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THE USE OF ANILINODIHYDROFURANS IN THE SYNTHESIS OF NOVEL HETEROCYCLIC COMPOUNDS

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Alkyl 4-oxo-2-phenylamino-4,5-dihydrofuran-3-carboxylates were used for the preparation of alkyl 5-amino-7-aryl-2-{[aryl(hydroxy)methyl](phenyl)amino}-4,6-dicyano-1-benzofuran-3-carboxylates, 4-oxo-2-phenylamino-N-(p-tolyl)-4,5-dihydrofuran-3-carboxamide, and ethyl 4-chloro-5-formyl-2-(phenylamino)furan-3-carboxylate. The latter was used for the synthesis of ethyl 4-chloro-5-(hydrazinylidenemethyl)-2-(phenylamino)furan-3-carboxylate and diethyl 5,5'-(hydrazine-1,2-diylidenemethylylidene)bis[4-chloro-2-(phenylamino)furan-3-carboxylate].

Keywords: anilinodihydrofurans, benzofurans, substituted furans.

The increasing importance of furano-fused heterocycles as biologically active compounds [1–5] has led to continuing development of new simple procedures for their synthesis. In the light of these findings and our continuing interest in the synthetic importance of the enaminones and synthesis of some functionally substituted heterocycles [6–9], we have investigated the behavior of some furans of the enaminone type towards cinnamonitriles.

When arylidenemalononitriles **1a–c** [10] were subjected to reaction with alkyl 4-oxo-2-phenylamino-4,5-dihydrofuran-3-carboxylates **2a,b** [11] in refluxing 1-propanol in the presence of a catalytic amount of piperidine (Scheme 1), the 1-benzofuran derivatives **5a–c** were obtained, instead of the expected furo-[3,2-*b*]pyrans **4a–c**. Similar behavior has been reported previously [12–16].

The NMR spectrum of compound **5a** exhibited two one-proton singlets at δ 5.50 (CH benzyl) and δ 5.60 (OH) ppm. The mass spectrum of compound **5b** showed the molecular ion at *m/z* 584.

Formation of compound **5** could be explained by addition of two molecules of compound **1** to compound **2** to form the intermediate **3** *via* retro Knoevenagel reaction followed by cyclization and elimination of hydrogen cyanide. This reaction represents an interesting method for the construction and functionalization of the 1-benzofuran ring systems. In addition, this method has the advantages of ready accessibility of the reagents, good yields, and experimental simplicity.

In view of the above findings and in connection with the present work aiming to explore the synthetic importance of enaminones, we studied the conversion of compound **2a** into some new substituted furan derivatives.

