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**ARTICLE TYPE** 

# Versatile Polyiodopyrazoles: Synthesis and Biocidal Promise<sup>†</sup>

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<sup>5</sup> An efficient route to polyiodopyrazoles, 3, 4, 5-triiodopyrazole (1), 1-methyl-3, 4, 5-triiodopyrazole (2) and 1-diiodomethyl-3, 4, 5-triiodopyrazole (3), opens the door to prospective biocides. Nitration of 1 and 2 gives the previously inaccessible compounds, 3, 4-dinitro-5-iodopyrazole (4), and 3, 4-dinitro-10 5-iodo-1-methylpyrazole (5), respectively. These synthetic pathways will open many fronts for pyrazole chemistry.

Modern warfare is no longer limited to the use of conventional weapons; there is believed to be a huge store of chemical and biological weapons distributed among various countries as well <sup>15</sup> as illegitimate groups around the world. As a result interest in developing Agent Defeat Weapons (ADWs) has grown significantly during the last few years.<sup>[1]</sup> ADWs are airborne warheads which contain anti bioagent materials which may be iodine-rich compounds that form large amounts of elemental

- <sup>20</sup> iodine, and hydroiodic acid (HI) as detonation products strong biocides against such agents as viruses, spores, bacteria, and parasites.<sup>[2, 3]</sup> ADWs demand easily containable, non sublimable, and thermally stable sources of iodine or iodine-containing species (Figure 1).<sup>[3]</sup>
- <sup>25</sup> Various periodo heterocyclicarenes including tetraiodofuran (TIF) and 3, 4, 5-triiodopyrazole have been synthesized in our lab and studied systematically.<sup>[3a]</sup> They are being tested as effective antibioagent ingredients suitable for application as ADWs. Polyiodide salts which have low vapor pressure, high densities,
- <sup>30</sup> and high iodine content also provide another opportunity to increase the iodine concentration in target compounds.<sup>[3b]</sup>



Figure 1: Possible ADWs - (a) Tetraiodofuran (TIF); (b) 2,3,4,5-Tetraiodo-1H pyrrole; (c) 3,4,5-Triiodo-1H-pyrazole; (d) Ethane-1,2-35 diammonium-bis(triiodide).

35 diaminomum-ois(unodide).

Current methods for the iodination of pyrazoles suffer from a variety of difficulties. Pyrazoles with electron donating

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substituents have been iodinated using iodine-iodide (I<sub>2</sub>-KI) or iodine monochloride (ICl); both routes often use large quantities of reactants.<sup>[4]</sup> An iodine-aqueous ammonia combination gives a mixture of 3, 4-diiodo- and 3, 4, 5-triiodopyrazoles in very low <sup>50</sup> yields.<sup>[5]</sup> Only diiodo derivatives were obtained when an oxidative iodination methodology – I<sub>2</sub>-HIO<sub>3</sub> – was attempted.<sup>[6]</sup> Likely because of the lack of good synthetic routes, the chemistry and properties of polyiodopyrazoles have not been studied widely.

Now we report an efficient synthesis route for polyiodopyrazoles, viz., 3, 4, 5-triiodopyrazole (1), 1-methyl-3, 4, 5-triiodopyrazole (2) and 1-diiodomethyl-3, 4, 5-triiodopyrazole (3) in good to excellent yields. The introduction of the diiodomethyl group is an effective way to increase iodine
concentration. Nitration of 1 and 2 leads to the formation of the previously inaccessible 3, 4-dinitro-5-iodopyrazole (4) and 1-methyl-3, 4-dinitro-5-iodopyrazole (5), respectively, giving rise to more energetic iodopyrazoles.

Our continuing interest in ADWs, led us to seek alternative <sup>65</sup> and more lucrative routes to the synthesis of polyiodopyrazoles. Thus a recent report where it was possible to synthesize various polyiodobenzenes by employing molecular iodine under electrophilic conditions, appeared to be useful,<sup>[7]</sup> although the analytical purity of the products was not established using <sup>70</sup> elemental analysis. Potassium persulfate was used as an oxidant in the presence of trifluoroacetic and sulfuric acids to generate the electrophilic species, I<sup>+</sup>. It is likely that only highly stable substrates could survive under these harsh conditions thus suggesting pyrazoles known for their stability as excellent <sup>75</sup> candidates for electrophilic substitution reactions.

