Tetrahedron Vol. 43, No. 19, pp. 4321 to 4328, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00

THE INVENTION OF RADICAL REACTIONS. PART XVI. RADICAL DECARBOXYLATIVE BROMINATION AND IODINATION OF AROMATIC ACIDS

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(*Received in Belgium* 23 *July* 1987)

Abstract: Thiohydroxamic esters of aromatic carboxylic acids undergo clean decarboxylative bromination or iodination on treatment with bromotrichloromethane, iodoform or diiodomethane in the presence of a radical initiator.

Decarboxylative halogenation of carboxylic acids (the Hunsdiecker-Borodin reaction) has traditionally been accomplished by treating anhydrous silver carboxylates with bromine or iodine.[1] The reaction is very sensitive to the presence of water and to the purity of the silver carboxylate but otherwise works well with saturated aliphatic, and especially primary carboxylic acids. Aromatic acids bearing electron withdrawing groups also undergo the reaction but yields are variable. In contrast, electron rich aromatic acids are subject to electrophilic ring bromination and therefore are not useful substrates. The difficulties and expense inherent in the preparation and dessication of very pure silver carboxylates has encouraged the development of other more practical variants which obviate these problems. These include in situ formation of the silver salt by treatment of the acid chloride with silver oxide and bromine[2] and the use of mercury[3] or thallium[4] salts in place of silver. Other alternate methods for producing acyloxy radicals ($RCO_2^{\bullet}$) have also been exploited to achieve similar decarboxylative halogenations. These, however, invariably involve strong oxidising conditions such as treating the carboxylic acid with lead tetraacetate-iodine and visible light or with t-butyl hypoiodite[5] or heating with lead tetraacetate[6] or iodobenzene diacetate[7] in the presence of a halogen donor (cupric halides, N-halo succinimide, iodine etc..).

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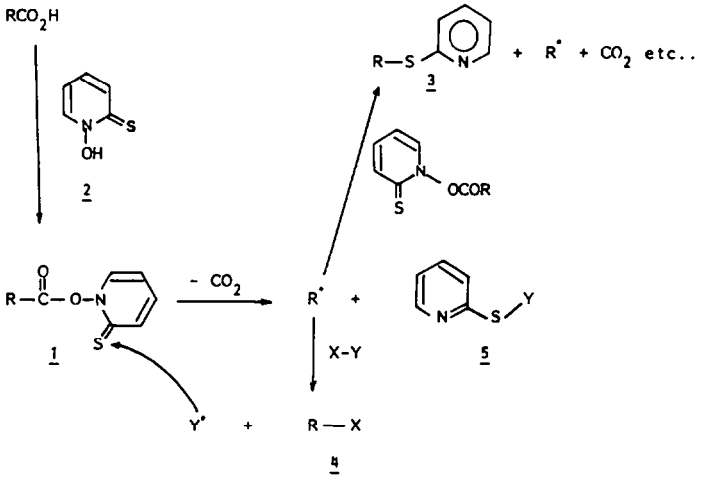
In a recent series of papers,[8] we have described the various synthetic facets of a novel radical decarboxylation reaction which requires neither heavy metals nor strong oxidants. In particular, we have shown that decarboxylative halogenation was especially easy and efficient for aliphatic and alicyclic acids.[9] Moreover, by a judicious choice of the experimental conditions we were able to achieve the decarboxylative bromination of aromatic and α,β-unsaturated acids.[10] We would now like to describe this latter work in detail as well as present more recent results concerning the corresponding decarboxylative iodination.

The chemical process which underlies our novel method is outlined in Scheme 1. We have found that if esters 1, derived from carboxylic acids and N-hydroxy-2-thiopyridone 2, are heated or irradiated with visible light, they undergo a radical chain reaction resulting in overall loss of carbon dioxide. In the absence of an efficient trap, the intermediate carbon radical propagates the chain by reacting with another molecule of 1 to give ultimately the pyridyl sulphide 3. If however, the reaction is conducted in the presence of a good halogen donor (CCl_4, $BrCCl_3$, CHI_3 etc...), the intermediate carbon radical is converted into the halide 4 with concomitant formation of another radical (Y· = $\cdot CCl_3$, $\cdot CHI_2$ etc...) which serves as the chain propagator (Scheme 1). This decarboxylative halogenation[9] proved exceptionally efficient in the case of primary, secondary and tertiary aliphatic or alicyclic carboxylic acids being by far superior to the Hunsdiecker-Borodin reaction or any of its more recent variants. The reason for this superiority is that esters of type 1 are not electrophilic, whereas the normal Hunsdiecker-Borodin hypohalites are strongly electrophilic (see below).



