Diheteroarylmethanes. 5.[1] *E*−*Z* Isomerism of Carbanions Substituted by 1,3-Azoles: ^{13}C and ^{15}N π-Charge/Shift Relationships as Source for Mapping Charge and Ranking the Electron-Withdrawing Power of Heterocycles

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Received October 23, 1995[⊗]

Previously proposed π-charge/shift relationships have been applied to ^{13}C and ^{15}N shifts of the carbanions of 2-benzylazoles (thiazole, oxazole, and imidazole), their corresponding benzo-fused analogs, and bis(2-azolyl)methanes (azolyl groups as above). In this way it is possible to rank the π electron-withdrawing power of these heterocycles in terms of charge demands c_X, a quantity representing the fraction of π negative charge withdrawn (delocalized) by the ring. The results indicate that $c_{thiaz} > c_{oxaz} > c_{imidaz}$; furthermore, benzoazoles are more efficient than monocyclic systems in delocalizing the negative charge. The charge demand c_X of imidazole is the smallest among the heteroaromatics so far considered, being even smaller than that of the phenyl ring. As a consequence, the negative charge in the anion of 2-benzyl-*N*-methylimidazole is predominantly transferred from the carbanionic carbon to the phenyl group rather than to the imidazolyl residue. The high double bond character of the bond linking the carbanionic and *ipso* phenyl ring carbons leads to room temperature ^{13}C shift anisochrony of the *meta* and *meta′* and *ortho* and *ortho′* positions of the phenyl ring. In all of the other cases, hindered rotation is observed at room temperature between the carbanionic carbon and position 2 of the heterocycle. A single set of resonances is presented by the bis(heteroaryl)methyl carbanions. π-Charge/shift relationships allow for the accurate π-charge mapping in these carbanionic systems, and the results point to considerable delocalization of the electron pair(s) of the oxygen and pyrrolic nitrogen atoms at position 1 in oxazole and imidazole toward the pyridic nitrogen at position 3 of the rings (in both the neutrals and the carbanionic species). On the contrary, not only does the sulfur atom in thiazole derivatives not delocalize any negative charge in the anions but it is barely involved in any π-donation to the pyridic nitrogen atom at position 3 also in the neutrals.

Once the chemical shift of the carbanionic carbon and the shielding contributions A_i[3] of the *i* groups bonded to it are known, the π-charge/^{13}C-shift relationship (1) allows empirical calculation of the π-electron density q_C^{π} [3,4] on a trigonal carbanionic carbon $XYCH^-$.

$$\delta^{13}C = 122.8 + \Sigma A_i - 160(q_C^{\pi} - 1) \qquad (1)$$

We have previously defined[4−6] the charge demand *c* of a substituent group as the fraction of π-charge withdrawn from an adjacent charged trigonal carbon atom and have subsequently used charge demands as a measure of the capacity of substituents to delocalize positive or negative charges.[4−10] The values of substituent charge demands depend on the system studied. In charge demand notation, the subscript identifies the group and the superscript the system or family of carbanions. Thus, benzyl carbanions $PhCH^-X$ (in which Y = Ph) originated the c_X^{Ph} values,[4] and symmetrically diactivated carbanions X_2CH^- originated the c_X^X values.[6] Strong electron-withdrawing groups X or Y (with the exception of Y = Ph) have the same charge demands in X_2CH^- and $XYCH^-$ ($c_X^X = c_X^Y$). The charge demands c_X and c_Y are in turn related to q_C^{π}. In diactivated carbanions X_2CH^-, the charge demand c_X^X is related to the experimentally obtained q_C^{π} by relationship 2; in benzyl carbanions $PhCH^-X$, the c_X^{Ph} is related to the value of q_C^{π} by relationship 3.

$$c_X^X = (2 - q_C^{\pi})/2 \qquad (2)$$

$$c_X^{Ph} = 2 - c_{Ph} - q_C^{\pi} \qquad (3)$$

In (3) c_{Ph} is the charge delocalized by the phenyl group in $PhCH^-X$. It varies with X but can be calculated[4] according to relationship 4 by adding the local variations

[⊗] Abstract published in *Advance ACS Abstracts,* February 15, 1996.

(1) For part 4, see ref 2a. For part 3, see ref 7b. For part 2, see ref 2b. For part 1, see ref 2c.

(2) (a) Bradamante, S.; Facchetti, A.; Pagani, G. *Gazz. Chim. Ital.* In press. (b) Abbotto, A.; Bradamante, S.; Pagani, G. *Gazz. Chim. Ital.* **1994**, *124*, 301−308. (c) Abbotto, A.; Alanzo, V.; Bradamante, S.; Pagani, G. A.; Rizzoli, C.; Calestani, G. *Gazz. Chim. Ital.* **1991**, *121*, 365−368.

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0022-3263/96/1961-1761$12.00/0

of the π-electron densities at all of the positions of the phenyl ring. Analogously, after exploiting the π-charge/

$$c_{Ph} = \Sigma\Delta q^{\pi}_{C\text{-ring}} = -\Sigma\Delta\delta^{13}C_{ring}/160 \quad (4)$$

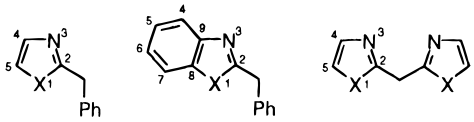
^{15}N-shift relationship (5),[8−11] the charge demand c^{Ph}_{Het} of an aromatic nitrogen heterocycle in benzyl carbanions $PhCH^{-}X$ with X = Het is given by the relationship 6.

$$\Delta\delta^{15}N = -366.34\Delta q^{\pi}_{N} \quad (5)$$

$$c^{Ph}_{Het} = \Sigma\Delta q^{\pi}_{C\text{-ring}} + \Sigma\Delta q^{\pi}_{N} = -[\Sigma\Delta\delta^{13}C_{ring}/160 + \Sigma\Delta\delta^{15}N/366.34] \quad (6)$$

We have so far been mainly involved in ranking the resonance electron-withdrawing power of primary organic functionalities,[4−6] along with pyridyl[7] and azine[5,8] heterocyclic rings contiguous to a carbanionic center. In this way, we have obtained two sets of values, c^{Ph}_{X} and c^{X}_{X}, for various X groups, depending on whether α-substituted benzyl anions $PhCH^{-}X$ or diactivated systems X_2CH^{-} are being considered. The ranking of electron-withdrawing groups has allowed a precise prediction of the ^{13}C shift of the carbanionic carbon to be made in many di-[9,10] and trisubstituted[12] carbanions. It has also been possible to describe the variation in the π-electron density between neutral and conjugated anionic species (charge mapping).[4−10] In particular, benzyl carbanions $PhCH^{-}Het$ with Het = 2- and 4-pyridyl and 2- and 4-quinolyl and heterocyclic azine rings show *E*−*Z* isomerism for the bond linking the heterocycle and the carbanionic carbon.[7,8]

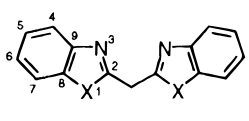
We have now extended this approach to the carbanions substituted by heterocyclic 1,3-azoles (oxazole, thiazole, and imidazole) and their benzo-fused analogs. The systems we have considered are 2-benzylthiazole (BnTz) (**1**), 2-benzyloxazole (BnOx) (**2**), 2-benzyl-*N*-methylimidazole (BnIm) (**3**), 2-benzylbenzothiazole (BnBTz) (**4**), 2-benzylbenzoxazole (BnBOx) (**5**), and 2-benzyl-*N*-methylbenzimidazole (BnBIm) (**6**). However, the extension also covered the bis(heteroaryl)methanes, bis(2-thiazolyl)-methane (bisTzM) (**7**), bis(*N*-methylimidazol-2-yl)methane (bisImM) (**8**), bis(2-benzothiazolyl)methane (bisBTzM) (**9**), bis(2-benzoxazolyl)methane (bisBOxM) (**10**), and bis(*N*-methylbenzimidazol-2-yl)methane (bisBImM) (**11**).



