Synthesis of Imidazoles via Hetero-Cope Rearrangements[1]

Ivan Lantos,*,† Wei-Yuan Zhang†,[2] Xiuqi Shui,‡ and Drake S. Eggleston*,‡

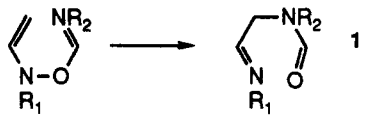
Synthetic Chemistry Department and Physical and Structural Chemistry Department, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania 19406-0939

Received June 28, 1993•

A novel synthetic approach to heterocycles containing the imidazole moiety based on the multihetero-Cope rearrangement is described. Oximes are reacted with benzenecarboximidoyl chlorides **4** affording adducts that readily undergo the hetero-Cope rearrangement at slightly elevated temperatures. Acid treatment of the resulting amidines **8** provides imidazoles in very high yields.

Introduction

In connection with the syntheses of a number of imidazole-containing drug substances, we sought to find methods that could provide convenient entries into the imidazole ring system. In surveying the literature, we have found that since the introduction of the TOSMIC method of van Leusen[3] very few fundamentally new approaches for the imidazole nucleus have appeared. It occurred to us that the multihetero-Cope rearrangement, involving three heteroatoms in an appropriately assembled molecular framework, could be suitably applied to this problem. Such an approach would have the advantage of affording compounds with substituent patterns not readily accessible by currently existing routes. Support for the feasibility of this approach came from the highly favorable thermodynamics associated with the reaction due largely to the formation of the very strong carbon–hetero (C=N) double bond and carbon–hetero (C–NMe) single bond at the expense of the energy required to break the weak hetero–hetero (N–O) bond. Using the method of Hendrickson,[4] the enthalpy change in the process depicted by eq 1 was calculated to be −65 kcal/mol.



It was surprising therefore to find that in spite of the extensive application of this rearrangement to the synthesis of a number of heterocyclic systems[5] it has found only limited application in imidazole chemistry.[6] Blechert,[7] in a study of the rearrangement of arylhydroxamic acid derived imidates, has obtained compounds related to benzo-fused imidazolin-2-ones, and Lobo and Prabhakar[8] likewise carried out 3.3 sigmatropic rearrangements resulting in similarly fused compounds. The fundamental difference, however, between these systems and ours is that they utilize arylhydroxamic acid derived sigmatropic frameworks wherein the olefinic framework essential for the rearrangement is already suitably in place. The design of our system, on the other hand, is based on oxime-derived imidates which required an initial protomeric shift before the Π-framework was properly established. This tautomeric change, as described in what follows, was difficult to accomplish.

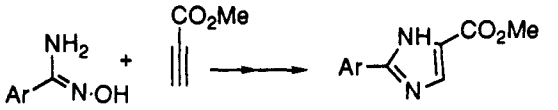
To explore the feasibility of the intended transformation, we decided to study the rearrangement of adducts formed between oximes and benzenecarboximidoyl chlorides **4** (R_3 = Me and Ph) previously used by Blechert.[7]

Results and Discussion

In our first attempts at the reaction, oximes of undefined stereochemistry were treated with the *N*-methylbenzenecarboximidoyl chloride **4** (R_3 = Me), and the *in situ* preformed imidate adducts **5** were treated with a mixture of acetic anhydride/acetyl chloride. It was hoped that this treatment would effect the acetylation of the oxime nitrogen and thus the protomeric shift required for setting up the essential 3.3 framework. However, only erratic results were obtained. The situation considerably improved when the oximes were reacted with a 2-fold excess of the imidoyl chlorides (**4**; R_3 = Me or Ph) in a THF solution containing 3 molar equiv of triethylamine. The facile formation of new compounds with generalized structure **8** was observed, clearly resulting from the desired sigmatropic rearrangement of intermediate **6**. Proof of structure for the rearranged products is based on an X-ray structure determination of compound **8c** (R_1 and R_2 being *trans*, Figure 1 in supplementary material),[9] the compound derived from deoxybenzoin oxime **3c**, as well as from

† Synthetic Chemistry Department.
‡ Physical and Structural Chemistry Department.
• Abstract published in *Advance ACS Abstracts,* October 15, 1993.

