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Synthesis of 5-Substituted 1,3-Dimethylpyrazolo[4,3-*e*][1,2,4]triazines

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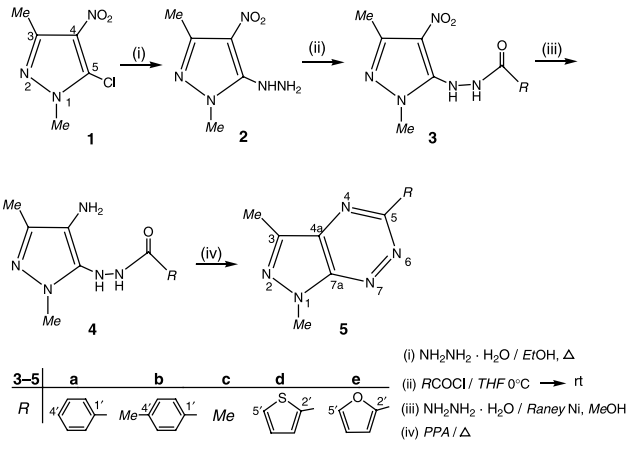
Summary. A novel method for the synthesis of a new series of 5-substituted 1,3-dimethyl pyrazolo[4,3-*e*][1,2,4]triazines is described. The new synthetic strategy is based on the classical *Bischler* 1,2,4-benzotriazine synthesis. This approach involves the preparation of 5-hydrazinopyrazole from 5-chloro-1,3-dimethyl-4-nitropyrazole followed by acylation and nitro group reduction to form the corresponding 4-amino-3-(acylhydrazino)pyrazoles. Intramolecular oxidative cyclization of the latter derivatives, using polyphosphoric acid, produced the respective target pyrazolotriazines.

Keywords. Pyrazolotriazines; *Bischler* reaction; Oxidative cyclisation.

Introduction

The pyrazolo-1,2,4-triazines have received considerable attention due to their pharmacological applications as antiviral [1], antitumor [2], antifungal [3], analgesic, anti-inflammatory, and antipyretic agents [4]. The pyrazolo[4,3-*e*][1,2,4]triazine skeleton is also found in many natural products such as *pseudoiodinine* [5] and *nostocine* A [6]. The latter systems inhibit the growth of *Gram*-positive and *Gram*-negative bacteria with somewhat weaker action against fungi [7, 9] as well as antitumor activity [6, 8]. The most widely used routes to synthesize 1,3,5-trisubstituted pyrazolo[4,3-*e*][1,2,4]triazines involve intramolecular cyclization of the respective hydrazones using phosphorous oxychloride or ethanolic HCl [8, 9]. In literature, the reported procedures illustrate that the pyrazole ring was constructed onto the 1,2,4-triazine nucleus. To the best of our knowledge, the only report concerned with construction of a triazine skeleton onto pyrazole was reported by *Youssef et al.* [10]. Herein, we report a new approach for the construction of the 1,2,4-triazine nucleus on a pyrazole derivative based on the classical *Bischler* 1,2,4-benzotriazine synthesis (Scheme 1) [11].



Scheme 1

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Results and Discussion

5-Chloro-1,3-dimethyl-4-nitro-1*H*-pyrazole (**1**) is utilized as synthon in the preparation of the target compounds. Hydrazinolysis of **1**, using hydrazine hydrate and ethanol at reflux, yielded the corresponding 5-hydrazino derivative **2** in an S_N Ar addition-elimination reaction. Acylation of **2** with the appropriate acyl chloride in dry *THF* furnished the respective acid hydrazides **3a**–**3e**. The nitro group of the latter compounds was reduced chemically (using hydrazine hydrate and *Raney* nickel) into their respective 4-amino analogs **4a**–**4e**, which were relatively unstable intermediates (Scheme 1). Of these, **4b** was characterized whilst the others were not purified, but were used directly (as crude products) for the final cyclization step. Intramolecular oxidative cyclodehydration of **4a**–**4e** into the corresponding targeted bicycles was accomplished using polyphosphoric acid (*PPA*).

