A Convenient One-Pot Preparative Method for 4,5-Diarylisoxazoles Involving Amine Exchange Reactions

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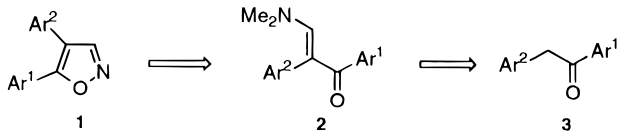
4,5-Diarylisoxazoles **1** are efficiently prepared by submitting enaminones **2**, readily obtained from deoxybenzoins **3**, to oximation conditions. This conversion implies an uncommon amine group exchange reaction. Preparation of 4-isoxazolines **5** and ring-opening transformations to β-keto nitriles **4** and 1,3-amino alcohol derivatives **7** are also described.

In the context of our ongoing interest in the synthetic potential of enamino ketones **2**,[1] we set out to study the synthesis and reactivity of 4,5-diarylisoxazoles **1**[2] using compounds **2** as key intermediates (Scheme 1).

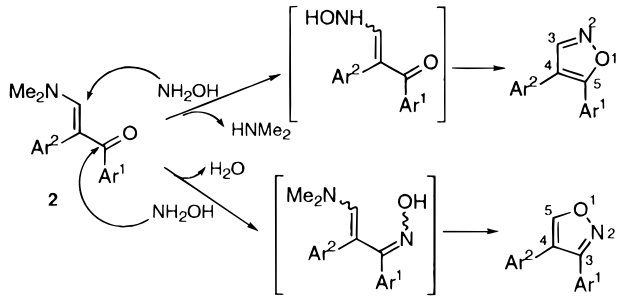
Enamino ketones,[3] β-diketones,[4] and β-chlorovinyl ketones[5] have been used *inter alia* as starting materials for the preparation of isoxazoles.[6] In every case, the cyclization reaction can be typified as a C−C−C + N−O ring closure process. However, only the use of enamino ketone provides a single isomer,[7] which is the result of an unusual amine exchange reaction.[1b,8] Nevertheless, in all cases the cyclization reaction may proceed by two possible mechanisms,[9] which differ in their sequential nucleophilic attack/amine exchange reactions (Scheme 2). As such, the identification of the reaction products provides unequivocal proof[4a,9] of the mechanism involved in the transformation.

The isoxazole ring has wide synthetic applications.[10] Particularly, a 4,5-diaryl substituted heterocycle adequately functionalized can be used as a substrate for Ullmann or Suzuki diaryl coupling reactions,[11−13] leading to tetracyclic planar systems of great interest. Therefore, and taking into account the few examples of this type of heterocycle in the literature,[14] it appeared worthwhile to find a simple high-yielding method for the synthesis of 4,5-diaryl-substituted isoxazoles.

Scheme 1



Scheme 2



Results and Discussion

Enamino ketones **2a**−**g**, readily obtained from the corresponding deoxybenzoins **3**,[1] were submitted to reaction with hydroxylamine hydrochloride under standard oximation conditions,[15] yielding 4,5-diarylisoxazoles **1a**−**g** in a "one-pot" reaction, as shown in Table 1 and Scheme 3.

The results allowed us to propose a mechanism for the formation of the target isoxazoles in which the first step is an amine exchange reaction (Scheme 4). Subsequent nucleophilic attack of the so-obtained hydroxylamine derivative to the carbonyl group, followed by elimination, yields the target heterocycle.

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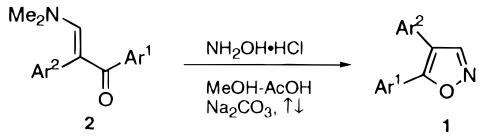
Table 1. 4,5-Diarylisoxazoles 1 Prepared

isoxazoles	Ar^1	Ar^2	yield[a] (%)	mp[b] (°C)
1a	Ph	Ph	90	68−70[14]
1b	3,4-$(MeO)_2$Ph	3,4-$(MeO)_2$Ph	99	126−128
1c	3,4-$(MeO)_2$Ph	Ph	91	62−63
1d	2,3,4-$(MeO)_3$Ph	3,4-$(MeO)_2$Ph	96	52−54
1e	2,3,4-$(MeO)_3$Ph	Ph	97	69−71
1f	3,4-$(MeO)_2$Ph	3,4,5-$(MeO)_3$Ph	95	82−84
1g	2,3,4-$(MeO)_3$Ph	3,4,5-$(MeO)_3$Ph	88	oil

[a] Yield of pure crystallized compound. [b] Crystallized from methanol.

Scheme 3



Scheme 4

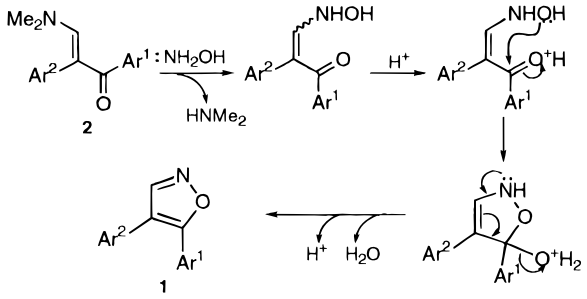


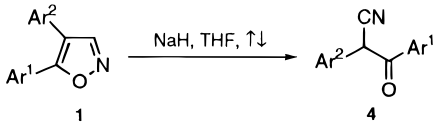
Table 2. β-Ketonitriles 4 Prepared

β-ketonitriles	Ar^1	Ar^2	yield[a] (%)	mp[b] (°C)
4a	Ph	Ph	70	81−82
4b	3,4-$(MeO)_2$Ph	3,4-$(MeO)_2$Ph	91	103−105
4c	3,4-$(MeO)_2$Ph	Ph	81	113−114
4d	2,3,4-$(MeO)_3$Ph	3,4-$(MeO)_2$Ph	88	114−115

[a] Yield of pure crystallized compound. [b] Crystallized from hexane−diethyl ether (1:1).

