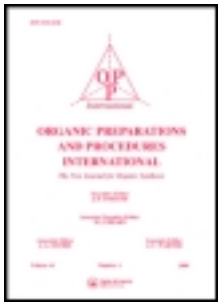

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N-BROMOSUCCINIMIDE-CHLOROFORM, A MORE CONVENIENT METHOD TO NUCLEAR BROMINATE REACTIVE AROMATIC HYDROCARBONS

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N-BROMOSUCCINIMIDE - CHLOROFORM, A MORE CONVENIENT METHOD TO NUCLEAR BROMINATE REACTIVE AROMATIC HYDROCARBONS

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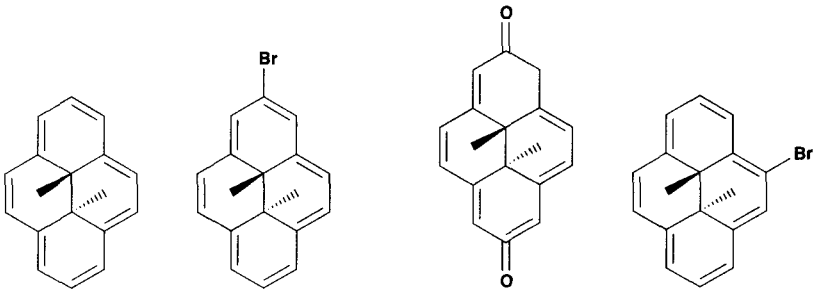
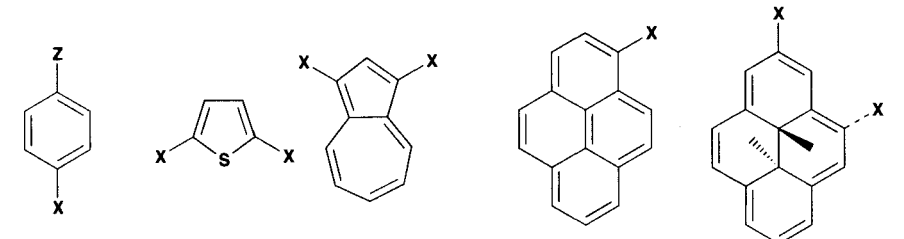
Although NBS is well known as a free radical brominating reagent for allylic and benzylic hydrogens, its use in the electrophilic bromination of aromatic rings is much less known. In 1979, we reported the use of NBS-DMF as a mild, selective nuclear monobromination reagent for reactive aromatic compounds.[1] Even though DMF is not the easiest solvent to handle, this reagent has since that time, found use in a variety of cases,[2] many of which are quite complex natural products. However, we have noted[3] that if the DMF is wet, problems can occur; for example, the dihydropyrene **1** gives bromide **2** with dry DMF, but quinone **3** if the DMF contains traces of water. Others[4] have also observed that



1 **2** **3** **4**

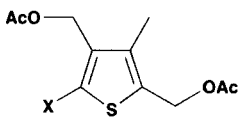
DMF is not an easy solvent to remove, having both a high boiling point and limited solubility in water, and thus investigated acetonitrile as an alternative solvent for methoxybenzenes and naphthalenes. In cases that are sensitive to water, the use of acetonitrile can present problems. Nevertheless, in order to obtain reasonable reaction rates at room temperature, some polarity in the solvent is

required. Therefore we investigated the much easier handled solvent, chloroform and now report that NBS-$CHCl_3$ at room temperature provides a convenient method to effect the nuclear bromination of reactive aromatic substrates such as anilines, anisoles, phenols, thiophene, mesitylene, azulene, pyrene and *trans*-10b,10c-dimethyldihydropyrene to give products which are easily isolated. Two or more bromine atoms can be introduced for thiophene, azulene and *trans*-dimethyldihydropyrene. Rather than optimize each individual case, we have attempted to establish conditions that work well for a variety of substrates.

