A Convenient Strategy for the Synthesis of 4,5-Bis(*o*-haloaryl)isoxazoles

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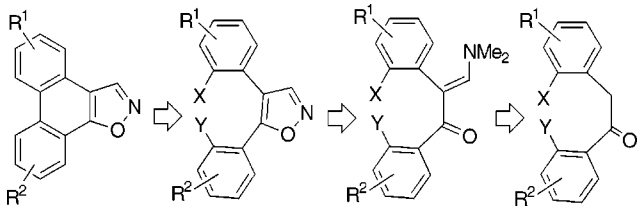
A series of new 1,2-bis(*o*-haloaryl)ethanones is efficiently prepared and applied to the synthesis of 4,5-bis(*o*-haloaryl)isoxazoles. Isolation of intermediate hydroxyisoxazolines, which are structurally examined, provides a definitive proof for a heterocyclization mechanism based on an amine exchange process. The isolation and X-ray crystallographic studies of significant side products such as benzamides and triarylpropionitriles are also described.

Introduction

Following our research on enaminoketones as precursors of several heterocyclic systems,[1] we planned the preparation of new 4,5-diarylisoxazoles adequately functionalized for a subsequent biaryl coupling reaction which would provide a novel entry to phenanthro-fused isoxazoles. 4,5-Bis(2-haloaryl) isoxazoles (X,Y= Br, I) were chosen as suitable substrates for a final biaryl coupling step, since the commonly used biaryl coupling methodologies are currently carried out with halogenated compounds.[2]



As an efficient synthesis of 4,5-diaryl-substituted isoxazoles starting from diarylethanones has been already reported,[1c] a similar protocol could be applied to adequately dihalogenated deoxybenzoins in order to have a ready access to the target halogenated heterocyclic systems. In addition to this synthetic aim, several unknown mechanistic features of the heterocyclization process and some relevant discoveries on the pharmacological properties of isoxazoles[3] prompted us to explore this interesting path leading to new 4,5-bis(2-haloaryl)-isoxazoles. The most outstanding results are presented in this paper.

With regard to deoxybenzoins, since they constitute valuable synthons of a large number of compounds,[4] several methodologies have been developed for their preparation.[5] Although the classical Friedel−Crafts acylation of arenes with arylacetyl chlorides is the generally employed strategy,[5a] nucleophilic substitution of benzyl halides with acyl carbanions has been reported as a versatile alternative.[5b]

Results and Discussion

1. Synthesis of 2,2′-Dihalodeoxybenzoins. On the basis of the easy preparation of nonhalogenated deoxybenzoins such as **1**,[6] several assays were carried out in order to insert the target halogen substitution at 2,2′-positions. In our hands, bromination of deoxybenzoin **1** in both acidic and neutral media only afforded 2-bromo-

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(1) (a) Domínguez, E.; Mtez. de Marigorta, E.; Olivera, R.; SanMartin, R. *Synlett* **1995**, 955−956. (b) Olivera, R.; Pascual, S.; Herrero, M.; SanMartin, R.; Domínguez, E. *Tetrahedron Lett.* **1998**, *39*, 7155−7158. (c) Domínguez, E.; Ibeas, E.; Mtez. de Marigorta, E.; Palacios, J. K.; SanMartin, R. *J. Org. Chem.* **1996**, *61*, 5435−5439.

(2) (a) Suzuki, H.; Enya, T.; Hisamatsu, Y. *Synthesis* **1997**, 1273−1276. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (c) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73−78.

(3) Several isoxazole derivatives have been reported to exhibit very interesting pharmacological applications, e.g., in the treatment of Alzheimer's disease, as bactericides or as antineoplasic agents. See: (a) Simoni, D.; Manfredini, S.; Tabrizi, M. A.; Bazzanini, P. G.; Baraldi, P. G.; Ferroni, R.; Traniello, F.; Nastruzzi, C.; Feriotto, G.; Gambari, R. *Drug. Res. Discov.* **1992**, *8*, 165−177. (b) Scobie, M.; Threadgill, M. D. *J. Org. Chem.* **1994**, *59*, 7009−7013. (c) Diana, G. D.; Rudewicz, P.; Pevear, D. C.; Nitz, T. J. *J. Med. Chem.* **1995**, *38*, 1355−1371. (d) Shivakumar, B. *Indian J. Heterocycl. Chem.* **1998**, *8*, 27−30. (e) Xue, C. B. *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 3499−3504. The use of isoxazoles as fungicides or herbicides is described in: Hamper, B. C.; Leschinsky, K. L.; Massey, S. S.; Bell, C. L.; Brannigan, L. H.; Prosch, S. D. *J. Agric. Food Chem.* **1995**, *43*, 219−228.

(4) (a) Grinshaw, J.; Thompson, N. *J. Chem. Soc., Chem. Commun.* **1987**, *4*, 240−241. (b) Hoyle, C. E.; Cranford, M.; Trapp, M.; No, Y. G.; Kim, K. J. *Polymer* **1988**, *29*, 2033−2040. (c) Anstead, G.; Srinivasan, R.; Peterson, C. S.; Wilson, S. R.; Katzenellenboguen, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 1378−1385. (d) Mogestern, O.; Richter, P. H.; Ahrens, H. *Pharmazie* **1992**, *47*, 25−27.

(5) (a) Wähälä, K.; Hase, T. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3005−3008. (b) Katritzky, A. R.; Oniciu, D. C. *Bull. Soc. Chim. Belg.* **1996**, *105*, 635−638. (c) Sato, T.; Narusse, K.; Enokiya, M.; Fujisawa, T. *Chem. Lett.* **1981**, 1135−1136. (d) Ueki, M.; Okamura, A.; Yamaguchi, J.-I. *Tetrahedron Lett.* **1995**, *36*, 7467−7470. (e) Miyashita, A.; Matsuoka, Y.; Suzuki, Y.; Iwamoto, K. I.; Higashino, T. *Chem. Pharm. Bull.* **1997**, *45*, 1235−1242.

(6) Badía, D.; Carrillo, L.; Domínguez, E.; Cameno, A. G.; Martinez de Marigorta, E.; Vicente, T. *J. Heterocycl. Chem.* **1990**, *27*, 1287−1292.

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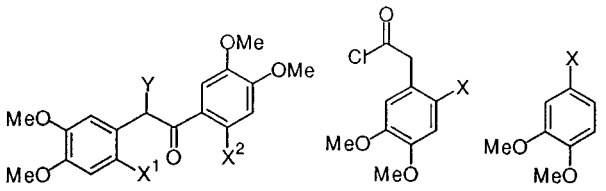
ethanone **2** (95% yield), whereas iodination of the same ketone **1** with ICl[7] provided monoiodo derivative **3** with good yield (82%). Attempts to insert the second halogen in **3** with ICl or thallium(III)-mediated iodination[8] failed, as only traces of 2,2′-diiodo ketone **4** were obtained.

We then assayed Friedel−Crafts acylation of haloarenes with haloarylacetyl chlorides. Despite a previous report,[9] the reaction between 2-bromo-4,5-dimethoxyphenylacetyl chloride **5a** and bromoveratrole **6a** provided only 25% of the corresponding deoxybenzoin **4**, probably due to a lack of reactivity of derivative **6a**. Similar attempts to prepare diiodo ketone **4** were also unsuccessful, as iodoveratrole **6b** underwent a Lewis acid-promoted dehalogenation.[10] Thus, although iodohomoveratryl chloride **5b** and iodoveratrole **6b** were regioselectively obtained by iodination with ICl, the subsequent Friedel−Crafts acylation step only provided monoiodinated ketone **3** (63% yield).



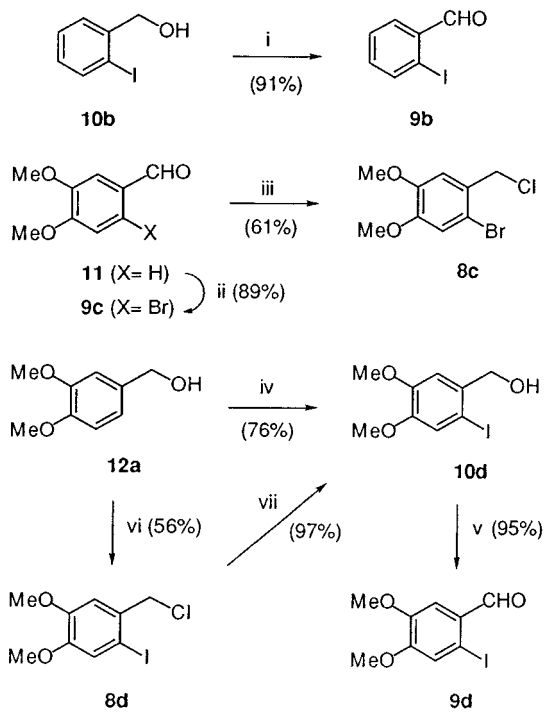
1 (X^1=X^2=Y= H)
2 (X^1=X^2= H; Y= Br)
3 (X^1= I; X^2=Y= H)
4 (X^1=X^2= I,Br; Y= H)

5a (X= Br)
5b (X= I)

6a (X= Br)
6b (X= I)

As Friedel−Crafts strategy failed, the preparation of dihalogenated deoxybenzoins **4** was then attempted by reaction of 2-haloaryl α-aminocarbonitriles **7** with 2-haloarylmethyl chlorides **8**. Apart from commercially available 2-bromobenzaldehyde **9a**, the preparation of the required 2-haloarenecarbaldehydes **9b**−**d**, synthons of the corresponding α-aminocarbonitriles **7**,[11] was accomplished as shown in Scheme 1. Oxidation of *o*-iodobenzyl alcohol **10b** with activated manganese dioxide and *ortho*-bromination of veratraldehyde **11** afforded haloaldehydes **9b** and **9c**, respectively. On the other hand, as iodination of veratraldehyde **11** afforded an inseparable mixture of the 2- and 3-iodoveratraldehydes, the problem was overcome by iodinating veratryl alcohol **12a** with I_2−CF_3COOAg[12] to **10d** followed by oxidation with pyridinium dichromate to obtain aldehyde **9d**. Although the attempts for the aromatic iodination of **12a** with ICl unexpectedly afforded iodoveratryl chloride **8d**, the latter derivative was readily hydrolyzed to benzyl alcohol **10d**. It must be pointed out that **12a** → **8d** transformation constitutes a straightforward access to one of the required benzyl chloride precursors **8**.[13] Finally,

Scheme 1



i: MnO_2, $CHCl_3$; ii: Br_2, $CHCl_3$; iii: 1. $NaBH_4$, MeOH; 2. NCS·Me_2S; iv: I_2, CF_3CO_2Ag; v: PDC, CH_2Cl_2; vi: ICl, $CHCl_3$; vii: $AgNO_3$, H_2O, MeCOMe

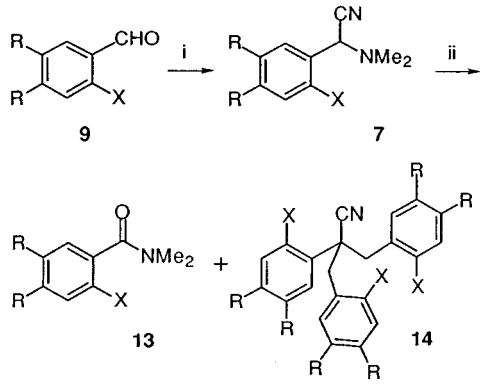
2-bromo-4,5-dimethoxybenzyl chloride **8c** was prepared from **9c** by means of a reduction/chlorination sequence.

The transformation of 2-halobenzaldehydes **9** into the corresponding α-aminonitriles **7** was accomplished by standard procedures (KCN/Me_2NH·HCl),[11] though the acetonitrile−water mixture of solvents was preferred to typical methanol in order to avoid acetal formation, thus α-aminonitriles **7a**−**d** were obtained with good yields (Table 1). The next step, the alkylation of derivatives **7** with halobenzyl chlorides **8** provided unexpected results. In fact, as shown in Table 1, it was observed a marked tendency of aminonitriles **7** to undergo oxidation to amides **13** under standard deprotonation conditions (NaH, DMF).[14] In addition, unexpected polyalkylated nitriles **14** were also obtained due to the presence of alkylating chlorides **8**.

This kind of oxidation leading to amides has been rarely observed, and in most cases a bubbling of oxygen through the reaction mixture is required.[15] Therefore, it can be proposed that the *ortho*-halogen substituent activates the benzylic position toward oxidation processes. Taking into account that the captodative effect provoked by amino and cyano functionalities[16] can stabilize a free radical generated by loss of an electron from the α-aminocarbonitrile carbanion, we suggest a mechanism where a peroxide intermediate[17] promotes the formation of amides **13** (Scheme 2).

(7) Merkusev, E. B. *Synthesis* **1988**, 923−937.
(8) McKillop, A.; Hunt, J. D.; Zelesku, M. J.; Fowler, J. S.; Taylor, E. C.; McGilliuray, G.; Kienzle, F. *J. Am. Chem. Soc.* **1971**, *93*, 4841.
(9) (a) Castedo, L.; Iriondo, I.; Domínguez, E.; Lete, E.; Villa, M. J. *An. Quim.* **1985**, *81C*, 61−65. (b) Domínguez, E.; Lete, E.; Iriondo, C.; Villa, M. J. *Bull. Soc. Chim. Belg.* **1984**, *93*, 1099−1103. In our hands, the procedure for the preparation of **5a** reported therein provided only a 25% yield of the target intermediate, probably due to a lack of reproducibility.
(10) Gore, P. H. In *Friedel−Crafts and related reactions*; Olah, G., Ed.; Wiley-Interscience: New York, 1964; Vol. 3, pp 44−46.
(11) (a) Dyke, S. F.; Tiley, S. E.; White, A. C.; Gale, D. P. *Tetrahedron* **1975**, *31*, 1219. (b) Aidhen, I. S.; Narasimham, N. S. *Tetrahedron Lett.* **1991**, *32*, 2171−2174.
(12) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959−6964.
(13) 2-Bromobenzyl chloride **8a** and 2-iodobenzyl chloride **8b** are commercially available, from Lancaster Co. and Aldrich, respectively.
(14) Badía, D.; Domínguez, E.; Iriondo, C. *Bull. Soc. Chim. Belg.* **1986**, *95*, 207.
(15) Chuang, T.-H.; Yang, C.-C.; Chang, C.-J.; Fang, J.-M. *Synlett* **1990**, 733−734.
(16) Viehe, H. G.; Janusek, Z.; Merenyl, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148−154.
(17) Dibiase, S. A.; Wolak, R. P.; Dishong, D. M.; Gokel, G. W. *J. Org. Chem.* **1980**, *45*, 3630−3634.

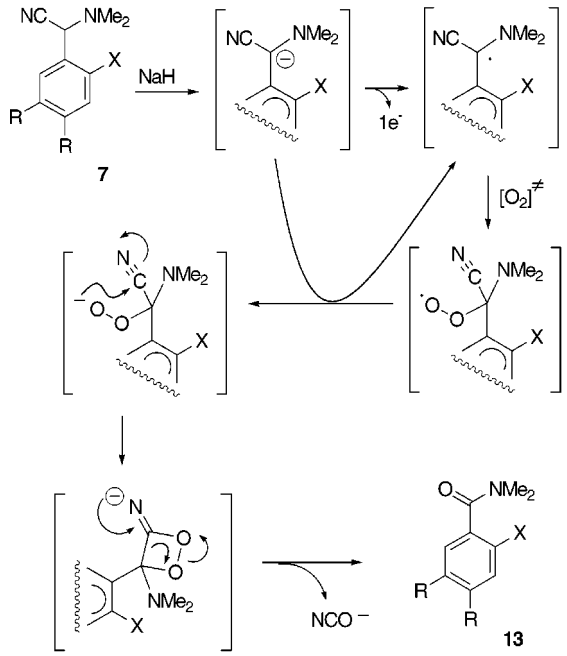
Table 1. Aminonitriles 7, Amides 13, and Nitriles 14 Prepared



i: KCN, $Me_2NH{\cdot}HCl$, MeCN, H_2O; ii: NaH, DMF, **8**

R	X	**7** (%)	**13** (%)	**14** (%)
H	Br	**7a** (87)	**13a** (62)	**14a** (32)
H	I	**7b** (85)	**13b** (65)	**14b** (31)
OMe	Br	**7c** (89)	**13c** (70)	**14c** (28)
OMe	I	**7d** (89)	**13d** (55)	**14d** (41)

Scheme 2



Although the autoxidation problem was overcome by means of using degassed DMF, triaryl nitrile derivatives **14** were still obtained as main products (59−72%) along with the expected intermediate enamines **15** (22−31%) when submitting α-aminonitriles **7** to alkylation conditions.

