Phenacyl Bromides Revisited: Facile Synthesis of Some New Pyrazoles, Pyridazines, and Their Fused Derivatives

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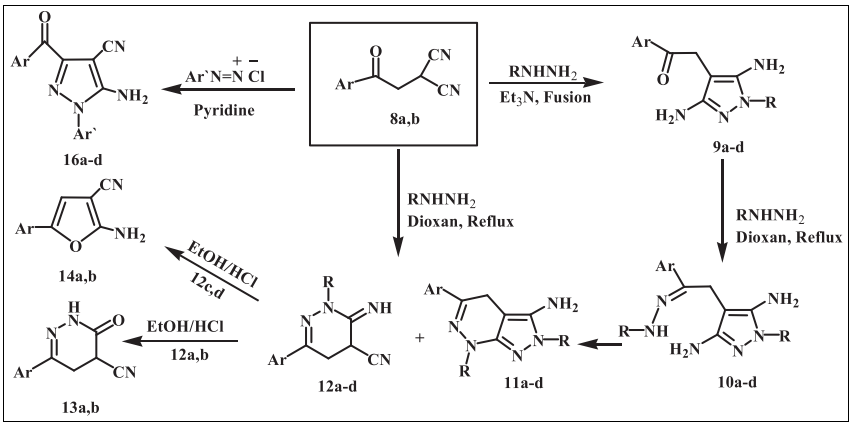

Phenacylmalononitriles **8a**,**b** react with hydrazines under dry conditions to afford the pyrazole derivatives **9a–d** and in refluxing dioxane to afford the pyrazolo[3,4-*c*]pyridazine derivatives **11a–d** and the pyridazine-6-imine derivatives **12a–d**. Compounds **12a**,**b** were transformed into their oxo analogs **13a**,**b** upon reflux in ethanolic HCl, whereas **12c**,**d** were transformed into the furan derivatives **14a**,**b** under the same reaction conditions (reflux in ethanolic HCl). Compounds **8a**,**b** could be transformed directly into the benzoyl-pyrazole derivatives **16a–d** upon coupling with diazotized aromatic amines in pyridine. The structures of the new compounds were substantiated by elemental analyses and spectral data as well as x-ray crystallographic analysis. Plausible mechanisms for the unexpected transformations are suggested.

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INTRODUCTION

In the past few years, we have been involved in a program aimed at the synthesis of some new heterocyclic systems of biological interest to be tested as biodegradable agrochemicals [1–5]. In the context of this program, we have previously reported several syntheses starting from 2-bromo-1-phenylethanone (ω-bromoacetophenone) **2a** (obtained from acetophenone **1** by bromination; Fig. 1) [6–9]. Some new pyrrole, pyrazole, and pyridazine derivatives were required for such biological studies. 2-(2-Bromo-1-phenylethylidene)-malononitrile derivatives **5b**,**c** seemed good precursors to fulfill this objective via their reaction with differently substituted aromatic amines to obtain the pyrrole derivatives **7** presumably via the intermediates **6** [10] (Scheme 1).

The parent compound of this series **5a** was eventually obtained via Knoevenagel condensation of acetophenone **1** with malononitrile **3** to afford 2-(1-phenylethylidene)-malononitrile **4** and then brominating this latter compound to afford **5a** [10] (Fig. 1). Because we already have the bromo derivatives **2b**,**c**, it was thought that their condensation with malononitrile **3** under dry conditions will lead to the desired condensation products **5b**,**c** (Scheme 1).

RESULTS AND DISCUSSION

Thus, the reaction between **2b**,**c** and malononitrile **3** was conducted in dry conditions without solvent and was catalyzed by piperidine; however, after treatment and purification of the products, we have found that they are not the desired condensation products **5b**,**c** but rather the phenacyl malononitrile derivatives **8a**,**b**. The elemental analyses showed that these products did not show any bromine content, and their ^{1}H NMR spectra showed generally the doublet and triplet signals at $\delta = 3.6$ (d, 2H) and 4.35 (t, 1H) ppm, respectively. It should be mentioned that compounds **8a** has been previously described in the literature and was obtained via another route with approximately the same yield [11].

In spite of not obtaining the desired condensation products **5b**,**c**, however, the obtained phenacyl malononitrile derivatives **8a**,**b** seemed also excellent precursors to fulfill our target via their reaction with hydrazine hydrate and

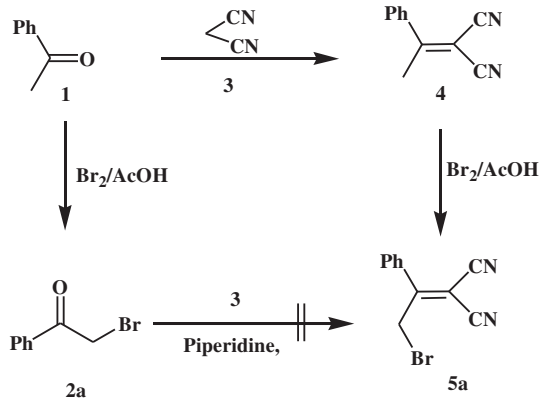


Figure 1. Synthesis of 2-(2-bromo-1-phenylethylidene) malononitrile.

phenyl hydrazine and the coupling reaction. The results of the reaction of **8a**,**b** with hydrazine hydrate and phenyl hydrazine were found to depend on the applied reaction conditions.

Thus, when **8a**,**b** were allowed to react with hydrazine hydrate and phenyl hydrazine under dry conditions without solvent at room temperature, the obtained products were found to be 1:1 adducts. The IR spectrum of the isolated products showed absorption bands at $\upsilon_{max} = 3330$, 3220, 3100, and 1660 cm^{-1} corresponding to NH, NH_2, and CO groups, respectively, and no cyano absorption bands were revealed except in the *p*-cyano derivatives.

