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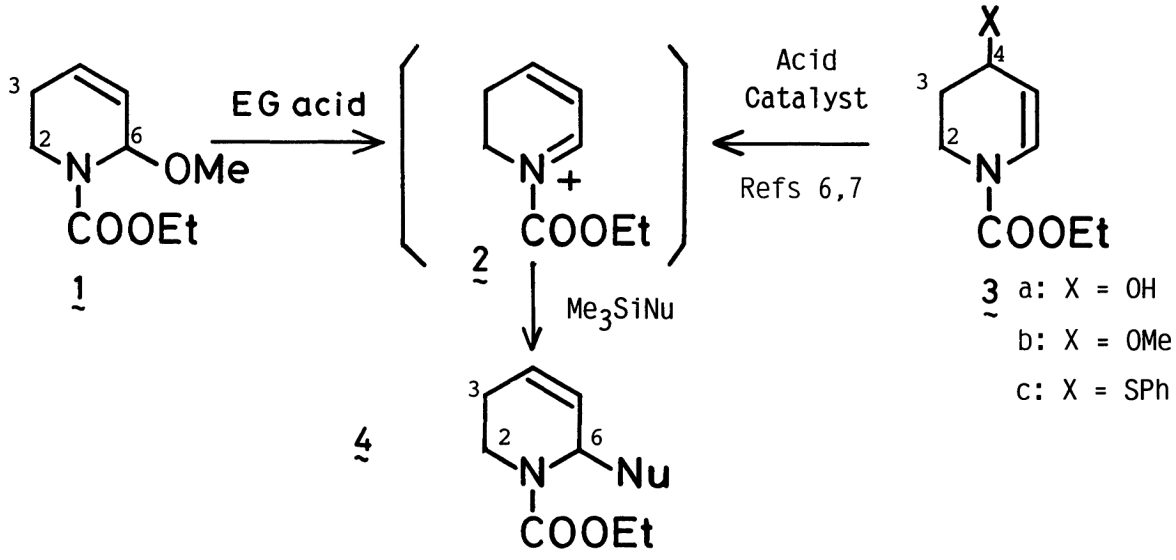
Regioselective Alkylation of Vinylogous N-Acyliminium Ion, Leading to 6-Alkyl-1,2,3,6-tetrahydropyridines, by Using Electrogenerated Acid (EG acid) as a Catalyst†

Sigeru TORII,* Tsutomu INOKUCHI, Sadahito TAKAGISHI, Fumihiko AKAHOSHI, and Kenji UNEYAMA
Department of Industrial Chemistry, School of Engineering, Okayama University, Tsushima, Okayama 700

Alkylation of 6-methoxy-1,2,3,6-tetrahydro- and 4-methoxy-1,2,3,4-tetrahydropyridines with organo-silicon compounds as a carbon nucleophile by using electrogenerated acid as an acid catalyst proceeds regioselectively at the C-6 position via vinylogous acyliminium ion, while sulfenylation and methoxylation occurs at the C-4 position.

6-Alkyl-1,2,3,6-tetrahydropyridine ring is embodied in a large number of piperidine alkaloids such as streptazolin,[1] palustrine,[2] sedinine,[3] and so on.[4] Among various approaches leading to this kind of skeleton, regioselective addition of carbon nucleophile to N-acyliminium ion is currently of synthetic interest.[5] Recently, Kozikowski[6] and Comins[7] have shown the generation of vinylogous N-acyliminium ion **2** from 4-hydroxyenecarbamate **3a** and have succeeded in the regioselective alkylation at the C-6 position. However, these reactions have been achieved with a stoichiometric amount of acids such as $SnCl_4$, $TiCl_4$, $BF_3{\cdot}Et_2O$, and Me_3SiOTf. In seeking a versatile and direct route to **4**, the

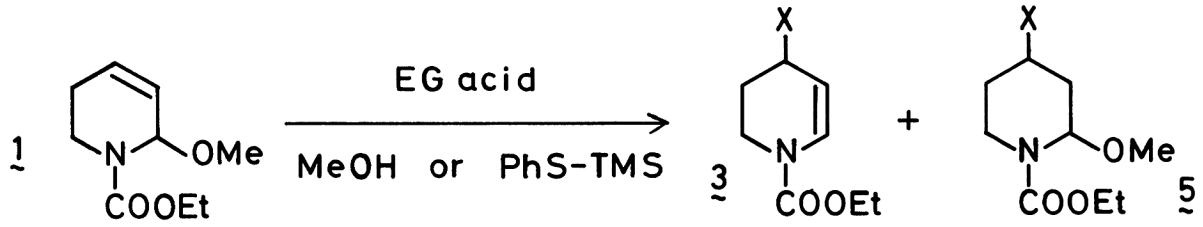


† Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.

