An efficient synthesis of pyridazinoindazolones

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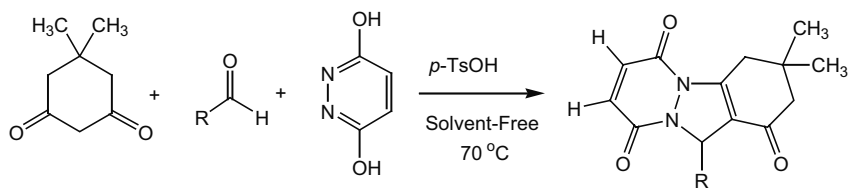
An efficient synthesis of biologically interesting pyridazinoindazolone derivatives was achieved via a one-pot three-component *p*-toluenesulfonic acid-catalysed reaction of dimedone, differently substituted aldehydes, and 3,6-dihydroxypyridazine under solvent-free conditions. Two plausible mechanisms for the formation of pyridazinoindazolones are proposed.

Keywords: aldehydes, dimedone, heterocycles, multicomponent reactions

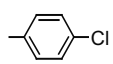
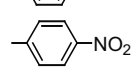
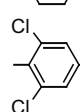
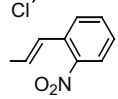
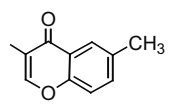
Among a large variety of nitrogen-containing heterocyclic compounds, heterocycles containing bridgehead hydrazine have received considerable attention because of their pharmacological properties and clinical applications.[1-13] For example, benzydamine is the first reported indazole derivative recognised in the management of pain and inflammation topically.[6] In this direction, many efforts were focused on the development of new non-steroidal anti-inflammatory drugs (NSAIDs) with an indazole ring system.[2-8] Later, several orally active indazole derivatives such as triazolo[1,2-*a*]indazoles, triazepino[1,2-*a*]indazoles and pyrazolo[1,2-*a*]indazole-1,3,9-trione derivatives were reported to possess 5-lipoxygenase inhibition with antiinflammatory, analgesic activities.[9,10] On the other hand, another fused polycyclic heteroring system such as diftalone, a phthalazino[2,3-*b*]phthalazine-5,12(7*H*,14*H*)-dione has been used as a NSAID.[11] Recently, a series of new *N*[2] substituted 1,2-dihydro-3*H*-indazol-3-ones as well as their condensed pyrazolo, pyridazino derivatives such as pyridazino[1,2-*a*]indazole-6,9,11-triones and 3,9-dioxo-3*H*,9*H*-pyrazolo[1,2-*a*]indazole were synthesised.[12,13] The anti-inflammatory activity of some of these synthesised compounds was determined by carrageenan-induced rat paw oedema technique using diclofenac as a reference drug. The pharmacological data showed that most of the tested compounds exhibited a significant long lasting anti-inflammatory activity, which in some cases was superior to that of diclofenac.

In connection with our recent interest aimed at the development of efficient protocols for the preparation of biologically active heterocycles,[14-16] we report here an efficient *p*-toluenesulfonic acid-catalysed one-pot condensation reaction of dimedone, differently substituted aldehydes, and 3,6-dihydroxypyridazine under solvent-free conditions at 70 °C which afforded 2,3,4,11-tetrahydro-1*H*-pyridazino[1,2-*a*]indazole-1,6,9-trione derivatives in good to moderate isolated yields.

The one-pot three-component condensation reactions of dimedone **1** with various aldehydes **2** and 3,6-dihydroxy-



1 **2** **3** **4**

	R	Yield/%
4a	-CH_3	55
4b	-$CH_2CH_2CH_3$	61
4c		80
4d		73
4e		85
4f		91
4g		51
4h		63

Scheme 1

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pyridazine **3** in the presence of a catalytic amount (30 mol%) of *p*-toluenesulfonic acid (*p*-TsOH) proceeded spontaneously at 70 °C under solvent-free conditions and were complete after 10 minutes to afford 2,3,4,11-tetrahydro-1*H*-pyridazino[1,2-a] indazole-1,6,9-triones **4a–h** in moderate to good yields (Scheme 1). The ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of fused pyridazinoindazolone **4**. Any product other than **4** could not be detected by NMR spectroscopy. All the products were characterised by FT-IR, ^{1}H and ^{13}C NMR spectra, and elemental analysis.

