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CONJUGATE ADDITION TO 5-PHENYLSULFINYL 2-SUBSTITUTED 2-CYCLOPENTENONES: A NEW ROUTE TO 4,5-DISUBSTITUTED 2-CYCLOPENTENONES

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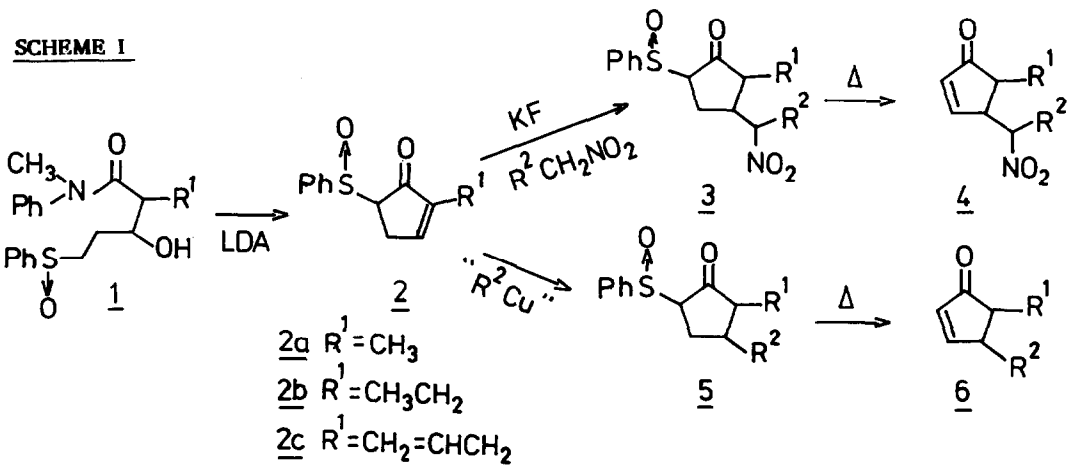
Summary: 4,5-Disubstituted 2-cyclopentenones have been prepared by conjugate addition of nitroalkanes and of organocopper reagents to 5-phenylsulfinyl 2-substituted 2-cyclopentenones, followed by pyrolysis.

Among the substituted cyclopentenones, 4,5-di substituted 2-cyclopentenones are of important because they are well known as the basic structural units in cyclopentanoid natural products, especially the PGA-type compounds.[1] Considerable attention has been paid to the practical and efficient synthesis of 4,5-disubstituted 2-cyclopentenones.[2] We recently reported a convenient preparation of functionalised cyclopentenones of type 2 by the intramolecular acylation of α-sulfinyl carbanions derived from 1 and showed that 2 could be useful intermediates for the synthesis of 5-alkylidene 2-cyclopentenones.[3,4] Our interest in developing a new general approach for the construction of 4,5-disubstituted 2-cyclopentenones has led us to investigate the synthetic utility of the functionalised cyclopentenones 2 as valuable starting materials. The conjugate addition of anions to 2 followed by pyrolysis should provide a convenient route to 4,5-disubstituted 2-cyclopentenones (Scheme I).

SCHEME I



Initially, we explored the conjugate addition reaction of nitronate anions derived from the corresponding nitroalkanes to the cyclopentenone 2. It was found that treatment of nitromethane (2 equiv.) with 2a (1 equiv.) in the presence of potassium fluoride (2 equiv.) in isopropanol[5] at room temperature provided the desired adduct 3a in 76%. Employing KF/isopropanol as the standard reaction conditions, the conjugate adducts 3b-h were obtained as mixtures of diastereomers. Neat pyrolysis of the adducts 3a-h at 110-130° under reduced pressure (0.02 Torr) afforded the expected 4,5-disubsdtituted 2-cyclopentenones 4a-h in 40-82%. The results are summarized in Table I.

Table I Preparation of 3 and 4 by conjugate addition of nitroalkane to 2 followed by pyrolysis.

