Table II. Some Notable Bond Distances (Å) and Angles (deg) for the New Product $C_{11}H_8NCl_3$

Bond Distances	
C(8)-C(8a)	1.70
C(5)-C(9)	1.68
C(1)-C(8b)	1.29
C(N)-C(5)	1.48
C(5)-C(5a)	1.48
C(N)-C(3)	1.30
Bond Angles	
C(5a)-C(6)-C(7)	102
C(6)-C(7)-C(8)	114
C(5)-C(9)-C(8)	98
C(5a)-C(5)-C(9)	105
C(5)-C(5a)-C(6)	114
C(7)-C(8)-C(8a)	95

brown reaction mixture containing the products: **2** (GLC, t_r = 12.5 min), **2a** (GLC, t_r = 14.5 min), and **2b** (GLC t_r = 11.5 min), was evaporated and the residue chromatographed on 100 g of silica gel with hexane as the eluent. Fractions 4-6 containing compound **2b** were evaporated, and the residue were recrystallized from 2-propanol to give 0.21 g (3%) of white crystal: mp 45 °C; mass spectrum, m/z 260 ($M^{\cdot+}$), 225 ($M^{\cdot+}$ - Cl), 190 ($M^{\cdot+}$ - 2Cl), 155 ($M^{\cdot+}$ - 3Cl), 182 (trichloropyridine), 78 (benzene); ^{1}H NMR (δ) H5 4.33, H5a 3.30, H6 5.84, H7 6.47, H8 2.76, H8a 3.46, $H9_{endo}$ 1.27, $H9_{exo}$ 0.79, (J, Hz) 5,5a 2.0, 5a,8a 1.0, 5a,6 3.2, 6,7 5.8, 7,8 3.1, 8,8a 1.0, $8,9_{exo}$ 4.5, $9_{endo},9_{exo}$ 12.0, $5,9_{endo}$ 4.0; ^{13}C NMR (δ) C5 58, C5a 59.5, C6 127, C7 142, C8 49, C8a 61.4, C8b 132, C9 36.5, C1 104, C2 108, C3 110, (J, Hz) 5 163, 5a 147, 6 172, 7 172, 8 153, 8a 151, 9 137.

Anal. Calcd for $C_{11}H_8NCl_3$: C, 50.69; H, 3.09; N, 5.38. Found: C, 50.22; H, 3.12; N, 5.51.

X-ray Crystallography of 2b. Single crystals of the compound were sealed in thin-walled glass capillaries prior to examination. Final lattice parameters as determined from a least-squares refinement of the angular settings of 15 reflections (θ > 20°) accurately centered on an Enraf-Nonius CAD-4 diffractometer are given in Table I. Data were collected on the diffractometer by using procedures which have been previously described.[5] Three standard reflections were used during data collection; none of the intensities decayed by more than 8%. One independent quadrant was measured out to 2θ = 44° and a slow scan was performed on a total of 1546 unique reflections. The final value of R = 0.098 was achieved. The bond lengths and angles of **2b** are shown in Table II; the positional and thermal parameters in Table III (supplementary material).

Supplementary Material Available: Figure 1 (ORTEP drawing of **2b**) and Table III (positional and thermal parameters for **2b**) (2 pages). Ordering information is given on any current masthead page.

Synthesis of 4(5)-Acyl-, 1-Substituted 5-Acyl-, and 1-Substituted 4-Acyl-1*H*-imidazoles from 4-Aminoisoxazoles

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4-Aminoisoxazoles can be acylated with a wide variety of activated carboxylic acids. Hydrogenation of the resulting amides gives α-(acylamino)enaminones, which cyclize to 4(5)-acylimidazoles upon treatment with base. This method allows for the synthesis of acylimidazoles with a wide range of substituents at C-2. Utilization of N-substituted 4-aminoisoxazoles in the same sequence of reactions yields 1-substituted 5-acylimidazoles, a substitution pattern not otherwise easily prepared. Treatment of α-(acylamino)enaminones, derived from N-unsubstituted isoxazoles, with primary amines leads to incorporation of the amine at the β-position with concomitant expulsion of ammonia. This sequence efficiently yields 1-substituted and 1,2-disubstituted 4-acylimidazoles but does not give satisfactory yields of 5-substituted 4-acylimidazoles due to steric inhibition of the amine exchange.

Friedel-Crafts acylation of imidazoles is not possible because of the deactivation that occurs upon complexation of the basic imidazole with the Lewis acid.[1] As a result, other strategies must be employed to synthesize *C*-acylimidazoles. 2-Acylated derivatives can be synthesized indirectly through manipulation of the corresponding hydroxymethyl derivatives, obtained by hydroxymethylation,[2] or directly through carbanions derived from suitably N-protected imidazoles[3,4] and through the photochemical rearrangement of *N*-acylimidazoles.[5] Depending on the substituent pattern, the latter method can also provide 4-acylated imidazoles.[6] As in the 2-acyl series, 4(5)-acylimidazoles can be indirectly prepared through manipulation of the hydroxymethyl compounds obtained by either hydroxymethylation[2,7] or ring synthesis.[8] Metalation chemistry has also been applied to the synthesis of 4(5)-acylimidazoles; however, in addition to N-protection, this generally requires that the 2-position be suitably blocked by a protecting group or an unreactive substituent.[3,9] Our specific interest in 4(5)-acetylimidazoles as pharmaceutical intermediates led us to pursue efficient syntheses of these compounds that proceeded through ring-forming reactions. The first such synthesis developed utilized 3-bromo-4-ethoxy-3-buten-2-

(1) Grimmett, M. R. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1970; Vol. 12, p 179.
(2) Grimmett, M. R. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1980; Vol. 27, p 297. Reference 1, p 172.
(3) Iddon, B. *Heterocycles* **1985**, *23*, 417. Iddon, B.; Khan, N. *Tetrahedron Lett.* **1986**, *27*, 1635.
(4) Ohta, S.; Hayakawa, S.; Moriwaki, H.; Tsuboi, S.-i.; Okamoto, M. *Heterocycles* **1985**, *23*, 1759.
(5) Iwasaki, S. *Helv. Chim. Acta* **1976**, *59*, 2738.
(6) LaMattina, J. L.; Suleske, R. T.; Taylor, R. L. *J. Org. Chem.* **1983**, *48*, 897.
(7) Cue, B. W. Eur. Patent 116 205a, 22 Aug 1984.
(8) (a) Griffith, R. K.; DiPietro, R. A. *Synthesis* **1983**, 576. Paul, R.; Menschik, J. U.S. Patent 4 107 307, 15 Aug 1978. Antonini, I.; Cristalli, G.; Franchetti, P.; Grifantini, M.; Martelli, S. *Synthesis* **1983**, 47. (b) Kokosa, J. M.; Szafasz, R. A.; Tagupa, E. *J. Org. Chem.* **1983**, *48*, 3605.
(9) Carpenter, A. J.; Chadwick, D. J. *Tetrahedron* **1986**, *42*, 2351. Kirk, K. L. *J. Heterocycl. Chem.* **1985**, *22*, 57.

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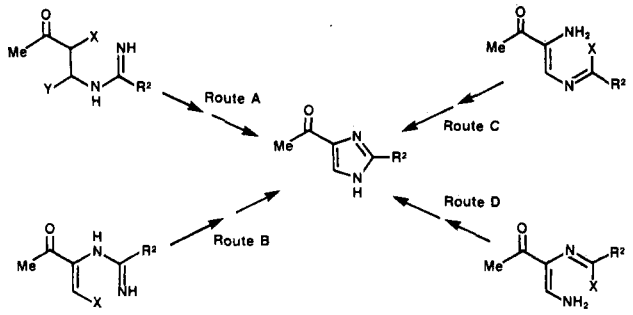
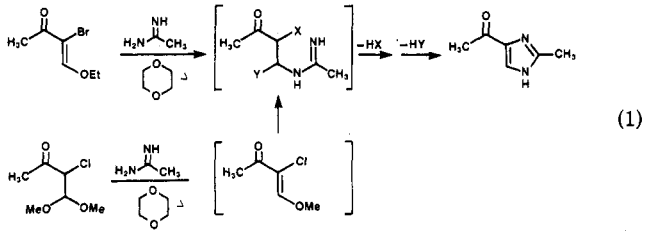
Scheme I[a]



[a] Note that the numbering of R groups in this and subsequent schemes reflects the ultimate positioning of these groups on the acylimidazole product.

one, which when treated with amidines gives the expected 4-acetylimidazoles (eq 1).[10] The synthesis of relatively

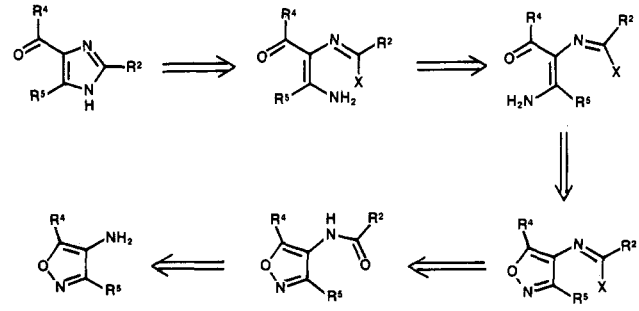


(1)

large quantities of the butenone was, however, not readily accomplished. As a result, we developed an alternative starting material for the sequence, i.e., 3-chloro-4,4-dimethoxy-2-butanone, which could be easily and reproducibly synthesized on a large scale.[11] This allowed us to prepare a few hundred grams of 4-acetyl-2-methylimidazole, which was required for development work. While this chemistry was well suited to satisfy our particular need for 4-acetyl-2-methylimidazole, because of the limited availability and reactivity of complex amidines, it was not so well suited for discovery work wherein we desired 4-acetylimidazoles with a wide variety of substituents on C-2. Since none of the methods cited above nor other available syntheses of acylimidazoles[12] appeared to satisfy our needs, we sought to develop new syntheses and, in particular, we considered potential routes in which the formation of a carbon–nitrogen bond would lead to the desired ring system.

Four possible routes to acetylimidazoles in which carbon–nitrogen bond formation leads to ring closure are shown in Scheme I. Route A had already been exemplified by our earlier work,[11] and route B involved an intermediate whose ring closure was regiochemically equivocal. Route C had no obvious drawbacks; however, a synthesis of the requisite α-amino-β-imidoylbutenones was not readily identified. In contrast, the α-imidoyl-β-aminobutenones required for implementation of route D were recognized to be the hydrogenation products of 4-imidoylisoxazoles. This is shown retrosynthetically in Scheme II. Such isoxazole imidates could be prepared from the amides, which would in turn be derived from the corresponding amines by acylation. The substituent on C-2 of the imidazole product would be derived from the acylating agent, and thus a wide range of groups could potentially be easily incorporated at this position. The

Scheme II



isoxazolamine required for the synthesis of 4-acetylimidazoles, i.e., 4-amino-5-methylisoxazole, is a known compound.[13] Thus, we engaged in an effort to synthesize 2-substituted 4-acetylimidazoles by such a sequence of reactions, and the success of this effort has been communicated.[14] Herein, we describe the full details of this work, its application to the synthesis of all but a few of the possible 4(5)-acylimidazole substitution patterns, and some improvements that we have made toward the synthesis of the aminoisoxazole precursors.

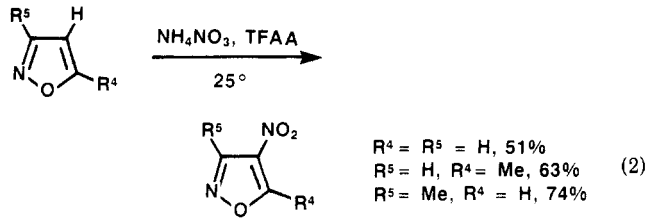
Discussion

Preparation of 4-Aminoisoxazoles. The generality of the sequence outlined in Scheme II is obviously limited by the availability of 4-aminoisoxazoles. These amines can be prepared by the aluminum amalgam,[15] zinc,[16] or stannous chloride mediated[13] reduction of the corresponding 4-nitroisoxazoles. These reductions are generally very efficient. The requisite nitroisoxazoles can be prepared by nitration of the corresponding 4-unsubstituted compounds. For example, 4-nitro-5-methylisoxazole, the isoxazole needed for the synthesis of 4-acetylimidazoles, has been prepared by nitrating 5-methylisoxazole with concentrated nitric acid in fuming sulfuric acid.[13] These conditions are typical of those used to prepare nitroisoxazoles containing aliphatic substituents; the isoxazole ring, being somewhat deactivated toward electrophilic substitution, requires potent nitrating conditions. Many functional groups, however, will not tolerate such drastic conditions, and the need to handle these strong acids is always somewhat hazardous. As a result, we sought other nitration methods that would be more convenient and would permit more functionality to be included.

Acetyl nitrate was found to be ineffective for nitrating 5-methylisoxazole; apparently a more potent agent is needed. One such agent, nitronium tetrafluoroborate, in refluxing acetonitrile was found to be effective, giving a 44% yield of the desired 4-nitro-5-methylisoxazole. One problem with this method, however, was the difficulty in monitoring the progress of the reaction and determining whether additional nitrating agent was needed to bring the reaction to completion. Another potent nitrating agent is trifluoroacetyl nitrate, which is presumably generated when nitrate salts are added to trifluoroacetic anhydride.[17] Application of this method gave a significantly better yield of the desired nitroisoxazole (63%). In addition, monitoring the progress of the reaction was easily accomplished by ^{1}H NMR; a neat aliquot of the reaction mixture had few interfering protons. This method, when applied to 3-methylisoxazole and isoxazole itself, gave the desired

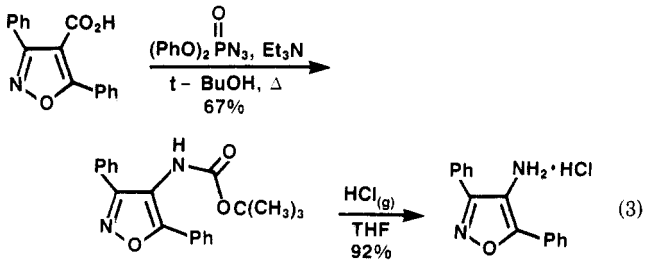
(10) Lipinski, C. A.; Blizniak, T. E.; Craig, R. H. *J. Org. Chem.* **1984**, *49*, 566.
(11) Reiter, L. A. *J. Org. Chem.* **1984**, *49*, 3494.
(12) Raghu, S.; Farina, J. S.; Peake, S. L. U.S. Patent 4 395 547, 26 July 1983. Veronese, A. C.; Vecchiati, G.; Sferra, S.; Orlandini, P. *Synthesis* **1985**, 300.
(13) Quilico, A.; Musante, C. *Gazz. Chim. Ital.* **1941**, *71*, 327.
(14) Reiter, L. A. *Tetrahedron Lett.* **1985**, *26*, 3423.
(15) Morgan, G. T.; Burgess, H. *J. Chem. Soc., Trans.* **1921**, *119*, 697.
(16) Keana, J. F. W.; Little, G. M. *Heterocycles* **1983**, *20*, 1291.
(17) Crivello, J. V. *J. Org. Chem.* **1981**, *46*, 3056.

nitroisoxazoles in 74% and 51% yields, respectively (eq 2). The extremely base-sensitive 4-nitroisoxazole had



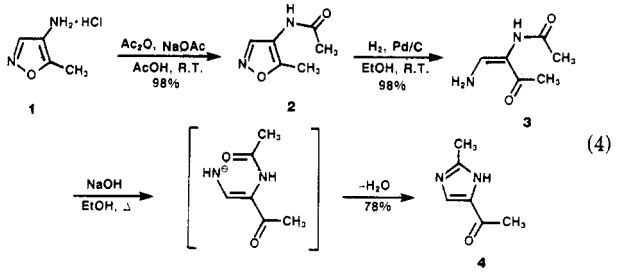
previously been best prepared by nitration with nitronium tetrafluoroborate in sulfolane, which gave 35% yield;[18] nitric acid in sulfuric acid gave only a 3.5% yield of 4-nitroisoxazole.[19] The trifluoroacetyl nitrate method then is a significant improvement over the earlier nitration procedures and should be applicable to any isoxazole with substituents that are not in themselves easily nitrated or otherwise reactive to the relatively mild, although acidic, reaction conditions.