X-ray crystallographic studies accomplished on a monocrystal of nitrile **14a** confirmed the already proposed structure and showed some remarkable structural features of this unexpected byproduct. As shown in Figure 1, there is a clear symmetry plane defined by the *o*-bromoacetonitrile moiety (torsion angles C5−C6−C7−C15 and C1−C6−C7−C15 are 0° and 180°, respectively), and both *o*-bromobenzyl moieties adopt such a conformation that minimizes repulsive interactions between Br substituent, allowing the formation of four C−H···Br and one C−H···N intramolecular hydrogen bonds. Further stabilization is provided by the intermolecular packing

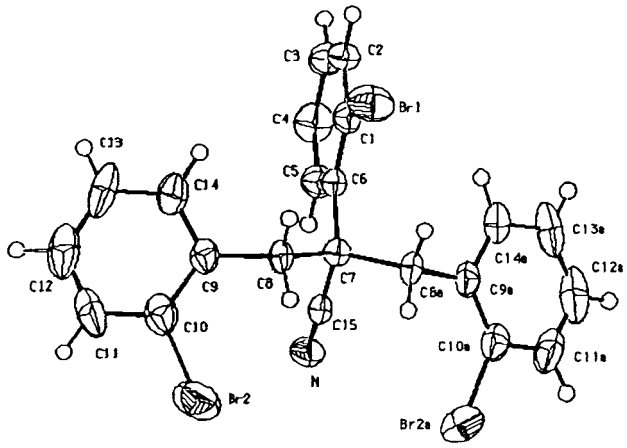


Figure 1. Ortep III view of nitrile **14a** showing the atomic numbering scheme.

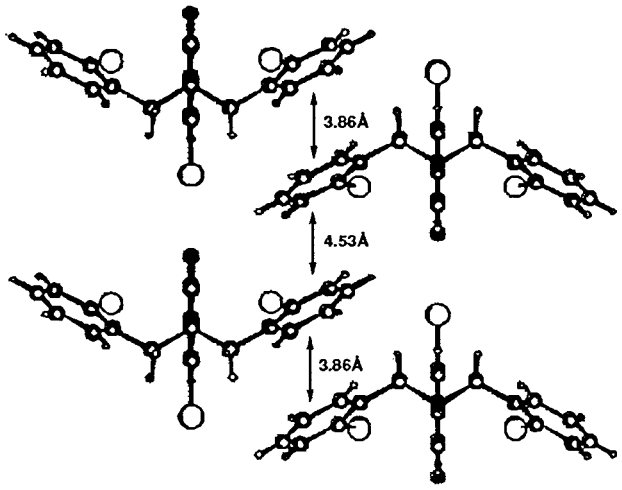


Figure 2. Packing diagram of nitrile showing π interactions.

where additional hydrogen bonding and weak $\pi-\pi$ interactions between aromatic rings[18a−c] form a "zip type" arrangement (Figure 2).[18d]

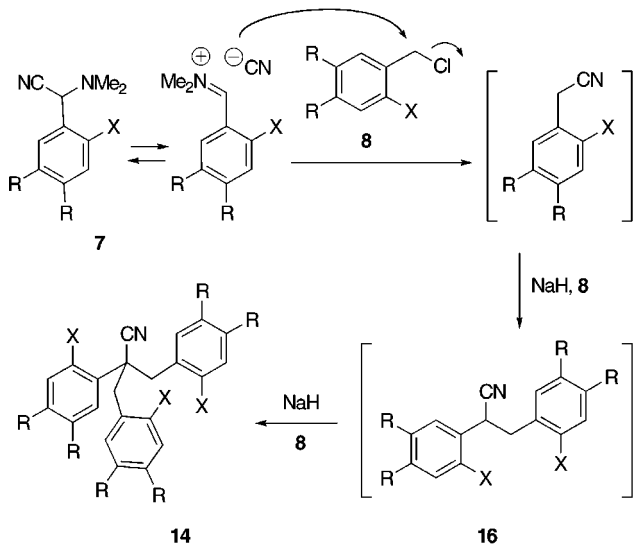
To explain the formation of nitriles **14**, it must be considered an initial α-aminonitrile/iminium cyanide equilibrium based on a push−pull type mechanism.[19] In fact, decyanation of α-aminonitriles has been observed in reductive, strongly basic conditions, or mediated by mercury(II) trifluroacetate,[20] but not in so high a proportion, probably due to a fast removal of cyanide ion from the equilibrium as it reacts with halobenzyl chlorides **8**. Thus, strongly nucleophilic cyanide ion would replace chloride from halobenzyl derivatives **8** and the so-formed

(18) (a) Nishio, M.; Hirota, M.; Umezawa, Y. in *The CH−Pi Interaction: Evidence, Nature and Consequences*; Marchland, A. P., Ed.; Wiley-VCH: New York, 1998. (b) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525−5534. (c) The nature and extent of the $\pi-\pi$ interactions was evaluated by CONTACTOS program. See: Albert, A.; Cano, F. H. In *Cristalografía*; Hernández-Cano, F., Foces-Foces, C. Martínez-Ripoll, M., Eds.; Publicaciones CSIC: Madrid, 1995; p 183. (d) See Supporting Information for hydrogen bonding and other selected geometric parameters of nitrile **14a**, including $\pi-\pi$ interaction parameters.

(19) Ogura, K.; Shimamura, Y.; Fujita, M. *J. Org. Chem.* **1991**, *56*, 2920−2922.

(20) (a) Yamada, S. I.; Akimoto, H. *Tetrahedron Lett.* **1969**, *16*, 3105−3108. (b) Jenning, M. J.; Biles, C.; Romero, D. L. *Tetrahedron Lett.* **1993**, *34*, 4301−4304. (c) Sassaman, M. B. *Tetrahedron* **1996**, *52*, 10835−10840.

Scheme 3



arylacetonitriles would undergo an iterative deprotonation/alkylation process to give triaryl nitriles **14** (Scheme 3). The isolation of intermediate **16** (X = Br, R = OMe) provided an additional proof to support our mechanistic proposal.[21]

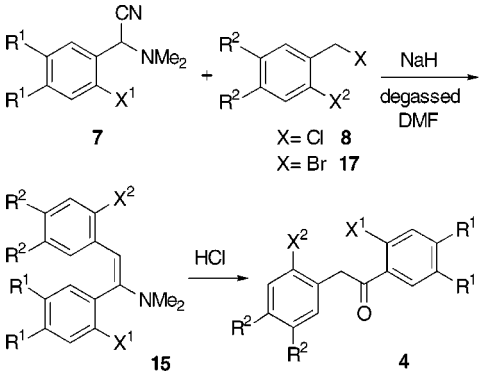
Finally, enamine derivatives **15a**,**b** were obtained with good yields when α-aminonitriles **7a**,**b** were added onto a mixture of NaH and halobenzyl chlorides **8a**,**b** (method A in Table 2) at −19 °C, as a fast alkylation of **7** avoided the α-aminonitrile/iminium cyanide equilibrium and the subsequent side reactions. However, the same conditions applied to substrates **7c**,**d** and chlorides **8c**,**d** afforded unreacted material and low proportion of the target enamines **15c**,**d**, probably due to a marked instability of the methoxylated benzyl chlorides employed in the presence of NaH.[22] To promote a faster alkylation step, halobenzyl bromides **17**[23] were assayed as alkylating agents (method B in Table 2), affording enamines **15c**,**d** with good yields. This behavior can be explained considering that, when using bromides **17**, a much higher alkylation rate overcomes by far the decomposition rate. Although enamine type intermediates had been proposed by Dyke,[11a] no diarylenamines such as **15** have been isolated so far. Moreover, strongly acidic conditions and high temperatures (HCl concentrated, 145 °C, 12 h) were required to effect hydrolysis of these halogenated intermediates, although milder conditions (HCl 6 M, 115 °C, 8 h) were enough for some enamines bearing alkoxy substitution.

(21) In fact, triarylnitriles **14** have been also prepared by addition of sodium cyanide to halogenated benzyl halides in the presence of base. These results will be published elsewhere.

(22) ^{1}H NMR tecniques showed complete decomposition of methoxylated halobenzyl chlorides **8c**,**d** in the presence of NaH at temperatures above −10 °C. Attempts to carry out the alkylation reaction at lower temperatures afforded enamines **15c**,**d** with moderate yields (40−55%). Although no decomposition product was isolated, the autoalkylation of benzyl chlorides under basic conditions has been reported. See: Hauser; C. R.; Brasen, W. R.; Skell, P. S.; Kantor, S. W.; Brodhay, A. E. *J. Am. Chem. Soc.* **1956**, *78*, 1653−1658.

(23) (a) Iodoarylmethyl bromides **17b** and **17d** were obtained by treatment of alcohols **10b** and **10d** with HBr−H_2O and HBr−CH_3-COOH, respectively. See: Vögtle, N.; Eisen, N.; Franken, S.; Büllesbach, P.; Puff, H. *J. Org. Chem.* **1987**, *52*, 5560−5564. (b) Bromoarylmethyl bromides **17c** and **17e** were prepared by treatment of veratryl alcohol **12a** and homopiperonyl alcohol **12b** with Br_2−$CHCl_3$, respectively. See: Landais, Y.; Robin, J.-P.; Leburn, A. *Tetrahedron* **1991**, *47*, 3787−3804 and Cochran, J. E.; Padwa, A. *J. Org. Chem.* **1995**, *60*, 3438−3439.

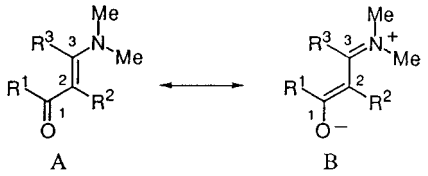
Table 2. Synthesis of Enamines 15 and Dihalodeoxybenzoins 4



R^1	R^2	X^1	X^2	**15** (%)	**4** (%)[c]
H	H	Br	Br	**15a** (87)[a]	**4a** (82)[d]
H	H	I	I	**15b** (83)[a]	**4b** (79)[d]
OMe	OMe	Br	Br	**15c** (79)[b]	**4c** (71)[e]
OMe	OMe	I	I	**15d** (81)[b]	**4d** (76)[e]
OMe	H	Br	Br	**15e** (80)[a]	**4e** (75)[d]
OMe	H	I	I	**15f** (80)[a]	**4f** (74)[d]
H	OMe	Br	Br	**15g** (79)[b]	**4g** (72)[d]
H	OMe	I	I	**15h** (78)[b]	**4h** (70)[d]
H	OMe	Br	I	**15i** (71)[b]	**4i** (60)[d]
H	OMe	I	Br	**15j** (74)[b]	**4j** (66)[d]
H	OCH_2O[f]	Br	Br	**15k** (81)[b]	**4k** (77)[e]

[a] Method A: 1. **8**, degassed DMF, NaH, −19 °C, 1 min; 2. **7**, degassed DMF, −19 °C, 10 min → rt. [b] Method B: 1. **7**, degassed DMF, NaH, −19 °C, 60 min; 2. **17**, degassed DMF, −19 °C, 10 min → rt. [c] Overall yield of pure crystallized compound (MeOH). [d] Hydrolysis was effected by HCl concentrated, 145 °C, 12 h. [e] Hydrolysis was effected by HCl 6 M, 115 °C, 8 h. [f] $R^2 + R^2 = OCH_2O$.

2. Spectroscopic Nonequivalence in Vinylogous Amide Systems. As shown in Table 4, enaminoketones **18** were efficiently prepared from diaryl ethanones **4** by treatment with Vilsmeier−Haack type reagent dimethylformamide dimethyl acetal (DMFDMA). Some of the former derivatives **18** showed spectroscopic nonequivalence of the *N*-methyl groups, an effect related to previous observations with nonhalogenated enaminoketones **19a**−**d**.[24]



In the vinylogous amide system, the contribution of resonance form B causes hindered rotation around C_3−N. We proposed that depending on the electron-withdrawing nature of the R^1 substituent (alkyl, *p*-methoxyphenyl, phenyl, and *p*-nitrophenyl) this contribution varies, affecting the rotational barrier for C_3−N bond which can be observed by ^{1}H and ^{13}C NMR techniques (Figure 3).

However, nonhalogenated 1,2-diarylenaminones **20**, previously prepared by our group,[24] showed only one sharp singlet for NMe_2 moiety at room temperature, suggesting that steric factors had to be considered in our theory. As shown in Figure 4, molecular modeling

(24) SanMartin, R.; Mtez. de Marigorta, E.; Domínguez, E. *Tetrahedron* **1994**, *50*, 2255−2264.

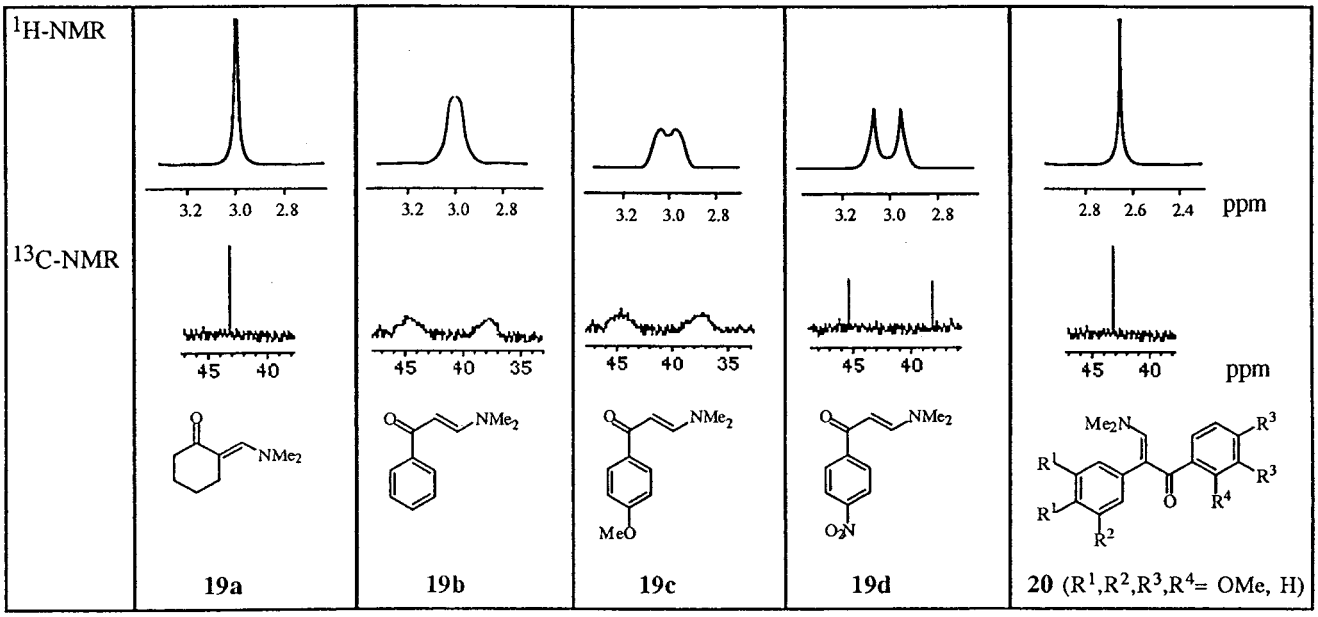


Figure 3. ^{1}H NMR and ^{13}C NMR signal shapes corresponding to the NMe_2 moiety of enaminoketones **19** and **20**.

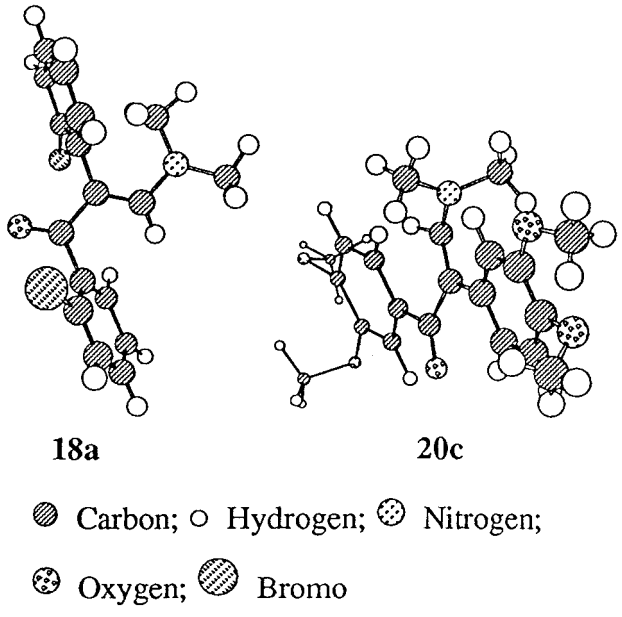


Figure 4. View of low energy conformations of enaminoketones **20c** and **18a**.

calculations of **20c** ($R^1 = R^3 = OMe$, $R^2 = R^4 = H$) provided such a low-energy conformation for **20c** where the dimethylamino group, due to the steric interaction with bulky aryl group at C-2, would be located in a perpendicular plane with respect to the latter aryl substituent; thus, the nitrogen lone pair would be almost perpendicular to the enone π orbital system and unable to overlap with it. Therefore, dihaloaryl enaminones **18** would be quite interesting, since according to our calculations the bulky halogen substituent could force the aryl ring to deviate from coplanarity with the enone system, thus allowing resonance with the dimethylamino group and, consequently, spectroscopic nonequivalence of the already mentioned methyl groups attached to nitrogen (Figure 4).