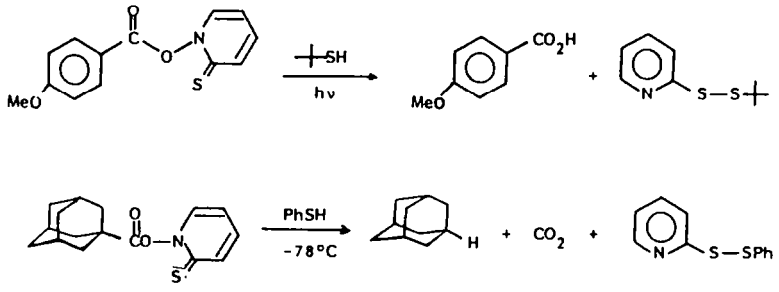
X-Y = Cl-CCl_3, Br-CCl_3, I-CHI_2

1, 3, 4	5
a) R = p-MeO-C_6H_4	a) Y = CCl_3
b) R = 1-adamantyl	b) Y = CHI_2
c) R = p-O_2N-C_6H_4-	c) Y = $-(CF_2)_5CF_3$

Scheme 1

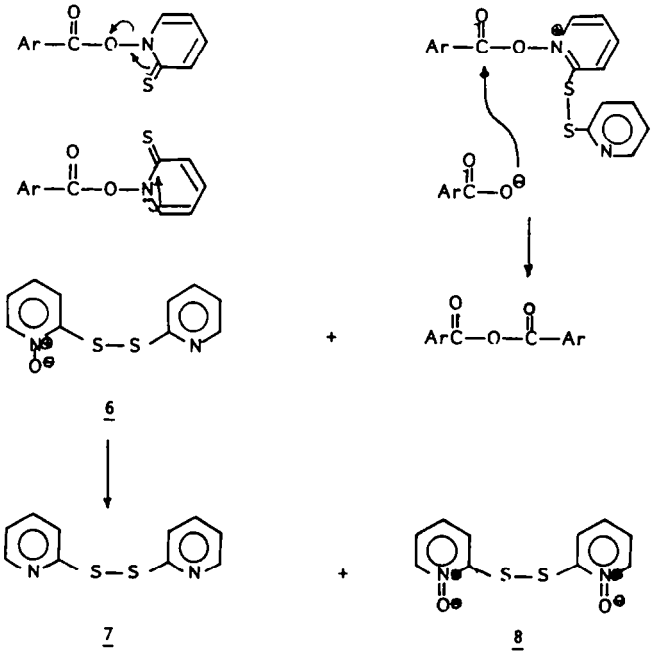
Aromatic and α,β-unsaturated carboxylic acids on the other hand are rather problematic. The difficulties arise from the somewhat persistent nature of the carboxylic radical in this case[11] (10^4-10^5 s^{-1} for $ArCO_2\cdot$ as compared with ~10^9 s^{-1} for $RCO_2\cdot$). For

example irradiation of ester 1a in the presence of t-butyl mercaptan afforded an excellent yield of p-methoxy benzoic acid produced by capture of the intermediate carboxylic radical by the thiol. In sharp contrast, no adamantanoic acid could be detected in the case of ester 1b even at -78°C. The reaction produced only adamantane as the sole acid derived product[12] (Scheme 2).



Scheme 2

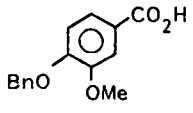
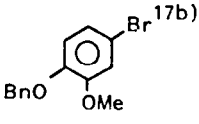
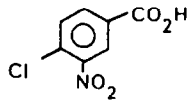
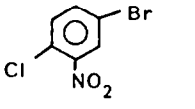
The special nature of esters 1 derived from aromatic acids manifested itself when, in a preliminary series of experiments, we examined their behaviour towards heat and light. Whereas aliphatic esters gave cleanly the corresponding sulphides 3 on heating or irradiating with visible light, ester 1c derived from p-nitrobenzoic acid produced only a low yield (< 10%) of sulphide 3c in a rather unclean reaction. The major products were p-nitrobenzoic acid and its anhydride. The formation of anhydride was found to be quite general and of probably ionic origin as shown in Scheme 3. The initial unsymmetrical disulphide 6 may disproportionate into dipyridyl disulphide 7 and its di-N-oxide 8 both of which have been detected in the reaction mixture. The homolytic fission of the N-O bond is probably slow enough in this case to allow interference by unwanted ionic processes.



