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Nucleic Acid Related Compounds. 118. Nonaqueous Diazotization of Aminopurine Derivatives. Convenient Access to 6-Halo- and 2,6-Dihalopurine Nucleosides and 2′-Deoxynucleosides with Acyl or Silyl Halides[1]

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Abstract: Treatment of 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2-amino-6-chloropurine (**1**) with TMS-Cl and benzyltriethylammonium nitrite (BTEA-NO_2) in dichloromethane gave the crystalline 2,6-dichloropurine nucleoside **2**, and acetyl chloride/BTEA-NO_2 was equally effective (~85%, without chromatography). TMS-Br/*tert*-butyl nitrite/dibromomethane gave crystalline 2-bromo-6-chloro analogue **3** (85%). (Chloro or bromo)-dediazoniation of 3′,5′-di-*O*-acetyl-2′-deoxyadenosine (**4**) gave the 6-[chloro (**5**, 63%) or bromo (**6**, 80%)]purine deoxynucleosides, and 2′,3′,5′-tri-*O*-acetyladenosine (**8**) was converted into the 6-chloropurine nucleoside **9** (71%).

Introduction

Nonaqueous diazotization/halo-dediazoniations[2,3] provide efficient transformations of (amino → halo)purine nucleosides.[4,5] Halogen-functionalized derivatives can be converted into biologically important analogues by nucleophilic aromatic displacement[6−9] and organometallic cross-coupling chemistry.[10] Halo-dediazoniations of aminopurines can be performed under milder conditions[4,5] than halo-deoxygenation of oxopurine derivatives (phosphoryl halides[8,11] or Vilsmeier−Haack reagents[7,8]). Conversion of 6-(oxo → halo)purine derivatives with a positive halogen source and hexamethylphosphorus triamide (HMPT) gave 6-(bromo or chloro)purine ribonucleosides,[9] but failed with an acid-sensitive 2′-deoxynucleoside.[9b] We have communicated a new functionalization of 6-oxopurine nucleoside *and* 2′-deoxynucleoside derivatives, which provides 6-(imidazol-1-yl) compounds in excellent yields.[12] The imidazolyl group can be substituted by common nucleophiles, but it is not displaced as readily as a halogen. Halo-dediazoniation provides economical access to base-functionalized nucleosides in comparison with lithiation/stannylation procedures.[13]

Nitrosylation of weakly basic amines is often rate limiting in dediazoniation, and nitrosyl halides are potent nitrosylating agents.[3b] Nitrosyl halides are likely generated in situ during nonaqueous diazotization of aminopurine nucleosides with antimony trihalides and a nitrite source.[4,5] However, diazotization/dediazoniation mechanisms can be complex and are influenced to a significant degree by minor changes in reaction conditions.[5] Antimony(III) halides are effective catalysts for diazotization/halo-dediazoniation, and have Lewis acidic properties as well as serving as halogen donors. Because antimony compounds are toxic and $SbCl_3$ has been shown to bind to DNA,[14] efficient halo-dediazoniation procedures that do not employ SbX_3 are needed.[5]

Nitrosyl chloride, as a component of aqua regia, was recorded in eighth-century Arabic literature,[15] and in situ generation of NOCl with acetyl chloride and nitrous acid or alkyl nitrites replaced aqua regia a millenium later.[16] Generation of NOCl with $AlCl_3$, PCl_3, $AsCl_3$, or $TiCl_4$ is known,[17,18] and such sources have been used for in situ diazotization of aliphatic amines.[19] Generation of NOCl from silicon chlorides and alkyl nitrites was noted in early patent literature,[15] and TMS-Cl/MX has been used for halo-dediazoniation of aryl triazenes.[20] TMS-Cl, $NaNO_2$, and phase transfer agents have been used for deoximation of aldehyde and ketone oximes[21a] as well as halo-

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(1) (a) Patent application filed. (b) Paper 117: Miles, R. W.; Nielsen, L. P. C.; Ewing, G. J.; Yin, D.; Borchardt, R. T.; Robins, M. J. *J. Org. Chem.* **2002**, *67*, 8258−8260.

