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5-AMINOIMIDAZOLE CHEMISTRY

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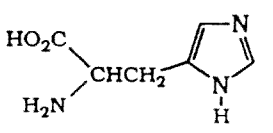
Contrary to reports in the early literature, 5-aminoimidazoles can be prepared in good yield as crystalline compounds. A study of their chemistry has shown that they behave as either C- or N-nucleophiles depending upon the nature of the electrophile. These addition and addition–elimination reactions provide useful new routes to nitrogen heterocycles. An important naturally occurring 5-aminoimidazole, aminoimidazole ribonucleotide (AIR) is a biosynthetic precursor of purines and thiamine. The chemistry of 5-aminoimidazoles is discussed and a synthesis of the aminoimidazole ribonucleoside (AIRs) and its biomimetic transformation to novel purine analogues is presented.

INTRODUCTION

Imidazoles are an important class of heterocycles. The imidazole ring occurs naturally in the α-amino acid histidine **1** and is a component of a number of synthetic products such as, for example, the antiulcer drug cimetidine **2**. Because imidazoles are of such fundamental interest it is surprising to find that the chemistry of the simple 4- and 5-aminoimidazoles **3** and **4**, respectively, which are potentially useful and versatile synthetic intermediates, has received little attention [1].



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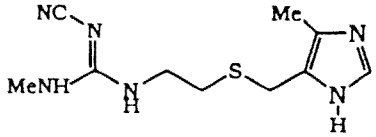

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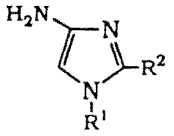

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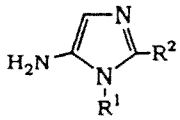

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This paucity of information is particularly remarkable since a simple 5-aminoimidazole derivative is an intermediate in the biosynthesis of purines and thiamine (Scheme 1). Mother Nature has been using a 5-aminoimidazole as a synthetic intermediate for millions of years.

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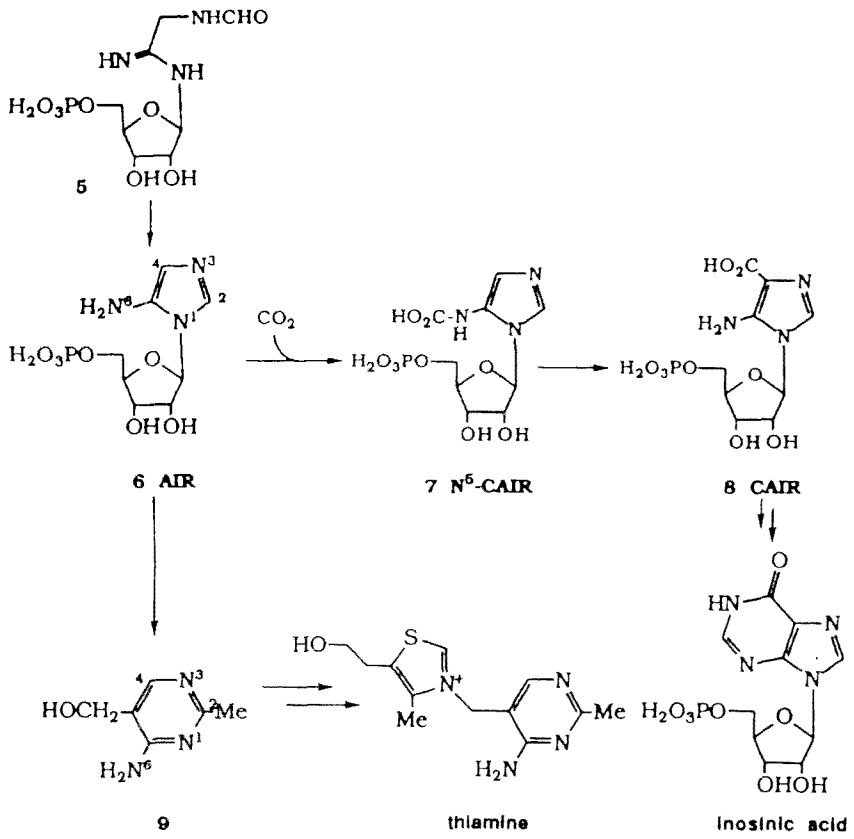
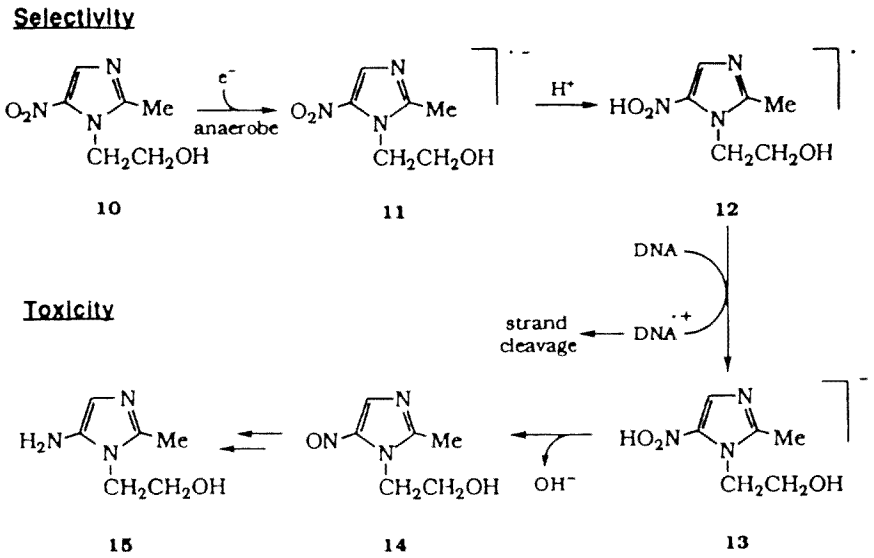


