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Improved Synthesis of 2-Chlorocyclobutanone Derivatives

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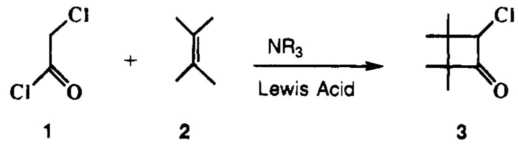
2-Halocyclobutanones are valuable intermediates for the synthesis of cyclopropanecarboxylic acid derivatives, which are useful components for biologically active compounds such as pesticides.[1] Various syntheses of 2-halocyclobutanones have been reported, but most of them were complicated and few were achievable in a single step.[1,2] For example, reductive dehalogenation of 2,2-dichlorocyclobutanones, prepared by the reaction of dichloroketene and olefins, was necessary to give 2-chlorocyclobutanones.[3] The reaction of alkylchloroketene and terminal olefins gave 2-alkyl-2-chlorocyclobutanones, which were subsequently rearranged into 2-alkyl-4-chlorocyclobutanones.[4] The only report of a one-step synthetic procedure was the reaction of α,α-dichloroacetyl chloride and olefins.[5] In this reaction, the generation of chloroketene fom α,α-dichloroacetyl chloride by the reaction with zinc dust was proposed. α-Chloroacetyl chloride has been considered quite useless for the generation of chloroketene, although it is one of the most readily available reagents.[2,5] Chloroketene has been estimated to be very unstable in contrast with rather stable dichloroketene, and its synthetic applications for [2 + 2] cycloaddition with ketenophiles, such as olefins, have been thought to be rather limited.[2,6]

In order to investigate a new synthetic method for preparing 2-halocyclobutanone derivatives, we attempted to generate chloroketene from α-chloroacetyl chloride and allow it to react it with olefins in situ. In this paper, we report an improved synthesis of 2-chlorocyclobutanone derivatives from α-chloroacetyl chloride and olefins (Schemes1 and 2). Some remarkable effects of tertiary amines and Lewis acid catalysts[7,8] on the generation of chloroketene and the formation of 2-chlorocyclobutanones are also described.

Preliminary examinations involved the dropwise addition of 1 equiv of *N*,*N*-dimethylaniline over 1 h at 20 °C under nitrogen to α-chloroacetyl chloride (**1**; 1.0 equiv) and 2,3-dimethyl-2-butene (**2**; 2.0 equiv) in 1,2-dichloroethane. The reaction solution was subsequently stirred at 20 °C for 4 h. None of the expected addition product, 2-chlorocyclobutanone **3**, was produced in the reaction of **1** and **2** in the absence of Lewis acid catalysts. In spite of the presence of excess base, the addition of $ZnCl_2$ proved effective for the activation of chloroketene and led to 16% yield of **3**, which was confirmed by GLC, mass, and ^{1}H-NMR analyses using an authentic sample[6] of **3** for reference. The yield of **3** was increased to 44% when the reaction was carried out at 60 °C, in spite of the instability of chloroketene. This reaction proceeded highly selectively, and no other addition products, such as 1,4-dichloro-3,3,4-trimethylpentan-2-one,[9] were detected by GLC analysis.

Scheme 1



Scheme 2

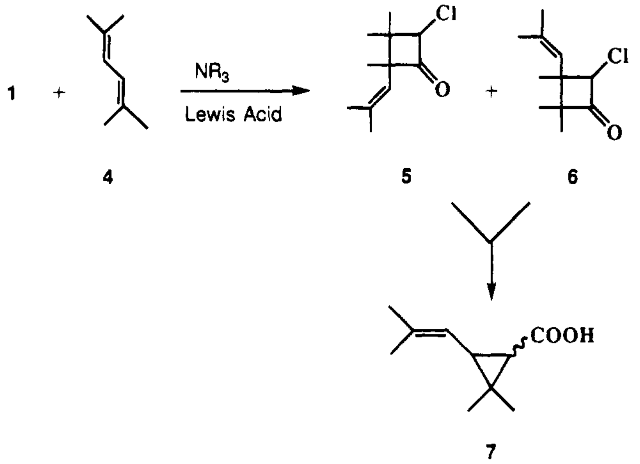


Table 1. Effect of Lewis Acids on Chloroketene Addition Reactions[a] of 1 and 2

entry	Lewis acid	yield of **3**[b] (%)
1	$AlCl_3$	0.9
2	$FeCl_3$	5.6
3	$ZnCl_2$	44.3
4	$ZnBr_2$	56.6
5	$SnCl_4$	52.4
6	$SnBr_4$	78.3

[a] Molar ratio of reagents employed was **1**:**2**:$PhNMe_2$:Lewis acid = 1.0:2.0:1.0:0.5. All reactions were carried out in $ClCH_2CH_2Cl$ at 60 °C for 4 h under N_2 after the addition of $PhNMe_2$ over 1 h. [b] Yields of **3** were determined based on **1** by GLC analysis.

Examination of Lewis acid catalysts (Table 1) suggested that the yield of **3** might be enhanced by suitable combinations of appropriate soft acids and tertiary amines. Hard acids such as $TiCl_4$ and $AlCl_3$ were presumed to be almost inactive because they complex tightly with tertiary amine bases.

The effects of various tertiary amine bases combined with Lewis acid catalysts were also examined (Table 2). The relatively high yield of **3** obtained with triisobutylamine suggests the essential role of a sterically hindered structure in preventing inactivation of the Lewis acid catalysts. Further increases in the yields of **3** were obtained with *N*,*N*-dialkylanilines, especially with *N*,*N*,2,4,6-pentamethylaniline (Table 2). This evidence suggests that soft amine bases and soft Lewis acid

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[9] Prepared according to the procedure reported in: *Chem. Abstr.* **1986**, *106*, 101790v; JP 86229838, 86229839.