Phenyl-substituted 4-nitroisoxazoles are examples of compounds that cannot be efficiently prepared through nitration because in many instances the phenyl ring is more active toward electrophilic substitution than is the isoxazole.[20] As a result, other strategies must be chosen to synthesize these compounds. Direct synthesis of 4-nitroisoxazoles containing phenyl groups can be achieved through various ring-forming reactions.[21] Likewise, compounds containing other sensitive functionalities (e.g., acetals or esters) can be prepared through ring-forming reactions.[16,22] Another potential route to 4-aminoisoxazoles is the rearrangement of the corresponding 4-carboxylic acids in a Curtius, Hofmann, or Schmidt reaction. Such chemistry has received little attention, the only example of which we are aware is the Hofmann rearrangement of 3-phenylisoxazole-4,5-carboxylic acid diamide to 3-phenyl-4-aminoisoxazole-5-carboxylic acid amide.[23] Since isoxazole-4-carboxylates with a variety of 3- and 5-substituents are readily availble through 1,3-dipolar cycloadditions,[24] we felt that a more relevant demonstration of the utility of this route would be worthwhile. Thus, 3,5-diphenylisoxazole-4-carboxylate was subjected to a modified Curtius rearrangement using diphenylphosphoryl azide in *tert*-butyl alcohol (eq 3).[25] The resulting *tert*-



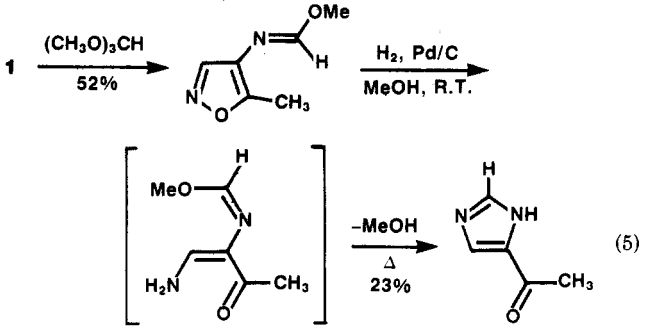
butyl carbamate was obtained in 67% yield. The carbamate was then cleaved with HCl(g) in THF, giving the desired amine as its salt in 92% yield. In the Curtius rearrangement, the use of alcohols other than *tert*-butyl alcohol (e.g., phenol) to capture the isocyanate intermediate would allow deprotection of the amine under nonacidic conditions. Through this sequence, the improved nitration procedure and the cited ring-forming reactions, a wide variety of 4-aminoisoxazoles is available.

Preparation of 4(5)-Acyl-1*H*-imidazoles. In beginning, our investigations aimed at applying the reactions outlined in Scheme II, we initially focused on the synthesis of 4-acetyl-2-methylimidazole, a compound with which we had considerable experience. The synthesis of 4-acetylimidazoles requires that the reaction sequence be begun with 4-amino-5-methylisoxazole (1), and the synthesis of the 2-methylimidazole derivative requires that 1 be acetylated (eq 4). Aminoisoxazole 1 was prepared by the



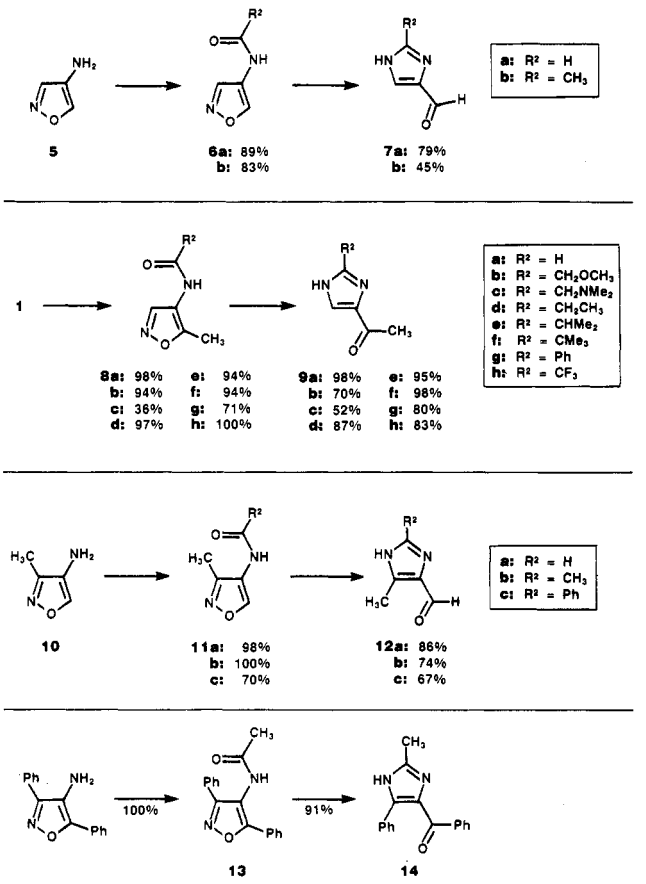
aluminum amalgam reduction of the corresponding nitroisoxazole and was quantitatively acetylated with acetic anhydride. Rather than convert the resulting amide **2** to an imidate, which was the initial plan, we first investigated its direct utilization. Thus, hydrogenation of **2** over 10% palladium on carbon gave the expected ring-cleaved product, the 2-acetamidoenaminone **3**, an isolable substance. Subsequent refluxing of **3** in ethanol led to no reaction; however, addition of 1 mol equiv of sodium hydroxide led to relatively rapid cyclization, with complete conversion occurring after 30–60 min. Workup consisted of a quench with solid ammonium chloride and removal of the inorganic salts by filtration. Such a workup is particularly useful because it avoids contacting by the products with aqueous solutions in which many of the lower molecule weight acylimidazoles are quite soluble. Utilization of potassium carbonate as the base to induce cyclization of **3** was not nearly as effective as sodium hydroxide; the reaction was very slow, taking about 20 h of reflux with a large excess of potassium carbonate. Organic bases such as *N,N,N′,N′*-tetramethylguanidine or DBN were even less effective, with the reaction occurring more slowly and less cleanly. Potassium *tert*-butoxide in *tert*-butyl alcohol was effective at inducing the dehydrative cyclization, and presumably, other alkoxides would be as well.

Although direct utilization of an *N*-isoxazolylamide had been successfully demonstrated, we still explored the use of an imidate in the reaction sequence. Thus, amine 1 was treated with an excess of trimethyl orthoformate to give the desired imino ester in 52% yield (eq 5). The relatively



(18) Kusumi, T.; Nakanishi, K. U.S. Patent 4 288 445, 8 Sept 1981.
(19) Kochetkov, N. K.; Khomutova, E. D. *Zh. Obshch. Khim.* **1959**, *29*, 535; *Chem. Abstr.* **1960**, *54*, 498c.
(20) Katritzky, A. R.; Konya, M.; Tarhan, O.; Burton, A. G. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1627.
(21) Dal Piaz, V.; Pinzauti, S.; Lacrimini, P. *Synthesis* **1975**, 664. Hauff, J.-P.; Tuaillon, J.; Perrot, R. *Helv. Chim. Acta* **1978**, *61*, 1207.
(22) Nesi, R.; Chimichi, S.; Sarti-Fantoni, P.; Buzzi, A.; Giomi, D. *Heterocycles* **1985**, *23*, 1465.
(23) Desimoni, G.; Grunanger, P. *Gazz. Chim. Ital.* **1967**, *97*, 25.
(24) Stork, G.; McMurry, J. *J. Am. Chem. Soc.* **1967**, *89*, 5461. Christl, M.; Huisgen, R.; Sustmann, R. *Chem. Ber.* **1973**, *106*, 3275.
(25) Shioiri, T.; Ninomiya, K.; Yamada, S.-i. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

Scheme III



low yield of this imidate was due to its high propensity to react further with aminoisoxazole, or to disproportionate, to give the *N,N'*-bis(isoxazolyl)amidine. Hydrogenation of chromatographically purified imino ester gave a more polar material, which when refluxed in methanol gave 4-acetylimidazole, although in quite low yield. Our experience with this one example and the earlier result in which the amide **2** was utilized directly indicated that there was no advantage in proceeding through an imidate intermediate and, in fact, doing so may even be disadvantageous.

With these results, we were prepared to exploit this chemistry for our needs, and our previous report showed that 4-acetylimidazoles with a wide variety of substituents at C-2 can be prepared by this sequence.[14] We now describe how this isoxazole to imidazole "rearrangement" can be applied to the synthesis of all but a few of the possible substitution patterns of 4(5)-acylimidazoles.

There are four substitution patterns of 4(5)-acylimidazoles in which there is no N-substitution. These are 4-acyl-, 2-substituted 4-acyl-, 5-substituted 4-acyl-, and 2,5-disubstituted 4-acylimidazoles. All of these can be prepared through this chemistry (Scheme III).

4-Acylimidazole synthesis requires that the starting isoxazole be unsubstituted at position 3 and that the 4-amino group be formylated. Thus, 4-aminoisoxazole (**5**) prepared by the aluminum amalgam reduction of 4-nitroisoxazole, and **1** gave the formamides **6a** and **8a**, respectively. Subsequent "reductive rearrangement" led to the monosubstituted 4-acylimidazoles **7a** and **9a**. While these are relatively simple imidazole derivatives, inclusion of a more complex group at position 5 of the isoxazole obviously would lead to a more elaborate imidazole ketone.

2-Substituted 4-acylimidazoles can be prepared from 3-unsubstituted 4-aminoisoxazoles that have been acylated with an activated carboxylic acid other than formic acid. Thus, isoxazoles **6b** and **8b–8i** led to the 2-substituted 4-acylimidazoles **7b** and **9b–9i**, respectively. As we had desired, the 2-substituent can be easily varied by acylating with diverse activated carboxylic acids. Incorporation of functionalized side chains such as methoxymethyl or (dimethylamino)methyl, highly hindered side chains such as 2-propyl or *tert*-butyl, or strongly electron-withdrawing side chains such as trifluoromethyl is easily accomplished, generally in very high yield. Such compounds, easily prepared here, could not have been readily prepared by any of the earlier methods. We have successfully acylated aminoisoxazoles with anhydrides, *N*-acylimidazolides, mixed anhydrides, and acid chlorides. Through one of these acylating procedures, or possibly others, virtually any carboxylic acid can be utilized. Subsequent intact incorporation onto C-2 of an acylimidazole requires only that the functionality and/or the protecting groups in the carboxylic acid be stable to hydrogenation and treatment with base, e.g., hydroxide or alkoxide.

5-Substituted 4-acylimidazoles are derived from 3-substituted or 3,5-disubstituted 4-aminoisoxazoles that have been formylated. Only a single example of this pattern is included here; amine **10**, prepared by the aluminum amalgam reduction of the corresponding nitroisoxazole, was formylated to give isoxazole **11a**, which yielded imidazole **12a**. Utilization of isoxazoles with substituents at C-3 other than a methyl group obviously would allow the synthesis of imidazoles with more complex substituents on C-5.

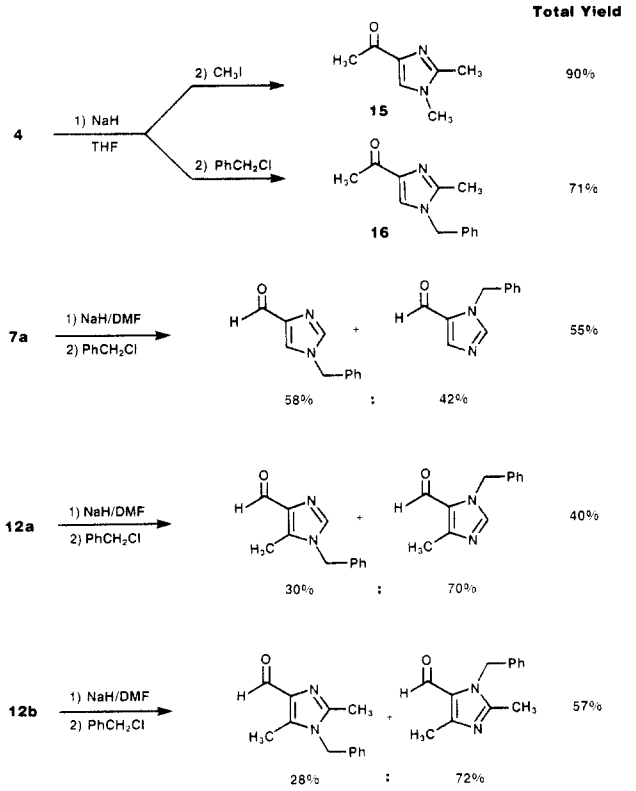
2,5-Disubstitued 4-acylimidazoles are also derived from 3-substituted or 3,5-disubstituted 4-aminoisoxazoles; however, in this case the 4-amino function must be acylated with a reagent other than a formate derivative. Thus, isoxazoles **11b**, **11c**, and **13** yielded the imidazoles **12b**, **12c**, and **14**, which exemplify this substitution pattern. Other exmaples of this pattern are provided in some earlier work by Ajello.[26]

Preparation of 1-Substituted 4-Acyl- or 5-Acylimidazoles. The regiospecific synthesis of N-substituted imidazoles is not always a straightforward operation. Direct alkylation may proceed to give a single isomer, or a mixture of the two possible isomers may result.[27] The outcome depends primarily on the relative sizes of the substituents at positions 4 and 5. In the case of acylimidazoles, an acetyl group is sufficiently larger than a proton to direct alkylation entirely toward the less sterically hindered nitrogen, yielding exclusively the 1-substituted 4-acetyl derivatives (Scheme IV). Thus, **4** gives the *N*-methyl and *N*-benzyl derivatives **15** and **16** exclusively. However, benzylation of **7a** gives a mixture of the 1,4- and 1,5-disubstituted imidazoles. Similarly, **12a** and **12b** both give mixtures of N-benzylated compounds.

