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A SIMPLE AND CONVENIENT METHOD FOR THE PREPARATION OF α-SUBSTITUTED-α-DIAZOESTERS

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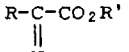
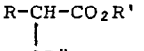
The first synthesis of diazoesters by direct diazotization of amino acid esters was reported by Curtius[1,2] around 1900. Although this method is well suited for the preparation of diazoacetic ester,[3] it is generally inapplicable to the syntheses of α-substituted-α-diazoesters (I),[2] because of very low yields and contamination with impure byproducts. Other indirect routes[4,5,6] have also been reported for preparing I from amino acid ester derivatives as starting materials. These are not only rather tedious and wasteful, but have also been attempted on a limited numbers of amino acid derivatives, e.g. glycine or alanine ester.

We have found a simpler and more convenient synthesis of I. When amino acid esters in chloroform or benzene are refluxed with isoamylnitrite and a small amount of acid, I is obtained in fairly good yields as shown in Table I. Purification of the products is successful by chromatography on alumina which removes slight amounts of byproducts, α-hydroxy acid derivatives (II), most effectively.



(I)



(II)

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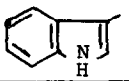
Diazo esters (I), prepared in this manner, are analitically pure. Their structures are evidenced by NMR, IR (liq : 2075-2085 cm^{-1} ($\rangle C=\overset{+}{N}=\overset{-}{N}$), 1680-1695 cm^{-1} ($-CO_2R'$)) and UV (ethanol : 262-264, 360-415 mμ ($-\underset{\underset{N_2}{\|}}{C}-CO_2R'$)) spectra. Id is

Table I

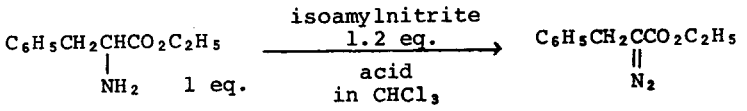
$$\underset{\underset{NH_2}{|}}{R-CH-CO_2R'}\ (1\ eq.) \xrightarrow[\text{AcOH (0.1-0.3 eq.)}]{\text{isoamylnitrite (1.1-1.2 eq.)}} \underset{\underset{N_2}{\|}}{R-C-CO_2R'}\ (I)$$

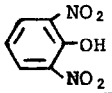
(I)	R	R'	solvent	condition	yield %
a	$(CH_3)_2CH-$	$-C_2H_5$	C_6H_6	50°C 4 hr.	60
b	$C_6H_5CH_2-$	$-C_2H_5$	$CHCl_3$	reflux 45 min.	88
c	$p-HOC_6H_4CH_2-$	$-CH_3$	$CHCl_3$	reflux 45 min.	41
d		$-CH_3$	C_6H_6	reflux 50 min.	62
e	$H_5C_2O_2CCH_2CH_2-$	$-C_2H_5$	C_6H_6	reflux 1 hr.	59
f	$CH_3SCH_2CH_2-$	$-CH_3$	$CHCl_3$	reflux 1 hr.	64
g	$C_6H_5CH_2OCONH(CH_2)_4-$	$-C_2H_5$	$CHCl_3$	reflux 50 min.	77

obtained as yellow prisms (mp 64-5°); the others as golden yellow oils. Although Chiles and Noyes[7] reported that Ie, prepared from diethyl L-glutamate by the Curtius method, showed some optical rotation (α_D^{20}=+1.68 (l, 1.0, neat)), the compound, obtained by the present procedure, is completely optically inactive; as expected from the chemical nature of aliphatic diazo compounds. All the I obtained from L-amino acid esters was also optically inactive.

This method, as shown in Table II, requires acid. But acid reacts slowly with I to afford II in chloroform or benzene. If an insufficient amount of acid

Table II



Acid	Acid eq.	Condition min.	Diazoester yield %
——	——	reflux 120	0
CH_3COOH	0.03	reflux 45	7
"	0.1	"	88
"	0.3	reflux 15	81
"	0.5	"	77
CF_3COOH	0.1	reflux 45	33
"	0.3	"	59*1
C_6H_5COOH	0.1	"	85
$(CH_3)_3CCOOH$	"	"	49
	"	"	53*2
HCl	1	room temp. 60	0

*1 contaminated by a slight amount of ethyl cinnamate.

*2 contaminated by a slight amount of byproduct, probably O-nitroso-2.6-dinitrophenol.

is used as the catalyst, it is consumed and diazotization stops before it is complete. When acid is used in fairly large quantities, the formation of II increases and the yield of I is lower. The optimum quantity of acid is 0.1-0.3 equivalent to amino acid ester. Of the several organic acids tested, CH_3COOH and C_6H_5COOH were best. Stronger acids are not suited for this reaction.

The following is a typical procedure. A mixture of phenylalanine ethyl ester (0.97 g, 5 mmole), acetic acid (0.09 g, 1.5 mmole) and isoamylnitrite (0.71 g, 6 mmole) in chloroform (30 ml) is refluxed for 15 min. Chloroform (30 ml) is added to the yellow solution obtained. The whole is cooled and washed with cold 1N H_2SO_4 solution, cold water, cold satd. $NaHCO_3$ solution and water, then dried over Na_2SO_4. The dried diazoester solution is filtered and chloroform and isoamylalcohol are completely distilled off in vacuo to afford crude Ib (0.87 g), which is purified on column chromatography using alumina (active grade, 2-3; 50 g; solvent, benzene:hexane 1:10). The fractions required are combined and evaporated to dryness in vacuo to give pure Ib (0.83 g, y. 81%) as a golden yellow oil. (IR (liq), 2085, 1690 cm^{-1}; UV (EtOH), 263, 415 mμ; NMR ($CDCl_3$), 2.71 (5H, s), 5.77 (2H, q), 6.39 (2H, s), 8.75 (3H, t) τ).

We have given a very convenient method for the preparation of various α-diazoesters of α-amino acids, which have not been easily accessible. We are now investigating the reactivities of I.

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