Three equivalents of pyrazole or 1-methylpyrazole were treated with two equivalents of iodine in the presence of equal amounts of potassium persulfate in dichloroethane to obtain 3, 4, 5-triiodopyrazole (1) or 1-methyl-3, 4, 5-triiodopyrazole (2) in 80 63% and 82% yields, respectively. Compounds 1 and 2 were characterized by NMR, and IR spectra, elemental analysis, and DSC measurements (Scheme 1). The carbon-bonded methylene group in acetic acid is considered to be an active group for electrophilic nitration; it can be converted into the trinitromethyl 85 group under nitrating conditions. The 1-acetic acid substituent in pyrazole has a similar active methylene group, and although it seemed likely that it should be possible to generate the triiodomethyl moiety using electrophilic iodination, only 1-diiodomethyl-3, 4, 5-triiodopyrazole (3) was obtained in 30% 90 yield (Scheme 1). It was fully characterized by using NMR, and

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IR spectra, elemental analysis, and DSC measurement techniques. Similar reactions with other heterocycles which contained the methylene group of acetic acid failed to react. However, apparently the nitrogen-linked acetic acid group has a sufficiently

Table 1. Physical properties of compounds 1-5

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s active methylene group for successful electrophilic iodination reactions under present conditions.

After discovering a reliable synthetic route to 3, 4, 5

Comp	$T_{\rm m}^{[a]}$	$T_{d}^{[b]}$	$d^{[c]}$	$\Delta H_f^{\circ [d]}$	$\Delta H_f^{\circ}$	$D^{[e]}$	$P^{[\mathrm{f}]}$	IS <sup>[g]</sup>	Iodine
-	[°C]	[°C	[gcm <sup>-3</sup> ]	[kJ mol <sup>-1</sup> ]	[kJ g <sup>-1</sup> ]	[ms <sup>-1</sup> ]	[GPa]	[J]	[%]
1	224	272	3.38	461.1	1.03	2859	5.32	>40	85.4
2	154	-	3.35	307.2	0.66	2919	5.42	>40	82.8
3	-	371	3.94	453.1	0.63	2605	4.59	>40	89.2
4	150	292	2.46	621.6	2.19	5922	20.63	>40	44.7
5	81	363	2.30	644.8	2.16	6443	24.02	>40	42.6

[a] melting point; [b] decomposition temperature; [c] density - gas pycnometer (25°C); heat of formation - Gaussian 03; [e] calculated detonation velocity - Cheetah 6.0; [f] calculated detonation pressure - Cheetah 6.0; [g] impact sensitivities - BAM drop hammer.

triiodopyrazole, attempts were made to introduce nitro groups <sup>10</sup> onto the pyrazole ring.



Scheme 1: Synthesis of 1-5

Although a variety of nitrating conditions were tried, it was not possible to obtain the 3, 4, 5-substituted trinitropyrazole.
<sup>15</sup> However, nitration of 3, 4, 5-triodopyrazole (1) or 1-methyl-3, 4, 5-triodopyrazole (2) with 100% nitric acid gave the new 3, 4-dinitro-5-iodopyrazole (4) or 1-methyl-3, 4-dinitro-5-iodopyrazole (5), respectively (Scheme 1), both of which previously had been inaccessible. Each was characterized by <sup>20</sup> NMR, and IR spectra, elemental analysis and DSC measurement techniques. Single crystal structure analysis was carried out for 5. Although 4 and 5 appeared to be susceptible to nucleophilic attack, e.g., to replace iodo at the 5-position, neither amination nor azidation of 4 and 5 under varying conditions was successful.
<sup>25</sup> This may arise from significant localization of a negative charge

at position 5 in the ring thus enhancing the strength of the carboniodine bond and precluding substitution (Scheme 2).



Scheme 2: Delocalization of electrons in 4

Heats of formation of all compounds were calculated with the Gaussian 03 program suite using isodesmic reactions <sup>[8]</sup> (Electronic Supporting Information Scheme S1). For these iodine-containing compounds, the (15s, 11p, 6d) basis of Strömberg et al. was augmented with other p shell and the five 35 valence exponents optimized resulting sp in а [521111111,41111111,3111] contraction scheme in

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elements.<sup>[9]</sup> Single-point energy (SPE) refinement on the <sup>40</sup> optimized geometries were performed with the use of MP2/6-311++G<sup>\*\*</sup> level. Corresponding iodine sets were constructed in MP2 method by using all electron calculations and quasi relativistic energy-adjusted spin-orbit-averaged seven-valenceelectron effective core potentials (ECPs). All compounds have <sup>45</sup> positive heats of formation; as expected, **4** and **5** with nitro substituents have higher positive heats of formation. The calculated values for heats of formation and experimental densities were used to predict the detonation velocities (*D*) and detonation pressures (*P*) using the Cheetah 6.0 program. All the <sup>50</sup> compounds have low detonation pressures which range from 4.59 to 24.02 GPa and the range of detonation velocities is 2605 to 6443 ms<sup>-1</sup>.

