the exo hydrogen of the methylene bridge (endo hydrogen being orthogonally oriented to the bridgehead hydrogen).[5] The alternative 4 + 2, head-to-head adduct (IIIa), though also not containing any vinyl hydrogens, cannot account for this pattern of coupling of three hydrogens and also the H-11's would appear at a much lower field. Also, consistent with structure III, the ^{13}C nmr spectrum of the photoproduct shows the presence of two quaternary olefinic carbons at δ 140.4 and 129.3, two cyano carbons at δ 115.9 and 112.9, and three aliphatic quaternary carbons at δ 49.0 (C-9), 41.2 (C-1), and 19.2 (C-10) along with other methyl, methylene, and methine carbon signals. Finally, structure III also accounts for the peaks at *m/e* 121 and 62 in its mass spectrum. The cyclopropenyl cation formed by the loss of the cyclobutane ring and an allylic hydrogen probably corresponds to the 121 peak and the associated metastable peak should have a *m/e* 62.

This reaction appears to have some generality because in a similar manner 3,4-dehydro-I gives 3,4-dehydro-III as the only end product: nmr, three methyl singlets at δ 1.08, 1.11, and 1.47, three coupled H's at 1.66 (d, J = 10.0 Hz, H-8_{endo}), 2.58 (d of d, J = 5.0, 10.0 Hz, H-8_{exo}), and 3.44 (d, J = 5.0 Hz, H-7), a broad methylene singlet at 2.56, and a singlet for two vinyl H's at 5.28 ppm.

Upon heating to 100°, II rearranges to three products: I (5%), III (35%), and a new isomeric compound, IV (60%). The formation of I is in line with other *retro*-γ-ionylidene compounds.[6] The nmr spectrum of the major product shows the presence of methyl singlets at δ 1.17, 1.19, and 1.35, a complex group of signals for 6 H's between δ 1.4 and 2.0. Most indicative of the structure is the presence of a vinyl hydrogen (t, δ 5.74, J = 3.0 Hz) coupled with two H's at δ 2.42 and two coupled hydrogens at 1.61 (d, J = 9.0 Hz) and 1.91 (d). These features are only consistent with a structure from 2 + 2 internal cycloaddition of II. Of the two possible structures (IV and IVa) we favor the head-to-tail adduct IV because of the chemical shifts of coupled methylene hydrogens being too high for hydrogens adjacent to a dicyanomethylene group and more importantly upon heating to 180°, IV undergoes further rearrangement to III. From structure IV, 1,3 migration of the dicyanomethylene group gives III, while from IVa, there is no direct pathway to III.

The unusual photo and thermal chemical properties of II are probably associated with the dicyano group. That electrocyclic products are not formed in direct irradiation reaction must be due to the absence of a di-s-cis conformer necessary for cyclization due to unfavorable steric interaction.[3] The internal cycloadditions are probably associated with the electron deficient property of the 9,10 double bond. It is interesting to note that the directions of addition (4 + 2 or 2 + 2) for the major products in thermal and photochemical reactions are opposite to those normally encountered in cycloaddition reactions. At this time it is not clear whether these cycloadditions are from concerted or stepwise processes. If concerted, the photochemical and thermal reactions must have proceeded by way of $_{\pi}4_s + _{\pi}2_a$ ($_{\pi}4_a + _{\pi}2_s$) and $_{\pi}2_s + _{\pi}2_a$ additions.[7] Such mechanistic and stereochemical questions can be answered with compounds of defined stereochemistry at C-9 and C-10.

Experimental Section

All pmr spectra were recorded on a Varian HA-100 spectrometer and cmr spectra on a Varian XL-100 spectrometer. Deuterated chloroform was used as solvent and TMS as internal standard.

***retro*-γ-Ionylidenemalononitrile (II).** A 10% ether or chloroform solution of β-ionylidenemalononitrile (I)[1b] was sealed in a Pyrex test tube and irradiated with a 200-W Hanovia medium pressure mercury lamp equipped with a Corning 0-51 filter. Progress of reaction was followed by nmr. After 2 days the reaction was complete. The major product was identified as the *retro*-γ-triene II by its nmr spectrum: 1 H (t, J = 7.0 Hz) at 4.90 ppm coupled with 2 H's at 3.19; two additional vinyl hydrogens at 4.48 and 4.98 ppm. Another minor product was also present in the irradiation mixture. The compound, however, was not isolated nor identified. Conditions of photochemical and thermal reactions of II are described in the text.

