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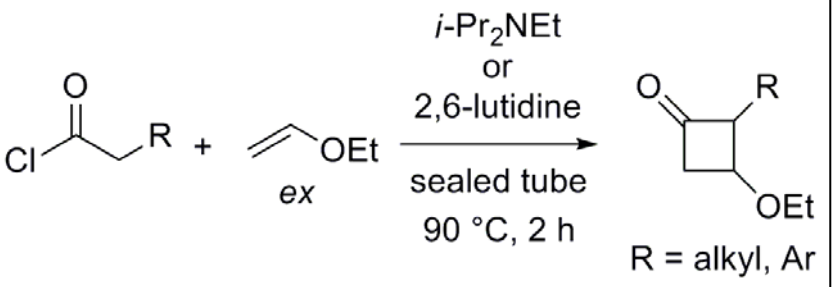

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An efficient procedure for preparation of 2-monoalkyl or 2-monoaryl-3-ethoxycyclobutanones

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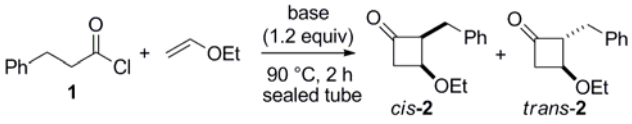
Abstract— Optimized reaction conditions for preparation of various 2-monosubstituted 3-ethoxycyclobutanones are described. 2-Monoalkyl 3-ethoxycyclobutanones were efficiently prepared by the reaction of the corresponding carboxylic acid chlorides and an excess amount of ethyl vinyl ether in the presence of diisopropylethylamine at 90 °C in a sealed tube. 2-Monoaryl 3-ethoxycyclobutanones were prepared by using 2,6-lutidine as a base in the above mentioned procedure.

Cyclobutanones are important and versatile compounds in organic synthesis.[1] Among them, 3-ethoxycyclobutanones have been employed for preparation of bicyclobutanes[2] and silyloxy dienes.[3] We recently found new synthetic utility of 3-ethoxycyclobutanones as a useful building block for synthesis of various types of six-membered cyclic compounds. Thus, Lewis acid activates 2,2-disubstituted 3-ethoxycyclobutanones by cleaving the more substituted C2-C3 bond of the cyclobutanone ring to form a zwitterionic intermediate, which reacts with carbonyl compounds,[4] allylsilanes,[5] or silyl enol ethers[6] to afford the corresponding cyclic compounds. In our investigation of these reactions, we encountered difficulty in preparation of 2-*mono*substituted or non-substituted 3-ethoxycyclobutanones. That is, 3-ethoxy-2-monoalkylcyclobutanones were synthesized in low yields (vide infra) by the conventional procedure of employing the corresponding carboxylic acid chloride, triethylamine, and ethyl vinyl ether (EVE) in refluxing acetonitrile.[7] We report here a widely applicable procedure for preparation of 2-*mono*substituted 3-ethoxycyclobutanones.

The conventional conditions for synthesis of 3-ethoxycyclobutanones by [2 + 2] cycloaddition of ethyl vinyl ether (EVE) and ketene, which was generated in situ from carboxylic acid chloride **1** with triethylamine in refluxing acetonitrile, gave the desired 2-benzyl-3-ethoxycyclobutanone **2** in 7% yield (Table 1, Entry 1). [2 + 2] Cycloaddition using an excess amount (10 equivalents) of EVE without acetonitrile in a sealed tube gave **2** in a slightly improved yield (12% yield, Entry 2). It was thought that an undesired side reaction such as dimerization of ketene via species **4**, which was formed by the addition of triethylamine hydrochloride to reactive monoalkyl ketene **3**,[7a,8] was the reason for low yields of cyclobutanone

Table 1. Optimization of Reaction Conditions

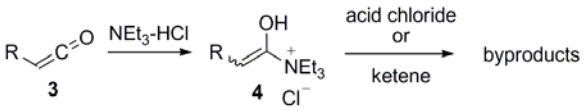


Entry	Base	EVE (equiv)	Yield (%)[a]	cis/trans[b]
1[c]	Et_3N	2	7	10:90
2	Et_3N	10	12	17:83
3	*i*-Pr_2NEt	10	80	62:38
4	Bu_3N	10	31	10:90
5	*i*-Bu_3N	10	trace	—
6	2,6-lutidine	10	36[b]	61:39
7	*i*-Pr_2NEt	5	54	61:39

[a] Isolated yield unless otherwise mentioned.

