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Short Report

N-Chloro and *N*-Bromosaccharins: Valuable Reagents for Halogenation of Electron Rich Aromatics and Cohalogenation of Alkenes

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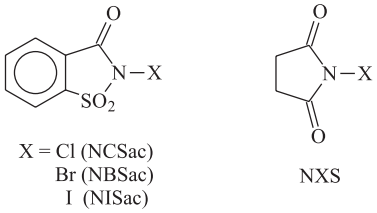
N-Cloro e *N*-bromo-sacarinas reagem com compostos aromáticos ricos em elétrons (anisol, acetanilida, *N*,*N*-dimetilanilina) para fornecer os produtos de halogenação do anel. As reações com a *N*-bromo-sacarina fornecem somente os produtos com substituição na posição *para*, enquanto que a utilização de *N*-cloro-sacarina gera mistura de produtos *orto* e *para*, com predominância do isômero *para* (*ca.* 4-5 : 1). Já as reações das halo-sacarinas com alquenos (cicloexeno, estireno, α-metilestireno e 1-hexeno) em acetona aquosa fornecem as respectivas haloidrinas.

N-Chloro- and *N*-bromosaccharins react with electron rich aromatic compounds (anisole, acetanilide, *N*,*N*-dimethylaniline) producing halogenated compounds. The reaction with *N*-bromosaccharin gives *para*- substituted compounds only, whereas *N*-chlorosaccharin produces *orto* and *para* mixtures (*para* isomer predominantly, *ca.* 4-5 : 1). The reactions of the *N*-halosaccharins with alkenes (cyclohexene, styrene, α-methylstyrene, and 1-hexene) give the corresponding halohydrins.

Keywords: cohalogenation, aromatic halogenation, *N*-halosaccharin

Introduction

Although *N*-halosaccharins (NXSac, Scheme 1) are more electrophilic than the structurally analogue *N*-halosuccinimides (NXS), they have found little attention in synthetic organic chemistry.[1] Recently, Dolenc published the reaction of NISac with alkenes and aromatic compounds.[1] On the other hand, NCSac and NBSac are easily prepared from the readily available sodium salt of saccharin[2] and they are used in mild oxidation reactions,[3-7] analytical chemistry,[8] and as halogenating reagents for allylic,[9] benzylic[9,10] and α-carbonylic[10,11] positions. Surprisingly, to the best of our knowledge, there is no description of the reaction of those halosaccharins with alkenes and aromatic compounds and we now present our results on this area.



Scheme 1.

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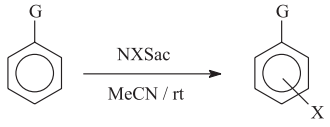
Results and Discussion

NCSac and NBSac react smoothly and fast with electron rich aromatics and the results are summarized in Table 1. The reactions were performed at room temperature stirring together a solution of NXSac (5 mmol) and the aromatic compound (5 mmol) in acetonitrile. The products were characterized by coinjection with authentic commercial

Table 1. Halogenation of aromatics with NXSac

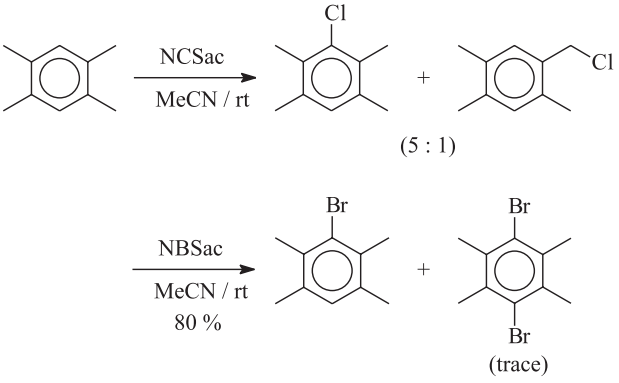


G	X	t / min	%[a]	*p* / *o*[b]
H	Cl	> 240	0[c]	-
H	Br	> 240	0[c]	-
Me	Cl	> 240	0[c]	-
Me	Br	> 240	0[c]	-
OMe	Cl	110	53	4.3 / 1
OMe	Br	5	60	100 / 0[d]
NHAc	Cl	55	78	4.5 / 1
NHAc	Br	10	77	100 / 0[d]
NMe_2	Cl	30	79	5.0 / 1
NMe_2	Br	5	75	100 / 0[d]

[a] Yield of pure product based on aromatic compound; [b] Determined by HRGC; [c] Substrate recovered; [d] Not detected.

samples in high-resolution gas chromatography (HRGC) and spectroscopic methods.