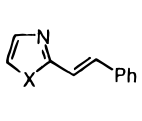
1: X = S
2: X = O
3: X = NMe

4: X = S
5: X = O
6: X = NMe

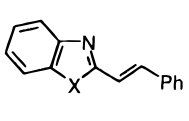
7: X = S
8: X = NMe



9: X = S
10: X = O
11: X = NMe



12: X = S
13: X = NMe



14: X = S
15: X = O
16: X = NMe

We considered the bis(heteroaryl)methanes **7**−**11** attractive for at least three reasons. First, unlike substituted diphenylmethanes, bis(heteroaryl)methanes of azines and azoles are compounds that have so far received little attention in the literature, notwithstanding their potentially great interest as activated carbon acids.[13] Indeed, many of them manifest "active methylene behaviour" [2b] insofar as they undergo easy nitrosation, azo-coupling, and condensation with carbonyl reagents. Second, we wanted to compare the charge demands c^{Ph}_{Het} and c^{Het}_{Het} of these heterocycles with the charge demand of the phenyl ring c^{Ph}_{Ph}. Third, although bis(2-benzothiazolyl)methane (bisBTzM) (**9**) and transition metal ions are known[2c] to give neutral methanates [ML_2] in which the ligand is present as bis(2-benzothiazolyl)methyl carbanion, not all bis(*o-aza*heteroaryl)methanes behave as good carbanionic ligands.[7b,15] As a rough estimate of the stability of the carbanion, the charge demand of the heterocycle may prove to be a valid discriminating threshold below which the formation of neutral metal chelates can be prevented.

To apply relationship 1 to carbanions **1**$^{-}$−**10**$^{-}$ and obtain the c_{Het} values, we needed to know the shielding contributions A_i of the different azoles and benzoazoles. Following a previous approach,[6] the A_i terms were calculated as the difference between the ^{13}C chemical shifts of the β carbon in styrene and those of the same carbon atoms in the styryl derivatives **12**−**16.**

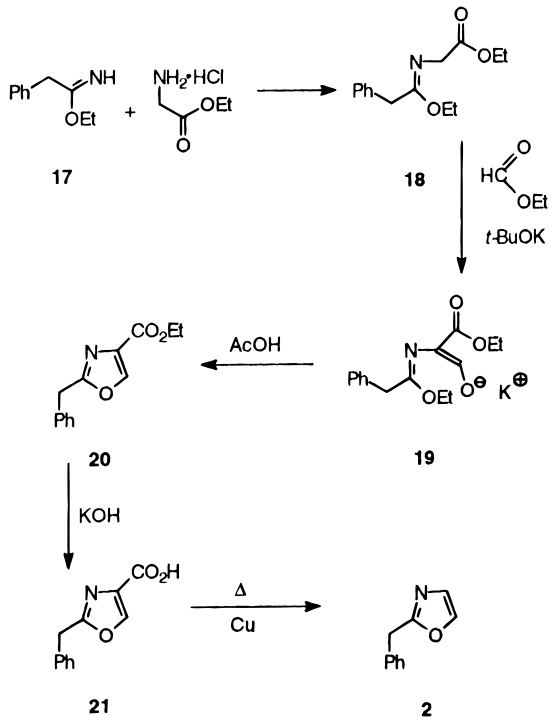
Results

Synthesis of Neutrals and Preparation of Carbanions. 2-Benzyloxazole (BnOx) (**2**) appears to be unknown. It was prepared according to Scheme 1 following Cornforth's approach[17] for 2-substituted oxazoles. Phenylacetimidoyl ethyl ether (**17**) was reacted with the hydrochloride of glycine methyl ester to give substituted imido ether **18** which, upon condensation with ethyl formate under basic conditions, gave hydroxymethylene sodium salt **19**. Cyclization to 2-benzyl-4-(ethoxycarbonyl)oxazole (**20**) was performed in refluxing glacial acetic acid. Subsequent careful basic hydrolysis to acid **21** and decarboxylation afforded **2** in an overall yield of 32%. Compound **2** was also prepared using an alternative route based on a recently reported synthesis of oxazole derivatives.[18] The mixture of 1- and 2-(phenylacetyl)-1,2,3-triazoles (**22** and **23**) (respectively), as obtained from the reaction of phenylacetyl chloride and 2-(trimethylsilyl)-1,2,3-triazole (Scheme 2),was thermolyzed in sulfolane.

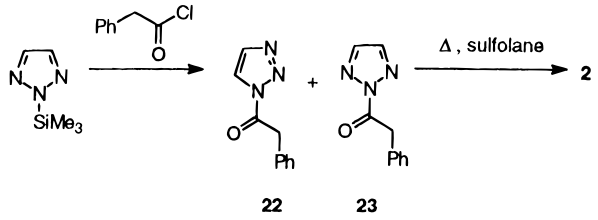
Bis[4-(ethoxycarbonyl)thiazol-2-yl]methane (**24**) was prepared (Scheme 3) according to the general Hantzsch synthesis of thiazoles by condensing malonodithioamide[2b] with ethyl bromopyruvate. Subsequent acidic hydrolysis

(11) Gatti, C.; Ponti, A.; Gamba, A.; Pagani, G. *J. Am. Chem. Soc.* **1992**, *114*, 8634−8644.
(12) Barchiesi, E.; Bradamante, S.; Ferraccioli, R.; Pagani, G. A. *J. Chem. Soc., Chem. Commun.* **1987**, 1548−1549.
(13) Bordwell has reported[14] particularly high carbon acidity for 2-benzylbenzothiazole in DMSO (pK_a = 20.8): since the phenyl ring is much less electron-withdrawing than the benzothiazolyl ring, we estimate that the pK_a of bis(2-benzothiazolyl)methane is in the upper region of the 10−20 pK_a units.
(14) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.
(15) We have reported[2c] that bis(2-benzothiazolyl)methane (**9**) acts as a carbanionic ligand L^{-} toward the acetates of divalent transition metal ions [Zn(II), Cu(II), Co(II), Ni(II)], leading to neutral metal methanates [ML_2]. Further work from this laboratory[16] has shown that this behavior is common to a number of other bis(*o-aza*heteroaryl)-methanes, including bis(2-benzoxazolyl)methane (**10**). The *aza* analog of the series, bis(*N*-methylbenzimidazol-2-yl)methane (**11**), fails to react with metal acetates to give neutral methanates.
(16) Abbotto, A. Ph.D. Thesis, University of Milano, 1993.
(17) Cornforth, J. W.; Fawaz, E.; Goldsworthy, L. J.; Robinson, R. *J. Chem. Soc.* **1949**, 1549−1553.
(18) Williams, E. L. *Tetrahedron Lett.* **1992**, *33*, 1033−1036.

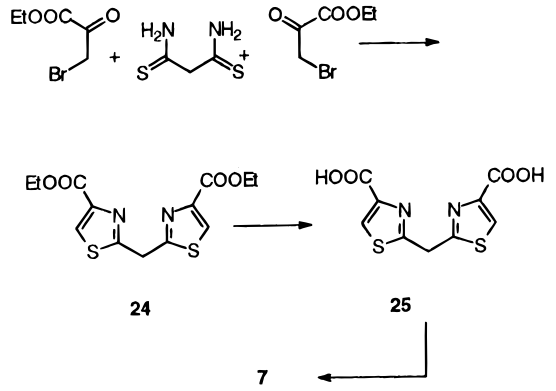
Scheme 1



Scheme 2



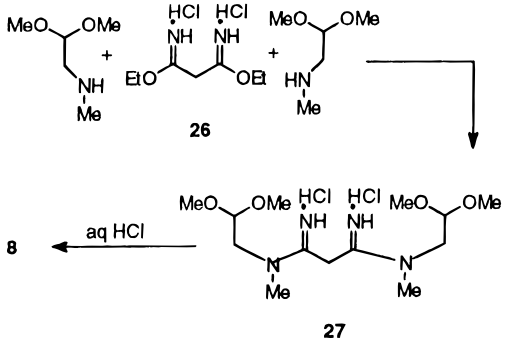
Scheme 3



and decarboxylation of acid **25** gave (bisTzM) (**7**). This compound is rather unstable in air but can be stored for some time and with little decomposition under nitrogen and in the cold.

