

Addition of silyl enol ethers to imidazoles and thiazoles in the presence of alkyl chloroformate

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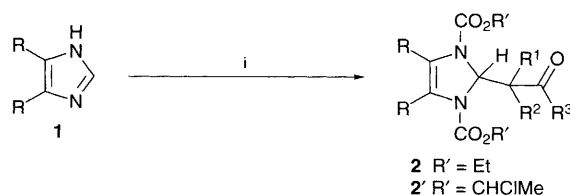
Various kinds of silyl enol ethers and ketene silyl acetals react with imidazole, thiazole and their benzo-derivatives in the presence of an alkyl chloroformate to give 2-substituted imidazolines and thiazolines in good yields.

Recently we have been investigating the reactivity of *N*-alkoxycarbonyl quaternary salts of azaaromatics, and their application to new synthetic methods.¹ Although they are unstable and unisolable, except for the salts of pyridines,² *in situ* trapping by nucleophiles is possible when the reagents used are unreactive to the azaaromatic itself and the alkoxycarbonyl group. By this method, allyl and ethynyl groups were readily introduced into a variety of azaaromatics, using allyltributyltin and bis(tributylstannyl)acetylene as nucleophiles, respectively.³ Other organotin reagents, however, were found to be inert to most azaaromatics.⁴ These results prompted us to search for other nucleophiles which are suitable for this system, and it was revealed that silyl enol ethers and ketene silyl acetals are good nucleophiles that afford dihydro-adducts of imidazoles and thiazoles in excellent yields in the presence of alkyl chloroformate. This paper describes our results.

1,3-di(alkoxycarbonyl)- and 1,3-diacyl-imidazolium salts were reported to be unstable⁵ and the use of their electrophilic reactivities has been limited to a few reports.⁶ However, when imidazoles were treated with alkyl chloroformate (1.2 equiv.) and triethylamine (1.2 equiv.)[‡] followed by the addition of alkyl chloroformate (1.2 equiv.) and silyl enol ether (or ketene silyl acetal) (1.2 equiv.), 1,3-di(alkoxycarbonyl)-2-substituted-4-imidazolines were obtained in good yields§ (Scheme 1, Table 1). The products were obtained as rotational and/or diastereoisomeric isomers in almost all cases, which were observed by ¹H and ¹³C NMR.¶

The reaction system was next applied to thiazole and benzothiazole, as shown in Scheme 2 and Table 2. The reaction proceeded smoothly regardless of the order of adding the reagents, and 2-substituted 4-thiazolines were obtained in high yields.

As shown in Tables 1 and 2, the use of 1-chloroethyl chloroformate made the reaction much faster than with ethyl chloroformate. The yields are good in almost all cases regardless of the R' group of alkyl chloroformate. Thus, the other alkyl chloroformates were found to be also available for the reaction, and the results are shown in Scheme 3, using benzimidazole and methyl trimethylsilyldimethylketene acetal as a typical example.



Scheme 1 Reagents and conditions: i, alkyl chloroformate (1.2 equiv.), triethylamine (1.2 equiv.), MeCN, 0 °C, 10 min, then alkyl chloroformate (1.2 equiv.), a silyl enol ether (1.2 equiv.), 0 °C, 10 min–24 h

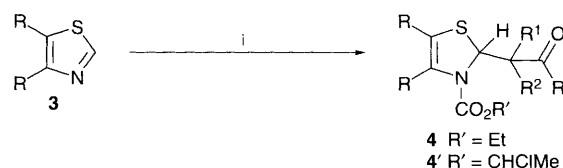
Until now, chemistry of *N*-alkoxycarbonyl quaternary salts were almost limited to that of pyridine derivatives,⁷ and there have been few reports concerning reactions of *N*-alkoxycarbonyl quaternary salts with silyl reagents. Akiba *et al.* reported that pyridinium salts reacted with silyl enol ether at their 4-positions, and that some silyl enol ethers have a tendency to afford the products which do not release the silyl group.⁸ Although this phenomenon was observed when the reaction was performed in CH₂Cl₂, the use of acetonitrile as a solvent circumvented the side reaction.

In conclusion, we have developed a new, versatile method for the synthesis of 2-substituted 4-heteroazoline** in one step. This reaction system seems to have wide application, since it is found to be available for various kinds of silyl reagents and

Table 1 Reaction of imidazole and benzimidazole with silyl enol ethers (or ketene silyl acetals) in the presence of alkyl chloroformate

R	R ¹	R ²	R ³	Conditions ^a	Yield of 2 or 2' (%)
H	Me	Me	OMe	0 °C, 10 min	94 (2)
				0 °C, 10 min	93 (2')
	Me(H)	H(Me)	OMe	0 °C, 2 h	85 (2)
				0 °C, 10 min	85 (2')
	H	–CH=CH–O–		0 °C, 20 min	84 (2) ^b
				0 °C, 20 min	99 (2') ^b
	H	H	Me	0 °C, 1 h	87 (2)
				0 °C, 10 min	75 (2')
	H	H	Ph	0 °C, 2 h	76 (2)
				0 °C, 30 min	87 (2')
–CH=CH–	H	–CH=CH–O–		0 °C, 3 h	29 (2)
				0 °C, 40 min	58 (2')
	Me	Me	OMe	0 °C, rt, 24 h	100 (2)
				0 °C, 1 h	99 (2')
	Me(H)	H(Me)	OMe	0 °C, 2 h	66 (2)
				0 °C, 1 h	97 (2')
	H	–CH=CH–O–		0 °C → rt, 18 h	92 (2) ^b
				0 °C, 1 h	99 (2') ^b
	H	H	Me	0 °C → rt, 18 h	72 (2)
				0 °C, 30 min	96 (2')
H	H	H	Ph	0 °C → rt, 20 h	74 (2)
				0 °C, 30 min	86 (2')
	H	–CH=CH–O–		0 °C → rt, 24 h	82 (2)
				0 °C → rt, 3 h	96 (2')

^a rt = room temp. ^b In the case of 2-trimethylsilyloxyfuran as nucleophile, an addition occurred at its 5-position to give a 2-[5-[2(5*H*)-furanoyl]]-4-imidazoline derivative.