The elucidation of the structure of **4** using ^{1}H and ^{13}C NMR spectroscopic data is discussed with **4a** as an example. The central pyrazole moiety in compound **4a** has an asymmetric carbon atom bearing a hydrogen atom. In fact, these products **4a–h** are chiral molecules. The ^{1}H NMR spectrum of **4a** consisted of two singlet signals for the geminal methyl protons (δ_H 1.15 and 1.16 ppm) and a doublet for the methyl group directly attached to the central pyrazole ring (δ_H 1.64 ppm). Two AB-quartet resonances (δ_H 2.33–2.34 and 3.05–3.13 ppm) were observed for the two methylene groups. The methine group of the pyrazole moiety (N-C*H*-C=) resonated as a quartet (δ_H 5.44 ppm). An AB-system was observed for two vicinal vinylic protons (δ_H 6.87 and 6.93 ppm).

The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 14 distinct resonances in agreement with the suggested structure. The structural assignments made on the basis of the ^{1}H and ^{13}C NMR spectra of compound **4a** were supported by measurement of its IR spectra. The IR spectrum of **4a** showed strong absorptions at 1700, 1662 and 1658 cm^{-1} due to the carbonyls and the C=C bond at 1579 cm^{-1} as a weak broad band. The ^{1}H decoupled ^{13}C NMR spectra of **4b-h** are similar to those of **4a** except for the R groups, which exhibit characteristic signals with appropriate chemical shifts.

The scope and limitations of this simple process with respect to the aldehyde component was examined and it was found that aliphatic aldehydes, substituted aromatic aldehydes and α,β-unsaturated aldehydes all tolerate the reaction conditions with moderate to good yields. Although the mechanism of the reaction has not yet been established experimentally, two possible pathways are by reaction of dimedone first with either 3,6-dihydroxypyridazine or with an aldehyde. In conclusion, some merits of this method are its generalisation with respect to aldehydes, shorter reaction times, easy work-up and no need for toxic organic solvents.

Experimental

Melting points were measured on a Büchi 535 apparatus. Elemental analyses (C, H, N) were conducted using an elementar vario EL *III* instrument. FT-IR Spectra were recorded on a Bruker Equinox-55 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avance spectrometer at 400.13 and 100.77 MHz, with $CDCl_3$ as solvent. The solvents and reagents used in this work were purchased from Merck. All reagents were used without further purification.

Typical procedure for the preparation of **4a**

In a 20-mL screw-capped vial, a mixture of dimedone (0.140 g, 1.0 mmol), 3,6-dihydroxypyridazine (0.112 g, 1.0 mmol), acetaldehyde (0.066 g, 1.5 mmol) and *p*-TSA (0.05 g, 0.3 mmol) was heated at 70 °C for 10 min and the completion of reaction was confirmed by TLC (EtOAc–hexane 1:2). After cooling, the reaction mixture was washed with water (10 mL) and the residue recrystallised from CH_2Cl_2:*n*-hexane (1:6) to afford pure **4a** as yellow crystals (0.143 g, 55%).

3,3,11-Trimethyl-2,3,4,11-tetrahydro-1H-pyridazino[1,2-a]-indazole-1,6,9-trione (**4a**): M.p. 166–168 °C (dec.); IR (KBr): ν = 1700, 1662, 1658 (C=O), 1579 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ_H 1.15 and 1.16 (2 s, 2 C(CH_3)$_2$), 1.64 (d, $^3J_{HH}$ = 6.2 Hz, CH–CH_3), 2.33 and 2.34 (AB system, $^2J_{HH}$ = 16.4 Hz, CH_2), 3.05 and 3.13 (AB system, $^2J_{HH}$ = 19.2 Hz, CH_2), 5.44 (q, $^3J_{HH}$ = 6.2 Hz, C*H*–CH_3), 6.87 and 6.93 (AB system, $^3J_{HH}$ = 10.2 Hz, CH=CH) ppm; ^{13}C NMR ($CDCl_3$, 100.7 MHz): 192.7, 155.0, 153.7, 150.4, 135.8, 134.7, 119.6, 59.5, 51.0, 37.5, 34.5, 28.6, 28.2, 16.9 ppm. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.54; H, 6.22; N, 10.80%.

