An effective Method for the Generation of Dibromocarbene and Its Application to Organic Synthesis

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An Effective Method for the Generation of Dibromocarbene and Its Application to Organic Synthesis[1)]

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Dibromocarbene is effectively generated from bromoform and aqueous sodium hydroxide by use of tertiary amine as catalyst in two-phase system. Dibromocarbene thus generated reacts with olefins to give dibromocyclopropane derivatives in good yields. Dimethyldodecylamine (DMDA) acts as the most effective catalyst. Dibromocarbene generated in the presence of DMDA has a high reactivity and inserts into the C-H bond of saturated hydrocarbons; adamantane and 1-methylcyclohexane.

1. Introduction

Dibromocarbene is a versatile intermediate in organic synthesis[2)]. However, no effective method for the generation of this carbene has so far been reported. Makosza has shown that dichlorocarbene can be generated with high efficiency from a heterogeneous mixture of chloroform and aqueous sodium hydroxide by use of benzyltriethylammonium chloride as catalyst[3)]. The application of this method (the so-called "Phase-transfer catalysis") to the generation of dibromocarbene gave, however, far less satisfactory results. Previously, we have shown that tertiary amines serve as effective catalyst in two-phase system for the generation of dichlorocarbene[4)]. The extension of this study has revealed that certain tertiary amines act also as a good catalyst for the generation of dibromocarbene.

In this paper we report a simple and effective method for the generation of dibromocarbene in two-phase system and its application to organic synthesis**.

2. Results and Discussion

The reaction of bromoform with aqueous sodium hydroxide proceeds at very slow rate in benzene in the absence of tertiary amines. Accordingly, when this reaction was carried out in the presence of cyclohexene (**1a**) at 50°C for 20 h, 7,7-dibromobicyclo [4.1.0] heptane (**2a**) was obtained only in less than 1% yield. The generation of dibromocarbene was found to proceed at much faster rate in the presence of catalytic amounts of tertiary amines. Dibromocarbene thus generated reacted with olefins to give the

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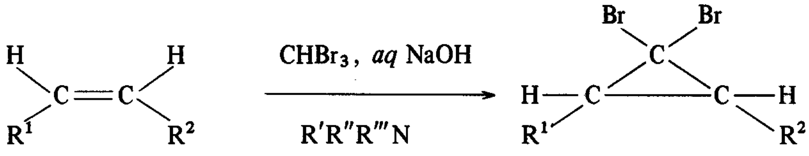
** Recently, Makosza has pointed out independently that tributylamine can be utilized as catalyst for this reaction[5)].

corresponding dibromocyclopropane derivatives in good yields.



1 **2**

a: $R^1, R^2 = -(CH_2)_4-$ c: $R^1 = H$, $R^2 = CH_3(CH_2)_5$

b: $R^1 = H$, $R^2 = C_6H_5$ d: $R^1 = H$, $R^2 = CH_3(CH_2)_3$

The yield of **2a** depended on the structure of tertiary amines employed. The results are given in Table 1. Use of dimethyldodecylamine (DMDA) afforded **2a** in the highest yield (84%). Use of tributylamine gave less satisfactory result. In general, trialkylamines of the type $[CH_3(CH_2)_n]_3N$ having the alkyl groups of C_5 and C_6 had better catalytic ability. Relation between number of carbon atoms of the amines and the yield of **2a** are shown in Fig. 1. Primary or secondary amines were ineffective as catalyst. Aromatic tertiary amines such as N,N-dibutylaniline and pyridine showed poor catalytic ability. The result of Table 1 also indicates that in the generation of dibromocarbene the amine-catalyzed reactions offer much more satisfactory results than the phase-transfer catalyzed ones: use of TEBA (a phase-transfer catalyst) gave **2a** only in 14% yield.

