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A NEW APPROACH TO α-ALKOXY- AND α-ALKYLTHIOKETONES FROM CONJUGATED NITROALKENES

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α-Substituted ketones are obtained in two steps by reduction of the α,β-unsaturated nitroalkenes using $SnCl_2 \cdot 2H_2O$ in alcoholic media followed by hydrolysis with levulinic acid.

α-Alkoxycarbonyl compounds have found widespread utility in the synthesis of macrolide antibiotics and polyether ionophores.[1,2] Although α-alkoxyaldehydes are accessible via several routes,[1-4] the corresponding ketones are not as readily available. They are generally prepared via the decomposition of α-diazoketones[5] or the dimers of α-hydroxyketones[6] in the presence of alcohols. α-Alkoxyketones have also been reported to be formed as by-products in the fragmentation of ionic peroxides[7] and in the methanolysis of arylcyclopropanone methyl hemiacetals.[8]

We have been investigating the use of nitroalkenes as precursors to a variety of useful synthetic intermediates such as nitroalkanes,[9] N-substituted hydroxylamines,[10] amines,[11] ketones,[12] chromenes[13] and oxime derivatives.[14]

We now wish to describe a useful two-step preparation of α-substituted ketones.[15] The sequence involves the reduction of readily accessible nitroalkenes with stannous chloride in an appropriate alcohol (or thiol) at room temperature. The resulting α-substituted oxime derivatives, obtained in high yields, are then hydrolyzed using levulinic acid[17] (Scheme 1). The use of non-aqueous, non-acidic media (for the preparation of oximes), shorter reaction times and the overall efficiency of this procedure make it an especially practical route to a variety of α-substituted ketones. Our results are summarized in Table 1.

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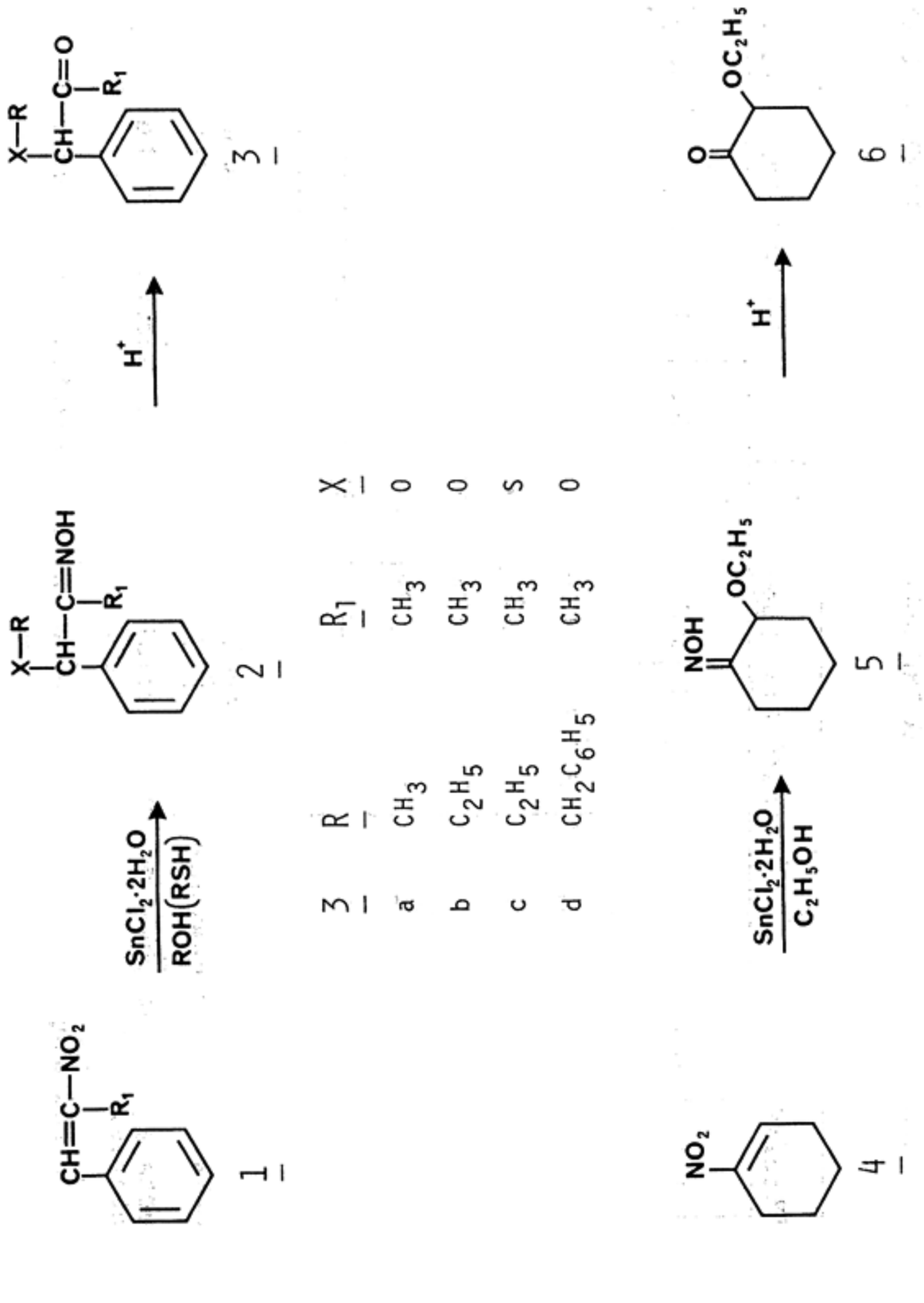
EXPERIMENTAL

