An Improved Rapid Method for the Synthesis of N-Carboxy α-Amino Acid Anhydrides Using Trichloromethyl Chloroformate

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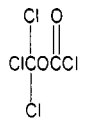
N-Carboxy anhydrides (NCA's) of α-amino acids are very important compounds in peptide chemistry, because they are used for the preparation of poly(α-amino acids)[1] and peptides.[2-4] 2-Nitrophenylsulfenyl (Nps) derivatives of them[5] are also used for syntheses of peptides[6,7] and depsipeptides[8] protected by the Nps group. The NCA's are usually synthesized by reaction of the corresponding α-amino acids with phosgene.[9] The conventional procedure for the phosgenation of an amino acid involves passing gaseous phosgene through a suspension of the amino acid in a dry solvent such as dioxane or tetrahydrofuran until a clear solution is obtained. Goodman et al.[10] have established a routine method for the preparation of the NCA's which involves the use of a stock solution of phosgene in benzene to remove the potential danger of using a large amount of gaseous phosgene.

An alternate method for the preparation of the NCA's using trichloromethyl chloroformate (TCF) (1) has been reported.[11,12] The method first involves the decomposition



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of TCF to phosgene in a warm solvent, followed by reaction of the resulting phosgene with the amino acids.[11] In the TCF method, however, the advantage of using a calculated amount of liquid TCF is offset by very slow decomposition of TCF to phosgene (4 to 6 h at 60 °C). Without this decomposition of TCF prior to the reaction with the amino acids, the formation of the NCA's is usually unsuccessful.[11]

We have developed a facile method for the preparation of the NCA's using TCF. This improved method involves the rapid decomposition of TCF with activated charcoal and the simultaneous reaction of the resulting phosgene with the amino acids in the same reaction vessel. TCF decomposes instantly to give phosgene when catalyzed by the activated charcoal. Thus, the reaction time in this modified method is now as short as that of the phosgene stock solution method.[10] The preparative procedure is very simple: the amino acid and activated charcoal are suspended in tetrahydrofuran and 0.75 M TCF is added. The mixture is magnetically stirred at 55 °C until the amino acid dissolves. The reaction is complete within 30 min for almost all amino acids. Then the activated charcoal is removed by filtration through Celite placed on a glass filter. The filtrate is concentrated and the residual oil crystallizes upon the addition of hexane.

The amount of TCF needed for complete reaction with amino acids has been examined. Theoretically, a half mole of TCF should be enough to react with a mole of the amino acids, because a mole of TCF yields two moles of phosgene. Experimentally, however, even when a 10% excess of TCF was allowed to react with amino acids, 16% of the amino acid was left unreacted. The use of a 40% excess of TCF afforded total amino acid conversion to the NCA.

Results of the syntheses of NCA's by the modified TCF method are summarized in Table I. The phosgenation reaction is complete within 30 min (except for L-alanine) and gives the NCA's in high yields. Since TCF is an easily handled liquid, the method reported here should facilitate rapid syntheses of NCA's.

Table I. Preparation of *N*-Carboxy Anhydrides of Some α-Amino Acids by the Modified TCF Method

NCA	reactn time, min	yield, %	mp, °C	lit. mp, °C
L-Ala	90	85	91–92	92[11]
L-Val	40	93	70–71	71[11]
L-Leu	30	89	76–77	76–77[13]
L-Phe	30	86	95–96	95–96[14]
L-Met	30	78	43–44	42–44[15]
L-Glu(OBzl)	30	88	93–94	93–94[16]
L-Glu(OMe)	30	91	99–100	100[11]
L-Asp(OBzl)	25	93	127–128	126.5–127.5[17]

Experimental Section

Melting points were obtained with a capillary melting point apparatus and are uncorrected. TCF was purchased from Hodogaya Chemical Co., Tokyo, and activated charcoal was purchased from Wako Chemicals, Osaka, and used without further treatments. Infrared spectra were recorded as KBr disks by a JASCO A702 spectrophotometer controlled by a JASCO A330 data processor.

Typical Procedure for the Preparation of NCA's. L-Leucine (26.2 g, 0.2 mol) and activated charcoal (0.5 g) were suspended in tetrahydrofuran (250 mL). To the suspension was added TCF (18 mL, 0.15 mol) with vigorous stirring. The temperature was gradually raised to 55 °C, and stirring was continued at 55 °C until the amino acid dissolved. The solution was then filtered through Celite placed on a glass filter. The filtrate was concentrated at 40 °C under reduced pressure to give a pale yellow oil, which was crystallized by addition of hexane. The product was twice recrystallized from diethyl ether–hexane to give colorless crystals of the NCA. The infrared spectrum showed the C=O stretching bands of the anhydride at 1816 and 1754 cm^{-1}. The NCA's of L-alanine, L-valine, L-leucine, L-phenylalanine, and L-methionine were recrystallized from diethyl ether–hexane and the NCA's of γ-benzyl and methyl L-glutamates and β-benzyl L-aspartate were recrystallized from ethyl acetate–hexane.