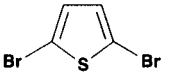


Azulene does not form a monobromide cleanly, but can be dibrominated (below). Anthracene only forms about 30% of 9-bromoanthracene under the above conditions. It is interesting that dihydropyrene **1** gives almost exclusively (>95%) the 2-bromide **2** in dried DMF, whereas in acetonitrile a 3:1 mixture of **2** and **4** is obtained; in $CHCl_3$ the ratio of these two isomers is 1:1. The use of $CHCl_3$ is thus especially useful, since access to the 4-derivatives of dihydropyrene has been very restricted until now.[7]

The use of larger quantities of NBS permits higher brominated products to be obtained. With 2 equivalents of NBS, thiophene gave 56% of 2,3-dibromothiophene[5a,c] **7**. Azulene cleanly yields 86% of 1,3-dibromoazulene, **8**, mp 76-77°,[8] if acetic acid (2 mL/100mL) is added to the $CHCl_3$;



5 X = H
6 X = Br



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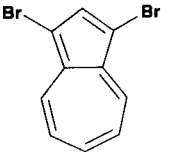
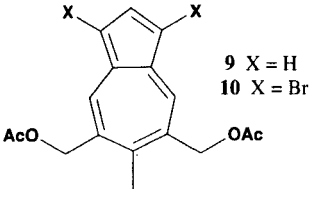
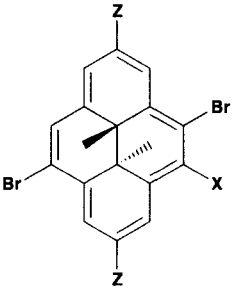


8



9 X = H
10 X = Br



11 Z = *t*-Bu, Y = Br, X = H
12 Z = *t*-Bu, Y = H, X = Br
13 Z = H, Y = Br, X = H
14 Z = H, Y = X = Br

otherwise reaction is not complete. Likewise the substituted azulene **9** yields dibromoazulene **10**, in 57% yield. The 2,7-di-*tert*-butyl derivative of **1** with 2 equivalents of NBS in $CHCl_3$ yields >95% of the 1:1 mixture of dibromides **11** and **12**.[9]

With 4 equivalents of NBS in $CHCl_3$ at room temperature for 24 h and followed by reflux for 24 h, Dihydropyrene (**1**) actually yields about 60% of tetrabromide, from which 36% of the tetrabromide **13** can be obtained pure by fractional recrystallization. Further bromination of **13** is slow, 10 equivalents of NBS yield pentabromide, from which **14** can be obtained in 21% yield by fractional recrystallization.

In summary, we believe that NBS-$CHCl_3$ is a useful addition to the reagents that can nuclear brominate reactive aromatic hydrocarbons under mild conditions.

EXPERIMENTAL SECTION

Melting points were determined on a Reichert 7905 melting point apparatus. IR spectra, major peaks only, were recorded on a Bruker IFS25 FT-IR as KBr disks. Proton NMR spectra were recorded at 300 MHz in $CDCl_3$ on a Bruker AC300 (^{13}C NMR at 75.5 MHz). Mass spectra were measured on a Kratos Concept-H instrument. Elemental analyses were carried out by Canadian Microanalytical Services, Ltd, Vancouver, BC. All evaporations were carried out at reduced pressure, and the silica gel was Merck, 70-230 mesh.

TABLE 1. Monobromination of Substrates using NBS-$CHCl_3$ (General Procedure).

Substrate	Product	Yield	Identity[a]
Aniline	*p*-bromoaniline	90%	**2**, 482A
Anisole	*p*-bromoanisole	84%	**2**, 187A
Phenol	*p*-bromophenol	81%	**2**, 253C
m-Cresol	4-bromo-*m*-cresol	85%	b
Mesitylene	2-bromomesitylene	90%	**2**, 122A
Pyrene	2-bromopyrene	96%	b
Thiophene	2-bromothiophene	71%	c
5	**6**	95%	d
1	**2** and **4** (1:1)	80%	e

a) Samples were compared to authentic samples by ^1H and ^{13}C NMR, and by mp where appropriate; *e. g.* **2**, 482A refers to the Aldrich Library of ^{13}C and ^1H FT NMR Spectra, Edition I, spectrum number. b) Prepared by us previously.[1] c) Oil[5]; Reference 5c gives the ^1H NMR spectra of both 2- and 3-bromothiophene which are completely different. d) Oil; properties below. e) ^1H NMR spectrum below.

