Synthesis of isoxazolidines using polymer supported perruthenate (PSP)

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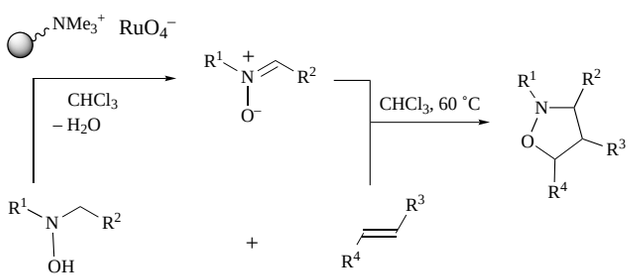
COMMUNICATION

Polymer supported perruthenate (PSP) has been used in mild and selective oxidations of secondary hydroxylamines to give nitrones; in the presence of dipolarophiles isoxazolidines are obtained in one-pot processes in good yields.

The synthesis of chemical libraries is of great importance in the pharmaceutical and agrochemical industries. These libraries of small molecules are normally prepared either in solution or on a solid support. The greater flexibility of the solution-chemistry approach is outweighed by the need for purification of the library.[1] As a consequence solid supported reagents[2] have been developed which allow the synthesis of chemical libraries in solution using an excess of reagent which can finally be removed by simple filtration without the need for a chromatographic work-up. We have recently reported the use of polymer supported perruthenate (PSP) as a mild oxidant for the clean conversion of primary and secondary alcohols to carbonyl compounds.[3] Here we report the use of PSP for the *in situ* preparation of nitrones to give isoxazolidines in one-pot processes.

Nitrones are synthetically useful intermediates since they provide, *via* [2 + 3]cycloadditions, an excellent route to isoxazolidines which are not only interesting targets in themselves, but are also precursors for highly functionalised open chain derivatives.[4] These 1,3-dipoles are commonly prepared either from secondary hydroxylamines by oxidation with HgO,[5] TPAP[6] or $PdCl_2$[7] or from condensation of aldehydes and monosubstituted hydroxylamines.[8]

Hydroxylamines can be prepared either sequentially or *in situ* from the corresponding amines using dimethyldioxirane (DMDO).[9] PSP can oxidise these substrates to the corresponding nitrones (Scheme 1). Owing to their limited stability it

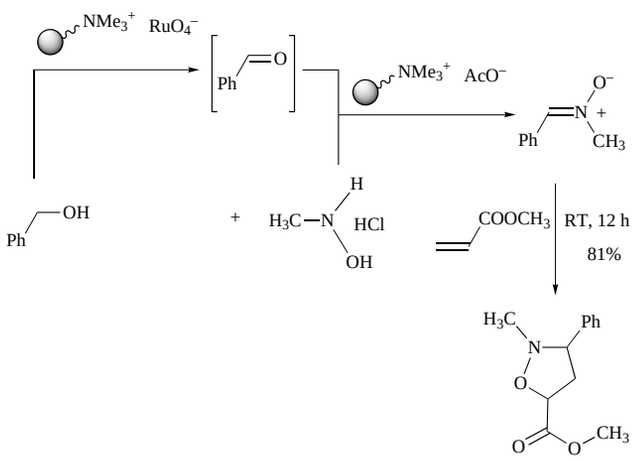


Scheme 1

is advantageous to perform this oxidation in the presence of an electron-poor dipolarophile. The oxidation and the cycloaddition reaction can be performed as a one-pot process affording isoxazolidines in good yields after removal of the solid supported reagent by filtration (Table 1). The immobilised oxidant can be regenerated by stirring it over a solution of *N*-methylmorpholine *N*-oxide (NMO).

