Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 21 Aug 2006.

To cite this article: Jean-Louis Delépine, Pascal Pecquet, Marie-christine Betton & François Huet (1996) Preparation of Diethyl 2-Alkoxymethyl-, 2-Phenylselenomethyl- and 2-Phenylthiomethylmalonate, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:15, 2819-2829, DOI: 10.1080/00397919608005216

To link to this article: http://dx.doi.org/10.1080/00397919608005216

SYNTHETIC COMMUNICATIONS, 26(15), 2819-2829 (1996)

Preparation of Diethyl 2-Alkoxymethyl-, 2-Phenylselenomethyl- and 2-Phenylthiomethylmalonate

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Abstract : Title compounds were obtained either by alkylation of the sodium derivative of diethyl malonate or by the conjugate addition to diethyl methylenemalonate **4**. When reactions with **4** were run in basic medium two successive Michael additions occured.

Preparation of dialkyl 2-alkoxymethylmalonates is usually performed by alkylation of dialkyl malonates with chloromethyl alkyl ethers.[1-6] This reaction gives good results from monosubstituted dialkyl malonates[6] but some difficulties were encountered in the case of the unsubstituted starting materials.[5] Other preparative procedures such as the reaction of the organozinc derivative of diethyl

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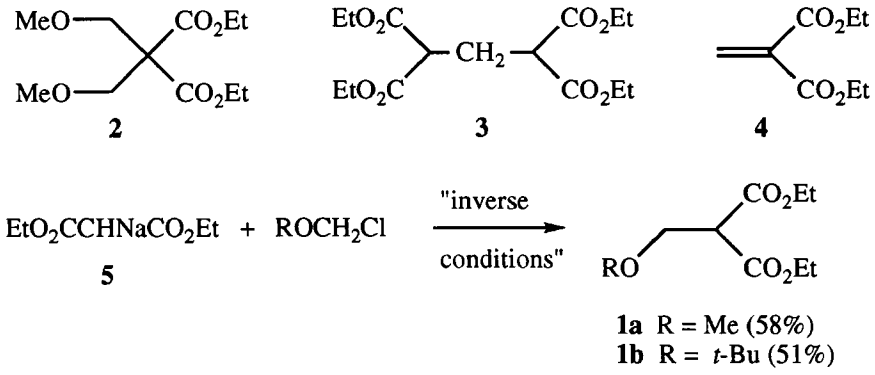
malonate with acetyl chloride[7] and the catalytic hydrogenation of diethyl ethoxymethylenemalonate[8] were also described.

In our hands, attempts to prepare compound **1a** by reaction between chloromethyl methyl ether and the diethyl malonate sodium derivative **5** by the procedure of Simonsen[1] or with several modifications[5] led to poor results. Therefore we carefully examined results according to the experimental conditions.



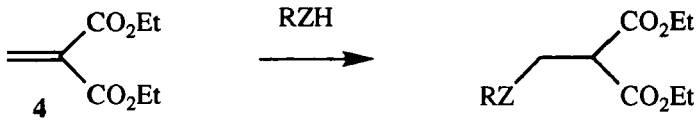
We firstly found that addition of chloromethyl methyl ether to the sodium derivative **5** ("direct conditions") in refluxing THF, only led to a small amount of the expected product **1a** (<5%) together with the dialkylated product **2** (18%), a part of the starting material and unidentified products. In another experiment chloromethyl methyl ether was added to the sodium derivative **5** at -5°C, the reaction mixture was slowly warmed to room temperature, then the reaction was allowed to proceed for 3 h at this temperature. We thus obtained tetraester **3** as the main product (79% isolated yield). This compound, which was also obtained by Simonsen,[1] is probably issued from the conjugate addition of the sodium derivative **5** to the

elimination product **4** which should be obtained *in situ* from **1a**. A similar result was pointed out in Knoevenagel reactions.[9]

Finally a more satisfactory result was achieved in a reproducible way when the sodium derivative **5** was added to a dilute THF solution of chloromethyl methyl ether and a 58% isolated yield of **1a** was thus obtained in these "inverse conditions". However isolation of **1a** ned successive short pad then spinning band column distillations ; when the crude product was directly distillated through a spinning band column, the elimination occured and a 58% isolated yield of **4** was obtained.