3,3-Dimethyl-11-propyl-2,3,4,11-tetrahydro-1H-pyridazino[1,2-a]-indazole-1,6,9-trione (**4b**): Yellow powder (0.176 g, 61%). M.p. 168–170 °C (dec.); IR (KBr): ν = 1688, 1654, 1648 (C=O), 1582 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ_H 0.87 (t, $^3J_{HH}$ = 7.0 Hz, $CH_2CH_2CH_3$), 1.16 and 1.17 (2 s, 2 C(CH_3)$_2$), 2.01–2.04 (m, $CH_2CH_2CH_3$), 2.26 and 2.27 (AB system, $^2J_{HH}$ = 16.4 Hz, CH_2), 3.06 and 3.15 (AB system, $^2J_{HH}$ = 19.0 Hz, CH_2), 3.75-3.77 (m, $CH_2CH_2CH_3$), 5.52 (t, $^3J_{HH}$ = 6.0 Hz, CH), 6.87 and 6.93 (AB system, $^3J_{HH}$ = 10.2 Hz, CH=CH) ppm; ^{13}C NMR ($CDCl_3$, 100.7 MHz): 197.1, 163.8, 154.1, 150.7, 135.8, 134.6, 118.8, 63.5, 51.0, 40.9, 37.5, 28.7, 28.3, 25.5, 18.6, 14.2 ppm. Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.73; H, 7.02; N, 9.70%.

3,3-Dimethyl-11-phenyl-2,3,4,11-tetrahydro-1H-pyridazino[1,2-a]-indazole-1,6,9-trione (**4c**): Yellow powder (0.258 g, 80%). M.p. 203–205 °C (dec.); IR (KBr): ν = 1690, 1661, 1650 (C=O), 1580 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ_H 1.16 and 1.17 (2 s, 2 C(CH_3)$_2$), 2.29 (s, CH_2), 3.13 and 3.25 (AB system, $^2J_{HH}$ = 19.2 Hz, CH_2), 6.27 (s, CH), 6.89 (s, CH=CH), 7.27–7.33 (m, C_6H_5) ppm; ^{13}C NMR ($CDCl_3$, 100.7 MHz): 192.0., 154.9, 153.2, 150.3, 136.0, 135.1, 134.8, 128.9, 128.8, 127.1, 119.0, 65.4, 51.0, 37.5, 34.7, 28.7, 28.3 ppm. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.85; H, 5.66; N, 8.73%.

11-(4-Chlorophenyl)-3,3-dimethyl-2,3,4,11-tetrahydro-1H-pyridazino[1,2-a]-indazole-1,6,9-trione (**4d**): Yellow powder (0.260 g, 73%). M.p. 201–203 °C (dec.); IR (KBr): ν = 1720, 1659, 1622 (C=O), 1588 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ_H 1.13 and 1.17 (2 s, 2 C(CH_3)$_2$), 2.28 and 2.30 (AB system, $^2J_{HH}$ = 16.4 Hz, CH_2), 3.12 and 3.24 (AB system, $^2J_{HH}$ = 19.2 Hz, CH_2), 6.24 (s, CH), 6.89 (s, CH=CH), 7.28 and 7.31 (AA'BB' system, $C_6H_4NO_2$) ppm; ^{13}C NMR ($CDCl_3$, 100.7 MHz): 191.9, 154.8, 153.2, 150.6, 135.9, 135.0, 134.8 133.7, 129.0, 128.5, 118.5, 64.8, 50.9, 37.5, 34.7, 28.7, 28.3 ppm. Anal. Calcd for $C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.08; N, 7.85. Found: C, 64.03; H, 4.77; N, 7.80%.

3,3-Dimethyl-11-(4-nitrophenyl)-2,3,4,11-tetrahydro-1H-pyridazino[1,2-a]-indazole-1,6,9-trione (**4e**): Yellow powder (0.312 g, 85%). M.p. 209–211 °C (dec.); IR (KBr): ν = 1680, 1658, 1623 (C=O), 1589 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ_H 1.13 and 1.18 (2 s, 2 C(CH_3)$_2$), 2.28 and 2.30 (AB system, $^2J_{HH}$ = 16.4 Hz, CH_2), 3.14 and 3.24 (AB system, $^2J_{HH}$ = 19.2 Hz, CH_2), 6.33 (s, CH), 6.91 and 6.95 (AB system, $^3J_{HH}$ = 10.3 Hz, CH=CH), 8.51 and 8.18 (2 d, $^3J_{HH}$ = 8.7 Hz, $C_6H_4NO_2$) ppm; ^{13}C NMR ($CDCl_3$, 100.7 MHz): 191.9, 154.7, 153.3, 151.1, 148.0, 142.2, 135.7, 135.3, 128.1, 124.1, 117.7, 64.5, 50.8, 37.5, 34.7, 28.9, 28.3 ppm. Anal. Calcd for $C_{19}H_{17}N_3O_5$: C, 62.12; H, 4.66; N, 11.44. Found: C, 62.06; H, 4.61; N, 11.50%.

