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REGIOSELECTIVE SYNTHESIS OF 4-(2-OXOALKYL)PYRIDINES VIA 1, 4-DIHYDROPYRIDINE DERIVATIVES USING SILYL ENOL ETHERS AND PYRIDINIUM SALTS

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Abstract : Trimethylsilyl enol ethers (1) reacted with 1-ethoxycarbonylpyridinium chloride (3) at 4-position with high regioselectivity to afford 1-ethoxycarbonyl-4-(2-oxoalkyl)-1, 4-dihydropyridines (4) in 42 - 87% yields. When 2, 2, 2-trichloroethyl chloroformate was employed, yields of the corresponding 1, 4-dihydropyridines (8) were higher (80 - 100% yields). 4 and 8 were oxidized by oxygen or $AgNO_3$ to give 4-(2-oxoalkyl)pyridines (12 : 30 - 65%).

Considerable efforts have been paid to introduce substituents into 4-position of pyridine regioselectively, and recently successful and easily applicable methods were reported on introduction of alkyl or aryl substituents by several groups such as Akiba,$^{1)}$ Piers,$^{2)}$ Katritzky,$^{3)}$ and Comins.$^{4)}$ In relation to this subject, we next tried to introduce 2-oxoalkyl group into 4-position of pyridine. Doering et al.,$^{5)}$ Sheinkman et al.,$^{6)}$ and Katritzky et al.$^{3b)}$ have reported some methods on the same project, but these attempts should be improved essentially because the reaction conditions are drastic and the yields are low,$^{5,6)}$ or because specially prepared pyridiniopyridone is employed as a starting material.$^{3b)}$ In this communication we wish to report a regioselective reaction of trimethyl- and t-butyldimethylsilyl enol ethers (1 and 2) at 4-position of ethoxycarbonyl- or 2, 2, 2-trichloroethoxycarbonylpyridinium chlorides (3 and 7) as shown in the scheme.

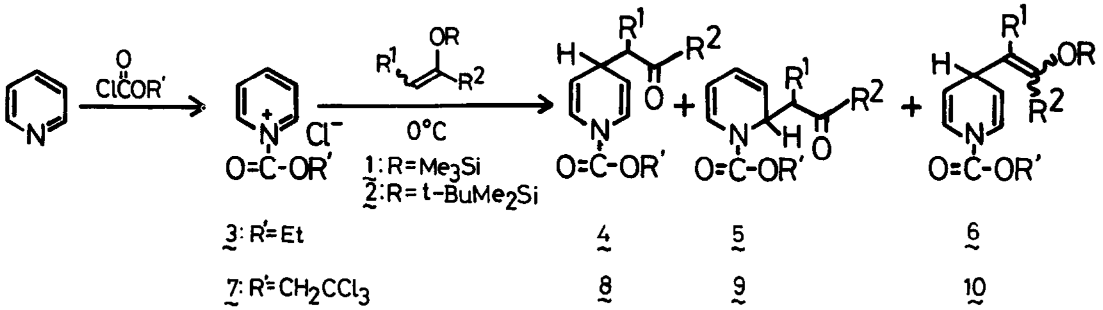
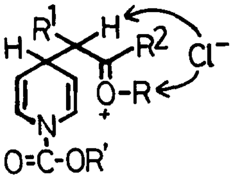


Table I Yields of Dihydropyridine Derivatives Using Ethyl Chloroformate

	R	R^1	R^2	Reaction Time (h)	Yield (%)i) **4**ii)	**5**ii)	**6**ii)
a	Me_3Si	Me	OMe	0.5	87	0	0
b	Me_3Si	Ph	OMe	0.5	86	0	0
c	Me_3Si	Me	Ph	10	51	0	0
d	Me_3Si	Me	Et	10	67	0	0
e	Me_3Si	$-(CH_2)_4-$		9	42	3iii)	17
f	Me_3Si	$PhCH_2$	H		no reaction		
g	Me_3Si	H	Me	4	54	37	0
h	Me_3Si	H	Ph	5	69	21	0
i	$t\text{-}BuMe_2Si$	H	Ph	8	11	6	71

i) Isolated yield by flash column chromatography (hexane : AcOEt = 9 : 1) or Kugelrohr distillation. Product distribution (**4** : **5**) was determined by ^1H NMR. ii) Satisfactory IR, ^1H NMR, MS data were obtained for these compounds. iii) A mixture of diastereoisomers. The ratio could not be determined because of difficulty in their quantitative separation by flash column chromatography and instability of the products under the conditions of GC analysis. iv) Each reaction was carried out by using the pyridinium salt (3 - 5 mmol) and the molar ratio of silyl enol ether to the salt was 1.1 - 1.2.

