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Towards a Robust and Reliable Method for the Reduction of Functionalized Sulfoxides

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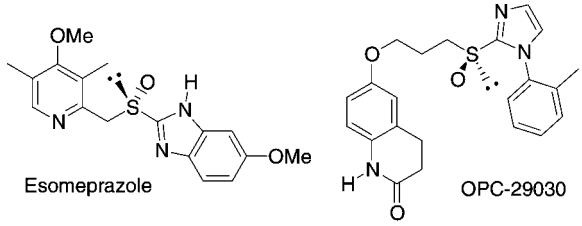
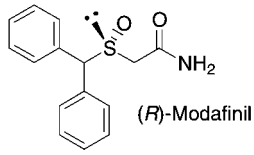
Abstract:

Several functionalized sulfoxides in the modafinil series, which bear another reducible function, were chemoselectively reduced to thioethers using the KI/AcCl system.

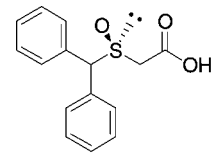
Introduction

Organosulfur compounds that contain a chirogenic sulfoxide unit play an important role in asymmetric synthesis (as either chiral auxiliaries or ligands), or in pharmaceutical chemistry.[1,2] For example, esomeprazole (a powerful proton pump inhibitor used as an antiulcer agent), OPC-29030 (a platelet adhesion inhibitor), or (*R*)-modafinil (an atypical psychostimulant recently approved in the United States as a treatment for excessive daytime sleepiness associated with narcolepsy and work-shift sleep disorder), among others, exhibit such a chiral functional group.

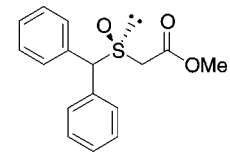




As part of our ongoing studies on the synthesis (*R*)-modafinil and its derivatives, we previously described both resolution[3] and enantioselective methods.[4] (*R*)-Modafinil can be obtained by resolution using either chiral chromatography or preferential crystallization of its precursor, (*RS*)-modafinic acid.[3,5] However, such nondynamic resolution procedures suffer from a major drawback with respect to enantioselective syntheses, i.e. the inherent limitation to 50% maximum theoretical yield. In order to improve the maximum theoretical yield, one can either racemize the unwanted enantiomer during the resolution process (dynamic resolution) or after isolation, allowing it to be submitted to the resolution procedure again. As the sulfoxide function of modafinil and its derivatives is configurationally stable in both resolution conditions, we focused on the study of the *ex situ* racemization of (*S*)-modafinil and its derivatives, modafinic acid and methyl 2-(diphenylmethylsulfinyl)acetate (DMSAM).



(*S*)-Modafinic acid



(*S*)-DMSAM

The more interesting substrate for this purpose is modafinic acid, which can be resolved by preferential crystallization using the AS3PC method.[6]

Our first attempts using reported racemization methods for chiral sulfoxides (i.e., thermal activation,[7] acid[8] or base[9] catalysis) were unsuccessful, owing mainly to the *S*-benzhydryl labile bond that is easily cleaved in these rather drastic conditions. We therefore turned to a second strategy based on a reduction/oxidation sequence (Scheme 1).

Since the oxidation by H_2O_2 had previously been optimized on an industrial scale,[10] our primary goal was to develop a reliable method for reducing a sulfoxide unit with complete chemoselectivity in the presence of reducible functions such as carboxylic acid, amide, and ester, as well as the labile benzhydryl unit. Indeed, most of the reported sulfur deoxygenation methods do not show any chemoselectivity when other reducible functions are present on the same molecule.[11–13] From the many available methods, we selected the reduction systems using activated iodide salts or sodium borohydride (Table 1).

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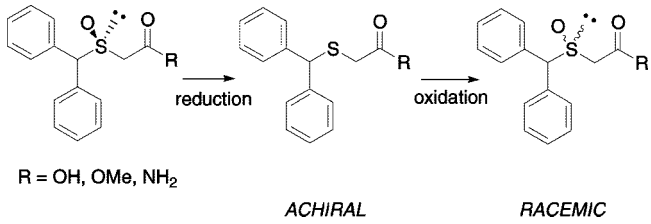
Scheme 1. **Reduction/oxidation sequence**



However, NaI/$(COCl)_2$ and $NaBH_4/I_2$ are not convenient for the reduction of modafinic acid, as they can react with the carboxylic acid function, and were therefore discarded from this study.

