# Preparation of a novel bromine complex and its application in organic synthesis

Yuya Nishio, Kotaro Yubata, Yutaro Wakai, Kotaro Notsu, Katsumi Yamamoto, Hideki Fujiwara, Hiroshi Matsubara

PII: S0040-4020(19)30094-8
DOI: https://doi.org/10.1016/j.tet.2019.01.055
Reference: TET 30107

To appear in: *Tetrahedron*

Received Date: 6 December 2018
Revised Date: 16 January 2019
Accepted Date: 24 January 2019

Please cite this article as: Nishio Y, Yubata K, Wakai Y, Notsu K, Yamamoto K, Fujiwara H, Matsubara H, Preparation of a novel bromine complex and its application in organic synthesis, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.01.055.

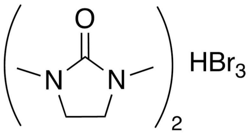
## Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

### Preparation of a novel bromine complex and its application in organic synthesis

Leave this area blank for abstract info.

Yuya Nishio[a] , Kotaro Yubata[a], Yutaro Wakai[a], Kotaro Notsu[b], Katsumi Yamamoto[b], Hideki Fujiwara[a], and Hiroshi Matsubara[a]*
[a]*Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan* [b]*Research Laboratory, Manac Incorporation, Fukuyama, Hiroshima 721-0956, Japan*



Air stable $Br_2$ source

Tetrahedron
journal homepage: www.elsevier.com

# Preparation of a novel bromine complex and its application in organic synthesis

Yuya Nishio[a] , Kotaro Yubata[a], Yutaro Wakai[a], Kotaro Notsu[b], Katsumi Yamamoto[b], Hideki Fujiwara[a], and Hiroshi Matsubara[a] *

[a]*Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan*
[b]*Research Laboratory, Manac Incorporation, Fukuyama, Hiroshima 721-0956, Japan*

## ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

*Keywords:*
Bromine alternative
DMI
Bromination
Hofmann rearrangement
X-ray crystal structure analysis

## ABSTRACT

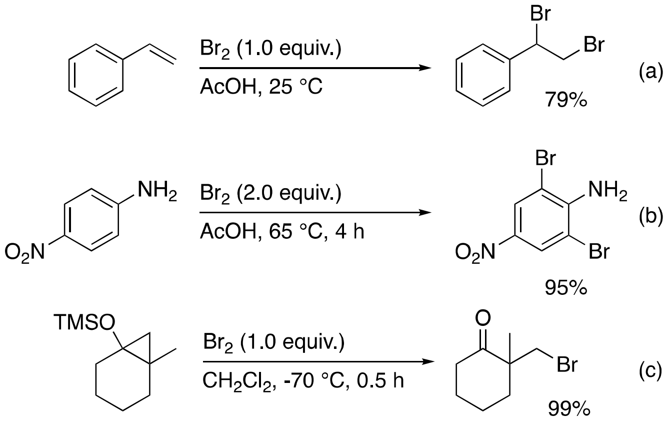
Although molecular bromine ($Br_2$) is a useful brominating reagent, it is not easy to handle. Herein, we describe the preparation of a novel air-stable bromine complex prepared from 1,3-dimethylimidazolidinone (DMI) and $Br_2$, which was identified to be $(DMI)_2HBr_3$ by spectral and X-ray techniques. This complex was then used to brominate olefins, carbonyl compounds, and aromatics, as well as in the Hofmann rearrangement. Yields of reaction products using this complex were almost the same or superior to those using other bromine alternatives.

---

* Corresponding author. Tel.: +81-72-254-9698; fax: +81-72-254-9163; e-mail: matsu@c.s.osakafu-u.ac.jp

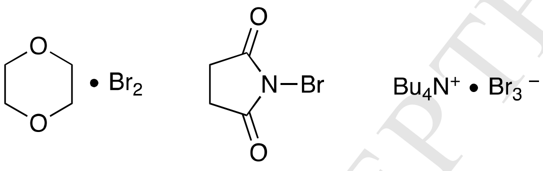
## 1. Introduction

Molecular bromine ($Br_2$), which is a simple diatomic substance composed of two bromine atoms, is highly reactive and has primarily been employed in bromination reactions in organic synthesis [1]. Since bromination reactions of olefins, as well as carbonyl and aromatic compounds using $Br_2$ are traditional transformations in organic chemistry, $Br_2$ is widely used as a brominating reagent. Some examples of its use are shown in **Scheme 1** [2].



**Scheme 1.** Bromination with $Br_2$.

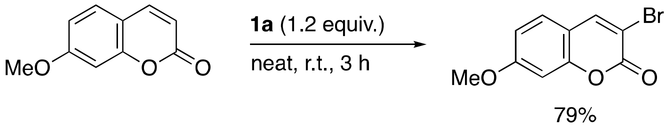
However, $Br_2$ is known to be a 'non-user-friendly' reagent, and some significant issues in connection with its use have been raised. $Br_2$ is a toxic and corrosive liquid with a low boiling point (58.8 °C) that evaporates readily to form a dangerous gas [1]. Accordingly, many $Br_2$ alternatives have been developed to overcome the drawbacks associated with the application of $Br_2$ in organic synthesis [3]; some of these alternatives are shown in **Scheme 2**.



DDB (**1a**) NBS (**1b**) TBATB (**1c**)

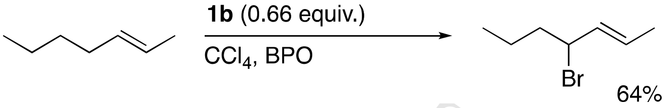
**Scheme 2.** $Br_2$ alternatives.

1,4-Dioxane dibromide (DDB, **1a**) [4] is a 1:1 complex between $Br_2$ and 1,4-dioxane; **1a** is a mild brominating reagent and can be used to brominate aromatics, such as coumarins, under solvent-free conditions (**Scheme 3**) [5]. DDB is not robust at ambient temperature, which prevents the wide use of this reagent.



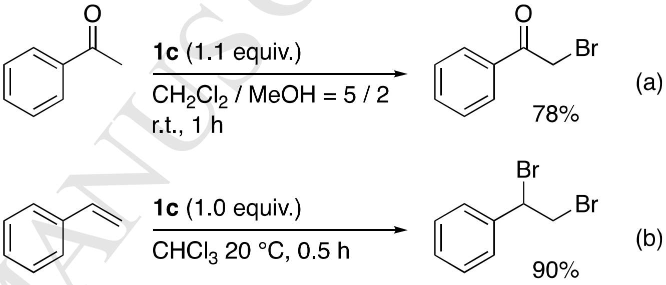
**Scheme 3.** Bromination with **1a**.

*N*-Bromosuccinimide (NBS, **1b**) [6] is a useful brominating reagent that facilitates the Wohl–Ziegler reaction [7], namely brominations at allylic and benzylic positions in the presence of a radical initiator, such as benzoyl peroxide (BPO) or 2,2'-azobis(isobutyronitrile) (AIBN). A typical allylic bromination procedure using **1b** is shown in **Scheme 4** [8].



