FURANS AND PYRANS FROM γ-AND δ-KETONITRILES#

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Abstract - The spontaneous cyclization of δ-ketonitriles resulting from the reaction of malononitrile with either 1,2,3-triaryl-3-chloropropanones (II) or 1,2,3-triarylpropenones (III) in a basic medium leads to 2-amino-4,5,6-triaryl-3-cyano-4H-pyrans (V). On the other hand II and III react with potassium cyanide and an aromatic aldehyde in a hydroalcoholic medium to give γ-ketonitriles which cyclize to 2-arylideneimino-3,4,5-triarylfurans (VIII).

Some work has been previously reported on a synthesis of pyrans involving a cyclization through a cyano group and a carbonyl group [1-3]. This leads to 2-amino-4H-pyrans which are little known compounds[4]. Cyclization of a nitrile and a carbonyl group has also led to other heterocycles[5,6].

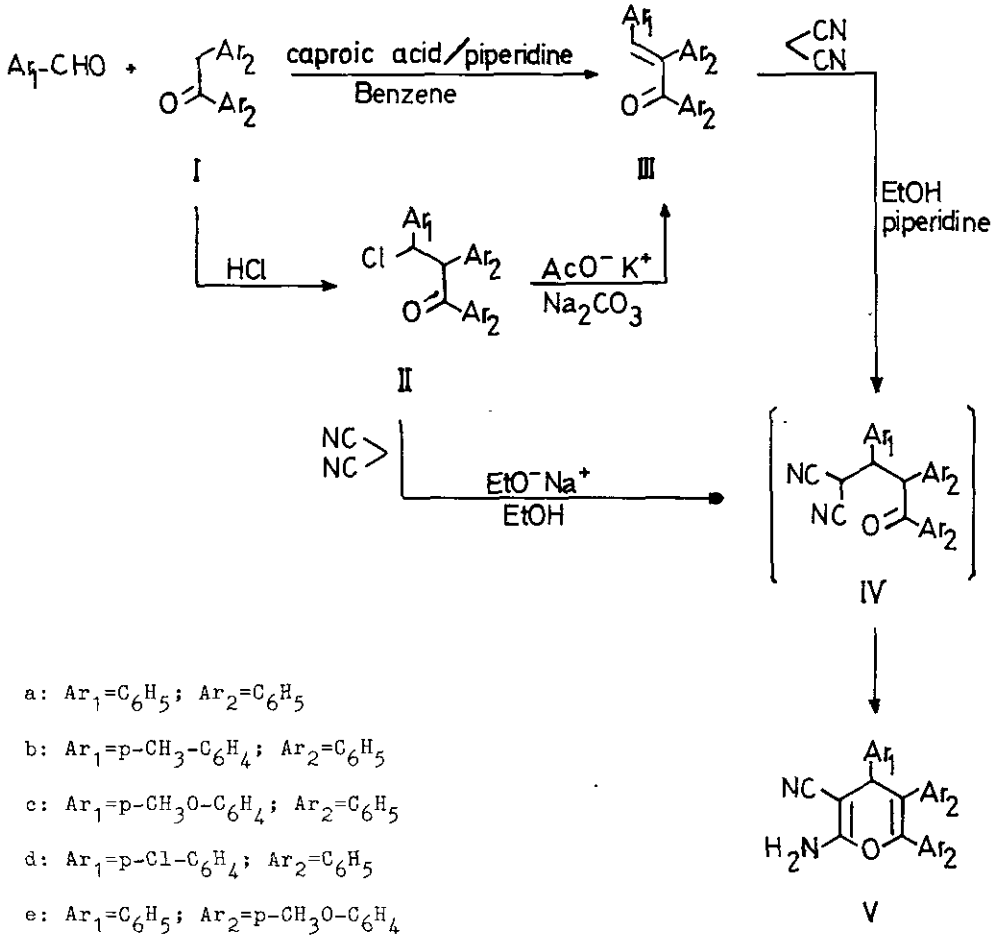
Now we wish to report on the cyclization of δ and γ-ketonitriles resulting from the reaction of either malononitrile or potassium cyanide with 1,2,3-triaryl-3-chloropropanones (II) or 1,2,3-triarylpropenones (III).