Scheme 3

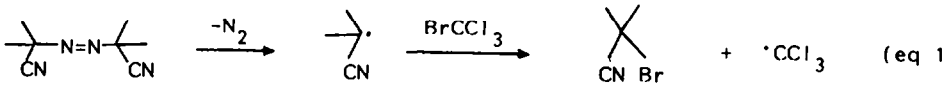
To favour the unimolecular decarboxylation step we were thus compelled to operate at a somewhat high temperature. Indeed slow addition of the carboxylic acid chloride to a suspension of the sodium salt in a mixture of o-dichlorobenzene and bromotrichloromethane heated to ca 130°C effected a relatively clean decarboxylative bromination of p-nitrobenzoic and α-naphtoic acids. p-Bromonitrobenzene and bromonaphthalene were thus produced in 69 and 80% respectively. (Table 1, entries 1 and 2). However, extension of these conditions to other acids was not so successful. Yields were variable and formation of anhydride in some cases could not be easily suppressed especially when the temperature was lowered. For example, the yield of trans bromostyrene from cinnamic acid was a poor 12-15% (Table 1, entry 4) reflecting perhaps the thermal fragility of the product. Lowering the temperature produced a slight increase in the yield (22%) but also resulted in the formation of large amounts of cinnamic anhydride.

Table 1

Entry	Acid	Bromo derivative[a]	Yield (%)	Yield of 5a (%)	Lit. Yield (%)
1	P-Nitrobenzoic Acid	4-Bromonitrobenzne	69[b]	79[1a] 66[b] 42[3d]	95[15]
2	1-Naphthoic acid	1-Bromo-naphthalene	82	90 80[b]	4.5[1a] 60[b]
3	2-Naphthoic acid	2-Bromo-naphthalene	85	78	0[1a]
4	$PhCH{=}CHCO_2H$	$PhCH{=}CHBr$	68	70 12.5[b]	17.5[1a] 39[b]
5	$p\text{-}MeOC_6H_4CO_2H$	$p\text{-}MeOC_6H_4Br$	84	87	0[1a]
6	3,4,5-Trimethoxy-benzoic acid	3,4,5-Trimethoxybromo benzene[17a]	62	68	26[6]
7	p-Toluic acid	p-Bromotoluene	55[c]	78	17[1a] 11[3d]
8		 [17b]	45	55	-
9	2,6-Dimethoxy-benzoic acid	2,6-Dimethoxy bromo benzene[17c]	60	61	-
10	m-Iodobenzoic acid	m-Iodobromobenzne	81	81	-
11			43	49	-

[a] Bromo derivatives with no reference are described in "Dictionary of Organic Compounds", 5th Ed., Chapman and Hall, 1982. [b] Reactions performed without AIBN at Ca 130°C. All others at 100°C with 15-30% AIBN. [c] Low yield due to volatility of the product.

Even under such drastic conditions, the sluggish decarboxylation was seriously hampering the efficienty of the radical chain process causing a buildup of ester concentration with the consequent side reactions. One way of circumventing this difficulty was to increase the number of radical chains in operation at a given time by incorporating an external initiator such as azobisisobutyronitrile (AIBN). The isobutyronitrile radicals produced by the decomposition of AIBN would react with the bromotrichloromethane to give trichloromethyl radicals (eq. 1) which being efficient chain propagators in our system, would keep the ester concentration low and therefore favour the desired radical pathway.



(eq 1)

Indeed when AIBN (up to 30%) was incorporated to the acid chloride prior to addition to the hot suspension of the sodium salt of 2 in $BrCCl_3$ a cleaner and more reproducible decarboxylative bromination was observed. Furthermore, the reaction could be run at the lower temperature of 100°C which made it applicable to a wider variety of aromatic carboxylic acids as shown by the results collected in Table 1.

