ALLYLATION OF *N*-ACYL QUATERNARY SALTS OF AZAAROMATICS WITH ALLYLTRIMETHYLSILANE IN THE PRESENCE OF TRIFLATE ION[1]

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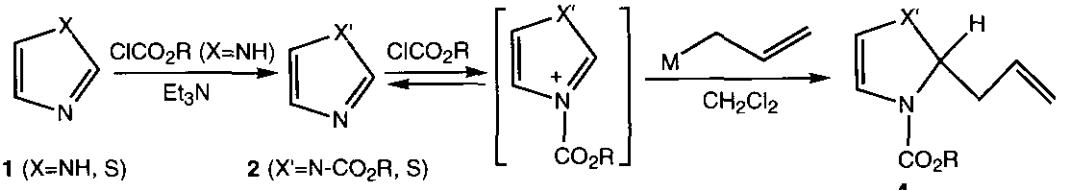
Abstract - Imidazoles and thiazoles were allowed to react with allyltrimethylsilane in the presence of chloroformate and triflate ion to give *N*-acyl 2-allyl adducts in good yields. The same reaction was also proceeded in the cases of pyridazines and phthalazine as substrates.

Allylation is one of the most important organic reactions because of diverse usefulness of allyl functional group, and there are a lot of synthetic methods for this purpose.[2] In the course of our studies on the reaction of unstable *N*-alkoxycarbonyl quaternary salts of azaaromatics, we found that allyltributyltin[3] is a useful reagent for introduction of allyl group toward many heterocycles such as pyridazine, imidazole, thiazole, 1,2,3-triazine, and so on (Scheme 1).[4] Although this process afforded a general method for allylation of azaaromatics, there are two disadvantages in this system that allyltributyltin is highly toxic, and that tributyltin chloride formed by the reaction is difficult to be removed completely from the reaction mixture.[5] Thus a search was made to replace allyltributyltin with other allyl metals. In our reaction system, *N*-alkoxycarbonyl quaternary salts (e.g. **3** in Scheme 1) were formed in low concentration and equilibrium lies so far to the left, thus nucleophiles used here must react only with *N*-alkoxycarbonyl quaternary salts in the presence of excess amounts of parent azaaromatics and chloroformates.[6]



1 (X=NH, S) **2** (X'=N-CO_2R, S) **3** unstable salt **4**

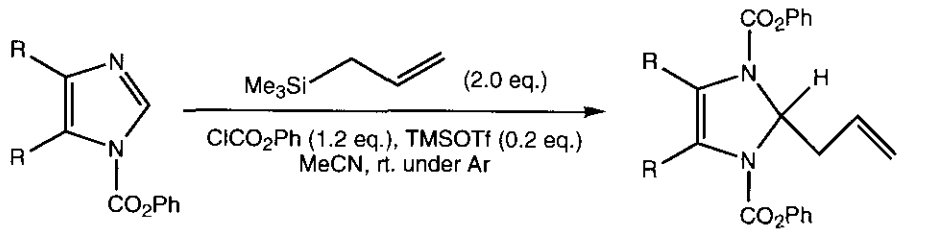
X'=N-CO_2Et, M=$SnBu_3$, R=Et: y 96%
X'=N-CO_2Et, M=$SiMe_3$, R=CHClMe: y 9%
X'=S, M=$SnBu_3$, R=Et: y 61%
X'=S, M=$SiMe_3$, R=Et: y 0%

Scheme 1

Thus various allylation reagents such as allylmagnesium bromide, allyllithium, and allylzinc were revealed to be ineffective to the reaction. Although allyltrimethylsilane does not react with azaaromatics or chloroformate, it gave only low yields of the allyl adducts because of its lower nucleophilicity than that of allyltributyltin (Scheme 1).[7]

In a recent paper,[8] Yamaguchi *et al.* reported that displacement of chloride ion of 1-alkoxycarbonylquinolinium salt to triflate ion increased an electrophilic character of the quinolinium salt. Thus we utilized this method for imidazoles and the reaction yields were improved to reach practical level. This system was applied to thiazole, pyridazine and their benzo derivatives, and the reaction also proceeded smoothly, though the cause of the acceleration was varied with respect to the reported one.[8] This paper describes these results.

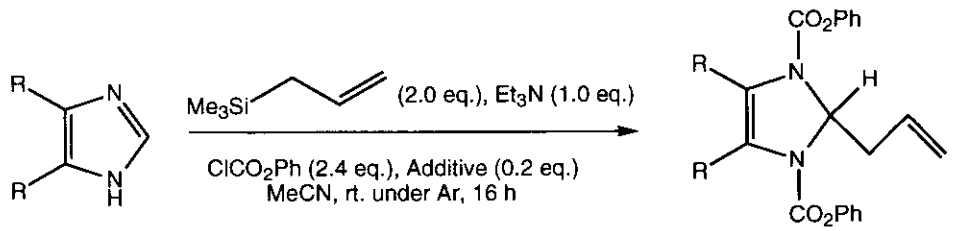
1-Phenoxycarbonylimidazole and its benzo derivative (**5**) were allowed to react with allyltrimethylsilane and phenyl chloroformate in the presence of 0.2 equiv of trimethylsilyl triflate (TMSOTf) to give 2-allyl-1,3-di(phenoxycarbonyl)-4,5-imidazolines in quantitative yields (Scheme 2).



