Difluoramination of Heterocyclic Ketones: Control of Microbasicity

Robert D. Chapman,*[,1a,b] Mark F. Welker,[1b] and Charles B. Kreutzberger[1b]

Research and Technology Group (Code 4B2200D), Naval Air Warfare Center Weapons Division, China Lake, California 93555, and TPL, Inc., 3921 Academy Parkway North NE, Albuquerque, New Mexico 87109

Received October 6, 1997

Difluoramination of a tetrahydro-1,5-diazocine-3,7(2*H*,6*H*)-dione to the corresponding 3,3,7,7-tetrakis(difluoramino)diazocine was achieved by a judicious choice of protecting group. Arenesulfonyl protecting groups for the diazocine nitrogens proved superior to acetyl during the slow disruption of the transannular bridge in 9-oxa-3,7-diazabicyclo[3.3.1]nonane intermediates by difluorosulfamic acid. While a 1,5-ditosyl derivative failed to proceed beyond the product of addition of difluoramine to one ketone carbonyl (hemiaminal **6**), the use of 4-nitrobenzenesulfonyl as the protecting groups lowered the nitrogens' basicities below that of the oxygen site in the dione and intermediates, allowing the reaction to proceed to a *gem*-bis(difluoramino)diazocine product (**11**). A safer procedure for handling difluoramine is described.

Introduction and Background

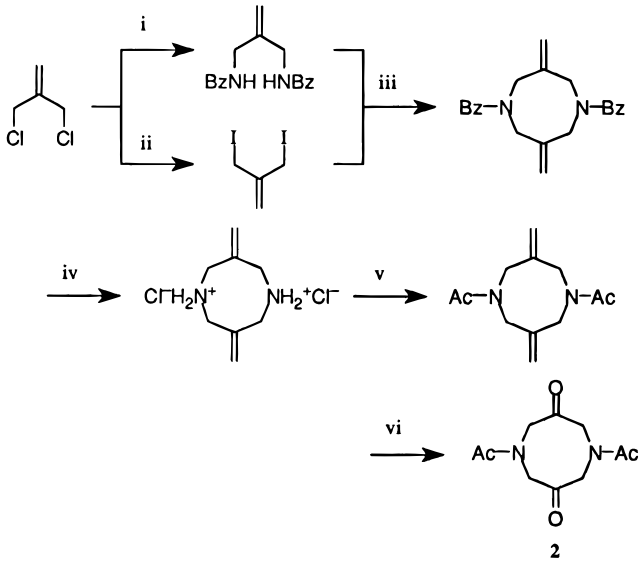
A new class of compounds was proposed a few years ago independently by Zheng et al.[2] and by Baum and coworkers[3] as potentially superior explosives or solid propellant oxidizers: *gem*-bis(difluoramino)-substituted heterocyclic nitramines. The example of this class that has received the most attention in the United States is 3,3,7,7-tetrakis(difluoramino)octahydro-1,5-dinitro-1,5-diazocine (HNFX, **1**).[4] The first reported example of a

1

tetrahydro-1,5-diazocine-3,7(2*H*,6*H*)-dione was prepared as a potential intermediate toward **1** by ozonation of a tetrahydro-3,7-bis(methylene)-1,5-diazocine, formed by cyclization between a methallyl dihalide and an alkylamine followed by dealkylation and protection (Scheme 1).[3]

Attempts by one of us (R.D.C.) to convert 1,5-diacetyltetrahydro-1,5-diazocine-3,7(2*H*,6*H*)-dione (**2**) to the corresponding 3,3,7,7-tetrakis(difluoramino)diazocine led to facile addition of one difluoramine to one carbonyl site,[5] but prolonged reaction to disrupt the stable transannular bridge resulted only in degradation of the organic substrate (Scheme 2). Using nitro as an alternative N-protecting group allowed further progress of the sequence to **1**. Thus, nitrolysis of *trans*-3,7-diacetyl-5-(difluoramino)-9-oxa-3,7-diazabicyclo[3.3.1]nonan-1-ol produced an unprecedented nitrate ester of a hemiacetal, 5-(difluoramino)-3,7-dinitro-9-oxa-3,7-diazabicyclo[3.3.1]non-1-yl nitrate,

Scheme 1[a]



[a] Reagents and conditions (yield):[3] (i) $PhCH_2NH_2$, 60 °C (93%); (ii) NaI, acetone (86%); (iii) K_2CO_3, EtOH, reflux (77%); (iv) (1) $CH_3CHClOCOCl$, $ClCH_2CH_2Cl$, reflux, (2) CH_3OH, reflux (90%); (v) $(CH_3CO)_2O$, aq K_2CO_3 (100%); (vi) (1) O_3, CH_3OH, −78 °C (2) Me_2S (56%).

* E-mail: Robert_Chapman@imdgw.chinalake.navy.mil. Phone (760) 939-1663. FAX (760) 939-1617.

(1) (a) Present affiliation: Naval Air Warfare Center Weapons Division. (b) TPL, Inc.

(2) Zheng, Y.; Huang, T.; Zhang, M.; Wang, X. *International Symposium on Pyrotechnics and Explosives [Proceedings]*, Beijing, China, Oct 1987; China Academic Publishers: Beijing, 1987; pp 234−240.

