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Prospects of fused polycyclic nitroazines as thermally insensitive energetic materials

Robert D. Chapman[a,*], William S. Wilson[a,1], John W. Fronabarger[b], Lawrence H. Merwin[a], Gregory S. Ostrom[a]

[a]*Chemistry & Materials Division (Code 4T4200D), Naval Aviation Science & Technology Office, Naval Air Warfare Center Weapons Division, China Lake, CA 93555, USA*

[b]*Pacific Scientific Energetic Materials Co., 7073 W. Willis Drive, Chandler, AZ 85226, USA*

Abstract

Novel chemical structures originally proposed as new thermally insensitive explosives were certain zero- to low-hydrogen-content, polynitro, polycyclic heteroaromatic compounds based on nitrogenous heterocycles. The proposed compounds were expected to be high-density materials with explosive yields in the RDX-to-HMX range, but with high melting points, good shock sensitivity, and significantly better thermal stabilities. Originally proposed candidates incorporated 3,6-dinitropyridazine as a structural feature. Based on the experimental results and on conclusions drawn from a careful consideration of principles of reactivity of this general class of compound—polynitroazines—important lessons were learned that are applicable to future choices of practical new energetic materials targets. A conclusion is drawn that the intractability of certain polynitroazine target compounds unavoidably arises from an extraordinary susceptibility to ubiquitous environmental contaminants such as water. The recognition of this structure–property relationship should have an important payoff toward future choices of target compounds.

Keywords: Nitropyridazines; Polynitroazines; Nitroheterocycles; Nitroheteroaromatic; Nucleophilic substitution

1. Introduction

Classical approaches to high-output secondary explosives have included the development of cyclic and cage nitramines, such as octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX) and hexanitrohexaazaisowurtzitane (CL-20). Although the representatives of this category of explosive exhibit superior explosive outputs, they are often more susceptible than is desired to degradation (including catastrophic reactive responses) via shock or thermal stimuli. Nitroaromatic and nitroheteroaromatic explosives tend generally to be more shock insensitive and thermally stable than high-energy materials in other classes such as nitramines. Examples of unsaturated nitroheterocycles that have received recent interest for demonstrated insensitivity properties include 3-nitro-1,2,4-triazolin-5-one (NTO) [1], 5-amino-3-nitro-1*H*-1,2,4-triazole (ANTA) [2,3], 2,4-dinitroimidazole (2,4-DNI) [4], and aminonitroheterocyclic *N*-oxides [5].

Polycyclic 3,6-dinitropyridazines—such as 1,4,5,8-tetranitropyridazino[4,5-*d*]pyridazine (**1**) and 2,4,7-trinitroimidazo[4,5-*d*]pyridazine (**2**)—are an unprece-

* Corresponding author. Tel.: +1-760-939-1663; fax: +1-760-939-1617.

E-mail address: chapmanrd@navair.navy.mil (R.D. Chapman).

[1] Present address: Weapons Systems Division, DSTO, Salisbury SA 5108, Australia.

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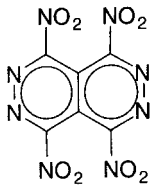
dented class of energetic compound that may have desirable stability properties.



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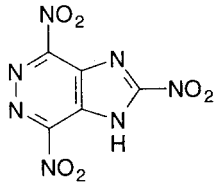

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Analogy of thermal and physical properties between related carbocyclic and heterocyclic compounds (Fig. 1) would predict the desired stability, e.g. the heterocyclic *skeleton* of compound **1**, pyridazino[4,5-*d*]pyridazine, has a melting point of 290 °C [6] compared to 83 °C for the carbocyclic analogue, naphthalene. The energetic carbocyclic derivative 1,4,5,8-tetranitronaphthalene has a melting point of 343 °C and density of 1.80 g cm^{-3} [7,8], so the corresponding tetraaza derivative **1** may be predicted to have a very attractive thermal stability. Its predicted density—according to the method of Stine [9]—is also attractive for energetic performance.

A similar trend may be seen in thermal properties—specifically, melting points—of indene and azaindene derivatives (Fig. 2), skeletons on which target **2** is based.

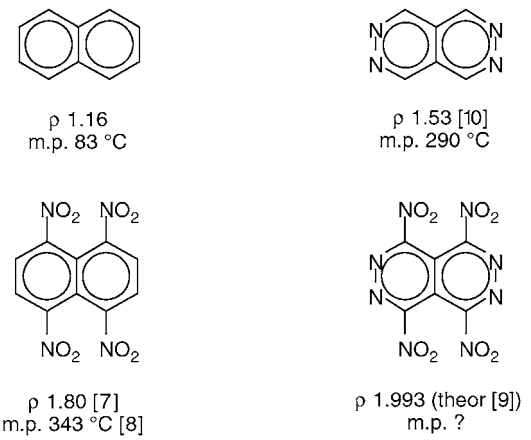

Fig. 1. Comparison of naphthalene and azanaphthalene physical properties [10].

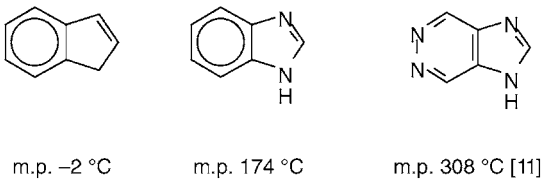

Fig. 2. Comparison of indene and azaindene melting points [11].

Because initiation by such stimuli as impact and friction is ultimately thermal in nature, these materials should also show exceptional insensitivity. Furthermore, empirical predictive codes estimate outstanding densities and detonation performance for these target molecules, with compound **1** predicted to have energetic performance comparable to that of HMX and compound **2** comparable to that of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX). Different tetranitrotetraazanaphthalene isomers have recently received attention in regard to their theoretical performance as energetic materials [12].

2. Experimental

Warning. ''Products from procedures described in this report are potentially explosive and may be subject to accidental initiation by such environmental stimuli as impact, friction, heat, or electrostatic discharge. Appropriate precautions should, therefore, be taken in their handling and/or use''. Reagents for which references are not specified were procured commercially; Aldrich Chemical Co. was a typical source. Melting points were determined in capillary tubes using a Mel-Temp II melting point apparatus or a DuPont Instruments DSC 2910 differential scanning calorimeter. IR spectra were determined as KBr disks using a Perkin-Elmer model 1330 spectrophotometer or as diffuse reflectance spectra run on a Nicolet 60SX FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on solutions using a Bruker AC-200 (200 MHz ^{1}H) or a Bruker AMX-400 (400 MHz ^{1}H). Chemical shift assignments were made on the basis of homonuclear decoupling, short- and long-range correlation (HMQC and HMBC) and GASPE experiments. Mass spectra were determined using a Perkin-Elmer 5985 gas chromatograph–mass spectrometer (GC–MS).