The method was extended to preparation of compound **1b**, from **5** and chloromethyl *t*-butyl ether,[10] in 51% isolated yield. However, in this case, the crude product was purified by column chromatography on silica gel.

We also succeeded in preparation of these compounds by the conjugate additions of the corresponding alcohols to diethyl methylenemalonate **4**.[11] The reaction gave good results in acidic medium. On the other hand, preparation of selenium and sulfur derivatives was also possible by the same way but without catalyst (Table 1).



1a Z=O, R = Me
1b Z=O, R = *t*-Bu
1c Z = Se, R = Ph
1d Z = S, R = Ph

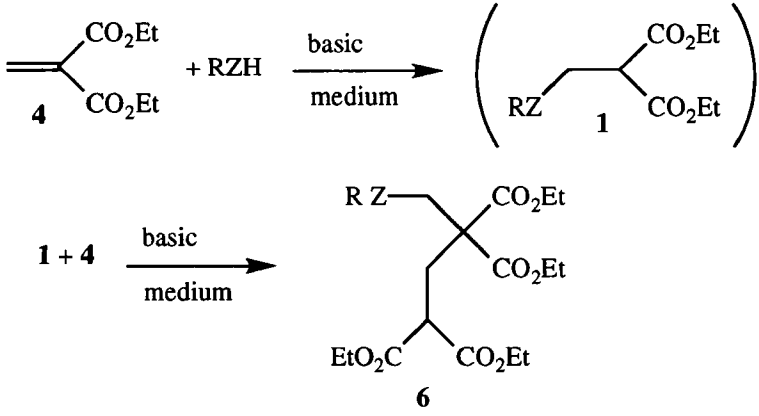
Table 1. Preparation of compounds 1 by the conjugate addition to 4

Reagent	Solvent, catalyst, time, temperature	Product	Isolated yield
MeOH	MeOH, dry *p*-TsOH[a], 1 h, reflux	**1a**,	98%
t-BuOH	*t*-BuOH, dry *p*-TsOH[b], 4 h, reflux	**1b**,	86%
PhSeH[c]	THF, without, 4 h, room temperature	**1c**,	76%
PhSH	THF, without, 12 h, room temperature	**1d**,	91%

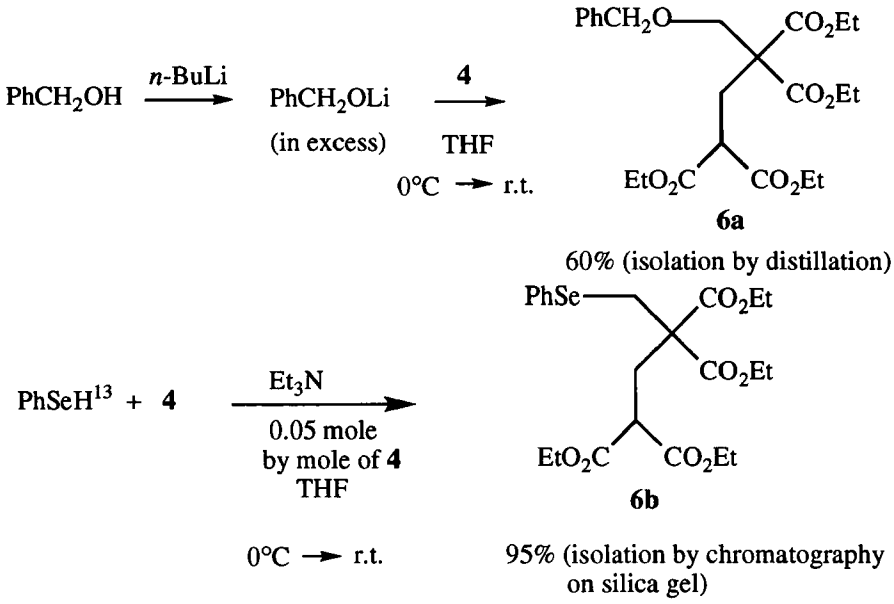
a 0.02 mole by mole of **4** ; b 0.03 mole by mole of **4**

c Freshly prepared by reduction of diphenyldiselenide[13]

When reactions with **4** were run in the presence of catalytic or stoechiometric amounts of base, we obtained either mixtures of the expected product **1** and of compound **6** corresponding to Michael reaction of **1** with **4**, or **6**, exclusively. Compound **6** probably reacts more slowly than **1** with **4** ; therefore reaction stops to **6**.