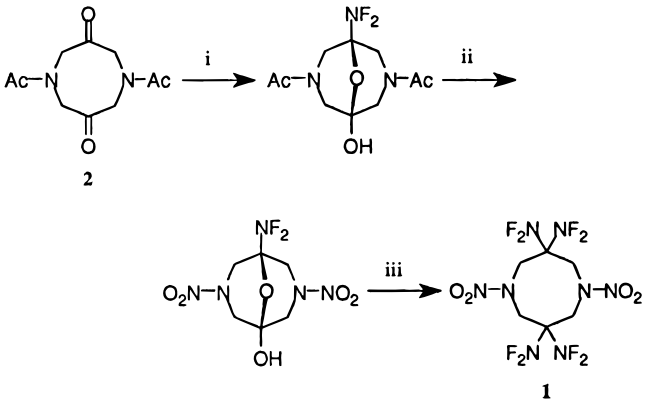
(3) Chapman, R. D.; Archibald, T. G.; Baum, K. *Research in Energetic Compounds*; Report ONR-7-1 (Interim); Fluorochem Inc.: Azusa, CA, Oct 1989; DIALOG Accession Number 1429659; NTIS Accession Number AD-A214106; available from the National Technical Information Service, U.S. Department of Commerce, Springfield, VA 22161.

(4) Miller, R. S. *Mater. Res. Soc. Symp. Proc.* **1996**, *418*, 3.

(5) *Research in Energetic Compounds*; Report ONR-7-1, final report to the Office of Naval Research (Arlington, VA) on Contract N00014-88-C-0536; Fluorochem Inc.: Azusa, CA, Sep 1991. Described by Baum et al.: Baum, K.; Trivedi, N. J.; Lovato, J. M.; Iyer, V. K. *Novel Approaches to the Synthesis of Fluorodinitromethane and Fluorodinitroethanol*; Report NRO-1-1; Fluorochem Inc.: Azusa, CA, Aug 1993; *Chem. Abstr.* **1995**, *123*, 339081*r*. NTIS Accession Number AD-A269158; available from the National Technical Information Service, U.S. Department of Commerce, Springfield, VA 22161.

S0022-3263(97)01839-2 CCC: $15.00
Published on Web 02/14/1998

Scheme 2[a]



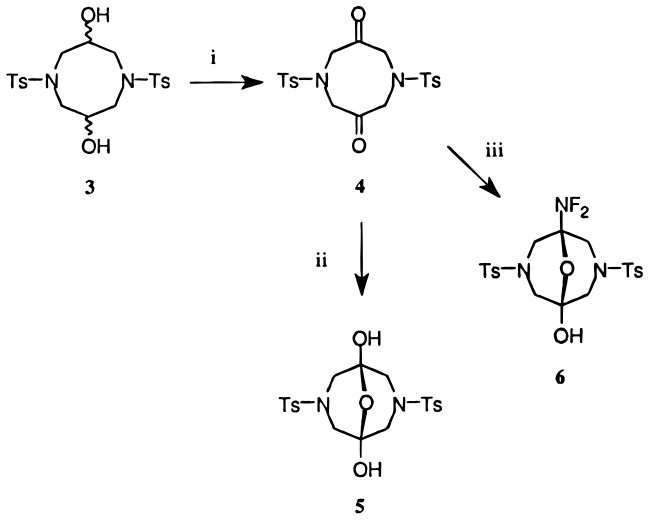
[a] Reagents and conditions (yield):[5] (i) HNF_2, H_2SO_4 (53%); (ii) (1) $HNO_3-(CF_3CO)_2O$, CH_2Cl_2, −27 °C, (2) NO_2 elimination (50%); (iii) $F_2NSO_3H-H_2SO_4$, −23 °C (∼1%).

which underwent slow spontaneous elimination of NO_2 after workup. Difluoramination of the nitro-protected diazocine under conventional conditions allowed the formation of desired nitramine **1**, but the yield was quite poor (∼1% in the last step) due to the known instability of nitramines in strong nonnitrating acids.[6]

Results and Discussion

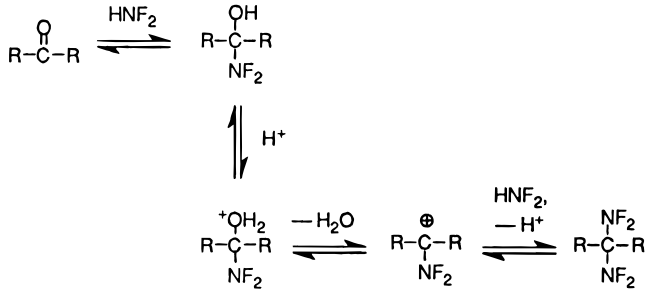
As a modified approach, we undertook the use of *N*-arenesulfonyl derivatives as yet another protected form of tetrahydro-1,5-diazocine-3,7(2*H*,6*H*)-dione expected to be more stable under the conditions of difluoramination in difluorosulfamic acid−sulfuric acid. Some alkanesulfonyl-[7] and arenesulfonyl-protected[8] amines are nitrolyzable to the corresponding nitramines. In our first system, octahydro-1,5-bis(4-methylbenzenesulfonyl)-1,5-diazocine-3,7-diol ("ditosyldiazocinediol", **3**) was prepared according to the method of Paudler et al.[9] The diol was oxidized to the corresponding dione by Swern oxidation, analogous to the oxidation of 1,5-cyclooctanediol;[10] dione **4** was isolated upon workup as the corresponding bis(hemiacetal) (**5**); hemiacetal **5** is readily dehydrated to dione **4**.[11] Difluoramination of **4** or of **5** produced a result similar to the initial finding in the reaction with the 1,5-diacetyl derivative (**2**): facile addition of one difluoramine occurred at the site of one carbonyl or hemiacetal equivalent, producing a transannularly bridged hemiacetal−hemiaminal (**6** in Scheme 3). Despite treatment with difluorosulfamic acid under a variety of conditions, including prolonged reaction for several days, there was no distinct progress toward a 3,3,7,7-tetrakis(difluoramino)diazocine. The structural nature of (difluoramino)-diazocines can be diagnosed by ^{19}F NMR: chemical shifts

