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REACTION OF POLYCHLOROACETAMIDES WITH AMINES: REDUCTIVE DECHLORINATION AND AZIRIDINE FORMATION

Takeaki Naito,* Ayako Saito, Masafumi Ueda, and Okiko Miyata

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan *e-mail:* taknaito@kobepharma-u.ac.jp

Abstract – Treatment of trichloroacetamides with amines undergoes reductive dechlorination *via* single-electron transfer process to afford dichloroacetamides in good yields. Reaction of trichloro- and dichloroacetamides with DBU provides a new synthetic method of aziridinopyrrolidines.

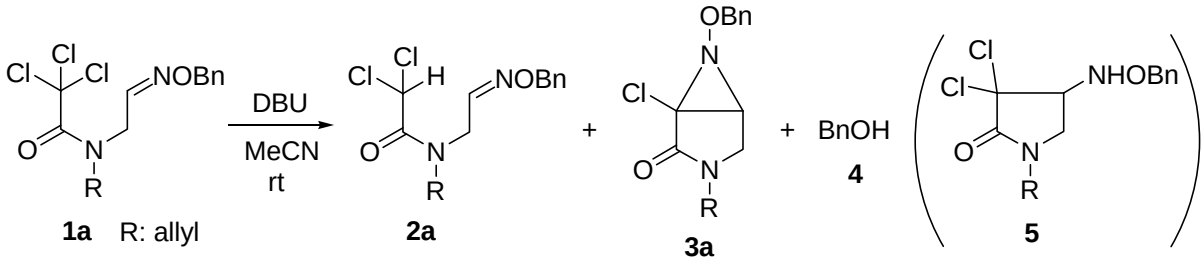
INTRODUCTION

Radical reactions have emerged as a valuable tool for organic chemists, exhibiting great advantages over ionic chemistry.[1-10] Free radical synthetic methods largely relied on toxic organomercury or organotin chemistry. Therefore, the radical reactions including atom- and group-transfer processes or single-electron transfer (SET) processes have been a subject of current interest. [1-10] Among known SET reactions, there have been only a few examples[11-14] using organic amines as an electron donor compared with so many examples using metals. Synthetic methods using metals are not generally tolerant of the removal of even a trace amount of metals which are often included in foods and drugs. Considering these backgrounds, we investigated to develop an environmentally benign SET reaction employing amines as an electron donor and found two types of novel reactions which are a novel reductive dehalogenation reaction *via* SET and a simple method for preparing aziridine skeletons *via* aza-Darzens type reaction.

There have been several examples of cyclization of trichloroacetamides with olefins in which the first step of cyclization proved to be SET reaction from metals such as ruthenium, [15] copper, [16] and nickel[17] to the trichloroacetamide group. Actually Nagashima[16] and Zard[17] groups provided novel method for preparing pyrrolidones *via* the route involving transition-metal catalyzed radical cyclization of trichloroacetamides. Ishibashi group[14] has independently reported that upon treatment of *p*-dihydroquinone and amine, trichloroacetamides carrying the enamide moiety undergo cyclization to give hydroindolones *via* SET.

RESULTS AND DISCUSSION

Aiming at the development of a new environmentally benign cyclization reaction *via* the route involving SET process from organic molecule, we started to investigate the reaction of trichloroacetamide (**1a**) under the same reaction conditions reported by Ishibashi group.[14]



1a R: allyl **2a** **3a**

Scheme 1

Table 1. Reaction of 1a with DBU

entry	conc. (M)	DBU (eq.)	temp.	time	yield (%)		
					2a	**3a**	**4**
1	0.02	1	reflux	10 (h)	25	0	23
2	0.02	3	rt	18 (d)	13	8	9
3[a]	0.02	3	rt	19 (d)	0	7	25
4[b]	0.02	3	rt	3 (d)	0	2	27
5	0.1	3	rt	3 (d)	23	11	5
6	0.5	3	rt	17 (h)	22	10	trace

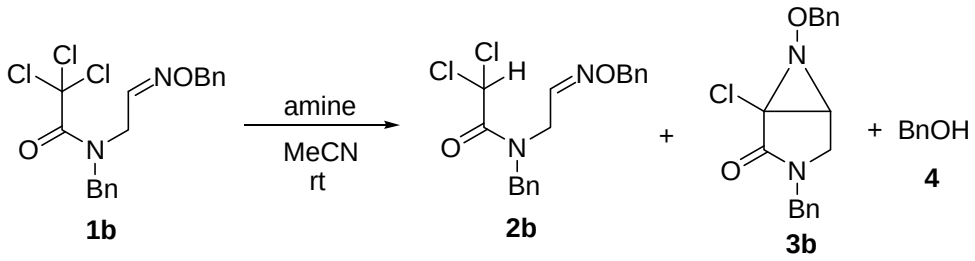
[a]The reaction was carried out in the dark.

[b]The reaction was carried out in the presence of EtOH (3 eq.).

Employment of **1a** as a substrate which carries two types of double bonds, olefin and oxime ether, would lead to informative and instructive suggestions regarding each double bond as a radical acceptor (Scheme 1). However, the reaction conditions (*p*-dihydroquinone, DBU, reflux in MeCN) employed by Ishibashi[14] led only to a very sluggish reaction that gave no isolable compounds from the reaction mixture. Therefore we investigated the reaction of **1a** with either hydroquinone or DBU. In the presence of hydroquinone, trichloroacetamide (**1a**) was completely recovered while three products (**2a**, **3a**) and benzyl alcohol (**4**) were obtained from the reaction of **1a** with DBU (entry 2). Product (**2a**) has the dichloroacetamide group and another one (**3a**) was proved an aziridine compound from the spectral data. Intramolecularly cyclized product (**5**) was not isolated.

Optimization of the reaction was attempted by changing concentration, amount of base, reaction temperature and time as shown in Table 1. Stirring 0.5 M solution of trichloroacetamide (**1a**) and DBU (3 eq.) in acetonitrile for 17 h gave dichloroacetamide (**2a**) and aziridine (**3a**) in 22% and 10% yields, respectively, with a small amount of benzyl alcohol (**4**) (entry 6).

Generality of this reaction was proved by the reaction of *N*-benzyl trichloroacetamide (**1b**) with either DBU or other organic bases summarized in Table 2.



