# SOLVENT EFFECT ON THE BISCHLER-NAPIERALSKI REACTION. SYNTHESIS OF 3-ARYL-3,4-DIHYDROISOQUINOLINES.

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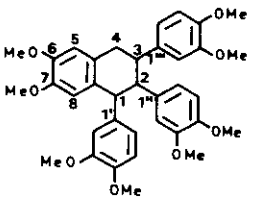
Abstract - The classical Bischler-Napieralski cyclization of 1,2-diaryl-ethylamides always led to neutral compounds: the 3,4,3',4'-tetramethoxystilbene (5) and/or the triaryl substituted tetralin (6). These characteristic by-products of the Bischler-Napieralski reaction arise as a consequence of competing equilibria involving nitrilium ions. The desired 3-aryl-3,4-dihydroisoquinolines were obtained in acceptable yields when the "appropiate" nitrile was used as solvent.

The Bischler-Napieralski reaction[1] is one of the most convenient methods for the preparation of 3,4-dihydroisoquinolines[2], but it has failed in the cyclization of 1,2-diaryl-ethylamides to 3-aryl-3,4-dihydroisoquinolines[3,4,5,6]. Only when the above amides have no substituents in the A-ring[5,7], or when the corresponding formamides are used[4,5], the desired 3-aryldihydroisoquinolines are obtained. The failure of 1,2-diaryl-ethylamides to undergo cyclization has been rationalized[6] in terms of fragmentation of the intermediate nitrilium salts into stilbenes, being the formation of the conjugated π-systems the driving force for this reaction. Even under the very mild conditions described by Fodor et al,[6] the retro-Ritter reaction predominated in the above mentioned cases.

We now wish to report a preparation of 3-aryl-3,4-dihydroisoquinolines (4) by cyclodehydration of 1,2-diaryl-ethylamides (1) with phosphorous pentachloride as condensing agent and the "appropriate" nitrile as solvent. We hope this modification of the Bischler-Napieralski reaction will be an advantageous synthetic method for isoquinoline derivatives.

Several amides (1) were prepared[8] and cyclized to the corresponding dihydroisoquinolines (4) (Table 1). We have also observed that the action of an excess of $P_2O_5$, $POCl_3$ or $PCl_5$ on the 1,2-diaryl-ethylamides (1) in boiling toluene for 0.5 h gave not the desired 3,4-dihydroisoquinolines (4), but the 3,4,3',4'-tetramethoxystilbene (5) in about 70% yield as a colorless crystalline solid mp 151-152°C (reported[4] mp 153-154°C). However, a similar procedure heating the amides (1) in toluene under reflux for 2 h afforded a white solid mp 151-152°C (64% yield), which was proved to be a dimer of the stilbene (5).

In a recent publication[5] on the unusual products in the Bischler-Napieralski cyclization of 1,2-diaryl-ethylamides, it is claimed that the "dimeric stilbene", already mentioned in the pioneering studies of Battersby et al,[4] posseses the indane structure (7). However the structural assignment lied on rather loose grounds: a) the non symmetrical nature of the product as revealed by its pmr spectrumn and b) the presence of "an intense signal at m/e=449" in its mass spectrum (which however is not described). Nevertheless we have concluded, on the basis of its spectral data[9], that the dimeric compound has actually the triaryl substituted structure (6).

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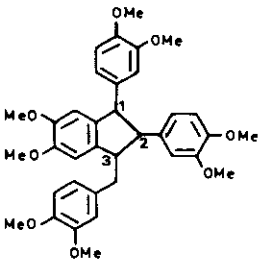