Scheme 3[a]



[a] Reagents and conditions: (i) (1) $(COCl)_2$−DMSO, CH_2Cl_2, −78 °C, (2) Et_3N; (ii) aq HCl−acetone, reflux; (iii) $F_2NSO_3H-H_2SO_4$/$CFCl_3$, −10 °C, 3 h.

Scheme 4. Mechanism of Difluoramination of Ketones



in the range of δ 18−25 are characteristic of internal mono(difluoramino)alkanes (e.g., **6**), while internal *gem*-bis(difluoramino) derivatives exhibit absorptions in the range of δ 27−33.[12] The great propensity of eight-membered-ring systems to transannularly bridge[3,13] leads here to the stable 9-oxa-3,7-diazabicyclo[3.3.1]nonanes. Some deactivation toward further difluoramination is therefore a reasonable expectation; however, the complete absence of the desired final product suggested a fundamental flaw in this system.

We reasoned that this flaw involved the competing sites of microbasicity within dione hemiacetal **5** and intermediate **6**. The process of difluoramination leading to *gem*-bis(difluoramino)alkanes proceeds as in Scheme 4.[14] An intermediate *N*,*N*-difluorohemiaminal (e.g., **6**) must be capable of generating a difluoramino-substituted carbocation to further alkylate another difluoramine molecule. Upon considering simpler models of structural

(6) (a) Holstead, C.; Lamberton, A. H. *J. Chem. Soc.* **1952**, 1886. (b) Semel, S.; Laccetti, M. A.; Roth, M. *Anal. Chem.* **1959**, *31*, 1050. (c) Šimeček, J. *Anal. Chem.* **1961**, *33*, 260.

(7) (a) Franchimont, A. P. N.; Klobbie, E. A. *Rec. Trav. Chim.* **1886**, *5*, 274. (b) Robson, J. H.; Reinhart, J. *J. Am. Chem. Soc.* **1955**, *77*, 2453.

(8) (a) van Romburgh, P. *Rec. Trav. Chim.* **1884**, *3*, 7. (b) Axenrod, T.; Watnick, C.; Yazdekhasti, H.; Dave, P. R. *J. Org. Chem.* **1995**, *60*, 1959.

(9) (a) Paudler, W. W.; Gapski, G. R.; Barton, J. M. *J. Org. Chem.* **1966**, *31*, 277. (b) Paudler, W. W.; Zeiler, A. G. *J. Org. Chem.* **1967**, *32*, 2425.

(10) Schreiber, S. L.; Smith, D. B.; Schulte, G. *J. Org. Chem.* **1989**, *54*, 5994.

(11) Dave, P. R.; Forohar, F.; Axenrod, T.; Das, K. K.; Qi, L.; Watnick, C.; Yazdekhasti, H. *J. Org. Chem.* **1996**, *61*, 8897.

(12) (a) Jones, K.; Mooney, E. F. *Annu. Rep. NMR Spectrosc.* **1970**, *3*, 261. (b) Emsley, J. W.; Phillips, L. *Prog. Nucl. Magn. Reson. Spectrosc.* **1971**, *7*, 1.

(13) (a) Paquette, L. A.; Fischer, J. W.; Engel, P. *J. Org. Chem.* **1985**, *50*, 2524. (b) Waykole, L. M.; Shen, C.-C.; Paquette, L. A. *J. Org. Chem.* **1988**, *53*, 4969. (c) Perlmutter, H. D. *Adv. Heterocycl. Chem.* **1989**, *46*, 1. (d) Shen, C.-C.; Paquette, L. A. *J. Org. Chem.* **1989**, *54*, 3324. (e) Haufe, G.; Alvernne, G.; Laurent, A. *J. Fluorine Chem.* **1990**, *46*, 83. (f) Zajac, W. W., Jr.; Speier, G. J.; Buzby, J. H.; Walters, T. R. *J. Org. Chem.* **1996**, *61*, 3545.

(14) (a) Baum, K. *J. Am. Chem. Soc.* **1968**, *90*, 7083. (b) Graham, W. H.; Freeman, J. P. *J. Org. Chem.* **1969**, *34*, 2589. (c) Fokin, A. V.; Kosyrev, Yu. M.; Makarov, V. A.; Novoselov, N. P. *Doklady Chem. (Engl. Transl.)* **1969**, *186*, 350.

components of the 1,5-ditosyldiazocinedione system, we elucidated the mechanistic problem. Typical ketones have basicities producing an acid dissociation constant of $pK_a \sim -7$ for the conjugate acid.[15] Tosylamide itself has a $pK_a \approx -6.37$ for the conjugate acid; *N*,*N*-dimethyltosylamide's $pK_a \approx -6.19$.[16] It was therefore reasonable that the 1,5-ditosyldiazocinedione system would undergo protonation initially at the diazocine nitrogen sites. Such protonation would seriously deactivate or prohibit subsequent formation of a requisite carbocation two carbons away.

