

General Procedure for Carboxylation:

To a magnetically stirred solution of diisopropylamine (12.5 g, 124 mmol) in tetrahydrofuran (40 ml) under nitrogen at 0° was added *n*-butyllithium (124 mmol). The solution was stirred for 10 minutes, then cooled to -78°. A solution of the *ortho*-toluic acid **1a** or **1b** (31 mmol) and dimethyl carbonate (6.65 ml, 62 mmol) in tetrahydrofuran (40 ml) was added dropwise over 10 minutes. When the addition was completed, the cooling bath was removed and the reaction was allowed to warm to room temperature, during which time a precipitate formed in the yellow solution. The reaction mixture was stirred for 4 h, then water (50 ml) was added and stirring was continued overnight. The basic solution was evaporated at reduced pressure until water began to distill.

For homophthalic acid (**2a**), the solution was acidified (pH=1) and extracted with ethyl acetate (4 × 75 ml). After drying (MgSO₄), ethyl acetate was removed at reduced pressure and the resulting solid was triturated with boiling chloroform, cooled, and filtered to give pure homophthalic acid; yield: 4.75 g (85%); m.p. 140–141 (Lit.², m.p. 140–141°).

For 6-methoxyhomophthalic acid (**2b**), the solution was acidified, then further evaporated until an oil precipitated. This mixture was extracted with hot ethyl acetate (4 × 75 ml). After drying (MgSO₄) and evaporation of the solvent, the residue was triturated with boiling ether (50 ml), cooled, and filtered to give pure 6-methoxyhomophthalic acid (**2b**); yield: 2.73 g. The filtrate was evaporated, the oily residue was diluted with water (50 ml) and a small amount of methanol, and heated in the steam bath for 15 min. After re-extraction with ethyl acetate, drying, evaporation of the solvent and ether treatment, an additional crop of pure product **2b** was obtained; yield: 2.54 g. The filtrate was again evaporated, the residue was dissolved in hot acetone which was then diluted with benzene. The resulting crystals (580 mg) were collected to bring the overall yield of pure **2b** to 5.85 g (90% yield), m.p. 164–165° (Lit.³, m.p. 165°). An identical yield of **2b** was obtained when the reaction scale was tripled.

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¹ P. E. Pfeffer, L. S. Silbert, J. M. Chirinko, *J. Org. Chem.* **37**, 451 (1972).

² O. Grummitt, R. Egan, A. Buck, *Org. Syn., Coll. Vol.* **III**, 449 (1955).

³ M. Matsui, S. Arasaki, K. Mori, *Agr. Biol. Chem. Tokyo* **28**, 896 (1964).

Sodium Dithionite as a Reductant for Aldehydes and Ketones

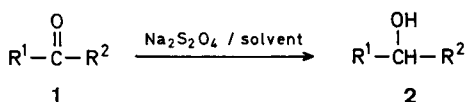
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Sodium dithionite, Na₂S₂O₄, is a reducing agent widely applied both in the laboratory and industry¹. It is commonly

used in biochemistry for the reduction of a variety of coenzymes and enzymes² and in organic chemistry to reduce several types of functional groups, especially those containing nitrogen^{3,4}.

One is struck, however, at the sparseness of reports of the reduction of carbonyl compounds by this commonly available reagent. The reductions of acetone and benzaldehyde were claimed (without experimental detail) over a century ago⁵ and more recently the reductions of benzil to benzoin^{6,7} and of cyclohexanone to cyclohexanol⁸ (in 10% yield) have been reported. We are unaware of other pertinent literature.



We have now developed experimental conditions under which a variety of aldehydes and relatively unhindered ketones (**1**) can be reduced to the corresponding alcohols (**2**) by sodium dithionite. The experimental procedures are simple, the yields are good, and the dangers, inconvenience, and expense of metal hydride reagents are avoided.

A number of examples are given in the Table. Roughly the same procedure was used for all reductions. If sufficiently soluble the substrate is dissolved in water, otherwise a 50:50 mixture of water and dioxan is used. Excess sodium hydrogen carbonate is used to keep the reaction mixture basic (otherwise no reaction occurs). The reaction mixture is held at reflux for 4 h and the sodium dithionite is added in portions (a batch of the reagent loses most of its reducing properties after one hour under the conditions used).