Results and Discussion

Allenmark developed in 1966 a reductive system based on the use of potassium iodide and acetyl chloride, primarily intended as an analytical tool for sulfoxide assay.[14] This system was successfully used on a sulfoxide compound having structural similarities to modafinic acid (Table 1, line 1). We applied the same experimental procedure (Scheme 2) and set up a workup (quenching with ice/water, followed by addition of solid sodium thiosulfate until disappearance of the brown coloration and extraction) because the initial analytical method did not require isolation of the obtained thioether.

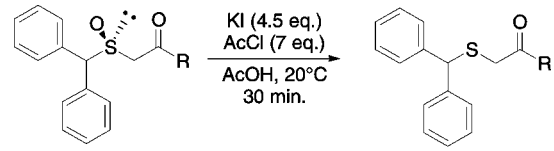
Thioethers were obtained from modafinic acid and modafinil in excellent isolated yields (87−88%) on a 2 mmol scale in 45 mL of acetic acid. The reduction of DMSAM gave an even better yield of 95%. No reduction of the acid, amide, or ester function was observed. These encouraging results proved that the deoxygenation of our substrates was efficient and chemoselective using this method. Fractional factorial design of experiments was used to optimize temperature and concentrations of the modafinic acid, KI, and AcCl, confirming that the more efficient procedure relied on the initial Allenmark conditions (Scheme 2). Lowering the amount of KI (and, to a lesser degree, of acetyl chloride), or increasing the reaction temperature, led to an increased formation of benzhydrol as a side product. Nevertheless in order to scale up the reaction, we needed to improve the productivity of the method. As the solubility of the (benzhydrylthio)acetic acid is higher than that of modafinic acid, we devised an alternative procedure using a saturated solution of sulfoxide and KI, in which the solid reagents slowly dissolve as the reaction proceeds. The concentration of sulfoxide and KI can therefore be kept constant throughout most of the reaction, and the acetyl chloride is always in large excess to the dissolved sulfoxide, preventing the formation of benzhydrol.

Table 1. **Selected literature conditions for sulfoxide reduction**

method	R^1	R^2	yield (%)	ref
KI/AcCl	$C_6H_5-CH_2$	$(CH_2)_2-COOH$	quant.	14
NaI/$(COCl)_2$	$C_6H_5-CH_2$	$C_6H_5-CH_2$	99	15
KI/PTSA[a]	methionine sulfoxide		93	16
NaI/$TiCl_4$	$C_6H_5-CH_2$	$C_6H_5-CH_2$	90−98	17
$NaBH_4/I_2$	$C_6H_5-CH_2$	$C_6H_5-CH_2$	98	18

[a] *p*-Toluenesulfonic acid.

Scheme 2. **Reduction of modafinil derivatives using KI/AcCl system**



First, the amounts of potassium iodide and acetyl chloride were optimized to 2.25 equiv and 1.75 equiv, respectively, for the reduction of 15 g of modafinic acid in 450 mL of acetic acid (12×10^{-2} mol·L^{-1}) (Figure 1). Then the amounts of modafinic acid, potassium iodide, and acetyl chloride were increased, the solvent volume being kept constant (Figure 1).

Up to 30 g of modafinic acid was reduced in 450 mL of solvent (24×10^{-2} mol·L^{-1}) without any decrease of the yield. This improved procedure uses a much lower amount of potassium iodide and acetyl chloride and operates at higher concentration than the initial procedure devised by Allenmark. After addition of a water/ice mixture, the iodine generated during the reaction is reduced by addition of sodium thiosulfate, and the solid