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Registry No. 1, 503-38-8; L-Ala-NCA, 2224-52-4; L-Val-NCA, 24601-74-9; L-Leu-NCA, 3190-70-3; L-Phe-NCA, 14825-82-2; L-Met-NCA, 15776-11-1; L-Glu(OBzl)-NCA, 3190-71-4; L-Glu(OMe)-NCA, 1663-47-4; L-Asp(OBzl)-NCA, 13590-42-6; L-Ala-OH, 56-41-7; L-Val-OH, 72-18-4; I-Leu-OH, 61-90-5; L-Phe-OH, 63-91-2; L-Met-OH, 63-68-3; L-Glu(OBzl)-OH, 1676-73-9; L-Glu(OMe)-OH, 1499-55-4; L-Asp(OBzl)-OH, 2177-63-1.

Spectrophotometric and Titrimetric Studies on Alkyl Hypobromites

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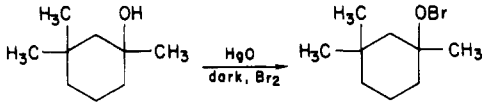
Investigations on the oxidation of simple alcohols by bromine in aqueous solution were initiated by Bugarszky.[1] He found that oxidation of dilute aqueous solutions of ethanol (1 to 4% by weight) gave acetic acid as the main product. Swain et al.[2] studied the oxidation of 2-propanol by bromine in aqueous solution and found 2-propanone. Kudesia[3] had investigated the oxidation of *n*-butanol and found butyraldehyde to be the only product.

Little work had been done on the reaction of alcohols with bromine in nonaqueous solution. Sneen and Matheny[4] treated a pentane solution of 1,3,3-trimethylcyclohexanol with Br_2 and HgO in the dark to give a hypobromite intermediate:



(1)

They did not isolate the hypobromite intermediate but confirmed its identity through ultraviolet and infrared spectroscopy and compared the spectroscopic data to those of known hypobromites, which had been reported by Anbar and Dostrovsky.[5]

We investigated the formation of alkyl hypobromites from tertiary and secondary alcohols. A titrimetric method was adopted to determine the percent yield of the alkyl hypobromites. Molar absorptivities for each reaction were calculated from the spectrophotometric and titrimetric data.

Results and Discussion

Factors that effected the most favorable condition for the formation of the alkyl hypobromites were light, solvent, temperature, and the concentration of the reactants.

Tertiary hypobromites are stable in the dark at a 0 °C temperature for prolonged periods. Secondary hypobromites deteriorate over prolonged periods under the same conditions. The nature of the products formed from the decomposition of hypobromites is discussed in a report by Brun and Waegell.[6]

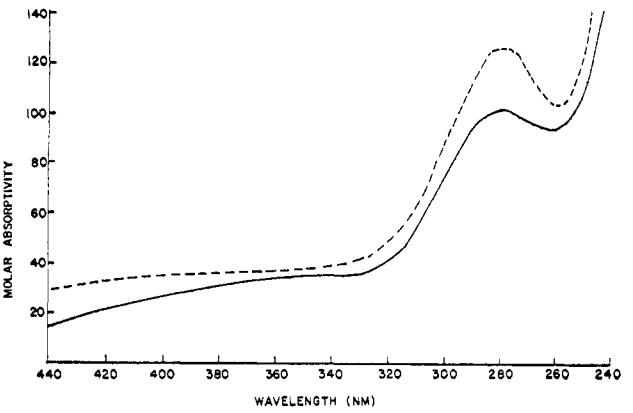
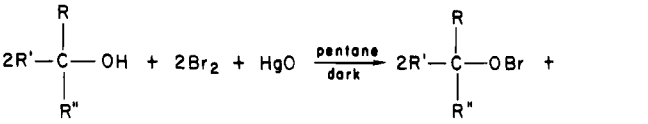


Figure 1. Absorption spectra. Reaction of alcohols with bromine and mercuric oxide in pentane with a reaction time of 60 min: *tert*-amyl alcohol (--); 2-pentanol (—).

The reaction to form alkyl hypobromite proceeded at room temperature with the mercuric oxide and distilled pentane as solvent:



R" = H or alkyl

Mercuric oxide is assumed to act as it does in the reaction with water and bromine to generate hypobromous acid.[7]

The reaction flask was covered with Al foil as the alkyl hypobromite was found to be stable in the dark.[4]

Earlier work[2] suggested that secondary alcohols reacted directly with bromine to give their corresponding ketones and the HBr produced would cause the acid-catalyzed addition of bromine to the enol form of the ketone product to take place.[8] Hence, when secondary alcohols were employed, Na_2CO_3 was added.

Reaction of Alcohols with Bromine and Mercuric Oxide in Pentane. Twelve alcohols were employed in the preparation of their corresponding alkyl hypobromites. After 1 h, samples were removed for the spectrophotometric and titrimetric studies.

Absorption Spectra. The absorption spectra, measured after 1 h, displayed no appearance of Br_2 at 415 nm and a strong absorbance of the alkyl hypobromite at 280 nm. Representative spectra of the alkyl hypobromites prepared from a secondary alcohol and a tertiary alcohol are displayed (Figure 1).

Tritrimetric Determination. The alkyl hypobromite was analyzed by two methods, following treatment of an aliquot of the solution with excess KI and a known excess of HCl (eq 3). The liberated iodine was estimated by

$$ROBr + H^+ + 2I^- \rightarrow ROH + I_2 + Br^- \quad (3)$$

titration against standard sodium thiosulfate, following which the excess HCl remaining after decomposition of the hypobromite was determined by titration against standard alkali. Each titration gives an independent estimate of the amount of alkyl hypobromite present, i.e.,

$$[\text{alkyl hypobromite}] = [I_2] = [H^+ \text{ used in reaction 3}]$$

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