It was observed that the reactions with NBSac were faster with exclusive formation of 4-substituted bromides, whereas reactions with NCSac produced a mixture of 2- and 4-substituted chlorides (the 4-isomer predominated in all cases by *ca.* 4-5 : 1). Less reactive substrates such as benzene and toluene did not react after 4 h. On the other hand, durene showed interesting results (Scheme 2). Although the reactions were incomplete after several hours, it was observed that using NCSac it was obtained products arising from the reaction with both aromatic nucleus and methyl group, whereas NBSac produced almost exclusive aromatic bromination.

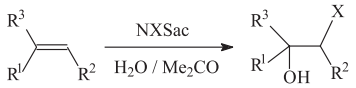


Scheme 2.

The formation of halodurenes could be rationalized by a nucleophilic attack of the aromatic ring to the electrophilic halogen in NXSac. On the other hand, the chlorination of the methyl in the reaction of durene with NCSac is probably a radical reaction. The difference between NCSac (electrophilic and radical attack) and NBSac (electrophilic attack only) are in accordance with the fact that NCSac is more efficient than NBSac for benzylic halogenation, whereas NBSac is more efficient than NCSac for electrophilic reactions.[7,9]

The cohalogenation (halogenation in the presence of a nucleophilic solvent[12]) of representative alkenes was also easily achieved with NCSac and NBSac. The reactions were performed at room temperature with equimolar amounts of alkene and NXSac in aqueous acetone to produce the corresponding halohydrins and the results are summarized in Table 2. In general, the regioselectivity was very high and no regioisomeric products were detected by the analytical methods employed (HRGC and ^{1}H and ^{13}C NMR). The exception was 1-hexene that afforded a regioisomeric mixture of halohydrins in which the 1-halo-2-alkanols predominated (*ca.* 3 : 1 by high-resolution GC). The products were characterized by spectroscopic methods and, wherever possible, by coinjection in HRGC with authentic commercial samples or prepared by an alternative route.[13]

Table 2. Cohalogenation of alkenes with NXSac



R^1	R^2	R^3	X	t / min	%[a]
- $(CH_2)_4$-		H	Cl	30	80[b]
- $(CH_2)_4$-		H	Br	30	82[b]
Bu	H	H	Cl	45	74[c]
Bu	H	H	Br	35	76[c]
Ph	H	H	Cl	10	71
Ph	H	H	Br	10	66
Ph	H	Me	Cl	10	91
Ph	H	Me	Br	10	93

[a] Yield of pure product based on alkene; [b] *trans*; [c] Obtained predominantly (*ca.* 3:1 by HRGC) with its regioisomer.

In summary, NCSac and NBSac are alternative and attractive reagents to perform halogenation of electron rich aromatic compounds and cohalogenation of alkenes. Furthermore, the reaction conditions are simple, safe and these halosaccharins are easily prepared by commercial sodium saccharin.

Experimental

All chemicals were used without further purification. NCSac and NBSac were prepared by reaction of sodium salt of saccharin with KCl or KBr and oxone®.[2] ^{1}H NMR and ^{13}C NMR spectra were acquired on a Bruker AC-200 (200 MHz and 50 MHz, respectively) spectrometer in $CDCl_3$ (otherwise stated) solutions with TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer (KBr film). MS were obtained on a Hewlett-Packard HP5896-A HRGC-MS using electron impact (70 eV). Analyses by HRGC were performed on a HP-5890-II gas chromatograph with FID by using a 30 m (length), 0.25 mm (ID) and 25 μm (phase thickness) RTX-5 silica capillary column and H_2 (flow rate 50 cm s^{-1}) as carrier gas (split 1:20).

