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Article

{[K.18-Crown-6]Br_3}$_n$: A tribromide catalyst for the catalytic protection of amines and alcohols

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ABSTRACT

{[K.18-Crown-6]Br_3}$_n$, a unique tribromide-type catalyst, was utilized for the *N*-boc protection of amines and trimethylsilylation (TMS) and tetrahydropyranylation (THP) of alcohols. The method is general for the preparation of *N*-boc derivatives of aliphatic (acyclic and cyclic) and aromatic, and primary and secondary amines and also various TMS-ethers and THP-ethers. The simple separation of the catalyst from the product is one of the many advantages of this method.

1. Introduction

Crown ethers have attracted significant attention in various fields of science. Crown ether moieties are popular host compounds in host-guest chemistry, and these ligands have a remarkable ability to selectively form strong complexes with organic and inorganic cations [1–3] and anions [4,5]. Among the crown ethers, the 18-crown-6 forms a very stable complex with K^+, and it has the maximum stability constant among alkali complexes with metal cations [6,7].

Organic tribromide (OTB) reagents are preferred oxidants over molecular bromine because of the hazards associated with bromine. Several tribromides have been reported, including 1-butyl-3-methylpyridinium tribromide for the bromination of anilines and phenols [8], pyridinium tribromide for the oxidation of sulfides [9], phenyltrimethylammonium tribromide for the conversion of aromatic epoxide [10], *N*-benzyl-DABCO-tribromide for the deprotection of dithioacetals [11], tetrabutylammonium tribromide for the synthesis of aurones and flavones [12], 1,2-dipyridiniumditribromide–ethane for the bromination of aromatic compounds [13], and oxidation of alcohols by hexamethylenetetramine-bromine [14], and DABCO-bromine [15]. In addition, some ionic liquid tribromides (IL-Br_3^-) for the preparation of bromoesters from aromatic aldehydes [16] and bromination of aromatic substrates [17] have been reported.

In 2007, we reported a class of unique tribromide compounds with a columnar nanotube-like structure, {[K.18-crown-6]Br_3}$_n$, which was confirmed by X-ray crystallography. These compounds have a high active bromine content per molecule and they act as excellent bromine carriers for the oxidation of thiols and the bromination of aromatic sub-

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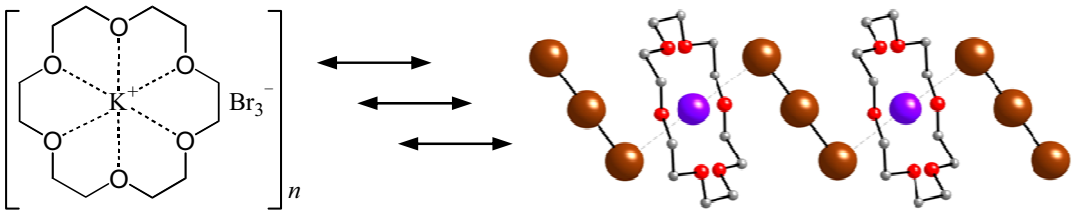


Fig. 1. View of X-ray structure of {[K.18-Crown-6]Br_3}$_n$.

strates (Fig. 1) [18].

These are very useful compounds, and the development of further catalytic application for these compounds, especially {[K.18-crown-6]Br_3}$_n$, is of interest [18,19].

When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, the other reactive functional groups must be blocked to prevent undesired reactions. For this purpose, many protective groups have been developed [20]. For a functional group, there are various protecting protocols: *N*-*tert*-butoxycarbonylation of amines by *di*-*tert*-butyl dicarbonate (Diboc) [21] and silylation and tetrahydropyranylation (THP) of alcohols by hexamethyldisilazane (HMDS) and 3,4-dihydro-2*H*-pyran (DHP) [22]. In this paper, we show the catalytic use of {[K.18-crown-6]Br_3}$_n$ in the efficient *N*-boc protection of amines and protection in the reaction of alcohols to trimethylsilylation (TMS)-ether and THP-ether.

2. Experimental

Chemicals were purchased from Merck. The protected products were characterized by the comparison of their spectral (IR, ^{1}H-NMR, and ^{13}C-NMR) and physical data with those of known samples [21–28]. {[K.18-crown-6]Br_3}$_n$ was prepared according our previously reported procedure [18].

