Syntheses of α-Keto Amides and Acids from Ethyl Alkylidenecyanoacetate

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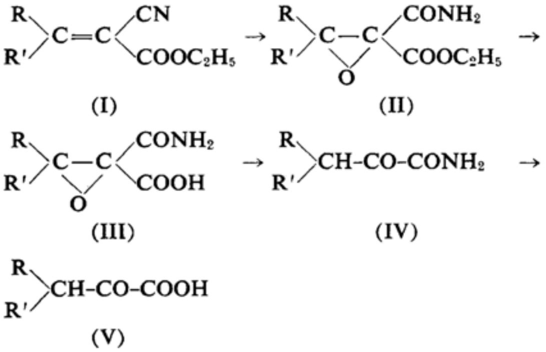
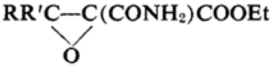
The present paper deals with a novel preparation of α-keto amides and acids from ethyl alkylidenecyanoacetate as starting material. The synthetic steps are shown in the following scheme.



Payne and Williams[1] have shown that α, β-unsaturated acids such as crotonic and maleic

TABLE I. PREPARATION OF EPOXYAMIDE II FROM ETHYL ALKYLIDENECYANOACETATE (I)


$$\underset{\diagdown O \diagup}{RR'C-C}(CONH_2)COOEt$$

R	R'	M. p., °C	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N%
Methyl	Methyl	101	61	$C_8H_{13}O_4N$	51.33	7.00	7.48	50.89	6.53	7.45
Methyl	Ethyl	77	80	$C_9H_{15}O_4N$	53.72	7.51	6.96	53.28	7.45	7.01
Methyl	Isobutyl	69	71	$C_{11}H_{19}O_4N$	57.62	8.35	6.11	57.37	8.01	6.15
Methyl	Hexyl	88	64	$C_{13}H_{23}O_4N$	60.98	9.01	5.44	60.62	8.78	5.42
Propyl	Propyl	99	50	$C_{12}H_{21}O_4N$	59.24	8.70	5.76	58.85	8.40	5.84
Methyl	Phenyl	91	70	$C_{13}H_{15}O_4N$	62.64	6.07	5.62	62.40	6.01	5.59
Cyclohexyl		111	65	$C_{11}H_{17}O_4N$	58.13	7.54	6.16	58.23	7.45	6.07
Cyclopentyl		123	75	$C_{10}H_{15}O_4N$	56.32	7.09	6.57	55.99	6.83	6.53

TABLE II. PREPARATION OF α-KETOAMIDE IV FROM III

$RR'CHCOCONH_2$

R	R'	M. p., °C	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N%
Methyl	Methyl	112	50	$C_5H_9O_2N$	52.16	7.88	12.17	51.89	7.77	11.99
Methyl	Ethyl	71	52	$C_6H_{11}O_2N$	55.79	8.58	10.85	55.81	8.59	10.85
Propyl	Propyl	63	80	$C_9H_{17}O_2N$	63.13	10.00	8.18	62.84	9.49	8.20
Methyl	Phenyl	116	64	$C_{10}H_{11}O_2N$	67.78	6.26	7.91	67.53	6.11	7.84
Cyclohexyl		120	48	$C_8H_{13}O_2N$	61.91	8.44	9.03	62.07	8.18	9.02
Cyclopentyl		144	40	$C_7H_{11}O_2N$	59.55	7.85	9.92	59.37	7.62	9.91

TABLE III. PREPARATION OF α-KETO ACID V FROM III

$RR'CHCOCOOH$

R	R'	M. p., °C (B. p., °C/mmHg)	Yield, %	Oxime M. p., °C	Oxime Formula	Oxime Calcd. N	Oxime Found N%
Methyl	Ethyl	40 (82~84/18)	75	164	$C_6H_{11}O_3N$	9.65	9.51
Methyl	Isobutyl	89 (140~143/7)	80	132 (decomp.)	$C_8H_{15}O_3N$	8.09	8.03
Methyl	Hexyl	(126~129/8)	92	90 (decomp.)	$C_{10}H_{19}O_3N$	6.96	6.81
Propyl	Propyl	(145~148/7)	80	144 (decomp.)	$C_9H_{17}O_3N$	7.48	7.33
Methyl	Phenyl	53	90	120 (decomp.)	$C_{10}H_{11}O_3N$	7.25	7.02
Cyclohexyl		50	98	170	$C_8H_{13}O_3N$	8.18	8.18
Cyclopentyl		54	60	131 (decomp.)	$C_7H_{11}O_3N$	8.91	8.92

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[1] G. B. Payne and P. H. Williams, *J. Org. Chem.*, **24**, 54 (1959).

acids are efficiently epoxidized with hydrogen peroxide using sodium tungstate as catalyst, and Payne[2] has also established that ethyl isopropylidenecyanoacetate is converted to the corresponding epoxyamide by the use of hydrogen peroxide and sodium hydroxide.

In the present work, ethyl alkylidenecyanoacetate was epoxidized at 70~80°C in ethanol containing 30% hydrogen peroxide and sodium tungstate dihydrate. The resulting epoxyamide II reacted with alcoholic alkali at room temperature to give the compound III. Decarboxylation and rearrangment of III to α-ketoamide IV was readily accomplished by heating with a small amount of water. Further, the treatment of III and IV with dilute hydrochloric acid afforded α-keto acid V in a good yield. The compounds IV and V formed the corresponding oximes. The compounds which were prepared by this process are listed in Tables I–III.

The method appears to be generally applicable in the synthesis of α-keto amide and acid.

Details of this study will be published elsewhere.

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[2] G. B. Payne, ibid., 26, 654 (1961).