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Synthesis of 3,3-bis(difluoramino)octahydro-1,5,7,7-tetranitro-1,5-diazocine (TNFX), a diversified energetic heterocycle

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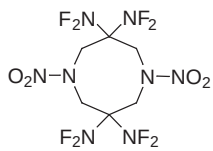
Abstract—The syntheses of new 3,3-dinitro derivatives of the 1,5-diazocine ring system are described. Highly deactivated precursor ketones hexahydro-7,7-dinitro-1,5-bis(2- and 4-nitrobenzenesulfonyl)-1,5-diazocin-3(2*H*)-ones (**18**) have been difluoraminated to the corresponding *gem*-bis(difluoramino)diazocines (**19**). The 1,5-bis(4-nitrobenzenesulfonyl)diazocine derivative undergoes *N*-nitrolysis with the protonitronium reagent formed in the nitric acid–trifluoromethanesulfonic acid–antimony pentafluoride system to produce 3,3-bis(difluoramino)octahydro-1,5,7,7-tetranitro-1,5-diazocine **2** (TNFX), containing nitramine, *gem*-dinitro, and *gem*-bis(difluoramino) structural components.

As first proposed by Zheng et al.[1] and by Baum and co-workers,[2] *gem*-bis(difluoramino)-substituted heterocyclic nitramines, such as structures **1** and **2**, are of interest because of their potentially high density, high energy, and superior properties as solid propellant oxidizers.[3] A superior synthesis of compound **1** (HNFX) was recently reported,[4,5] and, in this communication, we report the first synthesis of a *gem*-dinitro-substituted analog, **2** (TNFX). Although the symmetric analogs, HNFX and octahydro-1,3,3,5,7,7-hexanitro-1,5-diazocine,[6] have been reported, the asymmetric derivative **2**, incorporating both difluoramino and *C*-nitro substituents in addition to nitramine, may offer potentially superior propellant performance in certain formulations, based either on arguments involving qualitative chemical features of the ingredient[2] or on computational estimates of its thermodynamic properties.[7] Of course, the asymmetric functionalization of the C^3 and C^7 carbons of the 1,5-diazocine system required development of a judicious protection strategy, as we describe here.



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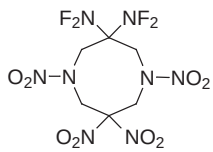

2

The introduction of two geminal difluoramino groups generally requires strongly acidic conditions (e.g. anhydrous H_2SO_4) starting from precursor ketones or certain *gem*-bromonitro intermediates.[8] This severe synthetic constraint limits the types of functional groups that will survive this treatment. In this report, we detail two approaches affording important new *gem*-dinitro-1,5-diazocine derivatives that have been successfully developed as difluoramination precursors to **2**.

With a view toward subsequent hydrolysis of the *O*-acetyl group to the alcohol followed by oxidation to the corresponding ketone, several unsuccessful attempts to prepare the analogous *gem*-dinitro compound from oxime **3** were carried out. Oxime **3**, available from on-going related studies, was made by ozonolysis of 3-acetoxy-1,5-diacetyloctahydro-7-methylene-1,5-diazocine[9] followed by oximation of the intermediate ketone.

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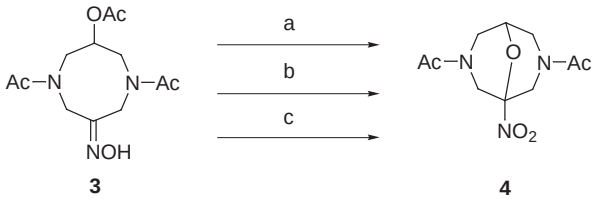
As outlined in Scheme 1, the conventional oxidation methods[10] for the conversion of oximes to the *gem*-dinitro group that were investigated included ~100% HNO_3, *N*-bromosuccinimide and *m*-chloroperbenzoic acid. In each case transannular bridging intervened and only the 3,7-diacetyl-5-nitro-9-oxa-3,7-diazabicyclo-[3.3.1]nonane derivative **4** was obtained.