Bis(*N*-methylimidazol-2-yl)methane (bisImM) (**8**) was prepared according to the method shown in Scheme 4. Bis-malonimido ethyl ether **26** was reacted with (*N*-methylamino)acetaldehyde diethyl acetal to give bis-amidine **27**; this compound was cyclized in hydrochloric acid to bis(*N*-methylimidazol-2-yl)methane (bisImM) (**8**). Because of the solubility of **8** in water, its isolation required continuous extraction with hexane in a Kumagawa apparatus from the basified, dry residue obtained from the cyclization step.

Scheme 4



Carbanions $\mathbf{1}^{-}$–$\mathbf{10}^{-}$ were prepared in DMSO using dimsylsodium as a base. We have documented the reasons for our choice of DMSO as a solvent elsewhere.[3–10] Under these conditions, the sodium salts should have the form of solvent separated ion pairs or of free ions. The insufficient solubility of the carbanion sodium salt of compound **11** prevented us from obtaining its ^{13}C and ^{15}N NMR spectra.

NMR Shift Assignments. The ^{13}C and ^{15}N NMR shifts of compounds **1**–**6** and $\mathbf{1}^{-}$–$\mathbf{6}^{-}$ are shown in Table 1; those relating to compounds **7**–**11** and $\mathbf{7}^{-}$–$\mathbf{10}^{-}$ are given in Table 2. Here, we only provide a detailed interpretation of NMR data when the assignments were not straightforward.

(a) ^{13}C Shifts. The ^{13}C shift assignments in the neutral compounds **1**–**11** were based on coupling constants[19a] and the known heteroatom substituent effects operating in the heterocycles.[19b] Benzothiazole, benzoxazole, and *N*-methylbenzimidazole[20] were used as model compounds for comparison. When ambiguities occurred, a complete analysis of the spectrum was performed and discrimination was based on the multiplicity of patterns and the values of the long-range coupling constants.

In compound **2** the assignments to C_{para}, C(4), and C(5) were as follows: 126.82 ppm, C_{para}, double triplet, $^3J_{C,H(ortho)} = 6.9$ Hz; 127.03 ppm, C(4), double doublet, $^1J_{C,H(4)} = 193.9$ Hz, in line with $^1J_{C,H(4)} = 195$ Hz in oxazole,[19a] $^2J_{C,H(5)} = 16.0$ Hz; 139.72 ppm, C(5), double doublet, $^1J_{C,H(5)} = 209.6$ Hz, in line with $^1J_{C,H(5)} = 209$ Hz in oxazole,[19a] $^2J_{C,H(4)} = 18.5$ Hz. In compound **3**, the peak at 121.23 ppm was attributed to C(5), given that this was a double double quartet, $^1J_{C,H(5)} = 188.5$ Hz, in analogy with $^1J_{C,H(5)} = 189$ Hz in imidazole,[19a] $^2J_{C,H(5)} = 13.0$ Hz, $^3J_{C,H(Me)} = 3.0$ Hz; at 126.39 ppm C(4) was present as a double doublet, $^1J_{C,H(4)} = 186.6$ Hz, $^2J_{C,H(5)} = 9.7$ Hz.

In the phenyl ring of anions $\mathbf{1}^{-}$–$\mathbf{6}^{-}$, the carbon atoms *para* to the carbanionic center showed the largest high-field displacement in comparison with neutrals. In anions $\mathbf{1}^{-}$–$\mathbf{3}^{-}$, $\mathbf{7}^{-}$, and $\mathbf{8}^{-}$, C(5) proved to be the most shielded position of the heterocycle; in anions $\mathbf{4}^{-}$–$\mathbf{6}^{-}$, $\mathbf{9}^{-}$, and $\mathbf{10}^{-}$, C(4), C(6), C(7), and C(8) showed shielding effects to varying degrees. Anion $\mathbf{1}^{-}$ was present as a mixture of the *E* and *Z* geometrical isomers in a ratio of 1:1, not interchangeable in the NMR time scale at room temperature. Discrimination between the signals of the two isomers was not possible because of the lack of ring protons proximate to the carbanionic proton susceptible to an NOE experiment. Two isomers were also present

(19) (a) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; VCH: Weinheim, 1987; pp 288–289. (b) Reference 19a, p 282.
(20) Stefaniak, L. *Org. Magn. Reson.* **1978**, *11*, 385–389.

Table 1. $^{13}C^{a}$ and ^{15}N NMR Shifts^{b} (ppm) of 2-Benzyl-1,3-azoles 1−6 and Conjugate Carbanions 1^{-}−6^{-} in DMSO^{c}

	azole ring positions									phenyl ring positions				CH_2/	^1J/	other
compd	1	2	3	4	5	6	7	8	9	*ortho*	*meta*	*para*	*ipso*	CH^-	Hz^{d}	groups
1		170.12	316.82	142.60	120.36					129.22	129.00	127.23	138.56	38.68	129.9	
1$^-$ 50%^{e}		165.83	231.56	141.61	93.58					119.18	127.55	111.64	143.68	82.87	150.6	
50%		163.92	230.98	140.00	93.26					119.01	127.15	111.22	142.92	79.90	150.2	
2		162.64	245.35	127.03	139.72					128.72	128.56	126.82	135.95	33.59	130.1	
2$^-$		168.48	190.2^{f}	127.01	125.30					117.64	127.22	109.12	144.84	65.10^{g}	150.6	
3	155.78	146.17	257.72	126.39	121.23					128.30	128.38	126.21	137.89	32.30	128.2	CH_3 = 32.32
3$^-$	122.54	154.73	216.40	124.22	111.56					117.74^{g}	127.52^{g}	105.16	145.42	62.59	147.5	CH_3 = 31.47
										114.70^{g}	126.78^{g}					
4		170.98	308.02	122.30	126.08	124.86	122.08	135.05	152.89	129.15	128.70	127.07	137.52	39.41	*h*	
4$^-$ 85%		160.37	218.33	111.59	124.30	114.05	118.26	130.58	159.96	121.36	127.33	114.96	143.20	82.60	151.4	
15%		159.51	*i*	111.28	124.71	112.83	118.81	129.90	156.46	120.78	127.83	114.68	142.83	85.20	150.4	
5		165.18	242.53	119.30	124.72	124.20	110.44	150.30	140.84	128.90	128.53	126.92	135.06	34.07	130.6	
5$^-$ 90%		168.10	179.62	108.99	121.28	113.58	104.38	149.26^{j}	148.88^{j}	120.85	127.25	113.74	143.77	67.13	152.0	
10%		168.47	*i*	108.63	121.96	112.46	104.84	150.11^{k}	147.59^{k}	120.40	127.72	114.01	143.42	69.23	152.0	
6	138.73	153.67	242.22	118.47	121.62	121.28	109.84	135.87	142.23	128.56	128.66	126.53	136.87	32.99	129.0	CH_3 = 29.78
6$^-$	109.54	158.52	193.49	108.63	117.81	112.72	102.08	136.88	148.20	119.89	127.04	111.10	145.05	65.86	148.0	CH_3 = 28.29

^{a} Relative to Me_4Si (0.0 ppm). ^{b} Relative to liquid NH_3 (0.0 ppm), 380.23 ppm from neat nitromethane. ^{c} 0.50 M solutions at 27 °C. ^{d} Relative to the benzylic methylene or methine group. ^{e} Values of corresponding positions in the two isomers can be exchanged. ^{f} Obtained for a 1 M solution at 35 °C (broad peak at 27 °C). ^{g} Broad. ^{h} Covered by solvent peaks. ^{i} Nitrogen of minor isomer was not detected. ^{j} Values can be exchanged. ^{k} Values can be exchanged.

