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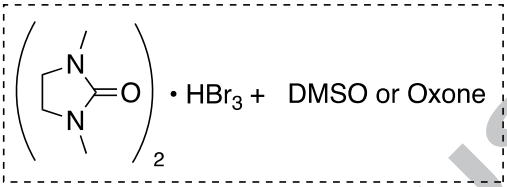

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Atom-economical brominations with tribromide complexes in the presence of oxidants

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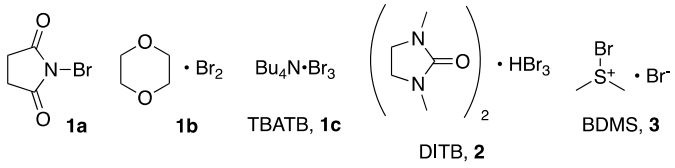
ABSTRACT

Bromination is an important transformation in organic synthesis, and novel efficient bromination techniques are still required. Herein, we demonstrate atom-economical brominations using $(DMI)_2HBr_3$, a novel tribromide complex, with oxidants such as DMSO and Oxone. Using this system, olefinic and aromatic brominations, as well as selective α-monobrominations of ketones proceeded well to afford the desired bromides in good yields. Importantly, in these reactions all of the bromine atoms in this complex are used to brominate.

1. Introduction

Bromination is a fundamental process in organic chemistry and the products of bromination reactions, namely organobromides, are useful as building blocks in organic synthesis as well as functional materials, such as fire retardants. Traditionally, molecular bromine (Br_2) has been used in this chemistry [1]; however, Br_2 is troublesome to handle due to its intrinsic toxicity and volatility. In order to circumvent this problem, various brominating reagents, such as *N*-bromosuccinimide (**1a**) [2], dioxane dibromide (**1b**) [3], and tetrabutylammonium tribromide (TBATB, **1c**) [4], have been reported. Recently, a novel brominating reagent, namely bis(1,3-dimethylimidazolidinone) hydrotribromide (DITB, **2**), was developed in our research group [5]. DITB (**2**, $(DMI)_2HBr_3$) is a complex between two 1,3-dimethylimidazolidinone (DMI) molecules and HBr_3. The brominating ability of complex **2** was examined in several organic reactions. This complex provided reaction products in yields that were almost the same or superior to those using other bromine alternatives; hence **2** can be used in many bromination reactions as an alternative to Br_2.



1a **1b** TBATB, **1c** DITB, **2** BDMS, **3**

Unfortunately, complex **2** has a fundamental drawback for practical use. As is evident from its molecular formula, complex **2** contains HBr_3, from which Br_2 is used to brominate, while HBr is always discarded. In order to improve atom economy of bromine, we focused on the use of the HBr 'discarded' from complex **2**. It is known that Br_2 is generated by the oxidation of bromide ion. For example, Karki *et al.* reported the preparation of bromodimethylsulfonium bromide (BDMS, **3**) from HBr and dimethyl sulfoxide (DMSO) [6], applied **3** in many bromination reactions, and concluded that compound **3** is a useful brominating reagent. During the preparation of **3**, HBr is oxidised with DMSO. With this in mind, we applied the concept used to prepare **3** to the generation of Br_2 from the HBr in DITB **2**. In this study, we used complex **2** for several reactions, including olefinic and aromatic brominations, and α-bromination of carbonyl compounds in the presence of an oxidant. On the other hand, aromatic brominations and the α-brominations of carbonyl compounds generate HBr as the byproduct, which we also used as a source of Br_2 in this system.