Silyl enol ethers (**1** and **2**) were allowed to react with **3** in CH_2Cl_2 at 0 °C under nitrogen and some of the results are shown in Table I. As is evident from the Table, ketene silyl acetals (**1a** and **1b**) reacted with **3** to afford the corresponding 1,4-dihydropyridine derivatives (**4a** and **4b**) in good yields. Similarly, trimethylsilyl enol ethers of ketones (**1c** and **1d**) led to **4c** and **4d**, respectively, but in somewhat lower yield. When **1e** was employed, **4e** was obtained in 42% yield accompanied with the corresponding 1,2-dihydropyridine derivative (**5e**, 3%) and trimethylsilyl enol ether of **4e** (**6e**, 17%). On the other hand, when trimethylsilyl enol ether of β-phenylpropionaldehyde (**1f**) was used, the desired product was not obtained at all and **1f** was recovered under the conditions probably due to low nucleophilicity of **1f**. The reaction of **1g** and **1h** (R^1 = H in **1**) with **3** gave 1,2- and 1,4-dihydropyridine derivatives as a mixture. Then, in order to obtain 4-(2-oxoalkyl)-1,4-dihydropyridine derivatives (**4**) regioselectively in case of silyl enol ethers prepared from acetone and acetophenone, we examined the reaction utilizing a bulky silyl enol ether, i.e., t-butyldimethylsilyl enol ether (**2**). However, to our great surprise, when **2i** was reacted with **3**, t-butyldimethylsilyl enol ether of **4i** (**6i**) was obtained in 71% yield accompanied with 4i (11%) and 5i (6%). From these results, we speculated that the oxonium salt (11) is a possible intermediate, and that the chloride ion attacked the proton predominantly rather than bulky t-butyldimethylsilyl group, but the chloride ion attacked trimethylsilyl group of 11a predominantly to give 4 in the reaction using trimethylsilyl enol ether. This rationalization is supported by the literature that the reaction of t-butyldimethylsilyl chloride with nucleophiles is slower by 10^4 times than that of trimethylsilyl chloride.[7)]

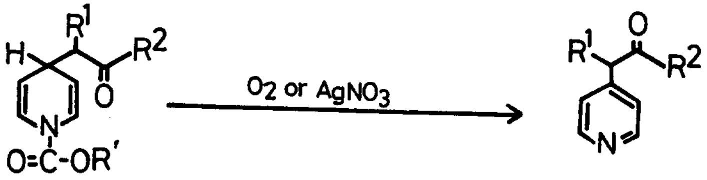


11a : R = Me_3Si-

11b : R = t-$BuMe_2Si$-

In the next, we tried the reaction using 2, 2, 2-trichloroethyl chloroformate instead of ethyl chloroformate expecting to increase the yield of 1, 4-dihydropyridine derivatives. As a result, 1-(2, 2, 2-trichloroethoxycarbonyl)-4-(2-oxoalkyl)-1, 4-dihydropyridines (8) were obtained in high yields (8b - d ; 83 - 100%) and the corresponding 9 and 10 were not detected. Acetonitrile was employed as a solvent due to higher solubility of 7 than that in dichloromethane. When 1h was allowed to react with 7, 8h was obtained in 65% yield accompanied with 9h (22%) and 10h (4%). However, when 2i was employed, t-butyldimethylsilyl enol ether of 8i (10i) was obtained quantitatively. 10i could be converted to the corresponding ketone (8h ≡ 8i) in 86% yield by treating with tetrabutylammonium fluoride. Accordingly, it was established that 8 could be obtained in high yield and selectivity utilizing various silyl enol ethers.

The final stage of the synthesis of 4-(2-oxoalkyl)pyridines (12) is oxidation of 4 and 8. When 4 and 8 were allowed to stirr under a stream of oxygen in a similar manner as 4-alkyl-1, 4-dihydropyridine derivatives,[1b, 1c)] the reaction was too slow and the yields were unsatisfactory. However, the oxidation of 4d by use of $AgNO_3$ in THF for 3 h afforded the corresponding pyridine derivative (12d : R^1 = Me, R^2 = Et) in 65% yield as shown in Table II. Unfortunately, in case of 8, 12 was not obtained at all by $AgNO_3$ and a complicated mixture was obtained.



4: R'=Et

8: R'=CH_2CCl_3

12

Table II Yields of 4-(2-Oxoalkyl)pyridines (12)[i]

R'		R^1	R^2	[O]	Solvent	Reaction Time	Yield[ii](%)
CH_2CCl_3	c	Me	Ph	O_2	CH_2Cl_2	7 day	40
CH_2CCl_3	e	-(CH_2)$_4$-		O_2	CH_2Cl_2	1 day	24
CH_2CCl_3	h	H	Ph	O_2	CH_2Cl_2	7 day	32
Et	a	Me	OMe	O_2	neat	7 day	41
CH_2CCl_3	d	Me	Et	O_2	neat	5 day	38
Et	d	Me	Et	$AgNO_3$	THF	3 h	65

i) Satisfactory IR, ^{1}H NMR, MS, and elemental analyses (or high resolution MS) data were obtained for these compounds. ii) Isolated yield by flash column chromatography or Kugelrohr distillation.

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