Scheme 2

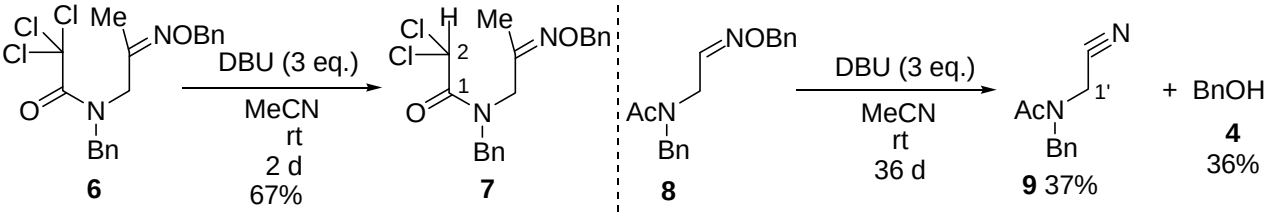
Table 2. Reaction of 1b with amines

entry	conc.	amine	time	yield (%)			
	(M)	(eq.)	(d)	**2b**	**3b**	**4**	**1b**
1	0.02	DBU (3)	1	44	2	14	trace
2	0.1	DBU (3)	2.5	21	14	11	trace
3	0.1	DBN (3)	2	25	6	13	0
4	0.1	TMG (3)	2	36	3	0	37
5	0.1	Et_3N (3)	14	no reaction			
6	0.1	DABCO (3)	7	no reaction			

Product ratio and yield of three products (**2b**, **3b**, and **4**) are found to be slightly depending upon reaction conditions used. It is worth to note that amines such as DBU, DBN, and TMG (tetramethylguanidine) containing an amidine moiety in the molecule are effective in this reaction (entries 1-4). Bases carrying the amidine group exhibit strong basicity and are also suitable for SET while DABCO carrying bridgehead nitrogen would be unable to supply α-hydrogen of the nitrogen moiety.

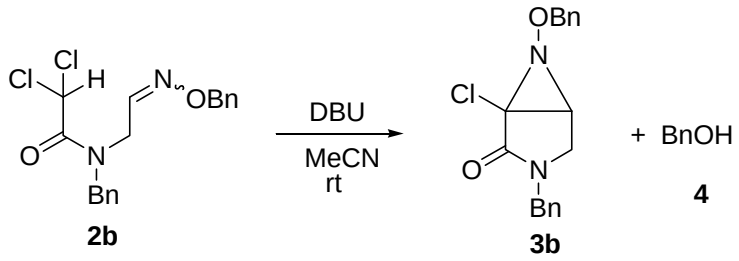
In order to propose reaction pathway to three products, we next investigated reaction of the related substrates, ketoxime ether (**6**) and acetamide (**8**) with DBU (Scheme 3). Upon treatment with DBU, ketoxime ether (**6**) gave dichloroactamide (**7**) in 67% yield with no formation of benzyl alcohol (**4**). Similar treatment of acetamide (**8**) with DBU gave nitrile (**9**) and benzyl alcohol (**4**) in 37% and 36%

yields, respectively, with recovering 47% yield of starting material (**8**).



Scheme 3

We also extended reaction with DBU to dichloroacetamide (**2b**) in order to disclose the reaction pathway to aziridine formation. Additionally, both *E*- and *Z*-oxime ethers (**2b**) were isolated and subjected to the reaction as shown in Table 3.



Scheme 4

Table 3. Reaction of 2b with DBU

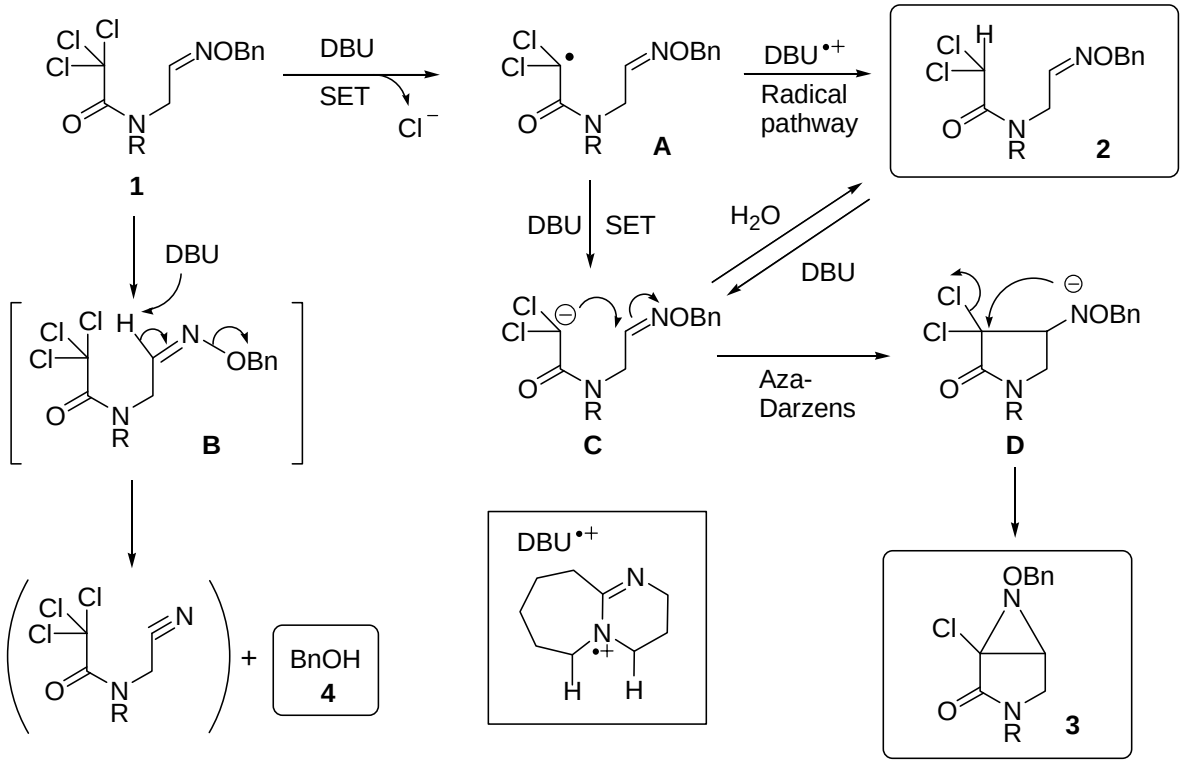
entry	**2b** (*E*/*Z*)	conc. (M)	DBU (eq.)	time (d)	yield (%)		
					3b	**4**	**2b**
1	*E*	0.02	3	4	29	trace	18
2	*E*	0.1	6	3	51	4	3
3	*Z*	0.02	6	1.5	27	27	25
4	*Z*	0.1	3	2	27	26	6
5	*Z*	0.1	6	3	29	20	6