conjunction with 6-31+G\*\* for first row and second row

The detonation products,  $I_2$ , and in some cases, HI, and I, which are strong biocides, were predicted using Cheetah 6.0 <sup>55</sup> calculations. Compound **1** with one hydrogen atom was found to liberate HI while the other compounds do not liberate more than one percent HI or I. As shown in Figure 3, while compound **3** has the highest iodine concentration in its detonation products at ~89%, the detonation products of **1** - **3** each contains a high <sup>60</sup> percentage of iodine that makes them good candidates as effective bio agent-defeat materials (Table 2).



Figure 3: The sums of iodine-containing species in the detonation <sup>65</sup> products of compounds 1, 2, 3, 4, and 5 (weight percent).

The structure of **5** was obtained by X-ray single crystal crystallography. The crystallographic data are summarized in the Electronic Supporting Information. Suitable crystals were obtained by the slow evaporation of a solution of **5** in benzene <sup>70</sup> and diethyl ether. The crystals are triclinic falling in the P2<sub>1</sub> space

Table 1: Major detonation products shown by Cheetah 6.0 calculations [wt. % kg kg<sup>-1</sup>]

		6 6 1			
Comp	N <sub>2</sub> [g]	$I_2[g]$	HI [g]	I [g]	C [s]
1	6.22	52.1	22.87	10.34	8.00
2	6.09	81.9	-	-	8.51
3	3.93	88.6	-	-	6.34
4	22.2	49.6	-	-	8.36
5	18.8	41.7	-	-	5.07

group with two molecules per crystal lattice (Figure 4). The bond length between N1 and N2 is 1.364(6) Å falling in the typical range of N–N single bonds (1.363(11)–1.366(12) Å).<sup>[10a]</sup> The distance between the C(4) ring carbon and nitrogen of the nitro group 5 bonded to C(4) – N(8) is 1.419(8) Å. Similarly, the C(5) –N(11) bond length in 3, 4, 5-trinitropyrazole is 1.4538 (14) Å.<sup>[11]</sup> Thus the effect of iodine substituents is clearly seen in shortening of the C(4)-N(8) bond and lengthening of the C(5)-N(11) bond in comparison to similar bonds in 3, 4, 5-trinitropyrazole. The 10 carbon-iodine bond length for C(3)-I(7) is 2.039(5) Å which is shorter than the normal carbon-iodine single bond length, 2.13 Å. <sup>[10]</sup>The shorter bond length may account for the failure of the amination or azidation reactions of **5**.



15 Figure 4: (a) Thermal ellipsoid plot (50%) of 5. Hydrogen atoms are included but are unlabeled for clarity. (b) Ball and stack packing diagram of 5 viewed down the a-axis.

<sup>1</sup>H and <sup>13</sup>C spectra were recorded on 300 MHz (Bruker Avance 300) nuclear magnetic resonance spectrometer operating at 300.13 and 75.48 MHz by using [D<sub>6</sub>]DMSO as solvent and locking solvent unless otherwise stated. The chemical shifts in <sup>1</sup>H and <sup>13</sup>C spectra are reported relative to Me<sub>4</sub>Si. The decomposition temperatures (onset) were obtained using a differential scanning calorimeter (TA Instruments Co., Model Q 10) at a scanning rate <sup>25</sup> of 5 °C per minute in closed aluminum containers with a small hole in the lids. IR spectra were recorded using KBR pellets for solids on a BIORAD model 3000 FTS spectrometer. Densities were determined at room temperature employing a Micromeritics AccuPyic 1330 gas pycnometer. Elemental analyses were carried <sup>30</sup> out using an Exeter CE-440 elemental analyzer

3, 4, 5-Triodopyrazole (1): A mixture of pyrazole (2 g, 29.3 mmol), iodine (12.4 g, 48.8 mmol) and potassium persulfate (13.1 g, 48.8 mmol) in dichloroethane (DCE, 50 mL) in a 500 mL round-bottomed flask was stirred in an ice bath for five minutes.