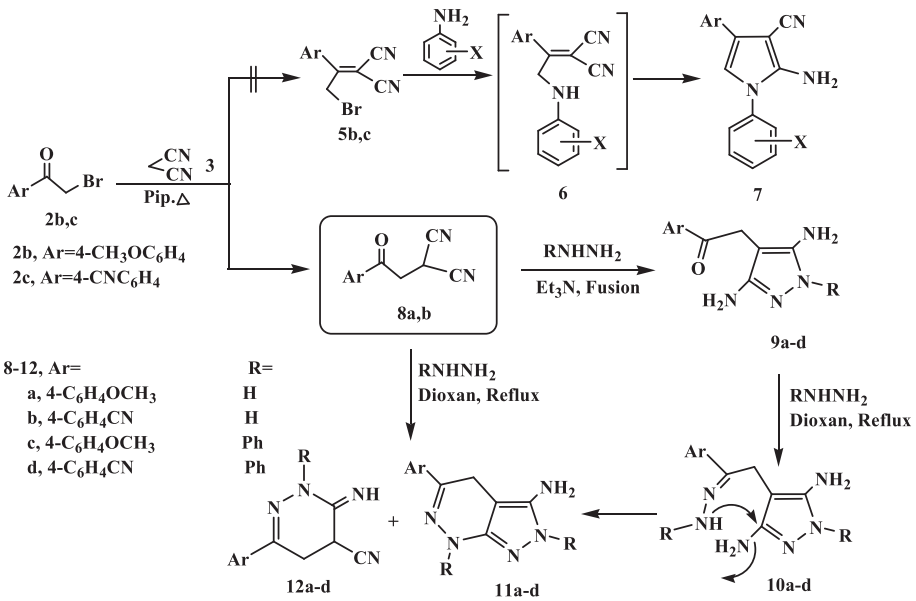
The ^1H NMR spectrum of the isolated product revealed a singlet (2H) at $\delta = 3.60$ ppm and a singlet (1H, D_2O exchangeable) at δ 11.20 and 10.45 ppm because of NH in the derivatives obtained from **8a**,**b** with hydrazine, whereas this NH signal disappeared in the derivatives obtained from **8a**,**b** with phenyl hydrazine. On the basis of these spectral as well as elemental analytical data, the *p*-substituted 4-phenacyl-3,5-diaminopyrazole structures **9a–d** were assigned to these products. ^{13}C NMR data of these compounds confirmed these structures. The mass spectra showed also molecular ion peaks that fit correctly to these structures (*cf*. Experimental).

The reaction of **8a**,**b** with hydrazine hydrate was carried out in refluxing dioxane, and we could isolate two products in each case (fractional crystallization) with melting points 235 and 290°C and 240 and 293°C, respectively. On the basis of the analytical and spectral data, the higher mp products (290 and 293°C) were recognized as the pyrazolo [3,4-*c*]pyridazine derivatives **11a**,**b**, whereas the lower mp products (235 and 240) were recognized as the tetrahydropyridazine-6-imines **12a**,**b**.

Similarly, compounds **8a**,**b** reacted with phenyl hydrazine in refluxing dioxane to afford in each case two compounds that were separated and analyzed. They were found to be the pyrazolo[3,4-*c*]pyridazine derivatives **11c**,**d** and the pyridazine-6-imine derivatives **12c**,**d**, respectively (*cf*. Experimental).

The IR spectra of the higher mp compounds **11a–d** showed no carbonyl absorptions and only the presence of NH_2 and NH absorption bands at $\upsilon_{max} = 3320–3150\ cm^{-1}$ in **11a**,**b**, but no NH bands were revealed in **11c**,**d**. The ^1H NMR spectra of **11a–d** revealed generally a singlet (2H) at $\delta = 2.4$ ppm and two aromatic doublets (4H) at $\delta = 7.45–7.85$ ppm. Compounds **11a**,**b** displayed, in addition, a D_2O exchangeable singlets (1H) at $\delta = 8.50$ and 11.6 ppm attributable to two NH protons, but the aromatic integration was 14H in case of **11c**,**d** with no signals because of NH protons.

Scheme 1. Synthesis of compounds 8, 9, 10, 11 and 12.



The IR spectra of the lower mp products **12a–d** revealed, generally, absorption bands at $\upsilon_{max} = 3280$, 3190, and 2231 cm^{-1}, attributable to NH and CN groups, respectively, and no carbonyl absorption bands appeared. The ^1H NMR spectra of these reaction products are in complete agreement with the assigned structures. A further support for this structural assignment was gained from the ^{13}C NMR spectrum of **12a** that showed signals at $\delta = 22.54$ (t), 25.84 (d), 115.30 (s), and 166.54 (s) attributable to methylene, methine, cyano, and the imine carbon atoms, respectively, beside the other expected signals because of the other carbons (*cf.* Experimental). The mass spectra of these products showed their correct molecular ion peaks. On the basis of the aforementioned data, the imino-pyridazine structures **12a–d** were confirmed for these products (*cf.* Experimental; Scheme 1).

It seems that in refluxing dioxane, two competitive reactions are working: first is the cycloaddition of hydrazine or phenyl hydrazine to the two cyano groups of **8** to afford the 4-phenacyl-3,5-diaminopyrazole **9a–d** that undergoes an *in situ* condensation with hydrazine hydrate or phenyl hydrazine to afford the hydrazone intermediates **10a–d**, which in its role undergoes cyclization with elimination of ammonia via the nucleophilic attack of the hydrazone NH_2 or PhNH on the ring amino group to give **11a–d**. Second is the condensation of hydrazine hydrate or phenyl hydrazine with the carbonyl group of **8** followed by addition of the hydrazone NH_2 or PhNH to one of the cyano groups to afford **12a–d**.