(2) Bunnett's nomenclature[3] is used. Replacement of a diazonium species by another group is termed dediazoniation regardless of mechanism. The name of the entering group is added as a prefix (e.g., chloro-dediazoniation and bromo-dediazoniation).

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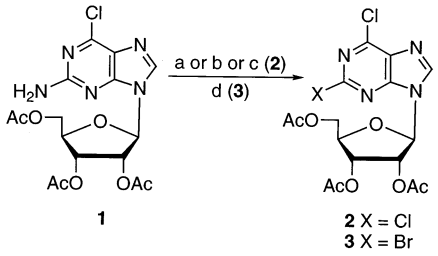
SCHEME 1[a]



[a] Reagents and conditions: (a) TMS-Cl/BTEA-NO_2/CH_2Cl_2 (83%); (b) TMS-Cl/BTEA-NO_2/$NaNO_2$/CH_2Cl_2 (86%); (c) AcCl/BTEA-NO_2/CH_2Cl_2/0−5 °C (84%); (d) TMS-Br/TBN/CH_2Br_2 (85%).

dediazoniation of anilines.[21b] Olah reported generation of nitryl chloride from $NaNO_3$/TMS-Cl, and nitrations with NO_2Cl were catalyzed by $AlCl_3$.[22] Facilitation of halo-dediazoniation of arylamines occurs with tetraalkylammonium halides.[21,23,24]

We have employed SbX_3 and nitrite sources for nucleosides,[4a,b,5] but nitrosyl halides have rarely been used in nucleoside chemistry.[8,25] Chlorine, *tert*-butyl nitrite (TBN), and copper(I) chloride[26] were used for chloro-dediazoniation of a 2-amino-6-chloropurine nucleoside, and adenosine and guanosine derivatives underwent fluoro-dediazoniation with *tert*-butylthionitrites and $NaBF_4$.[27] We now report nonaqueous halo-dediazoniations of aminopurine nucleosides with convenient reagent combinations for generation of NOCl or NOBr in situ.

Efficient chloro-dediazoniation of 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2-amino-6-chloropurine[28,29] (**1**) (Scheme 1) was effected with TMS-Cl (9 equiv) and benzyltriethylammonium nitrite (BTEA-NO_2) (3 equiv) in CH_2Cl_2 at ambient temperature. The process was rapid (<30 min), and crystalline 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2,6-dichloropurine[4c,5] (**2**) (83%, without chromatography) was obtained. Comparable yields were obtained at 0 °C. TMS-Cl (3.5 equiv) and BTEA-NO_2 (1.5 equiv) with powdered $NaNO_2$ (5 equiv) gave **2** (86%) within 1 h. By contrast, another method for nonaqueous chloro-dediazoniation of **1** employed Cl_2/TBN/CuCl in a strongly exothermic reaction, and removal of colloidal material by filtration was required prior to crystallization of **2**.[26]

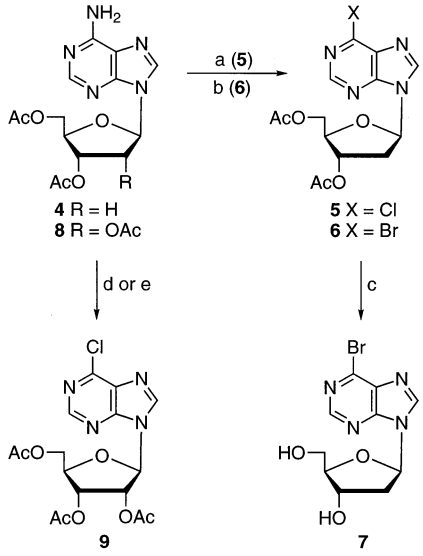
We found that **1** underwent efficient bromo-dediazoniation with TMS-Br and TBN. Competing redox with nitrite anion and TMS-Br precluded the use of $NaNO_2$. Crystalline 2-bromo-6-chloropurine nucleoside **3**[4c,5] (85%, without chromatography) was obtained with TMS-Br (9 equiv)/TBN (20 equiv)/CH_2Br_2/ambient temperature within 1 h.