**Scheme 4.** Bromination with **1b**.

Although **1b** is highly reactive, it gradually decomposes even at room temperature, and excess amounts of this reagent are often required in some reactions. Tetrabutylammonium tribromide (TBATB, **1c**) [9] has been used to α-brominate acetophenone in a 5:2 mixture of dichloromethane and methanol at ambient temperature, to afford α-bromoacetophenone in good yield (**Scheme 5a**) [10].



**Scheme 5.** Bromination with **1c**.

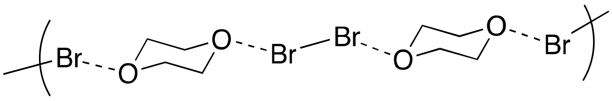
In addition, olefins, such as styrene, have been brominated with equimolar amounts of **1c** to afford the corresponding dibromides in good yields (**Scheme 5b**) [11]. While this reagent is highly stable, its solubility is generally low in protic solvents such as water, methanol, and ethanol.

Since bromination with $Br_2$ is an important transformation in organic synthesis, and the organobromide products useful as synthetic intermediates as well as functional materials, the development of $Br_2$ alternatives that overcome the drawbacks associated with the use of $Br_2$ is quite important. In particular, highly reactive and robust $Br_2$ alternatives are still strongly required. In this study, we prepared a novel bromine alternative based on 1,3-dimethylimidazolidinone (DMI) and evaluated its brominating ability in several reactions.

## 2. Results and Discussion

### *2.1. Synthesis of a new bromine complex*

To develop a novel bromine complex, we focused on **1a**, which was initially reported in 1952 [12]; **1a** is a charge-transfer complex that acts as a $Br_2$ equivalent owing to interactions between 1,4-dioxane and $Br_2$ (**Scheme 6**). Specifically, the 1,4-dioxane and $Br_2$ molecules act as donors and acceptors [13], respectively.

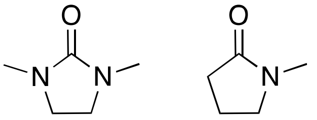


**Scheme 6.** Crystal structure of **1a**. [13]

Unfortunately, the interactions in **1a** are very weak, rendering the complex unstable. Hence, in order to prepare a more stable $Br_2$ complex, we examined several solvents by following the procedure used for the preparation of **1a**. 1,4-Dioxane (20 mL) was cooled to 0 °C, $Br_2$ (1.0 mmol) was then added to the solvent, and the reaction mixture was stirred at 0 °C for 1 h. The addition of diethyl ether (100 mL) to the mixture at 0 °C led to the formation of **1a** as a yellow crystalline solid (**Table 1**, entry 1).

**Table 1**
Formation of bromine complex.

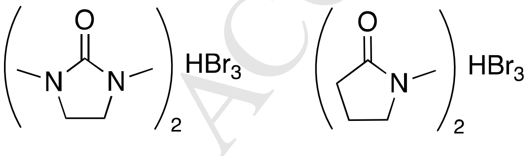
| Entry | Solvent | Formation of $Br_2$ complex |
|---|---|---|
| 1 | 1,4-dioxane | + |
| 2 | Tetrahydrofuran (THF) | – |
| 3 | 1,2-Dimethyxyethane (DME) | – |
| 4 | 1,3-Dimethylimidazolidinone (DMI, **2a**) | + |
| 5 | *N*-methylpyrrolidone (NMP, **2b**) | + |
| 6 | Thioanisole | – |



DMI (**2a**) NMP (**2b**)

Reaction conditions: $Br_2$ (1.0 mmol), solvent (20 mL), 0 °C, 1 h.

1,3-Dimethyl-2-imidazolidinone (DMI, **2a**) and *N*-methylpyrrolidone (NMP, **2b**) both afforded orange crystalline solids (entries 4 and 5) whereas tetrahydrofuran (THF) or dimethoxyethane (DME) did not form a complex; rather a brown liquid was obtained instead (entries 2 and 3), while thioanisole reacted with $Br_2$ to generate hydrogen bromide (entry 6). The prepared orange crystalline solids were identified by iodometric and acid-base titrations. As a result, these crystals were found not to be $Br_2$ complexes, but rather hydrogen tribromide ($HBr_3$) complexes consisting of HBr and $Br_2$.



DITB (**3a**) MPHT (**3b**)

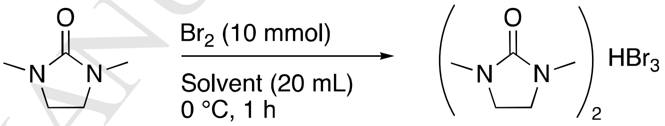
**Scheme 7.** Prepared $HBr_3$ complexes.

The molecular formulas of the two $HBr_3$ complexes were determined by NMR spectroscopy and elemental analysis. The $HBr_3$ complexes of **2a** and **2b** were identified to be bis(1,3-dimethyl-2-imidazolidinone) hydrotribromide (DITB, **3a**) and di(*N*-methylpyrrolidone) hydrotribromide (MPHT, **3b**) (**Scheme 7**). While **3b** is a known compound that has been prepared by another method [14], **3a** is a novel complex.

The conditions for the preparation for **3a** were then optimised (**Table 2**). When DMI (**2a**) was selected as both the solvent and the substrate, **3a** was obtained in 83% yield (entry 1). Shielding the reaction from light resulted in a slightly lower yield of **3a** (entry 2), while reducing the amount of DMI from 20 mL to 4.3 mL (4 equiv.) lowered the yield to 57% (entry 3). However, the yield of **3a** was dramatically improved when diethyl ether was added as the solvent (entry 4). On the other hand, the target complex was obtained in 65% yield when the reaction conditions reported for the preparation of **3b** [14] were employed (entry 5). In known methods, the preparation of an $HBr_3$ complex requires an HBr source such as HBr/AcOH, while methanol is used to quench the excess acetic acid after the completion of the reaction. Since **3a** dissolves well in methanol, the use of this solvent was found to decrease the yield of the product (entry 5).

By comparing entries 4 and 5, we conclude that the procedure developed in this study (entry 4) is superior to that previously reported (entry 5), since our method does not require an HBr source and provides a higher yield of the desired product.

**Table 2**
Optimization of the reaction conditions.



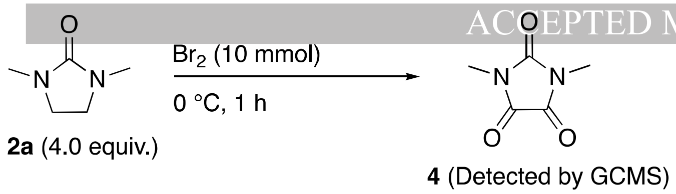
**2a** **3a**

| Entry | Solvent | **2a** (equiv.) | Additive (equiv.) | Yield[a,b] (%) |
|---|---|---|---|---|
| 1 | **2a** | – | – | 83 |
| 2[c] | **2a** | – | – | 75 |
| 3 | – | 4.0 | – | 57 |
| 4 | $Et_2O$ | 4.0 | – | 89 |
| 5 | MeOH | 3.0 | HBr/AcOH (1.6) | 65 |

[a] Isolated yield. [b] Based on bromine atoms. [c] In the dark.