Reaction of *E*-**2b** with DBU gave the expected aziridine (**3b**) as a major product with a small amount of benzyl alcohol (**4**) (entry 1). When 6 eq. of DBU and 0.1 M solution were employed, we obtained aziridine (**3b**) in moderate yield (entry 2). On the other hand, under the same reaction conditions, *Z*-**2b** gave almost same yield (27%) of aziridine (**3b**) and benzyl alcohol (**4**) (27%).

There are a few examples of reductive dehalogenation of α-halogenocarbonyl compounds with organic amines but they are mostly focused on reaction mechanism using α-bromo ketones, [11]

α-chloroacetophenone, [12] and hexachloroacetone[13] as a substrate.

Based on the results mentioned above and related works,[11-13] we propose possible reaction pathway to three products (**2**-**4**) as shown in Scheme 5.



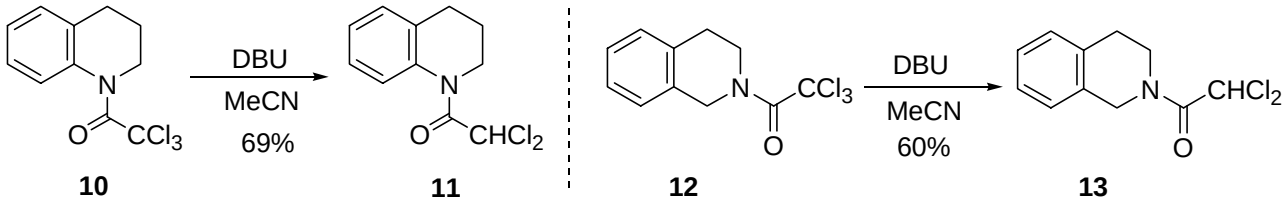
Scheme 5

SET from DBU to trichloroacetamide (**1**) occurs to form α-carbamoyl radical (**A**) that would be hydrogenated by radical cation of DBU produced to afford dichloroacetamide (**2**). As another possible pathway, product (**2**) would be formed *via* SET from DBU to intermediate radical (**A**) leading to the formation of the corresponding anion (**C**) followed by its protonation.

In aziridine formation, two reaction pathways would be possible. Since dichloroacetamide (**2**) worked well, **2** is first deprotonated by DBU to form anion (**C**) that would undergo aza-Darzens type of reaction to afford aziridine (**3**). When trichloroacetamide (**1**) is used as a substrate, anion (**C**) is formed from radical (**A**) and also by deprotonation of **2** with DBU.

Formation of by-product benzyl alcohol (**4**) would be explained in *anti*-elimination fashion from *Z*-aldoxime ether group (**B**) with DBU.

Potentiality of reductive dechlorination of trichloroacetamides has been proved by two other reactions of *N*-trichloroacetamides (**10**) and (**12**) prepared from tetrahydroquinoline and tetrahydroisoquinoline which afforded the respective dichloroacetamides (**11**) and (**13**) in good yields (Scheme 6).



10 **11** **12** **13**

Scheme 6

CONCLUSION

We have now established an effective method for preparing dichloroacetamides by simple treatment of trichloroacetamides with DBU and found that reactions of tri- and dichloroacetamides carrying oxime ether with DBU gave aziridine compounds via aza-Darzens reaction. The resulting aziridinopyrrolidines are closely related to the partial structure of mitomycin-mitosene antitumor antibiotics.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 200, 300, or 500 MHz and at 75 or 125 MHz, respectively. IR spectra were recorded using FTIR apparatus. MS spectra were obtained by EI method. Flash column chromatography (FCC) was performed using E. Merck Kieselgel 60 (230-400 mesh). Medium-pressure column chromatography (MCC) was performed using Lobar größe B (E. Merck 310-25, Lichroprep Si60). Preparative TLC (PTLC) was performed on pre-coated Silica gel 60F-254 plates (0.5 mm thick, Merck). All extracts were dried over $MgSO_4$ and then concentrated under reduced pressure.

2,2,2-Trichloro-*N*-(2-phenylmethoxyiminoethyl)-*N*-(2-propenyl)acetamide (1a) To 2-chloroacetaldehyde *O*-phenylmethyloxime[18] (25 g, 136 mmol) was added allylamine (38 mL, 507 mmol) with stirring under a nitrogen atmosphere at 0 °C. The mixture was stirred at rt for 2 days. Water was added and then the mixture was extracted with AcOEt. The organic phase was dried and concentrated at reduced pressure to give the residue. ^{1}H-NMR spectrum of the residue proved the formation of desired *sec*-amine (*E* : *Z* = 1 : 1) which without further purification was subjected to next acylation reaction.

(*E/Z*)-2-Propenylaminoacetaldehyde *O*-Phenylmethyloxime: ^{1}H-NMR (300 MHz) δ : 7.47-7.31 (5H + 1/2H, m, ArH + iminoic H), 6.81 (1/2H, t, *J*=5.0 Hz, iminoic H), 5.90-5.66 (1H, m, olefinic H), 5.18-5.09 (2H, m, olefinic H), 5.08 (2/2H, s, OC*H*$_2$Ph), 5.07 (2/2H, s, OC*H*$_2$Ph), 3.20 (2H, d, *J*=6.2 Hz, NC*H*$_2$CH=CH$_2$), 3.09 (2H, d, *J*=5.0 Hz, C*H*$_2$CH=NOBn).

