The Reaction of Vinyl Ethers with Acridine

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The reaction of vinyl ethers with acridine gives new acridine derivatives in the presence of an organic ammonium salt and alcohol. An organic ammonium salt such as acridinium chloride affect this reaction. All of the addition products were obtained as dihydroacridinyl derivatives. Moreover, in the reaction of ketene silyl acetal with acridine, the addition products were also obtained as the dihydroacridine derivatives.

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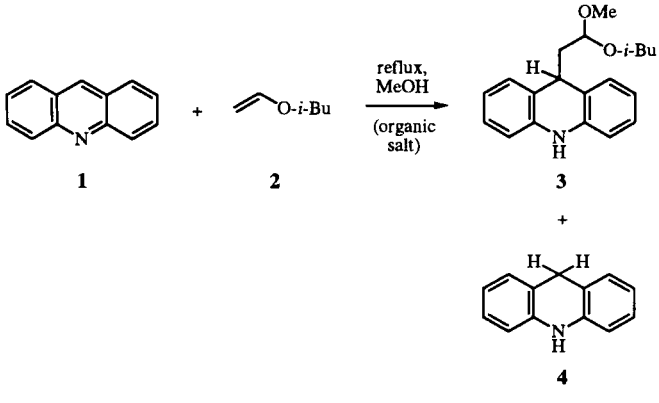
Many reactions of acridine with nucleophilic reagents are substitution reactions, and these products always have acridine rings [1,2].

In this paper, we report new 9-substituted dihydroacridine derivatives from the reaction of acridine with vinyl ethers. The mixture of acridine **1** and isobutyl vinyl ether **2** dissolved in methanol was heated under reflux for 24 hours. Addition products such as 9-(2'-isobutoxy-2'-methoxy)ethyl-9,10-dihydroacridine **3**, were obtained in trace amounts (Scheme 1).

Scheme 1



1 + **2** → **3** + **4**

On the other hand, the reaction of acridinium chloride with a vinyl ether gave only dimethyl acetal, (2-isobutoxy-2-methoxy)ethane, and acetaldehyde which was detected only by use of gc-ms. It was known that the reaction of a vinyl ether with alcohol in the presence of acid gave an acetal as the product [3]. It was suggested that the acridine hydrochloride attacked the vinyl ether from the data presented above. Therefore, when the salt was added to the mixture under the reaction conditions shown in Table 1, products **3** and 9,10-dihydroacridine **4** were obtained (Scheme 1). Product **4** was already reported in the previous article [1].

The organic ammonium salt used for these reactions were aromatic hetrocyclic ammonium salts (acridinium chloride, phenanthridinium chloride, quinolinium chloride) and dimethylamine hydrochloride as shown in Table 1. The reaction of vinyl ether with acridine in the presence of 10 mole% acridinium chloride to acridine gives product **3** at the highest yield (46%) in these experiments.

Table 1

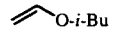
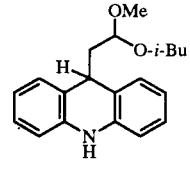
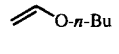
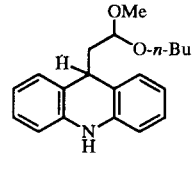
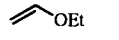
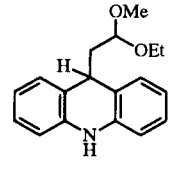
Effects of Organic Ammonium Salts

Organic ammonium salts	Addition quantity (mole%)	Reaction time(h)	Yield (%) **3**	**4**	Recovery (%) **1**
None	0	24	1	0	87
acridinium chloride .	100	4	0	0	100
acridinium chloride	10	4	46	20	11
phenanthridinium chloride	10	4	32	22	26
quinolinium chloride	10	4	30	17	28
dimethylamine hydrochloride	10	4	7	trace	74

Reaction conditions: Acridine (**1**) 1.5 mmoles, vinyl ether (**2**) 3.0 mmoles, in 5 ml of methanol, were refluxed.

Table 2

Reaction Products of Vinyl Ether Derivatives with Acridine

Vinyl ether	Product		Yield (%)	Recovery (%)
		**3**	46	11
		**5**	31	25
		**6**	30	35

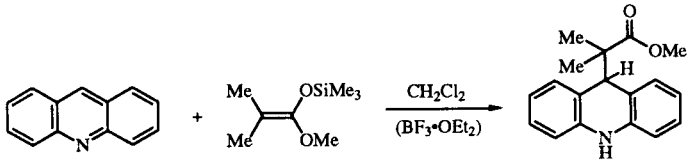
Reaction conditions: Acridine (**1**) 1.5 mmoles, vinyl ether 3.0 mmoles, acridinium chloride (10 mole %) in 5 ml of methanol, were refluxed for 4 hours.

