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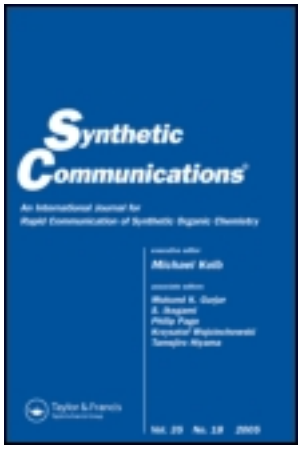

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Novel Synthesis of Some New Pyridazine and Pyridazino[4,5-d]pyridazine Derivatives

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NOVEL SYNTHESIS OF SOME NEW PYRIDAZINE AND PYRIDAZINO[4,5-*d*]PYRIDAZINE DERIVATIVES

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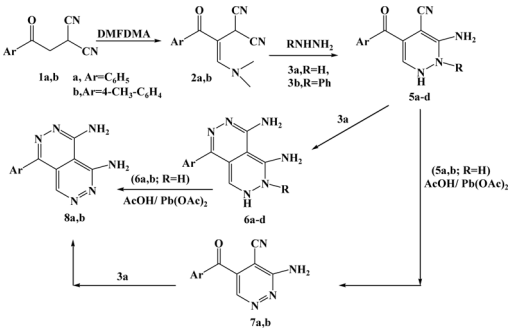
GRAPHICAL ABSTRACT



Abstract *Phenacyl-malononitrile derivatives* **1a** *and* **b** *react with dimethylformamide dimethylacetal (DMFDMA) in refluxing toluene to afford the enaminones* **2a** *and* **b** *respectively. Compounds* **2a** *and* **2b** *react with the hydrazine hydrate* **3a** *and phenyl hydrazine* **3b** *in refluxing ethanol to afford the pyridazine derivatives* **5a–d**, *presumably via the intermediates* **4**. *Compounds* **5a–d,** *react with hydrazine hydrate* **3a** *to afford the pyridazino[4,5-*d*]pyridazines* **6a–d** *respectively. The pyridazines* **5a** *and* **b** *and the pyridazino[4,5-*d*] pyridazines* **6a** *and* **b** *could be oxidized into the full aromatic systems* **7a** *and* **b** *and* **8a** *and* **b** *respectively. Compounds* **7a** *and* **b** *react also with hydrazine hydrate* **3a** *to afford* **8a** *and* **b** *respectively.*

Keywords Dimethylformamide-dimethylacetal; phenacyl-malononitrile; pyridazine; pyridazino[4,5-*d*]pyridazine

INTRODUCTION

Pyridazine derivatives have received considerable attention in the past two decades because of their diverse biological activities.[1,2] This class of compounds

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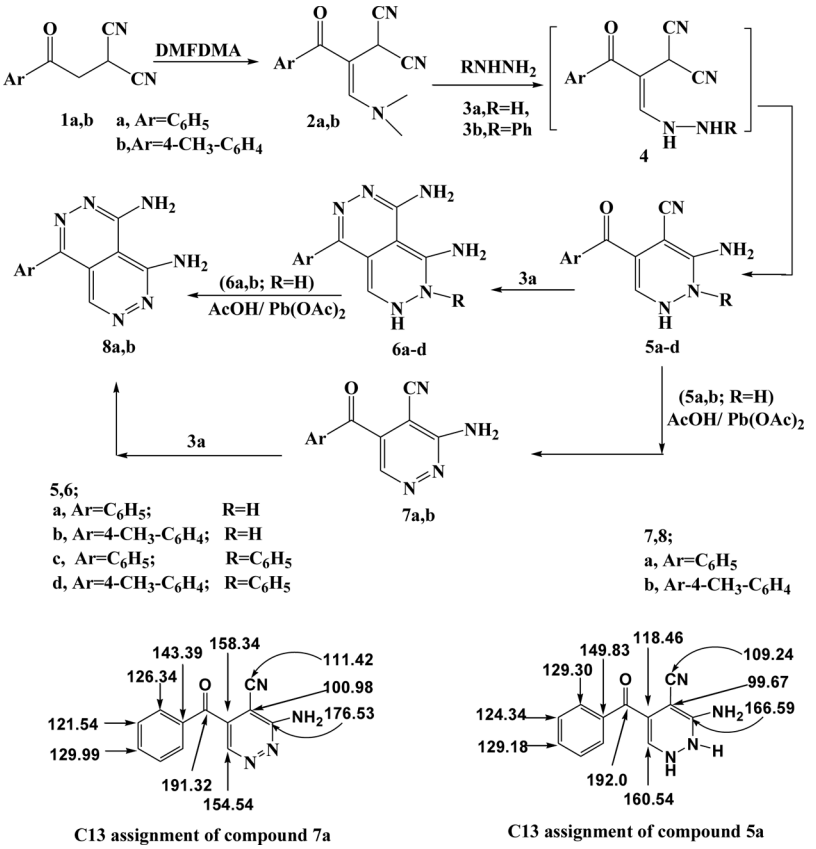

