

Note

Alkali cleavage of α,α -disubstituted β -ketoesters, nitriles and β -diketones

T H Bennur & N N Joshi*

Division of Organic Synthesis,
National Chemical Laboratory, Pune 411 008, India

Received 9 October 2001; accepted (revised) 26 February 2002

Nucleophilic cleavage of several α,α -disubstituted β -ketoesters, nitriles and β -diketones has been examined. Only alkali hydroxides participated in the reaction yielding substituted esters, nitriles and ketones.

Cleavage of the keto group at α -position is an unusual reaction in organic chemistry. There are scattered examples in the literature describing such deacylation process. One of the earliest examples is the classical Haller-Bauer reaction¹ involving the cleavage of ketones with NaNH_2 . Fission of non-enolizable ketones has also been accomplished² with KO^tBu . The reaction proceeds through the formation of a tetrahedral intermediate followed by cleavage of the C-C bond with the generation of a carbanion³. It is therefore obvious that in the cases where the carbanion is stabilized, the cleavage would be more facile. Whereas unsubstituted and monosubstituted β -ketoesters undergo normal saponification⁴ on treat-

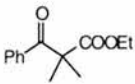
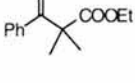
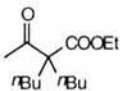
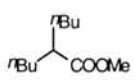
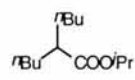
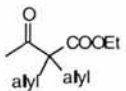
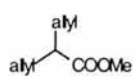
ment with alkali, α,α -disubstituted derivatives undergo deacylation⁵. This could be the combined effect of the relief of the steric strain and stability of the carbanion.



X = COOR, CN, COR

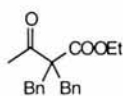
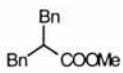
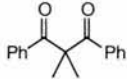

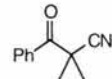
We decided to investigate this interesting reaction and present generalized results for the deacylation of β -ketoesters, nitriles and β -diketones. The results are summarized in the **Table I**. A variety of α,α -disubstituted derivatives were prepared and treated with several nucleophiles. Only hydroxy nucleophile leads to the cleavage of the keto group. Other nucleophiles *e.g.* RONa , PhSK and RNH_2 did not participate in the reaction. Whereas the β -diketone (entry 10) and β -ketonitrile (entry 11) behaved as expected, the cleavage of β -ketoesters posed mechanistic problem. The cleavage could occur *via* the stabilized (by the ester group) carbanion as in the case of diketone and ketonitrile or the reaction could involve a ketene intermediate. In either case, the carbon-carbon bond cleavage proved to be more facile than expected saponification. The newly generated ester from the

Table I—Deacylation of β -ketoesters, nitriles and β -diketones

Entry	Substrate	Nucleophile	Temp. °C	Time (hrs)	Product	Yield* (%)
1		NaOH / MeOH	25	3	PhCOOH	90
2		LiOH / MeOH	25	4	PhCOOH	77
3		BuNH_2 / THF	reflux	12	no reaction	
4		BuONa / THF	reflux	12	no reaction	
5		PhSK / DMF	80	12	no reaction	
6		NaOH / MeOH	reflux	2		84(97)
7		NaOH / PrOH	reflux	2		81(90)
8		NaOH / MeOH	25	24		79(87)

—Contd

Table I—Deacylation of β -ketoesters, nitriles and β -diketones (—Contd)

Entry	Substrate	Nucleophile	Temp. °C	Time (hrs)	Product	Yield* (%)
9		NaOH / MeOH	25	48		77(81)
10		NaOH / MeOH	25	2	PhCOOH 	74 (92)
11		NaOH / MeOH	25	3	PhCOOH	85

* The figures in parenthesis are yields as estimated by GC.

cleavage was always the ester of the alcohol used as the solvent (*e.g.* entry 7). Blank experiments ruled out the possibility of any transesterification under the conditions employed. For example, ethyl benzoate does not undergo significant transesterification in isopropanol in the presence of catalytic amount of sodium hydroxide.

In summary, we have examined the alkali-mediated deacylation of α,α -disubstituted β -ketoesters, nitriles and β -diketones with a view to present the aspects hitherto unknown or undocumented. The reaction has potential synthetic utility for the preparation of a variety of substituted esters, nitriles and ketones.

Experimental Section

All the reactions were monitored by GC. The authenticity of the products was confirmed by mp (solid compounds), co-injection on GC (volatile compounds) and spectroscopy (new compounds).

General procedure. To a solution of the title compound (5 mM) in appropriate alcohol (10 mL), sodium hydroxide (5 mM) was added and the reaction mixture was stirred at the temperature indicated in

Table I. The reaction was monitored by GC for the disappearance of the starting material. Usual work-up was then followed to isolate the product. Amongst the two products formed, only the larger unit was isolated. Water-soluble products (*e.g.* acetic acid, entry 6-9), volatile products (*e.g.* ethyl butyrate, entry 1 & 2) were not isolated. In the case of entry 10, both benzoic acid and isobutyrophenone were isolated in comparable yield.

Acknowledgement

One of the authors (THB) is thankful to the CSIR, New Delhi for the grant of a Research Fellowship.

References

- 1 Hamlin K E & Weston A W, *Organic Reactions*, 9, 1957, 1.
- 2 Gassmann P G, Lumb J T & Zalar T V, *J Am Chem Soc*, 89, 1969, 946.
- 3 Stetter H in *Newer Methods of Preparative Organic Chemistry*, Vol II, edited by W Foerst, (Academic Press Inc, New York), 1963, pp 51.
- 4 (a) Swain C G, Bader R F W, Esteve (Jr) R M & Griffin R N, *J Am Chem Soc*, 83, 1961, 1951.
(b) Straub T S & Bender M L, *J Am Chem Soc*, 94, 1972, 8881.
- 5 Stotter P L & Hill K A, *Tetrahedron Lett*, 1972, 4067.