A Simple Preparation of 1,3-Dimethylisoquinoline and its Derivatives

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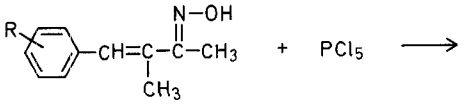
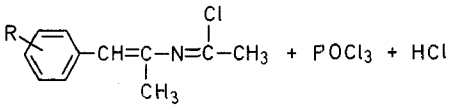
There are serious difficulties in the preparation of isoquinoline derivatives substituted in the 3-position by the general methods used for preparing isoquinoline compounds. In both Pomeranz-Fritsch and Pictet-Spengler reactions these compounds were obtained only in a few cases[1]. Under conditions of the Bischler-Napieralski reaction and its Pictet-Gams modification the α-substituted β-arylethylamides undergo mainly a dealkylation reaction[2]. For this reason, the expected 3,4-dihydroisoquinoline or isoquinoline derivatives substituted in the 3 position were not obtained in many cases or their yields were very low[1]. A few attempts at cyclization of α-substituted *N*-styrylamides of carboxylic acids[3,4] resulted in the 3-substituted isoquinoline derivatives with good yields as a result of the greater stability of the C N bond. However, the preparation of styrylamides[5,6] is rather difficult and, therefore, this method seems to be inconvenient for synthesis of isoquinoline derivatives.

In this work, 1,3-dimethylisoquinoline and its derivatives substituted at the benzene ring were prepared from the oximes of 4-aryl-3-methyl-3-buten-2-ones. The oximes of these compounds **1** exist only in the stable (*E*)-configuration[7] and, in the presence of phosphorus pentachloride, they undergo a rearrangement reaction to yield *N*-α-methylstyrylacetimidoyl chlorides **2**[8].



1



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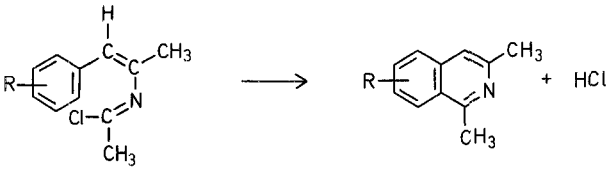
The imidochlorides **2** without previous separation were subjected to cyclization to give the isoquinoline derivatives **3**.



2 **3**

The imidochlorides **2** may undergo cyclization to the isoquinoline derivatives **3** at elevated temperatures in the absence of a catalyst but in the presence of phosphorus pentoxide the yield of the cyclization reaction is higher.

The reaction was carried out in decalin for two reasons. It was found that isoquinoline derivatives were obtained in higher yields at the boiling temperature of decalin, i.e., higher than that usually used in the Bischler-Napieralski reaction (110–140 °C). Decalin is a non-polar solvent and does not contain any nucleophilic centres. For these reasons, the side reactions of fragmentation of imidochlorides and solvent alkylation[2] are suppressed.

Among the isoquinoline derivatives obtained (Table 1), 1,3-dimethylisoquinoline[4] and 1,3-dimethyl-6,7-methylenedioxyisoquinoline[9] were previously prepared by other methods. The chemical constitutions of the other compounds were determined by microanalysis, U.V., and N.M.R. methods.

The electronic spectra of the isoquinoline derivatives prepared are similar and are characterized by the presence of E_1, E_2, and B bands. A strong bathochromic B bond displacement in an acidic medium in comparison with the spectra run in an alkaline medium as well as the occurrence of the E_2 band in acidic solutions prove the presence of isoquinoline moiety[10]. It was possible to confirm fully the chemical constitution of the compounds synthesized by comparing the N.M.R. spectra of the isoquinoline deriva-

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Table 1. 4-Aryl-3-methyl-3-buten-2-one Oximes **1** and 1,3-Dimethylisoquinolines **3** Prepared

