# Solvent-free synthesis of 3,5-di-*tert*-butylpyrazole and 3,5-di-substitutedbutylpyrazol-1-ylethanol Juanita L. van Wyk<sup>a</sup>, Bernard Omondi<sup>a</sup>, Divambal Appavoo<sup>a</sup>, Ilia A. Guzei<sup>a,b</sup>, and James Darkwa<sup>a</sup>\*

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A high-yield, solvent-free approach to the synthesis of 1,3,5-trisubstituted pyrazoles is reported. Four compounds, (3,5-di-*tert*-butyl-1H-pyrazole, (2-(3,5-dimethyl-1H-pyrazol-1-yl)ethanol, 2-(3,5-di-*tert*-butyl-1H-pyrazol-1-yl)ethanol, 2-(3,5-diphenyl-1H-pyrazol-1-yl)ethanol were readily prepared by solvent-free condensation of the appropriate diketone and the respective hydrazine. The crystal structures of the three pyrazolyl-ethanols are typical of N-substituted pyrazoles. All three pyrazolyl compounds show interesting inter-molecular hydrogen bonding. For the 3,5-dimethyl compound the molecules form discrete hydrogen bonded dimers within a unit cell, while for the others the hydrogen bonding is in a head-to-tail arrangement resulting in the formation of chains.

Keywords: solvent-free synthesis, pyrazoles, pyrazolyl

Pyrazoles and their derivatives continue to receive attention because they are valuable compounds as pharmaceuticals,1-3 as intermediates for industrial products,<sup>4,5</sup> as ligands in coordination chemistry<sup>6</sup> and in catalysis.<sup>7</sup> However, access to pyrazoles usually involve tedious synthetic routes and organic solvents that are not environmentally friendly. One such synthesis is that of 3,5-di-tert-butylpyrazole which takes four days of refluxing and purification, followed by sublimation.<sup>8,9</sup> A recent report by Wang and Qin<sup>10</sup> has shown that grinding 2,4pentanedione with hydrazines gives the appropriate pyrazole derivatives, which represents a marked improvement on the Elguero method.8 The report by Wang and Qin includes the synthesis of 3,5-di-tert-butylpyrazole. It is, however, difficult to see how the liquid starting materials for the synthesis of 3,5-di-tert-butylpyrazole, 2,2',6,6'-tetramethyl-3,5-heptanedione and hydrazine hydrate, are ground to form the product. We have prepared 3,5-di-tert-butylpyrazole and the di-substituted pyrazolylethanol by heating a mixture of liquid synthons, 2,2',6,6'-tetramethyl-3,5-heptanedione and hydrazine hydrate or di-substituted 2,4-propanedione and hydrazine ethanol respectively at 60-70 °C in a solvent-free procedure. We report here these syntheses.

## **Results and discussion**

The four compounds (1-4) were readily prepared at mild temperatures *via* the condensation of 2,2',6,6'-tetramethyl-3,5-heptandedione with hydrazine in the case of compound 1, and for the rest of the compounds *via* the condensation of the corresponding dione with 2-hydroxyethylhydrazine. All reactions were performed under solvent-free conditions (Scheme 1), a critical finding that has produced promising results. All four compounds were isolated and worked up using a minimal



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amount of solvent. In fact for compound **1** there was no need for any solvent at all making this is the first truly green process for its synthesis. In contrast, the corresponding synthetic procedure reported by Wang and Qin<sup>10</sup> involves a drop of concentrated sulfuric acid, washing with 10% Na<sub>2</sub>CO<sub>3</sub> solution and







**Fig. 2** ORTEP diagram of pyrazole **3** with the ellipsoids drawn at 50% probability level.



Fig. 3 ORTEP diagram of pyrazole 4 with the ellipsoids drawn at 40% probability level. Some H atoms are omitted for clarity.

water. Our yield of 89% compares favourably with the 96% yield reported by Wang and Qin.<sup>10</sup> Our reaction time for the synthesis of **1** is also considerably shorter than the procedure reported by Elquero and co-workers,<sup>8</sup> which is the most commonly followed procedure for the synthesis of **1**.

