ONE POT REACTION OF UNSTABLE *N*-ACYL QUATERNARY SALT OF THIAZOLES OR IMIDAZOLES WITH SILYL ENOL ETHERS FORMED *IN SITU* [1]

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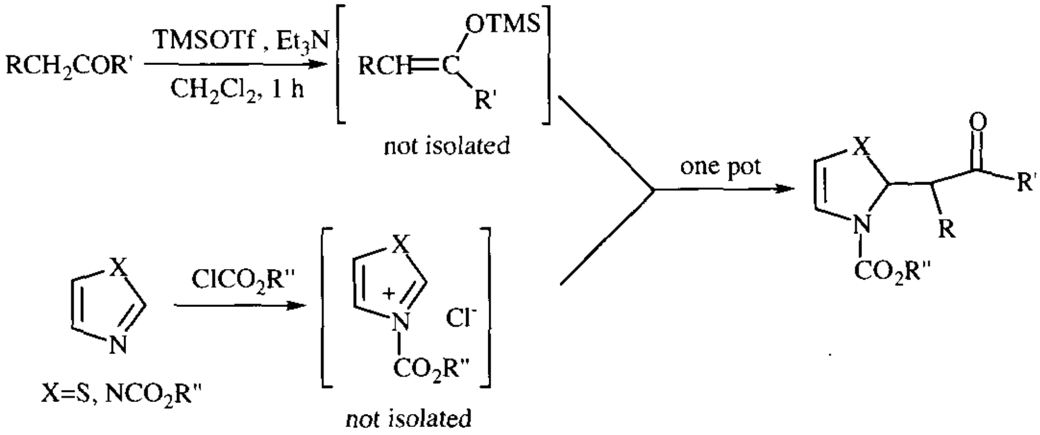
Abstract - Ketone, trimethylsilyl triflate, triethylamine, thiazole or imidazole, and alkyl chloroformate were sequentially added to methylene chloride to form 2-substituted *N*-alkoxycarbonylated thiazoline or imidazoline derivatives in good yields.

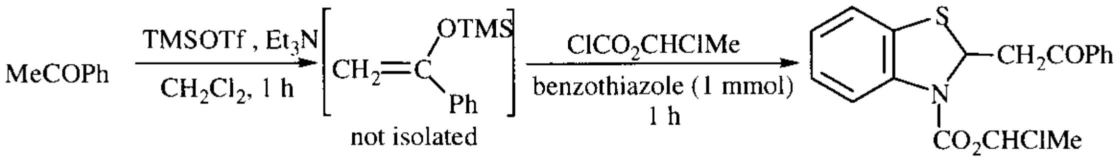
In recent years, we have been interested in the chemistry of *N*-acyl quaternary salts of azaaromatics, and reported that allylstannane[2] and silyl enol ethers[3] are good nucleophiles toward these unstable salts. Therefore, we investigated more versatile method for the preparation of these adducts, and found that silyl enol ether which was prepared *in situ* attack *N*-acyl quaternary salts formed *in situ* to give the adducts. The reaction completed simply by a sequential addition of five commercially available reagents in one pot. This paper describes these results.



Scheme 1

Our previous paper described that silyl enol ether was subjected to the reaction with *N*-acyl quaternary salts of azaaromatics to afford the corresponding *N*-acyl dihydro derivatives in high yields, and the reaction proceeded without any side-products.[3] Thus silyl enol ethers were found to react with the salts with complete chemoselectivity in the presence of parent azaaromatics and alkyl chloroformate. These results suggest that more convenient procedure, that is, the use of silyl enol ethers formed *in situ* also might be possible.

Benzothiazole was selected as a starting material, and the reaction with enolate formed *in situ* was investigated (Table 1). Although the yields of the adduct were low in the cases of excess amounts of acetophenone, use of 1.5 molar amounts of acetophenone, trimethylsilyl triflate (TMSOTf), and triethylamine resulted in the formation of the adduct in a good yield.

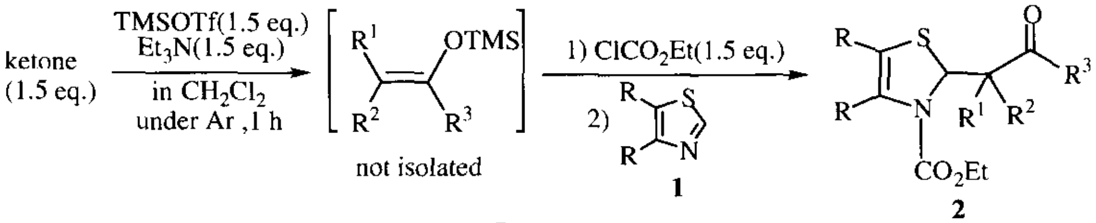


Scheme 2

Table 1. Optimization of Reaction Conditions Using Benzothiazole as a Substrate

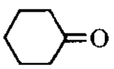
entry	MeCOPh (mmol)	TMSOTf (mmol)	Et_3N (mmol)	$ClCO_2CHClMe$ (mmol)	yield (%)
1	1.5	1.5	1.5	1.5	91
2	2	2	2	1.5	89
3	1.2	1.2	1.2	1.5	74
4	2	1.5	1.5	1.5	40
5	2	1.2	1.2	1.5	32
6	4	2	2	1.5	34