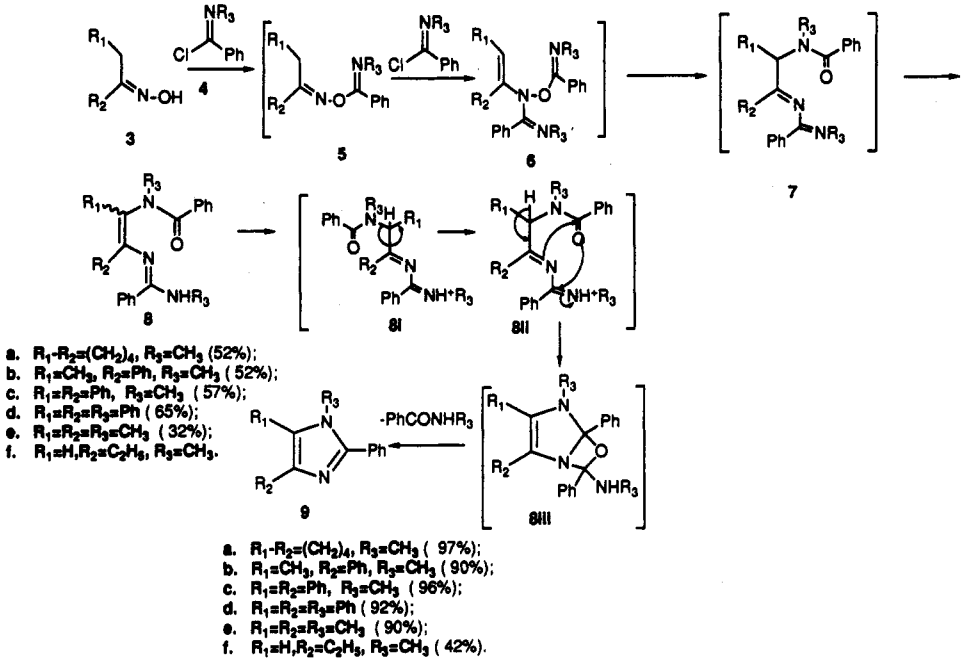
(1) Presented in part at the 205th National Meeting of the American Chemical Society, Denver, March 1993, ORGN 243.
(2) SmithKline Beecham postdoctoral fellow.
(3) van Leusen, A. M.; Wilderman, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153.
(4) Hendrickson, J. B. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 47.
(5) (a) Blechert, S. *Synthesis* **1989**, 71. (b) For pyrroles: Trofimov, B. A. In *Advances in Heterocyclic Chemistry*, Katritzky, A. R., Ed., Academic Press: New York, **1990**; Vol. 51. (c) For indoles: Blechert, S. *Tetrahedron Lett.* **1984**, *25*, 1547. (d) Other substituted aryl derivatives: Coates, R. M.; Said, I. Md. *J. Am. Chem. Soc.* **1977**, *99*, 2355.
(6) To the best of our knowledge only one other synthesis of imidazoles not fused to an aromatic moiety, based on the multihetero-Cope rearrangement, appears in the literature. Heindel (Heindel, N. D. *Tetrahedron Lett.* **1971**, 1439) describes the reaction between aryl amidoximes and propiolic esters yielding imidazoles, after acid treatment of the rearranged adducts.



(7) Blechert, S.; Hofeilmeier, R. *Tetrahedron Lett.* **1985**, 5281.
(8) Almeida, P. S.; Lobo, A. M.; Prabhakar, S. *Heterocyclics* **1989**, *28*, 653. We thank one of the reviewers for bringing this article to our attention.
(9) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambrdge, CB2 1EZ, UK.

