution of oxalyl chloride (0.96 ml, 11 mmol) in dichloromethane (15 ml) at −60 to −65 °C under an inert atmosphere. After 5 min, the carboxylic acid (solid/neat) (10 mmol) was added to the reaction mixture and stirring was continued for 15 min. Triethylamine (6.97 ml, 50 mmol) was added dropwise and after 5 min, the reaction mixture was allowed to attain room temperature and then diluted with dichloromethane (20 ml). Water (30 ml) was added to the reaction mixture and the aqueous layer was extracted with dichloromethane (50 ml). The combined organic extract was washed with water (30 ml), then brine (30 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography/crystallization. All the products[17] have been fully characterised by ^{1}H NMR, ^{13}C NMR and mass spectroscopy, and by mp and elemental analysis.

Acknowledgements

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14. *Spectral data on methylthiomethyl-2-formyl-4,5-dimethoxybenzoate* **5**: mp 90–92 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (3H, s, CH_3S), 3.99 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 5.44 (2H, s, CH_2S), 7.47 (1H, s, Ar), 7.51 (1H, s, Ar), 10.66 (1H, s, CHO); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.97, 165.51, 152.39, 152.17, 131.35, 125.59, 112.60, 109.73, 69.77, 56.37, 56.31, 15.89; IR (KBr, cm^{-1}) 1721, 1675, 1590, 1521, 1359, 1287, 1210, 1134; MS (CI, 70 eV) *m/z* 271 (M^++H); HRMS calcd for $C_{12}H_{14}O_5S$, 270.0556; found, 270.0556; Anal. Calcd for $C_{12}H_{14}O_5S$: C, 53.32; H, 5.22; S, 11.86. Found: C, 53.47; H, 5.18; S, 11.58.
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17. *Spectroscopic data for novel products*: (Table 1, entry 2): Oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (3H, s, CH_3S), 3.91 (3H, s, OCH_3), 5.36 (2H, s, CH_2S), 6.97–7.02 (2H, m, Ar), 7.48 (1H, t, $J = 6$ Hz, Ar), 7.83 (1H, d, $J = 6$ Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.69, 159.42, 133.93, 131.83, 120.15, 119.54, 112.04, 68.49, 55.99, 15.48; MS (EI, 70 eV), *m/z* 212 (M^+); IR (neat, cm^{-1}) 1731, 1600, 1491, 1288, 1238; HRMS calcd for $C_{10}H_{12}O_3S$, 212.0514; found, 212.0515; (Table 1, entry 6): oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (3H, s, CH_3S), 5.38 (2H, s, CH_2S), 5.39 (1H, d, $J = 9$ Hz), 5.87 (1H, d, $J = 18$ Hz), 6.75 (1H, dd, $J = 18$, 9 Hz), 7.47 (2H, d, $J = 8.4$ Hz, Ar), 8.02 (2H, d, $J = 8.4$ Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.04, 142.29, 135.97, 130.08, 128.91, 126.19, 116.76, 68.80, 15.53; IR (neat, cm^{-1}) 1720, 1607, 1260, 1087; MS (EI, 70 eV) *m/z* 208 (M^+); Anal. calcd for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81; S, 15.40; found C, 63.29; H, 6.00; S, 15.72; (Table 1, entry 8): oil turns solid on keeping, mp 40–42 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (3H, s, CH_3S), 4.02 (2H, d, $J = 5.4$ Hz, $NHCH_2CO$), 5.12 (2H, S, OCH_2Ph), 5.24 (2H, s, CH_2S), 5.34 (1H, bs, NH), 7.35 (5H, s, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): 169.86, 156.27, 136.16, 128.57, 128.25, 128.14, 69.42, 67.19, 42.89, 15.51; IR (neat, cm^{-1}) 1722, 1525, 1260, 1171; HRMS calcd for $C_{12}H_{15}NO_4S$, 269.0709; found, 269.0710; (Table 1, entry 9): mp 50–52 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06–2.16 (2H, m, $PhCOCH_2CH_2$), 2.24 (3H, s, CH_3S), 2.50 (2H, t, $J = 7.2$ Hz, $PhCOCH_2$), 3.08 (2H, t, $J = 7.2$ Hz, CH_2CH_2CO), 5.15 (2H, s, CH_2S), 7.44–7.50 (2H, m, Ar), 7.55–7.61 (1H, m, Ar), 7.96–7.99 (2H, m, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.31, 172.92, 136.77, 133.14, 128.63, 128.03, 68.16, 37.28, 33.39, 19.28, 15.45; MS(EI) *m/z* 253 (M^++H); HRMS calcd for $C_{13}H_{16}O_3S$, 252.0813; found, 252.0814; (Table 1, entry 10), oil turns solid on keeping, mp 44–46 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (3H, t, $J = 6.2$ Hz, CH_3CH_2), 1.25–1.40 (18H, m, $9 \times CH_2$), 1.54–1.67 (6H, m), 2.31 (3H, s, CH_3S), 2.32–2.42 (6H, m, CH_2CH_2CO), 5.12 (2H, m, CH_2S); ^{13}C NMR (75 MHz, $CDCl_3$): 211.83, 173.53, 67.92, 42.84, 42.81, 34.35, 31.62, 29.69, 29.38, 29.25, 29.21, 29.05, 28.94, 24.86, 23.86, 22.50; IR (neat, cm^{-1}) 2920, 2850, 1734, 1463, 1417; HRMS calcd for $C_{20}H_{38}O_3S$, 358.2507; found, 358.2508.