NOVEL CONDENSING AGENTS FOR BISCHLER-NAPIERALSKI TYPE CYCLODEHYDRATION

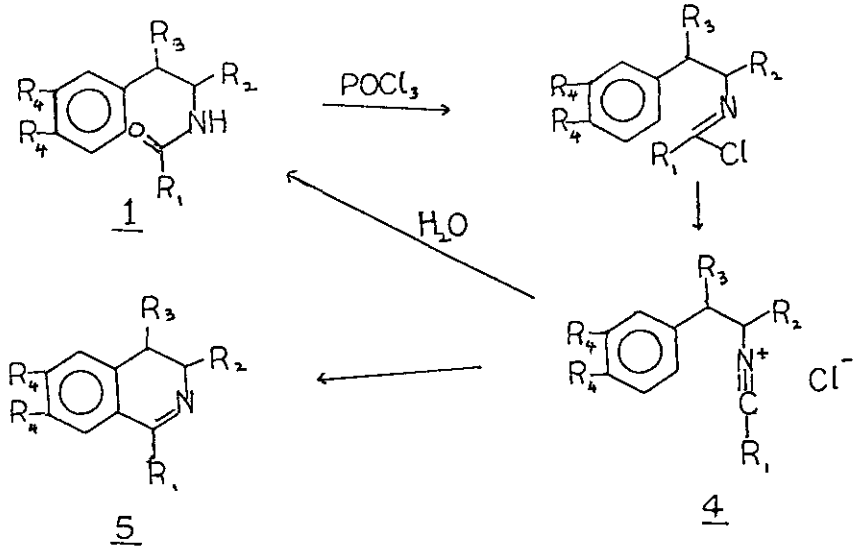
Sreeramulu Nagubandi* and G. Fodor

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506

*Present address: Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901

Abstract - Trifluoroaceticanhydride and trifluoromethyl sulfonyl anhydride are used in Bischler-Napieralski type cyclization. Starting from the appropriate amides, the dihydroisoquinolines are formed in excellent yields.

Bischler-Napieralski (BN) reaction is very widely used[1] in the synthesis of isoquinoline derivatives, however, classical Bischler type cyclizations require drastic conditions of refluxing the amide with phosphoryl chloride or phosphorus pentoxide, in xylene or toluene etc. During the elucidation[2-4] of the mechanism for BN cyclization, we felt the need for milder conditions for the cyclization. The imidoyl halide formed as an intermediate in BN reaction dissociates to a nitrilium salt[2] (Scheme 1) and this induced a search for better leaving groups than chloride of the imidoyl derivatives.



Scheme 1

R_1 = Ph, CH_3 pOMePh, R_2 = H,Ph, R_4 = H,OCH_3.

Two such groups are trifluoroacetic anhydride (TFAA) and trifluoromethyl sulfonic anhydride (TFMSA). The reaction between the amide (1) and TFAA or TFMSA is very fast to give the imidoyl trifluoroacetate (isoimide)[5] and imidoyl trifluoromethyl sulfonate (mixed anhydride) respectively (Scheme 1). Even though the reaction of TFMSA with aldoximes is known, the above imidoyl derivitives are not well known in the literature. Campagna et al,[6] proposed a mechanism for preparation of nitriles from amides, where the imidoyl trifluoroacetate structure was assumed to be an intermediate, but they did not isolate the intermediate. Prior to their publication, we already have isolated[2] various imidoyl trifluoroacetates and imidoyl trifluoromethyl sulfonates (Tables 1 and 2) from N-substituted amides.

TABLE 1

Preparative and Spectroscopic Data for Imidoyl Trifluoroacetates

Structure 2 $R_1R_2R_3R_4$	X	Yield	IR (NaCl) Nujol. 1500-1800 cm^{-1}	=N-CHR"*	=NCHR'CHR"-*	Other	Aryl Signals
PhHHOMe	$COCF_3$	100%	1780(m),1720(vs), 1700(vs),1595(s), 1510(s)	3.98 (t) J = 6.5Hz	2.88 (t) J = 7Hz ($-OCH_3$)	3.77(t) 3.83(s)	6.58(m) 7.53(s)
PhHHH	$COCF_3$	100%	1800(m),1730(vs), 1601(vs),1580(w), 1525(vs)	3.97 (t) J = 7.5Hz	2.92 (t) J = 8.5Hz	----	7.17(s) 7.50(s)
PhPhHH	$COCF_3$	90%	1730(m),1690(s), 1600(m),1575(w)	a multiplet# 3.25 and 4.12	between	12.00(s)	5.75(d) 7.25(s)
MePhHH	$COCF_3$	91%	≠	3.63 (dd)	5.46 (t)	2.00(s) $-CH_3$ 11.93(s)	7.23(s) 7.67(s)
pMeOPhPhHH	$COCF_3$	93%	1800(m),1740(m), 1690(s),1605(s), 1505(s)	5.90 (t)	3.52 (d)	3.85(s)	6.90 and 7.53(AA'XX')± 7.32(s) 6.72(s)
PhHPhH	$COCF_3$	100%	1720,1700&1680(vs) 1600(s),1575(w)	4.45(broad singlet)+			6.85(s) 7.33(s)
pMeOPhHHMeO	$COCF_3$	94%	1760(w),1720(s), 1660(s),1600(vs), 1495(s)	4.03 (t)	2.98 (t) J = 7Hz	3.93 and (OCH_3)	7.63(AA'XX') 6.77(d)

