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Investigation of hydrazine addition to functionalized furans: synthesis of new functionalized 4,4′-bipyrazole derivatives

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Abstract—The addition of hydrazine to functionalized furans **2a–d** leads to a variety of 4,4′-bipyrazoles **4a–c** depending on the structure of the starting materials. In one example, compound **2c** was first converted to an intermediate, furo[3,4-*d*]pyridazine **3c** which was then transformed into 4,4′-bipyrazole **4c** on reacting with hydrazine.

1. Introduction

This work arose from the attempts to synthesize pyrrolo[3,4-*d*]pyridazine since a few reports in the literature indicated interesting biological properties for the members of this system.[1–3] Pyrrolopyridazines can be obtained by the reaction of 3,4-diacetyl-2,5-disubstituted furans with 2 equiv of hydrazine.[4] Thus, it was necessary to prepare suitably functionalized furans. The required furans **2a–d** were synthesized by reacting active methylene compounds such as malononitrile and ethyl cyanoacetate with 3-chloro-2,4-dicarbonyl compounds **1a–b** according to previously described procedures.[5] As depicted in Scheme 1, the enolic oxygen of the intermediates **1′c–d** could attack either the nitrile or the carbonyl group to produce products **2c–d** or **2′c–d**. On the basis of spectral data, the sole products were **2c–d**.

The attempts to prepare pyrrolo[3,4-*d*]pyridazine from the reaction of hydrazine hydrate with compounds **2a–d** following Mosby[4] failed but instead gave 4,4′-bipyrazoles **4a–c**, which are reported as pharmacologically important compounds with an array of biological activities.[6–9]

The structures of compounds **4a–c** were confirmed from analytical data. For example, the ^{1}H NMR spectrum of **4a** exhibited signals assignable to the six protons of the methyl groups at δ 2.03 ppm, and the protons of one NH_2 and three NH groups at δ 5.56 ppm and 8.50–10.50 ppm, respectively, which were removed on deuteration. The ^{13}C NMR spectrum exhibited signals for the two methyl carbons and the quaternary carbons next to the methyl groups at δ 12.34 ppm and 142.84 ppm and those for C-4′, C-4, C-5 and C-3 at δ 80.46, 107.83, 157.92 and 170.61 ppm, respectively. The IR spectrum showed an absorption at 1633 cm^{-1} assignable to an amide carbonyl group and two absorptions at 3300 and 3100 cm^{-1} attributed to the NH_2 and NH groups. The ultraviolet spectrum of this product showed only one absorption band with a λ_{max} (H_2O) at 243 nm, which resembles the curve of a reported 4,4′-bipyrazole.[4] All this evidence plus the molecular ion peak at m/z 193 and microanalytical data strongly support the pyrazole-like structure of compound **4a**.

Note that in this multi-step synthesis, the likely key intermediate, the furo[3,4-*d*]pyridazine was not isolated except for intermediates **2c** and **2e** (acyl derivative of **2a**) which were isolated and their structures identified by spectral analysis. Mosby and Jones have also reported the formation of such intermediates during the reaction of functionalized furans with hydrazine. Further reaction with hydrazine produced pyrrolo[3,4-*d*]-pyridazine[4] and 4,4′-bipyrazole.[10]

When intermediates **3c,e** were treated with hydrazine hydrate, only **3c** underwent ring opening followed by a ring closure to 4,4′-bipyrazole **4c** (Scheme 2). On the basis of these observations a plausible mechanism is depicted for the formation of these compounds