3,4-Dehydro-β-ionylidenemalononitrile. In 200 ml of CCl_4, 24 g of I was allowed to react with 17.8 g of NBS with 0.5 g of benzoyl peroxide. The nmr spectrum of the product agreed with that of 4-bromo-β-ionylidenemalononitrile. The crude product was allowed to react with a mixture of *N,N*-dimethylaniline (70 ml) and pyridine (30 ml) at 95°. After the usual work-up, the crude product was purified by column chromatography (silica gel with benzene as solvent). The overall yield of 3,4-dehydro-β-ionylidenemalononitrile is 50%: ir (film) 2220, 970, and 730 cm^{-1}; nmr δ 1.12 (s, 6 H), 1.96 (s, 3 H), 2.32 (s, 3 H), 5.92 (s, 2 H), 6.90 (d, J = 16 Hz, 1 H), 7.14 (d, 1 H).

Conditions for photochemical reactions of the tetraenenitrile are similar to those described for I.

Acknowledgment. This work was partially supported by a grant from the Public Health Services (EY-AM 00918). Cmr spectra were obtained by Mr. J. Loo on a Varian XL-100 instrument made available through a NSF-DSD grant (GU 3855).

Registry No.—I, 52699-42-0; 3,4-dehydro-I, 52665-36-8; II, 52665-37-9; III, 52665-38-0; 3,4-dehydro-III, 52665-39-1; IV, 52665-40-4; 4-bromo-β-ionylidenemalononitrile, 52665-41-5.

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(7) See, *e.g.*, R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970.

Biological Probes. II. Ring Labeled Nicotinamide

T. A. Bryson,* J. C. Wisowaty, R. B. Dunlap, R. R. Fisher, and P. D. Ellis

Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

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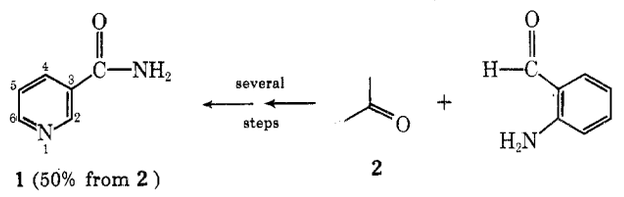
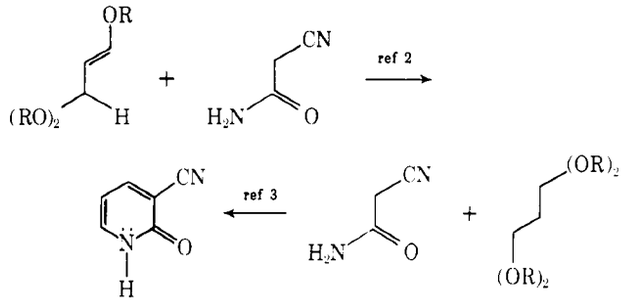
A growing interest in nonradioactive labels for use as general biological probes has led us to the development of efficient methods for the preparation of ring labeled nicotinamide (1). Previously we had described a high yield, six-step synthesis of $^{13}C_6$-amide 1 starting with carbon-13 labeled acetone.[1] We now wish to report a versatile labeling



1 (50% from 2) 2

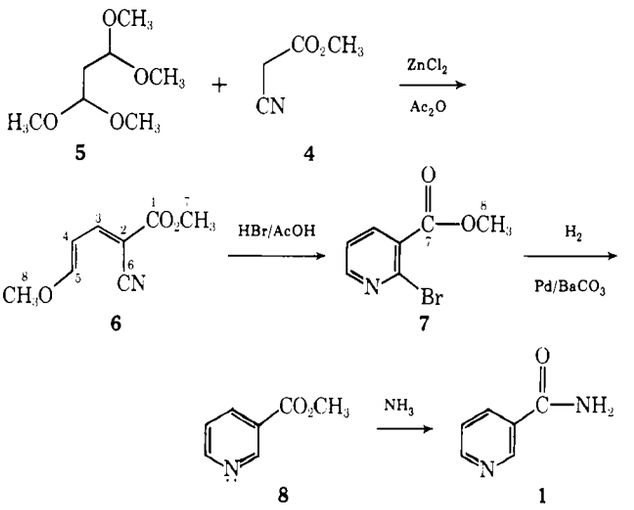
technique that can be applied to regiospecific labeling of pyridines and one which constitutes a vast improvement in the synthesis of 2-halonicotinic acid derivatives. Initially,