0022-3263/93/1958-7092$04.00/0

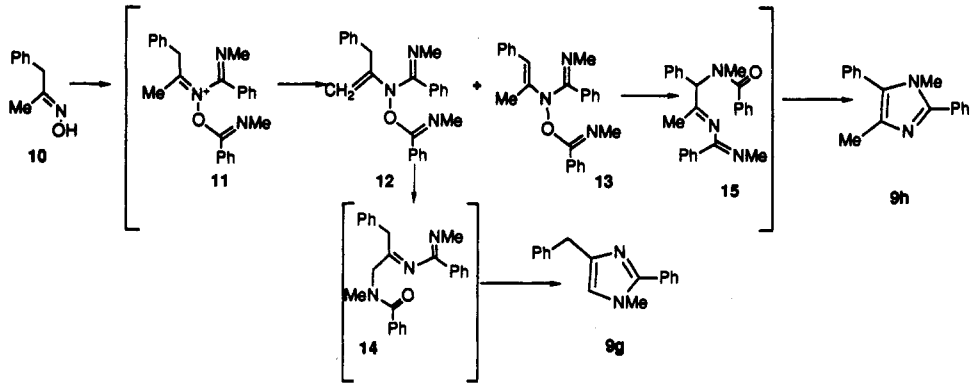
Scheme I



a. R_1-R_2=$(CH_2)_4$, R_3=CH_3 (52%);
b. R_1=CH_3, R_2=Ph, R_3=CH_3 (52%);
c. R_1=R_2=Ph, R_3=CH_3 (57%);
d. R_1=R_2=R_3=Ph (65%);
e. R_1=R_2=R_3=CH_3 (32%);
f. R_1=H, R_2=C_2H_5, R_3=CH_3.

a. R_1-R_2=$(CH_2)_4$, R_3=CH_3 (97%);
b. R_1=CH_3, R_2=Ph, R_3=CH_3 (90%);
c. R_1=R_2=Ph, R_3=CH_3 (96%);
d. R_1=R_2=R_3=Ph (92%);
e. R_1=R_2=R_3=CH_3 (90%);
f. R_1=H, R_2=C_2H_5, R_3=CH_3 (42%).

Scheme II



further transformations to the imidazoles (*vide infra*). It is noteworthy that deprotonation of the initial product of rearrangement **7c** occurs from a conformation where the two bulky phenyl groups are *trans* disposed. Acid treatment of the amidines **8** led in a smooth conversion to the variously substituted imidazoles **9**. We found it gratifying that *anti*-amidine **8c** readily underwent isomerization and ring closure.

It was of interest to consider a possible mechanism for these reactions. Our current view is shown in Scheme I. Protonation α to the amido moiety affords intermediate **8i** which undergoes a 180° rotation around the C–C single bond to form **8ii**. This intermediate is well positioned to cyclize to bicyclic intermediate **8iii** from which the imidazole is derived by a simple fragmentation. Currently, our only experimental support for this proposed mechanism comes from the finding that in all experiments almost equivalent amounts of *N*-alkylbenzamides are produced along with the imidazoles. This would otherwise not be expected from a reaction performed under azeotropic conditions.

This new imidazole synthesis proved to be equally facile for the formation of N_1-methyl- as well as N_1-phenylimidazoles. Oximes having α-protons only on one of the substituents afford, by this new procedure, a single product whereas oximes with protons on both α-substituents produce mixtures. Compounds **9a–f** are a few examples of the variously substituted imidazoles that could be prepared by this new process.

Up to this point, our synthetic efforts were based on the transformation of mixtures of *syn*- and *anti*-oximes, it was therefore not surprising that mixtures of amidines resulted (e.g., **8e** and **8f**). As an extension of this work, it became of interest to investigate the rearrangement of oximes of known and homogeneous stereochemistry. Specifically, it was of interest to determine what influence, if any, the initial oxime stereochemistry would have on the stereochemical outcome of the rearrangement. It was hoped that deprotonation of the initial adduct, e.g., **12**, would be faster than equilibration to the isomer **13** and thus the *syn*-oxime would predominantly afford rearranged compound **14** (Scheme II), while the *anti*-derived oxime similarly would afford **15**.

To test this experimentally we studied the rearrangement of the *syn*-oxime **10** (the isomer having the oxime-hydroxy cis to the CH_3 group) of methyl benzyl ketone, which is the only oxime we could obtain in pure form. The *syn* stereochemistry, as shown, was determined by a comparison of the NMR signal of the methylene protons of **10** with the signals due to the same protons in the purified mother liquors, a mixture enriched in the *anti*

isomer. Karabatsos and Teller have noted[10] that the signals due to the α-methylene protons cis to the oxime-hydroxyl occurred at a 0.2 ppm lower field in the ^{1}H NMR spectra of ketoximes than the signals due to the trans methylene protons. We observed that methylene proton signals of **10** were at 3.55 ppm in contrast to the methylene signals of the isomer at 3.79 ppm. When subjected to standard rearrangement conditions, this oxime afforded a 1.5:1 ratio of products **14** and **15**, respectively, a result which indicates partial equilibration at either the oximino (**11**) or the deprotonation (**12** and **13**) stages. It is interesting to note, however, that the original stereochemistry was still retained to a reasonable extent. Further exploration of these multihetero-Cope rearrangements is currently ongoing in our laboratory.

