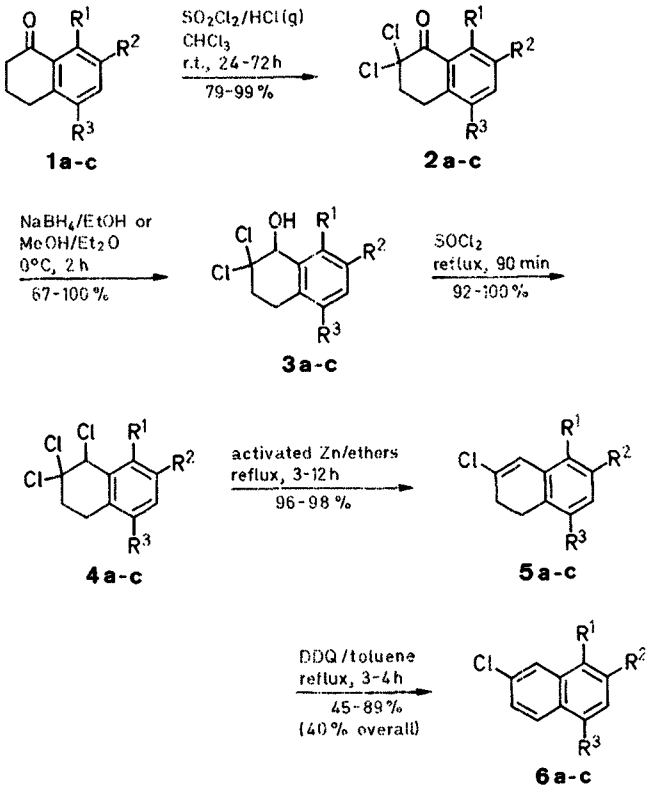
A Convenient and Unambiguous Synthesis of 2 (or 7)-Chloronaphthalenes from Substituted α-Tetralones

John D. Prugh,* Albert A. Deana, J. Mark Wiggins

Department of Medicinal Chemistry, Merck Sharp and Dohme Research Laboratories, West Point, PA, 19486, USA

2(or 7)-Chlornaphthalenes are unambiguously prepared from α-tetralones(1-oxo-1,2,3,4-tetrahydronaphthalenes) by introducing two chlorines in the 2-position with sulfuryl chloride, reducing the ketone with sodium borohydride, and then converting the resulting hydroxy to chloro with thionyl chloride. Vicinal chlorines are then removed with activated zinc giving a vinyl chloride which is aromatized with 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (DDQ) to give the desired 2(or 7)-chloronaphthalenes.

In our work preparing naphthalene analogues of the natural product lovastatin, we had occasion to prepare multisubstituted 7-chloronaphthalenes. Methodology was needed to introduce the 7-chloro substituent unambiguously. Since substituted α-tetralones (1-oxo-1,2,3,4-tetrahydronaphthalenes) are readily available from substituted benzenes by Friedel–Crafts acylation with succinic anhydrides followed by ketone reduction to the methylene and a second Friedel–Crafts acylation[2] to give the tetralone,[1] we opted to introduce the 7-chloro substituent via these α-tetralones.[3] The methodology developed for this purpose is outlined in the Scheme.



1-6	R¹	R²	R³
a	$CH_2CH_2CH_2O_2CPh$	CH_3	CH_3
b	$CH_2CH_2CO_2Et$	CH_3	Cl
c	$CH_2CH_2CO_2Et$	Cl	CH_3

Geminal chlorination of **1a** proceeded smoothly with sulfuryl chloride in chloroform using hydrogen chloride gas as a catalyst.[4] Alternatively, the chloro substituents could be introduced stepwise by first monochlorinating with sulfuryl chloride in dichloromethane using hydrogen chloride as catalyst. After removing the solvent and volatile reagents at reduced pressure, the resultant crude product was treated with sulfuryl chloride in chloroform saturated with hydrogen chloride gas to slowly introduce the second chloro group. Compounds **1b** and **1c** were chlorinated in this way. Although the two-step method seemed a little cleaner, it does not offer any great advantage. Sodium borohydride reduction of the ketone followed by conversion of the alcohol to the corresponding chloro derivative proved uneventful. Indeed, up to this point all three compounds in the sequence **1** → **4** performed in about the same way. However, in the next step involving dechlorination with activated zinc dust[5] great differences were observed. Compound **4a** proceeded exothermically in refluxing ether as solvent. Compound **4c** required refluxing dry glyme. Compound **4b** would not react in either ether or glyme but when heated to 140 °C with dry diglyme as a solvent, the reaction became exothermic and caused the solvent to reflux. Aromatization with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing toluene gave the desired 7-chloronaphthalene.

