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A CONVENIENT SYNTHETIC METHOD OF 1,3-DISUBSTITUTED ISOQUINOLINES USING SILVER TRIFLUOROMETHANESULFONATE AS A KEY REAGENT

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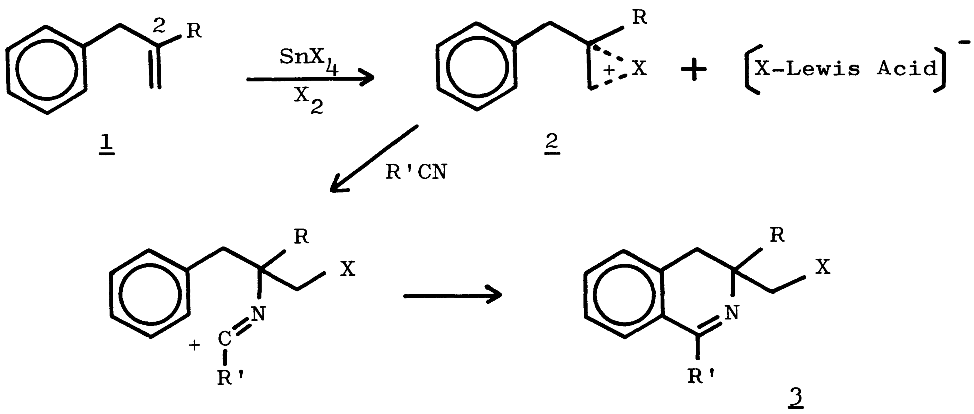
1,3-Disubstituted isoquinolines were prepared under mild conditions from allylbenzenes and nitriles using silver trifluoromethanesulfonate and iodine.

In the course of our studies on the metal-catalyzed organic reactions, we expected that a metal trifluoromethanesulfonate (triflate) would exhibit unique effects as characterized by the extremely weak nucleophilicity of the anion and the more naked nature of the metal cation.[1)] In the present study we utilized silver triflate and iodine as key reagents for the reaction of allylbenzenes and nitriles, which proved to be a convenient synthetic method of 1,3-disubstituted isoquinolines.

Hassner et al[2)] described the formation of 3,4-dihydroisoquinolines by the reaction of allylbenzenes with halogen (Br_2 or I_2) and nitriles in the presence of a Lewis acid. What makes this reaction a useful synthetic method of the dihydroisoquinolines is the ready availability of various types of allylbenzene substrates as compared with β-phenylethylamine derivatives or other types of the substrates required for the well-known Bishler-Napieralski reaction or some other isoquinoline syntheses. The same authors have claimed that the Lewis acid suppressed the nucleophilicity of the halogen anion due to a complex formation, thus allowing the nitrile to open the halonium ion 2 as shown in the scheme 1. The resulting nitrilium ion then underwent ring closure to the dihydroisoquinoline. Although the reaction proceeded satisfactorily with 2-substituted allylbenzenes (1, R = alkyl), the reaction from allylbenzenes having no substituents on this position (1, R = H) was accompanied by the extensive nucleophilic attack by halide ion to produce dihalides, and the yields of the dihydroisoquinolines 3 were quite low (15 - 20%). As it is requisite to start from allylbenzenes having no substituents on this position for the isoquinoline synthesis, we introduced silver triflate and iodine as the reagents. Although silver triflate and iodine did not react with each other upon mixing in acetonitrile, the presence of allylbenzene 4 in the mixture induced the precipitation of silver iodide. The primary product in the solution was a dihydroisoquinoline produced from iodonium ion by nitrile attack and ensuing cyclization of the resulted nitrilium ion. The intermediate dihydroisoquinoline was identified by the NMR analysis. The present reaction is characteristic in that the triflate ion is the sole anion in the solution. The triflate ion has dual characteristics: first, it is hardly nucleophilic, thus providing an ample opportu-



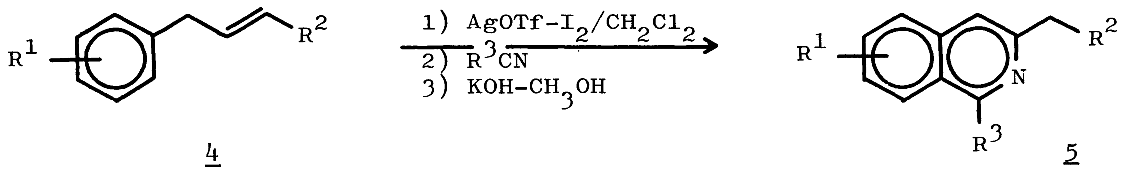
Scheme 1.

nity for the nitrile molecule to attack the iodonium ion, and second, it hardly associates with the counter cation, thus furnishing the intermediate nitrilium ion with the more ability to cyclize.

