Heterocyclic Synthesis with ω-bromoacetophenone: Synthesis of Some New Pyrazole, Pyridazine and Furan Derivatives

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Síntesis heterocíclica con w*-bromoacetofenona: Síntesis de nuevos derivados de pirazol, piridazina y furano*

Síntesi heterocíclica amb w*-bromoacetofenona: Síntesi de nous derivats de pirazole, piridazina i furà*

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RESUMEN

Los derivados de p-bromofenacilnitrilo 3a,b reaccionan con derivados de hidrazina bajo diferentes condiciones para dar los diaminopirazoles 4a,b, las piridazin-6-iminas 5a,b y los 5-aminopirazoles 11a,b. Al calentar a reflujo 5a en una mezcla etanol / ácido clorhídrico, éste se transforma en la piridazin-6-ona 6 mientras que, bajo las mismas condiciones de reacción, 5b experimenta contracción de anillo con eliminación de fenilhidrazina rindiendo el derivado de furano 7. El compuesto 7 también se puede obtener a partir de 3a calentando este producto a reflujo en etanol usando catálisis de trietilamina. El fenacilcianoacetato de etilo 3b reacciona con hidrato de hidrazina y fenilhidrazina para dar los derivados de 4-fenacilpirazol 11a,b, respectivamente. El compuesto 3b rinde una mezcla de los dos derivados de furano 12 y 13 al calentarlo a reflujo en etanol usando catálisis de trietilamina. Además, el compuesto 3b experimenta la reacción de acoplamiento con las sales de diazonio aromáticas 14a-d para dar los derivados de pirazol 16a-d, presumiblemente vía los correspondientes derivados hidrazo 15a-d.

Palabras clave: ***p*-Bromofenacilnitrilos. Piridaziniminas. Piridazinona. 3,5-Diaminopirazoles. Furanos.**

SUMMARY

***p*-Bromophenacylnitrile derivatives 3a,b react with hydrazine derivatives under different conditions to afford the diaminopyrazoles 4a,b, the pyridazine-6-imines 5a,b, and 5-aminopyrazoles 11a,b. Refluxing of 5a in ethanol/hydrochloric acid mixture furnished its transformation into the pyridazine-6-one 6 while 5b under the same reaction conditions, underwent ring contraction expelling phenyl hydrazine to afford the furan derivative 7. Compound 7 could also be obtained from 3a upon reflux in ethanol catalyzed by triethylamine. Ethyl phenacylcyanoacetate 3b reacts with hydrazine hydrate and phenylhydrazine to afford the 4-phenacylpyrazole derivatives 11a,b respectively. Compound 3b afforded a mixture of the two furan derivatives 12 and 13 upon reflux in ethanol catalyzed by triethylamine. Compound 3b also undergoes the coupling reaction with the aromatic diazonium salts 14a-d to afford the pyrazole derivatives 16a-d presumably via the hydrazo derivatives 15a-d respectively.**

Key words: ***p*-Bromophenacylnitriles. Pyridazineimines. Pyridazinone. 3,5-Diaminopyrazoles. Furans.**

RESUM

Els derivats de p-bromofenacilnitril 3a,b reaccionen amb derivats d'hidrazina sota diferents condicions per donar les diaminopirazoles 4a,b, les piridazin-6-imines 5a,b i les 5-aminopirazoles 11a,b. L'escalfament a reflux de 5a en una barreja etanol / àcid clorhídric el transforma en la piridazin-6-ona 6 mentre que, sota les mateixes condicions de reacció, 5b experimenta contracció d'anell amb eliminació de fenilhidrazina rendint el derivat de furà 7. El compost 7 també es pot obtenir a partir de 3a en escalfar aquest producte a reflux en etanol emprant catàlisi de trietilamina. El fenacilcianoacetat d'etil 3b reacciona amb hidrat d'hidrazina i fenilhidrazina per donar els derivats de 4-fenacilpirazole 11a,b, respectivament. El compost 3b rendeix una barreja dels dos derivats de furà 12 i 13 en ésser escalfat a reflux en etanol emprant catàlisi de trietilamina. A més, el compost 3b experimenta la reacció d'acoblament amb les sals de diazoni aromàtiques 14a-d per donar els derivats de pirazole 16a-d, presumiblement via els corresponents derivats hidrazo 15a-d.