To a solution of *sec*-amine prepared above (26.7 g, 130 mmol) in CH_2Cl_2 (300 mL) were added dropwise Et_3N (14.5 mL, 254 mmol) and then TCAA (trichloroacetic anhydride) (23 mL, 127 mmol) under a

nitrogen atmosphere at 0 °C. The mixture was stirred at rt for 23 h. Water was added and then the mixture was extracted with CH_2Cl_2. The organic phase was dried and concentrated to give a residue which was purified by FCC (hexane : AcOEt (20 : 1)) to afford **1a** (24 g, 44%) as a colorless oil. ^{1}H-NMR spectrum showed the existence of a geometrical mixture (*E* : *Z* = 1 : 1) of the oxime ether group and rotational isomer around the amide group. IR ν_{max} cm^{-1} : 1682 (CON). ^{1}H-NMR (300 MHz) δ : 7.44 (1/2H, t, *J*=5.7 Hz, iminoic H), 7.40-7.27 (10H, m, ArH), 6.84-6.66 (1/2H, br m, iminoic H), 5.86-5.70 (1H, m, olefinic H), 5.30-5.16 (2H, br m, olefinic H), 5.13 (1H, s, OC*H*$_2$Ph), 5.09 (1H, s, OC*H*$_2$Ph), 4.66-3.99 (4H, br m, NC*H*$_2$CH=CH$_2$ + C*H*$_2$CH=NOBn). ^{13}C-NMR (50 MHz) δ : 160.5, 147.1, 144.5, 137.1, 131.1, 130.4, 128.3, 128.24, 128.16, 128.0, 127.9, 127.8, 119.8, 118.8, 92.5, 92.4, 77.2, 76.4, 76.0, 53.4, 51.9, 50.3, 47.5, 46.2, 45.2, 44.2. MS *m/z* (relative intensity) : 354 (1.5), 352 (13.5), 350 (40.0), 348 (40.5). HRMS *m/z* : Calcd for $C_{14}H_{15}N_2O_2Cl_3$ (M^+) 348.0198. Found : 348.0195.

2,2,2-Trichloro-*N*-(2-phenylmethoxyiminoethyl)-*N*-phenylmethylacetamide (1b) According to the procedure given for **1a**, the amide (**1b**) was prepared from 2-chloroacetaldehyde *O*-phenylmethyloxime[18] (3.4 g, 18.3 mmol), benzylamine (4 mL, 36.6 mmol), and TCAA (4 mL, 22 mmol) via the corresponding benzyliminoethylamine. The amide (**1b**) (3 g, 48%) obtained is colorless oil and found to be a geometrical mixture (*E* : *Z* = 1 : 1) of the oxime ether group and rotational isomer around the amide group from ^{1}H-NMR spectrum. IR ν_{max} cm^{-1} : 1685 (CON). ^{1}H-NMR (300 MHz) δ : 7.42-7.18 (10H + 1/2H, m, ArH + iminoic H), 6.73 (1/2H, br s, iminoic H), 5.07 (2H, br s, OC*H*$_2$Ph), 4.91 (2/2H, br s, NC*H*$_2$Ph), 4.61 (2/2H, br s, NC*H*$_2$Ph), 4.46-3.96 (2H, br m, C*H*$_2$CH=NOBn). ^{13}C-NMR (50 MHz) δ : 160.9, 147.2, 144.5, 137.2, 137.1, 134.7, 128.8, 128.7, 128.3, 128.1, 128.0, 127.9, 92.7, 92.6, 76.4, 76.1, 65.4, 60.2. MS *m/z* (relative intensity) : 404 (0.7), 402 (6.5), 400 (18.0), 398 (18.0). HRMS *m/z* : Calcd for $C_{18}H_{17}N_2O_2Cl_3$ (M^+) 398.0356. Found : 398.0350.

General Procedure for Reaction of Trichloroacetamides (1a, b) with DBU A solution of trichloroacetoamides (**1a, b**) (140 mg, 0.4 mmol) and DBU in MeCN was stirred under the reaction conditions shown in Tables 1 and 2. After the solution was concentrated, the residue was purified by either FCC, MCC, or PTLC (hexane : AcOEt (3 : 1) to afford dichloroacetamide (**2a, b**), aziridine (**3a, b**), benzyl alcohol (**4**), and starting compounds (**1a, b**) in the yields shown in Tables 1 and 2.

2,2-Dichloro-*N*-(2-phenylmethoxyiminoethyl)-*N*-(2-propenyl)acetamide (**2a**). Colorless oil. Spectral data are collected as a geometrical mixture of the oxime ether group and rotational isomer around the amide group (2 : 2 : 3 : 1). IR ν_{max} cm^{-1} : 1685 (CON). ^{1}H-NMR (300 MHz) δ : 7.46-7.32 (5H + 1/8H + 2/8H, m, ArH + iminoic H), 6.77 (2/8H, t, *J*=4.5 Hz, iminoic H), 6.69 (3/8H, t, *J*=4.5 Hz, iminoic H), 6.25 (2/8H, s, COCCl_2H), 6.19 (2/8H, s, COCCl_2H), 6.17 (3/8H, s, COCCl_2H), 6.15 (1/8H, s, COCCl_2H),

5.88-5.64 (1H, m, olefinic H), 5.30-5.17 (2H, m, olefinic H), 5.15 (2/8H, s, OC*H*$_2$Ph), 5.13 (4/8H, s, OC*H*$_2$Ph), 5.10 (4/8H, s, OC*H*$_2$Ph), 5.08 (6/8H, s, OC*H*$_2$Ph), 4.41 (2/8H, d, *J*=4.5 Hz, C*H*$_2$CH=NOBn), 4.26 (4/8H, d, *J*=4.5 Hz, C*H*$_2$CH=NOBn), 4.18 (4/8H, d, *J*=5.4 Hz, C*H*$_2$CH=NOBn), 4.10 (6/8H, d, *J*=5.4 Hz , C*H*$_2$CH=NOBn), 4.09-3.97 (2H, m, NC*H*$_2$CH=CH$_2$). ^{13}C-NMR (50 MHz) δ : 164.1, 163.6, 147.0, 146.8, 144.6, 137.2, 136.9, 131.6, 131.4, 131.1, 130.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 118.9, 118.8, 188.5, 76.7, 76.3, 76.0, 65.1, 64.9, 64.6, 64.5, 51.5, 50.1, 49.9, 49.3, 46.1, 45.3, 43.1, 43.0. MS *m/z* (relative intensity) : 318 (7.0), 316 (43.0), 314 (64.0). HRMS *m/z* : Calcd for $C_{14}H_{16}N_2O_2Cl_2$ (M^+) 314.0606. Found : 314.0601.