- <sup>35</sup> Trifluoroacetic acid (39 mL) was added drop wise followed by concentrated sulfuric acid (1.75 mL). The reaction mixture was stirred for half an hour in an ice bath. After stirring at room temperature for fifteen minutes, the reaction mixture was heated for eight to twelve hours at 70-80 °C. The mixture was cooled to
- <sup>40</sup> room temperature and the solvent was evaporated by blowing air on the solution The residue was washed with cold water and dissolved in ethanol with heating. The solution was filtered. Water (~ 15 mL) was added before evaporating the solution by blowing air to remove unreacted iodine. Finally the residue was

<sup>45</sup> again dissolved in ethanol and a little water was added. The solvent was removed using a rotary evaporator to give a white solid which was further washed with cold water to obtain a pure product (yield = 8.26g, 63.3%).

$$\begin{split} T_{melt} &= 224.0 ~^\circ\text{C}; ~ T_{dec} ~(\text{onset}) = 272.~ 2 ~^\circ\text{C}; ~ IR ~(\text{KBr}) \lor ~ 3398, \\ {}_{50} ~3075, ~2953, ~2875, ~2733, ~1647, ~1516, ~1417, ~1314, ~1242, \\ 1130,982, 961, 854, 449 ~\text{cm}^{-1}; ~^1\text{H} ~\text{NMR} ~\delta ~13.94 ~(\text{broad}, ~\text{NH}), 4.7 \\ ; ~^{13}\text{C} ~\text{NMR} ~\delta ~94.2, ~85.1; ~\text{elemental analysis:} ~(\%) ~\text{calculated for} \\ C_3\text{H} ~I_3 ~N_2 ~(445.77): ~\text{C}, ~8.08; ~\text{H}, ~0.23; ~\text{N}, ~6.28; ~\text{found} ~\text{C}, ~8.27; ~\text{H}, \\ 0.22; ~\text{N}, ~6.20. \end{split}$$

<sup>55</sup> 1-Diiodomethyl-3, 4, 5-triodopyrazole (3): Pyrazole-1-acetic acid was prepared according to the literature.<sup>[12]</sup> Pyrazole (12.5 g, 183.6 mmol) was added to sodium hydroxide (16.2 g, 405 mmol) dissolved in water (185 mL) in a one liter round-bottomed flask. Then bromoacetic acid (28.1 g, 202.2 mmol) was added in <sup>60</sup> portions with stirring and the resulting mixture heated at reflux for 2 hours. After cooling, the mixture was carefully acidified (2 M HCl) to ~ pH 3 with vigorous stirring whereupon the product precipitated from the solution (Note: product does not precipitate if HCl is added too fast) (yield, 15.26 g, 67 %).

<sup>65</sup> Pyrazole acetic acid (0.18 g, 1.5 mmol,), iodine (1.27 g, 5 mmol) was stirred for five minutes in a 100 mL round-bottomed flask and then trifluoroacetic acid (4 mL) was added drop wise followed by sulphuric acid (0.18 mL). The reaction mixture was stirred in an ice bath for ten minutes and at room temperature for

<sup>70</sup> half an hour. Then stirring continued at 70 °C to 80°C for fortyeight hours and allowed to cool to room temperature before pouring in ice-water. The residue was filtered and washed with cold water; dissolved in ethanol and ~ 5 mL water was added. Ethanol was removed by blowing air. The residue was filtered 75 and washed with cold water (yield: 0.32 g, 30%).

 $T_{dec}$  (onset) = 371 °C; IR (KBr) v 3448, 2922, 1637, 1401, 1344, 1296, 1273, 1107, 983, 439 cm<sup>-1</sup>; <sup>1</sup>H NMR δ 13.61 (CHI<sub>2</sub>); <sup>13</sup>C NMR δ 109.8, 107.4, 85.1, 83.9; elemental analysis: (%) calculated for C<sub>4</sub>H I<sub>5</sub> N<sub>2</sub> (711.59): C, 6.75; H, 0.14; N, 3.94; s0 found C, 6.94; H, 0.19; N, 4.89

3, 4-Dinitro-5-iodopyrazole (4): 3, 4, 5-Triiodopyrazole (5g. 11.2 mmol) was added portion wise to 100% nitric acid (50 mL) in 100 mL round-bottomed flask and the reaction mixture was stirred overnight at 100 °C. After cooling to room temperature the <sup>85</sup> mixture was poured into crushed ice; the resulting solution was neutralized with solid sodium bicarbonate. The solution was acidified to pH 1 with concentrated hydrochloric acid and extracted with diethyl ether (3 x 20 mL). The combined extracts were washed with water and dried over anhydrous magnesium <sup>90</sup> sulphate. A slightly yellow compound was obtained after evaporating the solvent using a rotary evaporator (yield, 2.3 g, 73.6%).

