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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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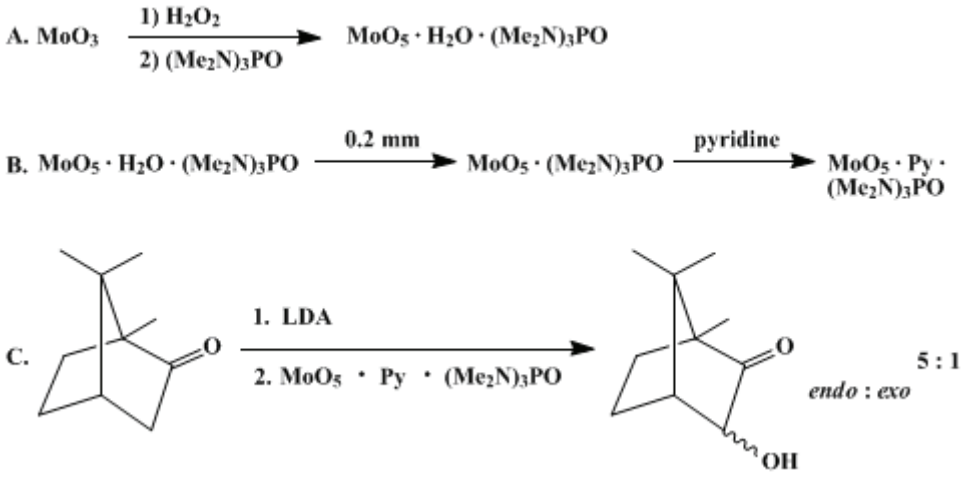
HYDROXYLATION OF ENOLATES WITH OXODIPEROXYMOLYBDENUM(PYRIDINE) (HEXAMETHYLPHOSPHORIC TRIAMIDE), MoO_5·Py·HMPA (MoOPH): 3-HYDROXY-1,7,7-TRIMETHYLBICYCLO[2.2.1] HEPTAN-2-ONE

[Bicyclo[2.2.1]heptan-2-one, 3-hydroxy-1,7,7-trimethyl-]



Submitted by Edwin Vedejs and S. Larsen[1].
Checked by Gordon Hill and K. Barry Sharpless.

1. Procedure

Caution! Reactions using peroxides should be performed behind a safety shield to minimize explosion hazards (Note 1). Hexamethylphosphoric triamide (HMPA) and methanol are toxic and must be handled in a hood (Note 2).

A. *Oxodiperoxymolybdenum(aqua)(hexamethylphosphoric triamide), MoO_5·H_2O·HMPA.*[2] A 500-mL, three-necked flask is fitted with an internal thermometer and a mechanical paddle stirrer. The flask is charged, with stirring, with 30 g (0.2 mol) of molybdenum oxide (MoO_3) (Note 3) and 150 mL of 30% hydrogen peroxide (H_2O_2) (Note 4). An oil bath equilibrated at 40°C is placed under the rection mixture and heating is continued until the internal temperature reaches 35°C. The heating bath is removed and replaced by a water bath to control the mildly exothermic reaction so that an internal temperature of 35–40°C is maintained. After the initial exothermic period (approximately 30 min), the reaction flask is placed in the 40°C oil bath and stirred a total of 3.5 hr to form a yellow solution with a small amount of suspended white solid (Note 5).

After cooling to 20°C, the solution is filtered through a 1-cm mat of Celite pressed into a coarse-porosity sintered-glass filter. The yellow filtrate is cooled to 10°C (with an ice bath and magnetic stirring) and 37.3 g (0.21 mol) of hexamethylphosphoric triamide (HMPA) (Note 2) is added dropwise over 5 min, resulting in the formation of a yellow crystalline precipitate. Stirring is continued for a total of 15 min at 10°C, and the product is filtered using a Büchner funnel and pressed dry with a spatula. After 30 min in the funnel (aspirator vacuum), the filtercake is transferred to a 1-L Erlenmeyer flask. Methanol (20 mL) is added and the mixture is stirred in the 40°C bath. More methanol is slowly added until the crystals have dissolved. Cooling the saturated solution in the refrigerator gives yellow needles. The crystal mass is broken up with a spatula, the product is filtered and washed with 20–30 mL of cold methanol to give MoO_5·H_2O·HMPA, 46–50 g (59–64%) (Note 5) and (Note 6).