We determined ratios of halo-dediazoniation products with competing halogen sources (TMS-X/$CH_2X'_2$) by ^{1}H NMR analysis of purified mixtures (H8 signals at δ 8.27 for **2** and 8.14 for **3**). Products were separated (preparative TLC) and quantitated (UV), and their identities were confirmed (MS). Treatment of **1** with TMS-X (9 equiv) and TBN (20 equiv) in $CH_2X'_2$ at ambient temperature for 3 h gave results summarized in Table 1.

TABLE 1. Products from Halo-dediazoniations of 1

		products (%)		
reagent	solvent	**2**	**3**	**9**
TMS-Cl/TBN	CH_2Br_2	72	15	2.5
TMS-Br/TBN	CH_2Cl_2	16	69	

SCHEME 2[a]



[a] Reagents and conditions: (a) TMS-Cl/BTEA-NO_2/CH_2Cl_2/0 °C (63%); (b) TMS-Br/TBN/CH_2Br_2/0−5 °C (80%); (c) (i) NaOH/H_2O, (ii) XAD-4 (80%); (d) AcCl/BTEA-NO_2/CH_2Cl_2/0 °C (71%); (e) $SOCl_2$/BTEA-NO_2/−78 °C to ambient temperature (62%).

Yields of (reagent and solvent)-derived halo-dediazoniation products were remarkably constant in both reactions. Products in which halogen was derived from TMS-X exceeded the solvent-derived halo-dediazoniation products by a factor of ∼4.5. Nitrosyl halides decompose by both homolytic and heterolytic pathways, which precludes mechanistic inferences regarding these halo-dediazoniations. However, enhanced formation of products derived from TMS-X versus those from solvent is analogous to our results with TBN/($SbBr_3$ and/or BTEA-Br).[5]

Halo-dediazoniation with likely in situ generation of NOCl or NOBr also was effective at C6 of acetylated adenosine derivatives. Chloro-dediazoniation of the acidlabile 3′,5′-di-*O*-acetyl-2′-deoxyadenosine[30] (**4**) (TMS-Cl/BTEA-NO_2/CH_2Cl_2/0 °C/3 h) (Scheme 2) gave 9-(3,5-di-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-6-chloropurine (**5**) (63%). Bromo-dediazoniation of **4** (TMS-Br/TBN/CH_2Br_2/0−5 °C/5−7 h) proceeded more cleanly to give the important intermediate 9-(3,5-di-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-6-bromopurine[5,9b] (**6**) (80%). Minor quantities (<15%) of 6-oxopurine deriva-

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tives were produced with halo-dediazoniations at C6 as previously noted.[5] This bromo-dediazoniation of the acid-sensitive 2′-deoxynucleoside (**4** → **6**) gave yields comparable to those reported by Véliz and Beal for conversion of protected inosine into a 6-bromopurine ribonucleoside derivative with HMPT/(NBS or CBr_4),[9] whereas the latter conditions caused glycosyl bond cleavage with a protected 2′-deoxyinosine.[9b]

Montgomery and Thomas[31] identified polymerization of 9-(β-D-ribofuranosyl)-6-chloropurine in aqueous base (displacement of chloride by sugar hydroxyl groups), and the enhanced S_NAr reactivity of 6-bromopurine derivative **6** was recently noted.[9b] We deprotected **6** with alcoholic ammonia at lowered temperatures,[5] but accompanying displacement of bromide by sugar hydroxyl groups can occur. We investigated deacetylation with NaOH/H_2O/DME or Dowex 1 (OH^-)/H_2O/DME, but observed (TLC) minor conversion of **6** to 2′-deoxyinosine and/or other byproducts. Clean deprotection was effected by treatment of **6** on a large surface (flask) with dilute NaOH/H_2O (0.01 M, 5 equiv) followed by adsorption of the product on a polystyrene resin (Amberlite XAD-4). Elution with acetonitrile and flash evaporation of volatiles at lowered temperatures gave the elusive 2′-deoxynucleoside **7**[5] without significant side reactions. This procedure[5] allows isolation of other 6-halopurine nucleosides (>80% yields) as clean powders.