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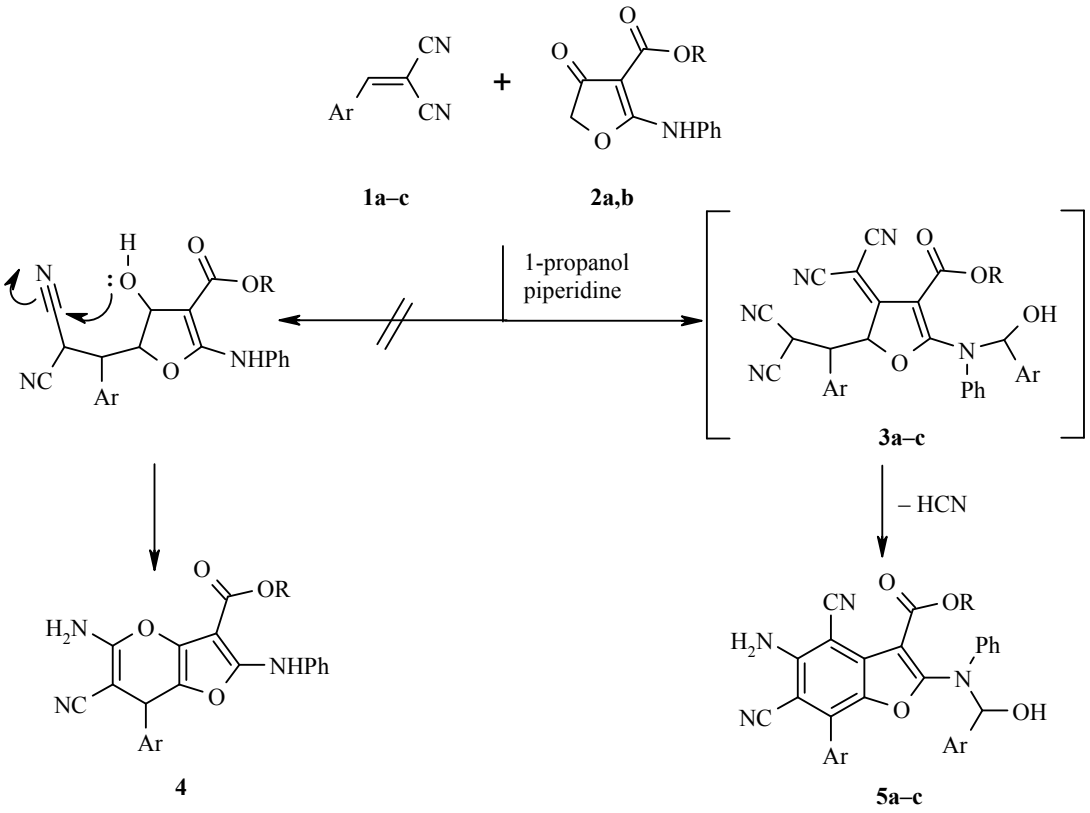
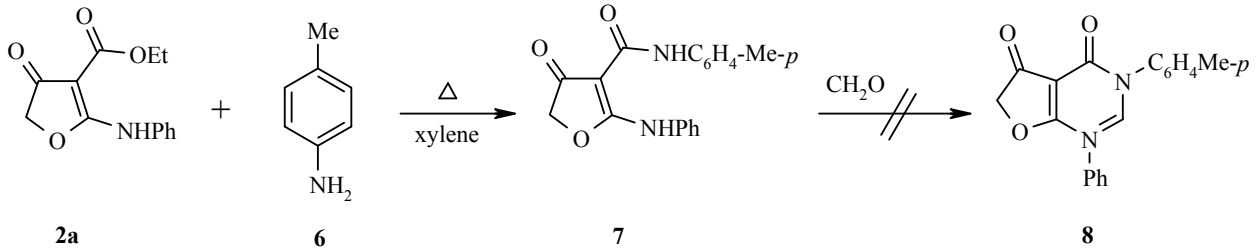
Scheme 1



2 a R = Et, **b** R = Me; **3,5 a** R = Et, Ar = Ph, **b** R = Me, Ar = *p*-ClC_6H_4,
c R = Me, Ar = *p*-BrC_6H_4

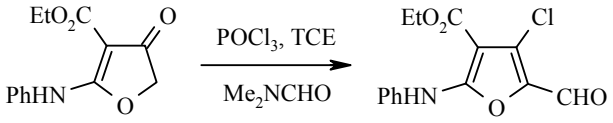
In the present work, the heterocyclic enaminone **2a** has been condensed with aromatic amine **6** in refluxing xylene to give compound **7,** which we could not convert into compound **8** when treated with formaldehyde (Scheme 2). The product **7** was characterized by analytical and spectral data (cf. Experimental).

Scheme 2



Treatment of compound **2a** with the Vilsmeier reagent (Me_2NCHO + $POCl_3$) in tetrachloroethylene at room temperature afforded the aldehyde **9** (Scheme 3). The structure of **9** was supported by its mass spectrum, which showed the molecular ion at *m/z* 293.