Routinely, basic treatment of C-3-unsubstituted isoxazoles induces ring opening to give β-keto nitriles,[6,16] useful difunctionalized compounds.[17] In our case, treatment of heterocycles **1** with EtONa/EtOH[17b] under various reaction conditions provided the expected β-keto nitriles **4** in 30−36% yield. Low yields (20−28%) also resulted as well by using LDA as a base, although it has been reported that this reagent has been successfully applied to 5-substituted isoxazoles.[16b] Furthermore, though $LiAlH_4$ has been reported to selectively reduce isoxazoles,[18c] in our hands β-keto nitriles **4** were obtained *via* a ring-opening process, only with low yields (19−25%). Finally, β-keto nitriles **4** were prepared in high yield using NaH (Table 2, Scheme 5).

Scheme 5



In the light of these results, we propose that the observed ring-opening reaction not only represents a practical synthesis of the mentioned ketonitriles, but also a valuable method for checking the position of the substituents in the parent heterocycle,[3,9a] thus establishing unambiguously the mechanism previously proposed for the construction of isoxazoles **1**. In fact, only the 4,5-substituted isoxazole, and not the 3,4-disubstituted isoxazole, would be able to react with base to directly produce a cyanoketone.

Similar to isoxazoles,[18] isoxazolines also have pharmacological,[19] industrial,[20] and synthetic applications.[21] Among these compounds, 4-isoxazolines **5**[2,22] are quite rare, and as far as we know, no general method for their preparation has been reported to date. In order to perform the selective reduction of isoxazoles **1** to 4-isoxazolines **5**, we first carried out *N*-methylation[17a,23] reactions with trimethyloxonium tetrafluoroborate (Meerwein salt).[24] The so-obtained *N*-methylisoxazolinium salts **6** were then submitted to reduction with both $LiAlH_4$ and $NaBH_4$,[22] affording quite different results. In fact, while low yields of 4-isoxazolines **5** were obtained with the former, the use of $NaBH_4$ considerably improved the outcome (Table 3, Scheme 6).

On the other hand, although 2-isoxazolines are known to be good precursors[22,25,26] of 1,3-amino alcohols, versatile building blocks for natural product synthesis[27] as well as useful chiral inductors,[28] no examples of reductive cleavage of 4-isoxazolines of type **5** to 1,2-diaryl-substituted 1,3-amino alcohols **7** are known. Toward this goal, we attempted the tandem reduction of the stilbenic C−C double bond/cleavage of the N−O bond of isoxazolines **5**,

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Table 3. Isoxazolinium Salts 6 and 4-Isoxazolines 5 Prepared

			6		5	
	Ar^1	Ar^2	yield[a] (%)	mp[b] (°C)	yield[a] (%)	mp (°C)
a	Ph	Ph	85	139−141	84	oil
b	3,4-$(MeO)_2$Ph	3,4-$(MeO)_2$Ph	94	161−163	64	109−111[c]
c	3,4-$(MeO)_2$Ph	Ph	96	158−160	90	oil
d	2,3,4-$(MeO)_3$Ph	3,4-$(MeO)_2$Ph	99	152−153	93	oil

[a] Yield of pure compound. [b] Crystallized from ethyl acetate. [c] Crystallized from methanol.

Scheme 6

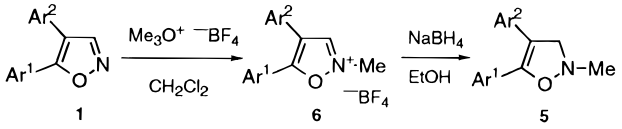
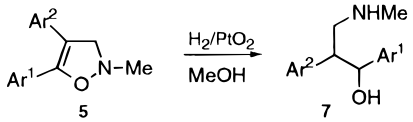


Table 4. 1,3-Amino Alcohols 7 Prepared

1,3-amino alcohols	Ar^1	Ar^2	yield[a] (%)	mp (°C)
7a	Ph	Ph	47	oil
7b	3,4-$(MeO)_2$Ph	3,4-$(MeO)_2$Ph	55	117−119[b]

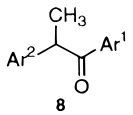
[a] Yield of pure compound. [b] Crystallized from methanol.

Scheme 7



but neither BBN[29] nor DIBAL-H,[26b,30] under a wide range of conditions, induced reaction.

Nevertheless, while Pd−C catalytic hydrogenation only produced 1,2-diarylpropanones **8**, the use of the Adams



catalyst furnished the expected 1,3-amino alcohols **7** though in moderate yields (47% and 55%) (Table 4, Scheme 7).

To summarize, we have accomplished an efficient conversion of deoxybenzoins to 4,5-diarylisoxazoles and we have studied their behaviour under ring opening reaction conditions in basic medium, thus isolating the corresponding β-ketonitriles, which represents a proof of the structure of the original heterocycles. We have also prepared a series of 4,5-diaryl-4-isoxazolines by submitting the parent heterocycles to tandem *N*-quaternization/reduction conditions. Apart from that, the so-obtained isoxazolines were regioselectively converted to the corresponding 1,2-diaryl-substituted 1,3-aminoalcohols.