The 1,2,3-triaryl-3-chloropropanones needed for this work were prepared by reaction of deoxybenzoin, or its substituted derivatives, (I) with aromatic aldehydes and hydrogen chloride[7]. Dehydrohalogenation of II with potassium acetate and sodium carbonate leads to 1,2,3-triarylpropenones (III). The latter compounds can also be prepared directly from deoxybenzoin and aromatic aldehydes in the presence of caproic acid and piperidine[8].

Reaction of either 1,2,3-triaryl-3-chloropropanones (II) or 1,2,3-triarylpropenones (III) with malononitrile in a basic medium allows the synthesis of 2-amino-4,5,6-triaryl-3-cyano-4H-pyrans (V). In both cases, the reaction takes place easily in alcoholic solution and, monitored by means of analytical TLC, are complete in a few minutes at room temperature. Pyrans (V) are obtained in high

yields and are easily isolated in a pure state after precipitation.

The reaction can be explained (Scheme I) through the formation of an intermediate δ-ketonitrile (IV) which is not isolated, the cyclization of which by nucleophilic attack of the carbonyl oxygen at the cyano group, followed by an imino-enamino tautomerization leads to the 2-amino-4H-pyran ring. Ketonitrile IV originates from a nucleophilic displacement of chlorine by the anion of malononitrile if propanones II are used as the starting materials and from a Michael addition when propenones III are the reaction substrates.



a: $Ar_1=C_6H_5$; $Ar_2=C_6H_5$

b: $Ar_1=p\text{-}CH_3\text{-}C_6H_4$; $Ar_2=C_6H_5$

c: $Ar_1=p\text{-}CH_3O\text{-}C_6H_4$; $Ar_2=C_6H_5$

d: $Ar_1=p\text{-}Cl\text{-}C_6H_4$; $Ar_2=C_6H_5$

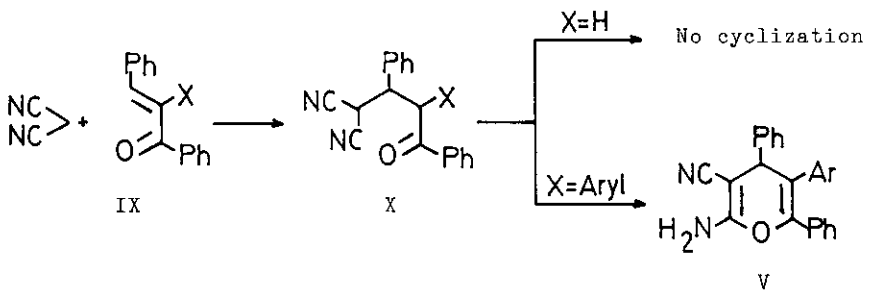
e: $Ar_1=C_6H_5$; $Ar_2=p\text{-}CH_3O\text{-}C_6H_4$