5 **6** R=H: y 99%
R= -CH=CH-: y 98%

Scheme 2

Parent imidazole and benzimidazole also afforded the adducts in the presence of 2 equiv of phenyl chloroformate and 1 equiv of triethylamine (Scheme 3). In the typical experiment, imidazole (1 mmol) was dissolved in MeCN (10 mL) and the air was replaced with Ar. To the solution were added allyltrimethylsilane (2 mmol), triethylamine (1 mmol), TMSOTf (0.2 mmol), and phenyl chloroformate (2.4 mmol) successively at room temperature, and the mixture was allowed to react for 16 h. Then aqueous sodium bicarbonate solution (5 mL) and CH_2Cl_2 (10 mL) were added and the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (10 mL x 2), and the organic layer was combined and dried over $MgSO_4$, and evaporated off to leave a residue, which was chromatographed on silica gel (hexane-ether) to give the product. Instead of TMSOTf, use of tetrabutylammonium triflate resulted in a lowering of the yield (Table 1, entry 2), probably because the ineffective exchange of the counter anion of quaternary salts, and tetrabutylammonium perchlorate gave less yield of the product although quinolinium salts were activated by the anion.[8]



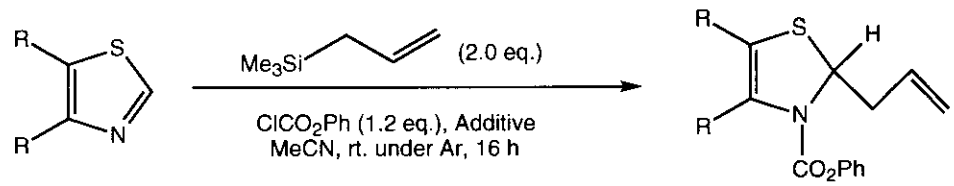
1 **6**

Scheme 3

Table 1

entry	R	Additive	yield (%)of **6**
1	H	TMSOTf	93
2	H	nBu_4NOTf	63
3	H	nBu_4NClO_4	45
4	H	-	trace
5	-CH=CH-	TMSOTf	97

Although benzothiazole also reacted by the use of a catalytic amount of TMSOTf to give corresponding allyl adduct in a good yield (Scheme 4 and Table 2, entry 4), the reaction did not proceed smoothly when thiazole was a substrate. The use of an equimolar amount of *t*-butyldimethylsilyl triflate (TBDMSOTf) improved the reaction yield to a moderate one (Table 2, entry 3).



7 **8**

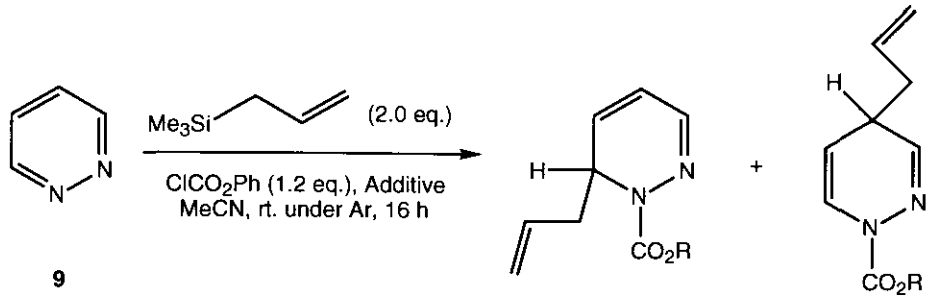
Scheme 4

Table 2

entry	R	Additive	yield of **8** (%)
1	H	TMSOTf (0.2 eq.)	38
2	H	TMSOTf (1.0 eq.)	50
3	H	TBDMSOTf (1.0 eq.)	68
4	-CH=CH-	TMSOTf (0.2 eq.)	99

In the case of pyridazine, the use of a catalytic amount of TMSOTf resulted in a complicated mixture of products, and the equimolar TBDMSOTf was necessary for quantitative formation of the product. The adducts included both 1,6- and 1,4-isomers, and the former was obtained dominantly as same as in the case

of allyltributyltin. Thus, allylsilane was revealed to act as a hard nucleophile. Phthalazine gave a quantitative yield of the 1,2-adduct in the presence of 0.2 equiv of TMSOTf.