Scheme 1. Synthesis of some new pyridazine and pyridazino[4,5-*d*]pyridazine derivatives.

is reported to show aldose-reductase inhibitory,[3] antihypertensive, anticonvulsant, antispasmodic, and muscle relaxant effects, and inhibits blood platelet aggregation. They are also used as antihistaminic, analgesic, anti-inflammatory, and cardiotonic agents with vasodilator activity.[4–6] In addition, these compounds were also reported to show herbicidal and fungicidal[7,8] activities. In the past two decades, we have been involved in a program aiming at the synthesis of heterocyclic compounds of expected biological activity to be tested as biodegradable agrochemicals.[9–18] In the context of this program and because of increased interest in pyridazine derivatives, some new pyridazine derivatives were required for biological activity studies. 2-(1-Aroyl-2-dimethylamino-vinyl)-malononitrile compounds **2a** and **b**[19] (Scheme 1) seemed to be good precursors to fulfill this objective via their reaction with hydrazine and phenyl hydrazine.

RESULTS AND DISCUSSION

Thus compounds **1a** and **b** were prepared according to our previously reported methods.[20,21] Compounds **1a** and **b** were allowed to react with dimethylformamide

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dimethylacetal (DMFDMA) in refluxing toluene to afford the enamines **2a** and **b** respectively as recently described by us.[19]

Compounds **2a** and **b** react with hydrazine hydrate **3a** and phenyl hydrazine **3b** in refluxing ethanol to afford the dihydropyridazine derivatives **5a–d** respectively. This reaction is assumed to take place via the substitution of the dimethylamine by the hydrazines to give the intermediate **4**, which undergoes in situ cyclization to give the final isolable products **5a–d**. The infrared (IR) spectra of these products showed a cyano and a carbonyl absorption bands at $\upsilon_{max} \approx 2200$ and $1655\,cm^{-1}$ respectively. The ^1H NMR spectra of these compounds show generally the pyridazine H at $\delta \approx 7.25$ ppm and the two NH protons at $\delta \approx 8.2$ and 9.05 ppm in the case of **5a** and **b** and only one NH at $\delta \approx 9.05$ in the case of **5c** and **d** with increased aromatic proton integration by 5H.

We have explored the β-ketonitrile moiety in compounds **5a–d** for further reactions. Thus **5a–d** were refluxed in ethanol with hydrazine hydrate **3a** to afford yellow to brown products.

The IR spectra of these products did not reveal any absorption bands that can be attributed to cyano or carbonyl functions. Based on this, as well as the analytical and NMR data, structures **6a–d** were assigned to these products.

The dihydropyridazines **5a** and **b** could be oxidized easily upon reflux in acetic acid in the presence of lead acetate in an open atmosphere to afford the full aromatic 3-aminopyridazine derivatives **7a** and **b** respectively. Under the same reaction conditions, the dihydropyridazino[4,5-*d*]pyridazines **6a** and **b** were successfully oxidized to the corresponding full aromatic derivatives **8a** and **b**. The ^1H NMR spectra of **7a** and **b** and **8a** and **b** were all void from the NH signals. The oxidation process perhaps occurred by atmospheric oxygen.

Compounds **7a** and **b** were allowed to react with hydrazine hydrate in refluxing ethanol to afford the pyridazino[4,5-*d*]pyridazines **8a** and **b** respectively. Analytical and spectral data are in complete agreement with the assigned structures, and some of them are substantiated with ^{13}C NMR data.

EXPERIMENTAL

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 NMR and ^{13}C NMR spectra were taken on a Varian Gemini 300-MHz spectrometer in dimethylsulfoxide (DMSO-d_6) using tetramethylsilane (TMS) as internal standard, and chemical shifts are expressed in δ ppm values. Mass spectra (MS) were taken on a Shimadzu GCMS-GB 1000 PX instrument (70 ev). Elemental analyses were carried out at the Micro-analytical Center at Cairo University.