Table 2. $^{13}C^{a}$ and ^{15}N NMR Shifts^{b} (ppm) of Bis-2-(1,3-azolyl)methanes 7−11 and Their Conjugate Carbanions 7^{-}−10^{-} in DMSO^{c}

	azole ring positions											
compd	1	2	3	4	5	6	7	8	9	CH_2/CH^-	^1J/Hz^{d}	other groups
7		165.54	319.04	142.42	120.76					35.88	135.0	
7$^-$		166.63	247.52	140.49	100.41					79.91	156.9	
8^{e}	157.46	143.69	259.43	126.20	121.48					25.30	129.0	CH_3 = 32.45
8$^{-\,e,f}$	122.60	154.55	201.94	123.93	112.02					47.10	149.5	CH_3 = 31.40
9		166.30	311.22	122.55	126.28	125.28	122.21	135.25	152.58	37.78	133.8	
9$^-$		164.76	241.32	115.43	124.42	117.45	119.62	132.11	155.97	81.42	157.8	
10		160.60	245.72	119.62	125.30	124.57	110.75	150.46	140.58	28.58	133.8	
10$^-$		168.71	187.10	114.20	122.30	118.16	107.01	148.59	145.65	55.81	160.2	
11	140.50	150.51	242.16	118.51	121.77	121.27	109.82	135.90	142.13	26.73	130.1	CH_3 = 29.92

^{a} Relative to Me_4Si (0.0 ppm). ^{b} Relative to liquid NH_3 (0.0 ppm), 380.23 ppm from neat nitromethane. ^{c} 0.50 M solutions at 27 °C. ^{d} Relative to the methylene or methine bridge. ^{e} 0.25 M solution. ^{f} 50 °C.

in the NMR spectrum of anions **4**$^-$ and **5**$^-$ with similar ratios of respectively 85:15 and 90:10. Once again, it was impossible to discriminate the signals of the two isomers. In anion **2**$^-$, the assignment of the double doublets at 125.30, 127.01, and 127.22 ppm to C(5), C(4) and C_{meta}, respectively, was based on the different values of $^1J_{C,H}$ (125.30 ppm, C(5), $^1J_{C,H(5)}$ = 199.6 Hz, $^2J_{C,H(4)}$ = 19.1 Hz; 127.01 ppm, C(4), $^1J_{C,H(4)}$ = 181.7 Hz, $^2J_{C,H(5)}$ = 15.5 Hz; 127.22 ppm, C_{meta}, $^1J_{C,H(meta)}$ = 151.5 Hz, $^3J_{C,H(meta')}$ = 7.0 Hz). In anion **3**$^-$, the long-range coupling with the methyl group allowed the assignment to C(5) and C(4): 111.56 ppm, C(5), double double quartet, $^1J_{C,H(5)}$ = 180.9 Hz, $^2J_{C,H(4)}$ = 15.9 Hz, $^3J_{C,H(Me)}$ = 3.2 Hz; 124.22 ppm, C(4), double doublet, $^1J_{C,H(4)}$ = 178.8 Hz, $^2J_{C,H(5)}$ = 9.6 Hz. In anion **7**$^-$, the different values of the $^2J_{C,H}$ allowed the discrimination between C(4) and C(5): 100.41 ppm, C(5), double doublet, $^2J_{C,H(4)}$ = 15.0 Hz, could be compared with $^2J_{C(5),H(4)}$ = 15.3 Hz in compound **7**; and 140.49, C(4), double doublet, $^2J_{C,H(5)}$ = 5.5 Hz, with $^2J_{C(4),H(5)}$ = 6.6 Hz in compound **7**. As with anion **3**$^-$, the discrimination between C(5) and C(4) in anion **8**$^-$ was based on the long-range coupling constant with the methyl group: 112.02 ppm, C(5), double double quartet, $^2J_{C,H(4)}$ = 15.6 Hz, $^3J_{C,H(Me)}$ = 2.8 Hz; 123.93 ppm, C(4), double doublet, $^2J_{C,H(5)}$ = 9.8 Hz.

(b) ^{15}N Shifts. As expected from previous results obtained investigating carbanions with pyridine-like nitrogen atoms,[7,8] the ^{15}N shift underwent high-field displacement when passing from the neutrals to the carbanions. This must be related to the increase of π-electron density on the nitrogen atoms in the anions. The shift assignments of the two nitrogen atoms of the imidazole ring in compounds **3** and **8**, and of the benzimidazole ring in compounds **6** and **11**, were based on known nitrogen shieldings in simple heterocyclic systems.[21] In anions **3**$^-$, **6**$^-$, and **8**$^-$, both nitrogen atoms are shielded in relation to their corresponding atoms in the neutrals. It is assumed that the pyrrolic nitrogen atom remained at a higher field than the pyridic nitrogen atom, as in the neutrals.

***E*−*Z* Isomerism in the Anions.** The ^{13}C NMR spectra of benzyl anions **1**$^-$, **2**$^-$, **4**$^-$, **5**$^-$, and **6**$^-$ provide evidence for a mixture of both the *E* and *Z* isomers along the bond linking the carbanionic carbon and the heterocycle. The carbanion of 2-benzyl-*N*-methylimidazole (**3**$^-$) is one of the rare cases in which there is evidence at room temperature that hindered rotation is present along the bond linking the carbanionic carbon and the phenyl ring. Figure 1 shows the variations in the spectrum as the sample temperature increased. In the other cases, no evident variation was detected as the temperature was increased to 55 °C; in view of the instability of the dimsyl anion above 60 °C,[22] we did not try higher temperatures. The NOE experiment[8] that allowed the determination of the double bond configuration in the case of the benzylazine anions could not be used for anions **1**$^-$, **2**$^-$, **4**$^-$, **5**$^-$, and **6**$^-$ because of the lack of protons at the *ortho,ortho*′

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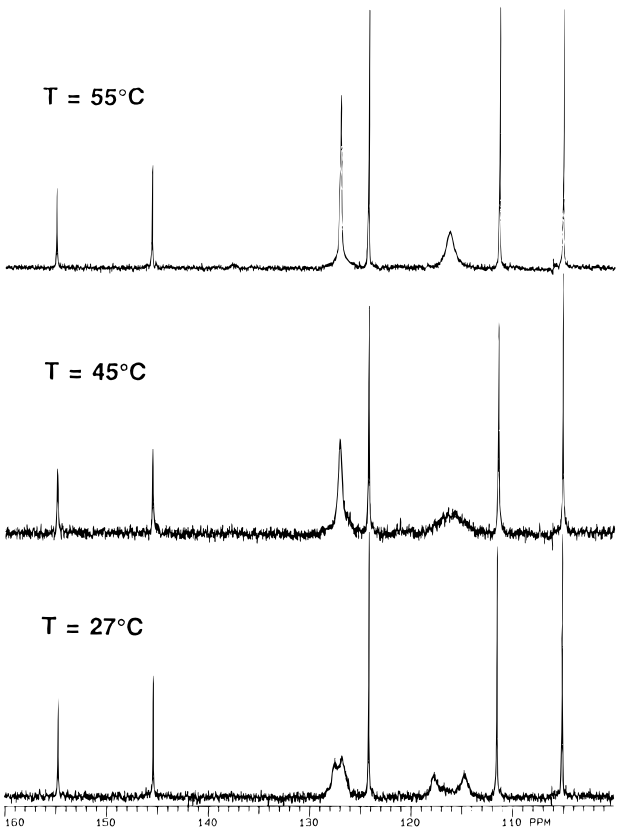
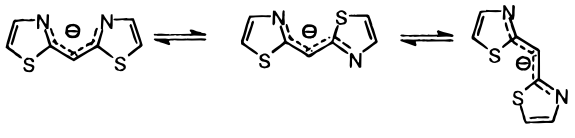


Figure 1. Temperature-dependent ^{13}C NMR spectrum of the carbanion of 2-benzyl-*N*-methylimidazole (**3**$^-$) in DMSO (aromatic region).

positions of the heterocycle. In these anions, we found that the phenyl ring prefers to stay *syn* to the ring nitrogen atom, and it is possible that there is an analogous preference in the case of benzyl azoles. The anion of 2-benzylbenzothiazole has been reported[23] to react with benzaldehyde in THF to give the *threo* aldol product with moderate diastereoselectivity (80%). Unfortunately, this result is of no help for the stereochemical assignment of the *E* and *Z* isomers of **4**$^-$ because the lithium salt of the same anion was reported to be unreactive in HMPA, that is, under conditions analogous to those of the sodium salt in DMSO described herein.