Similarly, all the (pyrazol-1-yl)ethanol compounds (2–4) were formed in the absence of solvents, in contrast to the 3,5-dimethyl-<sup>11,12</sup> and 3,5-diphenyl-<sup>12</sup> analogues reported in the literature where the reactions were performed in absolute ethanol. Even with the work-up for 2–4 that requires small amounts of solvents, our procedure<sup>11,12</sup> is substantially greener than the reported literature procedures for 1–4. Another major advantage of our processes is short reaction times; hence using less energy. The yields for 2–4 are also very good to excellent.

We were able to grow crystals of **2**–**4** by slow evaporation of methanol solutions of **2** and **4**, whilst crystals of **3** were grown from hexane. Table 1 lists the crystallographic data and refinement details for compounds **2**, **3** and **4**. The molecular parameters of the three structures are similar and fall in the usual ranges. The N–C–C–O torsion angles in the three compounds differ, presumably due to different packing effects and hydrogen bonding interactions. The most interesting aspect of the structures are the intermolecular interactions. In solid state, compound **2** forms O–H…N bonded dimers with the O…N separation of 2.8512(14) Å and O–H…N angle of 177.6(15)°. The dimers can be described with a first order graph set notation  $R_2^2(12)$ .

Whereas compounds 2 and 3 crystallised with one molecule each in the asymmetric unit, compound 4 has four symmetryindependent molecules in the asymmetric unit. In the crystals of all three compounds the molecules are linked together through intermolecular O–H...N hydrogen bonds (Table 3). In the crystal the molecules of 3 are arranged in a head-to-tail fashion. The strong hydrogen bonds of the type O–H...N (O... N distance is 2.8216(16) Å, the O–H...N angle spans  $171(1)^{\circ}$ ) link molecules into spiral chains running parallel to the crystallographic *b* axis. The graph set notation for this hydrogen bonding interaction is C(6). Similar spiral chains are observed in the crystal structure of compound 4, but they are formed differently and run in the crystallographic *a* direction. In 4, the four molecules are arranged pairwise in a head-to-tail fashion and there are four discrete hydrogen bonds among them. These O–H...N type bonds are fairly strong with the average O...N separation of 2.823(14) Å and average O-H...N angle of  $172(1)^{\circ}$ . The graph set notation for each interaction is the same, D(2). Thus, the four symmetry independent molecules can be considered as one "set", and these "sets" are linked by hydrogen bonds and propagate along the *a* axis in the crystal.

## Conclusions

In summary this paper reports new solvent-free synthesis of four known pyrazoles using very mild reaction conditions that lead to high to excellent yields. The scale on which we performed our reactions is small but the reactions can be scaled up, thereby offering those who need large amounts of these compounds suitable procedures to make them.

#### Experimental

All chemicals were of reagent grade and used as received. All solvents were dried over the appropriate drying agent and distilled prior to use. Reactions and manipulation were carried out using a dual vacuum/ nitrogen line and standard Schlenk techniques unless otherwise stated. <sup>1</sup>H NMR and <sup>13</sup>C{<sup>1</sup>H}NMR were recorded on a Bruker Ultrashield 400 (<sup>1</sup>H NMR 400MHz, <sup>13</sup>C{<sup>1</sup>H} NMR 100MHz) in CDCl<sub>3</sub> and chemical shifts were referenced to residual protons in CDCl<sub>3</sub>.