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Thus, the cmr spectrum of this compound showed the characteristic signals of three methine carbons and a methylene carbon, a fact which indicated that only structures (6) and (7) are viable for the dimer. The interpretation of its 300 MHz pmr spectrum, allowed us to propose for our dimer the structure of 1,2,3-tris(3,4-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (6) with a 1,2-trans 2,3-trans conformation being the three aryl substituents pseudoequatorial. Thus, in the pmr spectrum the most significant signal is a doublet at $\delta$4.25 (J=10.5 Hz) due to the $C_1$-H. The chemical shift and large coupling constant between $C_1$-H and $C_2$-H is characteristic of 1,2,3-triaryl substituted tetralins[10] with trans-diaxial coupling. These data let us to exclude the indane structure (7) in which this doublet should appear at a lower field ($\delta$4.45-4.95 vs. $\delta$4.25)[10] with a smaller coupling constant (J=9-9.5 Hz). In addition, its mass spectral fragmentation pattern fitted well[11] with the proposed structure (6). In fact, it showed the molecular ion at m/e=600 and the base peak at m/e=300, which is due to a fragmentation involving a retro-Diels-Alder type process. The "intense signal at m/e=449"[5], in our hands was only a 5% of the base peak (m/e=300). Furthermore, we believe its formation can be explained rationally from the tetralin radical cation at m/e=600. The combined pmr, cmr, uv, ir and ms data support (6) as the structure for this compound.

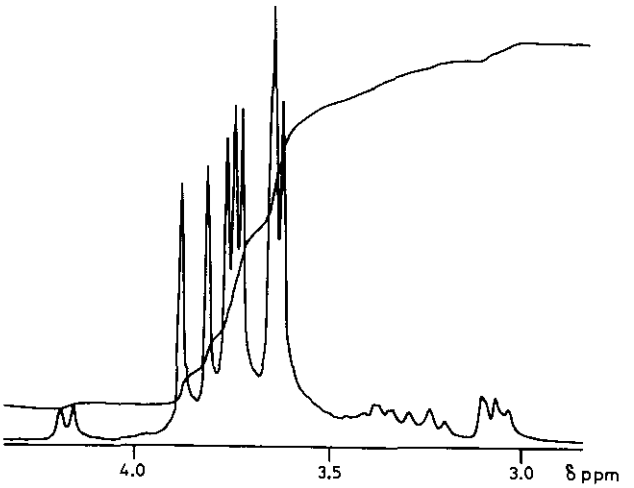
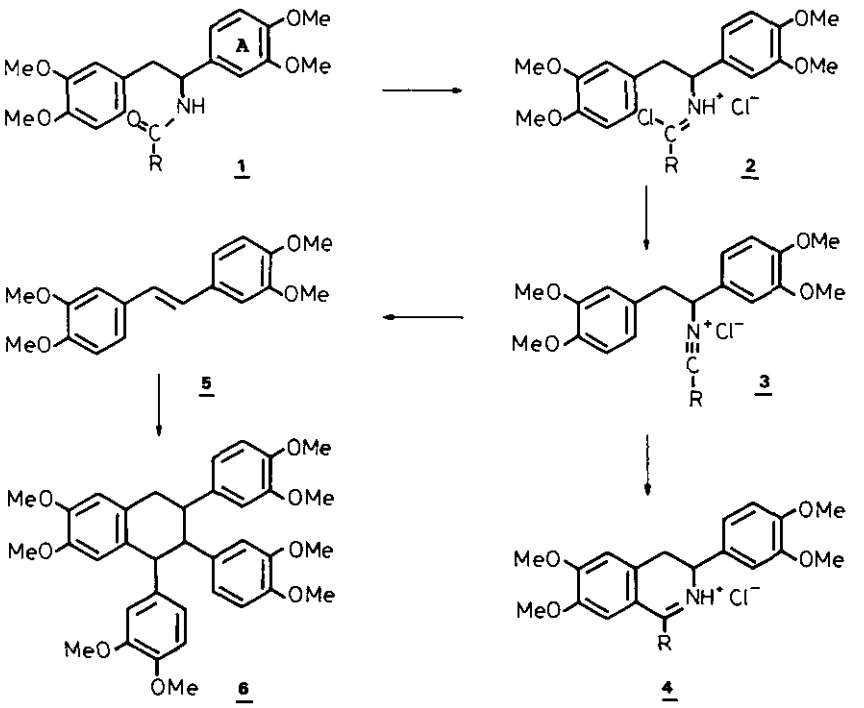