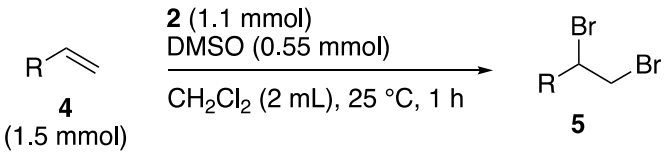
2. Results and discussion

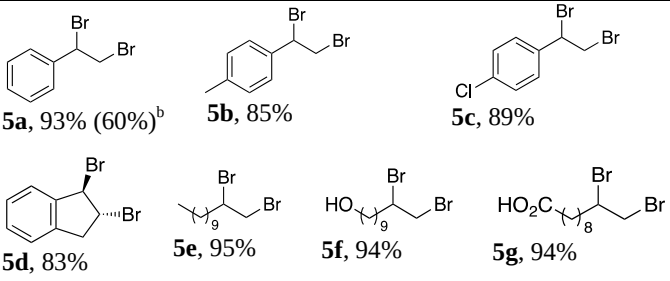
2.1. Bromination of alkenes

We began our investigation by brominating aliphatic and aromatic alkenes with complex **2** in the presence of DMSO. Ideally, this complex should be able to brominate 1.5 equivalents of an alkene since **2** contains three bromine atoms; hence, we brominated styrene (**4a**, 1.5 mmol, 1.5 equiv.) with **2** (1.10 mmol) in CH_2Cl_2 (2 mL) in the presence of DMSO (0.55 mmol, 0.5 equiv.) at 25 °C for 1 h, to afford the corresponding dibrominated product, 1-phenyl-1,2-dibromoethane (**5a**), in 93% yield. This result demonstrates that all of the bromine atoms in complex **2** were used in the bromination chemistry. The yield of **5a** decreased to 60% when the reaction was carried out in the absence of DMSO, which demonstrates that DITB alone is unable to brominate more than two equivalents of the substrate. Styrene derivatives **4b** and **4c** were brominated to afford the

corresponding dibromides **5b** and **5c** in good yields. Indene (**4d**) was transformed to the desired product **5d** in 83% yield without any side products, while aliphatic alkenes **4e**-**4g** furnished the corresponding dibromides **5e**-**5g** in excellent yields.

Table 1
Bromination of alkenes[a] with DITB **2**/DMSO.



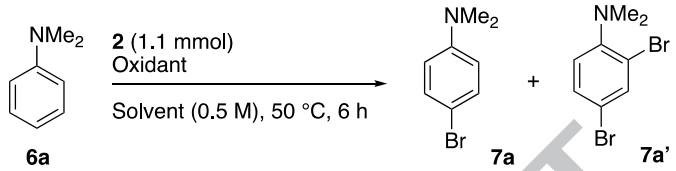


[a]Isolated yield. [b]Without DMSO.

2.2. Aromatic bromination

We next focused on aromatic brominations with DITB in the presence of an oxidant. Since HBr is generated as the by-product in this reaction, complex **2** can ideally brominate three equivalents of an aromatic compound. Using *N*,*N*-dimethylaniline (**6a**) as the substrate, we began to optimise the reaction conditions for bromination, the results of which are listed in Table 2. DITB has been reported to brominate one molar equivalent of **6a** in 93% yield (entry 1) [5]. However, the use of DMSO as the oxidant did not result in an increased yield of brominated product **7a** (52%, entry 2). Changing the oxidant to Oxone ($2KHSO_5•KHSO_4•K_2SO_4$) afforded a similar yield (53%) of **7a**, together with 31% of the dibrominated product **7a'** (entry 3), while the use of acetonitrile as the solvent resulted in a similar result to that obtained in AcOH: **7a** and **7a'** were obtained in yields of 52% and 25% yields (entry 4). Fortunately, increasing the amount of **6a** to three equivalents relative to oxone led to the formation of the desired product **7a** in 76 and 92% yields without by-product, **7a'** (entries 5 and 6). These results indicate that acetonitrile is a better solvent than acetic acid for this bromination chemistry. Oxidants other than oxone gave lower yields of the product (entries 7 and 8). Based on these results, the optimal conditions were established to involve substrate (3.0 mmol), **2** (1.1 mmol), and oxone (1.1 mmol) in acetonitrile (6 mL) at 50 °C for 6 h (entry 6). The scope of this protocol was examined under these conditions, the results of which are summarised in Table 3.

Table 2
Optimization of reaction conditions for bromination of **6a** with **2**.

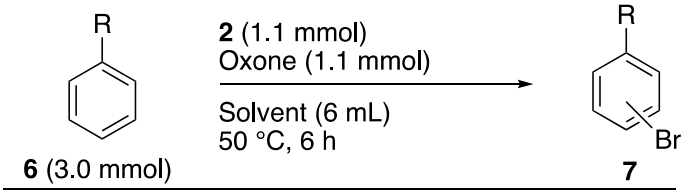


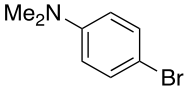
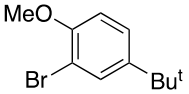
Entry	Amount of **6a** /mmol	Solvent	Oxidant /mmol	Yield of **7a** / %[a]
1	1.0	AcOH	--	93[b]
2	2.0	AcOH	DMSO/1.1	52
3	2.0	AcOH	Oxone/1.1	53(31)[c]
4	2.0	CH_3CN	Oxone/1.1	52(25)[c]
5	3.0	AcOH	Oxone/1.1	76
6	3.0	CH_3CN	Oxone/1.1	92
7	3.0	AcOH	H_2O_2aq/1.1	62
8	3.0	AcOH	$NaClO·5H_2O$/1.1	35

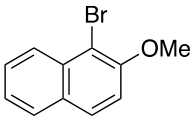
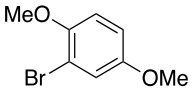
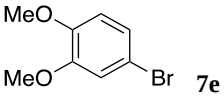
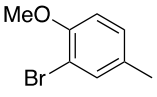
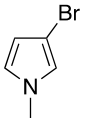
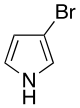
[a]Determined by NMR. [b]Isolated yield. [c]Yield of dibromide **7a'**.