Commercially available 1-nitro-1-cyclohexene (Aldrich) was used a obtained. β-Methyl-β-nitrostyrene was prepared by procedure as described earlier.[18] The products were characterized by their physical properties and spectral characteristics (^{1}H-NMR, ^{13}C-NMR etc.).



SCHEME 1

TABLE I. α-ALKOXYKETONE FORMATION VIA THE REDUCTION AND HYDROLYSIS OF NITROALKENES.[a]

Product[b]	Yield[c]	I.R.	^{1}H-NMR($CDCl_3$, δ ppm)				^{13}C-NMR($CDCl_3$, δ ppm)			
	[%]	$\nu_{max}\cdot cm^{-1}$	CH	XCH_2/CH_3	$COCH_3$	CH_3	C=O	CH	XCH_2/CH_3	CH_3
3a	93	1710	4.66s	3.37s	2.11s	-	206.7	89.39	57.16	-
3b	95	1710	4.75s	3.48q	2.12s	1.20t	206.9	87.77	65.13	15.26
3c	90	1700	4.64s	2.47q	2.17s	1.22t	203.6	60.40	26.50	14.20
3d	88	1710	4.81s	4.54d	2.13s	-	206.8	86.74	71.09	-
6	79	1715	3.82m	3.53m	-	1.23t	210.4	82.68	65.43	15.32

a - The nitroalkenes were reduced with $SnCl_2\cdot 2H_2O$ and oximes obtained were then hydrolyzed with levulinic acid.

b - Products exhibited physical and spectral properties in accord with the assigned structures.

c - Isolated and unoptimized yields based on oxime derivatives;[14] all products are thick oils.

NMR spectra were recorded on a JEOL-FX 90Q Spectrometer and referenced to Me_4Si. I.R. spectra were determined on a Perkin-Elmer 1330 infrared spectrophotometer as thin films. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

General Procedure for the Synthesis of Oxime Derivatives

The synthesis of α-benzyloxyphenylacetone is representative of the procedure employed. Benzyl alcohol (25 mL), β-methyl-β-nitrostyrene (0.652 g, 4 mmol) and stannous chloride (1.35 g, 6 mmol) were placed in a 50 mL Erlenmeyer flask and the mixture stirred at room temperature. A mildly exothermic reaction ensued which was accompanied by the disappearance of yellow coloration (nitroalkene). After 30 min, the reaction mixture was carefully poured onto ice. The pH of the solution was adjusted to ∿8 via the addition of 5% aqueous sodium bicarbonate and then the product extracted into ether. The organic phase was washed with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The high boiling benzyl alcohol impurity was distilled off using a Kugelrohr, to yield essentially pure α-benzyloxyphenylacetone oxime, m.p. 78-80°C (79%); ^{1}H-NMR ($CDCl_3$) δ8.2 (brs,1H,NOH,exch. with D_2O), 7.4-7.2 (m,5H,Ar-H), 5.04(s,1H,CH), 4.57(s,2H,OCH_2Ph), 1.78 (s,3H,CH_3); ^{13}C-NMR($CDCl_3$) δ158.79(C=NOH), 81.33(CH), 70.68(OCH_2Ph) and 9.39(CH_3).

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.29, H, 6.67 , N, 5.49
Found: C, 75.17; H, 6.55, N, 5.62.

General Procedure for the Hydrolysis of Oximes

A stock solution of levulinic acid was prepared by mixing 9 volumes of levulinic acid with 1 volume of 1.0N HCl. An excess of this reagent (normally 30 fold) was added to α-benzyloxyphenylacetone oxime (0.51 g, 2 mmol) in a round-bottomed flask containing a magnetic stirring bar. The reaction mixture was stirred at 80°C (oil bath) for 3.5 hr. and then diluted with water (20 mL). The product was extracted into ether (3 x 40 mL) and the combined extracts were washed with 5% aqueous sodium bicarbonate, water, dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was purified by column chromatography on silica gel (4% ether/petroleum ether) to yield α-benzyloxyphenylacetone,[19] as thick oil (88%); I.R. ν_{max} 1710 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.45-7.3 (m,5H,Ar-H), 4.82(s,1H,CH), 4.54(d,2H,OCH_2Ph), 2.14 (s,3H,$COCH_3$); ^{13}C-NMR ($CDCl_3$) δ 206.85(C=O), 86.74(CH), 71.09(OCH_2PH) and 25.31($CO\underline{C}H_3$).

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