generation of **2**[8] from 6-methoxy-1,2,3,6-tetrahydropyridine **1** is an attractive alternative in terms of easy availability of **1** from simple piperidines.[9] In this paper, we report the regioselective alkylation of **1** with organo-silicon compounds bearing a nucleophilic site to give **4**, exclusively, by using electrogenerated acid (EG acid) as an acid catalyst.[10]

The starting compounds **1** and **6** were prepared in 70-80% yield from N-ethoxycarbonyl-2,3-dehydropiperidines by (1) electrochemical halomethoxylation and (2) dehydrohalogenation with 1,3-diazabicyclo[5.4.0]undec-7-ene.[9] The EG acid catalyzed alkylations of **1** were carried out as follows. To the electrolysis vessel was placed $LiClO_4$ (5.3 mg, 0.05 mmol) and Bu_4NClO_4 (17 mg, 0.05 mmol) and these stuffs were dried at 120-150 °C under a reduced pressure. To this mixture was added a solution of N,O-acetal **1** (93 mg, 0.5 mmol) and allyltrimethylsilane (86 mg, 0.75 mmol) in CH_2Cl_2 (3 ml) and then the vessel was equipped with two platinum foil electrodes (1.5 cm^2). The entire mixture was electrolyzed under a constant applied voltage of 15 V (current: 10 mA) at room temperature. Progress of the reaction was monitored by TLC (SiO_2, hexane:AcOEt 3:1) and the reaction was quenched with Et_3N (3 drops) when the starting material **1** was completely consumed (it required 0.19 F/mol of electricity). The volatiles were removed on a rotary evaporator and the residue was purified by column chromatography (SiO_2, hexane:AcOEt 20:1) to give 71 mg (73%) of the desired **4a** (R_f 0.6) and 17 mg (18%) of the enamide **3b** (R_f 0.4).

Allylation has occurred at the C-6 position in accordance with that of **3b** reported by Kozikowski.[6] Formation of the methoxylated **3b** is ascribed to the reaction of **1** with methoxytrimethylsilane or methanol which is liberated during the reaction. Apparently, the regiochemical outcome of this reaction indicates different reactivity of the intermediary vinylogous N-acyliminium ion **2** toward the carbon or oxygen nucleophiles. Thus, alkylation at the C-6 position may be the result of an initial kinetic attack of carbon nucleophile, while the methoxylation at the C-4 position represents a thermodynamic addition. Similar C-4 substitutions were found in the electrolysis of **1** either in methanol, giving the corresponding **3b** in 87% yield, or in CH_2Cl_2 containing phenylthiotrimethylsilane, yielding the sulfenylated **3c** in 67% yield. In addition to the regioselective alkylation of **1**, EG acid catalyzed allylation of 4-methoxy analogue **3b** with allyltrimethylsilane resulted in the formation of **4a** (44%) along with the methoxylated **5b** (25%).

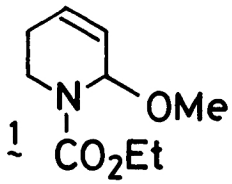
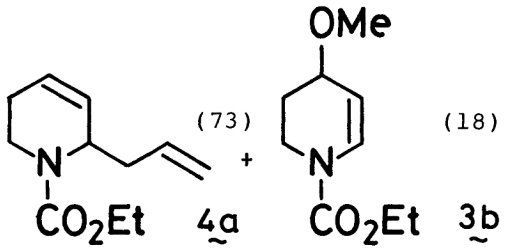
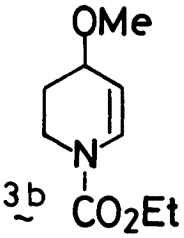
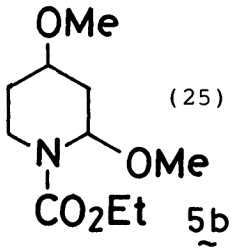
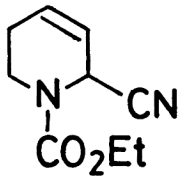
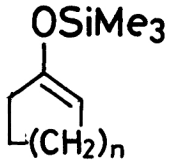
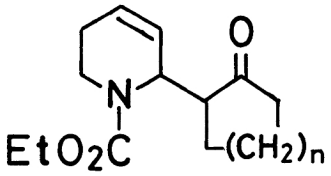
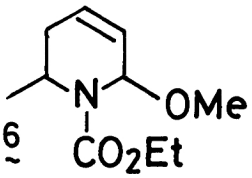
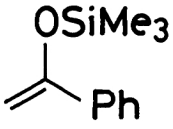
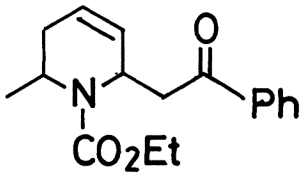
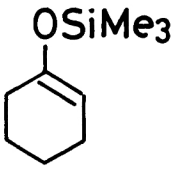
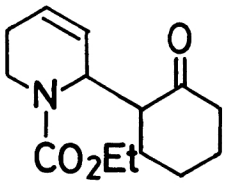