Synthesis of 3-Amino-5-aroyl-1,2-dihydro-pyridazine-4-carbonitrile Derivatives 5a–d

Hydrazine hydrate or phenyl hydrazine (10 mmol) was added to a solution of each of compounds **2a** and **b** (10 mmol) in ethanol (10 ml). The reaction mixture was refluxed for ≈3–5 h [thin-layer chromatography (TLC) control using ethyl

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acetate–petroleum ether 1:1]. The mixture was left to cool to room temperature in each case, then poured onto ice-cold water and acidified with a few drops of HCl until it was just neutral. The solids so formed were collected by filtration and recrystallized from ethanol to give the products **5a–d**.

Selected Data

3-Amino-5-benzoyl-1,2-dihydropyridazine-4-carbonitrile 5a. Yellow product; yield 1.5 g (67%); mp 227–229 °C. $\upsilon_{max} = 3410$, 3332, 3065 & 2130 (NH_2 & NH), 2203 (CN), 1658 (CO); $\delta_H = 4.76$ (br, 2H, NH_2, D_2O exchangeable), 7.30 (s, 1H, pyridazine H), 7.40–7.84 (m, 5H, Ar-H), 8.22 (br, 1H, NH, D_2O exchangeable), 9.10 (br, 1H, NH, D_2O exchangeable); $\delta_C = 99.67$ (s), 109.24 (s), 118.46 (s), 124.34 (d), 129.18 (d), 129.30 (d), 149.83 (s), 160.54 (d), 166.59 (s), 192.00 (s). MS: m/z (%) 226 (M^+). Anal. calcd. for $C_{12}H_{10}N_4O$ (226.23): C, 63.71; H, 4.46; N, 24.76. Found: C, 63.55; H, 4.40; N, 24.90.

3-Amino-5-(4-methylbenzoyl)-1,2-dihydropyridazine-4-carbonitrile 5b. Dirty yellow product; yield 1.5 g (63%); mp 213–215 °C. $\upsilon_{max} = 3400$, 3329, 3063 & 2132 (NH_2 & NH), 2196 (CN), 1655 (CO); $\delta_H = 2.3$ (s, 3H, Me), 4.74 (br, 2H, NH_2, D_2O exchangeable), 7.25 (s, 1H, pyridazine H), 7.28 & 7.72 (2d, 4H, Ar-H), 8.17 (br, 1H, NH, D_2O exchangeable), 9.02 (br, 1H, NH, D_2O exchangeable). MS: m/z (%) 240 (M^+). Anal. calcd. for $C_{13}H_{12}N_4O$ (240.26): C, 64.99; H, 5.03; N, 23.32. Found: C, 65.05; H, 5.15; N, 23.25.

3-Amino-5-benzoyl-2-phenyl-1,2-dihydropyridazine-4-carbonitrile 5c. Dark yellow product; yield 2 g (66%); mp 239–240 °C. $\upsilon_{max} = 3408$, 3330, 3068 & 2132 (NH_2 & NH), 2205 (CN), 1658 (CO); $\delta_H = 4.82$ (br, 2H, NH_2, D_2O exchangeable), 7.25 (s, 1H, pyridazine H), 6.65–7.85 (m, 10H, Ar-H), 9.05 (br, 1H, NH, D_2O exchangeable); MS: m/z (%) 302 (M^+). Anal. calcd. for $C_{18}H_{14}N_4O$ (302.33): C, 71.51; H, 4.67; N, 18.53. Found: C, 71.55; H, 4.48; N, 18.65.

3-Amino-5-(4-methylbenzoyl)-2-phenyl-1,2-dihydropyridazine-4-carbonitrile 5d. Dark brown powder; yield 1.9 g (62%); mp 232–234 °C. $\upsilon_{max} = 3395$, 3330, 3060 & 2130 (NH_2 & NH), 2204 (CN), 1656 (CO); $\delta_H = 2.3$ (s, 3H, Me), 4.75 (br, 2H, NH_2, D_2O exchangeable), 7.25 (s, 1H, pyridazine H), 6.65–7.72 (m, 9H, Ar-H), 9.08 (br, 1H, NH, D_2O exchangeable). MS: m/z (%) 316 (M^+). Anal. calcd. for $C_{19}H_{16}N_4O$ (316.36): C, 72.13; H, 5.10; N, 17.71. Found: C, 72.28; H, 5.15; N, 17.80.