Scheme 1. Role of AIR in the biosynthesis of purine and thiamine

Relevant stages in the biosynthesis of purines are shown in Scheme 1. Aminoimidazole ribonucleotide (AIR) **6** is made by cyclization of N-formylglycinamidine ribonucleotide (**5**) which is carboxylated to give 4-carboxyaminoimidazole ribonucleotide (CAIR) (**8**). In a recent study using *E. coli*, Stubbe and coworkers have shown that AIR **6** is first transformed enzymatically into the carbamate **7** (N^5-CAIR), and a second enzyme then transforms this carbamate into CAIR **8** [2]. The transformation (**7** → **8**) is a key step in purine biosynthesis and is the only stage which gives a new C—C bond. In the context of this enzymatic process, it is relevant to note earlier studies by Shaw and coworkers, who showed that saturated aqueous bicarbonate in the absence of enzymes can transform 5-aminoimidazoles into their 4-carboxy derivatives [3]. A carbamate is also implicated in this process [4].

The enzymatic transformation of AIR **6** to the pyrimidine precursor **9** of thiamine in bacteria is a fascinating process. It is known that all the carbon atoms in the pyrimidine ring are derived from AIR **6** [5], and the relationship between atoms common to the imidazole and pyrimidine rings is shown in Scheme 1. How the enzyme achieves the insertion of a substituted carbon atom from the ribosyl fragment into the imidazole ring is not known.

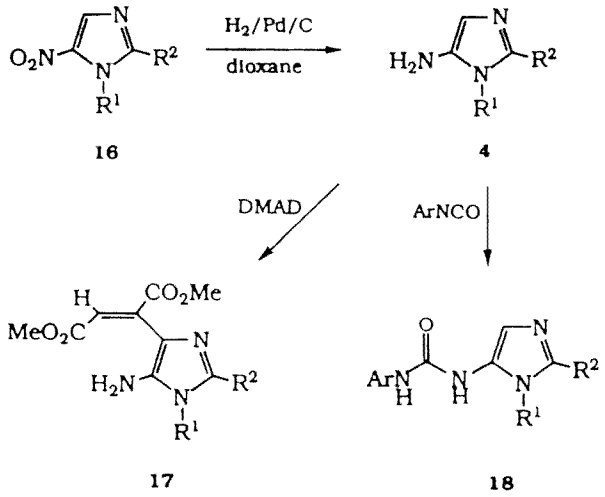
5-Aminoimidazoles are also of interest as metabolites of antibacterial 5-nitroimidazoles. Metronidazole **10** is an important drug which is effective against anaerobic bacteria [6]. It is used extensively to prevent and treat bacterial infections after surgery. The antibacterial action is achieved by selective bioreduction in the anaerobic environment of the microorganism (Scheme 2). Only in this environment do reducing enzymes occur with a suitably low reduction potential to achieve the one-electron reduction of the 5-nitroimidazole to its radical anion **11**. It is believed that this radical anion undergoes protonation to give a neutral radical **12**, which readily accepts an electron from DNA. The oxidized DNA subsequently undergoes strand cleavage leading to cell death [7]. The anion **13** formed by oxidation of DNA leads to the nitroso derivative **14**, which can undergo further reduction to the amine **15**. This 5-aminoimidazole **15** is known to be formed as a bacterial metabolite of metronidazole **10** [8] but, contrary to early speculation, it is not bactericidal [9].