Scheme 3

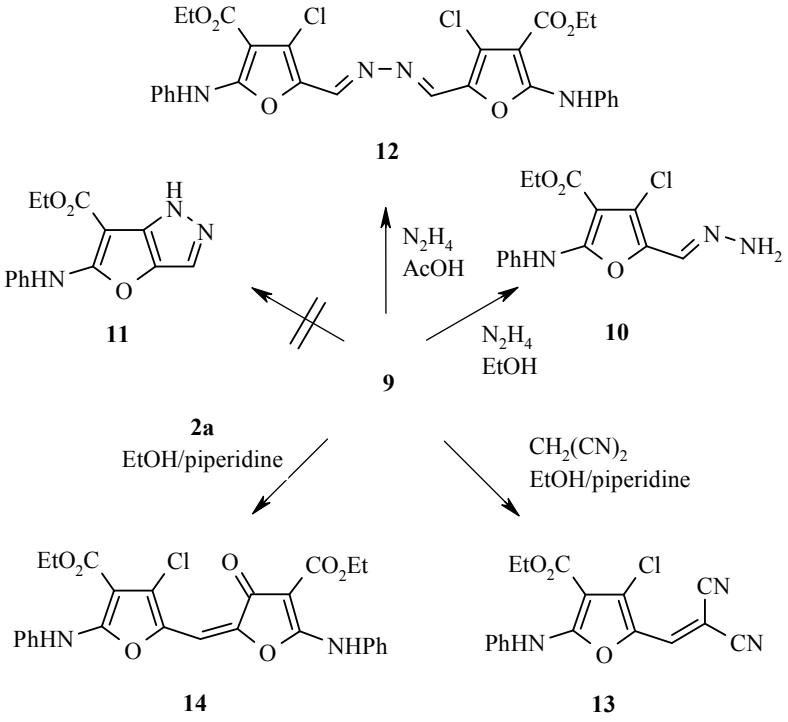


2a **9**

In view of the considerable chemical reactivity of ß-halo ketones, the authors felt it would be valuable to investigate the reaction of the aldehyde **9** with hydrazines as a possible route to the furo[3,2-*c*]pyrazoles. However, the treatment of compound **9** with hydrazine in a 1:1 molar ratio in absolute ethanol afforded the corresponding hydrazone **10** instead of the expected product **11**. On the other hand, the treatment of compound **9** with hydrazine in acetic acid afforded the azine **12** (Scheme 4). The structure **10** assigned to the product is based on analytical and spectral data.

Several nucleophilic condensation reactions of compound **9** were also studied: this compound reacted with malononitrile and with compound **2a** to give furan derivatives **13** and **14**, respectively (Scheme 4). The structures assigned to the products are based on their analytical and spectral data. The mass spectrum of compound **14** showed the molecular ion at *m/z* 522 (cf. Experimental).

Scheme 4



EXPERIMENTAL

Melting points (uncorrected) were taken on a Fisher electric melting point apparatus. Elemental analyses were carried out in the Microanalytical Unit, Faculty of Science, Mansoura and Cairo Universities.

Infrared spectra (pellets, KBr) were recorded on a SP-2000 Pye-Unicam spectrometer. ^{1}H NMR spectra were obtained with Varian-Gemini (200 MHz) and Brucker (250 MHz) spectrometers, internal standard TMS. Mass spectra (EI) were recorded on a GCMS QP1000EX Shimadzu mass spectrometer (EI, 70 eV). The purity of the synthesized compounds were tested by TLC using Merck TLC aluminum sheets, Cellulose F254, layer thickness 0.10 mm (ethyl acetate–ether, 9:1 as eluent), and no by-products were noticed in all cases.

Synthesis of Alkyl 5-Amino-7-aryl-2-{[aryl(hydroxy)methyl](phenyl)amino}-4,6-dicyano-1-benzofuran-3-carboxylates 5a-c. A mixture of compound **2a** or **2b** (0.003 mol) and the appropriate arylidenemalononitrile **1a-c** (0.006 mol) in 1-propanol (30 ml) and piperidine (0.1 ml) was refluxed for 8 h. The solid products that precipitated after cooling were filtered off and crystallized from ethanol.

Ethyl 5-Amino-2-{[hydroxy(phenyl)methyl](phenyl)amino}-7-phenyl-4,6-dicyano-1-benzofuran-3-carboxylate (5a) obtained as yellow crystals. Yield 83%; mp 205–207°C. IR spectrum, ν, cm^{-1}: 3399 (OH), 3337, 3238 (NH_2), 2198 (C≡N), 1660 (C=O ester). ^{1}H NMR spectrum (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.25 (3H, t, *J* = 7.0, CH_3 ester); 4.15 (2H, q, *J* = 7.0, CH_2 ester); 5.05 (2H, s, NH_2); 5.50 (1H, s, CH benzyl); 5.6 (1H, s, OH); 7.19-7.45 (15H, m, H Ar). Found, %: C 72.51; H 4.71; N 10.82. $C_{32}H_{24}N_4O_4$. Calculated, %: C 72.72; H 4.58; N 10.60.