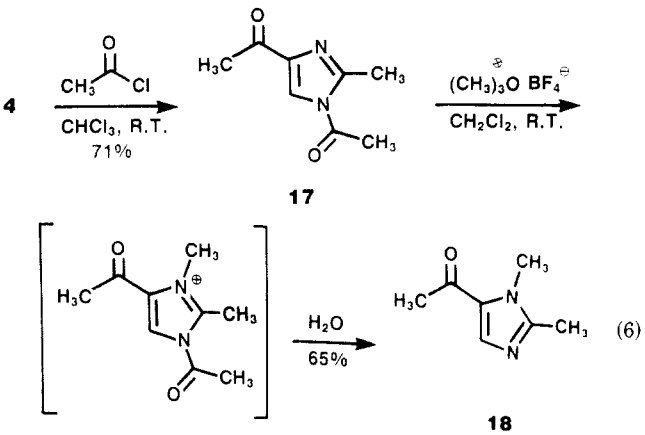
In the cases where a single product can be obtained, this will have a 1,4-relationship between the N substituent and the larger of the groups on C-4 and C-5. If a 1,5-relationship is desired, however, another route must be taken. One route to such compounds involves initial protection of the least hindered ring nitrogen followed by alkylation of the more hindered nitrogen and final deprotection.[28]

(26) Ajello, E. *Ann. Chim. (Rome)* **1970**, *60*, 343; *Chem. Abstr.* **1970**, *73*, 87857p.
(27) Lipshutz, B. H.; Morey, M. C. *J. Org. Chem.* **1983**, *48*, 3745.
(28) Olofson, R. A.; Kendall, R. V. *J. Org. Chem.* **1970**, *35*, 2246.

Scheme IV



This procedure can be applied to *C*-acylimidazoles; thus, **4** was selectively N-acetylated to give **17**, which was then alkylated with trimethloxonium tetrafluoroborate (eq 6).



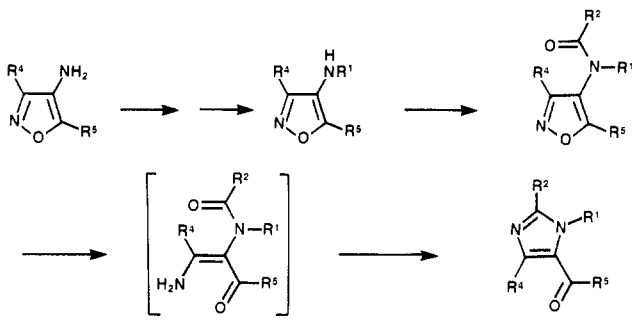
(6)

Deprotection by quenching the reaction with water gave 1,2-dimethyl-5-acetylimidazole, the "more hindered" isomer **18**. When applying this procedure, other workers have utilized alkylating agents besides oxonium salts, e.g., benzyl bromide;[29] however, in the present case this does not appear to be possible. The presence of two acyl groups on the imidazole ring deactivates it to such an extent that refluxing **17** in neat methyl iodide led to no reaction. As a result, this procedure is significantly limited by the availability of alkylating agents potent enough to react with the very electron-poor diacylimidazole.

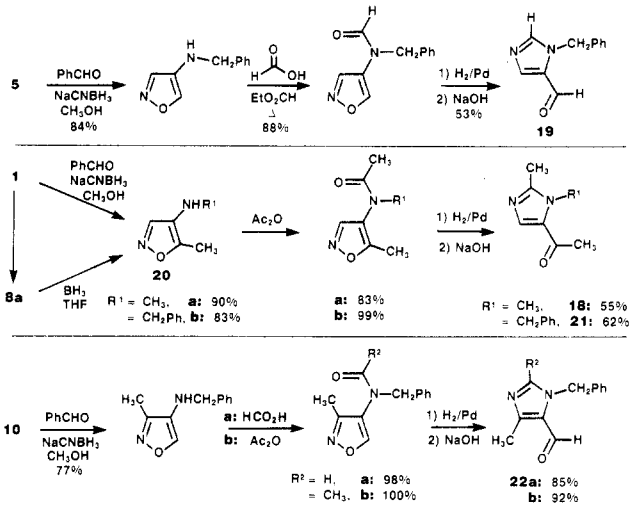
While few 1-substituted 5-acylimidazoles can be prepared through the above protection/alkylation/deprotection procedure, a relatively simple modification of the sequence described in Scheme II allows the preparation of a wide variety of these compounds. Thus, if the 4-amino

(29) Godefroi, E. F.; Mentjens, J. H. F. M. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 56.

Scheme V



Scheme VI

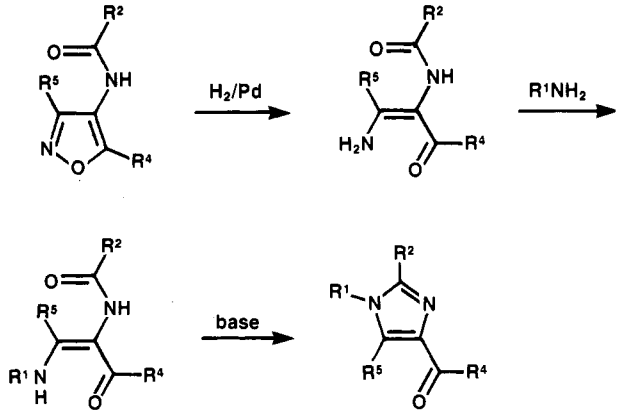


group is substituted and then carried through the standard sequence of acylation, hydrogenation, and base-induced ring closure, 1-substituted 5-acylimidazoles are obtained (Scheme V). The success of this sequence was described for a single substitution pattern in our earlier report.[14] We now describe its application to all possible 1-substituted 5-acylimidazole substitution patterns, which include 1-substituted, 1,2-disubstituted, 1,4-disubstituted, and 1,2,4-trisubstituted 5-acylimidazoles (Scheme VI).

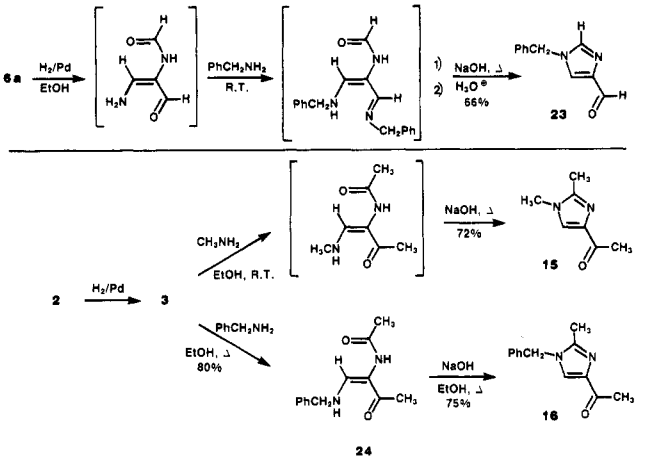
Reductive benzylation of 4-aminoisoxazole (**5**) followed by formylation, hydrogenative ring opening, and base-induced dehydrative ring closure gave the first of these substitution patterns, a 1-substituted 5-acylimidazole **19**. The 1,2-disubstituted 5-acyl pattern is illustrated with two examples. Thus, the substituted amines **20a** and **20b**, prepared in one or two steps from **1**, were acetylated and reductively rearranged to give the trisubstituted imidazoles **18** and **21**. The *N*-methyl derivative **18** prepared in this manner was identical with that prepared by Olofson's procedure[28] as described above. A trisubstituted imidazole having the 1,4,5-trisubstitution pattern was prepared by reductive benzylation of amine **10** followed by formylation and reductive rearrangement yielding **22a**. The final variation, which has substitution at all possible positions, was again derived from amine **10**; reductive benzylation, acetylation, and reductive rearrangement gave the 1,2,4-trisubstituted 5-acylimidazole **22b**.

Some 1-substituted 4-acylimidazoles may be prepared through simple alkylation, as was discussed above; however, there are many imidazoles that will not selectively alkylate to give a single isomer (e.g., see Scheme IV). Since we had found that the 2-(acylamino)enaminone intermediate **3** required a strong base to induce cyclization, we reasoned that treatment of any of the intermediate 2-(acylamino)enaminones with a primary amine would lead

Scheme VII



Scheme VIII

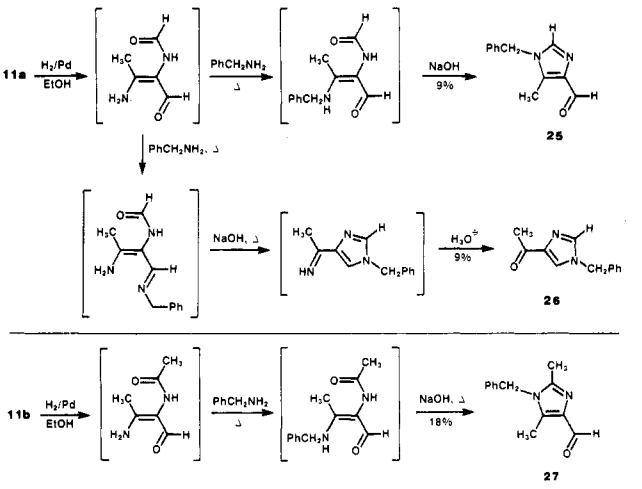


to exchange of the β-amino group rather than imidazole formation. Such an exchange would allow us to synthesize 1-substituted 4-acylimidazoles (Scheme VII). This possibility is of particular interest in those cases where the synthesis of 1-substituted 4-acylimidazoles cannot be selectively prepared through alkylation. This sequence has been investigated, and of the four possible imidazoles with a 1,4-relationship between the N-substituent and the acyl group, the 1-substituted and 1,2-disubstituted 4-acylimidazoles are available through this chemistry, while the 1,5-disbustituted and 1,2,5-trisubstituted 4-acylimidazoles cannot be obtained efficiently through such a sequence of reactions.

Hydrogenation of **6a** gave the expected 2-(acylamino)-enaminone, which when treated with an excess of benzylamine at room temperature led to the desired exchange of benzylamine for ammonia (Scheme VIII). The benzylamine adduct was not isolated but was directly treated with sodium hydroxide to induce cyclization. This gave the benzylimine of the desired imidazolecarboxaldehyde, and the free aldehyde **23** was obtained in 66% yield after acid hydrolysis of the imine. Thus, 1-substituted 4-acylimidazoles are available by this method, and although this particular example was somewhat complicated by the imine formation, this problem is probably restricted to imidazolecarboxaldehydes. Note that the product of this particular reaction could not be selectively prepared by alkylation of **7a** (see Scheme IV).

In a similar fashion, two examples of the 1,2-disubstituted 4-acylimidazoles were synthesized. The 2-acetamidoenaminone **3** was treated with methylamine or benzylamine to give the expected exchange products (Scheme VIII). The methylamine adduct was not isolable,

Scheme IX



and so it was directly cyclized with base, giving a 72% overall yield of 4-acetyl-1,2-dimethylimidazole (**15**), which was identical with the material prepared by methylation of **4**. The benzylamine adduct **24** was isolable and was obtained in an 80% recrystallized yield. Cyclization with sodium hydroxide in ethanol gave a 75% yield of 4-acetyl-1-benzyl-2-methylimidazole (**16**), which was identical with material prepared by benzylation of **4**. In neither of these two cases was the imine of the desired imidazole ketone detected. Aniline did not readily react with **3**, suggesting that an amine with nucleophilicity on the order of a primary aliphatic amine is required for the exchange reaction to occur. Thus, the N-substituent introduced through this chemistry can be derived from a wide range of aliphatic amines, and perhaps electron-rich aromatic amines, as long as the functionality or protecting groups therein are stable to sodium hydroxide or alkoxide.

While the above examples were executed with little trouble, attempts to apply this sequence to 1,5-disubstituted and 1,2,5-trisubstituted 4-acylimidazoles were much less successful. Thus, hydrogenation of **11a** gave the desired 2-(acylamino)enaminone, but treatment with benzylamine did not lead to a single predominant product, as had been observed in the earlier cases (Scheme IX). Complete consumption of the 2-(acylamino)enaminone was forced by refluxing with excess benzylamine; the mixture was then treated with sodium hydroxide in the standard fashion, quenched, and treated with aqueous acid to hydrolyze any imine that might have formed. Chromatography then gave a 19% yield of a 1:1 mixture of two isomeric compounds, 1-benzyl-5-methylimidazole-4-carboxaldehyde (**25**), the expected product, and 1-benzyl-4-acetylimidazole (**26**). This result indicates that the exchange of benzylamine for ammonia is significantly impaired by the β-methyl group on the 2-(acylamino)enaminone. As a result, in this case benzylamine also reacts with the aldehyde of the acyclic intermediate, giving the corresponding imine. The benzyl-substituted nitrogen of this adduct then reacts with the neighboring amide, giving an imidazole. Hydrolysis of the imine during workup leads to the observed acetylimidazole. In addition to this undesired reaction path, others must also be operating to account for the low mass balance.

An attempt to apply the same sequence of reactions to **11b** led to a similar complex reaction mixture; however, in this case only the expected product **27** was obtained in 18% yield (Scheme IX). Again, other undesired reactions must be occurring to account for the low mass balance. The conclusion, therefore, must be made that the reaction sequence in Scheme VII will not be suitable for any case

where $R^5 \neq H$ due to the steric inhibition by such a substituent on the amine exchange.