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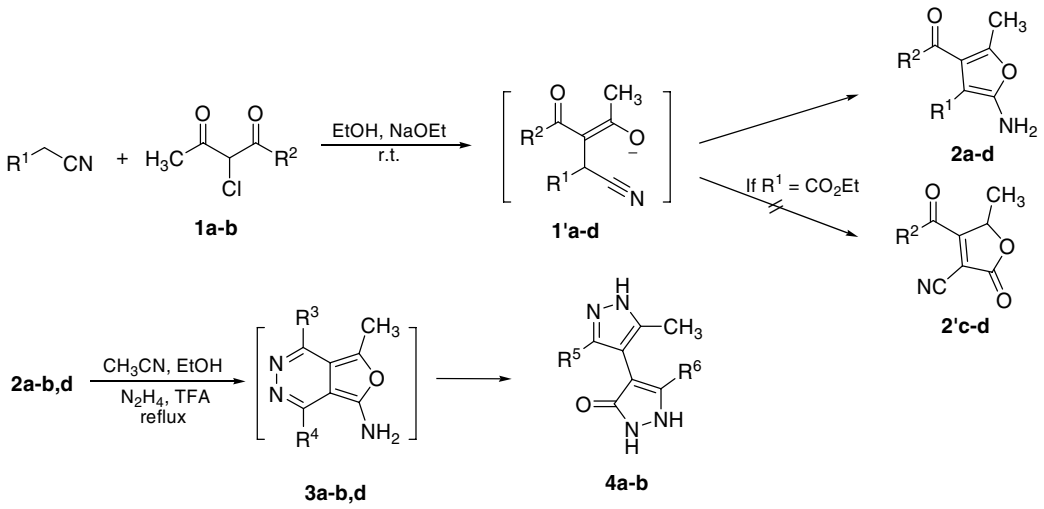
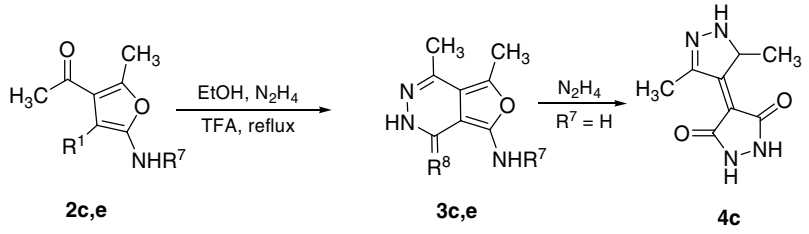


2a $R^2 = CH_3$, $R^1 = CN$
2b $R^2 = OEt$, $R^1 = CN$
2c $R^2 = CH_3$, $R^1 = CO_2Et$
2d $R^2 = OEt$, $R^1 = CO_2Et$

3a $R^3 = CH_3$, $R^4 = NH_2$
3b $R^3 = OH$, $R^4 = NH_2$
3d $R^3 = OH$, $R^4 = OH$

4a $R^5 = CH_3$, $R^6 = NH_2$ (from **2a**)
4b $R^5 = OH$, $R^6 = NH_2$ (from **2b** and **2d**)

Scheme 1.



2c $R^7 = H$, $R^1 = CO_2Et$
2e $R^7 = Ac$, $R^1 = CN$

3c $R^7 = H$, $R^8 = O$
3e $R^7 = Ac$, $R^8 = NH$

Scheme 2.

(Schemes 3 and 4). As depicted in Scheme 4, both compounds **2b,d** on treatment with hydrazine hydrate give a single product **4b**. The structure of this compound was confirmed from spectral and analytical data.

In summary, we have found an easy and reliable synthetic pathway to 4,4′-bipyrazoles, which are valuable precursors for the synthesis of a number of heterocyclic ring systems such as pyrazolo[1,5-*a*]pyrimidines, which are of considerable biological importance.

2. General procedure for the preparation of the aminofurans 2a–d

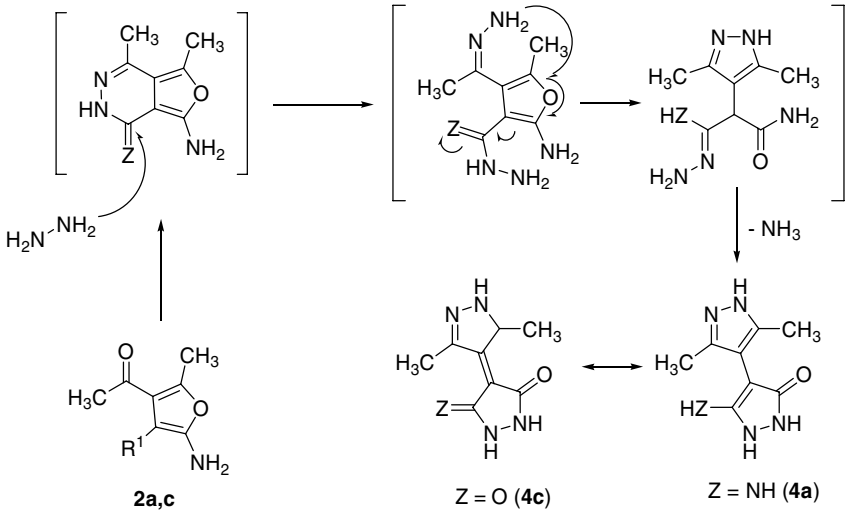
A solution of the 3-chloro-2,4-dicarbonyl compound **1a**–**b** (50 mmol) and malononitrile or ethyl cyanoacetate (50 mmol) in absolute ethanol (7 ml) was added dropwise at room temperature to a solution of sodium (50 mmol) in absolute ethanol (30 ml). The reaction mixture was stirred at room temperature for 4–6 h, and then cold water (250 ml) was added. The resulting solid material was filtered off, and either washed with water (3×10 ml) and ethanol (10 ml) in the case of **2a**–**b**, or recrystallized from ethanol/water in the case of **2c**–**d**, to give the pure product.