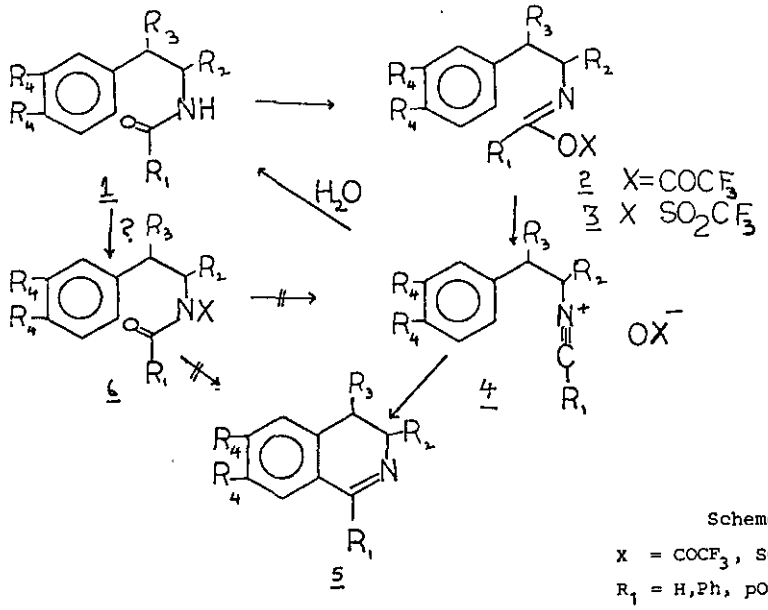
#Appears as a cluster of doublets. ≠IR spectra of the isoimide could not be obtained as the decomposition was very fast even at room temperature. ±For the para disubstituted aryl ring protons. + Appears to have superimposed on a doublet. *This peak is somewhat superimposed by other ($-OCH_3$) peaks.

TABLE 2: Preparative and Spectral Data of Various Imidoyl Trifluoromethylsulfonates

Structure 3 $R_1R_2R_3R_4$	X	Yield	IR (NaCl) Nujol. 1500-1700 cm^{-1}	NMR =NCHR'-	NMR =NCHR'CH_2#	NMR Other#	NMR Aryl Signals
PhHHH	SO_2CF_3	80-90%	1725(m)	4.00+	3.33	14.73(s)	7.47(m)
			1650(m)				
			1580(s)				
MeOPhHHH	SO_2CF_3	90-92%	1725(m)+	4.57(t)	3.30(t)	3.90(s)	7.04(d)
			1650(m)	J= 7Hz	J = 7Hz	(OCH_3)	7.93(d)
			1610(s)				7.32(s)
			1500(m)				
PhHHMeO	SO_2CF_3	90-94%	1630(s)				
			1605(m)	3.90≠	3.20(t)	3.73(s)	6.93(s)
			1550(s)		J = 7Hz	4.02(s)	7.07(s)
			1515(s)			($-OCH_3$)	7.70(s)
MeOPhHHOMe	SO_2CF_3	90%	1640(m)	4.45+	2.97(s)+	3.70(s)+	6.87(d)+
			1620(s)				7.60(d)+
			1570(m)				
			1525(m)				
MeHHH	SO_2CF_3	90%		decomposes			
MeOPhPhHH	SO_2CF_3		1700(s)				
			1600(s)	decomposes very fast#			
			1545 and				
			1525(m)				
			1500(s)				

#Also see experimental section for complete spectral data. +Broad peak. ≠Approximate since this peak is superimposed by other ($-OCH_3$) peaks.

Similar to the mechanism we worked out[2,3], these imidoyl derivatives (isoimides and mixed anhydrides) cyclize, via the nitrilium salt (4) to yield the corresponding dihydroisoquinoline derivatives (Scheme 2). Formation of an isoimide (3,X=$COCF_3$) is instantaneous upon the addition of the reagent, but the cyclization is slow enough to monitor with NMR. The amide shows two singlet absorptions at 3.73 ppm and 3.79 ppm for the six methoxy protons which became two singlet absorptions at 3.70 ppm and 3.83 ppm in the imidoyl derivative (for = N-$\underline{CH_2}$ -). The reaction of triflyl anhydride with various amides is instantaneous to give the mixed anhydride which cyclizes rapidly, especially when electron-donating groups are available in the phenyl ring.



