ISOQUINOLINE DERIVATIVES FROM THE RITTER-TYPE REACTION OF VINYL CATIONS

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Both silver-assisted reaction of β -arylvinyl bromides and the photolysis in nitriles gave isoquinoline derivatives, indicating that the Ritter reaction involving a vinyl cation took place.

Although reaction of a carbenium ion with a nitrile is well-known as the Ritter reaction,¹⁾ the great majority of work on the Ritter reaction has dealt with a saturated carbenium ion. The example involving an unsaturated carbenium ion, i. e., a vinyl cation, is little known.²⁾ If the Ritter reaction generally takes place in the case of β -arylvinyl cations, it can be applied to the one-pot synthesis of isoquinoline derivatives as shown in Eq. 1. The synthetic method



described in Eq. 1 is especially useful for synthesis of highly substituted isoquinolines because the starting vinyl bromides which produce the corresponding vinyl cations can be easily prepared. In the present paper we wish to report the one-pot synthesis of isoquinolines which proves that the Ritter reaction generally occurs even in β -arylvinyl cations.

Two methods were performed for the generation of β -arylvinyl cations. One is silver-assisted solvolysis² and the other is photolysis of vinyl halides.³

First we describe the silver-assisted solvolysis. Solvolysis of α -arylvinyl bromides generally requires a fairly high temperature even in the presence of silver salts.⁴⁾ In the case of α -anisyl- β -arylvinyl bromides the reaction took

place at the refluxing temperature in acetonitrile, while the reaction of α -phenylvinyl bromides needed a further high temperature. Therefore, the following method was performed in practice. A mixture of β -arylvinyl bromide 1 (0.5 mmol), silver triflate or tetrafluoroborate (0.6 mmol), and a nitrile (10 ml) was heated in a hard-glass ampoule under the conditions described in Table 1. Silver bromide was filtrated and then the nitrile was removed under the reduced pressure. After the residue was hydrolyzed with sodium hydroxide solution (2 mol·dm⁻³), isoquinoline derivative $\underline{2}^{5}$ was extracted with ether-benzene, and then isolated by column chromatography on alumina. In addition, photolysis by a high-pressure Hg lamp (400 W) for 3 h at room temperature after the thermolysis gave a slightly higher yield than the thermolysis without the photolysis. Table 1 shows that silver triflate is better than silver tetrafluoroborate and the isoquinoline 2^{5} was obtained in a high yield. α -Substituent effect on the reactivity of the silverassisted reaction (p-An > p-Tol > Ph) suggests the intervention of a vinyl cation similarly to the case of vinylation of aromatic substrates.²⁾ All nitriles used, i. e., acetonitrile, propionitrile, and benzonitrile, gave the corresponding isoquinolines in a high yield, indicating that any kinds of nitriles can be applied to this isoquinoline synthesis. Furthermore, even the β -arylvinyl bromide which was substituted by only one phenyl group at the β position gave a high yield of isoquinoline 2.

Next we carried out photolysis of β -arylvinyl bromides in a nitrile. Formation of vinyl cations by photolysis of vinyl bromides is confirmed by previous works.³⁾ Irradiation of β -arylvinyl bromide <u>1</u> (1 mmol) was carried out in a nitrile (100 ml) through a Pyrex-filtered high-pressure Hg lamp (100 W) under N₂ atmosphere at 5 °C. After evaporation of the nitrile the isoquinoline <u>2</u> was obtained by the workup similar to the above experiment. As shown in Table 1, for example, a high yield of isoquinoline <u>2d-Me⁵</u> was obtained in the photolysis of triphenylvinyl bromide <u>1d</u> in acetonitrile, while the photolysis in propionitrile led to a lower yield of isoquinoline <u>2d-Et⁵</u> with the formation of 9-phenylphenanthrene. Therefore, the formation of isoquinoline <u>2</u> in the photolysis is disturbed by the formation of a phenanthrene derivative.

Both the silver-assisted reaction and the photolysis afford the isoquinoline derivatives, which is explained as follows. Reaction of the β -arylvinyl bromide <u>1</u> with silver ion or photolysis results in the generation of the corresponding vinyl cation, followed by reaction with a nitrile to give a nitrilium ion. Cyclization



