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PHENYL DICHLOROPHOSPHATE AS AN ACTIVATING AGENT IN THE PFITZNER-MOFFATT OXIDATION

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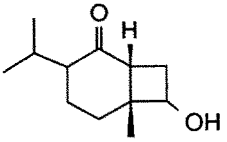
Summary: Phenyl dichlorophosphate has been shown to be a highly efficient activating agent for dimethyl sulfoxide in the Pfitzner-Moffatt oxidation. Alcohols are readily converted to the corresponding ketones and aldehydes with this reagent under very mild conditions by a simple procedure.

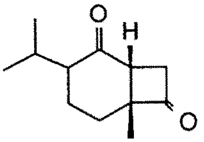
Towards the total synthesis of dendrobine, it was necessary to transform keto alcohols **1** to the corresponding ketones **2**. Swern oxidation using oxalyl chloride[1] was attempted for this conversion. To our surprise, the reaction gave an unexpected product which was characterized as the undesired chloro diketone 3,[2] apparently resulting from the concomitant α-chlorination of the existing cyclohexanone moiety. Presumably, complex **4** was involved as a source of positive chlorine.[2] Although this problem could be circumvented by using acetic anhydride[3] or trifluoroacetic anhydride (TFAA)[4] as activating agents, the reaction was shown to be slow when the former was used, while with the latter reagent, the results were not highly reproducible. Moreover, in both cases the yields of the desired product **2** were only modest (~60%). In order to improve the reaction, we have investigated other possible activating agents. In this communication, we wish to report a general and highly efficient dimethyl sulfoxide (DMSO) activator in the Pfitzner-Moffatt oxidation.[5]

In principle, any compound which can react preferentially with the oxygen of DMSO can be used as an activator in the Pfitzner-Moffatt oxidation. Thus, phosphorus-containing compounds are of particular interest because of their high reactivity towards oxygen functionalities. In fact, phosphorus oxychloride and phosphorus trichloride have been examined, though these reagents were found to be markedly inferior to oxalyl chloride.[1a]

Upon examination of a series of other phosphorus-containing compounds which also includes diphenyl chlorophosphate and diethyl chlorophosphate, phenyl dichlorophosphate (PDCP) has emerged as an efficient activator. For



1



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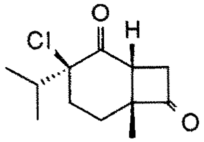


3

$[(CH_3)_2\overset{+}{S}Cl]Cl^-$

4

$[(CH_3)_2\overset{+}{S}OPO(Cl)OPh]Cl^-$

5

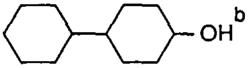
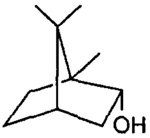
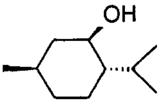
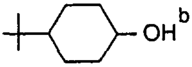
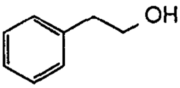
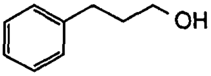
example, the oxidation of compound 1 with PDCP and DMSO in dichloromethane in the presence of triethylamine consistently gave high yields (>80%) of the desired diketone **2**. Only occasionally, a trace amount of the chloro diketone **3** was produced simultaneously. Most likely, complex 5 (generated from DMSO and PDCP) instead of **4** which could also be derived from 5 was involved as the oxidant.

PDCP proved to be generally useful as an activator for DMSO in the Pfitzner-Moffatt oxidation. The oxidation of a number of alcohols has been examined and the results are summarized in Table 1. An examination of the results reveals that the yields of the products are consistently high and, wherever applicable, compare favourably with those reported for oxalyl chloride and TFAA with a few exceptions. For cholesterol (Entry 6), our method is inferior with the yield lower by ca. 20% and with substantial amount of the rearranged product (4-cholesten-3-one) produced. On the other hand, our method is superior in the oxidation of phenethyl alcohol (Entry 10). A 62% yield of β-phenylacetaldehyde was isolated compared to 32-50% yield using TFAA and 23% yield for oxalyl chloride, each determined by gas chromatography.[1c,4a]

A salient feature of the procedure lies in its operational simplicity as illustrated by the following typical experiment. To a solution of DMSO (0.35 mL, 5 mmol) in dichloromethane (10 mL) at -10°C under an argon atmosphere, were added sequentially with stirring, PDCP (0.45 mL, 3 mmol),[6] triethylamine (0.70 mL, 5 mmol) and a solution of 2-octanol (0.16 mL, 1 mmol) in dichloromethane (5 mL).[7] The reaction mixture was stirred at -10°C for 5 min, then allowed to slowly warm up to room temperature. After 30 min, water (10 mL) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 15 mL). The organic solution was washed with a saturated aqueous sodium chloride solution (20 mL), dried with magnesium sulfate, filtered and concentrated. The residue was subjected to flash

Table 1. Oxidation of Alcohols Using PDCP

$$RR'CHOH \xrightarrow[Et_3N\ (5eq),\ CH_2Cl_2,\ -10^\circ C \rightarrow 20^\circ C]{DMSO\ (5eq),\ PDCP\ (3eq)} RCOR'$$

Entry	Substrate	Time(min.)	% Yield[a]
1	**1**[b]	45	84
2	$CH_3(CH_2)_5CH(OH)CH_3$	35	92
3	 [b]	30	90
4		30	81
5	6-Ketocholestanol	45	96
6	Cholesterol	60	75[c]
7		30	92
8	 [b]	30	94
9	$CH_3(CH_2)_{16}CH_2OH$	45	77
10		75	62
11		30	80

[a] All yields given are for isolated products.

[b] A mixture of diastereomers was used.

[c] A mixture of two isomers ($\Delta^4 : \Delta^5 = 2 : 1$) was obtained.

column chromatography on silica gel. Elution with 10% diethyl ether in petroleum ether gave 118 mg (92% yield) of 2-octanone (Entry 2).

The above procedure, which was successfully applied to all the cases listed in Table 1, is more convenient than those involving oxalyl chloride or TFAA. In Swern oxidation, depending on the type of substrates, several sets of conditions are used in order to achieve the best results.[1b,4c] Moreover, in a typical experiment, it is necessary to introduce the base at a certain temperature range after the reaction has proceeded for a period of time. Otherwise the yield of the desired product would be reduced drastically.[4a,c] In our hand, the attempted oxidation of 1-octadecanol (Entry 9) with oxalyl chloride, DMSO and triethylamine at -10°C using the procedure described above failed to give any detectable amount of the corresponding aldehyde and the starting alcohol was recovered intact.[8]

In conclusin, PDCP has proved to be an efficient activator for DMSO in the Pfitzner-Moffatt oxidation. It compares favorably with other commonly used activators such as dicyclohexylcarbodiimide, acetic anhydride, TFAA and oxalyl chloride. A broad synthetic utility of this reagent is expected in view of its high efficiency and operational simplicity.[9]

References and Notes

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6. When lesser amounts of PDCP and DMSO were used, the reaction was found to be slower as expected and the product yield lower.
7. The yield of the desired product was not affected when the reaction was carried out in the following manner. A solution of DMSO, PDCP and the alcohol in dichloromethane was stirred at -10°C or below for a period of time (5-15 min) then triethylamine was added at -10°C.
8. On the other hand, octadecanal was formed in ca. 86% yield (based on gas chromatography) when triethylamine was added after the reaction had proceeded for 15 min.[1b]

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