We investigated acetyl chloride and BTEA-NO_2 for in situ generation of NOCl. It had been shown that different ratios of nitrite, acetate, and substrate determined proportions of NOCl, AcONO, and N_2O_3 in solution, and these affected nitrosylation pathways.[32] An approximately equimolar ratio of AcCl/BTEA-NO_2 was effective for chloro-dediazoniation of (2 or 6)-aminopurine nucleosides. Treatment of 2′,3′,5′-tri-*O*-acetyladenosine[33] (**8**) with a 5-fold excess of AcCl/BTEA-NO_2 in CH_2Cl_2 at 0−5 °C for 3 h gave 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-chloropurine[5,28] (**9**) (71%). Yields were decreased with larger quantities of AcCl or BTEA-NO_2. Treatment of **1** under analogous conditions gave **2** (83%, without chromatography) (Scheme 1).

We also evaluated thionyl chloride for in situ generation of NOCl. Moss and Matsuo[34] had treated alkane diazoates with $SOCl_2$ and obtained alkyl chlorides, N_2, and SO_2. Our treatment of **8** with BTEA-NO_2 (3 equiv) in $SOCl_2$ gave **9** (62%) plus the 6-oxo byproduct (2′,3′,5′-tri-*O*-acetylinosine[33]). This procedure did not work well at the gram scale, and extensive glycosyl bond cleavage occurred with **8**/TBN/$SOCl_2$.

In summary, we have likely effected in situ generation of NOCl/CH_2Cl_2 or NOBr/CH_2Br_2 from (Me_3SiX or AcCl) and (TBN or BTEA-NO_2). Our procedures provide efficient halo-dediazoniation of protected (2 or 6)-aminopurine nucleosides as well as the acid-sensitive 2′-deoxynucleosides. These reactions are cost-effective and proceed at or below ambient temperature with convenient reagents and standard laboratory equipment and conditions.

Experimental Section

UV spectra were recorded with solutions in EtOH unless otherwise indicated. ^1H NMR spectra ($Me_4Si/CDCl_3$) were recorded at 200 MHz unless otherwise indicated. "Apparent" peak shapes are in quotation marks when first-order splitting would be more complex or when peaks were poorly resolved. Mass spectra (MS) were determined with FAB (glycerol) or CI (CH_4 or isobutane). Chemicals and solvents were of reagent quality. CH_2Cl_2 and CH_2Br_2 were dried by reflux over and distillation from CaH_2. Benzyltriethylammonium nitrite (BTEA-NO_2) was prepared from BTEA-Cl by ion exchange [Dowex 1 × 2 (Cl^-) + 1 M $NaNO_2/H_2O$ (until no AgCl with 2% $AgNO_3$/EtOH) → Dowex 1 × 2 (NO_2^-); BTEA-NO_2/H_2O solution was evaporated, EtOH/toluene was added and evaporated in vacuo (5×), and the granular solid was stored over P_2O_5 with protection from light]. Filtration chromatography was performed with silica gel (60−200 mesh). TLC was performed with silica gel on aluminum plates ($CHCl_3$/MeOH, 95:5, unless otherwise indicated). "Cold" or "cooled" indicates use of an ice−water bath. Substrates **1**,[29] **4**,[30] and **8**[33] were prepared as described.

9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-dichloropurine (2). Method A: TMS-Cl (1.14 mL, 978 mg, 9.0 mmol) was added dropwise to a stirred solution of **1** (428 mg, 1.0 mmol) in CH_2Cl_2 (30 mL) under N_2. BTEA-NO_2 (714 mg, 3.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise (1 drop/2 s) and the solution was stirred at ambient temperature for 30 min (TLC). The solution was diluted (CH_2Cl_2, 200 mL) and washed (5% $NaHCO_3$/H_2O, 5 × 100 mL). The combined aqueous phase was extracted (CH_2Cl_2, 2 × 100 mL), and the combined organic phase was dried ($MgSO_4$) and filtered. Volatiles were evaporated, Et_2O was added to and evaporated (3 ×) from the yellow oil, and the residue was recrystallized (EtOH) to give **2** (373 mg, 83%) as pale-yellow crystals with mp, UV, ^1H NMR, and MS data as reported.[5]