B. *Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) MoO_5·Py·HMPA=MoOPH*.[2] The recrystallized product from above is dried over phosphorus oxide (P_2O_5) in a vacuum desiccator, shielded from the light, for 24 hr at 0.2 mm to give a somewhat hygroscopic yellow solid, MoO_5·HMPA. A 36.0-g (0.101 mol) portion of MoO_5·HMPA is dissolved in 150 mL of dry tetrahydrofuran (THF) (Note 7) and the solution is filtered through a Celite mat, if needed, to remove a small amount of amorphous precipitate. The filtrate is then stirred magnetically in a 20°C water bath while 8.0 g (0.101 mol) of dry pyridine (Note 8) is added over 10 min. The crystalline, yellow product is collected on a Büchner funnel, washed with dry tetrahydrofuran (25 mL) and anhydrous ether (200 mL) and dried in a vacuum desiccator (1 hr, 0.2 mm) to yield 36–38 g (51–53% overall from MoO_3) of finely divided yellow crystalline MoO_5·Py·HMPA (Note 9).

The product is stored in a dark glass jar inside a second container partly filled with Drierite, and the container is kept in the refrigerator. Before opening the jar, the container is allowed to warm to room temperature to avoid condensation of moisture inside. Properly stored MoOPH is a freely flowing crystalline powder and can be used over a period of several months (Note 10).

C. *Hydroxylation of camphor*: *1,7,7-trimethyl-3-hydroxybicyclo*[*2.2.1*]*-heptan-2-one*. A solution of lithium diisopropylamide (LDA) is prepared as follows: A 250-mL, three-necked flask and magnetic stirrer are flame-dried under a slow stream of nitrogen. After cooling, the flask is charged with 40 mL of approximately 1.5 *M* butyllithium in hexane (Note 11) under nitrogen flow using a syringe. The flask is cooled in a dry ice–acetone bath and 9.2 mL (66 mmol) of diisopropylamine (Note 8) is added by syringe, followed by 40 mL of dry THF (Note 7). The resulting LDA solution is allowed to reach room temperature under a slow flow of nitrogen. For titration, 0.312 g (2 mmol) of menthol is dissolved in 5 mL of dry THF with a few crystals of phenanthroline (Note 12) under nitrogen flow at −70°C. The LDA solution is added dropwise (using a nitrogen-purged syringe) to the stirred menthol solution until the yellow color of menthoxide–phenanthroline turns to the rust color of LDA–phenanthroline (2.67 mL of LDA solution is needed, 0.75 M).

An aliquot of 47.1 mL (35.3 mmol) of LDA solution is transferred by nitrogen-filled syringe into a nitrogen-swept, 500-mL, three-necked flask equipped with a magnetic stirrer and a device for addition of solid MoOPH. The latter is an L-shaped glass tube with male joints at each end. A round-bottomed flask containing 20.9 g (48.1 mmol) of MoOPH is wired to the L-tube, which is wired to the reaction vessel at such an angle that rotation of the L-tube causes addition of MoOPH to the enolate. The MoOPH container is temporarily suspended using clamps, and the entire apparatus is maintained under a slow flow of nitrogen. After the LDA solution is cooled in a dry ice–acetone bath, 4.88 g (32.1 mmol) of camphor (Note 13) in 200 mL of dry THF is added dropwise with stirring over 0.5 hr. Then 10 min later the reaction is placed in a dry ice–carbon tetrachloride bath and after 15 min the MoOPH is added over 1–2 min by rotating the L-tube and gently tapping it to dislodge the powder. The reaction immediately turns orange and eventually fades to a pale tan (Note 14). Stirring is continued at approximately −23°C for 20 min, and the reaction is quenched by adding 100 mL of saturated aqueous sodium sulfite (Na_2SO_3). Vigorous stirring is maintained and the mixture is allowed to warm to room temperature. After 10 min at 20°C, the mixture is shaken with 100 mL of saturated sodium chloride solution, and the aqueous layer is extracted twice with 70 mL of ether. The combined organic layers are washed once with a mixture of 50 mL of 10% aqueous hydrochloric acid and 50 mL of saturated sodium chloride solution. The hydrochloric acid–sodium chloride aqueous layer is back-extracted with 50 mL of ether, and the combined organic layers are dried over $MgSO_4$, filtered, and evaporated under an aspirator to yield a blue–green oil. Residual molybdenum salts are removed by filtration over 100 g of silica gel (Note 15) in a 2.5-cm column wet-packed and eluted with 1:1 ether–hexane. The product is eluted with approximately 750 mL of ether–hexane. Evaporation (aspirator) yields a white semisolid, which is crystallized from 15 mL of hexane at −20°C and collected by washing with hexane cooled to −70°C. The mother liquors are crystallized in a similar manner from 2-4 mL of hexane to give a total of five crops, 4.14 g (77%) of colorless needles, mp 170–183°C, a 5:1 mixture of endo : exo isomers (Note 16). Recrystallization did not affect the isomer ratio (literature mp; endo, 192–195°C, exo, 210–211° C).[3]