Conclusions

Herein, we have described a versatile synthesis of 4-(5)-acylimidazoles that allows the unequivocal placement of substituents at all positions of the imidazole ring. The substituent at C-2 of the imidazole is derived from a carboxylic acid. As a result, diverse groups can easily be incorporated at this position; this we have amply demonstrated. The substituents on C-5(4) and the adjacent acyl group depend, respectively, on the substituents at positions 3 and 5 of the starting isoxazole. These too can be widely varied, although some preliminary synthesis may be required in order to obtain the appropriate 4-aminoisoxazole. The method can be easily adapted to provide imidazoles with a 1,5-relationship between the nitrogen substituent and the acyl group, and the choice of substituents that can be placed at position 1 is limited only by what groups can be placed on the amino group of a 4-aminoisoxazole. Simple alkyl, functionalized alkyl (e.g., heteroatom substituted), and aralkyl groups can all be readily introduced. Aryl and hindered alkyl groups can probably be incorporated, although not as easily. The method can also be utilized to synthesize imidazoles with a 1,4-relationship between the nitrogen substituent and the acyl group, provided that C-5 of the imidazole product is unsubstituted. In this case, the nitrogen substituent is derived from a primary amine that must be sufficiently nucleophilic to add to the β-position of a β-amino-α,β-unsaturated ketone. We have utilized only aliphatic amines; however, nucleophilic aromatic amines should also be suitable. Of all the possible imidazole substitution patterns, only 1,5-disubstituted and 1,2,5-trisubstituted 4-acylimidazoles are not available through this chemistry. 4-Aminoisoxazoles, the key starting materials, can be prepared by a number of methods, some of which we have improved and described herein. The availability of 4-aminoisoxazoles with diverse substituent patterns and the general utility of the imidazole acyl groups for the elaboration of complex functionality should allow this reductive rearrangement method to be exploited for the synthesis of imidazoles in general.

Experimental Section

NMR spectra were obtained on a Varian EM-390 spectrometer, and chemical shifts are reported from the standard tetramethylsilane. IR spectra were obtained on a Perkin-Elmer 283 spectrophotometer. Low-resolution mass spectra were obtained on a Finnigan EI-CI mass spectrometer, and exact masses were determined on a A.E.I. MS30 spectrometer. Melting points are uncorrected and were determined in open capillaries. Elemental analyses were performed by the Analytical Department of Pfizer, Inc. Solvents and reagents were used as obtained from commerical sources unless otherwise noted. Flash chromatography refers to the procedure described by Still et al.[30]

5-Methyl-4-nitroisoxazole. 5-Methylisoxazole (8.31 g, 0.100 mol) was dissolved in trifluoroacetic anhydride (74 g, 0.35 mol = 50 mL, $d = \sim 1.487$ g/mL), and ammonium nitrate (8.00 g, 0.100 mol) was added in 0.5-g portions, keeping the reaction temperature between 25 and 30 °C. After complete addition, ^{1}H NMR of a neat aliquot showed the mixture to contain 65% product and 35% starting isoxazole. Thus, another portion of ammonium nitrate (3.60 g, 0.045 mol) was added as above. After complete addition, ^{1}H NMR analysis indicated that less than 5% of starting material remained. The mixture was poured onto ice water and extracted with chloroform (4 × 50 mL). The extracts were washed with water (250 mL), and this aqueous wash was extracted with chloroform (3 × 25 mL). The combined chloroform extracts were dried over magnesium sulfate and filtered, and the filtrate was concentrated giving a yellow oil [12.34 g (96%)], which was virtually pure as determined by ^{1}H NMR. The oil was distilled to give 8.04 g (63%) of product as a pale yellow liquid: bp 88–90 °C (18 Torr) [lit.[13] bp 187–189 °C (760 Torr)]; ^{1}H NMR (CD_3OD) δ 8.98 (1 H, s), 2.82 (3 H, s).

3-Methyl-4-nitroisoxazole was prepared from 3-methylisoxazole[31] by the same procedure as 5-methyl-4-nitroisoxazole. Thus, the reaction of 3-methylisoxazole (8.31 g, 0.100 mol) gave, after distillation, 9.44 g (74%) of pale yellow liquid, bp 90–94 °C (24 Torr) [lit.[13] bp 103–107 °C (26 Torr)]. This material was redistilled because of some bumping that occurred at the end of the first distillation that caused slight contamination of the product; this yielded 5.53 g (43%) of product as a pale yellow liquid: ^{1}H NMR ($CDCl_3$) δ 9.20 (1 H, s), 2.60 (3 H, s).

4-Nitroisoxazole was prepared from isoxazole by the same procedure as 5-methyl-4-nitroisoxazole with the modifications described below. Thus, the combined chloroform extracts obtained from the reaction of isoxazole (6.91 g, 0.100 mol) were dried over magnesium sulfate and filtered, and the filtrate was concentrated giving a yellowish green oil, which was covered with hexane and reconcentrated in vacuo without any warming. This caused solidification of the oil. After the addition of further hexane and cooling at 5 °C, the solid was collected, washed with cold hexane, and dried, giving 5.82 g (51%) of pale yellow solid that contained only trace impurities as judged by ^{1}H NMR: mp 45–46.5 °C (lit.[18] mp 46–47.5 °C); ^{1}H NMR ($CDCl_3/Me_2SO$-d_6) δ 9.83 (1 H, s), 9.00 (1 H, s); mass spectrum, *m/e* (relative intensity) M^+, 114 (97.8), 95 (18.9), 85 (58.6), 69 (100), 45 (92.5).

3,5-Diphenyl-4-isoxazolylcarbamic Acid 1,1-Dimethylethyl Ester. 3,5-Diphenylisoxazole-4-carboxylic acid[32] (1.38 g, 5.20 mmol), diphenylphosphoryl azide (1.43 g, 5.20 mmol), and triethylamine (530 mg, 5.20 mmol) were refluxed in *tert*-butyl alcohol (52 mL, dried over molecular sieves) for 24 h. The solvent was removed in vacuo, and the residue was taken up in ethyl acetate (50 mL). This mixture was washed with 1 N hydrochloric acid (3 × 25 mL) and saturated sodium bicarbonate solution (3 × 25 mL). The ethyl acetate solution was then dried over magnesium sulfate, filtered, and concentrated in vacuo, yielding 1.54 g (88%) of a pale yellow solid. Recrystallization from cyclohexane (50 mL)/ethyl acetate gave 1.17 g (67%) of short thin colorless needles: mp 173–174 °C; mass spectrum, *m/e* (relative intensity) M^+, 336 (13.0), 280 (19.9), 263 (12.2), 236 (53.5), 208 (13.2), 160 (7.7), 133 (53.6), 105 (83.6), 57 (100); ^{1}H NMR ($CDCl_3$) δ 1.09, 1.46 (9 H, 2 br s), 5.81 (1 H, br s), 7.5 (6 H, m), 7.7 (2 H, m), 7.8 (2 H, m) (at 330 K, the *tert*-butyl group appeared as a broad singlet at δ 1.35, and the aromatic protons were better resolved, but still multiplets). Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.44; H, 5.99; N, 8.33. Found: C, 71.29; H, 6.03; N, 8.28.

4-Amino-3,5-diphenylisoxazole Hydrochloride. 3,5-Diphenyl-4-isoxazolylcarbamic acid 1,1-dimethylethyl ester (1.167 g, 3.47 mmol) was added to a saturated solution of HCl(g) in THF (20 mL), and the resultant mixture was stirred at room temperature for 16 h. The THF was removed in vacuo. The residual solid was slurried in ether, collected by filtration, washed with ether, and dried, giving 872 mg (92%) of a white crystalline solid: mp 192–195 °C; mass spectrum, *m/e* (relative intensity) M^+, 236 (63.4), 133 (39.6), 105 (100), 77 (45.2); ^{1}H NMR (Me_2SO-d_6) δ 7.5 (6 H, m), 7.8 (4 H, m), 8.16 (3 H, s). Anal. Calcd for $C_{15}H_{12}N_2O$·HCl: C, 66.06; H, 4.80; N, 10.27. Found: C, 66.18; H, 4.85; N, 10.17.

4-Amino-5-methylisoxazole (1). 5-Methyl-4-nitroisoxazole was reduced by the procedure of Morgan and Burgess[15] with modification as described below. 5-Methyl-4-nitroisoxazole (19.32 g, 0.151 mol) in THF (100 mL) was added dropwise to aluminum amalgam (from 8.14 g, 0.302 mol of aluminum foil), which was suspended in THF (500 mL) and water (10.9 mL, 0.604 mol), keeping the temperature about 25 °C. After one-third, two-thirds, and complete addition of the nitroisoxazole solution, further aluminum foil (8.14 g each addition) and water (11 mL each

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(34) Streith, J.; Leibovici, C.; Martz, P. *Bull. Soc. Chim. Fr.* **1971**, 4152.

addition) were added. After complete addition of the nitroisoxazole solution, the mixture was stirred at room temperature for 3 h. The mixture was then filtered, and the aluminum salts were washed with THF until no UV-active material could be detected by TLC in the filtrate. The combined filtrates were concentrated in vacuo, and the residue was diluted with absolute ethanol (250 mL) and reconcentrated. The residual oil was diluted with ether, and this solution was dried with magnesium sulfate, filtered, and concentrated. The residue was dissolved in 2-propanol (200 mL), and 12 N hydrochloric acid (17 mL, 0.200 mol) was added. Crystallization occurred while standing overnight. The solid was collected, washed with 2-propanol and dried, giving 11.32 g (56%) of chunky white crystals. The filtrate was concentrated in vacuo to a solid, which was slurried in acetone, collected, washed, and dried, giving 6.43 g (31%) of off-white fine crystals: total yield 87%; mp 184–195 °C (lit.[13] mp 149 °C);[35] mass spectrum, *m/e* (relative intensity) M^+, 98 (74.8), 71 (86.5), 43 (100); ^1H NMR (Me_2SO-d_6) δ 2.58 (3 H, s), 8.53 (1 H, s), 10.02 (3 H, br s).

***N*-(5-Methyl-4-isoxazolyl)acetamide (2).** 1·HCl (1.35 g, 10.0 mmol) was treated with sodium acetate (820 mg, 10.0 mmol) and excess acetic anhydride (5 mL) in acetic acid (45 mL) for 2 h at room temperature. The reaction mixture was then concentrated in vacuo and the residue taken up in ether, dried with magnesium sulfate, and filtered. The filtrate was concentrated in vacuo, and a trace of acetic anhydride was removed under high vacuum to give 1.38 g (98%) of white solid: mp 94–97 °C (lit.[13] mp 87 °C); mass spectrum, *m/e* (relative intensity) M^+, 140 (11.1), 98 (49.4), 71 (27.4), 43 (100); ^1H NMR ($CDCl_3$) δ 2.17 (3 H, s), 2.40 (3 H, s), 8.57 (1 H, s), 8.73 (1 H, br s).

3-Acetamido-4-amino-3-buten-2-one (3). 2 (281 mg, 2.0 mmol) was hydrogenated over 10% palladium on carbon (100 mg) at 45 psi in methanol (20 mL) at room temperature for 1 h. The catalyst was removed by filtration and washed with methanol. The filtrate was concentrated in vacuo, yielding 280 mg (98%) of a grayish white solid. This was purified by flash chromatography (20:80 methanol/chloroform) and subsequently recrystallized from acetone: mp 184–185 °C; mass spectrum, *m/e* (relative intensity) M^+, 142 (72.2), 125 (9.4), 100 (100), 85 (24.1), 72 (35.7), 57 (66.0), 43 (86.8); ^1H NMR (CD_3OD) δ 2.10 (3 H, s), 2.14 (3 H, br s), 7.66 (1 H, s); IR (KBr) 1668, 1683, 3179, 3266, 3351 cm^{-1}. Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.41; H, 6.99; N, 19.32.

General Procedure for Conversion of 4-(Acylamino)-isoxazoles to 4(5)-Acylimidazoles. Compounds **4**, **7a**, **7b**, **9a–9i**, **12a–12c**, **14**, **18**, **19**, **22a**, and **22b** were prepared by the following procedure:

The 4-(acylamino)isoxazole was hydrogenated at 40 psi over 10% palladium on carbon (25%–50% by weight) in ethanol (ca. 10 mL/mmol of reactant). After 1 h, the reaction was usually complete as determined by TLC (10:90 methanol/chloroform) and the catalyst removed by filtration and washed with ethanol. (If the reaction was not complete after 1 h, then a second portion of 10% palladium on carbon was added and the hydrogenation continued for another hour; none of the examples herein required more catalyst or time than this.) The filtrate containing the intermediate β-amino-α,β-unsaturated ketone was treated with sodium hydroxide (pellets, 1.1 equiv) at reflux for 1 h. Solid ammonium chloride (1.2 equiv) was then added, the reaction allowed to cool to room temperature, and the ethanol removed in vacuo. The residue was slurried in acetone and the mixture filtered. Concentration of the filtrate gave the crude product, generally as a solid, which can be flash chromatographed or recrystallized to give pure imidazole.

4(5)-Acetyl-2-methyl-1*H*-imidazole (4) was prepared from **2** by the General Procedure. Recrystallization of the crude product from ethyl acetate/isopropyl ether (1:1) gave a 37% yield of product, mp 128–130 °C (lit.[6] mp 127–129 °C). Evaporation of the filtrate and flash chromatography (acetone) of the residue gave an additional 41% of product: total yield 78%; mass spectrum, *m/e* (relative intensity) M^+, 124 (47.5), 109 (100), 81 (98.1), 54 (68.3); ^1H NMR (Me_2SO-d_6) δ 2.33 (3 H, s), 2.38 (3 H, s), 7.68 (1 H, s).

4(5)-Acetyl-1*H*-imidazole from an Imidate. 1·HCl (777 mg, 5.77 mmol) was heated in trimethyl orthoformate (6 mL) at 90 °C for 4 h. After the mixture stood at room temperature overnight, the solvent was removed in vacuo and the residue flash chromatographed (2.5:97.5 methanol/chloroform) to give 421 mg (52%) of methyl *N*-(5-methyl-4-isoxazolyl)methanimidoate as a yellow oil: mass spectrum, *m/e* (relative intensity) $M^+ + 1$, 141 (9.8), M^+, 140 (10.2), 113 (13.5), 85 (13.5), 71 (36.6), 43 (100); ^1H NMR ($CDCl_3$) δ 2.40 (3 H, s), 3.85 (3 H, s), 7.87 (1 H, s), 8.17 (1 H, s).