This sequence is made particularly convenient because the product of each step can be carried on without purification until the 2(or 7)-chlorinated naphthalene is reached. Thus **6a** was obtained in 40% overall yield without purification of the intermediates.

Melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. Analytical TLC plates were Analtech, and silica gel (230–400 mesh) was purchased from E M Reagents. Mass spectra were obtained using a VG MMZAB-HF mass spectrometer. ^{1}H-NMR spectra were obtained using a Varian XL-300, Varian T-60A, Nicolet 360, or Varian EM-390.

1-(3-Benzoyloxypropyl)-7,7-dichloro-2,4-dimethyl-8-oxo-5,6,7,8-tetrahydronaphthalene (2a):
Gaseous HCl is bubbled into a solution of **1a** (6.5 g, 19.3 mmol) dissolved in $CHCl_3$ (20 mL) until saturated. SO_2Cl_2 (15.6 mL, 26.05 g, 193 mmol) is added dropwise and stirred at r.t. for 3 h. SO_2Cl_2 (15.6 mL) is added again, and the reaction mixture is stirred at r.t. overnight. The excess SO_2Cl_2 and solvent are removed at reduced pressure then chased with dry toluene (2 × 20 mL) leaving 7.8 g (99%) of product; a gum, R_f = 0.71 (silica, CH_2Cl_2). This product is used in the next step without further purification.

MS (70 eV): Exact Mass ($C_{22}H_{22}Cl_2O_3$): calc. 404.0946, found 404.0950.

^{1}H-NMR ($CDCl_3$/TMS; 360 MHz): δ = 2.07 (m, 2H, CH_2); 2.25 (s, 3H, CH_3); 2.38 (s, 3H, CH_3); 2.97 (d, 2H, J = 6 Hz, CH_2); 3.03 (d, 2H, J = 6 Hz, CH_2); 3.09 (t, 2H, J = 6 Hz, CH_2); 4.47 (t, 2H, J = 6 Hz, CH_2O); 7.15–7.6 (m, 4H, H_{arom}); 8.08 (m, 2H, H_{arom}).

1-(3-Benzoyloxypropyl)-7,7-dichloro-8-hydroxy-2,4-dimethyl-5,6,7,8-tetrahydronaphthalene (3a):
$NaBH_4$ (1.51 g, 40 mmol) is added to a solution of **2a** (7.82 g, 19.3 mmol) in MeOH (100 mL) and Et_2O (50 mL), which has been cooled in an ice-water bath. The reaction mixture is stirred for 2 h. TLC (silica, CH_2Cl_2) showed the reaction complete. The reaction mixture is partitioned between Et_2O (300 mL) and H_2O (200 mL). The ether layer is extracted with H_2O (5 × 50 mL), dried ($MgSO_4$), filtered, and the solvent is evaporated under reduced pressure to give 7.86 g (100%) of product as a gum, R_f = 0.51 (1% acetone/CH_2Cl_2). This product is used in the next step without further purification.

MS (70 eV): Exact Mass ($C_{22}H_{24}O_3$ ($M^+ - Cl_2$): calc. 336.1725, found 336.1726.^{1}H-NMR ($CDCl_3$/TMS; 60 MHz): δ = 1.63–2.55 (m, 2H, CH_2); 2.15 (s, 3H, CH_3); 2.30 (s, 3H, CH_3); 2.55–3.1 (m, 4H, $2CH_2$); 4.4 (t, 2H, J = 6 Hz, CH_2O); 5.08 (s, 1H, HOCH); 6.92 (s, 1H, H_{arom}); 7.04–7.6 (m, 3H, H_{arom}); 7.9–8.16 (m, 2H, H_{arom}).