1-Chloro-6-phenylmethoxy-3-(2-propenyl)-3,6-diazabicyclo[3.1.0]hexan-2-one (3a). Colorless oil. IR ν $_{max}$ cm^{-1} : 1714 (CON). ^{1}H-NMR (300 MHz) δ : 7.38-7.34 (5H, m, ArH), 5.73-5.60 (1H, m, olefinic H), 5.24-5.16 (2H, m, olefinic H), 4.88 (2H, s, OC*H*$_2$Ph), 3.85 (2H, m, NC*H*$_2$CH=CH$_2$), 3.49 (1H, dd, *J*=11.4, 4.2 Hz, 4-H), 3.39 (1H, d, *J*=11.4 Hz, 5-H), 3.27 (1H, d, *J*=4.2 Hz, 4-H). ^{13}C-NMR (50 MHz) δ : 165.0, 135.8, 131.0, 129.0, 128.4, 128.3, 118.7, 76.0, 64.1, 47.1, 46.9, 45.6. MS *m/z* (relative intensity) : 280 (4.0), 278 (12.0). HRMS *m/z* : Calcd for $C_{14}H_{15}N_2O_2Cl$ (M^+) 278.0821. Found : 278.0824.

2,2-Dichloro-*N*-(2-phenylmethoxyiminoethyl)-*N*-phenylmethylacetamide (2b). Colorless oil. Spectral data are collected as a geometrical mixture of the oxime ether group and rotational isomer around the amide group (1 : 1 : 1 : 1). IR ν $_{max}$ cm^{-1} : 1674 (CON). ^{1}H-NMR (300 MHz) δ : 7.39-7.13 (10H + 1/4H + 1/4H, m, ArH + iminoic H), 6.67 (1/4H + 1/4H, dt, *J*=9.9, 4.5 Hz, iminoic H), 6.30 (1/4H, s, COCCl_2H), 6.24 (1/4H, s, COCCl_2H), 6.21 (1/4H, s, COCCl_2H), 6.19 (1/4H, s, COCCl_2H), 5.11 (2/4H, s, OC*H*$_2$Ph), 5.09 (2/4H, s, OC*H*$_2$Ph), 5.06 (2/4H, s, OC*H*$_2$Ph), 5.05 (2/4H, s, OC*H*$_2$Ph), 4.71 (2/4H, s, NC*H*$_2$Ph), 4.64 (2/4H, s, NC*H*$_2$Ph), 4.61 (2/4H, s, NC*H*$_2$Ph), 4.57 (2/4H, s, NC*H*$_2$Ph), 4.35 (2/4H, d, *J*=4.5 Hz, C*H*$_2$CH=NOBn), 4.22 (2/4H, d, *J*=4.5 Hz, C*H*$_2$CH=NOBn), 4.11 (2/4H, d, *J*=5.7 Hz, C*H*$_2$CH=NOBn), 4.07 (2/4H, d, *J*=5.7 Hz, C*H*$_2$CH=NOBn). ^{13}C-NMR (50 MHz) δ : 164.2, 164.0, 144.5, 144.3, 137.2, 136.9, 135.4, 134.6, 129.0, 128.7, 128.4, 128.3, 128.27, 128.2, 128.0, 127.8, 126.7, 76.3, 76.0, 65.1, 64.6, 50.8, 49.6, 45.7, 45.0. MS *m/z* (relative intensity) : 368 (3.0), 366 (17.0), 364 (26.5). HRMS *m/z* : Calcd for $C_{18}H_{18}N_2O_2Cl_2$ (M^+) 364.0744. Found : 364.0741.

1-Chloro-6-phenylmethoxy-3-phenylmethyl-3,6-diazabicyclo[3.1.0]hexan-2-one (3b) Colorless crystals mp 107-108 °C (hexane / AcOEt). IR ν $_{max}$ ($CHCl_3$) cm^{-1} : 1711 (CON). ^{1}H-NMR (300 MHz) δ : 7.39-7.17 (10H, m, ArH), 4.89 (2H, s, OC*H*$_2$Ph), 4.51, 4.30 (2H, ABq, *J*=14.7 Hz, NC*H*$_2$Ph), 3.37 (1H, dd, *J*=11.1, 4.2 Hz, 4-H), 3.27 (1H, d, *J*=11.1 Hz, 5-H), 3.22 (1H, d, *J*=4.2 Hz, 4-H). ^{13}C-NMR (50 MHz) δ : 165.3, 135.8, 134.9, 129.0, 128.8, 128.4, 128.0, 127.9, 76.1, 64.0, 47.1, 47.0, 46.8. MS *m/z* (relative

intensity) : 330 (4.0), 328 (11.5). HRMS *m/z* : Calcd for $C_{18}H_{17}N_2O_2Cl$ (M^+) 328.0978. Found : 328.0973. *Anal*. Calcd for $C_{18}H_{17}N_2O_2Cl$: C, 65.75; H, 5.21; N, 8.52. Found : C, 65.92; H, 5.27; N, 8.48.

2,2,2-Trichloro-*N*-(2-phenylmethoxyiminopropyl)-*N*-phenylmethylacetamide (6) According to the procedure given for **1b**, alkylation of benzylamine (3.3 mL, 30 mmol) with chloroacetone *O*-phenylmethyloxime (1.9 g, 10 mmol) afforded (*E*/*Z*)-1-phenylmethylamino-2-propanone *O*-phenylmethyloxime which without purification was acylated with TCAA (1.8 mL, 10 mmol) to give **6** (1.3 g, 30%) as a colorless oil.

(*E*/*Z*)-1-Phenylmethylamino-2-propanone *O*-Phenylmethyloxime. ^{1}H-NMR (300 MHz) δ : 7.34-7.22 (10H, m, ArH), 5.10 (2H, s, OC*H*$_2$Ph), 3.70 (2H, s, NC*H*$_2$Ph), 3.28 (2H, s, C*H*$_2$C(Me)=NOBn), 1.89 (3H, s, Me).