2.1. Diazotization of 1,4-diaminophthalazine (3)

Procedure a. 1,4-Diaminophthalazine (**3**) (0.100 g, 0.63 mmol) [13,14] was added to dilute sulfuric acid (10 ml) to give a white suspension, to which was added a solution of sodium nitrite (0.500 g, 7.24 mmol) in water (10 ml), and the reaction mixture was stirred at ambient temperature for 2 h. Filtration and washing with water gave a white solid (0.060 g, 59%) identified as phthalhydrazide (2,3-dihydrophthalazine-1,4-dione) (**5**) by comparison of its ^{1}H and ^{13}C NMR spectra in DMSO with library spectra. *Procedure b.* Copper nitrate trihydrate (0.500 g, 2.1 mmol) was dissolved in water (10 ml), and 1,4-diaminophthalazine (**3**) (0.100 g, 0.63 mmol) was added, together with sodium nitrite (0.500 g, 7.24 mmol). The reaction mixture was stirred at ambient temperature for 2 h, and then slowly acidified by the dropwise addition of dilute hydrochloric acid. The resultant precipitate was filtered off and tentatively identified as the iminodiazo compound **6** (0.20 g, 19%) on the basis of its ^{1}H NMR spectrum in acetone-d_6 [δ 8.19 (dd, 1H), 8.03 (dd, 1H), 7.93 (ddd, 1H), 7.80 (ddd, 1H)], its ^{13}C spectrum in the same solvent (δ 135.6, 134.3, 132.1, 130.7, 117.8, 112.1), its FT-IR spectrum (2230 cm^{-1}), and its mass spectrum [*m*/*z* 171, 143, 115, 88 (base peak)].

2.2. Nitration of phthalazine (7)

Potassium nitrite (1.04 g, 12.2 mmol) was suspended/dissolved in DMSO (10 ml) containing phthalazine (**7**) (0.120 g, 0.92 mmol), and a solution of acetic anhydride (1.2 g, 12 mmol) in DMSO (8 ml) was added dropwise, with stirring, at ambient temperature. When the addition was ca. one-third complete, the solution became yellowish-brown accompanied by the evolution of oxides of nitrogen; on completion of the addition the solution became clear yellow. The solution was stirred at ambient temperature for 2 h, during which time an orange hue developed. The reaction mixture was worked-up by quenching in dichloromethane (30 ml) and water (30 ml), separation, washing the aqueous layer with dichloromethane (2 × 30 ml), washing the combined organic extracts with brine (3 × 50 ml), drying over magnesium sulfate and then evaporation of the solvent under reduced pressure over the weekend to give a semi-solid residue (0.230 g). Washing with ether left a pale yellow solid (0.075 g), shown by ^{1}H NMR to be essentially a mixture of 1-nitrophthalazine (**9**) and 2*H*-Phthalazin-1-one (**8**) (ca. 42 and 58%). Flash chromatography (silica/chloroform) gave 2*H*-Phthalazin-1-one (**8**) (0.065 g, 44%, mp 187–189 °C), recrystallized from water, and trace fractions identified as phthalonitrile (**10**) and phthalimide (**11**). 2*H*-phthalazin-1-one (**8**) was characterized by its ^{1}H NMR (acetone-d_6): δ 11.7 (br s, 1H, NH), 8.31 (d, 1H, H_8), 8.27 (s, 1H, H_4), 7.90 (ddd, 1H, H_6), 7.89 (dd, 1H, H_5), 7.82 (ddd, 1H, H_7); ^{13}C NMR (acetone-d_6): δ 160.5 (C_1), 139.1 (C_4), 133.7 (C_6), 131.9 (C_7), 130.2 (C_{4a}), 128.1 (C_{8a}), 126.5 (C_8), 126.3 (C_5); GC–MS *m*/*z* 146 (base peak and parent ion), 118, 89. 1-Nitrophthalazine (**17**) could not be isolated, but was characterized by its ^{1}H NMR [acetone-d_6: δ 9.94 (s, 1H, H_4), 8.46 (ddd, 1H), 8.25–8.30 (m, 3H); chloroform-*d*: δ 9.71 (s, 1H, H_4), 8.26 (dd, 1H), 8.19 (dd, 1H), 8.12 (ddd, 2H, $H_{6,7}$)] and confirmed by GC–MS [*m*/*z* 175 (parent ion), 129, 102, 89 (base peak)].

2.3. Oxidation of 4,7-diaminoimidazo[4,5-d]pyridazine (12) with hypofluorous acid–acetonitrile

The 20% fluorine in nitrogen was passed through a well stirred solution of water (0.5 ml) in acetonitrile (70 ml) cooled to −15 °C, to generate the oxidant solution (ca. 12.3 mmol). A suspension of 4,7-diaminoimidazo[4,5-*d*]pyridazine [14,15] (**12**) (0.100 g, 0.67 mmol) in acetonitrile (40 ml) was added in portions, and the mixture was stirred at −15 °C overnight to give a clear yellow solution. Evaporation to dryness and washing/trituration with ether gave a yellow solid (0.080 g) identified by ^{1}H, ^{13}C and ^{19}F NMR as ammonium tetrafluoroborate etherate. No other organic product remained.

2.4. Oxidation of 1,4-diaminophthalazine (3) with hypofluorous acid–acetonitrile

The 20% fluorine in nitrogen was passed through a well stirred solution of water (1 ml) in acetonitrile (70 ml) cooled to −15 °C, to generate the oxidant solution (ca. 12.3 mmol). A suspension/solution of 1,4-diaminophthalazine (**3**) (0.100 g, 0.63 mmol) in

acetonitrile (40 ml) was added in portions, and the mixture was stirred at −15 °C overnight to give a clear yellow solution. Warming to ambient temperature, filtration and evaporation of the solvent left a tacky semi-solid (0.250 g) with a pungent odor suggesting residual acid(s). Dissolution/suspension in dichloromethane (100 ml), quenching with aqueous sodium bicarbonate, separation and drying of the organic layer gave a cream colored solid residue (0.090 g). ^{1}H NMR (acetone-d_6) suggested the presence of three compounds; the major product (60 mol%) was identified as phthalonitrile (**10**) and a minor product (5 mol%) as phthalimide (**11**); the remaining product (35 mol%) was characterized as 4-nitro-2*H*-phthalazin-1-one (**13**). GC–MS also confirmed the presence of phthalonitrile [*m*/*z* 128 (base peak and parent ion)] and 4-nitro-2*H*-phthalazin-1-one (**13**) [*m*/*z* 191 (parent ion), 145, 117, 90 (base peak)]. Washing with ether (30 ml) removed the phthalonitrile to leave **13** (0.020 g, 17% overall), contaminated with a trace of **11**; re-crystallization from ethanol gave off-white needles, mp 245–246 °C. ^{1}H NMR (acetone-d_6): δ 12.30 (br s, 1H, NH), 8.42 (ddd, 1H, H_8), 8.25 (ddd, 1H, H_5), 8.10 (ddd, 1H, H_6), 8.02 (ddd, 1H, H_7); ^{13}C NMR (acetone-d_6): δ 160.2 (C_1), 148.0 (C_4), 135.6 (C_6), 134.0 (C_7), 129.6 (C_{8a}), 127.9 (C_8), 125.5 (C_5), 123.8 (C_{4a}); FT-IR: 3167, 3109, 3061, 3019, 2948, 2905, 1703, 1543, 1322, 1147, 845, 777 cm^{-1}; GC–MS *m*/*z* 191 (parent ion), 145, 117, 90 (base peak). Variation of reaction times and modification of work-up procedures had a minor effect on the product distribution. Reaction time of 150 min and addition of sodium fluoride to scavenge traces of acid, followed by dissolution in dichloromethane and washing with aqueous sodium bicarbonate, gave 0.080 g of pale yellow product, shown by GC–MS to consist of phthalic anhydride (**16**) (18.5%), phthalonitrile (**10**) (45.5%), phthalimide (**11**) (13.0%) and 4-nitro-2*H*-phthalazin-1-one (**13**) (23.1%). Reduction of reaction time to 30 min and addition of silica gel to adsorb both acid residues and water, followed by dissolution in dichloromethane and washing with aqueous sodium bicarbonate, gave 0.070 g of yellow solid, shown by ^{1}H NMR (acetone-d_6) to consist of phthalonitrile (**10**) (57%), phthalimide (**11**) (10%) and 4-nitro-2*H*-phthalazin-1-one (**13**) (33%), without sign of phthalic anhydride (**16**).