(6) The initial system (solvent + substrate) containing an enantiomeric excess (e.g. of *R*) is heated at T_B so that only the *S*-enantiomer in default is completely dissolved. Thus, the slurry is composed of crystals of the enantiomer in excess in thermodynamic equilibrium with its saturated solution. The system (a suspension and not a solution) is therefore self-seeded by crystals of the pure enantiomer; one-third of the future crops is already present in the system as fine crystals (an *in situ* wet grinding can be applied if necessary). The suspension is then submitted to an adapted cooling program and stirring mode without any need of additional seeds so that the crystal growth is favoured instead of an uncontrolled secondary nucleation. At the end of the entrainment, the crystals of the *R*-enantiomer are collected by filtration or centrifugation, and the mother liquor contains an excess of the antipode *S*. A mass of racemic mixture, equal to the collected mass of *R* crystals, is then added to the mother liquor which is then reheated at T_B. This process can be repeated as many times as necessary, allowing by alternative crystallization of *R* and *S* enantiomers the resolution of any quantities of racemic mixture crystallizing as a stable conglomerate. (a) Coquerel, G.; Petit, M.-N.; Bouaziz, R. Method of Resolution of Two Enantiomers by CrystallizationPatent WO9508522. March 30, 1995. (b) Coquerel, G. Preferential Crystallization In *Novel Optical Resolution Technologies*; Sakai, K., Hirayama, N., Tamura, R. Eds.;Topics in Current Chemistry 619; Springer GmbH: Berlin, Heidelberg, 2007; pp 1−50.
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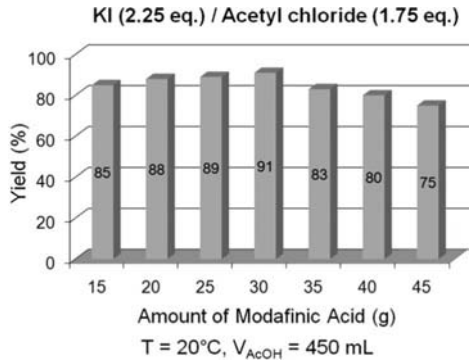


Figure 1. **Reduction of modafinic acid at constant volume with KI/AcCl system for 1 h.**

modafinic acid is collected by filtration, dissolved in dichloromethane, washed with a sodium thiosulfate solution, and concentrated *in vacuo*. Simple washing of the resulting solid with a water/cyclohexane mixture (5:1 v/v) allowed the obtention of pure (benzhydrylthio)acetic acid. After oxidation with H_2O_2, the resulting racemic sulfoxide (71% overall yield from the optically pure modafinic acid) was suitable for resolution by means of preferential crystallization using the AS3PC procedure.[19]

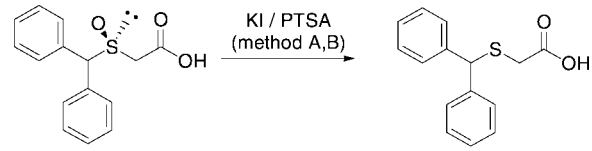
In addition we carried out the reduction of DMSAM in the same conditions[20] on up to 6 g scale in 45 mL of acetic acid and were delighted to obtain a quantitative yield (99%). However, attempts to reduce modafinil were not as successful as when using "unoptimized" Allenmark conditions (Scheme 2). Indeed, the reaction was performed four times and gave a yield ranging from 52 to 76% along with various amounts of benzhydrol, benzophenone, and benzhydrylacetate, showing a lower efficiency for this substrate than the two others investigated in this study.

The system described by Fujiki[16] using potassium iodide and a solid Brønsted acid as activating agent is an appealing alternative to avoid the use of solvent (Scheme 3). Indeed, the reaction proceeds upon grinding the three reagents in the solid state (Scheme 3).

The reduction of 5 g of modafinic acid using a Brønsted acid as the activating agent without any solvent and under mechanical stirring (method A, Scheme 3) gave 78% yield. Attempts to decrease the duration of the reaction by either microwave or ultrasound activation resulted in low yields and partial or complete degradation of the starting material. We also wanted to assess this deoxygenating system in acetic acid (method B, Scheme 3). Thus 2.5 g of sulfoxide was reduced with 80% yield in 1 h. The use of solvent significantly decreased the reaction time from 18 to 1 h without loss of efficiency.