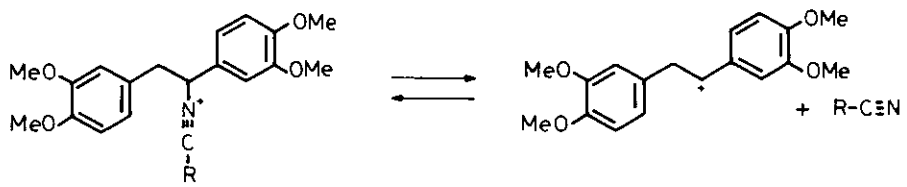

Figure 1. Pmr spectrum of compound (6) on 300 MHz in $CDCl_3$.

As described previously, under the classical "one-pot" conditions (toluene, $POCl_3$, $P_2O_5$ or $PCl_5$, reflux), 1,2-diaryl-ethylamides (1) always led to neutral compounds: the 3,4,3',4'-tetramethoxystilbene (5) and/or the triaryl-substituted tetralin (6). In all cases, the retro-Ritter reaction predominated, except when the formamide (1a) was treated with $PCl_5$ in dichloromethane at room temperature, in which case the 3-aryldihydroisoquinoline (4a) was obtained with better yields than those reported in the literature[5] for this compound.




a: R=H; b: R=$CH_3$; c: R=$CH_3CH_2$; d: R=Ph; e: R=$PhCH_2$

The above experiments and the hypothesis that the intermediate nitrilium salts (3) may reversibly dissociate into a nitrile and a carbonium ion (8)[6], induced us to search for a way of shifting this equilibrium towards the nitrilium salts (3), thus favouring isoquinoline formation. In addition, acetonitrile is known[12] to be a good solvent in some Bischler-Napieralski cyclizations. Therefore, we planned a slight modification of this reaction, which consisted in the use of the "appropriate" nitrile RCN as solvent.

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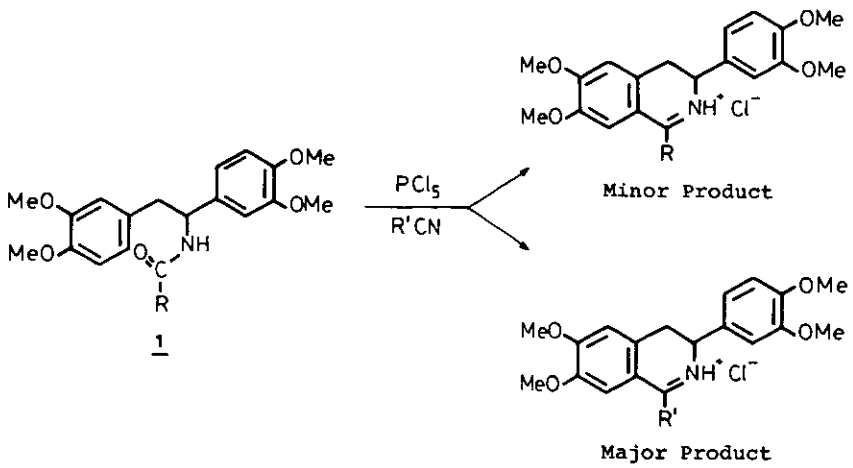
Thus, to a magnetically stirred solution of the 1,2-diaryl-ethylamides (1) (0.1 mol) in the corresponding nitrile (freshly distilled from $P_2O_5$), anhydrous phosphorous pentachloride (0.8 mol) was added. The addition was carried out in portions under nitrogen atmosphere at 0°C. After 1 h at 0°C the cooling bath was removed and the stirring was continued for 3-5 h (the progress of the reaction could be followed by tlc on silica gel, chloroform/methanol 9.5:0.5). The solvent was removed under reduced pressure and the oily residue purified by column chromatography on silica gel with dichloromethane as eluent to afford the corresponding dihydroisoquinolines (4) as yellow solids in acceptable yields (Table 1).