Reaction of 3-Amino-5-aroyl-1,2-dihydro-pyridazine-4-carbonitrile Derivatives 5a–d with Hydrazine Hydrate 3a (Preparation of 6a–d)

A mixture of each of compounds **5a–d** (10 mmol) and hydrazine hydrate (10 mmol) in ethanol (15 ml) was refluxed for 1 h. The reaction mixture was left to cool to room temperature in each case, then poured onto ice water and acidified with a few drops of HCl until it was just neutral. The solids so formed were collected by filtration and recrystallized from ethanol/dimethylformamide (DMF) to give products **6a–d**.

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Selected Data

5-Phenyl-2,3-dihydropyridazino[4,5-*d*]pyridazine-1,8-diamine 6a. Yellow product; yield 1.5 g (63%); mp 222–223 °C. $\upsilon_{max} = 3390$, 3328, 3065 & 2129 (NH_2 & NH); $\delta_H = 4.74$ (br, 2H, NH_2, D_2O exchangeable), 5.14 (br, 2H, NH_2, D_2O exchangeable), 6.05 (s, 1H, pyridazine H), 7.32 & 7.65 (m, 5H, Ar-H), 8.15 (br, 1H, NH, D_2O exchangeable), 9.00 (br, 1H, NH, D_2O exchangeable). MS: m/z (%) 240 (M^+). Anal. calcd. for $C_{12}H_{12}N_6$ (240.26): C, 59.99; H, 5.03; N, 34.98. Found: C, 59.86; H, 5.10; N, 35.09.

5-(4-Tolyl)-2,3-dihydropyridazino[4,5-*d*]pyridazine-1,8-diamine 6b. Dirty yellow product; yield 1.5 g (63%); mp 205–206 °C. $\upsilon_{max} = 3392$, 3330, 3065 & 2130 (NH_2 & NH); $\delta_H = 2.32$ (s, 3H, Me), 4.75 (br, 2H, NH_2, D_2O exchangeable), 5.15 (br, 2H, NH_2, D_2O exchangeable), 6.07 (s, 1H, pyridazine H), 7.15 & 7.52 (2d, 4H, Ar-H), 8.15 (br, 1H, NH, D_2O exchangeable), 9.05 (br, 1H, NH, D_2O exchangeable). MS: m/z (%) 254 (M^+). Anal. calcd. for $C_{13}H_{14}N_6$ (254.29): C, 61.40; H, 5.55; N, 33.05. Found: C, 61.32; H, 5.50; N, 33.15.

2,5-Diphenyl-2,3-dihydropyridazino[4,5-*d*]pyridazine-1,8-diamine 6c. Yellowish brown product; yield 1.5 g (63%); mp 243–244 °C. $\upsilon_{max} = 3392$, 3329, 3067 & 2127 (NH_2 & NH); $\delta_H = 4.78$ (br, 2H, NH_2, D_2O exchangeable), 5.16 (br, 2H, NH_2, D_2O exchangeable), 6.03 (s, 1H, pyridazine H), 7.28–7.65 (m, 10H, Ar-H), 9.10 (br, 1H, NH, D_2O exchangeable). MS: m/z (%) 316 (M^+). Anal. calcd. for $C_{18}H_{16}N_6$ (316.36): C, 68.34; H, 5.10; N, 26.56. Found: C, 68.38; H, 5.17; N, 26.65.

2-Phenyl-5-(4-tolyl)-2,3-dihydropyridazino[4,5-*d*]pyridazine-1,8-diamine 6d. Coffee-brown product; yield 1.5 g (63%); mp 253–255 °C. $\upsilon_{max} = 3391$, 3325, 3065 & 2135 (NH_2 & NH); $\delta_H = 2.35$ (s, 3H, Me), 4.76 (br, 2H, NH_2, D_2O exchangeable), 5.18 (br, 2H, NH_2, D_2O exchangeable), 6.08 (s, 1H, pyridazine H), 7.25–7.62 (m, 9H, Ar-H), 9.12 (br, 1H, NH, D_2O exchangeable). MS: m/z (%) 330 (M^+). Anal. calcd. for $C_{19}H_{18}N_6$ (330.39): C, 69.07; H, 5.49; N, 25.44. Found: C, 69.0; H, 5.45; N, 25.35.

