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CROSSED CLAISEN CONDENSATION OF 2-ALKYL-4,4-DIMETHYL-2-OXAZOLINES WITH ACID ANHYDRIDES BY ALUMINUM CHLORIDE AND TRIETHYLAMINE

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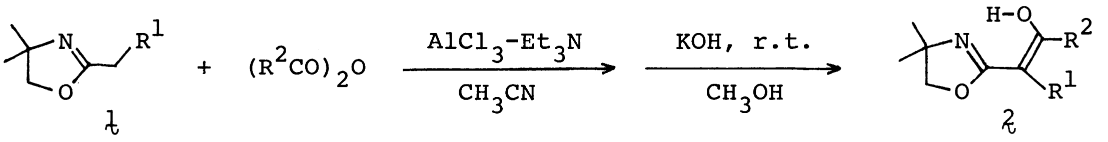
Reactions of 2-*prim*-alkyl-4,4-dimethyl-2-oxazolines with alkanoic acid anhydrides having alpha hydrogens in the presence of aluminum chloride and triethylamine gave an oxazoline derivative of β-keto acids in moderate yields.

Selective crossed Claisen condensation of acid derivatives with acylating reagents having alpha hydrogens is very difficult because of their self-dimerization.$^{1)}$ A considerably reactive reagent must be used for the nucleophilic component of the reaction, e.g., *O*-silyl ketene acetal$^{2)}$ or lithium enolate.$^{3)}$ We report here a novel crossed Claisen condensation of 2-*prim*-alkyl-4,4-dimethyl-2-oxazolines (**1**), which are stable and readily available compounds,$^{4)}$ with alkanoic acid anhydrides in the presence of aluminum chloride and triethylamine to give an oxazoline derivative of β-keto acids (**2**).



Results are summarized in Table 1. 2-Methyloxazoline was more reactive than 2-ethyl or 2-isobutyl derivative. 2-Isopropyloxazoline gave no expected product. Acetic anhydride was most reactive and other alkanoic acid anhydrides were applicable. Acid chlorides having alpha hydrogens did not give **2** under the similar conditions probably due to decomposition of the reagents. The acid anhydrides did not react with **1** in the absence of aluminum chloride, while acid chlorides lacking alpha hydrogens react with **1** to give **2** in good yields.$^{5)}$ These facts suggest that the acid anhydrides are activated by the aluminum chloride to quaternarize the nitrogen of **1**.

This novel method of the crossed condensation is more convenient than others using more reactive nucleophiles,$^{2,3)}$ although the yields of **2** are not so high. The obtained 2-acylmethyl-2-oxazolines (**2**) are versatile materials for the β-keto ester synthesis because **2** can be monoalkylated selectively$^{5)}$ and 2-oxazoline group is known to be converted to various functional groups.$^{4)}$

Representative procedure is following: A mixture of **1** (20 mmol) and triethylamine (160 mmol) was added to a solution of aluminum chloride (30 mmol) in acetonitrile (40 ml). Acid anhydride (60 mmol) was added to the mixture below 0 °C during 30 min. The mixture was kept at the temperature shown in Table 1. The reaction was quenched by adding 3 M aqueous sodium hydroxide (60 ml) at 0 °C and the products were extracted with chloroform. The extract was dissolved in 1.5 M methanolic potassium hydroxide (20 ml) and allowed to stand at room temperature for 10 h in order to decompose diacylated products.[5] Purification of **2** is shown at notes b) and c) in Table 1.

Table 1. Yields and properties of oxazoline derivatives of β-keto acids (**2**)

Product **2**		Melting Point	E/K Ratio[a]	Reaction Conditions		Yields of **2**
R^1	R^2	θ_m/°C		θ_m/°C	Time/h	%
H	CH_3	125-127	94/6	0	6	71
H	C_2H_5	95-98	87/13	50	3	56[b]
H	C_3H_7	74-79	87/13	50	3	55[b]
H	i-C_3H_7	96-97.5	91/9	50	3	31[b]
H	C_4H_9	64-66	89/11	50	3	64[b]
H	i-C_4H_9	90-92	93/7	50	3	62[b]
H	C_5H_{11}	55-58	91/9	50	3	55[b]
CH_3	CH_3	113-115[d] (45 mmHg)	61/39	0	15	57[c]
i-C_3H_7	CH_3	65-70[d] (4 mmHg)	73/27	0	15	50[c]

a) Enol-keto ratio of **2** in $CDCl_3$. b) Crude product was co-distilled with ethylene glycol (20 ml) under reduced pressure and recrystallized from benzene-hexane. c) Crude product was distilled under reduced pressure.
d) Boiling point.

References

1) C. R. Hauser and B. E. Hudoson, Jr., Org. React., 1, 266 (1942).
2) M. W. Rathke and D. F. Sullivan, Tetrahedron Lett., 1973, 1297; G. Rousseau and L. Blanco, ibid., 26, 4195 (1985).
3) A. I. Meyers, D. L. Temple, R. L. Nolen, and E. D. Mihelich, J. Org. Chem., 39, 2778 (1974); D. A. Evans, M. D. Ennis, T. Le, N. Mandel, and G. Mandel, J. Am. Chem. Soc., 106, 1154 (1984); Y. Ito, T. Katsuki, and M. Yamaguchi, Tetrahedron Lett., 25, 6015 (1984).
4) A. I. Meyers and E. D. Mihelich, Angew. Chem., Int. Ed. Engl., 15, 270 (1976).
5) Y. Tohda, T. Kawashima, M. Ariga, R. Akiyama, H. Shudoh, and Y. Mori, Bull. Chem. Soc. Jpn., 57, 2329 (1984).

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