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INTRAMOLECULAR ACYLATION OF α-SULFINYL CARBANION: A NEW GENERAL ROUTE TO 5-SUBSTITUTED Δ^2-CYCLOPENTENONES

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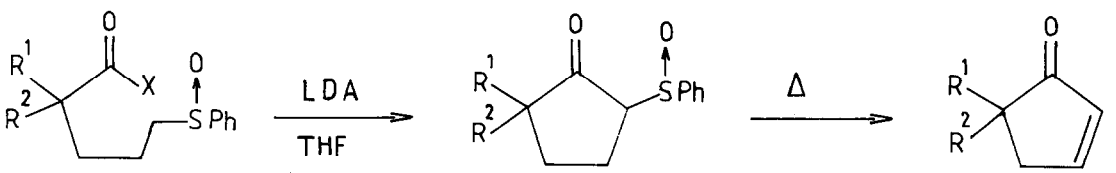
Abstract: A general method for the preparation of 5-substituted Δ^2-cyclopentenones via the intramolecular acylation of α-sulfinyl carbanions has been demonstrated.

α-Sulfinyl carbanions have long been known to undergo intermolecular acylation reactions leading to β-keto sulfoxides which are important intermediates for syntheses of ketones and α,β-unsaturated ketones[1]. However, there are few reports on the intramolecular acylation of the carbanions[2]. The reactions might be valuable for construction of cycloalkanones, cycloalkenones or even highly functionalized cycloalkanones, especially Δ^2-cyclopentenones[3] which are key compounds for the synthesis of natural products such as prostanoids[4]. Recently there has been an increasingly large amount of research devoted to developing synthetic routes to substituted cyclopentenone derivatives. One of the representative and attractive routes to cyclopentenones involves the cyclodehydration of 1,2-diketones[3]. Many other methods have involved the cyclodehydration of γ-butyrolactones[5], the intramolecular Wittig reaction[6], the Nazarov cyclization of divinyl ketones and related reactions[7], intramolecular acylation of vinylsilanes[8], and pyrolysis of α-alkynones[9]. Our interest concerning the chemistry in this area led us to investigate the intramolecular acylation of α-sulfinyl carbanions as a possible synthetic route for synthesis of the substituted cyclopentenones. Our synthetic approach was outlined as belows.



1, X=OCH_3; R^1,R^2=alkyl or phenyl
2, X=$N-C_6H_5$ (CH_3); R^1=alkyl; R^2= H

3, R^1,R^2=alkyl or phenyl
4, R^1=alkyl; R^2= H

5, R^1,R^2=alkyl or phenyl
6, R^1=alkyl; R^2=H

First, we studied the cyclisation of the ester sulfoxide 1. Thus, treatment of 1a-d with 2.2-2.5 equivalents of lithium diisopropylamide in THF (10 ml per 1 mmol of the ester sulfoxide 1) at -78°C for 1 hr and then at 0°C for 1 hr provided the β-keto sulfoxide 3a-d in good yield after quenching with saturated NH_4Cl solution. The formation of the β-keto sulfoxide 3 resulted from the intramolecular acylation reaction of the initially formed α-sulfinyl carbanion. Having succeeded in obtaining the ketosulfoxide 3, we therefore next examined the possibility for the preparation of the keto sulfoxide 4, a precursor for 5-alkylsubstituted 2-cyclopentenone 6, by the same synthetic approach. We used the amide sulfoxide 2 as the starting material for our investigation because of the difference in acidity of both α-protons adjacent to the carbonyl function and the sulfur atom, which could avoid the competitive proton abstraction. As expected, the cyclisation of the amide sulfoxides 2a-e proceeded smoothly by using the standard conditions as above to give the β-keto sulfoxides 4a-e in high yields. Pyrolysis of the β-keto sulfoxides 3 and 4 gave the desired cyclopentenones 5 and 6 in high yields: this was carried out by refluxing in CCl_4 under argon atmosphere (entries 2 and 3) or by heating neat at 110-120°C under reduced pressure (0.03-0.05 Torr) following by preparative thin-layer chromatography (entry 9) or direct distillation (entries 1,4 and 5-8). The results were summarized in Table 1.