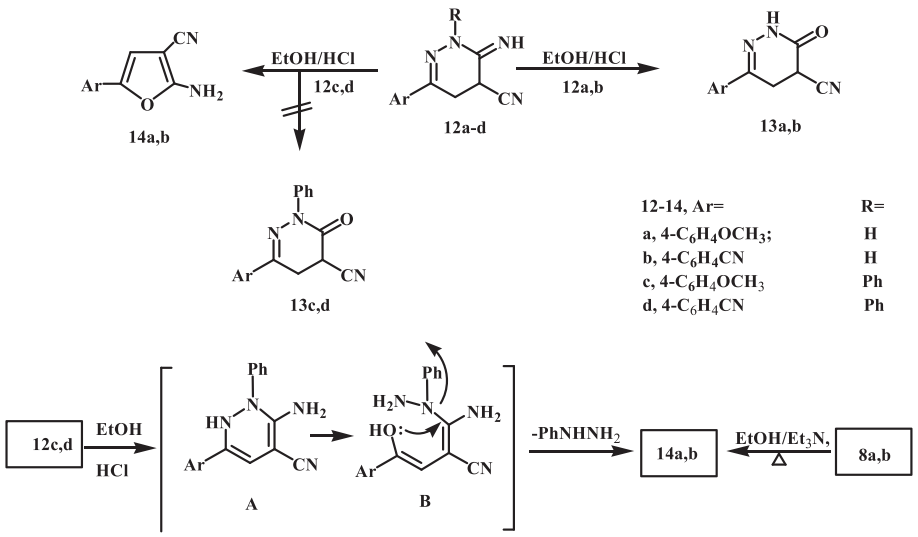
To prove this assumption, compounds **9a**,**b** were allowed to react with hydrazine hydrate in refluxing dioxane, and we could obtain the hydrazone compounds **10a**,**b** as orange colored products. Refluxing these latter compounds in ethanolic sodium ethoxide furnished their cyclization to afford **11a**,**b**, and analogously, **9c**,**d** were allowed to react with phenyl hydrazine under the same conditions to afford dark orange products that were formulated as the phenyl hydrazones **10c**,**d**. These were also successfully cyclized into **11c**,**d**, respectively. The identity of the compounds was deduced from their melting points and TLC analysis.

This behavior of **8a**,**b** towards hydrazines is in agreement with our previously reported behavior of phenacyl malononitrile towards the same reagents [12].

Compounds **12a–d** were refluxed in ethanol/conc. HCl mixture (4:1 by volume) aiming to transform them to the corresponding pyridazinone derivatives **13a–d** (Scheme 2). However, only **12a**,**b** (R = H; obtained from hydrazine) could undergo this transformation, and compounds **13a**,**b** were obtained. Under these conditions, compounds **12c**,**d** afforded light brown products. The IR spectrum of these products did not show any carbonyl absorption band, but absorption bands at $\upsilon_{max} = 3010–2280$ and 2226 corresponding to NH_2 and CN groups were revealed. The mass spectra of these two products showed molecular ion peaks at $m/z = 213$ and 209 ($M^+ - 1$ and M^+). These data correspond to the molecular masses of **12c**,**d** after elimination of phenyl hydrazine. On the basis of the aforementioned data, the furan structures **14a**,**b** were thus suggested for these products. The ^1H NMR spectrum of **14a** revealed broad singlets at $\delta = 3.92$ ppm (2H, D_2O exchangeable) attributed to NH_2 and $\delta = 7.30$ ppm integrated for 1H (furan H) beside two doublets in the aromatic region. The ^1H NMR spectrum of **14b** revealed the furan proton at the same position ($\delta = 7.3$ ppm) but the NH_2 at $\delta = 7.9$ ppm.

The ^{13}C NMR data of these products showed the four carbons of furan beside the other signals at their expected positions. This unexpected formation of these furan derivatives urged us to have an X-ray for any of these products, and luckily, we could obtain it for **14a** that showed unambiguously the furan structure (Fig. 2) [13,14].

Scheme 2. Synthesis of the pyridazines 12 and 13 and the furans 14.



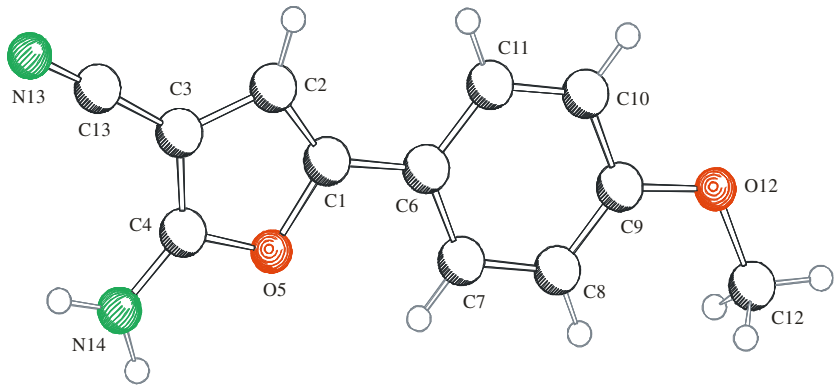


Figure 2. X-ray crystallographic structure of the furan derivative **14a** [13,14]. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

A plausible mechanism for the transformation of **12c**,**d** to **14a**,**b** is depicted in Scheme 2. It is assumed to proceed via initial tautomerization of the pyridazine rings **12c**,**d** under the effect of HCl to give the intermediates **A** followed by hydrolytic ring opening to afford the intermediates **B**. These intermediates **B** in their role undergo recyclization with loss of phenyl hydrazine to afford the furan derivatives **14a**,**b**. This behavior is observed only in case of **12c**,**d** because the phenyl ring presumably stabilizes and facilitates the elimination of phenyl hydrazine. The furan derivative **14a** was obtained via an alternative route by refluxing **8a** in ethanol catalyzed by triethylamine [11].

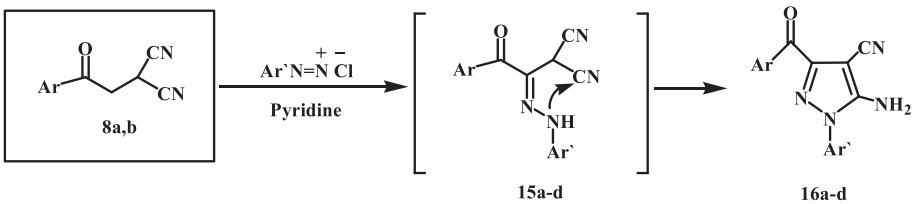
Aroyl pyrazoles are also interesting compounds from the point of view of their biological activity studies as well as their further transformations [15]. The obtained phenacyl malononitriles **8a**,**b** were coupled with aromatic diazonium salts (phenyl- and *p*-chlorophenyl-) in pyridine solution to afford bright colored compounds. It was thought that we have obtained the hydrazo derivatives **15a–d**. However, the ^{1}H NMR spectra of these products did not reveal any singlet signals that can be attributed to a methine proton or the hydrazone proton. Therefore, we had the impression that our obtained products are the already cyclized pyrazole derivatives **16a–d**. All analytical and spectral data were in complete agreement with the pyrazole structures **16a–d** that were assigned for these products. Furthermore, the ^{13}C NMR spectrum of **16a** as a representative example revealed 14 C signals that are applicable to this structure (*cf*. Scheme 3 and Experimental).