A typical procedure is as follows: To a solution of silver triflate (1.94 mmol) in dichloromethane (10 ml), or in acetonitrile in case of the reaction with acetonitrile, was added an allylic compound (1.94 mmol) at room temperature. After a solution of iodine (1.94 mmol) in dichloromethane (15 ml) or acetonitrile was poured dropwise at 0° within 10 min, and an appropriate nitrile (1.94 mmol) was added, the solution was warmed slowly to an ambient temperature. After the reaction mixture was kept under the conditions shown in the table 1, silver iodide was filtered off, and the filtrate was mixed with a methanol solution of potassium hydroxide (9.70 mmol). The solution was kept at 40° for 1 hr, water was added, and the product was extracted with dichloromethane. The extract was washed with sodium thiosulfate, and the evaporation of the solvent gave the corresponding isoquinoline in almost pure state. Each product was purified by distillation, and identified by the spectroscopic analysis. The melting points of the picrates 5a,4) 5c,5) and 5d4) coincided with those reported. The present reaction can be contrasted to the similar dihydroisoquinoline synthesis under Ritter reaction conditions (allylbenzene, nitrile, and sulfuric acid), in which only activated benzene ring by the electron-donating substituents can participate in the cyclization.3)

The formation of isoquinoline nucleus indicates that the attack of nitrile molecule occurs at the position 2 of the allylbenzene. Although this is reasonable in view of the Markownikoff rule, we checked the general trend of the regioselectivity of the nucleophilic attack on the halonium ion using methanol as a nucleophile. As shown in the table 2, the reaction proceeded in the expected way in case of styrene (6e), while the reaction with other substrates (6a - 6d) gave a mixture of two regioisomers 7 and 8. Notably in case of 6d (= 4d), the opposite isomer 8d was the major product. In view of the fact that the isoquinoline derivatives were obtained as a sole product in the present reaction, we concluded that the addition

Table 1. Products and Yields of the Reaction of Nitriles with Olefins.



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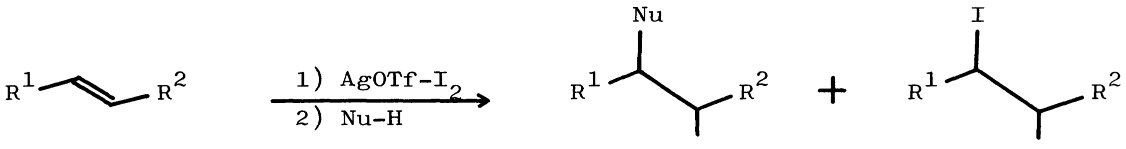
Entry	Olefin		Nitrile	Time(h) / Temp / Solvent			Product yield(%)
	R^1	R^2	R^3				
a	H	H	CH_3	1	rt	CH_3CN	65
b	H	H	C_2H_5	3	40°	CH_2Cl_2	47
c	H	H	C_6H_5	1	40°	CH_2Cl_2	36
d	H	CH_3	CH_3	1	rt	CH_3CN	66
e	4-OCH_3	H	CH_3	1	80°	CH_3CN	61

Table 2. Products and Yields of the Reaction of Nucleophiles with Olefins.



6 7 8

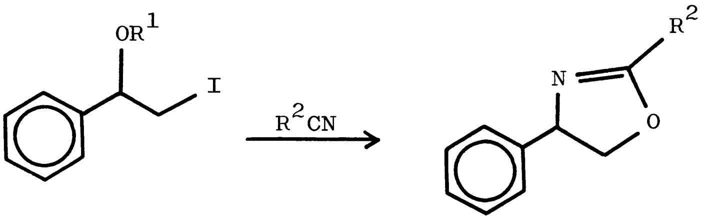
Entry	Olefin		Nu	Yield (%)	
	R^1	R^2		7	8
a	C_6H_{13}	H	CH_3O	38	8
b	$C_6H_5CH_2$	H	CH_3O	42	21
b	$C_6H_5CH_2$	H	HO	27	16
c	C_6H_5O	H	CH_3O	22	22[a]
d	$C_6H_5CH_2$	CH_3	CH_3O	7	27[b]
e	C_6H_5	H	CH_3O	60	0
e	C_6H_5	H	HCOO	100	0
e	C_6H_5	H	CF_3CH_2O	100	0

a) 14% of 6c was recovered.

b) 57% of 6d was recovered.

of nitrile to the halonium ion proceeded reversibly, thus ultimately resulting in the position-2 attack which favored the ensuing cyclization to the six-membered ring system.

With an aim at the synthesis of 3-unsubstituted isoquinolines, we carried out the reaction of iodohydrin derivatives 9a and 9b with nitriles in the presence of silver triflate as a modification of Pictet-Gams reaction. Similarly to the cyclization of various 2-acylamino-1-arylalkan-1-ols under typical Pictet-Gams conditions,6) the product was not isoquinolines but oxazolines 10a and 10b, which were obtained in 32% and 61% yields, respectively. The oxazoline 10b was identical with the authentic sample prepared from styrene oxide and acetonitrile according to the known method.7) Evidently the present reaction proceeded with the migration of oxygen atom involving oxonium ion 11.



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a: $R^1 = CH_3$

b: $R^1 = CHO$

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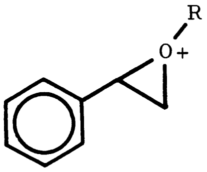
a: $R^2 = CH_3$

b: $R^2 = C_2H_5$



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