For the *N*-boc protection of amines, to a solution of diboc (1 mmol) in ethanol (5 ml) was added {[K.18-crown-6]Br_3}$_n$ (0.001 mmol). The solution was stirred at room temperature for 1 min. The amine (1 mmol) was then added and the solution was stirred at room temperature for an appropriate time (Table 1). After completion of the reaction, the solvent was removed by water bath distillation. To the residue was added ethyl acetate (5 ml) and the mixture was filtered (the catalyst is insoluble in *n*-hexane and ethyl acetate). The solid was washed with ethyl acetate (10 ml × 2) and the combined filtrates were reduced to dryness to yield the pure products.

For the tetrahydropyranylation or trimethylsilylation of alcohols, to a solution of the DHP (1 mmol) or HMDS (1 mmol) in CH_3CN (5 ml) were added {[K.18-crown-6]Br_3}$_n$ (0.001 mmol). The solution was stirred at room temperature for 1 min. Then alcohol (1 mmol for THP and 2 mmol for TMS) was added and the solution was stirred at room temperature for an appropriate time (Table 2). After completion of the reaction, CH_3CN was removed by water bath distillation. To the residue was added *n*-hexane or ethyl acetate (5 ml) and the mixture was filtered (the catalyst is insoluble in *n*-hexane and ethyl acetate). The filtrate was washed with *n*-hexane or ethyl acetate (10 ml × 2). The solvent was removed by distillation to yield pure products.

3. Results and discussion

In this continuation of our studies on the host-guest chemistry of crown ethers [18,21–24] on the synthesis and application of tribromide reagents [18,19,21,22] and the protection of organic functional groups [21,22,25,26], we report that {[K.18-crown-6]Br_3}$_n$ is an excellent catalyst for the *tert*-butoxycarbonylation of various amines and TMS and THP of alcohols under mild conditions. Thus, we prepared a range of *tert*-butoxycarbonylated amines under the following reaction conditions: amines (1 mmol), Diboc (1 mmol), {[K.18-crown-6]Br_3}$_n$ (0.001 mmol), and ethanol (5 ml) as the optimized solvent for this reaction (Scheme 1 and Table 2). Likewise, we prepared a range of TMS-ethers and THP-ethers under the following reaction conditions: alcohols (1 mmol) protective group (DHP or HMDS (1 mmol)), {[K.18-crown-6]Br_3}$_n$ (0.001 mmol), and CH_3CN (5 ml) as the optimized solvent for these reactions (Scheme 1 and Table 2).

As shown in Table 2, a wide range of amines and alcohols (aliphatic and aromatic) were protected using the above procedure to afford the corresponding products in moderate to excellent yields. In the case of amines, aliphatic amines gener-

Table 1
Protection of amines with {[K.18-crown-6]Br_3}$_n$ (0.1 mol%) and Diboc (1 mmol) in the conversion to the *N*-boc compounds in ethanol at room temperature.

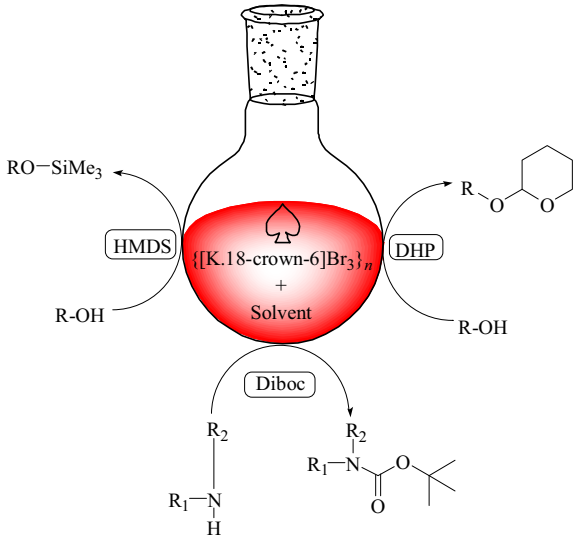
Entry	Substrate	Time (min)	Isolated yield (%)
1	4-Chloroaniline	420	94
2	4-Bromoaniline	240	90
3	4-Methoxyaniline	60	85
4	4-Hydoxyaniline	30	90
5	2-Hydoxyaniline	40	95
6	2-Methylaniline	210	85
7	3-Methylaniline	180	70
8	Dibenzylamine	15	85
9	4,4'-Methylenedianiline	210	70
10	4-Methylbenzene-1,2-diamine	255	65
11	1-Naphtylamine	360	84
12	Azepane	3	75
13	Piperazine	1	93
14	2-(Piperazin-1-yl)ethanol	2	78
15	2-Methylpiperidine	3	73
16	1-Phenylpiperazine	1	80
17	1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane	3	96
18	1,4,7,10,13-Pentaoxa-16-azacyclooctadecane	5	90
19	1*H*-imidazole	240	45
20	Cyclohexane-1,2-diamine	90	82
21	Naphthalene-1,5-diamine	360	—