2. Notes

1. There are no reports that $MoO_5 \cdot H_2O \cdot HMPA$, $MoO_5 \cdot HMPA$, or $MoO_5 \cdot Py \cdot HMPA$ are shock-sensitive. On heating on a hot plate, the crystalline solids ignite and burn, but do not detonate. These compounds can be stored in a refrigerator with precautions to exclude light. Prolonged storage at room temperature in the light may cause decomposition with gas evolution and an exotherm sufficient to crack a glass container.
2. Hexamethylphosphoric triamide is toxic and a suspected carcinogen.
3. Molybdenum oxide was obtained from Mallinckrodt, Inc.
4. Hydrogen peroxide was obtained from Mallinckrodt, Inc.
5. Failure to maintain the internal temperature below 40°C results in formation of amorphous, insoluble products.
6. The purity of this material is decisive because the quality of subsequent products cannot be improved by recrystallization because of some decomposition.
7. Tetrahydrofuran was distilled from sodium–benzophenone and stored under nitrogen.
8. Pyridine was distilled from barium oxide.
9. The product melts with vigorous evolution of gas at 103–105°C.
10. Prolonged exposure to light, or failure to control exothermic reactions in prior steps, results in a sticky product that smells of pyridine. No method for purifying partly decomposed MoOPH has been found, and "sticky" product should not be used for enolate hydroxylation. Suspect material can be decomposed by stirring with aqueous sodium sulfite (Na_2SO_3) solution.
11. Butyllithium was obtained from the Foote Mineral Company.
12. Menthol and phenanthroline were obtained from the Aldrich Chemical Company, Inc.
13. Camphor was obtained from Eastman Organic Chemicals.
14. The colors are somewhat substrate-dependent. Some enolate hydroxylations acquire a green–blue color.
15. Silica gel, 60–200 mesh, was obtained from Davison Chemical Division.
16. The endo : exo ratio is determined by comparing the NMR CHOH signal areas of the endo (4.21 ppm, d, $J = 4.8$ Hz) and exo (3.75 ppm, br s) isomers.

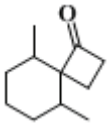
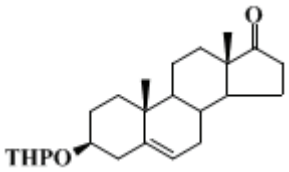
3. Discussion

Enolate hydroxylation is a problem of long standing. Direct oxygenation succeeds with the fully substituted enolates of certain α,α-disubstituted ketones[4] and a variety of carboxylic acid derivatives (ester anions, acid dianions, amide anions),[5] but the reaction of enolates, $RCH{=}C(O^-)R'$ or $CH_2{=}C(O^-)R'$, with oxygen results in complex products of overoxidation. The stable molybdenum peroxide reagent $MoO_5 \cdot Py \cdot HMPA$ (MoOPH),[2] first prepared by Mimoun, allows the conversion of $RCH{=}C(OLi)R'$ into $RCH(OH)COR'$ in generally good yields (Table I).[6] In some cases, the α-diketone is formed as a by-product. The MoOPH reagent also hydroxylates branched or unbranched ester, amide, and nitrile anions.[6,7] For unknown reasons, MoOPH hydroxylations seldom give complete conversion of enolates into products, and recovery of 5–15% of the starting carbonyl substrate is to be expected.

Methyl ketone enolates are hydroxylated by MoOPH, but the products tend to undergo condensation with the starting enolate, resulting in poor yields.[6] Methyl ketone hydroxylation has been described by Moriarty, using $C_6H_5I{=}O/CH_3OH/OH^-$.[8]

TABLE I
CONVERSION OF $RCH{=}C(OLi)R'$ INTO $RCH(OH)COR'$

Ketone	Oxidation Temperature (°C)	α-Hydroxy Ketone (%)	α-Diketone (%)
Valerophenone	−22	60	13
	−44	62	<2
Deoxybenzoin	−44	34	26
Isobutyrophenone	−22	65	
α-Tetralone	−22	48	
Camphor	−22	77	<2
	−22 → 60, 16 hr	44	11