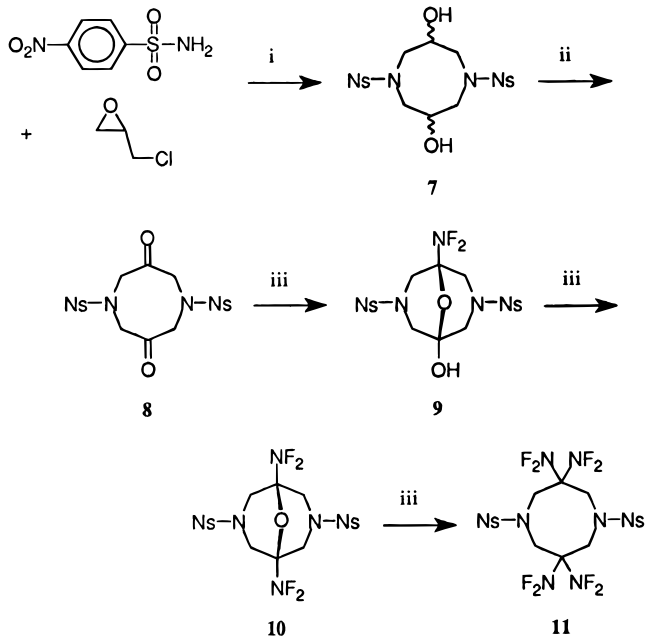
While simple addition of difluoramine to ketone carbonyls is facile—even proceeding without strong acid,[17] although it is catalyzed by acid—leading to the observed hemiaminals, formation of *gem*-bis(difluoramino)diazocines would be mechanistically prevented by protonation of the ring nitrogens before the ketone carbonyls or hemiaminal oxygens. We assumed that the basicity of the *N*,*N*-difluorohemiaminal oxygen sites is comparable to that of ketones, on the basis of the known group electronegativity of the difluoramino substituent.[18] Although precise microbasicities of the oxygen and nitrogen sites in the ditosyldiazocines have not been measured, it has been demonstrated that relatively small differences in microbasicity within polyamines lead to kinetically completely selective protonation of the most basic site and not to extents of protonation proportional to the thermodynamic basicities.[19]

Our solution to the recalcitrance of ditosyl derivatives was to modify the protecting group in order to favorably affect the microbasicities. 4-Nitrobenzenesulfonamide (nosylamide) exhibits a $pK_a \approx -8.5$,[16] so we chose nosyl as our preferred protecting group: in this system the diazocine nitrogens should be *less* basic than the ketone and hemiaminal oxygens, and the difluoramination should proceed as desired. We found this to be the result.

Octahydro-1,5-bis(4-nitrobenzenesulfonyl)-1,5-diazocine-3,7-diol ("dinosyldiazocinediol", **7**) was prepared analogously to the ditosyl derivative by base-catalyzed condensation between commercial nosylamide and epichlorohydrin (Scheme 5), producing a similar 29% yield. The diol was oxidized to the dione (**8**) by Swern oxidation in up to 94% purified yield. Electronegatively N-substituted tetrahydro-1,5-diazocine-3,7(2*H*,6*H*)-diones tend to be hygroscopic and susceptible to hydration to corresponding hemiacetals (e.g., **5**) or even to ketone hydrates (*gem*-diols).[20]

Because of serious hazards inherent in the use of difluoramine,[21−23] typically used in conventional difluoraminations of ketones,[14] we also modified the conditions

Scheme 5[a]



[a] Reagents and conditions (yield): (i) NaOH, aq EtOH, reflux (29%); (ii) (1) $(COCl)_2$−DMSO, CH_2Cl_2, −78 °C, (2) Et_3N (94%); (iii) HNF_2, $F_2NSO_3H-H_2SO_4/CFCl_3$, −15 ↔ 0 °C, 15 days (60%).

of the difluoramine reactions with ketones in order to alleviate most of this hazard. Historically, difluoramine has been most prone to detonation in the neat, condensed phase (e.g., as a liquid refluxing at its boiling point during the formation of difluorosulfamic acid upon condensation into fuming sulfuric acid, or upon addition of organic substrates to these solutions). We have moderated its chemical and physical sensitivity by employing a volatile inert solvent in the presence of the fuming sulfuric acid. We chose trichlorofluoromethane as a solvent expected to be completely inert even during the prolonged reaction with the 3,7-bis(4-nitrobenzenesulfonyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane intermediates. Salient characteristics of a good solvent for this process include inertness for the duration of the difluoramination reaction, good solvent properties toward difluoramine, appreciable volatility if the difluoramine is condensed at low temperature (e.g., by dry ice) so that concomitant solvent condensation will moderate the sensitivity of difluoramine, and preferably low solubility of organic intermediates in order to facilitate their transport into the strong acid necessary for difluoramination.

A difluoramination of dinosyldiazocinedione (**8**) held at −15 °C for 9 days produced a 24% total yield of difluoramine derivatives consisting of expected intermediates (**9**, **10**) plus desired product (**11**) in a mole ratio of 52:9:39. Another run held at −10 °C for 24 days produced a 45% isolated yield of **11**. Under atypical conditions described in the Experimental Section, a reaction cycled between ca. −15 and 0 °C took the reaction to completion in 15 days with a 60% yield of desired product **11**. A reaction conducted in CH_2Cl_2 instead of $CFCl_3$, but otherwise by the typical procedure, produced a 48% yield of a 10:9:81 (molar) mixture of **9** + **10** + **11** after 15 days at −15 to −8 °C. Intermediates **9**

(15) (a) Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; John Wiley & Sons: New York, 1972; pp 60−62. (b) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992; p 250.