1-(3-Benzoyloxypropyl)-7,7,8-trichloro-2,4-dimethyl-5,6,7,8-tetrahydronaphthalene (4a):
Alcohol **3a** (7.86 g, 19.3 mmol) is dissolved in $SOCl_2$ (40 mL) and slowly brought to reflux, then refluxed for 90 min. The reaction mixture is then cooled to 23 °C and the excess $SOCl_2$ is evaporated under reduced pressure and then chased with dry toluene (2 × 50 mL) to leave 7.60 g (92%) of a gum, R_f = 0.36 (silica, 33% CH_2Cl_2 in hexane), which is used in the next step without purification.

MS (70 eV): Exact Mass ($C_{22}H_{23}Cl_3O_2$): calc. 424.0764, found 424.07635.

^{1}H-NMR ($CDCl_3$/TMS; 60 MHz): δ = 1.55–2.64 (m, 4H, $2CH_2$); 2.15 (s, 3H, CH_3); 2.34 (s, 3H, CH_3); 2.66–3.24 (m, 4H, $2CH_2$); 4.4 (t, 2H, J = 6 Hz, CH_2O); 5.6 (s, 1H, ClCH); 6.95 (s, 1H, H_{arom}); 7.05–7.6 (m, 3H, H_{arom}); 7.95–8.15 (m, 2H, H_{arom}).

1-(3-Benzoyloxypropyl)-7-chloro-2,4-dimethyl-5,6-dihydronaphthalene (5a):
Activated Zn dust[5] (1.35 g, 20.65 mmol) is added to a solution of **4a** (7.60 g, 17.9 mmol) in dry Et_2O (6 mL). The reaction is stirred and heated with a heat gun intermittently to maintain reflux, then heated at reflux for 3 h. TLC (silica, 33% CH_2Cl_2 in hexane) showed the reaction complete. The reaction mixture is diluted with Et_2O (100 mL) and filtered from unreacted Zn; then the Et_2O is washed successively with dilute HCl (10%, 40 mL), H_2O (4 × 30 mL), then sat. $NaHCO_3$ (30 mL); dried ($MgSO_4$), filtered and the Et_2O evaporated at reduced pressure to leave 6.10 g (96%) of product as a gum. This compound is used in the next step without purification.

MS (70 eV): Exact Mass ($C_{22}H_{23}ClO_2$: calc. 354.1386, found 354.1384.
^{1}H-NMR ($CDCl_3$/TMS; 90 MHz): δ = 1.75–2.38 (m, 2H, CH_2); 2.17 (s, 3H, CH_3) 2.26 (s, 3H, CH_3); 2.45–2.95 (m, 6H, $3CH_2$); 4.38 (t, 2H, J = 6 Hz, CH_2O); 6.85 (m, 2H, H_{vinyl}, H_{arom}); 7.18–7.64 (m, 3H, H_{arom}); 8.0–8.16 (m, 2H, H_{arom}).

1-(3-Benzoyloxypropyl)-7-chloro-2,4-dimethylnaphthalene (6a):
A solution of DDQ (5.75 g, 25.35 mmol) in toluene (50 mL) is added to a solution of **5a** (6.00 g, 16.9 mmol) in toluene (50 mL) and the stirred reaction mixture is heated in a bath at 100–110 °C for 3 h. The reaction mixture is cooled to r.t., filtered from the solid, and the solvent is evaporated at reduced pressure to leave a gum which is flash chromatographed on an 80 mm × 300 mm silica gel column eluting with CH_2Cl_2/hexane (1:1) to give 2.7 g (45%) of the product as a gum which slowly solidifies, mp 84–90 °C. This product is used in the next step as is. A small sample is recrystallized from EtOH for analysis, mp 96–97 °C. Overall yield for 5 steps 40%.

$C_{22}H_{21}ClO_2$	calc.	C 74.89	H 6.00
(352.9)	found	75.08	6.10

^{1}H-NMR ($CDCl_3$/TMS; 60 MHz): δ = 1.95–2.38 (m, 2H, CH_2); 2.45 (s, 3H, CH_3); 2.6 (s, 3H, CH_3); 3.15 (m, 2H, CH_2); 4.4 (t, 2H, J = 6 Hz, CH_2O); 7.05–8.14 (m, 9H, H_{arom}).