The reactions were complete when an aliquot did not produce a color change in a wet iodide-starch test paper.

Typical procedure for the chlorination and bromination of aromatics

To a stirred solution of the aromatic compound (5 mmol) in acetonitrile (5 cm^3), NXSac (5 mmol) was added at rt. After termination of the reaction, CH_2Cl_2 (20 cm^3) was

added. The solution was washed with 10 % $NaHCO_3$ (2 x 10 cm^3), 10 % $NaHSO_3$ (2 x 10 cm^3) and then dried (Na_2SO_4). Evaporation of the solvent on a rotatory evaporator gave the haloaromatic compound.

p-chloroanisole. ^{1}H NMR: δ 3.70 (s, 3H), 6.74 (d, *J* 8.98 Hz, 2H), 7.15 (d, *J* 8.96 Hz, 2H) ppm. ^{13}C NMR: δ 55.6 (CH_3), 115.4 (C), 125.7 (CH), 129.5 (CH), 158.4 (C) ppm.

o-chloroanisole. ^{1}H NMR: δ 3.82 (s, 3H), 6.80 (d, *J* 7.72 Hz, 2H), 7.20 (d, *J* 8.51 Hz, 2H) ppm. ^{13}C NMR: δ 56.2 (CH_3), 112.3 (C), 121.5 (CH), 122.4 (CH), 127.9 (CH), 130.4 (CH), 156.0 (C) ppm.

p-bromoanisole. ^{1}H NMR: δ 3.79 (s, 3H), 6.79 (d, *J* 9.00 Hz, 2H), 7.39 (d, *J* 9.00 Hz, 2H) ppm. ^{13}C NMR: δ 55.6 (CH_3), 113.0 (C), 115.9 (CH), 132.4 (CH), 158.9 (C) ppm. IR ν_{max}/cm^{-1} : 3094, 3072, 3004, 2958, 2938, 2905, 2837, 1590, 1578, 1489, 1290, 1247, 1033, 822, 804, 792, 601, 507. MS: *m/z* 50, 62, 63, 64, 77, 79, 92, 117, 119, 143, 145, 171, 173, 186 (M^+, 100%), 188 ($M+2^+$, 100%).

p-chloroacetanilide. ^{1}H NMR: δ 2.04 (s, 3H), 7.33 (d, *J* 8.58 Hz, 2H), 7.61 (d, *J* 8.40 Hz, 2H), 10.06 (broad s, 1H, NH) ppm. ^{13}C NMR: δ 24.4 (CH_3), 120.9 (CH), 127.0 (C), 129.0 (CH), 138.7 (C), 168.9 (C) ppm. MS: *m/z* 43, 63, 73, 92, 99, 127 (100%), 129, 169 (M^+, 24%), 171 ($M+2^+$, 8%).

o-chloroacetanilide. ^{1}H NMR: δ 2.09 (s, 3H), 7.18 (d, *J* 7.74 Hz, 1H), 7.47 (d, *J* 8.34 Hz, 2H), 7.70 (d, *J* 7.72 Hz, 1H), 9.51 (broad s, 1H, NH) ppm. ^{13}C NMR: δ 24.7 (CH_3), 121.8 (CH), 122.7 (CH), 124.6 (CH), 127.6 (CH), 128.9 (CH), 134.6 (C), 168.2 (C) ppm. MS: *m/z* 43, 65, 73, 92, 99, 127 (100%), 129, 134, 135, 169 (M^+, 13%), 171 ($M+2^+$, 5%).

p-bromoacetanilide. ^{1}H NMR (DMSO-d_6): δ 2.04 (s, 3H), 7.45 (d, *J* 8.34 Hz, 2H), 7.56 (d, *J* 8.52 Hz, 2H), 10.06 (broad s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ 24.4 (CH_3), 114.9 (C), 121.3 (CH), 131.9 (CH), 139.1 (C), 168.9 (C) ppm. IR ν_{max}/cm^{-1} : 3293, 3260, 3186, 3115, 3052, 1668, 1644, 1601, 1586, 1532, 1487, 1394, 1309, 1290, 1255, 1007, 831, 819, 740, 687, 504. MS: *m/z* 43, 63, 65, 92, 171 (100%), 173, 213 (M^+, 27%), 215 ($M+2^+$, 26%).