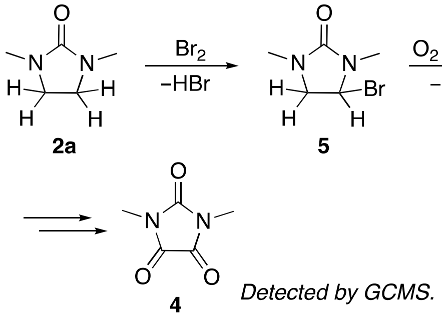
### *2.2. Investigation of the reaction mechanism in the preparation of DITB (3a)*

A novel attractive procedure for the preparation of $HBr_3$ complexes in the absence of an HBr source was developed. We presumed that HBr was generated in this process; consequently, we next investigated how HBr is formed under these conditions. Initially, the NMR spectra of the reaction mixture and the filtrate were acquired during each phase of the preparation of **3a**. The reaction mixture immediately exhibited a broad peak at 10.5 ppm in its $^1H$ NMR spectrum after the addition of $Br_2$ to DMI (**2a**), which was assigned to the proton of HBr. This $^1H$ NMR spectrum reveals that $Br_2$ reacted with **2a** or moisture in the air to generate HBr. In addition, the GCMS spectrum (**Fig. S1** in the Supplementary Data) shows that the reaction of **2a** with $Br_2$ provided 1,3-dimethylparabanic acid **4** (**Scheme 8**), while no brominated **2a** was observed.



**Scheme 8.** Control experiments for formation of **3a**.

On the basis of these results, a plausible reaction mechanism for the generation of HBr was proposed (**Scheme 9**). The C-H bonds of the methylene groups of **2a** are more easily cleaved than the C-H bonds of the methyl groups. Therefore, **2a** reacts with $Br_2$ to give brominated product **5** and HBr. Subsequently, bromide **5** is transformed to 1,3-dimethyl-2,4-imidazolidinedione (**6**) upon exposure to aerobic oxygen or moisture. This series of reactions is repeated, to afford 1,3-dimethylparabanic acid **4**, which was detected by GCMS.



**Scheme 9.** Plausible reaction mechanism for the generation of hydrogen bromide.

### 2.3. Physical properties of DITB (3a)

We next examined the physical properties of DITB (**3a**). Firstly, we tested the solubility of **3a** along with the other hydrotribromide complexes **3b** and **1c** (**Table 3**). Complexes **3a**, **3b**, and **1c** did not dissolve in hexane or diethyl ether ($Et_2O$) (entries 1 and 4). While ethyl acetate (AcOEt) was a poor solvent (entry 2), these complexes dissolved well in chloroform ($CHCl_3$), dichloromethane ($CH_2Cl_2$), and DMF (entries 3, 5 and 10). Complex **3a** was completely soluble in $CH_2Cl_2$ to give 0.5 or 1 M solutions, while **3b** and **1c** were partly soluble at these concentrations (entries 6 and 7). In addition, the solubility of **3a** in methanol or ethanol was superior to that of **3b** and **1c** (entries 8 and 9). Although **3b** and **1c** were completely insoluble in benzene and toluene, **3a** was only slightly soluble (entries 11 and 12). Based on these results, we conclude that the solubility of **3a** in organic solvents is generally higher than that of **3b** or **1c**.

**Table 3**
Solubility test[a,b] of $HBr_3$ complexes.

| Entry | Solvent | **3a** | **3b** | **1c** |
|---|---|---|---|---|
| 1 | Hexane | – | – | – |
| 2 | AcOEt | ± | ± | ± |
| 3 | $CHCl_3$ | ++ | ++ | ++ |
| 4 | $Et_2O$ | – | – | – |
| 5 | $CH_2Cl_2$ | ++ | ++ | ++ |
| 6 | $CH_2Cl_2$ (0.5 M) | ++ | + | + |
| 7 | $CH_2Cl_2$ (1.0 M) | ++ | + | + |
| 8 | MeOH | ++ | ++ | + |
| 9 | EtOH | ++ | + | ± |
| 10 | DMF | ++ | ++ | ++ |
| 11 | Benzene | ± | – | – |
| 12 | Toluene | ± | – | – |

[a] Conditions: 0.1 M at 20 °C. [b] ++: completely soluble, +: partially soluble, ±: slightly soluble, –: insoluble.

The physical properties of **3a** are summarised in **Table 4**. As mentioned above, the molecular formula of **3a** was determined to be $C_{10}H_{21}O_2N_4Br_3$ by $^1H$ and $^{13}C$ NMR spectroscopies and elemental analysis. Complex **3a** is an orange crystalline solid, as shown in **Fig. 1**. The $Br_2$ content of **3a** is approximately 34 wt% (determined by iodometric titration), while its melting point is 117-118 °C. In addition, **3a** was found to be robust in air, but corrosive towards metals.

**Table 4**
Physical properties of **3a**.

| | |
|---|---|
| Name | Bis(1,3-dimethylimidazolidinone)hydrotribromide |
| Molecular formula | $C_{10}H_{21}N_2O_2Br_3$ |
| Colour and shape | Orange prisms |
| $Br_2$ contents | 34 wt% |
| Mp | 117–118 °C |
| Density | 1.73 g/cm$^3$ |
| Other properties | Stable in air, corrosive |

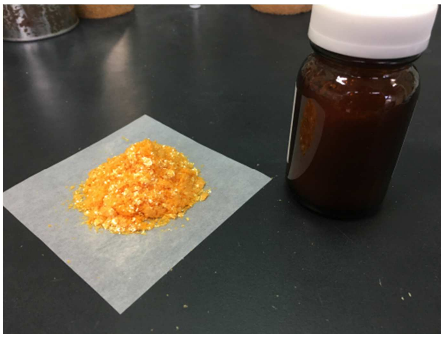


**Fig. 1.** Colour and crystal shape of **3a**.

### 2.4. X-ray crystal structure analysis of DITB (3a) [15]

The X-ray crystal structure of **3a** was determined at room temperature on an orange prismatic single crystal recrystallised from methanol. The crystal structure of **3a** was found to belong to the monoclinic $P2_1/c$ space group. As shown in **Fig. 2**, H11 and Br1 are located at the inversion centre of the unit cell, with half of them in a crystallographically independent unit. The distance between the bridging hydrogen and the carbonyl oxygen is 1.202(5) Å, suggesting that the two oxygen atoms of adjacent

DMI units are linked by strong hydrogen bonds (O1•••H11•••O1 = 2.404 Å). This hydrogen bonding distance is almost the same as that of complex **3b** (2.415(5) Å) [16]. Because the Br$_3^-$ unit is located at the inversion centre, it is completely linear, with a Br1-Br2 bond length of 2.5386(9) Å that is almost identical to that of complex **3b** (2.531(1) Å). Each Br$_3^-$ unit is surrounded by four DMI units in the *bc*-plane of the unit cell that are located in parallel with the Br$_3^-$ unit, as shown in **Fig. 3a**. Furthermore, such a Br$_3^-$ unit is blocked by other DMI units in the *a*-direction (**Fig. 3b**). Therefore, the Br$_3^-$ unit is highly stable in the crystalline solid, which is why solid **3a** is so robust in air.