2.1. 4-Acetyl-2-amino-5-methylfuran-3-carbonitrile 2a

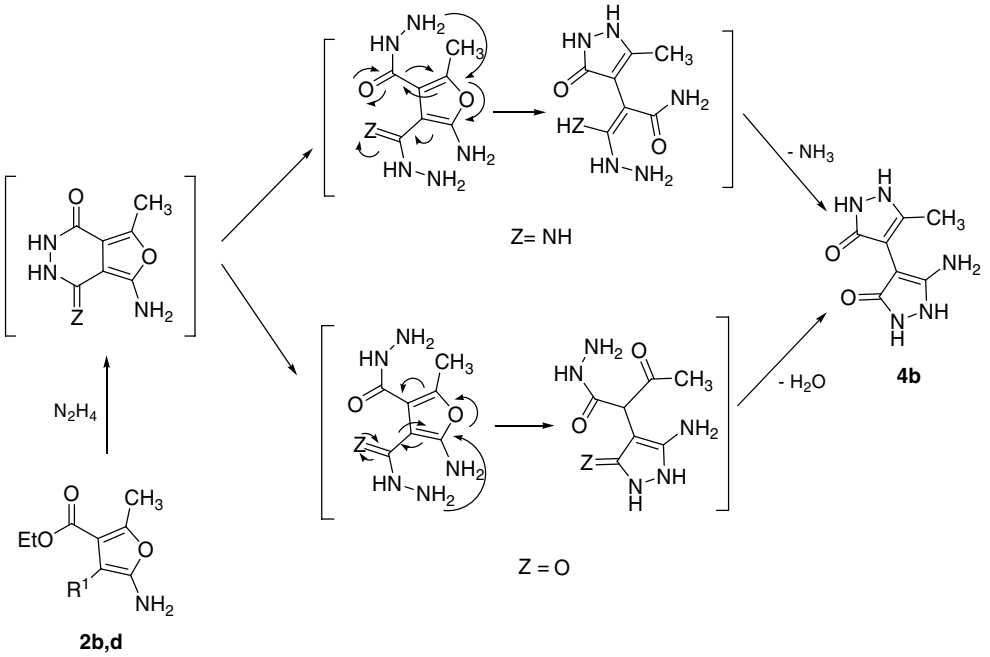
Reaction of 3-chloroacetylacetone (**1a**) and malononitrile: pale yellow powder, yield (78%), mp: 245 °C, ^{1}H NMR (100 MHz, DMSO-d_6) δ 2.35 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 7.40 (s, 2H, NH_2), IR (KBr disc) ν 3300, 2990, 2200, 1664, 1588 cm^{-1}, EIMS m/z 164 (M^+), Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.45; H, 4.72; N, 16.99.

2.2. Ethyl 5-amino-4-cyano-2-methylfuran-3-carboxylate 2b

Reaction of ethyl 2-chloro acetoacetate (**1b**) and malononitrile: pale yellow powder, yield (77%), mp: 210 °C, ^{1}H NMR (100 MHz, acetone-d_6): δ 1.32 (t, $J = 7.4$ Hz, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.27 (q, $J = 7.4$ Hz, 2H, CH_2),



Scheme 3. Conversion of **2a,c** to the corresponding bipyrazoles **4a,c**.



Scheme 4. Conversion of **2b,d** to bipyrazole **4b**.

6.70 (s, 2H, NH_2), IR (KBr disc) ν 3374, 2990, 2205, 1688, 1647 cm^{-1}, EIMS m/z 192 (M^+), Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.66; H, 5.24; N, 14.35.