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3,5-di-tert-Butyl-1H-pyrazole (1): A mixture of 2,2',6,6'-tetramethyl-3,5-heptanedione (0.22 g, 1.0 mmol) and hydrazine monohydrate (0.05 g, 1.0 mmol) was heated at 70 °C in a round bottom flask for 2 h. The reaction mixture started to solidify after 1 h during the heating process. By the end of the reaction time the product was a white solid mass which needed no further purification. Yield: 0.16 g (89%); m.p. 194.0 °C (lit. 193.0 °C).<sup>8</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.29 (s, 18H, C(CH<sub>3</sub>)<sub>3</sub>); 5.88 (s, 1H, pz-<u>H</u>). <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>):  $\delta$  30.4, 31.8, 97.2.

2-(3,5-Dimethyl-1H-pyrazol-1-yl)ethanol (2): 2,4-Pentanedione (1.03 g, 10 mmol) was added to 2-hydroxyethylhydrazine (0.76 g, 10.0 mmol) in a round bottom flask immersed in an ice bath. This was

Compound	2	3	4
Empirical formula	C <sub>7</sub> H <sub>12</sub> N <sub>2</sub> O	C <sub>13</sub> H <sub>24</sub> N <sub>2</sub> O	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O
Formula weight	140.19	224.34	264.32
Temperature (K)	100(2)	100(2)	100(2)
Wavelength (Å)	1.54178	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	P2 <sub>1</sub> /c	C2/c	ΡĪ
a (Å)	4.4035(15)	a = 28.801(4)	<i>a</i> = 10.5400(8)
b (Å)	16.165(5)	b = 5.7090(8)	b = 12.2432(9)
c (Å)	10.366(3)	c = 18.589(3)	c = 22.0008(17)
α (°)	90.	α = 90	$\alpha = 85.087(2)$
β (°)	99.46(2)	$\beta = 115.851(3)$	$\beta = 76.369(2)$
γ (°)	90	$\gamma = 90$	$\gamma = 89.665(2)$
Volume (Å <sup>3</sup> )	727.8(4)	2750.6(7)	2748.7(4)
Z	4	8	8
ρ (calcd) (Mg m <sup>-3</sup> )	1.279	1.083	1.277
μ (mm- <sup>1</sup> )	0.707	0.069	0.081
F(000)	304	992	1120
Crystal size (mm <sup>3</sup> )	0.40 x 0.29 x 0.20	0.49 x 0.08 x 0.08	0.32 x 0.13 x 0.05
Theta range for data collection (°)	5.12 to 71.94.	1.57 to 28.60°.	0.96 to 28.50°.
Index ranges	-5<=h<=5,	-38<=h<=38,	-14<= <i>h</i> <=14,
	-19<= <i>k</i> <=18,	-7<= <i>k</i> <=7,	-16<= <i>k</i> <=16,
	-12<=/<=12	-24<=/<=25	-29<=/<=29
Reflections collected	10782	38715	103128
Independent reflections	1411 [R(int) = 0.0183]	3512 [R(int) = 0.0770]	13837 [R(int) = 0.0442]
Completeness to theta = 28.60°	100.0%	99.4%	99.1%
Absorption correction	Empirical with SADABS	Semi-empirical from	Semi-empirical from
		equivalents	equivalents
Max. / min. transmission	0.8691 and 0.7641	0.9945 and 0.9671	0.9960 and 0.9746
Refinement method	Full-matrix least-squares on F2	Full-matrix least-squares on F2	Full-matrix least-squares on F2
Data / restraints / parameters	1411 / 0 / 140	3512 / 0 / 153	13837 / 0 / 725
Goodness-of-fit on <i>F</i> 2	1.053	1.024	1.149
Final R indices [I>2sigma(I)]	$R^1 = 0.0324$ , $wR^2 = 0.0842$	$R^1 = 0.0457$ , $wR^2 = 0.1023$	$R^1 = 0.0503$ , $wR^2 = 0.1210$
R indices (all data)	$R^1 = 0.0330$ , $wR^2 = 0.0846$	$R^1 = 0.0850$ , $wR^2 = 0.1270$	$R^1 = 0.0665$ , $wR^2 = 0.1299$
Extinction coefficient	0.0058(9)	0.0024(5)	0.302
Largest diff. peak and hole (e Å-3)	0.273 and –0.204	0.282 and –0.186 e Å-₃	–0.285 e Å⁻³

