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Single Step Synthesis of Substituted Lactic Acids from Ketones using Nitrobenzene as an Oxidant

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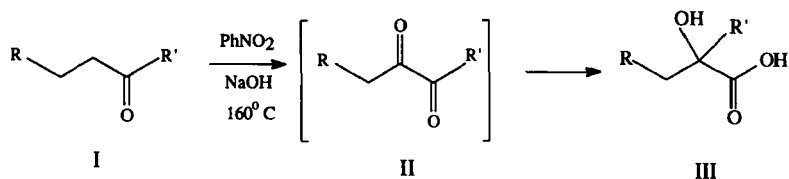
SINGLE STEP SYNTHESIS OF SUBSTITUTED LACTIC ACIDS FROM KETONES USING NITROBENZENE AS AN OXIDANT

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Abstract: A single step conversion of ketones to α,β -disubstituted lactic acids is described.

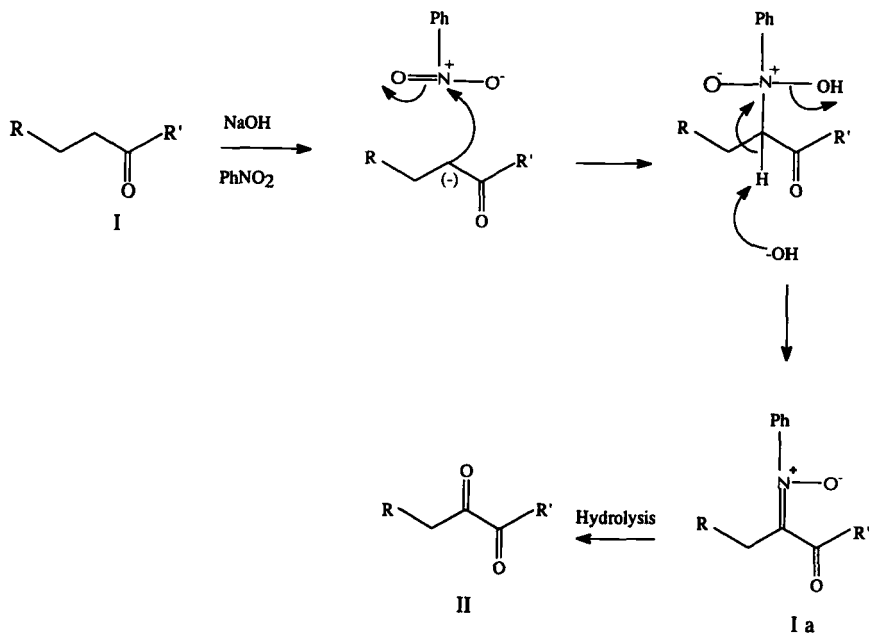
Lactic acids have been synthesised by various methods including hydrogenation or hydride reduction of α -keto acids, hydrocyanation of ketones followed by hydrolysis,¹ rearrangement of α -disubstituted β -amino esters,² rearrangement of α -ketoepoxides using sodium hydroxide³ and other methods.^{4,5} Recently a useful synthesis of β -aryl lactic acids has appeared.⁶ Most of the methods reported for lactic acids involve multistep synthesis. We herein report a simple, one-pot oxidative synthesis of α,β -disubstituted lactic acids from readily available starting material using nitrobenzene as an oxidant. Nitrobenzene has been previously used in the oxidative degradation of lignins and some ketones.⁷

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**Scheme I****Table**

Products	R	R'	mp. °C	% yield
IIIa	Phenyl	Methyl	95-96	48
IIIb	Phenyl	Phenyl	153-56	60
IIIc	p-Methoxy-phenyl	Phenyl	184	57
IIId	p-Methoxy-phenyl	Methyl	89	40
IIIe	Phenyl	2-Phenylethyl	137-38	35

Thus as shown in Scheme I, the ketone (I) on oxidation with nitrobenzene in the presence of sodium hydroxide in a laboratory autoclave yielded lactic acid (III) presumably through the intermediacy of α -diketone (II). Since the starting ketones can be structurally varied widely, this method appears to be a general method for the synthesis of diversely substituted lactic acids (Table). The yields of the reaction are moderate to good. Interestingly, it has been reported that β -aryl lactic acids are unstable⁶ whereas the lactic acids reported in this paper appear to be stable on storage.

**Scheme II**

The suggested mechanism for the oxidation of the ketone I to the α -diketone II is illustrated in Scheme II.

The ketone I is first deprotonated at the α -position. The anion then attacks the nitrogen of nitrobenzene to give an intermediate which undergoes dehydration to give the corresponding imine oxide Ia. The imine oxide finally gets hydrolysed to give the desired α -diketone which under the reaction conditions undergoes a benzilic acid rearrangement to give the substituted lactic acid.

The simplicity of the method as well as the wide structural variation that appears possible for the final lactic acids recommends the method for adoption and further exploration.

General procedure for the preparation of lactic acids (IIIa-IIIe)

A mixture of the ketone (0.10 mole) in nitrobenzene (0.65 mole) and aqueous sodium hydroxide solution (1 mole, 2N soln.) was heated to 160°C in an autoclave for 6 hr. The internal pressure rose to 50 psi. After cooling, the crude reaction mixture was washed with 200 ml chloroform to remove nitrobenzene and other neutral organics. The aqueous layer was then carefully acidified with conc. hydrochloric acid to pH 7. The resultant mixture was extracted with 200 ml chloroform, dried and the solvent evaporated to give the desired lactic acid. The final compound was recrystallised using toluene as the solvent.

¹H NMR (IIIa, CDCl₃, ppm): 1.5, (s, 3H); 2.92 (d, J=11 Hz, 1H)
3.22(d, J=11 Hz, 1H); 6.7 (bs, 2H); 7.3 (s, 5H).

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