This is the first successful Bischler-Napieralski reaction of 1,2-diaryl-ethylamides to 1-substituted 3-aryl-3,4-dihydroisoquinolines with electron-donating substituents in the A-ring.

To prove the role of the nitrile in this reaction, the behaviour of each amide (1) towards various nitriles was examined. Thus, the experiments showed in Table 2 were carried out and in all the cases, the major product was the 3-aryldihydroisoquinoline corresponding to the nitrile used as solvent. For example, when the acetamide (1b) was treated with phosphorous pentachloride in dry benzonitrile, following the general procedure above described, and the crude product was subjected to column chromatography on silica gel (eluent toluene/dichloromethane), the following compounds were isolated: 3,4,3',4'-tetramethoxystilbene (5) (yield 19%), 1-phenyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (4d) (yield 50%) and 1-methyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (4b) (yield 8%).

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All those facts substantiate the role assigned to the nitrile in this modified Bischler-Napieralski reaction.

Table 1. - 3-aryl-3,4-dihydroisoquinolines (4) prepared from 1,2-diaryl-ethylamides (1).

| Product No. | R | Yield (%) | mp °C (solvent) | React. Condit. time (h) (solvent) | ir (KBr) $\nu_{C=N}$ ($cm^{-1}$) | uv (EtOH) $\lambda_{max}$ nm(log ε) | pmr ($CDCl_3$/TMS) δ(ppm), J(Hz) |
|---|---|---|---|---|---|---|---|
| 4a | H | 81 | 240-242[5] (acetone) | 3 (dichloromethane) | 1630 | 237(4.33) 282(3.80) 313(3.88) 370(3.62) | 3.45(d,J=8,2H,$CH_2$), 3.80(s,6H,$CH_3O$), 3.90(s,3H,$CH_3O$), 4.0(s,3H,$CH_3O$), 5.3 (t,J=8,1H,CH), 7.0-7.6(m,5H$_{aromatic}$), 9.05(s,1H,CH=N). |
| 4b | $CH_3$ | 66 | 158-160 (methanol/ acetone) | 6 (acetonitrile) | 1645 | 236(4.30) 285(3.79) 307(3.93) 358(3.75) | 3.0(s,3H,$CH_3$C=N), 3.5(d,J=8,2H,$CH_2$), 3.8(s,3H,$CH_3O$), 3.9(s,3H,$CH_3O$), 4.0 (s,3H,$CH_3O$), 4.1(s,3H,$CH_3O$), 5.3(t, J=8,1H,CH), 6.8-7.3(m,5H$_{aromatic}$). |
| 4c | $CH_3CH_2$ | 65 | 169-170 (methanol/ acetone) | 6 (propionitrile) | 1650 | 245(4.27) 285(3.73) 308(3.93) 360(3.83) | 1.5(t,J=7.5,3H,$CH_3CH_2$), 3.1(m,4H,2 2×$CH_2$), 3.8(s,3H,$CH_3O$), 3.9(s,3H,$CH_3O$), 3.95(s,3H,$CH_3O$), 4.05(s,3H,$CH_3O$), 5.3 (m,1H,CH), 6.8-7.3(m,5H$_{aromatic}$) |
| 4d | Ph | 70 | 130-132 (methanol/ acetone) | 6 (benzonitrile) | 1630 | 236(4.33) 261(4.01) 316(3.94) 375(3.70) | 3.6(d,J=8,2H,$CH_2$), 3.75(s,3H,$CH_3O$), 3.8(s,3H,$CH_3O$), 3.9(s,3H,$CH_3O$), 4.05 (s,3H,$CH_3O$), 5.6(m,1H,CH), 6.7-7.1 (m,4H$_{arom.}$), 7.3-7.9(m,6H$_{arom.}$). |
| 4e | $PhCH_2$ | 58 | 177-180 (ethanol/ acetone) | 8 (phenylaceto-nitrile) | 1650 | 232(4.37) 278(4.02) 313(3.96) 359(3.62) | 3.3(d,J=8,2H,$CH_2$), 3.80(s,3H,$CH_3O$), 3.85(s,6H,2×$CH_3O$), 4.0(s,3H,$CH_3O$), 4.7(s,2H,$CH_2$C=N), 5.4(m,1H,CH), 6.7--7.2(m,4H$_{arom.}$), 7.2-7.5(m,6H$_{arom.}$). |

