DECARBOXYLATION OF β-KETOESTERS IN HEXAMETHYLPHOSPHORIC TRIAMIDE

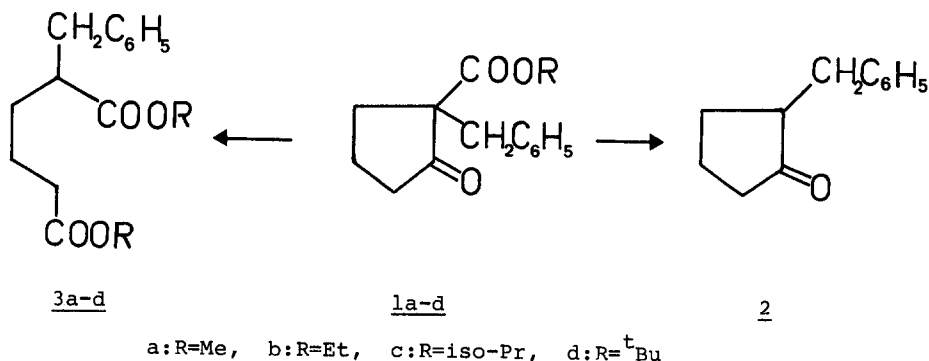Paul Müller and Bernard Siegfried

Département de Chimie Organique, Université de Genève,

30, quai de l'Ecole-de-Médecine, 1211 Genève 4

Ester cleavage by halide ions in dipolar aprotic solvents is believed to proceed by an S_N2 process involving nucleophilic displacement of carboxylate ion from the alcohol (1,2,3). The synthetic methods making use of this reaction require elevated temperature (4), strong base (5) or air-sensitive reagents (6,7,8) which limits their general applicability. Ester cleavage by nucleophilic attack on the alcohol is much more subjected to structural effects on the alcohol than is ester hydrolysis. Thus the reactivity of methylacetate is only 2.3 times that of ethyl acetate in the hydroxide ion catalyzed hydrolysis at 25° in 70% acetone (9). However, displacement of dihydroxy benzoate by thiocyanate in an S_N2 process in molten salt medium occurs 49 times faster from the methyl than from the ethyl ester (10). This allows selective cleavage of methyl esters.

In previous studies on nucleophilic reactivities we have investigated the substitution of tosylates by halide ions in various dipolar aprotic solvents (11). The most reactive combination of solvent and halide salt, hexamethylphosphoric triamide (HMPT) and lithium chloride, has now been applied to the cleavage of 2-benzyl-2-carbomethoxycyclopentanone (1a), a compound studied previously by Eschenmoser and Elsinger (1) in the lithium iodide-dimethylformamide (DMF) system. Attack by the halide ion may lead to the carboxylate which undergoes decarboxylation to 2 in a subsequent step. Ester cleavage and decarboxylation, however, could also be concerted.

$$\underline{3a\text{-}d} \qquad\qquad \underline{1a\text{-}d} \qquad\qquad\qquad \underline{2}$$

$$a:R=Me, \quad b:R=Et, \quad c:R=iso\text{-}Pr, \quad d:R={}^tBu$$

    Treatment of $\underline{1a}$ with a two-fold excess of lithium chloride in HMPT for 24 hours at 75° resulted in a ca. 90% yield of 2-benzyl-cyclopentanone ($\underline{2}$). The reaction time was reduced to 60 min. when lithium chloride was replaced by sodium cyanide in HMPT, a system that could not be studied previously owing to the low solubility of the salt at 25° (11). In a typical experiment 0.57 g (11.6 mmole) sodium cyanide was dissolved in 100 ml dry HMPT at 75° under nitrogen atmosphere. 1.5 g (6.4 mmole) of ester $\underline{1a}$ was added and the mixture stirred for 60 min. After cooling it was poured into 500 ml of 2N hydrochloric acid (hood!). Extraction with CCl_4 yielded $\underline{2}$, contaminated by 2.5% of a side product (see below). Pure $\underline{2}$ (0.89 g, 80%) was obtained after chromatography and distillation and identified by IR, NMR and MS. The semicarbazone had M.P. 198° (Lit. 204-205° (1)).

    From an experiment with 2-methyl-2-carbomethoxycyclopentanone as substrate acetonitrile was isolated in 70% yield. This demonstrates that attack of the cyanide takes place at the alkyl group.