Mots clau: ***p*-Bromofenacilnitrils. Piridazinimines. Piridazinona. 3,5-Diaminopirazoles. Furans.**

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INTRODUCTION

Nitriles are versatile synthones for a wide variety of heterocyclic compounds that are interesting as pharmaceuticals, pesticides and dyes[1]. Pyridazine derivatives have received considerable attention in recent decades due to their biological activity as antiplatetet agents[2], inhibitors of glycogen synthase kinase[3] and antimicrobial agents[4]. Recently aminopyrazoles were found to be potentially useful to prevent protein aggregation which is the first phase of Alzheimer[5]. Substituted furans also served as building blocks in material sciences[6].

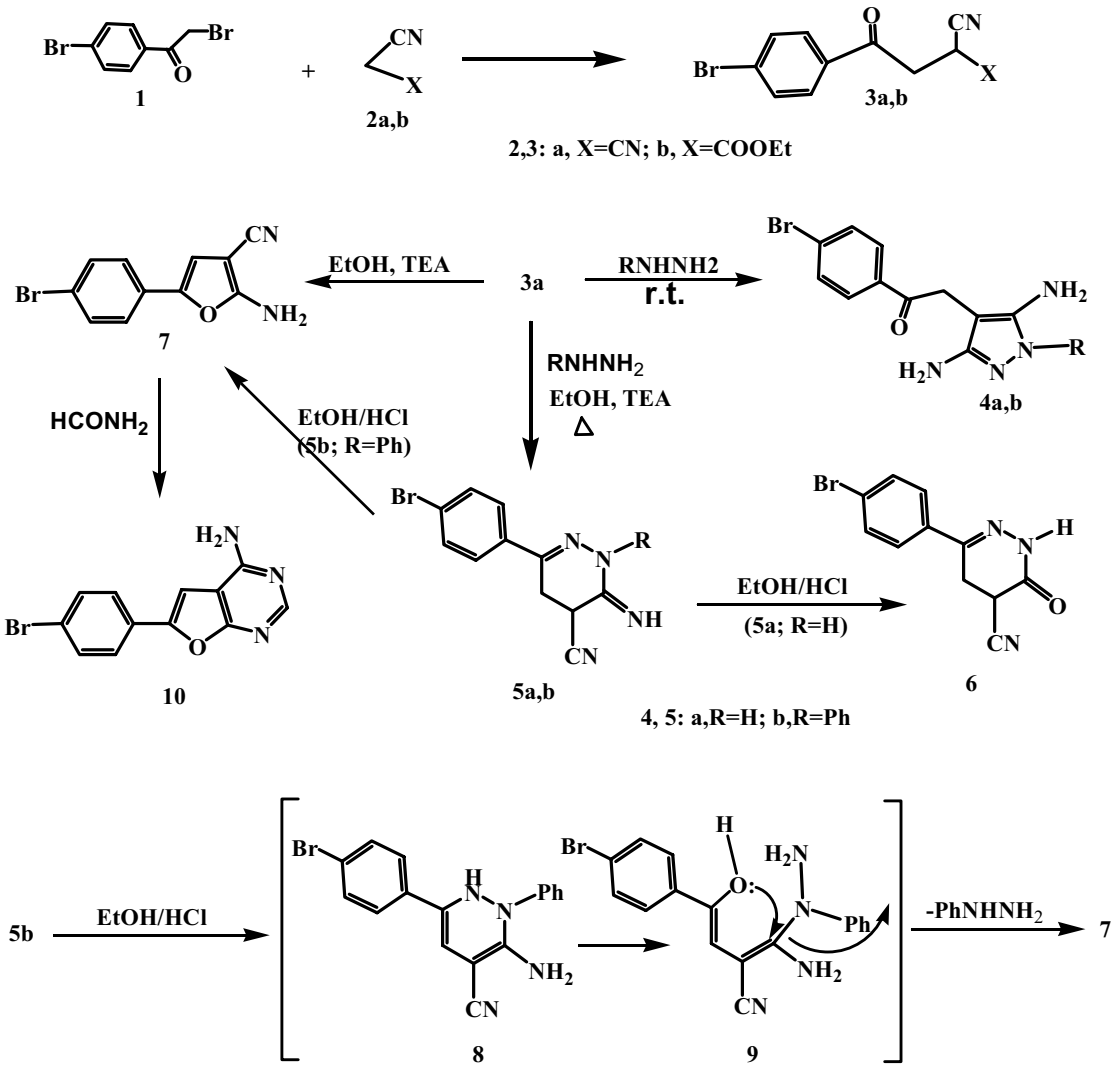
In the last two decades we have been involved in a program aiming to develop new simple routes for the synthesis of heterocyclic compounds of biological interest[7-10]. Recently some new bromo-substituted pyridazine, pyrazole and furan derivatives were required for biological evaluation. *p*-Bromophenacylnitrile derivatives **3a,b** seemed good candidates to fulfill this objective.