Unlike the above benzyl carbanions, the ^{13}C NMR spectra of the anions of bis(heteroaryl)methanes **7**$^-$−**10**$^-$ show a single set of resonances and therefore indicate either a single species [e.g., either the (*E*,*E*)-**7**$^-$, the (*E*,*Z*)-**7**$^-$, or the (*Z*,*Z*)-**7**$^-$] or a rapid (on the NMR time scale) equilibrium between the three interconverting isomers.



Discussion

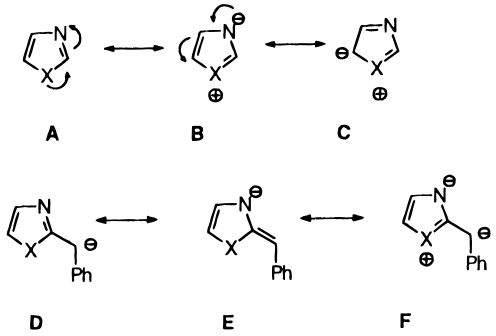
The Nature of X in Azoles and Delocalization in Carbanions. Carbons C(5) and C(4) of monocyclic benzyl azoles can be considered as being respectively *para* and *meta* to the benzyl residue. Therefore, as expected, deprotonation of the benzylic methylene involves a much greater high-field displacement of C(5) than C(4) (which remains almost constant). Similarly, in benzo-fused systems, only C(4), C(6), and, to a lesser extent, C(8) undergo the greatest high-field shift. The nitrogen at position 3 of the heterocycles is the nucleus that undergoes the largest shift when passing from the neutrals to carbanions. In benzyl derivatives, this increase amounts to ca. 85−90 ppm for the thiazole ring, 50 ppm for the oxazolyl derivatives, and 40 ppm for the imidazole ring. The results are similar in the bis(heteroaryl)methanes.

Table 3. Shielding Contributions A_X (ppm) of Heteroaryl Substituents at C(β) in β-Substituted Styrenes

substituent	$^{13}C(\beta)$ shift	A_X[a]
H	113.2[b]	0.0
thiazol-2-yl	120.8	7.6
oxazol-2-yl		0.5[c]
N-methylimidazol-2-yl	114.6	1.4
benzothiazol-2-yl	121.9	8.7
benzoxazol-2-yl	113.7	0.5
N-methylbenzimidazol-2-yl	114.4	1.2

[a] Positive values mean low-field displacements. [b] Kalinowski, H. O.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy*; John Wiley & Sons: Chichester, 1988; p 161. [c] The same value of the corresponding benzo-fused substituent is assumed.

A preliminary question arising before calculation of the charge demands of the heterocycles concerns the resonance contribution made to limit formulas (see below) by the second heteroatom in thiazole, oxazole, and imidazole derivatives (respectively sulfur, oxygen, and nitrogen). In particular, do resonance ring structures A−C make a substantial contribution to charge delocalization in benzyl anions D−F? To answer this question



it is worth noting, first, that the ^{15}N chemical shift of the nitrogen atom in thiazolyl derivatives is strictly analogous to that of the pyridyl systems.[21] Furthermore, the high-field displacement of ^{15}N following deprotonation of 2-benzylthiazole and 2-benzylbenzothiazole is almost the same as that found for 2-benzylpyridine[24] and 2-benzylquinoline.[7b] It therefore seems that the -S- group in neutral and carbanionic thiazole derivatives offers an electronic and magnetic contribution which is no more and no less than that offered by the −CH=CH− fragment in pyridine.

Second, a totally different situation is presented by oxazole and imidazole derivatives. The ^{15}N shift at position 3 of the neutrals (Tables 1 and 2) is considerably more high field than that of thiazole. Although not exclusively so, this result can be ascribed to the π donation of X(1) to N(3) and regarded as providing evidence for a considerable contribution of the limit formula B for X = O and NMe. In the anions, the

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Table 4. Variations of the Local π-Electron Densities (millielectrons) for Each *i*th Position on Going from the Neutral 2-Benzyl-1,3-azoles 1−6 to the Conjugate Anions 1^-−6^- [a]

		azole ring positions									phenyl ring positions			
compd		1	2	3	4	5	6	7	8	9	*ortho*	*meta*	*para*	*ipso*
$\mathbf{1}^-$	50%		27	233	6	167					63	9	97	−32
	50%		39	234	16	169					64	11	100	−27
$\mathbf{2}^-$			−36	150	0	90					69	8	111	−56
$\mathbf{3}^-$		91	−54	113	14	60					66	5	132	−47
											85	10		
$\mathbf{4}^-$	85%		66	245	67	11	68	24	28	−44	49	9	76	−36
	15%		72		69	9	75	20	32	−22	52	5	77	−33
$\mathbf{5}^-$	90%		−18	172	64	22	66	38	6	−50	50	8	82	−54
	10%		−21		67	17	73	35	1	−42	53	5	81	−52
$\mathbf{6}^-$		80	−30	133	62	24	54	48	−6	−37	54	10	96	−51

[a] Positive values correspond to an increment of π-electron density.

Table 5. Variations of the Local π-Electron Densities (millielectrons) for Each *i*th Position on Going from the Neutral Bis-2-(1,3-azolyl)methanes 7−10 to the Conjugate Anions 7^-−10^- [a]

	azole ring positions								
compd	1	2	3	4	5	6	7	8	9
$\mathbf{7}^-$		−7	195	12	127				
$\mathbf{8}^-$	95	−68	157	14	59				
$\mathbf{9}^-$		10	191	44	12	49	16	20	−21
$\mathbf{10}^-$		−51	160	34	19	40	23	12	−32

[a] Positive values correspond to an increment of π-electron density.

benzylic negative charge can partition between both N(3) and X(1), and the high-field displacement of the ^{15}N shift of the NMe at position 1 of the anionic imidazolyl derivatives confirms this interpretation. To have access to a quantitative measure of the charge mapping in the anions, we adopted the working hypothesis that relationship 5 is a valid means of correlating the displacement of the ^{15}N shift with π-electron density variations not only for the pyridine-like N(3) but also for the pyrrole-like N(1) of the NMe group. The same trigonal electronic configuration at N(3) and at N(1) justifies this assumption and predominantly ascribes the high-field displacement of N(1) to the increase in π-electron density at this site.

The following approach in the evaluation of the charge demands of the heterocycles takes all of this into account.