Oxidation of 5a and b and 6a and b

Lead acetate (3.25 g; 10 mmol) was added to a solution of each of **5a**, **5b**, **6a**, or **6b** (10 mmol) in glacial acetic acid (15 ml), and the reaction mixture was refluxed for ≈2–3 h in each case [TLC control]. The reaction mixture was filtered off while hot to remove any insoluble residues, and the filtrate was left to cool and then poured onto ice-cold water. The precipitated solids, thus formed, were collected by filtration and recrystallized from ethanol to give dark yellow products of **7a**, **7b**, **8a**, and **8b** respectively.

Selected Data

3-Amino-5-benzoyl-pyridazine-4-carbonitrile 7a. Dirty yellow product; yield 1.42 g (63%); mp 147–149 °C. $\upsilon_{max} = 3213$ & 2232 (NH_2), 2215 (CN), 1655 (CO); $\delta_H = 5.56$ (br, 2H, NH_2, D_2O exchangeable), 7.55–8.10 (m, 5H, phenyl-H),

8.48 (s, 1H, pyridazine 6-H). $\delta_C = 100.98$ (s), 111.42 (s), 121.54 (d), 126.34 (d), 129.99 (d), 143.39 (s), 154.54 (d), 158.34 (s), 176.53 (s), 191.32 (s). MS: m/z (%) 224 (M^+). Anal. calcd. for $C_{12}H_8N_4O$ (224.22): C, 64.28; H, 3.60; N, 24.99. Found: C, 64.35; H, 3.65; N, 25.09.

3-Amino-5-(4-methylbenzoyl)-pyridazine-4-carbonitrile 7b. Dirty yellow product; yield 1.5 g (63%); mp 142–143 °C. $\upsilon_{max} = 3329$, 3218 (NH_2), 2196 (CN), 1658 (CO); $\delta_H = 2.3$ (s, 3H, Me), 4.74 (br, 2H, NH_2, D_2O exchangeable), 7.28 & 7.72 (2d, 4H, Ar-H), 8.17 (s, 1H, pyridazine 6-H). MS: m/z (%) 238 (M^+). Anal. calcd. for $C_{13}H_{10}N_4O$ (238.24): C, 65.54; H, 4.23; N, 23.52. Found: C, 65.58; H, 4.45; N, 23.68.

4-Phenylpyridazino[4,5-d]pyridazine-1,8-diamine 8a. Yellow product; yield 1.59 g (67%); mp 214–215 °C. $\upsilon_{max} = 3410$, 3332 (NH_2); $\delta_H = 7.25$–7.65 (m, 5H, Ar-H), 7.92 (br, 4H, $2NH_2$, D_2O exchangeable), 8.25 (s, 1H, pyridazine H). MS: m/z (%) 238 (M^+). 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, 4.30; N, 35.35.

4-(4-Tolyl)-pyridazino[4,5-d]pyridazine-1,8-diamine 8b. Yellow product; yield 1.63 g (65%); mp 212–213 °C. $\upsilon_{max} = 3412$, 3335 (NH_2); $\delta_H = 2.33$ (s, 3H, Me), 7.10–7.45 (2d, 4H, Ar-H), 7.90 (br, 4H, $2NH_2$, D_2O exchangeable), 8.35 (s, 1H, pyridazine H). MS: m/z (%) 252 (M^+). Anal. calcd. for $C_{13}H_{12}N_6$ (252.27): C, 61.89; H, 4.79; N, 33.31. Found: C, 61.95; H, 4.87; N, 33.46.

Transformation of 7a and b into 8a and b

A mixture of each of compounds **7a** or **7b** (10 mmol) and hydrazine hydrate (10 mmol) in ethanol (15 ml) was refluxed for 1 h. The reaction mixture was left to cool to room temperature in each case, then poured onto ice-water and acidified with a few drops of HCl until it was just neutral. The solids thus formed were collected by filtration and recrystallized from ethanol/DMF to give products identical in all respects with compounds **8a** and **8b**.

CONCLUSION

We could prepare series of substituted pyridazine and pyridazino[4,5-*d*]pyridazine derivatives of anticipated diverse biological activities from laboratory-available starting materials. The synthetic methods used throughout are rather simple, and no hazardous solvents were involved.

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