Experimental Section

General Procedures. Solvents were either purified according to methods described by Perrin *et al.*[31] or used as received from the manufacturers, depending on their purity. Thin layer chromatography (TLC) was performed on plates coated to a thickness of 0.2 mm with Merck Kieselgel 60 F_{254} using UV light (254 nm) and Dragendorff's reagent[32] as developing agents. Flash column chromatography[33] was performed on Merck Kieselgel 60 (230−400 mesh ASTM); air-pressure chromatography was carried out on Kieselgel 60 (70−230 mesh ASTM) or on neutral alumina 90 (activity I, 70−230 mesh ASTM). Evaporation of solvents under reduced pressure was performed in a rotatory evaporator. Melting points are uncorrected. Infrared spectra were recorded as KBr plates, as a neat liquid, or in $CHCl_3$, and peaks are reported in cm^{-1}. NMR spectra were recorded at 250 MHz for ^1H and 62.83 MHz for ^{13}C. Chemical shifts (δ) were measured in ppm relative to tetramethylsilane (δ 0.00) or chloroform (δ 7.26 for ^1H or 77.00 for ^{13}C) as internal standards; dimethyl sulfoxide-d_6 (δ 2.49 for ^1H or 39.5 for ^{13}C) has been used when indicated. Multiplicities are indicated by s (singlet), b s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or dd (doublet of doublets). Coupling constants, *J*, are reported in hertz. ^{13}C DEPT experiments were used to assist with the assignment of the signals. Data for mass spectra (EI) are reported in the form *m*/*z* (intensity relative to base = 100).

Enamino ketones **2e** and **2g** were prepared in accordance with our previous reports,[1] and the following results were obtained.

3-(*N*,*N*-Dimethylamino)-2-phenyl-1-(2,3,4-trimethoxyphenyl)propenone (2e) (77%): pale yellow powder; mp 137−138 °C (diethyl ether); R_f (hexane−EtOAc, 2:8) 0.4; ν_{max} 1640 (C=O), δ_H 2.60 (6H, s, NMe_2), 3.78 (6H, s, OMe), 3.83 (3H, s, OMe), 6.64 (1H, d, J = 8.5, H-5′$_{arom}$), 6.87 (1H, d, J = 8.5, H-6′$_{arom}$), 7.11 (1H, s, =CHN), 7.1−7.2 (5H, m, H_{arom}); δ_C 43.1 (NMe), 55.7, 60.6, and 61.6 (OMe), 106.6, 113.1 ($C_{arom}H$), 123.1 (=*C*CO), 126.0, 127.2, and 131.8 ($C_{arom}H$), 129.5, 136.4 ($C_{arom}C$), 141.5, 150.5, and 153.5 ($C_{arom}O$), 153.9 (=CHN), 192.6 (CO). Anal. Calcd for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.45; H, 6.85; N, 4.20.

3-(*N*,*N*-Dimethylamino)-1-(2,3,4-trimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)propenone (2g) (88%): pale yellow powder; mp 139−141 °C (diethyl ether); R_f (hexane−EtOAc, 2:8) 0.1; ν_{max} 1635 (C=O); δ_H 2.67 (6H, s, NMe_2), 3.77 (9H, s, OMe), 3.81 (6H, s, OMe), 3.85 (3H, s, OMe), 6.39 (2H, s, H-2″$_{arom}$ and H-6″$_{arom}$), 6.58 (1H, d, J = 8.5, H-5′$_{arom}$), 6.87 (1H, d, J = 8.5, H-6′$_{arom}$), 7.07 (1H, s, =CHN); δ_C 43.3 (NMe), 55.9, 60.6, 60.7, and 61.8 (OMe), 106.7, 109.1 ($C_{arom}H$), 113.3 (=*C*CO), 123.1 ($C_{arom}H$), 129.5, 131.9 ($C_{arom}C$), 136.4, 141.8, 150.7, 152.2, and 153.7 ($C_{arom}O$), 154.1 (=CHN), 192.9 (CO). Anal. Calcd for $C_{23}H_{29}O_7N$: C, 64.02; H, 6.77; N, 3.25. Found: C, 63.96; H, 6.87; N, 3.58.

4,5-Diphenylisoxazole (1a). Typical Procedure. NH_2-OH·HCl (210 mg, 3.15 mmol) and Na_2CO_3 (170 mg, 1.6 mmol) were added to a stirred solution of enamino ketone **2a**[1] (720 mg, 2.86 mmol) in methanol (30 mL) and water (15 mL) at room temperature. The reaction mixture was acidified with glacial acetic acid up to pH 4−5 and refluxed for 2 h. After cooling, the reaction mixture was basified to pH 8 with ammonium hydroxide solution and extracted with dichloromethane (4 × 30 mL). The organic extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* to afford a yellow oil, which was crystallized in methanol, providing isoxazole **1a** (570 mg, 90%) as a white powder: mp 68−70 °C (methanol); R_f (CH_2Cl_2−EtOAc, 9:1) 0.8; ν_{max} 1630 (C=N); δ_H 7.3−7.4 (8H, m, H_{arom}), 7.6−7.7 (2H, m, H_{arom}), 8.34 (1H, s,

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H-3); δ_C 116.1 (C-4), 127.2 ($C_{arom}H$), 127.5 ($C_{arom}C$), 127.9, 128.5, 128.7, and 128.9 ($C_{arom}H$), 129.9 ($C_{arom}C$), 151.7 (C-3), 163.9 (C-5); *m*/*z* 221 (M^+, 23), 193 (22), 165 (60), 143 (11), 116 (15), 105 (55), 77 (32). Anal. Calcd for $C_{15}H_{11}ON$: C, 81.42; H, 5.01; N, 6.33. Found: C, 81.39; H, 4.98; N, 6.40.