2.3. Ethyl 4-acetyl-2-amino-5-methylfuran-3-carboxylate 2c

Reaction of 3-chloroacetylacetone (**1a**) and ethyl cyanoacetate: white needles, yield (94%), mp: 134 °C, ^1H NMR (100 MHz, $CDCl_3$): δ 1.32 (t, $J = 7.2$ Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 4.26 (q, $J = 7.2$ Hz, 2H, CH_2), 5.5 (s, 2H, NH_2), IR (KBr disc) ν 3300, 2990, 1676, 1632 cm^{-1}, EIMS m/z 211 (M^+). Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 57.01; H, 6.06; N, 6.50.

2.4. Diethyl 2-amino-5-methylfuran-3,4-dicarboxylate 2d

Reaction of ethyl 2-chloro acetoacetate (**1b**) and ethyl cyanoacetate: white needles, yield (92%) mp: 94 °C, ^1H NMR (100 MHz, $CDCl_3$): δ 1.33 (m, 6H, $2CH_3$), 2.23 (s, 3H, CH_3), 4.27 (m, 4H, $2CH_2$), 5.30 (s, 2H, NH_2), IR (KBr disc) ν 3300, 2998, 1698, 1676, 1640 cm^{-1}, EIMS m/z 241 (M^+), Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.33; H, 6.03; N, 5.68.

2.5. *N*-(4-acetyl-3-cyano-5-methylfuran-2-yl)acetamide 2e

A mixture of aminofuran **2a** (10 mmol) in acetic anhydride (15 ml) was refluxed for 4 h. The solvent was then

evaporated under reduced pressure and the residue was crystallized from water to give **2e** as white needles.

Yield (68%), mp: 204 °C, ^{1}H NMR (100 MHz, acetone-d_6): δ 2.12 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 10.12 (s, 1H, NH), IR (KBr disc) ν 3300, 2990, 2220, 1691, 1662, 1547 cm^{-1}, EIMS m/z 206 (M^+), Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.17; H, 4.73; N, 13.66.

3. General procedure for the preparation of furo[3,4-*d*]-pyridazines 3c,e

Hydrazine hydrate (1 ml) was added to a mixture of **2c,e** (5 mmol) in ethanol (5 ml) and TFA (0.5 ml). The reaction mixture was then refluxed for 5–6 h. The resulting solid material was filtered off and washed with water (10 ml) and ethanol (5 ml) to afford the pure products **3c,e**.

3.1. 7-Amino-4,5-dimethylfuro[3,4-*d*]pyridazin-1(2*H*)-one 3c

Reaction of **2c** with hydrazine: pale yellow powder, yield (47%), mp: 278 °C, ^{1}H NMR (100 MHz, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 6.88 (s, 2H, NH_2), 10.6 (s, 1H, NH), IR (KBr disc) ν 3300, 2990, 1647 cm^{-1}, EIMS m/z 179 (M^+), Anal. Calcd for $C_8H_9N_3O_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.45; H, 5.12; N, 23.38.

3.2. *N*-(1-Amino-4,5-dimethylfuro[3,4-*d*]pyridazin-7-yl)-acetamide 3e

Reaction of **2e** with hydrazine hydrate, yellow powder, yield (65%), mp: 260 °C, ^{1}HNMR (100 MHz, DMSO-d_6): δ 2.38 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 7.25 (s, 2H, NH_2), 11.13 (s, 1H, NH), IR (KBr disc) ν 3300, 2990, 1680, 1650, 1600 cm^{-1}, EIMS m/z 220 (M^+), Anal. Calcd for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.62; H, 5.41; N, 25.32.

4. General procedure for the preparation of aminobi-pyrazoles 4a–b

Hydrazine hydrate (10–12 ml) was added to a solution of **2a**, **2b** or **2d** (30 mmol) in acetonitrile (12 ml), ethanol (6 ml) and TFA (1 ml). The reaction mixture was heated under reflux for 20–24 h. The resulting solid material was then filtered off and washed with 10 ml of cold ethanol to give pure **4a**–**b**.

4.1. 5-Amino-1,2-dihydro-4-(3,5-dimethyl-1*H*-pyrazol-4-yl)pyrazol-3-one 4a

Reaction of **2a** with hydrazine: white powder, yield (63%), mp: 315 °C (dec) ^{1}H NMR (100 MHz, DMSO-d_6): δ 2.03 (s, 6H, $2CH_3$), 5.56 (s, 2H, NH_2), 8.5–10.5 (3H, 3NH), ^{13}C NMR (125 MHz, DMSO-d_6) δ 12.34, 80.47, 107.83, 142.84, 157.92, 170.61, UV (H_2O) λ_{max} 243 nm, IR (KBr disc) ν 3300, 3100, 2990, 1633 cm^{-1}, EIMS m/z 193 (M^+), Anal. Calcd for $C_8H_{11}N_5O$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.47; H, 5.49; N, 36.54.