Thus various ketones were used for the reaction, and the results are shown in Scheme 3 and Table 2. In the typical procedure, ketone (0.3 mmol) was dissolved in CH_2Cl_2 (1 mL), and TMSOTf (0.3 mmol) and triethylamine (0.3 mmol) were added successively at room temperature under Ar. The mixture was stirred for 1 h, then ethyl chloroformate (0.3 mmol) and benzothiazole (0.2 mmol) were added to the mixture, which was allowed to react for 30 min to 24 h depending upon the progress of the reaction. Then the solvent was evaporated off to leave a residue, which was chromatographed on silica gel to give the product. All the products were obtained as mixtures of conformational and/or diastereomeric isomers.



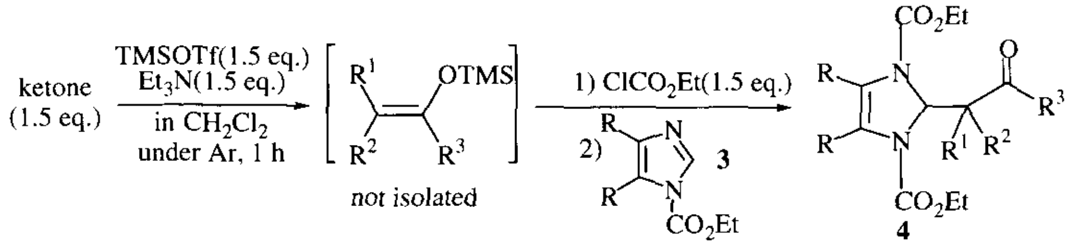
Scheme 3

Table 2. **Reaction of Thiazole and Benzothiazole with Silyl Enol Ethers Prepared *in situ***

entry	ketone	R^1	R^2	R^3	R	conditions	yield of **2** (%)
1	MeCOPh	H	H	Ph	H	rt, 30 min	78
2					-(CH=CH)-	rt, 24 h	91
3		H	$-(CH_2)_4-$		H	rt, 30 min	86
4					-(CH=CH)-	rt, 24 h	96
5	MeCOMe	H	H	Me	H	rt, 30 min	83
6					-(CH=CH)-	rt, 24 h	86
7	EtCOEt	H(Me)	Me(H)	Et	H	rt, 30 min	82
8					-(CH=CH)-	rt, 24 h	89

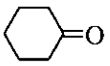
The yields were high in every case, and comparison with the previous data[4a] showed that this system afforded comparable or better yields than those of the isolated silyl enol ethers.

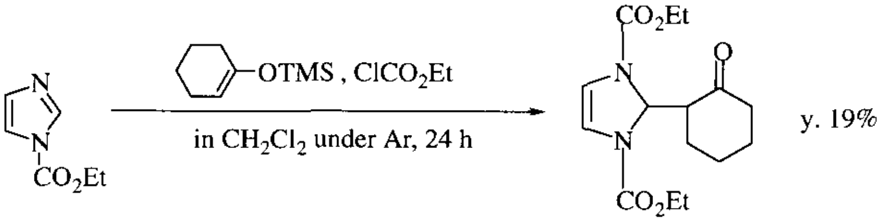
The reaction was applied to imidazole and benzimidazole, and the results are summarized in Scheme 4 and Table 3. In the case of imidazole, a most remarkable difference from the previous system was obtained when cyclohexane silyl enol ether was adopted as a nucleophile (see Scheme 5 and Table 3, entry 3). This fact also revealed that the one pot synthesis is superior to the previous one both from the practical and operational viewpoints. It was reported that triflate ion as a counter anion of *N*-acyl quaternary salts of quinoline increased the electrophilicity of the azaaromatic nucleus.[5] Therfore, the existence of triflate ion in the one pot system might accelerate the addition reaction to afford better results than previous ones.