f: $Ar_1=p\text{-}CH_3\text{-}C_6H_4$; $Ar_2=p\text{-}CH_3O\text{-}C_6H_4$

SCHEME I

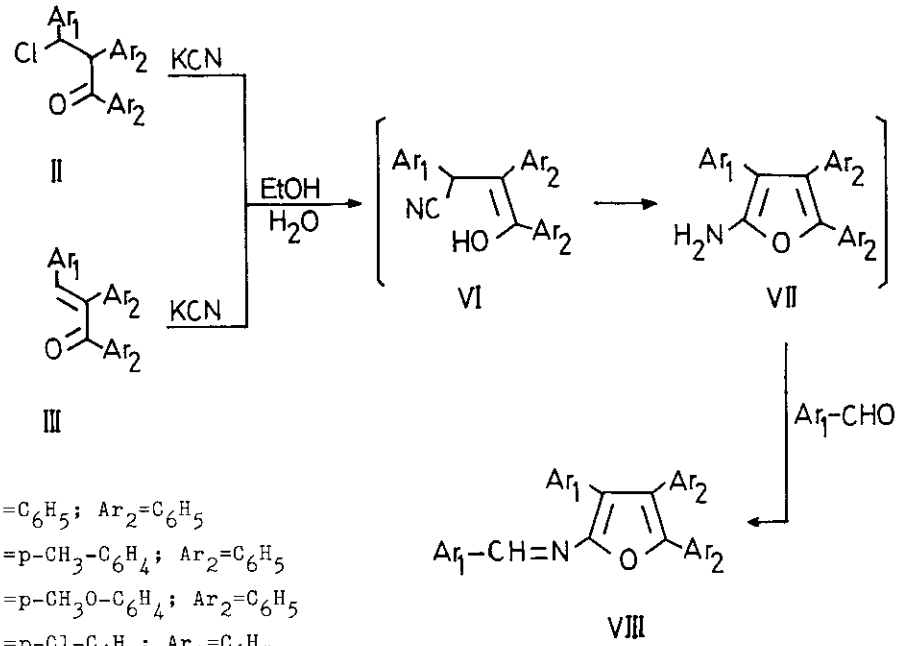
Pyrans V show in their IR spectra, together with the amino stretching band at 3500-3200 cm^{-1} and the cyano stretching band at 2200-2190 cm^{-1}, two strong bands at 1685-1670 cm^{-1} and 1660-1640 cm^{-1} due to the amino bending band and the C=C double bond of the pyran ring, as well as two strong bands at 1270-1250 cm^{-1} due to the enolic C-O-C bonds. In the ^{1}H-NMR spectra, the hydrogen at position 4 appears as a sharp singlet at 4.5-4.2 ppm and the amino group gives rise to a broad band which is usually included in the aromatic multiplet and can be identified by adding trifluroacetic acid to the sample.

It must be pointed out that the presence of the aryl group at position 5 is important for the cyclization. Thus, when malononitrile reacts with benzylideneacetophenone (IX,X=H), the cyclization does not take place and the adduct X (X=H)[5] is the product isolated from the reaction. Probably, the conjugation of the phenyl group with the enolic form of the carbonyl group in the intermediate δ-ketonitrile is responsible for the ease of cyclization.



Treatment of II or III with potassium cyanide in a hydroalcoholic medium should lead to a γ-ketonitrile. The cyclization of this by means of a nucleophilic attack of the carbonyl oxygen at the nitrile, should afford a 2-aminofuran ring[6], but the reaction failed and only a mixture of decomposition products was obtained in a number of attempts in different conditions (Note 1). This result is in agreement with the known instability of 2-aminofurans, which are only stable when the ring bears electron-withdrawing substituents[9,10].

However, if the starting materials are treated with potassium cyanide in the presence of an aromatic aldehyde, a cyclization does occur and furans VIII (Scheme II), in which the amino group is protected as a Schiff base, are obtained. The reaction takes place in one step and the intermediate adducts are not isolated.



a: Ar_1=C_6H_5; Ar_2=C_6H_5

b: Ar_1=p-CH_3-C_6H_4; Ar_2=C_6H_5

c: Ar_1=p-CH_3O-C_6H_4; Ar_2=C_6H_5

d: Ar_1=p-Cl-C_6H_4; Ar_2=C_6H_5

e: Ar_1=C_6H_5; Ar_2=p-CH_3O-C_6H_4

g: Ar_1=p-CH_3O-C_6H_4; Ar_2=p-CH_3O-C_6H_4

SCHEME II

The reaction is favoured if a small excess of potassium cyanide and aromatic aldehyde is used. The aromatic aldehyde to be put in the reaction medium must contain the same aryl group (Ar_1) as the one previously used for the preparation of III in order to rule out the possibility of a retro-Knoevenagel decomposition of this could provide another aldehyde to the reaction medium, thus allowing the formation of a mixture of two final furans. Furans VIII are easily isolated in a pure state as yellow, crystalline compounds and are obtained in good yield when 1,2,3-triarylpropenones (III) are used as starting materials; the yields resulting from 1,2,3-triaryl-3-chloropropanones (II) are much lower. The yields are also greatly influenced by the nature of the substituents present in the aromatic rings.