EXPERIMENTAL

Melting points were determined on an electrothermal (9100) apparatus (Kleinfeld, Gehrden, Germany) and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer (Perkin Elmer, Norwalk, CT). The ^{1}H NMR and ^{13}C NMR spectra were taken on a Varian Gemini 300 MHz spectrometer (Varian, Oxford, UK) 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 (Shimadzu, Kyoto, Japan) (70 eV). Elemental analyses were carried out by the Microanalytical Center at Cairo University. The X-ray crystallography as well as a considerable part of the spectra were carried out in the Institute of Organic Chemistry, Technical University of Dresden, Germany.

Preparation of the phenacyl malononitrile derivatives 8a,**b**. A mixture of the respective ω-bromoacetophenone derivative **2b** or **2c** (100 mmol) and malononiotrile **3** (6.6 g; 100 mmol) was warmed under dry conditions on a water bath untill a homogeneous solution is obtained and then allowed to cool to room temperature. Piperidine (8.50 g,

Scheme 3. Synthesis of the pyrazoles 16.



15, 16: Ar=	Ar`=	Ar=	Ar`=
a, 4-$C_6H_4OCH_3$;	Ph	c, 4-$C_6H_4OCH_3$;	4-C_6H_4Cl
b, 4-C_6H_4CN	Ph	d, 4-C_6H_4CN	4-C_6H_4Cl

100 mmol) was added portionwise to this solution with shaking; each portion is being added after the vigorous reaction and evolution of fumes have ceased. After complete addition, the reaction mixture was heated on a boiling water bath for 1 h, and then allowed to stand overnight. The crystalline products thus obtained were triturated with ethanol, filtered off, and then recrystallized from ethanol.

2-[2-(4-Methoxyphenyl)-2-oxo-ethyl]-malononitrile 8a. Light yellow crystals: yield (18.0 g, 84%); mp 188–189°C (Lit. [11] 191–192°C); υ_{max} = 2257 (CN), 1684 (CO) cm^{-1}; *m/z* = 213 [$M^+ - 1$]. δ_H = 3.60 (d, 2H, CH_2; *J* = 4.1 Hz), 3.85 (s, 3H, CH_3), 4.35 (t, 1H, CH; *J* = 4.1 Hz), 6.90 and 7.85 (2d, 4H, Ar-H; *J* = 7.15 Hz). δ_C = 17.77 (d, CH), 39.12 (t, CH_2), 55.65 (q, CH_3) 112.52 (s, CN), [114.31 (d), 130.66 (d), 131.33 (s), 164.79 (s) Ph Carbons], 189.80 (s) (C=O). *Anal*. Calcd for $C_{12}H_{10}N_2O_2$ (214.22): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.35; H, 4.82; N, 13.25.

2-[2-(4-Cyanophenyl)-2-oxo-ethyl]malononitrile 8b. Light coffee brown crystals: yield (17.8 g, 85%); mp 180–182°C; υ_{max} = 2261 (CN), 2229 (CN), 1691 (CO) cm^{-1}; *m/z* = 209 [M^+]. δ_H = 4.12 (d, 2H, CH_2; *J* = 4.0 Hz), 5.15 (t, 1H, CH; *J* = 4.0 Hz), 8.03 and 8.20 (2d, 4H, Ar-H; *J* = 7.15 Hz). δ_C = 17.89 (d, CH), 39.08 (t, CH_2), 114.20 (s, CN), 116.10 (s, CN), [118.14 (s), 128.84 (d), 132.78 (d), 137.90 (s) Ph Carbons], 193.95 (s) (C=O). *Anal*. Calcd for $C_{12}H_7N_3O$ (209.20): C, 68.89; H, 3.37; N, 20.09. Found: C, 68.75; H, 3.35; N, 20.19.

Preparation of 3,5-diaminopyrazole derivatives 9a–d: general procedure. A mixture of each of **8a**,**b** (0.01 mol) and hydrazine hydrate or phenyl hydrazine (0.015 mol) is warmed under dry conditions on a water bath where a vigorous reaction took place. Few drops of triethylamine may be added to activate the reaction. The solid masses formed on standing at room temperature were triturated with ethanol and then poured onto cold water and acidified by few drops of conc. HCl. The solid products so formed were filtered off and recrystallized from ethanol/dimethylformamide (DMF) mixture (4:1).

2-(3,5-Diamino-1*H*-pyrazol-4-yl)-1-(4-methoxyphenyl)-ethanone 9a. Yellow crystals: yield (1.85 g, 75%); mp 236–237°C; υ_{max} = 3332, 3216, 3118 (NH_2 and NH), 1658 (CO) cm^{-1}; *m/z* = 242 [$M^+ - 4$]. δ_H = 3.80 (s, 2H, CH_2), 3.90 (s, 3H, CH_3), 7.25 and 7.65 (2d, 4H, Ar-H; *J* = 7.12 Hz.), 8.52 (br, 4H, $2NH_2$), 11.20 (s, 1H, NH). *Anal*. Calcd for $C_{12}H_{14}N_4O_2$ (246.27): C, 58.53; H, 5.73; N, 22.75. Found: C, 58.65; H, 5.60; N, 22.55.

4-[2-(3,5-Diamino-1*H*-pyrazol-4-yl)-acetyl]-benzonitrile 9b. Yellow crystals: yield (1.64 g, 68%); mp 253–255°C; υ_{max} = 3335, 3226, 3078 (NH_2 and NH), 2225 (CN), 1678 (CO) cm^{-1}; *m/z* = 241 [M^+]. δ_H = 3.60 (s, 2H, CH_2), 4.65 (s, 2H, NH_2) 7.40 and 7.80 (2d, 4H, Ar-H; *J* = 7.10 Hz), 10.30 (s, 2H, NH_2), 10.45 (s, 1H, NH). *Anal*. Calcd for $C_{12}H_{11}N_5O$ (241.25): C, 59.74; H, 4.60; N, 29.03. Found: C, 59.60; H, 4.65; N, 29.20.