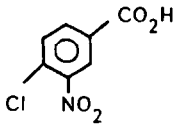
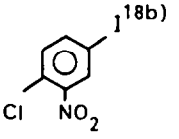
This decarboxylation is effective for electron poor as well as for electron rich aromatic acids. This generality strongly vindicates the utility of this procedure. As can be seen from the comparison made in Table 1 (entries 2-7), aromatic acids with electron donating substituents give poor results with the classical methods of the Hunsdiecker-Borodin type. This shortcoming is a consequence of the highly electrophilic nature of the intermediate acyl hypobromide implicated in the Hunsdiecker-Borodin and other related reactions. Undesired ionic bromination of the aromatic ring is difficult to avoid in these cases. No strongly electrophilic species is involved in our method. Furthermore a dramatic improvement is observed in the case of cinnamic acid using this modification of the experimental procedure. Thus, the yield of bromostyrene is increased to 68% as compared with the original 12.5% (Table 1, entry 4).

The success with the decarboxylative bromination encouraged us to examine briefly the more difficult case of iodination. Aromatic iodo compounds are invaluable as starting materials for the preparation of a number of very useful organometallic reagents (Grignard reagents, organo- lithium, mercury or palladium derivatives to name but a few).

We initially tested iodoform, CHI_3 as the iodine atom donor, in view of the satisfactory results obtained in the aliphatic and alicyclic series.[9] A similar slow addition of a solution of the acid chloride and AIBN in toluene to a refluxing suspension of the sodium salt of 2 in toluene containing iodoform did afford reasonable yields of the expected iodoaromatic compounds (Table 2, entries 1, 4, 6, 8). For reasons which are not yet clear, the reaction with 4-chloro-3-nitrobenzoyl chloride proceeded poorly resulting in only a low yield of the desired iododerivative (Table 2, entry 10).

Overall, the reaction is less efficient than the decarboxylative bromination. Furthermore, the reaction mixtures acquire a dark brown colour charateristic of iodine which is discharged by thiosulphate. We were thus inclined to ascribe the modest performance to the slow thermal decomposition of the iodoform as well as of the coproduced pyridine derivative 5b. This apparead to be corroborated by the poorer yields observed when the temperature was increased.

Table 2

Entry	Acid $ArCO_2H$	Iodine source	Yield (%) of Iodo derivative ArI[b]	
1	1-Naphthoic acid	CHI_3	1-Iodonaphthalene	(69)
2	"	$CF_3(CF_2)_5$-I[a]	"	(57)
3	"	CH_2I_2	"	(60)
4	$3,4,5$-$(MeO)_3C_6H_2CO_2H$	CHI_3	$3,4,5$-$(MeO)_3C_6H_2I$[18a]	(31)
5	"	CH_2I_2	"	(40)
6	4-$MeC_6H_4CO_2H$	CHI_3	4-MeC_6H_4I	(52)
7	"	CH_2I_2	"	(54)
8	4-$O_2NC_6H_4CO_2H$	CHI_3	4-$O_2NC_6H_4I$	(54)
9	"		"	(16)
10		CHI_3	 [18b]	(13)
11	"	CH_2I_2	"	(16)

[a] In this case, sulphide 5c could also be isolated in 52% yield.

[b] Products with no reference are described in "Dictionary of Organic Compounds", 5th Ed., Chapman and Hall, 1982.

Iodotrichloromethane and iodotribromomethane would have probably been ideal sources of iodine but unfortunately they are described as unstable substances.[13] We therefore turned to the more stable, but expensive, perfluoroiodohexane.

Using this reagent, the appearance of the reaction mixture was indeed more pleasing but the actual yield of the desired iodonaphthalene was not improved (Table 2, entry 2). The corresponding sulphide 5c could be isolated in this case in comparable yield (52%), confirming that 5b was indeed unstable and was in large part the source of the iodine produced in the previous experiments.

Other potential iodine donors were also examined. Diiodomethane was practically as good as iodoform (Table 2, entries 3, 5, 7, 11) but neopentyl iodide gave mediocre results (Table 2, entry 9).

Although on the whole the yield of iodoaromatics is only modest, the radical decarboxylative iodination of an aromatic acid does not seem to have been reported. This method could allow an expedient entry into otherwise inaccessible compounds.

Experimental

Melting points are uncorrected. NMR data are for deuterochloroform solutions with tetramethylsilane as internal standard. N-Hydroxy pyridine-2-thione 2 and its sodium salt are available commercially. Aromatic acid chlorides were prepared by standard methods using thionyl chloride.