The C=N double bond of furans VIII gives rise to a quite strong band at about 1610 cm^{-1} and the C-O-C bonds to a band at about 1250 cm^{-1} and the proton of the -CH= group appears as singlet at 9.05-8.65 ppm in the ^{1}H-NMR spectra.

EXPERIMENTAL

Melting points were determined in a Buchi melting point apparatus in open capillary and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer in potassium bromide pellets. The ^{1}H-NMR spectra were obtained on a Varian T-60A spectrometer in the solvents as indicated. Chemical shifts are quoted in δ values, using TMS as an internal standard. Mass spectra were recorded on a Varian MAT 711 at 100 ev. Analytical TLC was performed on silica gel plates, using benzene/ethyl acetate as the eluent. Microanalyses were performed by "Centro Nacional de Química Orgánica" de Madrid.

1,2,3-Triaryl-3-chloropropanones (II).- 1,2,3-Triphenyl-3-chloropropanone (IIa) was prepared according to Kholer and Nygaard[7], 1,2-diphenyl-3-(p-methylphenyl)-3-chloropropanone (IIb) was obtained as reported by Klages[11] and the method of Das and Ghosh[12] was used for the preparation of 1,2-diphenyl-3-(p-methoxyphenyl)-3-chloropropanone (IIc). The remaining compounds, not reported in the literature, were prepared according to the following general procedure: 0.04 mole of deoxybenzoin (or its substituted derivative) and 0.08 mole of the appropriate aromatic aldehyde are dissolved in ca. 20 ml of ethyl ether. A stream of dry hydrogen chloride is bubbled into the solution for 7-14 hours. The solution is then chilled and the resulting precipitate is filtered off and washed with a small volume of chilled ether. The product is purified by recrystallization in an appropriate solvent.

3-Chloro-3-(p-chlorophenyl)-1,2-diphenylpropanone (IId).- This compound was obtained in 43% yield. M.p. 113-115 ºC (from ethanol). IR (KBr): ν_{max}= 1670, 1600, 1580, 1495, 1280, 1220, 1090, 1020, 760, 740, 690 cm^{-1}. ^{1}H-NMR (Cl_3CD): δ = 7.6-6.8 (m, 14H,arom), 5.5 (d,1H,CH), 5.0 (d,1H,CH).

Anal. Calcd. for $C_{21}H_{16}Cl_2O$: C, 70.99; H, 4.50; Cl, 20.00. Found: C, 71.00; H, 4.43; Cl, 19.97.

3-Chloro-1,2-di(p-methoxyphenyl)-3-phenylpropanone (IIe).- This compound was obtained in 52% yield. M.p. 175-176 ºC (from ethanol). IR (KBr): ν_{max}= 2960, 1660, 1600, 1570, 1510, 1260, 1170, 1025, 790, 700 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 7.7-6.5 (m,13H,arom), 5.5 (d,1H,CH), 5.0 (d,1H,CH), 3.6 (s,6H, $2CH_3O$).

Anal. Calcd. for $C_{23}H_{21}O_3Cl$: C, 72.53; H, 5.51. Found: C, 72,83; H, 5.14.

3-Chloro-3-(p-methylphenyl)-1,2-di(p-methoxyphenyl)propanone (IIf).- This compound was obtained in 17% yield. M.p. 132-134 ºC (from ethanol). IR (KBr): ν_{max}= 2950, 1660, 1600 1570, 1510, 1260, 1170, 1030, 785 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 7.8-6.4

(m,12H,arom), 5.5 (d,1H,CH), 5.0 (d,1H,CH), 3.7 (s,3H,CH_3O), 3.5 (s,3H,CH_3O), 2.2 (s,3H,CH_3).