3

we had hoped to use the known 3-cyano-2-pyridone (3) as a precursor of amide 1 since the preparation of this pyridone 3 proceeds from readily accessible malonic acid derivatives. Unfortunately, neither the procedure of Dornow[2] nor that of Protopopova[3] could be modified to give a suitable yield of 3. High yield preparations of pyridines were finally realized through the reaction sequence in Scheme I.

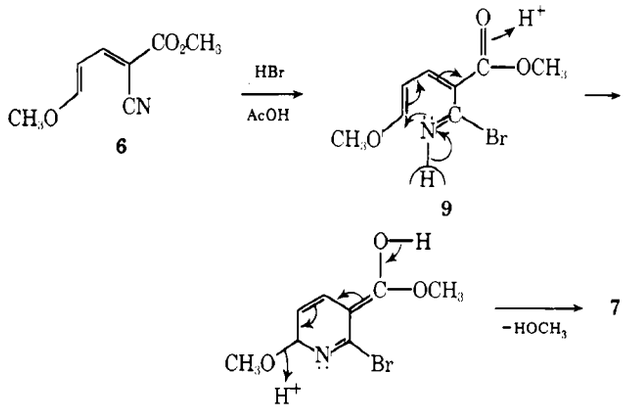
Scheme I



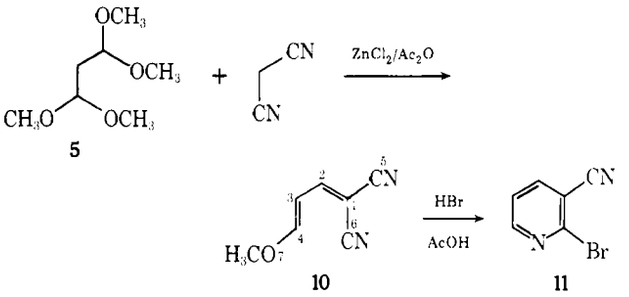
The zinc chloride catalyzed condensation of methyl cyanoacetate (4) and 1,1,3,3-tetramethoxypropane (5) in acetic anhydride afforded enol ether 6 (90%).[4] Ether 6, on treatment with HBr in acetic acid, undergoes a very facile intramolecular cyclization–elimination reaction forming methyl 2-bromonicotinate (7, 97%).[5] This ester 7 was converted to the desired amide 1 by catalytic hydrogenation (7 → 8, 93%) followed by treatment with aqueous ammonia (8 → 1); thus providing a convenient, high yield conversion of methyl cyanoacetate to nicotinamide (1, 60% from 5).

Presumably, this cyclization reaction is initiated by addition of HBr to the nitrile group of 6, forming iminobromide 9 (below) which, in turn, could add to the terminus of the conjugated ester system in a Michael-like reaction. Bromopyridine 7 would then be formed by simple elimination of methanol. It is interesting to note that the pmr and cmr spectrum of enol ether 6 indicated the presence of only one of several possible geometric isomers,[6] a fact which might fortuitously account for the nearly quantitative conversion of 6 to 7. It would seem more likely that under these strongly acidic conditions (HBr/AcOH) the geometry of the conjugated enol ether–nitrile is of little consequence.

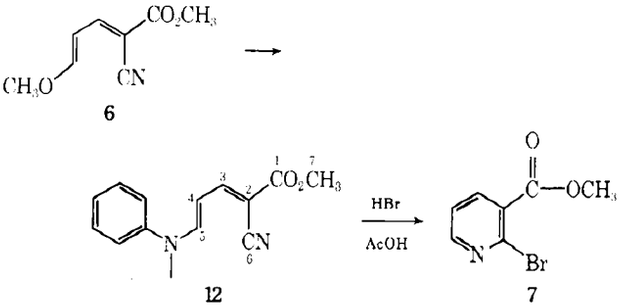
The reaction sequence operates with equal facility in forming 2-bromonicotinonitrile (11) from malononitrile.