(16) Virtanen, P. O. I.; Heinämäki, K. *Suom. Kemist. B* **1969**, *42*, 142; *Chem. Abstr.* **1969**, *70*, 118627h.

(17) (a) Freeman, J. P.; Graham, W. H.; Parker, C. O. *J. Am. Chem. Soc.* **1968**, *90*, 121. (b) Fokin, A. V.; Kosyrev, Yu. M.; Galakhov, I. V.; Ragulin, L. I. *Doklady Chem. (Engl. Transl.)* **1969**, *192*, 326.

(18) (a) Ettinger, R. *J. Phys. Chem.* **1963**, *67*, 1558. (b) Baum, K. *J. Org. Chem.* **1970**, *35*, 1203.

(19) Delfini, M.; Segre, A. L.; Conti, F.; Barbucci, R.; Barone, V.; Ferruti, P. *J. Chem. Soc., Perkin Trans. 2* **1980**, 900.

(20) Other examples include 1,5-diacetyloctahydro-1,5-diazocine-3,3,7,7-tetraol formed from **2**,[3] and octahydro-1,5-dinitro-1,5-diazocine-3,3,7,7-tetraol formed from tetrahydro-1,5-dinitro-1,5-diazocine-3,7-(2*H*,6*H*)-dione (Chapman, R. D.; Kreutzberger, C. B., unpublished results).

(21) Lawton, E. A.; Weber, J. Q. *J. Am. Chem. Soc.* **1963**, *85*, 3595.

(22) Parker, C. O.; Freeman, J. P. *Inorg. Synth.* **1970**, *12*, 307.

(23) Christe, K. O.; Wilson, R. D. *Inorg. Chem.* **1987**, *26*, 920, and references therein.

and **10** have appreciable solubility in CH_2Cl_2.[24] Progress of the difluoramination is conveniently monitored by ^{19}F NMR analysis of small aliquots as the reaction proceeds through intermediates **9** (δ 22.3 in 96% H_2SO_4) and **10** (δ 23.2) toward product **11** (δ 28.9).

Conclusion

The successful preparation of the first [β,β-bis(difluoramino)alkyl]sulfonamide (diazocine **11**) demonstrates the criticality of a judicious choice of protecting group in a system in which difluoramination of a ketone carbonyl to *gem*-bis(difluoramino)alkylene must be achieved at a position β to nitrogen within the same molecule. The replacement of tosyl by nosyl effects a sufficient lowering of basicity of the diazocine nitrogen to make the difluoramination reaction feasible. The recognition of this criticality has applicability to other situations in which substrates with sites of comparable and competing basicity or nucleophilicity are present. The handling of difluoramine is made significantly safer by the use of appropriate inert solvents.

The novel nitrolysis of highly deactivated amide **11** to the corresponding nitramine (**1**) will be described in a future publication.

Experimental Section

General Experimental Procedures. Elemental analyses were by Desert Analytics (Tucson, AZ) or by Galbraith Laboratories (Knoxville, TN). All chemicals were reagent grade or better, unless specified by source; typically, Aldrich Chemical Co. was the source.

Improved Procedure for Difluoramination of Ketones. Difluoramine was generated by acidic hydrolysis of *N,N*-difluorourea, prepared by direct fluorination of aqueous urea.[14,22] ***WARNING:*** Under certain conditions, difluoramine can be an extremely sensitive, detonable material![21−23] Although the procedural modifications described here alleviate much of this sensitivity, difluoramine should be handled only by appropriately qualified personnel. Adequate shielding should be used to contain a possible detonation.

The difluoramination reaction is conducted in a jacketed flask, for example, European-style flask #CG-1576 by Chemglass, Inc. (Vineland, NJ). A refrigerated circulator—we used a Neslab Instruments Model RTE-8 (50:50 ethylene glycol−H_2O) or an FTS Systems Model RS25AL00 (60:30:10 glycol−H_2O−MeOH)—is used to cool the jacketed flask, to which is added an inert solvent such as trichlorofluoromethane.[24] The reaction flask is also fitted with an auger-style powder addition funnel to add dry ketone substrate (unless the ketone is liquid or is soluble in the inert solvent used; then a liquid addition funnel may be used). To contain volatiles otherwise swept through by the inert gas flow, the flask may be optionally fitted with a Dewar-style condenser cooled by dry ice−solvent (e.g., ethanol or acetone), which causes $CFCl_3$ as well as difluoramine to reflux under typical gas flow rates. Alternatively or additionally, a jacketed addition funnel (such as Chemglass #AF-0552) containing an additional quantity of cooled inert solvent may be fitted onto the reaction flask; volatiles are thus passed through the auxiliary solvent sample before condensation at the condenser, even further diluting the volatile difluoramine and moderating its sensitivity.