2-(3,5-Diamino-1-phenyl-1*H*-pyrazol-4-yl)-1-(4-methoxyphenyl)-ethanone 9c. Yellow crystals: yield (2.45 g, 76%); mp 212–213°C; υ_{max} = 3329–3115 (NH_2), 1660 (CO) cm^{-1}. *m/z* = 322 [M^+]. δ_H = 3.62 (s, 2H, CH_2), 3.91 (s, 3H, CH_3), 7.15–7.65 (m, 9H, Ar.H), 8.1 (br, 2H, NH_2), 8.17 (br, 2H, NH_2). *Anal*. Calcd for $C_{18}H_{18}N_4O_2$ (322.36): C, 67.07; H, 5.63; N, 17.38. Found: C, 67.00; H, 5.55; N, 17.50.

4-[2-(3,5-Diamino-1-phenyl-1*H*-pyrazol-4-yl)-acetyl]-benzonitrile 9d. Yellow crystals: yield (2.10 g, 66%); mp 242–243°C; υ_{max} = 3335–3138 (NH_2), 2227 (CN), 1667 (CO) cm^{-1}; *m/z* = 317 [M^+]. δ_H = 3.64 (s, 2H, CH_2), 7.25–7.80 (m, 9H, Ar-H), 8.15 (br, 2H, NH_2), 8.21 (br, 2H, NH_2). *Anal*. Calcd for $C_{18}H_{15}N_5O$ (317.34): C, 68.13; H, 4.76; N, 22.07. Found: C, 68.18; H, 4.80; N, 22.27.

The reaction of phenacyl-malononitriles 8a,b with hydrazines in solution: synthesis of 11a–d and 12a–d. A solution of **8a** or **8b** (0.01 mol) and hydrazine hydrate or phenyl hydrazine (0.01 mol) in 25 mL of dioxane was refluxed for 2 h. The reaction mixture was allowed to cool to room temperature. The solid precipitate was filtered off, boiled in ethanol where a part dissolved, filtered while hot, and left to recrystallize. The insoluble part was recrystallized from DMF/dioxane mixture (1:1) and identified as **11a–d**. The precipitated part from ethanol was identified as **12a–d**. Compounds **11a–d/12a–d** were found to be approximately 1/1 in each case.

5-(4-Methoxyphenyl)-4,7-dihydro-2*H*-pyrazolo[3,4-*c*]pyridazin-3-yl amine 11a. zDirty yellow crystalline solid, yield (0.90 g, 75%) mp 290–291°C. υ_{max} = 3305, 3215, 3138, 3130 (NH_2 and NH) cm^{-1}; *m/z* = 243 [M^+]. δ_H = 2.40–2.48 (s, 2H, CH_2), 3.68 (s, 3H, CH_3), 6.80 (br s, 2H, NH_2), 7.45–7.82 (2d, 4H, Ar-H; *J* = 7.20 Hz), 8.54 (br s, 1H, NH), 11.63 (br s, 1H, NH). δ = 15.48 (t), 55.90 (q), 89.32 (s), 114.15(d), 123.63 (s), 130.4 (d), 132.25 (s), 152.10 (s), 155.65 (s), 164.85 (s). *Anal*. Calcd for $C_{12}H_{13}N_5O$ (243.26): C, 59.25; H, 5.39; N, 28.79. Found C, 59.35; H, 5.24; N, 28.85.

4-(3-Amino-4,7-dihydro-2*H*-pyrazolo[3,4-*c*]pyridazin-5-yl) benzonitrile 11b. Dirty yellow crystalline solid, yield (0.87 g, 73%) mp 293–294°C. υ_{max} = 3325, 3220, 3135, 3132 (NH_2 and NH), 2225 (CN) cm^{-1}; *m/z* = 238 [M^+]. δ_H = 2.42–2.46 (s, 2H, CH_2), 7.47–7.85 (2d, 4H, Ar-H; *J* = 7.18 Hz), 8.35 (br s, 2H, NH_2), 8.55 (br s, 1H, NH), 11.65 (br s, 1H, NH). *Anal*. Calcd for $C_{12}H_{10}N_6$ (238.25): C, 60.50; H, 4.23; N, 35.27. Found C, 60.56; H, 4.32; N, 35.20.

5-(4-Methoxyphenyl)-2,7-diphenyl-4,7-dihydro-2*H*-pyrazolo [3,4-*c*]pyridazin-3-yl amine 11c. Brown crystalline solid, yield (1.25 g, 63%) mp 305–307°C. υ_{max} = 3325–3220 (NH_2) cm^{-1}; *m/z* = 395 [M^+]. δ_H = 2.43–2.48 (s, 2H, CH_2), 3.72 (s, 3H, CH_3), 8.72 (br s, 2H, NH_2), 7.25–7.95 (m, 14H, Ar-H). *Anal*. Calcd for $C_{24}H_{21}N_5O$ (395.46): C, 72.89; H, 5.35; N, 17.71. Found C, 72.95; H, 5.25; N, 17.60.

4-(3-Amino-2,7-diphenyl-4,7-dihydro-2*H*-pyrazolo[3,4-*c*] pyridazin-5-yl)benzonitrile 11d. Brown crystalline solid, yield (1.27 g, 65%) mp 312–314°C. υ_{max} = 3325–3225 (br, NH_2); 2223 (CN) cm^{-1}; *m/z* = 390 [M^+]. δ_H = 2.45–2.49 (s, 2H, CH_2), 6.75–8.15 (m, 16H, Ar-H + NH_2). *Anal*. Calcd for $C_{24}H_{18}N_6$ (390.44): C, 73.83; H, 4.65; N, 21.52. Found C, 73.90; H, 4.55; N, 21.40.