Table 2
Protection of alcohols with {[K.18-crown-6]Br_3}$_n$ (0.1 mol%) in their conversion to the TMS- and THP-ethers in acetonitrile at room temperature.

Entry	Substrate	Time (min)		Yield (%)	
		TMS-ether	THP-ether	TMS-ether	THP-ether
1	1-Phenylethanol	40	125	75	48
2	2-Phenylethanol	15	120	95	95
3	Benzyl alcohol	8	20	85	93
4	Menthol	20	180	90	60
5	Diphenylmethanol	12	40	97	96
6	(4-Chlorophenyl)methanol	50	45	95	85
7	(4-Fluorophenyl)methanol	7	20	97	84
8	1-Adamantanol	180	190	88	80
9	2-Adamantanol	—	80	—	73
10	Octan-1-ol	60	90	83	74
11	Cyclododecanol	10	120	96	70
12	Cyclohexanol	15	25	92	64
13	1-Indanol	—	20	—	95
14	2-Methyl-1-phenylpropan-2-ol	120	140	82	45
15	(2,4-Dichlorophenyl)methanol	55	65	74	80
16	3-Methylpent-1-yn-3-ol	50	55	80	45
17	2-Phenylpropan-1-ol	16	120	82	50
18	(4-Methoxyphenyl)methanol	5	25	92	98
19	1-Cyclohexylethanol	20	40	94	86
20	(4-Nitrophenyl)methanol	20	100	85	71
21	Thiophen-2-ylmethanol	60	60	—	—
22	Phenol	60	60	—	—

ally reacted more rapidly than aromatic amines. Furthermore, organic tribromide reagents are well known as brominating agents for aromatic species [13,18]. Our results in the protection of aromatic amines further showed the chemoselectivity of the {[K.18-crown-6]Br_3}$_n$/diboc combination, as the *N*-boc protected amine was the only product observed in all cases, and bromination of the aromatic ring in the aromatic amines did not occur (Table 1).

In the protection of alcohols, the alcoholic –OH was protected and the phenolic –OH remained intact. Although it was reported in Refs. [14] and [15] that these reagents can oxidize alcohols, under our reaction conditions, the oxidation reaction did not occur (Table 2).



Scheme 1. Catalytic protection of amines and alcohols using {[K.18-Crown-6]Br_3}$_n$.

4. Conclusions

{[K.18-crown-6]Br_3}$_n$, a unique tribromide-type catalyst, is an excellent bromine carrier for the catalytic *N*-boc protection of amines and trimethylsilylation and tetrahydropyranylation of alcohols. The simple separation of the catalyst from the product mixture is only one of the many advantages of this method. The reactions were carried out under mild conditions and the products were obtained with moderate to excellent yields.

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Graphical Abstract

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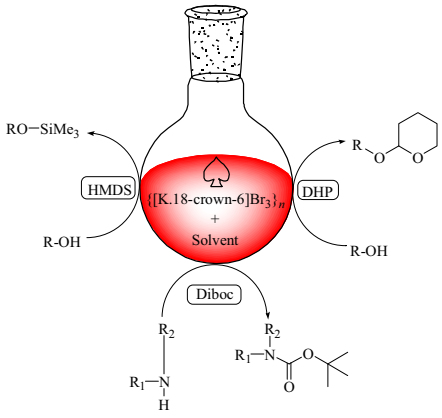

{[K.18-Crown-6]Br_3}$_n$ as a unique tribromide-type catalyst was utilized for the *N*-boc protection of amines and the trimethylsilylation/tetrahydropyranylation of alcohols. The simple separation of the catalyst from the products is only one of the many advantages of this method.

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