Anal. Calcd. for $C_{24}H_{23}O_3Cl$: C, 73.00; H, 5.83; Found: C, 73.41; H, 5.79.

1,2,3-Triarylpropenones (III).- 1,2,3-Triphenylpropenone (IIIa)[7], 1,2-diphenyl-3-(p-methylphenyl)propenone (IIIb)[11], 1,2-diphenyl-3-(p-methoxyphenyl)propenone (IIIc)[13] and 1,2-diphenyl-3-(p-chlorophenyl)propenone (IIId)[14] were prepared from the appropriate compounds II according to the Black and Lutz method[15]. 1,2-Di(p-methoxyphenyl)-3-phenylpropenone (IIIe)[14], 1,2-di(p-methoxyphenyl)-3-(p-methylphenyl) propenone (IIIf)[14] and 1,2,3-tri(p-methoxyphenyl)propenone (IIIg)[14] were prepared either by Black and Lutz method[15] or by direct condensation of aromatic aldehydes with deoxybenzoin (I) in the presence of caproic acid/piperidine[8].

2-Amino-4,5,6-triaryl-3-cyano-4H-pyrans (V). General procedures.-

a) To a solution of 0.0015 mole of sodium in ca. 10 ml of absolute ethanol, 0.0015 mole of malononitrile are added and then 0.0015 mole of the appropriate 1,2,3-triaryl-3-chloropropanone (II). The reaction mixture is stirred at room temperature for a few minutes. The solid that separates is filtered off, washed with a little methanol and recrystallised from the appropriate solvent.

b) To a suspension of the appropriate 1,2,3-triarylpropenone (III) in ca. 20 ml of dry ethanol, 0.01 mole of malononitrile are added under stirring at room temperature, together with a few drops of piperidine. After a few minutes, a copious precipitate separates and is filtered off, washed and recrystallised.

2-Amino-3-cyano-4,5,6-triphenyl-4H-pyran (Va).- This compound was obtained in 97% yield by method a) and 91% yield by method b). M.p. 239-240 ºC (recrystallised from ethanol). IR (KBr): ν_{max}= 3450, 3325, 2200, 1675, 1645, 1600, 1420, 1270, 1140, 700 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 7.3-6.6 (m,17H,arom,NH_2), 4.3 (s,1H,CH). MS: m/e (relative intensity) = 350(M^+,22), 284(50), 273(46), 178(46), 105(100).

Anal. Calcd. for $C_{24}H_{18}N_2O$: C, 82.29; H, 5.14; N, 8.00. Found: C, 82.59; H, 5.58; N, 7.96.

2-Amino-3-cyano-4-(p-methylphenyl)-5,6-diphenyl-4H-pyran (Vb).- This compound was obtained in 72% yield by method b). M.p. 227-228 ºC (recrystallised from ethanol). IR (KBr): ν_{max}= 3440, 3310, 2190, 1670, 1640, 1590, 1400, 1260, 1210, 1130 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 7.3-6.6 (m,16H,arom.,NH_2), 4.3 (s,1H,CH), 2.3 (s,3H,CH_3).

Anal. Calcd. for $C_{25}H_{20}N_2O$: C, 82.41; H, 5.49; N, 7.69. Found: C, 82.18; H, 5.49; N, 7.73.

2-Amino-3-cyano-4-(p-methoxyphenyl)-5,6-diphenyl-4H-pyran (Vc).- This compound was obtained in 70% yield by method b). M.p. 194-195 ºC (recrystallised from ethanol). IR (KBr): ν_{max}= 3440, 3320, 2190, 1670, 1640, 1595, 1410, 1260, 1240, 1130 cm^{-1}. ^{1}H-NMR(DMSO-d_6): δ = 7.4-6.8 (m,16H,arom.,NH_2), 4.3 (s,1H,CH), 3.6 (s,3H,CH_3O).

