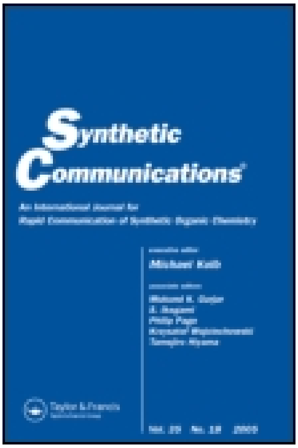

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MMPP (Magnesium Monoperoxyphthalate) in Acetonitrile; A New Approach to the Synthesis of Lactones via Baeyer-Villiger Oxidation of Cyclic Ketones

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MMPP (MAGNESIUM MONOPEROXYPHTHALATE) IN ACETONITRILE; A NEW APPROACH TO THE SYNTHESIS OF LACTONES *VIA* BAEYER-VILLIGER OXIDATION OF CYCLIC KETONES

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Abstract: A variety of unsubstituted and mono- or di-substituted cycloalkanones can be oxidised with modest excess of magnesium monoperoxyphthalate hexahydrate in acetonitrile to produce the corresponding lactones in a facile, selective, and high yielding manner.

Magnesium monoperoxyphthalate, *MMPP*, has been manufactured on an industrial scale as a bleaching agent in a detergent composite owing to its mild oxidative property.[1] The laboratory reagent,[2] available as the hexahydrate,[3] is a free-flowing white powder and can be utilised much more safely than conventionally widely-used *mCPBA*, which is shock-sensitive and potentially explosive in nature. *MMPP* is therefore a likely candidate for an alternative to *mCPBA* as a safe, inexpensive, and easily accessible peroxygen source in organic synthesis. Heaney's

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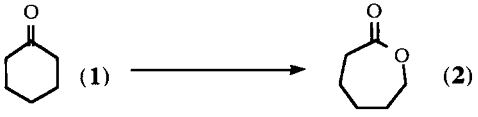
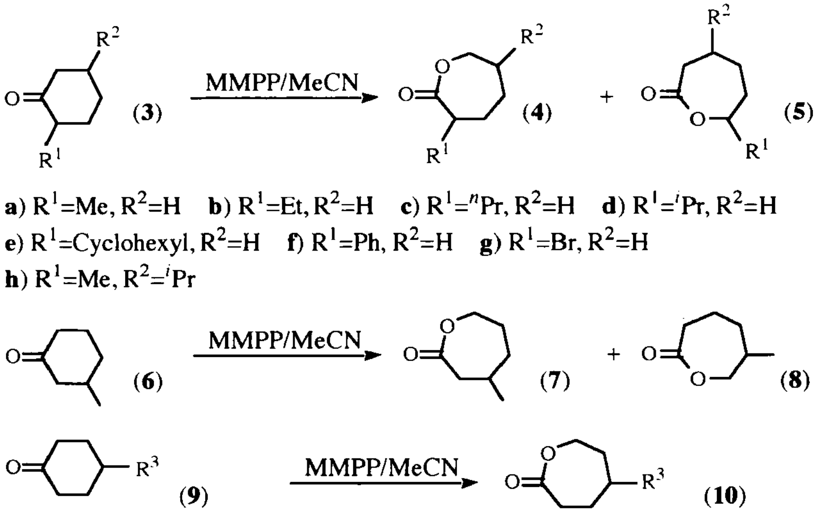
group first called attention to the applicability of *MMPP* to typical oxygen-donating type reactions including epoxidation, Baeyer-Villiger reaction, sulfide-to-sulfoxide and amine-to-N-oxide oxidations under semiaqueous or phase-transfer conditions.[4] Since then many interesting facets of *MMPP* chemistry have been documented,[5] but *MMPP* chemistry in a water-free medium has hitherto been unexplored. This article describes a novel use of *MMPP* in acetonitrile since this procedure offers a convenient tool for synthesizing a variety of seven-membered lactones *via* Baeyer-Villiger oxidation[6] of cyclohexanone and its derivatives (Scheme 1 and 2).

Scheme 1



The oxidations of cyclic ketones were readily carried out by adding *MMPP* in one (Method A) or several portions (Method B), depending on the concentration of *MMPP* used,[7] to a mixture of the ketone and acetonitrile and by efficiently stirring the resultant milky suspension. Table 1 collects together the reaction conditions, yields, and relative proportions of the structural isomers of lactones. Thus, the *MMPP/MeCN* system obviously works in an efficient and high yielding manner. For example, the excellent yield of ε-caprolactone **2** in the current case (90% isolated yield; Scheme 1, Entry 1) can be favourably compared to that obtained by Heaney's procedure (57% GC yield).[4] Lactones can be produced from 2- (Entries 2-9), 3- (Entry 10) and 4-substituted cyclohexanones (Entries 11-12) in excellent to quasi quantitative yields (Scheme 2). The regiochemical outcomes of the competing rearrangements of skeleton carbons attached to the carbonyl groups in the 2-substituted cyclohexanone **3** series (Scheme 2, Entries 2-9), *viz.* methine *vs.* methylene migration, are in keeping with the expected relative stabilities of the migrating carbons. In addition, our observations that in contrast to the susceptibility of norcamphor which gives a mixtures of the lactones in 73% isolated yield, inertness of 2-*t*-butylcyclohexanone and camphor towards *MMPP* may be explained by the unfavourable steric environment around their oxo-functionalities blocking attack of the bulky peracid[3b] on them. Accordingly, these facts coupled with the tabulated results indicate that the oxidative susceptibility of ketones under these conditions is governed by electrosteric factors.

