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SYNTHESIS OF α-AMINO KETONES FROM α,β-EPOXY SULFOXIDES

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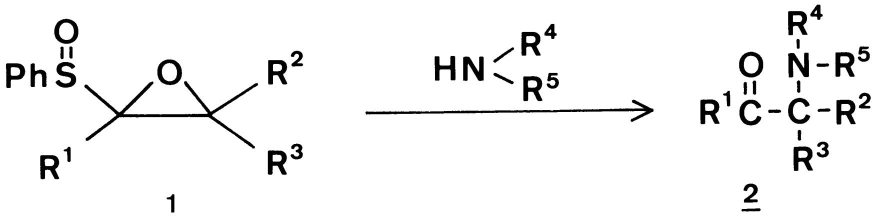
Various kinds of α-amino ketones and α-arylamino ketones are synthesized in good yields by aminolysis of α,β-epoxy sulfoxides which are easily prepared from alkylated chloromethyl phenyl sulfoxide and carbonyl compounds.

α-Amino ketones (2) are very important and versatile compounds in synthetic organic chemistry. They are useful intermediates for drugs[1,8)] or as building blocks for nitrogen containing heterocyclic compounds.[2)] In spite of the impressive development of the methods for the synthesis of β-amino ketones, such as Mannich reaction[3)] or Michael addition of amines to α,β-unsaturated carbonyl compounds,[4)] only limited numbers of methods for the construction of α-amino ketones (2) are reported. Aminolysis of α-halo ketones[5)] usually gives poor yields. Reduction of acyl cyanides[6)] gives only one type ($RCOCH_2NH_2$) of α-amino ketones. The Neber rearrangement[7)] gives only α-amino ketones having no substituents on the nitrogen atom. Aminolysis of enediol silyl ether[1)] was reported to give about 45% yield of α-amino ketones. Aminolysis of epoxy-ether is good method, and practically used in a preparation of some drugs but only syntheses of phenyl α-amino ketones were reported.[8)]

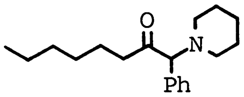
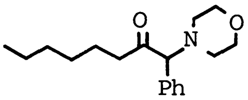
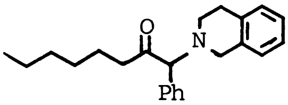
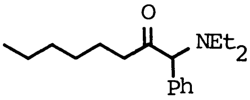
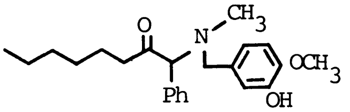
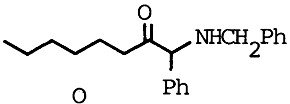
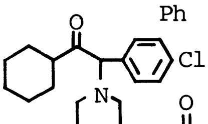
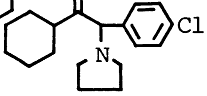
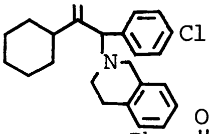
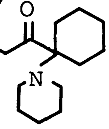
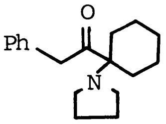
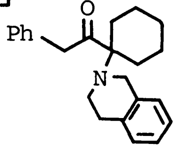
Recently we reported a method for the synthesis of dialkyl ketones and α-sulfenylated carbonyl compounds from α,β-epoxy sulfoxides (1).[9)] In the course of the studies on the synthesis of α-substituted carbonyl compounds from α,β-epoxy sulfoxides (1), here a new and efficient method for the synthesis of α-amino ketones (2) is reported according to Eq. 1.



(1)

α,β-Epoxy sulfoxides (1) are very easily prepared in good overall yields from alkyl halides (R^1), carbonyl compounds (R^2, R^3), and chloromethyl phenyl sulfoxide.[10)] We have found that the β-carbon of the α,β-epoxy sulfoxides is