Scheme 2

X = $COCF_3$, SO_2CF_3 R_2 = H

R_1 = H,Ph, $pOCH_3Ph$ R_3 = H,Ph

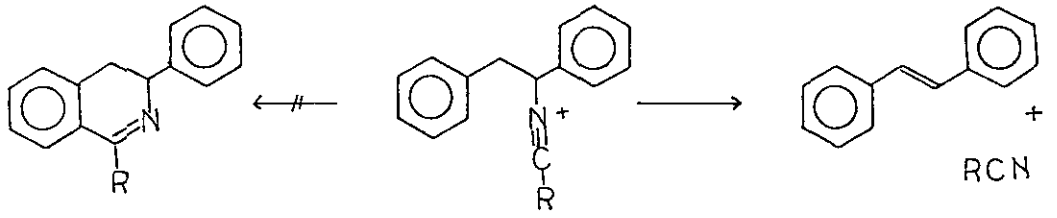
R_4 = H, OCH_3

Whenever TFAA reacted with 2-phenethyl amides, the reaction products depend on the competition between the N-trifluoroacetylation (6) and O-trifluoroacetylation (2). However, Thomson[7] stated that low temperatures appeared to be a prerequisite to N,N-diacylation and that at temperatures above 0° C, the reaction was accompanied by dehydration to a large extent. In all the preparations of isoimides and mixed anhydrides, the temperatures were never lowered below room temperature (around 20-25° C). Our attempt to N-acylate or benzoylate various amides (of the type shown in Table 1) at room temperature was unsuccessful. Similarly, the reaction between amides and TFMSA could result in two different compounds. Again, the O-trifluoromethyl sulfonation was preferred over the N-trifluoromethyl sulfonation.

Thus, the O-acylation prodominates and this is proved by isolation, and mass spectral analysis[4] of the intermediate. In addition, the dihydroisoquinoline formation is not possible from the N,N-diacylated derivative unless it later rearranges to O-acylated compound.

The formation of "retro-Ritter" reaction products, as observed[2-4] with other condensing agents, from 1,2-diphenethyl benzamide were inevitable when TFAA or TFMSA were used. The transition state for the retro-Ritter products probably very much resembles the extended conjugation in products. The N-(1,2-diphenethyl)-acetamide shows a single absorption at 1.83 ppm for the three methyl protons. When TFMSA was added, this singlet moved to 1.87 ppm, and within 5-6 hours at room temperature, a new singlet appeared at 2.28 ppm (for CH_3CN) which later increased in intensity

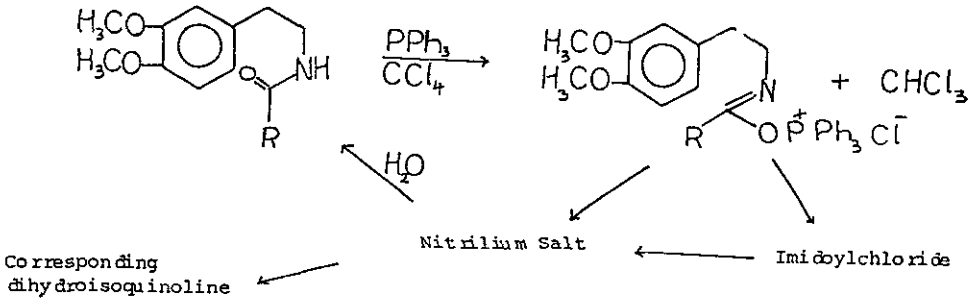
while the singlet absorption at 1.87 ppm decreased. If the nitrilium salt is stabilized by delocalization of electrons, the undesirable decomposition of the nitrilium salt should be overcome. Accordingly, an appropriate amide, the N-(1,2-diphenethyl)-p-methoxy benzamide was reacted with TFAA and TFMSA. However, only olefin and no cyclized product was isolated, as expected from the retro-Ritter reaction (Scheme 3).



Scheme 3

R = CH_3, ph, pOCH_3ph

Appel et al[8] observed that triphenylphosphine and carbon tetrahalides convert amides into imidoyl halides. This observation offered us a possibilty of cyclodehydration using similar systems. We assumed that the mechanism involved an imidoyl oxyphosphonium intermediate. Indeed N-(2[3,4-dimethoxyphenyl]-ethyl)-benzamide underwent cyclization upon heating with triphenylphosphine and carbon tetrachloride. We suggest Scheme 4 to account for the reaction.



Scheme 4

The above novel condensing agents are very convenient to use[9] at low temperatures in the cyclodehydration of Bischler-Napieralski and related type of reactions.

