

A New Synthesis of Carboxylic Acids from Ketones

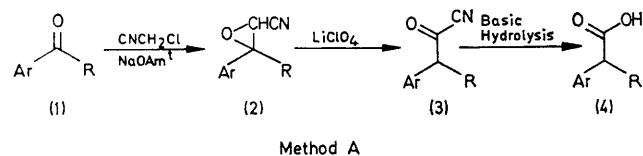
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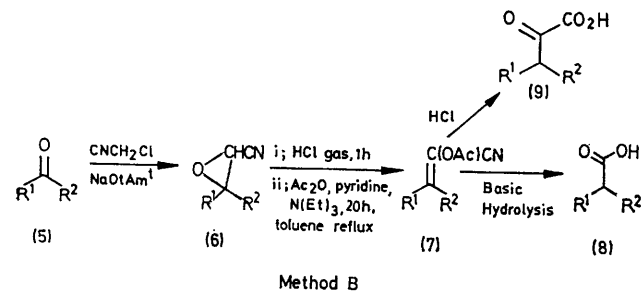
Summary The use of glycidonitriles allows a convenient conversion of aromatic and aliphatic ketones into carboxylic acids with the addition of one carbon atom.

WE describe a new conversion of ketones into carboxylic acids with the addition of one carbon atom. The application to aromatic ketones, in particular, has advantages over other alternatives.¹

Chloroacetonitrile is known to condense with a variety of ketones to give glycidonitriles (6) in good yields.² We have now modified this Darzens condensation to give glycidonitriles isolable in greater than 95% yield after distillation,



and have also found that the compounds can be converted into α -ketonitriles³ (3) (Method A) or α -acetoxyacrylonitriles (7) (Method B) and then to carboxylic acids. In Method A, crude β -arylglycidonitriles (2) are converted to α -ketonitriles (3) by a catalytic amount (4%) of potassium hydrogen sulphate, lithium trifluoroacetate or preferably lithium perchlorate⁴ in refluxing toluene or xylene (caution: HCN is evolved³). The α -ketonitrile (3) is then directly hydrolysed in aqueous base. Alternatively, heating (3) with an amine gives the corresponding amide.



Products and overall isolated yields are shown in the Table.

¹ E. L. Eliel and J. P. Freeman, *Org. Synth.*, 1953, **33**, 7; F. E. Ziegler and P. A. Wendler, *J. Amer. Chem. Soc.*, 1971, **93**, 4318; S. Cacchi, L. Caglioti, and G. Paolucci, *Chem. and Ind.*, 1972, 213; H. L. Cohen and G. F. Wright, *J. Org. Chem.*, 1953, **18**, 432; Y. S. Salkind and M. S. Peschkerowa, *J. Russ. Phys. Chem.*, 1914, 476; U. Schollkopf and R. Schroder, *Angew. Chem.*, 1972, **84**, 289; D. Seebach, *Synthesis*, 1969, **1**, 17.

² F. F. Blicke and J. A. Faust, *J. Amer. Chem. Soc.*, 1954, **76**, 3156; G. Stork, W. S. Worrall, and J. J. Pappas, *ibid.*, 1960, **82**, 4315; V. F. Martynov and A. V. Shchelkunov, *J. Gen. Chem. U.S.S.R.*, 1957, **27**, 1271.

³ Physical data show that under our reaction conditions (Method A) the α -keto nitriles are largely converted further to the dimeric form. Both monomers and dimers are hydrolyzed to carboxylic acids in aqueous base. J. Thesing and D. Witzel, *Angew. Chem.* 1956, **13**, 434.

⁴ This catalyst has been used to convert simple epoxides to ketones and aldehydes under somewhat less vigorous conditions. B. Rickborn and R. M. Gerkin, *J. Amer. Chem. Soc.*, 1971, **93**, 1693. Since completion of our work, the action of lithium perchlorate on glycidic esters has been reported to give mainly olefinic products. B. C. Hartman and B. Rickborn, *J. Org. Chem.*, 1972, **37**, 943.

⁵ A. Bayer, *Annalen*, 1891, **266**, 184.

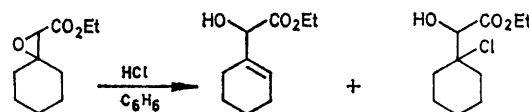
TABLE

Ketone	Product ^a	Yield/%	
		Method A	Method B
<i>p</i> -Isobutylacetophenone	2-(<i>p</i> -isobutylphenyl)-propionic acid ^b	72	73
α -Tetralone	1,2,3,4-tetrahydro-1-naphthoic acid ^c	47	68
Cyclohexanone	cyclohexanecarboxylic acid ^b		57
Cyclopentanone	cyclopentanecarboxylic acid ^b		51
2-Pentanone	2-methylpentanoic acid ^b		57

^a All products were purified by distillation or crystallization.

^b Identical with authentic samples. ^c M.p. 85°; lit.⁵ 85°.

A less direct route is preferred to convert aliphatic ketones into carboxylic acids (Method B). Dry HCl is allowed to convert the glycidonitrile (6) in to an α -hydroxy- β -chloronitrile which is acetylated and dehydrohalogenated to give an α -acetoxyacrylonitrile (7). Basic hydrolysis and acidification gives the desired carboxylic acid (8) (Table). In contrast to the clean addition of HCl to glycidonitriles, we found the action of HCl on glycidic esters gives α -hydroxy-



Scheme

$\beta\gamma$ -unsaturated esters and α -hydroxy- β -chloro esters in approximately equal amounts (Scheme). This propensity of glycidic esters to give elimination products, perhaps due to intramolecular deprotonation of the tertiary carbonium ion by the carboalkoxy group, shows that glycidonitriles are unique as precursors to α -ketoacids. The α -acetoxyacrylonitriles (7) may be treated with cold mineral acid to give α -ketoacids (9).

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