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SYNTHESIS OF 1-HETERARYLISOQUINOLINES BY CYCLIZATION OF NITRILIUM SALTS

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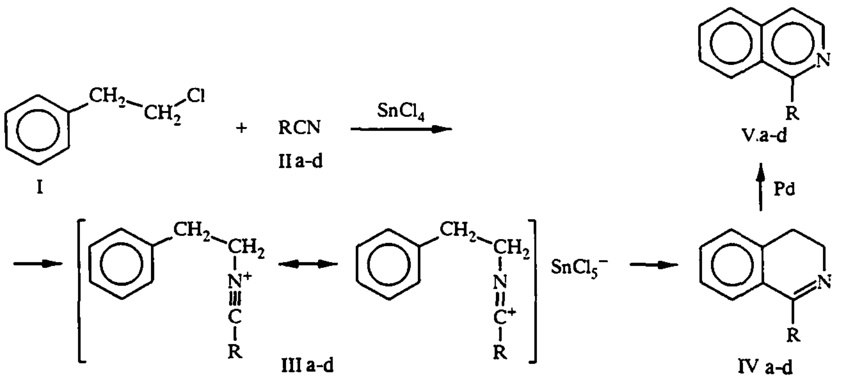
1-Heteraryl substituted 3,4-dihydroisoquinolines and their aromatic analogs have been synthesized from heterocyclic carbonitriles, β-phenylethyl chloride and tin(IV) chloride.

The intramolecular cyclization of nitrilium salts, formed from the interaction of equimolar amounts of β-halogenoethylbenzenes, carbonitriles and tin(IV) chloride, is a suitable method for the synthesis of 1-substituted 3,4-dihydroisoquinolines [1]. The yields of the 3,4-dihydroisoquinoline derivatives varies widely and depends on the nature of the nitrile. High yields (90-100%) are obtained with aliphatic nitriles, whereas the yields of 3,4-dihydroisoquinolines from acrylonitrile and its homologs did not exceed 13%. With benzonitrile and phenylacetonitrile the yields did not exceed 55-65%, and introduction of an electron donor substituent in the benzene ring of the nitrile starting material reduced the yield sharply [2].

We have investigated the use of heterocyclic nitriles for the synthesis of 3,4-dihydroisoquinolines with heteraryl substituents in position 1. The following compounds have been used: 2-cyanofuran, 5-methyl-2-cyanofuran, 2-cyanopyrrole, N-methyl-2-cyanopyrrole, 3-cyanoindole and 3-cyanopyridine. When the nitrilium salt, obtained by mixing the nitrile, β-chloroethylbenzene and tin(IV) chloride, has significant crystallinity and does not resinify on heating, the subsequent cyclization occurs successfully to give the corresponding 3,4-dihydroisoquinoline. Positive results were obtained with the following compounds: 2-cyanofuran (IIa), 5-methyl-2-cyanofuran (IIb), N-methyl-2-cyanopyrrole (IIc) and 3-cyanopyridine (IId). As a result of the cyclization a series of 3,4-dihydroisoquinolines IVa-d was obtained with furan, pyrrole and pyridine substituents at position 1. The structures of the products were confirmed by high resolution ^1H NMR spectroscopy. The signals of the protons 3-H and 4-H of the isoquinoline nucleus, which appear as two doublets at 2.74-2.88 and 3.61-3.88 ppm with $J = 7.1$-7.7 Hz, are characteristic for compounds IIa-d. Signals for protons of the benzene and heterocyclic nuclei are also observed.



II-V a) R = 2-furyl; b) R = 5-methyl-2-furyl; c) R = N-methyl-2-pyrrolyl; d) R = 3-pyridyl

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TABLE 1. Elemental Analyses, Physical Constants and Yields of the Compounds Synthesized

Compound	Molecular formula of the picrate	Picrate: (Found, %)/ (Calc., %)			mp of picrate, °C	bp, °C/ mmHg	Yield, %
		C	H	N			
IVa	$C_{19}H_{14}N_4O_8$	53,82 53,52	2,96 3,29	13,37 13,15	167	130...132/2	22
IVb	$C_{20}H_{16}N_4O_8$	54,60 54,55	3,64 3,64	12,71 12,73	137	130...132/2	26
IVc	$C_{20}H_{17}N_5O_7$	54,97 54,67	3,58 3,87	15,84 15,95	165	187...190/7	13
IVd	$C_{20}H_{15}N_5O_7$	54,09 54,92	3,05 3,43	16,94 16,02	172	146...148/2	21
Va	$C_{19}H_{12}N_5O_8$	54,48 53,77	2,75 2,83	13,27 13,21	153	135...137/2	50
Vc	$C_{20}H_{14}N_5O_8$	54,13 54,80	2,53 3,20	12,26 12,79	162; 63*	135...138/1	86
Vc	$C_{20}H_{15}N_5O_7$	54,51 54,92	3,24 3,43	15,98 16,02	198; 90*	138...140/2	48
Vd	$C_{20}H_{13}N_4O_7$	54,83 55,17	2,39 2,99	15,83 16,09	190	143/2	80

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*mp of substituted isoquinoline.