The above imidate was hydrogenated at 15 psi over 10% palladium on carbon (100 mg) in methanol. After 0.5 and 2.5 h, additional portions (100 mg each) of catalyst were added. After 3.5 h of hydrogenation, the catalyst was removed by filtration and the filtrate refluxed for 18 h. The reaction mixture was concentrated in vacuo and the residue flash chromatographed (10:90 methanol/chloroform) to give 78 mg (23%) of an off-white solid: mp 153–156 °C (lit.[5] mp 172 °C). Despite the low melting point, the TLC behavior, mass spectrum, and ^1H NMR of this sample were identical with those of an authentic sample prepared from **6a**.

4-Aminoisoxazole (5) was prepared from 4-nitroisoxazole by the same procedure as **1**. Thus, 4-nitroisoxazole (5.82 g, 51.0 mmol) was reduced with aluminum amalgam (from 2.75 g, 0.102 mol of aluminum foil) in THF (150 mL)/water (4 mL). After the reaction mixture was filtered through Celite, the combined filtrates were concentrated in vacuo, and the residue was dissolved in ethanol (200 mL) and treated with 12 N hydrochloric acid (8 mL, 96 mmol). This solution was evaporated, diluted with toluene, and reevaporated. The residue was dried under high vacuum, and 3.84 g (62%) of tan solid was obtained. An analytical sample was prepared by treating a portion with sodium acetate, flash chromatographing the resulting free base, and reconverting the pure amine to its hydrochloride with HCl(g) in ethyl acetate: mp 160–163 °C; mass spectrum, *m/e* (relative intensity) M^+, 84 (47.7), 71 (12.4), 57 (100); ^1H NMR (Me_2SO-d_6) δ 8.77 (1 H, s), 9.13 (1 H, s). Anal. Calcd for $C_3H_4N_2O$·HCl: C, 29.89; H, 4.18; N, 23.24. Found: C, 29.61; H, 4.14; N, 22.91.

***N*-(4-Isoxazolyl)formamide (6a).** 5·HCl (1.33 g, 11.0 mmol) was refluxed in a mixture of formic acid (11 mL) and ethyl formate (110 mL) for 24 h. The reaction mixture was then concentrated in vacuo and the resulting oil diluted with toluene and reevaporated. The resulting dark tan solid was flash chromatographed (5:95 methanol/chloroform), yielding 1.09 g (89%) of product, mp 125–129 °C. An analytical sample was prepared by recrystallization from cyclohexane/ethyl acetate: mp 128–129 °C; mass spectrum, *m/e* (relative intensity) M^+, 112 (49.4), 57 (100); ^1H NMR ($CDCl_3/CD_3OD$) δ 8.25 (1 H, s), 8.38 (1 H, s), 8.93 (1 H, s); IR (KBr) 1675 cm^{-1}. Anal. Calcd for $C_4H_4N_2O_2$: C, 42.86; H, 3.60; N, 24.99. Found: C, 42.67; H, 3.60; N, 24.85.

***N*-(4-Isoxazolyl)acetamide (6b)** was prepared from **5** by the same procedure as **2**. Thus, the reaction of 5·HCl (723 mg, 6.0 mmol) gave, after flash chromatography (5:95 methanol/chloroform), 632 mg (83%) of a light tan solid: mp 146–148 °C; mass spectrum, *m/e* (relative intensity) M^+, 126 (19.5), 97 (9.6), 84 (10.9), 57 (22.0), 43 (100); ^1H NMR ($CDCl_3/CD_3OD$) δ 2.10 (3 H, s), 8.35 (1 H, s), 8.90 (1 H, s); IR (KBr) 1664 cm^{-1}. Anal. Calcd for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.23; H, 4.78; N, 22.11.

1*H*-Imidazole-4(5)-carboxaldehyde (7a) was prepared from **6a** as in the General Procedure except that the intermediate α-amino-α,β-unsaturated aldehyde precipitated, and therefore, the catalyst was not filtered off until after the sodium hydroxide treatment and ammonium chloride quench: yield 79% after flash chromatography (10:90 methanol/chloroform); mp 170–171 °C (lit.[33] mp 173–174 °C); mass spectrum, *m/e* (relative intensity) M^+, 96 (100), 67 (36.1); ^1H NMR (Me_2SO-d_6) δ 7.90 (1 H, s), 7.97 (1 H, s), 9.73 (1 H, s); IR (KBr) 1669 cm^{-1}.

2-Methyl-1*H*-imidazole-4(5)-carboxaldehyde (7b) was prepared from **6b** as in the General Procedure: yield 45% after flash chromatography (10:90 methanol/chloroform); mp 161–162 °C (lit.[34] mp 160–162 °C); mass spectrum, *m/e* (relative intensity) M^+, 110 (100), 81 (51.7), 54 (48.2); ^1H NMR (CD_3OD) δ 2.38 (3 H, s), 7.73 (1 H, s), 9.60 (1 H, s); IR (KBr) 1693, 1668 cm^{-1}.

(35) The large discrepancy between the melting point of **1** as prepared by us and the literature value is unaccounted for. The melting points of two derivatives of **1**, i.e., **2** and **8g**, are in reasonable agreement with the literature values.

N-(5-Methyl-4-isoxazolyl)formamide (8a) was prepared from 1 by the same procedure as **6a**. Thus, the reaction of 1·HCl (3.36 g, 25.0 mmol) gave, upon concentration, 3.10 g (98%) of a tan solid, mp 73–77 °C. An analytical sample was prepared by recrystallization from hexane/ethyl acetate: mp 77–78 °C; mass spectrum, *m/e* (relative intensity) M^+, 126 (1.6), 98 (1.1), 71 (6.6), 56 (10.1), 43 (100); ^1H NMR (CD_3OD) δ 2.42 (3 H, s), 8.18 (1 H, s), 8.57 (1 H, s); IR (KBr) 1680 cm^{-1}. Anal. Calcd for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.50; H, 4.80; N, 22.30.

2-Methoxy-N-(5-methyl-4-isoxazolyl)acetamide (8b). Methoxyacetic acid (4.50 g, 50.0 mmol) in dry THF (250 mL) was treated with 1,1′-carbonyldiimidazole (8.10 g, 50.0 mmol) in one portion at room temperature. After 5 h, 1·HCl (5.61 g, 41.7 mmol) was added and the mixture stirred overnight at room temperature. The THF was then removed in vacuo and the residue taken up in sufficient 1 N hydrochloric acid to bring the pH to 2. This aqueous mixture was extracted with chloroform (4 × 75 mL). The combined extracts were washed with saturated sodium bicarbonate solution (2 × 50 mL) and then dried over magnesium sulfate. Filtration and concentration in vacuo gave 6.65 g (94%) of a yellow oil. An analytical sample was prepared by flash chromatographing (2.5:97.5 methanol/chloroform) a portion of this oil followed by recrystallization from hexane: mp 53–55 °C; mass spectrum, *m/e* (relative intensity) M^+, 170 (10.1), 125 (2.4), 111 (24.0), 72 (13.0), 45 (100); ^1H NMR (CD_3OD) δ 2.33 (3 H, s), 3.40 (3 H, s), 3.97 (2 H, s), 8.27 (1 H, s). Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.47. Found: C, 49.51; H, 5.98; N, 16.85.

2-(Dimethylamino)-N-(5-methyl-4-isoxazolyl)acetamide (8c). *N,N*-Dimethylglycine hydrochloride (2.51 g, 18.0 mmol) was finely powdered, slurried in chloroform (150 mL) and treated with triethylamine (5.68 g, 56.1 mmol) in one portion. This light yellow solution was cooled to −30 °C, and isobutyl chloroformate (2.46 g, 18.0 mmol) was added, keeping the temperature below −20 °C. After the mixture was cooled to −30 °C, finely ground 1·HCl (2.02 g, 15.0 mmol) was added in one portion. After 15 min at −30 °C, the solution was allowed to warm slowly to 0 °C. After 2 h at 0 °C, the solution was washed with saturated sodium bicarbonate solution (50 mL), dried with magnesium sulfate, filtered, and concentrated in vacuo. The residual yellow oil was flash chromatographed (ethyl acetate) to give 1.00 g (36%) of thick yellow oil: mas spectrum, *m/e* (relative intensity) M^+, 183 (1.5), 141 (2.1), 58 (100); ^1H NMR ($CDCl_3$) δ 2.37 (9 H, s), 3.05 (2 H, s), 8.52 (1 H, s); exact mass calcd for $C_8H_{13}N_3O_2$ 183.1007, found 183.0998.

N-(5-Methyl-4-isoxazolyl)propionamide (8d). 1·HCl (1.61 g, 12.0 mmol) was treated with sodium propionate (1.15 g, 12.0 mmol) and propionic anhydride (1.87 g, 14.4 mmol) in propionic acid (12 mL) for 6 h at room temperature. The solvent was then removed in vacuo, and the residue was taken up in ether, which was then dried with magnesium sulfate, filtered, and evaporated in vacuo to give a pale yellow oil. Crystallization was induced by trituration with a cold mixture of hexane and ethyl acetate. The solid was collected, washed, and air dried, giving 1.79 g (97%) of white powder: mp 56–58 °C; mass spectrum, *m/e* (relative intensity) $M^+ + 1$, 155 (100), M^+, 154 (46.4), 138 (7.5), 112 (19.9), 57 (89.5); ^1H NMR ($CDCl_3$) δ 1.22 (3 H, t, J = 7 Hz), 2.35 (3 H, s), 2.36 (2 H, q, J = 7 Hz), 8.33 (1 H, br s), 8.47 (1 H, s); IR (KBr) 1650 cm^{-1}. Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.28; H, 6.31; N, 17.99.

2-Methyl-N-(5-methyl-4-isoxazolyl)propionamide (8e). 1·HCl (2.02 g, 15.0 mmol) in chloroform (65 mL) was treated with pyridine (2.85 g, 36.0 mmol) in one portion. 2-Methylpropionyl chloride (2.13 g, 20.0 mmol) in chloroform (10 mL) was then added in a slow stream. The temperature rose to 35 °C, and most of the starting amine dissolved. After the mixture was stirred for 1 h, it was warmed to reflux for 1 h. Pyridine (240 mg, 3.0 mmol) and 2-methylpropionyl chloride (320 mg, 3.0 mmol) were added, and reflux was continued for an additional 30 min. The cooled solution was washed with 1 N hydrochloric acid (75 mL). The aqueous wash was extracted with chloroform (2 × 25 mL). The combined organic extracts were washed with saturated sodium carbonate solution (100 mL). The aqueous layer was extracted with chloroform (2 × 25 mL). The combined organic extracts were dried with magnesium sulfate, filtered, and concentrated in vacuo yielding 2.38 g (94%) of a yellow solid, which was recrystallized from cyclohexane (50 mL)/ethyl acetate to give 1.83 g (73%) of fine white needles, mp 79–82 °C. Analytical sample: mp 81–82 °C; mass spectrum, *m/e* (relative intensity) $M^+ + 1$, 169 (25.7), M^+, 168 (16.4), 126 (22.2), 98 (10.1), 71 (95.5), 43 (100); ^1H NMR ($CDCl_3$) δ 1.19 (6 H, d, J = 7.5 Hz), 2.30 (3 H, s), 2.55 (1 H, heptet, J = 7.5 Hz), 7.62 (1 H, br s), 8.48 (1 H, s); IR (KBr) 1656 cm^{-1}. Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 56.83; H, 7.13; N, 16.59.

2,2-Dimethyl-N-(5-methyl-4-isoxazolyl)propionamide (8f). 1·HCl (2.02 g, 15.0 mmol) in chloroform (60 mL) was treated with pyridine (2.85 g, 36 mmol). To this mixture was added dropwise a solution of 2,2-dimethylpropionyl chloride (2.41 g, 20 mmol) in chloroform (15 mL) without cooling; a slight exotherm ensued. After complete addition, the mixture was stirred at room temperature for 2 h and then refluxed for 30 min. The cooled mixture was washed with 1 N hydrochloric acid (50 mL) and the aqueous layer extracted with chloroform (2 × 25 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (50 mL), and the aqueous layer was extracted with chloroform (2 × 25 mL). The combined organic extracts were dried with magnesium sulfate, filtered, and concentrated in vacuo to give, after drying under high vacuum, 2.73 g (100%) of a white powder. This was recrystallized from cyclohexane (50 mL)/ethyl acetate to give 2.56 g (94%) of fine white needles: mp 113–115 °C; mass spectrum, *m/e* (relative intensity) M^+, 182 (10.4), 140 (4.6), 126 (8.7), 85 (16.3), 71 (11.1), 57 (100); ^1H NMR ($CDCl_3$) δ 1.26 (9 H, s), 2.33 (3 H, s), 7.10 (1 H, br s), 8.41 (1 H, s); IR (KBr) 1661 cm^{-1}. Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.30; H, 7.77; N, 15.38.

N-(5-Methyl-4-isoxazolyl)benzamide (8g). 1·HCl (673 mg, 5.0 mmol) was finely ground, slurried in chloroform (20 mL), and treated with pyridine (870 mg, 11 mmol). After a few minutes, benzoyl chloride (773 mg, 5.5 mmol) was added in one portion. After 2 h, the chloroform solution was washed with 1 N hydrochloric acid (25 mL) and saturated sodium bicarbonate solution (25 mL) and dried with magnesium sulfate. Filtration and concentration in vacuo gave a gummy white solid, which was flash chromatographed (5:95 methanol/chloroform), yielding 724 mg (71%) of white solid: mp 148–149 °C (lit.[13] mp 140 °C); mass spectrum, *m/e* (relative intensity) M^+, 202 (9.6), 160 (21.9), 105 (100), 77 (71.0); ^1H NMR (CD_3OD/acetone-d_6) δ 2.43 (3 H, s), 7.4 (3 H, m), 7.8 (2 H, m), 8.5 (1 H, s).

N-(5-Methyl-4-isoxazolyl)-2,2,2-trifluoroacetamide (8h). 1·HCl (2.02 g, 15.0 mmol) was dissolved in trifluoroacetic anhydride (15.7 g, 75.0 mmol = 10.6 mL, d = ~1.487 g/mL) and stirred at room temperature for 1 h. The solvent was removed in vacuo and the residual oil dissolved in toluene (20 mL) and reconcentrated. The toluene treatment was repeated twice, and the oil was dried under high vacuum, during which time it solidified, yielding 2.92 g (100%) of white powder; mp 59–61 °C; mass spectrum, *m/e* (relative intensity) M^+, 194 (32.6), 152 (8.7), 125 (26.5), 97 (10.1), 69 (32.9); ^1H NMR ($CDCl_3$) δ 2.45 (3 H, s), 8.43 (1 H, s); IR (KBr) 1730 cm^{-1}. Anal. Calcd for $C_6H_5F_3N_2O_2$: C, 37.12; H, 2.60; N, 14.43. Found: C, 36.97; H, 2.71; N, 14.37.