<b>Table I</b> Crystallographic data for the compounds <b>Z</b>	Table 1	lographic data for the compound	ds <b>2–4</b>
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Table 2 Selected bond distances and angles for compounds 2-4

		Во	ond distances/Å			
	2	3	4A	4B	4C	4D
O(1)–C(1)	1.4153(13)	1.4129(18)	1.420(2)	1.419(2)	1.419(2)	1.422(2)
N(1)-C(3)	1.3527(14)	1.3614(18)	1.361(2)	1.362(2)	1.359(2)	1.361(2)
N(1)–N(2)	1.3644(13)	1.3672(16)	1.3563(18)	1.3580(18)	1.3589(18)	1.3572(18)
N(1)-C(2)	1.4536(14)	1.4530(18)	1.466(2)	1.466(2)	1.466(2)	1.466(2)
N(2)–C(5)	1.3354(14)	1.3330(18)	1.345(2)	1.343(2)	1.344(2)	1.338(2)
			Bond angles/°			
N(1)–N(2)–C(5)	105.16(9)	105.58(11)	105.37(13)	105.44(13)	105.45(13)	105.26(13)
C(2)-N(1)-N(2)	119.91(9)	116.59(11)	118.68(13)	118.77(13)	118.79(13)	118.67(13)
C(2)-N(1)-C(3)	128.06(9)	131.19(12)	129.03(13)	129.52(13)	129.13(13)	129.18(13)
C(3)-N(1)-N(2)	112.01(9)	112.07(11)	112.04(13)	111.65(13)	111.80(13)	112.00(13)
N(1)-C(3)-C(4)	106.38(9)	105.37(12)	106.37(14)	106.63(14)	106.44(14)	106.34(14)
N(2)-C(5)-C(4)	110.54(9)	109.95(13)	110.47(14)	110.61(14)	110.62(14)	110.86(14)

accompanied by evolution of heat. The addition was maintained at a rate precluding overheating, but was generally completed within 10 min. The resultant liquid was stirred in an ice bath for 1 h and the solid product started forming within 30 min. The product was recrystallised from a minimum amount of diethylether at -20 °C. Yield: 1.17 g (84%); m.p. 62.0–63.5 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.10 (3H, s, pz-CH<sub>3</sub>), 2.16 (3H, s, pz-CH<sub>3</sub>), 3.81 (2H, t, J = 5.4 Hz, CH<sub>2</sub>), 3.94 (2H, t, J = 5.4 Hz, CH<sub>2</sub>) 4.85 (1H, br s, OH) 5.70 (1H, s, pz-H). <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>):  $\delta$  10.6, 12. 9, 49.8, 60.8, 104.5, 139.4, 147.1. Anal. Calcd for C<sub>7</sub>H<sub>12</sub>N<sub>2</sub>O (140.19): C, 59.98; H, 8.63; N, 19.98. Found: C, 59.51; H, 8.88; N, 20.03%.

2-(3,5-di-tert-Butyl-1H-pyrazol-1-yl)ethanol (3): A mixture of 2,2',6,6'-tetramethyl-3,5-heptanedione (0.21 g, 1.0 mmol) and 2-hydroxyethyl-hydrazine (0.11 g, 1.5 mmol) was heated at 70 °C in a round-bottom flask for 2 h. The reaction mixture was cooled to -20 °C, and the resultant sticky solid mass was washed with cold water and dried in