By use of the same procedure the following isoxazoles were prepared:

4,5-Bis(3,4-dimethoxyphenyl)isoxazole *(*1b) (99%): mp 126−128 °C (methanol); R_f (CH_2Cl_2−EtOAc, 9:1) 0.8; ν_{max} 1630 (C═N); δ_H 3.76 (3H, s, OMe), 3.79 (3H, s, OMe), 3.89 (3H, s, OMe), 3.91 (3H, s, OMe), 6.8−7.0 (4H, m, H_{arom}), 7.2−7.3 (2H, m, H_{arom}), 8.29 (1H, s, H-3); δ_C 55.8, 55.9 (OMe), 109.9, 110.9, 111.5, and 111.9 ($C_{arom}H$), 114.9 (C-4), 119.3, 121.3 ($C_{arom}H$), 122.8 ($C_{arom}C$), 148.8, 149.1, and 150.3 ($C_{arom}O$), 151.9 (C-3), 163.5 (C-5); *m*/*z* 341 (M^+, 34), 298 (10), 165 (100), 137 (8), 77 (3). Anal. Calcd for $C_{19}H_{19}O_5N$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.70; H, 5.52; N, 4.01.

5-(3,4-Dimethoxyphenyl)-4-phenylisoxazole (1c) (91%): mp 62−64 °C (methanol); R_f (CH_2Cl_2−EtOAc, 9:1) 0.7; ν_{max} 1620 (C═N); δ_H 3.58 (3H, s, OMe), 3.75 (3H, s, OMe), 6.71 (1H, d, J = 8.4, H-5′$_{arom}$), 7.02 (1H, d, J = 1.9, H-2′$_{arom}$), 7.12 (1H, dd, J = 8.4, 1.9, H-6′$_{arom}$), 7.2−7.3 (5H, m, H_{arom}), 8.21 (1H, s, H-3); δ_C 55.1, 55.3 (OMe), 109.5, 110.7 ($C_{arom}H$), 114.6 (C-4), 119.7, 119.8, 127.5 and 128.3 ($C_{arom}H$), 128.4, 129.9 ($C_{arom}C$), 148.4, 149.9 ($C_{arom}O$), 151.3 (C-3), 163.4 (C-5); *m*/*z* 281 (M^+, 100), 238 (10), 195 (4), 166 (8), 165 (55), 116 (5). Anal. Calcd for $C_{17}H_{15}O_3N$: C, 72.58; H, 5.37; N, 4.98. Found: C, 71.98; H, 5.33; N, 5.13.

4-(3,4-Dimethoxyphenyl)-5-(2,3,4-trimethoxyphenyl)-isoxazole (1d) (96%): mp 98−100 °C (methanol); R_f (CH_2Cl_2−EtOAc, 9:1) 0.6; ν_{max} 1620 (C═N); δ_H 3.51 (6H, s, 2 × OMe), 3.70 (9H, s, OMe), 6.5−6.9 (5H, m, H_{arom}), 8.34 (1H, s, H-3); δ_C 55.0, 55.2, 55.5, 60.3, and 60.7 (OMe), 106.8, 110.0, 110.8 ($C_{arom}H$), 114.2 (C-4), 116.7 ($C_{arom}C$), 119.2 ($C_{arom}H$), 122.1 ($C_{arom}C$), 125.0 ($C_{arom}H$), 141.8, 147.9, and 148.4 ($C_{arom}O$), 149.7 (C-3), 151.7, 155.1 ($C_{arom}O$), 161.4 (C-5); *m*/*z* 371 (M^+, 32), 238 (10), 340 (5), 195 (100), 152 (7), 77 (3). Anal. Calcd for $C_{20}H_{21}O_6N$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.58; H, 5.73; N, 4.02.

4-Phenyl-5-(2,3,4-trimethoxyphenyl)isoxazole (1e) (97%): mp 69−71 °C (methanol); R_f (CH_2Cl_2−EtOAc, 9:1) 0.8; ν_{max} 1620 (C═N); δ_H 3.57 (3H, s, OMe), 3.79 (3H, s, OMe), 3.81 (3H, s, OMe), 6.64 (1H, d, J = 8.7, H-5′$_{arom}$), 7.02 (1H, d, J = 8.7, H-6′$_{arom}$), 7.1−7.2 (5H, m, H_{arom}), 8.43 (1H, s, H-3); δ_C 55.6, 60.4, 60.7 (OMe), 107.0 ($C_{arom}H$), 114.2 (C-4), 116.9 ($C_{arom}C$), 125.1, 126.9, 127.1, and 128.3 ($C_{arom}H$), 129.8 ($C_{arom}C$), 140.0, 150.0, and 151.8 ($C_{arom}O$), 155.3 (C-3), 162.3 (C-5); *m*/*z* 311 (M^+, 4), 208 (42), 196 (45), 105 (100), 77 (33). Anal. Calcd for $C_{18}H_{17}O_4N$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.40; H, 5.43; N, 4.84.

5-(3,4-Dimethoxyphenyl)-4-(3,4,5-trimethoxyphenyl)-isoxazole (1f) (95%): mp 52−54 °C (methanol); R_f (CH_2Cl_2−EtOAc, 9:1) 0.8; ν_{max} 1620 (C═N); δ_H 3.76 (6H, s, 2 × OMe), 3.79 (3H, s, OMe), 3.87 (3H, s, OMe), 3.89 (3H, s, OMe), 6.59 (2H, s, H-2″$_{arom}$ and H-6″$_{arom}$), 6.85 (1H, d, J = 8.5, H-5′$_{arom}$), 7.19 (1H, d, J = 2.0, H-2′$_{arom}$), 7.26 (1H, dd, J = 8.5, J 2.0, H-6′$_{arom}$), 8.30 (1H, s, H-3); δ_C 55.6, 55.7, 55.9, 60.8, and 61.2 (OMe), 107.2, 110.5, and 111.2 ($C_{arom}H$), 114.8 (C-4), 117.1 ($C_{arom}C$), 119.7 ($C_{arom}H$), 122.7 ($C_{arom}C$), 125.5 ($C_{arom}H$), 142.3, 148.4, and 148.8 ($C_{arom}O$), 150.2 (C-3), 152.2, 155.5 ($C_{arom}O$), 161.9 (C-5). Anal. Calcd for $C_{20}H_{21}O_6N$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.62; H, 5.72; N, 4.01.