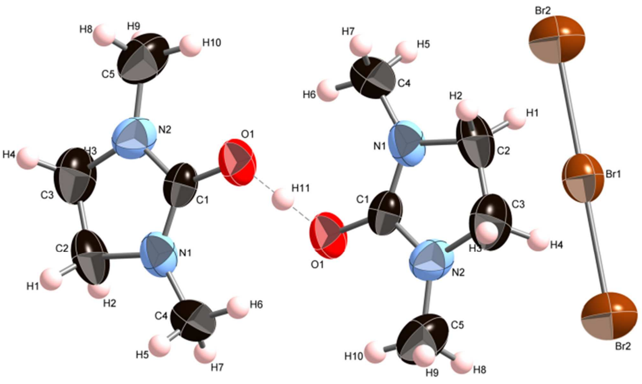


**Fig. 2.** ORTEP drawing of molecular structure of **3a**.

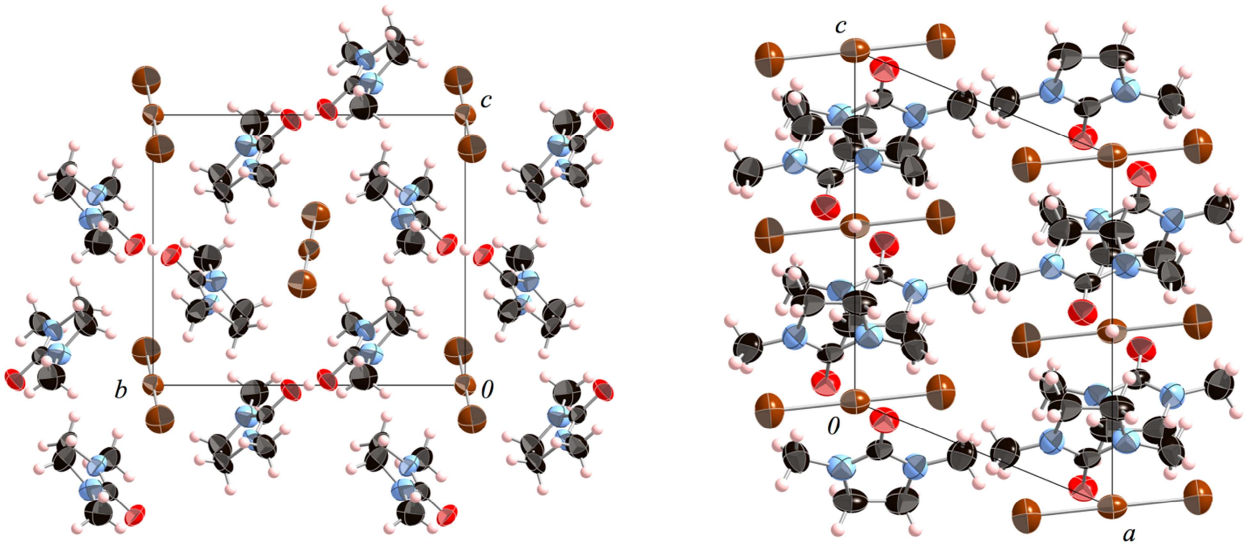


**Fig. 3.** Crystal structures of **3a** projected onto the (a) *bc*-plane and (b) *ac*-plane.

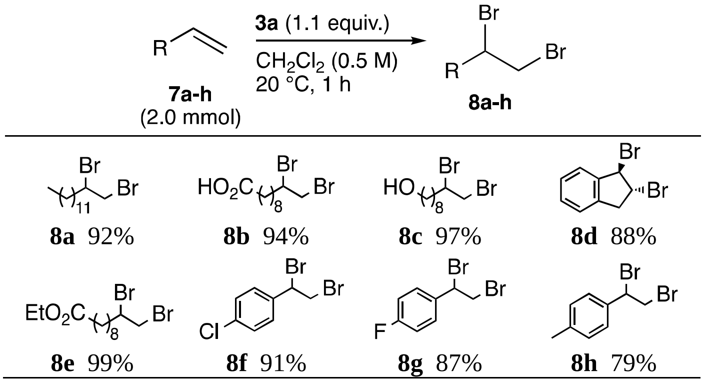
### *2.5. Bromination ability of DITB (3a)*

Since it is important for Br$_2$ alternatives to be highly reactive in organic syntheses, we investigated the reactivity of **3a**. For this purpose, we examined four reactions: (1) olefinic bromination, (2) the α-bromination of carbonyl compounds, (3) aromatic bromination, and (4) the Hofmann rearrangement.

### *2.5.1. Bromination of olefins with **3a***

Initially, we brominated a variety of olefins **7a-h** (2.0 mmol) by reacting them with **3a** (1.1 equiv.) in CH$_2$Cl$_2$ at 20 °C for 1 h, which afforded vicinal dibromides **8a-h** (**Table 5**) [17]. 1-Tetradecene (**7a**) and olefins bearing carboxyl (**7b**) and hydroxyl (**7c**) groups gave the corresponding dibromides **8a-c** in excellent yields. The bromination of unsaturated ester **7e** also proceeded without any decomposition of the ester group, to afford **8e** in quantitative yield.

**Table 5**
Bromination of olefins with **3a**.[a]

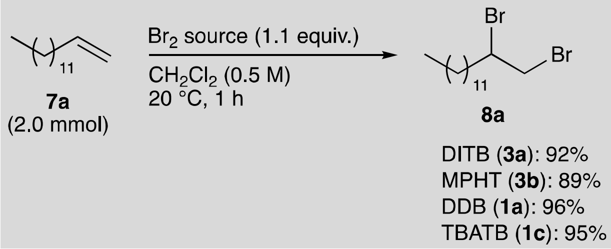


**8a** 92%
**8b** 94%
**8c** 97%
**8d** 88%
**8e** 99%
**8f** 91%
**8g** 87%
**8h** 79%

[a] Isolated yield.

Indene (**7d**) reacted with **3a** to furnish 1,2-dibromoindane (**8d**) in 88% yield, while styrene derivatives, such as halo-substituted styrenes (**7f-g**) and 4-methylstyrene (**7h**), were also dibrominated to provide the corresponding dibromides **8f-h** in yields of 79-91%. Based on these results, **3a** is as an efficient brominating reagent for olefins.