2.5. 1-Amino-4-chlorophthalazine (*14*)

1,4-Dichlorophthalazine (1.00 g, mmol) was dissolved in warm DMF (10 ml) and heated to 100 °C in an oil bath. Aqueous ammonia (40 ml) was added dropwise over 2 h at such a rate as to maintain steady reflux. The reaction was allowed to cool to ambient temperature, water (40 ml) was added, and the mixture was allowed to stand in the refrigerator overnight. Filtration and washing with water gave an off-white solid (0.55 g), shown by ^{1}H NMR (acetone-d_6) to be a mixture of starting material (36%) and product (64%) [16]. Washing with refluxing benzene to remove the starting material followed by recrystallization from benzene gave 1-amino-4-chlorophthalazine (**14**) (0.30 g, 33%), mp 221–223 °C (lit. 221–222 °C [17]). ^{1}H NMR (acetone-d_6): δ 8.29 (ddd, 1H), 8.15 (ddd, 1H), 8.01 (ddd, 1H), 7.98 (ddd, 1H), 6.61 (br s, NH_2); ^{13}C NMR (acetone-d_6): δ 157.6 (C_1), 145.9 (C_4), 133.7 (C_7), 133.1 (C_6), 127.0 (C_{4a}), 125.5 (C_5), 124.1 (C_8), 120.6 (C_{8a}); GC–MS *m*/*z* 179/181 (parent ion), 144, 123, 89 (base peak), 76, 75.

2.6. Oxidation of 1-amino-4-chlorophthalazine (*14*) with hypofluorous acid–acetonitrile

The 20% fluorine in nitrogen was passed through a well stirred solution of water (1 ml) in acetonitrile (70 ml) cooled to −15 °C, to generate the oxidant solution (ca. 14.6 mmol). Solid 1-amino-4-chlorophthalazine (**14**) (0.175 g, 0.98 mmol) was added, and the mixture was stirred at −15 °C for 2 h, giving a slurry of a white solid in a clear yellow solution. Filtration gave a white solid (0.070 g, 40%) identified by ^{1}H NMR as 4-chloro-2*H*-phthalazin-1-one (**15**). Evaporation of the filtrate left a yellowish-orange semi-solid residue (0.090 g), identified by ^{1}H NMR as a mixture of phthalonitrile (**10**) and phthalimide (**11**). Separation by flash chromatography gave phthalonitrile (**10**) (0.031 g, 25%) and phthalimide (**11**) (0.011 g, 8%).

2.7. Oxidation of 1,4-diaminophthalazine (*3*) with dimethyldioxirane

A solution of dimethyldioxirane in acetone was prepared as follows. A 2 l three-necked round-bottom flask was equipped with an efficient mechanical stirrer and an addition funnel, and was connected via a

U-tube to a 100 ml round-bottom flask cooled to −78 °C (dry ice–acetone). The reaction flask was charged with a mixture of water (127 ml), acetone (96 ml), and sodium bicarbonate (29 g), and cooled to 5–10 °C in an ice bath. With vigorous stirring, "Oxone®" (potassium peroxymonosulfate) (60 g) was added in five portions at 3 min intervals; 3 min after the last addition, the ice bath was removed and the dimethyldioxirane–acetone mixture was distilled under house vacuum and collected at −78 °C. The solution was allowed to warm to ambient temperature, and an attempt was made to dry it with anhydrous potassium carbonate. 1,4-Diaminophthalazine (**3**) (0.100 g, 0.63 mmol) was added, and the suspension was stirred in the dark at ambient temperature for 90 min to give a clean yellow solution. Evaporation of the solvent gave a suspension of yellow solid in ca. 1.5 ml liquid; clearly the attempted drying was inadequate. Freeze drying gave a dirty yellow solid residue (0.100 g), shown by GC–MS to consist of phthalic anhydride (**16**) (4.1%), phthalonitrile (**10**) (4.7%), phthalimide (**11**) (19.2%), 2-cyanobenzamide (**17**) (21.4%), 3-iminoisoindolin-1-one (**18**) (18.0%) and 4-nitro-2*H*-phthalazin-1-one (**13**) (32.7%). The reaction procedure was repeated using dimethyldioxirane in dichloromethane, prepared by diluting the acetone solution with water (70 ml), extracting twice with dichloromethane (20 ml), washing the organic phase three times with water, and then drying over anhydrous potassium carbonate. Evaporation of the reaction solution gave an orange solid residue (0.120 g), shown by GC–MS to consist of phthalic anhydride (**16**) (1.3%), phthalonitrile (**10**) (14.4%), phthalimide (**11**) (10.8%), 2-cyanobenzamide (**17**) (26.5%), 3-iminoisoindolin-1-one (**18**) (24.0%) and 4-nitro-2*H*-phthalazin-1-one (**13**) (23.0%). The products from the two reactions were combined and separated by flash chromatography (silica gel in chloroform transitioned to 1:1 chloroform–ethyl acetate) to give phthalonitrile (**10**) (0.010 g, 8% overall), phthalimide (**11**) (0.039 g, 21%, recrystallized from water as needles, mp 234–236 °C), 4-nitro-2*H*-phthalazin-1-one (**13**) (0.053 g, 22%, recrystallized from ethanol), and 2-cyanobenzamide (**17**) (0.029 g, 16%, recrystallized from methanol as needles, mp 170–171 °C; ^{1}H NMR (acetone-d_6): δ 7.87 (two overlapping ddd, 2H, $H_{4,5}$), 7.75 (ddd, 1H), 7.67 (ddd, 1H), 7.49 (br s, 1H, NH), 7.01 (br s, 1H, NH); ^{13}C NMR (acetone-d_6): δ 167.7 (CO), 139.9 (C_1), 135.1 (C_5), 133.4 (C_4), 131.8 (C_3), 129.1 (C_6), 118.2 (CN), 112.1 (C_2); FT-IR: 3370, 3170, 2230, 1670, 1620, 1590, 1575, 1400, 1130, 780, 760 cm^{-1}; GC–MS *m/z* 146 (parent ion), 130 (base peak), 102, 76. The phthalic anhydride (**16**) and 3-iminoisoindolin-1-one (**18**) were apparently retained on the silica column.

2.8. Oxidation of 1-amino-4-chlorophthalazine (*14*) with dimethyldioxirane

A solution of dimethyldioxirane in dichloromethane was prepared as described above. 1-Amino-4-chlorophthalazine (**14**) (0.200 g, 1.1 mmol) was added, and the mixture was stirred in the dark at ambient temperature for 2 h, giving a clear yellow solution. Evaporation and trituration with ethanol gave a reddish-brown solid shown by ^{1}H NMR to be impure 4-chloro-2*H*-phthalazin-1-one (**15**) (0.064 g). Evaporation of the filtrate and extraction with ether gave a yellow residue (0.080 g) shown by ^{1}H NMR to be a mixture of phthalonitrile (**10**) and phthalimide (**11**). Separation by flash chromatography gave phthalonitrile (**10**) (0.029 g, 20%) and phthalimide (**11**) (0.009 g, 6%).