The structures of the new compounds **3a**–**3e**, **4b**, and **5a**–**5e** were supported by elemental analysis, IR, MS, and NMR spectral data. Thus, the mass spectra displayed the correct molecular ions [M^+] suggested from their molecular formulae. Those of **5a**–**5e** are dominated by fragment ions corresponding to [M − 28] and [M − 43] due to successive loss of N_2 and methyl radical. The IR spectra of **5a**–**5e** showed strong bands in the range of $\bar{\nu} = 1510$–$1560\,cm^{-1}$ corresponding to C=N stretching, but lack those bands around $1660\,cm^{-1}$ attributed to the hydrazide C=O present in **4**. ^1H and ^{13}C signal assignments are based on DEPT and 2D (COSY, HMQC, and HMBC) experiments.

The ^1H NMR spectrum of **5b** lacks the signals corresponding to C(5)-NH, C(4)-NH_2 and C(5)-NHCO protons present in its precursor **4b**. Likewise, the ^{13}C NMR spectrum of **5b** lacks the signal around $\delta = 170$ ppm present in the spectrum of **4b**, assigned to the carbon of the CONH group.

Experimental

5-Chloro-1,3-dimethyl-4-nitropyrazole (**1**) was purchased from Maybridge CombiChem (UK) and the acyl chlorides employed in this study were purchased from Acros. Melting points were determined on a SMP2 Stuart melting point apparatus. IR spectra were measured as KBr discs with a Nicolet-MAGNA-IR-560 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or *DMSO*-d_6 on a Bruker DPX-300 instrument. Chemical shifts are expressed in ppm with reference to *TMS* as internal standard. Coupling constants are given in Hz. Electron impact mass spectra (MS-EI) were measured on a Varian MAT-112S spectrometer at 70 eV and at an ion source temperature of 200°C. Microanalyses were performed at the Microanalytical Laboratory of the Hashemite University, Zarqa-Jordan, and the results were found to be in good agreement (±0.4%) with the calculated values.

5-Hydrazino-1,3-dimethyl-4-nitro-1H-pyrazole (**2**, $C_5H_9N_5O_2$)

To a solution of 0.88 g **1** (5 mmol) in 30 cm^3 absolute ethanol, was added dropwise hydrazine hydrate (85%, 8 cm^3, 160 mmol). The resulting yellow solution was stirred for 15 min at ambient temperature, then refluxed (H_2O bath) for 2 h. The solvent was then removed under vacuum, and the residual solid product was recrystallized from ethanol to afford yellow crystals of **2**. Yield 0.59 g (69%); mp 179–180°C (Ref. [12] 175–176°C); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.39$ (s, C(3)-CH_3), 3.92 (br s, C(5)-NH_2), 3.95 (s, N(1)-CH_3), 8.07 (br s, C(5)-NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.4$ (C(3)-*C*H_3), 39.3 (N(1)-CH_3), 118.1 (C-3), 145.0 (C-4), 147.6 (C-5); IR: $\bar{\nu} = 3339$ (NH), 1664 (C=N), 1582, 1367 (NO_2) cm^{-1}.

*General Procedure for the Synthesis of N′-(1,3-Dimethyl-4-nitro-1H-pyrazol-5-yl) acid hydrazides **3a–3e***

To a cooled (0°C) solution of 0.17 g **2** (1 mmol) in 30 cm^3 dry *THF* was added dropwise 1.5 mmol of the appropriate acid chloride. The reaction mixture was further stirred at 0°C for 1.5 h and stirring was continued at ambient temperature for overnight. The solvent was then removed under vacuum and the residual solid product was collected by suction filtration, washed with petroleum ether (bp 40–60°C, 2 × 10 cm^3) and dried to give the respective products **3a**–**3e**.

N′-(1,3-Dimethyl-4-nitro-1H-pyrazol-5-yl)benzohydrazide (**3a**, $C_{12}H_{13}N_5O_3$)

Yield 95%; mp 230°C (dec); ^1H NMR (300 MHz, *DMSO*-d_6): $\delta = 2.30$ (s, C(3)-CH_3), 3.60 (s, N(1)-CH_3), 7.53 (m, H-3′ + H-4′ + H-5′), 7.85 (m, H-2′ + H-6′), 8.97 (br s, C(5)-NH), 10.93 (br s, HN-C=O) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 14.5$ (C(3)-*C*H_3), 38.2 (N(1)-CH_3), 118.7 (C-3), 128.0 (C-2′ + C-6′), 129.2 (C-3′ + C-5′), 132.0 (C-1′), 132.8 (C-4′), 144.0 (C-4), 147.0 (C-5), 167.2 (C=O) ppm; IR: $\bar{\nu} = 3254$ (NH), 1659 (C=O), 1577, 1357 (NO_2) cm^{-1}.