We subsequently evaluated the reactivities of the other bromine complexes for comparison; to that end 1-tetradecene (**7a**) was also brominated with MPHT (**3b**), DDB (**1a**), and TBATB (**1c**) (**Scheme 10**). As shown in **Scheme 10**, bromination with these bromine complexes gave the desired 1,2-dibromotetradecane (**8a**) in similarly high yields to that obtained using **3a**, which reveals that DITB is about as reactive as the other bromine alternatives **3b**, **1a**, and **1c**.

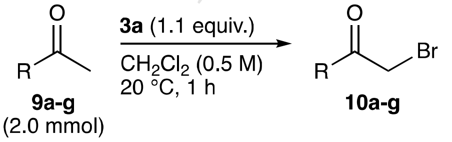


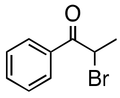
**Scheme 10.** Evaluation of the bromination of 1-tetradecene with **3a**.

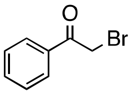
### *2.5.2. α-Bromination of carbonyl compounds with 1a*

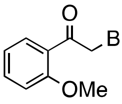
We next focused on α-brominating carbonyl compounds [18] with **3a**. As shown in **Table 6**, when acetophenone derivatives **9a-g** (2.0 mmol) were reacted with **3a** (1.1 equiv.) in $CH_2Cl_2$ (0.5 M) at 20 °C for 1 h, the corresponding α-brominated products **10a-g** were obtained in moderate-to-good yields. The bromination of propiophenone (**9a**) afforded 2-bromopropiophenone (**10a**) in 94% yield together with trace amounts of 2,2-dibromopropiophenone. 1-Bromoacetophenone (**10b**) was obtained in 73% yield when acetophenone (**9b**) was used as the substrate, while 2-methoxyacetophenone (**9c**) and 4-methoxyacetophenone (**9d**), bearing electron-donating groups at their ortho- and para-positions, respectively, furnished **10c** and **10d** in 77 and 56% yield, respectively, when reacted with **3a**. The acetophenone **9d** also provided the dibrominated product in 27% yield together with the desired monobromide **10d**, while steric hindrance associated with the ortho-methoxy group in **9c** presumably prevented overbromination, to afford **10c** in 77% yield. Methyl *tert*-butyl ketone (**9e**) afforded the corresponding α-bromoketone **10e** in lower yield (42%) due to high volatility of the bromide. Acetophenone derivatives with electron-withdrawing groups, such as 4-(trifluoromethyl)acetophenone (**9f**) and 4-chloroacetophenone (**9g**), were reacted with **3a** to provide **10f** and **10g** in 69 and 73% yield, respectively. These results are consistent with previously reported yields of α-brominated carbonyl compounds.

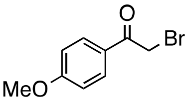
**Table 6**
α–bromination of carbonyl compounds with **3a**.

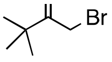


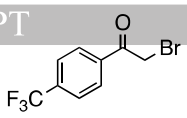

**10a** 94%

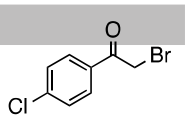

**10b** 73%


**10c** 77%


**10d** 56%

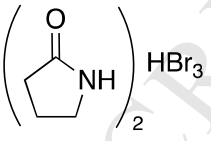

**10e** 42%[b]

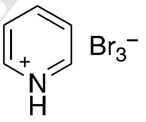

**10f** 69%

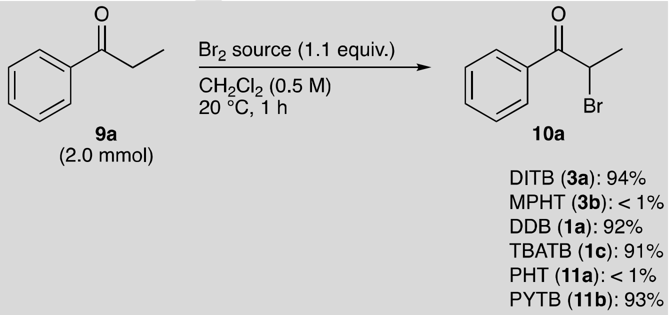

**10g** 73%

[a]Isolated yields. [b]Determined by $^1$H NMR.

Propiophenone **9a** was brominated with **3b**, **1a**, **1c**, pyrrolidone hydrotribromide (PHT, **11a**), and pyridinium tribromide (PYTB, **11b**), in order to compare the reactivities of these five alternative reagents with that of **3a** (**Scheme 11**); **10a** was obtained in excellent yields when **3a**, **1a**, **1c** , and **11b** were used to brominate **9a**. Interestingly, the reaction did not proceed well in the presence of **3b** or **11a** due to their poor solubilities in $CH_2Cl_2$; hence, **3a** is superior to **3b** and **11a** for α-brominating carbonyl compounds in this solvent.


PHT (**11a**)


PYTB (**11b**)

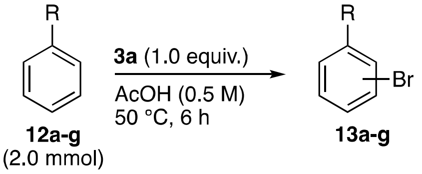


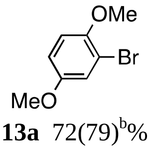
**Scheme 11.** Evaluation of the α–bromination of propiophenone with **3a**.

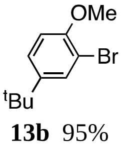
### *2.5.3. Bromination of aromatic compounds with 3a*

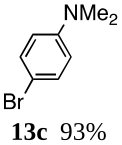
A typical application of $Br_2$ is represented by the electrophilic bromination of aromatic compounds [19]. This reaction is a significant transformation in organic synthesis, and aryl bromides have widely been used as useful building blocks in cross-coupling reactions or through the formation of Grignard reagents. Hence, we examined the brominations of aromatics **12a-g** (2.0 mmol) with **3a** in acetic acid (0.5 M) at 50 °C for 6 h, which afforded the corresponding aryl bromides **13a-g** (**Table 7**).

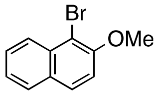
**Table 7**
Bromination of aromatic compounds with **3a**.[a]

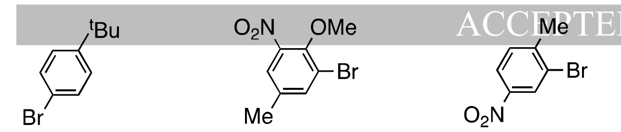



**13a** 72(79)[b]%


**13b** 95%


**13c** 93%


**13d** 99%



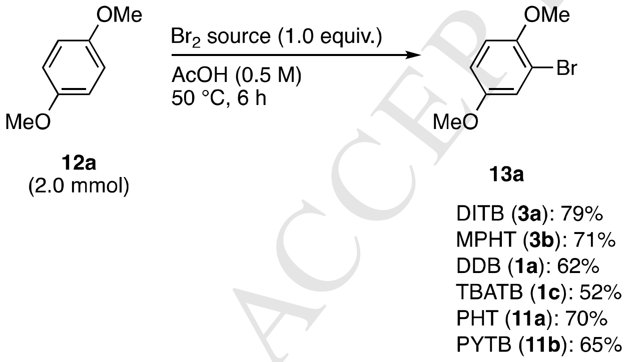
**13e** n.r. (< 2 %)[c] **13f** n.r. **13g** n.r. (n.r.)[d]

---

[a]Isolated yield. [b]Determined by GC. [c]Using Fe (12 mol%) in AcOH at 80 °C. [d]Using $H_2SO_4$ as the solvent at 80 °C.