RESULTS AND DISCUSSION

p-Bromophenacyl malononitrile **3a** and ethyl *p*-bromophenacyl cyanoacetate **3b** were prepared from the reaction of *p*-bromophenacyl bromide **1** with malononitrile **2a** or the sodium salt of ethyl cyanoacetate **2b** respectively according to literature procedures[11, 12] (Scheme 1).

p-Bromophenacyl malononitrile **3a** reacts with hydrazines to afford different products according to the reaction conditions. Thus it reacts with hydrazine hydrate at room temperature to afford a yellow crystalline product of mp. 252ºC. Elemental analysis of this product showed that it is 1:1 adduct. The IR spectrum of the isolated products showed absorption bands at υ_{max} 3352, 3215, 3078 and 1658 cm^{-1} corresponding to NH, NH_2 and CO groups, respectively and no cyano absorption bands were revealed. The ^1H NMR spectrum of the isolated product revealed a singlet (2H) at δ = 3.55 ppm, a broad singlet (4H, D_2O exchangeable) at 8.50 ppm attributable to two NH_2 and a singlet (1H, D_2O exchangeable) at 10.16 ppm due to NH, beside the other aromatic signals. The mass spectrum showed two molecular ion peaks at *m/z* 293 (M^+–1) and 295 (M^++1). Based on these spectral as well as elemental analytical data the diaminopyrazole structure **4a** was assigned to this product (*cf.* experimental & Scheme 1). Similarly, the reaction of **3a** with phenyl hydrazine under the same reaction conditions afforded the corresponding N-phenylpyrazole derivative **4b**. Elemental analysis and spectral data agree with structure **4b**.

The reaction of **3a** with hydrazine hydrate in refluxing ethanol catalyzed by few drops of triethylamine afforded another pale yellow solid product with mp. 310ºC. The IR



Scheme 1.

spectrum of this isolated product revealed absorption bands at υ_{max} 3280, 3120 and 2231 cm^{-1}, attributable to NH and CN groups, respectively and no carbonyl absorption bands appeared. The ^1H NMR spectrum of this reaction product revealed a multiplet (2H) at δ = 1.78 ppm, a signal (dd, 1H) at δ = 2.44-2.54 ppm, and two D_2O exchangeable singlet signals 7.50 and 11.46 ppm (1H) attributable to the ring and imino group NH's, beside the expected aromatic signals at their proper position. The pyridazine structure **5a** was suggested to this product. A support for this structural assignment was gained from the ^{13}C NMR spectrum of this compound which showed signals at δ = 25.55 (t), 29.86 (d), 116.80 (s) and 159.73 (s) attributable to methylene, methine, cyano and the imine carbon atoms, respectively, beside the other expected signals due to the other carbons (*cf*. Scheme 1 & experimental). The mass spectrum of this product showed correct molecular ion peaks at *m/z* 276 & 278 (M^+–1 & M^++1). Based on the above data the iminopyridazine structure **5a** was assigned for this product (*cf*. experimental; Scheme 1).

The reaction of **3a** with phenyl hydrazine in refluxing ethanol catalyzed by few drops of triethylamine afforded a new canary yellow solid product. The IR spectrum of this product showed the absorption bands at υ_{max} 3182 and 2215 cm^{-1}, corresponding to NH and CN groups, respectively. The ^1H NMR spectrum of this reaction product revealed a multiplet (2H) at δ = 1.75 ppm, a signal (dd, 1H) at δ = 2.45-2.56 ppm, and only one D_2O exchangeable singlet at 11.50 ppm (1H) attributable the imine NH, beside other aromatic signals at their proper position. The mass spectrum of this product showed correct molecular ion peaks at *m/z* 352 (M^+–1) and 354 (M^++1). Based on the above data the pyridazineimine structure **5b** was assigned for this product.

The appearance of the methylene protons as multiplets and of the methine protons as doublet of doublet in the 1H NMR spectra of compounds **5a** and **5b** as well as **6** is presumably attributed to the non chemical equivalence of the two methylene protons which are axial and equatorial in a chair form of diazacyclohexenes.

This behavior of **3a** towards hydrazines is in agreement with our recently reported behavior of phenacyl malononitrile towards the same reagents[13].