Scheme 4

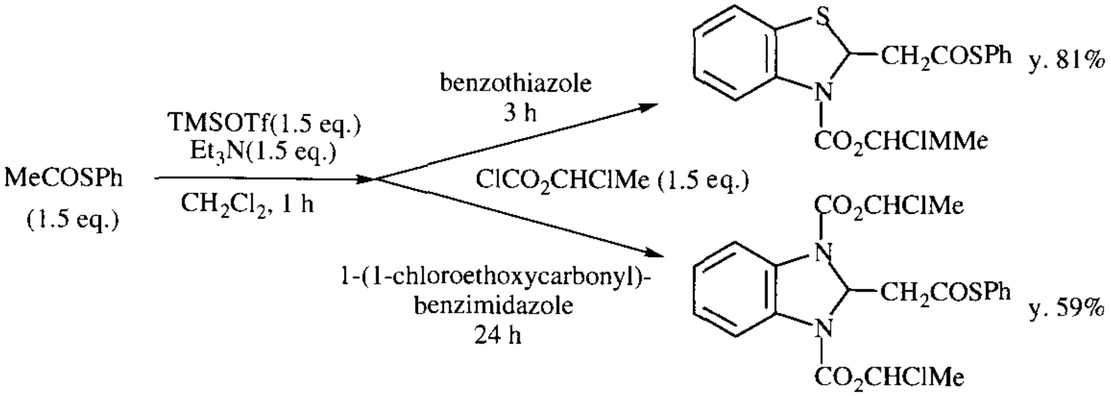
Table 3. Reaction of *N*-Ethoxycarbonyl Imidazole and Benzimidazole with Silyl Enol Ethers Prepared *in situ*

entry	ketone	R^1	R^2	R^3	R	conditions	yield of **4** (%)
1	MeCOPh	H	H	Ph	H	rt, 30 min	94
2					-(CH=CH)-	rt, 24 h	79
3		H	$-(CH_2)_4-$		H	rt, 30 min	86
4					-(CH=CH)-	rt, 24 h	quant.
5	MeCOMe	H	H	Me	H	rt, 12 h	65
6					-(CH=CH)-	rt, 24 h	86
7	EtCOEt	H(Me)	Me(H)	Et	H	rt, 30 min	90
8					-(CH=CH)-	rt, 24 h	93



Scheme 5

The applications of the above methods to esters were failed because α-proton of ester moiety is less acidic than that of ketones. The use of thioester, however, was revealed to be effective in the system to afford the similar adducts shown in Scheme 6. It was reported that α-proton of thioester shows similar reactivity to that of ketones rather than esters.[6]



Scheme 6

In this paper, we described that ketone (or thioester), TMSOTf, triethylamine, thiazole or imidazole, and alkyl chloroformate were sequentially added to methylene chloride to afford 2-substituted *N*-alkoxycarbonylated thiazoline or imidazoline derivatives in quantitative yields. The procedure is quite simple and the isolation and purification of silyl enol ethers can be omitted. The application of the reaction to other heterocycles is under investigation.

REFERENCES AND NOTES

1. This paper is dedicated to the commemorative issue (Vol. 50) of *Heterocycles*.

2. a) T. Itoh, H. Hasegawa, K. Nagata, M. Okada, and A. Ohsawa, *Tetrahedron Lett.*, **1992**, *33*, 5399. b) T. Itoh, H. Hasegawa, K. Nagata, and A. Ohsawa, *J. Org. Chem.*, **1994**, *59*, 1319. c) T. Itoh, H. Hasegawa, K. Nagata, Y. Matsuya, and A. Ohsawa, *Heterocycles*, **1994**, *37*, 709. d) T. Itoh, H. Hasegawa, K. Nagata, M. Okada, and A. Ohsawa, *Tetrahedron*, **1994**, *50*, 13089. e) T. Itoh, H. Hasegawa, K. Nagata, Y. Matsuya, M. Okada, and A. Ohsawa, *Chem. Pharm. Bull.*, **1994**, *42*, 1768.

3. a) T. Itoh, M. Miyazaki, H. Hasegawa, K. Nagata, and A. Ohsawa, *Chem. Commun.*, **1996**, 1217. b) T. Itoh, M. Miyazaki, K. Nagata, and A. Ohsawa, *Heterocycles*, **1997**, *46*, 83. c) T. Itoh, M. Miyazaki, K. Nagata, H. Hasegawa, A. Ohsawa, and K. T. Nakamura, *Heterocycles*, **1998**, *47*, 125.

4. For example, in the cases of isolated acetophenone silyl enol ether as a nucleophile, the adducts were obtained in 55% (thiazole), 90% (benzothiazole), 76% (imidazole), and 74% (benzimidazole) yields, respectively.

5. a) R. Yamaguchi, B. Hatano, T. Nakayasu, and S. Kozima, *Tetrahedron Lett.*, **1997**, *38*, 403. b) R. Yamaguchi, Y. Omoto, M. Miyake, and K. Fujita, *Chem. Lett.*, **1998**, 547.

6. a) C. Gennari, A. Bernardi, S. Cardani, and C. Scolastico, *Tetrahedron Lett.*, **1985**, *26*, 797. b) C. Gennari, M. G. Beretta, A. Bernardi, G. Moro, C. Scolastico, and R. Todeschini, *Tetrahedron*, **1986**, *42*, 893.

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