1 → **3**: b: X = MeO (87%); c: X = PhS (67%)

1 → **5**: (trace) (8%)

The present alkylation method is also applicable to the reaction with

Table 1. EG Acid Catalyzed Alkylation of N-Ethoxycarbonyltetrahydropyridines[a)]

Entry	Substrate 1, 3b, 6	Nucleophile	Product (Yield/%[b)])
1		$H_2C{=}CHCH_2SiMe_3$	 (73) + (18)
2		$H_2C{=}CHCH_2SiMe_3$	4a (44) +  (25)
3	1	Me_3SiCN	 (50)
4	1		 (n = 1, 73) (n = 2, 95) (n = 8, 93)
5			 (73)[c)]
6	3b		 (95)

a) Electrolyses were carried out in a similar manner as the text by using 0.5-1.0 mmol of the substrate and 1.2-1.5 equivalent of the nucleophile by passing 0.10-0.25 F/mol of electricity in an undivided cell. b) Based on isolated products after chromatography. c) A separable mixture (ca. 4:3) was obtained.

another nucleophilic organo-silicon compounds such as trimethylsilyl cyanide and enol silyl ethers as summarized in Table 1. Aldol reactions of **1**, **3b**, or **6** with enol silyl ethers proceeded selectively at the C-6 position to give the corresponding adducts **4c-e** and **7** in good yields (Entries 4-6). Unfortunately, stereoselective alkylation was not attained in the reaction of **6** with enol silyl ether (entry 5).

EG acid generated from perchlorate salts has proven to be an efficient catalyst for generation of iminium ion **2** from both **1** and **3b** in the reaction with organo-silicon nucleophile. Application to the alkaloid synthesis is currently under investigation in our laboratory.

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11) The selected spectral data are as follows. **4a**; IR (neat) 3060, 3020, 1695 (C=O), 1657 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3, CH_3), 1.70-2.50 (m, 2, CH_2), 2.29 (m, 2, CH_2-C=C), 2.62-3.16 (m, 1, CH_2), 4.09 (q, J = 7 Hz, 2, CH_2O), 4.00-4.65 (m, 2, CH_2N, CHN), 4.80-5.18 (m, 2, C=CH_2), 5.40-6.15 (m, 3, CH=CH, CH=C). **4b**; IR (neat) 3037, 2245 (C≡N), 1705 (C=O), 1658 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3, CH_3), 1.95-2.20 (m, 2, CH_2), 2.80-3.30 (m, 1, CH_2-N), 4.22 (q, J = 7 Hz, 2, CH_2-O), 4.05-4.40 (m, 1, CH_2-N), 5.30 (m, 1, CH-N), 5.50-5.58 (m, 1, CH=CH), 5.93-6.30 (m, 1, CH=CH); ^{13}C NMR ($CDCl_3$) δ 14.6 (q), 24.5 (t), 38.1 (t), 43.4 (d), 62.5 (t), 116.8 (s), 119.7 (d), 130.2 (d), 154.6 (s). **4d**; IR (neat) 3025, 1705 (C=O), 1656 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3, CH_3), 1.40-3.20 (m, 12, $5CH_2$, CH-CO, CH_2N), 3.95-4.35 (m, 1, CH_2N), 4.12 (q, 2, CH_2O), 4.53-5.10 (m, 1, CHN), 5.55-6.10 (m, 2, CH=CH). **7** (Minor product); IR (neat) 3040, 1700 (C=O), 1693 (C=O), 1655 (C=C), 1600, 1580 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 14.7(q), 19.7 (q), 30.0 (t), 45.8 (t), 47.3 (d), 49.0 (d), 61.1 (t), 123.8 (d), 128.2 (d, 3C), 128.5 (d, 2C), 133.0 (d), 137.0 (s), 156.0 (s), 198.4 (s). **7** (Major prod.); IR (neat) 3040, 1695 (C=O), 1600, 1588 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 14.7 (q), 20.8 (q), 30.0 (t), 43.5 (d), 44.8 (t), 48.1 (d), 61.3 (t), 122.3 (d), 125.9 (d), 128.2 (d, 2C), 133.2 (d), 136.7 (s), 155.1 (s), 198.0 (s).

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