3-Imino-6-(4-methoxyphenyl)-2,3,4,5-tetrahydropyridazine-4-carbonitrile 12a. Pale yellow crystalline solid, yield (0.78 g, 69%) mp 235–236°C. υ_{max} = 3280, 3190 (NH) and 2231 (CN) cm^{-1}; *m/z* = 228 [M^+]. δ_H = 1.75–1.80 (d, 2H, CH_2; *J* = 3.6 Hz), 2.40–2.52 (t, 1H, CH; *J* = 3.6 Hz), 3.92 (s, 3H, CH_3), 7.42 (s, 1H, ring NH), 7.44–7.58 (2d, 4H, Ar-H; *J* = 7.14 Hz), 11.45 (s, 1H, =NH). δ_c = 22.54(t), 25.84(d), 54.95(q), 114.54(d), 115.30(s), 123.75(s), 130.16(d), 155.73(s), 163.75(s), 166.54(s). *Anal*. Calcd for $C_{12}H_{12}N_4O$ (228.25): C, 63.15; H, 5.30; N, 24.55. Found C, 63.12; H, 5.35; N, 24.62.

6-(4-Cyanophenyl)-3-imino-2,3,4,5-tetrahydropyridazine-4-carbonitrile 12b. Brownish yellow crystalline solid, yield (0.75 g, 67%) mp 240–242°C. IR: υ_{max} = 3283, 3195 (NH), 2224 and 2232 (2CN) cm^{-1}; *m/z* = 223 [M^+]. δ_H = 1.74–1.79 (d, 2H, CH_2; *J* = 3.5 Hz), 2.41–2.53 (t, 1H, CH; *J* = 3.5 Hz), 7.40 (s, 1H, ring NH), 7.42–7.65 (2d, 4H, Ar-H; *J* = 7.12 Hz), 11.48 (s, 1H, NH). *Anal*. Calcd for $C_{12}H_9N_5$ (223.23): C, 64.56; H, 4.06; N, 31.37. Found C, 64.55; H, 4.15; N, 31.25.

3-Imino-6-(4-methoxyphenyl)-2-phenyl-2,3,4,5-tetrahydropyridazine-4-carbonitrile 12c. Yellow crystalline solid, yield (1.18 g, 78%) mp 238–239°C. υ_{max} = 3198, 3090 (NH), 2234 (CN) cm^{-1}; *m/z* = 304 [M^+]. δ_H = 1.74–1.81 (d, 2H, CH_2; *J* = 3.6 Hz), 2.41–2.50 (t, 1H, CH; *J* = 3.6 Hz), 3.82 (s, 3H, CH_3), 7.45–7.82 (m, 9H, Ar-H), 11.55 (s, 1H, NH). *Anal*. Calcd for $C_{18}H_{16}N_4O$ (304.35): C, 71.04; H, 5.30; N, 18.41. Found C, 71.14; H, 5.37; N, 18.50.

6-(4-Cyanophenyl)-3-imino-2-phenyl-2,3,4,5-tetrahydropyridazine-4-carbonitrile 12d. Dirty yellow crystalline solid, yield (1.12 g, 75%) mp 242–243°C. υ_{max} = 3215, 3130 (NH), 2226 and 2235 (2CN) cm^{-1}; *m/z* = 299 [M^+]. δ_H = 1.76–1.82 (d, 2H, CH_2; *J* = 3.5 Hz), 2.40–2.48 (t, 1H, CH; *J* = 3.5 Hz), 7.47–7.85 (m, 9H, Ar-H), 11.63 (s, 1H, NH). *Anal*. Calcd for $C_{18}H_{13}N_5$ (299.33): C, 72.23; H, 4.38; N, 23.40. Found C, 72.28; H, 4.35; N, 23.45.

Alternative preparation of 11a–d. a) Preparation of the hydrazones 10a–d. A solution of the *p*-substituted 4-phenacylpyrazole derivatives **9a**,**b** (0.01 mol) with hydrazine hydrate (0.01 mol) and of the *p*-substituted 4-phenacyl-1-phenylpyrazole derivatives **9c**,**d** (0.01 mol) with phenyl hydrazine (0.01 mol) in 30 mL of ethanol was refluxed for 2 h where solid orange precipitates appeared. The reaction mixture was then left to cool to room temperature, filtered off, and recrystallized from ethanol/DMF to afford orange yellow crystals that were identified as the hydrazones **10a**,**b** and the phenyl hydrazones **10c**,**d**, respectively.

4-[2-Hydrazono-2-(4-methoxyphenyl)-ethyl]-1*H*-pyrazole-3,5-diamine 10a. Orange crystalline solid, yield (1.85 g, 71%) mp 172–174°C. υ_{max} = 3327, 3225, 3142, 3038 (NH_2 and NH) cm^{-1}; *m/z* = 260 [M^+]. δ_H = 2.65 (s, 2H, CH_2), 3.85 (s, 3H, CH_3), 5.64 (br s, 4H, $2NH_2$), 6.78–8.18 (m, 6H, Ar-H + NH_2), 11.85 (s, 1H, NH). *Anal*. Calcd for $C_{12}H_{16}N_6O$ (260.30): C, 55.37; H, 6.20; N, 32.29. Found C, 55.45; H, 6.10; N, 32.14.

4-[2-(3,5-Diamino-1*H*-pyrazol-4-yl)-1-hydrazonoethyl]-benzonitrile 10b. Orange crystalline solid, yield (1.76 g, 69%) mp 176–177°C. υ_{max} = 3330, 3226, 3143, 3067 (NH_2 and NH) cm^{-1}; *m/z* = 255 [M^+]. δ_H = 2.66 (s, 2H, CH_2), 5.68 (br s, 4H, $2NH_2$), 6.48–7.58 (2d, 4H, Ar-H; *J* = 7.05 Hz), 8.34 (br s, 2H, NH_2), 11.88 (s, 1H, NH). *Anal*. Calcd for $C_{12}H_{13}N_7$ (255.28): C, 56.46; H, 5.13; N, 38.41. Found C, 56.50; H, 5.25; N, 38.12.

