REACTION OF PYRIDAZINE AND QUINOLINE WITH SILYL ENOL ETHERS IN THE PRESENCE OF ALKYL CHLOROFORMATE#

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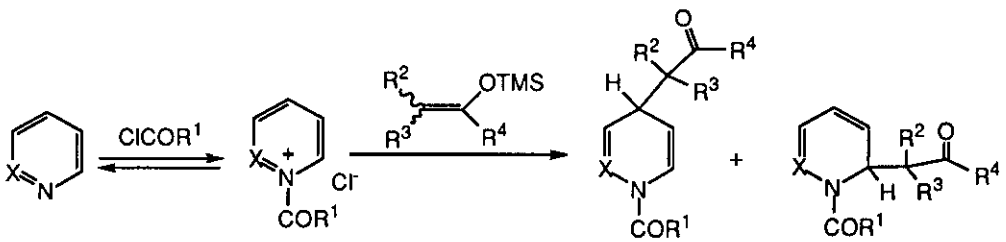
Abstract - Pyridazine was allowed to react with silyl enol ethers (or ketene silyl acetals) in the presence of ethyl chloroformate to give 4- and 6-substituted 1-ethoxycarbonyldihydropyridazines in good yields. The vicinal substituents of silyl enol ethers considerably affected the regioselectivity, and one of the two dihydroadducts was selectively obtained by the use of appropriate silyl enol ethers. Similar substituent effect was observed in the reaction of quinolines under the same conditions.

Silyl enol ethers (or ketene silyl acetals) have been revealed to be versatile nucleophiles toward carbonyl groups in the presence of Lewis acids,[1] and the application to stereoselective syntheses has been extensively investigated.[2] In the cases of azaaromatics, however, silyl enol ethers have been seldom used as nucleophiles because of their selective but low reactivity, and there are few reports concerning the reaction of silyl reagents with azaaromatics.[3]

Akiba *et al.* reported that pyridine ring was activated through quaternization by alkyl chloroformate to react with silyl enol ethers to give 1,4-dihydropyridine derivatives.[4] They also showed that pyrimidine gave complicated products whose formation was rationalized by the intermediary of 1,2,3,4-tetrahydro adducts in the same reaction system.[5]



1 (X=CH) **2** (X=CH) **3** (X=CH) **4** (X=CH)
5 (X=N) **6** (X=N) **7** (X=N) **8** (X=N)

Scheme 1

#This paper is dedicated to the memory of the late Professor Shun-ichi Yamada.

Table 1. The Reaction of the Pyridinium Salt (**2**) with Silyl Enol Ethers

entry	R^1	R^2	R^3	R^4	yield of **3** (%)[a]	yield of **4** (%)[a]
1	OEt	Me	Me	OMe	94	0
2	OEt	Me	H	OMe	74 (87)[b]	7 (0)[b]
3	$OC_{10}H_7$[c]	Me	H	OMe	58	0
4	OEt	H	$\{CH_2\text{-}CH_2\}_2$		42[b]	3[b]
5	$OC_{10}H_7$[c]	H	$\{CH_2\text{-}CH_2\}_2$		65	0
6	OEt	H	H	Ph	69[b]	21[b]
7	$OC_{10}H_7$[c]	H	H	Ph	61	16
8	OEt	H	H	Me	30 (54)[b]	30 (37)[b]
9	OEt	H	H	OMe	66	33
10	OEt	H	H	OPh	41	41
11	OEt	H	H	OBn	49	49
12	OEt	TMS	H	OMe	70 [6]	0

a) Product distribution was determined by ^{1}H-NMR. b) reference 4a. c) β-naphthoxy group.

In the course of our study of *N*-alkoxycarbonyl quaternary salts of azaaromatics,[7] we have been interested in regioselectivity of the reaction. Although the reports claimed the γ(1,4)-selectivity of the reaction, close investigation using various silyl enol ethers showed that the α(1,2 or 1,6)-adducts were formed in considerable yields (Scheme 1(X=CH) and Table 1). Especially, in the cases of R^2=R^3=H, α-adducts were obtained in almost as same yields as those of γ-adducts. A bulky alkoxycarbonyl group only slightly decreased the formation of α-adducts (Table 1, entries 6 and 7). These facts suggest that silyl enol ethers do not always have exclusive γ-selectivity. Upon these results, we investigated the reaction of silyl enol ethers with other six-membered azaaromatics, and found that pyridazine and quinoline react with unsubstituted silyl enol ethers (R^2=R^3=H) to give α-adducts almost exclusively.

The results of the reaction of pyridazine with silyl enol ethers in the presence of alkyl chloroformate are shown in Table 2 (Scheme 1, X=N). In the typical experiment, pyridazine (1 mmol) and a silyl enol ether (1.1 mmol) were dissolved in CH_2Cl_2 (5 mL) and the solution was cooled to 0°C. To the mixture, ethyl chloroformate (1.1 mmol) was added dropwise, and the mixture was allowed to stir at 0°C for 10 min to 2 h. Thereafter, the solvent was evaporated to leave a residue, which was chromatographed on silica gel to give the product. When pyridazine and ethyl chloroformate were treated in the absence of silyl enol ether, corresponding *N*-ethoxycarbonylpyridazinium salt was seldom obtained,[8] and a slow decomposition of pyridazine was observed by TLC. Thus, it is necessary for the nucleophile to trap a trace amount of *N*-alkoxycarbonylpyridazinium salt in the presence of unreacted pyridazine and alkyl chloroformate. And silyl enol ethers are found to be selective nucleophiles toward the salt, which might be formed in a low yield in the reaction mixture. As is in the case of pyridine, a silyl enol ether which has two substituents at vicinal position afforded a 1,4-adduct as a sole product (entry 1). However, the decrease of the substituents changed the reaction site to α-position. In particular, unsubstituted