Table 1 Preparation of 2a from 1a by Use of Various Tertiary Amines as Catalysts[a)]

Amine	Yield of 2a, %	Amine	Yield of 2a, %
none	0	Benzyldiethylamine	19
Triethylamine	5	Dimethyldodecylamine	84
Tripropylamine	53	Didodecylmethylamine	73
Tributylamine	68	Dimethyloctadecylamine	73
Tripentylamine	79	Dodecylamine	1
Trihexylamine	80	N,N,N',N'-Tetramethylpropylenediamine	8
Trioctylamine	70		
Tridecylamine	50	Benzyltriethylammonium[b)] chloride (TEBA)	14
Tridodecylamine	19		

[a)] 1a; 44 mmol, bromoform; 66 mmol, amine; 2.2 mmol, 33% aqueous sodium hydroxide; 15 g, benzene; 5 ml, temperature; 50°C, time; 20 h. [b)] A typical phase-transfer catalyst.

The rate of formation of **2a** in the presence of tertiary amines obeyed a pseudo-first-order kinetics as expressed in Equation 1. Table 2 shows the pseudo-first-order rate

$$\frac{d\,[2a]}{dt} = k\,[1a] \qquad (1)$$

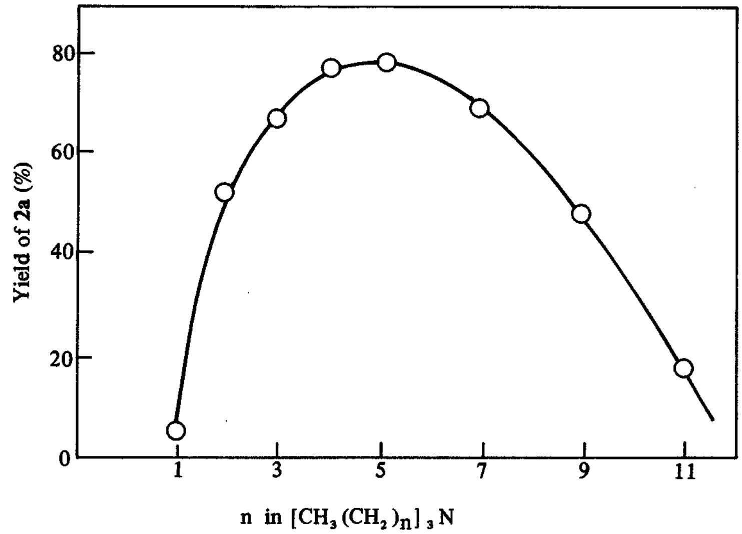


Fig. 1. Relation between number of carbon atoms of the alkylgroup in $[CH_3(CH_2)_n]_3N$ and the yields of **2a** in the reaction of **1a** with dibromocarbene at 50°C for 20 h in the presence of the tertiary amines.

Table 2 Pseudo-first-order Rate Constants for the Addition of Dibromocarbene to **1a** in the Presence of Tertiary Amines[a)]

Amine	$10^5 k_{obsd}$, s^{-1}
Dimethyldodecylamine (DMDA)	6.67
Dimethylhexadecylamine	3.33
Tributylamine	1.11

[a)] **1a**; 2.0 M, $CHBr_3$; 3.0 M, amine; 0.01 M, 33% NaOH; 12.5 M, temperature, 50°C.

constants determined under the conditions indicated in this table. The rate of formation of **2a** in the presence of DMDA is much faster than the rates in the presence of other amines. This result suggests that dibromocarbene generated in the presence of DMDA has a higher reactivity. The enhanced reactivity of this carbene was demonstrated by the reaction with other olefins. Dibromocarbene generated in the presence of DMDA reacted with 1-octene (**1c**) and 1-hexene (**1d**) to give the dibromocyclopropane derivatives, **2c** and **2d**, in 80 and 78% yields, respectively (Table 3). In contrast, the reaction of 1-octene and 1-hexene with dibromocarbene generated in the presence of a phase-transfer catalyst (TEBA) resulted in the recovery of the starting olefins. Furthermore, the reaction of styrene (**1b**) with dibromocarbene in the presence of DMDA gave 1,1-dibromo-2-phenylcyclopropane (**2b**) in 70% yield only for 4 h. On the other hand, when tributylamine was used as catalyst, much longer reaction time (20 h) was needed to obtain **2b** in a com-

Table 3 Addition of Dibromocarbene to Olefins in the Presence of Amine Catalysts.

