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α-BROMINATION OF ACID HALIDES

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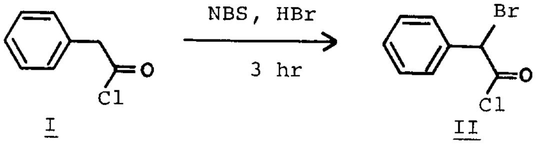
The α-bromination of acids may be accomplished by the Hell-Volhard-Zelinski (HVZ) reaction[2]. Although this reaction is believed to proceed by bromination of the acyl halide which is generated *in situ*,[3,4] the direct bromination of an acid chloride, in most cases, proceeds with difficulty[5]. Extended reaction times[5a], free radical initiators[5b] and high intensity light[5c] are often utilized to realize such a bromination. Although N-bromosuccinimide (NBS) is well known as a brominating agent[6] there appears to be no report of this reagent being employed to directly brominate acid chlorides.

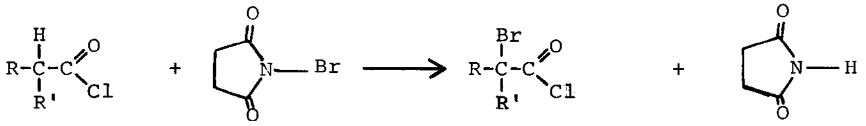
We wish to report that N-bromosuccinimide in the presence of acid catalysts, effects the bromination of acid halides in relatively short reaction times and in high yield. For example, phenylacetyl chloride (I) is quantitatively coverted (nmr) to the α-bromo derivative II. This was accomplished

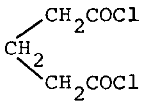
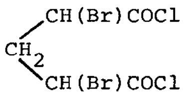
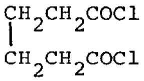
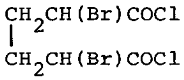
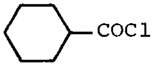
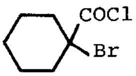


by refluxing the acid chloride with a 20% excess of N-bromosuccinimide for 3 hours in carbon tetrachloride solution to which had been added 3-5 drops of HBr/HOAc solution. Filtration of the insoluble succinimide and removal of solvent afforded crude acid chloride II which was shown to be homogeneous by vpc analysis. Distillation provided the α-bromo acid chloride in 75% yield. In a similar manner, a variety of primary and secondary acid chlorides and diacid chlorides were converted to their α-bromo derivatives.

TABLE I

BROMINATION OF ACID CHLORIDES BY NBS.



Acid Chloride	Reaction time, hr	Product	% Yield[a]
$C_6H_5CH_2COCl$	3	$C_6H_5CH(Br)COCl$	75
$ClCH_2CH_2COCl$	4	$ClCH_2CH(Br)COCl$	70
	1		75[b]
 CH_2CH_2COCl CH_2CH_2COCl	1[e]	 $CH_2CH(Br)COCl$ $CH_2CH(Br)COCl$	60[c]
	4.5		58
			70[d]

a) Reactions were quantitative (nmr), yields reported are of pure distilled product. b) Isolated as the methyl ester. c) Isolated as the meso diacid. d) Isolated as the amide. e) With molecular bromine, the reaction time is 14 hr (Ref. 5c).

These results are summarized in Table I. Yields in all cases were quantitative as determined by nmr. These compounds could be isolated in high yield and purity. Thus, this bromination reaction permits the convenient preparation of many α-brominated acyl derivatives such as esters, amides, aldehydes and ketones as well as α-bromo acids.

That the bromination of acid chlorides by N-bromosuccinimide proceeds not by a free radical process, but rather by way of an ionic mechanism could be readily demonstrated. Addition of benzoyl peroxide, a free radical initiator[7], suppressed the rate of bromination to a considerable extent while the addition of a trace of a mineral acid had a strong catalytic effect (Fig. 1).

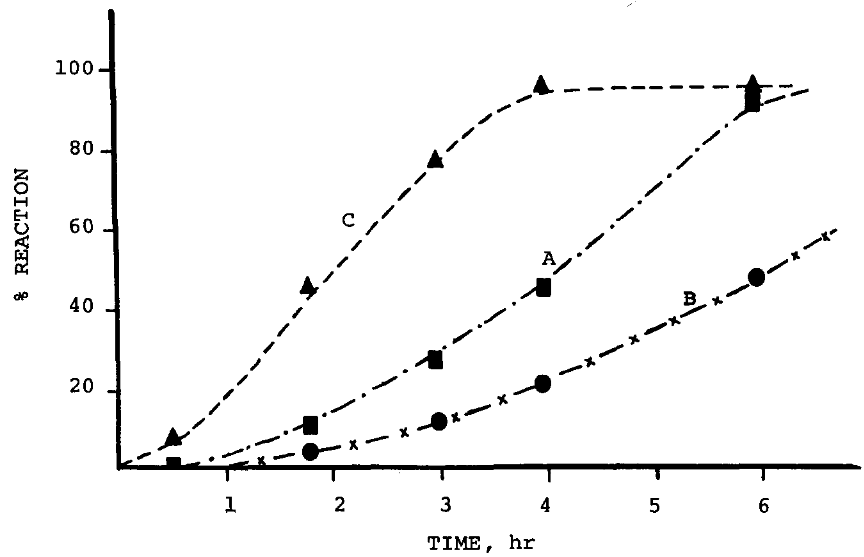
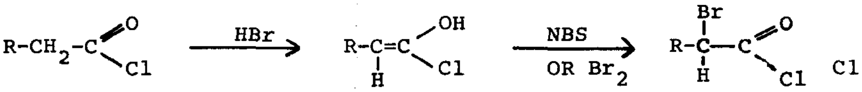


Figure 1. Bromination of Phenylacetyl Chloride (1)
A) refluxing carbon tetrachloride (1 M.).
B) as (A), benzoyl peroxide added.
C) as (A), 1 drop HBr/HOAc added.

The function of the acid is presumably to effect enolization of the acid chloride. This enol may then undergo bromination either by reaction with N-bromosuccinimide itself, or with bromine generated by the reaction of NBS



with acid. Bromine is generated during the reaction as evidenced by the development of a deep red coloration.

This bromination appears to be both convenient and general; the high yields and short reaction times make it competitive with the HVZ reaction. Since this bromination permits the isolation of the α-bromo acid chloride, from which a wide variety of acyl derivatives may be prepared, the reaction is thus more versatile than the classical HVZ procedure.

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