3 **4**

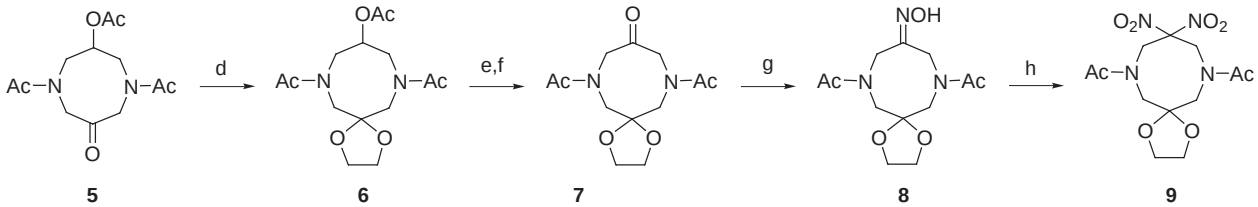
Scheme 1. Reagents and conditions (yield): (a) HNO_3, NH_4NO_3, urea, CH_2Cl_2, reflux (29%); (b) NBS, $NaHCO_3$, dioxane–H_2O, rt (40%); (c) *m*-CPBA, Na_2HPO_4, urea, MeCN, reflux (49%).

These findings substantiate previously observed difficulties in this eight-membered ring system.[2b,11] The marked propensity for transannular bridging to occur leads to stable 9-oxa-3,7-diazabicyclo[3.3.1]nonanes.[4,11c] Thus, satisfactory methodologies that circumvent bridging are needed for the preparation of asymmetric saturated *gem*-dinitro-1,5-diazocine precursors that will undergo difluoramination reactions.

In the first approach (Scheme 2), ketone **5**, the precursor to oxime **3**, was subjected to the sequence of transformations shown, to arrive at oxime **8**. 1,3-Dioxolane protection of the keto function in the latter oxime was employed to avoid transannular reactions and, under these conditions, smooth conversion of the oxime **8** to the corresponding *gem*-dinitro compound **9** took place. However, under a variety of conditions, deprotection of **9** to the corresponding ketone proved impossible in our hands.

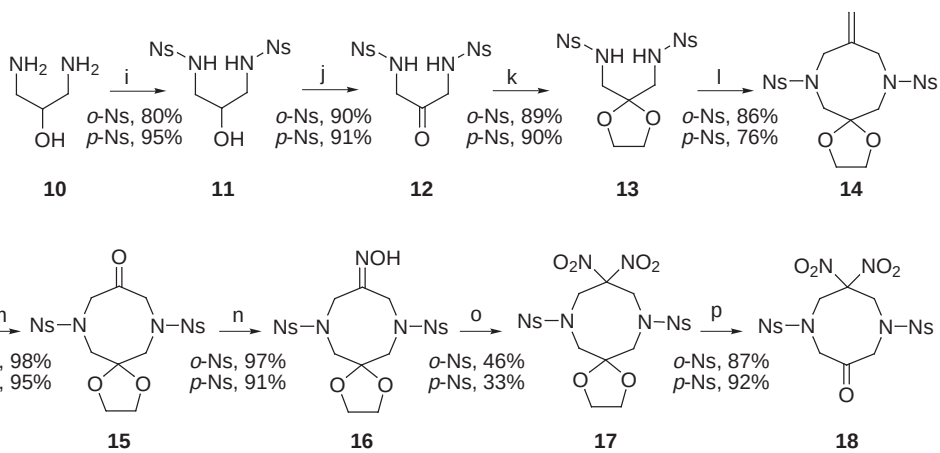
In the alternative strategy, outlined in Scheme 3, a commercially available starting material, 1,3-diaminopropan-2-ol (**10**),[12] was *N*-protected by *o*-nitrobenzenesulfonyl or *p*-nitrobenzenesulfonyl groups, followed by chromic acid oxidation to ketone **12**, and the latter carbonyl function was protected through reaction with ethylene glycol to form its 1,3-dioxolane derivative **13**. Cycloalkylation of **13** with methallyl dibromide[13] followed by ozonolysis of the readily formed *exo*-methylene-1,5-diazocine intermediate **14** afforded the monoprotected 1,5-diazocin-3(2*H*)-one **15**. Oximation followed by HNO_3 oxidation of **16** afforded the *gem*-dinitro derivative **17**, and hydrolysis of the latter produced the desired hexahydro-7,7-dinitro-1,5-diazocin-3(2*H*)-one derivative **18**.

