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A GENERAL SYNTHESIS OF α-AMINO ACID ORTHOESTERS FROM NITRILES VIA N-CHLOROIMIDATES

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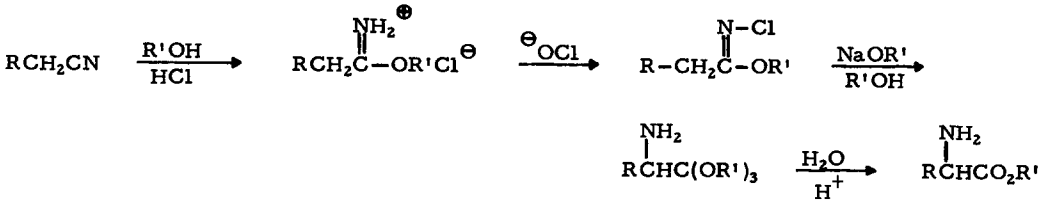
We wish to report a new general synthesis of α-amino acid orthoesters; the three-step synthesis involves conversion of a nitrile to an imino ester, conversion of the latter to an N-chloroimidate (1), and alkoxide treatment of the N-chloroimidate to form the α-aminoorthoester by mild acid hydrolysis.



The α-amino acid orthoesters have not been generally available previously. Specific syntheses have been reported for the cis-phloroglucinol orthoester of glycine (2) and N-benzyloxycarbonylglycine ethyl orthoester (3).

In Table I are listed examples of α-aminoorthoesters which have been prepared by this method. The yields in general are good and the product obtained directly is relatively free of impurities. The reaction has not been successful when carried out on α-disubstituted acetonitriles (4).

The reaction temperature depends upon the acidity of the α-methylene proton. When $R=C_6H_5$, reaction takes place at room temperature; the completely aliphatic nitriles require reaction temperatures in the range 60-70°.

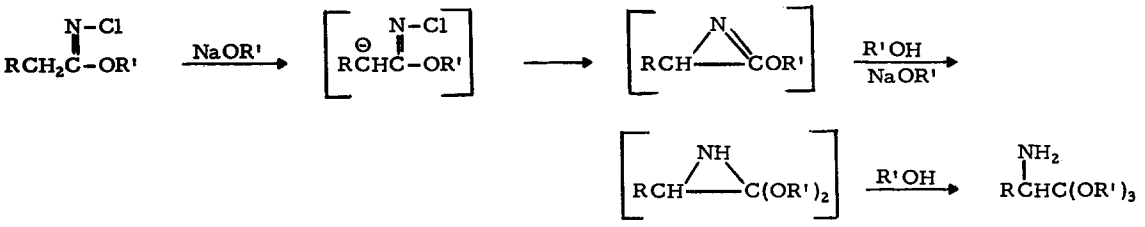
Table I. α-Aminoorthoesters Prepared from Nitriles

R	R'	Yield %	b.p.	Calc'd. %			Found		
				C	H	N	C	H	N
H	CH_3CH_2	38	35-37°/0.5 mm	54.2	10.81	7.91	54.9	11.1	7.47
CH_3CH_2	CH_3CH_2	67	50°/0.3 mm	58.5	11.3	6.82	58.4	11.45	7.29
C_6H_5	CH_3	82	70-80°/0.2 mm	62.5	8.11	6.63	63.4	7.89	6.62
CH_3OCH_2	CH_3CH_2	87	60-70°/0.2 mm	66.4	9.15	5.53	67.0	8.53	5.79
$NC(CH_2)_3$	CH_3CH_2	98	75°/0.2 mm	59.0	9.90	11.47	58.8	10.3	11.66
CH_3	CH_3CH_2	92	31-32°/0.45 mm	56.5	11.07	7.32	56.8	11.0	7.46

In a typical experiment sodium alkoxide solution (about 1.25 N) in alcohol is added to an alcohol solution of the N-chloroimidate and the contents heated if necessary for 1-3 hours. Reaction is indicated by precipitation of sodium chloride. The contents are poured into water and extracted with methylene chloride. The α-aminoorthoester is obtained as a residue after solvent removal. Purification if necessary, can be effected by distillation at reduced pressure. The α-aminoorthoester is readily converted to an α-amino acid ester by shaking a CH_2Cl_2 solution with a 10% aqueous acid solution.

Product identifications are based upon infrared and proton NMR spectra as well as elemental analyses and conversion to known α-amino acid esters. The infrared spectra all exhibited very strong ether-type absorptions near 1065 cm^{-1}; the NH_2 characteristically absorbed weakly at 3350 and 1600 cm^{-1}. The strong (three identical) alkoxy proton NMR patterns were apparent in all products. The rest of the proton spectra were consistent with assigned structures.

The reaction mechanism is apparently closely related to that of the Neber reaction, and can be written as follows:



Removal of the α proton by alkoxide forms a resonance stabilized carbanion which reacts by chloride displacement and ring closure to the 2-alkoxyazirine (5) intermediate. Under the basic reaction conditions, the 2-alkoxyazirine probably adds a mole of alcohol to give the intermediate 2,2-dialkoxyaziridine, which undergoes ring opening (6) and addition of another mole of alcohol to produce the α-aminoorthoester.

Earlier Baumgarten and co-workers (7) observed the conversion of N-chloroimidates to α-amino esters; however, their acid work-up procedure precluded isolation of the α-aminoorthoester.

The α-aminoorthoesters provide new and chemically reactive amino acid derivatives which may prove useful in peptide syntheses or as versatile organic intermediates.

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REFERENCE AND FOOTNOTES

1. For a review of the chemistry of imidates, see R. Roger and D. G. Neilson, Chem. Rev., 61, 179 (1961).

2. F. Bohlmann and W. Sucrow, Ber., 97, 1839 (1964).

3. J. Zemlicka and S. Chladek, Coll. Czech. Chem. Comm., 31 3775 (1966).

4. The mechanistically similar Neber rearrangement of oxime tosylates is also less successful with α-methinyl than with α-methylene compounds. See C. O'Brien, Chem. Rev., 64, 81 (1964) for a discussion.

5. In some cases it appears that the 2-alkoxyazirine intermediate can be isolated. Such compounds have not been previously reported, and will be the subject of a future paper.

6. Ring opening of a proposed 1-azirine intermediate under neutral alcoholic conditions was reported recently. See A. Hassner and F. W. Fowler, J. Am. Chem. Soc., 90, 2869 (1968).

7. H. E. Baumgarten, J. E. Dirks, J. M. Petersen and Robert L. Zey, J. Org. Chem., 31, 3708 (1966).