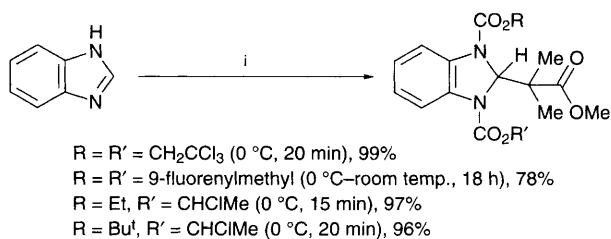


Scheme 2 Reagents and conditions: i, alkyl chloroformate (1.2 equiv.), a silyl enol ether (1.2 equiv.), MeCN, 0 °C, 10 min–24 h

Table 2 Reaction of thiazole and benzothiazole with silyl enol ethers (or ketene silyl acetals) in the presence of alkyl chloroformate

R	R ¹	R ²	R ³	Conditions ^a	Yield of 4 or 4' (%)
H	Me	Me	OMe	0 °C, 30 min	98 (4)
				0 °C, 10 min	94 (4')
	Me(H)	H(Me)	OMe	0 °C, 30 min	96 (4)
				0 °C, 10 min	98 (4')
	H	—CH=CH—O—		0 °C, 1 h	72 (4) ^b
				0 °C, 20 min	89 (4') ^b
	H	H	Me	0 °C, 20 min	70 (4)
				0 °C, 10 min	72 (4')
	H	H	Ph	0 °C, 2 h	55 (4)
				0 °C, 10 min	74 (4')
{CH=CH}	H	{CH ₂ } ₄		0 °C, 2 h	65 (4)
				0 °C, 10 min	90 (4')
	Me	Me	OMe	0 °C → rt, 5 h	92 (4)
				0 °C, 10 min	88 (4')
	Me(H)	H(Me)	OMe	0 °C → rt, 20 h	96 (4)
				0 °C, 20 min	96 (4')
	H	—CH=CH—O—		0 °C → rt, 24 h	98 (4) ^b
				0 °C, 2 h	99 (4') ^b
	H	H	Me	0 °C → rt, 24 h	99 (4)
				0 °C, 30 min	99 (4')
H	H	H	Ph	0 °C → rt, 24 h	90 (4)
				0 °C, 30 min	97 (4')
	H	{CH ₂ } ₄		0 °C, 8 h	96 (4)
				0 °C, 30 min	100 (4')

^a Rt = room temp. ^b In the cases of 2-trimethylsilyloxyfuran as a nucleophile, an addition occurred at its 5-position to give 2-{5-[2(5H)-furanoyl]}-4-thiazoline derivatives.

**Scheme 3** Reagents and conditions: i, as in Scheme 1

alkyl chloroformates. The application of this system to the six-membered azaaromatics, and transformation of the obtained adducts are now in progress.^{††}

Footnotes

[†] On leave from the Central Research Laboratories, SS Pharmaceutical Co. Ltd., Narita (Japan).

[‡] The formation of 1-(1-chloroethoxycarbonyl)imidazole was confirmed by the isolation of the compound at this step. But, the isolation yield was below 50% due to its instability. Therefore, the one-pot process is useful both from the viewpoints of convenience and practice.

§ Simultaneous addition of a substrate, alkyl chloroformate (2.4 equiv.), triethylamine (1.2 equiv.), and a silyl enol ether also afforded the same adduct, but the yields were lowered to 70–80%.

¶ The measurement of NMR at high temperature (65–100 °C) excluded signals derived from rotational isomers.

|| Introduction of a Boc group was performed using di-*tert*-butyl dicarbonate in dioxane, and 1-Boc-benzimidazole was isolated for the next addition reaction in this case.

** Benzoxazole also afforded this type of adducts in good yields.

†† For example, aromatization to 2-substituted imidazole was performed using several adducts. 2,4-Fmoc derivatives and 2-(1-chloroethoxycarbonyl)-4-ethoxycarbonyl derivatives afforded aromatized products in 70–100% yields.

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- 4 It was reported that benzyltributyltin reacts selectively with *N*-alkoxycarbonyl pyridinium salts at the C-4 positions; see: R. Yamaguchi, M. Moriyasu and M. Kawanishi, *Tetrahedron Lett.*, 1986, **27**, 211. Ethyl(tributylstannyl)acetate was shown to be a versatile reagent for the carboethoxymethylation of functionalized pyridines; see T. G. Murali Dhar and C. Gluchowski, *Tetrahedron Lett.*, 1994, **35**, 989. These reagents showed poor reactivity towards other heterocycles such as imidazole, thiazole and pyridazine.
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