Table 1.
α-Amino ketones from α,β-epoxy sulfoxides with amines

Run	Epoxy sulfoxide	Amine[a]	Solvent	Temp	Time	α-Amino ketones	Yield[b] %
1	3 L	A	-	r.t.	3 h		97
	P	A	-	r.t.	21 h		100
2	3 L	B	-	r.t.	4 h		100
	P	B	-	r.t.	23 h		99
	P	B	-	80 °C	90 min		90
	P	B	DMSO	80 °C	100 min		100
	P	B	HMPA	80 °C	150 min		94
3	3 L	C	HMPA	r.t.	27 h		89
	P	C	HMPA	110 °C	40 min		100
4	3 L	D	-	r.t.	8 d		96
	P	D[c]	DMSO	50 °C	31 h		44
5	3 L	E[d]	DMSO	60 °C	3 h		53
	P	E[d]	DMSO	60 °C	5 h		52
6	3 L	F[c]	DMSO	55 °C	1 h		72
	P	F[c]	DMSO	55 °C	1 h		73
7	4 L	A	-	100 °C	2 h		97
	P	A	-	100 °C	12 h		85
8	4 L	G	-	80 °C	1 h		100
	P	G	-	80 °C	6 h		85
9	4 L	C[e]	DMSO	100 °C	7 h		94
	P	C[e]	DMSO	100 °C	20 h		80
10	5	A	-	100 °C	6 h		76
11	5	G	-	80 °C	4 h		100
12	5	C[e]	DMSO	100 °C	30 h		48

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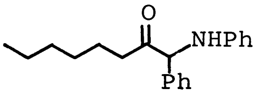
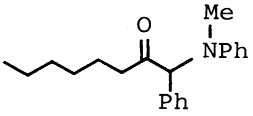
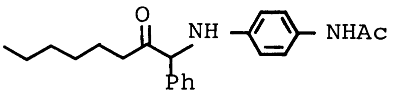
a) A: piperidine, B: morpholine, C: 1,2,3,4-tetrahydroisoquinoline, D: diethylamine, E: N-(3-hydroxy-4-methoxy)benzyl-N-methylamine, F: benzylamine, G: pyrrolidine. b) Isolated yields after silica gel column chromatography. c) 45 equiv. of amine was used. d) 4 equiv. of amine was used. e) 40 equiv. of amine was used and the concentration of the epoxy sulfoxide was 0.07 M.

very reactive to various kinds of nucleophiles[9] including amines or aromatic amines to afford α'-substituted ketones in good yields under mild conditions.

The results of the reaction of the α,β-epoxy sulfoxides 3 (R^1= n-hexyl, R^2, R^3= phenyl, H), 4 (R^1= cyclohexyl, R^2, R^3= p-chlorophenyl, H), and 5 (R^1= benzyl, R^2, R^3= $-(CH_2)_5-$) with various kinds of amines are summarized in Table 1. The epoxides 3 and 4 have two isomers (L and P), respectively, but the stereochemistries have not yet been determined. The reaction were usually conducted in DMSO or HMPA (0.5 M concentration of epoxy sulfoxide and 10 equiv. of amines are used unless otherwise noted) or in amine without solvent in the case of volatile amines under nitrogen atmosphere.

As shown in Table 1, many kinds of α-amino ketones are synthesized from the epoxy sulfoxides in good yields. The amine having a complex structure (Run 5) can be used to afford α-amino ketone, though the yield is moderate, which implies that this method would have practical value. Isomers L and P showed some differences in reactivity toward the amines. The epoxides having cyclohexane ring in R^1 (4) showed less reactivity than those of normal alkyl group in R^1 (3) due to steric hinderance on the β carbon of the epoxide by cyclohexyl group (see Run 1 and 7). The dipolar aprotic solvent known to be effective for nucleophilic bimolecular reaction[11] was used in this reaction. Run 3 shows that DMSO is slightly more effective than HMPA. Monoalkylamines usually gave a complex mixture but only benzylamine afforded an α-amino ketone in about 70% yield (Run 6).

Table 2.
α-Arylamino ketones from α,β-epoxy sulfoxides with aromatic amines

Epoxy sulfoxide	Aromatic amine (equiv.)[a]	Temp	Time	α-Anilino ketones	Yield[b] %
3 L	H (50)	100 °C	1 h		97
P	H (50)	100 °C	2 h		81
3 L	I (90)	100 °C	2 h		73
P	I (90)	100 °C	2 h		56
3 L	J (5)	100 °C	3 h		63
P	J (5)	100 °C	5 h		47

a) H: aniline, I: N-methylaniline, J: p-aminoacetanilide; The reaction was conducted in HMPA and the concentration of 3 was 0.4 M. b) Isolated yields after silica gel column chromatography.

The results of the reaction of 3 with aromatic amines are summarized in Table 2. As the nucleophilicity of aromatic amines is decreased by the delocalization of the nitrogen lone pair of electrons, the reaction of aromatic amines with the α,β-epoxy sulfoxide required a higher temperature than those of amines and the reaction gave moderate yields.

The other methods reported to be effective for opening of epoxides, such as aminosilanes[12)] or reactions at alumina surfaces[13)] were not effective in this reactions.

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