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Efficient One Step Transformation of Carboxylic Acids to Nitriles with the Carbon Chain Shortened by One Carbon Atom

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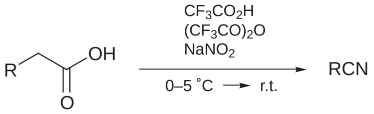
Nitrozation of ω-substituted alkanoic acids of the general formula $X(CH_2)_nCO_2H$ ($X = Cl, CO_2H, CO_2Me$, PhthN), bulky substituted alkanoic acids, arylacetic acids containing electron withdrawing substituents in the aromatic ring, *o*-tosylhydroxyphenylacetic acids and *N*-phtaloilaminophenylacetic acids yield nitriles with the carbon chain shortened by one (or two for dicarboxylic acids) carbon atom.

In 1975 in a preliminary communication[1] we reported the reaction of carboxylic acids yielding nitriles with the carbon chain shortened by one carbon atom. Although this reaction, which we termed as nitrosative cleavage had been used for shortening the carbon chain of natural bile acids,[2] its area of action has not been studied. The present work has been aimed to determine the area of action of this reaction.



1 **2**

1a–d	R = $(CH_2)_nCl$, n = 2, 3, 7, 9	**2a–d**	R = $(CH_2)_nCl$, n = 2, 3, 7, 9
1e,**f**	R = $(CH_2)_nCO_2Et$, n = 2, 7	**2e**,**f**	R = $(CH_2)_nCO_2Et$, n = 2, 7
1g,**h**	R = $(CH_2)_nCO_2Me$, n = 3, 2	**2g**,**h**	R = $(CH_2)_nCO_2Me$, n = 3, 2
1i,**j**	R = $(CH_2)_nCO_2H$, n = 8, 7	**2i**,**j**	R = $(CH_2)_{n-1}CN$, n = 8, 7
1k–m	R = $(CH_2)_n$NPhth, n = 2, 4, 5	**2k–m**	R = $(CH_2)_n$NPhth, n = 2, 4, 5
1n	R = Bu^t	**2n**	R = Bu^t
1o	R = Ph_2CH	**2o**	R = Ph_2CH
1p	R = adamantyl	**2p**	R = adamantyl
1q	R = 4-nitrophenyl	**2q**	R = 4-nitrophenyl
1r	R = 2, 4-dinitrophenyl	**2r**	R = 2, 4-dinitrophenyl
1s	R = 4-tosyloxyphenyl	**2s**	R = 4-tosyloxyphenyl
1t	R = 4-phthaloylaminophenyl	**2t**	R = 4-phthaloylaminophenyl

Scheme 1

We have found that ω-chloroalkanoic acids **1a**–**d**, ω-phthalimidoalkanoic acids **1k**–**m**, monoesters of dicarboxylic acids **1g**–**h** and dicarboxylic acids undergo this reaction giving nitriles with good yields (Tables 1–4, see full text). The only exceptions were dicarboxylic acids (succinic, glutaric and adipic) which readily cyclize to anhydrides when treated with trifluoroacetic acid anhydride. Bulky substituents R do not inhibit the reaction significantly so that 3,3-dimethylbutanoic acid, adamantylacetic acid and 3,3-diphenylpropionic acid smoothly react giving the corresponding nitriles (Table 5, see full text). The only exception was 3,3,3-triphenylpropionic acid: our attempt to carry out nitrosative cleavage failed, the reaction proceeding to give the unexpected 10-cyano-10-phenyl-9-anthrone.[3]

Phenylacetic acid is smoothly cleaved giving benzonitrile in 72% yield. The introduction of electron-withdrawing substituents into the phenyl ring do not inhibit the nitrosative cleavage so that 4-nitrophenylacetic acid **1q** gave 4-nitrobenzonitrile **2q** and 2,4-dinitrophenyl acetic **1r** acid gave 2,4-dinitrobenzonitrile **2r**. By contrast, the introduction of strong electron-donating substituents (hydroxy, alkoxy, or amino groups) into the benzene ring retard the reaction. Reaction of 4-hydroxyphenylacetic acid, 3,4-dimethoxyphenylacetic acid and 4-aminophenylacetic acid resulted in the formation of a complex mixture of products. No nitriles were isolated. However, the protection of the hydroxy group in 4-hydroxyphenylacetic acid by *O*-tosylation and in 4-aminophenylacetic acid by *N*-phthalation allowed us to obtain nitrile **2s** (55% yield) and nitrile **2t** (72% yield).

Techniques used: IR, ^1H NMR

References: 22

Scheme: 1

Tables: 5

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