Table 1

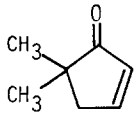
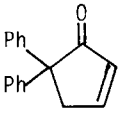
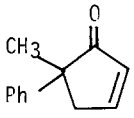
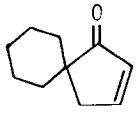
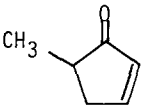
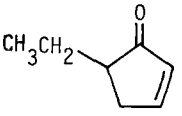
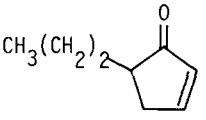
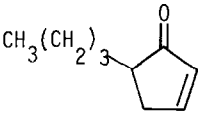
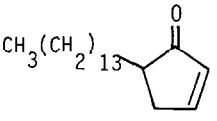
Entry	Ester 1 or Amide 2 (%)[a,b]	β-Keto Sulfoxide 3 or 4[a,b,c] % (m.p.)	Cyclopentenone 5 or 6[a,b] % (m.p.)
1	1a: $R^1 = R^2 = CH_3$ (42)	3a: 88 (102-104°)	 5a: 76 (liq.)
2	1b: $R^1 = R^2 =$ Ph (50)	3b: 67 (128-130°)	 5b: quantitative(85-87°)
3	1c: $R^1 = CH_3$; $R^2 =$ Ph (51)	3c: 74 (liq.)	 5c: 90 (liq.)
4	1d: R^1-R^2= -$(CH_2)_5$- (63%)	3d: 70 (143-144°)	 5d: 68 (liq.)

Table 1 (cont.)

Entry	Ester 1 or Amide 2 (%)[a,b]	β-Keto Sulfoxide 3 or 4[a,b,c] % (m.p.)	Cyclopentenone 5 or 6[a,b] % (m.p.)
5	2a: $R^1 = CH_3$; $R^2 = H$ (80)	4a: 81 (liq.)	 6a: quantitative (liq.)
6	2b: $R^1 = CH_3CH_2$; $R^2 = H$ (75)	4b: 74 (50-54°)	 6b: 95 (liq.)
7	2c: $R^1 = CH_3(CH_2)_2$-; R^2=H(68)	4c: 91 (liq.)	 6c: 72 (liq.)
8	2d: $R^1 = CH_3(CH_2)_3$-; R^2=H(77)	4d: 98 (liq.)	 6d: 74 (liq.)
9	2e: $R^1 = CH_3(CH_2)_{13}$-; R^2=H(69)	4e: 83 (liq.)	 6e: 85 (45-46°)

a) Yields of isolated products.

b) The spectral data of these products are fully consistent with the assigned structures.

c) These products have been obtained as diastereomeric mixtures.

Preparation of the starting sulfoxides 1 and 2 began with the corresponding esters or amides (R^1R^2CHCOX, X=OMe or -NMePh). Reaction of the enolate anion derived from the corresponding ester or amide (LDA/THF, 0°C, 1 hr)[10] with 1-bromo-3-phenylthiopropane (-78°→ RT, overnight) in the presence of hexamethylphosphortriamide (HMPA) followed by oxidation of the resulting alkylated product with m-chloroperbenzoic acid (MCPA) (CH_2Cl_2, -78°)[11] provided the desired sulfoxides 1 and 2, generally in good overall yield (see Table).

Our work has thus established the utility of the intramolecular acylation of the α-sulfinyl carbanions as a useful synthetic method for the preparation of 5-substituted cyclopentenones, especially the cyclopentenones of type 6 which are versatile intermediates in

organic synthesis because of their ready ability to equilibrate to the thermodynamically more stable 2-alkyl substituted Δ^2-cyclopentenones[12]. Considering the high yields, the present method appears to provide an easy entry to certain cyclopentanoid natural products.

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