When 1,4-dimethoxybenzene (**12a**), a highly electron-rich aromatic compound, was reacted with **3a** (1.0 equiv.), the brominated product **13a** was produced in 72% yield. 4-*tert*-Butylanisole did not afford 3-bromo-4-*tert*-butylanisole, rather 2-bromo-4-*tert*-butylanisole (**13b**) was exclusively obtained in 95% yield. Aromatics bearing electron-donating groups, such as *N*,*N*-dimethylaniline (**12c**) and 2-methoxynaphthalene (**12d**), were brominated at the expected positions, to afford 4-bromo-*N*,*N*-dimethylaniline (**13c**) and 3-bromo-2-methoxynaphthalene (**13d**) in excellent yields, respectively. *tert*-Butylbenzene (**12e**) did not produce 4-bromo-*tert*-butylbenzene (**13e**), presumably because the *tert*-butyl group is an insufficiently strong electron-donating group to effect bromination with **3a**. Moreover, even in the presence of an iron (12 mol%) [20], **3a** hardly brominated **12e** to furnish **13e**. Aromatic compounds bearing strong electron-withdrawing groups, such as **12f** and **13g**, were not brominated at all. In addition, the reaction of **12g** with **3a** in sulfuric acid at 80 °C returned starting material, with none of the desired product **13g** formed.

1,4-Dimethoxybenzene (**12a**) was brominated with **3b**, **1a**, **1c**, **11a**, and **11b** under the same conditions used to brominate **3a**, the results of which are summarised in **Scheme 12**. When **3a**, **3b**, and **11a** were employed, the desired product **13a** was obtained in yields of 79, 71, and 70%, respectively; however, the bromination of **12a** with **1c** gave **13a** in 52% yield. It seems that **1c** does not dissolve well in acetic acid. On the other hand, when **1a** was used, some 1,4-dioxane-decomposition products were detected by GCMS, and a 62% yield of **13a** was obtained. In addition, complex **11b** afforded **13a** in 65% yield. Based on these results, we conclude that the reactivity of **3a** is similar to those of **3b** and **11a**, but superior to those of **1a**, **1c**, and **11b**.



**Scheme 12.** Evaluation of the bromination of 1,4-dimethoxybenzene with **3a** (Yields were determined by GC).

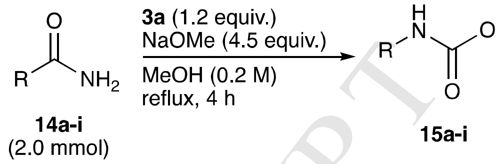
### 2.5.4. Hofmann rearrangement with 3a

The Hofmann rearrangement is a degradation reaction used to convert a primary amide into a primary amine [21]. In this work, we carried out this reaction with sodium methoxide or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methanol, which afforded carbamates instead of amines.

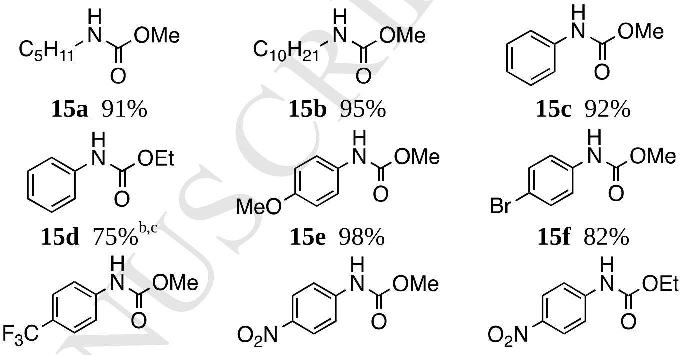
Initially, we examined the rearrangement of hexyl amide (**14a**) under the variety of conditions listed in **Table S1** in the Supplementary Data; the following optimised reaction conditions were determined: substrate (2.0 mmol), **3a** (1.2 equiv.), sodium methoxide (4.5 equiv.), methanol (0.2 M), reflux, 4 h.

**Table 8**

Hofmann rearrangement with **3a**.[a]



---



**15a** 91% **15b** 95% **15c** 92%

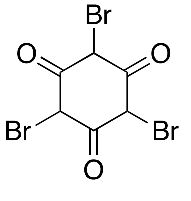
**15d** 75%[b,c] **15e** 98% **15f** 82%

**15g** 71% **15h** 57%[b] **15i** 22%[b,c]

---

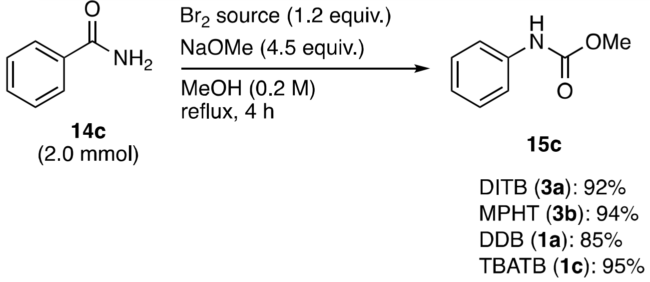
[a]Isolated yield. [b]Determined by $^1H$ NMR. [c]Using EtOH/DMSO = 2:1 (0.2 M) and NaOEt (4.5 equiv.).

The substrate scope of the Hofmann rearrangement using **3a** is summarised in **Table 8**. Aliphatic amides **14a,b** furnished **15a,b** in excellent yields. While the Hofmann rearrangement of benzamide (**14c**) proceeded well to afford the corresponding carbamate **15c** in 92% yield; the rearrangement in EtOH/DMSO (2/1 v/v) instead of methanol gave the corresponding ethyl carbamate **15d** in 75% yield. Methyl (4-methoxyphenyl) carbamate (**15e**) was obtained almost quantitatively. The reaction of benzamides bearing electron-withdrawing substituents, such as 4-bromobenzamide (**14f**), and 4-(trifluoromethyl)benzamide (**14g**), afforded the corresponding carbamates **15f** and **15g** in 82, and 71% yield, respectively. In addition, 4-nitrobenzamide **13h**, with its strong electron-withdrawing group, provided the desired products **15h** and **15i** in 57 and 22% yield, respectively, when reacted under the two reaction conditions. It should be noted that the Hofmann rearrangement of **14h** with NBS (**1b**) or tribromoisocyanuric acid (**16**) has previously been reported to give a poor yield [22a] or require a long reaction time [22b].