Table 1. Isoquinoline 2 from the reaction of vinyl bromide 1 with a nitrile

Ving	yl b	romi	de <u>1</u> a)	Nitrile	Conditions of thermolysis			Yield of isoquinoline 2		
	R ₁	^R 2	^R 3	R ₄	Ag salt	Temp/°C	Time/h	Therm ^{b)}	Therm- hv^{c})	hν ^d)
<u>1a</u> :	An	An	MeO	Me	AgBF4	reflux	2		52	
<u>1b</u> :	An	Ph	н	Me	$AgBF_4$	120	2		68	37 ^{e)}
<u>1b</u> :	An	Ph	н	Me	AgOTÍ	150	3	84	96	37 ^{e)}
<u>1b</u> :	An	Ph	н	Et	AgOTf	150	3		95	
<u>1b</u> :	An	Ph	н	Ph	AgOTf	150	8		89	
<u>1c</u> :	Tol	Ph	н	Me	AgOTf	150	4	80	78	52
<u>1c</u> :	Tol	Ph	н	Et	AgOTf	150	4	79	82	
<u>1c</u> :	Tol	Ph	н	Ph	AgOTf	150	8		83	
<u>1d</u> :	Ph	Ph	н	Me	AgOTf	160	12	68	86	77
<u>1d</u> :	Ph	Ph	н	Et	AgOTf	160	12	55	64	52
<u>1d</u> :	Ph	Ph	н	Ph	AgOTf	160	24		88	
<u>1e</u> :	Ph		н	Me	AgOTf	160	48	66	66	12
<u>1e</u> :	Ph		н	Et	AgOTf	160	48	65	72	
<u>1e</u> :	Ph		н	Ph	AgOTf	160	48		82	

a) An = $p-CH_3OC_6H_4$ -; Tol = $p-CH_3C_6H_4$ -. b) Ag-assisted reaction. c) Ag-assisted reaction and then photolysis. d) Photolysis only. e) Filtered by a hard glass.

of the nitrilium ion forms the isoquinoline skeleton. This cyclization takes palce thermally at a high temperature (150-160 °C) but photochemically at a low temperature because the silver-assisted reaction of trianisylvinyl bromide <u>la</u> in acetonitrile at the refluxing temperature gives N-acetylamino-trianisylethylene after alkaline hydrolysis.²⁾ In the photolysis, as discussed before,³⁾ hydrogen atom abstraction by the vinyl radical competes with the vinyl cation formation and this is the reason of low yields in the case of photolysis.

In summary, the Ritter reaction of β -aryl-substituted vinyl cations gives rise to isoquinoline derivatives, indicating a convenient synthesis of highly substituted isoquinolines.



References

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 5) 2a-Me: Mp 148-149 °C(EtOH); NMR δ(CCl₄) 2.87(s, Me), 3.68(s, OMe), 3.76(s, OMe), 3.88(s, OMe), and 6.49-7.73(m, ArH). <u>2b-Me</u>: Mp 170-172 °C(EtOH); NMR δ(CCl₄) 3.00(s, Me), 3.67(s, OMe), and 6.53-8.20(m, ArH). <u>2b-Et</u>: Mp 118-119 °C(EtOH); NMR δ(CCl₄) 1.52(t, J=7.5 Hz, Me), 3.37(q, J=7.5 Hz, CH₂), 3.68(s, OMe), and 6.48-8.18(m, ArH). <u>2b-Ph</u>: Mp 153-155 °C(EtOH); NMR δ(CCl₄) 3.69(s, OMe) and 6.60-8.23(m, ArH). <u>2c-Me</u>: Mp 126-128 °C(EtOH); NMR δ(CCl₄) 2.23(s, Me), 3.00 (s, Me), and 6.80-8.12(m, ArH). <u>2c-Et</u>: Mp 153-154 °C(EtOH); NMR δ(CCl₄) 1.52 (t, J=7.5 Hz, Me), 2.27(s, Me), 3.37(q, J=7.5 Hz, CH₂), and 6.79-8.21(m, ArH). <u>2c-Ph</u>: Mp 160-162 °C(EtOH); NMR δ(CCl₄) 2.24(s, Me) and 6.89-8.25(m, ArH). <u>2d-Me</u>: Mp 156-158 °C(EtOH); NMR δ(CCl₄) 1.50(t, J=7.5 Hz, Me), 3.38(q, J=7.5 Hz, CH₂), and 6.95-8.26(m, ArH). <u>2d-Ph</u>: Mp 155-157 °C(EtOH); NMR δ(CCl₄) 7.08-8.26(m, ArH). <u>2e-Me</u>: Mp 97-98 °C(aq. EtOH); NMR δ(CCl₄) 2.59(s, Me), 2.91 (s, Me), and 7.27-8.15(m, ArH). <u>2e-Et</u>: Mp 72-73 °C(aq. EtOH); NMR δ(CCl₄) 1.45(t, J=7.5 Hz, Me), 2.61(s, Me), <u>3.29(q, J=7.5 Hz, CH₂), and 7.27-8.20(m, ArH). 2e-Ph</u>: Mp 80-82 °C(EtOH); NMR δ(CCl₄) 2.69(s, Me) and 7.14-8.21(m, ArH).

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