Oxime **1**				1,3-Dimethylisoquinoline **3**					
	R	m.p.	R_f[a]	R	Yield [%][b]	m.p. or b.p./torr	R_f[a]	Molecular formula[c]	m.p. of picrate
a	H	109–111 °C	0.62	H	65	134–135 °C/15	0.21	—[d]	181–182 °C
b	3-H_3C	94–95 °C	0.73	6-H_3C	45	154–155 °C/15	0.19	$C_{12}H_{13}N$ (171.2)	180–181 °C
c	3-H_3CO	74–76 °C	0.62	6-H_3CO	41	62–63 °C	0.14	$C_{12}H_{13}NO$ (187.2)	170 °C
d	3-Cl	94–95 °C	0.59	6-Cl	48	55–56 °C	0.20	$C_{11}H_{10}ClN$ (191.7)	220–221 °C
e	4-H_3C	142–143 °C	0.74	7-H_3C	58	148–149 °C/17[f]	0.23	$C_{12}H_{13}N$ (171.2)	212–213 °C
f	4-H_3CO	118–120 °C	0.72	7-H_3CO	5.8	77–78 °C	0.19	$C_{12}H_{13}NO$ (187.2)	197 °C
g	4-Cl	123–124 °C	0.67	7-Cl	31	75–76 °C	0.24	$C_{11}H_{10}ClN$ (191.7)	226 °C
h	3,4-O—CH_2—O	118–119 °C	0.61	6,7-O—CH_2—O	32	146–146.5 °C	0.08	—[e]	227 °C

[a] Stationary phase: silica gel; mobile phase: 3:1 v/v benzene/ethyl acetate.
[b] Based on oxime **1**
[c] The microanalyses of products and their picrates were in satisfactory agreement with the calculated values (N ±0.38, Cl ±0.15); exceptions: **3g** Cl +0.85, **3d** picrate N +0.56.
[d] Lit. [4] b.p. 134–135 °C/torr, picrate m.p.181–182 °C [earlier: T. N. Ghosh, B. Bhattacharya, *J. Indian Chem. Soc.* **36**, 425 (1959), picrate m.p. 181–182 °C].
[e] Lit. [9] m.p. 146 °C, picrate m.p. 227 °C.
[f] m.p. 33–34 °C.

Table 2. Spectral Data of 1,3-Dimethylisoquinolines **3**

Product	U.V. (methanol/water) λ_{max} [nm] ($\varepsilon \cdot 10^{-3}$) medium	E_1 band	E_2 band	B band	^{1}H-N.M.R. (acetone-d_6) δ [ppm]
3a	basic	218 (65.7)	272 (4.39)	330 (3.59)	7.66 (m, 4H_{arom}); 7.22 (s, 1H, 4-H); 2.79 (s, 3H, 1-CH_3); 2.52 (s, 3H, 3-CH_3)
	acidic	228 (49.7)	274 (2.71)	344 (5.75)	
3b	basic	227 (67.9)	278 (4.21)	328 (3.58)	7.79 (d, 1H, 8-H, J_o=8 Hz); 7.30 (d, 1H, 5-H, J_m=2 Hz); 7.19 (q, 1H, 7-H, J_o=8, J_m=2 Hz); 7.09 (s, 1H, 4-H); 2.73 (s, 3H, 1-CH_3); 2.49 (s, 3H, 3-CH_3); 2.37 (s, 3H, 6-CH_3)
	acidic	236 (50.8)	285 (2.81)	343 (5.38)	
3c	basic	235 (51.9)	284 (4.09)	321 (2.35)	7.90 (d, 1H, 8-H, J_o=9.5 Hz); 7.18 (s, 1H, 4-H); 7.02 (q, 1H, 7-H, J_o=9.5, J_m=2.5 Hz); 7.01 (d, 1H, 5-H, J_m=2.5 Hz); 3.81 (s, 3H, 6-H_3CO); 2.70 (s, 3H, 1-CH_3); 2.42 (s, 3H, 3-CH_3)
	acidic	246 (41.3)	309 (6.6)		
3d	basic	227 (51.3)	268 (4.0)	331 (3.5)	7.84 (d, 1H, 8-H, J_o=9 Hz); 7.49 (d, 1H, 5-H, J_m=2 Hz); 7.25 (q, 1H, 7-H, J_o=9, J_m=2 Hz); 7.07 (s, 1H, 4-H); 2.67 (s, 3H, 1-CH_3); 2.42 (s, 3H, 3-CH_3)
	acidic	235 (53.5)	275 (2.9)	343 (5.6)	
3e	basic	223 (67.5)	271 (5.41)	337 (4.08)	7.65 (d, 1H, 8-H, J_m=1 Hz); 7.42 (d, 1H, 5-H, J_o=8 Hz); 7.26 (q, 1H, 6-H, J_o=8, J_m=1 Hz); 7.09 (s, 1H, 4-H); 2.72 (s, 3H, 1-CH_3); 2.48 (s, 3H, 3-CH_3); 2.35 (s, 3H, 7-CH_3)
	acidic	233 (55.3)	276 (3.1)	352 (5.35)	
3f	basic	227 (50.1)	268 (5.92)	349 (3.08)	7.58 (d, 1H, 5-H, J_o=8.5 Hz); 7.27 (d, 1H, 8-H, J_m=2 Hz); 7.21 (s, 1H, 4-H); 7.19 (q, 1H, 6-H, J_o=8.5, J_m=2 Hz); 3.83 (s, 3H, 7-H_3CO); 2.72 (s, 3H, 1-CH_3); 2.43 (s, 3H, 3-CH_3)
	acidic	241 (46.0)	277 (5.06)	368 (4.22)	
3g	basic	222 (60.9)	273 (5.73)	338 (3.23)	7.95 (d, 1H, 8-H, J_m=2 Hz); 7.64 (d, 1H, 5-H, J_o=9 Hz); 7.44 (q, 1H, 6-H, J_o=9, J_m=2 Hz); 7.24 (s, 1H, 4-H); 2.72 (s, 3H, 1-CH_3); 2.44 (s, 3H, 3-CH_3)
	acidic	235 (60.5)	276 (3.67)	353 (3.53)	
3h	basic	235 (50.0)	278 (4.67)	335 (4.18)	7.22 (s, 1H, 8-H); 7.12 (s, 1H, 4-H); 6.92 (s, 1H, 5-H); 6.02 (s, 2H, 6,7-O—CH_2—O); 2.63 (s, 3H, 1-CH_3); 2.38 (s, 3H, 3-CH_3)
	acidic	248 (59.7)	308 (8.56)	346 (5.25)	
3i[a]	basic	238 (16.8)	299 (3.2)	331 (4.04)	
	acidic	250 (15.7)	306 (2.5)	371 (4.98)	