N′-(1,3-Dimethyl-4-nitro-1H-pyrazol-5-yl)-4-methylbenzohydrazide (**3b**, $C_{13}H_{15}N_5O_3$)

Yield 93%; mp 221°C (dec); ^1H NMR (300 MHz, *DMSO*-d_6): $\delta = 2.29$ (s, C(4′)-CH_3), 2.36 (s, C(3)-CH_3), 3.58 (s, N(1)-CH_3), 7.29 (d, $J = 7.8$ Hz, H-3′ + H-5′), 7.76 (d, $J = 7.8$ Hz, H-2′ + H-6′), 8.94 (br s, C(5)-NH), 10.84 (br s, HN–C=O) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 14.5$ (C(3)-*C*H_3), 21.5 (C(4′)-*C*H_3), 38.2 (N(1)-CH_3), 118.7 (C-3), 128.0 (C-2′ + C-6′), 129.1 (C-1′), 129.7 (C-3′ + C-5′), 143.0 (C-4′), 144.0 (C-4), 147.1 (C-5), 167.0 (HN–C=O) ppm; IR: $\bar{\nu} = 3272$ (NH), 1669 (C=O), 1577, 1352 (NO_2) cm^{-1}.

N′-(1,3-Dimethyl-4-nitro-1H-pyrazol-5-yl) acetohydrazide (**3c**, $C_7H_{11}N_5O_3$)
Yield 85%; mp 235°C (dec); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.86$ (s, O=C–CH_3), 2.26 (s, C(3)-CH_3), 3.58 (s, N(1)-CH_3), 8.66 (br s, C(5)-NH), 10.36 (br s, HN–C=O) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 14.5$ (C(3)-*C*H_3), 20.5 (C(4)-*C*H_3), 38.1 (N(1)-CH_3), 118.5 (C-3), 143.9 (C-4), 146.9 (C-5), 170.1 (HN–C=O) ppm; IR: $\bar{\nu} = 3276$ (NH), 1667 (C=O), 1582, 1357 (NO_2) cm^{-1}.

N′-(1,3-Dimethyl-4-nitro-1H-pyrazol-5-yl)-2-thienohydrazide (**3d**, $C_{10}H_{11}N_5O_3S$)
Yield 82%; mp 170°C (dec); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 2.28$ (s, C(3)-CH_3) 3.60 (s, N(1)-CH_3), 7.17 (dd, $J = 4.1$, 5.3 Hz, H-4′), 7.84 (d, $J = 5.3$ Hz, H-3′), 7.92 (d, $J = 4.1$ Hz, H-5′), 9.00 (br s, C(5)-NH), 11.08 (br s, HN–C=O) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 14.5$ (C(3)-*C*H_3), 38.3 (N(1)-CH_3), 118.7 (C-3), 128.9 (C-4′), 130.2 (C-5′), 132.9 (C-3′), 136.4 (C-2′), 144.0 (C-4), 146.9 (C-5), 162.1 (HN–C=O) ppm; IR: $\bar{\nu} = 3233$ (NH), 1651 (C=O), 1572, 1357 (NO_2) cm^1.

N′-(1,3-Dimethyl-4-nitro-1H-pyrazol-5-yl)-2-furohydrazide (**3e**, $C_{10}H_{11}N_5O_4$)
Yield 95%; mp 175°C (dec); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 2.28$ (s, C(3)-CH_3), 3.57 (s, N(1)-CH_3), 6.65 (br , H-4′), 7.26 (br d, $J = 3.1$ Hz, H-3′), 7.91 (br d, $J = 2.8$ Hz, H-5′), 8.96 (br s, N(1)H), 10.86 (br s, HN=C=O) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 14.5$ (C(3)-*C*H_3), 38.2 (N(1)-CH_3), 112.6 (C-4′), 116.0 (C-3′), 118.6 (C-3), 144.0 (C-4), 145.8 (C-5), 146.8 (C-5′), 146.9 (C-2′), 158.6 (HN–C=O) ppm; IR: $\bar{\nu} = 3235$ (NH), 1654 (C=O), 1579, 1357 (NO_2) cm^{-1}.