Olefin	Catalyst	Reaction time, h	Product	(Yield, %)
1a	DMDA[a]	20	**2a**	(84)
1a	Bu_3N[b]	20	**2a**	(68)
1a	TEBA[c]	20	**2a**	(14)
1b	DMDA	4	**2b**	(70)
1b	Bu_3N	4	**2b**	(45)
1c	DMDA	20	**2c**	(80)
1c	TEBA	20	**2c**	(0)
1d	DMDA	20	**2d**	(78)
1d	TEBA	20	**2d**	(0)

[a] DMDA, dimethyldodecylamine. [b] Bu_3N, tributylamine. [c] TEBA, benzyltriethylammonium chloride.

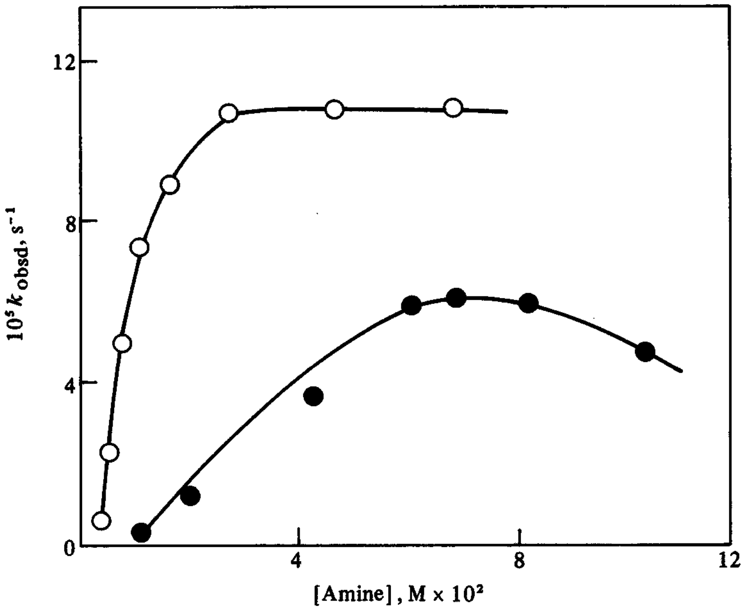


Fig. 2. Effect of concentrations of tertiary amines on the rate constants for the formation of 7,7-dibromobicyclo[4.1.0]heptane at 50°C. The reaction was conducted by stirring a heterogeneous mixture of cyclohexene (20 mmol) and bromoform (30 mmol), and 33% sodium hydroxide (10 ml) in 10 ml of benzene at 50°C.

—○—○— ; $C_{12}H_{25}N(CH_3)_2$, —●—●— ; $(C_4H_9)_3N$.

parable yield. Fig. 2 shows the relation between concentrations of amines and pseudo-first-order rate constants for the formation of **2a**. For DMDA, the rate constants (k_{obsd}) first increased with increasing its concentrations, and then reached to a constant value at the concentration of about 2 x 10^{-2}M. For tributylamine, the rate constants first increased with increasing its concentrations, then decreased through a maximum value.

On the other hand, in the case of cetyltrimethylammonium bromide (CTABr) the rate constants increased linearly with its concentrations (Fig. 3). This result suggests that CTABr acts as a phase-transfer catalyst, but not as a micellar catalyst. A comprehensive understanding of the concentration effects of the amines on the rates is not attained at present. However, it seems conceivable that tertiary amines somehow stabilizes a reactive intermediate.