Azoles Charge Demands. Experimental access to the empirical evaluation of how much negative charge is delocalized by the heterocyclic rings in the carbanions can be provided by two alternative calculations. The first, through eq 3, provides c_X values that are homogeneous with those previously[4,5] obtained for a number of other classic EWGs of organic chemistry (CO_2R, C(O)R, CN, SO_nR, NO_2, etc.) and whose uncertainty depends on q^{π}_{C}. The second approach provides the c_{Het} value through eq 6 and involves a large number of terms in the summation of all the local π-charge densities. The calculation of c_{Het} was based on the following premises: (1) The sulfur atom in the carbanions of thiazole derivatives does not delocalize any negative charge, this being present only on the carbon and nitrogen skeleton (in short, $(\Delta q^{\pi})_{S(1)} = 0$). (2) The ^{15}N shift/$\pi$-charge relationship (5) is valid not only for the pyridine but also for the pyrrole-like nitrogen atoms of imidazole derivatives. (3) The π-charge density variation at the oxygen atom in oxazoles is identical to that at the pyrrole nitrogen atom in imidazoles. In short, $(\Delta q^{\pi})_{O(1)} = (\Delta q^{\pi})_{N(1)}$ (this appears reasonable in view of the close resemblance of the ^{15}N shift behavior of oxazolyl and imidazolyl derivatives). The calculations reported in Tables 6 and 7 for the oxazolyl derivatives were performed considering either $(\Delta q^{\pi})_{O(1)} = 0$ or $(\Delta q^{\pi})_{O(1)} = (\Delta q^{\pi})_{N(1)}$ (numbers in parentheses).

Table 6. Experimental π-Electron Densities *q* (electrons) for Conjugate Anions 1^-−6^- of 2-Benzyl-1,3-azoles 1−6

compd		q_{Ph} [a]	q_{Het} [b]	q_C [c]	$q_{Ph} + q_{Het} + q_C$ [d]
$\mathbf{1}^-$	50%	6.209	6.433	1.378	14.020
	50%	6.223	6.458	1.397	14.078
$\mathbf{2}^-$		6.209	6.204 (6.295)[e]	1.445	13.858 (13.949)[e]
$\mathbf{3}^-$		6.251	6.224	1.466	13.941
$\mathbf{4}^-$	85%	6.156	10.465	1.387	18.008
	15%	6.158	10.500[f]	1.371	18.029
$\mathbf{5}^-$	90%	6.144	10.300 (10.380)[g]	1.432	17.876 (17.956)[g]
	10%	6.145	10.302[f] (10.382)[g]	1.419	17.866 (17.946)[g]
$\mathbf{6}^-$		6.173	10.328	1.445	17.946

[a] π-Electron density resident on the phenyl ring. [b] π-Electron density resident on the azole ring. [c] π-Electron density resident on the carbanionic carbon. [d] Total π-electron density of the anionic system (to be compared with the theoretical value of 14 and 18 π-electrons for simple and benzo-fused derivatives, respectively). [e] Value in parentheses calculated by assuming $\Delta q^{\pi}_{O(1)}$ equal to $\Delta q^{\pi}_{N(1)}$ of corresponding imidazole derivative $\mathbf{3}^-$. [f] Same $\Delta q^{\pi}_{N(3)}$ of major isomer assumed. [g] Value in parentheses calculated by assuming $\Delta q^{\pi}_{O(1)}$ equal to $\Delta q^{\pi}_{N(1)}$ of corresponding imidazole derivative $\mathbf{6}^-$.

Table 7. Experimental π-Electron Densities *q* (electrons) for Conjugate Anions 7^-−10^- of Bis-2-(1,3-azolyl)methanes 7−10

compd	q_{Het} [a]	q_C [b]	$2q_{Het} + q_C$ [c]
$\mathbf{7}^-$	6.327	1.363	14.017
$\mathbf{8}^-$	6.257	1.491	14.005
$\mathbf{9}^-$	10.321	1.367	22.009
$\mathbf{10}^-$	10.205 (10.300)[d]	1.425	21.835 (22.025)[d]

[a] π-Electron density resident on the azole ring. [b] π-Electron density resident on the carbanionic carbon. [c] Total number of π-electrons in the anionic system (to be compared with the theoretical values of 14 and 22 π-electrons for monocyclic and benzo-fused derivatives, respectively). [d] Value calculated by assuming $\Delta q^{\pi}_{O(1)}$ equal to $\Delta q^{\pi}_{N(1)}$ of similar imidazole derivative $\mathbf{8}^-$.

In order to ascertain whether the above assumptions were acceptable, we compared the theoretical number of total π-electrons of the systems (14 in $\mathbf{1}^-$−$\mathbf{3}^-$, $\mathbf{7}^-$, and $\mathbf{8}^-$; 18 in the benzo-fused $\mathbf{4}^-$−$\mathbf{6}^-$, $\mathbf{9}^-$, and $\mathbf{10}^-$) and the total number of electrons calculated by summing the electron densities on the rings (the phenyl and the heterocycle in $PhCH^-Het$, or the two heterocycles in Het_2CH^-) and on the carbanionic carbon CH^- (eqs 7 and 8). Tables 6 and 7 show that the agreement between the experimental and

$$q^{\pi}_{Het} + q^{\pi}_{Ph} + q^{\pi}_{C} = \text{total number of } \pi \text{ electrons} \quad (7)$$

$$2q^{\pi}_{Het} + q^{\pi}_{C} = \text{total number of } \pi \text{ electrons} \quad (8)$$

Table 8. Charge Demands of Heteroaryl Substituents in $PhCH^-X$(c_X^{Ph}) and in X_2CH^-(c_X^X)

X	c_X^{Ph}	c_X^X
thiazol-2-yl	0.413−0.380[a,b]	0.318
oxazol-2-yl	0.346	
N-methylimidazol-2-yl	0.283	0.254
benzothiazol-2-yl	0.457−0.471[a]	0.316
benzoxazol-2-yl	0.424−0.436[a]	0.288
N-methylbenzimidazol-2-yl	0.382	

[a] Values referred to the major and minor anionic geometric isomer, respectively. [b] 1:1 mixture of geometrical isomers.

theoretical values is excellent. In particular, the calculations for the thiazole and benzothiazole rings show that no negative charge is delocalized onto the sulfur atom in the anions of thiazoles **1**$^-$ and **7**$^-$ and benzothiazoles **4**$^-$ and **9**$^-$. The consequence of this is that the sulfur electron pair in the neutral thiazole derivatives is barely involved in delocalization toward the nitrogen or the aromatic carbon atoms of the ring. Incorporation of relationship 5 for N(1) of the imidazole derivatives into q^{π}_{Het} of relationships 7 and 8 leads to a total "experimental" number of electrons that is in excellent agreement with theory. A similarly excellent result is obtained for the oxazole systems if q^{π}_{Het} takes into account that $(\Delta q^{\pi})_{O(1)} = (\Delta q^{\pi})_{N(1)}$.

Data in Table 8 show that the charge demands of the heterocycles decrease in the series $c_{thiaz} > c_{oxaz} > c_{imid}$. The result that N(3) of imidazole is more reluctant than that of oxazole and, even more so, that of thiazole to accept negative charge from the carbanionic carbon is due to the already very efficient "internal" donation to N(3) from N(1) in imidazole and from O(1) in oxazole. Benzo-fused rings are more efficient than monocyclic rings in delocalizing the charge.