4-(3,4,5-Trimethoxyphenyl)-5-(2,3,4-trimethoxyphenyl)isoxazole (1g) (88%): colorless oil; R_f (CH_2Cl_2−EtOAc, 9:1) 0.9; ν_{max} 1610 (C═N); δ_H 3.69 (3H, s, OMe), 3.71 (6H, s, 2 × OMe), 3.82 (3H, s, OMe), 3.85 (3H, s, OMe), 3.89 (3H, s, OMe), 6.49 (2H, s, H-2″$_{arom}$ and H-6″$_{arom}$), 6.72 (1H, d, J = 8.6, H-5′$_{arom}$), 7.08 (1H, d, J = 8.6, H-6′$_{arom}$), 8.47 (1H, s, H-3); δ_C 55.9, 56.1, 55.9, 60.8, 60.9, 61.4 (OMe), 104.6, 107.3 ($C_{arom}H$), 114.7 (C-4),117.1, 121.8 ($C_{arom}C$), 125.6 ($C_{arom}H$), 137.5, 142.4 ($C_{arom}O$), 150 ($C_{arom}H$), 142.3, 148.4, and 148.8 ($C_{arom}O$), 150.2 (C-3), 152.3, 153.3, 155.6 ($C_{arom}O$), 162.6 (C-5). Anal. Calcd for $C_{21}H_{23}O_7N$: C, 62.83; H, 5.77; N, 3.49. Found: C, 62.90; H, 5.72; N, 3.41.

2,3-Diphenyl-3-oxopropanonitrile 4a. Typical Procedure. NaH (106 mg, 4.4 mmol) was added in one portion to a solution of isoxazole **1a** (114 mg, 0.52 mmol) in dry THF (25 mL) under argon at room temperature. The resulting slurry was refluxed for 10 h, cooled, quenched with saturated aqueous NH_4Cl (20 mL), and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated to give a yellow oil. Flash column chromatography (hexane/EtOAc 2:8) afforded a colorless oil, which was crystallized from hexane−diethyl ether, providing β-ketonitrile **4a** (80 mg, 70%) as a white solid: mp 91−92 °C (hexane−diethyl ether, 1:1) (lit.[34] mp 93−94 °C); R_f (hexane/EtOAc 2:8) 0.8; ν_{max} 2245 (CN), 1695 (C═O); δ_H 5.61 (3H, s, CHCN), 7.4−7.5 (8H, m, H_{arom}), 7.9−8.0 (2H, m, H_{arom}); δ_C 46.6 (*C*HCN), 116.5 (CN), 128.2, 129.1, 129.2, 129.6, 130.3 ($C_{arom}H$), 133.6, 134.4 ($C_{arom}C$), 188.8 (C═O). Anal. Calcd for $C_{15}H_{11}ON$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.20; H, 5.10; N, 6.40.

By use of the same procedure the following compounds were prepared:

2,3-Bis-(3,4-dimethoxyphenyl)-3-oxopropanonitrile (4b) (91%): mp 103−105 °C (hexane/diethyl ether, 1:1); R_f (hexane/EtOAc 2:8) 0.8; ν_{max} 2240 (CN), 1685(C═O); δ_H 3.84 (3H, s, OMe), 3.86 (3H, s, OMe), 3.89 (3H, s, OMe), 3.92 (3H, s, OMe), 5.51 (1H, s, CHCN), 6.83 (1H, d, J = 8.2, H-5″$_{arom}$), 6.85 (1H, d, J = 8.4, H-5′$_{arom}$), 6.91 (1H, d, J = 2.2, H-2″$_{arom}$), 6.97 (1H, dd, J = 8.2, 2.2, H-6″$_{arom}$), 7.49 (1H, d, J = 2.1, H-2′$_{arom}$), 7.57 (1H, dd, J = 8.2,J 2.1, H-6′$_{arom}$); δ_C 45.9 (*C*HCN), 55.9, 56.0, 56.2 (OMe), 110.1, 111.2, 111.6 ($C_{arom}H$), 116.9 (CN), 120.7 ($C_{arom}H$), 123.0 ($C_{arom}C$), 124.1 ($C_{arom}H$), 126.5 ($C_{arom}C$), 149.3, 149.6, 149.8, 154.3 ($C_{arom}O$), 187.5 (C═O). Anal. $C_{19}H_{19}O_5N$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.81; H, 5.50; N, 4.19.

3-(3,4-Dimethoxyphenyl)-2-phenyl-3-oxopropanonitrile (4c) (91%): mp 113−114 °C (hexane/diethyl ether, 1:1); R_f (hexane/EtOAc 2:8) 0.5; ν_{max} 2245 (CN), 1685(C═O); δ_H 3.77 (3H, s, 2 × OMe), 3.81 (3H, s, OMe), 5.62 (1H, s, CHCN), 6.77 (1H, d, J = 8.4, H-5′$_{arom}$), 7.2−7.3 (5H, m, H_{arom}), 7.40 (1H, d, J = 1.8, H-2′$_{arom}$), 7.52 (1H, dd, J = 8.4, 1.8, H-6′$_{arom}$); δ_C 46.0 (*C*HCN), 55.7, 55.9 (OMe), 110.0, 110.9, ($C_{arom}H$), 116.9 (CN), 126.6, ($C_{arom}C$), 127.9, 128.8, 129.3 ($C_{arom}H$), 130.8 ($C_{arom}C$), 149.1, 154.2 ($C_{arom}O$), 187.4 (C═O). Anal. Calcd for $C_{17}H_{15}O_3N$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.66; H, 5.30; N, 5.01.