In fact, ^{1}H NMR spectra of enaminones **18a** and **18c** at room temperature showed for the NMe_2 moiety significant broad singlets (2.41−2.84 ppm in $CDCl_3$, 2.39−2.82 ppm in DMSO-d_6 for **18a**, 2.59−3.08 ppm in $CDCl_3$, 2.44−2.91 ppm in DMSO-d_6 for **18c**), and two signals could be found in ^{13}C NMR (47.1 and 38.5 ppm in $CDCl_3$, 47.4 and 38.8 ppm in DMSO-d_6 for **18a**, 47.2 and 38.6 ppm in $CDCl_3$, 46.7 and 37.9 ppm in DMSO-d_6 for **18c**). NMR experiments at different temperatures of enaminoketones **18a** and **18c** in DMSO-d_6 showed a coalescence temperature of 45 °C and only a sharp singlet in both ^{1}H and ^{13}C NMR spectra at 68 °C (Figure 5). According to the coalescence temperature, the $\Delta G^{\ddagger}$ for the rotational barrier has an approximate value of 15.0 kcal/mol. Similar experiments and calculations performed on enaminones **19d** and **20c** provided $\Delta G^{\ddagger}$ values of 16.4 and 12.5 kcal/mol, respectively, which is consistent with our proposal based on electronic and steric factors.

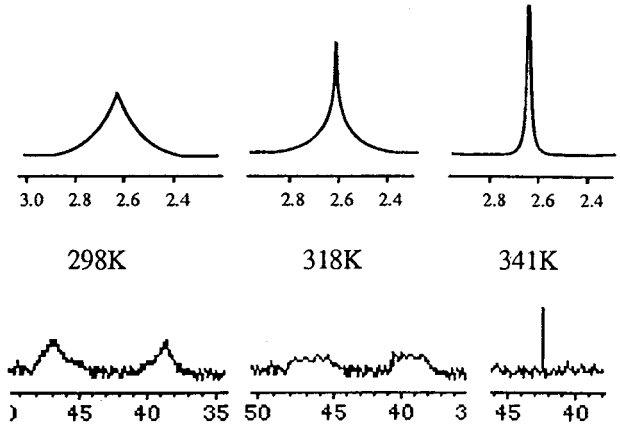


Figure 5. ^{1}H NMR and ^{13}C NMR signal shapes corresponding to the NMe_2 moiety of enaminoketone **18a** in DMSO-d_6 at several temperatures.

3. Synthesis of Dihalogenated Diarylisoxazoles. To obtain the target diarylisoxazoles **21**, enaminoketones **18** were submitted to heterocyclization conditions according to our procedure.[1c] However, only mixtures of 4,5-bis(2-haloaryl)-5-hydroxy-2-isoxazolines **22** and deoxybenzoins **4** were obtained under the latter conditions (Table 3). These results are worth examining, as the

Scheme 4

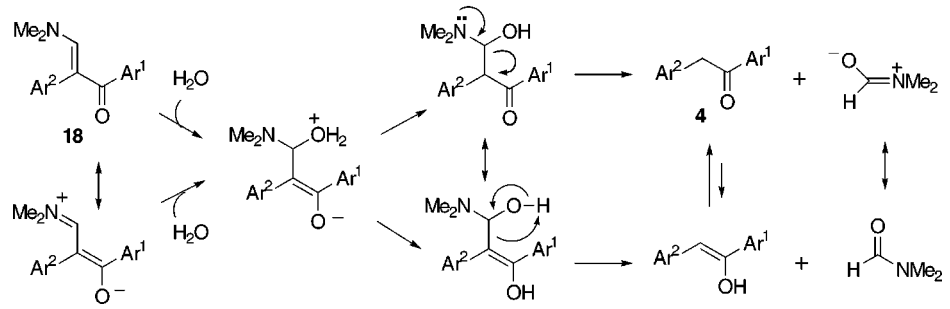
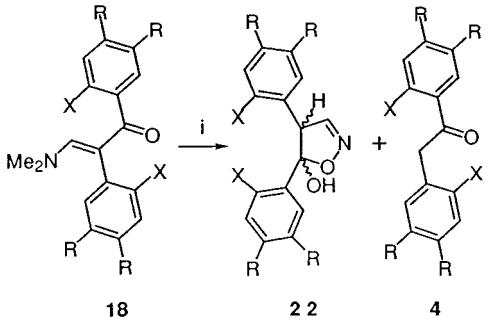


Table 3. Isoxazolines 22 and Ketones 4 from Enaminoketones 18



i: $NH_2OH{\cdot}HCl$, AcOH, K_2CO_3, MeOH-H_2O, ↑↓, 11h

R	X	**22** (%)	**4** (%)
H	Br	**22a** (58, 36/64[a])	**4a** (37)
H	I	**22b** (61, 22/78[a])	**4b** (31)
OMe	Br	**22c** (66, 46/54[a])	**4c** (29)
OMe	I	**22d** (60, 44/56[a])	**4d** (35)

[a] Cis/trans ratio, calculated from the relative integration of the ^{1}H NMR signals (m) corresponding to H-4.

isolation of hydroxyisoxazolines **22** provides a valuable proof of an amine exchange-based mechanism,[1] and the formation of deoxybenzoins illustrates an unusual process in the chemistry of enaminoketones.

With regard to hydroxyisoxazoline intermediates **22a**−**d**, which were obtained as mixtures of *cis*/*trans* diastereoisomers, their lack of reactivity toward dehydration might be the reason for their isolation. The structure of these isoxazolines **22**, confirmed by X-ray difraction techniques performed on a monocrystal of the *trans*-4*S**,5*S**-isomer of **22b** (owing to the $P2_1/c$ space-group centrosymmetry, both the *R*,*R* and *S*,*S* enantiomers are present in the crystal and only the *S*,*S*-configuration is represented in Figure 6), showed the isoxazoline ring in an almost ideal envelope-type conformation (puckering parameters Q, θ, and φ[25] are 0.262−0.267, n/c, and 323.4−328.4°, respectively).

On the other hand, the formation of deoxybenzoins **4** from enaminoketones **18** illustrates an unusual behavior of enaminoketones related to a retro-Mannich reaction. We propose that enaminones **18** could undergo a conjugate addition of water leading to an adduct which eliminates DMF, giving rise to ketones **4** (Scheme 4). In fact, DMF was isolated along with derivatives **4** from the reaction mixture.[26]

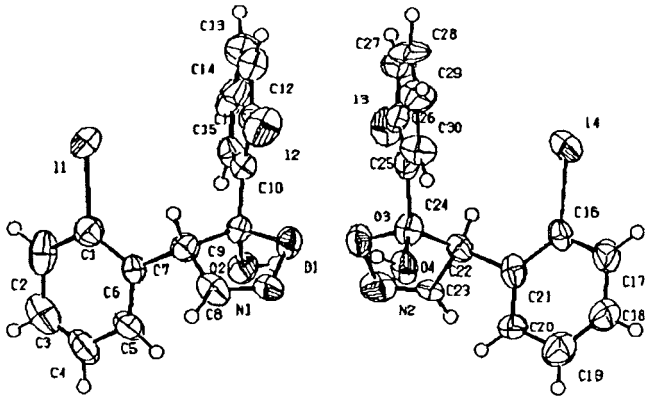


Figure 6. PLATON view of hydroxyisoxazoline **22b**. The asymmetric unit is composed of two slightly different conformers of the same molecule.

The formation of deoxybenzoins **4** was avoided by sonication of the reaction mixture at 65 °C, consequently the yield of hydroxyisoxazolines **22** was much improved (78−84%). However, the target isoxazoles **21** could not be obtained by simple heating, sonication, or treatment under acidic (*p*-TsOH, H_2SO_4 aq) or basic (K_2CO_3, NaOAc, or pyridine) conditions to effect dehydration of derivatives **22**. A related behavior has already been reported by Anjaneyulu et al.[27] This problem was sorted out by performing the reaction in a heavy wall pressure tube. The effect of working at higher temperatures than the boiling point of the solvent and higher pressures than the atmospheric[28] was crucial, as target isoxazoles **21** were regioselectively obtained in short reaction times (1.5−2.0 h). Table 4 shows the results obtained for the synthesis of these bis(haloaryl) heterocycles **21** along with their precursors **18**.

In addition to the observed regioselectivity of the heterocyclization reaction, the isolation of intermediates **22** rules out the possibility of a mechanism based on a hydroxylamine attack to form the corresponding oxime A whose hydroxy group would displace dimethylamino moiety. Therefore, our mechanistic proposal,[1c] based on an initial amine-exchange process followed by nucleophilic addition of hydroxylamine derivative B to the carbonyl group and dehydration, is clearly confirmed (Scheme 5).

To sum up, an efficient strategy for the preparation of *o*,*o*′-dihaloarylethanones is reported. This methodology overcomes a number of synthetic problems associated to the presence of the *o*,*o*′-dihalo substituents, presenting

(25) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354−1358.

(26) See Experimental Section for more details. An alternative mechanism based on the hydrolysis of **18** to the aldehyde followed by oxidation to the corresponding keto-acid and subsequent decarboxylation was discarded as it could not explain the formation of DMF.

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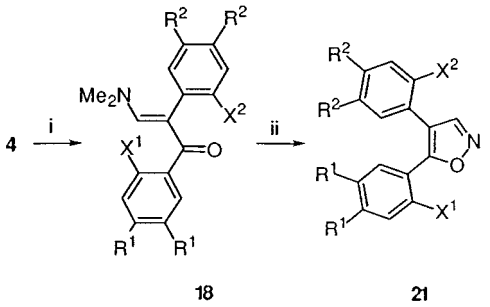
Table 4. Synthesis of Dihaloaryl Enaminones 18 and Isoxazoles 21



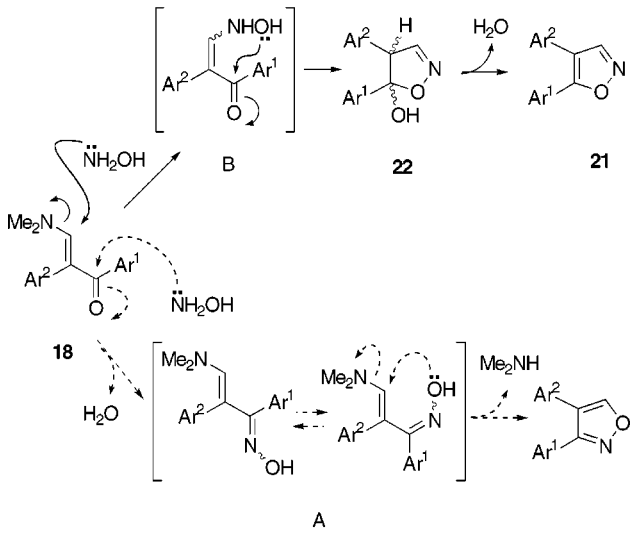
i: DMFDMA, toluene, ↑↓

ii: $NH_2OH{\cdot}HCl$, AcOH, K_2CO_3, ROH (R= Me, ^{i}Pr), 115°C, sealed tube

R^1	R^2	X^1	X^2	**18** (%)[a]	**21** (%)[a]
H	H	Br	Br	**18a** (77)	**21a** (92)
H	H	I	I	**18b** (78)	**21b** (90)
OMe	OMe	Br	Br	**18c** (75)	**21c** (89)
OMe	OMe	I	I	**18d** (70)	**21d** (98)[b]
OMe	H	Br	Br	**18e** (79)	**21e** (91)
OMe	H	I	I	**18f** (71)	**21f** (89)[b]
H	OMe	Br	Br	**18g** (81)	**21g** (92)
H	OMe	I	I	**18h** (86)	**21h** (88)
H	OMe	Br	I	**18i** (82)	**21i** (81)
H	OMe	I	Br	**18j** (77)	**21j** (78)
H	OCH_2O[c]	Br	Br	**18k** (84)	**21k** (93)

[a] Yield of pure crystallized compound (MeOH). [b] The reaction was performed using ^{i}PrOH as solvent. MeOH was the solvent of choice in the synthesis of the rest of isoxazoles **21**. [c] $R^2 + R^2 = OCH_2O$.

Scheme 5



at the same time interesting side products and significant intermediates, such as triarylpropionitriles, benzamides, deoxybenzoins, and 5-hydroxyisoxazolines. In addition, X-ray structural examination of some of the latter compounds and a general explanation for the spectroscopic behavior of enaminoketones based on electronic/conformational factors are also reported.

Experimental Section

General. For general experimental details, see ref 1c. MM2 parameters[29] were applied by MOLGEN[30] and CSChem3D[31] programs to perform conformational calculations. The data collection and cell refinement of crystallographic analysis were performed by CAD-4 software.[32] The crystallographic data reduction was carried out by Xtal3.2,[33] and the structure was solved by SHELXL86 and refined by SHELXL93 programs.[34]

Preparation of Chloride, Bromide, and Aldehyde Precursors.

2-Iodobenzaldehyde (9b). MnO_2 (82.5 g, 0.854 mol) was added in little portions to a stirred solution of alcohol **10b** (10 g, 42.7 mmol) in chloroform (200 mL) at room temperature. After stirring for 1 h, the mixture was filtered, and the filtrate was evaporated in vacuo to provide a colorless oil which was crystallized from hexane. 2-Iodobenzaldehyde **9b** (9.0 g, 91%) was obtained as a brown powder: mp 37−38 °C (hexane) (lit.[35] 37 °C (hexane)); R_f 0.54 (5% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 7.26 (1H, ddd, J = 7.5, 7.5, 1.9 Hz), 7.46 (1H, ddd, J = 7.5, 7.5, 1.9 Hz), 7.85 (1H, dd, J = 7.5, 1.9), 7.93 (1H, dd, J = 7.5, 1.9 Hz) 10.04 (1H, s); ^{13}C NMR ($CDCl_3$) δ 101.2, 128.6, 130.1, 134.6, 135.2, 140.5 195.1; FTIR (neat film, cm^{-1}): 1693; EIMS (*m*/*z*, %) 232 (M^+, 100), 104 (71).

2-Bromo-4,5-dimethoxybenzaldehyde (9c). Typical Procedure. A solution of bromine (3.2 mL, 62.5 mmol) in dry chloroform (8 mL) was added dropwise to a stirred solution of veratraldehyde (10.0 g, 60.1 mmol) in dry chloroform (80 mL) under argon at room temperature. The mixture was heated to 60 °C for 6 h, and after cooling, it was concentrated in vacuo. The residue was washed with chloroform and evaporated under reduced pressure. Crystallization from MeOH afforded bromoveratraldehyde **9c** (13.1 g, 89%) as a white powder: mp 147−148 °C (MeOH) (lit.[36] 149−151 °C (MeOH)); R_f 0.54 (3% EtOAc/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.92 (3H, s), 3.96 (3H, s), 7.06 (1H, s), 7.42 (1H, s) 10.19 (1H, s); ^{13}C NMR ($CDCl_3$) δ 55.9, 56.3, 110.2, 115.3, 120.2, 126.3, 148.7, 154.3 190.5; FTIR (neat film, cm^{-1}): 1669; EIMS (*m*/*z*, %) 246 (M + 1, 94), 244 (M − 1, 100), 231 (16), 229 (18).

The same procedure applied to (3,4-dimethoxyphenyl)-methanol **12a** afforded (2-bromo-3,4-dimethoxyphenyl)methyl bromide **17c** (91%) as a white powder: mp 118−119 °C (hexane) (lit.[37] 121−123 °C (cyclohexane))

The same procedure applied to 5-(hydroxymethyl)-1,3-benzodioxole **12b** afforded 5-bromo-6-(bromomethyl)-1,3-benzodioxole **17e** (93%) as a white powder: mp 88−90 °C (Et_2O) (lit.[38] 92−93 °C (MeOH))

(4,5-Dimethoxy-2-iodophenyl)methyl Chloride (8d). A solution of ICl (5.44 g, 32.8 mmol) in dry $CHCl_3$ (15 mL) was added to a stirred solution of veratryl alcohol (4.61 g, 27.4 mmol) in dry $CHCl_3$ (75 mL) under argon at room temperature. After stirring for 2 h, water (400 mL) and $Na_2S_2O_5$ were added until the purple iodine color was discharged. After decantation, the organic layer was washed with saturated aqueous $Na_2S_2O_5$, dried over anhydrous sodium sulfate, and evaporated in vacuo. Crystallization of the residue from 15% EtOAc/hexane afforded iodo derivate **8d** (4.79 g, 56%) as a red powder: mp 80−81 °C (Et_2O) (lit.[39] 84−85 °C (MeOH)).

