Tetrahedron Letters,Vol.23,No.18,pp 1875-1876,1982 0040-4039/82/181875-02$03.00/0
Printed in Great Britain

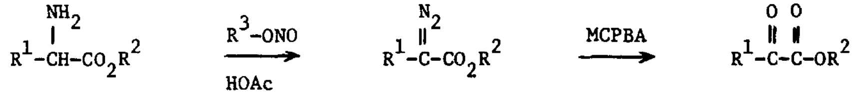
CONVERSION OF α-AMINOESTERS TO α-KETOESTERS

E. D. Thorsett

New Lead Discovery Department, Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc., P.O. Box 2000, Rahway, N.J. 07065 USA

Summary: A one-pot method for converting α-aminoesters to α-ketoesters *via* peracid oxidation of diazoesters is described.

Several years ago Curci and co-workers[1] reported that α-diazoketones gave α-diketones on treatment with m-chloroperbenzoic acid (MCPBA). Although the authors were primarily interested in mechanistic data, their results indicated that the conversion could be of potential synthetic value. Since we were interested in α-ketoesters as intermediates for enzyme inhibitor design studies,[2] the reaction of interest became the conversion of α-diazoesters to α-ketoesters. Takamura and collaborators[3] had published a convenient method for conversion of α-aminoesters to α-diazoesters using isoamylnitrite in the presence of acetic acid. Thus, the desired transformation became the conversion of α-aminoesters (1) to α-ketoesters (3) as described by the equation:



$$R^1\text{-}\overset{NH_2}{\overset{|}{C}}H\text{-}CO_2R^2 \xrightarrow[HOAc]{R^3\text{-}ONO} R^1\text{-}\overset{N_2}{\overset{\|}{C}}\text{-}CO_2R^2 \xrightarrow{MCPBA} R^1\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{O}{\overset{\|}{C}}\text{-}OR^2$$

1 2 3

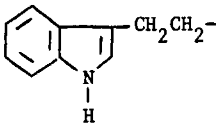
In the initial investigation of this reaction sequence, the diazoesters (2) were isolated as described.[3] Treatment of 2 with 1 equivalent of MCPBA in either chloroform or methylene chloride resulted in an exothermic reaction accompanied by vigorous nitrogen evolution. When gas evolution ceased, the reaction was concentrated, diluted with pentane and filtered. The filtrate was washed with dilute sodium bicarbonate, dried and concentrated. The products were then purified by silica gel chromatography or distillation.

Subsequently it was found that the reaction sequence could be run in one-pot thus avoiding the isolation of the α-diazoesters (2). Furthermore, replacement of isoamyl nitrite by t-butyl nitrite afforded a cleaner α-ketoester by virtue of easier removal of t-butanol. Thus, in the one-pot procedure the cooled diazotization mixture[3] was treated with one mole m-chloroperbenzoic acid[4] per mole of starting amino ester to afford the α-ketoester.

In Table 1 are collected the results of several experiments. Readily oxidizable functionalities are incompatible with the reaction conditions. Thus, sulfur and indole[5] containing compounds suffered decomposition. However, hydrocarbon and Cbz-protected amino containing compounds diazotized and oxidized without incident. In general, the results reported here appear to parallel those observed by Poisel[6] who recently reported a similar overall transformation. Although this reaction is subject to certain limitations, it does appear to provide a facile route from α-aminoesters to α-ketoesters in those cases where it is applicable.

Table 1

Yields of α-Ketoesters (3)

3	R^1	R^2	% Yield*	
a.	CH_3-	$CH_2C_6H_5$	61 (94)	semicarbazide: mp. 175-176 (lit.: 176)[7]
b.	$(CH_3)_2CH$-	CH_3	66 (83)	bp.: 68-70 at 10 mm 2,4-DNP: mp. 104-105 (lit.: 104-106)[8]
c.	Cbz-NH-$(CH_2)_4$-	CH_3	54	2,4-DNP: mp. 168-169
d.	$C_6H_5CH_2CH_2$-	C_2H_5	55	bp: 97-101 at 0.1 mm
e.	CH_3-S-$(CH_2)_2$-	CH_3	0	
f.		C_2H_5	0	

*Chromatographically pure products from one-pot procedure.

Yields in parentheses are for ketoesters derived from pure α-diazoesters.

References

1. R. Curci, F. DiFuria, J. Ciabattoni and P. W. Concannon, J. Org. Chem., 39, 3295 (1974).
2. A. A. Patchett, E. E. Harris, E. W. Tristram, M. J. Wyvratt, et al., Nature, 288, 280 (1980).
3. N. Takamura, T. Mizoguchi, K. Koga and S. Yamada, Tetrahedron, 31, 227 (1975).
4. The MCPBA is added in small portions to the reaction mixture. In larger scale runs (e.g. >50 mmole), external cooling is recommended. The oxidation reaction is generally allowed to proceed 30 minutes after completion of MCPBA addition.
5. Experiment run by Dr. D. Hangauer.
6. H. Poisel, Chem. Ber., 111, 3136 (1978).
7. Dictionary of Organic Compounds (4th Ed.), 5, 2829 (1965).
8. Y. Iwakura, F. Toda and Y. Torii, J. Org. Chem., 31, 2875 (1966).

(Received in USA 12 February 1982)