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CONVENIENT SYNTHESES OF AROYLAMINO ACIDS AND α-AMINO KETONES[1)]

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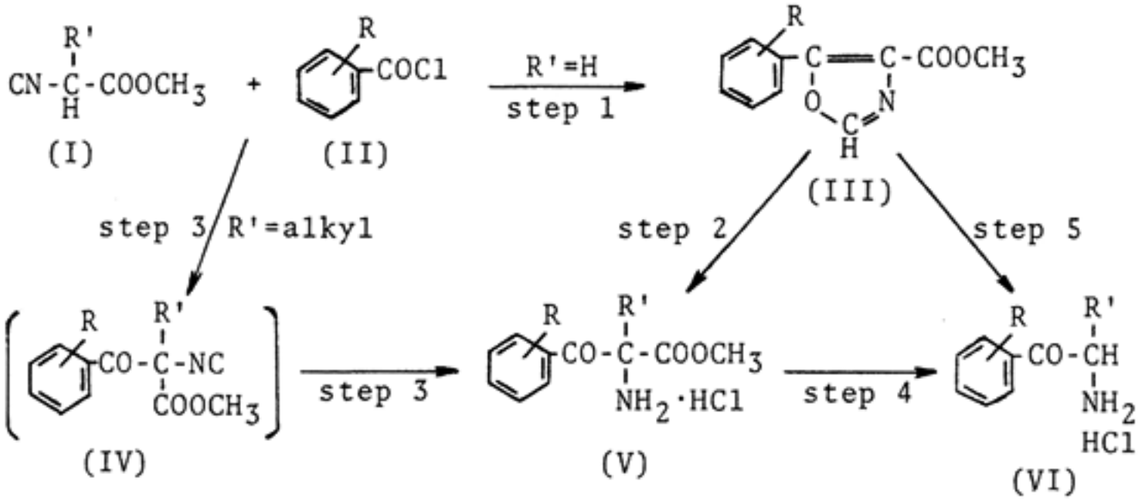
C-Acylamino acid, especially aroylamino acid is a key and still currently interest compound for the pharmaceutical intermediate in which β-arylserine prepared by the reduction in an example would be physiologically important.

On the other hand, phenyl derivatives of α-amino ketone are also more useful compounds for the synthesis of those of amino alcohol which are important compounds including physiologically interest substances such as ephedrine and adrenaline used as sympathomimetic agents.

Several syntheses methods of the aroylamino acid[2)] and α-amino ketone[3)] have been reported. However those methods require various limited conditions and are not advantageous for the practical preparation.

Within the framework of our studies on the synthesis of amino acid, isocyano compound which is readily synthesized from N-formyl amino acid ester[4)] was known to be particularly

interest and valuable. In this paper we report that a new convenient synthesis which we believe is more generally suited for the preparation of aroylamino acids and α-amino ketones as shown in scheme.



The reaction of α-isocyano acetate (I, R'=H) with various acyl halides (II) in the presence of base afforded oxazole compounds (III) in good yield (step 1). In most recent, the reaction by the use of BuLi or t-BuOK as a base was independently described by Schöllkopf et al.[5]. However, in the course of studies on the synthesis of amino acids from the isocyanide, we found the same reaction took place too in the presence of not only metallic base such as NaH, but also organic base such as triethylamine or 1,5-diazabicyclo [5·4·0] undec-5-ene (DBU). A typical example is as follows; A mixture of methyl α-isocyano acetate (2.0 g), benzoylchloride (2.8 g) and triethylamine (8.4 ml) in THF (30 ml) was stirred for 48 hr at room temperature. After the reaction was over, the mixture was evaporated to remove the solvent. To the obtained residue was added ethyl acetate, and the solution was washed

with water, dried and then evaporated *in vacuo*. The obtained precipitate was washed with n-hexane and collected by filtration. Recrystallization from methanol gave 4-carbomethoxy-5-phenyloxazole (III, R=H) in 91% yield. In a similar way, several oxazole derivatives were prepared and those results were shown in Table I.