Scheme 2



a) R^1=Me, R^2=H **b)** R^1=Et, R^2=H **c)** R^1=^{n}Pr, R^2=H **d)** R^1=^{i}Pr, R^2=H
e) R^1=Cyclohexyl, R^2=H **f)** R^1=Ph, R^2=H **g)** R^1=Br, R^2=H
h) R^1=Me, R^2=^{i}Pr

a) R^3=Me **b)** R^3=^{t}Bu

MMPP can be successfully utilised for ring enlargement of cyclopentanone by Method A (Scheme 3), but larger ring ketones (seven or more membered) resist oxidation. Further work on technical improvements to overcome these limitations are in progress.

Scheme 3

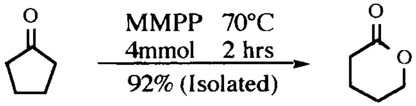


Table 1. Oxidation of Cyclohexanones with *MMPP* in Acetonitotrile

Entry No.	Ketone	*MMPP* (mmol)	Temp (°C)	Time (hr)	Yields (%)[a)]	Lactone	Isomers ratios[b)]
1	(**1**)	3	60	2	90	(**2**)	
2	(**3a**)	4	70	2	92	(**4a**)+(**5a**)	5:95
3	(**3b**)	4	70	2	80	(**5b**)	
4	(**3c**)	4	70	2	94	(**5c**)	
5	(**3d**)	4	70	2	85	(**5d**)	
6	(**3e**)	5	70	4	83	(**4e**)+(**5e**)	6:94
7	(**3f**)	5	70	4	56	(**5f**)	
8	(**3g**)	6	reflux	6	55[c)]	(**4e**)	
9	(**3h**)	5	80	4	83	(**5h**)	
10	(**6**)	4	70	2	97	(**7**)+(**8**)	53:47
11	(**9a**)	3	60	2	87	(**10a**)	
12	(**9b**)	4	70	2	93	(**10b**)	

a) Isolated yields of chromatographically purified lactones based on starting cyclohexanones. b) Determined by NMR. c) GC yields.

Experimental Section

The ^1H NMR spectra were recorded with a JNM FX-200 (200 MHz) spectrometer using deuteriochloroform solution with TMS as an internal standard. The IR spectra were measured on a JASCO A-100 spectrophotometer as thin films (neat) or KBr disks. Analytical gas chromatography was performed on a Shimadzu GC-14B instrument equipped with a flame ionization detector through a 2 mx5mmØ glass column packed with 20% PEG-20M on Chromosorb WAW-DMCS (60-80 mesh) and interfaced with a Shimadzu Chromatopac C-R6A integrator, with temperature programming. Wakogel B-5F was used for the preparative thin layer chromatography. Magnesium monoperoxyphthalate hexahydrate was purchased from *Tokyo Chemical Industry Co., Ltd.*, and its purity was determined by iodometry (*ca.* 86%). Ketones, except for the following three, were commercial chemicals and were employed as received. 2-Ethylcyclohexanone was prepared by the oxidation of the parent alcohol with aqueous sodium dichromate.[8] 2-Isopropylcyclohexanone was prepared by Raney nikel[9] catalysed hydrogenation of 2-isopropylphenol under modified conditions (H_2 pressure 100 kg/cm^2, 110 °C, 30 h) of original method[10] followed by the sodium dichromate oxidation[8] of the resultant alcohol. 2-Bromocyclohexanone was obtained by bromination of cyclohexanone.[11] The purities of all ketones were checked by GC just before use. Acetonitrile was distilled and stored over molecular sieves.

Oxidation Procedures.— General oxidation procedures were as follows. A ketone (2 mmol), acetonitrile (10mL), and a Teflon-coated magnetic stirring bar were placed in a 30 mL round-bottom two-necked flask equipped with a glass stopper and *ca.* 25 cm long reflux condenser. The mixture was heated in a thermostatic oil-bath at 60 °C to reflux temperature with stirring. To this was added *MMPP* (3-6 mmol) in one (Method A; Entries 1-5 and 10-12) or several portions[7] at constant intervals (Method B; Entries 6-9), upon which loose replacement of the glass stopper followed every addition. After completion of the addition of *MMPP*, the vigorous stirring of the resultant mixture was continued for two hours. After cooling to room temperature, the reaction mixture was filtered through a sintered glass funnel, and the residue was thoroughly washed with portions of dry ether (*in toto* 100 mL). Concentration of the combined filtrate on a rotary evaporator *in vauo* followed by separation by preparative TLC afforded the single lactone (Entries 1, 3-5, 7-9, 11, and 12) or a mixture of the structural isomers of the lactones (Entries 2, 6, and 10), the ratios of which were determined by NMR. If the lactone was contaminated with a trace of any oxidant residue, the satisfactorily pure (GC, NMR, and TLC) product was obtained by repeated chromatography.

References and Notes

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2 *MMPP* is commercially available from *Tokyo Chemical Industry Co., Ltd., Aldrich Chemical Co., Ltd.*, and *Interox Chemicals Ltd.*

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7 It appears expedient to add *MMPP* in portions as described in *Method B* in cases where a large amount of the reagent is employed. If this is not done, formation of a solid crust on the wall of the reaction vessel is sometimes observed, which leads not only to a decrease in conversion of the ketone and the yield of the lactone, but also to poor reproducibility of the reaction.

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