Spectral data of **6** are collected as a geometrical mixture of the oxime ether group and rotational isomer around the amide group. IR ν $_{max}$ cm^{-1} : 1682 (CON). ^{1}H-NMR (300 MHz) δ : 7.35-7.29 (8H, m, ArH), 7.10 (2H, br m, ArH), 5.07 (2H, br s, OC*H*$_2$Ph), 4.85 (10/8H, br s, NC*H*$_2$Ph), 4.56 (6/8H, br s, NC*H*$_2$Ph), 4.33 (6/8H, br s, C*H*$_2$C(Me)=NOBn), 4.02 (10/8H, br s, C*H*$_2$C(Me)=NOBn), 1.83 (3H, br s, Me). ^{13}C-NMR (50 MHz) δ : 160.9, 151.7, 138.0, 135.4, 134.9, 128.6, 128.2, 128.0, 127.7, 127.1, 92.9, 77.2, 75.7, 52.3, 51.8, 51.1, 49.8, 12.8. MS *m/z* (relative intensity) : 418 (0.3), 416 (2.5), 414 (8.0), 412 (8.0). HRMS *m/z* : Calcd for $C_{19}H_{19}N_2O_2Cl_3$ (M^+) 412.0511. Found : 412.0513.

2,2-Dichloro-*N*-(2-phenylmethoxyiminopropyl)-*N*-phenylmethylacetamide (7) A solution of **6** (165 mg, 0.4 mmol) and DBU (0.18 mL, 1.2 mmol) in MeCN (20 mL) was stirred at rt for 2 days. The reaction mixture was concentrated and the residue was purified by MCC (hexane : AcOEt (5 : 1)) to give **7** (102 mg, 67%) as a colorless oil and starting compound (**6**) (29 mg, 17%). Spectral data of **7** are collected as a geometrical mixture of the oxime ether group and rotational isomer around the amide group (1 : 1). IR ν $_{max}$ cm^{-1} : 1679 (CON). ^{1}H-NMR (300 MHz) δ : 7.34-7.27 (8H, m, ArH), 7.15-7.06 (2H, m, ArH), 6.32 (1/2H, s, COCCl_2H), 6.22 (1/2H, s, COCCl_2H), 5.08 (2/2H, s, OC*H*$_2$Ph), 5.07 (2/2H, s, OC*H*$_2$Ph), 4.56 (2/2H, s, NC*H*$_2$Ph), 4.53 (2/2H, s, NC*H*$_2$Ph), 4.08 (2/2H, s, C*H*$_2$C(Me)=NOBn), 3.98 (2/2H, s, C*H*$_2$C(Me)=NOBn), 1.85 (3/2H, s, Me), 1.77 (3/2H, s, Me). ^{13}C-NMR (50 MHz) δ : 164.6, 164.4, 152.5, 151.6, 138.0, 137.6, 135.7, 134.8, 129.0, 128.7, 128.35, 128.26, 128.0, 127.9, 127.8, 127.7, 126.5, 76.2, 75.7, 65.0, 64.8, 50.4, 50.2, 50.1, 49.1, 12.9, 12.6. MS *m/z* (relative intensity) : 382 (2.0), 380 (12.5), 378 (18.5). HRMS *m/z* : Calcd for $C_{19}H_{20}N_2O_2Cl_2$ (M^+) 378.0900. Found : 378.0906.

***N*-(2-Phenylmethoxyiminoethyl)-*N*-phenylmethylacetamide (8)** Acetylation of (*E*/*Z*)-2-propenylaminoacetaldehyde *O*-phenylmethyloxime (1.3 g, 5 mmol) used for preparation of **1** with

Ac_2O under the usual reaction conditions afforded **8** (1.1 g, 76%) as a colorless oil. Spectral data are collected as a geometrical mixture of the oxime ether group and rotational isomer around the amide group (3 : 4 : 4 : 6). IR ν_{max} cm^{-1} : 1658 (CON). ^{1}H-NMR (300 MHz) δ : 7.42-7.10 (10H + 6/17H + 4/17H, m, ArH + iminoic H), 6.70 (4/17H, t, *J*=4.2 Hz, iminoic H), 6.55 (3/17H, t, *J*=4.2 Hz, iminoic H), 5.08 (6/17H, s, OC*H*$_2$Ph), 5.06 (16/17H, s, OC*H*$_2$Ph), 5.04 (12/17H, s, OC*H*$_2$Ph), 4.59 (6/17H, s, NC*H*$_2$Ph), 4.56 (8/17, s, NC*H*$_2$Ph), 4.50 (8/17H, s, NC*H*$_2$Ph), 4.45 (12/17H, s, NC*H*$_2$Ph), 4.25 (8/17H, d, *J*=4.2 Hz, C*H*$_2$CH=NOBn), 4.13 (6/17H, d, *J*=4.2 Hz, C*H*$_2$CH=NOBn), 4.09 (12/17H, d, *J*=5.7 Hz, C*H*$_2$CH=NOBn), 3.89 (8/17H, d, *J*=5.7 Hz, C*H*$_2$CH=NOBn), 2.17 (12/17H, s, COMe), 2.14 (18/17H, s, COMe), 2.12 (12/17H, s, COMe), 2.09 (9/17H, s, COMe). ^{13}C-NMR (50 MHz) δ : 170.6, 170.5, 170.3, 170.0, 148.3, 147.6, 145.5, 144.7, 137.0, 136.6, 135.7, 128.4, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.33, 127.29, 127.2, 127.0, 126.1, 126.0, 75.9, 75.5, 75.3, 52.4, 50.8, 48.9, 48.0, 46.0, 43.4, 41.6, 21.0, 20.9, 20.8. HRMS *m/z* : Calcd for $C_{18}H_{20}N_2O_2$ (M^+) 296.1524. Found : 296.1530.

Reaction of *N*-(2-Phenylmethoxyiminoethyl)-*N*-phenylmethylacetamide (8) with DBU According to the procedure given for **7**, reaction of **8** (296 mg, 1 mmol) with DBU (0.45 mL, 3 mmol) for 36 days afforded **9** (70 mg, 37%), benzyl alcohol (**4**) (39 mg, 36%), and **8** (140 mg, 47%).

N-Cyanomethyl-*N*-phenylmethylacetamide (**9**). Colorless oil. IR ν_{max} cm^{-1} : 2254 (CN), 1662 (CON). ^{1}H-NMR (200 MHz) δ : 7.41-7.20 (5H, m, ArH), 4.66 (2H, s, NC*H*$_2$Ph), 4.25 (2H, s, C*H*$_2$CH=NOBn), 2.25 (3H, s, NCOMe). ^{13}C-NMR (50 MHz) δ : 170.7, 134.4, 129.3, 129.0, 128.5, 126.8, 115.3, 32.6, 30.9, 21.2. HRMS *m/z* : Calcd for $C_{11}H_{12}N_2O$ (M^+) 188.0949. Found : 188.0947.