EXPERIMENTAL

Melting points were determined on a model 1A 6304 electrothermal appartus and are uncorrected. B.P.'s are also uncorrected. IR spectra were recorded on Perkin-Elmer models 137 and 137G, Beckman IR-8 or Bausch and Lomb 250 spectrophotometers. The term "solution" is used with chloroform-d as the solvent (unless another solvent is mentioned) and the term "mull" is used for nujol. The proton nmr spectra (H_{nmr}) were obtained using Varian Associates model T-60, EM-360, and HA-60 with TMS an interral standard.

N-(2-phenethyl)-benzimidoyl trifluoroacetate (2a) (General Procedure).

The N-(2-phenethyl)-benzamide (1 g, 0.0044 mole) was suspended in anhydrous ether (25 ml) and trifluoroacetic anhydride (1.85 g, 0.0088 mole) was added dropwise, in the dry box. The solvent was evaporated from the reaction mixture. The H_{nmr} ($CDCl_3$) spectrum showed that the residue consisted of the O-trifluoroacetyl isoimide and partly its trifluoroacetate salt. The latter could be converted to the isoimide by heating the oily residue in a vacuum, in a 60°C oil bath for 1-2 hr. The oily isoimide was obtained in quantitative yield and was not further purified.

IR (neat): 3010 (w), 2950 (m), 2925 (w), 2845 (m), 1800 (m), 1730 (vs), 1710 (vs), 1601 (vs, -C=N), 1580 (w), 1525 (vs), 1470 (s), 1420 (m), 1395 (w), 1370 (m), 1325 (m), 1270 (vs), 1205 (m), 1170 (vs), 1120 (m), 1025 (vs), 970 (w), 855 (s), 815 (m), 770 (s), 735 (m), 695 (m) cm^{-1}.

H_{nmr} ($CDCl_3$): 2.92 (t, J = 8.5Hz, 2H, $C_6H_5CH_2CH_2$-), 3.97 (t, J = 7.5Hz, 2H, $C_6H_5CH_2CH_2$-), 7.17 (broad s, 5H, C_6H_5), 7.50 (broad s, 5H, C_6H_5).

Cyclization of N-(2-[3,4-dimethoxyphenyl]-ethyl)-benzimidoyl trifluoroacetate (2e) to 1-phenyl-3,4-dihydro-6,7-dimethoxyisoquinoline.

The compound 2e (0.98 g, 0.0026 mole) was heated under vacuum, at 60-70°C (bath temperature) for about 5-6 hr. The reaction was monitored by nmr of withdrawn samples. A yellow solid was obtained upon tituration of the reaction mixture with anhydrous ether (10-15 ml). The H_{nmr} (in $CDCl_3$) spectrum indicated that the solid was the cyclized, isoquinoline salt. The above yellowish solid was dissolved in water (15 ml), and made alkaline by 15% KOH solution (25 ml). Upon stirring for 30 min. a white solid was precipitated and filtered, yield 90.1%, m.p. 123-125°C. The spectral characteristics were identical with those of the authentic sample.

Cyclization of an amide via the imidoyl trifluoroacetate without isolation of the intermediate.

In a three necked flask (150 ml) equipped with a reflux condenser, dropping funnel, the N-(2-phenethyl)-benzamide (1a) (2 g, 0.0088 mole) was suspended in anhydrous xylene (75 ml). To this stirred suspension, trifluoroacetic anhydride (4.2 g, 0.20 mole) was added dropwise under a continuous flow of dry nitrogen. At the end of the addition, the reaction mixture became homogeneous and was refluxed for about 6 hr. After cooling, the contents of the reaction vessel

were poured onto crushed ice (100 g). The organic layer was separated and the aqueous layer was basified with 15% aqueous sodium carbonate solution. Then the aqueous layers were extracted with chloroform, the extracts combined, dried and the amide collected upon the evaporation of the solvent. The spectra were identical to thos of the authentic sample of the amide.

Attempted cyclization of N-(1,2-diphenethyl)-benzimidoyl trifluoroacetate (2b).

A. The isoimide (1 g) was dissolved in anhydrous chloroform (15 ml) and was allowed to cyclize for about 5 days and was occasionally stirred. The solvent was removed on the Rotavapor and 15% KOH solution (30 ml) was added to the residue. The yellow oil which separated was extracted with chloroform (2 x 15 ml). The IR and H_{nmr} spectrum of the oily residue of the solvent, indicated to consist of a mixture of trans-stilbene, benzonitrile and some amide based on comparison with authentic samples.

B. N-(1,2-diphenethyl)-benzimidoyl trifluoroacetate (2b) (1.18 g, 0.0029 mole) was heated (bath temperature of 60°C) under vacuum (0.04 torr) for about 50-70 min. The reaction mixture was dissolved in anhydrous ether (15 ml) after cooling. Petroleum ether was added drop by drop to the etheral solution until a slight turbidity appeared. After standing for several hours, the mixture of trans-stilbene and N-(1,2-diphenethyl)-benzamide (1b) precipitated and were filtered by suction. The latter had to be formed by hydration of the nitrilium salt (4b). The filtrate contained benzonitrile and was obtained after removing the solvent. The spectra of thus obtained benzonitrile was identical with that of the authentic sample. The stilbene and the amide were separated through their difference in the solubility in ethyl ether. The yield of stilbene was 66.6% and was identified by comparing the spectra with that of the authentic sample.

