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Chlorination and Bromination of Aromatic Molecules by an N-Halosaccharin / Pyridinium Poly(Hydrogen Fluoride) System

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CHLORINATION AND BROMINATION OF AROMATIC MOLECULES BY AN N-HALOSACCHARIN / PYRIDINIUM POLY(HYDROGEN FLUORIDE) SYSTEM

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Abstract: The title chlorination and bromination procedure can be used for ring halogenation of monosubstituted benzene derivatives. Reactions do not need the addition of any catalyst and take place under mild conditions.

Halogenation of organic molecules are of general interest. Chlorination of reactive aromatic compounds can be effected using aqueous chlorine, N-chloroamides and anilides[1]. When chlorine is used as a reagent the reactions are generally carried out in the presence of electrophilic catalyst. Reactions with aromatic molecules having a bonded methyl group take place also at the side chain, if light or a free radical initiator is present. Chlorination of the methyl group of toluene with N-chloroimines[2] resulted in the formation of benzyl chloride, but the reaction time, temperature, presence of free-radical initiator or light have an influence on the conversion of toluene and percent of the product formed.

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Many procedures have been described for the direct introduction of bromine into aromate nucleus. The majority of these can be classified into one of three categories depending on the nature of the bromine source which is employed, namely

-molecular bromine, as such, or generated in situ

-molecular bromine activated by a catalyst

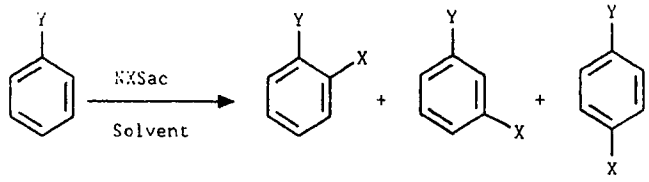
-positive bromine species.

Bromination with bromine of activated aromatic rings occurs readily with ortho- and para- isomers formation. The isomers distribution depends on the type of substituent and solvent used. On the other hand, aromatic rings bearing deactivating substituents require large amounts of Friedel-Crafts catalyst. The main role of the catalyst in aromatic electrophilic bromination is to polarise the reagent in such way that the bromine atom will be as positive as possible. One such molecule in which the bromine is highly polarized is bromine monofluoride. Rosen et al[3] reported that BrF, prepared by passing flourine through a cold suspension of bromine in CCl_3F can be used in electrophilic bromination and dibromination of various mono- and disubstituted aromatic compounds bearing activated or deactivated substituents, under very mild reaction conditions.

It is also known that an anhydrous hydrogen-fluoride/ N-bromoacetamide system[4] serves as a source of BrF. Recently, we have determined that N-bromosaccharin (NBSac) in the presence of pyridinium poly(hydrogen fluoride)[5] can be used as a very efficient reagent for stereospecific and regioselective bromofluorination of various phenyl substituted olefines and acetylenes. NBSac can also be used as a brominating agent for benzylic and α-carbonylic positions[6]. Reflux or irradiation with a sunlamp dramatically reduced the reaction time, while added radical initiators increased the yields of products.

We now report the results of chlorination and bromination of substituted aromatic molecules using an N-halosaccharin (NXSac)/ pyridinium poly(hydrogen fluoride) system (Scheme, Table 1, Table 2).

Chlorination of anisole at room temperature results in complete conversion of the starting compound in 2 hours into a mixture



1a-e			2a-e	3a-e	4a-e
Y:	$-OCH_3$	1a	2a	3a	4a
	$-CH_3$	1b	2b	3b	4b
	$-NO_2$	1c	2c	3c	4c
	-F	1d	2d	3d	4d
	-Cl	1e	2e	3e	4e

SCHEME

of ortho- and para- chloro derivatives when 20 percent excess of NCSac was used. A small amount of dichloroanisole was also formed. As the halogenation reaction is quite sensitive to changes in the polarity of the reaction medium, we have also studied chlorination of anisole with NCSac in acetic acid and methanol and determined that the reactivity of NCSac is lower in these solvents than in the case when pyridinium poly(hydrogen fluoride) was used (Table 1).