General Procedure.- The arene (2 mmol) and NBS (2.1 mmol) were stirred in reagent grade $CHCl_3$ (as obtained, 25 mL) at 15-20° for 24 h. The mixture was then washed with water, and additional $CHCl_3$ was added if needed, and then the organic layer was dried and evaporated to give product. Further purification was generally not necessary but if required, chromatography over silica gel with

hexane as eluant was used. The results are shown in Table 1. On the 100 mmol scale, 300 mL of $CHCl_3$ can be used.

Compound 6: ^{1}H NMR 5.06 (s, 2H, -CH_2O-), 4.94 (s, 2H, -CH_2O-), 2.16 (s, 3H, -CH_3), 2.00 (s, 6H, -$COCH_3$); ^{13}C NMR: δ 170.7, 170.6, 137.0, 135.1, 132.5, 115.1, 59.2, 58.2, 20.8, 20.7, 12.7; IR (KBr) 1743 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}BrO_4S$: C, 41.14; H, 4.08. Found: C, 40.86; H, 4.52

Compound 4: ^{1}H NMR 8.90 (d, H-3), 8.85 (s, H-5), 8.64-8.54 (m, H-1,6,8,9,10), 8.20 (t, H- 2), 8.13 (t, H-7), -4.14 and -4.15 (s, -CH_3). This compound could not be separated pure from **2**, but is easily distinguished by ^{1}H NMR (see reference 6 for ^{1}H NMR of **2**).

1,3-Dibromoazulene (8), from azulene (256 mg, 2.0 mmol) and NBS (712 mg, 4.0 mmol) in $CHCl_3$ (49 mL + 1 mL acetic acid) using the general procedure above gave 492 mg (86%) of **8**, mp 76-77° (lit[8] mp 76-77°); ^{1}H NMR: δ 8.29 (d, 2H, J = 9.5 Hz), 7.79 (s, 1H), 7.67 (t, 1H, J = 9.5 Hz), 7.26 (t, 2H, J = 9.5 Hz); ^{13}C NMR: δ 140.1, 138.2, 136.7, 135.8, 124.1, 102.7.

1,3-Dibromo-5,7-*bis*(methylcarbonyloxymethyl)-6-methylazulene (10), from **9** (240 mg, 0.84 mmol), NBS (300 mg, 1.7 mmol) and $CHCl_3$-AcOH (49 mL + 1 mL) was obtained 210 mg (57%) of **10**, mp 148-150°; ^{1}H NMR: δ 8.30 (s, 2H), 7.72 (s, 1H), 5.32 (s, 4H), 4.82, (s, 2H), 2.61 (s, 3H), 2.14 (s, 6H); ^{13} C NMR: δ 170.8, 152.2, 138.9, 138.3, 133.0, 130.0, 104.5, 69.7, 21.0, 20.8; IR (KBr) 1730 cm^{-1}; MS (FAB) M^+ at *m/z* 442, 444, 446.

Anal. Calcd for $C_{17}H_{16}Br_2O_4$: C, 45.98; H, 3.63. Found: C, 46.12; H, 3.61

2,4,7,9-Tetrabromo-10b,10c-dimethyl-10b,10c-dihydropyrene (13), by the general procedure using 4 equiv. of NBS, followed by an additional 24 hours at reflux. Three recrystallizations from methanol yielded 36% of dark green crystals, mp 231-232°; ^{1}H NMR: δ 8.99 (s, 2H), 8.69 (s, 2H), 8.64 (s, 2H), -3.76 (s, 6H); ^{13}C NMR: δ 137.0, 132.9, 128.2, 127.9, 127.6, 121.1, 117.2, 31.9, 14.3.

Anal. Calcd for $C_{18}H_{12}Br_4$: C, 39.46; H, 2.21. Found: C, 39.28; H, 2.25

2,4,5,7,9-Pentabromo-10b,10c-dimethyl-10b,10c-dihydropyrene (14).- As for **13**, except 10 equiv. NBS used. Three recrystallizations from methanol gave 21% of dark green crystals of **14**, mp 247-248°; ^{1}H NMR: δ 9.15 (s, 1H), 9.12 (s, 1H), 9.01 (s, 1H), 8.67 (s, 1H), 8.63 (s, 1H), -3.62 (s, 3H), -3.64 (s, 3H); HRMS calcd for $C_{18}H_{11}{}^{79}Br_5$: 621.6778. Found: 621.6771.

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