Experimental Section

General Procedures. Unless otherwise stated, all experiments were performed under a slight positive pressure of nitrogen. Tetrahydrofuran was freshly distilled from sodium under a nitrogen atmosphere, using benzophenone as an indicator. Cyclohexanone oxime and 2-butanone oxime were purchased from Aldrich Chemical Co., and deoxybenzoin oxime, phenylacetone oxime, and propiophenone oxime were prepared by the procedure of House et al.[11] They were used as a *syn* and *anti* isomeric mixture without purification. *N*-Methylbenzenecarboximidoyl chloride and *N*-phenylbenzenecarboximidoyl chloride were prepared according to Vaughan et al.[12]

General Procedure for the Preparation of Amidine Intermediates 8. To a cooled solution of *N*-methylbenzenecarboximidoyl chloride[12] in dry THF (50 mL) at −78 °C was added a 3.5 molar excess of triethylamine. The mixture was stirred for 0.5 h, and a solution of the oxime (0.5 equiv) was added. The solution was refluxed for 12 h. Water was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with saturated NaCl and dried (Na_2SO_4). The solvent was removed at reduced pressure, and the crude product was purified by "flash-column" chromatography.

***N*-Methyl-*N*-[2-[[(methylamino)phenylmethylene]amino]-1-cyclohexen-1-yl]benzamide (8a).** From **4** (R_3 = Me) (3.1 g, 20 mmol) and cyclohexanone oxime (1.13 g, 10 mmol) was obtained 1.8 g of **8a** as an oil in 52% yield, after chromatography with 20% ethyl acetate in hexane: FT-IR (neat) 2843, 1622, 1599, 1575, 1523 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.60–7.16 (m, 10 H), 6.89 (s, 1 H), 2.97 (s, 3 H), 2.75 (s, 3 H), 2.31–1.22 (m, 8 H); mass spectrum 347 (*m/z*).

***N*-Methyl-*N*-[2-[[(methylamino)phenylmethylene]amino]-1-(1-methyl-2-phenyl)ethenyl]benzamide (8b).** From **4** (R_3 = Me) (1.24 g, 8.0 mmol) and propiophenone oxime (600 mg, 4.0 mmol, *syn:anti* = 92:8[10]) was obtained 800 mg of **8b** in 52% yield, after chromatography with 20% ethyl acetate in hexane: mp 171–173 °C; FT-IR (KBr) 1613, 1592, 1575, 1535 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.54–6.90 (m, 15 H), 2.93 (s, 3 H), 2.87 (s, 3 H), 2.53 (s, 1 H), 1.84 (s, 3 H); mass spectrum 383 (*m/z*). Anal. Calcd for $C_{25}H_{25}N_3O$: C, 78.30; H, 6.57. Found: C, 78.26; H, 6.61.

***N*-Methyl-*N*-[2-[[(methylamino)phenylmethylene]amino]-1,2-diphenylethenyl]benzamide (8c).** From **4** (R_3 = Me) (3.06 g, 20 mmol) and deoxybenzoin oxime (2.11 g, 10 mmol, 100% *syn* to benzyl group[11]) was obtained 2.54 g of crystalline product **8c** in 57% yield, after chromatography with 20% ethyl acetate in hexane: mp 196–198 °C; FT-IR (KBr) 1616, 1592, 1566, 1535 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39–6.90 (m, 20 H), 4.56 (s, 1 H), 3.01 (s, 3 H), 2.85 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.5, 144.4, 140.1, 136.7, 136.3, 129.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 127.2, 127.1, 126.7, 126.5, 126.4, 126.3, 126.2, 123.9, 38.1, 29.3; mass spectrum 445 (*m/z*). Anal. Calcd for $C_{30}H_{27}N_3O$: C, 80.87; H, 6.11; N, 9.43. Found: C, 80.73; H, 6.13; N, 9.27.