Table 2. - Reaction of 1,2-diaryl-ethylamides (1) with $PCl_5$ using different nitriles as solvents.

| Substrate No. | R | Solvent | Product No. | R | Yield* (%) |
|---|---|---|---|---|---|
| 1b | $CH_3$ | Propionitrile | 4b | $CH_3$ | 9 |
| | | | 4c | $CH_3CH_2$ | 54 |
| | $CH_3$ | Benzonitrile | 4b | $CH_3$ | 8 |
| | | | 4d | Ph | 50 |
| | $CH_3$ | Phenylacetonitrile | 4b | $CH_3$ | 7 |
| | | | 4e | $PhCH_2$ | 47 |
| | $CH_3$ | Acetonitrile/ Benzonitrile (1:1) | 4b | $CH_3$ | 30 |
| | | | 4c | Ph | 35 |
| 1d | Ph | Acetonitrile | 4d | Ph | 9 |
| | | | 4b | $CH_3$ | 53 |
| | Ph | Phenylacetonitrile | 4d | Ph | 7 |
| | | | 4e | $PhCH_2$ | 40 |
| 1e | $PhCH_2$ | Acetonitrile | 4e | $PhCH_2$ | 8 |
| | | | 4b | $CH_3$ | 51 |
| | $PhCH_2$ | Benzonitrile | 4e | $PhCH_2$ | 8 |
| | | | 4d | Ph | 48 |

*Yield of pure, isolated product.

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8. General procedure: To a stirred solution of the N-1,2-bis(3,4-dimethoxyphenyl) ethylamine ( 1 mmol) in dry pyridine (15 ml), the corresponding acid chloride (1.1 mol) was added dropwise at room temperature. The stirring was continued for the required period of time (tlc monitoring). Solvent was removed, ice was added and the 1,2-diaryl-ethylamides (1) were obtained by filtration and further purified by crystallization.
9. mp 151-152°C. Anal. Calcd. for $C_{36}H_{40}O_8$: C, 71.98%; H, 6.71%. Found: C, 71.84%; H, 6.50%. Uv $\lambda_{max}^{EtOH}$ nm (log ε) 283(4.22). Pmr ($CDCl_3$), δ 3.06-3.6 (4H, m, $2\times H_4$, $H_3$, $H_2$), 3.63 (3H, s, $CH_3O$), 3.64 (6H, s, $2\times CH_3O$), 3.73 (3H, s, $CH_3O$), 3.75 (3H, s, $CH_3O$), 3.77 (3H, s, $CH_3O$), 3.82 (3H, s, $CH_3O$), 3.90 (3H, s, $CH_3O$), 4.25 (1H, d, J=10.5 Hz, $H_1$), 6.28-6.63 (11H, m, aromatic protons). Cmr ($CDCl_3$) δ $C_4$, 39.9 (t); $C_3$, 46.7 (d); $C_2$, 55.0 (d); $C_1$, 56.4 (d); $CH_3O$-, 55.9 (q); aromatic -CH-, 110.8 (d), 111.4 (d), 112.1 (d), 112.9 (d), 119.8 (d), 120.6 (d), 121.6 (d); $C_{4a}$, 129.2 (s); $C_{1'}$, $C_{1''}$, $C_{1'''}$ ,131.6 (s), 132.2 (s), 135.7 (s); $C_{8a}$, 138.1 (s); aromatic C-O, 147.5 (s), 147.1 (s). Ms, m/e(%): 600($M^+$, 5), 449(5), 300(100).
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13. All new compounds reported gave satisfactory microanalyses and were identified on the basis of their ir, uv, nmr and ms spectral data.

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