2.9. 4-Amino-2H-phthalazin-1-one (*19*)

2-Amino-4-chlorophthalazine (**14**) (0.20 g, mmol) was added to 80% sulfuric acid (5 ml) and heated at 150 °C for 30 min. The reaction mixture was cooled to ambient temperature and quenched in ice–water (100 ml) [17]. Filtration and washing with water gave 4-amino-2*H*-phthalazin-1-one (**19**) as an off-white solid (0.15 g, 84%), recrystallized from water as off-white needles (0.08 g), mp 265–266 °C (lit. 265–266 °C [17]). ^{1}H NMR (acetone-d_6): δ 10.6 (br s, 1H, NH), 8.31 (ddd, 1H, H_8), 8.01 (br d, 1H, H_5), 7.88 (ddd, 1H, H_6), 7.81 (ddd, 1H, H_7), 5.3 (br s, 2 H, NH_2); ^{13}C NMR (acetone-d_6): δ 158.0 (C_1), 146.1 (C_4), 132.7 (C_6), 131.0 (C_7), 128.3 (C_{8a}), 126.1 (C_8), 124.9 (C_{4a}), 123.9 (C_5); GC–MS *m/z* 161 (base peak and parent ion), 130, 104, 103, 77, 76.

2.10. Oxidation of 4-amino-2H-phthalazin-1-one (*19*) with dimethyldioxirane

A solution of dimethyldioxirane in dichloromethane was prepared as described above. 4-Amino-

2*H*-phthalazin-1-one (**19**) (0.050 g, 0.31 mmol) was added, and the mixture was stirred in the dark at ambient temperature for 75 min, giving a clear yellow solution. Evaporation of the solvent under reduced pressure gave an off-white solid (0.054 g, 91%), shown by ^{1}H NMR (acetone-d_6) to be essentially pure 4-nitro-2*H*-phthalazin-1-one (**13**), which was recrystallized from ethanol as cream needles (0.039 g).

2.11. Oxidation of 4,7-diaminoimidazo[4,5-d]pyridazine (12) with dimethyldioxirane

A solution of dimethyldioxirane in dichloromethane was prepared as described above. 4,7-Diaminoimidazo[4,5-*d*]pyridazine [14,15] (**12**) (0.200 g, 1.33 mmol) was added, and the suspension was stirred at ambient temperature in the dark for 90 min, leaving a solid suspended in a clear yellow solution. The solid was filtered off (0.190 g, 95%) and shown by ^{1}H NMR (DMSO-d_6) to be pure unreacted starting material. The filtrate was evaporated to leave a yellow semi-solid (0.026 g), shown to include miscellaneous unidentified aromatic residues. Oxidation with dimethyldioxirane in acetone gave essentially the same result.

2.12. 1-Chloro-4-(S,S-diphenylsulfilimino)phthalazine (20)

Following the general procedure of Millar et al. [18], 1,4-dichlorophthalazine (0.48 g, 2.41 mmol) in 15 ml THF was added via addition funnel to *S*,*S*-diphenylsulfilimine (Aldrich 99%, 1.00 g, 4.92 mmol) in 15 ml THF, and the funnel was washed out with 2 ml THF. The solution was heated at reflux for 24 h and then cooled. The white precipitate (*S*,*S*-diphenylsulfilimine hydrochloride) was filtered off, and the filtrate was dried by rotary evaporation. The residue was chromatographed (silica gel, 0.5 in. × 20 in., CH_2Cl_2 transitioned to 1:1 CH_2Cl_2–EtOH), and the major eluate of the last fraction was impure **20**, which was re-chromatographed (silica gel, 0.5 in. × 20 in., CH_2Cl_2 transitioned to 1:9 THF–CH_2Cl_2), yielding 0.7019 g (80%) of **20**. The solid residue was recrystallized from CCl_4, followed by vacuum-drying of the filtered white crystalline solid over P_4O_{10}, yielding 0.5777 g (66%) of pure **20** according to ^{1}H and ^{13}C NMR. ^{1}H NMR (acetone-d_6): δ 8.68 (m, 1H, H_8), 8.04 (m, 5H, H_5, Ph-$H_{2,6}$), 7.91–7.96 (m, 2H, $H_{6,7}$), 7.55–7.65 (m, 6H, Ph-$H_{3–5}$); ^{1}H NMR ($CDCl_3$): δ 8.63 (dd, 1H, H_8), 8.04 (dd, 1H, H_5), 7.91 (dd, 4H, Ph-$H_{2,6}$), 7.83 (d, 1H, H_7), 7.80 (d, 1H, H_6), 7.50 (m, 6H, Ph-$H_{3–5}$); ^{13}C NMR (acetone-d_6): δ 161.7 (C_1), 145.0 (C_4), 133.2 (C_7), 132.7 (C_7, Ph-C_4), 130.8 (Ph-$C_{3,5}$), 128.2 (Ph-$C_{2,6}$), 127.1 (C_{4a}), 126.5 (C_5), 126.1 (C_{8a}), 124.9 (C_8).

2.13. Oxidation of 1-chloro-4-(S,S-diphenylsulfilimino)phthalazine (20)

To **20** (0.53 g, 1.46 mmol) in 10 ml 1,2-dichloroethane (DCE) was added *m*-chloroperoxybenzoic acid (Acros Organics, 1.51 g, 8.74 mmol), which had been recrystallized from DCE, and 15 ml DCE. The solution was refluxed for 3.2 h. After storing the product solution at −80 °C and re-warming to melt the solution, insoluble precipitate was filtered off and washed with $CHCl_3$; after vacuum-drying, the solid was identified as *m*-chlorobenzoic acid. The filtrate's solute was chromatographed (silica gel, $CHCl_3$ transitioned to CH_2Cl_2 transitioned to THF), yielding eluates containing diphenyl sulfone (the expected oxidation product of diphenylsulfilimine) and several colored eluates, none of which was consistent with a desired nitrophthalazine according to multinuclear NMR analysis.

