1,8-Diazabicyclo[5.4.0]undec-7-ene Hydrobromide Perbromide: A New Mild Stable Brominating Agent for Aromatic Compounds

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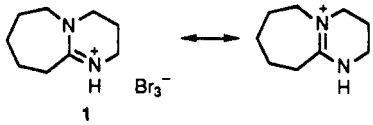
Received August 29, 1991

Bromination of aromatic compounds with elementally bromine is a well-known reaction.[1] Owing to the hazards associated with bromine, several solid brominating agents have been prepared, i.e., pyridine hydrobromide perbromide ($PyHBr_3$),[2] tetramethylammonium tribromide,[3] and phenyltrimethylammonium tribromide.[4] These crystalline tribromides constitute a convenient source of bromine because of their ease of handling. They have been used occasionally as nuclear brominating agents, particularly with reactive aromatic compounds, i.e., phenols[4] and anilines.[5] The chief drawbacks of these reagents are their limited application to reactive rings,[4,5] the relatively low yields of products,[6] and the deterioration of the reagents during long periods of storage[7].

It would be useful to have alternative sources of bromine that offer advantages of wide application, mild reaction conditions, high reaction rates, and stability.

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) is a well-known reagent that found application because of its nonnucleophilic and strongly basic properties.[8] The bicyclic imidine reacts with inorganic and organic acids, forming crystalline salts which have a stable imidinium cation structure 1. We now report the brominating properties of $DBUHBr_3$ (1) with a number of aromatics and heteroaromatics.



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Results and Discussion

$DBUHBr_3$ was readily obtained in almost quantitative yield by the action of an equimolar amount of bromine on DBU in the presence of HBr in acetic acid. The orange crystalline bromine complex $DBUHBr_3$ showed a remarkable stability over $PyHBr_3$. In separate samples, titration of the active bromine of each tribromide left exposed to air for a period of 1 month has shown that $PyHBr_3$ had lost about 30% of its active bromine, while 1 remained unchanged, not only for 1 month, but for several months.

The structure of 1 was confirmed by spectroscopy. The ^1H NMR spectrum shows a broad singlet at δ 8.35 ppm for the N-H proton, which undergoes a slow exchange. The UV spectrum exhibits an intense absorption band centered at 275 nm (ϵ = 36 000 M^{-1} cm^{-1}), the λ_{max} typical for the Br_3^- anion.[9]

Bromination of Aromatic Compounds with DBUH-Br_3. Four general procedures have been employed for aromatic bromination with 1 depending on the nature of the aromatic ring (Table I). Activated aromatics and heteroaromatics such as aniline and thiophene are brominated very smoothly at room temperature in aqueous DMF.

Fairly reactive aromatic systems, like mesitylene, acenaphthene, and biphenylene, can be similarly brominated with 1 in the presence of $HgCl_2$ as a catalyst. This method is particularly advantageous with biphenylene, since direct bromination with bromine gives 2-bromobiphenylene in a moderate yield together with some polybromides.[10]

Polycyclic aromatic compounds, such as naphthalene, anthracene, and phenanthrene, undergo bromination with 1 in acetic acid at reflux. Both 9-bromo- and 9,10-dibromoanthracene can be selectively prepared, depending upon the molar ratio of the reagent.

Unreactive and deactivated rings, like benzene, bromobenzene, and nitrobenzene, were brominated in good yields by the Derbyshire–Waters method.[11] A solution of the aromatic substrate and Ag_2SO_4 in H_2SO_4 was treated with 1 to give the corresponding bromide.

The reagent is also capable of brominating some heteroaromatics, usually sensitive to normal bromination, like indole and imidazole. 3-Bromoindole was isolated in 72% yield following the method of Piers for bromination of indole with $PyHBr_3$.[12] Imidazole was brominated with 1 according to the Kajigaeshi method.[4] Treatment of imidazole with 1 in a mixture of CH_2Cl_2 and CH_3OH afforded 2,4,5-tribromoimidazole in 60% yield. The literature methods usually give the tribromide in a lower yield due to oxidative degradation of imidazole.[13]

In all cases $DBUHBr_3$ can be regenerated and recovered from the reaction medium after isolation of bromination products. Treatment of the aqueous reaction medium with hydrobromic acid and $NaBrO_3$ gives 1 in yields ranging from 60% to 68%.