    Quantitative information on the rate enhancement in the sodium cyanide/HMPT system compared with other systems was obtained by kinetic measurements. Aliquots of the reaction mixture were withdrawn at appropriate time intervals. After work up, progress of the reaction was determined by comparison of the NMR signals of the methyl or benzyl protons with that of the aromatic protons. The data were analyzed in terms of the commonly used second-order rate equation by

Table. Rate constants for ester cleavage at 75.0°

Salt	Solvent	Ester	$10^3 k_{obs}$ $[M^{-1}min^{-1}]$	$10^3 k_{rel} S_N 2^{a)}$	$r^{b)}$
NaCN	HMPT	1a	249.	243.	0.9733
NaCN	DMF	1a	8.17	-	0.9841
LiCl	HMPT	1a	9.49	-	0.9996
LiBr	HMPT	1a	3.86	-	0.9573
NaCN	HMPT	1b	3.97	3.37	0.9576
NaCN	HMPT	1c	0.94	0.81	0.9597
NaCN	HMPT	1d	1.02	-	0.9627

a) Corrected for side reaction; b) Correlation coefficient

means of a computer program. The results are summarized in the Table. Transfer

of the reaction with sodium cyanide from DMF to HMPT results in a rate increase

of a factor of 30. In HMPT the reactivities of CN^-, Cl^-, Br^- towards 1a are 65,

2.45, and 1.0 respectively. Using relative halide ion reactivities in DMF from

the literature (12,13), the rates of the sodium cyanide/HMPT system are accele-

rated by a factor of 5-10'000 over lithium iodide/DMF.

The reactions of the ethyl-(1b), isopropyl-(1c), and tert.butyl-(1d) esters

with sodium cyanide are more complex. A secondary reaction contributed up to

20% to the observed rate constants. The rate constants k_{obs} in the Table are

corrected for this side reaction, assuming a scheme of two parallel reactions

consuming one equivalent of cyanide ion each. With this assumption the methyl

ester 1a is 72 times more reactive than 1b. The reactivity of the other esters

(1c and 1d) agrees with the proposed $S_N 2$ mechanism with some E2 contribution.

The structures of the side products 3a-d (see Scheme) are evident from

their spectral data. 3b was also obtained by ethoxide induced ring opening of

1b in refluxing ethanol (14) and showed identical spectral properties as the

side product of the reaction of 1b with cyanide ion. The formation of 3 from 1

may be rationalized by nucleophilic displacement of alcoholate via attack by

cyanide on the carboxyl group (15). The alcoholate, in turn, could induce a

retro-Dieckmann reaction by attack on the ketone function of the ketoester (14).

The reaction may be applied to other esters as well, although longer reac-
tion times are required. Thus methyl benzoate yields benzoic acid (24 hrs, 75°,
yield 85%) and phthalide under the same conditions gives α-cyano-o-toluic acid
(80%). A mixture of methylmesitoate (5.6 mmole) and ethylbenzoate (5.8 mmole)
upon treatment with sodium cyanide (5.9 mmole) in 50 ml of HMPT (24 hrs, 75°)
afforded mesitoic acid (4.8 mmole, 85%), methyl mesitoate (0.5 mmole, 9%) and
ethylbenzoate (5.4 mmole, 93%). Accordingly the methyl specificity would appear
to be not restricted to β-ketoesters.

The synthetic applicability and the mechanistic aspects of this reaction
are currently under investigation.

BIBLIOGRAPHY

(1)   F. Elsinger, J. Schreiber, and A. Eschenmoser, Helv. Chim. Acta 43, 113
      (1960); F. Elsinger, Org. Synth. 45, 7 (1965).

(2)   E. Taschner and B. Libereck, Roczniki Chem. 30, 323 (1956), Chem. Abstr.
      51, 1039 (1957).

(3)   E. Cherbuliez, J.P. Leber, and M. Bouvier, Helv. Chim. Acta 36, 1203 (1953)

(4)   A.P. Krapcho, G.A. Glynn, and B.J. Grenon, Tetrahedron Letters 1967, 215;
      A.P. Krapcho and A.J. Lovey, Tetrahedron Letters 1973, 957.

(5)   F.C. Chang and N.F. Wood, Tetrahedron Letters, 1964, 2969.

(6)   P.A. Bartlett and W.S. Johnson, Tetrahedron Letters 1970, 4459.

(7)   G.I. Fentrill and R.N. Mirrington, Ausl. J. Chem. 25, 1731 (1972);
      W.R. Vaughan and J.B. Baumann, J. Org. Chemistry 27, 739 (1962).

(8)   J.C. Sheehan and G.D. Daves, Jr., J. Org. Chemistry 29, 2006 (1964).

(9)   R.W. Jones and J.D.R. Thomas, J. Chem. Soc. (B) 1966, 661.

(10) E.W. Thomas and T.I. Crowell, J. Org. Chemistry 37, 744 (1972).

(11) P. Müller and B. Siegfried, Helv. Chim. Acta 55, 2400, 2965 (1972).

(12) W.M. Weaver and J.D. Hutchison, J. Amer. Chem. Soc. 86, 261 (1964).

(13) R. Alexander, E.C.F. Ko, A.J. Parker, and T.J. Broxton, J. Amer. Chem.
      Soc. 90, 5049 (1968).

(14) W. Foerst, Neuere Methoden der präparativen organischen Chemie, Verlag
      Chemie Weinheim, 1960, p. 69-87.

(15) Hydrolysis of the intermediate during work-up would yield 2.