T<sub>melt</sub> = 150.0 °C; T<sub>dec</sub> (onset) = 291. 9 °C; IR (KBr) v 3219, 1618, 1550, 1468, 1421, 1362, 1326, 1109, 790, 848, 814, 511 cm<sup>-1</sup>; <sup>13</sup>C <sup>95</sup> NMR δ 148.8, 129.6 91.7; elemental analysis: (%) calculated for C<sub>3</sub>H I N<sub>4</sub> O<sub>4</sub> (283.97): C, 12.69; H, 0.35; N, 19.73; found C, 12.86; H, 0.37; N, 19.60.

3, 4-Dinitro-5-iodo-1-methylpyrazole (5): 1-Methyl-3, 4, 5triodopyrazole (5 g, 10.8 mmol) was added portion wise to 100% <sup>100</sup> nitric acid (50 mL) and the reaction mixture was stirred overnight at 100 °C. After cooling to room temperature, the mixture was poured into crushed ice to obtain a white precipitate.

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The mixture was filtered and the residue washed with cold water to leave a white solid (yield, 2.3 g, 74%).

 $\begin{array}{l} T_{melt} = 81.0 \ ^{\circ}C; \ T_{dec} \ (onset) = 363.0 \ ^{\circ}C; \ IR \ (KBr) \ \nu \ \ 2924, \ 1554, \\ 1531, \ 1491, \ 1454, \ 1413, \ 1355, \ 1325, \ 1229, \ 1124, \ 1080, \ 1020, \\ {}_{5} \ 879, \ 808, \ 760, \ 732, \ 623 \ cm^{-1}; \ ^{1}H \ NMR \ \delta \ 4.0 \ (CH_3) \ ; \ ^{13}C \ NMR \ \delta \\ 147.9, \ 130.5, \ 96.7; \ elemental \ analysis: \ (\%) \ calculated \ for \ C_{4}H_3 \ I \\ N_{4}O_{4} \ (298.00): \ C, \ 16.12; \ H, \ 1.01; \ N, \ 18.80; \ found \ C, \ 16.15; \ H, \\ 0.91; \ N, \ 18.54. \end{array}$ 

### **10** Conclusions

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Polyiodopyrazoles, 3, 4, 5-triiodopyrazole (1), 1-methyl-3, 4, 5triiodopyrazole (2) and N-diiodomethyl-3, 4, 5-triiodopyrazole (3), were synthesized in efficient electrophilic reactions using molecular iodine in the presence of trifluoroacetic and sulphuric <sup>15</sup> acid; the calculated detonation properties and products suggest that the compounds may be effective bio agent defeat agents. A synthetic method was developed as an effective strategy for introducing an N-diiodomethyl group into pyrazole. Nitration of 1 and 2 with 100% HNO<sub>3</sub> resulted in the formation of the pheretofore inaccessible iodo dinitropyrazoles **4** and **5**. These

- <sup>20</sup> heretofore inaccessible iodo dinitropyrazoles, **4** and **5**. These polyiodopyrazoles may have application not only as ADWs but also in other areas such as medicinal chemistry, materials science, and synthetic organic chemistry.
- The authors gratefully acknowledge Dr. J. P. Hooper, Naval <sup>25</sup> Postgraduate School, Monterey, CA 93943 for Cheetah 6.0 calculations. This work was supported by the Defence Threat Reduction Agency (HDTRA1–11–1–0034) and the ONR (NOOO14-12-1-0536).

## Notes and references

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- Fax:+1 208-885-9146
- ‡ *Crystal data* for **5**: C<sub>2</sub>H<sub>7</sub>N<sub>5</sub>O<sub>4</sub>, FW = 298.00, Crystal dimensions  $0.17 \times 35 \ 0.10 \times 0.07 \ \text{mm}$ , Monoclinic, space group *P*2<sub>1</sub>, *a* = 6.082(9) Å, *b* =

8.835(14) Å, *c* = 8.067(13) Å, *β* = 107.606(19)°, *V* = 413.2(11) Å<sup>3</sup>, *Z* = 2, *D<sub>c</sub>* = 2.395 mg/m<sup>3</sup>,  $\lambda$  = 0.71073 Å,  $\mu$  = 3.866 mm<sup>-1</sup>, *F*(000) = 280, *R*<sub>1</sub> = 0.0229 for 1073 observed (*I* > 2σ*I*) reflections and 0.0252 for all 1073 reflections, Goodness-of-fit = 0.970, 119 parameters. Further details are 40 provided in the ESI†. CCDC 1031880.

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