In initial experiments, diethylhydroxylamine (0.5 mmol) was added to a mixture of dichloromethane or deuteriochloroform (3 cm^3) and PSP (500 mg, 1.0 mmol RuO_4^- per gram resin) at room temperature. Upon consumption of the starting material as indicated by thin layer chromatography the yield of the corresponding nitrone was estimated to be 94% by ^1H NMR spectroscopy. When this oxidation was performed in the presence of electron-poor dipolarophiles *e.g.* methyl acrylate, acrylonitrile or methyl vinyl ketone the corresponding isoxazolidines were obtained in good yields. Similarly, hydroxypyrrolidine has been oxidised to the corresponding 1,3-dipole and reacted *in situ* with diethyl fumarate to give an isoxazolidine in good yield (Table 1, entry 3). Owing to the high chemoselectivity of the perruthenate oxidant these transformations are possible in the presence of other functional groups. For example the tertiary amine functionality in a piperazine derivative (Table 1, entry 2a,b) was inert under the reaction conditions and the cycloaddition products from the reaction with methyl acrylate and diethyl fumarate were obtained in good yields. In summary, this process allows the preparation of isoxazolidines from symmetrical secondary hydroxylamines.

A second route towards isoxazolidines starts from an alcohol (Scheme 2). After oxidation with PSP the resulting carbonyl



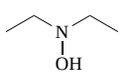
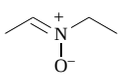
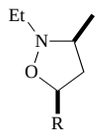
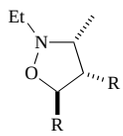
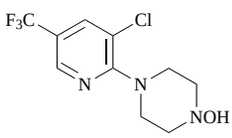
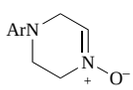
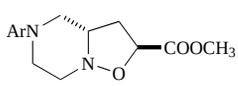
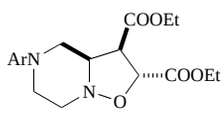
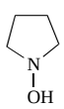
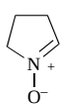
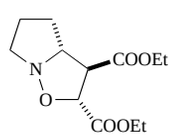
Scheme 2

compound can be condensed with a primary hydroxylamine to afford the corresponding nitrone which can then be used in a cycloaddition to afford isoxazolidines. This process is illustrated in the synthesis of *N*-methyl-5-methoxycarbonyl-3-phenylisoxazolidine from benzyl alcohol, hydroxymethylamine and methyl acrylate (Scheme 2). After PSP-oxidation of benzyl alcohol† (0.5 mmol) the solution of crude benzaldehyde in dichloromethane (1 cm^3) was added to a mixture of solid supported acetate,‡ hydroxymethylamine hydrochloride salt (1.1 equiv.) and methanol (3 cm^3) and stirred at room temper-

† This is a quantitative reaction, as reported earlier (ref. 3).

‡ This reagent is used to buffer the reaction mixture and was prepared from an ion exchange resin (IR 27, OH^--form) by washing the resin thoroughly with glacial acetic acid and drying *in vacuo* for several days.

Table 1 Oxidations of secondary hydroxylamines in the presence of dipolarophiles to yield isoxazolidines

Entry	Hydroxylamine	Nitrone	Dipolarophile	Isoxazolidine[a]		Reaction time/h	Yield/%
1a			methyl acrylate		R = $COOCH_3$	16	91[b]
1b	"	"	acrylonitrile		R = CN	13	89[b]
1c	"	"	methyl vinyl ketone		R = $COCH_3$	17	81[b]
1d	"	"	diethyl fumarate		R = COOEt	13	72[c]
2a[d]			methyl acrylate			16	89[c]
2b[d]			diethyl fumarate			19	55[b]
3			diethyl fumarate			14	84[c]

[a] The products indicated correspond to the major diastereoisomer. The assignment of regio- and stereo-chemistry is based on literature precedence (ref. 11). [b] Yield determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] Ar = 2-(3-Chloro-5-trifluoropyridyl).

ature for 12 h.[10] The solution of the crude nitrone was then transferred to a mixture of methyl acrylate (1.5 equiv.) and toluene (3 cm^3) and stirred overnight. The cycloaddition product was isolated in 81%.

In conclusion we have shown the use of Polymer Supported Perruthenate (PSP) in the preparation of nitrones for the synthesis of isoxazolidines. We believe the processes described are suitable for automated synthesis and thus offer interesting opportunities for the synthesis of chemical libraries.

We gratefully acknowledge financial support from the Swiss National Science Foundation (Fellowship to B. H.), the BP endowment and the Novartis Research Fellowship (to S. V. L.).

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Paper 7/07340B
Received 10*th October* 1997
Accepted 4*th November* 1997