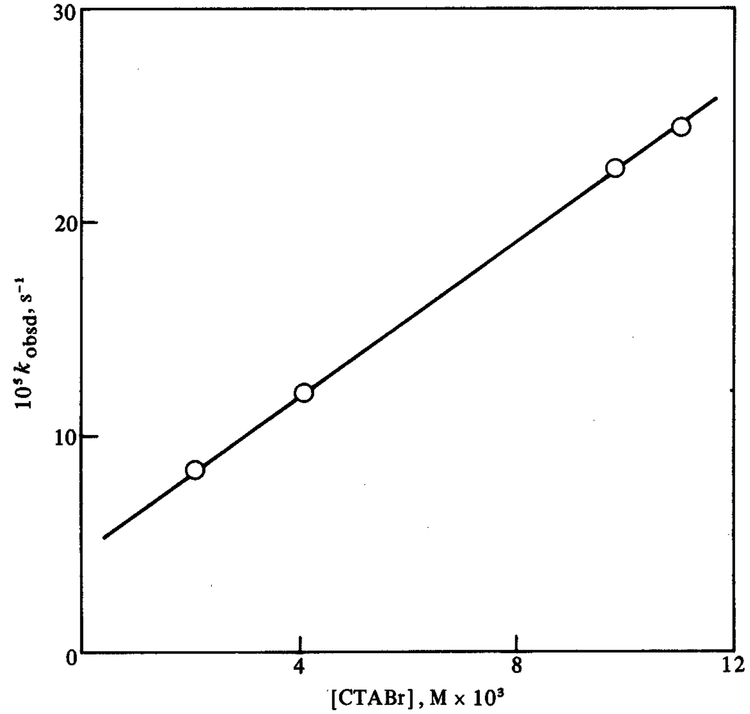


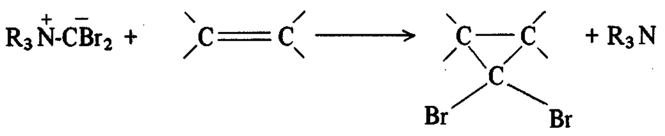
Fig. 3 Effect of concentrations of cethyltrimethylammonium bromide on the rate constants for the formation of 7,7-dibromobicyclo[4.1.0]heptane at 50°C. The reaction was conducted by stirring a heterogeneous mixture of 20 mmol of cyclohexene, 30 mmol of bromoform, and 10 ml of 33% sodium hydroxide in 10 ml of benzene at 50°C.

Scheme 1 represents a plausible mechanism for the formation of dibromocarbene in the amine-catalyzed reaction.

$$CHBr_3 + NaOH \longrightarrow NaCBr_3 + H_2O \qquad (2)$$

$$NaCBr_3 \longrightarrow NaBr + :CBr_2 \qquad (3)$$

$$:CBr_2 + R_3N \longrightarrow R_3\overset{+}{N}\text{-}\overset{-}{C}Br_2 \qquad (4)$$



(5)

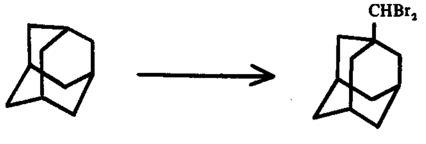
Scheme 1

Dibromocyclopropane derivatives are produced in high yield in this reaction, although dibromocarbene is readily hydrolyzed with aqueous sodium hydroxide in homogeneous system in the absence of tertiary amines. This fact can be rationalized by assuming that dibromocarbene is stabilized by tertiary amine in two-phase system probably as a ylide $R_3\overset{+}{N}\text{-}\overset{-}{C}Br_2$ (Eq. (4)). A support for the formation of ylide has been given in the dichlorocarbene generation in the presence of tertiary amines[6),7)].

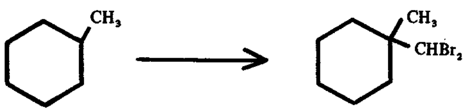
The insertion of dichlorocarbene to the carbon-hydrogen bond of saturated hydrocarbons is known[8)], but there is no such example for dibromocarbene. Treatment of adamantane (**3a**) with bromoform-aqueous sodium hydroxide in benzene in the presence of TEBA or tributylamine resulted in the recovery of the starting material. However, dibromocarbene generated in the presence of DMDA inserted into adamantane to give dibromomethyladamantane (**4a**) in 6% yield (23% yield based on consumed adamantane), along with 1-bromoadamantane. In a similar manner, 1-methyl-1-dibromomethylcyclohexane (**4b**) was obtained in 7% yield from methylcyclohexane (**3b**). In this case, no bromination product of **3b** was obtained.

We see again in these examples that dibromocarbene generated in the presence of DMDA has a high reactivity: the reactivity appears to be as high as that of a free carbene.

In summary, we emphasized that the amine-catalyzed reaction in two-phase system provides a convenient and efficient method for the generation of dibromocarbene under mild conditions, and that the carbene generated in the presence of DMDA has especially high reactivity. Hence, this method provides a wide applicability in organic synthesis.



3a **4a**



3b **4b**

3. Experimental

General Procedure for the Preparation of Dibromocyclopropane Derivatives.