Compounds **5a,b** were refluxed in ethanol / conc. HCl mixture (4:1 by volume) aiming to transform them to the corresponding pyridazinone derivatives. However, only **5a** could undergo this transformation and compound **6** was obtained. Under these conditions compound **5b** has afforded light brown crystals of mp. 240ºC. The IR spectrum of this product did not show any carbonyl absorption band but absorption bands at υ_{max} 3410, 3313 and 2217 corresponding to NH_2 and CN groups were revealed. The ^1H NMR spectrum of this isolated product revealed a broad singlet at δ = 6.46 ppm (2H, D_2O exchangeable) attributed to NH_2, a singlet signal at δ = 6.55 ppm integrated for (1H) beside two doublets in the aromatic region. The mass spectrum of this product showed a molecular ion peaks at *m/z* = 262 & 264 (M^+–1 & M^++1). Based on the above data the furan structure **7** was thus assigned for this product. The formation of **7** from **5b** is assumed to proceed via initial tautomerization of the pyridazine ring under the effect of HCl to give the intermediate **8** followed by hydrolytic ring opening to afford the intermediate **9**. Compound **9** in its role undergoes cyclization with loss of phenyl hydrazine to afford the furan derivative **7** (Scheme 1). This furan structure **7** was unambiguously established through its alternative preparation by refluxing **3a** in ethanol catalyzed by triethylamine. The obtained product was completely identical to **7** in all respects.

Refluxing the furan **7** in formamide afforded the furo[2,3-d]pyrimidine derivative **10**. The elemental analysis and spectral data supported structure **10** (*cf*. Scheme 1 & experimental).

On the other hand compound **3b** reacts with hydrazines to afford the 4-phenacylpyrazole derivatives **11a,b** (Scheme 2). The IR spectra of both compounds showed a broad absorption bands at υ_{max} ~ 3425-3157 cm^{-1} assignable to the ring NH, NH_2 and OH beside carbonyl absorption bands at υ_{max} 1685 and 1666 cm^{-1} respectively. The ^1H NMR spectrum of **11a** revealed four singlets at δ = 3.53 (2H), 3.72 (2H), 4.66 (1H) and 11.35 (1H) ppm attributable to NH_2, CH_2, OH and NH beside two doublets at δ =7.50-7.64 ppm (4H) for the aromatic protons. The ^1H NMR spectrum of **11b** showed approximately the same pattern except that the signal at δ =11.35 ppm is missing and the aromatic integral is increased to (9H). Mass spectra and elemental analyses are in good agreement with structures **11a,b** (*cf*. experimental & Scheme 2).

Compound **3b** has afforded a mixture of two compounds with overall yield of 76% (1:1 ratio) upon reflux in ethanol catalyzed by triethylamine. These were separated and identified as the furan derivatives **12** and **13**. Compound **12** is assumed to be formed via cyclization with loss of ethanol. This was confirmed by the absence of the ester carbonyl absorption band at υ_{max} ~ 1720 cm^{-1} in the IR spectrum and the presence of CN absorption band at υ_{max} 2215 cm^{-1} and the presence of OH in the ^1H NMR spectrum. Compound **13** on the other hand, is formed apparently via cyclization to the cyano group. Again in this case no cyano absorption band in the IR spectrum while the ester carbonyl absorption band is clearly defined at 1712 cm^{-1}, the characteristic ethoxy protons are also revealed in the ^1H NMR spectrum.

Aroyl pyrazoles are interesting compounds from the point of view of biological activity studies as well as their further transformations[14]. Therefore it was planned to obtain *p*-bromophenyl pyrazolyl ketones from **3a,b** via their azo/hydrazo derivatives of the type **15** (Scheme 2) which then can be cyclized into the desired compounds. Therefore we carried out the coupling reaction of **3a** and **3b** with aromatic diazonium salts. Unfortunately we could not isolate any products from **3a**; while **3b** underwent a successful azocoupling reaction to afford highly colored products. It was thought that we have obtained the azo derivatives **15a-d** or their hydrazo tautomers, however the IR spectra did not show ester carbonyl absorptions and the ^1H NMR spectra did not reveal the usual quartet and triplet signals of the ester group, or the hydrazo NH proton singlet.