Method B: TMS-Cl (444 μL, 380 mg, 3.50 mmol) was added dropwise to a stirred mixture of **1** (428 mg, 1.0 mmol) and powdered $NaNO_2$ (345 mg, 5.0 mmol) in CH_2Cl_2 (25 mL) under N_2. BTEA-NO_2 (357 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise (1 drop/s) and the solution was stirred at ambient temperature for 1 h (TLC). The mixture was cooled for 15 min and added dropwise to a cold, vigorously stirred mixture of saturated $NaHCO_3/H_2O$ (200 mL)//CH_2Cl_2 (200 mL). The aqueous layer was extracted (CH_2Cl_2), and the combined organic phase was washed (H_2O) and dried ($MgSO_4$). Volatiles were evaporated, and the yellow oil was recrystallized (BuOH) to give **2** (384 mg, 86%).

Method C: A solution of AcCl/CH_2Cl_2 (1 M, 2.5 mL, 2.5 mmol) was added to dried CH_2Cl_2 (10 mL) under N_2, and the solution was cooled for 15 min. BTEA-NO_2 (535.5 mg, 2.25 mmol) in CH_2Cl_2 (5 mL) was then added dropwise (1 drop/2 s) to the cold, stirred solution of AcCl/CH_2Cl_2. A cold solution of **1** (214 mg, 0.5 mmol) in dried CH_2Cl_2 (5 mL) was then added dropwise to the cooled, stirred AcCl/BTEA-NO_2/CH_2Cl_2 solution (TLC, hexanes/EtOAc, 3:7). Immediate workup and recrystallization (method B) gave **2** (187 mg, 84%).

9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-2-bromo-6-chloropurine (3). TMS-Br (1.2 mL, 1.38 g, 9.0 mmol) was added dropwise to a stirred solution of **1** (428 mg, 1.0 mmol) in CH_2Br_2 (30 mL) under N_2. TBN (2.4 mL, 2.06 g, 20 mmol) was added dropwise, and stirring was continued at ambient temperature for 1 h (TLC). Workup (as for **2**, method B) and recrystallization (EtOH) gave **3** (416 mg, 85%) with mp and spectral data as reported.[5]

9-(3,5-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-chloropurine (5). TMS-Cl (3.81 mL, 3.26 g, 30 mmol) was added dropwise to a cold (0 °C), stirred solution of **4** (335 mg, 1.0 mmol) in dried CH_2Cl_2 (30 mL) under N_2. BTEA-NO_2 (2.38 g, 10 mmol) in dried CH_2Cl_2 (10 mL) was added dropwise, the flask was sealed (glass or Teflon stopper), and stirring was continued for 1−2 h with cooling (TLC showed conversion of **4** → **5** plus a minor product). The solution was added dropwise to a vigorously stirred mixture of cold, saturated $NaHCO_3/H_2O$ (200 mL)//CH_2Cl_2 (200 mL). The organic layer was washed (H_2O and brine), dried ($MgSO_4$), and filtered through 20 g of silica gel in

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a fritted glass funnel. Product was eluted (CH_2Cl_2/MeOH, 99.9:0.1), and volatiles were evaporated to give **5** (223 mg, 63%) as a pale-yellow solid foam: UV max 264 nm (ϵ 9700), min 225 nm; ^{1}H NMR δ 2.06, 2.13 (2 × s, 2 × 3H), 2.61−2.72 (ddd, J = 14.2, 6.2, 2.8 Hz, 1H), 2.90 ("quint", J = 6.4 Hz, 1H), 4.31−4.43 (m, 3H), 5.42−5.44 (m, 1H), 6.47 ("t", J = 5.8 Hz, 1H), 8.30, 8.75 (2 × s, 2 × 1H); LRMS (CI) m/z 355/357 (MH^+ [$C_{14}H_{16}{}^{35/37}ClN_4O_5$] = 355/357). Anal. Calcd for $C_{14}H_{15}ClN_4O_5$: C, 47.40; H, 4.26; N, 15.79. Found: C, 47.42; H, 4.35; N, 15.77.