Whereas the aromatic bromination of *N*,*N*-dimethylaniline (**6a**) with **2**/oxone was carried out successfully, anisole derivatives **6b**-**6d** afforded the corresponding bromides in moderate yields (entries 2, 4, 6). It is well known that 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) [7] facilitates many reactions including Friedel–Crafts acylations [8], Baeyer–Villiger oxidations [9], and epoxidations [9a][10]. HFIP also promotes the hydrochlorination of alkynes using HCl [11]. Hence, we added HFIP to the reaction mixture with extension of reaction time to 24 h; the mixed solvent (3:1 acetonitrile/HFIP) [12] effectively promoted the aromatic bromination, with the yields of bromides **7b**, **7c**, and **7d** improved to 81, 85, and 80%, respectively (entries 3, 5, 7). Using HFIP as the co-solvent, anisoles **6e** and **6f** were brominated in 85 and 72% yields, respectively (entries 8 and 9); however, pyrrole derivatives **6g**-**6h** did not afford the desired products, rather the starting materials were observed to decompose.

Table 3
Aromatic bromination[a] with DITB **2**/oxone



Entry	Prodcut	Solvent	Yield / %
1	 **7a**	CH_3CN	92(87)[b]
2	 **7b**	CH_3CN	48
3[c]		CH_3CN/HFIP = 3/1	81

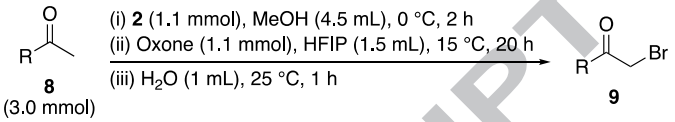
4	 **7c**	CH_3CN	63
5[c]		CH_3CN/HFIP = 3/1	85(81)[b]
6	 **7d**	CH_3CN	40
7[c]		CH_3CN/HFIP = 3/1	80(55)[b,d]
8[c]	 **7e**	CH_3CN/HFIP = 3/1	85(69)[b,d]
9[c]	 **7f**	CH_3CN/HFIP = 3/1	72
10[c]	 **7g**	CH_3CN/HFIP = 3/1	ND[e]
11[c]	 **7h**	CH_3CN/HFIP = 3/1	ND[e]

[a]Determined by NMR. [b]Isolated yield. [c]Reaction time 24 h. [d]See Reference and Note [13]. [e]Not detected by GCMS.

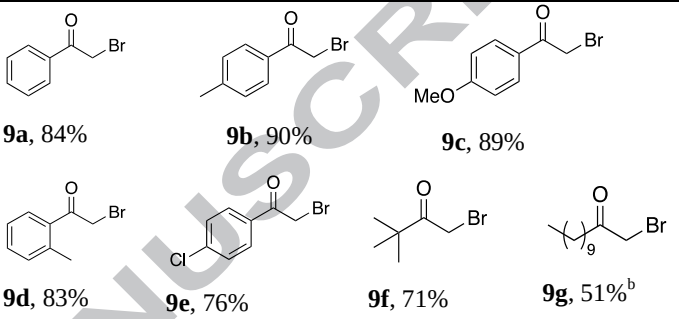
2.3. Selective α–monobromination of ketones

We also examined the α-brominations of ketones using DITB/oxidant. In a similar manner to an aromatic system, the α-brominations of ketones also generates HBr; consequently, we attempted to reuse this HBr as a bromine source. In addition, we also tried to monobrominate at the α-positions of ketones in a manner that avoided dibromination. Significant amounts of dibromides are usually formed during α-bromination reactions due to the high reactivities of the generated monobromides. Nevertheless, we suppressed the formation of the dibromide using methanol (MeOH) as the solvent; the formation of the acetal during the reaction is the key to achieving this outcome. As shown in Table S1 in the Supplementary Material, we selectively monobrominated the α-positions of carbonyl compounds using HBr/DMSO in MeOH. We then applied these reaction conditions to α-brominate ketones with DITB/oxidant. Oxone was employed as the oxidant since DMSO was a less-reactive oxidant in this reaction, as shown in Table S2. Based on these results, the optimal conditions were established to be: (i) substrate (3.0 mmol), DITB (1.1 mmol) in MeOH (4.5 mL) at 0 °C for 2 h, (ii) addition of oxone (1.1 mmol) and HFIP (1.5 mL) at 15 °C followed by stirring at the temperature for 20 h, and (iii) addition of water (1.0 mL) at 25 °C followed by stirring at the temperature for 1 h. The substrate scope of this reaction is shown in Table 4. Acetophenones bearing electron-donating substituents were transformed into the desired monobromides in yields in excess of 80% (**9a**-**9d**), while 4-chloroacetophenone (**8e**) afforded the corresponding product in 76% yield, together with recovered substrate (9%). Unfortunately, acetophenones bearing strong electron-withdrawing groups, such as trifluoromethyl or nitro, did not afford the desired monobromide using this technique. Pinacolone (**8f**), an aliphatic ketone, was also examined, giving the desired product in 71% yield, while 2-dodecanone (**8g**) bearing two α-carbons provided monobromide **9g**, in which the terminal methyl group was brominated, in 51% yield.