4(5)-Acetyl-1H-imidazole (9a) was prepared from **8a** by the General Procedure: yield 98% after flash chromatography (5:95 methanol/chloroform); mp 169–170 °C (lit.[5] mp 172 °C); mass spectrum, *m/e* (relative intensity) M^+, 110 (100), 95 (88.4), 81 (3.3), 68 (32.4), 67 (36.6); ^1H NMR (acetone-d_6/Me_2SO-d_6) δ 2.45 (3 H, s), 7.67 (2 H, s).

4(5)-Acetyl-2-(methoxymethyl)-1H-imidazole (9b) was prepared from **8b** by the General Procedure: yield 70% after flash chromatography (5:95 methanol/chloroform); mp 90–92 °C; mass spectrum, *m/e* (relative intensity) M^+, 154 (26.9), 139 (26.0), 124 (100), 107 (85.4), 81 (71.4), 53 (42.9), 43 (78.2); ^1H NMR (CD_3OD) δ 2.43 (3 H, s), 3.37 (3 H, s), 4.47 (2 H, s), 7.70 (1 H, s); IR (KBr) 1649 cm^{-1}. Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.13; H, 6.42; N, 18.05.

4(5)-Acetyl-2-[(dimethylamino)methyl]-1H-imidazole (9c) was prepared from **8c** by the General Procedure: yield 52% after flash chromatography (15:85 methanol/chloroform) of free base as an oil: mp (dihydrochloride salt) 219–225 °C dec; mass spectrum, *m/e* (relative intensity) $M^+ + 1$, 168 (17.4), 124 (100), 106 (41.4), 82 (32.6), 58 (32.9); ^1H NMR ($CDCl_3$) δ 2.37 (6 H, s), 2.52 (3 H, s), 2.68 (2 H, s), 7.67 (1 H, s). Anal. Calcd for $C_8H_{13}N_3O$·2HCl: C, 40.01; H, 6.30; N, 17.50. Found: C, 39.74; H, 6.20; N, 17.28.

4(5)-Acetyl-2-ethyl-1H-imidazole (9d) was prepared from

8d by the General Procedure: yield 87% after flash chromatography (5:95 methanol/chloroform); mp 117–119 °C (lit.[6] mp 120–121 °C); mass spectrum, *m/e* (relative intensity) M^+, 138 (100), 123 (93.8), 95 (48.8), 81 (12.7), 68 (28.3); ^1H NMR ($CDCl_3$) δ 1.37 (3 H, t, J = 7 Hz), 2.52 (3 H, s), 2.88 (2 H, q, J = 7 Hz), 7.70 (1 H, s).

4(5)-Acetyl-2-(2-propyl)-1*H*-imidazole (9e) was prepared from **8e** by the General Procedure: yield 95% after flash chromatography (5:95 methanol/chloroform); mp 152–154 °C; mass spectrum, *m/e* (relative intensity) M^+, 152 (41.8), 137 (100), 119 (21.6), 95 (15.8); ^1H NMR ($CDCl_3$) δ 1.37 (6 H, d, J = 7 Hz), 2.45 (3 H, s), 3.17 (1 H, heptet, J = 7 Hz), 7.65 (1 H, s); IR (KBr) 1658 cm^{-1}. Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 56.83; H, 7.13; N, 16.59.

4(5)-Acetyl-2-(2,2-dimethylpropyl)-1*H*-imidazole (9f) was prepared from **8f** by the General Procedure: yield 98% after flash chromatography (5:95 methanol/chloroform); mp 198–199 °C; mass spectrum, *m/e* (relative intensity) M^+, 166 (36.9), 151 (100), 133 (25.6), 109 (18.1); ^1H NMR ($CDCl_3$) δ 1.38 (9 H, s), 2.43 (3 H, s), 7.63 (1 H, s); IR (KBr) 1666 cm^{-1}. Anal. Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.80; H, 8.38; N, 16.86.

4(5)-Acetyl-2-phenyl-1*H*-imidazole (9g) was prepared from **8g** by the General Procedure: yield 80% after flash chromatography (5:95 methanol/chloroform); mp 155–156 °C (lit.[8b] mp 158–158.5 °C); mass spectrum, *m/e* (relative intensity) M^+, 186 (89.0), 171 (100), 143 (13.2), 116 (68.9), 104 (15.7), 89 (36.4), 77 (24.4); ^1H NMR ($CDCl_3$/Me_2SO-d_6) δ 2.52 (3 H, s), 7.3 (3 H, m), 7.72 (1 H, s), 8.0 (2 H, m).

4(5)-Acetyl-2-(trifluoromethyl)-1*H*-imidazole (9h) was prepared from **8h** by the General Procedure: yield 83% after flash chromatography (3:97 methanol/chloroform); mp 187–188 °C; mass spectrum, *m/e* (relative intensity) M^+, 178 (63.9), 163 (100), 143 (82.6), 115 (16.6); ^1H NMR ($CDCl_3$) δ 2.57 (3 H, s), 7.73 (1 H, s); IR (KBr) 1660 cm^{-1}. Anal. Calcd for $C_6H_5F_3N_2O$: C, 40.46; H, 2.83; N, 15.73. Found: C, 40.35; H, 2.84; N, 15.55.

4-Amino-3-methylisoxazole (10) was prepared from 3-methyl-4-nitroisoxazole by the same procedure as **1**. Thus, 3-methyl-4-nitroisoxazole (14.94 g, 0.113 mol) was reduced with aluminum amalgam (from 6.10 g, 0.226 mol of aluminum foil) in THF (600 mL)/water (8.1 mL). After the reaction mixture was filtered through Celite, the combined filtrates were treated with 12 N hydrochloric acid (14.1 mL) and concentrated in vacuo to a wet solid. This was dissolved in ethanol and reconcentrated. The resulting white solid was slurried in ethyl acetate, filtered, and washed with ethyl acetate. Drying gave 9.95 g (65%) of slightly pink crystals: mp 188–189 °C dec (lit.[13] mp 184 °C dec); mass spectrum, *m/e* (relative intensity) M^+, 98 (25.0), 57 (71.5), 42 (100); ^1H NMR (Me_2SO-d_6) δ 2.32 (3 H, s), 8.03 (3 H, br s), 9.00 (1 H, s).

***N*-(3-Methyl-4-isoxazolyl)formamide (11a)** was prepared from **10** by the same procedure as **6a**. Thus, the reaction of **10**·HCl (2.69 g, 20.0 mmol) gave, after flash chromatography (ethyl acetate), 2.48 g (98%) of white powdery solid: mp 99–101 °C; mass spectrum, *m/e* (relative intensity) M^+, 126 (27.0), 97 (10.5), 57 (73.4), 42 (100); ^1H NMR ($CDCl_3$) δ 2.32 (3 H, s), 8.28 (1 H, s), 8.92 (1 H, s), 9.65 (1 H, br s); IR (KBr) 1671 cm^{-1}. Anal. Calcd for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.47; H, 4.74; N, 22.25.

***N*-(3-Methyl-4-isoxazolyl)acetamide (11b)** was prepared from **10** by the same procedure as **2**. Thus, the reaction of **10**·HCl (2.02 g, 15.0 mmol) gave, after flash chromatography (5:95 methanol/chloroform), 2.11 g (100%) of a broad-melting white solid, which was apparently a partial hydrate. A portion recrystallized from water was obtained as a monohydrate: mp 89–91 °C (lit.[13] mp 90–91 °C); mass spectrum, *m/e* (relative intensity) M^+, 140 (22.2), 125 (1.7), 111 (12.7), 98 (29.9), 84 (5.3), 71 (6.8), 57 (32.4), 43 (100); ^1H NMR ($CDCl_3$/Me_2SO-d_6) δ 2.10 (3 H, s), 2.27 (3 H, s), 2.78 (2 H, s, H_2O), 8.87 (1 H, s), 9.17 (1 H, br s); IR (KBr) 1671 cm^{-1}. Anal. Calcd for $C_6H_8N_2O_2$·H_2O: C, 45.56; H, 6.37; N, 17.71. Found: C, 45.38; H, 5.99; N, 17.66.

***N*-(3-Methyl-4-isoxazolyl)benzamide (11c).** **10**·HCl (673 mg, 5.0 mmol) was slurried in chloroform (50 mL) and treated with pyridine (870 mg, 11.0 mmol) and then benzoyl chloride (773 mg, 5.5 mmol). After the mixture was stirred at room temperature for 1 h, it was washed with 1 N hydrochloric acid (25 mL) and the aqueous layer extracted with chloroform (2 × 20 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (25 mL), and the aqueous layer was extracted with chloroform (2 × 20 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo to give a white solid. This was flash chromatographed (5:95 methanol/chloroform) to give a waxy solid, which was recrystallized from cyclohexane (25 mL)/ethyl acetate to give 710 mg (70%) of white crystals: mp 148–149 °C (lit.[13] mp 148–149 °C); mass spectrum, *m/e* (relative intensity) M^+, 202 (5.8), 173 (13.9), 105 (100), 77 (47.7), 51 (18.2); ^1H NMR ($CDCl_3$) δ 2.33 (3 H, s), 7.5 (3 H, m), 7.8 (2 H, m), 8.67 (1 H, br s), 8.97 (1 H, s); IR (KBr) 1650 cm^{-1}.

5(4)-Methyl-1*H*-imidazole-4(5)-carboxaldehyde (12a) was prepared from **11a** by the General Procedure: yield 86% after flash chromatography (10:90 methanol/chloroform); mp 162–163.5 °C; mass spectrum, *m/e* (relative intensity) M^+, 110 (100), 95 (7.6), 81 (34.0), 68 (18.0), 54 (69.0); ^1H NMR ($CDCl_3$) δ 2.50 (3 H, s), 7.57 (1 H, s), 9.82 (1 H, s); IR (KBr) 1664 cm^{-1}. Anal. Calcd for $C_5H_6N_2O$: C, 54.53; H, 5.49; N, 25.44. Found: C, 54.52; H, 5.58; N, 25.20.

2,5(4)-Dimethyl-1*H*-imidazole-4(5)-carboxaldehyde (12b) was prepared from **11b** by the General Procedure: yield 74% after flash chromatography (5:95 methanol/chloroform); mp 159–161 °C; mass spectrum, *m/e* (relative intensity) M^+, 124 (100), 109 (3.8), 95 (15.5), 83 (21.6), 68 (25.4), 54 (30.7); ^1H NMR (CD_3OD) δ 2.32 (3 H, s), 2.42 (3 H, s), 9.63 (1 H, s); IR (KBr) 1665 cm^{-1}. Anal. Calcd for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 57.84; H, 6.60; N, 22.40.

5(4)-Methyl-2-phenyl-1*H*-imidazole-4(5)-carboxaldehyde (12c) was prepared from **11c** by the General Procedure: yield 67% after flash chromatography (2.5:97.5 methanol/chloroform); mp 156–158 °C; mass spectrum, *m/e* (relative intensity) M^+, 186 (100), 171 (7.4), 158 (9.9), 130 (26.6), 116 (8.5), 104 (61.3), 83 (48.7), 77 (32.5), 55 (59.9); ^1H NMR (CD_3OD) δ 2.52 (3 H, s), 7.4 (3 H, m), 7.9 (2 H, m), 9.78 (1 H, s); IR (KBr) 1665, 2819 cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.31; H, 5.35; N, 14.83.

***N*-(3,5-Diphenyl-4-isoxazolyl)acetamide (13)** was prepared from 4-amino-3,5-diphenylisoxazole by the same procedure as **2**. Thus, the reaction of 4-amino-3,5-diphenylisoxazole hydrochloride (724 mg, 2.65 mmol) gave 767 mg (100%) of white solid. A 100-mg portion was recrystallized from cyclohexane (10 mL)/ethyl acetate, giving fine colorless needles: mp 186–187 °C; mass spectrum, *m/e* (relative intensity) M^+, 278 (30.7), 236 (78.1), 186 (40.4), 133 (40.0), 105 (100), 77 (49.8); ^1H NMR ($CDCl_3$/Me_2SO-d_6) δ 1.98 (3 H, s), 7.3 (6 H, m), 7.6 (2 H, m), 7.7 (2 H, m), 9.19 (1 H, s). Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.43; H, 4.97; N, 10.03.

4(5)-Benzoyl-2-methyl-5(4)-phenyl-1*H*-imidazole (14) was prepared from **13** by the General Procedure: yield 91% after flash chromatography (ethyl acetate) as a glass; mass spectrum, *m/e* (relative intensity) M^+, 262 (100), 261 (99.0), 233 (23.2), 185 (58.0), 165 (19.3), 131 (19.2), 116 (16.1), 105 (20.3), 89 (50.7), 77 (46.2); ^1H NMR ($CDCl_3$) δ 2.45 (3 H, s), 7.2 (8 H, m), 7.6 (2 H, m); exact mass calcd for $C_{17}H_{14}N_2O$ 262.1106, found 262.1060.

4-Acetyl-1,2-dimethylimidazole (15) by Methylation of 4. **4** (1.24 g, 10.0 mmol) was added to a slurry of sodium hydride (50% in oil; 528 mg, 11.0 mmol) in THF (50 mL), and the resultant mixture was stirred at room temperature for 30 min. Methyl iodide (1.49 g, 10.5 mmol) was then added and stirring continued for 4 h. Ammonium chloride (107 mg, 2 mmol) was added, and after the mixture was stirred overnight at room temperature, the solids were removed by filtration and washed with THF. Concentration of the filtrate in vacuo gave only 0.5 g of material, indicating that the solids removed by filtration probably contained additional product. These solids were therefore dissolved in water, and this solution was saturated with ammonium chloride and thoroughly extracted with chloroform (12 × 25 mL). The combined extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo, giving a yellow oil. This was combined with the material obtained from the THF filtrates and flash chromatographed (7.5:92.5 methanol/chloroform), yielding 1.25 g (90%) of a white solid: mp 88–91 °C; mass spectrum, *m/e* (relative intensity) M^+, 138 (87.6), 123 (100), 95 (29.2), 82 (42,6), 68 (28.2), 54 (58.6), 42 (73.3); ^1H NMR (CD_3OD) δ 2.37, 2.40 (6

H, 2 s), 3.67 (3 H, s), 7.67 (1 H, s); IR (KBr) 1664 cm^{-1}. Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.63; H, 7.28; N, 20.06.