[b] Determined by ^1H NMR.

[c] The reaction was performed by using acetonitrile as a solvent at reflux under N_2.

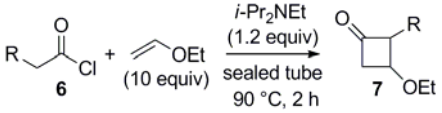


Scheme 1. Undesired formation of reactive intermediate **4**

2 (Scheme 1). Therefore, hindered amines were employed in order not to form **4**. It was then found that diisopropylethylamine was a suitable amine for the cycloaddition reaction, and cyclobutanone **2** was obtained

in 80% yield (Entry 3).[9] Tributylamine, triisobutylamine, and 2,6-lutidine were not effective (Entries 4–6). Decreasing the amount of EVE from 10 to 5 equivalents resulted in decrease in the yield of **2** to 54% (Entry 7). The use of inorganic bases such as K_2CO_3 and Cs_2CO_3 in the presence of a catalytic amount of diisopropylethylamine was not effective. Raising the reaction temperature from 90 °C to 120 °C did not improve the yield of cyclobutanone **2**, and the reaction at 60 °C gave **2** in a trace amount.

Table 2. Synthesis of various 2-monoalkyl 3-ethoxycyclobutanones **7a–i**



Entry	R	7	Yield (%)[a]	cis/trans[b]
1	H	**7a**	37	—
2	Me	**7b**	77	53:47
3	Et	**7c**	78	16:84
4	Pr	**7d**	71	27:73
5	Bu	**7e**	76	30:70
6	Hex	**7f**	77	58:42
7	*i*-Bu	**7g**	77	24:76
8	*i*-Pr	**7h**	50	31:69
9	*t*-Bu	**7i**	48	36:64
			(74)[c]	(54:46)[c]

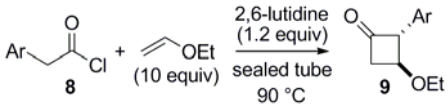
[a] Isolated yield.

[b] Determined by ^{1}H NMR.

[c] Triethylamine was used instead of diisopropylethylamine.

Next, several 2-alkyl-3-ethoxycyclobutanones **7** were prepared by using the corresponding carboxylic acid chloride **6**, diisopropylethylamine and 10 equivalents of EVE in a sealed tube at 90 °C (Table 2). It should be noted that 2-nonsubstituted 3-ethoxycyclobutanone **7a**, which was not obtained by the conventional method of using triethylamine as a base, was obtained in 37% yield (Entry 1).[10] This is a convenient method for preparation of **7a** because a special apparatus (ketene lamp) is not required in the present method. Linear nonbranched ketenes such as methyl ketene, ethyl ketene, propyl ketene, and butyl ketene, which were reported to dimerize easily,[7a] reacted with EVE smoothly to afford the corresponding cyclobutanones in good yields (Entries 2–6). Ketenes bearing a β-blanched alkyl group generated from acid chloride **6g** gave the corresponding cyclobutanone **7g** in 77% yield, whereas α-branched ketenes generated from acid chlorides **6h** and **6i** gave the corresponding cyclobutanones **7h** and **7i** in 48–50% yields (Entries 7–9). In the reaction of **6i**, triethylamine was found to be more suitable than diisopropylethylamine probably because smooth abstraction of the α-proton of **6i** with triethylamine took place, and formation of undesired **4** from *tert*-butyl ketene was difficult due to its steric hindrance.