9-(3,5-Di-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-6-bromopurine (6). TMS-Br (396 μL, 459 mg, 3.0 mmol) was added dropwise to a cold (0 °C), stirred solution of **4** (335 mg, 1.0 mmol) in CH_2Br_2 (40 mL) under N_2. TBN (2.4 mL, 2.06 g, 20 mmol) was added dropwise, the flask was sealed (glass or Teflon stopper), and stirring was continued at 0−5 °C for 5−7 h (TLC showed conversion of **4** → **6** plus a minor product). Workup and evaporation of volatiles (as for **5**) gave **6**[5,9b] (319 mg, 80%) as a pale-yellow oil with UV and ^{1}H NMR data as reported.[5] HRMS (FAB) m/z 399.0313 (MH^+ [$C_{14}H_{16}{}^{79}BrN_4O_5$] = 399.0304). Anal. Calcd for $C_{14}H_{15}BrN_4O_5 \cdot 0.5H_2O$: C, 41.18; H, 3.92; N, 13.73. Found: C, 41.00; H, 3.79; N, 13.79.

6-Bromo-9-(2-deoxy-*β*-D-*erythro*-pentofuranosyl)purine (7). Volatiles were evaporated from a solution of **6** (299 mg, 0.75 mmol) in CH_2Cl_2 (75 mL) in a 2000-mL flask to form a thin film. NaOH/H_2O (0.01 M, 380 mL, 3.8 mmol) was added, and the solution was stirred at ambient temperature for 1−2 h (*maximum* 2 h, byproduct formation occurs; TLC, $CHCl_3$/MeOH, 9:1). Adsorption on Amberlite XAD-4 resin (145 mL) and processing (see method 5[5]) gave **7** (189 mg, 80%) as an off-white solid. A sample was chromatographed (silica gel; CH_2Cl_2/Me_2CO, 1:1) to give **7** as a white powder with UV and ^{1}H NMR data as reported.[5] HRMS (FAB) m/z 315.0106 (M^+ [$C_{10}H_{11}{}^{79}BrN_4O_3$] = 315.0093). Anal. Calcd for $C_{10}H_{11}BrN_4O_3$: C, 38.11; H, 3.52; N, 17.78. Found: C, 38.30; H, 3.60; N, 17.54.

9-(2,3,5-Tri-*O*-acetyl-*β*-D-ribofuranosyl)-6-chloropurine (9). Method A: BTEA-NO_2 (595 mg, 2.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a cold (0 °C), stirred solution of AcCl (225 μL, 250 mg, 3.2 mmol) in CH_2Cl_2 (2.5 mL) under N_2. A solution of **8** (197 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the dark-orange solution, and stirring was continued at 0 °C for 4 h (TLC showed conversion of **8** → **9** plus a minor product). The solution was added dropwise to a vigorously stirred mixture of cold, saturated $NaHCO_3$/H_2O (200 mL)//CH_2Cl_2 (200 mL). The aqueous layer was extracted (CH_2Cl_2), and the combined organic phase was dried ($MgSO_4$) and filtered through silica gel (15 g) in a fritted glass funnel. Product was eluted (CH_2Cl_2/MeOH, 99.9:0.1), and volatiles were evaporated to give **9**[5] (147 mg, 71%) as a pale-yellow solid foam: UV (MeOH) max 264 nm (ϵ 9700), min 227 nm; LRMS (FAB) m/z 413/415 (MH^+ [$C_{16}H_{18}{}^{35/37}ClN_4O_7$] = 413/415).

Method B: BTEA-NO_2 (357 mg, 1.5 mmol) and **8** (196 mg, 0.5 mmol) were cooled (−78 °C) under N_2. $SOCl_2$ (15 mL) was added dropwise with stirring, the dark-orange solution was allowed to warm slowly to ambient temperature, and stirring was continued for 4 h (TLC showed conversion of **8** → **9** plus a minor product). The solution was added dropwise to a vigorously stirred mixture of saturated Na_2CO_3/H_2O (250 mL)//CH_2Cl_2 (250 mL). The organic layer was washed (H_2O and brine), and the combined aqueous phase was extracted (CH_2Cl_2). The combined organic phase was dried ($MgSO_4$) and volatiles were evaporated to give **9** (128 mg, 62%) as a white solid foam.

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