4.2. 5-Amino-1,2-dihydro-4-(2,3-dihydro-5-methyl-3-oxo-1*H*-pyrazol-4-yl)pyrazol-3-one 4b

Reaction of **2b** or **2d** with hydrazine: (note: for the reaction of **2d** only 2 equiv of hydrazine hydrate is used) recrystallized from DMF/methanol (1:3) a pale yellow powder, yield (73% for **2b**, 62% for **2d**), mp: 318–320 °C (dec), ^{1}H NMR (100 MHz, DMSO-d_6): δ 2.13 (s, 3H, CH_3), 5.71 (s, 2H, NH_2), 7.12 (s, 1H, NH), 8.50–10.50 (3H, 3NH), UV (MeOH) λ_{max} 252 nm, IR (KBr disc) ν 3400, 3250, 2994, 1640 cm^{-1}, EIMS m/z 194 (M^+), Anal. Calcd for $C_7H_9N_5O_2$: C, 43.08; H, 4.62; N, 35.9. Found: C, 42.71; H, 4.79; N, 35.96.

4.3. 4-(3,5-Dimethyl-1*H*-pyrazol-4(5*H*)-ylidene)pyrazolidine-3,5-dione 4c

Hydrazine hydrate 98% (1.2 ml) was added to a solution of **2c** (2 mmol) in ethanol (8 ml), DMF (2 ml) and TFA (0.5 ml). The reaction mixture was heated under reflux for 18 h. The solvent was then evaporated to dryness under reduced pressure and the residue washed with chloroform (10 ml), and then subjected to column chromatography using ethyl acetate–MeOH (90/10%) to give 0.09 g (23%) of compound **4c** as a yellow powder. mp: 189 °C, ^{1}H NMR (100 MHz, pyridine-d_5): δ 1.35 (d, $J = 6.9$ Hz, 3H, CH_3), 2.17 (s, 3H, CH_3), 5.42 (q, $J = 6.9$ Hz, 1H, CH), 6.50 (s, 3H, 3NH), IR (KBr disc) ν 3300, 3400, 2990, 1696, 1676 cm^{-1}, EIMS m/z 195 (M+1), Anal. Calcd for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.28; H, 5.25; N, 28.64.

References and notes

1. Stearns, B. A.; Anker, N.; Arruda, J. M.; Campbell, B. T.; Chen, C.; Cramer, M.; Hu, T.; Jiang, X.; Park, K.; Ren, K. K.; Sablad, M.; Santini, A.; Schaffhauser, H.; Urbanb, M. O.; Munoz, B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1295.
2. Malinka, W.; Redzicka, A.; Lozach, O. *IL Farmaco* **2004**, *59*, 457.
3. Inel, S.; Jones, C.; Gretir, C. O. *Tetrahedron* **1984**, *40*, 3979.
4. Mosby, W. L. *J. Chem. Soc.* **1957**, 3997.
5. Watanuki, S.; Sakamoto, S.; Harada, H.; Kikuchi, K.; Kuramochi, T.; Kawaguchi, K.; Okazaki, T.; Tsukamoto, S. *Heterocycles* **2004**, *62*, 127, and references cited therein.
6. Cuadro, A. M.; Elguero, J.; Navarro, P. *Chem. Pharm. Bull.* **1985**, *33*, 2535.
7. Mardin, M.; Seuter, F.; Perzborn, E.; Schlossmann, K.; Mayer, D.; Fiedler, V. (Bayer, A.-G.) Ger. Offen. DE 3,308,881 (Cl. A61K31/415), 13 September 1984, Appl. 12 March 1983 (*Chem. Abstr.* **1984**, *101*, 222712b).
8. Bayer, A.-G. Jpn. Kokai Tokyo Koho Jp 59,175,469 [84,175,469] (Cl. C07D231/20), 04 October 1984, DE Appl. 3,308,881, 12 March 1983 (*Chem. Abstr.* **1985**, *102*, 56154v).
9. Igarashi, T.; Sakurai, K.; Oi, T.; Obara, H.; Ohya, H.; Kamada, H. *Free Radical Biol. Med.* **1999**, *26*, 1339.
10. Jones, G. *J. Am. Chem. Soc.* **1956**, *78*, 159.