Fuming sulfuric acid is added to the inert solvent in a quantity sufficient to chemically absorb about half of the introduced quantity of difluoramine (via reaction with SO_3). The generated difluoramine gas is passed (with a nitrogen or argon flow) via Teflon spaghetti tubing first through a water-cooled Liebig condenser on the generator flask followed by an ice−water-cooled trap, a Drierite U-tube, and into the reaction's inert solvent layer just above the oleum. $CFCl_3$ readily absorbs difluoramine, which gradually reacts with the SO_3 in contact with the organic layer. Raising the flask temperature to ≥0 °C—nearer to the melting point of oleum—during difluoramine absorption facilitates the combination by liquefaction. The mixture of difluorosulfamic acid and sulfuric acid formed by complete reaction of 30% oleum with difluoramine will remain liquid down to the boiling point of difluoramine (−23 °C), but difluoramination reactions are typically run at −15 to 0 °C.

Volatile gases are ultimately passed out—via the dry ice condenser—through an auxiliary flask containing desiccant, which allows pressure release without moisture absorption into the system. Optionally, the gas flow may then be passed through an aqueous KI trap to qualitatively monitor any loss of difluoramine.

One of the present investigators (R.D.C.) has conducted almost 30 runs by the present procedure with no untoward behavior of the systems. In some runs, the apparatus was intentionally vigorously agitated, even during reflux of the HNF_2−$CFCl_3$ mixture, with no adverse reaction.

Tetrahydro-1,5-bis(4-methylbenzenesulfonyl)-1,5-diazocine-3,7(2*H*,6*H*)-dione (4) and 3,7-Bis(4-methylbenzenesulfonyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-1,5-diol (5). Swern reagent was made from a solution of oxalyl chloride (85.0 g, 0.670 mol) in 750 mL of CH_2Cl_2, cooled in a dry ice−acetone bath, to which was added DMSO (67.97 g, 0.870 mol) by syringe over 20 min. A solution of ditosyldiazocinediol[9] **3** (98.1 g, 0.216 mol) in 150 mL of DMSO was added over 5 min. After 3.5 h with stirring, the temperature being maintained in the range of −78 to −50 °C by a dry ice−acetone bath, triethylamine (242.9 g, 2.40 mol) was added quickly. The mixture was stirred for 30 min at −78 °C and then at room temperature for 2.5 h. Water (500 mL) was added, and the solid suspension was filtered, yielding ∼15 g of crude **5**. Sequent washings of the filtrate with saturated aqueous NH_4Cl and saturated aqueous Na_2CO_3 followed by slow concentration produced a crop of solid at each step; the collective later crops were a mixture of dione **4** and hemiacetal **5**. The crude product was purified by converting it all to hemiacetal: to crude dione (70 g) in 500 mL of acetone was added 50 mL of H_2O and 50 mL of concentrated HCl; the mixture was refluxed overnight, gradually dissolving. The solution was poured onto ice and diluted with H_2O to 3 L; the white precipitate was filtered off and vacuum-dried, yielding 63.60 g of purified **5**. The first crop above was similarly purified to yield 12.40 g. The total yield was 76.00 g (75%) of **5**.

Hemiacetal **5** is readily dehydrated to dione **4** by azeotropic drying.[11] It may also be dehydrated under vacuum at 100 °C. Variations on the workup procedure have preferentially produced dione **4** over hemiacetal **5** but at a significant cost in yield.

Dione **4**. ^1H NMR (200 MHz, acetone-d_6, 50 °C): δ 2.47 (s, 6 H), 4.19 (s, 8 H), 7.50 (d, 8.3 Hz, 4 H), 7.80 (d, 8.3 Hz, 4 H). ^{13}C NMR (50 MHz, acetone-d_6): δ 21.4, 60.7, 128.2, 131.2, 135.6, 145.8, 205.1. IR (KBr): ν_{CO} 1738.7 cm^{-1}. Anal. Calcd for $C_{20}H_{22}N_2S_2O_6 \cdot 0.18H_2O$: C, 52.93; H, 4.97; N, 6.17; S, 14.13. Found: C, 52.91; H, 4.87; N, 6.08; S, 14.25. Hemiacetal **5**. ^1H NMR (200 MHz, acetone-d_6): δ 2.46 (s, 6 H), 2.36, 3.70 (AB quartet, 10.6 Hz, 8 H), 6.06 (s, 2 H), 7.48 (d, 8.3 Hz, 4 H), 7.70 (d, 8.3 Hz, 4 H). ^{13}C NMR (50 MHz, acetone-d_6): δ 21.4, 52.3, 94.0, 128.9, 130.7, 133.0, 144.9. Anal. Calcd for $C_{20}H_{24}N_2S_2O_7 \cdot 0.63H_2O$: C, 50.05; H, 5.31; N, 5.84; S, 13.36. Found: C, 49.95; H, 5.30; N, 5.93; S, 13.38.