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(31) *Chem3D Pro 3.5.2*, 1997, CambridgeSoft Corporation, Cambridge, MA.

(32) Enraf-Nonius *CAD-4 Software 5.0*, Enraf-Nonius, Delft, The Netherlands.

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(36) *Dictionary of organic compounds*; Buckingham, J.; Donoghy, S. M. Ed.; Chapman & Hall: Easton, Pennsylvania, 1982; Vol 5, p 786.

(37) Shono, T.; Hamaguchi, H.; Sasaki, M.; Fujita, S.; Nagami, K. *J. Org. Chem.* **1983**, *48*, 1621−1628.

(38) Barthel; W. F.; Alexander, B. H. *J. Org. Chem.* **1958**, *28*, 1012−1014.

4,5-Dimethoxy-2-iodophenylmethanol (10d). A solution of iodine (18.2 g, 70.4 mmol) in dry $CHCl_3$ (50 mL) was added to a stirred solution of veratryl alcohol **12a** (9.8 g, 58.7 mmol) and silver trifluoroacetate (14.1 g, 64.6 mmol) in dry $CHCl_3$ (250 mL) under argon at room temperature. After stirring for 2 h, the mixture was filtered, and the filtrate was concentrated under reduced pressure, giving a yellow oil which was triturated with Et_2O to afford alcohol **10d** (15.7 g, 91%) as a yellow powder: mp 96−97 °C (Et_2O) (lit.[39] 77−78 °C (Et_2O))

An alternative procedure for the preparation of 4,5-dimethoxy-2-iodophenylmethanol **10d** is described below:

A solution of chloride **8d** (6.43 g, 206 mmol) in acetone (15 mL) was added dropwise to a stirred suspension of $AgNO_3$ (3.64 g, 212 mmol) in acetone (50 mL) and water (50 mL) at room temperature. After being stirred for 1 h, the mixture was filtered, and the filtrate was washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure, and the residue was triturated with Et_2O to provide alcohol **10d** (6.0 g, 99%) as a white powder.

2-Bromo-4,5-dimethoxyphenylmethanol (10c). $NaBH_4$ (1.66 g, 44 mmol) was added in little portions to a stirred solution of aldehyde **9c** (10.8 g, 44 mmol) in dry MeOH (27 mL) and dry $CHCl_3$ (13 mL) at 0 °C under argon. After stirring at the same temperature for 1 h, water (400 mL) was added, and the aqueous layer was extracted with $CHCl_3$ (3 × 70 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated in vacuo to give a residue which was crystallized from Et_2O. Alcohol **10c** (8.0 g, 74%) was obtained as a white powder: mp 91−93 °C (Et_2O) (lit.[40] 82.5 °C); R_f 0.15 (5% EtOAc/$CHCl_2$); ^{1}H NMR ($CDCl_3$) δ 3.69 (3H, s), 3.70 (3H, s), 4.48 (2H, s), 6.82 (1H, s) 6.85 (1H, s); ^{13}C NMR ($CDCl_3$) δ 55.3, 55.7, 63.8, 110.6, 111.1, 114.1, 131.6, 147,9, 148.2; FTIR (neat film, cm^{-1}): 3388; EIMS (*m*/*z*, %) 249 (M + 2, 9), 248 (M + 1, 76), 247 (M$^+$, 13), 246 (M − 1, 16), 231 (18), 229 (10), 167 (29), 139 (100).

2-Bromo-4,5-dimethoxyphenylmethyl Chloride (8c). Me_2S (1.14 mL, 14.6 mmol) was added to a stirred suspension of NCS (1.83 g, 13.4 mmol) in dry CH_2Cl_2 (70 mL) at −25 °C under argon. After the mixture was stirred at the same temperature for 15 min, a solution of alcohol **10c** (3.0 g, 12.1 mmol) in dry CH_2Cl_2 (5 mL) was added, and the resulting suspension was allowed to warm to 0 °C. The stirring at 0 °C was continued for 2 h, and then the reaction mixture was poured onto an ice−water mixture (20 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, and evaporated in vacuo. The resulting yellow oil was purified by flash chromatography using 10% EtOAc/hexane as eluent, affording chloride **8c** (2.64 g, 82%) as a white powder: mp 60−61 °C (20% hexane/Et_2O); (lit.[41] 55 °C (CCl4); R_f 0.91 (hexane); ^{1}H NMR ($CDCl_3$) δ 3.81 (3H, s), 3.82 (3H, s), 4.60 (2H, s), 6.85 (1H, s) 6.97 (1H, s); ^{13}C NMR ($CDCl_3$) δ 46.3, 55.8, 55.9, 113.0, 114.3, 115.3, 128.3, 148.3, 148.5; FTIR (neat film, cm^{-1}): 1440 (CH_2); EIMS (*m*/*z*, %) 266 (M + 1, 25), 264 (M − 1, 19), 231 (100), 229 (94).

4,5-Dimethoxy-2-iodobenzaldehyde (9d). A solution of alcohol **10d** (10 g, 34 mmol) in dry CH_2Cl_2 (20 mL) was added to a stirred suspension of PDC[17] (20.1 g, 51 mmol) in dry CH_2Cl_2 (300 mL) under argon at 0 °C. After stirring for 45 min at the same temperature, Et_2O (200 mL) was added, the mixture was filtered, the filtrand was repeatedly washed with Et_2O. The combined organic layers were concentrated in vacuo to give aldehyde **9d** (9.43 g, 95%) as a white powder: mp 115−117 °C (Et_2O) (lit.[39] 85−95 °C (dec) ($CHCl_3$)) R_f 0.33 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.90 (3H, s), 3.94 (3H, s), 7.29 (1H, s), 7.40 (1H, s) 9.85 (1H, s); ^{13}C NMR ($CDCl_3$) δ 56.0, 56.4, 92.7, 111.0, 121.7, 128.3, 149.7, 154.4 194.8; FTIR (neat film, cm^{-1}): 1670; EIMS (*m*/*z*, %) 292 (M$^+$, 100), 164 (11).

(4,5-Dimethoxy-2-iodophenyl)methyl Bromide (17d). A solution of alcohol **10d** (15.0 g, 51.0 mmol) in dry CH_2Cl_2 (45 mL) was added slowly to a stirred solution of HBr (120 mL, 47% in water) under argon at 0 °C. After being stirred for 1 h, the mixture was allowed to warm, and it was diluted with water (500 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over anhydrous sodium sulfate, and evaporated in vacuo. The resulting red oil was purified by flash chromatography using 20% EtOAc/hexane as eluent, providing bromide **17d** (16.2 g, 89%) as a white powder: mp 89−90 °C (Et_2O); R_f 0.36 (15% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 3.82 (3H, s), 3.83 (3H, s), 4.53 (2H, s), 6.92 (1H, s) 7.18 (1H, s); ^{13}C NMR ($CDCl_3$) δ 39.3, 55.5, 55.7, 88.3, 112.3, 121.1, 131.8, 148.8, 148.9; FTIR (neat film, cm^{-1}): 1452; EIMS (*m*/*z*, %) 358 (M + 1, 10), 356 (M − 1, 10), 277 (100).

(2-Iodophenyl)methyl Bromide (17b). A solution of HBr (105 mL, 33% in AcOH) was added to a stirred solution of 2-iodobenzyl alcohol **10b** (10.5 g, 44.4 mmol) in AcOH (5 mL) under argon at 0 °C. After the mixture was stirred at the same temperature for 45 min, water (600 mL) was added, and the resulting white precipitate was filtered and redissolved in CH_2Cl_2 (100 mL). This organic layer was washed with saturated aqueous $NaHCO_3$ and water, dried over anhydrous sodium sulfate, and evaporated in vacuo. The residue was crystallized from MeOH to provide 2-iodobenzyl bromide **17b** (12.4 g, 95%) as a white powder: mp 48−50 °C (MeOH), (lit.[42] 56−57 °C (Et_2O)); R_f 0.76 (20% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 4.60 (2H, s), 6.99 (1H, ddd, J = 7.7, 7.7, 1.7 Hz), 7.33 (1H, ddd, J = 7.5, 7.5, 1.0 Hz), 7.47 (1H, dd, J = 7.7, 1.7 Hz) 7.85 (1H, dd, J = 7.5, 1.0 Hz); ^{13}C NMR ($CDCl_3$) δ 38.8, 100.0, 128.8, 130.0, 130.4, 139.9, 140.0; FTIR (neat film, cm^{-1}): 1463; EIMS (*m*/*z*, %) 298 (M + 1, 12), 296 (M − 1, 12), 217 (100).

Synthesis of Aminonitriles.

2-(2-Bromo-4,5-dimethoxyphenyl)-2-(*N*,*N*-dimethylamino)acetonitrile (7c). Typical Procedure. Veratraldehyde **11** (5.14 g, 21.0 mmol) was dissolved in CH_3CN (85 mL), and the resulting solution was added dropwise to a stirred solution of NaCN (1.72 g, 34.4 mmol) and Me_2N·HCl (4.78 g, 58.0 mmol) in water (34 mL) at room temperature. After stirring for 18 h, the reaction mixture was concentrated in vacuo, and the residue was redissolved in water (150 mL) and extracted with diethyl ether (4 × 75 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), water (50 mL), and brine (50 mL), dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was crystallized from methanol to afford α-aminonitrile **7c** (5.59 g, 89%) as a yellow powder: mp 72−73 °C (MeOH); R_f 0.39 (5% EtOAc/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.33 (6H, s, NMe), 3.86 (3H, s), 3.89 (3H, s), 4.95 (1H, s), 7.04 (1H, s), 7.05 (1H, s); ^{13}C NMR ($CDCl_3$) δ 241.6, 56.2, 62.2, 104.7, 112.4, 114.9, 115.1, 116.1, 148.1, 149.9; FTIR (neat film, cm^{-1}): 2230; EIMS (*m*/*z*, %) 300 (M + 1, 9), 298 (M − 1, 9), 257 (13), 255 (13), 254 (100). Anal. Calcd for $C_{12}H_{15}BrN_2O_2$: C, 48.18; H, 5.05; N. 9.36. Found: C, 48.29; H, 5.11; N, 9.47.

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

2-(2-Bromophenyl)-2-(*N*,*N*-dimethylamino)acetonitrile (7a) (87%), as a yellow oil; R_f 0.67 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.34 (6H, s), 5.04 (1H, s), 7.21 (1H, ddd, J = 7.7, 7.7, 1.7 Hz), 7.33 (1H, ddd, J = 7.7, 7.7, 1.5 Hz), 7.57 (1H, dd, J = 7.7, 1.7 Hz), 7.91 (1H, dd, J = 7.7, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 41.1, 62.1, 114.3, 124.3, 127.0, 129.6, 130.2, 132.6, 133.3; FTIR (neat film, cm^{-1}): 2218; EIMS (*m*/*z*, %) 240 (M + 1, 9), 238 (M − 1, 9), 196 (12), 194 (10), 116 (10), 83 (100). Anal. Calcd for $C_{10}H_{11}BrN_2$: C, 50.23; H, 4.64; N, 11.72. Found: C, 50.31; H, 4.72; N, 11.61.

2-(*N*,*N*-Dimethylamino)-2-(2-iodophenyl)acetonitrile (7b) (85%), as a yellow powder; mp 30−32 °C (hexane); R_f 0.60 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.34 (6H, s), 4.90 (1H, s), 7.07 (1H, ddd, J = 7.6, 7.6, 1.5 Hz), 7.40 (1H, ddd, J = 7.6, 7.6, 1.1 Hz), 7.58 (1H, dd, J = 7.6, 1.5 Hz), and 7.91 (1H, dd, J = 7.6,

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1.1 Hz); ^{13}C NMR ($CDCl_3$) δ 41.0, 66.1, 100.2, 114.4, 127.8, 129.1, 130.2, 132.6, 135.1 (C_{arom}-C), 140.2; FTIR (neat film, cm^{-1}): 2216; EIS (*m*/*z*, %) 286 (M^+, 24). Anal. Calcd for $C_{10}H_{11}IN_2$: C, 41.98; H, 3.88; N, 9.79. Found: C, 42.09; H, 3.96; N, 9.86.

2-(*N*,*N*-Dimethylamino)-2-(4,5-dimethoxy-2-iodophenyl)-acetonitrile (7d) (89%), as a white powder; mp 76−77 °C (MeOH); R_f 0.36 (25% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 2.34 (6H, s), 3.88 (3H, s), 3.91 (3H, s), 4.81 (1H, s), 7.08 (1H, s), 7.30 (1H, s); ^{13}C NMR ($CDCl_3$) δ 41.2, 55.9, 56.0, 66.0, 88.5, 112.0, 115.0, 122.2, 128.0, 148.8, 149.4; FTIR (neat film, cm^{-1}): 2224; EIMS (*m*/*z*, %) 346 (M^+, 24), 302 (100), 176 (15). Anal. Calcd for $C_{12}H_{15}IN_2O_2$: C, 41.64; H, 4.37; N, 8.09. Found: C, 41.84; H, 4.33; N, 8.22.

Synthesis of Diarylenamines.

(*E*)-1,2-Bis(2-bromophenyl)-*N*,*N*-dimethylethenylamine (15a). Typical Procedure (Method A). A solution of 2-bromobenzyl chloride **8a** (5.7 g, 27.6 mmol) in dry degassed DMF (18 mL) was quickly added to a stirred suspension of NaH (95%, 1.39 g, 55.0 mmol) in dry degassed DMF (15 mL) under argon at −19 °C. A solution of α-aminonitrile **7a** (6.0 g, 25.1 mmol) in dry DMF (6 mL) was immediately added to this mixture, as the solution was turning red. After stirring for 15 min at the same temperature, the reaction mixture was allowed to warm to room temperature and stirring was continued for an additional 1.5 h. Water (∼30 mL) was added until hydrogen bubbling stopped. Evaporation of the solvent under reduced pressure (1 mmHg, T ∼90 °C) afforded a brown oil which was purified by flash chromatography using 10% EtOAc/hexane as eluent, providing enamine **15a** (8.31 g, 87%) as a white powder, mp 82−83 °C (EtOH); R_f 0.38 (30% CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$) δ 2.76 (6H, s), 5.60 (1H, s), 6.45−6.49 (1H, m), 6.71−6.75 (2H, m), 7.17−7.21 (3H, m), 7.40−7.44 (1H, m), 7.55 (1H, d, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 40.0, 102.1, 123.9, 124.7, 125.1, 126.4, 127.5, 129.2, 129.5, 132.1, 132.2, 132.9, 138.0, 138.6, 150.0; FTIR (neat film, cm^{-1}): 1584; EIMS (*m*/*z*, %) 383 (M + 2, 30), 381 (M^+, 59), 379 (M − 2, 29), 302 (71), 300 (100). Anal. Calcd for $C_{16}H_{15}Br_2N$: C, 50.42; H, 3.97; N, 3.68%). Found: C, 50.81; H, 3.74; N, 3.77.

The same procedure on α-aminonitrile **7b** and chloride **8b** provided (*E*)-*N*,*N*-dimethyl-1,2-bis(2-iodophenyl)ethenylamine **15b** (83%) as a white powder: mp 102−103 °C (Et_2O); *Rf* 0.32 (30% CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$) δ 2.76 (6H, s), 5.49 (1H, s), 6.47 (1H, dd, J = 7.9, 1.3 Hz), 6.56 (1H, ddd, J = 7.5, 7.5, 1.5 Hz), 6.78 (1H, ddd, J = 7.9, 7.9, 0.9 Hz), 6.96 (1H, ddd, J = 7.9, 7.9, 1.3 Hz), 7.14 (1H, dd, J = 7.5, 1.8 Hz), 7.23 (1H, ddd, J = 7.5, 7.5, 1.5 Hz), 7.72 (1H, dd, J = 7.9, 1.8 Hz), 7.82 (1H, dd, J 7.5, 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 40.0, 100.8, 101.8, 107.1, 125.3, 127.3, 128.2, 128.6, 129.3, 131.5, 138.6, 139.5, 141.4, 141.6, 152.4; FTIR (neat film, cm^{-1}): 1596; EIMS (*m*/*z*, %) 475 (M^+, 100), 348 (65), 346 (23). Anal. Calcd for $C_{16}H_{15}I_2N$: C, 40.45; H, 3.18; N, 2.95. Found: C, 40.59; H, 3.09; N, 3.18.