**16**

As shown in **Scheme 13**, the Hofmann rearrangement of **14c** was conducted with **3b**, **1a**, and **1c** under the same reaction conditions as those used with **3a**. Methyl carbamate **15c** was obtained in excellent yields in the presence of **3a**, **3b**, and **1c**, while the reaction using **1d** led to a lower yield. These results clearly show that **3a** is as reactive as bromine alternatives **3b** and **1c**, but is superior to **1a**.



**Scheme 13.** Evaluation of the Hofmann rearrangement of benzamide with **3a**.

## 3. Conclusion

We developed bis(1,3-dimethyl-2-imidazolidinone) hydrotribromide (DITB, **3a**) as novel bromine alternative. In addition, a novel procedure for the preparation of $HBr_3$ complexes was established. Our procedure is significant since it uses lower amounts of reagents and provides higher yields of products than previous methods. Specifically, since $Br_2$ also produces HBr, no HBr source is required in this new method. The physical properties of **3a** reveal that this complex is robust in air. In addition, **3a** is more soluble in a variety of organic solvents than MPHT (**3b**) and TBATB (**1c**). X-ray crystallography revealed that the $Br_3^-$ unit is surrounded by four DMI units, which indicates that $Br_3^-$ is highly stable within the crystal. Olefins, carbonyl compounds, and aromatics were brominated with **3a**, which also facilitated the Hofmann rearrangement, providing the desired products in good-to-excellent yields. To evaluate the reactivity of **3a**, the above four reactions were also carried out with **3b**, **1c**, and DDB (**1a**). The reactivity of **3a** was observed to be almost identical to that of alternatives **3b, 1a**, and **1c** during the bromination of olefins and in the Hofmann rearrangement. On the other hand, the use of **3a** for the α-bromination of carbonyl compounds yielded the desired products in much higher yields than **3b** owing to its superior solubility. Similarly, when brominating aromatics, **1c** afforded 2-bromo-1,4-dimethoxybenzene in moderate yield due to its poor solubility in acetic acid, while **3a** provided the product in higher yield. In conclusion, DITB (**3a**) is a simple to prepare, air stable, and convenient alternative to molecular bromine in many bromination reactions.

## 4. Experimental section

### *4.1. Preparation of Bis (1,3-dimethyl-2-imidazolidinone) hydrotribromide (DITB, **3a**)*

To a 50 mL round-bottom-flask equipped with a drying tube containing calcium chloride, was added 1,3-dimethyl-2-imidazolidinone (2.54 g, 22.2 mmol) in diethyl ether (20 mL) at 0 °C. Molecular bromine (809 mg, 5.06 mmol) was slowly added to the flask at the temperature, and the mixture was stirred at 0 °C for 1 h. Diethyl ether (30 mL) was added to the mixture, separating an orange precipitation, which was then filtered and washed with ether (10 mL × 3) to afford an orange crystalline solid (1.41 g, 89%). Mp: 117-118 °C; $\nu_{max}$ (KBr) 1625 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 2.98 (s, 12H, $NCH_3$), 3.63 (s, 8H, $CH_2$), 10.5 (bs, 1H, HBr); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 32.15, 46.30, 161.76. Found: C, 25.58; H, 4.50; N, 11.99; Br, 51.13. $C_{10}H_{21}N_2O_3Br_3$ requires C, 25.61; H, 4.51; N, 11.95, Br, 51.11%.

### *4.2 Typical procedure for the bromination of olefins with **3a** (Table 5, **8a**)*

To a solution of 1-tetradecene (**7a**, 408 mg, 2.08 mmol) in $CH_2Cl_2$ (4 mL) was added **3a** (990 mg, 2.11 mmol), and the mixture was stirred at 20 °C for 1 h. The reaction mixture was then diluted with hexane (50 mL) and washed with water (20 mL × 2). The organic layer was dried over $Na_2SO_4$ (15 g) and concentrated in vacuo. The crude residue (690 mg) was purified using silica gel column chromatography (eluent: hexane) to afford 1,2-dibromotetradecane (**8a**, 683 mg, 92 %) [23] as a colourless liquid; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.27–1.45 (m, 20H), 1.73–1.82 (m, 1H), 2.10-2.18 (m, 1H), 3.62 (dd, *J* = 9.7 Hz, *J* = 10.1 Hz, 1H), 3.84 (dd, *J* = 4.1 Hz, *J* = 10.1 Hz, 1H), 4.17 (ddt, *J* = 9.7 Hz, *J* = 4.1 Hz, *J* = 5.5 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 14.21, 22.78, 26.82, 28.91, 29.45, 29.49, 29.63, 29.74 (3C), 32.01, 36.07, 36.32, 53.09.

### *4.3. Typical procedure for the α-bromination of carbonyl compounds with **3a** (Table 6, **10a**)*

To a solution of propiophenone (**9a**, 285 mg, 2.15 mmol) in $CH_2Cl_2$ (4 mL) was added **3a** (1.23 g, 2.62 mmol), and the mixture was stirred at 20 °C for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution and then extracted with diethyl ether (15 mL × 3). The combined organic layers were washed with water (20 mL × 2), dried over $Na_2SO_4$ and concentrated in vacuo. The resulting crude residue was purified using silica gel column chromatography (eluent: hexane/chloroform = 1:2) to afford bromide **10a** (433 mg, 94 %) [24] as a white crystalline solid; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.90 (d, *J* = 6.7 Hz, 3H), 5.30 (q, *J* = 6.7 Hz, 1H), 7.48 (t, *J* = 8.1 Hz, 2H), 7.59 (t, J = 8.1 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 20.25, 41.60, 128.87, 129.04, 133.81, 134.14, 193.46.

### *4.4. Typical procedure for the bromination of aromatic compounds with **3a** (Table 7, **13a**)*

To a mixture of 1,4-dimethoxybenzene (**12a**, 277 mg, 2.01 mmol) in acetic acid (4 mL), was added **3a** (1.02 g, 2.17 mmol) and the mixture was stirred at 50 °C for 6 h. The reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution and then extracted with diethyl ether (15 mL × 3). The combined organic layers were washed with water (20 mL × 2), dried over $Na_2SO_4$ and concentrated in vacuo. The resulting crude residue was purified using silica gel column chromatography (eluent: hexane/benzene = 1:1) to afford bromide **13a** (310 mg, 71%) [25] as a pale brown crystalline solid; $^1H$ NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.81 (s, 3H), 6.77–6.82 (m, 2H), 7.10 (d, *J* = 2.3 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 55.81, 56.74, 111.84, 112.98, 113.53, 118.96, 150.19, 153.95.