Ethyl 3-(4,7,7-Trichloro-2-methyl-8-oxo-5,6,7,8-tetrahydro-1-naphthyl)-propanoate (2b):
Introduction of the First Chlorine: A solution of **1b** (5.70 g, 20.3 mmol) in CH_2Cl_2 (20 mL) is saturated with dry gaseous HCl, and SO_2Cl_2 (16.4 mL, 27.5 g, 203 mmol) is added dropwise and stirred at r.t. for 2 h. Work-up as in **2a** gives 6.40 g (100%) of the product. This is used in the next step without purification.

MS (70 eV): Exact Mass ($C_{16}H_{17}O_3Cl$(M^+ – HCl): calc. 292.0866, found 292.0869.

Introduction of the Second Chlorine: Dry HCl gas is bubbled into a solution of ethyl 3-(4,7-dichloro-2-methyl-8-oxo-5,6,7,8-tetrahydro-1-naphthyl)propanoate (6.40 g, 203 mmol) in $CHCl_3$ (20 mL) until saturated. SO_2Cl_2 (16.4 mL, 27.5 g, 203 mmol) is added. With an atmosphere of HCl gas covering the reaction, it is stoppered and then stirred at r.t. for 72 h at which time TLC (silica, CH_2Cl_2) showed the reaction complete. Work-up as above leaves 7.08 g (100%) of product as a gum. This is used in the next step without purification.

MS (70 eV): Exact Mass ($C_{16}H_{16}Cl_2O_3$(M^+ – HCl): calc. 326.0476, found 326.0475.

^{1}H-NMR ($CDCl_3$/TMS; 300 MHz): δ = 1.28 (t, 3H, J = 7 Hz, CH_2CH_3); 2.38 (s, 3H, CH_3); 2.61 (t, 2H, J = 7 Hz, CH_2); 2.96 (t, 2H, J = 7 Hz, CH_2); 3.17–3.24 (m, 4H, $2CH_2$); 4.17 (q, 2H, J = 7 Hz, CH_2CH_3); 7.45 (s, 1H, H_{arom}).

Ethyl 3-(2,7,7-Trichloro-4-methyl-8-oxo-5,6,7,8-tetrahydro-1-naphthyl)-propanoate (2c):
By the above procedure two chlorines are introduced α to the ketone of **1c** giving after crystallization from EtOH the product 6.2 g (79%); mp 94–96°C.

$C_{16}H_{17}Cl_3O_3$	calc.	C 52.84	H 4.71
(363.7)	found	52.61	4.89

^{1}H-NMR (CDCl$_3$/TMS; 360 MHz): δ = 1.28 (t, 3H, J = 7 Hz, CH_2CH_3); 2.28 (s, 3H, CH_3); 2.67 (br t, 2H, J = 7 Hz, CH_2); 2.99 (m, 4H, $2CH_2$); 3.55 (br t, 2H, J = 7 Hz, CH_2); 4.18 (q, 2H, J = 7 Hz, CH_2CH_3); 7.44 (s, 1H, H_{arom}).

Ethyl 3-(4,7,7-Trichloro-8-hydroxy-2-methyl-5,6,7,8-tetrahydro-1-naphthyl)propanoate (3b):
$NaBH_4$ (0.19 g, 5.02 mmol) is added to a solution of **2b** (7.84 g, 20.3 mmol) in EtOH (60 mL) which has been cooled in an ice-water bath. The reaction mixture is allowed to stir for 15 min when TLC (silica, CH_2Cl_2) shows the reaction not complete. $NaBH_4$ (20 mg) is added three times with 15 min intervals of stirring between each addition. The complete reaction mixture is worked up as in **3a** to leave 7.25 g (98%) of product as a gum R_f = 0.41 (2% acetone/CH_2Cl_2). This is used in the next step without purification.

MS (70 eV): Exact Mass calc. ($C_{16}H_{18}Cl_2O_2$(M^+ – HOCl): 312.0684, found 312.0681.

^{1}H-NMR (CDCl$_3$/TMS; 300 MHz): δ = 1.28 (t, 3H, J = 7 Hz, CH_2CH_3); 2.38 (s, 3H, CH_3); 2.4–2.7 (m, 2H, CH_2) 2.8–3.2 (m, 6H, $3CH_2$); 4.2 (q, 2H, J = 7 Hz, CH_2CH_3); 5.1 (s, 1H, HOCH); 7.35 (s, 1H, H_{arom}).