***(E/Z)*-2,2-Dichloro-*N*-(2-phenylmethoxyiminoethyl)-*N*-phenylmethylacetamide (2b)** To a solution of (*E/Z*)-2-phenylmethylaminoacetaldehyde *O*-phenylmethyloxime (3.04 g, 12 mmol) and Et_3N (3.3 mL, 24 mmol) in $CHCl_3$ (50 mL) was added dropwise dichloroacetyl chloride (1.27 mL, 13.2 mmol) at 0 °C and then the mixture was stirred at rt for 2 h. Water was added and the mixture was extracted with $CHCl_3$. The extract was dried and concentrated to give a residue which was purified with FCC (hexane : AcOEt (5 : 1)) to afford **2b** (2.2 g, 50%) as colorless oil and as a geometrical mixture of the oxime ether group and rotational isomer around the amide group (1 : 1 : 1 : 1). Further purification by MCC (hexane : AcOEt (7 : 1)) gave *E*- and *Z*-oxime ethers as a single geometrical isomer. Both NMR spectral data were collected as a 1 : 1 mixture of rotational isomer around the amide group.

E-Oxime ether. Colorless oil. IR ν_{max} cm^{-1} : 1682 (CON). ^{1}H-NMR (300 MHz) δ : 7.39-7.13 (10H + 1H, m, ArH + iminoic H), 6.30 (1/2H, s, $COCCl_2H$), 6.21 (1/2H, s, $COCCl_2H$), 5.08 (2/2H, s, OC*H*$_2$Ph), 5.05 (2/2H, s, OC*H*$_2$Ph), 4.64 (2/2H, s, NC*H*$_2$Ph), 4.57 (2/2H, s, NC*H*$_2$Ph), 4.11 (2/2H, d, *J*=5.7 Hz, C*H*$_2$CH=NOBn), 4.07 (2/2H, d, *J*=5.7 Hz, C*H*$_2$CH=NOBn). ^{13}C-NMR (50 MHz) δ : 164.3, 164.1, 146.6,

144.5, 144.4, 137.0, 135.5, 134.7, 129.1, 128.9, 128.8, 128.5, 128.42, 128.37, 128.3, 128.1, 128.0, 126.9, 126.8, 76.8, 76.5, 76.1, 65.2, 65.0, 64.8, 52.5, 50.9, 50.7, 49.7, 45.8, 45.2, 43.1, 42.9.
HRMS *m/z* : Calcd for $C_{18}H_{18}N_2O_2Cl_2$ (M^+) 364.0744. Found : 364.0741.
Z-Oxime ether. Colorless oil. IR ν_{max} cm^{-1} : 1682 (CON). ^{1}H-NMR (300 MHz) δ : 7.39-7.15 (10H, m, ArH), 6.69 (1/2H, t, *J*=4.5 Hz, iminoic H), 6.65 (1/2H, t, *J*=4.5 Hz, iminoic H), 6.24 (1/2H, s, $COCCl_2H$), 6.19 (1/2H, s, $COCCl_2H$), 5.11 (2/2H, s, OC*H*$_2$Ph), 5.06 (2/2H, s, OC*H*$_2$Ph), 4.71 (2/2H, s, NC*H*$_2$Ph), 4.60 (2/2H, s, NC*H*$_2$Ph), 4.35 (2/2H, d, *J*=4.5 Hz, C*H*$_2$CH=NOBn), 4.22 (2/2H, d, *J*=4.5 Hz, C*H*$_2$CH=NOBn). ^{13}C-NMR (50 MHz) δ : 164.4, 164.2, 146.7, 144.5, 144.4, 135.5, 134.7, 129.1, 128.9, 128.8, 128.5, 128.42, 128.38, 128.30, 128.2, 128.1, 128.0, 126.9, 126.8, 76.8, 76.4, 76.1, 65.2, 65.0, 64.8, 52.5, 50.9, 50.7, 49.7, 45.8, 45.2, 43.1. HRMS *m/z* : Calcd for $C_{18}H_{18}N_2O_2Cl_2$ (M^+) 364.0745. Found : 364.0748.

General Procedure for Reaction of Dichloroacetamide (2b) with DBU A solution of *E*- or *Z*-oxime ether (**2b**) (365 mg, 1 mmol) and DBU in MeCN was stirred under the reaction conditions shown in Table 3. After the solution was concentrated, the residue obtained was purified by either FCC, MCC, or PTLC (hexane : AcOEt (3 : 1) to afford aziridine (**3b**), benzyl alcohol (**4**), and starting compound (**2b**) in the yields shown in Tables 3. Both aziridine (**3b**) and benzyl alcohol (**4**) were identical with the respective products obtained from **1b**.

1-Trichloroacetyl-1,2,3,4-tetrahydroquinoline (10) To a solution of 1,2,3,4-tetrahydroquinoline (3.76 mL, 30 mmol) and Et_3N (8.4 mL, 60 mmol) in $CHCl_3$ (60 mL) was added TCAA (8.1 mL, 46 mmol) under a nitrogen atmosphere at 0 °C. The mixture was stirred at rt for 30 h. Water was added and the mixture was extracted with $CHCl_3$. The extract was dried and concentrated to give a solid which was recrystallized with hexane / AcOEt to give colorless needles of **6** (4.57 g, 55%), mp 117-118 °C. IR ν_{max} ($CHCl_3$) cm^{-1} : 1683 (CON). ^{1}H-NMR (200 MHz) δ: 7.72 (1H, d, *J*=7.4 Hz, 8-H), 7.35-7.23 (3H, m, ArH), 4.18 (2H, t, *J*=7.4 Hz, 2-H$_2$), 3.00 (2H, t, *J*=7.4 Hz, 4-H$_2$), 2.24 (2H, quint, *J*=7.4 Hz, 3-H$_2$). ^{13}C-NMR (50 MHz) δ: 159.4, 139.0, 131.0, 129.1, 126.0, 125.8, 125.1, 93.7, 47.5, 25.5, 23.0. MS *m/z* (relative intensity) : 283 (0.9), 281 (8.0), 279 (25.0), 277 (25.5). HRMS *m/z* : Calcd for $C_{11}H_{10}Cl_3NO$ (M^+) 276.9827. Found : 276.9828. *Anal*. Calcd for $C_{11}H_{10}NOCl_3$: C, 47.43; H, 3.62; N, 5.03. Found : C, 47.53; H, 3.63; N, 5.02.