4-Acetyl-1-benzyl-2-methylimidazole (16) by Benzylation of 4. 4 (1.24 g, 10.0 mmol) was added to a slurry of sodium hydride (50% in oil; 528 mg, 11.0 mmol) in THF (50 mL), and the resultant mixture was stirred at room temperature for 20 min. Benzyl chloride (1.33 g, 10.5 mmol) was then added and the mixture warmed to reflux for 16 h. The cooled mixture was quenched with saturated ammonium chloride solution (25 mL) and extracted with ether (3 × 50 mL). The combined extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo, giving a yellow oil. This was flash chromatographed (ethyl acetate), yielding 1.53 g (71%) of a pale yellow oil: mass spectrum, *m/e* (relative intensity) M^+, 214 (67.4), 199 (59.8), 91 (100), 65 (55.9), 43 (31.6); ^1H NMR (CD_3OD) δ 2.33 (3 H, s), 2.40 (3 H, s), 5.17 (2 H, s), 7.5 (5 H, m), 7.77 (1 H, s); IR (neat) 1670 cm^{-1}; exact mass calcd for $C_{13}H_{14}N_2O$ 214.1105, found 214.1098.

Benzylation of 7a. 7a (96 mg, 1.0 mmol) was dissolved in dry DMF (5 mL) and treated with 50% sodium hydride in oil (58 mg, 1.2 mmol). After 5 min, benzyl chloride (152 mg, 1.2 mmol) was added and the mixture stirred at room temperature. After 5 h, additional portions of 50% sodium hydride in oil (0.2 mmol) and benzyl chloride (0.2 mmol) were added, and the reaction was allowed to stir overnight at room temperature. The reaction was then quenched with saturated sodium bicarbonate solution (25 mL), diluted with water (25 mL), and extracted with ether (9 × 25 mL). The extract was dried with magnesium sulfate, filtered, and concentrated in vacuo. The residual oil was flash chromatographed (2.5:97.5 methanol/chloroform), and fractions containing the two products were combined. A second chromatography (isopropyl ether, 2 column lengths; then ethyl acetate) was performed to eliminate residual benzyl chloride and DMF. This yielded 102 mg (55%) of a colorless oil, which by ^1H NMR was determined to be a mixture of 1-benzylimidazole-4-carboxaldehyde (58%) and 1-benzylimidazole-5-carboxaldehyde (42%): ^1H NMR ($CDCl_3$) δ 5.13 (15 mm/2 H, 1,4-isomer), 5.50 (11 mm/2 H, 1,5-isomer).

Benzylation of 12a. 12a (110 mg, 1.0 mmol) in dry DMF was treated with sodium hydride (50% in oil, 72 mg, 1.5 mmol), and the resultant mixture was stirred at room temperature for 5 min. Benzyl chloride (158 mg, 1.25 mmol) was then added and stirring continued for 20 h. The mixture was then quenched with saturated sodium carbonate solution (25 mL), diluted with water (25 mL), and extracted with ethyl acetate (4 × 25 mL). The combined extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting yellow oil was flash chromatographed (ethyl acetate), yielding 80 mg (40%) of a pale yellow oil, which by ^1H NMR was determined to be a mixture of 1-benzyl-4-methylimidazole-5-carboxaldehyde (70%) and 1-benzyl-5-methylimidazole-4-carboxaldehyde (30%): ^1H NMR ($CDCl_3$) δ 5.08 (7 mm/2 H, 1-benzyl-4-acyl isomer), 5.43 (16 mm/2 H, 1-benzyl-5-acyl isomer).

Benzylation of 12b. 12b (124 mg, 1.0 mmol) in dry DMF was treated with sodium hydride (50% in oil, 72 mg, 1.5 mmol), and the resultant mixture was stirred at room temperature for 5 min. Benzyl chloride (158 mg, 1.25 mmol) was then added and stirring continued for 24 h. The mixture was then quenched with saturated sodium bicarbonate solution (25 mL), diluted with water (25 mL), and extracted with ethyl acetate (3 × 25 mL). The combined extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting yellow oil was flash chromatographed (2.5:97.5 methanol/chloroform), giving a yellow oil that still contained considerable DMF; thus, this was rechromatographed (ethyl acetate), yielding 122 mg (57%) of a pale yellow oil, which by ^1H NMR was determined to be a mixture of 1-benzyl-2,4-dimethylimidazole-5-carboxaldehyde (72%) and 1-benzyl-2,5-dimethylimidazole-4-carboxaldehyde (28%): ^1H NMR ($CDCl_3$) δ 5.07 (9 mm/2 H, 1-benzyl-4-acyl isomer), 5.52 (23 mm/2 H, 1-benzyl-5-acyl isomer).

1,4-Diacetyl-2-methylimidazole (17). 4 (2.50 g, 20.1 mmol) and triethylamine (2.24 g, 22.1 mmol) were combined in chloroform (100 mL), and acetyl chloride (1.74 g, 22.1 mmol) was added dropwise. After 4.5 h, the reaction mixture was washed with water (3 × 50 mL) and dried with magnesium sulfate. Filtration and concentration in vacuo gave 2.39 g (71%) of light yellow solid: ^1H NMR ($CDCl_3$) δ 2.50 (3 H, s), 2.60 (3 H, s), 2.65 (3 H, s), 7.77 (1 H, s).

5-Acetyl-1,2-dimethylimidazole (18) from 17. Crude 17 (2.39 g, 14.4 mmol) was dissolved in methylene chloride (30 mL), and the resultant mixture was treated with trimethyloxonium tetrafluoroborate (2.34 g, 15.8 mmol). After the mixture was stirred for 24 h at room temperature, another portion of oxonium salt (1.17 g, 7.9 mmol) was added. After 20 h more, the reaction mixture was concentrated in vacuo and the residue dissolved in water. This solution was basified with solid sodium carbonate and the mixture extracted with chloroform (5 × 25 mL). The combined extracts were dried with magnesium sulfate, filtered, and concentrated to a brown oil, which was flash chromatographed (5:95 methanol/chloroform), giving 1.30 g (65%) of light yellow solid, mp 80.5–81.5 °C, whose mass spectrum, ^1H NMR, and TLC behavior were identical with that of material prepared from **20a**.

4-(*N*-Benzylamino)isoxazole. 5·HCl (603 mg, 5.0 mmol), sodium acetate (410 mg, 5.0 mmol), and benzaldehyde (584 mg, 5.5 mmol) were combined in methanol (50 mL). After 15 min at room temperature, sodium cyanoborohydride (346 mg, 5.5 mmol) was added in one portion. After 4 h the mixture was concentrated in vacuo and the residue taken up in saturated sodium bicarbonate solution (25 mL) and extracted with chloroform (3 × 20 mL). The extracts were dried with magnesium sulfate, filtered, and concentrated in vacuo. The residue was dissolved in ethanol, treated with 12 N hydrochloric acid (1 mL), and evaporated, yielding a solid that was recrystallized from 2-propanol (10 mL) to give 242 mg (23%) of off-white crystals, mp 159–161 °C dec. A second crop was obtained by evaporating the 2-propanol filtrate, drying the residual solid under high vacuum, and collecting this after slurrying it in ether to yield 646 mg (61%) of product: mass spectrum, *m/e* (relative intensity) M^+, 174 (7.7), 146 (3.4), 118 (4.7), 97 (12.3), 91 (100); ^1H NMR (CD_3OD) δ 4.60 (2 H, s), 7.43 (5 H, s), 8.63 (1 H, s), 9.00 (1 H, s). Anal. Calcd for $C_{10}H_{10}N_2O$·HCl: C, 57.01; H, 5.26; N, 13.30. Found: C, 57.13; H, 5.26; N, 13.15.

***N*-Benzyl-*N*-(4-isoxazolyl)formamide** was prepared from 4-(*N*-benzylamino)isoxazole by the same procedure as **6a**. Thus, the reaction of 4-(*N*-benzylamino)isoxazole hydrochloride (843 mg, 4.0 mmol) gave, after flash chromatography (20:80 ethyl acetate/isopropyl ether), 714 mg (88%) of yellow solid: mp 71–73 °C; mass spectrum, *m/e* (relative intensity) M^+, 202 (8.3), 173 (7.1), 97 (12.9), 91 (100); ^1H NMR (CD_3OD) δ 4.87, 4.95 (2 H, 2 s), 7.23 (5 H, s), 8.43, 8.50, 8.57, 8.63 (2 H, 4 s), 8.92 (1 H, s); IR (KBr) 1671, 1681 cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.99; N, 13.86. Found: C, 65.28; H, 4.94; N, 13.58.

1-Benzylimidazole-5-carboxaldehyde (19) was prepared from *N*-benzyl-*N*-(4-isoxazolyl)formamide by the General Procedure; yield 53% of a yellow oil after flash chromatography (5:95 methanol/chloroform). The product solidified upon standing, and a portion was recrystallized from pentane: mp 53–55 °C (lit.[8b] mp 51–52 °C), mass spectrum, *m/e* (relative intensity) M^+, 186 (59.9), 168 (8.7), 130 (4.3), 91 (100); ^1H NMR ($CDCl_3$) δ 5.48 (2 H, s), 7.2 (5 H, m), 7.63 (1 H, s), 7.77 (1 H, s), 9.70 (1 H, s); IR (KBr) 1674, 2824 cm^{-1}.

5-Methyl-4-(methylamino)isoxazole (20a). Solid 8a (2.96 g, 23.5 mmol) was carefully treated with excess borane–methyl sulfide complex (25.8 mL, 51.6 mmol, M in THF) at room temperature. After complete addition, the reaction mixture was stirred at room temperature for 30 min and then warmed to reflux for 30 min. To the cooled reaction mixture was then added methanol (4.96 g, 155 mmole = 6.3 mL) and stirring at room temperature continued for 30 min. HCl(g) (>857 mg, 23.5 mmol) in THF (20 mL) was then added, keeping the temperature about 0 °C with ice cooling. After the mixture was stirred at 0 °C for 1 h, the resulting precipitate was collected, washed with THF, and air dried yielding 2.51 g (72%) of fine white powder. A second crop of product [627 mg (18%)] was obtained from the filtrate after it stood for 48 h. A portion of the first crop was sublimed (100 °C, 2 Torr) to provide an analytical sample: mp 125–128 °C; mass spectrum, *m/e* (relative intensity) M^+, 112 (11.8), 85 (24.0), 43 (100); ^1H NMR (Me_2SO-d_6) δ 2.61 (3 H, s), 2.90 (3 H, s), 9.00 (1 H, s), 10.75 (2 H, br s). Anal. Calcd for $C_5H_8N_2O$·HCl: C, 40.41; H, 6.11; N, 18.85. Found: C, 40.10; H, 6.11; N, 18.65.

***N*-Methyl-*N*-(5-methyl-4-isoxazolyl)acetamide** was prepared from **20a** by the same procedure as **2**. Thus, the reaction

of **20a**·HCl (627 mg, 4.22 mmol) gave, after flash chromatography (75:25 ethyl acetate/hexane), 543 mg (83%) of colorless oil, which solidified upon standing. An analytical sample was prepared by recrystallization from hexane (20 mL)/ethyl acetate: mp 45–47 °C; mass spectrum, *m/e* (relative intensity) M^+, 154 (11.7), 112 (22.8), 85 (15.8), 43 (100); ^1H NMR ($CDCl_3$) δ 1.92 (3 H, s), 2.58 (3 H, s), 3.15 (3 H, s), 8.20 (1 H, s). Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.20; H, 6.32; N, 18.01.

5-Acetyl-1,2-dimethylimidazole (18) was prepared from *N*-methyl-*N*-(5-methyl-4-isoxazolyl)acetamide by the General Procedure: yield 55% after flash chromatography (5:95 methanol/chloroform); mp 79–82 °C; mass spectrum, *m/e* (relative intensity) M^+, 138 (78.4), 123 (100), 95 (28.8), 54 (22.4); ^1H NMR ($CDCl_3$) δ 2.47 (6 H, s), 3.87 (3 H, s), 7.67 (1 H, s); IR (KBr) 1658 cm^{-1}. Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.82; H, 7.28; N, 20.18.

4-(Benzylamino)-5-methylisoxazole (20b) was prepared from **1** by the same procedure as for 4-(*N*-benzylamino)isoxazole. Thus, the reaction of **1**·HCl (2.02 g, 15.0 mmol) gave, after recrystallization from 2-propanol (40 mL), 2.81 g (83%) of fine white needles: dec pt (without melting) 145–170 °C; mass spectrum, *m/e* (relative intensity) M^+, 188 (7.0), 187 (14.4), 160 (3.6), 118 (12.9), 111 (36.0), 91 (100), 65 (22.4), 43 (82.5); ^1H NMR (Me_2SO-d_6) δ 2.31 (3 H, s), 4.42 (2 H, s), 7.4 (5 H, m), 8.58 (1 H, s). Anal. Calcd for $C_{11}H_{12}N_2O$·HCl: C, 58.80; H, 5.83; N, 12.47. Found: C, 58.58; H, 5.93; N, 12.39.

***N*-Benzyl-*N*-(5-methyl-4-isoxazolyl)acetamide** was prepared from **20b** by the same procedure as **2**. Thus, the reaction of **20b**·HCl (2.57 g, 11.4 mmol) gave 2.60 g (99%) of a white powder. An analytical sample was prepared by recrystallization from hexane: mp 84–85.5 °C; mass spectrum, *m/e* (relative intensity) M^+, 230 (12.7), 187 (11.5), 145 (5.6), 111 (22.3), 91 (100), 65 (16.5), 43 (85.6); ^1H NMR ($CDCl_3$) δ 1.87 (3 H, s), 1.95 (3 H, s), 4.68 (2 H, s), 7.2 (5 H, m), 7.83 (1 H, s); IR (KBr) 1660 cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.56; H, 5.94; N, 12.20.