Enone	$R^2CH_2NO_2$	3(%)[a,b]	4(%)[a,b]
2a	R^2=H	3a, 76	4a, 52
2a	R^2=n-C_5H_{11}	3b, 59	4b, 65
2a	R^2=CH_2CH_2CH 	3c, 60	4c, 82
2a	R^2=n-C_6H_{13}	3d, 59	4d, 40
2b	R^2=H	3e, 74	4e, 50
2b	R^2=n-C_4H_9	3f, 63	4f, 61
2b	R^2=n-C_5H_{11}	3g, 70	4g, 53
2b	R^2=n-C_6H_{13}	3h, 66	4h, 74

a. Yield of pure product isolated by SiO_2 preparative thin-layer chromatography. All products gave satisfactory spectral data (IR, ^{1}H-NMR and MS) and elemental analyses.

b. Obtained as diastereomeric mixtures.

Having succeeded in preparing the cyclopentenones 4, we next investigated the conjugate addition of some organocopper reagents to the cyclopentenones of type 2. Thus, treatment of 2b (1 equiv.) with Bu_2CuLi (2 equiv.) in ether at -78° for 3 hr in the absence or presence of chlorotrimethylsilane (TMCS) and hexamethylphosphortriamide (HMPA)[6] furnished the adduct 5a in about 38% yield together with 17-34% of the recovered enone 2b (Table II, entries 1 and 2). A better yield of 5a (46%, entry 3) was observed when the reaction was carried out in THF (-78°, 3 hr, TMCS/HMPA). The reactions employing the higher order organocuprate[7] $Bu_2Cu(CN)Li_2$ in ether with or without BF_3,OEt_2[8] (entries 4 & 5) resulted in the formation of 5a in 44 and 36%. The conjugate adduct 5b was achieved in 48% yield when 2a (1 equiv.) was treated with $Bu_2Cu(CN)Li_2$

(2 equiv.) in THF at -78° in the presence of HMPA/TMCS (entry 7). Attempts to improve the yield of the conjugate adduct by using a large excess of the organocopper reagents or by performing the reactions at 0° or at room temperature were unsuccessful: the reactions provided complex mixtures of products as indicated by thin-layer chromatography analysis. To gain further insight into the reactivity of the functionalised cyclopentenone of type 2, other organocopper reagents were tried as summarized in Table II (entries 6, 8 and 9). Pyrolysis of 5a-e in refluxing toluene followed by preparative thin-layer chromatography (SiO_2) gave the 4,5-disubstituted 2-cyclopentenones 6a-e in 61-72%.

Table II Conjugate addition reactions of organocopper reagents to 2 leading to 5, followed by pyrolysis giving 6.

Entry	2	Reagent	Solvent	Additive[a]	5(%)[b,c,d]	6(%)[c,d]
1	2b	Bu_2CuLi	Et_2O	-	5a, 38 (17)	-
2		Bu_2CuLi	Et_2O	TMCS/HMPA	5a, 38 (34)	-
3		Bu_2CuLi	THF	TMCS/HMPA	5a, 46 (37)	-
4		$Bu_2Cu(CN)Li_2$	Et_2O	-	5a, 31 (26)	-
5		$Bu_2Cu(CN)Li_2$	Et_2O	$BF_3.OEt_2$	5a, 44 (15)	6a, 68
6		$(t\text{-}Bu)_2Cu(CN)Li_2$	THF	TMCS/HMPA	5b, 32 (12)	6b, 72
7	2a	$Bu_2Cu(CN)Li_2$	THF	TMCS/HMPA	5c, 48 (29)	6c, 62
8		$(t\text{-}Bu)_2Cu(CN)Li_2$	THF	TMCS/HMPA	5d, 30 (3)	6d, 61
9	2c	$Bu_2Cu(CN)Li_2$	THF	$BF_3.OEt_2$	5e, 40 (12)	6e, 66

All reactions were run at -78° for 3 hr, using 2 equiv. of cuprate.

a. $BF_3.OEt_2$ (1 equiv.) or a mixture of TMCS (2 equiv.) and HMPA (10% solution) was employed.

b. Isolated yields after PLC (SiO_2): Yields given in parentheses are the percentage yields of the recovered starting enones.

c. All products exhibited physical and spectral characteristics (IR, NMR, MS and analyses) in accordance with the assigned structures.

d. Obtained as mixtures of isomers.

The above results clearly demonstrated the synthetic potential of 5-phenylsulfinyl-2-cyclopentenones as useful intermediates. The sequence thus provides a new general method for the preparation of 4,5-disubstituted 2-cyclopentenones. We are now intensively investigating to use this approach for the synthesis of prostaglandin A and derivatives.

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