A mixture of olefin (44 mmol), bromoform (16.6 g, 66 mmol), 33% aqueous sodium hydroxide (15 g), and a tertiary amine (2.2 mmol) in benzene (5 ml) was stirred for 20 h at 50°C. The reaction mixture was poured into ice-water and extracted with ether-benzene. The organic layer was dried (Na_2SO_4), evaporated, and the residue was distilled to give a product. The structure of the product was identified by its NMR, IR, and Mass spectra. The yield of the product was determined by GLC.

7,7-Dibromobicyclo[4.1.0] heptane (2a). This compound was obtaine from cyclohexene (**1a**): bp 93–94°C/6 Torr (lit[9], 100°C/8 Torr), n_D^{22} = 1.5572 (lit[9], 1.5578). The Mass spectrum exhibited peaks at *m/e* 252 (M^+): 254 (M^++2): 256 (M^++4) = 1: 2: 1 (dibromide).

1,1-Dibromo-2-phenylcyclopropane (2b). This compound was obtained from styrene (**1b**): bp 131–132°C/10 Torr (lit[10], 97°C/1 Torr), n_D^{25} = 1.5963 (lit[10], 1.5963). ^{1}H-NMR (CCl_4): δ = 1.94 (dd, 1H, J = 8.8 and 7.6 Hz), 2.09 (dd, 1H, J = 9.8 and 7.6 Hz), 2.90 (dd, 1H, J = 9.8 and 8.8 Hz), and 7.22 *ppm* (s, 5H).

1,1-Dibromo-2-hexylcyclopropane (2c). This compound was obtained from 1-octene: bp 98–99°C/4 Torr. The Mass spectrum exhibited peaks at *m/e* = 282 (M^+), 284, and 286.

1,1-Dibromo-2-butylcyclopropane (2d) This compound was obtained from 1-hexene: bp 97–98°C/6 Torr.

Dibromomethyladamantane (4a). A mixture of adamantane (**3a**) (1.47 g, 10.8 mmol), bromoform (14 g, 55 mmol), 33% NaOH (9 g), and dimethyldodecylamine (DMDA) (45 mg, 0.24 mmol) in benzene (3 ml) was stirred for 43 h at 46°C. The resulting mixture was poured into ice-water and extracted with ether-benzene. The organic layer was dried (Na_2SO_4), evaporated *in vacuo*, and the residue was distilled (bp 140–145°C/7 Torr). The distillate, which was solidified upon standing, was recrystallized from methanol to give 0.20 g (6%) of dibromomethyladamantane (**4a**): mp 62–63°C. ^{1}H-NMR (CCl_4): δ = 1.50–1.90 (m, 12 H), 1.90–2.20 (m, 3H), and 5.37 *ppm* (s, 1H, $CHBr_2$). Found: C, 42.74; H, 5.40%; M^+, 306. Calcd for $C_{11}H_{16}Br_2$: C, 42.89; H, 5.23%; M, 306.

1-Methyl-1-dibromomethylcyclohexane (4b). This compound was obtained from methylcyclohexane (**3b**) in 7% yield in a similar manner: by 100–101°C/7 Torr. ^{1}H-NMR (CCl_4): δ = 1.14 (s, 3H, CH_3), 1.45–1.75 (m, 10H), and 5.60 *ppm* (s, 1H, $CHBr_2$). Found; C, 35.52; H, 5.18%; M^+, 268. Calcd for $C_8H_{14}Br_2$: C, 35.59; H, 5.23%; M, 268.

Kinetic Measurements. A heterogeneous mixture of olefin, bromoform, tertiary amine, and decane (internal standard for GLC analysis) in benzene and aqueous sodium hydroxide was stirred at a controlled temperature with the aid of "TAIYO-THERMO UNIT C-550" Electric Controller (Taiyo Kagaku Co.). The reaction was stopped at an appropriate time interval by cooling the reaction mixture. Amount of the product in organic layer was then determined by GLC. By employing the equation:

$\ln([a]/[a]-[x]) = kt$ where $[a] = [\text{olefin}]$ and $[x] = [\text{cyclopropane derivatives}]$, the rate constant ($k$) was calculated from a slope of the linear line.

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