Scheme 2. Bioreduction of metronidazole

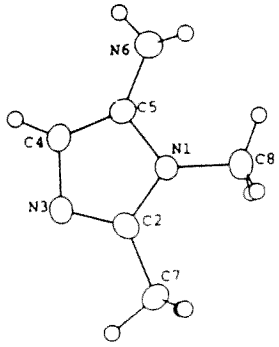
PREPARATION AND STRUCTURE

Although it was thought that the amine **15** might be the active antibacterial agent derived from metronidazole **10**, early attempts to prepare it were unsuccessful and contributed to the myth that 5-aminoimidazoles are too unstable to be isolated [10]. The first successful preparation of this amine **15** was by Sullivan and coworkers, who obtained it as a gummy solid by catalytic reduction of metronidazole in ethanol solution [9]. We also found that 5-aminoimidazoles **4** could be obtained in good yield by this method (Scheme 3) but we were only successful in isolating crystalline products **4** when we changed to using dioxane as solvent, which gave a much cleaner reaction than ethanol [11]. Prepared in this way, the amines are colorless crystalline compounds which slowly darken and decompose in air but which can be kept for long periods under an argon atmosphere in a freezer.



Scheme 3. Preparation and addition reactions of 5-aminoimidazoles

The spectroscopic properties of these amines **4** are all consistent with the 5-amino structure. The ^{1}H NMR spectrum of the 1,2-dimethylderivative (**4**; $R^1 = R^2 = Me$) is typical (δH($CDCl_3$) 2,1 (C—C$\underline{H}_3$), 3,2 (N—C$\underline{H}_3$), 4,15 (N$\underline{H}_2$), and 5,8



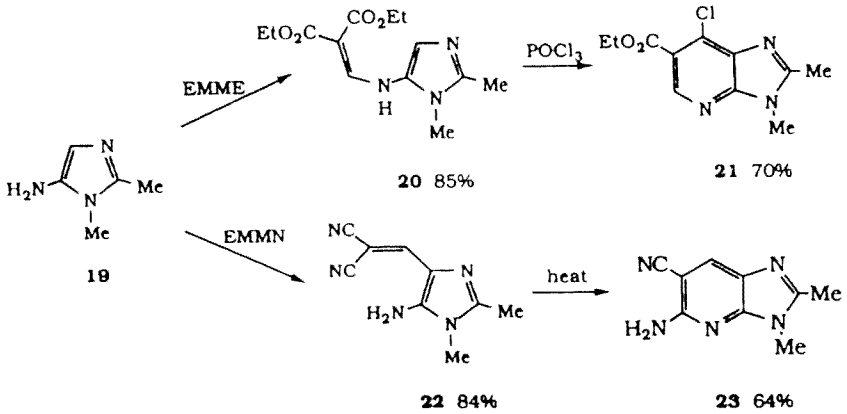
N(1)-C(2)	1.370 Å	C(5)-C(6)	1.400 Å
C(2)-N(3)	1.321 Å	C(5)-N(1)	1.391 Å
N(3)-C(4)	1.400 Å	N(1)-C(8)	1.463 Å
C(4)-C(5)	1.358 Å	C(2)-C(7)	1.486 Å

Fig. 1. Structure of 5-amino-1,2-dimethylimidazole determined by X-ray crystallography [12].