N-(p-Methoxy)-benzoyloxy-pyridine-2-thione 1a.

(This compound is sensitive to light and moisture. The reaction vessel, chromatography column etc.. should be corvered with aluminium foil).

To an ice cold solution of N-hydroxypyridine-2-thione 2 (635 mg, 5 mmoles) and pyridine (400 mg) in dry, degassed dichloromethane (10 ml) was added p-methoxybenzoylchloride (850 mg, 5 mmoles). After stirring for 30 min, the mixture was filtered through a silica column and the yellow product eluted with dichloromethane. Concentration under reduced pressure without heating gave essentially pure 1a (861 mg, 66%) which was used without further purification; ν_{max} (Nujol) 1775 cm^{-1}; m/e: 261 (M^+); δ_H: 8.13 (2H, d, J = 9 Hz), 7.55-7.80 (2H, m), 6.47-7.34 (2H, m), 6.95 (2H, d, J = 9 Hz), 4.90 (3H, s).

Irradiation of Ester 1a in the Presence of t-Butylmercaptan.

An ice-cold solution of ester 1a (150 mg) in dry, degassed dichloromethane (10 ml) containing an excess (Ca 0.5 ml) of t-butylmercaptan was irradiated with a 300 W tungsten lamp under an inert atmosphere until disappearance of the yellow colour. Concentration and chromatography of the residue on silica using dichloromethane gave t-butyl 2-pyridyl disulphide (115 mg, 86%), identical with an authentic sample.[19] Further elution with ethyl acetate:dichloromethane (1:1) afforded p-methoxybenzoic acid (87 mg, 98%), identical with an authentic specimen.

Decarboxylative Bromination General Procedures.

a) Procedure not involving AIBN. - To a suspension of the dry sodium salt of 2 (1.1 mmole) in a refluxing mixture of bromotrichloromethane and O-dichlorobenzene (2:3; 5ml) was added dropwise (30 min) under an inert atmosphere a solution of the acid chloride (1 mmole) in the same mixture (10 ml). After a further heating period of 5 min, the solvents were evaporated under reduced pressure and the residue was purified by chromatography on silica using dichloromethane-pentane mixtures. The bromoderivatives as well as the co-produced sulphide 5a are known products. The yields and references are collected in Table 1.

b) Procedure involving the use of AIBN. - To a suspension of the sodium salt of 2 (1.1 mmole) in refluxing bromotrichloromethane (5 ml) was added dropwise (30 min) a solution of the acid chloride (1 mmole) and AIBN (Ca 25 mg) in the same solvent (5 ml) under an inert atmosphere. After a further heating period of 5 min, the solvent was evaporated under reduced pressure and the residue purified as above by chromatography on silica.

Decarboxylative Iodination - General Procedure.

To a suspension of the sodium salt of 2 (1.1 mmole) in refluxing dry toluene (3 ml) was added under an inert atmosphere the iodine donor (1.1 mmole; see Table 2) followed by a solution of the acid chloride (1 mmole) and AIBN (Ca 25 mg) in the same solvent (5 ml). The addition took 30 min. After a further heating period of 5 min the solvent was evaporated under reduced pressure and the residue purified by chromatography on silica using dichloromethane:pentane mixtures. All the iodo derivatives are known compounds. Yields and references are collected in Table 2.

Perfluoro n-hexyl 2-pyridyl sulphide 5c which was isolated when using perfluorohexyliodide as the source of iodine was purified by bulb to bulb distillation: (oven temperature 150°C at 3 mmHg); ν_{max} (neat) 1580, 1220, 1205 cm^{-1}; m/e 429 (M^+), 410 $(M-F)^+$; δ_H 8.60-8.72 (1H, m), 8.40-8.60 (2H, m), 7.20-7.45 (1H, m); (Found: C, 31.00; H, 1.24; N, 3.35; S, 7.18. Calc. for $C_{11}H_4F_{13}NS$: C, 30.78; H, 0.94; N, 3.26; S, 7.47%).

Acknowledgement

We would like to thank Prof. E. Vogel (Cologne Univ., Federal Republic of Germany) for helpful discussion and for the suggestion to increase the concentration of trichlomethyl radicals by addition of an initiator. Prof. E. Vogel has successfully applied this method to the difficult problem of decarboxylative bromination of sensitive trieneacids.[14]

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