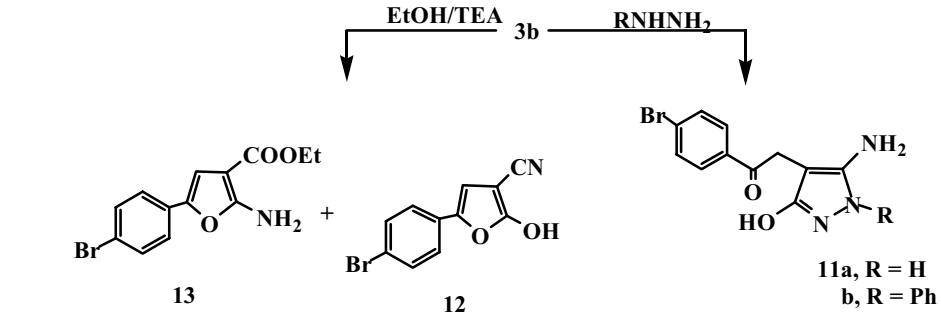
All analytical and spectral data are in complete agreement with the pyrazole structures **16a-d** which were assigned for these products. Furthermore the ^{13}C NMR spectrum of **16a** as a representative example revealed 13 signals which are applicable to this structure (*cf*. Scheme 2 & experimental).

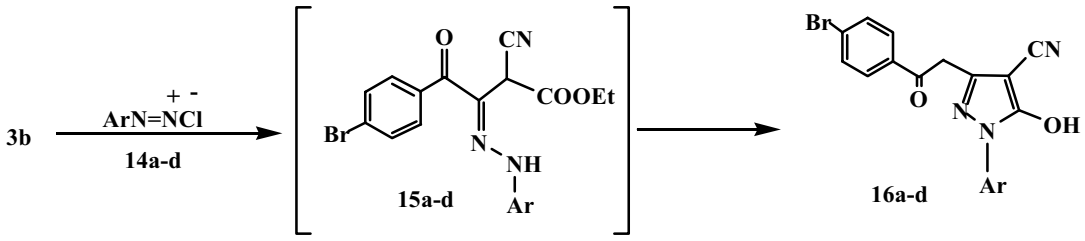
EXPERIMENTAL SECTION

Melting points were measured on an Electrothermal (9100) apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. The ^1H and C^{13} NMR spectra were taken on a Varian Gemini 300 MHz spectrometer in DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ ppm values. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 ev). Elemental analyses were carried out at the Micro-analytical Center at Cairo University.

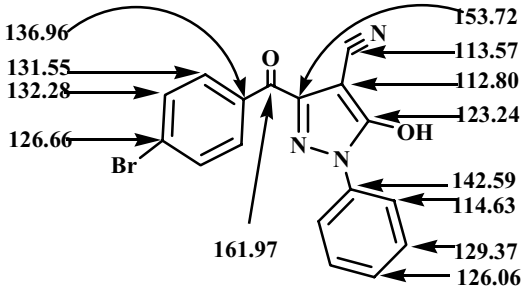
p-*Bromophenacylnitrile derivatives 3a,b (General Procedure)*.

These compounds were prepared according to literature procedure; **3a** according to ref.[11] and **3b** according to ref.[12].





14-16: a, Ar = C_6H_5 ; b, Ar = 4-$CH_3C_6H_4$; c, Ar = 4-$OCH_3C_6H_4$; d, Ar = 4-ClC_6H_4



C13 asignments of 16a

Scheme 2.

Preparation of 3,5-diaminopyrazole derivatives 4a,b: (General Procedure).

A mixture of **3a** (0.01 mol) and hydrazine hydrate or phenyl hydrazine (0.015 mol) is warmed under dry conditions on a water bath until a homogenous solution is obtained. The solid mass formed on standing at room temperature was triturated with ethanol then poured onto cold water acidified by few drops of conc. HCl. The solid products so formed were filtered off and recrystallized from ethanol / dimethylformamide (DMF) mixture (4:1).

1-(4-Bromophenyl)-2-(3,5-diamino-1H-pyrazol-4-yl)-ethanone 4a:

Yellow powder, mp. 252ºC, 63% yield. υ_{max} (KBr) 3352, 3215, 3078 (NH_2 & NH) and 1658 (CO) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 3.55 (s, 2H, CH_2), 7.55-7.64 (2d, 4H, arom.), 8.50 (br., 4H, $2NH_2$), 10.16 (s, 1H, NH). Anal. Calcd. for ($C_{11}H_{11}BrN_4O$) C, 44.77; H, 3.76; Br, 27.07; N, 18.98. Found: C, 44.61; H, 3.58; Br, 27.24; N, 18.78.

