A Novel Entry to Carbenoid Species *via* β-Ketosulfoxonium Ylides

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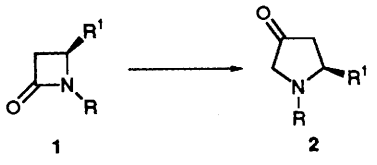
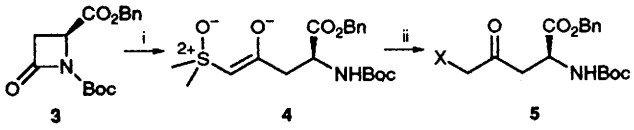
In the presence of suitable rhodium(II) catalysts, lactam derived β-ketosulfoxonium ylides can be transformed to β-oxonitrogen heterocycles, *e.g.* substituted 4-oxopyrrolidine, *via* intermediates of carbenoid nature.

In the course of our study into new routes to non-proteinogenic amino acids it proved necessary to develop a procedure that would convert a chiral azetidin-2-one (*e.g.* **1**) to a substituted 4-oxopyrrolidine **2** (Scheme 1). Previously, we reported that a suitably activated β-lactam **3** can be efficiently ring opened with dimethylsulfoxonium methylide to produce the β-ketosulfoxonium ylide **4**, which could then be converted to a series of δ-substituted γ-oxo-α-aminoacids **5** (Scheme 2).[1]



Scheme 1

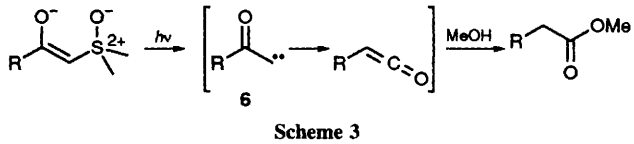


Scheme 2 *Reagents and conditions*: i, Me_2SOCH_2, dimethyl sulfoxide (DMSO), room temp., (97%); ii, see ref. 1, H–X, (Boc = *tert*-butyloxycarbonyl, Bn = benzyl)

Unfortunately, attempts to cyclise **5** (X = Br) directly to **2** failed and it was therefore necessary to investigate an alternative sequence.

In the initial report describing β-ketosulfoxonium ylides, Corey and Chaykovsky reported a photochemical rearrangement in methanol which yielded a homologated carboxylate ester possibly *via* the carbene **6** (Scheme 3).[2]

Sulfonium ylides have also been observed to undergo both photochemical and transition metal catalysed decomposition[3,4] to provide products characteristic of carbene type generation. Although, some doubt has been cast on the mechanism of these reactions as to the proposed intermediacy of carbenoids,[5] the observations of Cohen *et al.*[6] and more recently Cimetière and Julia[7] have suggested that such sulfonium ylides can indeed be precursors to metal carbenoid intermediates. We therefore considered that the β-ketosulfoxonium ylide **4** might be converted to a carbenoid, which could undergo intramolecular N–H insertion to form the desired 4-oxoproline derivative **7** (Scheme 4).



Scheme 3

Table 1

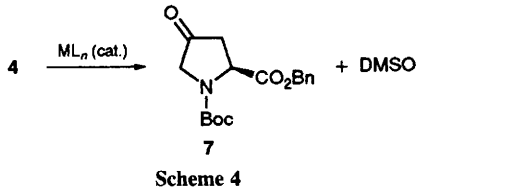
Catalyst	Amount (%) m/m	Solvent/*T*	Reaction time	7 (%)
$Rh_2(OAc)_4$	8	Benzene/reflux	16 h (6 h addition)	62
$Rh_2(OAc)_4$	10	DCM[a]/room temp.	3 weeks	No reaction
$Rh_2(O_2CCF_3)_4$	5	1,2-DCE/reflux	6 h (4 h addition)	77
$Rh_2(O_2CCF_3)_4$	5	Benzene/reflux	3 h (2 h addition)	70
$Rh_2(O_2CCF_3)_4$	3	$1,2\text{-}C_6H_4Cl_2$/reflux	6 h (4 h addition)	66
$Rh_2(O_2CCF_3)_4$	15	DCM/room temp.	1 week	No reaction
$Rh_2(O_2CMe_3)_4$	10	Benzene/reflux	16 h (6 h addition)	No reaction
$Rh_2(NHCOCF_3)_4$	10	Benzene/reflux	12 h (6 h addition)	Decomposition of **4**

[a] DCM = dichloromethane.

