Tetrahedron Letters,Vol.30,No.21,pp 2791-2794,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A NEW SYNTHESIS OF α-KETOETHERS VIA ANCHIMERICALLY ASSISTED SUBSTITUTION OF AN α-SULFINYL FUNCTION WITH ALCOHOLS

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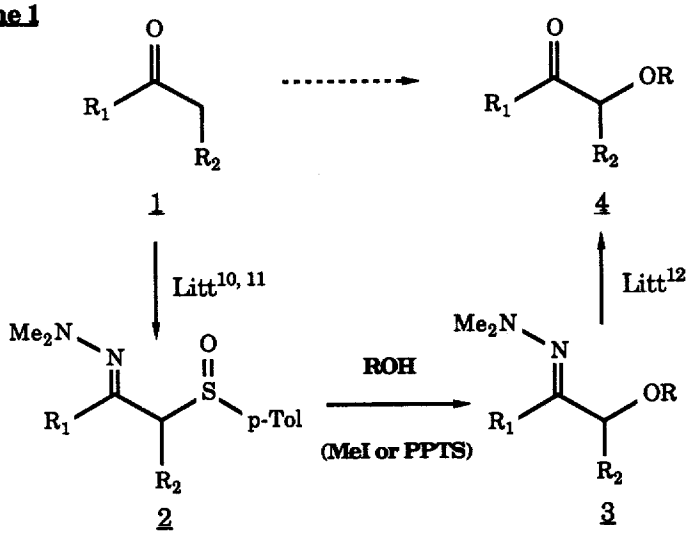
Abstract: The preparation of α-alkoxy-, α-allyloxy- and α-benzyloxyaldehydes and ketones, via substitution of a sulfinyl function in α-sulfinylhydrazones 2 with primary, secondary and tertiary alcohols is described.

α-Ketoethers are useful intermediates in the synthesis of macrolides[1,2], pheromones[3,4] and prostanoïds[5]. These intermediates are usually prepared by oxidative cleavage of various allyl ethers[6] and of the benzyl ether derivative of solketal[2] or nucleophilic additions to monoprotected α-ketoaldehydes[7].

In the course of our studies directed toward the synthesis of α-*p*-tolylsulfinylacetaldehyde[8] we observed during deprotection of α-sulfinylhydrazone 2a under standard conditions (1 eq MeI, EtOH 96%, reflux[9]) the formation of α-ethyloxyhydrazone 3a instead of α-*p*-tolylsulfinylacetaldehyde.

Herein, we report the scope of this new reaction allowing the synthesis of various α-alkoxy-, α-allyloxy- and α-benzyloxyaldehydes and ketones (scheme 1).

Scheme 1

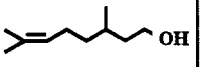
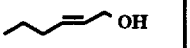


R_1	R_2	1 to 4
H	H	a
H	Me	b
$-(CH_2)_4-$		c

α-sulfinylhydrazones 2, prepared using already well documented procedures[10,11], were treated with various alcohols, to give the corresponding key intermediates 3 which is easily deprotected with copper chloride[12].

Investigation of this new reaction showed that primary alkyl, allyl and benzyl alcohols gave satisfactory yields (entries 1-5, 8-9), whereas a secondary gave only low conversion (entry 6). The results are summarized in the table.