Methyl 5-Amino-7-(*p*-chlorophenyl)-2-{[*p*-chlorophenyl(hydroxy)methyl](phenyl)amino}-4,6-dicyano-1-benzofuran-3-carboxylate (5b) obtained as brown crystals. Yield 63%; mp 278-280°C (decomp.). IR spectrum, ν, cm^{-1}: 3407 (OH), 3339, 3234 (NH_2), 2202 (C≡N), 1665 (C=O ester). Mass spectrum, *m/z* (*I*, %): 584 $[M]^+$ (30), 553 $[M\text{-}OMe]^+$ (34), 526 $[M+H\text{-}(CO_2Me)]^+$ (2), 442 $[553\text{-}C_6H_4Cl]^+$ (6), 330 $[553\text{-}C_6H_4Cl]^+$ (7), 93 (100). Found, %: C 63.61; H 3.32; N 9.51. $C_{31}H_{20}Cl_2N_4O_4$. Calculated, %: C 63.82; H 3.46; N 9.60.

Methyl 5-Amino-7-(*p*-bromophenyl)-2-{[*p*-bromophenyl(hydroxy)methyl](phenyl)amino}-4,6-dicyano-1-benzofuran-3-carboxylate (5c) obtained as yellow crystals. Yield 60%; mp 288-290°C (decomp.). IR spectrum, ν, cm^{-1}: 3395 (OH), 3310, 3210 (NH_2), 2198 (C≡N), 1670 (C=O ester). Mass spectrum, *m/z* (*I*, %): 674 $[M]^+$ (17.1), 643 $[M\text{-}OMe]^+$ (5.1), 485 $[643\text{-}(C_6H_4Br+2H)]^+$ (5.8), 93 (100). Found, %: C 55.21; H 3.12; N 8.11. $C_{31}H_{20}Br_2N_4O_4$. Calculated, %: C 55.38; H 2.99; N 8.33.

4-Oxo-2-phenylamino-N-(*p*-tolyl)-4,5-dihydrofuran-3-carboxamide (7). A mixture of compound **2a** (0.003 mol) and *p*-toluidine **6** (0.003 mol) in xylene (15 ml) was refluxed for 6 h. The solid product obtained after concentration and cooling was filtered off and crystallized from ethanol to give compound **7** as yellow crystals. Yield 59%; mp 218-220°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 1638 (C=O ketone), 1561 (C=O amide). Mass spectrum, *m/z* (*I*, %): 308 $[M]^+$ (24), 202 $[M\text{-}C_7H_8N]^+$ (29), 174 $[202\text{-}CO]^+$ (4), 107 $[C_7H_8N+H]^+$ (100), 92 $[C_7H_8N+H\text{-}Me]^+$ (2), 77 $[92\text{-}NH]^+$ (20). Found, %: C 70.25; H 5.38; N 9.25. $C_{18}H_{16}N_2O_2$. Calculated, %: C 70.12; H 5.23; N 9.09.

Ethyl 4-Chloro-5-formyl-2-(phenylamino)furan-3-carboxylate (9). A cold solution of $POCl_3$ (10 ml) in tetrachloroethylene (TCE) (10 ml) and 3.56 ml DMF in TCE (40 ml) was added dropwise to a solution of compound **2a** (4.37 g) in TCE (40 ml). The reaction mixture was stirred for 16 h at room temperature. The solid product that separated after neutralization with NaOH solution and extraction with $CHCl_3$ was crystallized from ethanol to give yellow crystals. Yield 70%; mp 129-131°C. IR spectrum, ν, cm^{-1}: 3261 (NH), 1680 (C=O ester), 1653 (C=O aldehyde). Mass spectrum, *m/z* (*I*, %): 293 $[M]^+$ (25), 195 (50), 130 (100). Found, %: C 57.31; H 4.23; N 4.85. $C_{14}H_{12}ClNO_4$. Calculated, %: C 57.25; H 4.12; N 4.77.