The charge demand of the 2-imidazolyl group is not only the smallest of the values of the 1,3-azoles but is also quite small on an absolute scale. While the thiazolyl ring in anion **1**$^-$ of 2-benzylthiazole accepts more charge ($q_{Het} = 6.44$) (Table 6) than the phenyl ring ($q_{Ph} = 6.215$), in anion **3**$^-$ of 2-benzyl-*N*-methylimidazole, the amount of negative π-charge accepted by the phenyl ring ($q_{Ph} = 6.251$) is greater than that accepted by the imidazole ring ($q_{Het} = 6.224$). Consequently, whereas the thiazolyl ring is a good competitor of the phenyl ring in delocalizing the negative charge, the imidazolyl ring is not. The net result is that hindered rotations occur along different bonds in the two cases. The anion of 2-benzylimidazole has high double bond character along the bond linking the carbanionic carbon and the *ipso* carbon of the phenyl ring, leading to the exceptional result of room temperature anisochrony of the *ortho* and *meta* positions. In contrast, the anion of 2-benzylthiazole has high double bond character along the bond linking the carbanionic carbon and C(2) of the heterocycle. The results of the benzo-fused systems can be rationalized on similar grounds.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker AC-300 instrument operating at 300 MHz. ^{13}C and ^{15}N NMR spectra were recorded at 27 °C on a Varian XL-300 spectrometer, operating at 75.47 and 30.45 MHz, respectively, and using 0.50 M solutions in DMSO. Spectral parameters and calibrations have been previously reported.[8] Coupling constant values, *J*, are given in hertz throughout. Elemental analyses were performed on a Perkin-Elmer 240 instrument by the microanalysis laboratory of our department. Melting points are uncorrected. Anhydrous solvents were prepared by continuous distillation over sodium sand, in the presence of benzophenone and under nitrogen or argon, until the blue color of sodium ketyl was permanent. Extracts were dried over Na_2SO_4. Anions were prepared following the procedure already described.[3] **2-Benzylthiazole (1)**,[25] **2-benzylbenzothiazole (4)**,[26] **2-benzylbenzoxazole (5)**,[27] **bis(2-benzothiazolyl)-methane (9)**,[28] **bis(2-benzoxazolyl)methane (10)**,[29] **bis(*N*-methylbenzimidazol-2-yl)methane (11)**,[2a] **2-(*β*-styryl)-benzothiazole (14)**,[30] [^{13}C NMR (DMSO-d_6) δ 166.54, 153.60, 137.53, 135.27, 134.19, 129.61, 129.01, 127.80, 126.61, 125.57, 122.68, 122.26, 121.93], and **2-(*β*-styryl)benzoxazole (15)**[30] [^{13}C NMR (DMSO-d_6) δ 162.23, 149.72, 141.64, 139.32, 134.73, 129.72, 128.78, 127.73, 125.30, 124.54, 119.46, 113.67, 110.40] were prepared according to the literature.

2-Benzyl-4-(ethoxycarbonyl)oxazole (20). A mixture of ethyl formate (2.90 g, 39.1 mmol) and *N*-((ethoxycarbonyl)-methyl)phenylacetimidoyl ethyl ether (**18**)[17] (6.09 g, 24.4 mmol) was added to a suspension of potassium *tert*-butoxide (3.00 g, 26.7 mmol) in anhydrous diethyl ether (40.0 mL) at −4 °C. After stirring for 2 h at −4 °C, anhydrous ether (20 mL) was added, and then the yellow mixture was kept overnight at 4 °C. The white precipitate was rapidly separated under a nitrogen stream and washed with anhydrous diethyl ether (20 mL) to give the very hygroscopic hydroxymethylene potassium salt **19** (6.94 g, 22.0 mmol, 90.2%): ^{1}H NMR ($CDCl_3$) δ 8.50 (s, 1 H), 7.35−7.10 (m, 5 H), 4.00 (q, 2 H, $J = 7.5$), 3.90 (q, 2 H, $J = 7.5$), 1.11−1.09 (m, 6 H). The product was treated almost immediately in the subsequent reaction. Potassium salt **19** (6.94 g, 22.0 mmol) was added to refluxing glacial AcOH (50.0 mL), and after refluxing for 1 h, AcOH was removed at reduced pressure to leave a residue that was neutralized with a saturated aqueous solution of $NaHCO_3$ (20.0 mL) and extracted with diethyl ether (5 × 15 mL). The solvent was removed from the dried extracts to give the product as a brown solid (4.07 g, 17.6 mmol, 80.0%), mp 63 °C, which was used without any further purification in the next step. An analytical sample was purified to give a white solid: mp 72 °C (EtOH) (lit.[17] mp 74−75 °C); ^{1}H NMR ($CDCl_3$) δ 8.15 (s, 1 H), 7.35−7.20 (m, 5 H), 4.35 (q, 2 H, $J = 7.5$), 4.15 (s, 2 H), 1.40 (t, 3 H).

2-Benzyl-4-carboxyoxazole (21). A mixture of 2-benzyl-4-(ethoxycarbonyl)oxazole **(20)** (3.07 g, 13.2 mmol) and 6% aqueous KOH (12 mL) in H_2O (6 mL) was refluxed for 10 min, cooled, and acidified to pH 4 with 1 N H_2SO_4. The resulting pale yellow precipitate was separated to give the product as monohydrate, used without any further purification in the next step (2.66 g, 12.0 mmol, 90.9%), mp 153 °C. A sample was purified to give a white solid: mp 153 °C (H_2O, charcoal) (lit.[17] mp 156−158 °C); ^{1}H NMR ($CDCl_3$) δ 8.20 (s, 1 H), 7.40−7.20 (m, 5 H), 4.20 (s, 2 H), 3.00 (broad). The peak at δ 3.00 disappears upon deuteration. Anal. Calcd for $C_{11}H_9NO_3 \cdot H_2O$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.41; H, 4.70; N, 5.95.

2-Benzyloxazole (2). **Method A.** A mixture of 2-benzyl-4-carboxyoxazole·H_2O **(21)** (1.66 g, 7.5 mmol) and electrolytic copper powder (3.32 g) was heated at 250 °C in a Kugelrohr apparatus. The pale green oil that distilled (bp 250 °C/25 mmHg) was taken up with diethyl ether (15 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL). The solvent was removed from the dried organic layer to leave the practically pure product as a pale green oil (0.54 g, 3.4 mmol, 45.3%), which was further purified by distillation in Kugelrohr to give a colorless oil, bp 135−145 °C/0.08 mmHg: ^{1}H NMR ($CDCl_3$) δ 7.56 (d, 1 H, $J = 0.8$), 7.36−7.22 (m, 5 H), 7.04 (d, 1 H), 4.10 (s, 2 H); MS (EI) *m/z* 159 ($M^{+\bullet}$, 100), 130 (27), 103 (20), 91 (80). Anal. Calcd for $C_{10}H_9NO$: C, 75.44; H, 5.71; N, 8.80. Found: C, 75.15; H, 5.69; N, 9.02.

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Method B. A procedure reported for the synthesis of 2-substituted oxazoles was adopted.[18] A solution in anhydrous sulfolane (70 mL) of a 95:5 mixture of 1-(phenylacetyl)-1,2,3-triazole **(22)** and 2-(phenylacetyl)-1,2,3-triazole **(23)** as obtained in the preparation described below (2.24 g, 12.0 mmol) was stirred for 4.5 h at 160 °C under nitrogen. The originally colorless solution became dark red. The mixture was cooled to room temperature, poured into H_2O (100 mL), and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with H_2O (2 × 500 mL) to eliminate the sulfolane, dried, and evaporated to dryness to give a brown oil which was submitted to Kugelrohr distillation, affording the product as a colorless oil (1.61 g, 10.1 mmol, 84%), bp 130 °C/0.08 mmHg.

2-(Trimethylsilyl)-1,2,3-triazole. A procedure reported in the literature for the synthesis of 1-(trimethylsilyl)tetrazole was used.[31] To a solution of 1,2,3-triazole (1.02 g, 14.8 mmol) and Et_3N (1.62 g, 16.0 mmol) in anhydrous benzene (20 mL) was added dropwise trimethylsilyl chloride (1.59 g, 14.6 mmol), maintaining the temperature below 10 °C. A white precipitate was formed. The reaction mixture was stirred for 24 h at room temperature and then cooled to 0 °C and the triethylammonium chloride filtered off (2.00 g, 14.5 mmol, 99%). The obtained benzene solution of the product was used for the next step. After removal of the solvent at atmospheric pressure, a sample was obtained by distillation at reduced pressure, bp 68 °C/20 mmHg (lit.[32] bp 147−149 °C): ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 2 H), 0.53 (s, 9 H).