***N*-[1,2-Diphenyl-2-[[(phenylamino)phenylmethylene]-amino]ethenyl]-*N*-phenylbenzamide (8d).** From **4** (R_3 = Ph) (860 mg, 4 mmol) and deoxybenzoin oxime (420 mg, 2 mmol) was obtained 740 mg of **8d** in 65% yield, after chromatography with 20% ethyl acetate in hexane: mp 85–87 °C; FT-IR (KBr) 1639, 1577, 1539 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.75–6.35 (m, 30 H), 2.30 (s, 1 H); mass spectrum 569 (*m/z*). Anal. Calcd for $C_{40}H_{31}N_3O$: C, 84.33; H, 5.8; N,7.38. Found: C, 83.84; H, 5.73; N, 6.81.

***N*-Methyl-*N*-[1-methyl-2-[[(methylamino)phenylmethylene]amino]-1-propenyl]benzamide (8e).** From **4** (R_3 = Me) (3.1 g, 20 mmol) and 2-butanone oxime (0.87 g, 10 mmol, *syn:anti* = 74:26[13]) was obtained 1.01 g of **8e** as pale yellow solid in yield of 32% after chromatography with 20% ethyl acetate in hexane: mp 136–138 °C; FT-IR (KBr) 1650, 1607, 1595, 1538 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52–7.01 (m, 10 H), 3.10 (s, 3 H), 2.87 (s, 3 H), 2.26 (s, 1 H), 1.65 (s, 3 H), 1.62 (s, 3 H); mass spectrum 321 (*m/z*). Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N,13.07. Found: C, 74.65; H, 7.30; N, 12.56.

***N*-Methyl-*N*-[2-ethyl-2-[[(methylamino)phenylmethylene]amino]ethenyl]benzamide (8f).** From the above experiment, **8f** was not isolated in pure form but was used as an isomeric mixture (*vide infra*) in the next step.

Amidines 14 and 15. From **4** (R_3 = Me) (0.78 g, 5 mmol) and phenylacetone oxime (0.375 g, 2.5 mmol, 100% *syn*) was obtained 0.98 g of **14** and **15** as a crude mixture (1.5:1, respectively) which was used in the next step without futher purification.

Preparation of Imidazoles. General Procedure. The amidine was heated with *p*-toluenesulfonic acid (2.5 molar equiv) in toluene at reflux in a Dean–Stark apparatus for 12 h. The solution was cooled to ambient temperature and was washed with 1 N NaOH solution. The organic solution was concentrated at reduced pressure, and the residue was purified by chromatography.

1-Methyl-2-phenyl-3,4-tetramethyleneimidazole (9a). Prepared from corresponding amidine **8a** (1 g, 2.86 mmol) to afford 580 mg of white crystals in 97% yield after chromatography with 10% ethyl acetate in hexane: mp 119–120 °C; FT-IR (KBr) 1592, 1472, 1451 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48–7.17 (m, 5 H), 3.37 (s, 3 H), 2.53 (m, 2 H), 2.38 (m, 2 H), 1.70 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 145.8, 136.0, 131.2, 128.3, 128.3, 127.9, 127.6, 31.3, 24.2, 23.4, 23.0, 21.0; mass spectrum 212 (*m/z*). Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.40; H, 7.53; N, 13.36.

1,5-Dimethyl-2,4-diphenylimidazole (9b). Prepared from the corresponding amidine **8b** (700 mg, 1.83 mmol) to afford 410 mg of white crystals in 91% yield after chromatography with 10% ethyl acetate in hexane: mp 135–136 °C; FT-IR (KBr) 1605, 1580, 1488, 1475 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.71–7.24 (m, 10 H), 3.62 (s, 3 H), 2.46 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.9, 137.4, 135.3, 131.1, 129.1, 128.5, 128.3, 127.4, 126.2, 125.0, 31.9, 10.5; mass spectrum 248 (*m/z*). Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.17; H, 6.59; N, 11.32.

1-Methyl-2,4,5-triphenylimidazole (9c). Prepared from amidine **8c** (190 mg, 0.4 mmol) to afford 127 mg of white needles in 96% yield after chromatography with 10% ethyl acetate in hexane: mp 141–143 °C (lit.[13] mp 143–144 °C); FT-IR (KBr) 1600, 1502, 1477 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.74–7.13 (m, 15 H), 3.45 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 147.8, 137.7, 134.6, 131.2, 130.9, 130.8, 130.4, 129.0, 129.0, 128.7, 128.5, 128.0, 126.9, 126.2, 33.1; mass spectrum 310 (*m/z*). Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03. Found: C, 85.03; H, 6.01; N, 9.03.