11-(2,6-Dichlorophenyl)-3,3-dimethyl-2,3,4,11-tetrahydro-1H-pyridazino[1,2-a]-indazole-1,6,9-trione (**4f**): Yellow powder (0.356 g, 91%). M.p. 280–282 °C (dec.); IR (KBr): ν = 1715, 1658, 1624 (C=O), 1588 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ_H 1.17 and 1.18 (2 s, 2 C(CH_3)$_2$), 2.28 and 2.31 (AB system, $^2J_{HH}$ = 16.4 Hz, CH_2), 3.13 and 3.22 (AB system, $^2J_{HH}$ = 19.2 Hz, CH_2), 6.86 and 6.91 (AB system, $^3J_{HH}$ = 10.3 Hz, CH=CH), 7.15 (s, CH), 7.16-7.18 and 7.40–7.43 (2 m, $C_6H_3Cl_2$) ppm; ^{13}C NMR ($CDCl_3$, 100.7 MHz): 191.8, 155.2, 152.9, 152.3, 135.1, 135.0, 132.7, 130.0, 129.7, 129.2, 115.4, 61.8, 50.9, 37.5, 34.5, 28.8, 28.4 ppm. Anal. Calcd for $C_{19}H_{16}Cl_2N_2O_3$: C, 58.33; H, 4.12; N, 7.16. Found: C, 58.40; H, 4.10; N, 7.19%.

3,3-Dimethyl-11-[2-(2-nitrophenyl)-1-ethenyl]-2,3,4,11-tetrahydro-1H-pyridazino[1,2-a]-indazole-1,6,9-trione (**4g**): Yellow powder (0.200 g, 51%). M.p. 175–177 °C (dec.); IR (KBr): ν = 1720, 1683, 1641 (C=O), 1580 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ_H 1.08 and 1.10 (2 s, 2 C(CH_3)$_2$), 2.28 and 2.31 (AB system, $^2J_{HH}$ = 16.4 Hz, CH_2), 2.43 and 2.47 (AB system, $^2J_{HH}$ = 19.2 Hz, CH_2), 6.63 (dd, $^3J_{HH}$ = 6.3 Hz, $^4J_{HH}$ = 1.0 Hz, CH), 7.15 (s, CH), 7.24 (s, CH=CH), 7.28–7.8.11 (m, CH=CH-$C_6H_4NO_2$ and CH=CH) ppm; ^{13}C NMR ($CDCl_3$, 100.7 MHz): 192.6, 152.1, 149.3, 145.8, 133.4, 132.7, 131.1, 130.4, 129.6, 129.2, 128.8, 125.2, 125.0, 124.4, 117.3, 54.2, 52.4, 50.8, 40.9, 29.1, 28.6 ppm. Anal. Calcd for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68. Found: C, 64.04; H, 4.81; N, 10.73%.

3,3-Dimethyl-11-(6-methyl-4-oxo-4H-chromen-3-yl)-2,3,4,11-tetrahydro-1H-pyridazino[1,2-a]-indazole-1,6,9-trione (**4h**): Yellow powder (0.255 g, 63%). M.p. 271–273 °C (dec.); IR (KBr): ν = 1715, 1710, 1681, 1644 (C=O), 1581 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ_H 1.15 and 1.16 (2 s, 2 C(CH_3)$_2$), 2.26 and 2.28 (AB system,

$^2J_{HH}$ = 16.4 Hz, CH_2), 2.36 (s, CH_3), 3.11 and 3.29 (AB system, $^2J_{HH}$ = 19.2 Hz, CH_2), 5.97 (s, CH), 6.81 and 6.89 (AB system, $^2J_{HH}$ = 10.2 Hz, CH=CH), 7.33–7.84 (m, arom. H) ppm; ^{13}C NMR ($CDCl_3$, 100.7 MHz): 193.1, 177.2 164.4, 156.9, 154.7, 152.8, 135.5, 135.4, 135.1, 135.0, 134.7, 124.8, 124.5, 118.0, 117.2, 116.9, 61.1, 50.9, 37.5, 34.7, 28.7, 28.3, 20.9 ppm. Anal. Calcd for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93. Found: C, 68.40; H, 5.02; N, 6.94%.

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