Most ketones are only sluggishly reduced in water or water/dioxan. However, the yields improve dramatically on using as solvent dimethylformamide/water in a 50:50 mixture (for comparison see Table). A satisfactory explanation for the beneficial effect of dimethylformamide is lacking.








Carboxylic acids and amides are not reduced under these circumstances and esters and nitriles are hydrolyzed. The reduction of levulinic acid gives an example of a selective transformation with sodium dithionite.

In summary we believe that this procedure offers a simple and useful alternative to metal hydride reductions of unhindered carbonyl compounds. Sodium dithionite is inexpensive and easy to use; this recommends its use. A fuller description of the chemistry of this reagent will be published in due course.

General Procedure for the Reduction of Aldehydes and Ketones:

A solution of substrate (50 mmol) in dioxan (175 ml) or dimethylformamide for more difficultly reducible substrates (see Table), is added to water (175 ml) containing sodium hydrogen carbonate (27.5 g). When no cosolvent is used, the substrate is added neat. Sodium dithionite (12.5 g) is added and the reaction mixture refluxed for 4 h during which time three additional 12.5 g portions of sodium dithionite are added. The reaction is carried out under an atmosphere of nitrogen. After cooling to room temperature, water is added until the solution becomes clear and thereafter the solution is extracted with ether (furfuryl alcohol and γ -valerolactone were isolated by continuous extraction with ether for 7 and 72 hours respectively). When dimethylformamide is used as cosolvent the ether extracts are back-washed twice with water to remove traces of dimethylformamide. After drying (MgSO₄) and removal of the ether, the products are isolated by either distillation or recrystallization. Identification is based

Table. Reduction of Aldehydes and Ketones (1) to Alcohols (2) with Sodium Dithionite ($\text{Na}_2\text{S}_2\text{O}_4$)

Substrate 1	Product 2	Solvent	Yield [%]	m.p. or b.p./torr	Lit. m.p. or b.p./torr	$^1\text{H-N.M.R.}$ δ [ppm]
$n\text{-C}_5\text{H}_{11}\text{-C(=O)-H}$	$n\text{-C}_5\text{H}_{11}\text{-CH}_2\text{-OH}$	H_2O	63	157°/760	158°/760 ⁹	0.16–1.76 (m, 11H), 1.89 (s, 1H), 3.63 (t, 2H)
$\text{C}_6\text{H}_5\text{-C(=O)-H}$	$\text{C}_6\text{H}_5\text{-CH}_2\text{-OH}$	$\text{H}_2\text{O}/\text{dioxan}$ (1:1)	84	89°/8	93°/10 ⁹	4.37 (s, 2H), 4.38 (s, 1H), 7.17 (s, 5H)
		H_2O	90	65.5°/9	68 69°/20 ⁹	3.49 (s, 1H), 4.51 (s, 2H), 6.29 (m, 2H), 7.40 (m, 1H)
		H_2O	80	160°/760	161.1°/760 ⁹	0.67–2.60 (m, 10H), 3.38 (s, 1H), 3.58 (m, 1H)
		$\text{H}_2\text{O}/\text{dioxan}$ (1:1)	97	296–300°	296.2–297.7° ¹⁰	1.30–2.36 (m, 15H), 3.91 (s, 1H)
$\text{C}_6\text{H}_5\text{-C(=O)-CH}_3$	$\text{C}_6\text{H}_5\text{-CH(OH)-CH}_3$	$\text{H}_2\text{O}/\text{dioxan}$ (1:1)	30 ^a	—	—	—
$\text{C}_6\text{H}_5\text{-C(=O)-CH}_3$	$\text{C}_6\text{H}_5\text{-CH(OH)-CH}_3$	$\text{H}_2\text{O}/\text{DMF}$ (1:1)	94	85.5°/9	100°/18 ⁹	1.39 (d, 3H), 3.47 (s, 1H), 4.76 (q, 1H), 7.26 (s, 5H)
$\text{C}_6\text{H}_5\text{-C(=O)-C}_6\text{H}_5$	$\text{C}_6\text{H}_5\text{-CH(OH)-C}_6\text{H}_5$	$\text{H}_2\text{O}/\text{dioxan}$ (1:1)	50 ^a	—	—	—
$\text{C}_6\text{H}_5\text{-C(=O)-C}_6\text{H}_5$	$\text{C}_6\text{H}_5\text{-CH(OH)-C}_6\text{H}_5$	$\text{H}_2\text{O}/\text{DMF}$ (1:1)	94	65.5–67°	69° ⁹	3.14 (s, 1H), 5.56 (s, 1H), 7.22 (s, 10H)
$n\text{-C}_6\text{H}_{13}\text{-C(=O)-CH}_3$	$n\text{-C}_6\text{H}_{13}\text{-CH(OH)-CH}_3$	$\text{H}_2\text{O}/\text{DMF}$ (1:1)	84	70–71°/9	86–87°/20 ⁹	0.64–1.60 (m, 13H), 1.84 (s, 1H), 3.75 (m, 1H)
$\text{H}_3\text{C-C(=O)-CH}_2\text{-CH}_2\text{-COOH}$		H_2O	54	79°/9	86–90°/14 ⁹	1.42 (d, 3H), 1.63–2.80 (m, 4H), 4.70 (m, 1H)