2-(3,4-Dimethoxyphenyl)-3-(2,3,4-trimethoxyphenyl)-3-oxopropanonitrile (4d) (88%): mp 114−115 °C (hexane/diethyl ether, 1:1); R_f (hexane/EtOAc 2:8) 0.3; ν_{max} 2245 (CN), 1695 (C═O); δ_H 3.69 (3H, s, OMe), 3.70 (3H, s, OMe), 3.71 (3H, s, OMe), 3.74 (3H, s, OMe), 3.86 (3H, s, OMe), 5.74 (1H, s, CHCN), 6.54 (1H, d, J = 8.9, H-5′$_{arom}$), 6.66 (1H, d, J = 8.1, H-5"$_{arom}$), 6.74 (1H, d, J = 2.0, H-2"$_{arom}$), 6.77 (1H, dd, J = 8.1, 2.0, H-6"$_{arom}$), 7.28 (1H, d, J = 8.9, H-6′$_{arom}$); δ_C 48.5 (*C*HCN), 55.6, 55.7, 55.9, 60.6, 61,7 (OMe), 107.2, 110.9, 111.1 ($C_{arom}H$), 117.2 (CN), 120.8 ($C_{arom}C$), 121.8 ($C_{arom}H$), 122.9 ($C_{arom}C$), 126.7 ($C_{arom}H$), 141.2, 149.1, 153.1, 158.3 ($C_{arom}O$), 189.5 (C═O). Anal. Calcd for $C_{20}H_{21}O_6N$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.40; H, 5.61; N, 3.89.

***N*-Methyl-4,5-diphenylisoxazolium Tetrafluoroborate (6a). Typical Procedure.** Isoxazole **1a** (500 mg, 2.2 mmol) was dissolved in freshly distilled dichloromethane and added dropwise into a stirred suspension of trimethyloxonium tetrafluoroborate (500 mg, 3.3 mmol) in dichloromethane under argon at room temperature. After being stirred overnight, the reaction mixture was evaporated *in vacuo* and the resulting oil was treated with diethyl ether (2 mL) to give a yellow powder, which was filtered and crystallized in ethyl acetate, affording **6a** (600 mg, 85%) as white needles:[35] mp 139−141 °C (ethyl acetate); R_f (CH_2Cl_2) 0.5; ν_{max} 1645 (C═N^+); δ_H (DMSO-d_6) 4.63 (3H, s, NMe), 7.4−7.7 (10H, m, H_{arom}), 9.76 (1H, s, H-3); δ_C (DMSO-d_6) 45.1 (NMe), 125.3(C_4), 128.7, 130.9, 127.7, and 134.7 ($C_{arom}H$), 154.1 (C-*3*), 172.8 (C-5). Anal. Calcd for $C_{16}H_{14}ONBF_4$: C, 59.48; H, 4.37; N, 4.33. Found: C, 59.40; H, 4.41; N, 4.39.

(34) Kascheres,A.; Marchi, D. *J. Org. Chem.* **1975**, *40*, 2985−2987.

(35) Similarly to some other isoxazolium salts of the literature (see ref 23), **6a** turned yellow and decomposed in 1−2 months at room temperature.

By use of the same procedure the following compounds were prepared:

***N*-Methyl-4,5-bis(3,4-dimethoxyphenyl)isoxazolium tetrafluoroborate (6b)** (94%): white powder; mp 161−163 °C (ethyl acetate); R_f (CH_2Cl_2) 0.5; ν_{max} 1650 (C═N^+); δ_H (DMSO-d_6) 3.71 (3H, s, OMe), 3.77 (3H, s, OMe), 3.87 (3H, s, OMe), 3.91 (3H, s, OMe), 4.60 (3H, s, NMe), 7.10 (1H, d, J = 8.3, H-5′$_{arom}$), 7.12 (1H, s, H-2″$_{arom}$), 7.16 (2H, dd, J = 7.5, 1.5, H-5″$_{arom}$ and H-6″$_{arom}$), 7.33 (1H, d, J = 2.1, H-2′$_{arom}$), 7.43 (1H, dd, J = 8.3, J 2.1, H-6′$_{arom}$), 9.61 (1H, s, H-3); δ_C 40.9 (NMe), 55.6, 55.9 (OMe), 110.3, 112.2 ($C_{arom}H$), 115.2 (C-4), 117.3, 117.9 ($C_{arom}H$), 121.5 ($C_{arom}C$), 149.0, 149.2, and 150.0 ($C_{arom}O$), 152.9 (C-3), 165.6 (C-5). Anal. Calcd for $C_{20}H_{22}O_5NBF_4$: C, 54.20; H, 5.00; N, 3.16. Found: C, 54.29; H, 5.08; N, 3.20.