(C—H)) and is significantly different to that of the 5-nitroimidazole precursor (**16**; $R^1 = R^2 = Me$) (δH($CDCl_3$) 2,45 (C—CH_3), 3,9 (N—CH_3), and 7,9 (C—H)) [11]. We have recently confirmed the structure (**4**; $R^1 = R^2 = Me$) by X-ray crystallography [12], and the geometry is in accord with expectation (Fig. 1). The 5-amino group is slightly twisted out of conjugation with the imidazole ring, but this can be attributed to intermolecular hydrogen bonding in the crystal.

ADDITION AND ADDITION–ELIMINATION REACTIONS

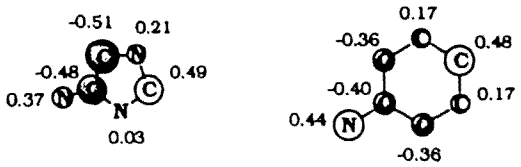
The preparation of the 5-aminoimidazoles **4** in good yield provided the opportunity of investigating their chemistry. We have found that they are N,C-ambident nucleophiles: with electrophilic reagents they undergo C- or N-addition (Scheme 3). Examples of C-addition are reactions of the amines with dimethylacetylenedicarboxylate (DMAD), which give the C-adducts – **17** in moderate yields. None of the isomeric N-adducts are detected. In contrast, aryl isocyanates react by N-addition, giving only the ureas – **18** [11]. For most reactions we have found it to be unnecessary to isolate the 5-aminoimidazoles. Instead we generate them in dioxane solution and use them immediately by addition of the appropriate reagent. In this way the addition–elimination reactions of a number of derivatives have been investigated, and results obtained using the 1,2-dimethyl derivative **19** are shown in Scheme 4. Reaction with diethylethoxymethylenemalonate (EMME) gave exclusively and in good yield (85%) the product derived from initial N-addition **20**. Cyclization of these diesters (e.g., **20**) using phosphorus oxychloride gives good yields (~70%) of 1-deazapurine derivatives (e.g., **21**). These are particularly useful intermediates from which a wide variety of purine analogues can be made [11].



Scheme 4. Formation of 1-deazapurine derivatives via addition–elimination reactions of 5-amino-1,2-dimethylimidazole

TABLE 1. Calculated (AMI) LUMO Energies for Selected Electrophilic Reagents

Species	Energy (eV)
CO_2	0.85
$EtOCH{=}CHCO_2Et$	0.18
$HC{\equiv}CCO_2Et$	0.14
$EtOCH{=}NCO_2Et$	-0.08
$EtOCH{=}NCN$	-0.14
PhNCO	-0.24
$EtOCH{=}C(CO_2Et)_2$	-0.40
$EtOCH{=}C(CN)CO_2Et$	-0.51
$(MeS)_2C{=}NCN$	-0.58
$EtOCH{=}C(CN)_2$	-0.62
$EtO_2CC{\equiv}CCO_2Et$	-0.80
$EtO_2CN{=}NCO_2Et$	-1.08



HOMO
ε = - 8.15 eV

HOMO
ε = - 8.53 eV

Fig. 2. Calculated HOMOs for 5-amino-1,2-dimethylimidazole and aniline.

When we reacted the same amines with the closely related reagent ethoxymethylenemalononitrile (EMMN), an unexpected result was obtained. Instead of N-addition, we observed exclusively C-addition in 84% yield. Typically, the 1,2-dimethyl derivative **19** gave the product **22**. The structure **22** is readily assigned from the ^1H NMR spectrum: the imidazole ring proton is absent and there is a broad singlet due to the primary amino group. The formation of the C—C bond (i.e., **19** → **22**) in this reaction is particularly interesting in that it is analogous to the important C—C bond-forming step in purine biosynthesis (i.e., **6** → **8**) (Scheme 1) and thus provides the opportunity of devising a biomimetic synthesis of purine analogues. When heated at 90°C in aqueous alcoholic alkali, compound **22** cyclized (64% yield) to the 1-deazapurine derivative **23**, which is an example of another useful class of intermediate for further synthesis.