1-(4-Bromophenyl)-2-(3,5-diamino-1-phenyl-1H-pyrazol-4-yl)- ethanone 4b:

Brownish yellow powder, mp. 225ºC, 65% yield. υ_{max} (KBr) 3311-3135 (NH_2) and 1661 (CO) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 3.65 (s, 2H, CH_2), 7.15-7.68 (m, 9H, arom.), 8.1 (br. s., 2H, NH_2), 8.15 (br. s, 2H, NH_2). Anal. Calcd. for ($C_{17}H_{15}BrN_4O$) C, 55.00; H, 4.07; Br, 21.52; N, 15.09. Found: C, 54.80; H, 4.20; Br, 21.30; N, 15.40.

Preparation of 3-(4-bromophenyl)-2,3,4,5-tetrahydro-6-iminopyridazine-5-carbonitriles 5a,b: (General Procedure).

To a solution of **3a** (0.01 mol) in ethanol (20 mL) was added 0.01 mol of either hydrazine hydrate or phenyl hydrazine. The reaction mixture was refluxed for 2h in each case, left overnight. The reaction mixture is poured on ice cold water and acidified with dil. HCl till just neutral. The precipitated solid was filtered off and recrystallized from acetic acid.

6-(4-bromophenyl)- 3-imino-2,3,4,5-tetrahydro-pyridazine-4-carbonitrile 5a:

Pale yellow powder, mp. 310ºC, 73% yield. υ_{max} (KBr) 3280, 3210 (NH) and 2231 (CN) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 1.73-1.82 (m, 2H, CH_2), 2.44-2.54 (dd, 1H, CH), 7.50 (s, 1H, ring NH), 7.44-7.58 (2d, 4H, arom.), 11.46 (s, 1H, =NH). δc (300 MHz, DMSO-d_6) 25.55(t), 29.86(d), 116.80(s), 123.31(s), 127.88(s), 131.55(d), 134.18(d), 147.71(s), 159.73(s).

Anal. Calcd. for ($C_{11}H_9BrN_4$) C, 47.68; H, 3.27; Br, 28.83; N, 20.22. Found: C, 47.50; H, 3.40; Br, 28.60; N, 20.30.

6-(4-Bromophenyl)- 3-imino-2-phenyl-2,3,4,5-tetrahydro-pyridazine-4-carbonitrile 5b:

Yellow powder, mp. 235ºC, 78% yield. υ_{max} (KBr) 3182 (NH) and 2215 (CN) cm^{-1}. δH (300 MHz, DMSO-d_6) 1.75-1.84 (m, 2H, CH_2), 2.45-2.56 (dd, 1H, CH), 6.65-7.55 (m, 9H, arom.), 11.50 (s, 1H, C=NH). Anal. Calcd. for ($C_{17}H_{13}BrN_4$) C, 57.81; H, 3.71; Br, 22.62; N, 15.86. Found: C, 57.60; H, 3.60; Br, 22.40; N, 15.70.

6-(4-Bromophenyl)- 3-oxo-2,3,4,5-tetrahydro-pyridazine-4-carbonitrile 6:

Compound **5a** (2.77 g; 0.01 mol) was refluxed in ethanol / conc. HCl mixture for 2h then left to cool to room temperature. The precipitated solid was filtered off, washed thoroughly with water and recrystallized from ethanol. Orange powder, mp. 239ºC, 58% yield. υ_{max} (KBr) 3215, 3128 (NH), 2227 (CN) and 1679 (C=O) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 1.93-2.05 (m, 2H, CH_2), 3.38-3.42 (dd, 1H, CH), 7.58 (s, 1H, ring NH), 7.48-7.60 (2d, 4H, arom.). Anal. Calcd. for ($C_{11}H_8BrN_3O$) C, 47.51; H, 2.90; Br, 28.73; N, 15.11. Found: C, 47.65; H, 2.80; Br, 28.60; N, 14.90.

Preparation of 2-amino-5-(4-bromophenyl)-furan-3-carbonitrile 7:

Method A: To a solution of **5b** (3.53 g; 0.01 mol) in 20 mL absolute ethanol was added 5 mL of conc. HCl. The reaction mixture was refluxed 1h and left to cool overnight. The precipitated solid was filtered off and recrystallized from ethanol.