It was confirmed that the reaction of other vinyl ethers with acridine gave the addition products corresponding to each vinyl ether as shown in Table 2. Instead of acridine, quinoline and phenanthridine were used for the reactant. There were no reaction products with each vinyl ether under the same reaction conditions.

The mechanism of this addition reaction is thought to be the following: First, the cation-like moiety in the aliphatic part was produced by the addition of the vinyl ether to C-9 which was activated by the hydrochloride binding to N-10 of the acridine ring as the intermediate in this reaction. Second, C-2' of this cation-like moiety was neutralized by the methanol. Then, **3** was obtained in the form of a dihydroacridine derivative.

Recently the reaction of ketene silyl acetal with 10-methylacridinium perchlorate was reported [4,5]. When a mixture of **1** and ketene silyl acetal **7** in dichloromethane was stirred at 0° for 3 hours, the product 9-(1'-methoxycarbonyl-1'-methyl)ethyl-9,10-dihydroacridine **8** was obtained in a 49% yield (Scheme 2, Table 3). This reaction was carried out in the presence of boron trifluoride diethyl etherate as the Lewis acid under the same reaction conditions described above; product **8** was obtained in a yield as high as 85% (Table 3). Neither quinoline nor phenanthridine reacted with ketene silyl acetal **7** in dichloromethane.

Scheme 2



1 **7** **8**

Table 3
The Reaction of Ketene Silyl Acetal with Acridine

Lewis acid	Yield of **8** (%)	Recovery (%)
–	49	35
BF_3•OEt_2	85	13

Reaction conditions: Acridine (**1**)1.5 mmoles, Ketene silyl acetal (**7**) 3.0 mmoles, in 5 ml of CH_2Cl_2.

It is worth noting that the products **3, 5, 6** and **8** which were obtained are the dihydroacridine derivatives; these products are new acridine derivatives. This is the first synthesis of the dihydroacridine derivatives containing an aliphatic side chain, and only acridine has this characteristic reaction with vinyl and silyl ethers.

EXPERIMENTAL

Measurements.

The melting points were determined on a Yamato melting point apparatus model MP-21 and are uncorrected. The ir spectra were taken on a Shimadzu FTIR 4200 spectrophotometer. The EI mass spectra were taken on a Shimadzu GC-MS-QP1000EX spectrometer. The ^1H nmr and ^{13}C nmr spectra were measured with a FT-NMR OMEGA 300 spectrometer (300MHz) with TMS as internal reference.

9-(2'-Isobutoxy-2'-methoxy)ethyl-9,10-dihydroacridine **3**.

Acridine (0.269 g, 1.5 mmoles) and acridine hydrochloride (0.15 mmoles) in methanol (5 ml) were added to isobutyl vinyl ether (0.39 ml, 3 mmoles). The solution was refluxed for 4 hours. After cooling, the mixture was neutralized with 2*N* sodium hydroxide solution. The mixture was extracted with ether, washed with a saturated sodium chloride solution and dried with magnesium sulfate. The solvent was dried after filtering. Compound **3** could be separated by column chromatography, eluting with benzene, to provide a yield of 46%, mp 95-96° as white crystals; ir (potassium bromide): 3337, 2961, 1120, 1053 cm^{-1}; ms: EI (m/z) 311; ^1H nmr (deuteriochloroform): 0.96 (d, 6H, J = 6.6 Hz), 1.78-1.96 (m, 1H), 1.87 (dd, 2H, J = 7.5, 6.0 Hz), 3.17 (dd, 1H, J = 8.7, 6.6 Hz), 3.33 (dd, 1H, J = 8.7, 6.6 Hz), 3.34 (s, 3H), 4.15 (t, 1H, J = 7.5 Hz), 4.34 (t, 1H, J = 6.0 Hz), 6.15 (s, 1H), 6.78 (d, 2H, J = 7.5 Hz), 6.95 (t, 2H, J = 7.5 Hz), 7.15 (t, 2H, J = 7.5 Hz), 7.21 (d, 2H, J = 7.5 Hz).

Anal. Calcd. for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09; N, 4.50. Found: C, 77.17; H, 8.22; N, 4.50.

9-(2'-Butoxy-2'-methoxy)ethyl-9,10-dihydroacridine **5**.