General Procedure for the Synthesis of N′-(4-Amino-1,3-dimethyl-1H-pyrazol-5-yl) Acid Hydrazides ***4a–4e*** *Exemplified by* ***4b***

N′-(4-Amino-1,3-dimethyl-1H-pyrazol-5-yl)-4-methylbenzohydrazide (**4b**, $C_{13}H_{17}N_5O$)
A solution of hydrazine hydrate (85%, 20 cm^3, 0.41 mol) was added dropwise to a solution of 0.58 g **3b** (2 mmol) in 25 cm^3 methanol and 0.8 g of *Raney* nickel catalyst at room temperature. After addition of 10 cm^3 hydrazine hydrate, another 0.4 g of *Raney* nickel were added, then the rest of hydrazine hydrate was added dropwise. The reaction mixture was refluxed for 1 h, cooled and the catalyst removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from chloroform-petroleum ether to give 0.15 g (29%) **4b**. Mp 149–150°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.07$ (s, C(4′)-CH_3), 2.35(s, C(3)-CH_3), 3.66(s, N(1)-CH_3), 7.17 (d, $J = 7.4$ Hz, H-3′ + H5′), 7.61 (d, $J = 7.4$ Hz, H-2′ + H-6′), 3.24 (br s, C(5)-NH + C(4)-NH_2), 8.52 (s, NH–C=O) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 11.3$ (C(3)-*C*H_3), 21.6 (C(4′)-*C*H_3), 34.9 (N(1)-CH_3), 119.1 (C-3), 127.1 (C-2′ + C-6′), 129.0 (C-1′), 129.5 (C-3′ + C-5′), 133.0 (C-4′), 137.1(C-4), 143.0 (C-5), 168.6 (NH–C=O) ppm; IR: $\bar{\nu} = 3375$ (NH), 1636 (C=O) cm^{-1}.

The following compounds of this series **4a** and **4c–4e** were prepared by adopting the same procedure and experimental conditions described above for **4b**:

N′-(4-Amino-1,3-dimethyl-1H-pyrazol-5-yl)benzohydrazide (**4a**, $C_{12}H_{15}N_5O$)
N′-(4-Amino-1,3-dimethyl-1H-pyrazol-5-yl)acetohydrazide (**4c**, $C_7H_{13}N_5O$)
N′-(4-Amino-1,3-dimethyl-1H-pyrazol-5-yl)-2-thienohydrazide (**4d**, $C_{10}H_{13}N_5OS$)
N′-(4-Amino-1,3-dimethyl-1H-pyrazol-5-yl)-2-furohydrazide (**4e**, $C_{10}H_{13}N_5O_2$)

However, these compounds were directly used as crude products, without characterization, for the synthesis of the respective target compounds **5a–5e**.

General Procedure for the Synthesis of 5-Substituted 1,3-Dimethylpyrazolo[4,3-e][1,2,4]triazines ***5a–5e***
A stirred suspension of substituted *N′*-(4-amino-1,3-dimethyl-1*H*-pyrazol-5-yl) acid hydrazides **4a–4e** in 15 cm^3 *PPA* was heated in an oil bath at 140°C for 1 h. The reaction mixture was then slowly poured with stirring onto crushed ice (50 cm^3). Sodium hydrogen carbonate was added until the solution was basic, then the mixture was extracted with $CHCl_3$ (3×75 cm^3). The combined organic extracts were dried (anhydrous Na_2CO_3) and the solvent was concentrated under reduced pressure to give the respective title products **5a–5e** which were further purified on silica gel TLC plates using $CHCl_3$:*Me*OH (98:2, *v*:*v*) as the developing solvent mixture.

1,3-Dimethyl-5-phenyl-1H-pyrazolo[4,3-e][1,2,4]triazine (**5a**, $C_{12}H_{11}N_5$)
Yield 24%; mp 122–123°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.71$ (s, C(3)-CH_3), 4.29 (s, N(1)-CH_3), 7.54 (m, H-3′ + H-4′ + H-5′), 8.60 (dd, $J = 7.6$, 2.0 Hz, H-2′ + H-6′) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.1$ (C(3)-*C*H_3), 34.8 (N(1)-CH_3), 128.1 (C-2′ + C-6′), 128.9 (C-3′ + C-5′), 130.7 (C-4′), 136.0 (C-3), 142.3 (C-3a), 147.6 (C-7a), 159.1 (C-5) ppm; IR: $\bar{\nu} = 1511$ (C=N) cm^{-1}; MS-EI: m/z (%) = 225 (25) [M$^+$], 197 (100), 182 (39),156 (66), 141 (56).