The same procedure on α-aminonitrile **7c** and chloride **8a** provided (*E*)-1-(2-bromo-4,5-dimethoxyphenyl)-2-(2-bromophenyl)-*N*,*N*-dimethylethenylamine **15e** (80%) as a red oil: R_f 0.45 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 2.58 (6H, s), 3.88 (3H, s), 3.90 (3H, s), 5.57 (1H, s), 6.53 (1H, dd, J = 7.5, 2.0 Hz), 6.69 (1H, s), 6.74 (1H, ddd, J = 7.5, 7.5, 2.4 Hz), 6.80 (1H, ddd, J = 7.5, 7.0, 2.0 Hz), 6.97 (1H, s), 7.43 (1H, dd, J = 7.0, 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 39.4, 55.3, 101.5, 113.6, 114.0, 114.8, 123.2, 124.5, 125.9, 128.4, 129.0, 131.4, 138.1, 147.9, 148.6, 149.3; FTIR (neat film, cm^{-1}): 1594; EIMS (*m*/*z*, %) 443 (M + 2, 46), 441 (M^+, 92), 439 (M − 2, 47), 362 (92), 360 (100). Anal. Calcd for $C_{18}H_{19}Br_2NO_2$: C, 49.01; H, 4.34; N, 3.17. Found: C, 49.37; H, 4.31; N, 2.94.

The same procedure on α-aminonitrile **7d** and chloride **8b** provided (*E*)-1-(4,5-dimethoxy-2-iodophenyl)-*N*,*N*-dimethyl-2-(2-iodophenyl)ethenylamine **15f** (80%) as an amber oil: R_f 0.43 (40% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 2.74 (6H, s), 3.71 (3H, s), 3.83 (3H, s), 5.44 (1H, s), 6.52 (1H, dd, J = 7.3, 1.4 Hz), 6.59 (1H, ddd, J = 7.5, 7.5, 1.4 Hz), 6.66 (1H, s), 6.82 (1H, ddd, J = 7.5, 7.3, 1.2 Hz), 7.17 (1H, s), 7.72 (1H, dd, J = 7.3, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 39.9, 55.8, 55.9, 88.3, 101.8, 107.1, 113.7, 121.3, 125.3, 127.3, 128.5, 133.5, 141.6, 148.7, 149.0, 152.1; FTIR (neat film, cm^{-1}): 1589; EIMS (*m*/*z*, %) 535 (M^+, 22), 408 (74). Anal. Calcd for $C_{18}H_{19}I_2NO_2$: C, 40.40; H, 3.58; N, 2.62. Found: C, 40.72; H, 3.51; N, 2.81.

(*E*)-1,2-Bis(2-bromo-4,5-dimethoxyphenyl)-*N*,*N*-dimethylethenylamine (15c). Typical Procedure (Method B). A solution of α-aminonitrile **7c** (6.8 g, 22.7 mmol) in dry degassed DMF (17 mL) was added dropwise to a stirred suspension of NaH (95%, 1.26 g, 50.0 mmol) in dry degassed DMF (13 mL) under argon at −19 °C. After the mixture was stirred for 1 h at the same temperature, a solution of arylmethyl bromide **17c** (12.7 g, 40.9 mmol) in dry degassed DMF (22 mL) was added, and the reaction mixture was stirred for 15 min at −19 °C, warmed to room temperature, and stirred for an additional 1.5 h. Water (∼10 mL) was slowly added until bubbling stopped, and the solvent was evaporated in vacuo (1 mmHg, $T \sim 90$ °C). The residue was purified by flash chromatography using 30% EtOAc/hexane as eluent to afford enamine **15c** (8.98 g, 79%) as a white powder: mp 138−140 °C (MeOH); R_f 0.57 (40% hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.74 (6H, s), 3.37 (3H, s), 3.73 (3H, s), 3.77 (3H, s), 3.84 (3H, s), 5.49 (1H, s), 6.18 (1H, s), 6.70 (1H, s), 6.90 (1H, s), 6.97 (1H, s); ^{13}C NMR ($CDCl_3$) δ 39.5, 54.6, 55.4, 55.6, 55.7, 101.5, 111.5, 113.0, 113.9, 114.2, 114.3, 114.9, 129.8, 130.6, 145.7, 146.8, 148.2, 148.7; FTIR (neat film, cm^{-1}): 1595; EIMS (*m*/*z*, %) 503 (M + 2, 52), 501 (M^+, 100), 499 (M − 2, 50). Anal. Calcd for $C_{20}H_{23}Br_2NO_4$: C, 47.93; H, 4.62; N, 2.79. Found: C, 48.09; H, 4.71; N, 2.54.

The same procedure on α-aminonitrile **7d** and bromide **17d** provided (*E*)-1,2-bis(4,5-dimethoxy-2-iodophenyl)-*N*,*N*-dimethylethenylamine **15d** (81%) as a yellow powder: mp 111−112 °C (50% acetone/MeOH); R_f 0.29 (40% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 2.74 (6H, s), 3.37 (3H, s), 3.71 (3H, s), 3.76 (3H, s), 3.82 (3H, s), 5.38 (1H, s), 6.20 (1H, s), 6.67 (1H, s), 7.12 (1H, s), 7.18 (1H, s); ^{13}C NMR ($CDCl_3$) δ 39.8, 55.0, 55.8, 55.9, 88.5, 89.1, 106.6, 112.0, 114.0, 120.4, 121.3, 134.1, 134.7, 146.0, 148.1, 148.8, 149.3, 151.5; FTIR (neat film, cm^{-1}): 1598; EIMS (*m*/*z*, %) 595 (M^+, 4), 469 (100). Anal. Calcd for $C_{20}H_{23}I_2NO_4$: C, 40.36; H, 3.89; N, 2.35. Found: C, 40.64; H, 3.77; N, 2.49.

The same procedure on α-aminonitrile **7a** and bromide **17c** provided (*E*)-2-(2-bromo-4,5-dimethoxyphenyl)-1-(2-bromophenyl)-*N*,*N*-dimethylethenylamine **15g** (79%) as a yellow oil: R_f 0.44 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 2.70 (6H, s, 3.25 (3H, s, 3.72 (3H, s, 5.51 (1H, s), 6.05 (1H, s), 6.87 (1H, s), 7.05−7.19 (3H, m), 7.52 (1H, dd, J = 7.7, 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 40.0, 55.0, 55.8, 101.9, 111.9, 113.2, 114.7, 124.5, 127.6, 129.3, 122.0, 132.2, 132.8, 138.2, 145.6, 146.9, 148.9; FTIR (neat film, cm^{-1}): 1571; EIMS (*m*/*z*, %) 443 (M + 2, 51), 441 (M^+, 100), 439 (M − 2, 52), 428 (18), 426 (35), 424 (21), 362 (68), 360 (78). Anal. Calcd for $C_{18}H_{19}Br_2NO_2$: C, 49.01; H, 4.34; N, 3.17. Found: C, 49.31; H, 4.36; N, 2.99.

The same procedure on α-aminonitrile **7b** and bromide **17d** provided (*E*)-*N*,*N*-dimethyl-2-(4,5-dimethoxy-2-iodophenyl)-1-(2-iodophenyl)ethenylamine **15h** (78%) as a yellow oil: R_f 0.41 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 2.74 (6H, s), 3.29 (3H, s), 3.76 (3H, s), 5.42 (1H, s), 6.08 (1H, s), 6.95 (1H, ddd, J = 7.9, 7.9, 1.5 Hz), 7.11−7.17 (2H, m), 7.27 (1H, ddd, J = 7.9, 7.9, 1.4 Hz), 7.83 (1H, dd, J = 7.9, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 39.9, 55.0, 55.8, 88.9, 100.6, 106.8, 111.6, 120.5, 128.3, 129.2, 131.5, 134.1, 139.4, 141.9, 146.0, 148.0, 151.6; FTIR (neat film, cm^{-1}): 1598; EIMS (*m*/*z*, %) 535 (M^+, 100), 520 (19), 408 (44). Anal. Calcd for $C_{18}H_{19}I_2NO_2$: C, 40.40; H, 3.58; N, 2.62. Found: C, 40.66; H, 3.49; N, 2.41.

The same procedure on α-aminonitrile **7a** and bromide **17d** provided (*E*)-1-(2-bromophenyl)-*N*,*N*-dimethyl-2-(4,5-dimethoxy-2-iodophenyl)ethenylamine **15i** (71%) as an amber oil: R_f 0.47 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 2.75 (6H, s), 3.31 (3H, s), 3.76 (3H, s), 5.44 (1H, s), 6.14 (1H, s, 7.08−7.22 (4H, m), 7.54 (1H, dd, J = 7.9, 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 40.0, 55.0, 55.8, 89.0, 107.0, 111.5, 120.6, 124.8, 127.5, 129.3, 132.2, 132.7, 134.5, 138.3, 146.1, 148.1, 149.2; FTIR (neat film, cm^{-1}): 1586; EIMS (*m*/*z*, %) 489 (M + 1, 33), 487 (M − 1, 34), 362 (17), 360 (23), 291 (100). Anal. Calcd for $C_{18}H_{19}BrINO_2$: C, 44.29; H, 3.92; N, 2.87. Found: C, 44.64; H, 3.66; N, 2.95.

The same procedure on α-aminonitrile **7b** and bromide **17c** provided (*E*)-2-(2-bromo-4,5-dimethoxyphenyl)-*N*,*N*-dimethyl-1-(2-iodophenyl)ethenylamine **15j** (74%) as a yellow oil: R_f 0.40

(30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 2.76 (6H, s), 3.27 (3H, s), 3.75 (3H, s), 5.52 (1H, s), 6.04 (1H, s), 6.90 (1H, s), 6.94 (1H, ddd, J = 7.9, 7.5, 1.9 Hz), 7.17 (1H, dd, J = 7.5, 1.9 Hz), 7.25 (1H, ddd, J = 7.5, 7.5, 1.0 Hz), and 7.83 (1H, dd, J = 7.9, 1.0 Hz); ^{13}C NMR ($CDCl_3$) δ 40.4, 55.6, 56.3, 101.0, 102.2, 112.5, 113.8, 115.8, 128.8, 129.7, 131.0, 132.0, 139.9, 142.5, 146.4, 147.6, 152.0; FTIR (neat film, cm^{-1}): 1596. Anal. Calcd for $C_{18}H_{19}BrINO_2$: C, 44.29; H, 3.92; N, 2.87. Found: C, 44.60; H, 3.84; N, 2.99.

The same procedure on α-aminonitrile **7a** and bromide **17e** provided (*E*)-2-(2-bromo-4,5-methylendioxyphenyl)-1-(2-bromophenyl)-*N*,*N*-dimethylethenylamine **15k** (81%) as a yellow oil: R_f 0.44 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 2.72 (6H, s), 5.51 (1H, s), 5.76 (2H, s), 5.99 (1H, s), 6.92 (1H, s), 7.15 (1H, ddd, J = 7.7, 7.7, 1.4 Hz), 7.19−7.28 (2H, m), 7.56 (1H, dd, J = 7.5, 1.1 Hz); ^{13}C NMR ($CDCl_3$) δ 40.0, 101.0, 102.4, 118.8, 112.0, 114.2, 124.5, 127.5, 129.5, 132.0, 132.1, 133.0, 137.8, 144.8, 146.4, 149.2; FTIR (neat film, cm^{-1}): 1584; EIMS (*m*/*z*, %) 427 (M + 2, 38), 425 (M$^+$, 84), 423 (M − 2, 42), 346 (71), 344 (100)**.** Anal. Calcd for $C_{17}H_{15}Br_2NO_2$: C, 48.03; H, 3.56; N, 3.29. Found: C, 48.19; H, 3.49; N, 3.58.

2-Bromo-*N*,*N*-dimethylbenzamide (13a) and 2-(2-Bromophenylmethyl)-2,3-bis(2-bromophenyl)propionitrile (14a). Typical Procedure. A solution of α-aminonitrile **7a** (0.60 g, 2.51 mmol) in dry DMF (2 mL) was added dropwise to a stirred suspension of NaH (95%, 0.21 g, 3.76 mmol) in dry DMF (3 mL) under argon at 0 °C. After the mixture was stirred for 1 h at the same temperature, a solution of chloride **8a** (0.67 g, 3.26 mmol) in dry DMF (2 mL) was added. The reaction mixture was stirred for 15 min at 0 °C, warmed to room temperature, and stirred for an additional 1.5 h. Water (∼5 mL) was added until hydrogen bubbling stopped, and the mixture was evaporated in vacuo (1 mmHg, $T \sim 90$ °C). Flash chromatography of the residue, eluting with a solvent gradient of 10%, 30%, 50%, 80%, and 95% EtOAc/hexane, afforded the following products:

2-Bromo-*N*,*N*-dimethylbenzamide (13a) (0.35 g, 62%) as a colorless oil, R_f 0.57 (20% EtOAc/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.83 (3H, s), 3.11 (3H, s), 6.98 (1H, d, J = 7.7, 1.5 Hz), 7.17−7.25 (2H, m), 7.32 (1H, ddd, J = 7.7, 7.3, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 34.5, 38.1, 119.0, 127.6, 130.1, 132.6, 138.5, 169.1; FTIR (neat film, cm^{-1}): 1643; EIMS (*m*/*z*, %) 229 (M + 1, 18), 227 (M − 1, 18), 228 (65). Anal. Calcd for $C_9H_{10}BrNO$: C. 47.39; H. 4.42; N. 6.14. Found: C. 47.42; H. 4.49; N. 6.11.

2-[(2-Bromophenyl)methyl)]-2,3-bis(2-bromophenyl)-propionitrile (14a) (0.42 g, 32%) as colorless prismatic crystals: mp 153−154 °C (10% EtOAc/hexane), R_f 0.63 (20% hexane/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.89 (2H, d, J = 14.8 Hz), 4.04 (2H, d, J = 14.9 Hz), 7.03−7.12 (6H, m), 7.20−7.27 (2H, m), 7.43−7.49 (1H, m), 7.55 (2H, m), 7.73 (1H, m); ^{13}C NMR ($CDCl_3$) δ 41.1, 51.6, 120.3, 121.5, 126.3, 127.0, 127.8, 128.8, 130.0, 131.9, 133.1, 134.4, 134.8, 136.3 (C_{arom}-H); FTIR (neat film, cm^{-1}): 2241; EIMS (*m*/*z*, %) 537 (M + 3, 5), 535 (M + 1, 15), 533 (M − 1, 15), 531 (M − 3, 5). Anal. Calcd for $C_{22}H_{16}Br_3N$: C, 49.47; H, 3.02; N, 2.62. Found: C, 49.53; H, 3.08; N, 2.58.

The same procedure on α-aminonitrile **7b** and chloride **8b** provided the following products:

***N*,*N*-Dimethyl-2-iodobenzamide (13b)** (65%) as a colorless oil, R_f 0.42 (20% EtOAc/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.84 (3H, s), 3.13 (3H, s), 7.05 (1H, ddd, J = 7.8, 7.6, 1.8 Hz), 7.20 (1H, dd, J = 7.6, 1.7 Hz), 7.36 (1H, ddd, J = 7.8, 7.6, 1.8 Hz), 7.81 (1H, dd, J = 7.8, 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 34.7, 38.4, 92.4, 126.9, 128.4, 130.0, 139.0, 142.8, 170.7 (CO); FTIR (neat film, cm^{-1}): 1640 (C═O); EIMS (*m*/*z*, %) 275 (M$^+$, 45), 231 (100). Anal. Calcd for $C_9H_{10}INO$: C, 39.30; H, 3.66; N, 5.09. Found: C, 39.45; H, 3.39; N, 5.10.

2-[(2-Iodophenyl)methyl)]-2,3-bis(2-iodophenyl)propionitrile (14b) (31%) as a white powder: mp 193−194 °C (10% EtOAc/hexane), R_f 0.42 (50% hexane/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.73 (2H, d, J = 15.2 Hz), 4.14 (2H, d, J = 15.1 Hz), 6.86−7.34 (8H, m), 7.86 (2H, d, J = 7.8 Hz), 8.12 (2H, d, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 46.5, 51.6, 94.3, 103.1, 120.1, 127.8, 128.5, 128.9, 130.0, 130.9, 131.9, 136.8, 138.0, 140.1, 144.1; FTIR (neat film, cm^{-1}): 2231; EIMS (*m*/*z*, %) 548 (M − I, 3), 421 (12), 217 (100). Anal. Calcd for $C_{22}H_{16}I_3N$: C, 39.14; H, 2.39; N, 2.07. Found: C, 39.23; H, 2.29; N, 2.22.