Two examples of preparation of compounds **6** by this way are given below.



In this paper we show that compounds **1a** and **1b** are efficiently obtained by the two preceding ways. The second method avoids using of the toxic chloromethyl alkyl ethers. The selenium and sulfur derivatives **1c** and **1d** were prepared by the second method only and without catalyst. On the other hand an unexpected preparative way to compounds **6**, involving two successive Michael reactions was pointed out.

Experimental

^{1}H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Bruker AC 400 instrument, unless otherwise stated, in deuteriochloroform

solution. Elemental analyses were performed by the service of microanalyses, CNRS, ICSN, Gif sur Yvette. High resolution mass measurements were performed at the CRMPO (Rennes) with a Varian Mat 311 Spectrometer. Products were isolated either by distillation of by flash column chromatography on silica gel.

Synthesis of 1a and 1b by alkylation

Diethyl malonate (40g, 0.25 mol) was added dropwise under stirring to a suspension of NaH (10g of 60% mineral oil dispersion, prewashed with cyclohexane, 0.25 mol) in THF (250 mL) under argon at 60°C. The reaction was allowed to proceed at the same temperature until the gas evolution ceases, then the reaction mixture was cooled to 0°C and cannulated, in 3 min, under argon pressure, into a stirred and cooled (-5°C) solution of chloromethyl methyl ether (20.15 g, 0.25 mol) in THF (200 mL). Reaction proceeded for 1 min and iced water (200 mL) was added. Extraction (Et_2O, 2 x 200 mL), drying ($MgSO_4$) and evaporation led to the crude product which was quickly distillated through a short column. A second distillation through a 80 plate spinning band column (or a 50 cm filled column) led to 29.6 g of **1a** as an oil (58%) ; bp 118°C/13 mm Hg (Lit[12] 121-122°C/15 mm Hg) ; ^{1}H NMR : δ 1.27 (t, 6H, J = 7.1 Hz), 3.37 (s, 3H), 3.70 (t, 1H, J = 7,6 Hz), 3.85 (d, 2H, J = 7.6 Hz), 4.23 (q, 4H, J = 7.1 Hz).

Compound **1b** was obtained at lower scale from chloromethyl *t*-butyl ether[10] (1.03 g, 8.41 mmol) in the same experimental conditions except that the crude **1b** was chromatographed on silica gel (cyclohexane/ethyl acetate 85 : 15). Pure **1b** was thus obtained as an oil (1.05 g, 51%) ; ^{1}H NMR : δ 1.18 (s, 9H), 1.27 (t, 6H, J = 7.1 Hz), 3.60 (t, 1H, J = 7.6 Hz), 3.81 (d, 2H, J = 7.6 Hz), 4.21

(q, 4H, J = 7.1 Hz) ; ^{13}C NMR : δ 14.0 ($\underline{C}H_3$ of C_2H_5), 27.1 ($\underline{C}H_3$ of *t*-Bu), 59.6, 60.7, 61.3 (2C), 73.4 (quat. C), 167.9 ($\underline{C}$=O) ; Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.52 ; H, 9.00. Found ; C, 58.34 ; H, 8.79.

Synthesis of 1a and 1b by Michael reaction

A mixture of diethyl methylenemalonate **4**[11] (15.0 g, 87.3 mmol) dry MeOH (100 mL) and *p*-toluenesulfonic acid (0.34 g, 2.0 mmol) was refluxed for 1h. The reaction mixture was then cooled and evaporated, 10% aqueous $NaHCO_3$ (75 mL) was added and extraction with Et_2O (3 x 150 mL) followed by drying ($MgSO_4$) and evaporation led to the practicaly pure product **1a**. It could be purified by distillation or chromatography on silica gel (cyclohexane/Et_2O 80 : 20). Yield of pure product 98% (17.4 g).