We also studied the reaction with toluene. It is known that NCSac[7] has been successfully used for benzylic chlorination when the reaction is assisted by a free-radical initiator. On the other hand, no side chain chlorination took place when the NCSac/ pyridinium poly(hydrogen fluoride) system was applied and o-chlorotoluene and p-chlorotoluene were obtained.

Higher reaction temperature and longer reaction time had to be used when the reaction of toluene and NCSac was carried out in acetic acid solution. We also determined that the NCSac/ pyridinium poly(hydrogen fluoride) system served as an efficient reagent for electrophilic chlorination of fluorobenzene and

TABLE 1: Chlorination of monosubstituted benzene derivatives

Substrate	Solvent	Reaction temp. (°C)	Reaction time (h)	Conversion (%)	Relative ratio of product (isolated yields) (%) 2	3	4	others
1a	HF/pyr	20	2	100	28(20)	/	66(56)	6(3)
1a	CH_3COOH	20	4	88	30(20)	/	70(51)	/
1a	CH_3COOH	50	2	86	33(21)	/	67(48)	/
1a	CH_3OH	20	4	83	35(19)	/	65(40)	/
1a	CH_3OH	64	2	95	36(25)	/	64(48)	/
1b	HF/pyr	20	2	74	72(41)	/	28(12)	/
1b*	HF/pyr	20	2	95	71(55)	/	29(20)	/
1b	CH_3COOH	80	4	63	60(28)	/	40(17)	/
1c	HF/pyr	20	2	0	/	/	/	/
1c	HF/pyr	20	24	0	/	/	/	/
1c	CH_3COOH	80	4	0	/	/	/	/
1d	HF/pyr	20	2	63	13 (5)	/	87(42)	/
1d	HF/pyr	20	7	100	10 (8)	/	90(72)	/
1d	CH_3COOH	80	4	0	/	/	/	/
1e	HF/pyr	20	2	59	38(14)	/	62(27)	/
1e	HF/pyr	20	7	65	40(18)	/	60(24)	/
1e	CH_3COOH	80	4	0	/	/	/	/

*: 1,7 mmol of NCSac per 1 mmol of toluene was used.

TABLE 2: Bromination of monosubtituted benzene derivatives

Substrate	Solvent	Reaction temp. (°C)	Reaction time (h)	Conversion (%)	Relative ratio of product (isolated yields)(%) 2	3	4	others
1a	HF/pyr.	20	2	100	6(4)	/	94(66)	/
1a	CH_3COOH	20	4	100	7(5)	/	93(66)	/
1a	CH_3COOH	50	2	100	9(6)	/	91(66)	/
1a	CH_3OH	20	4	100	10(7)	/	90(63)	/
1a	CH_3OH	64	2	100	11(8)	/	89(64)	/
1b	HF/pyr.	20	2	94	65(47)	/	35(25)	/
1b	CH_3COOH (85%)	80	4	100	48(36)	/	52(38)	/
1b	CH_3COOH (75%)	80	4	100	44(32)	/	56(40)	/
1c	HF/pyr.	20	2	87	/	100(72)	/	/
1c	CH_3COOH	80	4	/	/	/	/	/
1d	HF/pyr.	20	2	79	2(1)	/	70(35)	28(15)
1d	CH_3COOH	80	2	54	17(6)	/	81(30)	2(1)
1e	HF/pyr.	20	2	79	19(11)	/	81(57)	/
1e	CH_3COOH	80	2	46	44(16)	/	56(20)	/

chlorobenzene with the predominant formation of para isomers. No reaction was observed when acetic acid was used as a reaction medium.

Chlorination of highly deactivated benzene derivative such as nitrobenzene did not occur out even if pyridinium poly(hydrogen fluoride) was used.

We also studied reactions with NBSac / pyridinium poly(hydrogen fluoride) system and determined that it represents very efficient reagent for bromination of activated and deactivated monosubstituted benzene derivatives.