As shown in Scheme 4, the *gem*-bis(difluoramino) derivative **19** was obtained by a modified difluoramination[4] of ketone **18** with difluoramine–



5 **6** **7** **8** **9**

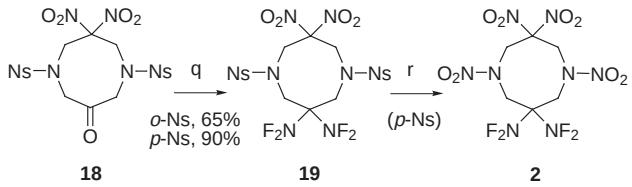
Scheme 2. Reagents and conditions (yield): (d) ethylene glycol, *p*-TsOH, benzene (69%); (e) K_2CO_3, MeOH–H_2O, rt (86%); (f) Jones reagent, 0°C (69%); (g) $NH_2OH{\cdot}HCl$, NaOAc, MeOH, reflux (97%); (h) HNO_3, NH_4NO_3, urea (36%).



10 **11** **12** **13** **14**

15 **16** **17** **18**

Scheme 3. Reagents and conditions: (i) 2- or 4-nitrobenzenesulfonyl chloride, THF–H_2O, K_2CO_3, rt; (j) CrO_3, H_2SO_4, acetone, rt; (k) ethylene glycol, *p*-TsOH, toluene; (l) $CH_2{=}C(CH_2Br)_2$, K_2CO_3, acetone, reflux; (m) (1) O_3, CH_2Cl_2, −78°C, (2) Me_2S; (n) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, reflux; (o) HNO_3, NH_4NO_3, urea; (p) conc. H_2SO_4, rt.



Scheme 4. Reagents and conditions: (q) HNF_2–F_2NSO_3H–H_2SO_4–$CFCl_3$, −15°C; (r) HNO_3–CF_3SO_3H–SbF_5, rt.

difluorosulfamic acid in sulfuric acid. *N*-Nitrolysis of dinosyldiazocine **19** proved remarkably difficult. This could be anticipated for reasons elaborated in the previous report on the synthesis of HNFX by *N*-nitrolysis of a dinosyldiazocine precursor.[5] Sterically hindered and electronegatively substituted protected amines are especially resistant to *N*-nitrolysis, and diazocine **19** incorporates both of these features. A β,β-bis(difluoramino)alkyl plus a β,β-dinitroalkyl substituent impart even more electron-withdrawing character than the two bis(difluoramino)alkyl substituents of the HNFX precursor; for example, Taft's $\sigma^*(NO_2)=4.72$[14] versus $\sigma^*(NF_2)\approx 4.13$.[15] Thus, even extended nitrolysis (14 days) of **19** with the system nitric acid–trifluoromethanesulfonic acid, a source of the strongly nitrating species protonitronium (NO_2H^{2+}),[16] at elevated temperature (55°C) produced predominantly only the corresponding mononitramine. Only by addition of a strong Lewis acid, SbF_5, to the nitrating system—in order to generate a higher concentration of protonitronium[17]—followed by further nitrolysis (2 days) was **2** (TNFX) formed by a clean conversion as the major product, although thus far in an unquantified yield. Therefore, the second nitrolysis step of Scheme 4 may well be the most difficult *N*-nitrolysis ever successfully achieved, since the second nitrolysis step producing HNFX was complete in HNO_3–HOTf (without Lewis acid) in only ~40 h.[5] Also, only the *p*-nosyl isomer of **19** was useful for formation of TNFX because the *o*-nosyl derivative underwent *para*-C-nitration, and the resulting 2,4-dinitrobenzenesulfonyl derivative was not effectively nitrolyzed. The product (**2**) was identified by multinuclear NMR spectroscopy as well as X-ray crystallography. **CAUTION**: TNFX (**2**) is expected to be a relatively sensitive high explosive and should be prepared and handled only by qualified personnel!

In summary, the first successful synthesis of 3,3-bis(difluoramino)octahydro-1,5,7,7-tetranitro-1,5-diazocine **2** (TNFX) has been realized. All compounds and intermediates described here have been fully characterized (^1H, ^{13}C NMR, HRMS, and/or X-ray crystallography), and a complete report of the synthetic details and interesting crystallographic properties of TNFX will be published elsewhere.

Acknowledgements

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