The oxazole compounds (III) were readily converted into aroylamino acid derivatives (V, R'=H) under heating at 50-60°C in 3N HCl-MeOH for 3 hr in high yield. (Table I)

In the reaction of α-alkyl isocyano compounds (I, R'=CH_3, $CH(CH_3)_2$) with various acyl halides (step 3), the oxazole compounds described above were not formed, but aroyl compounds (IV) were obtained. The compounds were identified by IR spectra showing 2210-20, 1740 and 1690 cm^{-1} due to the NC, $COOCH_3$ and CO, respectively, and NMR spectra. For example,

Table I. Formation of Oxazole Compounds (III) and Aroylamino Acid Derivatives (V, R'=H)

R	III mp(°C)	Yield (%)	V (R'=H) mp(°C) (dec)	Yield (%)
H	91-3	91	185-6	84
3,4-<O-O-	130-2	92	170-1	85
3,4,5-tri-OMe-	137-9	79	174-5	80
3,4-di-Cl-	142-3	88	165-7	80
3,4- 	111-3	85	169-70	85

to a suspension of 69% NaH (1.5 g) in THF (80 ml) was added a mixture of methyl α-isocyano propionate (4.5 g) and THF (20 ml) at room temperature under stirring. After stirring for 2 hr at the same temperature, 3,4-methylenedioxy benzoyl chloride (7.24 g) dissolved in THF (20 ml) was added gradually to the mixture for a period of 1 hr at room temperature. After stirring was continued over night, the solvent was removed under reduced pressure. To the residue was added ethyl acetate, and the solution was washed with water, dried and then evaporated *in vacuo*. The resulted compound (IV) without purification was subsequently hydrolyzed with 1N HCl-MeOH for 1 hr at 50°C to obtain α-(3,4-methylenedioxy)benzoyl alanine methyl ester hydrochloride (V, R=3,4-methylenedioxy, R'=CH_3). In a similar way, several aroylamino acid derivatives were prepared and these results were shown in Table II.

Furthermore, when the aroylamino acid and oxazol compound obtained in this experiment were treated with 6N HCl-MeOH

Table II. Preparation of α-Alkyl Aroylamino Acid Derivatives (V) (step 3)

R	R'	mp(°C) (dec)	Yield (%)
3,4- 	CH_3	143-4	58
3,4,5-tri-OMe-	CH_3	155-7	62
H	$CH(CH_3)_2$	167-7.5	65
3,4-	$CH(CH_3)_2$	152-2.5	55
3,4- 	$CH(CH_3)_2$	129-32	55

under refluxing for 5-6 hr, the corresponding α-amino ketone hydrochlorides (VI) were obtained in nearly quantitative yield accompaning with decarboxylation (step 4,5 Table III). An example of the decarboxylation reaction is as follows; α-Benzoyl glycine methyl ester hydrochloride (V, R, R'=H, 4.58 g) was dissolved in a mixture of conc.HCl (50 ml) and MeOH (50 ml) and refluxed for 5 hr. After the solvent was removed under reduced pressure, to the residue was added ethyl acetate to precipitate. The precipitate was collected by filtration and washed with ethyl acetate. Recrystallization from ethyl acetate-methanol gave phenacylamine hydrochloride (VI, R, R'=H) in 90% yield (step 4). In the same way, the phenacylamine hydrochloride was obtained also from oxazole compound (III, R=H) in 92% yield. (step 5)

Table III. Formation of α-Amino Ketone Derivatives (VI)

R	R'	mp(°C) (dec)	Yield* (%) (A)	(B)
H	H	194-6	90	92
3,4-	H	187-91	93	94
3,4,5-tri-OMe-	H	243-4	91	94
3,4- 	H	256	91	90
3,4-	CH_3	206	93	
3,4,5-tri-OMe-	CH_3	237	95	
H	$CH(CH_3)_2$	198-9	87	
3,4-	$CH(CH_3)_2$	227-9	86	

* (A) : from step 4 (B) : from step 5

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