3. Results

Our initial approach toward polycyclic energetic products involved a variety of attempts to prepare the generic 3,6-dinitropyridazine system, an unknown structure that is a feature of the proposed targets (**1** and **2**). A potentially attractive transformation to prepare *C*-nitro-substituted heterocycles is the ''nitro-Sandmeyer reaction'' [19], involving diazotization of amino substituents with subsequent displacement of a diazonium leaving group by nitrite ion. An apparently suitable precursor to **1** might be the corresponding tetramine, 1,4,5,8-tetraaminopyridazino[4,5-*d*]pyridazine, which is, however, unknown [20]. Alternatively, attempts (Fig. 3) to prepare a model 3,6-dinitropyridazine, 1,4-dinitrophthalazine (**4**), by diazotization of 1,4-diaminophthalazine (**3**) were unsuccessful, leading only to formation of phthalhydrazide (**5**)—the apparent

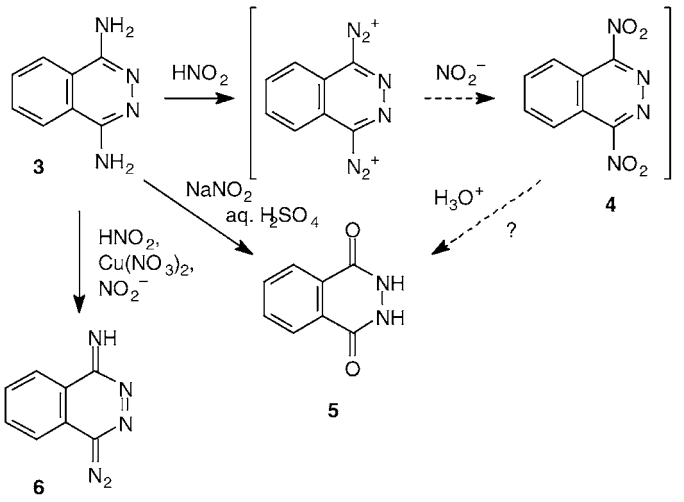

Fig. 3. Attempted nitro-Sandmeyer reaction of 1,4-diaminophthalazine.

product of hydrolytic displacement by water of both diazonium substituents in the initial intermediate or of both nitro substituents in the desired dinitrophthalazine—or, in the presence of copper(II) nitrate in an attempt to stabilize the diazonium intermediate against hydrolysis, a diazo-substituted imine tentatively identified as **6**.

During the course of this work, a novel nitration of an aromatic heterocycle was reported [21] in which isoquinoline was converted to 1-nitroisoquinoline by treatment with potassium nitrite and acetic anhydride in DMSO at ambient temperature, followed by aqueous work-up and extraction with dichloromethane. In an application of this transformation to systems of interest to us (Fig. 4), when phthalazine (**7**) was subjected to these conditions, the isolated product was 2*H*-phthalazin-1-one (**8**). Careful work-up of the crude reaction mixture and analysis of the product by ^{1}H NMR showed a mixture (ca. 4:3) of **8** and a compound identified as 1-nitrophthalazine (**9**) (although the reaction was carried out with a considerable excess of nitrating agent, there was no sign of a second nitration reaction at the four-position, nor of hydrolysis products derived therefrom). This compound showed a sharp singlet at δ 9.7 (assigned to H_4), in addition to a four-proton ABCD pattern in the range

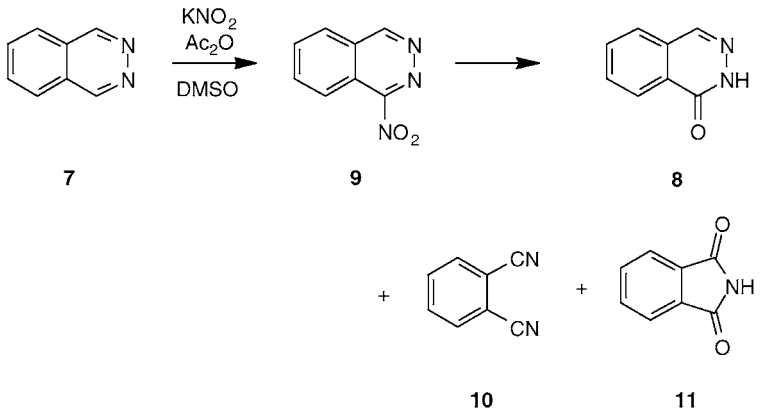

Fig. 4. Activated DMSO-promoted nitration of phthalazine.

δ 8.1–8.3, while GC–MS showed a prominent parent ion at mass 175. It did not survive flash chromatography (chloroform/silica gel), being converted to the phthalazinone (**8**), together with smaller amounts of phthalonitrile (**10**) and phthalimide (**11**) which were not apparent in the crude reaction product. These results show that a nitro group on C_1 of phthalazine is susceptible to hydrolysis both under the conditions of reaction and aqueous work-up, and during chromatography.

Our next approach toward a 3,6-dinitropyridazine was to try direct oxidation of 3,6-diaminopyridazines. The powerful oxidant hypofluorous acid (as the acetonitrile adduct, $HOF{\cdot}CH_3CN$) had been shown to effect clean amino-to-nitro oxidation on aromatic substrates [22,23], so we chose this as an attractive reagent for use in our heteroaromatic systems. ($HOF{\cdot}CH_3CN$ has since been applied to other azine substrates for amino and ring N-oxidation [24].) Oxidation of an attractive precursor, 4,7-diaminoimidazo[4,5-*d*]pyridazine (**12**), was adversely affected by its very limited solubility, being negligible in acetonitrile, the solvent of choice for this oxidation. Attempted overnight oxidation (Fig. 5) of a suspension of **12** in acetonitrile gave a clear yellow solution; however, work-up yielded only ammonium tetrafluoroborate (or an ether solvate). Fluorine came from the oxidant (perhaps via HF by-product), boron from the glassware, and ether from the work-up procedure. The apparent disruption of the imidazo[4,5-*d*]pyridazine skeleton is consistent with the reactivity of other azoles toward strong oxygen transfer reagents [25]. We, therefore, reverted to the

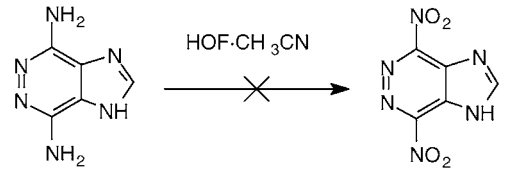

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Fig. 5. Attempted oxidation of 4,7-diaminoimidazo[4,5-*d*]pyridazine.

phthalazine (**3**) as a model for a polycyclic pyridazine.

Oxidation of **3** led to an initially promising result (Fig. 6). The isolated phthalazine derivative was 4-nitro-1(2*H*)-phthalazinone (**13**). This product is consistent with hydrolysis of the desired 1,4-dinitrophthalazine (**4**), perhaps by residual water from the $HOF{\cdot}CH_3CN$ reagent formed from water in acetonitrile or from water by-product from the amino-to-nitro oxidation by $HOF{\cdot}CH_3CN$.

A promising aspect of this result is that thermal properties of this nitrophthalazine (**13**) appear significantly improved over those of the nonnitrated analogue: mp 246 °C for **13** versus mp 189 °C for the commercially available reference compound 1(2*H*)-phthalazinone (**8**). The hydrolytic stability of a possible 1-amino-4-nitrophthalazine intermediate (from stepwise oxidation in this sequence) would be further evidence that the target 1,4-dinitrophthalazine was formed, but was hydrolytically reactive and would need to be prepared by anhydrous means.

To ascertain the hydrolytic stability of a 1-amino-4-nitrophthalazine intermediate during the oxidation, an

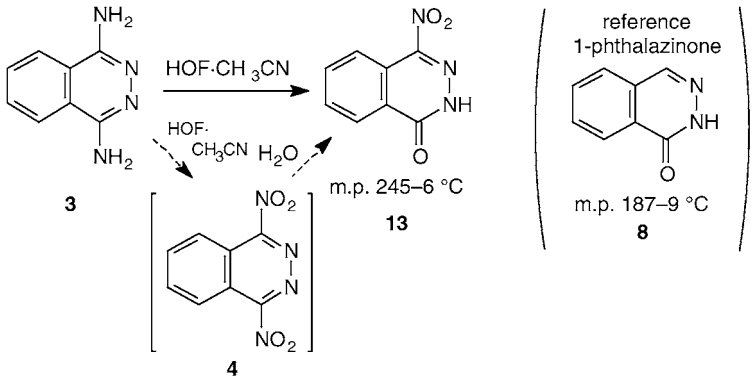

Fig. 6. Hypofluorous acid oxidation of 1,4-diaminophthalazine.