In summary, this versatile, stable, recoverable brominating agent acts as a new convenient source of bromine. From some nuclear bromination reactions conducted with both 1 and $(Bu)_4N^+Br_3^-$ (TBAT), it was evident that $DBUHBr_3$ is more reactive than TABT toward aromatic bromination. Longer reaction times and lower yields are usually associated with TBAT.

Experimental Section

Melting points are uncorrected. "Dried" refers to drying over anhydrous Na_2SO_4, followed by normal filtration.

$DBUHBr_3$ (1). To 1 L of glacial acetic acid, cooled to 20 °C, was added DBU (152.2 g, 1 mol) with sitrring at such a rate that the temperature did not rise above 25 °C (20 min). After the addition had been completed, 250 mL of 33% solution of HBr in acetic acid was added gradually. Bromine (60 mL) was then added dropwise, maintaining the temperature between 20 and 25 °C. The resulting orange solid was filtered in vacuo, washed with a little cold acetic acid and CCl_4, and dried under vacuum for 24 h over NaOH. Recrystallization from acetic acid (500 mL)

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0022-3263/92/1957-2740$03.00/0

Table I. Bromination of Aromatic Compounds with $DBUHBr_3$

no.	substrate	product	method	time, h	molar ratio, 1/subs.	yield,[a] %	mp, °C or bp, °C/Torr found	mp, °C or bp, °C/Torr lit.[15]
1	benzene	bromobenzene	D	0.5	1:2	70	153–155/760	152/760
2	mesitylene	2-bromomesitylene	B	1	1:1	76	103–106/16	105–107/16
3	acetanilide	4-bromoacetanilide	A	0.5	1:1	80	167–168	168
4	aniline	2,4,6-tribromoaniline	A	0.25	3:1	86	119–120	122
5	phenol	2,4,6-tribromophenol	A	0.25	3:1	89	92–94	95
6	nitrobenzene	1-bromo-3-nitrobenzene	D	12	1.1:1	62	53–55	56
7	naphthalene	1-bromonaphthalene	C	2	1.2:1	65	132–135/12	132–135/12
8	anthracene	9-bromoanthracene	C	0.25	1:1	70	96–98	100
		9,10-dibromoanthracene	C	0.5	2:1	95	223–225	226
9	phenanthrene	9-bromophenanthrene	C	3	1.2:1	60	62–64	65–66
10	biphenylene	2-bromobiphenylene	B	2	1:1	75	63–65	64–65[10]
11	thiophene	2-bromothiophene	A	0.25	1:2	68	152–154/760	155–156/760
		2,5-dibromothiophene	C	0.5	2:1	75	209–211/760	210/760

[a] Isolated pure product.

afforded 1: 92%; glittering-orange flakes; mp 120–122 °C; ^1H NMR ($CDCl_3$) δ 8.35 (br s, 1 H, NH), 3.60 (m, 6 H), 2.88 (m, 2 H), 2.17 (m, 2 H), 1.80 (m, 6 H); IR (KBr) ν 3350 (m, NH), 3250 (m, br) 2925 (m, CH), 1640 (s, N=C) cm^{-1}. Anal. Calcd for $C_9H_{17}Br_3N_2$: C, 27.51; H, 4.36; N, 7.16; Br, 61.07. Found: C, 27.60; H, 4.32; N, 7.13; Br, 60.85.

HBr acetic acid solution may be replaced by 45% hydrobromic acid (180 mL) to give $DBUHBr_3$ in 85% yield.

General Procedure for Bromination of Aromatics with 1. Method A. The appropriate proportion of the molar ratio of 1 was added to a vigorously stirred solution of the aromatic substrate (10 mmol) in 50% aqueous DMF (25 mL) over a period of 10 min. The mixture was stirred at room temperature for the specified reaction time and then diluted with water (100 mL). After complete precipitation of the product, it was filtered in vacuo and washed with water. For liquid products, the aqueous solution was extracted with ether, separated, washed with water, dried, and evaporated under reduced pressure.

Method B. $DBUHBr_3$ (4 g, 10 mmol) was added to a solution of the aromatic substrate (10 mmol) and $HgCl_2$ (10 mmol) in DMF (25 mL). The mixture was stirred vigorously at room temperature for the specified reaction time. Diluted HCl (100 mL) was added, and it was stirred continuously until precipitation was completed. The product was then filtered in vacuo and washed with water. Liquid products were extracted with ether, separated, and washed with water and aqueous $NaHCO_3$. They were then dried and evaporated under reduced pressure.