Reaction of 1-Trichloroacetyl-1,2,3,4-tetrahydroquinoline (10) with DBU According to the procedure given for reaction of **1**, reaction of **10** (111 mg, 0.4 mmol) with DBU (0.06 mL, 0.4 mmol) for 24 h afforded **11** (67 mg, 69%) and **10** (7 mg, 6%).

1-Dichloroacetyl-1,2,3,4-tetrahydroquinoline (**11**) Colorless oil. IR ν_{max} cm^{-1} : 2951 (Ar), 1679 (CON). ^{1}H-NMR (200 MHz) δ : 7.24 (4H, br s, ArH), 6.49 (1H, s, $COCCl_2H$), 3.87 (2H, t, *J*=6.6 Hz, 2-H), 2.76 (2H, t, *J*=6.6 Hz, 4-H), 2.03 (2H, quint, *J*=6.6 Hz, 3-H). ^{13}C-NMR (50 MHz) δ : 163.8, 137.4, 129.0, 126.9, 122.9, 64.0, 44.0, 26.2, 23.5. MS *m/z* (relative intensity) : 247 (5.0), 245 (29.0), 243 (44.5). HRMS *m/z* : Calcd for $C_{11}H_{11}NOCl_2$ (M^+) 243.0217. Found : 243.0216.

2-Trichloroacetyl-1,2,3,4-tetrahydroisoquinoline (12) According to the procedure given for **10**, acylation of 1,2,3,4-tetrahydroisoquinoline (3.75 mL, 30 mmol) with TCAA (6.1 mL, 33 mmol) gave colorless crystals of **12** (5.7 g, 69%), mp 69-70 °C (hexane / AcOEt). Spectral data are collected as a geometrical mixture of rotational isomer around the amide group. IR ν_{max} ($CHCl_3$) cm^{-1} : 1673 (CON). ^{1}H-NMR (300 MHz) δ : 7.25-7.11 (4H, m, ArH), 5.10-4.70 (2H, br m, 1-H), 4.20-3.82 (2H, br m, 3-H), 4.20-3.82 (2H, br m, 4-H). ^{13}C-NMR (50 MHz) δ : 159.3, 133.3, 131.8, 128.4, 126.9, 126.5, 126.1, 92.9, 77.2, 49.8, 47.6, 45.4, 28.2. MS *m/z* (relative intensity) : 283 (0.2), 281 (1.5), 279 (5.0), 277 (5.0). *Anal*. Calcd for $C_{11}H_{10}NOCl_3$: C, 47.43; H, 3.62; N, 5.03. Found : C, 47.52; H, 3.53; N, 5.04.

Reaction of 2-Trichloroacetyl-1,2,3,4-tetrahydroisoquinoline (12) with DBU According to the procedure given for reaction of **1**, reaction of **12** (278 mg, 1 mmol) with DBU (0.45 mL, 3 mmol) for 3 days afforded **13**[19] (144 mg, 60%) and **12** (32 mg, 12%).
2-Dichloroacetyl-1,2,3,4-tetrahydroisoquinoline (**13**). Colorless crystals, mp 87-88 °C (hexane / AcOEt) (lit.,[19] 86-87 °C). Spectral data were identical with those of authentic sample. [19]

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REFERENCES

1. P. Renaud and M. P. Sibi "*Radicals in Organic Synthesis*, Vol. 1, 2" Wiley-VCH, Weinheim, **2001**.
2. H. Miyabe, M. Ueda, and T. Naito, *Synlett*, **2004**, 1140.
3. H. Miyabe, M. Ueda, A. Nishimura, and T. Naito, *Tetrahedron*, 2004, **60**, 4227.
4. M. P. Sibi and N. A. Porter, *Acc. Chem. Res*., 1999, **32**, 163.
5. M. Ueda, H. Miyabe, A. Nishimura, O. Miyata, Y. Takemoto, and T. Naito, *Org. Lett*., 2003, **5**, 3835.

6. H. Miyabe, M. Ueda, A. Nishimura, and T. Naito, *Org*. *Lett*., 2002, **4**, 131.
7. H. Miyabe, M. Ueda, and T. Naito, *Chem*. *Commun*., **2000**, 2059.
8. H. Miyabe, M. Ueda, and T. Naito, *J*. *Org*. *Chem*., 2000, **65**, 5043.
9. I. Ryu, N. Sonoda, and D. P. Curran, *Chem. Rev*., 1996, **96**, 177.
10. B. Giese, B. Kopping, T. Gobel, J. Dickhaut, G. Thoma, K. J. Kulicke, and F. Trach, *Org. React*., 1996, **48**, 301.
11. A. G. Giumanini, *Chimia*, 1967, **21**, 464.
12. D. D. Tanner and J. J. Chen, *J*. *Org*. *Chem*., 1989, **54**, 3842.
13. D. C. Dittmer, A. Lombardo, F. H. Batzold, and C. S. Greene, *J*. *Org*. *Chem*., 1976, **41**, 2976.
14. Y. Takeda, O. Tamura, and H. Ishibashi, Abstract papers of 122 Annual Meeting of The Pharmaceutical Society of Japan, **2002**, p83.
15. H. Nagashima, H. Wakamatsu, N. Ozaki, T. Ishii, M. Watanabe, T. Tajima, and K. Itoh, *J*. *Org*. *Chem*., 1992, **57**, 1682.
16. H. Nagashima, N. Ozaki, M. Ishii, K. Seki, M. Washiyama, and K. Itoh, *J*. *Org*. *Chem*., 1993, **58**, 464.
17. J. Boivin, M. Yousfi, and S. Z. Zard, *Tetrahedron Lett*., 1994, **35**, 5629.
18. L. J. Stach, U. S. Patent 3920772, 1975 (*Chem. Abstr*., 1976, **84**, 89603d).
19. A. P. Venkov and L. K. Lukanov, *Synthesis*, **1989**, 59.