The intermediate enol ether 10 likewise appears to be only one of two possible isomers and cyclizes to give bromonitrile 11 as the only product in high yield; thus demonstrating the ease by which various halopyridines can be prepared.



There are indications in the literature[7] that conjugated enamines analogous to ether 6 undergo similar acid-catalyzed cyclizations. To test this possibility methyl 2-cyano-5-*N*-methylanilino-2,4-pentadienoate (12)[8] was prepared by treating ether 6 with *N*-methylaniline in refluxing methanol (88% yield). Enamine 12 smoothly forms methyl 2-bromonicotinate (7) under the same acid conditions (HBr/AcOH) in high yield (87%).



The availability of methyl cyanoacetate specifically labeled at various positions with either ^{13}C and/or ^{15}N enhances the versatility of the procedure described above. Accordingly, nicotinamide-2-^{13}C has been prepared in excellent yield in four steps from methyl cyanoacetate[9] (^{13}C-nitrile labeled) and corresponding nmr labels at positions one and three of amide 1 are close at hand. In addition labeled nicotinamide (1) has been incorporated into NAD^+ through biosynthetic techniques.[1] Finally we note that (labeled or unlabeled) methyl 2-bromonicotinate can be readily converted into 2-aminonicotinic acid derivatives and similar structures[10] which are important antiinflammatory agents and therefore this facile enol ether cyclization provides a convenient synthetic route to a variety of important medicinal agents. Other aspects concerning the generality of this enol ether–nitrile cyclization will be forthcoming.

Experimental Section

Mass spectra or satisfactory elemental analysis was obtained for all compounds. Melting points were obtained on a Fisher-Johns hot stage melting point apparatus and are uncorrected. All boiling points reported are for bulb to bulb distillations and are the oven temperature recorded unless otherwise indicated. Coupling constants (J) are reported in Hz.

Methyl 2-Cyano-5-methoxy-2,5-pentadienoate (6). A mixture of tetramethoxypropane (12.3 g), acetic anhydride (25 ml), and $ZnCl_2$ (68 mg) was heated under reflux and methyl cyanoacetate (4.95 g, 0.5 mol) was added dropwise. Reflux was maintained for 18 hr after which the volatiles were distilled out until the distillation temperature reached 122°. The residue was cooled and filtered. The filtrate solidified on standing. The solid was distilled (Kugelrohr oven, 0.1 m) affording a yellow oil (bp 90°), acetate of diacetal 4 and a yellow solid (**6**, 7.5 g, 90%) 110–140° (partial decomposition): pmr $\delta_{TMS}(CDCl_3)$ 7.92 (d, J = 13, 1 H, C_3H), 7.42 (d, J = 13, 1 H, C_5H), 6.11 (t, J = 13, 1 H, C_4H) 3.95 and 3.89 (s and s, 6 H's, $-OCH_3$'s); ir (CH_2Cl_2) 2250, 1720, 1615 cm^{-1}; cmr (relative TMS, CH_2Cl_2 ppm) 117.03 (labeled CN); 167.3 (C_5), 164.1 (C_1), 156.2 (C_5), 117.0 (C_6), 104.0 (C_4), 99.0 (C_2), 59.7 (C_8), 53.5 (C_7); ir (C_7); ir (CH_2Cl_2) 2235, 1720, 1620, 1560 cm^{-1}.

Methyl 5-(*N*-Methylanilino)-2-cyano-2,4-pentadienoate. Enol ether (**6**, 5.0 g, 0.03 mol) was dissolved in methanol (400 ml) and *N*-methylaniline (4.8 g, 0.045 mol) added. The stirred mixture was heated under reflux for 6 hr, then cooled and volatiles were removed at reduced pressure. The darkened residue was titurated with ether–hexane (1:1) resulting in a solid that was recrystallized from CH_2Cl_2–ether and afford 6.35 g of **12** (88%, mp 145–146°); pmr δ_{CDCl_3}(TMS) 7.92 (d, J = 13, 1 H, C_3H), 7.5 (d, J = 13, 1 H, C_5H), 7.27 (m, 5 H, Ph-), 5.85 (t, J = 13, 1 H, C_4H), 3.74 (s, 3 H, OCH_3), 3.41 (s, 3 H, NCH_3); ir (CH_2Cl_2) 2230, 1700, 1615, 1560 cm^{-1}; cmr (relative to TMS, CH_2Cl_2 ppm) 118.09 (labeled nitrile), 164.3 (C_1),[11] 158.4 (C_5), 154.2 (C_3), 146.9 ($C_{1'}$), 130.8 ($C_{3',3'}$ or C_m), 127.0 ($C_{4'}$ or C_p) 121.6 ($C_{2',2'}$ or C_o), 118.1 (C_6), 101.1 (C_4), ~91 (C_2),[11] 52.9 (C_7 or $-OCH_3$), 38.7 (C_8 or NCH_3).