TABLE 2. ^1H NMR Spectra of the Compounds Synthesized

Compound	NMR Spectra, δ, ppm (*J*, Hz)
IVa	2,74 (2H, t, J_{43} = 7,1, 4-CH_2); 3,83 (2H, t, J_{34} = 7,1, 3-CH_2); 6,52 (1H, d.d, $J_{4'3'}$ = 3,2, $J_{4'5'}$ = 1,6, 4'-H); 6,86 (1H, d, $J_{3'4'}$ = 3,2, 3'-H); 7,26 (1H, dm, J_{56} = 7,1, 5-H); 7,33 (1H, d.d.d J_{67} = 7,8, J_{65} = 7,5, J_{68} = 1,4, 6-H); 7,40 (1H, d.d.d, J_{76} = 7,8, J_{78} = 7,5, J_{75} = 1,4, 7-H); 7,58 (1H, d.d, $J_{5'4'}$ = 1,6, $J_{5'3'}$ = 0,6, 5'-H); 7,71 (1-H, d.d, J_{87} = 7,5, J_{86} = 1,4, 8-H)
Va	6,64 (1H, d.d, $J_{4'3'}$ = 3,4, $J_{4'5'}$ = 1,8, 4'-H); 7,19 (1H, d.d, $J_{3'4'}$ = 3,4, $J_{3'5'}$ = 0,8, 3'-H); 7,58 (1H, d, J_{43} = 5,7, 4-H); 7,63 (1H, d.d.d, J_{67} = 6,8, J_{65} = 8,1, J_{68} = 1,4, 6-H); 7,69 (1H, d.d.d, J_{76} = 6,8, J_{78} = 8,5, J_{75} = 1,5, 7-H); 7,71 (1H, d, d, $J_{5'4'}$ = 1,9, $J_{5'3'}$ = 0,9, 5'-H); 7,84 (1H, d, J_{56} = 8,1, 5-H); 8,58 (1H, d, J_{34} = 5,6, 3-H); 8,78 (1H, d, J_{87} = 8,5, 8-H)
IVb	2,41 (3H, s, CH_3); 2,74 (2H, t, J_{43} = 7,1, 4-CH_2); 3,83 (2H, br.t, , J_{34} = 7,1, 3-CH_2); 6,12 (1H, dq, $J_{4'3'}$ = 3,1, 4'-H); 6,73 (1H, d, $J_{3'4'}$ = 3,1, 3'-H); 7,26 (1H, d, J_{56} = 7,7, 5-H); 7,32 (1H, d.d.d, J_{67} = 7,6, J_{65} = 7,6, J_{68} = 1,2, 6-H); 7,4 (1H, d.d.d, J_{76} = 7,6, J_{78} = 7,4, J_{75} = 1,4, 7-H); 7,72 (1H, d.d, J_{87} = 7,8, J_{86} = 1,2, 8-H)
Vb	2,50 (3H, s, CH_3); 6,23 (1H, dq, $J_{4'3'}$ = 3,4, $J_{4'\text{-}CH_3}$ = 0,7, 4'-H); 7,08 (1H, d, $J_{3'4'}$ = 3,4, 3'-H); 7,53 (1H, d, J_{43} = 5,4, 4-H); 7,61 (1H, d.d.d, J_{67} = 6,9, J_{65} = 8,3, J_{68} = 1,5, 6-H); 7,67 (1H, d.d.d, J_{76} = 6,9, J_{78} = 8,1, J_{75} = 1,5, 7-H); 7,82 (1H, d, J_{56} = 8,3, 5-H); 8,55 (1H, d, J_{34} = 5,4, 3-H); 8,75 (1H, d, J_{87} = 8,1, 8-H)
IVc	2,88 (2H, t, J_{43} = 7,1, 4-CH_2); 3,61 (2H, t, J_{34} = 7,1, 3-CH_2); 3,94 (3H, s, CH_3); 6,03 (1H, d.d, $J_{4'3'}$ = 3,9, $J_{4'5'}$ = 2,5, 4'-H); 6,38 (1H, d.d, $J_{3'4'}$ = 3,9, $J_{3'5'}$ = 2,5, 3'-H); 6,68 (1H, d.d, $J_{5'4'}$ = 2,0, $J_{5'3'}$ = 2,5, 5'-H); 7,23 (2H, m, 5-H, 6-H); 7,32 (1H, d.d.d, J_{76} = 7,0, J_{78} = 8,0, J_{75} = 1,0, 7-H); 7,70 (1H, d.d, J_{87} = 8,0, 8-H)
Vb	3,79 (3H, s, CH_3); 6,28 (1H, m, 4'-H); 6,54 (1H, m, 3'-H); 6,85 (1H, d, $J_{5'4'}$ = 2,5, 5'-H); 7,56 (2H, m, 4-H, 6-H); 7,68 (1H, d.d.d, J_{76} = 7,0, J_{78} = 8,1, J_{75} = 1,5, 7-H); 7,84 (1H, d, J_{56} = 7,8, 5-H); 8,40 (1H, d, J_{87} = 8,4, 8-H); 8,57(1H, d, J_{34} = 5,4, 3-H)
IVd	2,83 (2H, t, J_{43} = 7,5, 4-CH_2); 3,88 (2H, br.t. J_{34} = 7,5, 3-CH_2); 7,22 (1H, d, J_{56} = 6,7, 5-H); 7,27 (1H, d.d.d, J_{67} = 7,8, J_{65} = 6,7, 6-H); 7,29 (1H, br.d, J_{87} =7,8, 8-H); 7,37 (1H, d.d, $J_{5'6'}$ = 5,5, $J_{5'2'}$ = 0,8, 5'-H); 7,42 (1H, d.d.d, J_{78} = 7,6, J_{76} = 7,8, J_{75} = 1,5, 7-H); 7,94 (1H, d.d.d, $J_{4'5'}$ = 7,8, $J_{4'6'}$ = 1,9, $J_{4'2'}$ = 2,1); 8,68 (1H, d.d, $J_{6'5'}$ = 5,5, $J_{6'4'}$ = 1,9, 6'-H); 8,85 (1H, d.d, $J_{2'4'}$ = 2,1, $J_{2'5'}$ = 0,8, 2'-H)
Vd	7,50 (1H, d.d.d, $J_{5'6'}$ = 4,9, $J_{5'4'}$ = 6,8, $J_{5'2'}$ = 0,9, 5'-H); 7,58 (1H, d.d.d, J_{67} = 5,8, J_{65} = 8,5, J_{68} = 1,1, 6-H); 7,72 (1H, d.d.d, J_{76} = 5,8, J_{75} = 1,0, 7-H); 7,75 (1H, d, J_{34} = 4,8, 4-H); 7,92 (1H, d, J_{56} = 8,5, 5-H); 8,25 (2H, m, 4'-H, 8-H); 8,65 (1H, d, J_{34} = 4,8, 3-H); 8,75 (1H, d.d, $J_{6'5'}$ = 4,9, $J_{6'4'}$ = 1,7, 6'- H); 8,97 (1H, d.d, $J_{2'4'}$ = 2,3, $J_{2'5'}$ = 0,9, 2'-H)