The same procedure on α-aminonitrile **7c** and chloride **8c** provided the following products:

2-Bromo-*N*,*N*-dimethyl-4,5-dimethoxybenzamide (13c) (70%) as a colorless oil: R_f 0.42 (20% EtOAc/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.84 (3H, s), 3.13 (3H, s), 3.84 (3H, s), 3.86 (3H, s), 6.76 (1H, s), 6.98 (1H, s); ^{13}C NMR ($CDCl_3$) δ 34.7, 38.2, 56.1, 56.2, 109.5, 110.3, 115.2, 130.4, 148.7, 149.8, 169.1; FTIR (neat film, cm^{-1}): 1637; EIMS (*m*/*z*, %) 289 (M + 1, 23), 287 (M − 1, 22), 244 (100). Anal. Calcd for $C_{11}H_{14}BrNO_3$: C, 45.85; H, 4.90; N, 4.86. Found: C, 45.94; H, 5.08; N, 4.67.

2-[(2-Bromo-4,5-dimethoxyphenyl)methyl]-2,3-bis(2-bromo-4,5-dimethoxyphenyl)propionitrile (14c) (28%) as a white powder: mp 193−194 °C (10% EtOAc/hexane); R_f 0.49 (5% EtOAc/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.60 (6H, s), 3.73 (2H, d, J = 19.1 Hz), 3.83 (6H, s), 3.90 (6H, s), 3.91 (2H, d, J = 19.1 Hz), 6.58 (2H, s), 6.97 (1H, s), 7.00 (2H, s), 7.15 (1H, s); ^{13}C NMR ($CDCl_3$) δ 40.4, 51.5, 55.7, 55.9, 56.0, 56.3, 113.9, 115.1, 115.3, 116.1, 118.3, 118.4, 121.3, 126.7, 126.8, 147.6, 148.0, 148.5, 149.0; FTIR (neat film, cm^{-1}): 2249; EIMS (*m*/*z*, %) 714 (M$^+$, 3). Anal. Calcd for $C_{28}H_{28}Br_3NO_6$: C, 47.09; H, 3.95; N, 1.96. Found: C, 46.88; H, 3.90; N, 1.96.

The same procedure on α-aminonitrile **7d** and chloride **8d** provided the following products:

***N*,*N*-Dimethyl-4,5-dimethoxy-2-iodobenzamide (13d)** (55%) as a colorless oil: R_f 0.40 (35% EtOAc/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.85 (3H, s), 3.10 (3H, s), 3.82 (3H, s), 3.85 (3H, s), 6.71 (1H, s), 7.16 (1H, s); ^{13}C NMR ($CDCl_3$) δ 34.7, 38.2, 55.9, 56.2, 80.7, 110.3, 121.1, 135.1, 149.5, 170.6; FTIR (neat film, cm^{-1}): 1637; EIMS (*m*/*z*, %) 335 (M$^+$, 52), 291 (100). Anal. Calcd for $C_{11}H_{14}INO_3$: C, 39.42; H, 4.21; N, 4.18. Found: C, 39.31; H, 4.19; N, 4.55.

2-[(4,5-Dimethoxy-2-iodophenyl)methyl]-2,3-bis(4,5-dimethoxy-2-iodophenyl)propionitrile (14d) (36%) as a white powder: mp 206−207 °C (50% hexane/EtOAc); R_f 0.29 (50% hexano/EtOAc); ^{1}H NMR ($CDCl_3$) δ 3.55 (6H, s), 3.63 (3H, s), 3.65 (2H, d, J = 14.8 Hz), 3.80 (6H, s), 3.84 (3H, s), 4.03 (2H, d, J = 14.8 Hz), 6.52 (2H, s), 6.94 (1H, s), 7.23 (2H, s), 7.49 (1H, s); ^{13}C NMR ($CDCl_3$) δ 45.1, 51.9, 55.1, 55.7, 56.2, 81.8, 90.3, 113.5, 115.2, 119.8, 121.7, 130.0, 147.1, 147.4, 148.6; FTIR (neat film, cm^{-1}): 2254; EIMS (*m*/*z*, %) 855 (M$^+$, 3). Anal. Calcd for $C_{28}H_{28}I_3NO_6$: C, 39.32; H, 3.30; N, 1.64. Found: C, 39.35; H, 3.41; N, 1.87.

When the same procedure applied on α-aminonitrile **7a** and chloride **8a** was performed with freshly distilled, degassed DMF as solvent, the following products were obtained:

2-[(2-Bromophenyl)methyl)]-2,3-bis(2-bromophenyl)-propionitrile (14a) (68%).

(*E*)-1,2-Bis(2-bromophenyl)-*N*,*N*-dimethylethenylamine (15a) (25%).

When the same procedure applied on α-aminonitrile **7b** and chloride **8b** was performed with freshly distilled, degassed DMF as solvent, the following products were obtained:

2-[(2-Iodophenyl)methyl)]-2,3-bis(2-iodophenyl)propionitrile (14b) (59%).

(*E*)-*N*,*N*-Dimethyl-1,2-bis(2-iodophenyl)ethenylamine (15b) (31%).

When the same procedure applied on α-aminonitrile **7c** and chloride **8c** was performed with freshly distilled, degassed DMF as solvent, the following products were obtained:

2-[(2-Bromo-4,5-dimethoxyphenyl)methyl]-2,3-bis(2-bromo-4,5-dimethoxyphenyl)propionitrile (14c) (63%).

(*E*)-1,2-Bis(2-bromo-4,5-dimethoxyphenyl)-*N*,*N*-dimethylethenylamine (15c) (25%).

2,3-Bis(2-bromo-4,5-dimethoxyphenyl)propionitrile (16) (10%) as a white powder: mp 123−124 °C (10% EtOAc/hexane); R_f 0.71 (5% EtOAc/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.24 (1H, d, J = 6.7 Hz), 3.26 (1H, d, J 7.9 Hz), 3.81 (3H, s), 3.86 (6H, s), 3.87 (3H, s), 4.59 (1H, dd, J = 7.9, 6.7 Hz), 6.73 (1H, s), 6.91 (1H, s), 6.99 (1H,s), 7.00 (1H, s).; ^{13}C NMR ($CDCl_3$) δ 36.7, 39.3, 55.6, 55.7, 55.8, 111.2, 113.2, 113.7, 114.1, 115.1, 116.7, 119.6, 125.6, 126.6, 147.9, 148.6, 149.2; FTIR (neat film, cm^{-1}): 2249; EIMS (*m*/*z*, %) 485 (M$^+$, 2), 229 (100). Anal. Calcd

for $C_{19}H_{19}Br_2NO_4$: C, 47.04; H, 3.95; N, 2.89. Found: C, 46.87; H, 3.89; N, 2.79.

When the same procedure applied on α-aminonitrile **7d** and chloride **8d** was performed with freshly distilled, degassed DMF as solvent, the following products were obtained:

2-[(4,5-Dimethoxy-2-iodophenyl)methyl]-2,3-bis(4,5-dimethoxy-2-iodophenyl)propionitrile (14d) (72%).

(*E*)-1,2-Bis(4,5-dimethoxy-2-iodophenyl)-*N*,*N*-dimethylethenylamine (15d) (22%).

Hydrolysis of Enamines.

1,2-Bis(2-bromophenyl)ethanone (4a). Typical Procedure. A stirred mixture of enamine **15a** (7.84 g, 20.6 mmol), HCl (85 mL of a 12.2 M solution in water), and MeOH (15 mL) was heated at 140 °C for 12 h. After being cooled, the mixture was partially concentrated under reduced pressure, extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried over anhydrous sodium sulfate. Evaporation in vacuo gave a yellow oil which was purified by flash chromatography using 20% EtOAc/hexane as eluent, providing ethanone **4a** (6.85 g, 94%) as a white powder: mp 59−60 °C (MeOH); R_f 0.42 (40% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 4.43 (2H, s), 7.20−7.33 (1H, m), 7.37−7.50 (4H, m), 7.52−7.64 (3H, m); ^{13}C NMR ($CDCl_3$) δ 49.6, 118.7, 125.2, 127.5, 128.8, 129.0, 130.3, 131.9, 132.1, 132.7, 133.7, 140.3, 198.8; FTIR (neat film, cm^{-1}): 1690; EIMS (*m*/*z*, %) 275 (M − Br,^{79} 4), 273 (M − Br,^{81} 4), 185 (100). Anal. Calcd for $C_{14}H_{10}Br_2O$: C, 47.50; H, 2.85. Found: C, 47.59; H, 2.81.

By use of the same procedure, the following products were prepared:

1,2-Bis(2-iodophenyl)ethanone (4b) (95%) as a white powder, mp 79−80 °C (acetone); R_f 0.57 (40% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 4.40 (2H, s), 6.97 (1H, dd, J = 8.0, 7.5 Hz), 7.14 (1H, ddd, J = 7.9, 7.5, 1.2 Hz), 7.32−7.35 (2H, m), 7.38 (1H, ddd, J = 7.5, 7.6, 1.4 Hz), 7.54 (1H, dd, J = 7.6, 1.4 Hz), 7.86 (1H, dd, J = 8.0, 1.2 Hz), 7.93 (1H, dd, J = 7.9, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 53.2, 91.2, 101.4, 127.8, 127.9, 128.2, 128.7, 130.9, 131.6, 137.3, 139.1, 140.4, 143.6, 199.6; FTIR (neat film, cm^{-1}): 1702; EIMS (*m*/*z*, %) 321 (M − I, 13), 231 (100). Anal. Calcd for $C_{14}H_{10}I_2O$: C, 37.53; H, 2.25. Found: C, 37.59; H, 2.26.

1-(2-Bromo-4,5-dimethoxyphenyl)-2-(2-bromophenyl)-ethanone (4e) (94%) as a white powder: mp 85−87 °C (MeOH); R_f 0.40 (40% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 3.87 (3H, s), 3.92 (3H, s), 4.47 (1H, s), 7.06 (1H, s), 7.12 (1H, s), 7.11−7.18 (1H, m), 7.28−7.31 (2H, m), 7.57 (1H, dd, J = 7.7, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 49.2, 56.0, 56.2, 111.2, 112.3, 116.4, 124.9, 127.5, 128.7, 131.8, 132.1, 132.6, 134.8, 147.9, 151.3, 198.0 (CO); FTIR (neat film, cm^{-1}): 1695; EIMS (*m*/*z*, %) 246 (10), 245 (85), 243 (100). Anal. Calcd for $C_{16}H_{14}Br_2O_3$: C, 46.41; H, 3.41. Found: C, 46.78; H, 3.59.

1-(4,5-Dimethoxy-2-iodophenyl)-2-(2-iodophenyl)ethanone (4f) (92%) as a colorless oil: R_f 0.43 (40% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 3.88 (3H, s), 3.91 (3H, s), 4.42 (2H, s), 6.97 (1H, ddd, J = 7.9, 7.9, 2.4 Hz), 7.13 (1H, s), 7.29−7.37 (3H, m), 7.86 (1H, dd, J = 7.9, 1.4 Hz); ^{13}C NMR ($CDCl_3$) δ 52.8, 56.1, 56.2, 81.9, 101.3, 112.0, 123.3, 128.4, 128.8, 130.9, 138.1, 139.4, 134.6, 148.5, 151.2, 198.1; FTIR (neat film, cm^{-1}): 1691 (C═O); EIMS (*m*/*z*, %) 508 (M$^+$, 3), 291 (100). Anal. Calcd for $C_{16}H_{14}I_2O_3$: C, 37.82; H, 2.78. Found: C, 37.98; H, 2.88.

2-(2-Bromo-4,5-dimethoxy)-1-(2-bromophenyl)ethanone (4g) (91%) as a white powder: mp 115−118 °C (MeOH); R_f 0.54 (50% hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 3.86 (6H, s), 4.33 (2H, s), 6.80 (1H, s), 7.02 (1H, s), 7.31 (1H, ddd, J = 7.7, 7.6, 1.9 Hz), 7.37 (1H, ddd, J = 7.6, 7.6, 1.3 Hz), 7.46 (1H, dd, J = 7.6, 1.9 Hz), 7.61 (1H, dd, J = 7.7, 1.3 Hz); ^{13}C NMR ($CDCl_3$) δ 49.1, 56.0, 114.0, 115.0, 115.3, 118.6, 125.7, 127.3, 128.5, 131.6, 133.5, 141.0, 148.3, 148.7, 200.2; FTIR (neat film, cm^{-1}): 1701; EIMS (*m*/*z*, %) 335 (M − Br,^{79} 28), 333 (M − Br,^{81} 29). Anal. Calcd for $C_{16}H_{14}Br_2O_3$: C, 46.41; H, 3.41. Found: C, 46.26; H, 3.47.

2-(4,5-Dimethoxy-2-iodophenyl)-1-(2-iodophenyl)ethanone (4h) (89%) as a yellow powder: mp 83−85 °C (MeOH); R_f 0.37 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 3.85 (6H, s), 4.33 (2H, s), 6.81 (1H, s), 7.13 (1H, ddd, J = 7.7, 7.7, 2.0 Hz), 7.22 (1H, s), 7.41 (1H, ddd, J = 7.9, 7.7, 2.0 Hz), 7.51 (1H, dd, J = 7.7, 2.0 Hz), 7.92 (1H, d, J = 7.9, 1.9 Hz); ^{13}C NMR ($CDCl_3$) δ 52.9, 55.9, 56.0, 89.3, 91.4, 113.1, 121.3, 127.9, 128.0, 129.5, 131.7, 140.5, 143.6, 148.5, 149.2, 200.7; FTIR (neat film, cm^{-1}): 1701; EIMS (*m*/*z*, %) 381 (M − I, 49). Anal. Calcd for $C_{16}H_{14}I_2O_3$: C, 37.82; H, 2.78. Found: C, 37.69; H, 2.91.

1-(2-Bromophenyl)-2-(4,5-dimethoxy-2-iodophenyl)-ethanone (4i) (85%) as a yellow powder: mp 88−90 °C (MeOH); R_f 0.39 (40% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 3.85 (6H, s), 4.34 (2H, s), 6.81 (1H, s), 7.22 (1H, s), 7.30 (1H, ddd, J = 7.6, 7.6, 1.9 Hz), 7.36 (1H, ddd, J = 7.5, 7.6, 1.5 Hz), 7.48 (1H, dd, J = 7.5, 1.9 Hz), 7.61 (1H, dd, J 7.5, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 53.5, 55.8, 56.0, 89.2, 113.3, 118.0, 121.4, 127.2, 128.6, 129.6, 131.5, 133.5, 141.0, 148.5, 149.2, 200.0; FTIR (neat film, cm^{-1}): 1702; EIMS (*m*/*z*, %) 462 (M + 1, 14), 460 (M − 1, 14) 335 (42), 333 (41). Anal. Calcd for $C_{16}H_{14}BrIO_3$: C, 41.68; H, 3.06. Found: C, 41.84; H, 2.97.

2-(2-Bromo-4,5-dimethoxy)-1-(2-iodophenyl)ethanone (4j) (89%) as a white powder: mp 112−114 °C (MeOH), R_f 0.37 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 3.85 (6H, s), 4.30 (2H, s), 6.81 (1H, s), 7.02 (1H, s), 7.12 (1H, ddd, J = 7.9, 7.5, 1.9 Hz), 7.39 (1H, ddd, J = 7.5, 7.5, 1.0 Hz), 7.48 (1H, dd, J = 7.5, 1.9 Hz), 7.90 (1H, dd, J = 7.9, 1.0 Hz); ^{13}C NMR ($CDCl_3$) δ 48.3, 56.0, 91.3, 113.9, 115.0, 115.4, 125.5, 127.9, 128.0, 131.7, 140.6, 143.8, 148.4, 148.8, 200.7; FTIR (neat film, cm^{-1}): 1701; EIMS (*m*/*z*, %) 381 (M + 1 − Br,^{81} 41). Anal. Calcd for $C_{16}H_{14}BrIO_3$: C, 41.68; H, 3.06. Found: C, 41.79; H, 3.09.

1,2-Bis(2-bromo-4,5-dimethoxyphenyl)ethanone (4c). Typical Procedure. A stirred mixture of enamine **15c** (8.98 g, 17.9 mmol), HCl (73 mL of a 6.0 M solution in water), and MeOH (13 mL) was heated at 115 °C for 9 h. After being cooled, the mixture was partially concentrated under reduced pressure, extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried over anhydrous sodium sulfate. Evaporation in vacuo gave a yellow oil which was purified by flash chromatography using 40% EtOAc/hexane as eluent, providing ethanone **4c** (7.64 g, 90%) as a white powder: mp 130−131 °C (MeOH) (lit.[11b] 130−132 °C); R_f 0.30 (40% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 3.85 (6H, s), 3.87 (3H, s), 3.91 (3H, s), 4.36 (2H, s), 6.81 (1H, s), 7.02 (1H, s), 7.05 (1H, s), 7.10 (1H, s); ^{13}C NMR ($CDCl_3$) δ 48.7, 55.9, 56.0, 56.1, 56.2, 111.1, 112.3, 113.8, 114.8, 115.3, 116.3, 126.4, 132.1, 147.9, 148.3, 148.6, 151.3, 198.6; FTIR (neat film, cm^{-1}): 1690; EIMS (*m*/*z*, %) 474 (M$^+$, 3). Anal. Calcd for $C_{18}H_{18}Br_2O_5$: C, 45.60; H, 3.83. Found: C, 45.54; H, 3.87.