Method B: To a solution of **3a** (2.63 g; 0.01 mol) in 20 mL absolute ethanol was added 0.5 mL. of triethylamine. The reaction mixture was refluxed 1h and left to cool overnight, poured on ice cold water and neutralized by HCl. The precipitated solid was filtered off and recrystallized from ethanol to give: Pale brown crystals, mp 240ºC, 60% yield. υ_{max} (KBr) 3410, 3313 (NH_2) and 2217 (CN) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 6.46 (s, 2H, NH_2), 6.55 (s, 1H, furan H), 7.33 (d, 2H, arom.), 7.55 (d, 2H, arom.). Anal. Calcd. for ($C_{11}H_7BrN_2O$) C, 50.22; H, 2.68; Br, 30.37; N, 10.65. Found: C, 50.10; H, 2.50; Br, 30.20; N, 10.80.

Preparation of 4-amino-6-(4-bromophenyl)-furo[2,3-d]pyrimidine 10:

A solution of **7** (0.01 mol) in 20 mL formamide was refluxed for 6 h, and then left to cool overnight. The brownish precipitated solid was filtered off and recrystallized from ethanol / DMF mixture. Brown amorphous solid, mp. 290ºC, 61% yield. υ_{max} (KBr) 3330-3210 (NH_2) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 6.65 (s, 1H, furan H) 8.45 (s, 1H, CH pyrimidine), 7.35 (d, 2H, arom.), 7.58 (d, 2H, arom.). 8.1 (s, 2H, NH_2). Anal. Calcd. for ($C_{12}H_8BrN_3O$) C, 49.68; H, 2.78; Br, 27.54; N, 14.48. Found: C, 49.50; H, 2.50; Br, 27.40; N, 14.60.

Preparation of 5-aminopyrazole derivatives 11a,b (General Procedure).

To a solution of **3b** (3.1 g; 0.01 mol) in dioxan (20 mL) was added 0.01 mol of either hydrazine hydrate or phenyl hydrazine. The reaction mixture was refluxed for 2h in each case, left overnight where dark yellow crystalline products appeared. The products were filtered off and recrystallized from ethanol.

2-(5-Amino-3-hydroxy-1H-pyrazol-4-yl)-1-(4-bromophenyl) ethanone 11a:

Dark yellow crystals, mp. 185ºC, 60% yield. υ_{max} (KBr) 3425, 3225, 3157 (OH, NH_2 & NH) and 1685 (CO) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 3.72 (s, 2H, CH_2), 3.53 (br., 2H, NH_2), 4.66 (s, 1H, OH), 7.50&7.64 (2d, 4H, arom.), 11.35 (s, 1H, NH). Anal. Calcd. for ($C_{11}H_{10}BrN_3O_2$) C, 44.62; H, 3.40; Br, 26.98; N, 14.19. Found: C, 44.70; H, 3.50; Br, 27.20; N, 14.30.

2-(5-Amino-3-hydroxy-1-phenyl-1H-pyrazol-4-yl)-1-(4-bromophenyl)-ethanone 11b:

Orange crystals, mp. 130ºC, 67% yield. υ_{max} (KBr) 3380-3166 (OH & NH_2) and 1666 (CO) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 3.71 (s, 2H, CH_2), 3.67 (br., 2H, NH_2), 4.80 (s, 1H, OH), 7.30-7.79 (m, 9H, arom.). Anal. Calcd. for ($C_{17}H_{14}BrN_3O_2$) C, 54.86; H, 3.79; Br, 21.47; N, 11.29. Found: C, 54.70; H, 3.70; Br, 21.70; N, 11.40.

Formation of the furan derivatives 12 and 13:

To a solution of **3b** (3.1 g; 0.01 mol) in 20 mL of absolute ethanol was added few drops of triethylamine. The reaction mixture was refluxed for 3 h then left to cool overnight. The light brown solid so formed was filtered off and recrysallized from a mixture of ethanol and dioxan to afford the furan **13**. The mother liquor was poured onto cold water to afford the furan **12** which was filtered off and recrystallized from ethanol/water (5:1).

5-(4-Bromophenyl) 2-hydroxy furan-3-carbonitrile 12:

Light brown, mp. 125ºC, 38% yield. υ_{max} (KBr) 4230 (OH) and 2215 (CN) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 5.31 (s, 1H, OH), 6.65 (s, 1H, furan H), 7.41 (d, 2H, arom.), 7.62 (d, 2H, arom.). Anal. Calcd. For ($C_{11}H_6BrNO_2$) C, 50.03; H, 2.29; Br, 30.26; N, 5.30. Found: C, 50.12; H, 2.40; Br, 30.40; N, 5.18.

