Tetrahedron Letters No. 41, pp 3825 - 3828, 1971. Pergamon Press. Printed in Great Britain.

A METHOD FOR INTRODUCING A CARBOXYL SUBSTITUENT INTO AROMATIC COMPOUNDS

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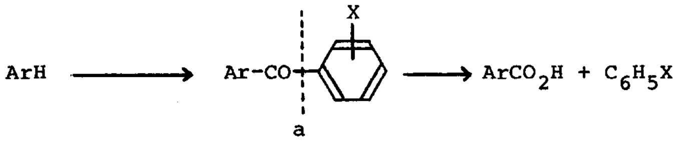
(Received in UK 3 August 1971; accepted for publication 8 September 1971)

When treated with the butoxide-water reagent many benzophenones are cleav to give high yields of benzoic acids.[1] As many classes of aromatic compounds are readily acylated to give benzophenones,[2] preparation of benzophenones in this way and cleavage of them with the butoxide-water reagent affords a simple method for introducing a carboxyl substituent into aromatic compounds. This is outlined in the Scheme. The method is of a similar type to some others such as acetylation[2] followed by the haloform reaction[3] or synthesis of a phenacylpyridinium halide, <u>via</u> acetylation[4] or chloroacetylation,[5] and cleavage of it with alkali.[4,5]



SCHEME

For the present method to be successful the substituent X must be such that cleavage occurs almost entirely at (a). An <u>ortho</u>-chloro substituent appears to be particularly suitable for this purpose because previous work[1] has shown that 2-chlorobenzophenone not only cleaves to give an acid fraction that is >99% benzoic acid, but it cleaves more easily than does benzophenone itself, treatment with the butoxide-water reagent for 5 minutes at 20° being sufficient to effect 92% cleavage. In addition 2-chlorobenzoyl chloride is readily available.

TABLE

	Acylation Reaction				Cleavage Reaction			
Substrate	Method[a]	Product	M.p.	Yield	Method[b]	Acid Product	% Of Desired Acid in Acid fraction[c]	Yield of Pure Acid[d]
Biphenyl	A	2-Chloro-4'-phenylbenzophenone[e]	91-92°	70%	A	Biphenyl-4-carboxylic acid	99%[f]	91%
o-Xylene	B	2-Chloro-3',4'-dimethylbenzophenone[e]	58-59°	75%	A	3,4-Dimethylbenzoic acid	>97%[g]	77%
Mesitylene	C	2-Chloro-2',4',6'-trimethylbenzophenone	100-101°[h]	77%	B	2,4,6-Trimethylbenzoic acid	>96%[g]	76%
1,2-Dimethoxybenzene	D	2-Chloro-3',4'-dimethoxybenzophenone[e]	141-143°	86%	B	3,4-Dimethoxybenzoic acid	98%[f]	85%
1,3-Dimethoxybenzene	E	2-Chloro-2',4'-dimethoxybenzophenone[e]	61-62°	87%	A	2,4-Dimethoxybenzoic acid	80%[f]	69%
Thiophen	F	2-(2-Chlorobenzoyl)-thiophen[e]	-[j]	62%	A	Thiophen-2-carboxylic acid	10%[f]	-
Thiophen	G	2-(2,6-Dichlorobenzoyl)thiophen[e]	97-99°	88%	A	Thiophen-2-carboxylic acid	-	72%

Notes for Table

a. A 2-Chlorobenzoyl chloride (1.1 equiv.) added to a mixture of substrate (1.0 equiv) and $AlCl_3$ (1.1 equiv.) in CH_2Cl_2 and mixture stirred at 20° for 6 hr.

B Substrate (1.0 equiv.) in CH_2Cl_2 added to $AlCl_3$ (1.1 equiv.) and 2-chlorobenzoyl chloride (1.1 equiv.) in CH_2Cl_2 and mixture heated under reflux for 1 hr.

C Substrate (1.0 equiv.) in CH_2Cl_2 added to $AlCl_3$ (1.1 equiv.) and 2-chlorobenzoyl chloride (1.1 equiv.) in CH_2Cl_2 and mixture stirred at 20° for 12 hr.

D A mixture of 2-chlorobenzoyl chloride (1.1 equiv.), substrate (1.0 equiv.) and iodine (0.01 equiv.) heated under reflux for 15 hr.

E 2-Chlorobenzoyl chloride (1.1 equiv.) added to a mixture of substrate (1.0 equiv.) and $AlCl_3$ (1.1 equiv.) in CH_2Cl_2 and mixture stirred at 20° for 14 hr.

F A mixture of 2-chlorobenzoyl chloride (1.1 equiv.), substrate (1.0 equiv.) and iodine (0.01 equiv.) heated under reflux for 7 hr.

G A mixture of 2,6-dichlorobenzoyl chloride (1.1 equiv.), substrate (1.0 equiv.) and iodine (0.01 equiv.) heated under reflux for 4 hr.

b. Reactions carried out using procedure given in ref.1. Reaction times and temperatures were as follows:-

A 2 hrs. at 20°

B 1 hr. at reflux temperature (*ca*.85°)

c. All cleavage reactions proceeded in >85% yield.

d. Yield after recrystallisation of the acid fraction to constant melting point. The final m.p.s. were in excellent agreement with literature values.

e. All new products had satisfactory analytical (C, H, Cl and, where relevant, S) and spectroscopic (i.r., u.v., and n.m.r.) data.

f. By g.l.c. analysis of methylated (ethereal CH_2N_2) acid fraction.

g. By n.m.r. spectral analysis.

h. Literature[7] value 99-101°.

j. Boiling point 133-135° @ 0.2 mm.

As a trial of the method biphenyl, *o*-xylene, mesitylene, 1,2-dimethoxybenzene 1,3-dimethoxybenzene, and thiophen were 2-chlorobenzoylated and the products obtained were cleaved using the butoxide-water reagent in 1,2-dimethoxyethane.[1] The results are summarised in the Table. The intermediate ketones were obtained in good yields[6] and were readily cleaved to afford high yields of acid products, the most vigorous cleavage conditions used being treatment with the butoxide-water reagent for 1 hr. at *ca*.85°. In every case except one the acid fraction obtained consisted mainly of the desired acid and recrystallisation of the fraction affordec the pure product in good yield.[6] The exception was the attempt to prepare thiophen-2-carboxylic acid. In this case the intermediate ketone only cleaved to a small extent in the desired direction. However, when 2,6-dichlorobenzoyl chlorid was used as the acylating reagent, i.e. when two *ortho*-chloro substituents were used to promote the required cleavage, the intermediate ketone cleaved to afford thiophen-2-carboxylic acid in good yield.

An attractive feature of this method of introducing a carboxyl substituent is that the butoxide-water reagent cleaves the intermediate ketones readily to give good yields of clean acid products.

Acknowledgement: We thank J.A.Licence and M.J.Pennell for technical assistance.

References

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