4,4-Diphenylcyclo-hexanone	−22	46	
2-Phenylcyclohexanone	−44	70	<5
	−22	81	
	−44	75 (16 α-OH)	

Several indirect methods for conversion of enolates into α-hydroxycarbonyl compounds are known. The most versatile is the reaction of enol silanes with *meta*-chloroperbenzoic acid developed by Rubottom.[9] This technique is often successful with substrates that are oxidized inefficiently by the MoOPH technique. Another alternative is to use the oxaziridine reagents developed by Davis et al.[10]

The method described for MoOPH hydroxylation of the camphor enolate is representative for ketone enolate hydroxylations, but optimization in each individual case to determine the best temperature and concentration is recommended. Large-scale oxidations may benefit from addition of reagent in several portions over time, and enolates that are sensitive to self-condensation may give higher yields if enolate is added slowly to excess MoOPH.

References and Notes

1. Department of Chemistry, University of Wisconsin, Madison, WI 53706.
2. Mimoun, H.; Seree de Roche, I.; Sajus, L. *Bull. Soc. Chim. Fr.* **1969**, 1481.
3. Thoren, S. *Acta Chem. Scand.* **1970**, *24*, 93.
4. Bailey, E. J.; Barton, D. H. R.; Elks, J.; Templeton, J. F. *J. Chem. Soc.* **1962**, 1578; Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294; Gardner, J. N.; Popper, T. L.; Carlon, F. E.; Gnoj, O.; Herzog, H. L. *J. Org. Chem.* **1968**, *33*, 3695.
5. Konen, D. A.; Silbert, L. S.; Pfeffer, P. E. *J. Org. Chem.* **1975**, *40*, 3253; Moersch, G. W.; Zwiesler, M. L. *Synthesis* **1971**, 647; Adam, W.; Cueto, O.; Ehrig, V. *J. Org. Chem.* **1976**, *41*, 370; Wasserman, H. H.; Lipshutz, B. H. *Tetrahedron Lett.* **1975**, 1731; Cuvigny, T.; Hullot, P.; Larchevêque, M.; Normant, H. *C. R. Hebd. Seances Acad. Sci., Ser. C.* **1975**, *218*, 251; Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.
6. Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.
7. Vedejs, E.; Telschow, J. E. *J. Org. Chem.* **1976**, *41*, 740.
8. Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett.* **1981**, *22*, 1283.
9. Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319; Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427; Rubottom, G. M.; Marrero, R. *J. Org. Chem.* **1975**, *40*, 3783.
10. Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402; Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

silica gel

Oxodiperoxymolybdenum(aqua)(hexamethylphosphoric triamide), $MoO_5 \cdot H_2O \cdot HMPA$

molybdenum oxide (MoO_3)

hydrogen peroxide (H_2O_2)

$MoO_5 \cdot H_2O \cdot HMPA$

Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) $MoO_5 \cdot Py \cdot HMPA$=MoOPH

$MoO_5 \cdot HMPA$

$MoO_5 \cdot Py \cdot HMPA$

MoOPH

LDA

$MoO_5 \cdot Py \cdot HMPA$ (MoOPH)

meta-chloroperbenzoic acid

OXODIPEROXYMOLYBDENUM(PYRIDINE)(HEXAMETHYLPHOSPHORIC TRIAMIDE), $MoO_5 \cdot Py \cdot HMPA$(MoOPH)

menthoxide

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

sodium sulfite (7757-83-7)

sodium chloride (7647-14-5)

oxygen (7782-44-7)

barium oxide

nitrogen (7727-37-9)

pyridine (110-86-1)

Benzophenone (119-61-9)

sodium (13966-32-0)

hydrogen peroxide (7722-84-1)

menthol (15356-60-2)

$MgSO_4$ (7487-88-9)

camphor (21368-68-3)

butyllithium (109-72-8)

Tetrahydrofuran,
THF (109-99-9)

α-Tetralone (529-34-0)

hexane (110-54-3)

deoxybenzoin (451-40-1)

2-phenylcyclohexanone (1444-65-1)

oxaziridine

phenanthroline

hexamethylphosphoric triamide (680-31-9)

isobutyrophenone (611-70-1)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

3-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one,
Bicyclo[2.2.1]heptan-2-one, 3-hydroxy-1,7,7-trimethyl-,
1,7,7-trimethyl-3-hydroxybicyclo[2.2.1]-heptan-2-one (21488-68-6)

molybdenum oxide

phosphorus oxide (1314-56-3)

molybdenum peroxide

Valerophenone (1009-14-9)

4,4-Diphenylcyclo-hexanone (4528-68-1)

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