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Table 2. Effect of *tert*-Amines on Chloroketene Addition Reactions[a]

entry	NR_3	yield of **3**[b] (%)
1	Et_3N	1.6
2	n-Pr_3N	4.3
3	i-Pr_3N	6.1
4	$allyl_3N$	18.3
5	i-Bu_3N	57.6
6	$PhNMe_2$	56.6
7	$PhNEt_2$	64.0
8	2,4,6-Me_3PhNMe_2	65.6

[a] Molar ratio of reagents employed was **1**:**2**:NR_3:$ZnBr_2$ = 1.0:2.0:1.0:0.5. All reactions were carried out in $ClCH_2CH_2Cl$ at 60 °C for 4 h under N_2 after the addition of NR_3 over 1 h. [b] Yields of **3** were determined based on **1** by GLC analysis.

catalysts enhance yields.[10] 1,8-Bis(dimethylamino)naphthalene (Proton Sponge) was not so effective as a base because of its low solubility in this case.

The best 91.2% yield of **3** was obtained when the reaction was carried out using tin(IV) bromide and *N*,*N*,2,4,6-pentamethylaniline (Table 2). In this reaction, crystalline complex salts[11] precipitated, and the ^{13}C- and ^{15}N-NMR spectra and elemental analysis were consistent with the structure $[Br_4SnCl_2]^{2-}\cdot(2,4,6\text{-}Me_3C_6H_2NMe_2)^+{}_2$.

In a similar reaction using 2,5-dimethylhexa-2,4-diene (**4**) as a ketenophile, mixed cycloaddition products **5** and **6** were obtained instead of **3** in 76.2% yield based on **1** (Scheme 2).[12] By means of the reported method,[3] mixed products **5** and **6** were readily transformed into racemic chrysanthemic acid **7** in 89.3% yield, and the cis- and trans-isomers were isolated by fractional crystallization after vacuum distillation. Their chemical properties were confirmed to be identical with those reported in the literature.[13]

In conclusion, a new and improved synthetic method for 2-chlorocyclobutanone derivatives starting from α-chloroacetyl chloride was found. The reactions of 2,3-dimethyl-2-butene and chloroketene generated in situ by the treatment of α-chloroacetyl chloride with tertiary amines were successfully achieved in the presence of Lewis acid catalysts, which play an important role in activating chloroketene to give 2-chloro-3,3,4,4-tetramethylcyclobutanone in high yields.

Experimental Section

General. All solvents and reagents were obtained from Wako Chemical and used without further purification. ^1H-, ^{13}C-, and ^{15}N-NMR spectra were recorded at 270, 68, and 27 MHz, respectively, using TMS as an internal referance.

Representative Experimental Procedure: 2-Chloro-3,3,4,4-tetramethylcyclobutanone (3). *N*,*N*,2,4,6-Pentamethylaniline (4.90 g, 30 mmol) was added dropwise with stirring to a solution of **1** (1.70 g, 20 mmol), **2** (3.37 g, 40 mmol), and $SnBr_4$ (4.38 g, 10 mmol) in 1,2-dichloroethane (3 mL) over 1 h at 60 °C under N_2 flow, and the reaction solution was stirred at 60 °C for 4 h. After the reaction, insoluble precipitates were filtered and the yield of product **3** was determined to be 91.2% based on **1** by GLC analysis. The solution of **3** was washed with 2 N HCl (aq) solution and water and then concentrated. Crude product **3** was purified by short silica gel column chromatography using an eluant of 2−5% acetone−n-hexane solution, and the oily pure product was isolated in 86.4% yield. Compound **3** seems rather thermally unstable, and considerable decomposition was observed when it was heated over 100 °C; bp 56−59 °C/0.2 Torr.; ^1H-NMR (270 MHz, $CDCl_3$) δ 1.08 (s, 6H), 1.30 (d, $J = 2.4$ Hz, 6H), 4.84 (s, 1H).

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(10) This result seems to relate to the unique reaction using tri-*n*-butylamine with $SnCl_4$ reported by Hirama et al.: Yamaguchi, M.; Hayashi, A.; Hirama, M. *J. Am. Chem. Soc.* **1993**, *115*, 3362.

(11) Slightly yellow powder: mp 227 °C dec; ^1H-NMR (270 MHz, DMSO-d_6) δ 2.25 (s, 3H), 2.51(s, 6H), 3.26(s, 6H), 7.03(s, 2H); ^{13}C-NMR (68 MHz, DMSO-d_6) δ 19.4, 20.0, 45.2, 131.1, 138.5; ^{15}N-NMR (27 MHz, DMSO-d_6) δ 43.7, 46.0. Anal. Calcd for $C_{22}H_{34}N_2SnBr_4Cl_2$: C, 31.5; H, 4.3; N, 3.3; Sn, 14.2; Br, 38.2; Cl, 8.5. Found: C, 31.4; H, 4.3; N, 3.3; Sn, 12.9; Br, 37.5; Cl, 8.2.

(12) The yield was determined by GLC analysis. Products **5** and **6** could not be separated by vacuum distillation.

(13) Bramwell, A. F.; Crombie, L.; Hemesley, P.; Pattendeu, G.; Elliott, M.; Jones, N. F. *Tetrahedron* **1969**, *25*, 1727.