Method C. The appropriate proportion of the molar ratio of 1 was added to a gently refluxing solution of the aromatic substrate (10 mL) in acetic acid over a period of 10 min. The mixture was stirred at reflux for the specified reaction time until no more HBr was evolved. The cold reaction mixture was diluted with water and extracted with ether. The organic layer was separated, washed with water and aqueous $NaHCO_3$, dried, and evaporated under reduced pressure. Anthracene products were isolated by filtration of the cold reaction mixture.

Method D. A mixture of the aromatic substrate (10 mmol), Ag_2SO_4 (4.70 g, 15 mmol), and concd H_2SO_4 (25 mL) was stirred vigorously at room temperature. $DBUHBr_3$ (4.4 g, 11 mmol) was added, over 30 min, and stirred continuously for the specified reaction time. The reaction mixture was then poured onto crushed ice (150 g), and the resulting AgBr was collected on a Buchner funnel. The filtrate and the precipitate were extracted with ether, and the combined extracts were washed several times with water to remove any remaining acid and evaporated under reduced pressure.

2,4,4,6-Tetrabromocyclohexa-2,5-dienone. The selective brominating agent was prepared from 2,4,6-tribromophenol according to Calo's method:[14] 78%; mp 122–124 °C. (lit.[15] mp 125 °C).

3-Bromoindole. The title compound was prepared as described in ref 12: 72%; mp 65–66 °C dec (lit.[12] mp 65–66 °C).

2,4,5-Tribromoimidazole. A mixture of imidazole (0.68 g, 10 mmol), $DBUHBr_3$ (4 g, 10 mmol), and $CaCO_3$ (2 g, 20 mmol) in CH_2Cl_2 (25 mL) and CH_3OH (10 mL) was stirred at room temperature for a period of 12 h, during which the orange color of the mixture disappeared. The solid $CaCO_3$ was filtered off, the filtrate was concentrated, and the residue was diluted with water. The aqueous mixture was extracted with ether, separated, dried, and evaporated under reduced pressure to give the title compound: 60% (based on $DBUHBr_3$) as white crystals; mp 220–222 °C (lit.[13] 221–222 °C).

Recovery of $DBUHBr_3$ from the Reaction Medium. The aqueous mother liquor, resulting after isolation of the product, was treated successively with 45% aqueous hydrobromic acid (1.7 equiv to $DBUHBr_3$, used in bromination process) and $NaBrO_3$ (0.34 equiv). The mixture was stirred until complete precipitation of 1, which was filtered and recrystallized from acetic acid: yield 60–68%.

Registry No. 1, 138666-59-8; DBU, 6674-22-2; $HgCl_2$, 7487-94-7; Ag_2SO_4, 10294-26-5; 2,4,5-tribromoimidazole, 2034-22-2; imidazole, 288-32-4; benzene, 71-43-2; mesitylene, 108-67-8; acetanilide, 103-84-4; aniline, 62-53-3; phenol, 108-95-2; nitrobenzene, 98-95-3; naphthalene, 91-20-3; anthracene, 120-12-7; phenanthrene, 85-01-8; biphenylene, 259-79-0; thiophene, 110-02-1; bromobenzene, 108-86-1; 2-bromomesitylene, 576-83-0; 4-bromoacetanilide, 103-88-8; 2,4,6-tribromoaniline, 147-82-0; 2,4,6-tribromophenol, 118-79-6; 1-bromo-3-nitrobenzene, 585-79-5; 1-bromonaphthalene, 90-11-9; 9-bromoanthracene, 1564-64-3; 9,10-dibromoanthracene, 523-27-3; 9-bromophenanthrene, 573-17-1; 2-bromobiphenylene, 17573-59-0; 2-bromothiophene, 1003-09-4; 2,5-dibromothiophene, 3141-27-3.

Supplementary Material Available: Table I containing bromination data for 12–24 with $DBUHBr_3$ and Table II containing ^1H NMR shifts of 1–27 (6 pages). Ordering information is given on any current masthead page.

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The Critical Role of β-CF_3 in the Regioselective Dehydrochlorination of 2-Chloro-4,4,4-trifluoro-2-methylbutane with Hindered Amines and Metal Oxides

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Received December 9, 1991

The use of steric effects to control the regiochemistry of 1,2-elimination reactions has been a recognized strategy since the mid-50's.[1,2] Since then, the understanding of

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