Ethyl 4-Chloro-5-(hydrazinylidenemethyl)-2-(phenylamino)furan-3-carboxylate (10). A mixture of compound **9** (0.003 mol) and hydrazine hydrate (0.003 mol) in absolute ethanol (25 ml) was refluxed for 5 h. The solid products that precipitated after cooling were filtered off and crystallized from the proper solvent to give the hydrazone **10** as yellow crystals from ethanol. Yield 82%; mp 125-127°C. IR spectrum, ν, cm^{-1}: 3349 (NH_2 hydrazone), 3289 (NH), 1669 (C=O ester), 1639 (C≡N). Mass spectrum, *m/z* (*I*, %): 307 $[M]^+$ (22), 262 $[M\text{-}OEt]^+$ (3), 234 $[M\text{-}CO_2Et]^+$ (4), 142 $[M\text{-}(C_6H_5NH+COOEt)]^+$ (9), 92 $[C_6H_5NH]^+$ (7), 77 $[C_6H_5]^+$ (100). Found, %: C 54.73; H 4.73; N 13.75. $C_{14}H_{14}ClN_3O_3$. Calculated, %: C 54.64; H 4.59; N 13.66.

Diethyl 5,5'-(Hydrazine-1,2-diylidenedimethanylylidene)bis[4-chloro-2-(phenylamino)-furan-3-carboxylate] (12). A mixture of compound **9** (0.003 mol) and hydrazine hydrate (0.003 mol) in acetic acid (20 ml) was refluxed for 6 h. The solid product that precipitated after cooling was filtered off and recrystallized from acetic acid to give golden-yellow crystals. Yield 37%; mp 227-229°C. IR spectrum, ν, cm^{-1}: 3293 (NH phenylamino), 1671 (C=O ester), 1621 (C≡N). Mass spectrum, *m/z* (*I*, %): 584 $[M]^+$ (30), 308 $[M+2H-C_{14}H_{12}NO_3Cl]^+$ (23), 77 $[C_6H_5]^+$ (100). Found, %: C 57.82; H 7.31; N 9.51. $C_{28}H_{24}Cl_2N_4O_6$. Calculated, %: C 57.64; H 4.15; N 9.60.

Ethyl 4-Chloro-5-(2,2-dicyanovinyl)-2-(phenylamino)furan-3-carboxylate (13). A mixture of compound **9** (0.003 mol) and malononitrile (0.003 mol) in absolute ethanol (25 ml) and piperidine (0.1 ml) was refluxed for 6 h. The solid product that precipitated out after cooling was filtered off and recrystallized from ethanol to give yellow crystals. Yield 63%; mp 139-141°C. IR spectrum, ν, cm^{-1}: 3324 (NH phenylamino), 2192 (C≡N), 1715 (C=O ester), 1633 (C=C). ^{1}H NMR spectrum (250 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.37 (3H, t, *J* = 7.0, CH_3 ester); 4.35 (2H, q, *J* = 7.0, CH_2 ester); 7.25–7.55 (6H, m, H Ar+vinyl); 10.1 (1H, s, NH). Found, %: C 59.86; H 3.61; N 12.41. $C_{17}H_{12}ClN_3O_3$. Calculated, %: C 59.73; H 3.54; N 12.29.

Ethyl 4-Chloro-5-[(4-ethoxycarbonyl-3-oxo-5-(phenylamino)furan-2(3H)-ylidene]methyl-2-(phenylamino)furan-3-carboxylate (14). A mixture of compound **9** (0.003 mol) and compound **2a** (0.003 mol) in absolute ethanol (30 ml) and piperidine (0.1 ml) was refluxed for 6 h. The reaction mixture was cooled, poured in water, and acidified with diluted HCl, 1:1. The precipitated material was filtered off and recrystallized from ethanol to give brown crystals. Yield 58%; mp 219-221°C. IR spectrum, ν, cm^{-1}: 3300 (NH phenylamino), 1664 (C=O ester), 1619 (CH=C). Mass spectrum, *m/z* (*I*, %): 523 $[M+1]^+$ (2), 522 $[M]^+$ (28), 487 $[M- HCl]^+$, probably the fused pyrylium ion (93), 395 $[M-HCl-(2EtO+2H)]^+$ (55), 77 $[C_6H_5]^+$ (100). Found, %: C 62.13; H 4.51; N 5.43. $C_{27}H_{23}ClN_2O_7$. Calculated, %: C 62.01; H 4.43; N 5.36.

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