FMO STUDY

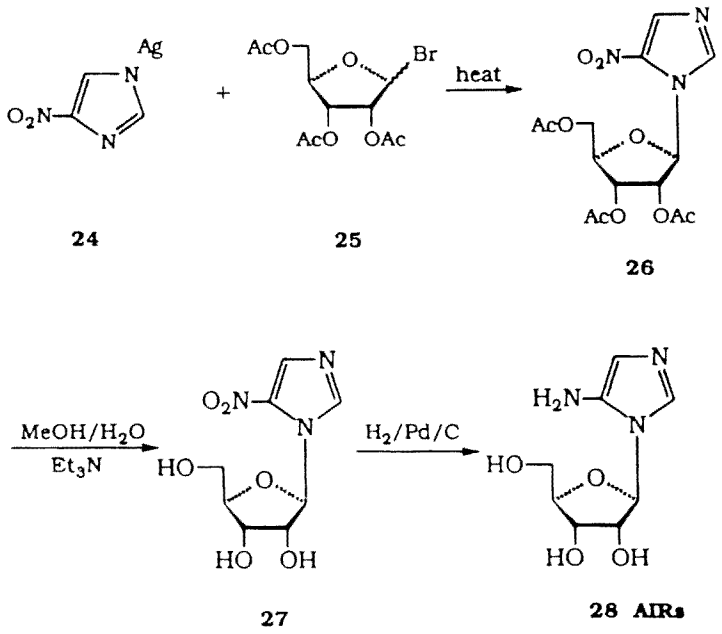
The N,C-ambident character of 5-aminoimidazoles prompted us to carry out semiempirical AM1 calculations on the 1,2-dimethyl derivative [11]. The highest occupied molecular orbital (HOMO) is of particular significance, and the orbital energy and coefficients are shown in Fig. 2 together with those for aniline. Based on the calculated HOMO energies the 5-aminoimidazoles are slightly more electron-rich than aniline and should be classified as borderline nucleophiles. The largest orbital coefficient of the HOMO occurs at the 4-position of the imidazole ring, and this coefficient is significantly larger than that on the exocyclic nitrogen atom. Note that, for aniline, one of the largest HOMO coefficients is on nitrogen. Based on these observations, we were encouraged to explore the hypothesis that soft electrophiles [HOMO (amine)—LUMO (electrophile) interactions] prefer to react at the 4-position, whereas harder electrophiles [Coulombic interactions] prefer reaction at the exocyclic nitrogen atom.

The transition states leading to N- and C-addition are, of course, different, and a variety of factors contribute to the relative reactivity. However, for a series of similar reagents we might reasonably expect the softer reaction center (C-4) to be increasingly favored as the reagents become softer. To further explore this possible rationalization of the observed regioselectivities, we calculated the LUMO energies of a series of electrophilic reagents using the AM1 method. The results are shown in Table 1.

The molecules in Table 1 are arranged in decreasing order of LUMO energy. Those at the top have the LUMOs with the highest energies and can be regarded as the hardest electrophiles. The results correlate well with our empirical observations [11, 13]. In our experience, those reagents with a calculated (AM1) LUMO energy greater than ca. 0.0 eV do not react with 5-aminoimidazoles. The group of reagents with LUMO energies in the range 0.0 to −0.5 eV tend to react by N-addition. The softer class of reagents with LUMO energies less than —0.5 eV are the ones that react primarily by C-addition. In this context it is interesting to note that aniline reacts with DMAD exclusively at the nitrogen atom to give anilinofumarate [14]. In contrast, 6-aminouracil, which is calculated to have an extremely large HOMO coefficient at C-5 [11], reacts exclusively at position 5, giving a C-adduct [15] in a manner analogous to the 5-aminoimidazoles.

BIOMIMETIC ROUTE TO NUCLEOSIDE ANALOGUES

The clean formation of 5-aminoimidazoles (**4**) from the corresponding 5-nitroimidazoles (**16**) (Scheme 3) provided us with the opportunity of investigating a new synthetic route to AIR **6** and of studying its chemical properties. In particular, we were interested in the possibility of C-addition of electrophilic reagents leading to a biomimetic route to nucleoside analogues.