Attempted cyclization of N-(1,2-diphenethyl)-p-methoxybenzimidoyl trifluoroacetate (2i).

The isoimide from the previous experiment was heated (bath temperature 60-70°C) under reduced pressure (0.04 torr) for about 6 hr. The reaction mixture was dissolved in anhydrous ether (20 ml), and was extracted with 15% KOH solution (2 x 30 ml). The ethereal layer was dried over anhydrous sodium sulfate and a pale yellowish oil was obtained on evaporation of the solvent. The spectral evidence (IR and nmr) indicated that the oil was indeed a mixture of trans-stilbene, p-methoxybenzonitrile and minor amounts of the corresponding amide (1i). The nitrilium salt was therefore not stabilized by an electron donor group in the benzimidoyl moiety.

Attempted cyclization of N-(1,2-diphenethyl)-acetimidoyl trifluoroacetate (2c).

N-(1,2-diphenethyl)-acetamide (1c) (1.05 g, 0.0044 mole), trifluoroacetic anhydride (4.40 g, 0.020 mole) and anhydrous ether (25 ml) were used to prepare this "mixed anhydride". The reaction of the amide and the formation of the "isoimide" was almost immediate. The NMR spectrum

of the reaction mixture, after the evaporation of the solvent, clearly indicated that the retro-Ritter reaction products formed, hence the cyclization of this to the corresponding isoquinoline (5c) was not successful.

H_{nmr} ($CDCl_3$): 2.00 (s, 3H, $-CH_3$), 3.63 (doublet of doublets due to the chemical shift of non-equivalance of the methylene protons, 2H, $C_6H_5CH_2-$), 5.46 (uneven q, 1H, $C_6H_5CHCH_2C_6H_5$), 7.23 (s) and 7.67 (s, for the aromatic protons), 11.93 (s, =NH-).

Preparation of imidoyl triflates.

N-(2-phenethyl)-benzimidoyl trifluoromethylsulfonate (3a).

The reaction between the N-(2-phenethyl)-benzamide (1a) (1 g, 0.0044 mole) and triflyl anhydride (2.82 g, 0.01 mole), occurred very fast according to the general technique described under VI. The H_{nmr} ($CDCl_3$) spectrum of the residue, after evaporation of the solvent, showed it to be a mixture of N-(2-phenethyl)-benzimidoyl trifluoromethylsulfonate (9a) and its salt with trifluoromethylsulfonic acid.

IR (neat): 2950 (s, broad), 1725 (m, broad), 1650 (m), 1600 (s), 1580 (s), 1480 (w), 1440 (m), 1390 (m), 1300 (vs, the traces of either can give rise to this very broad peak), 1020 (s), 920 (m, broad), 750 (m), 695 (s, broad) cm^{-1}.

H_{nmr} ($CDCl_3$): 3.33 (broad, 2H, $C_6H_5CH_2-$), 4.00 (broad, 2H, $C_6H_5CH_2CH_2O$), 7.47 (uneven multiplet, 10H), 14.73 (s, 1h).

The above "mixed anhydride" has failed to undergo cyclization to yield 1-phenyl-3,4-dihydroisoquinoline (5a); however, the corresponding amide (1a) was recovered upon alkaline hydrolysis.

N-(2-phenethyl)-p-methoxybenzimidoyl trifluoromethylsulfonate (3h).

The N-(2-phenethyl)-p-methoxybenzamide (1h) (1 g, 0.004 mole) triflyl anhydride (2.26 g, 0.008 mole) were allowed to react in anhydrous ether (25 ml) at 20°.

H_{nmr} ($CDCl_3$): 3.30 (t, J = 7Hz, 2H, $C_6H_5CH_2-$), 3.90 (s, 3H, $-OCH_3$), 4.57 (t, J = 7Hz, 2H, $C_6H_5CH_2CH_2-$), 7.04 and 7.93 (d, J = 9Hz, 4H, AB splitting, AA' XX' protons of $-C_6H_4OCH_3$), 7.32 (s, 5H, C_6H_5).

The mixed anhydride did not change its spectra even after several days and there was no indication of cyclization even after heating this mixture. However, this reaction mixture was hydrolyzed with a base to the amide (1h).

N-(2-[3,4-dimethoxyphenyl]-ethyl)-benzimidoyl trifluoromethylsulfonate (3e).

The N-(2-[3,4-dimethoxyphenyl]-ethyl benzamide (1e) (7.14 g, 0.025 mole) and triflyl anhydride (9 g, 0.0319 mole) were allowed to react at room temperature to give immediately an oil which later turned to a semisolid.