Ethyl 2-amino-5-(4-bromophenyl) furan-3-carboxylate 13:

Yellow, mp. 106ºC, 38% yield. υ_{max} (KBr) 3318-3281 (NH_2) and 1712 (CO) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 1.33 (t, 3H, CH_3), 4.31 (s, 2H, NH_2), 4.34 (q, 2H, CH_2), 6.66 (s, 1H, furan H), 7.31 (d, 2H, arom.), 7.52 (d, 2H, arom.). Anal. Calcd. for ($C_{13}H_{12}BrNO_3$) C, 50.34; H, 3.90; Br, 25.76; N, 4.52. Found: C, 50.16; H, 3.74; Br, 25.54; N, 4.72.

Preparation of 5-(4-bromophenyl)-1-aryl-1H-pyrazol-3-carbonitrile derivatives 16a-d:

Aryl diazonium salts **14a-d** (0.01 mol) were freshly prepared by adding a solution of 0.01 mol of sodium nitrite in 5 mL H_2O to a cold solution of the respective arylamine hydrochloride (0.01 mol) of the arylamine: aniline, *p*-toluidine, *p*-anisidine or *p*-chloroaniline respectively, in 5 mL conc. HCl) with stirring. The resulting solutions of the aryl diazonium salts were added to a cold solution of ethyl phenacyl cyanoacetate **3b** (0.01 mol), in ethanol (30 mL) containing sodium acetate (2 g). The reaction mixture was stirred at room temperature for 1h in each case and the solid products, so formed, were collected by filtration and recrystallized from ethanol.

3-(4-Bromo-benzoyl)-5-hydroxy-1-phenyl-1H-pyrazole-4-carbonitrile 16a:

Reddish violet crystals, mp. 260ºC, 70% yield. υ_{max} (KBr) 3430 (Br. OH), 2223 (CN), 1670 (CO) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 7.34-7.93 (m, 9H, arom.), 11.74 (s, 1H, OH). δc (300 MHz, DMSO-d_6) 112.80(s), 113.57(s), 114.63(d), 123.24(s), 126.06(d), 126.66(s), 129.37(d), 131.55(d), 132.28(d), 136.96(s), 142.59(s), 153.72(s), 161.97(s). Anal. Calcd. for ($C_{17}H_{10}BrN_3O_2$) C, 55.46; H, 2.74; Br, 21.70; N, 11.41. Found: C, 55.13; H, 2.55; Br, 21.49; N, 11.74.

3-(4-Bromo-benzoyl)-5-hydroxy-1-p-tolyl-1H-pyrazole-4-carbonitrile 16b:

Dark violet crystals, mp. 275ºC, 67% yield. υ_{max} (KBr) 3424 (Br. OH), 2219 (CN), 1668 (CO) cm^{-1}. δ_H (300 MHz, DMSO-

d_6) 2.35 (s, 3H, CH_3), 7.23-7.80 (4d, 8H, arom.), 11.76 (s, 1H, OH). Anal. Calcd. for ($C_{18}H_{12}BrN_3O_2$) C, 56.56; H, 3.16; Br, 20.91; N, 10.99. Found: C, 56.25; H, 3.42; Br, 20.45; N, 10.58.

3-(4-Bromo-benzoyl)-5-hydroxy-1-(4-methoxy-phenyl)-1H-pyrazole-4-carbonitrile 16c:

Dark violet crystals, mp. 250ºC, 72% yield. υ_{max} (KBr) 3426 (br. OH), 2220 (CN), 1678 (CO) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 3.74 (s, 3H, OCH_3), 6.94-7.91 (4d, 8H, arom.), 11.81 (s, 1H, OH). Anal. Calcd. for ($C_{18}H_{12}BrN_3O_3$) C, 54.29; H, 3.04; Br, 20.07; N, 10.55. Found: C, 54.61; H, 3.27; Br, 20.30; N, 10.73.

3-(4-Bromo-benzoyl)-1-(4-chloro-phenyl)-5-hydroxy-1H-pyrazole-4-carbonitrile 16d:

Red crystals, mp. 294ºC, 75% yield. υ_{max} (KBr) 3428 (Br. OH), 2222 (CN), 1675 (CO) cm^{-1}. δ_H (300 MHz, DMSO-d_6) 7.24-7.73 (4d, 8H, arom.), 11.75 (s, 1H, OH). Anal. Calcd. for ($C_{17}H_9BrClN_3O_2$) C, 50.71; H, 2.25; Br, 19.85; Cl, 8.81; N, 10.44. Found: C, 50.42; H, 2.37; Br, 19.46; Cl, 9.07; N, 10.58.

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