Methyl 2-Bromonicotinate (7) from Enamine 12. Enamine **12** (1 g, 0.004 mol) was dissolved in 5 ml of acetic acid and warmed to 40°. An acetic acid solution (10 ml) saturated with HBr (sat. at 0°) was added dropwise while maintaining the reaction mixture at 40–45°. After addition was complete the temperature was raised to 55° for 30 min. The darkened solution was cooled, poured into water, and neutralized by careful addition of Na_2CO_3. The aqueous solution was extracted with CH_2Cl_2 (3 × 125 ml). The organic extracts were combined, washed with water, and dried (Na_2SO_4). Evaporation of the volatiles at reduced pressure left a residue that was distilled (Kugelrohr oven at 0.1 m) affording a colorless liquid at 60° (*N*-methylaniline) and a viscous oil at 90–120° (**7**, 0.77 g, 87%): pmr δ_{CDCl_3}(TMS) 8.47 (dd, $J_{6,4}$ = 2, $J_{6,5}$ = 5, 1 H, C_6H), 8.07 (dd, $J_{4,5}$ = 8.5, $J_{4,6}$ = 2, 1 H, C_4H), 7.40 (dd, $J_{4\text{-}5}$ = 8.5, $J_{5,6}$ = 5, 1 H, C_5H), 3.95 (s, 3 H, OCH_3); ir = 1735 cm^{-1}; cmr (relative to TMS, CH_2Cl_2 ppm) 170.2 (C_7), 153.1 (C_6), 141.2 (C_2), 140.6 (C_4), 133.0 (C_3), 123.6 (C_5), 53.9 (C_8); cmr (relative to TMS, CH_2Cl_2 ppm) (C_2 label) 141.11, ir (CH_2Cl_2) 1735, 1580 cm^{-1}; pmr (labeled **7**) δ_{CDCl_3}(TMS) 8.47 (ddd, $J_{6,5}$ = 5, $J_{6,4}$ = 2, $J_{C_2,6}$ = 16, 1 H, C_6H), 8.07 (ddd, $J_{4,5}$ = 8.5, $J_{4,6}$ = 2, $J_{C_2,4}$ = 8, 1 H, C_4H), 7.40 (ddd, $J_{5,4}$ = 8.5, $J_{4,6}$ = 2, $J_{C_2,5}$ = 3, 1 H, C_5H).

Methyl 2-Bromonicotinate (7) from Vinyl Ether 6. Vinyl ether **6** (1.20 g, 0.007 mol) was treated with HBr in the exact manner described above for enamine **12** affording **7** (1.46 g, 97%, bp 105–120° (35 mm)); ir (film) 1735, 1580, 1560 cm^{-1}.

Methyl Nicotinate (8). At room temperature methyl 2-bromonicotinate (**7**, 1.65 g, 0.008 mol) was added to a vigorously stirred suspension of 1% Pd/$BaCO_3$ (10 g) in ethanol (150 ml) under hydrogen at atmospheric pressure. After 171 ml of H_2 was absorbed, the suspended catalyst was filtered and the volatiles were removed at reduced pressure. The resulting oil was distilled (bp 110–125° (~25 mm)) affording **8** (0.98 g, 93%, mp 42–43°); pmr δ_{CDCl_3}(TMS) 9.31 (dd, $J_{2,6}$ = 2 = $J_{2,4}$, 1 H, C_2H), 8.82 (dd, $J_{2,6}$ = 2, $J_{6,5}$ = 5), 8.43 (dt, $J_{4,5}$ = 8, $J_{2,4}$ = 2 = $J_{4,6}$, 1 H, C_4H), 7.40 (dd, $J_{4,5}$ = 8, $J_{4,6}$ = 5, 1 H, C_5H), 3.95 (s, 3 H, OCH_3), ir (CH_2Cl_2) 1725 and 1580 cm^{-1}; cmr (relative to TMS, CH_2Cl_2 ppm) 166.0 (C_7 or $-CO-$), 153.9 (C_6), 151.0 (C_2), 137.3 (C_4), 126.5 (C_3), 123.9 (C_5), 52.8 (C_8 or OCH_3); cmr (relative to TMS, CH_2Cl_2 ppm) (C_2 label) 151.16; ir (CH_2Cl_2) 1730 cm^{-1}.