Bromination of anisole was completed in 2 hours at room temperature, thus giving 94 percent of para- and 6 percent of ortho- bromoanisole isomers (Scheme, Table 2). A predominant ortho directing effect was observed in the case of toluene, while in the case of fluoro and chlorobenzene para bromination predominantly took place. A reaction with nitrobenzene under the same reaction conditions resulted in 87 percent conversion with only meta isomer formation. The regiospecifity of the bromination does not differ much from other aromatic electrophilic bromination methods, but it does not need the addition of any catalyst, and offers short reaction times and mild conditions.

We were also interested to determine the influence of pyridinium poly(hydrogen fluoride) in these reactions, and instead of pyridinium poly(hydrogen fluoride), acetic acid or methanol were used as solvents.

We determined that the reaction with anisole and NBSac in both solvents was not significantly altered by such a modification in solvent, while a lower conversion and change in product distribution were observed when reactions of toluene, fluorobenzene and chlorobenzene were carried out in acetic acid at 80°C (Table 2). Bromination of nitrobenzene with NBSac in acetic acid solution did not take place.

From the results obtained we can conclude that pyridinium poly (hydrogen fluoride) probably served not only as a solvent but, together with NXSac also as a source of XF species which then acted as the reagent for electrophilic aromatic chlorination and bromination.

It is also posible that the HF presence in NBSac / pyridinium poly(hydrogen fluoride) system formed a potential highly ionic species[3] $Br^{+}HF_2^{-}$.

EXPERIMENTAL SECTION

The ^1H NMR spectra were obtained in $CDCl_3$ using a Varian EM 360L spectrometer with Me_4Si as the internal standard. The IR spectra were determined on a Perkin-Elmer 1310 spectrometer. Gas chromatographic analyses were carried out on a Varian Model 3700 gas chromatograph fitted with a column packed with FFAP 30% on a Chromosorb A A/W and OV17 10% on a Chromosorb G A/W.

Reaction mixtures were separated by preparative gas chromatography on a Varian Aerograph series 2700 equipped with a preparative column of standard dimensions packed with FFAP 30% on a Chromosorb W H/P and OV17 15% on a Chromosorb W A/W.

We used commercially available substances as standards: 2-chloroanisole, 4-chloroanisole, 2-chlorotoluene, 4-chlorotoluene, 1,2-dichlorobenzene, 1,4-dichlorobenzene, 1-chloro-2-fluorobenzene, 1-chloro-4-fluorobenzene, 1-chloro-3-nitrobenzene, 2-bromoanisole, 4-bromoanisole, 2-bromotoluene, 4-bromotoluene, 1-bromo-2-chlorobenzene, 1-bromo-4-chlorobenzene, and 1-bromo-3-nitrobenzene (Aldrich, Fluka).

Pyridinium poly(hydrogen fluoride) (30% pyridine - 70% hydrogen fluoride) was prepared by Olah's methode[8].

NCSac was obtained by the method described by Bachhawat et al[7].

NBSac was prepared by the method described by Sanchez and Fumarola[9].

General halogenation procedure: 6.0 mmol of NXSac was added over 5 min to a mixture of 10 ml of pyridinium poly(hydrogen fluoride) (30% pyridine - 70% hydrogen fluoride) and 10 ml of Et_2O at 0°C. The reaction mixture was stirred for 10 min at room temperature, 5 mmol of substrate was added and stirring was continued at this temperature for two hours. The reaction mixture was poured into ice cold water and extracted with Et_2O.The ether layer was washed with an aqueous solution of $NaHCO_3$, then with water and dried over anhydrous Na_2SO_4. After evaporation of ether, the crude reaction mixture was analysed by

analytical GC using the temperature programme: T_{start}= 80°C, 6min, 10°/min, T_{end}= 180°C.

The products were isolated by preparative GC using the same temperature programme. Yields of isolated products are given in the Table 1 and Table 2. The structures were determined by comparison of physical and spectroscopic data with original samples.

Halogenation in methanol and acetic acid: we used the same procedure as in the previous case. Instead of a mixture of pyridinium poly(hydrogen fluoride) and Et_2O, 20 ml of methanol or acetic acid were used.

The appropriate reaction temperature, reaction time, product distribution and isolated yields are given in the Table 1 and Table 2.

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