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

1,2-Bis(4,5-dimethoxy-2-iodophenyl)ethanone (4d) (94%) as a white powder: mp 137−139 °C (acetone/MeOH); R_f 0.16 (40% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 3.84 (6H, s), 3.90 (6H, s), 4.33 (2H, s), 6.79 (1H, s), 7.10 (1H, s), 7.21 (1H, s), 7.32 (1H, s); ^{13}C NMR ($CDCl_3$) δ 52.2, 55.9, 56.0, 56.1, 85.8, 89.0, 111.9, 113.3, 121.7, 123.4, 130.3, 134.4, 148.6, 148.7, 149.2, 151.1, 198.4; FTIR (neat film, cm^{-1}): 1683; EIMS (*m*/*z*, %) 441 (M − I, 10), 291 (100). Anal. Calcd for $C_{18}H_{18}I_2O_5$: C. 38.05; H. 3.19. Found: C, 38.09; H, 3.12.

2-(2-Bromo-4,5-methylendioxyphenyl)-1-(2-bromophenyl)ethanone (4k) (95%) as a colorless oil: R_f 0.40 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 4.31 (2H, s), 5.98 (2H, s), 6.81 (1H, s), 7.02 (1H, s), 7.30 (1H, ddd, J = 7.7, 7.5, 1.9 Hz), 7.37 (1H, ddd, J = 7.6, 7.5, 1.4 Hz), 7.48 (1H, dd, J = 7.5, 1.9 Hz), 7.62 (1H, dd, J = 7.7, 1.4 Hz); ^{13}C NMR ($CDCl_3$) δ 49.3, 101.7, 111.1, 112.5, 115.4, 118.5, 126.6, 127.3, 128.5, 131.6, 133.5, 141.0, 147.3, 147.6, 200.5; FTIR (neat film, cm^{-1}): 1701; EIMS (*m*/*z*, %) 319 (M − Br,^{79} 34), 317 (M − Br,^{81} 34). Anal. Calcd for $C_{15}H_{10}Br_2O_3$: C. 45.26; H. 2.53. Found: C, 45.28; H, 2.59.

Synthesis of Enaminoketones.

1,2-Bis(2-bromophenyl)-3-(*N*,*N*-dimethylamino)propenone (18a). Typical Procedure. DMFDMA (4.54 mL, 325 mmol) was added dropwise to a stirred suspension of ketone **4a** (8.8 g, 25 mmol) in dry toluene (30 mL) under argon at room temperature. The resulting mixture was heated at 135 °C for 16 h, and after being cooled, it was concentrated in vacuo

to give a brown oil which was purified by flash chromatography using 50% EtOAc/hexane as eluent. Enaminoketone **18a** (7.873 g, 77%) was obtained as orange glassy solid: mp 41−42 °C (Et_2O); R_f 0.32 (50% hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 2.41−2.84 (6H, bs), 7.42−7.03 (6H, m, H_{arom}), 7.49 (1H, dd, J = 8.4, 1.4 Hz), 7.52 (1H, dd, J = 8.1, 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 38.5, 47.1, 111.2, 119.4, 126.4, 126.9, 128.2, 129.0, 131.4, 132.2, 133.6, 136.9, 142.6, 154.5, 191.2; FTIR (neat film, cm^{-1}): 1635, 1576; EIMS (*m*/*z*, %) 411 (M + 2, 6), 409 (M^+, 11), 407 (M − 2, 25), 330 (84), 328 (100). Anal. Calcd for $C_{17}H_{15}Br_2NO$: C, 49.91; H, 3.70; N, 3.42. Found: C, 50.08; H, 3.39; N, 3.21.

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

3-(*N*,*N*-Dimethylamino)-1,2-bis(2-iodophenyl)propenone (18b) (78%), as a white glassy solid: mp 59−60 °C (Et_2O); R_f 0.40 (50% hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 2.37−2.65 (6H, bs), 6.95−6.84 (3H, m), 7.21−7.38 (4H, m, H_{arom}), 7.76 (2H, m); ^{13}C NMR ($CDCl_3$) δ 43.0 (bs), 93.4, 105.2, 113.9, 127.0, 128.0, 128.9, 132.4, 137.5, 138.4, 141.0, 146.2, 154.0, 192.2; FTIR (neat film, cm^{-1}): 1637, 1569; EIMS (*m*/*z*, %) 503 (M^+, 11), 377 (18), 376 (100). Anal. Calcd for $C_{17}H_{15}I_2NO$: C, 40.58; H, 3.01; N, 2.78. Found: C, 40.39; H, 3.29; N, 2.64.

1,2-Bis(2-bromo-4,5-dimethoxyphenyl)-3-(*N*,*N*-dimethylamino)propenone (18c) (75%), as a yellow powder: mp 173−174 °C (Et_2O); R_f 0.33 (30% hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 2.39−3.12 (6H, bs), 3.77 (3H, s), 3.90 (9H, s), 6.76 (1H, s), 6.82 (2H, s), 6.88 (1H, s), 6.94 (1H, s); ^{13}C NMR ($CDCl_3$) δ 39.4, 46.8, 55.4, 109.4, 110.6, 113.9, 114.7, 116.0, 117.0, 129.6, 135.2, 147.3, 148.1, 148.6, 152.6, 191.2; FTIR (neat film, cm^{-1}): 1643, 1572; EIMS (*m*/*z*, %) 531 (M + 2, 5), 529 (M^+, 10), 526 (M − 2, 6), 450 (100), 448 (100). Anal. Calcd for $C_{21}H_{23}Br_2NO_5$: C, 47.66; H, 4.38; N, 2.65. Found: C, 48.64; H, 4.49; N, 2.48.

3-(*N*,*N*-Dimethylamino)-1,2-bis(4,5-dimethoxy-2-iodophenyl)propenone (18d) (70%), as a white powder: mp 202−203 °C (Et_2O); R_f 0.25 (40% hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 2.57−3.02 (6H, bs), 3.75 (6H, s), 3.78 (6H, s), 6.76 (1H, s), 6.83 (1H, s), 7.08 (2H, s), 7.13 (1H, s); ^{13}C NMR ($CDCl_3$) δ 38.7, 46.9, 55.9, 82.0, 94.2, 110.4, 111.0, 115.6, 119.8, 120.8, 139.7, 148.1, 148.3, 148.6, 148.8, 152.6, 193.7; FTIR (neat film, cm^{-1}): 1638, 1565; EIMS (*m*/*z*, %) 623 (M^+, 3), 496 (100),. Anal. Calcd for $C_{21}H_{23}I_2NO_5$: C, 40.47; H, 3.72; N, 2.25; Found: C, 40.79; H, 3.86; N, 2.19.

1-(2-Bromo-4,5-dimethoxyphenyl)-2-(2-bromophenyl)-3-(*N*,*N*-dimethylamino)propenone (18e) (79%), as a white powder: mp 73−75 °C (Et_2O); R_f 0.35 (30% hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 2.47−3.13 (6H, bs), 3.78 (3H, s), 3.84 (3H, s), 6.78 (1H, s), 6.93 (1H, s), 7.05−7.34 (4H, m), 7.54 (1H, m); ^{13}C NMR ($CDCl_3$) δ 39.0, 46.3, 55.8, 56.0, 110.1, 110.9, 115.0, 126.8, 127.3, 128.6, 131.7, 134.1, 135.1, 137.1, 145.1, 137.9, 147.5, 148.9, 153.5, 191.6; FTIR (neat film, cm^{-1}): 1639, 1575; EIMS (*m*/*z*, %) 471 (M + 2, 5), 469 (M^+, 10), 467 (M + 2, 5), 390 (84), 388 (100). Anal. Calcd for $C_{19}H_{19}Br_2NO_3$: C, 48.64; H, 4.08; N, 2.99. Found: C, 48.98; H, 3.92; N, 2.94.

3-(*N*,*N*-Dimethylamino)-1-(4,5-dimethoxy-2-iodophenyl)-2-(2-iodophenyl)propenone (18f) (71%), as a yellow oil: R_f 0.42 (40% EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 2.47−3.12 (6H, bs), 3.79 (3H, s), 3.83 (3H, s), 6.82−6.88 (2H, m), 7.15 (1H, m), 7.35 (1H, m), 7.79−7.82 (3H, m); ^{13}C NMR ($CDCl_3$) δ 37.2, 47.8, 55.8, 82.1, 105.7, 110.6, 112.6, 120.8, 127.4, 128.2, 132.8, 137.7, 138.9, 141.5, 148.1, 148.5, 154.4, 192.5 (CO); FTIR (neat film, cm^{-1}): 1637, 1572; EIMS (*m*/*z*, %) 563 (M^+, 100), 437 (22), 436 (100). Anal. Calcd for $C_{19}H_{19}I_2NO_3$: C, 40.52; H, 3.40; N, 2.49. Found: C, 40.77; H, 3.31; N. 2.59.

2-(2-Bromo-4,5-dimethoxyphenyl)-1-(2-bromophenyl)-3-(*N*,*N*-dimethylamino)propenone (18g) (81%) as a white glassy solid: mp 65−67 °C (50% hexane/EtOAc); R_f 0.35 (30% hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 2.52−2.94 (6H, bs), 3.74 (6H, s), 6.86 (1H, s), 6.97−7.24 (4H, m), 7.39−7.45 (2H, m); ^{13}C NMR ($CDCl_3$) δ 38.0, 47.0, 55.8, 114.2, 115.9, 117.2, 118.4, 126.5, 129.1, 132.1, 143.2, 147.5, 148.3, 153.0, 191.9; FTIR (neat film, cm^{-1}): 1637, 1576; EIMS (*m*/*z*, %) 469 (M^+, 5), 390 (98), 388 (100). Anal. Calcd for $C_{19}H_{19}Br_2NO_3$: C, 48.64; H, 4.08; N, 2.99. Found: C, 48.79; H, 4.12; N, 2.88.

3-(*N*,*N*-Dimethylamino)-2-(4,5-dimethoxy-2-iodophenyl)-1-(2-iodophenyl)propenone (18h) (86%) as a yellow glassy solid: mp 168−170 °C (Et_2O); R_f 0.40 (40% EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 2.54−3.13 (6H, bs), 3.84 (6H, s), 6.73−7.28 (5H, m), 6.73−7.28 (5H, m), 7.73−7.76 (2H, m); ^{13}C NMR ($CDCl_3$) δ 37.2, 47.3, 55.4, 93.5, 114.6, 119.6, 127.0, 129.0, 134.4, 138.3, 147.8, 148.1, 154.7, 193.0; FTIR (neat film, cm^{-1}): 1639, 1575; EIMS (*m*/*z*, %) 563 (M^+, 4), 436 (100). Anal. Calcd for $C_{19}H_{19}I_2NO_3$: C, 40.52; H, 3.40; N, 2.49. Found: C, 40.36; H, 3.62; N, 2.52.

1-(2-Bromophenyl)-3-(*N*,*N*-dimethylamino)-2-(4,5-dimethoxy-2-iodophenyl)propenone (18i) (82%): as a white powder: mp 168−170 °C (EtOAc); R_f 0.50 (20% hexane/EtOAc); ^1H NMR ($CDCl_3$) δ 2.56−2.85 (6H, bs), 3.83 (6H, s), 6.89 (1H, s), 7.19−7,0.1 (5H, m), 7.44 (1H, m); ^{13}C NMR ($CDCl_3$) δ 36.9, 47.6, 55.7, 55.8, 94.2, 115.1, 119.6, 120.1, 126.6, 129.1, 132.3, 133.7, 143.1, 148.2, 148.4, 154.8, 191.8; FTIR (neat film, cm^{-1}): 1637, 1576; EIMS (*m*/*z*, %) 517 (M + 1, 1), 515 (M − 1, 1), 390 (100), 388 (100). Anal. Calcd for $C_{19}H_{19}BrINO_3$: C, 44.21; H, 3.71; N, 2.71. Found: C, 44.47; H, 3.66; N, 2.89.

2-(2-Bromo-4,5-dimethoxyphenyl)-3-(*N*,*N*-dimethylamino)-1-(2-iodophenyl)propenone (18j) (77%) as a white powder: mp 167−169 °C (Et_2O); R_f 0.42 (20% EtOAc/CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 2.54−2.97 (6H, bs), 3.82 (6H, s), 6.87−7.31 (6H, m), 7.73 (1H, s); ^{13}C NMR ($CDCl_3$) δ 37.0, 47.0, 55.4, 93.1, 110.1, 113.7, 114.6, 115.5, 126.9, 128.7, 138.0, 146.4, 146.7, 147.8, 155.4, 192.9; FTIR (neat film, cm^{-1}): 1639, 1574; EIMS (*m*/*z*, %) 516 (M^+, 3), 436 (100). Anal. Calcd for $C_{19}H_{19}BrINO_3$: C, 44.21; H, 3.71; N, 2.71. Found: C, 44.37; H, 3.89; N, 2.75.

2-(2-Bromo-4,5-methylendioxyphenyl)-1-(2-bromophenyl)-3-(*N*,*N*-dimethylamino)propenone (18k) (84%) as a yellow glassy solid: mp 75−76 °C (MeOH); R_f 0.37 (40% EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 2.57−2.87 (6H, bs), 5.96 (2H, s), 6.86 (1H, s), 7.02−7.30 (4H, m), 7.52 (1H, m); ^{13}C NMR ($CDCl_3$) δ 39.6, 46.8, 107.2, 111.8, 113.1, 117.7, 119.8, 125.6, 126.8, 128.9, 129.4, 142.9, 146.8, 147.6, 160.0, 193.5 (CO); FTIR (neat film, cm^{-1}): 1636, 1576; EIMS (*m*/*z*, %) 455 (2), 453 (2), 451 (M^+, 3), 374 (100), 372 (97). Anal. Calcd for $C_{18}H_{15}BrNO_3$: C, 47.71; H, 3.34; N, 3.09. Found: C, 47.88; H, 3.36; N, 3.21.

Heterocyclization to Isoxazoles.

4,5-Bis(2-bromophenyl)isoxazole (21a). Typical Procedure. Ground Na_2CO_3 (0.462 g, 4.31 mmol) and $NH_2OH\cdot HCl$ (5.65 g, 66.0 mmol) were added to a solution of enaminoketone **18a** (2.71 g, 6.60 mmol) in dry methanol (100 mL)[43] in a heavy-wall screw capped tube at room temperature. The resulting mixture was acidified with glacial acetic acid (2.6 mL) to pH ∼ 4, and after closing the tube, it was heated at 115 °C for 2 h in a oven. After being cooled, the suspension was filtered, the filtrate washed with dichloromethane (100 mL), and the filtrate was evaporated in vacuo. The residue was redissolved with water (40 mL) and extracted with CH_2Cl_2 (5 × 15 mL), and the combined organic layers were washed with brine and water. The organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure, and the resulting yellow residue was triturated with methanol to afford isoxazole **21a** (2.301 g, 92%) as yellow flakes: mp 58−60 °C (MeOH); R_f 0.82 (6% EtOAc/CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.03−7.06 (1H, m), 7.15−7.18 (2H, m), 7.25−7.36 (3H, m), 7.56−7.62 (2H, m), 8.56 (1H, s); ^{13}C NMR ($CDCl_3$) δ 117.4, 122.8, 123.3, 127.4, 127.6, 128.5, 129.7, 131.5, 131.6, 131.8, 133.2, 133.5, 151.3, 164.8; FTIR (neat film, cm^{-1}): 1583; EIMS (*m*/*z*, %) 381 (M + 2, 33), 379 (M^+, 64), 377 (M − 2, 34), 300 (22), 298 (21). Anal. Calcd for $C_{15}H_9Br_2NO$: C, 47.53; H, 2.39; N, 3.70. Found: C, 47.81; H, 2.30; N, 3.61.

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

4,5-Bis(2-iodophenyl)isoxazole (21b) (90%) as a yellow powder: mp 129−130 °C (MeOH); R_f 0.80(6% EtOAc/CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.00−7.32 (6H, m), 7.89 (1H, dd, J = 7.9,

(43) 2-Propanol was used as solvent in the synthesis of isoxazoles **18d** and **18f**.

1.5 Hz), 7.92 (1H, dd, J = 7.1, 1.2 Hz), 8.56 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 97.2, 99.5, 120.0, 128.2, 128.9, 129.7, 131.1, 131.2, 132.6, 134.1, 139.6, 151.3, 166.6; FTIR (neat film, cm^{-1}): 1577; EIMS (m/z, %) 473 (M^+, 90), 346 (55), 219 (100). Anal. Calcd for $C_{15}H_9I_2NO$: C, 38.09; H, 1.92; N, 2.96. Found: C, 38.16; H, 1.79; N, 3.09.