Nicotinamide (1) was prepared from methyl nicotinate (**8**) as described earlier (approximately 75% from **8**):[1] ir (KBr) 3450, 1665, 1620 cm^{-1}; mp 130–131°.

1,1-Dicyano-4-methoxy-1,3-butadiene (10). Malononitrile (1.00 g, 0.015 mol) was converted to butadiene **10** following the procedure used to prepare vinyl ether **6** (1.23 g, 60%, bp 100–130° (10.01 mm)): ir (CH_2Cl_2) 2250, 1620 cm^{-1}; pmr δ_{CDCl_3}(TMS) 7.48 (d, J = 13, 1 H, C_3H), 7.40 (d, J = 13, 1 H, C_5H), 6.07 (t, J = 13, 1 H, C_4H), 3.92 (s, 3 H, OCH_3); cmr (relative to TMS, $CDCL_3$ ppm) 167.7 (C_4), 160.1 (C_2), 114.4 and 112.5 (C_5, C_6), 103.7 (C_3), 76.4 (C_1), 59.3 (C_7 or OCH_3).

Bromonicotinonitrile (11). Butadiene **10** (1.34 g, 0.01 mol) was converted to bromonicotinonitrile **11** following the procedure used to prepare methyl bromonicotinate (**7**, 1.59 g, 87%): ir (CH_2Cl_2) 2250 and 1580 cm^{-1}; pmr δ_{CDCl_3}(TMS) 7.49 (dd, $J_{4,5}$ = 8, $J_{6,5}$ = 5, 1 H, C_5), 8.03 (dd, $J_{4,5}$ = 8, $J_{4,6}$ = 2, 1 H, C_4), 8.70 (dd, $J_{6,5}$ = 5, $J_{6,4}$ = 2, 1 H, C_6H); cmr (relative to TMS, $CDCl_3$ ppm) 153.0 (C_6), 143.8 (C_2), 142.4 (C_4), 122.5 (C_5), 115.7 (C_3), 114.4 (C_7 or C ≡N).

Acknowledgment. We gratefully acknowledge the American Cancer Society (Grant Number BC-111) for support of this work.

Registry No.—**1**, 98-92-0; **4**, 105-34-0; **5**, 102-52-3; **6**, 52718-94-2; **7**, 52718-95-3; **8**, 93-60-7; **10**, 52718-96-4; **11**, 20577-26-8; **12**, 26932-71-8; *N*-methylaniline, 100-61-8; malononitrile, 109-77-3.

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(11) Estimated chemical shift from very weak signal.

Site of N-Amination of Adenine and Alkyladenines[1]

David F. Wiemer and Nelson J. Leonard*

Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

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In contrast to the many examples of heterocyclic *N*-oxides,[2] which are useful as synthetic intermediates and interesting because some, especially in the purine series,[3] have shown biological activity, there are fewer recorded examples of the isoelectronic *N*-imines and their corresponding *N*-amino salts.[4] The *N*-amino derivatives of the nucleic acid bases are of particular interest as intermediates and with respect to their possible biological activity. We wish to report the synthesis of 1-aminoadeninium salts and the effect of alkyl substituents on adenine upon the position of N-amination.[5]

Amination of a heterocyclic nitrogen is the most direct route to *N*-amino salts. Chloramine and hydroxylamine-*O*-sulfonic acid (HSA) are the traditional reagents used for N-amination,[4,6] while *O*-mesitylenesulfonylhydroxylamine (MSH)[7] and *O*-dinitrophenoxyamine[8] are enjoying increasing favor. Adenine (**1**) failed to aminate with HSA but with MSH in methanol yielded (≥65%) an *N*-aminoadeninium