The nitrilium salts from 2-cyanopyrrole and 3-cyanoindole are unstable under the reaction conditions which precluded the heterocyclization. The reaction was carried out at 100-115°C, except for cyclization of nicotinic acid nitrile IId, which required a temperature of 140-150°C which is connected to the high melting point of the corresponding nitrilium salt. Dehydrogenation over palladium black in xylene led to aromatization of the pyridine ring to give compounds Va-d, which are more stable than the starting materials IVa-d.

EXPERIMENTAL

The course of the reactions was monitored by TLC on Silufol UV-254 strips. ^{1}H NMR spectra of compounds IVa-d and Va-d were recorded in $CDCl_3$ with TMS as internal standard with a Varian VXR-400 spectrometer.

1-Heteraryl-3,4-dihydroisoquinoline (IVa-d) (general method). Tin(IV) chloride (0.1 mol) was added with stirring to a mixture of nitrile II (0.1 mol) and β-chloroethylbenzene (0.1 mol), and the mixture was heated at 110-115°C (nitriles IIa, b), 100-105°C (nitrile IIc) or 140-150°C (nitrile IId) for 3 h. The reaction mixture was poured into cold water and basified with concentrated sodium hydroxide solution. The organic layer was separated and the aqueous layer was extracted with ether. The ether extracts were combined, dried over magnesium sulfate, the ether evaporated and the residue distilled in vacuum.

1-Heterarylquinolines Va-d (general method). A mixture of dihydroisoquinoline IV (0.1 mol) and palladium black (0.1 g) in sulfur-free xylene (50 cm^3) was boiled for 6-8 h until hydrogen evolution ceased. The catalyst was filtered off, the solvent evaporated, and the residue was distilled in vacuum.

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