***N*-Methyl-5-(3,4-dimethoxyphenyl)-4-phenylisoxazolium tetrafluoroborate (6c)** (96%): white powder; mp 158−160 °C (ethyl acetate); R_f (CH_2Cl_2) 0.2; ν_{max} 1650 (C═N^+); δ_H (DMSO-d_6) 3.66 (3H, s, OMe), 3.90 (3H, s, OMe), 4.60 (3H, s, NMe), 7.12 (1H, d, J = 8.6, H-5′$_{arom}$), 7.25 (1H, d, J = 2.1, H-2′$_{arom}$), 7.38 (1H, dd, J = 8.6, 2.1, H-6′$_{arom}$), 7.59 (5H, m, H_{arom}), 7.04 (1H, s, H-2′$_{arom}$), 7.15 (1H, dd, J = 8.4, 1.9, H-6″$_{arom}$), 7.21 (1H, d, J = 1.9, H-2″$_{arom}$), 9.60 (1H, s, H-3); δ_C (DMSO-d_6) 41.5 (NMe), 56.0, 56.3 (OMe), 111.4, 112.8 ($C_{arom}H$), 116.2 (C-4), 119.3, 123.4 ($C_{arom}H$), 127.1, 130.3 ($C_{arom}C$), 150.5 ($C_{arom}O$), 154.6 (C-3), 186.3 (C-5). Anal. Calcd for $C_{18}H_{18}O_3NBF_4$: C, 56.43; H, 4.73; N, 3.65. Found: C, 56.39; H, 4.70; N, 3.70.

***N*-Methyl-4-(3,4-dimethoxyphenyl)-5-(2,3,4-trimethoxyphenyl)isoxazolium tetrafluoroborate (6d)** (99%): white powder; mp 152−153 °C (ethyl acetate); R_f (CH_2Cl_2) 0.6; ν_{max} 1670 (C═N^+); δ_H (DMSO-d_6) 3.34 (3H, s, OMe), 3.60 (3H, s, OMe), 3.67 (3H, s, OMe), 3.77 (3H, s, OMe), 3.90 (3H, s, OMe), 4.45 (3H, s, NMe), 6.92 (1H, dd, J = 8.4, 1.9, H-6″$_{arom}$), 7.00 (1H, d, J = 1.9, H-2″$_{arom}$), 7.05 (1H, d, J = 8.4, H-5″$_{arom}$), 7.06 (1H, d, J = 8.9, H-5′$_{arom}$), 7.31 (1H, d, J = 8.9, H-6′$_{arom}$), 10.09 (1H, s, H-3); δ_C (DMSO-d_6) 41.2 (NMe), 55.5, 56.3, 60.7, and 61.3 (OMe), 109.2, 111.0 ($C_{arom}H$), 118.1 (C-4), 120.5 ($C_{arom}H$), 126.2, 141.6 ($C_{arom}C$), 148.9, 149.8, and 151.9 ($C_{arom}O$), 157.7 (C-3), 164.1 (C-5). Anal. Calcd for $C_{21}H_{24}O_6NBF_4$: C, 53.30; H, 5.11; N, 2.96. Found: C, 53.24; H, 5.12; N, 2.99.

***N*-Methyl-4,5-diphenyl-4-isoxazoline (5a). Typical Procedure.** A stirred suspension of $NaBH_4$ (110 mg, 2.9 mmol) in dry ethanol (15 mL) was added *via cannula* to a stirred suspension of isoxazolium salt **6a** (108 mg, 0.33 mmol) in the same solvent (5 mL) under argon at room temperature. After being stirred for 6 h the reaction was quenched by adding saturated aqueous NH_4Cl solution (10 mL) and extracted with dichloromethane (5 × 20 mL). The aqueous layer was acidified to pH 8 with diluted hydrochloric acid and extracted again with dichloromethane (5 × 20 mL). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give a brown oil that was purified by flash chromatography using CH_2Cl_2 as eluent. Isoxazoline **5a** was obtained (66 mg, 84%) as a colorless oil; R_f (CH_2Cl_2) 0.5; ν_{max} 1661 (C═C); δ_H 2.92 (3H, s, NMe), 3.99 (1H, m, CH_aH_bN), 4.75 (1H, m, CH$_a$$H_b$N), 7.1−7.3 (8H, m, H_{arom}), 7.51 (2H, m, H_{arom}); δ_C 47.5 (NMe), 65.7 (CH_2), 105.8 (C_4), 126.4, 126.9, and 128.3 ($C_{arom}H$), 128.4 ($C_{arom}C$), 128.4, 129.2 ($C_{arom}H$), 133.6 ($C_{arom}C$), 147.3 (C-5). Anal. Calcd for $C_{16}H_{15}ON$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.06; H, 6.36; N, 5.92.

By use of the same procedure the following compounds were prepared:

***N*-Methyl-4,5-bis(3,4-dimethoxyphenyl)-4-isoxazoline (5b)** (64%): white powder; mp 109−111 °C (methanol); R_f (CH_2Cl_2) 0.3; ν_{max} 1655 (C═C); δ_H 2.82 (3H, s, NMe), 3.59 (3H, s, OMe), 3.67 (3H, s, OMe), 3.77 (3H, s, OMe), 3.78 (3H, s, OMe), 3.96 (1H, m, CH_aH_bN), 4.59 (1H, m, CH$_a$$H_b$N), 6.6−6.7 (4H, m, H_{arom}), 7.51 (2H, m, H_{arom}); δ_C 47.2 (NMe), 55.3, 55.5, 55.6 (OMe), 65.5 (C_3), 105.8 (C_4), 109.9, 110.5, 110.8, 119.1 and 120.9 ($C_{arom}H$), 121.7, 126.1 ($C_{arom}C$), 145.7, 147.4, 148.2, and 148.3 ($C_{arom}O$), 149.3 (C-5). Anal. Calcd for $C_{20}H_{23}O_5N$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.29; H, 6.44; N, 3.92.