Table 3. Synthesis of various 2-monoaryl 3-ethoxycyclobutanones **9a–i**



Entry	Ar	9	Yield (%)[a]	cis/trans[b]
1	Ph	**9a**	75 (trace)[c]	11:89
2	*p*-$MeOC_6H_4$	**9b**	74	14:86
3	*p*-MeC_6H_4	**9c**	56	11:89
4	*o*-MeC_6H_4	**9d**	74	6:94
5	*p*-ClC_6H_4	**9e**	56	12:88
6	1-Naph	**9f**	83	7:93
7	2-Naph	**9g**	64	6:94
8	2-Thienyl	**9h**	62	7:93
9	3-Thienyl	**9i**	70	7:93

[a] Isolated yield.

[b] Determined by ^{1}H NMR.

[c] Diisopropylethylamine was used instead of 2,6-lutidine.

Preparation of 2-aryl-3-ethoxycyclobutanones **9** from the corresponding α-aryl carboxylic acid chlorides **8** is shown in Table 3. The use of diisopropylethylamine gave the desired cyclobutanone **9a** in a trace amount, whereas the use of 2,6-lutidine gave **9a** in 75% yield (Entry 1). It was assumed that diisopropylethylamine-mediated formation of phenyl ketene took place too rapidly before cycloaddition with EVE because of increased acidity of the α-proton of carboxylic acid chloride **8a**. Other α-aryl carboxylic acid chlorides **8b–i** also reacted with EVE smoothly in the presence of 2,6-lutidine (Entries 2–9).

In summary, we have developed a convenient method for synthesis of 2-monoalkyl or 2-monoaryl 3-ethoxycyclobutanones by using the corresponding carboxylic acid chlorides and EVE in the presence of sterically hindered amines such as diisopropylethylamine or 2,6-lutidine.[11] Two points are thought to be important for the efficient synthesis of 2-monosubsituted 3-ethoxycyclobutanones from carboxylic acid chloride and EVE. One is smooth generation of ketene at 90 °C, a temperature at which ketene can react readily with EVE. The other is to avoid a reaction between ketene and amine hydrochloride to form intermediate **4**.

Acknowledgments

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9. **Typical Procedure** (Table 1, Entry 3): to a solution of diisopropylethylamine (0.28 mL, 1.64 mmol) and ethyl vinyl ether (1.28 mL, 13.4 mmol) was added 3-phenylpropionyl chloride **1** (0.20 mL, 1.35 mmol) in a sealed tube. The reaction mixture was heated with stirring at 90 °C (bath temperature) for 2 h. After cooling to room temperature, the reaction was quenched with saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate = 30:1 to 8:1) to afford 2-benzyl-3-ethoxycyclobutanone **2** (220 mg, 80%). Characterization data and NMR spectra are shown in the Supplemenrary Data.
10. Preparation of **7a** (10 times scale, Table 2, Entry 1): to a solution of diisopropylethylamine (2.8 mL, 16.4 mmol) and ethyl vinyl ether (13.0 mL, 136 mmol) was added acethyl chloride (0.96 mL, 13.5 mmol) in a sealed tube. The reaction mixture was heated with stirring at 90 °C (bath temperature) for 2 h. After cooling to room temperature, the reaction was quenched with saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (pentane/ether = 8:1) to afford 3-ethoxycyclobutanone **7a** (572 mg, 37%).
11. The present method was not suitable for preparation of 2,2-dialkyl 3-ethoxycyclobutanones. The reaction between isobutyryl chloride and EVE with diisopropylethylamine or triethylamine under the present reaction conditions gave 2,2-dimethyl-3-ethoxycyclobutaone in 8% or 46% yield, respectively.

Supplementary Data

Supplementary data including full characterization of all new cyclobutanones (**2**, **7a–i**, and **9a–i**) and their ^{1}H and ^{13}C NMR spectra are available in online version.