IR (mull): 2940 (vs, broad), 2870 (s), 1630 (s), 1605 (m), 1550 (s), 1515 (s), 1480 (w), 1460 (s, broad), 1410 (w), 1370 (s), 1325 (s), 1305 (w), 1280 (s), 1240 (s), 1220 (m), 1180 (w), 1150 (s), 1140 (s), 1025 (s), 980 (w), 875 (w), 780 (w), 725 (s), 700 (m), 635 (vs) cm^{-1}.

H_{nmr} ($CDCl_3$): 3.20 (t, J = 7Hz, 2H, $-NHCH_2CH_2-$), 3.73 (s, $-OCH_3$), 4.02 (s, $-OCH_3$), 6.93 (s), and 7.07 (s, 3H), 7.07 (s, 5H), 10.08 (s, broad, =NH, 1H), 14.68 (s, 1H, $-SO_3H$).

The other methylene group ($-NHCH_2CH_2-$) appears approximately around 3.90 ppm; however, it was superimposed by the two singlets (OCH_3) and the integration showed 8 protons.

N-(2-[3,4-dimethoxyphenyl]-ethyl)-p-methoxy-benzimidoyl trifluoromethyl-sulfonate (3i).

The N-(2-[3,4-dimethoxyphenyl]-ethyl)-p-methoxybenzamide (2.56 g, 0.008 mole) and triflyl anhydride (3.0 g, 0.0106 mole) were allowed to react at 20°. The mixed anhydride separated as an oil which upon stirring for 1 hr. solidified to an orange solid.

The above solid was filtered by suction and washed with anhydrous ether (20 ml), in the dry box. m.p. 173-175°C.

IR (neat): 2950 (vs. broad), 2865 (vs), 1540 (m), 1620 (s, -C=N), 1570 (m), 1525 (m), 1465 (s), 1380 (s), 1340 (m), 1280 (s), 1240 (s), 1225 (m), 1175 (s), 1125 (m), 1025 (s), 990 (w), 995 (w), 840 (m), 825 (m), 790 (m), 735 and 725 (w), 645 (m), 635 (s) cm^{-1}.

Thirty hours after the addition of the triflyl anhydride, the IR spectrum of the partly oily mixture showed a peak at 2350 (w) in addition to an overall blurred spectrum, indicating the presence of the nitrilium ion intermediate.

The amide and the triflyl anhydride were also allowed to react in $CDCl_3$ and this reaction mixture was used for spectral measurements.

H_{nmr} ($CDCl_3$): 2.97 (broad s, $=NCH_2CH_2-$), 3.70 (broad s, $-OCH_3$), 4.45 (broad s, $=NCH_2CH_2-$), 6.87 (broad d, J = 8Hz), 7.60 (broad d, J = 7.5Hz), and 11.57 (s, =HN).

As the reaction proceeded, a singlet appeared at 4.10 ppm ($-OCH_3$) which increased (relative to other $-OCH_3$ peak). At the end of five days at room temperature, the reaction appeared to have been completed and hence was worked up in an alkali media (to remove the acid, if any) to yield the required isoquinoline.

H_{nmr} ($CDCl_3$): 3.13 (uneven, t, J = 7.5Hz, $=HCH_2CH_2-$), 3.77 (s), and 4.05 (s -the two methoxy groups at carbons 6 and 7 in the isoquinoline), 3.92 (s, $-C_6H_4OCH_3$), 7.10 (d, J = 7.5Hz), and 7.73 (d, J = 8Hz), for the ortho and meta protons of aryl group at carbon 1 of the isoquinoline; 6.97 (d, J = 7Hz, the aromatic hydrogens of carbons 5 and 8 of the isoquinoline) was superimposed on the doublet centered at δ 7.10.

In an attempt to repeat the cyclization (after identifying the mixed anhydride), the amide was isolated, which formed due to the partial hydrolysis of the imidoyl triflate, or to hydration of the nitrilium salt.

N-(1,2-diphenethyl)-acetimidoyl trifluoromethylsufulfonate (3c).

The N-(1,2-diphenethyl)-acetamide (1c) (1.05 g, 0.004 mole) and triflyl anhydride (2.26 g, 0.0080 mole) were allowed to react in anhydrous ether. After evaporation of the solvent, the H_{nmr} ($CDCl_3$) spectrum showed the decomposition reaction in progress yielding acetonitrile and stilbene.

Attempts to isolate N-(1,2-diphenethyl)-p-methoxybenzimidoyl trifluoromethylsulfonate (3i).

The N-(1,2-diphenethyl)-p-methoxybenzamide (1i) (1 g, 0.003 mole) and triflyl anhydride (1.97 g, 0.007 mole) were used in the general procedure to prepare this mixed anhydride. The H_{nmr} ($CDCl_3$) spectrum of this oily residue showed it to be a mixture of trans-stilbene, p-methoxybenzonitrile (also matrix-bound ether, even after several days at low and reduced pressure).