Activation of NaI by $TiCl_4$ as a Lewis acid was also evaluated by using the protocol described by Balicki:[17] reduction of modafinic acid gave 77% yield in THF within 20 min. Although the NaI/$TiCl_4$ combination decreased significantly the reaction time, the isolation of thioether was difficult because of the formation of TiO_2 after hydrolysis. Furthermore, decomposition of modafinic acid into benzhydrol occurred when THF was replaced by acetic acid.

Scheme 3. **Reduction of modafinic acid using KIPTSA system**



Method A: KI (1.5 eq.), PTSA (2 eq.), 20°C, 18 h 78%
Method B: KI (2 eq.), PTSA (2.25 eq.), AcOH, 20°C, 1 h 80%

Conclusions

In this study, we have tested a series of reported methods for the deoxygenation of sulfoxides on modafinic derivatives that are important compounds in pharmaceutical area. It has been shown that a careful adaptation of the analytical Allenmark conditions[14] into a preparative procedure was the best method to reduce chemoselectively the sulfoxide function of polyfunctionalized materials, bearing both a labile benzhydryl moiety and another reducible function. The only drawback, high dilution, can be circumvented by an elegant use of the solubility of the resulting thioether, allowing multigram-scale reduction. In addition, a solvent-free method seems a powerful alternative, which remains to be optimized.

Experimental Section

General Methods. Infrared spectra were recorded on a Perkin-Elmer 16 PC FT-IR spectrometer, and NMR spectra were recorded on a Brüker Avance 300 (300 MHz). ^{13}C NMR spectra were determined with complete proton decoupling. Proton and carbon chemical shifts are reported in ppm (δ) downfield from signal of residual solvent in which NMR analysis was performed. High-pressure liquid chromatography (HPLC) was performed on a Thermoseparation products P100.

Reduction of (*S*)-(+)-Modafinic Acid. In a thermostatted 500 mL double jacket vessel, (*S*)-(+)-modafinic acid (25 g, 0.092 mol, 1 equiv) was partially dissolved in glacial acetic acid (450 mL) at 20 °C, then potassium iodide (68.85 g, 0.414 mol, 2.25 equiv) was added followed by acetyl chloride (11.34 mL, 0.161 mol, 1.75 equiv). Instantaneously, iodine was formed and strongly colored the mixture. After 1 h the reaction was quenched with 0.5 L of water + 0.5 L of ice with precipitation of thioether. Iodine was reduced with sodium thiosulfate until disappearance of the brown color. The precipitate was gathered on a sintered glass filter, then dissolved in CH_2Cl_2 (200 mL) in a 500 mL separatory funnel. The organic layer

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(20) Since DMSAM is a viscous liquid at room temperature, the workup was modified as follows: after addition of the water/ice mixture and destruction of the iodine formed with solid sodium thiosulfate, the sulfide was extracted with CH_2Cl_2 and washed with aqueous thiosulfate; the organic layer was dried on $MgSO_4$ and concentrated *in vacuo* to give a yellowish oil.

was washed with aqueous $Na_2S_2O_3$ solution (10 mL) to get ride of traces of iodine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification step was performed by washing with a 150 mL mixture of water/cyclohexane (5:1 v/v) in a 500 mL round-bottom flask. A white solid was filtered and dried at 60 °C to yield (benzhydrylthio)acetic acid (21.14 g, 89%). White solid; m.p.:128 °C; IR (cm^{-1}): $\nu_{C=O}$: 1697 and ν_{C-O}: 1303; ^1H NMR(300 MHz, DMSO-d_6): δ 12.66 (brs, ^1H, CO_2H); 7.24−7.45 (m, 10H, Ar−H); 5.39 (s, 1H, CH); 3.07 (s, 2H, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.1, 141.2, 129.0, 128.7, 128.5, 128.3, 127.9, 127.6, 53.2, 34.0. HPLC analysis (Inertsil ODS2 (15 cm × 4.6 mm i.d.); 1 mL/min; λ = 220 nm; eluent: acetonitrile 50% (v/v); phosphate buffer 0.05 mol·L^{-1} pH= 2.3, 50% (v/v)): t_R = 7.6 min).

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