Ethyl 3-(2,7,7-Trichloro-8-hydroxy-4-methyl-5,6,7,8-tetrahydro-1-naphthyl)propanoate (3c):
The title compound is prepared as its isomer **3b** (67%); mp 115–117°C from Et_2O/hexane (1:5).

$C_{16}H_{19}Cl_3O_3$	calc.	C 52.55	H 5.24
(365.7)	found	52.91	5.47

^{1}H-NMR (CDCl$_3$/TMS; 360 MHz): δ = 1.29 (t, 3H, J = 7 Hz, CH_2CH_3); 2.19 (s, 3H, CH_3); 2.58 (m, 2H, CH_2); 2.7–2.96 (m, 4H, $2CH_2$); 3.19 (m, 2H, CH_2); 4.17 (q, 2H, J = 7 Hz, CH_2CH_3); 5.09 (m, 1H, HOCH); 7.21 (s, 1H, H_{arom}).

Ethyl 3-(4,7,7,8-Tetrachloro-2-methyl-5,6,7,8-tetrahydro-1-naphthyl)propanoate (4b):
Compound **3b** (7.12 g, 19.4 mmol) is dissolved in $SOCl_2$ (40 mL) and then refluxed with stirring for 2.5 h, cooled to r.t., and the reaction mixture is worked up as in **4a** to give 7.48 g (100%) of crude product which is used in the next step without purification.

MS (70 eV): Exact Mass ($C_{16}H_{18}Cl_4O_2$): calc. 382.0061, found 382.0033.

^{1}H-NMR (CDCl$_3$/TMS; 300 MHz): δ = 1.31 (t, 3H, J = 7 Hz, CH_2CH_3); 2.32 (s, 3H, CH_3); 2.43–3.11 (m, 8H, $4CH_2$); 4.21 (q, 2H, J = 7 Hz, CH_2CH_3); 5.55 (d, 1H, J = 2 Hz, CH); 7.2 (s, 1H, H_{arom}).

Ethyl 3-(2,7,7,8-Tetrachloro-4-methyl-5,6,7,8-tetrahydro-1-naphthyl)propanoate (4c):
Using the procedure of **4b** this product is prepared, mp 92–94°C (yield quant.) from hexane.

$C_{16}H_{18}Cl_4O_2$	calc.	C 50.03	H 4.72
(384.1)	found	49.87	4.74

^{1}H-NMR (CDCl$_3$/TMS; 360 MHz): δ = 1.3 (t, 3H, J = 7 Hz, CH_2CH_3); 2.19 (s, 3H, CH_3); 2.48–3.23 (m, 8H, $4CH_2$); 4.21 (t, 2H, J = 7 Hz, CH_2CH_3); 5.61 (d, 1H, HOCH); 7.2 (s, 1H, H_{arom}).

Ethyl 3-(4,7-Dichloro-2-methyl-5,6-dihydro-1-naphthyl)propanoate (5b):
Activated Zn dust[5] (0.55 g, 8.43 mmol) is added to a solution of **4b** (2.49 g, 6.48 mmol) in dry diglyme (2.5 g) and heated and stirred in a bath to 140°C at which time the reaction vigorously and exothermically refluxes. The reflux subsides in ca. 1 min. Heating with a bath at 140 to 150°C is continued for 15 min. TLC (silica, $CHCl_3$) shows the reaction complete. The reaction mixture is cooled to r.t. and worked up as in **5a** to leave 1.99 g (98%) of product as a gum, R_f = 0.61 (silica, CH_2Cl_2), which is used in the next step without purification.

MS (70 eV): Exact Mass ($C_{16}H_{18}Cl_2O_2$): calc. 312.0684, found 312.0675.

^{1}H-NMR (CDCl$_3$/TMS; 300 MHz): δ = 1.29 (t, 3H, J = 7 Hz, CH_2CH_3); 2.28 (s, 3H, CH_3); 2.41 (t, 2H, J = 7 Hz, CH_2); 2.62 (t, 2H, J = 7 Hz, CH_2); 2.94 (dd, 2H, J = 6, 7.1 Hz); 3.04 (t, 2H, J = 8.8 Hz, CH_2); 4.17 (q, 2H, J = 7 Hz, CH_2CH_3); 6.78 (s, 1H, H_{vinyl}); 7.04 (s, 1H, H_{arom}).