1,2,4,5-Tetraphenylimidazole (9d). Prepared from amidine **8d** (460 mg, 0.81 mmol) to afford 276 mg of white crystals in 92% yield after chromatography with 10% ethyl acetate in hexane: mp 215–217 °C (lit.[14] mp 217–218 °C); FT-IR (KBr) 1598, 1496, 1479 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.61–7.03 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 146.9, 138.2, 137.0, 134.4, 131.1, 130.8, 130.6, 130.5, 129.0, 128.9, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.3, 126.5; mass spectrum (*m/z*) 372. Anal. Calcd for $C_{27}H_{20}N_2$: C, 87.07; H, 5.41; N, 7.52. Found: C, 86.90; H, 5.49; N, 7.33.

1,4,5-Trimethyl-2-phenylimidazole (9e). Prepared from amidine **8e** (0.1 g, 0.31 mmol) to afford 52 mg of a colorless oil in 90% yield after chromatography with 10% ethyl acetate in hexane. FT-IR (KBr) 1597, 1456 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52–

(10) Karabatsos,G. J.; Taller, R. A. *Tetrahedron* **1968**, *Vol. 24*, 3347.
(11) House, O. H.; Richey, A. F., Jr. *J. Org. Chem.* **1969**, *34*, 1430.
(12) Vaughan, W.; Carlson, D. R. *J. Am. Soc. Chem.* **1962**, *84*, 769.
(13) White D. M.; Sonnenberg, J. *J. Org. Chem.* **1964**, *29*, 1929.
(14) Gompper, R. *Chem. Ber.* **1957**, *90*, 37.

7.25 (m, 5 H), 3.46 (s, 3 H), 2.16 (s, 3 H), 2.11 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.7, 133.0, 131.3, 128.5, 128.3, 128.0, 124.1, 31.7, 12.6, 9.0; exact mass for $C_{12}H_{14}N_2$ calcd 186.1157, found 186.1159.

1-Methyl-2-phenyl-4-ethylimidazole (9f). Prepared from a mixture of amidines **8e:8f** (1.2:1, respectively, 1.8 g, 5.6 mmol) as a colorless oil (450 mg) in a yield of 42% after chromatography with 10% ethyl acetate in hexane: FT-IR (neat) 1563, 1472 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.60–7.32 (m, 5 H), 6.66 (s, 1 H), 3.65 (s, 3 H), 2.63 (q, 2 H), 1.24 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 147.0, 144.0, 130.8, 128.6, 128.3, 117.6, 34.1, 21.6, 13.6; exact mass for $C_{12}H_{14}N_2$ calcd 186.1157, found 186.1149.

1,4-Dimethyl-2,5-diphenylimidazole (9h) and 1-Methyl-2-phenyl-4-benzylimidazole (9g). Using the above method, a mixture of **15** and **14**, respectively (in a ratio of 1:1.5 made from phenylacetone oxime, 0.375 g, 2.5 mmol), afforded 93 mg of **9h** (15% yield) and 165 mg of **9g** (27% yield). **9h**: mp 62–64 °C; FT-IR (KBr) 1677, 1628, 1677, 1495, 1472 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.67–7.33 (m, 10 H), 3.50 (s, 3 H), 2.27 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 147.3, 135.0, 130.9, 130.6, 129.9, 128.7, 128.6, 128.5, 128.1, 127.7, 33.6, 13.3; mass spectrum 248 (*m/z*). Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 81.95; H, 6.54; N, 11.22. **9g**: FT-IR (KBr) 1603, 1580, 1494, 1469, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.60–7.25 (m, 10 H), 6.48 (s, 1 H), 3.97 (s, 2 H), 3.59 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 147.1, 141.2, 140.0, 130.0, 129.1, 128.9, 128.7, 128.5, 128.4, 126.2, 126.1, 119.3, 34.7, 34.3; mass spectrum 248 (*m/z*). Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 81.89; H, 6.22; N, 11.21.

Acknowledgment. The authors wish to acknowledge their gratitude to Ms. Edith Reich of the Analytical Sciences Department for elemental analyses and to Dr. Charlie DeBrosse for the str ural assignment of the anti-oxime and to thank the Mass spectrometry Facility of the Analytical Sciences Department. We are also grateful to our consultants, the late Professor Paul Gassman and Professor Larry Overman, for the kind advice they provided during this work.

Supplementary Material Available:[9] ORTEP of the X-ray structure determination for **8c** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.