4-[2-(4-Methoxyphenyl)-2-(phenyl-hydrazono)-ethyl]-1-phenyl-1*H*-pyrazole-3,5-diamine 10c. Dark orange crystalline solid, yield (2.68 g, 65%) mp 213–215°C. υ_{max} = 3327, 3225, 3142, 3038 (NH_2 and NH) cm^{-1}; *m/z* = 412 [M^+]. δ_H = 2.65 (s, 2H, CH_2), 3.75 (s, 3H, CH_3), 5.64 (br s, 2H, NH_2), 6.78–8.28 (m, 16H, Ar-H + NH_2), 12.85 (s, 1H, NH). *Anal*. Calcd for $C_{24}H_{24}N_6O$ (412.49): C, 69.88; H, 5.86; N, 20.37. Found C, 69.60; H, 5.80; N, 20.55.

4-[2-(3,5-Diamino-1-phenyl-1*H*-pyrazol-4-yl)-1-(phenyl-hydrazono)-ethyl]-benzonitrile 10d. Dark orange crystalline solid, yield (2.65 g, 63%) mp 233–235°C. υ_{max} = 3327, 3225, 3142, 3038 (NH_2 and NH) cm^{-1}; *m/z* = 407 [M^+]. δ_H = 2.71 (s, 2H, CH_2), 5.66 (br s, 2H, NH_2), 6.78–8.28 (m, 16H, Ar-H + NH_2), 12.90 (s, 1H, NH). *Anal*. Calcd for $C_{24}H_{21}N_7$ (407.47): C, 69.88; H, 5.86; N, 20.37. Found C, 69.60; H, 5.80; N, 20.55.

b) Cyclization of 10a–d. To a solution of each of **10a–d** (0.005 mol) in absolute ethanol (20 mL) was added 2 mL of freshly prepared sodium ethoxide (0.25 g of Na metal dissolved in 10 mL of ethanol), and the reaction mixture was refluxed for 2 h, and then left to cool to room temperature and poured on ice cold water and acidified with few drops of conc. HCl till neutral. The solid precipitates thus appeared was filtered off and washed thoroughly with cold water, dried, and recrystallized from ethanol to afford compounds completely identical with **11a–d**, respectively. The identity of these compounds was inferred from the matching melting points and IR spectra.

Transformation of 12a,**b** into **13a**,**b** and of **12c**,**d** into **14a**,**b**. Compounds **12a–d** (0.01 mol) were refluxed in ethanol (15 mL) containing conc. HCl (2 mL) for 2 h and then left to cool to room temperature, poured on crushed ice, and neutralized cautiously with ammonia solution. The precipitated solids were filtered off, washed thoroughly with water, and recrystallized from ethanol to afford **13a**,**b** and **14a**,**b**, respectively.

6-(4-Methoxyphenyl)-3-oxo-2,3,4,5-tetrahydropyridazine-4-carbonitrile 13a. Orange crystalline solid, yield (1.95 g, 85%) mp 240–242°C. υ_{max} = 3215, 3138 (NH), 2228 (CN), 1678 (C=O) cm^{-1}; *m/z* = 229 [M^+]. δ_H = 1.78–1.82 (d, 2H, CH_2; *J* = 3.5 Hz), 3.43–3.55 (t, 1H, CH; *J* = 3.5 Hz), 3.85 (s, 3H, CH_3), 7.43 (s, 1H, ring NH), 7.45–7.78 (2d, 4H, Ar-H; *J* = 7.14 Hz). δ_c = 26.94 (t), 35.96 (d), 55.92 (q), 114.58 (d), 116.32 (s), 123.62 (s), 130.21 (d), 155.63 (s), 163.95 (s), 181.56 (s). *Anal*. Calcd for $C_{12}H_{11}N_3O_2$ (229.23): C, 62.87; H, 4.84; N, 18.33. Found C, 62.85; H, 4.80; N, 18.40.

6-(4-Cyanophenyl)-3-oxo-2,3,4,5-tetrahydropyridazine-4-carbonitrile 13b. Orange crystalline solid, yield (1.93 g, 86%) mp 258–260°C. υ_{max} = 3225, 3144 (NH), 2225 and 2236 (2CN), 1679 (C=O) cm^{-1}; *m/z* = 225 [M^++1]. δ_H = 1.75–1.79 (d, 2H, CH_2; *J* = 3.4 Hz), 3.45–3.56 (t, 1H, CH; *J* = 3.4 Hz), 7.45 (s, 1H, ring NH), 7.54–7.82 (2d, 4H, Ar-H; *J* = 7.12 Hz). *Anal*. Calcd for $C_{12}H_8N_4O$ (224.22): C, 64.28; H, 3.60; N, 24.99. Found C, 64.30; H, 3.60; N, 25.15.

2-Amino-5-(4-methoxyphenyl)-furan-3-carbonitrile 14a. Yellow crystals: yield (1.67 g, 78%); mp 216–217°C (Lit. [11] 214–215°C); υ_{max} = 3008–2289 (NH_2), 2226 (CN) cm^{-1}; *m/z* = 213 [$M^+ - 1$]. δ_H = 3.85 (s, 3H, CH_3), 3.92 (s, 2H, NH_2), 6.9 (d, 2H, Ph; *J* = 7.20 Hz), 7.30 (s, 1H, Furan H-4), 7.85 (d, 2H, Ph; *J* = 7.20 Hz). δ_C = 55.62 (t, CH_3), 66.35 (s, Fur. C-3), 107.23 (d, Fur. C-4), 115.16 (s, CN), [114.18 (d), 127.96 (s), 130.55 (d), 164.59 (s) Ph Carbons], 142.63 (s, Fur. C-2), 164.95 (s, Fur. C-5). *Anal*. Calcd for $C_{12}H_{10}N_2O_2$ (214.22): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.32; H, 4.72; N, 13.12.