Anal. Calcd. for $C_{25}H_{20}N_2O_2$: C, 78.94; H, 5.26; N, 7.36. Found: C, 78.65; H, 5.31; N, 7.25.

2-Amino-3-cyano-4-(p-chlorophenyl)-5,6-diphenyl-4H-pyran (Vd).- This compound was obtained in 81% yield by method b). M.p. 216-217 ºC (recrystallised from ethanol). IR (KBr): ν_{max}= 3390, 3300, 2190, 1670, 1640, 1600, 1480, 1400, 1260, 1220, 1140, 1010 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 7.4-6.8 (m,16H,arom.,NH_2), 4.5 (s,1H,CH).

Anal. Calcd. for $C_{24}H_{17}N_2OCl$: C, 74.90; H, 4.42; N, 7.28; Cl, 9.23. Found: C, 74.62; H, 4.43; N, 7.40; Cl, 9.35.

2-Amino-3-cyano-4-phenyl-5,6-di(p-methoxyphenyl)-4H-pyran (Ve).- This compound was obtained in 32% yield by method b). M.p. 218-219 ºC (recrystallised from ethanol). IR (KBr): ν_{max}= 3435, 3350, 2190, 1675, 1645, 1610, 1410, 1250, 1130, 1025, 830 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 7.2-6.4 (m,15H,arom.,NH_2), 4.2 (s,1H,CH), 3.6 (s,3H, CH_3O), 3.52 (s,3H,CH_3O).

Anal. Calcd. for $C_{26}H_{22}N_2O_3$: C, 76.10; H, 5.36; N, 6.83. Found: C, 76.35; H, 5.18; N, 6.66.

2-Amino-3-cyano-4-(p-methylphenyl)-5,6-di(p-methoxyphenyl)-4H-pyran (Vf).- This compound was obtained in 32% yield by method b). M.p. 183-184 ºC (recrystallised from ethanol). IR (KBr): ν_{max}= 3430, 3360, 2200, 1685, 1660, 1610, 1510, 1420, 1250,1135, 1030, 840 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 7.1-6.4 (m,14H,arom.,NH_2), 4.16 (s,1H,CH), 3.6 (s,3H,CH_3O), 3.56 (s,3H,CH_3O), 2.2 (s,3H,CH_3).

Anal. Calcd. for $C_{27}H_{24}N_2O_3$: C, 76.41; H, 5.66; N, 6.60. Found: C, 76.41; H, 5.62; N, 6.72.

2-Arylideneimino-3,4,5-triarylfurans (VIII). General procedures.-

a) The starting 1,2,3-triaryl-3-chloropropanone (II) (0.005 mole) is dissolved in ca. 40 ml of ethanol/water (9:1 in volume) and 0.009 mole of potassium cyanide plus 0.009 mole of the appropriate aromatic aldehyde are added to the solution. The reaction mixture is heated at reflux temperature for a variable number of hours (4-18 hours) until the starting material is exhausted (TLC). The precipitate that separates on standing is filtered off and purified by recrystallization in an appropriate solvent.

b) To a solution of the starting 1,2,3-triarylpropenone (III) (0.005 mole) in ca.

40 ml of ethanol/water (9:1 in volume), 0.009 mole of potassium cyanide and 0.009 mole of the appropriate aromatic aldehyde are added. After heating the resulting solution at reflux temperature for 1-2.5 hours, a solid separates, is filtered off and recrystallised.

2-Benzylideneimino-3,4,5-triphenylfuran (VIIIa).- This compound was obtained in 16% yield by method a) and 90% yield by method b). M.p. 194-196 ºC (recrystallised from ethanol). IR (KBr): ν_{max}= 3050, 1600, 1500, 1480, 1445, 1260, 1075, 960 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 8.85 (s,1H,N=CH-Ph), 8.0-6.97 (m,20H,arom.). M.S.: m/e (relative intensity): 399(M$^+$,100), 398(15), 371(13), 294(13), 268(11), 267(13), 193(8), 165(8).