[a] R = 8-H_3CO.

tives obtained with data for isoquinoline and its 1-methyl and 3-methyl derivatives[11] (Table 2).

N-α-Methyl-β-arylvinylacetimidoyl chlorides containing substituents in the *para*-position undergo a cyclization reaction to the 7-substituted 1,3-dimethylisoquinolines while the *meta*-substituted imidochlorides cyclize to give the 6-substituted isoquinoline derivatives, confirming the principle of *para*-orientation[1]. A rapid cyclization of *N*-α-methyl-β-(*m*-methoxyphenyl)-vinylacetimidoyl chloride was the only reaction which resulted in formation of two basic products: 1,3-dimethyl-6-methoxyisoquinoline and 1,3-dimethyl-8-methoxyisoquinoline, the latter in small quantity. The constitution of the latter was determined by U.V. spectroscopy after its separation by preparative T.L.C.

The yields of the isoquinoline derivatives prepared varied greatly. They depend on the rate of isoquinoline ring closure in the intramolecular electrophilic substitution reaction of the intermediate iminocarbenium cations and the rates of side reactions of imidochlorides such as self-condensation and fragmentation[12]. However, 1,3-dimethylisoquinoline derivatives were obtained even when the rate of cyclization was considerably decreased owing to the electronic effects of substituents present at the benzene ring of the imidochlorides.

The influence of the ethylenic bond configuration in the initial oximes on the yield of isoquinolines was not, however, observed, because, within the group of the compounds examined, the intermediate products undergo a rapid isom-

erization to give a mixture of isomers in a ratio of ~1:1 under the reaction conditions[8].

1,3-Dimethylisoquinoline and Derivatives:
A solution of 4-aryl-3-methyl-3-buten-2-one oxime[7] (0.025 mol) in dry decalin (100 ml) is added dropwise to a suspension of phosphorus pentachloride (0.025 mol) in dry decalin (50 ml) with vigorously stirring at 0 °C. The reaction mixture is stirred and kept at a lowered temperature until the absence of the initial oxime is observed, usually after 5 to 15 min in the [samples being periodically taken from a batch and tested by means of the T.L.C. (silica gel plates/3:1 v/v benzene/ethyl acetate-eluent/iodine vapors-developer)]. Then, phosphorus pentoxide (25 g) is added to the reaction mixture with occasional stirring, followed by heating to the boiling point of decalin. The mixture is kept boiling for 30 min. After cooling, water (50 ml) is added dropwise to this mixture followed by steam distillation. The residue is made alkaline by addition of sodium hydroxide solution and again steam distilled. The isoquinoline derivatives prepared are isolated from the distillate by filtering or ether extraction.

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