Table

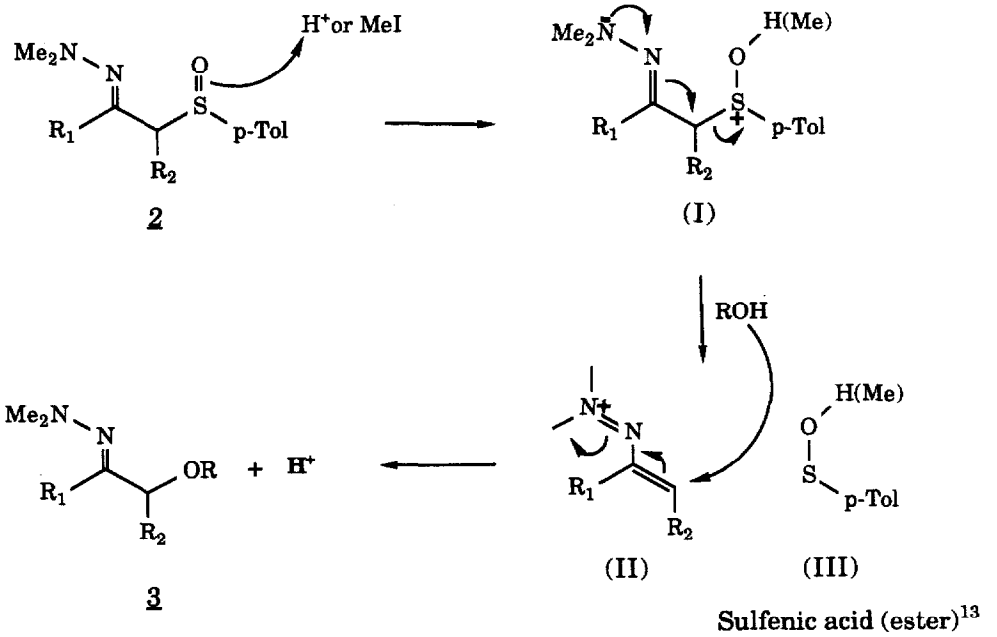
Hydrazone	Entry	ROH	Yield (reaction time h) MeI[a]	Yield (reaction time h) PPTS[b]
2a	1	MeOH	40 (4)	83 (0.3)
	2	EtOH	65 (1.5)	88 (0.3)
	3		70 (3.5)	
	4	$PhCH_2OH$	45 (1)	65 (1.5)
	5		40 (2)	63 (1.8)
	6	Me_2CHCH_2OH	10 (5)	70 (0.5)
	7	Me_3COH		60 (2.0)
2b(88/12)[c]	8	n-BuOH	70 racemic[d] (0.3)	
2c	9	MeOH		70 (0.75)

[a] alcoholic solution of 2, 1 eq MeI, 80°C or reflux; [b] alcoholic solution of 2, 0.1-0.3 eq pyridinium *p*-toluenesulfonate (PPTS), 60-70°C or reflux; [c] A THF solution of 2b (55/45 diastereoisomeric mixture obtained according litterature[11]) was treated with 1 eq of LDA, and after 1 h at -78°C quenched with a saturated NH_4Cl solution. A 88/12 diastereoisomeric mixture of 2b was obtained. [d] Optical purity was determined by ^1H NMR (200 MHz, $CDCl_3$) spectrometry using $Eu(hfc)_3$ using a procedure perfected with racemic samples (molar ratio substrate/shift reagent=1/0.48).

Replacement of methyliodide by octyliodide did not affect the course of the reaction , even

used in catalytical amount (approximatively 0.3eq). The alkyl halide was recovered after total conversion of 2 to 3. Therefore we thought that this reaction could be initiated either by the alkyl halide or by acid catalysis. A possible mechanism, starting by alkylation or protonation of the sulfoxide, and followed by anchimerically assisted elimination of sulfenic acid (or ester) (III)[13] is shown on scheme 2.

Scheme 2: Postulated reaction mechanism



In an attempt to justify this mechanism we discovered that the use of PPTS instead of alkyl halides was more efficient. Better yields were obtained by shorter reaction times and lower reaction temperatures. More interesting was the fact that secondary but also tertiary alcohols gave rise to substitution (see table). These results suggest that this reaction occurs most readily through an acid catalysis.

It is important to note that the formation of racemic α-butyloxypropionylhydrazone 3b (entry 8) suggests the existence of achiral intermediate (II), which may be formed by anchimerically assisted elimination of sulfenic acid (or ester) (III)[13] (scheme 2).

In summary we have shown the possibility to introduce various alcohols in α-position from carbonyl derivatives. The application of this new reaction to the synthesis of cyclic ethers is under investigation and will be published in due course.

Acknowledgement:

The authors thank Dr. A. GREINER (Rhône-Poulenc Agrochimie Lyon) and Dr. M. P. HEITZ (CNRS Strasbourg) for useful discussions.

References and notes

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13- Sulfenic acid has not been isolated. In fact it was shown that this compound dimerises easily[14], leading to *p*-tolyl *p*-toluenethiol sulfinate, which was observed during the course of the reaction.
With an alkyl halide, the reaction could be initiated by alkylation of the sulfoxide, followed probably by an acid catalysis with the proton liberated during the addition of the alcohol to intermediate (II).
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(Received in France 1 March 1989)