### *4.5. Typical procedure for the Hofmann rearrangement with **3a** (Table 8, **15c**)*

To a mixture of benzamide (**14c**, 244 mg, 2.01 mmol) in methanol (2 mL), was added NaOMe (498 mg, 9.21 mmol) in methanol (6 mL) and the mixture was stirred at 20 °C for 15 min. Complex **3a** (1.18 g, 2.52 mmol) and methanol (2 mL) were added to the mixture and stirred at reflux for 4 h. The reaction mixture was then cooled to room temperature, diluted with diethyl ether (20 mL) and quenched with a saturated $NH_4Cl$ aqueous solution (40 mL). After separation of the organic layer, the aqueous layer was further extracted with diethyl ether (15 mL × 3). The combined organic layers were washed with water (20 mL × 2), dried over $Na_2SO_4$, and concentrated in vacuo. The resulting crude residue was purified using silica gel column chromatography (eluent: hexane/chloroform = 1:1) to afford methyl phenylcarbamate (**15c**, 289 mg, 95 %) [26] as a white crystalline solid; $^1H$ NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.68 (bs, 1H), 7.06 (t, $J$ = 7.8 Hz, 1H), 7.30 (t, $J$ = 7.8 Hz, 2H), 7.40 (d, $J$ = 7.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 52.34, 118.83, 123.45, 129.02, 137.97, 154.33.

## Acknowledgments

This study was partially supported by JSPS KAKENHI Grant Number JP16K05755. HM acknowledges Prof. Hideki Yorimitsu for elemental analysis.

## References and notes

[1] A review of $Br_2$: 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.

[2] (a) J.H. Rolston, K. Yates, J. Am. Chem. Soc. 91 (1969) 1469–1477; (b) R.G. Shepherd, J. Org. Chem. 12 (1947) 275–283; (c) S. Murai, Y. Seki, N. Sonoda, J. Chem. Soc., Chem. Commun. (1974) 1032–1033.

[3] For example: I. Saikia, A.J. Borah, P. Phukan, Chem. Rev. 116 (2016) 6837−7042.

[4] A review of DDB: B. L. Finkelstein 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. 1505–1506.

[5] S.K. Chaudhuri, S. Roy, S. Bhar, Beilstein J. Org. Chem. 8 (2012) 323–329.

[6] Reviews of NBS: (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. 1657–1667; (b) J.S. Pizey in: Synthetic Reagents, vol. 2, Wiley, New York, 1974, pp. 1–63; (c) L.F. Fieser, M. Fieser in: Reagents for Organic Synthesis, vol. 1, Wiely, New York, 1967, pp.78–80.

[7] A review of the Wohl-Ziegler reaction: C. Djerassi, Chem. Rev. 43 (1948) 271–317.

[8] F.L. Greenwood, M.D. Kellert, J. Sedlak, Org. Synth. Col. Vol.4, 1963, 108–109.

[9] A review of TBATB: M.J.L. Fournier in: L.A. Paquette, D. Crich, P.L. Fuchs, G.A. Molander (Eds), Encyclopedia of Reagents for Organic Synthesis, 2nd. Ed., vol. 11, Wiely, Chichester, 2009, pp. 9135–9136.

[10] S. Kajigaeshi, T. Kakinami, T. Okamoto, S. Fujisaki, Bull. Chem. Soc. Jpn. 60 (1987) 1159–1160.

[11] J. Berthelot, M. Fournier, J. Chem. Educ. 63 (1986) 1011–1011.

[12] (a) L.A. Yanovskaya, A.P. Terent'ev, L.I. Belen'kii, Zh. Obshch. Khim. 22 (1952) 1635–1638; (b) L.A. Yanovskaya, A.P. Terent'ev, Zh. Obshch. Khim. 22 (1952) 1639–1642.

[13] O. Hassel. J. Hvoslef, Acta. Chem. Scand. 8 (1954) 873–873.

[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] Crystal data for DITB (**3a**), orange prism, 0.3 mm × 0.3 mm × 0.2 mm, chemical formula: $C_5H_{10.5}Br_{1.5}N_2O$, $Fw$ = 234.51, monoclinic, $P2_1/c$, $a$ = 8.1460(17), $b$ = , 10.998(3), $c$ = 10.326(3) Å, $\beta$ = 112.261(8)°, V = 856.1(4) Å$^3$, Z = 4, $D_{calcd.}$ = 1.819 g/cm$^3$, $\mu$ (Mo Kα) = 70.931 cm$^{-1}$, $F$ (000) = 460, 1967 unique reflections ($R_{int}$ = 0.0799), the final $R$ and $R_w$ were 0.0494 and 0.0422 (1007 reflections [$I > 2.0\sigma(I)$]), GOF = 1.142. CCDC-1877555.

[16] A. Bekaert, O. Barberan, E.B. Kaloun, A. Danan, J.D. Brion, P. Lemoine, B. Viossat, Z. Kristallogr. NCS, 216 (2001) 457–458.

[17] Bromination of **7a** with **3a** in $CH_2Cl_2$ in the presence of BPO (10 mol%) also exclusively afforded dibromide **8a** in quantitative yield (> 98% by GC).

[18] A review of α-bromination of carbonyl compounds: R.H. Vekariya, H.D. Patel, Tetrahedron, 2014, 70, 3949–3961.

[19] For example: M.B. Smith in: March's Advanced Organic Chemistry, 7th Ed. Wiely, Hoboken, 2013, pp. 603–608.

[20] J.F. Bunnett, M.M. Rauhut, Org. Synth. Coll. Vol. 4 (1963) 114–116.

[21] Reviews of the Hofmann rearrangement: (a) J. Aubé, C. Fehl, R. Liu, M.C. McLeod, H.F. Motiwala in: P.Knochel (Ed), Comp. Org. Synth. 2nd Ed., vol. 6, Elsevier, 2014, pp. 609–617; (b) T. Shioiri in: B.M. Trost, I. Fleming (Eds), Comp. Org. Synth. vol. 6, Pergamon, Oxford, 1991, pp. 800–806. (c) E.S. Wallis, J.F. Lane, Org. React. 1946, 3, 267–306.

[22] (a) L. S. M. Miranda, T. R. da Silva, L. T. Crespo, P. M. Esteves, L. F. de Matos, C. C. Diederichs, R. O. M. A. de Souza, Tetrahedron Lett. 52 (2011) 1639–1640; (b) X. Huang, M. Seid, J. W. Keillor, J. Org. Chem. 1997, 62, 7495–7496.

[23] G. Rolla, V. De Biasio, G.B. Giovenzana, M. Botta, L. Tei, Dalton Trans. 47 (2018) 10660–10670.

[24] Q. Jiang, W. Shenga, C. Guo, Green Chem. 15 (2013) 2175–2179.

[25] A. Bose, P. Mal, Tetrahedron Lett. 55 (2014) 2154–2156.

[26] L. Li, M. Xue, X. Yan, W. Liu, K. Xu, S. Zhang, Org. Biomol. Chem. 16 (2018) 4615–4618.

## Supplementary Material

Supplementary data (Table S1, Fig. S1, $^1$H and $^{13}$C NMR data of known compounds prepared in this study, and copies of $^1$H NMR, and $^{13}$C NMR spectra of new compounds.) associated with this article can be found online at https://doi.org/