Reaction with *t*-BuOH in the same experimental conditions, except that a larger amount of catalyst was used (0.03 mole by mole) and that the reaction mixture was refluxed for 4 h, yielded **1b** which was chromatographed (cyclohexane/ethyl acetate 85 : 15).Yield 86%.

Diethyl 2-phenylthiomethylmalonate 1c

Thiophenol (1.54 g, 14.0 mmol) in THF (10 mL) was added quickly at room temperature to a stirred solution of diethyl methylenemalonate **4**[11] (2.07 g, 12.0 mmol) in THF (5 mL). After 12 h stirring, THF was evaporated then Et_2O (30 mL) was added. Washing (10% aqueous NaOH then H_2O), drying ($MgSO_4$) evaporation and chromatography on silica gel (cyclohexane/Et_2O 98 : 2) led to 3.07 g of **1c** (91%) as an oil ; ^1H NMR : δ 1.26 (t, 6H, J = 7.1 Hz), 3.39 (d, 2H, J =

7.6 Hz), 3.55 (t, 1H, J = 7.6 Hz), 4.19 (q, 4H, J = 7.1 Hz), 7.29 (m, 3H), 7.41 (m, 2H) ; ^{13}C NMR : δ 14.0 (2C), 32.8 (2C), 52.2, 61.8, 127.1, 129.1 (2C), 131.0 (2C), 134.4, 168.0 (2C) ; Anal. Calcd for $C_{14}H_{18}O_4S$: C, 59.55 ; H, 6.43 ; S, 11.35. Found : C, 59.62 ; H, 6.47 ; S, 11.40.

Diethyl 2-phenylselenomethylmalonate 1d

Freshly prepared phenylselenol[13] (0.713 g, 4.54 mmol), diethylmethylemalonate **4**[11] (0.390 g, 2.27 mmol) and THF (10 mL) were stirred for 4 h at room temperature. Evaporation, addition of brine (10 mL), extraction with CH_2Cl_2 (3 x 10 mL), drying (Na_2SO_4), evaporation and chromatography on silica gel (cyclohexane/Et_2O 90 : 10) led to 0.568 g (76%) of **1d** as an oil ; ^1H NMR : δ 1.26 (t, 6H, J = 7.1 Hz), 3.30 (d, 2H, J = 7.7 Hz), 3.59 (t, 1H, J = 7.7 Hz), 4.19 (q, 4H, J = 7.1 Hz), 7.29 (m, 3H), 7.55 (m, 2H) ; ^{13}C NMR : δ 14.0 (2C), 25.0 (2C), 53.0 61.7, 127.7, 129.2 (2C), 133.8 (2C), 131.5, 168.3 (2C) ; Anal. Calcd for $C_{14}H_{18}O_4Se$: C, 51.07 ; H, 5.51 ; Se, 23.98. Found : C, 51.29 ; H, 5.46 ; Se, 24.43.

Preparation of 6a

n-Butyllithium (12.5 mL of 1.5 M solution in hexane, 20 mmol) was added dropwise at -5°C and under nitrogen to a stirred solution of $PhCH_2OH$ (2.5 g, 23 mmol) in THF (50 mL). Reaction was allowed to proceed for 30 min then diethyl methylenemalonate **4**[11] (3.4 g, 19.8 mmol) in THF (10 mL) was added dropwise at the same temperature. The reaction mixture was stirred for 30 min at 0°C then 30 min at room temperature. Addition of brine (10 mL), extraction with Et_2O (2 x 100 mL), drying ($MgSO_4$) evaporation and distillation (bp 125°C/0.025 mm Hg) led to

2.68 g of **6a** as an oil (60%) ; ^{1}H NMR (90 MHz) : δ 1.24 (t, 12H, J = 7.6 Hz), 2.75 (d, 2H, J = 7.5 Hz), 3.72 (t, 1H, J = 7.5 Hz), 3.91(s, 2H), 4.19 (q, 8H, J = 7.6 Hz), 4.52 (s, 2H), 7.35 (m, 5H) ; ^{13}C NMR : (20.1 MHz) : δ 13.8 (2C), 13.9 (2C), 30.2, 48.3, 57.3, 61.3 (2C), 61.4 (2C), 70.7, 73.2, 127.3-128.2 (4C), 137.6, 169.1 (4C) ; Anal Calcd for $C_{23}H_{32}O_9$: C, 61.05 ; H, 7.12. Found : C, 61.13 ; H, 7.07 ; HR-MS : calcd for $C_{23}H_{32}O_9$ 452.2046, Found : 452.2053.

