Reaction of 1,2-Diarylethylamides with Ethyl Polyphosphate (EPP): Correlation of the von Braun, Ritter and Bischler-Napieralski Reactions

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The Bischler-Napieralski cyclization of the 1,2-diarylethylamides in a "one-pot" process using ethyl polyphosphate as the reagent only yields the dihydroisoquinolines in certain cases. The *trans*-stilbenes and indanes are obtained as neutral products and sometimes as sole products. Results clearly indicate the effect of aryl group substitution on the course of the reaction and the relationship between the Bischler-Napieralski and Ritter reactions.

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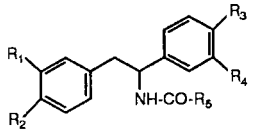
The biological activity attached to the isoquinoline nucleus has provided a great deal of interest in the synthesis of isoquinolines. Perhaps the most common approach to these compounds is the Bischler-Napieralski reaction (hereinafter referred to as the B-N reaction). Although several hundreds of references can be found in the literature [1] for the use of this reaction, the B-N synthesis has only sporadically been mentioned as the method of choice for the preparation of 3-arylisoquinoline derivatives and pertinent data are indeed scanty.

In 1958 Battersby and Binks [2], on heating the amide **9** in toluene with phosphoric acid or phosphorus oxychloride, obtained as the major product a nitrogen-free neutral compound that was recognized as the *trans*-3,3',4,4'-tetramethoxystilbene. Similar results were achieved by Narasimhan *et al*, in 1980 [3], when Fodor and Nagubandi [4] obtained *trans*-stilbene as the major product by treating several *N*-(1,2-diphenylethyl)acylamines with the reagents most widely employed in the B-N reaction, showing its correlation with the von Braun reaction as well as with the Ritter reaction and the Beckman reaction *via* a nitrilium salt. The failure of ring closure was attributed to the formation of a fully conjugated system as the *trans*-stilbene.

Table I



						Yield %		
	R_1	R_2	R_3	R_4	R_5	Dihydro-isoquinoline	*trans*-Stilbene	Indanes
1	H	H	H	H	H	---	77	---
2	H	H	H	H	Ph	---	79	---
3	H	OCH_3	H	H	H	---	71	---
4	H	OCH_3	OCH_3	H	H	---	82	---
5	OCH_3	OCH_3	H	H	H	89	---	---
6	OCH_3	OCH_3	H	H	CH_3	80	3	---
7	H	H	OCH_3	OCH_3	H	---	26	68
8	H	H	OCH_3	OCH_3	CH_3	---	42	55
9	OCH_3	OCH_3	OCH_3	OCH_3	H	---	---	99
10	OCH_3	OCH_3	OCH_3	H	H	8 [a]	10	37
11	OCH_3	H	H	H	H	63	---	---
12	OCH_3	OCH_3	NO_2	H	H	70	7	---
13	H	NO_2	OCH_3	OCH_3	H	---	80	7
14	H	NO_2	OCH_3	OCH_3	CH_3	---	67	25
15	-O-CH_2-O-		H	H	H	85	---	---
16	-O-CH_2-O-		H	H	CH_3	75	5	---

[a] Isolated as isoquinoline.

Bearing in mind these results, we attempted the synthesis of several *N*-(1,2-diarylethyl)acylamines (Table I) in order to determine whether the presence of substituents in the phenyl rings could modify the course of the reaction.

All the amides were treated with ethyl polyphosphate (EPP) in a "one-pot" reaction under the same conditions of temperature, time and concentration. This reagent was chosen for several reasons: 1) the high yields obtained by other authors in the B-N reaction [5]; 2) very smooth working conditions are readily achieved; and 3) it is a good leaving group [4].