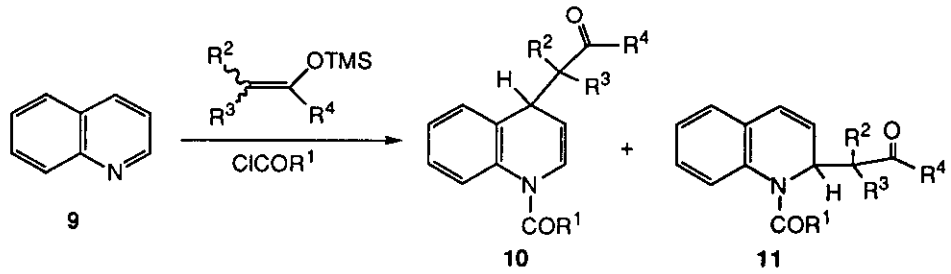
enolates gave α(1,6)-adducts exclusively (Table 2, entries 10-12). Thus, it was revealed that pyridazine afforded 1,4- or 1,6-adducts selectively by the use of appropriate silyl enol ethers.

Table 2 The Reaction of the Pyridazine (**5**) with Silyl Enol Ethers in the Presence of Chloroformate

entry	R^1	R^2	R^3	R^4	yield of **7** (%)[a]	yield of **8** (%)[a]
1	OEt	Me	Me	OMe	89	0
2	OEt	H	-CH=CH-O-[b]		83	13
3	OEt	Me	H	OMe	49	48
4	CH(OAc)Ph	Me	H	OMe	55	22
5	OEt	TMS	H	OMe	31	40
6	OEt	BnO	H	OPh	63	36
7	OEt	H	$-(CH_2-CH_2)_2-$		49	20
8	OEt	H	H	Me	18	72
9	OEt	H	H	Ph	35	54
10	OEt	H	H	OMe	10	70
11	OEt	H	H	OPh	6	78
12	OEt	H	H	OBn	trace	98

a) Product distribution was determined by ^{1}H-NMR. b) In the case where 2-trimethylsilyloxyfuran was used as a nucleophile, addition occurred at its 5-position to give 2,5-dihydro-2-oxo-5-furyl-derivatives.

Next, quinoline was allowed to react in the same reaction system. Although a stable *N*-ethoxycarbonyl quaternary salt was not obtained from quinoline,[9] the reaction proceeded smoothly to give the corresponding dihydro products. In the event, quinoline reacted slowly compared to pyridine and pyridazine, therefore 2 eq. of silyl enol ethers are required for the completion of the reaction within 2 h. The results are shown in Table 3 (Scheme 2).



Scheme 2

It is clearly shown that the regioselectivity is similar to that of pyridazine, but the α-orientation is more distinguishing.[10] Thus, unsubstituted silyl enol ethers afforded 1,2-adducts almost exclusively irrespective of the substituent R^4 (Table 3, entries 6-8). Moreover, the monosubstituted silyl enolates also gave 1,2-adducts dominantly (entries 3, 4).

In this paper, we reported the reaction of pyridazine and quinoline with silyl enol ethers in the presence of alkyl chloroformate. As is different from the reaction with pyridines, silyl enol ethers were revealed to react with pyridazine or quinoline at both α- and γ-positions depending upon the substituents. In particular, unsubstituted enolates tend to attack α-position almost exclusively, which might be useful for the synthesis of 6(or 2)-substituted pyridazines (or quinolines). The oxidation process of these adducts toward aromatization is now under investigation.

Table 3 The Reaction of Quinoline (**9**) with Silyl Enol Ethers in the Presence of Chloroformate

entry	R^1	R^2	R^3	R^4	yield of **10** (%)[a]	yield of **11** (%)[a]
1	OEt	Me	Me	OMe	70	28
2	OPh	Me	Me	OMe	74	26
3	OEt	Me	H	OMe	34 (28)[b]	58 (65)[b]
4	OEt	H	$-(CH_2)_3-$		8	83
5	OEt	TMS	H	OMe	7	66
6	OEt	H	H	Me	4 (5)[b]	95 (87)[b]
7	OEt	H	H	OPh	6	94
8	OEt	H	H	OBn	trace	89

a) Product distribution was determined by ^{1}H-NMR. *b) The data shown in ref. 10 using methyl* chloroformate as an activator.

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6. *[1-Methoxy-2-(trimethylsilyl)-vinyloxy]trimethylsilane was allowed to react under the same* conditions to afford a 1,4-adduct exclusively in 70% yield. The adduct was readily desilylated by treatment with Bu_4NF to afford a product (R^1=R^2=H). Thus, unsubstituted adducts could be prepared regioselectively at γ-position when this type of silyl enolate was used for pyridine.
7. a) T. Itoh, H. Hasegawa, K. Nagata, and A. Ohsawa, *J. Org. Chem.*, **1994**, *59*, 1319. b) T. Itoh, H. Hasegawa, K. Nagata, Y. Matsuya, M. Okada, and A. Ohsawa, *Chem. Pharm. Bull.*, **1994**, *42*, 1768. c) T. Itoh, H. Hasegawa, K. Nagata, M. Okada, and A. Ohsawa, *Tetrahedron*, **1994**, *50*, 13089.
8. The formation of *N*-ethoxycarbonylpyridazinium salt was not confirmed by the ^{1}H-NMR experiment, probably due to the low concentration of it.
9. In this case, ^{1}H-NMR experiment suggested that less than 5% of quinoline was quaternized in the reaction mixture.
10. Akiba *et al.* reported similar results in a communication; see, K. Akiba, T. Kobayashi, and Y. Yamamoto, *Heterocycles*, **1984**, *22*, 1519.

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