*vacuo.* Yield: 0.18g (80%); m.p. 88.9–90.0 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.14 (9H, s, pz-C(C<u>H<sub>3</sub>)<sub>3</sub>) 1.22</u> (9H, s, pz-C(C<u>H<sub>3</sub>)<sub>3</sub>) 3.85 (2H, t, *J* = 4.6 Hz, C<u>H<sub>2</sub>), 4.13 (2H, t, *J* = 4.6 Hz, C<u>H<sub>2</sub>), 5.77 (1H, s, pz-H).</u> <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>):  $\delta$  29.7, 30.1, 51.5, 61.4, 98.7, 152.0, 159.3. Anal. Calcd for C<sub>13</sub>H<sub>24</sub>N<sub>2</sub>O (224.34): C, 69.60; H, 10.78; N, 12.49. Found: C, 69.27; H, 10.95; N, 12.37%.</u></u>

2-(*3*,5-*Diphenyl-1H-pyrazol-1-yl)ethanol* (4): Synthesis of this compound was performed in a similar manner to **3** using dibenzoylmethane (0.23 g, 1.0 mmol) and 2-hydroxyethylhydrazine (0.11 g, 1.5 mmol). Yield: 0.22 g (90%); m.p. 101.4–103.0 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.75 (1H, br s, O<u>H</u>) 4.01 (2H, t, J = 5.5 Hz, C<u>H<sub>2</sub></u>), 4.22 (2H, t, J = 5.5 Hz, C<u>H<sub>2</sub></u>), 6.63 (1H, s, pz-<u>H</u>), 7.34 (1H, m, pz-C<sub>6</sub><u>H<sub>5</sub></u>), 7.42 (7H, m, pz-C<sub>6</sub><u>H<sub>5</sub></u>), 7.45 (2H, d, J = 7.10 Hz, pz-C<sub>6</sub><u>H<sub>5</sub></u>); <sup>13</sup>C{<sup>1</sup>H</sup>} NMR (CDCl<sub>3</sub>): δ 50.7, 61.6, 103.1, 125.4, 127.7, 128.6, 128.9, 130.0, 132.8,145.5, 150.7. Anal. Calcd for C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O (264.32): C, 77.25; H, 6.10; N, 10.60. Found: C, 77.10; H, 6.11; N, 10.48%.

Table 3 Geometric parameters for intermolecular O-H...N and C-H...O hydrogen bonding (Å, °)

Х-НҮ	X–H	HY	XY	<x–h…y< th=""><th>Symmetry code</th></x–h…y<>	Symmetry code
2					
O(1)–H(1)N(2)	0.867(18)	1.985(18)	2.812(15)	177.6(15)	1-x, 1-y, 1z
C(2)–H(8)O(1)	0.966(5)	2.586(15)	3.5095(19)	160.1(12)	$1+x, \frac{1}{2}-y, \frac{1}{2}+z$
3					
O(1)–H(1)N(1)	0.95(3)	1.88(3)	2.819(2)	171(3)	$\frac{1}{2}-x_{1}-\frac{1}{2}+y_{1}+\frac{1}{2}-z$
C(1)–H(1A)O(1)	0.98	2.57	3.484(3)	156	$\frac{1}{2}-x$ , $\frac{1}{2}+y$ , $\frac{1}{2}-z$
C(2)–H(8)O(1)	0.98	2.50	3.470(2)	170	$\frac{1}{2}-x, \frac{1}{2}-y, -z$
4					
O(1A)–H(1A)N(2C)	0.84	1.97	2.8051(19)	171	x, y, z
O(1B)–H(1B)N(2D)	0.84	2.00	2.8390(18)	172	X, V, Z
O(1C)-H(1C)N(2B)	0.84	1.99	2.8241(19)	171	X, V, Z
O(1D)–H(1D)N(2A)	0.4	1.99	2.8218(19)	171	1+x, y, z
C(1B)–H(1B2)O(1C)	0.99	2.60	3.475(2)	148	
C(13A)–H(13A)O(1A)	0.95	2.43	3.316(2)	155	
C(13C)-H(13C)O(1C)	0.95	2.44	3.327(2)	155	
C(1D)–H(1D2)O(1B)	0.99	2.57	3.4630(19)	150	

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