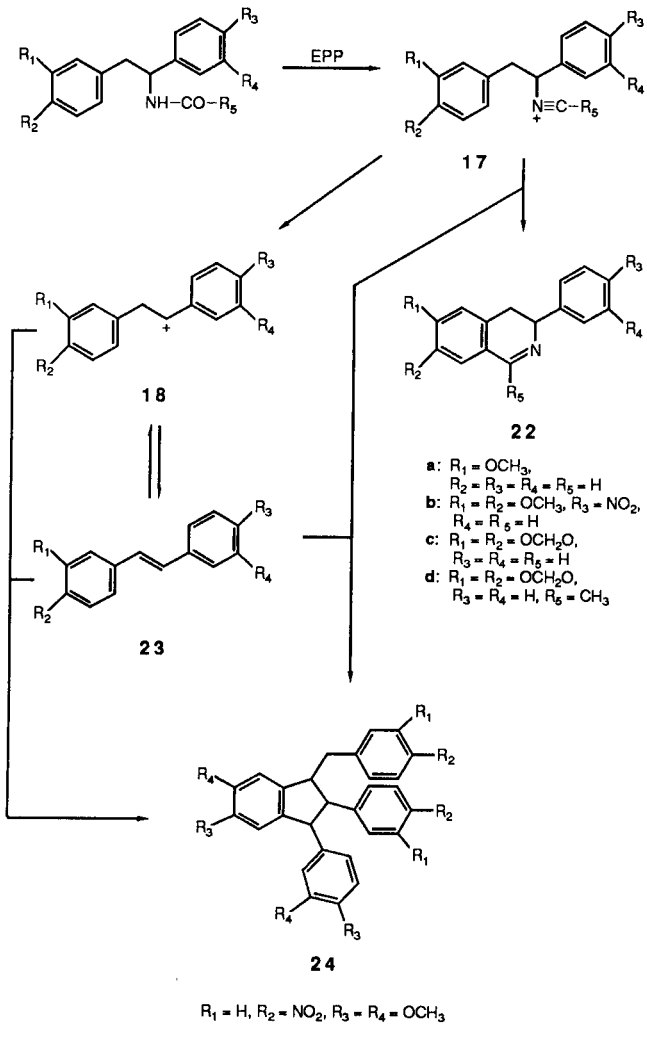
Our previous results [6], which are summarized in Table I, have shown that the course of the reaction is modified by the substituents as depicted in Scheme 1, as follows:

a) The prevalency of the "retro-Ritter" reaction (*via* A) is observed when the aryl group attached to the C-β is not nucleophilic enough in the cyclization position (amides **1, 2, 3, 4**).

b) The prevalency of the B-N reaction (*via* B) takes place when the aryl ring bonded to C-β is sufficiently nucleophilic in the cyclization position and there are no electron releasing groups in the phenyl ring attached to C-α-(amides **5, 6, 15**).

c) Whenever the "retro-Ritter" reaction affords a *trans*-stilbene with at least one aryl ring by the substitution of a veratryl group, a mixture of diastereoisomeric indanes

Scheme 1



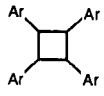
may be isolated.

d) The acyl group, whether formyl, acetyl or benzoyl (amides **7, 8, 9, 10, 14, 15**), is capable of modifying the yield slightly but fails to affect the overall course of the reaction.

Here we report our latest experimental results, which allow us to enlarge upon our previous findings.

The presence of a group capable of releasing electrons attached to the C-3 of the aryl ring bonded to C-β is necessary, together with a phenyl ring or an aryl ring with a substituent withdrawing electrons attached to C-α (amides **11, 12**), so that the B-N reaction should predominate over the "retro-Ritter" one.

However, it should be stressed that if the substitution is reversed in the amides (**5, 7** and **12, 13**) where the limiting reactions occur (B-N or "Retro-Ritter"), then the results of the reactions are also reversed. Taken together, these findings suggest that the final products of the reaction cannot be ascribed to the high conjugation stability of the *trans*-stilbene, but rather to the competitive stability of ions **18** and **17**.



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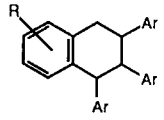

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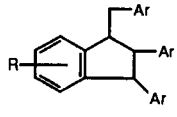

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Although it was possible to identify benzonitrile in the final mixture of the reaction between amide **2** and EPP, this fails to support the mechanism for the B-N reaction proposed by Fodor [4], because under reaction conditions the benzamide affords benzonitrile in a very high yield. At any rate, we accept Fodor's mechanism because it allows us to explain each and every one of the results.