4,5-Bis(2-bromo-4,5-dimethoxyphenyl)isoxazole (21c) (89%) as a white powder: mp 167−168 °C (MeOH); R_f 0.71 (6% EtOAc/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.59 (3H, s), 3.75 (3H, s), 3.84 (3H, s), 3.86 (3H, s), 6.54 (1H, s), 6.84 (1H, s), 7.02 (1H, s), 7.04 (1H, s), 8.51 (1H, s); ^{13}C NMR ($CDCl_3$) δ 55.6, 55.8, 55.9, 56.0, 113.5, 113.6, 115.4, 115.6, 117.1, 120.4, 122.3, 148.0, 148.1, 149.1, 150.6, 151.2, 164.6; FTIR (neat film, cm^{-1}): 1597; EIMS (m/z, %) 501 (M + 2, 9), 499 (M^+, 18), 497 (M − 2, 9), 419 (18), 417 (16), 339 (100). Anal. Calcd for $C_{19}H_{17}Br_2NO_5$: C, 45.72; H, 3.43; N, 2.81. Found: C, 45.86; H, 3.21; N, 2.76.

4,5-Bis(4,5-dimethoxy-2-iodophenyl)isoxazole (21d) (98%) as a white powder: mp 179−181 °C (MeOH); R_f 0.52 (50% hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 3.63 (3H, s), 3.75 (3H, s), 3.86 (3H, s), 3.87 (3H, s), 6.66 (1H, s), 6.80 (1H, s), 7.27 (2H, s), 8.51 (1H, s); ^{13}C NMR ($CDCl_3$) δ 55.7, 55.8, 56.0, 56.1, 86.0, 87.7, 113.7, 119.7, 121.4, 121.6, 124.5, 124.9, 148.7, 148.9, 149.0, 150.4, 151.3, 166.7; FTIR (neat film, cm^{-1}): 1590; EIMS (m/z, %) 593 (M^+, 18), 465 (11), 339 (100). Anal. Calcd for $C_{19}H_{17}I_2NO_5$: C, 38.47; H, 2.89; N, 2.36. Found: C, 38.31; H, 2.99; N, 2.19.

4-(2-Bromophenyl)-5-(2-bromo-4,5-dimethoxyphenyl)-isoxazole (21e) (91%) as a white powder: mp 58−60 °C (MeOH); R_f 0.35 (20% hexane/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.76 (3H, s), 3.89 (3H, s), 6.86 (1H, s), 6.88 (1H, s), 7.06 (1H, dd, J = 6.5, 2.3 Hz), 7.18−7.23 (2H, m), 7.65 (1H, dd, J = 6.7, 2.4 Hz), 8.55 (1H, s); ^{13}C NMR ($CDCl_3$) δ 55.8, 56.7, 113.2, 113.3, 115.6, 117.0, 119.9, 123.3, 127.3, 129.4, 130.5, 131.2, 132.9, 147.8, 150.5, 151.1, 164.7; FTIR (neat film, cm^{-1}): 1598; EIMS (m/z, %) 441 (M + 2, 19), 439 (M^+, 39), 437 (M − 2, 20), 279 (100). Anal. Calcd for $C_{17}H_{13}Br_2NO_3$: C, 46.50; H, 2.98; N, 3.29. Found: C, 46.57; H, 3.31; N, 3.29.

5-(4,5-Dimethoxy-2-iodophenyl)-4-(2-iodophenyl)isoxazole (21f) (89%) as a colorless oil: R_f 0.48 (20% hexane/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.72 (3H, s), 3.88 (3H, s), 6.78 (1H, s), 6.99−7.09 (2H, m), 7.24−7.30 (2H, m), 7.92 (1H, dd, J = 7.1, 1.7 Hz), 8.54 (1H, s); ^{13}C NMR ($CDCl_3$) δ 55.8, 56.1, 85.7, 99.8, 113.8, 119.7, 122.0, 124.7, 128.3, 129.7, 131.2, 134.6, 139.7, 148.8, 150.5, 151.4, 166.7 (C-5); FTIR (neat film, cm^{-1}): 1592; EIMS (m/z, %) 533 (M^+, 32), 291 (70), 279 (100). Anal. Calcd for $C_{17}H_{13}I_2NO_3$: C, 38.30; H, 2.46; N, 2.63. Found: C, 38.49; H, 2.20; N, 2.80.

4-(2-Bromo-4,5-dimethoxyphenyl)-5-(2-bromophenyl)-isoxazole (21g) (92%) as a white powder: mp 65−67 °C (MeOH); R_f 0.51 (20% hexane/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.56 (3H, s), 3.86 (3H, s), 6.51 (1H, s), 7.06 (1H, s), 7.26−7.38 (3H, m), 7.64 (1H, dd, J = 6.7, 1.6 Hz), 8.59 (1H, s); ^{13}C NMR ($CDCl_3$) δ 55.8, 56.1, 113.7, 115.7, 117.8, 122.2, 123.3, 127.4, 129.2, 131.6, 131.9, 133.4, 148.2, 149.4, 151.4, 164.9; FTIR (neat film, cm^{-1}): 1601; EIMS (m/z, %) 441 (M + 2, 40), 439 (M^+, 78), 437 (M − 2, 43), 360 (31), 358 (29). Anal. Calcd for $C_{17}H_{13}Br_2NO_3$: C, 46.50; H, 2.98; N, 3.19. Found: C, 46.57; H, 2.91; N, 3.29.

4-(4,5-Dimethoxy-2-iodophenyl)-5-(2-iodophenyl)isoxazole (21h) (88%) as a white powder: mp 120−122 °C (MeOH); R_f 0.37 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 3.58 (3H, s), 3.85 (3H, s), 6.54 (1H, s), 7.13 (1H, dd, J = 7.9, 7.6 Hz), 7.26−7.30 (2H, m), 7.38 (1H, dd, J = 7.6, 7.6 Hz), 7.91 (1H, d, J = 7.9 Hz), 8.58 (1H, s).; ^{13}C NMR ($CDCl_3$) δ 55.6, 55.9, 87.3, 97.5, 113.5, 119.9, 121.5, 126.1, 127.9, 131.4, 132.9, 139.6, 148.8, 149.0, 151.2, 166.7; FTIR (neat film, cm^{-1}): 1594; EIMS (m/z, %) 533 (M^+, 100), 406 (19). Anal. Calcd for $C_{17}H_{13}I_2NO_3$: C, 38.30; H, 2.46; N, 2.63. Found: C, 38.19; H, 2.59; N, 2.77.

5-(2-Bromophenyl)-4-(4,5-dimethoxy-2-iodophenyl)-isoxazole (21i) (81%) as a white powder: mp 60−62 °C (MeOH); R_f 0.41 (20% hexane/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.59 (3H, s), 3.86 (3H, s), 6.54 (1H, s), 7.27−7.42 (4H, m), 7.63 (1H, dd, J = 7.9, 2.0 Hz), 8.56 (1H, s); ^{13}C NMR ($CDCl_3$) δ 55.6, 56.0, 87.3, 113.4, 120.5, 121.6, 123.2, 126.4, 127.3, 128.9, 131.6, 131.8, 133.4, 149.0, 149.1, 151.4, 164.7; FTIR (neat film, cm^{-1}): 1586; EIMS (m/z, %) 487 (M + 1, 26), 485 (M − 1, 27), 359 (21). Anal. Calcd for $C_{17}H_{13}BrINO_3$: C, 42.00; H, 2.70; N, 2.88. Found: C, 42.09; H, 2.64; N, 2.86.

4-(2-Bromo-4,5-dimethoxyphenyl)-5-(2-iodophenyl)-isoxazole (21j) (78%) as a white powder: mp 68−70 °C (MeOH); R_f 0.41 (20% hexane/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.54 (3H, s), 3.87 (3H, s), 6.50 (1H, s), 7.06 (1H, s), 7.14 (1H, ddd, J = 7.9, 7.9, 2.0 Hz), 7.30 (1H, dd, J = 7.6, 1.6 Hz), 7.39 (1H, dd, J = 7.6, 7.6 Hz), 7.92 (1H, d, J 7.9 Hz), 8.63 (1H, s); ^{13}C NMR ($CDCl_3$) δ 55.3, 55.6, 97.2, 113.2, 113.3, 115.2, 116.8, 121.3, 127.2, 131.0, 131.1, 132.6, 139.3, 147.6, 148.8, 150.8, 166.5 (C-5); FTIR (neat film, cm^{-1}): 1600 (C═N); EIMS (m/z, %) 487 (M + 1, 22), 485 (M − 1, 23), 406 (17). Anal. Calcd for $C_{17}H_{13}BrINO_3$: C, 42.00; H, 2.70; N, 2.88. Found: C, 42.31; H, 2.35; N, 2.76.

4-(5-Bromo-1,3-benzodioxol-6-yl)-5-(2-bromophenyl)-isoxazole (21k) (93%) as a colorless oil: R_f 0.43 (20% hexane/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 5.96 (2H, s), 6.50 (1H, s), 7.07 (1H, s), 7.29−7.38 (3H, m), 7.64 (1H, dd, J = 6.4, 1.6 Hz), 8.50 (1H, s); ^{13}C NMR ($CDCl_3$) δ 101.9, 110.6, 113.0, 114.4, 117.5, 122.8, 123.0, 127.3, 128.5, 131.5, 131.7, 133.4, 147.2, 148.3, 151.5, 164.6; FTIR (neat film, cm^{-1}): 1586; EIMS (m/z, %) 425 (M + 2, 13), 423 (M^+, 25), 421 (M − 2, 14), 342 (19). Anal. Calcd for $C_{16}H_9Br_2NO_3$: C, 45.42; H, 2.14; N, 3.31. Found: C, 45.31; H, 2.19; N, 3.26.

Heterocyclization Procedures Leading to Ketones 4 and Hydroxyisoxazolines 21.

4,5-Bis(2-bromophenyl)-5-hydroxy-2-isoxazoline (22a) and 1,2-Bis(2-bromophenyl)ethanone (4a). Typical Procedure. $NH_2OH{\cdot}HCl$ (210 mg, 3.15 mmol) and Na_2CO_3 (170 mg, 1.6 mmol) were added to a stirred solution of enaminoketone **18a** (1.17 g, 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 11 h. After being cooled, 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 concentrated in vacuo (T < 30 °C). The residue (**A**) crystallized from 50% EtOAc/hexane, providing pure isoxazoline **22a** (658 mg, 58%) as a yellow powder, and the supernatant liquid was concentrated under reduced pressure (T < 30 °C) and crystallized from methanol to afford ethanone **4a** (374 mg, 37%) as a white powder. A simple distilation of supernatant liquid provided *N*,*N*-dimethylformamide (0.07 mL, 35%). Alternatively, a ^{1}H NMR spectrum ($CDCl_3$) of crude residue **A** showed both DMF and ethanone **4a** in the same proportion (from integration of signals at 8.2 ppm (1H, m) for DMF and at 4.43 ppm (2H, s) for **4a**).

4,5-Bis(2-bromophenyl)-5-hydroxy-2-isoxazoline (22a) was obtained as a mixture of diastereoisomers (**a**/**b** = 36/64) which showed the following selected data: ^{1}H NMR **a** ($CDCl_3$) δ 3.85 (1H, bs, O−H), 5.56 (1H, s, H-4); ^{1}H NMR **b** ($CDCl_3$) δ 3.79 (1H, bs, O−H), 5.71 (1H, s, H-4); ^{13}C NMR **a** ($CDCl_3$) δ 62.6 (C-4), 107.8 (C-5), 151.1 (C-3); ^{13}C NMR **b** ($CDCl_3$) δ 61.6 (C-4), 105.0 (C-5), 150.1 (C-3); FTIR (neat film, cm^{-1}): 3440 (O−H); EIMS (m/z, %) 399 (M + 2, 2), 397 (M^+, 4), 395 (M − 2, 2), 379 (M−H_2O, 2), 318 (M − Br,^{79} 7), 316 (M − Br,^{81} 7), 185 (100), 183 (99).

The same procedure on enaminone **18b** afforded the following products:

4,5-Bis(2-iodophenyl)-5-hydroxy-2-isoxazoline (22b) (61%) was obtained as a mixture of diastereoisomers (**a**/**b** = 22/78) which showed the following selected data: ^{1}H NMR **a** ($CDCl_3$) δ 3.19 (1H, bs, O−H), 5.44 (1H, s, H-4); ^{1}H NMR **b** ($CDCl_3$) δ 3.01 (1H, bs, O−H), 5.56 (1H, s, H-4); ^{13}C NMR **a** ($CDCl_3$) δ 66.7 (C-4), 106.9 (C-5), 150.6 (C-3); ^{13}C NMR **b** ($CDCl_3$) δ 67.2 (C-4), 105.2 (C-5), 149.4 (C-3); FTIR (neat film, cm^{-1}): 3435 (O−H); EIMS (m/z, %) 491 (M^+, 6), 473 (M − H_2O, 4), 364 (M − I, 12), 231 (100).

1,2-Bis(2-iodophenyl)ethanone (4b) (31%).

The same procedure on enaminone **18c** afforded the following products:

4,5-Bis(2-bromo-4,5-dimethoxyphenyl)-5-hydroxy-2-isoxazoline (22c) (66%) was obtained as a mixture of diastereoisomers (**a**/**b** = 46/54) which showed the following selected data: ^{1}H NMR **a** ($CDCl_3$) δ 2.05 (1H, bs, O−H), 5.56 (1H, s, H-4); ^{1}H NMR **b** ($CDCl_3$) δ 2.61 (1H, bs, O−H), 5.34 (1H, s, H-4); ^{13}C NMR **a** ($CDCl_3$) δ 62.7 (C-4), 106.6 (C-5), 151.5 (C-3); ^{13}C NMR **b** ($CDCl_3$) δ 65.4 (C-4), 107.4 (C-5), 159.5 (C-3); FTIR (neat film, cm^{-1}): 3390 (O−H); EIMS (*m*/*z*, %) 499 (M−H_2O, 7), 497 (3), 438 (M − Br,^{79} 4), 436 (M − Br,^{81} 4), 245 (100), 243 (96).

1,2-Bis(2-bromo-4,5-dimethoxyphenyl)ethanone (4c) (49%).

The same procedure on enaminone **18d** afforded the following products:

4,5-Bis(4,5-dimethoxy-2-iodophenyl)-5-hydroxy-2-isoxazoline (22d) (60%) was obtained as a mixture of diastereoisomers (**a**/**b** = 44/56) which showed the following selected data: ^{1}H NMR **a** ($CDCl_3$) δ 3.20 (1H, bs, O−H), 5.30 (1H, s, H-4); ^{1}H NMR **b** ($CDCl_3$) δ 3.49 (1H, bs, O−H), 5.39 (1H, s, H-4); ^{13}C NMR **a** ($CDCl_3$) δ 67.3 (C-4), 105.2 (C-5), 149.6 (C-3); ^{13}C NMR **b** ($CDCl_3$) δ 66.3 (C-4), 107.9 (C-5), 151.3 (C-3); FTIR (neat film, cm^{-1}): 3446 (O−H); EIMS (*m*/*z*, %) 593 (M − H_2O, 7), 484 (M − I, 4), 291 (100).

1,2-Bis(4,5-dimethoxy-2-iodophenyl)ethanone (4d) (35%).

Heterocyclization Assisted by Ultrasounds.

4,5-Bis(2-bromophenyl)-5-hydroxy-2-isoxazoline (22a). Typical Procedure. NH_2OH·HCl (210 mg, 3.15 mmol) and Na_2CO_3 (170 mg, 1.6 mmol) were added to a stirred solution of enaminoketone **18a** (1.17 g, 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 sonicated for 16 h at 65 °C. After being cooled, 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 give a yellow oil which was crystallized from 50% EtOAc/hexane, providing isoxazoline **22a** (80%) as a yellow powder (**a**/**b** diastereoisomers = 30/70).

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

4,5-Bis(2-iodophenyl)-5-hydroxy-2-isoxazoline (22b) (84%)(**a**/**b** diastereoisomers = 19/81).

4,5-Bis(2-bromo-4,5-dimethoxyphenyl)-5-hydroxy-2-isoxazoline (22c) (78%) (**a**/**b** diastereoisomers = 43/57).

4,5-Bis(4,5-dimethoxy-2-iodophenyl)-5-hydroxy-2-isoxazoline (22d) (81%) (**a**/**b** diastereoisomers = 41/59)

Supporting Information Available: Tables of fractional coordinates, equivalent isotropic and anisotropic parameters, bond lengths and bond angles, complete computational results in the form of Cartesian coordinates with the computed total energies. This material is available free of charge via the Internet at http://pubs.acs.org

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