1,3-Dimethyl-5-(4-methylphenyl)-1H-pyrazolo[4,3-e][1,2,4]triazine (**5b**, $C_{13}H_{13}N_5$)
Yield 21%; mp 152–153°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.43$ (s, C(4′)-CH_3), 2.70 (s, C(3)-CH_3), 4.28 (s, N(1)-CH_3), 7.34 (d, $J = 8.1$ Hz, H-3′ + H-5′), 8.49 (d, $J = 8.1$ Hz, H-2′ + H-6′) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.1$ (C(3)-*C*H_3), 21.5 (C(1)-*C*H_3), 34.7 (N(1)-CH_3) 128.0 (C-2′ + C-6′), 129.6 (C-3′ + C-5′), 133.3 (C-1′), 135.0 (C-3), 141.4 (C-4′), 142.1(C-3a), 147.6 (C-7a), 159.2 (C-5) ppm; IR: $\bar{\nu} = 1511$ (C=N) cm^{-1}; MS-EI: m/z (%) = 239 (21) [M$^+$], 211 (100), 196 (66), 170 (27), 155 (36).

1,3,5-Trimethyl-1H-pyrazolo[4,3-e][1,2,4]triazine (**5c**, $C_7H_9N_5$)
Yield 20%; mp 83–84°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.63$ (s, C(3)-CH_3), 3.04 (s, C(5)-CH_3), 4.24 (s, N(1)-CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.0$ (C(3)-*C*H_3),

23.6 (C(5)-CH_3), 34.7 (N(1)-CH_3), 134.6 (C-3), 141.1 (C-3a), 147.6 (C-7a), 161.3 (C-5) ppm; IR: $\bar{\nu} = 1557$ (C=N) cm^{-1}; MS-EI: m/z (%) = 163 (30) [M^+], 135 (58), 120 (22), 94 (100), 79 (43).

1,3-Dimethyl-5-(2-thienyl)-1H-pyrazolo[4,3-e][1,2,4]triazine (**5d**, $C_{10}H_9N_5S$)
Yield 32%; mp 138–140°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.66$ (s, C(3)-CH_3), 4.24 (s, N(1)-CH_3), 7.19 (dd, $J = 3.7$, 5.0 Hz, H-4′), 7.49 (d, $J = 5.0$ Hz, H-3′), 8.13 (d, $J = 3.7$ Hz, H-5′) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.1$ (C(3)-*C*H_3), 34.8 (N(1)-CH_3), 128.4 (C-4′), 128.7 (C-3′), 129.7 (C-5′), 134.5 (C-3), 140.7 (C-2′), 141.9 (C-3a), 147.2 (C-7a), 156.7 (C-5) ppm; IR: $\bar{\nu} = 1511$ (C=N) cm^{-1}; MS-EI: m/z (%) = 231 (58) [M^+], 203 (70), 188 (100), 162 (33), 147 (48).

l,3-Dimethyl-5-(2-furyl)-1H-pyrazolo[4,3-e][1,2,4]triazine (**5e**, $C_{10}H_9N_5O$)
Yield 26%; mp 143–145°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.70$ (s, C(3)-CH_3), 4.34 (s, N(1)-CH_3), 6.62 (dd, $J = 3.0$, 3.4 Hz, H-4′), 7.51 (d, $J = 3.4$ Hz, H-3′), 7.69 (br d, $J = 3.0$ Hz, H-5′) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 11.2$ (C(3)-*C*H_3), 34.8 (N(1)-CH_3), 112.4 (C-4′), 113.4 (C-3′), 134.8 (C-3), 142.1 (C-3a), 145.3 (C-5′), 147.0 (C-7a), 150.7 (C-2′), 156.6 (C-5) ppm; IR: $\bar{\nu} = 1521$ (C=N) cm^{-1}; MS-EI: m/z (%) = 215 (100) [M^+], 187 (5), 172 (4), 146 (7), 131 (4).

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