Lastly, we append a few comments on the experimental work. The 1-phenyl-2-(3-methoxyphenyl)ethanone [7] which affords the amide **11** could only be prepared by the Grignard reaction between the phenylmagnesium bromide and the 3-methoxyphenylacetonitrile. The preparation of the ketone 1-(4-nitrophenyl)-2-(3,4-dimethoxyphenyl)-ethanone [8], which affords the amide **12**, was troublesome and could only be obtained by the method described by Zimmer *et al* [9]. When the amide **12** was treated with EPP in the usual way, two compounds were obtained and clearly separated by preparative tlc. One of them was a *trans*-stilbene identical to the one we obtained as the minor product by treating amides **13** and **14** with EPP. The other compound proved to be a dimer of the *trans*-stilbene, having three possible structures (**19, 20** or **21**). The structure **19** is ruled out because there are several methoxy groups in the ^{1}H-nmr but no symmetry in the ^{13}C-nmr, and **20** is also untenable because of methylene group spin-spin multiplicity [10]. The mass spectrum of the dimer shows a clearcut peak corresponding to the m/e (M^+-4-nitrobenzyl) fragment, so that we accept structure **21**. Nevertheless, both the ^{1}H-nmr and ^{13}C-nmr spectra show the presence of several stereoisomers.

Work is currently under way on the purification of the indane stereoisomers and the determination of their configuration by means of the nmr spectra.

EXPERIMENTAL

Infrared spectra were performed on a Shimadzu IR 440 spectrometer as Nujol mulls. The ^{1}H nmr spectra were obtained on a Bruker WO 80 SYFT or a Varian FT 80A spectrometer in deuteriochloroform with

tetramethylsilane as internal standard. The mass spectrum was obtained on a Varian Mat Model CH7 A spectrometer and elemental microanalysis were performed in our Laboratories with a Coleman Analyzer. Melting points (uncorrected) were determined on a Thomas Hoover apparatus.

1-Phenyl-2-(3-methoxyphenyl)ethanone.

It was prepared from 3-methoxyphenylacetonitrile and phenylmagnesium bromide, following the procedure of Callen *et al* [12], yield 65%. Its analytical and spectral data are in agreement with those previously described [7].

1,2-Diarylethylamides.

They were prepared from the respective ketones according to a general procedure [13].

Amide **11**.

It was obtained as an oil, yield 73%; ir: 3350 (N-H), 1670 (C=O) cm^{-1}; nmr: δ 3.05 (2H, d, CH_2), 3.70 (3H, s, OCH_3), 5.25 (1H, br q, CH), 6.30 (1H, br d, NH), 6.50-7.50 (9H, m, Ar), 8.05 (1H, br s, CHO).

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.66; N, 5.49. Found: C, 75.38; H, 6.75; N, 5.41.

Amide **12**.

This compound had mp 141-142° (from methanol) yield 56%; ir: 3320 (N-H), 1660 (C=O), 1530 and 1340 (N-O) cm^{-1}; nmr: δ 3.05 (2H, d, J = 7.8 Hz, CH_2), 3.75 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.40 (1H, br q, CH_2), 6.00 (1H, br d, NH), 6.65 (3H, m, Ar), 7.37 (2H, d, J = 8.5 Hz, Ar), 8.17 (2H, d, J = 8.5 Hz, Ar), 8.20 (1H, s, CHO).

Anal. Calcd. for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.94; N, 8.48. Found: C, 61.72; H, 5.96; N, 8.51.

Amide **13**.

This compound had mp 170-172° (from ethanol), yield 80%; ir: 3280 (N-H), 1650 (C=O), 1510 and 1350 (N-O) cm^{-1}; nmr: δ 3.17 (1H, dd, CH_2), 3.32 (1H, dd, CH_2), 3.85 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.25 (1H, br q, CH), 5.85 (1H, br d, NH), 6.70 (3H, m, Ar), 7.25 (2H, d, J = 8.5 Hz, Ar), 8.08 (2H, d, J = 8.5 Hz, Ar), 8.17 (1H, s, CHO).

Anal. Calcd. for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.94; N, 8.48. Found: C, 61.73; H, 5.87; N, 8.45.

Amide **14**.

This compound had mp 145-146° (from ethanol), yield 65%; ir: 3325 (N-H), 1665 (C=O), 1530 and 1350 (N-O) cm^{-1}; nmr: δ 2.00 (3H, s, CH_3), 3.13 (1H, dd, CH_2), 3.30 (1H, dd, CH_2), 3.80 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.20 (1H, br q, CH), 6.05 (1H, br d, N-H), 6.75 (3H, m, Ar), 7.20 (2H, d, J = 8.5 Hz, Ar), 8.05 (2H, d, J = 8.5 Hz, Ar).