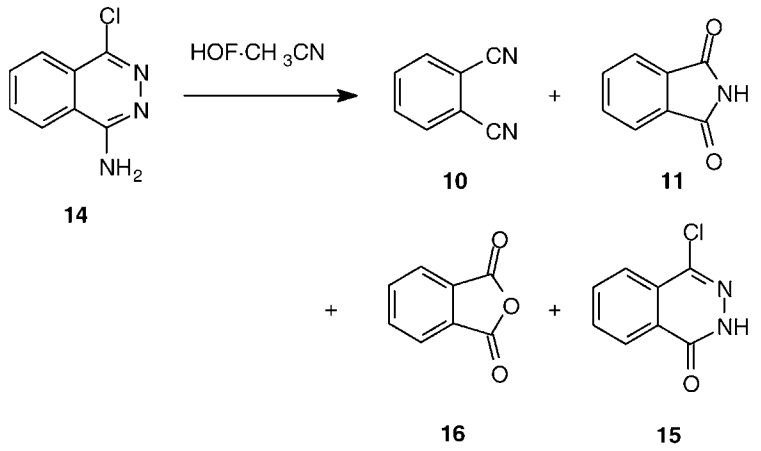

Fig. 7. Hypofluorous acid oxidation of 1-amino-4-chlorophthalazine.

attempt was made to prepare this compound via oxidation of 1-amino-4-chlorophthalazine (**14**) followed by aminolysis of a 1-chloro-4-nitrophthalazine intermediate. Oxidation by $HOF{\cdot}CH_3CN$ unfortunately produced only 4-chloro-1(2*H*)-phthalazinone (**15**) and hydrolysis products from the phthalazine system (Fig. 7), suggesting that in the desired 1-chloro-4-nitrophthalazine, the nitro group is hydrolytically more labile than the chloro substituent.

We next considered alternative oxidants, in case the acidity of $HOF{\cdot}CH_3CN$ contributed to the observed complications of hydrolysis. For example, dimethyldioxirane (generated in situ by the commercial peroxide Oxone® in acetone [26,27]) oxidizes 5-aminoindole to 5-nitroindole without effect on the heterocyclic nitrogen [28]. Oxidation of **3** with dimethyldioxirane in acetone at ambient temperature followed by evaporation of the solvent gave a slurry of yellow solid in water. Freeze drying gave the yellow solid, which was shown by ^1H NMR to be a complex mixture (Fig. 8) containing 4-nitro-2*H*-phthalazin-1-one (**13**). GC–MS showed the mixture also to contain phthalonitrile (**10**), phthalic anhydride (**16**), phthalimide (**11**), 2-cyanobenzamide (**17**), and 3-iminoisoindolin-1-one (**18**); with the exception of **18**, each was isolated by flash chromatography. The oxidation was repeated using a dried solution of dimethyldioxirane in dichloromethane [29], but the only change was a

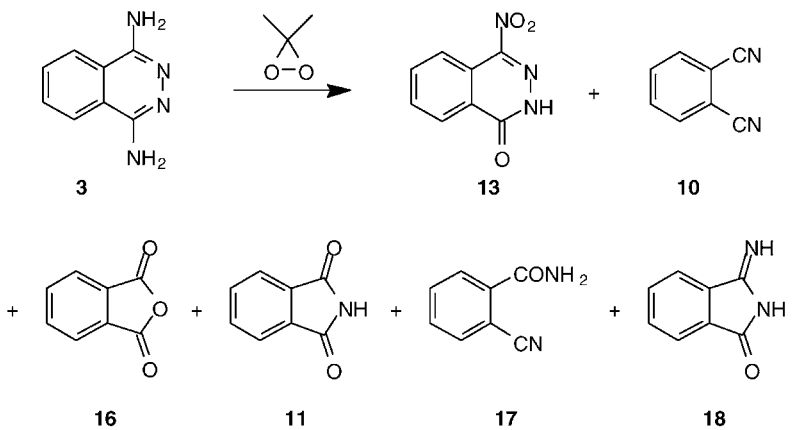

Fig. 8. Dimethyldioxirane oxidation of 1,4-diaminophthalazine.

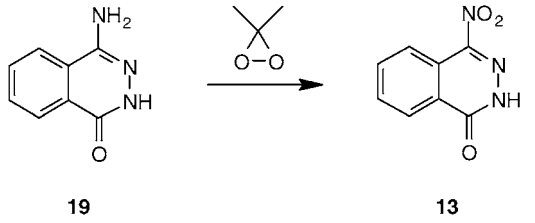

Fig. 9. Dimethyldioxirane oxidation of 4-amino-2*H*-phthalazin-1-one.

minor variation in the product distribution. In neither reaction was any trace of either 1-amino-4-nitrophthalazine or 4-amino-2*H*-phthalazin-1-one detected.

Oxidation of **14** with dimethyldioxirane in dichloromethane gave essentially the same mixture of products as did HOF·CH_3CN. However, oxidation of 4-amino-2*H*-phthalazin-1-one (**19**) with dimethyldioxirane in dichloromethane gave clean conversion to 4-nitro-2*H*-phthalazin-1-one (**13**) in essentially quantitative yield (Fig. 9). Thus, if **19** was formed during oxidation of 1,4-diaminophthalazine (**3**), by hydrolysis of either **3** itself or of 1-amino-4-nitrophthalazine, it was unlikely to survive the conditions of reaction.

A further alternative oxidation method that allows the prospect of amino-to-nitro conversion under anhydrous conditions is via sulfilimines. The nucleophilic substitution of sulfilimines and their salts onto aromatic substrates has been successfully demonstrated in recent years [30]. The resulting aromatic sulfilimine derivatives are furthermore susceptible to N-oxidation by reagents such as *m*-chloroperbenzoic acid to the corresponding nitroaromatic derivatives [18,31]. This route was undertaken to prepare and isolate 1-chloro-4-nitrophthalazine by anhydrous means in order to prove a tentative conclusion about relative lability of the substituents toward nucleophiles such as water. 1-Chloro-4-(*S*,*S*-diphenylsulfilimino)phthalazine (**20**), prepared by reaction of commercial 1,4-dichlorophthalazine with diphenylsulfilimine, was subjected to reaction with *m*-chloroperbenzoic acid (Fig. 10). Products chromatographically isolated from this reaction included *m*-chlorobenzoic acid and diphenyl sulfone, expected by-products from the desired N-oxidation reaction; however, no simple phthalazine product, such as the desired 1-chloro-4-nitrophthalazine, could be identified or isolated. This result is further consistent with the hypothesized high chemical reactivity toward nucleophiles of electronegatively 6-substituted 3-nitropyridazines.

4. Discussion

Although attempts to prepare the 3,6-dinitropyridazine substructure appear to be unprecedented, our observations about hydrolytic instability of various electronegatively 3,6-disubstituted pyridazines (including 1-chloro-4-nitrophthalazine and 1,4-dinitrophthalazine, **4**) prompted a thorough review of the known nucleophilic substitution chemistry of certain aromatic systems, particularly activated (polynitro) aromatics and especially activated azines, of which the nitropyridazines are an example.