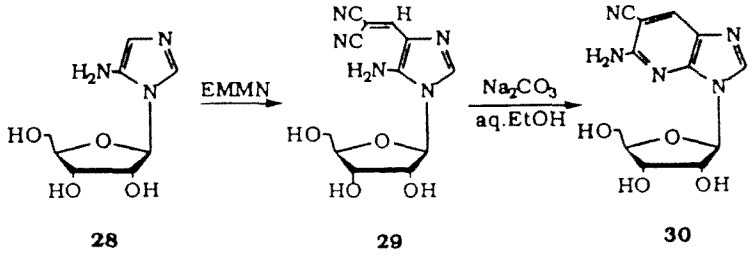


Scheme 5. Synthesis of aminoimidazole ribonucleoside (AIRs)

AIR **6** has previously been synthesized by Leonard and co-workers [16] by a route which involves decarboxylation of the nucleoside corresponding to CAIR **8**. Our approach is shown in Scheme 5. Using a modification of a method described by Imbach [17], the silver salt of 4(5)-nitroimidazole (**24**) was treated with 2,3,5-tri-O-acetyl-D-ribofuranosyl bromide (**25**) in hot xylene. The desired 5-nitro isomer **26** was obtained as the major product in 50% yield, and was easily separated from the 4-nitro isomer (30%) by chromatography. Deprotection of the sugar was straightforward, giving compound **27** in virtually quantitative yield. We were confident that the products **26** and **27** had the β-configuration, not only because of the mechanism of their formation but also because they meet the requirements of a number of NMR criteria which are diagnostic of β-anomers.

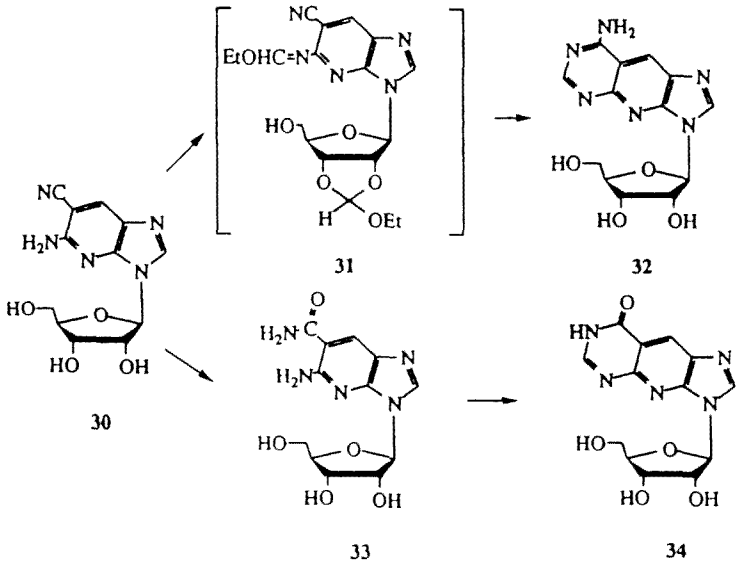
Finally, reduction of compound **27** in dioxane solution was extremely clean and gave a pure sample of aminoimidazole ribonucleoside (AIRs) **28** [18] which had spectroscopic properties identical with those described by Leonard and co-workers [16].

Treatment of AIRs **28** with EMMN, as expected from our previous studies, gave exclusively the C-addition–elimination product **29**. This was readily cyclized using a trace of base in hot ethanol to give the deazapurine derivative **30** (Scheme 6), which is suitable for further elaboration in a number of ways. Two examples are shown in Scheme 7.



28 **29** **30**

Scheme 6. Biomimetic 1-deazapurine synthesis



30 **31** **32** **33** **34**

Scheme 7. Synthesis of pyridine stretched nucleoside analogues

Reaction of compound **30** with excess diethoxymethyl acetate at reflux temperature gave a syrup, which we presume to be the intermediate **31**. Subsequent cyclization using methanolic ammonia gave the "pyridine stretched" analogue of adenosine **32** (55%). Attempts to achieve the transformation (**30** → **32**) using formamidine acetate were unsuccessful. Oxidation of the nitrile **30** using concentrated ammonia solution containing a catalytic amount of hydrogen peroxide gave the amide **33** (67%). This product **33** was cyclized using ethyl formate to give the "pyridine stretched" inosine analogue **34** (62%) [19].

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