H_{nmr} ($CDCl_3$): 3.83 (s, 3H, $-OCH_3$), 7.06 (s, 2H, $C_6H_5CH{=}CHC_6H_5$), 7.33 (m, all aromatic protons), 14.64 (s, CF_3SO_3H).

Cyclization of Imidoyl triflates.

The cyclization of the imidate, 3i, was comparatively fast, even at room temperature. The corresponding isoquinoline (5i) was collected after the usual work up in the basic media. The spectra was identical with that of the authentic sample.

H_{nmr} ($CDCl_3$): 2.70 (t, 2H, $=NCH_2CH_2$), 3.70 (s, 3H, $-OCH_3$), 3.92 (s, 3H, $-OCH_3$), 6.78 (s), and 7.45 (m, total of 7H). Here also the other methylene was around δ 3.98 superimposed by two singlets at δ 3.70 and δ 3.92.

The ratio of protons in the region δ 7 to 8, versus that in the region 3.83 ppm ($-OCH_3$) was 16:3. The 16 hydrogens included 14 aromatic hydrogens and 2 aliphatic hydrogens of the trans-stilbene. The traces of ether were also seen at δ 1.40 (t) and δ 4.03 (q).

The reaction between the N-(1,2-diphenethyl)-p-methoxybenzamide (1i) and triflyl anhydride was relatively fast and the resulting mixed anhydride almost immediately decomposed to yield the retro-Ritter reaction products.

Preparation of different carboxamides and sulfonamides.

N-(2-phenethyl)-trifluoroaceteamide (1s) (General Procedure).

To a magnetically stirred solution of 2-phenethylamine (6.05 g, 0.05 mole), in dry chloroform (20 ml), trifluoroacetic anhydride (15.75 g, 0.075 mole) was dropwise added under the hood. After the reactants were allowed to react for about 1 hr. the mixture was extracted with water and the organic layer was dried (Na_2SO_4). The crude amide was obtained and was recrystallized from ether-petroleum ether. m.p. 57-59°C.

Anal. Calcd. for $C_{10}H_{10}NOF_3$: C, 55.28%; H, 4.64%; N, 6.54%.

Found: C, 55.35%; H, 4.71%; N, 6.32%.

N-(2-phenethyl)-benzenesulfonylamide.

The sulfonylamide was prepared according to the procedure given for (1s) using 2-phenethylamine (3.25 g, 0.025 mole). Yield 55%, m.p. 68.570.5°C.

N-(2-[3,4-dimethoxyphenyl]-ethyl)-trifluoroacetamide (1u).

2-(3,4-dimethoxyphenyl)-ethylamine (5.43 g, 0.03 mole) was triturated with trifluoroacetic anhydride (10.5 g, 0.05 mole) at 0°C. After stirring the reaction mixture for about 30-45 min. water (35 ml) was added to the resulting solid. The precipitate was filtered with suction and washed thoroughly with water. The crude amide was recrystallized from dry ether-petroleum ether solvent mixture. Yield 65% (5.40 g), white fluffy crystals, m.p. 86-88°C.

Anal. Calcd. for $C_{12}H_{14}NO_3F_3$: C, 51.96%; H, 5.09%; N, 5.05%; O, 17.32%; F, 20.57%.

Found: C, 52.08%; H, 5.12%; N, 4.95%.

Preparation of N-(2-[3,4-dimethoxyphenyl]-ethyl)-benzene-sulfonylamide.

Excess benzenesulfonyl chloride (commercial grade) was added dropwise to 2-(3,4-dimethoxyphenyl)-ethylamine (1.81 g, 0.01 mole) and the reaction mixture was stirred for 1 hr. at 0°C. To this mixture, water was added and then it was extracted with ether (2 x 50 ml). The ethereal layers were combined, dried (Na_2SO_4) and the solvent was removed on Rotavapor. The resulting crude sulfonylamide was recrystallized in etherpetroleum ether solvent mixture. Yield 45% (1.45 g), m.p. 90.5-91.5°C.

Anal. Calcd. for $C_{16}H_{19}NO_4S$: C, 59.78%; H, 5.96%; N, 4.36%; O, 19.93%; S, 9.96%.

Found: C, 60.09%; H, 6.15%.

Attempts to benzoylate N-(2-[3,4-dimethoxyphenyl]-ethyl)-trifluoroacetamide (1u).