The literature of activated azines [32,33]—including the new examples of reactivity observed here—shows that polynitroazines (pyridines, pyridazines, pyrimidines, pyrazines) tend to be even more susceptible to nucleophilic attack than similar carbocycles. Nitroazines may be significantly more susceptible to nucleophilic attack than derivatives based on other leaving groups, including halides [34].

In nitroazines, a ring nitrogen imparts an activating effect (with *ortho*-, *para*-direction) on a nitro leaving group similar to that of a *C*-nitro substituent. Based on reactivities of nitropyridazine *N*-oxides, the relative

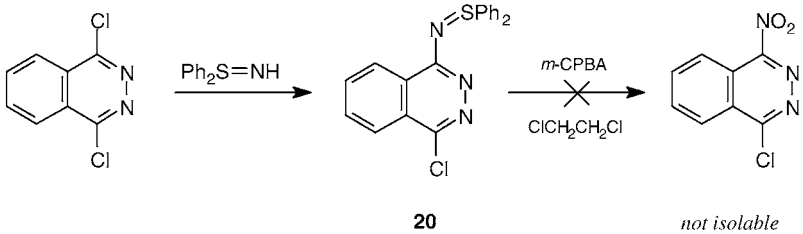

Fig. 10. Synthesis and attempted N-oxidation of 1-chloro-4-(*S*,*S*-diphenylsulfilimino)phthalazine.

activating effects of sites in the pyridazine 1-oxide structure are 5-(*para* to N) > 4-(*para* to N → O) > 3-(*ortho* to N) [35]. Although a few 3-alkoxy-4,6-dinitropyridazine 1-oxides have been prepared [36,37], these are not comparable models for the activating effects present in the 3,6-dinitropyridazine substructures we desired. Some of the 3-alkoxy-4,6-dinitropyridazine 1-oxides have been subjected to substitution by strong nucleophiles under forcing conditions; under basic conditions, the 3-alkoxy group [38,39] or the 6-nitro group [39] is displaced, while under acidic conditions, the 6-nitro group is displaced [39]. The 4,6-dinitropyridazine 1-oxides stabilized by the 3-alkoxy substituent posed no significant problem in their isolation. In contrast, our desired 3,6-dinitropyridazines would be *para*-activated by a *C*-nitro substituent as well as *ortho*-activated by an azine nitrogen. Under acidic conditions, this might be a protonated nitrogen, possibly further activating an *ortho*-nitro leaving group.

A few examples of theoretically attractive energetic target compounds have established a database of nucleophilic reactivity in superlatively activated nitroaromatics. For example, hexanitrobenzene can be isolated [40], but proved to be too susceptible to nucleophilic attack—such as by environmental moisture—to be useful as a deployed ingredient (although the intrinsic unimolecular instabilities of hexanitrobenzene and decanitrobiphenyl are believed to be due to nitro-to-nitrite rearrangement [41], that alternative decomposition mechanism did not preclude its high sensitivity toward nucleophiles, including water and ammonia [42]).

In comparison, another "target compound" that received significant attention in the past was 2,4,6-trinitro-1,3,5-triazine, whose interest as one example of a class of attractive, but synthetically intractable prospective ingredients led to this observation [43]: "over the past 20 years we have attempted the synthesis of these compounds by conventional techniques without success." A failure to appreciate the history of its synthetic problems due to the target's inherent chemical reactivity more recently produced this suggestion [44]: "we have designed and characterized theoretically 2,4,6-trinitro-1,3,5-triazine, and we encourage synthesis of it and its derivatives". However, only nitro-*sym*-triazines with electron-donating substituents (amino) have been successfully prepared, such as 2,4-bis(dialkylamino)-6-nitro-1,3,5-triazines formed via ozonation of 2,4-bis(dialkylamino)-6-hydroxylamino-1,3,5-triazines [45].

Another intractable class has proven to be highly electronegatively substituted *sym*-tetrazines, 3,6-dinitro-*sym*-tetrazine (**21**) in particular (Fig. 11).

Thus, replacing even three *C*-nitro components of a hexa substituted activated aromatic with azine nitrogens appears to make the product intractable. This target structure, therefore, offered another valuable example in the database of potential targets' chemical reactivities. Our current results further define the scope of practical highly activated energetic heterocycles, showing that replacement of even two *C*-nitro components by azine nitrogens (in the absence of stabilizing electron-donating substituents) makes the 3,6-dinitropyridazine substructure at least impractical if not intractable.

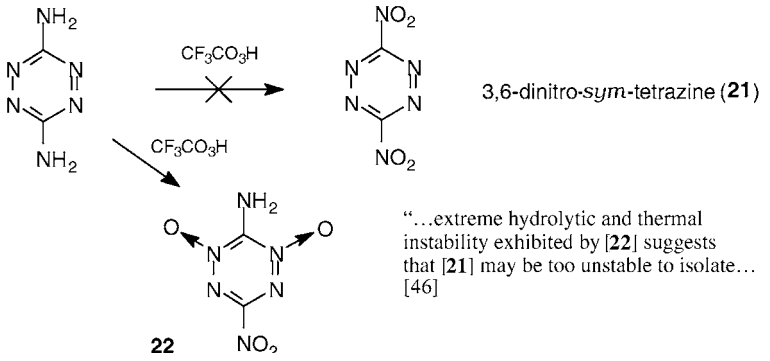

Fig. 11. Oxidation of 3,6-diamino-*sym*-tetrazine [46].

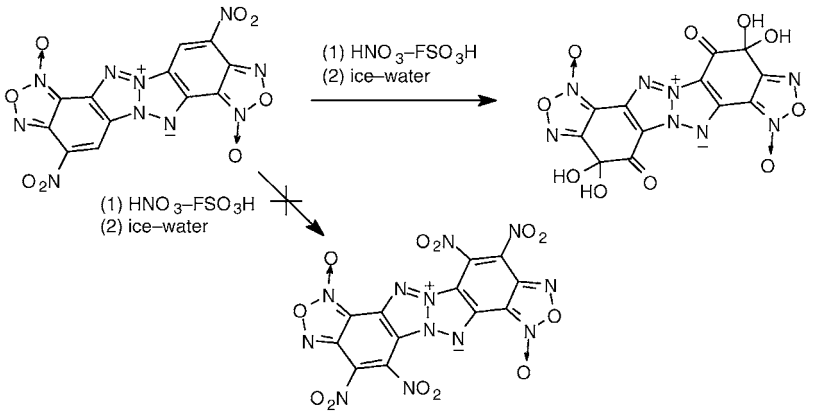

Fig. 12. Attempted nitration of 4,11-dinitro-14*H*-[1,2,5]oxadiazolo[3,4-*e*][1,2,5]oxadiazolo[3′,4′:4,5]benzotriazolo[2,1-*a*]benzotriazol-6-ium inner salt 1,8-dioxide [47].

Another recent example of inordinate nucleophilic reactivity was discovered in a failed attempt to produce a new, computationally superior derivative of a ''tetraazapentalene'' (Fig. 12) [47].

Reported precedents seem to suggest that the intended bis(*ortho*-dinitrobenzofuroxan) target compound would likely have problems with nucleophilic susceptibility that it ultimately exhibited. For example, 1,4-dinitrobenzofurazan (activated as a *para*-dinitroaromatic) shows facile lability of a nitro substituent (Fig. 13) [48–51].