Anal. Calcd. for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13. Found: C, 62.70; H, 5.81; N, 8.09.

3-Aryl-3,4-dihydroisoquinolines.

They were obtained from the amide and EPP in the usual way [6].

3-Phenyl-6-methoxy-3,4-dihydroisoquinoline (**22a**).

This compound was obtained as an oil, yield 63%; nmr: δ 2.85 (2H, m, CH_2), 3.82 (3H, s, OCH_3), 4.65 (1H, m, CH), 6.75 (2H, m, Ar), 7.25 (6H, m, Ar), 8.35 (1H, d, J = 2.5 Hz, CH=N).

Anal. Calcd. for $C_{16}H_{15}NO$: C, 81.01; H, 6.33; N, 5.91. Found: C, 81.12; H, 6.27; N, 5.97.

3-(4-Nitrophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**22b**).

This compound had mp 230° dec (from ethanol), yield 70%; nmr: δ 2.90 (2H, m, CH_2), 3.90 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 4.70 (1H, m, CH), 6.80 (1H, s, Ar), 7.00 (1H, s, Ar), 7.60 (2H, d, J = 8.6 Hz, Ar), 8.20 (2H, d, J = 8.6 Hz, Ar), 8.30 (1H, br s, CH=N).

Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.12; N, 8.97. Found: C, 65.29; H, 5.20; N, 8.91.

3-Phenyl-6,7-methylenedioxy-3,4-dihydroisoquinoline (**22c**).

This compound had mp 89-90° (from ethanol), yield 85%; nmr: δ 2.85 (2H, m, CH_2), 4.65 (1H, m, CH), 6.00 (2H, s, OCH_2O), 6.65 (2H, s, Ar), 7.35 (5H, m, Ar), 8.35 (1H, m, CH=N).

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.49; H, 5.18; N, 5.58. Found: C, 76.53; H, 5.12; N, 5.51.

1-Methyl-3-phenyl-6,7-methylenedioxy-3,4-dihydroisoquinoline (**22d**).

This compound had mp 62-63° (from ethanol), yield 75%; nmr: δ 2.65 (3H, s, CH_3), 3.00 (2H, m, CH_2), 4.70 (1H, m, CH), 6.15 (2H, s, OCH_2O), 6.80 (1H, s, Ar), 7.15 (1H, s, Ar), 7.50 (5H, m, Ar).

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.98; H, 5.66; N, 5.28. Found: C, 76.91; H, 5.59; N, 5.30.

trans-1-(3,4-Dimethoxyphenyl-2-(4-nitrophenyl)ethene (**23**).

It was obtained from **13** or **14** with EPP [6], yield, see Table I. This compound had mp 125-126° (from ethanol); ir: 1356 and 1535 (N-O), 960 (*trans* HC=CH) cm^{-1}; nmr: δ 3.95 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 6.75-7.25 (5H, m, Ar and CH=CH), 7.10 (2H, d, J = 8.7 Hz, Ar), 8.15 (2H, d, J = 8.7 Hz, Ar).

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.37; H, 5.26; N, 4.91. Found: C, 67.39; H, 5.21; N, 4.93.

1-(3,4-Dimethoxyphenyl)-2-(4-nitrophenyl)-3-(4-nitrobenzyl)-5,6-dimethoxyindane (**24**).

The diastereoisomeric mixture was obtained from **13** or **14** by treatment with EPP [14], yield, see Table I. The mixture had mp 84-90° (from ethanol); nmr (mixture): δ 2.58 (d, J = 7.4 Hz), 2.98 (d, J = 7.4 Hz), 3.14-3.50 (m), 3.58, 3.69, 3.76, 3.77, 3.84, 3.85, 3.93 (s, OCH_3), 4.00-4.26 (m), 4.48 (d, J = 8.1 Hz), 4.71 (d, J = 8.8 Hz), 5.98 (s), 6.37-6.78 (m, Ar), 6.98-7.52 (m, Ar), 7.91-8.23 (m, *p*-nitroPh); ms: m/z (% relative intensity) 570 (M^+, 10.3), 435 (100), 296 (12.6), 285 (13.8), 136 (12.6).

Anal. Calcd. for $C_{32}H_{30}N_2O_8$: C, 67.37; H, 5.26; N, 4.91. Found: C, 67.37; H, 5.20; N, 4.87.

Acknowledgements.

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