p-chloro-N,N-dimethylaniline. ^{1}H NMR: δ 3.01 (s, 3H), 6.55 (d, *J* 8.00 Hz, 1H), 7.12 (d, *J* 8.02 Hz, 1H) ppm. ^{13}C NMR: δ 43.6 (CH_3), 114.5 (CH), 125.4 (C), 130.1 (CH), 142.6 (C) ppm.

o-chloro-N,N-dimethylaniline. ^{1}H NMR: δ 3.05 (s, 3H), 6.83 (d, *J* 7.80 Hz, 2H), 7.10 (d, 8.89 Hz, 2H) ppm. ^{13}C NMR: δ 41.1 (CH_3), 114.5 (CH), 118.2 (C), 119.4 (CH), 127.3 (CH), 130.0 (CH), 145.0 (C) ppm.

p-bromo-N,N-dimethylaniline. ^{1}H NMR: δ 2.90 (s, 1H), 6.70 (d, *J* 9.00 Hz, 1H), 7.10 (d, *J* 9.00 Hz, 1H) ppm. ^{13}C NMR: δ 40.5 (CH_3), 108.4 (C), 114.0 (CH), 131.6 (CH), 149.4 (C) ppm.

bromodurene. ^{1}H NMR: δ 2.30 (s, 6H), 2.39 (s, 6H), 7.27 (s, 1H) ppm. ^{13}C NMR: δ 20.4 (CH_3), 21,1 (CH_3), 130.5 (CH), 131.2 (C), 134.1 (C), 134.9 (C), 135.2 (C) ppm. MS: *m/z* 65, 77, 91, 105, 115, 117, 133 (100%), 197, 199, 212 (M^+, 52%), 214 ($M+2^+$, 54%).

Typical procedure for the preparation of chloro- and bromohydrins

To a stirred solution of the alkene (5 mmol) in 10 cm^3 of water / acetone (1 : 3, v/v), NXSac (5 mmol) was added at rt. After termination of the reaction, Et_2O (10 cm^3) was added. The organic phase was washed with 10 % $NaHCO_3$ (2 x 8 cm^3), 10 % $NaHSO_3$ (2 x 8 cm^3) and then dried (Na_2SO_4). Evaporation of the solvent on a rotatory evaporator gave the halohydrin.

trans-2-chlorocyclohexanol. ^{1}H NMR: δ 1.05-2.84 (m, 8H), 2.60 (broad s, 1H, OH), 3.30 (s, 1H), 3.39 (s, 1H) ppm. ^{13}C NMR: δ 24.0 (CH_2), 25.6 (CH_2), 33.1 (CH_2), 35.1 (CH_2), 67.3 (CH), 75.2 (CH) ppm. MS: *m/z* 57 (100%), 80, 98, 116, 134 (M^+, 6%), 136 ($M+2^+$, 2%).

trans-2-bromocyclohexanol. ^{1}H NMR: δ 1.12-2.50 (m, 8H), 2.63 (broad s, 1H, OH), 3.61 (s, 1H), 3.91 (s, 1H) ppm. ^{13}C NMR: δ 24.1 (CH_2), 26.6 (CH_2), 33.6 (CH_2), 36.2 (CH_2), 61.6 (CH), 75.2 (CH) ppm.

1-chloro-2-hexanol. ^{1}H NMR: δ 0.90 (m, 3H), 1.10-1.80 (m, 6H), 2.25 (broad d, *J* 4.4 Hz, 1H, OH), 3.50 (dd, *J* 10.9 Hz and 6.4 Hz, 1H), 3.60 (dd, *J* 10.9 Hz and 3.2 Hz, 1H), 3.80 (m, 1H) ppm. ^{13}C NMR: δ 14.0 (CH_3), 22.6 (CH_2), 27.7 (CH_2), 34.0 (CH_2), 50.5 (CH), 71.5 (CH_2) ppm.