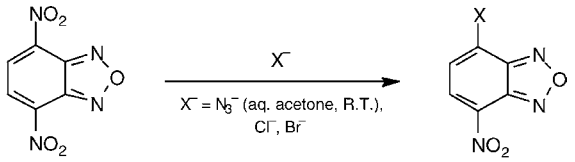

Fig. 13. Nucleophilic displacements of nitro in 1,4-dinitrobenzofurazan [48–51].

Even ''classical'' polynitroaromatics have been observed to undergo nucleophilic reactions that were unexpected by some researchers, when the compounds were subjected to attempts to modify their nuclear substitution [52]: ''although it is thermally very stable and explosively insensitive, 2,4,8,10-tetranitrobenzotriazolo[2,1-*a*]benzotriazole (TACOT) is surprisingly susceptible to a variety of nucleophilic substitution reactions'' (Fig. 14).

For comparison, however, an analogue of isomeric Y-TACOT activated by one azine nitrogen in each terminal ring—2,4,8,10-tetranitro-5*H*-pyrido[3″,2″:4′,5′][1,2,3]triazolo[1′,2′:1,2][1,2,3]triazolo[5,4-b]-pyridin-6-ium inner salt—can be isolated [53], avoiding the cumulative activating effects of *ortho*-dinitro adjacent to the furoxan ring and the ''tetraazapentalene'' core encountered in the previous example (Fig. 12).

The nucleophilic susceptibility that renders superlatively nitrated heterocycles impractical is not limited to aromatics. A past target compound in the US Navy

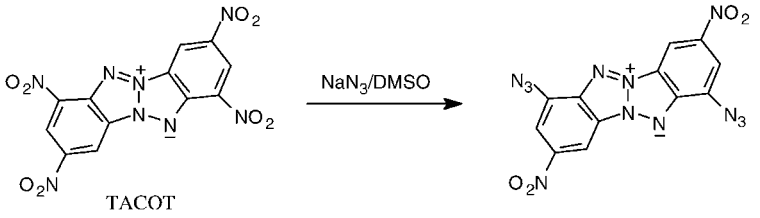

Fig. 14. Nucleophilic displacement of nitro substituents in Z-TACOT [52].

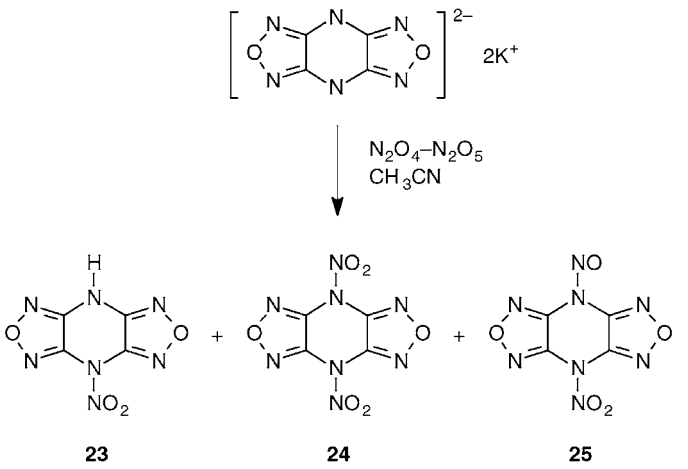

Fig. 15. Preparation of 4-nitro-4*H*,8*H*-difurazano[3,4-*b*:3′,4′-*e*]pyrazine derivatives [55].

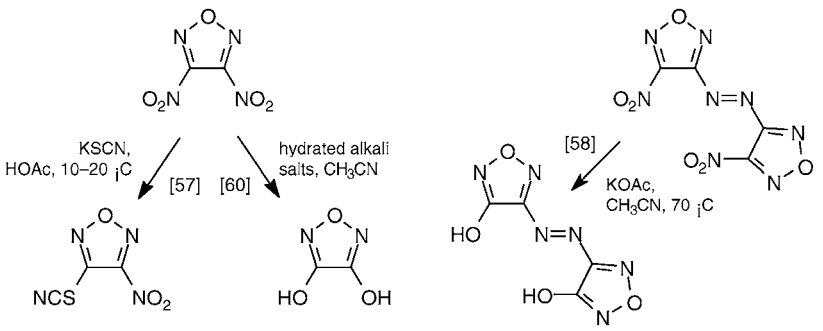

Fig. 16. Nucleophilic displacement of nitro in various nitrofurazans [56–60].

[54], 4,8-dinitro-4*H*,8*H*-difurazano[3,4-b:3′,4′-*e*]pyrazine (**24**), has been recently reported by Russian researchers (Fig. 15), who make the following observation [55]: ''unfortunately, we failed to examine *N*-nitro- and *N*-nitroso derivatives (**23–25**) in more detail due to their low hydrolytic stability''.

The nucleophilic susceptibility of 4,8-dinitro-4*H*,8*H*-difurazano[3,4-b:3′,4′-*e*]pyrazine (**24**) likely follows from the similar reactivity of the general class of electronegatively 3,4-disubstituted furazans (''electronegatively'' meaning substituents of electronegativity similar to or greater than nitramino, including nitro), and Sheremetev and coworkers have provided many examples of such susceptibility [56–60]. For example, several nitrofurazans have exhibited facile nucleophilic reactivities resulting in nitro-group displacement (Fig. 16).

5. Conclusions

An important conclusion has been drawn from our several unsuccessful attempts to prepare certain polynitroazines, especially model 3,6-dinitropyridazines, as well as from a retrospection of the chemistry of similar classes of compounds. Although some target compounds have potentially favorable performance properties and might appear to be synthetically tractable, the nucleophilic reactivity of some structures toward environmental contaminants, such as water,

limits their practical value as energetic ingredients. The nature and extent of this reactivity appear predictable a priori in many cases by a thoughtful review of precedent chemistry of structurally related compounds as well as of fundamental principles dictating the effects of certain structural components on this reactivity.

The following are some important lessons applicable to future choices of practical new energetic materials targets.

- It is clear that the intractability of certain polynitroazine target compounds unavoidably arises from their extraordinary susceptibility to incidental nucleophiles such as water (more so than *C*-polynitrocarbocycles).
- The 3,6-dinitropyridazine substructure is probably too chemically reactive (toward nucleophiles, including water) to be a useful ingredient unless stabilized by electron donation. Examples of this stabilization effect are apparent in the 2,4-bis(dialkylamino)-6-nitro-1,3,5-triazines [45] mentioned above and the aminonitroheterocyclic *N*-oxides [5], another recent example being 2,6-diamino-3,5-dinitropyrazine 1-oxide (LLM-105) [61]. Annelated imidazole or triazole (but not furazan or furoxan) rings may confer this stability. Thus, **2** may still be a reasonable target, although oxidation methods must be employed that do not disrupt the azolopyridazine skeleton.
- Computational methods have been investigated by others for estimating, a priori, nucleophilic reactivities of specific sites in aromatic (including heteroaromatic) molecules [62,63].
- Our conclusions and observations about reactivity of polynitroazines should have implications toward future choices of target compounds.
- Certain nitrogen heterocycles, especially fused polycyclic systems, would still be valuable for imparting good thermochemical and physical properties, not just to replace carbon for oxygen balance, i.e. not high-nitrogen for high-nitrogen's sake.

Acknowledgements

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