5-(Difluoramino)-3,7-bis(4-methylbenzenesulfonyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonan-1-ol (6). Following the

(24) For reactions with certain ketone substrates, dichloromethane may be a suitable solvent under typical difluoramination conditions. While ketone substrates have been added as dichloromethane solutions in other procedures (Mueller, K. F.; Cziesla, M. J. *J. Org. Chem.* **1969**, *34*, 917), we urge the use of an inert solvent throughout the entire process to avoid the presence of neat difluoramine in the reaction system. Other inert solvents with less ozone-depleting potential than $CFCl_3$, such as dichlorofluoromethane and perhaps chloroform, may also be usable for long-term reactions. Solvents with all of the salient characteristics described in the text are preferable.

improved difluoramination procedure described above, 8 mL of fuming sulfuric acid (30% SO_3) was added to 75 mL of $CFCl_3$ in a jacketed flask at −10 °C. While HNF_2 (6.66 g, 126 mmol) was being absorbed by the solvents, the temperature was gradually raised to 10 °C to liquefy the acid layer; upon immediate recooling to −10 °C, the acid remained liquid. Dione **4** (1.42 g, 3.15 mmol) was added gradually via powder addition funnel; 10 mL of $CFCl_3$ was used to wash the solid out of the funnel. After 3 h at −10 °C, the reaction mixture was quenched onto ice−water. The mixture was extracted with CH_2Cl_2 (3 × 500 mL). Rotary evaporation produced 1.02 g of solid, which was chromatographed on silica gel (25 mm × 35 cm) in ethanol-free HPLC-grade $CHCl_3$, eluting successively with $CHCl_3$ (250 mL), 1:9 acetone−$CHCl_3$ (250 mL), and then 2:8 acetone−$CHCl_3$ (250 mL); the content of **6** can be conveniently monitored in effluent fractions by ^{19}F NMR. Yield: 0.61 g (38%). Mp: 182−184 °C (dec). ^1H NMR (200 MHz, acetone-d_6): δ 2.46 (s, 6 H), 2.68, 3.75 (AB q, 11.1 Hz, 4 H), 2.91, 3.84 (AB q, 11.1 Hz, 4 H), 6.80 (s, 1 H), 7.49 (d, 8.0 Hz, 4 H), 7.74 (d, 8.3 Hz, 4 H). ^{13}C NMR (50 MHz, acetone-d_6): δ 21.6, 46.3 (t, 15 Hz), 52.6, 95.18, 95.32 (t, 10.0 Hz), 128.9, 131.0, 133.3, 145.4. ^{19}F NMR (188 MHz, acetone-d_6): δ 20.71.

Octahydro-1,5-bis(4-nitrobenzenesulfonyl)-1,5-diazocine-3,7-diol (7). 4-Nitrobenzenesulfonamide (25.17 g, 0.125 mol; Sigma-Aldrich-Fluka Bulk) and 12.5 mL of 10 *M* NaOH were mixed in 171 mL of 95% EtOH + 12.5 mL of H_2O. At reflux temperature, the nosylamide salt dissolved. A solution (45 mL) of epichlorohydrin (11.52 g, 0.125 mol) in 95% EtOH was added in one portion. In this, our best-quantified run, the mixture was held at reflux for 2 days, but we have also observed that an overnight reaction is sufficient. The EtOH solvent was removed by rotary evaporation. Additional H_2O (300 mL) was added to the reaction residue; this was boiled, cooled to lukewarm, and decanted off to remove salt byproducts. The organic residue was vacuum-dried overnight, redissolved in a minimum volume of boiling acetone, and filtered. Concentration by rotary evaporation precipitated a first crop (6.91 g) of diol **7**. The filtrate was taken to dryness by rotary evaporation, and the residue was boiled with 350 mL of absolute EtOH; upon cooling to lukewarm, the supernatant EtOH solution was decanted off and discarded. The residue was digested with 1:1 acetone−absolute EtOH, producing a second crop (2.28 g) of **7** for a total yield of 9.19 g (29%) [mp: 272.5−275.5 °C (dec)]. The collective light yellow product is usably pure but can be purified further by recrystallization from acetone (for purest product) or by digestion with 1:1 acetone−EtOH (for higher recovery). ^1H NMR (200 MHz, DMSO-d_6): δ 2.88 (m, ∼3 H, cis-**7**), 3.19 (m, ∼2 H, trans-**7**), 3.69 (dm, 14.8 Hz, ∼3 H, cis-**7**), 3.90 (bm, 2 H), 5.29 (d, 5.7 Hz, trans-**7**), 5.39 (d, 4.4 Hz, cis-**7**), 8.09 (dm, 8.8 Hz, 4 H), 8.46 (dm, 8.8 Hz, 4 H). cis-**7** ^{13}C NMR (50 MHz, DMSO-d_6): δ 52.7, 66.8, 124.8, 128.6, 142.9, 149.9. trans-**7** ^{13}C NMR (50 MHz, DMSO-d_6): δ 57.5, 69.4, 124.9, 128.3, 143.5, 149.9. NMR analysis showed a ratio of ∼68:32 for cis:trans isomers by analogy to assignments reported for **3**.[9] Anal. Calcd for $C_{18}H_{20}N_4S_2O_{10}$: C, 41.86; H, 3.90; N, 10.85. Found (mean of two): C, 41.68; H, 3.87; N, 10.70.