Ethyl 3-(2,7-Dichloro-4-methyl-5,6-dihydro-1-naphthyl)propanoate (5c):
Except for dry glyme as the solvent refluxing for 12 h the procedure of **5b** is used to prepare **5c** (97%) which is used in the next step without purification.

^{1}H-NMR (CDCl$_3$/TMS; 300 MHz): δ = 1.3 (t, 3H, J = 7 Hz, CH_2CH_3); 2.2 (s, 3H, CH_3); 2.5 (dd, 2H, J = 4.1, 4.1 Hz, CH_2); 2.6 (t, 2H, J = 4.1 Hz, CH_2); 2.84 (t, 2H, J = 4.1 Hz, CH_2); 3.1 (dd, 2H, J = 4.1, 4.1 Hz, CH_2); 4.18 (q, 2H, J = 7 Hz, CH_2CH_3); 6.8 (s, 1H, H_{vinyl}); 7.04 (s, 1H, H_{arom}).

Ethyl 3-(4,7-Dichloro-2-methyl-1-naphthyl)propanoate (6b):
Compound **5b** (2.00 g, 6.39 mmol), DDQ (2.18 g, 9.58 mmol), and dry toluene (75 mL) are mixed and heated at reflux with stirring for 2 h. The reaction mixture is allowed to stand overnight at r.t. when the ^{1}H-NMR of the work-up of a small aliquot showed 3% to 4% starting material. DDQ (0.5 g) is added, refluxed with stirring for 2 h when work-up of a small aliquot showed the reaction complete. The reaction mixture is worked up as in **6a** to give 1.78 g (89%) of the product as an oil.

MS (70 eV): Exact Mass ($C_{16}H_{16}Cl_2O_2$): calc. 310.0527, found 310.0527.

^{1}H-NMR (CDCl$_3$/TMS; 300 MHz): δ = 1.28 (t, 3H, J = 7 Hz, CH_2CH_3); 2.49 (s, 3H, CH_3); 2.56 (t, 2H, J = 8 Hz, CH_2); 3.33 (t, 2H, J = 8.6 Hz, CH_2); 4.19 (q, 2H, J = 7 Hz, CH_2CH_3); 7.42 (s, 1H, H_{arom}); 7.47 (dd, 1H, J = 2, 6.6 Hz, H_{arom}); 7.99 (d, 1H, J = 2 Hz, H_{arom}); 8.20 (d, 1H, J = 6.6 Hz, H_{arom}).

Ethyl 3-(2,7-Dichloro-4-methyl-1-naphthyl)propanoate (6c):
The procedure used to prepare **6b** is used to prepare **6c** (yield 73%), mp 71–73°C.

$C_{16}H_{16}Cl_2O_2$	calc.	C 61.75	H 5.18
(311.3)	found	61.71	5.18

^{1}H-NMR (CDCl$_3$/TMS; 360 MHz): δ = 1.28 (t, 3H, J = 7 Hz, CH_2CH_3); 2.62 (m, 2H, CH_2); 2.63 (s, 3H, CH_3); 3.48 (m, 2H, CH_2); 4.19 (q, 2H, J = 7 Hz, CH_2CH_3); 7.31 (s, 1H, H_{arom}); 7.47 (dd, 1H, J = 10, 2 Hz, H_{arom}); 7.92 (d, 1H, J = 10 Hz, H_{arom}); 8.01 (d, 1H, J = 2 Hz, H_{arom}).

Received: 20 September 1988; revised: 2 February 1989

(1) Peto, A.G. in: *Friedel–Crafts and Related Reactions*, Olah, G.A. (ed.), Coll. Vol. III, Part I, p. 550.
(2) Sethna, S. *ibid.*, Part 2, p. 911.
(3) The somewhat lengthy synthesis of the intermediate tetralones by known methods will be reported elsewhere.
(4) In a trial run, elemental chlorine gas was tried as a chlorinating reagent on α-tetralone in $CHCl_3$ saturated with HCl gas. This gave geminal chlorination, but also ca. 50% radical chlorination in the 4-position.
(5) Shriner, R.L., Newman, F.W. *Org. Synth. Coll. Vol. 3* **1955**, 73. In the experience of one referee, more reactive zinc is obtained by letting Zn dust react for 20–25 min at r.t. with excess 10% HCl.