^a Determined by G.L.C. (conditions: 6ft \times $\frac{1}{8}$ in column, SS 10% Carbowax 20M on Chromosorb WAW 80–100 mesh; column temperature: 150° (acetophenone reaction); 230° (benzophenone reduction).

on melting or boiling points, infrared, and $^1\text{H-N.M.R.}$ spectra, and comparison with authentic materials.

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¹ See, for example: U. Baumgarte, *Textilveredlung* **2**, 896 (1967).

² For some pertinent examples, see: D. O. Lambeth, G. Palmer, *J. Biol. Chem.* **248**, 6095 (1973).

³ E. Grandmougin, *J. Prakt. Chem.* **76**, 124 (1907).

⁴ L. F. Fieser, M. Fieser, *Reagents for Organic Synthesis*, Vol. I, Wiley, New York 1968, p. 1081.

⁵ M. P. Schützenberger, *Ann. Chim. Phys.* (4), **20**, 351 (1870).

⁶ E. Grandmougin, *Ber. Dtsch. Chem. Ges.* **39**, 3561 (1906).

⁷ M. J. Haddadin et al, *Tetrahedron* **30**, 659 (1974).

⁸ J. B. Jones, D. W. Sneddon, W. Higgins, A. J. Lewis, *J. Chem. Soc. Chem. Commun.* **1972**, 856.

⁹ *Handbook of Chemistry and Physics*, 52nd. Edit., Cleveland, Ohio, 1972.

¹⁰ P. v. R. Schleyer, R. D. Nicholas, *J. Am. Chem. Soc.* **83**, 182 (1961).

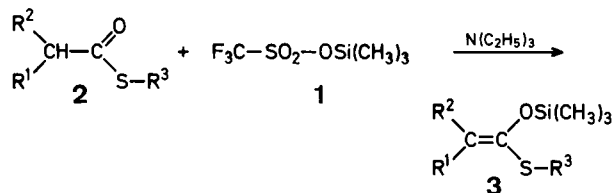
Synthese von Keten-*O*-trimethylsilyl-*S*-alkyl-monothioacetalen

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Die extreme Reaktionsfähigkeit von Trifluoromethansulfonsäure-trimethylsilylester (Trimethylsilyl-triflat, **1**) erlaubte erstmals die direkte Silylierung von Carbonsäure-estern². Wir fanden nun, daß Thiocarbonsäure-*S*-ester (**2**) bereits

bei 0–20° in Gegenwart molarer Mengen Triäthylamin in exothermer Reaktion durch **1** regioselektiv am Carbonyl-Sauerstoff zu Keten-*O*-trimethylsilyl-*S*-alkyl-monothioacetalen (**3**) silyliert werden.



Zur Erzielung hoher Ausbeuten empfiehlt es sich (insbesondere in Fällen von zu Kondensationen neigenden *S*-Ethern), die Ester **2** zusammen mit **1** vorzulegen und Triäthylamin zutropfen zu lassen. Mit *S*-Äthyl-thiocarboxylaten (**2**, $\text{R}^3 = \text{C}_2\text{H}_5$) führt die Reaktion im allgemeinen zu *Z/E*-Gemischen von **3**, mit *t*-Alkylestern (**2**, $\text{R}^3 = t\text{-C}_4\text{H}_9$) dagegen nur zu einem der beiden Stereoisomeren, wie die $^1\text{H-N.M.R.}$ -Spektren zeigen.

Ausgehend von *S,S'*-Dialkyl-1,4-dithiosuccinaten (**4**) erhält man analog die Bis-*O,S*-acetale **5**.