5-Acetyl-1-benzyl-2-methylimidazole (21). *N*-Benzyl-*N*-(5-methyl-4-isoxazolyl)acetamide (1.15 g, 5.0 mmol) was hydrogenated over 10% palladium on carbon (500 mg) at 45 psi in *tert*-butyl alcohol (50 mL) at room temperature for 1 h. The mixture was diluted with THF (50 mL) to inhibit crystallization of the *tert*-butyl alcohol, and then the catalyst was removed by filtration and washed with a mixture of *tert*-butyl alcohol/THF (1:1). To the filtrate was added potassium *tert*-butoxide (617 mg, 5.5 mmol) and the mixture refluxed for 1 h. Ammonium chloride (321 mg, 6.0 mmol) was then added, and after this had substantially dissolved, the mixture was allowed to cool to room temperature. The solvents were then removed in vacuo, and the residue was dissolved in acetone and filtered. The filtrate was concentrated to a yellow gum, which was triturated with hot hexane (6 × 50 mL). The hexane fractions were concentrated in vacuo, yielding 669 mg (62%) of a yellow oil that solidified upon standing. An analytical sample was prepared by recrystallization from hexane: mp 43–45 °C; mass spectrum, *m/e* (relative intensity) M^+, 214 (63.0), 199 (21.1), 91 (100), 65 (42.4), 43 (28.5); ^1H NMR ($CDCl_3$) δ 2.35 (3 H, s), 2.42 (3 H, s), 5.58 (2 H, s), 7.0 (3 H, m), 7.2 (2 H, m), 7.75 (1 H, s); IR (KBr) 1661 cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.06. Found: C, 72.73; H, 6.60; N, 13.20.

4-(Benzylamino)-3-methylisoxazole was prepared from **10** by the same procedure as 4-(*N*-benzylamino)isoxazole. Thus, the reaction of **10**·HCl (2.02 g, 15.0 mmol) gave, after recrystallization from 2-propanol (40 mL), 2.61 g (77%) of large white needles: mp 173–176 °C dec; mass spectrum, *m/e* (relative intensity) M^+, 188 (12.1), 146 (11.8), 118 (17.9), 91 (100), 65 (30.2), 42 (26.3); ^1H NMR (Me_2SO-d_6) δ 2.22 (3 H, s), 4.30 (2 H, s), 7.4 (5 H, m), 8.65 (1 H, s), 9.50 (2 H, br s). Anal. Calcd for $C_{11}H_{12}N_2O$·HCl: C, 58.80; H, 5.83; N, 12.47. Found: C, 58.58; H, 5.72; N, 12.31.

***N*-Benzyl-*N*-(3-methyl-4-isoxazolyl)formamide** was prepared from 4-(benzylamino)-3-aminoisoxazole by the same procedure as **6a**. Thus, the reaction of 4-(benzylamino)-3-aminoisoxazole hydrochloride (1.12 g, 5.0 mmol) gave, after flash chromatography (2:98 methanol/chloroform), 1.06 g (98%) of a pale yellow oil: mass spectrum, *m/e* (relative intensity) M^+, 216 (70.4), 187 (52.9), 146 (15.6), 91 (100), 65 (64.1), 42 (49.8); ^1H NMR ($CDCl_3$) δ 2.07 (3 H, s), 4.63, 4.72 (2 H, 2 s), 7.2 (5 H, m), 7.97, 8.05 (1 H, 2 s), 8.15, 8.47 (1 H, 2 s); IR (KBr) 1682 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.21; H, 5.68; N, 13.16.

1-Benzyl-4-methylimidazole-5-carboxaldehyde (22a) was prepared from *N*-benzyl-*N*-(3-methyl-4-isoxazolyl)formamide by the General Procedure: yield 85% after flash chromatography (ethyl acetate); mp 76–78 °C; mass spectrum, *m/e* (relative intensity) M^+, 200 (73.1), 91 (100); ^1H NMR ($CDCl_3$) δ 2.47 (3 H, s), 5.45 (2 H, s), 7.2 (5 H, m), 7.53 (1 H, s), 9.78 (1 H, s); IR (KBr) 1669, 2757, 2825 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.80; H, 6.04; N, 13.99. Found: C, 71.72; H, 6.01; N, 13.81.

***N*-Benzyl-*N*-(3-methyl-4-isoxazolyl)acetamide** was prepared from 4-(benzylamino)-3-methylisoxazole by the same procedure as **2**. Thus, the reaction of 4-(benzylamino)-3-methylisoxazole hydrochloride (1.12 g, 5.0 mmol) gave 1.51 g (100%) of product, mp 77–81 °C. An analytical sample was prepared by recrystallization of a portion from cyclohexane: mp 80–82 °C; mass spectrum, *m/e* (relative intensity) M^+, 230 (37.7), 187 (13.6), 159 (8.3), 146 (7.3), 111 (13.1), 91 (100), 65 (31.5), 43 (67.3); ^1H NMR ($CDCl_3$) δ 1.91 (3 H, s), 1.98 (3 H, s), 4.73 (2 H, s), 7.3 (5 H, m), 8.00 (1 H, s); IR (KBr) 1664 cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.48; H, 6.20; N, 12.29.

1-Benzyl-2,4-dimethylimidazole-5-carboxaldehyde (22b) was prepared from *N*-benzyl-*N*-(3-methyl-4-isoxazolyl)acetamide by the General Procedure: yield 92% of a pale yellow oil after flash chromatography (ethyl acetate); mass spectrum, *m/e* (relative intensity) M^+, 214 (100), 199 (10.6), 123 (14.7), 91 (77.0), 65 (34.2), 42 (29.6); IR (neat) 1661, 2847 cm^{-1}; exact mass calcd for $C_{13}H_{14}N_2O$ 214.1133, found 214.1106.

1-Benzylimidazole-4-carboxaldehyde (23). 6a (672 mg, 6.0 mmol) was hydrogenated at 45 psi over 10% palladium on carbon (350 mg) in methanol (60 mL) at room temperature. After 1 h the reaction was not complete; a second portion of catalyst (350 mg) was added, and the hydrogenation continued for another 1 h after which the reduction was complete. The catalyst was removed by filtration and washed well with methanol. The filtrate was treated with benzylamine (6.43 g 60.0 mmol) and stirred at room temperature for 20 h. Sodium hydroxide (264 mg, 6.6 mmol) was added and the reaction mixture warmed to reflux. After 2 h, ammonium chloride (385 mg, 7.2 mmol) was added, and after this had dissolved, the mixture was allowed to cool to room temperature. The methanol was removed in vacuo and the residue dissolved in ethyl acetate (50 mL). This solution was washed with saturated ammonium chloride solution (5 × 25 mL) to remove benzylamine. The ethyl acetate was dried with magnesium sulfate, filtered, and concentrated in vacuo to an orange oil. A mass spectrum indicated that this material contained a considerable amount of the benzylimine of the desired aldehyde: mass spectrum, *m/e* (relative intensity) M^+, 275 (100), 184 (95.7). Thus, the oil was dissolved in 3 N hydrochloric acid (10 mL) and stirred at room temperature for 16 h. This mixture was then neutralized with solid sodium carbonate and extracted with ethyl acetate (3 × 25 mL). The extract was dried, filtered, and concentrated in vacuo to give an orange oil, which was flash chromatographed [1:1 ethyl acetate/isopropyl ether (400 mL) and then ethyl acetate], giving 738 mg (66%) of product as a pale yellow oil:[8b] mass spectrum, *m/e* (relative intensity) M^+, 186 (49.1), 158 (3.4), 91 (100), 65 (30.4); ^1H NMR ($CDCl_3$) δ 5.13 (2 H, s), 7.2 (5 H, m), 7.55 (2 H, s), 9.82 (1 H, s); IR (KBr) 1689, 2822 cm^{-1}.

4-Acetyl-1,2-dimethylimidazole (15). 3 (284 mg, 2.0 mmol) was treated with excess methylamine (622 mg, 20 mmol = 1.55 g of 40% by weight in water) in ethanol (20 mL). After 5 h, the reaction mixture was concentrated in vacuo, yielding 3-acetamido-4-(methylamino)-3-buten-2-one as a yellow glass: mass spectrum, *m/e* (relative intensity) M^+, 156 (100), 139 (31.3), 114 (58.1), 86 (63.6), 71 (58.7). This was not purified but used directly in the subsequent reaction.

The methylamine adduct was dissolved in ethanol (20 mL) and treated with sodium hydroxide (97 mg, 2.42 mmol) at reflux for 1 h. Ammonium chloride (142 mg, 2.66 mmol) was added, and after this had substantially dissolved, the reaction was allowed to cool to room temperature and the solvent removed in vacuo. The residue was flash chromatographed (7.5:92.5 methanol/chloroform), yielding 200 mg (72%) of white solid, mp 84–87 °C, whose mass spectrum, ^1H NMR, and TLC behavior were identical

with that of the product of methylation of 4.

3-Acetamido-4-(benzylamino)-3-buten-2-one (24). 3 (142 mg, 1.0 mmol) was treated with benzylamine (118 mg, 1.2 mmol) in ethanol (10 mL) at reflux for 8 h. The cooled mixture was concentrated in vacuo and the residue recrystallized from ethyl acetate, giving 185 mg (80%) of fine white needles: mp 160–162 °C; mass spectrum, m/e (relative intensity) M^+, 232 (62.0), 215 (5.8), 189 (45.8), 147 (8.6), 99 (23.1), 91 (100), 72 (12.6), 43 (21.6); ^1H NMR (CD_3OD) δ 2.07 (3 H, s), 2.15 (3 H, br s), 4.48 (2 H, s), 7.3 (5 H, m), 7.75 (1 H, s); IR (KBr) 1678, 3256 cm^{-1}. Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.87; H, 6.89; N, 11.92.

4-Acetyl-1-benzyl-2-methylimidazole (16). 24 (180 mg, 0.77 mmol) was treated with sodium hydroxide (39 mg, 1.0 mmol) in ethanol (10 mL) at reflux for 2 h. Ammonium chloride (73 mg, 1.3 mmol) was added, and after this had substantially dissolved, the mixture was allowed to cool to room temperature and then concentrated in vacuo. The residue was flash chromatographed (ethyl acetate) to give 124 mg (75%) of pale yellow oil whose mass spectrum and ^1H NMR were identical with that of the product of benzylation of 4.

1-Benzyl-5-methylimidazole-4-carboxaldehyde (25). 11a (269 mg, 2.13 mmol) was hydrogenated at 45 psi over 10% palladium on carbon (135 mg) in ethanol (20 mL) at room temperature. After 1 h, the catalyst was removed by filtration and washed with ethanol. The filtrate was treated with benzylamine (2.28 g, 21.3 mmol); little reaction occurred during 24 h at room temperature, but after 4 h of reflux the hydrogenation product was consumed. Sodium hydroxide (94 mg, 2.34 mmol) was added, and reflux was continued for 1 h. Ammonium chloride (137 mg, 2.56 mmol) was then added, and after this had substantially dissolved, the mixture was allowed to cool to room temperature. The mixture was then concentrated in vacuo to a yellow oil, which was dissolved in 3 N hydrochloric acid (20 mL) and stirred at room temperature for 16 h. The mixture was then basified with solid sodium carbonate and extracted with chloroform (4 × 25 mL). The extract was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residual oil was flash chromatographed (2.5:97.5 methanol/chloroform). The product obtained was contaminated with benzylamine, so it was rechromatographed, giving 82 mg (19%) of a yellow oil, which was an equal mixture of 1-benzyl-5-methylimidazole-4-carboxaldehyde (25) and 4-acetyl-1-benzylimidazole (26): mass spectrum, m/e (relative intensity) M^+, 200 (59.2), $M^+ - 15$, 185 (31.2, methyl ketone fragment), 91 (100); ^1H NMR ($CDCl_3$) δ 2.40 (3 H, s, ketone), 2.46 (3 H, s, aldehyde), 5.06 (2 H, s, aldehyde), 5.10 (2 H, s, ketone), 7.2 (10 H, m, aldehyde and ketone), 7.45 (1 H, s, ketone), 7.48 (1 H, s, aldehyde), 7.50 (1 H, s, ketone), 9.88 (1 H, s, aldehyde).

1-Benzyl-2,5-dimethylimidazole-4-carboxaldehyde (27). 11b (1.346 g, 9.60 mmol) was hydrogenated at 45 psi over 10% palladium on carbon (673 mg) in methanol (96 mL) at room temperature for 1 h. A second portion of catalyst (673 mg) was added, and the hydrogenation continued for another 1 h. The catalyst was removed by filtration and washed with methanol. The filtrate was treated with benzylamine (10.27 g, 96 mmol) and allowed to stir at room temperature overnight. Sodium hydroxide (422 mg, 10.6 mmol) was then added and the mixture refluxed for 3 h. Ammonium chloride (616 mg, 11.5 mmol) was added, and after this had substantially dissolved, the mixture was allowed to cool to room temperature. The solvent was removed in vacuo and the residue dissolved in ethyl acetate. This solution was washed with saturated ammonium chloride solution, dried with magnesium sulfate, filtered, and concentrated. The residual oil was flash chromatographed (5:95 methanol/chloroform), giving 370 mg (18%) of pale yellow oil: mass spectrum, m/e (relative intensity) M^+, 214 (36.9), 213 (12.0), 123 (14.7), 122 (15.2), 105 (19.8), 91 (100); ^1H NMR (CD_3OD) δ 2.30 (3 H, s), 2.43 (3 H, s), 5.15 (2 H, s), 7.2 (5 H, m), 9.88 (1 H, s); exact mass calcd for $C_{13}H_{14}N_2O$ 214.1106, found: 214.1104.

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Reactions of 2-Cyclohexen-1-ones and Cyclohexane-1,3-diones with Chloro Methylene Iminium Salts

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Products are isolated and pathways established for the reactions of cyclohexane-1,3-diones with Vilsmeier reagents. Similarities between those reactions and the reactions of some 2-cyclohexen-1-ones with Vilsmeier reagents are demonstrated. The pathways proposed allow rationalization of products formed by the action of Vilsmeier reagents on a variety of cyclic and acyclic ketones.

In 1965, Holy and Arnold reported[1] some synthetically useful iminoalkylations of unsaturated ketones. Only a brief indication of mechanism was given for these interesting reactions, among which was the formation of 2,4-dichlorobenzaldehyde (3) in high yield by the action of $DMF/POCl_3$ upon acetylacetone (1). In the present work, we sought a deeper understanding of the action of iminoalkylating reagents upon acyclic and cyclic diketones and, in particular, answers to the following: (i) what the pathways are by which diketones produce a variety of products; (ii) the nature of the products when an acyclic ketone was employed, instead of a cyclic ketone; and (iii) how an unsaturated monoketone would react compared to a diketone. The present study provides some of the answers.

In our hands, a mixture of $DMF/POCl_3$ acted on acetylacetone (1) to give exclusively 2,4-dichlorobenzaldehyde (3), as reported by Holy and Arnold[1] (Scheme I). However, the action of *N*-formylmorpholine/$POCl_3$ on acetylacetone (1) at 85 °C gave a separable mixture of 2,4-dichlorobenzaldehyde (3) (17%) and 4,6-dichloroiso-

(1) Holy, A.; Arnold, Z. *Collect. Czech. Chem. Commun.* **1965**, *30*, 47.

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