To a stirred solution of benzoyl chloride (0.29 g, 0.00206 mole) in anhydrous chloroform (20 ml), spectral grade pyridine (0.987 g, 0.0124 mole) was added and the reaction mixture was cooled to about -60°C. To this thick slurry complex, a saturated solution of N-(2-[3,4-dimethoxyphenyl]-ethyl)-trifluoroacetamide (1u) (0.55 g, 0.00199 mole) in anhydrous acetone (spectral grade) was added. The reaction mixture was warmed slightly periodically to facilitate a continuous stirring for about 8 hr. The solvent was evaporated under reduced pressure and anhydrous ether added to the resulting thick slurry. The pyridine salt was filtered with suction. The filtrate was washed with water. The dried ethereal layer was concentrated and pteroleum ether was added until some turbidity appeared. The resulting white fluffy solid, which appeared on standing, was filtered with suction and was identified as the starting material by its spectra, superimposed on that of the amide. The above method was repeated by adding excess of benzoyl chloride (dissolved

in anhydrous chloroform) to the amide in chloroform. The work up (as in the previous case) gave the starting material in quantitative yield.

Reaction of Benzenesulfonyl chloride with N-(2-phenethyl)-benzamide (1a).

To the solution of N-(2-phenethyl)-benzamide (2.55 g, 0.01 mole) in chloroform (25 ml) and pyridine (0.49 g, 0.0062 mole) at 0°C, the benzenesulfonyl chloride (2.12 g, 0.012 mole) was added. The mixture was stirred and allowed to react for 2 hr. It was washed with water and then extracted with 15% aqueous Na_2CO_3 solution. The chloroform layer was dried and the solvent was removed. The crude product was obtained and its spectra were identical with that of the starting material.

Attempts to isolate the retro-Ritter reaction products from the reaction of N-(1,2-diphenethyl)-benzamide (1b) and benzenesulfonyl chloride.

The N-(1,2-diphenethyl)-benzamide (1b) was suspended in excess of pyridine and was cooled to 0°C. An excess amount of benzenesulfonyl chloride was added dropwise. The reaction mixture was stirred for 1 hr. The pyridine salt was precipitated out upon the addition of anhydrous ether and this salt was filtered by suction. The filtrate was twice washed with water (25 ml each) dried (Na_2SO_4), filtered and the solvent was evaporated. To this solid 15% Na_2CO_3 (25 ml) was added and the mixture was extracted with ether (2 x 25 ml). The extracts were combined, dried (Na_2SO_4) and concentrated (to a few ml). The petroleum ether was added to precipitate out the product, which later was filtered with suction and identified as the starting material.

Ring closure with triphenylphosphine and carbon tetrachloride.

The triphenylphosphine (1.32 g, 0.005 mole) was melted in a flask, fitted with a reflux condenser with a drying tube filled with anhydrous calcium chloride (indicating) and a magnetic stirrer. To this molten triphenylphosphine, carbon tetrachloride (spectral grade, 0.76 g, 0.005 mole) was added. The resulting complex was stirred and the N-(2-[3,4-dimethoxyphenyl]-ethyl)-benzamide (1) (1.14 g, 0.004 mole) was added. About 5 to 10 ml of anhydrous chloroform was added to facilitate the homogenity. The reaction mixture was refluxed for 1 to 1.5 hr. After cooling, the mixture was triturated with dry ether and then more ether was added. The resulting yellowish solid was filtered with suction. The H_{nmr} ($CDCl_3$) spectrum of this solid showed it to be a mixture of triphenyl phosphine oxide and 1-phenyl-3,4dihydro-6,7-dimethoxyisoquinoline (5e). The NMR spectrum indicates it to be a mixture of the corresponding isoquinoline (61%), amide (about 39%) and triphenylphosphine oxide.

H_{nmr} ($CDCl_3$): 1.86 (broad, 2H, $=NCH_2-$), 3.73 and 4.03 (s, 3H each, OCH_3 of the isoquinoline), 3.80 (s, 6H, $-OCH_3$ of the amide), 6.80 (d), 7.06 (s), 7.63 (m for Ph_3PO). The traces of ether can also be seeen at 1.20 (t) and 3.37 (broad q).

REFERENCES

1. For a review of BN reaction see: M. Whaley and T.R. Govindachari, Org. Reactions 6, 74 (1951).
2. S. Nagubandi. Dissertation to West Virginia University, Morgantown, West Virginia (1976).
3. G. Fodor and S. Nagubandi. Tetrahedron Report. In Press.
4. S. Nagubandi and G. Fodor. Submitted for Publication.
5. C.G. McCarty and L.A. Garner. The Chemistry of Amidines and Imidates, ed. by S. Patai, John Wiley and Sons, New York, 1975, p. 220.
6. F. Campagna, A. Carotti, and G. Casini. Tetrahedron Letters, 1813 (1977).
7. Q.E. Thompson. J. Am. Chem. Soc. 73, 5841 (1951).
8. R. Appel, K. Warning, and K.D. Ziehn. Chem. Ber. 106, 3450 (1973).
9. We thank a referee for drawing our attention to the limitation of this procedure when a hydroxy group is present in the benzene ring. However, we believe a protected hydroxy group should not cause any problems.

Received, 30th April, 1980