1-bromo-2-hexanol. ^{1}H NMR: δ 0.93 (m, 3H), 1.22-1.80 (m, 6H), 2.20 (d, *J* 4.8 Hz, 1H), 3.40 (dd, *J* 10.2 Hz and 7.0 Hz, 1H), 3.53 (dd, *J* 10.2 Hz and 3.4 Hz), 3.74 (m, 1H) ppm. ^{13}C NMR: δ 14.0 (CH_3), 22.6 (CH_2), 27.7 (CH_2), 34.8 (CH_2), 40.3 (CH_2), 71.0 (CH) ppm.

2-chloro-1-phenylethanol. ^{1}H NMR: δ 2.64 (broad s, 1H, OH), 3.71 (m, 2H), 4.89 (dd, *J* 3.50 Hz and 8.38 Hz, 1H), 7.37 (s, 5H) ppm. ^{13}C NMR: δ 51.0 (CH_2), 74.2 (CH), 126.2 (CH), 128.6 (CH), 128.8 (CH), 140.1 (C) ppm. IR ν_{max}/cm^{-1} : 3418, 3088, 3064, 3032, 2976, 2928, 2897, 1704, 1615, 1556, 1454, 1396, 1337, 1248, 1175, 1064, 873, 771, 725, 699, 616, 523. MS: *m/z* 51, 77, 79, 107 (100%), 156 (M^+, 4%), 158 ($M+2^+$, 1%).

2-bromo-1-phenylethanol. ^{1}H NMR: δ 2.73 (broad s, 1H, OH), 3.60 (m, 2H), 4.92 (dd, *J* 3.50 Hz and 8.60 Hz, 1H), 7.37 (s, 5H) ppm. ^{13}C NMR: δ 40.3 (CH_2), 74.0 (CH), 126.1 (CH), 128,6 (CH), 128.8 (CH), 140.5 (C) ppm. IR ν_{max}/cm^{-1} : 3419, 3087, 3063, 3031, 2963, 2918, 2896, 2850, 1705, 1681, 1614, 1453, 1420, 1336, 1258, 1217, 1198, 1016, 764, 701, 593. MS: *m/z* 51, 77, 79, 107 (100%), 200 (M^+, 3%), 202 ($M+2^+$, 3%).

1-chloro-2-phenyl-2-propanol. ^{1}H NMR: δ 1.63 (s, 3H),

2.63 (broad s, 1H, OH), 3.73 (d, *J* 11.17 Hz, 1H), 3.83 (d, *J* 11.17 Hz, 1H), 7.40 (m, 5H) ppm . ^{13}C NMR: δ 27.5 (CH_3), 55.6 (CH_2), 74.0 (C), 125.1 (CH), 127.7 (CH), 128.6 (CH), 144.3 (C) ppm. IR ν_{max}/cm^{-1} : 3445, 3089, 3061, 3029, 2978, 2933, 2851, 1730, 1495, 1447, 1377, 1337, 1290, 1249, 1181, 1070, 769, 966, 580. MS: *m/z* 43, 51, 77, 91, 121 (100%), 170 (M^+, 0.2%), 172 (M+2$^+$, 0.07%).

1-bromo-2-phenyl-2-propanol. ^{1}H NMR: δ 1.67 (s, 3H), 2.91 (broad s, 1H, OH), 3.68 (d, *J* 10.45 Hz, 1H), 3.76 (d, *J* 10.63 Hz, 1H), 7.37 (m, 5H) ppm. ^{13}C NMR: δ 28.2 (CH_3), 46.4 (CH_2), 73.3 (C), 125.0 (CH), 127.7 (CH), 128.6 (CH), 144.3 (C) ppm. IR ν_{max}/cm^{-1}: 3436, 3088, 3060, 3028, 2977, 2932, 2897, 1731, 1494, 1447, 1375, 1337, 1180, 1069, 1050, 766, 701, 591. MS: *m/z* 43, 51, 77, 78, 91, 105, 121 (100%), 214 (M^+, 0.3%), 216 (M+2$^+$, 0.2%).

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