X-ray crystallographic data: yellow crystals, $C_{12}H_{10}N_2O_2$ (M_r = 214.2 g*mol^{-1}), monoclinic, crystal size = 0.21 * 0.21 * 0.07 mm. space group $P2_1/c$ (No. 14), a = 19.275(1) Å, b = 5.402 (1) Å, c = 9.926(1) Å, α[°] = 90.00, β[°] = 99.13 (1), γ[°] = 90.00; *V*[$Å^3$] = 1020.4 (2), Z = 4, $D_{calc.}$ = 1.394 g*cm^{-3}, *F*(000) = 448 e, μ(M_o K_α) = 0.097 nm^{-1}; the final difference Fourier ρ = 0.18 (−0.19) e $Å^{-3}$. Max. resolution [sin θ/λ]$_{max}$ = 0.61 $Å^{-1}$/99.6%. Data were collected using a Bruker Nonius (Bruker, Rheinstetten, Germany) area detector at T[°C] = −75 (2), with graphite monochromator with Mo Kα radiation (λ = 0.71073 Å) using the CCD data collection and SADABS absorption correction method; min. 98.0% max: 99.3%. Total number of reflections collected = 16317. Number of independent reflections are 1873 and were counted with observed reflections 1519. R_{av} = 0.032. The final R and R_W^2 = 0.035 and 0.082, respectively.

2-Amino-5-(4-cyanophenyl)-furan-3-carbonitrile 14b. Brownish yellow crystals: yield (1.67 g, 80%); mp 240–241°C; υ_{max} = 3017–2287 (NH_2), 2254 and 2226 (2CN) cm^{-1}; *m/z* = 209 [M^+]. δ_H = 7.3 (s, 1H, Furan H-4), 7.58 (d, 2H, Ph; *J* = 7.19 Hz), 7.78 (d, 2H, Ph; *J* = 7.19 Hz), 7.90 (s, 2H, NH_2). δ_C = 67.30 (s), 107.81 (s), 111.38 (d), 115.54 (s), 119.01 (s), 122.11 (d), 132.85 (d), 133.25 (s), 139.97 (s), 164.63 (s). *Anal*. Calcd for $C_{12}H_7N_3O$ (209.20): C, 68.89; H, 3.37; N, 20.09. Found: C, 68.95; H, 3.42; N, 20.00.

The coupling reaction of 8a,b with diazonium salts: preparation of the pyrazoles 16a–d. Aryl diazonium salts (0.01 mol) were freshly prepared by adding a solution of 0.01 mol of sodium nitrite in 5 mL of water to a cold solution of the respective arylamine hydrochloride (aniline or *p*-chloroaniline in 5 mL conc. HCl; 0.01 mol) with stirring. The resulting solutions of the aryl diazonium salts were added to a cold solution of each of the phenacyl malononitriles **8a**,**b** (0.01 mol), in pyridine (50 mL). The reaction mixture was stirred at room temperature for 1 h in each case and then cold water was added (~100 mL), and to the whole solution was added conc. HCl dropwise until neutral. The precipitated solids were filtered off and recrystallized from ethanol/DMF (5:1) to afford the pyrazoles **16a–d**.

5-Amino-3-(4-methoxybenzoyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile 16a. Yellow crystals: yield (3.00 g, 79%); mp 222–223°C; $\upsilon_{max} = 3022$ (NH_2), 2222 (CN), 1663 (C=O) cm^{-1}; $m/z = 318$ [M^+]. $\delta_H = 3.90$ (s, 3H, CH_3), 4.78 (s, 2H, NH_2), 6.96 (d, 2H, Ar-H; $J = 7.08$ Hz), 7.35–7.96 (m, 5H, Ph), 8.40 (d, 2H, Ar-H; $J = 7.08$ Hz). $\delta_C = 56.32$ (q), 96.60 (s), 114.42 (d), 115.32 (s), 118.88 (d), 125. 62 (s), 126.22 (d), 129.15 (d), 130.62 (d), 139.42 (s), 142.40 (s), 152.46 (s), 166.54 (s), 186.92 (s). *Anal*. Calcd for $C_{18}H_{14}N_4O_2$ (318.33): C, 67.91; H, 4.43; N, 17.60. Found: C, 67.90; H, 4.45; N, 17.68.

5-Amino-3-(4-cyanobenzoyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile 16b. Yellow crystals: yield (2.13 g, 68%); mp 228–230°C; $\upsilon_{max} = 3028$ (NH_2), 2245 and 2222 (2CN), 1668 (C=O) cm^{-1}; $m/z = 313$ [M^+]. $\delta_H = 4.82$ (s, 2H, NH_2), 6.95 (d, 2H, Ar-H; $J = 7.06$ Hz), 7.33–7.95 (m, 5H, Ph), 8.39 (d, 2H, Ar-H; $J = 7.06$ Hz). *Anal*. Calcd for $C_{18}H_{11}N_5O$ (313.31): C, 69.00; H, 3.54; N, 22.35. Found: C, 69.15; H, 3.45; N, 22.30.

5-Amino-1-(4-chlorophenyl)-3-(4-methoxybenzoyl)-1*H*-pyrazole-4-carbonitrile 16c. Yellow crystals: yield (2.29 g, 65%); mp 156–158°C; $\upsilon_{max} = 3032$ (NH_2), 2221 (CN), 1667 (C=O) cm^{-1}; $m/z = 318$ [M^+]. $\delta_H = 3.92$ (s, 3H, CH_3), 4.79 (s, 2H, NH_2), 7.23–7.80 (m, 8H, Ar-H). *Anal*. Calcd for $C_{18}H_{13}ClN_4O_2$ (352.77): C, 61.28; H, 3.71; Cl, 10.05; N, 15.88. Found: C, 61.35; H, 3.82; Cl, 9.85; N, 15.69.

5-Amino-1-(4-chlorophenyl)-3-(4-cyanobenzoyl)-1*H*-pyrazole-4-carbonitrile 16d. Yellow crystals: yield (2.36 g, 68%); mp 128–130°C; $\upsilon_{max} = 3035$ (NH_2), 2225 and 2253 (2CN), 1672 (C=O) cm^{-1}; $m/z = 347$ and 349 [$M^+ \pm 1$]. $\delta_H = 4.85$ (s, 2H, NH_2), 6.95–8.30 (m, 8H, Ar-H). *Anal*. Calcd for $C_{18}H_{10}ClN_5O$ (347.76): C, 62.17; H, 2.90; Cl, 10.19; N, 20.14. Found: C, 62.35; H, 2.68; Cl, 10.32; N, 20.34.

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[13] Crystallographic data (excluding structure factors) for the structure **15** reported in this article have been deposited with the Cambridge Crystallographic Data Centre as a supplementary publication no. CCDC 848860. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) + 44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

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