Tetrahydro-1,5-bis(4-nitrobenzenesulfonyl)-1,5-diazocine-3,7(2*H*,6*H*)-dione (8). Dinosyldiazocinediol **7** (4.08 g, 7.90 mmol) was dissolved in 42 mL of DMSO (Aldrich anhydrous grade) + 9 mL of CH_2Cl_2. Swern reagent was made from a solution of oxalyl chloride (3.85 g, 30.3 mmol) in 100 mL of CH_2Cl_2, cooled in a dry ice−acetone bath, to which was added dropwise a solution of DMSO (3.26 g, 41.7 mmol) in 9 mL of CH_2Cl_2, washed in with 10 mL of CH_2Cl_2. The solution of **7** was added dropwise. After 3 h with stirring, cooling being maintained by a dry ice−acetone bath, triethylamine (7.99 g, 79.0 mmol) was added and washed in with 10 mL of CH_2Cl_2. The mixture was left stirring overnight, warming adventitiously to room temperature. Water (150 mL) was added to the mixture, producing a sludge which was filtered by filter paper, washed with water, and dried, to give a crude yield of 3.97 g (98%) of **8**. The crude product was boiled in 150 mL of acetone; the light-tan solid was filtered and oven-dried, for a purified yield of 3.79 g (94%). Pure **8** has quite low solubility in most organic solvents. ^1H NMR (200 MHz, DMSO-d_6, 110 °C): δ 4.28 (s, 8 H), 8.16 (d, 9.0 Hz, 4 H), 8.44 (d, 9.0 Hz, 4 H). Anal. Calcd for $C_{18}H_{16}N_4O_{10}S_2 \cdot 1.46H_2O$: C, 40.12; H, 3.54; N, 10.40; S, 11.90. Found: C, 40.09; H, 3.12; N, 10.09; S, 12.01.

3,3,7,7-Tetrakis(difluoramino)octahydro-1,5-bis(4-nitrobenzenesulfonyl)-1,5-diazocine (11). By the typical difluoramination procedure described above, 22 mL of 30% fuming sulfuric acid was added to 40 mL of CH_2Cl_2 cooled to −15 °C in a jacketed flask. The system used a dry ice-cooled Dewar condenser but no auxiliary addition funnel. Gaseous HNF_2 (0.20 mol) was absorbed into the CH_2Cl_2 layer. HNF_2−CH_2Cl_2 mixture refluxed from the dry ice condenser. Because the oleum was initially frozen, the temperature was briefly raised to 2 °C, which melted it; upon absorption of HNF_2 and recooling to −15 °C, it remained liquid. Solid dione **8** (3.458 g, 6.75 mmol) was added over ∼0.5 h and washed in with 15 mL of CH_2Cl_2. The mixture was stirred for 15 days; the temperature gradually rose from −15 to −8 °C. The reaction mixture was carefully poured into ice−water. The solution was basified to pH 8 with saturated aqueous sodium carbonate. Precipitated solids were filtered, dried, and Soxhlet-extracted with CH_2Cl_2 for 6 days; ^{19}F NMR analysis showed a 25:12:63 mole ratio of **9**:**10**:**11** among the CH_2Cl_2 extract. The Soxhlet extraction solvent was changed to acetone; extraction for 1 day yielded solute (1.28 g, 27%) which was 99% pure **11**. ^1H NMR (200 MHz, DMSO-d_6): δ 4.25 (s, 8 H), 8.25, 8.46 (AB q, J = 8.9 Hz, 8 H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 48.4 (m, $^3J_{CF}$ = 6.5 Hz), 96.1 (m), 125.0, 129.7, 141.4, 150.6. ^{19}F NMR (188 MHz, DMSO-d_6): δ 29.4. Anal. Calcd for $C_{18}H_{16}F_8N_8O_8S_2$: C, 31.40; H, 2.34; N, 16.28; F, 22.08; S, 9.31. Found: C, 31.94; H, 2.48; N, 15.66; F, 22.30; S, 9.48.

Concentration (∼2×) of the CH_2Cl_2 extract yielded another crop of solid (0.64 g); addition of an equal volume of $CHCl_3$ to the filtrate followed by concentration yielded another crop (0.27 g). the total yield of (difluoramino)diazocines was 3.27 mmol (48%) in a 10:9:81 mole ratio of **9**:**10**:**11**.

Modified (Atypical) Preparation of 3,3,7,7-Tetrakis(difluoramino)octahydro-1,5-bis(4-nitrobenzenesulfonyl)-1,5-diazocine (11). Dione **8** (13.22 g, 25.8 mmol) was added to a mixture of ∼425 mL of fuming sulfuric acid (containing 8−10% SO_3) plus 100 mL of $CFCl_3$ in a 1-L jacketed flask, into which was absorbed 13 g (0.25 mol) of HNF_2 while a refrigerated circulator cooled the reaction vessel to ca. −15 °C. Over the course of 48 h, organic solids separated out of this suspension into a single solid mass. Warming the mixture to ∼0 °C over 6 h produced a more-fluid suspension, which was recooled to ca. −15 °C over 6 h and then held there for 11 days. Additional (100 mL) fuming sulfuric acid (1−3% SO_3) was added; the reaction was warmed to ∼0 °C over 6 h, cooled to ca. −15 °C, and then held there overnight. A total of four more cycles of warming to ∼0 °C over 6 h followed by cooling to ca. −15 °C were conducted (a total of six cycles over six consecutive days). The reaction mixture was warmed once more to ∼0 °C over 6 h and then quenched by pouring it into a mixture of ice and saturated aqueous sodium carbonate. The quenched solution was neutralized to pH 7 with additional solid Na_2CO_3. Upon warming, the $CFCl_3$ evaporated. The precipitate was filtered, washed with water, and dried to yield 10.52 g (60%) of **11**.

Acknowledgment. The financial support of this work by the Office of Naval Research and the Ballistic Missile Defense Organization under ONR contract N00014-93-C-0126 to TPL, Inc. and Work Order N0001496WX20101 to NAWCWPNS, managed by Dr. Richard S. Miller (ONR), is gratefully acknowledged.

Supporting Information Available: ^1H, ^{13}C, and ^{19}F NMR spectra of compound **6** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9718399