***N*-Methyl-5-(3,4-dimethoxyphenyl)-4-phenyl-4-isoxazoline (5c)** (90%): colorless oil; R_f (CH_2Cl_2) 0.4; ν_{max} 1660 (C═C); δ_H 2.85 (3H, s, NMe), 3.65 (3H, s, OMe), 3.80 (3H, s, OMe), 3.99 (1H, m, CH_aH_bN), 4.65 (1H, m, CH$_a$$H_b$N), 6.74 (1H, d, J = 8.3, H-5′$_{arom}$), 6.95 (1H, d, J = 1.9, H-2′$_{arom}$), 7.05 (1H, dd, J = 8.3, 1.9, H-6′$_{arom}$), 7.1−7.2 (5H, m, H_{arom}); δ_C 47.1 (NMe), 55.3, 55.4 (OMe), 65.5 (C_3), 104.4 (C_4), 110.5, 110.7 ($C_{arom}H$), 120.8 ($C_{arom}C$), 121.4, 125.9, 126.6, and 127.9 ($C_{arom}H$), 133.5 ($C_{arom}C$), 146.7, 148.2 ($C_{arom}O$), 149.4 (C-5). Anal. Calcd for $C_{18}H_{19}O_3N$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.79; H, 6.36; N, 4.80.

***N*-Methyl-4-(3,4-dimethoxyphenyl)-5-(2,3,4-trimethoxyphenyl)-4-isoxazoline (5d)** (93%): colorless oil; R_f (CH_2Cl_2) 0.3; ν_{max} 1645 (C═C); δ_H 2.84 (3H, s, NMe), 3.47 (3H, s, OMe), 3.72 (3H, s, OMe), 3.76 (3H, s, OMe), 3.78 (3H, s, OMe), 3.79 (3H, s, OMe), 3.82 (1H, m, CH_aH_bN), 4.64 (1H, m, CH$_a$$H_b$N), 6.50 (1H, d, J = 8.3, H-5′$_{arom}$), 6.52 (1H, s, H-2″$_{arom}$), 6.61 (1H, d, J = 5.7, H-6″$_{arom}$), 6.65 (1H, d, J = 5.7, H-5″$_{arom}$), 6.93 (1H, d, J = 8.3, H-6′$_{arom}$); δ_C 47.4 (NMe), 54.8, 55.4, 55.7, 60.6, and 61.1 (OMe), 63.8 (C_3), 106.5, 107.3, 108.5, and 110.7 ($C_{arom}H$), 116.5 (C_4), 117.7 ($C_{arom}C$), 125.7 ($C_{arom}H$), 125.8 ($C_{arom}C$), 142.4, 145.1, 146.9, 148.1, 152.6 ($C_{arom}O$), 154.7 (C-5). Anal. Calcd for $C_{21}H_{25}O_6N$: C, 65.10; H, 6.50; N, 3.61. Found: C, 65.04; H, 6.58; N, 3.60.

3-(*N*-Methylamino)-1,2-diphenylpropanol (7a). Typical Procedure. A mixture of 4-isoxazoline **5a** (95 mg, 0.4 mmol), prereduced Adams catalyst (from 10 mg of platinum oxide), and HCl (0.5 mL of a 3 mol L^{-1} solution in water) in dry methanol (20 mL) was hydrogenated for 7 h (P_{H2} = 2.5 atm). The mixture was filtered, and the filtrate was evaporated to give a brown oil that was dissolved in diethyl ether and treated with 3 drops of concentrated HCl solution. The resulting solid hydrochloride was filtered, washed with dichloromethane, and redissolved in a mixture of methanol−water (9:1). This solution was basified to pH 9 with ammonium hydroxide solution to produce the free amino alcohol and extracted with dichloromethane (4 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated in vacuo to afford 1,3-amino alcohol **7a** (45 mg, 47%): colorless oil; R_f (CH_2Cl_2/MeOH 9.5:0.5) 0.7; ν_{max} 3500 (OH), 3300 (NH); δ_H 2.33 (3H, s, NMe), 2.51 (1H, bs, NH or OH), 2.83 (2H, d, J = 6.5, CH_2N), 3.29 (1H, q, J = 6.5, CHCH$_2$N), 4.93 (1H, d, J = 6.5, CHOH), 7.1−7.2 (10H, m, H_{arom}); δ_C 36.1 (NMe), 51.5 (CHCH$_2$N), 53.0 (CH_2N), 77.9 (CHOH), 126.6 126.8, 127.1, 127.8, 128.3, 128.4, and 129.4 ($C_{arom}H$), 139.7, 141.9 ($C_{arom}C$). Anal. Calcd for $C_{16}H_{19}ON$: C, 79.63; H, 7.93; N, 5.80. Found: C, 79.66; H, 7.98; N, 5.72.

By use of the same procedure 3-(*N*-methylamino)-1,2-bis-(3,4-dimethoxyphenyl)propanol (**7b**) was prepared (55%): pale yellow powder; mp 118−119 °C (dichloromethane); R_f (CH_2Cl_2/MeOH 9.5:0.5) 0.4; ν_{max} 3510 (OH), 3310 (NH); δ_H 2.33 (3H, s, NMe), 2.61 (1H, bs, NH or OH), 2.78 (2H, d, J = 6.7, CH_2N), 3.22 (1H, q, J = 6.7, CHCH$_2$N), 3.74 (3H, s, OMe), 3.78 (3H, s, OMe), 3.84 (6H, s, OMe), 4.85 (1H, d, J = 6.7, CHOH), 6.6−6.8 (6H, m, H_{arom}); δ_C 36.3 (NMe), 51.4 (CHCH$_2$N), 54.3 (CH_2N), 55.6, 55.8 (OMe), 78.1 (CHOH), 109.9, 110.3, 111.1, 111.9, 119.1, and 120.6 ($C_{arom}H$), 132.2, 134.4 ($C_{arom}C$), 147.8, 148.2, 148.3, and 148.7 ($C_{arom}O$). Anal. Calcd for $C_{20}H_{27}O_5N$: C, 66.46; H, 7.53; N, 3.87. Found: C, 66.50; H, 7.55; N, 3.91.

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