Acridine (0.269 g, 1.5 mmoles) and acridine hydrochloride (0.15 mmole) in methanol (5 ml) were added to butyl vinyl ether (0.36 ml, 3 mmoles). The solution was refluxed for 4 hours. After cooling, the mixture was neutralized with 2*N* sodium hydroxide solution. The mixture was extracted with ether, washed with a saturated sodium chloride solution and dried with magnesium sulfate. The solvent was dried after filtering. Compound **5** could be separated by column chromatography, eluting with benzene, to provide a yield of 31%, mp 80- 81° as white crystals; ir (potassium bromide): 3379, 2928, 1132, 1047 cm^{-1}; ms: EI (m/z) 279; ^1H nmr (deuteriochloroform): 0.93 (t, 3H, J = 7.5 Hz), 1.33-1.45 (m, 2H), 1.50-1.60 (m, 2H), 1.83 (dd, 2H, J = 7.5, 6.0 Hz), 3.29 (s, 3H), 3.37 (dt, 1H, J = 9.3, 6.6 Hz), 3.52 (dt, 1H, J = 9.3, 6.6 Hz), 4.12 (t, 1H, J = 7.5 Hz), 4.30 (t, 1H, J = 6.0 Hz), 6.10 (s, 1H), 6.77 (d, 2H, J = 7.5 Hz) 6.93 (t, 2H, J = 7.5 Hz), 7.11 (d, 2H, J = 7.5 Hz), 7.17 (t, 2H, J = 7.5 Hz).

Anal. Calcd. for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09; N, 4.50. Found: C, 76.95; H, 8.22; N, 4.51.

9-(2'-Ethexy-2'-methoxy)ethyl-9,10-dihydroacridine **6**.

Acridine (0.269 g, 1.5 mmoles) and acridine hydrochloride (0.15 mmole) in methanol (5 ml) were added to ethyl vinyl ether (0.29 ml, 3 mmoles), the solution was refluxed for 4 hours. After cooling, the mixture was neutralized with 2*N* sodium hydroxide solution. The mixture was extracted with ether, washed with a saturated sodium chloride solution, dried with magnesium sulfate. The solvent was dried after filtering. Compound **6** could be separated by column chromatography, eluting with benzene, to provide a yield of 30%, mp 98-99° as white crystals; ir (potassium bromide): 3383, 3001, 1113, 1059 cm^{-1}; ms: EI (m/z) 283; ^1H nmr (acetone-d_6): 1.12 (t, 3H, J = 6.9 Hz), 1.71 (dd, 2H, J = 7.5, 6.0 Hz), 3.23 (s, 3H), 3.38 (dq, 1H, J = 9.3, 6.9 Hz), 3.55 (dq, 1H, J = 9.3, 6.9 Hz), 4.05 (t, 1H, J = 7.5 Hz), 4.25 (t, 1H, J = 6.0 Hz), 6.83 (d, 2H, J = 7.5 Hz), 6.87 (t, 2H, J = 7.5 Hz), 7.07 (t, 2H, J = 7.5 Hz), 7.14 d, 2H, J = 7.5 Hz), 8.01 (s, 1H).

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47, N, 4.94. Found: C, 76.14; H, 7.68; N, 4.83.

9-(1'-Methoxycarbonyl-1'-methyl)ethyl-9,10-dihydroacridine **8**.

Method 1.

Acridine (0.269 g, 1.5 mmoles) and ketene silyl acetal **7** (0.504 g, 3 mmoles) in dichloromethane (5 ml) were stirred for 3 hours at 0° under a nitrogen atmosphere. After allowing to warm to room temperature, product **8** was extracted with dichloromethane, and dried over sodium sulfate. Compound **8** could be separated by column chromatography, eluting with benzene. It was obtained in a yield of 49%, mp 155-156°.

Method 2.

Acridine (0.269 g, 1.5 mmoles) and ketene silyl acetal **7** (0.504 g, 3 mmoles) were dissolved in dichloromethane (5 ml) then boron trifluoride diethyl etherate (0.213 g, 1.5 mmoles) in dichloromethane (5 ml) was added dropwise to the mixture under a nitrogen atmosphere. The mixture was stirred for 3 hours at 0°. The mixture was added to a saturated sodium hydrogen carbonate solution, and extracted with dichloromethane then washed with a saturated sodium chloride solution, and dried over sodium sulfate. The solvent was dried after filtering. Compound **8** could be separated by column chromatography, eluting with benzene. It was obtained in a yield of 85%, mp 155-156° as white needles; ir (potassium bromide): 3478, 1730, 1305, 1120 cm^{-1}; ms: EI (m/z) 180 ($C_{13}H_9N$), 101 ($C_5H_9O_2$); ^1H nmr (deuteriochloroform): 1.03 (s, 6H), 3.67 (s, 3H), 4.40 (s, 1H), 6.13 (s, 1H), 6.76 (d, 2H, J = 7.5 Hz), 6.91 (t, 2H, J = 7.5 Hz), 7.14 (t, 2H, J = 7.5Hz), 7.18 (d, 2H, J = 7.5 Hz).

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.85; H, 6.81; N, 5.03.

REFERENCES AND NOTES

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