Preparation of 6b

Triethylamine (15.2 mg, 0.15 mmol) was added dropwise at 0°C and under stirring to a mixture of diethyl methylenemalonate **4**[11] (0.526 g, 3.06 mmol) and of phenylselenol[13] (0.480 g, 3.06 mmol) in THF (10 mL). The reaction mixture was stirred for 12 h at room temperature, then THF was evaporated and Et_2O (50 mL) was added. Washing (10% aqueous NaOH then water), drying (Na_2SO_4), evaporation and chromatography on silica gel (cyclohexane/Et_2O 80 : 20) led to 0.729 g of **6b** (95%) as an oil ; ^{1}H NMR : δ 1.15 (t, 6H, J = 7.1 Hz), 1.26 (t, 6H, J = 7.1 Hz), 2.69 (d, 2H, J = 6.1 Hz), 3.43 (s, 2H), 3.50 (t, 1H, J = 6.1 Hz), 4.00 (m, 4H), 4.17 (m, 4H), 7.24 (m, 3H), 7.54 (m, 2H) ; ^{13}C NMR : δ 13.7 (2C), 14.0 (2C), 31.9 (2C), 32.1 (2C), 48.1, 57.3, 61.6, 61.7, 127.4, 129.0 (2C), 129.9, 133.7 (2C), 168.9 (2C), 169.6 (2C) ; Anal Calcd for $C_{22}H_{30}O_8Se$: C, 52.70 ; H, 6.03 ; Se, 15.75. Found : C, 52.99 ; H, 5.97 ; Se, 15.31.

Acknowledgment. We thank the local section of Sarthe of the Ligue Nationale contre le Cancer for a fellowship to J.-L.D.

References and notes

1. Simonsen, J.L. *J. Chem. Soc.*, **1908**, 1777-1789.
2. Musso, H. ; Naumann, K. ; Grychtol, K. *Chem. Ber.*, **1967**, *100*, 3614-3626.
3. Dowd, P. ; Shapiro, M. *J. Am. Chem. Soc.*, **1976**, *98*, 3724-3725.
4. Aeberhard, U. ; Keese, R. ; Stamm, E. ; Vögeli, U.-C. ; Lau, W. ; Kochi, J.K. *Helv. Chim. Acta*, **1983**, *66*, 2740-2759.
5. Elks, J. ; Elliott, D.F. ; Hems, B.A. *J. Chem. Soc.*, **1944**, 626-629 and references cited therein.
6. Luyten, M. ; Müller, S. ; Herzog, B. ; Keese, R. *Helv. Chim. Acta*, **1987**, *70*, 1250-1254.
7. Gaudemar-Bardone, F. ; Gaudemar, M. *Bull. Soc. Chim. Fr.*, **1970**, 2968-2972.
8. Feely, W. ; Boekelheide, V. *Organic Syntheses*, **1963**, Coll. Vol. IV, 298-301.
9 Jones, G. *in Organic Reactions*, **1967**, *15*, 204-599 ; Tietze, L.F. ; Beifuss, U. in Comprehensive Organic Synthesis, Trost, B.M. ; Fleming, I., Editors, Pergamon, **1991**, *Vol.* 2, 341-394.
10. Goff, D.A. ; Harris III, R.N. ; Bottaro, J.C. ; Bedford, C.D. *J. Org. Chem.*, **1986**, *51*, 4711-4714.
11. Diethyl methylenemalonate was easily prepared by the procedure of ref 12 and keeped in ether solution to avoid polymerization. Another preparation is possible from ref 8.
12. Bachman, G.B. ; Tanner, H.A. *J. Org. Chem.*, **1939**, *4*, 493-501.

13. Smith III, A.B. ; Scarborough Jr, R.M.*Tetrahedron Lett.*, **1978**, *19*, 1649-1652 ; see also Krief, A. ; Trabelsi, M. ; Dumont, W. *Synthesis*, **1992**, 933-935 and references cited therein.

(Received in the UK 31st December 1995)