Table 4
α-Bromination of ketones[a] using DITB **2**/oxone



8 (3.0 mmol) → **9**

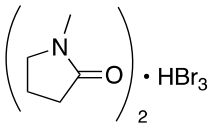


9a, 84% | **9b**, 90% | **9c**, 89% | **9d**, 83% | **9e**, 76% | **9f**, 71% | **9g**, 51%[b]

[a]Isolated yield. [b]Determined by NMR.

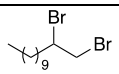
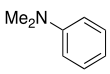
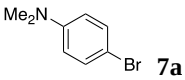
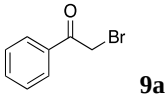
2.4. Bromination using other tribromide complexes in the presence of oxidants

Finally, we brominated 1-dodecene (**4e**) and *N*,*N*-dimethylaniline (**6a**), and acetophenone (**8a**), with other tribromide complexes, namely bis(N-methylpyrrolidone) hydrotribromide (MPHT, **10**) [14] and TBATB **1c** in the presence of oxidants under the optimised conditions, the results of which are summarised in Table 5.



MPHT, **10**

Table 5
Bromination using tribromide complexes in the presence of oxidants.

Substrate	Product	Isolated yield / %		
		DITB **2**	MPHT **10**	TBATB **1c**
 **4e**	 **5e**	95	93	77
 **6a**	 **7a**	87	85	80
 **8a**	 **9a**	84	83	4

Complex **10** was also an effective brominating agent and afforded the desired products in similar yields to those obtained using complex **2** [15], while tribromide **1c** gave lower yields than **2**. In particular, the α-bromination of acetophenone with **1c** proceeded very poorly, which is possibly due to the low solubility of the complex in MeOH.

3. Conclusion

We successfully performed atom-economical brominations in which all of the bromine atoms in DITB were consumed and incorporated into the desired products. In particular, 1.5 equiv. of an alkene, or 3 equiv. of an arene or a ketone, undergoes bromination with 1 equiv. of DITB in the presence of an appropriate oxidant, to afforded the desired product in good yield. A novel protocol for efficiently monobrominating the α-position of a ketone while suppressing dibromide formation was also developed. In addition, other tribromide complexes also participate in atom-economical brominations in this system.

Acknowledgments

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References and notes

[1] Reviews of Br_2: (a) R. R. Goehring in: L. A. Paquette, D. Crich, P. L. Fuchs, G. A. Molander (Eds), Encyclopedia of Reagents for Organic Synthesis, 2nd. Ed., vol. 3, Wiely, Chichester, 2009, pp.1496–1501; (b) I. Saikia, A.J. Borah, P. Phukan, Chem. Rev. 116 (2016) 6837–7042.

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[11] X. Zeng, S. Liu, G.B. Hammond, B. Xu, ACS Catalysis 8 (2018) 904–909.

[12] The acetonitrile/HFIP ratio used in reference 11 was also employed here. Increasing the acetonitrile/HFIP ratio from 3:1 to 11:1 (v/v) lowered the yield of the product to 74%.

[13] The significantly lower isolated yields are the results of difficulties associated with separating unreacted substrates **6d** and **6e** from products **7d** and **7e**, respectively.

[14] (a) A. Bekaert, O. Provot, O. Rasolojaona, M. Alami, J.-D. Brion, Tetrahedron Lett. 46 (2005) 4187–4191; (b) W.E. Daniels, E. Chiddix, S.A. Glickman, J. Org. Chem. 28 (1963) 573–574.

[15] It should be noted that complex **10** is poorly soluble in dichloromethane or ethanol; this complex is less reactive than complex **2** in some reactions. See reference 5 for details.

Supplementary Material

All compounds prepared in this study are known compounds. Supplementary data (Tables S1 and S2, Experimental details, ^{1}H and ^{13}C NMR data of isolated products in this study) can be found in the online version, at http://

Highlights

- Atom-economical brominations using $(DMI)_2HBr_3$ with oxidants was demonstrated.
- Using this system, olefinic and aromatic brominations were performed successfully.
- Selective α -monobrominations of ketones also proceeded well.
- All of the bromine atoms in the complex were used to brominate.