9 **10** **11**

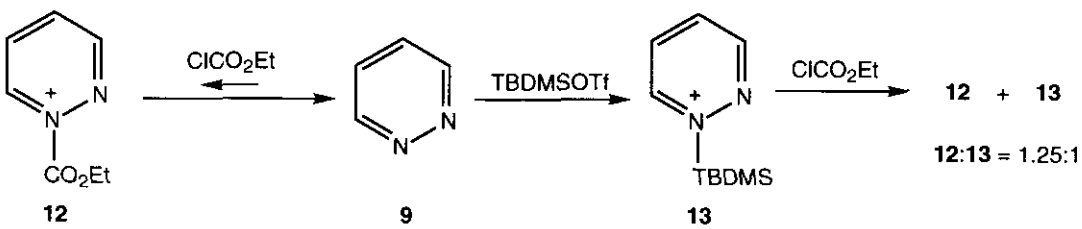
Scheme 5

Table 3

entry	Additive	R	yield of **10** (%)	yield of **11** (%)
1	TMSOTf (0.2 eq.)	Ph	- [a]	- [a]
2	TBDMSOTf (1.0 eq.)	Ph	90	9
3	TBDMSOTf (1.0 eq.)	Et	82	7

a) A complicated mixture of products was obtained.

In order to study the reaction mechanism, ^{1}H-NMR spectra were recorded for the samples described below. In the case of pyridazine (Scheme 6), the formation of an *N*-acylquaternary salt (**12**) was not observed by mixing of the substrate and ethyl chloroformate, while a mixture of **9** and TBDMSOTf showed new signals which were shifted downfield with respect to those of pyridazine.[9] These signals were supposed to be derived from *N*-silyl quaternary salt (**13**). When pyridazine, ethyl chloroformate, and TBDMSOTf were mixed, new downfield signals appeared other than those of **13**, and these were thought to be attributed to **12** (**12**:**13**= 1.3 : 1).[10] From these results, it was suggested that the TBDMSOTf promoted the formation of **12**, and also stabilized it. For parent thiazole, a similar process was observed by ^{1}H-NMR,[11] and the ratio of the TBDMS salt and the ethoxycarbonyl salt was 1 : 2.3.[12]



12 **9** **13**

Scheme 6

In this paper, we described that allylsilane was a versatile nucleophile toward *N*-alkoxycarbonyl quaternary salts of azaaromatics in the presence of triflate ion. Triflate ion was revealed to function as both a promoter of quaternary salts formation and a stabilizer of them. The application of the reaction system to other azaaromatics is now under investigation.

REFERENCES AND NOTES

1. This paper is dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday.
2. Y. Yamamoto and N. Asao, *Chem. Rev.*, **1993**, *93*, 2207, and references cited therein.
3. M. Pereyre, J. Quintard, and A. Rahm, "Tin in Organic Synthesis", Butterworth, London, 1987, pp. 185-258.
4. 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.
5. Although tributyltin chloride formed by the reaction was removed by the use of KF, it was difficult to perform a complete elimination of it from the reaction mixture.
6. Only when pyridines were used as substrates, corresponding *N*-acyl quaternary salts were formed dominantly in the reaction mixture, and the salts were used for the substrates of various nucleophiles. See, D. L. Comins and S. O'Conner, "Advances in Heterocyclic Chemistry", ed. by A. R. Katritzky, Academic Press, San Diego, 1992, Vol. 44, p. 199.
7. G. Hagen and H. Mayr, *J. Am. Chem. Soc.*, **1991**, *113*, 4954.
8. R. Yamaguchi, B. Hatano, T. Nakayasu, and S. Kozima, *Tetrahedron Lett.*, **1997**, *38*, 403.
9. The ^{1}H-NMR signals which were supposed to be derived from *N*-(*t*-butyldimethylsilyl)pyridazinium salt **13** were as follows (the data of pyridazine nucleus); (CD_3CN) δ: 8.32 (2H, br s), 9.45 (2H, br s).
10. The ^{1}H-NMR signals which were supposed to be derived from *N*-(ethoxycarbonyl)pyridazinium salt **12** were as follows (the data of pyridazine nucleus); (CD_3CN) δ: 8.70 (2H, br s), 9.54 (1H, br s), 10.19 (1H, br s).
11. The ^{1}H-NMR signals of *N*-(*t*-butyldimethylsilyl)thiazolium salt were as follows (the data of thiazole nucleus); (CD_3CN) δ: 7.96 (1H, br s), 8.18 (1H, dd, *J*=3.6, 0.9 Hz), 9.64 (1H, br s). The ^{1}H-NMR signals derived from *N*-(ethoxycarbonyl)thiazolium salt were as follows (the data of thiazole nucleus); (CD_3CN) δ: 8.28 (1H, br s), 8.63 (1H, br s), 10.51 (1H, br s).
12. In the case of imidazole, a mixture of equimolar amounts of 1-(ethoxycarbonyl)imidazole and ethyl chloroformate showed ^{1}H-NMR signals in which 4-H and 5-H was not equivalent, and two different ethyl groups appeared. The structure which has this spectrum could not be rationally speculated. When TBDMSOTf was added to this system, a simple spectrum was observed which was attributed to 1,3-di(ethoxycarbonyl)imidazolium salt.

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