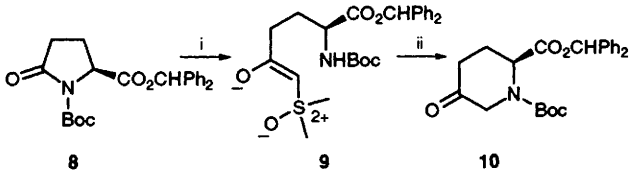
Table 2

Catalyst[a]	Amount (%) m/m	Solvent	Result
Copper bronze	50	Benzene–cyclohexene (1 : 5)	No reaction
CuO	50	Benzene–cyclohexene (1 : 5)	No reaction
Cu_2O	50	Benzene–cyclohexene (1 : 5)	No reaction
$Cu(acac)_2$	50	Benzene–cyclohexene (1 : 5)	No reaction
$Cu(acac)_2$	50	Benzene	No reaction
$CuTf_2$	50	Benzene/cyclohexene (1 : 5)	Decomposition of **4**
CuTf	40[b]	Benzene	Decomposition of **4**

[a] Hacac = pentane-2,4-dione, Tf = trifluoromethanesulfonate. [b] Mol%.



Scheme 4



Scheme 5 *Reagents and conditions*: i, Me_2SOCH_2, DMSO, room temp., (95%); ii, $Rh_2(O_2CCF_3)_4$, 1,2-DCE, reflux, (51%)

Thus, ylide **4** was treated with 10% m/m rhodium(II) acetate in boiling benzene for 18 h and significantly *N*-(*tert*-butyloxycarbonyl)-4-oxoproline benzyl ester **7** was isolated in 50% yield.† The yield was subsequently improved to 62% by carrying out the reaction with the slow addition of the substrate (over 6 h) to the suspension of 8% m/m rhodium(II) acetate in benzene, at reflux. To investigate possible ligand effects a number of alternative rhodium(II) catalysts were synthesised.[8] These reactions demonstrated that rhodium(II) pivalate was inactive under the conditions described for rhodium(II) acetate, whilst in contrast, rhodium(II) trifluoroacetate exhibited a marked enhancement in activity which led to a decreased reaction time, lower catalytic requirement, and increased yield. Optimised conditions required the use of 1,2-dichloroethane (1,2-DCE) as a solvent (5% m/m catalyst) and gave **7** in 77% yield (Table 1).

Treatment of sulfoxonium ylide **4** with a variety of copper compounds[4,6,7] (Table 2), however led to no useful reaction.

† DMSO detected in crude product prior to chromatography.

The ring opening/cyclisation sequence has also been extended to the synthesis of protected 5-oxopipecolic acid **10**, (Scheme 5). Thus, ring opening of **8** proceeded efficiently to produce the β-keto ylide **9** which was in turn treated with rhodium(II) trifluoroacetate (4% m/m), in refluxing 1,2-DCE, to afford the protected pipecolic acid derivative **10** in reasonable yield (51%). Such 5-oxopipecolic acid derivatives have recently been synthesised by a rhodium(II) acetate catalysed cyclisation of diazoketone precursors in 30–58% yield, and have been proposed as intermediates for the synthesis of *cis*-5-hydroxy-(L)-pipecolic acid.[9]

In summary, we have demonstrated that β-ketosulfoxonium ylides can be transformed, in the presence of suitable rhodium(II) species, into intermediates with carbenoid character. This process provides a novel entry to carbenoid species which has been exemplified during the two-step ring expansion sequences **3** to **7** and **8** to **10**.

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