Anal. Calcd. for $C_{29}H_{21}NO$: C,87.22; H, 5.26; N, 3.50. Found: C, 86.98; H, 5.24; N, 3.04.

2-(p-Methylbenzylideneimino)-3-(p-methylphenyl)-4,5-diphenylfuran (VIIIb).- This compound was obtained in 24% yield by method a) and 71% yield by method b). M.p. 195-196 ºC (recrystallised from ethanol). IR (KBr): ν_{max}= 1600, 1510, 1480, 1445, 1260, 960, 820, 770, 740, 705, 695 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 9.05 (s,1H,N=CH-Ph), 8.0-6.93 (m,18H,arom.), 2.46 (s,3H,CH_3), 2.38 (s,3H,CH_3).

Anal. Calcd. for $C_{31}H_{25}NO$: C, 87.12; H, 5.85; N, 3.28. Found: C, 87.23; H, 5.95; N, 2.92.

2-(p-Methoxybenzylideneimino)-3-(p-methoxyphenyl)-4,5-diphenylfuran (VIIIc).- This compound was obtained in 52% yield by method a) and 69% yield by method b). M.p. 169-171 ºC (recrystallised from ethanol). IR (KBr): ν_{max}= 1610, 1515, 1450, 1255, 1180, 1165, 1035, 840, 705, 695 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 8.64 (s,1H,N=CH-Ph), 7.86-6.5 (m,18H,arom.), 3.73 (s,3H,CH_3O), 3.63 (s,3H,CH_3O).

Anal. Calcd. for $C_{31}H_{25}NO_3$: C, 81.05; H, 5.45; N, 3.05. Found: C, 81.51; H, 5.43; N, 2.65.

2-(p-Chlorobenzylideneimino)-3-(p-chlorophenyl)-4,5-diphenylfuran (VIIId).- This compound was obtained in 93% yield by method b) . Method a) failed . M.p. 224-226 ºC (recrystallised from ethanol). IR (KBr): ν_{max}= 1590, 1490, 1445, 1260, 1090, 995, 840, 700 cm^{-1}. ^{1}H-NMR was not possible to register because of the insolubility of this compound, even in DMSO.

Anal. Calcd. for $C_{29}H_{19}NOCl_2$: C, 74.35; H, 4.06; N, 2.99. Found: C, 74.83; H, 4.53 N, 3.34.

2-Benzylideneimino-3-phenyl-4,5-di(p-methoxyphenyl)-furan (VIIIe).- This compound was obtained in 19% yield by method b). M.p. 153-154 ºC (recrystallised from etha-

nol). IR (KBr): ν_{max}= 1625, 1605, 1520, 1500, 1250, 1180, 835, 740, 700 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 8.66 (s,1H,N=CH-Ph), 8.0-6.5 (m,18H,arom.,), 3.66 (s,6H,2 CH_3O).

Anal. Calcd. for $C_{31}H_{25}NO_3$: C, 81.02; H, 5.48; N, 3.04. Found: C, 81.34; H, 5.64; N, 3.29.

2-(p-Methoxybenzylideneimino)-3,4,5-tri(p-methoxyphenyl)-furan (VIIIg).- This compound was obtained in 20% yield by method b). M.p. 154-155 ºC (recrystallised from ethanol). IR (KBr): ν_{max}= 1610, 1515, 1510, 1490, 1250, 1175, 1160, 1030, 840 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 8.65 (s,1H,N=CH-Ph), 7.8-6.6 (m,16H,arom.), 3.76 (s,3H,CH_3O), 3.73 (s,3H,CH_3O), 3.66 (s,6H,2CH_3O).

Anal. Calcd. for $C_{33}H_{29}NO_5$: C, 76.28; H, 5.62; N, 2.69. Found: C, 75.93; H, 5.79; N, 2.44.

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Note 1. 2-Arylideneiminofurans VIII (see below) were detected in trace amounts in the reaction mixture by means of analytical TLC when samples of them became available.

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