***N*-(Phenylacetyl)-1,2,3-triazoles 22 and 23.** The preparation follows a procedure reported[18] in the literature for *N*-acyltriazoles. Phenylacetyl chloride (2.20 g, 14.4 mmol) was added to the benzene solution of 2-(trimethylsilyl)-1,2,3-triazole as obtained in the previous step. The temperature raised spontaneously to 35 °C, and the formation of a white precipitate was observed. The solid was filtered off, and the solvent was removed to give the crude product (2.49 g, 13.3 mmol, 93%) as a pale pink oil. The product is a mixture of the two isomers 1-(phenylacetyl)-1,2,3-triazole and 2-(phenylacetyl)-1,2,3-triazole (95:5): ^{1}H NMR ($CDCl_3$) δ 8.26 (d, 0.95 H, J = 1.4), 7.89 (s, 0.1 H), 7.74 (d, 0.95 H), 7.41−7.22 (m), 4.61 (s, 1.90 H), 4.52 (s, 0.1 H).

2-Benzyl-*N*-methylimidazole (3). Powdery phenylacetimidoyl ethyl ether hydrochloride[33] (3.60 g, 18.0 mmol) was added to a solution of (methylamino)acetaldehyde dimethyl acetal (2.15 g, 18.0 mmol) in absolute EtOH (20 mL), maintaining the temperature between 0 and 5 °C. After stirring for 2.5 h at room temperature, anhydrous diethyl ether (100 mL) was added, giving ***N*-methyl-*N*-(2,2-dimethoxyethyl)-phenylacetamidine hydrochloride** as a white precipitate (3.65 g, 13.4 mmol, 74.4%): mp 162 °C; ^{1}H NMR ($CDCl_3$), two rotamers in the 30:70 ratio; 30% isomer, δ 10.5 (broad, 1 H), 9.9 (broad, 1 H), 7.37−7.25 (m, 5 H), 4.75 (t, 1 H, J = 5.6), 4.20 (s, 2 H), 3.88 (d, 2 H, J = 5.6), 3.48 (s, 3 H), 3.05 (s, 3 H); 70% isomer, δ 10.5 (broad, 1 H), 10.0 (broad, 1 H), 7.37−7.25 (m, 5 H), 4.27 (s, 2 H), 4.17 (t, 1 H, J = 5.6), 3.38 (s, 3 H), 3.37 (d, 2 H, J = 5.6), 3.35 (s, 3 H). Anal. Calcd for $C_{13}H_{20}N_2O_2$·HCl: C, 57.24; H, 7.76; N, 10.27. Found: C, 57.41; H, 7.55; N, 9.98. A solution of the hydrochloride (2.47 g, 9.0 mmol) in 37% HCl (1.10 g) and glacial AcOH (30 mL) was refluxed for 2 h. The solvent was removed at reduced pressure to leave a pale green residue that was taken up with diethyl ether (20 mL) and 30% NaOH (25 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (4 × 15 mL). The solvent was removed from the dried combined organic extracts to leave the product as a brown solid (1.31 g, 7.6 mmol, 84.4%) that was purified by Kugelrohr distillation (bp 135 °C/0.6 mmHg) to give the compound as a white solid (0.78 g, 4.5 mmol, 50.0%): mp 50−52 °C; ^{1}H NMR ($CDCl_3$) δ 7.30−7.10 (m, 5 H), 6.95 (d, 1 H, J = 0.8), 6.78 (d, 1 H), 4.10 (s, 2 H), 3.42 (s, 3 H); MS (EI, 10 eV) *m/e* 172 ($M^{+\bullet}$, 100), 171 (100), 157 (40), 91 (60), 81 (65). Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.64; H, 6.97; N, 16.18.

2-Benzyl-*N*-methylbenzimidazole (6). Powdery phenylacetimidoyl ethyl ether hydrochloride (1.60 g, 8.2 mmol) was added to a solution of *N*-methyl-*o*-phenylenediamine[34] (1.00 g, 8.2 mmol) in absolute EtOH (8 mL); the temperature spontaneously rose to 50 °C. The reaction mixture was stirred for 10 min at room temperature, the reaction was quenched with H_2O (15 mL), and then the mixture was extracted with diethyl ether (5 × 10 mL). The solvent was removed from the dried extracts to leave the product as a dark solid (1.45 g, 6.5 mmol, 79.3%) that was first purified by Kugelrohr distillation to give a pink-orange solid [(0.95 g, 4.3 mmol, 52.4%), bp 195 °C/0.5 mmHg, mp 68 °C], and then crystallized to a pale pink solid (0.7 g, 3.2 mmol, 30.0%), mp 72 °C (cyclohexane): ^{1}H NMR ($CDCl_3$) δ 7.75 (m, 1 H), 7.35−7.15 (m, 8 H), 4.35 (s, 2 H), 3.60 (s, 3 H). Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.00; H, 6.21; N, 12.45.

Bis[4-(ethoxycarbonyl)thiazol-2-yl]methane (24). A solution of ethyl bromopyruvate (26.10 g, 133.8 mmol) in DMF (10 mL) was added dropwise to a solution of malonodithioamide[2b] (9.00 g, 67.0 mmol) in DMF (40 mL), maintaining the temperature below 25 °C. The reaction mixture was stirred for 24 h at room temperature, treated with an aqueous solution (100 mL) of stoichiometric $NaHCO_3$, and extracted first with diethyl ether−AcOEt 2:1 (100 mL) and then with diethyl ether−AcOEt 1:1 (100 mL). After washing several times with H_2O and drying the combined extracts, elimination of the solvent left a dark oil that was extracted with diethyl ether (4 × 50 mL). The residue obtained after evaporation of the solvent from the combined extracts (yellowish solid, 13.40 g) was submitted to flash chromatography (CH_2Cl_2−AcOEt, 2:1) on silica gel to give the product as a yellowish solid (8.31 g, 25.4 mmol, 37.9%): mp 94−97 °C (a white sample was obtained by recrystallization from H_2O with no mp increase); ^{1}H NMR ($CDCl_3$) δ 8.06 (s, 2 H), 4.77 (s, 2 H), 4.34 (q, 4 H, J = 7.1), 1.32 (t, 6 H); MS (EI) *m/e* 326 ($M^{+\bullet}$, 40), 281 (59), 254 (100), 208 (30), 182 (56). Anal. Calcd for $C_{13}H_{14}N_2O_4S_2$: C, 47.84; H, 4.32; N, 8.58. Found: C, 48.17; H, 4.16; N, 8.46.

Bis(4-carboxythiazol-2-yl)methane (25). A suspension of bis[(4-(ethoxycarbonyl)thiazol-2-yl]methane **(24)** (5.00 g, 15.3 mmol) in 10% HCl (50 mL) was refluxed for 10 h. After 1 h from the homogeneous solution at reflux temperature a yellowish precipitate was observed, turning to light brown during the reaction. After cooling to room temperature, the brownish precipitate was collected and dried over $CaCl_2$ at reduced pressure, overnight, and at room temperature, and then for further 30 min at 60 °C, to afford the product (3.73 g, 13.8 mmol, 90.2%): mp > 220 °C; ^{1}H NMR (DMSO-d_6) δ 13 (broad, 2 H), 8.45 (s, 2 H), 4.92 (s, 2 H). Anal. Calcd for $C_9H_6N_2O_4S_2$: C, 40.00; H, 2.24; N, 10.36. Found: C, 40.15; H, 2,27; N, 10.13.

Bis(2-thiazolyl)methane (7). A mixture of bis(4-carboxythiazol-2-yl)methane **(25)** (2.37 g, 8.8 mmol) and electrolytic copper powder (3.00 g) was heated in a Kugelrohr apparatus at 260−270 °C at 25 mmHg. The distilled oil (0.99 g) resulted a mixture of the reactant and of the product; it was taken up with CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL). The solvent was removed from the dried organic layer to leave a dark brown oil (0.52 g) that was submitted to Kugelrohr distillation, affording the product as a pale yellow oil (0.43 g, 2.4 mmol, 27.3%): bp 145 °C/0.05 mmHg; ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 2 H, J = 3.0), 7.28 (d, 2 H), 4.80 (s, 2 H); MS (EI) *m/e* 182 ($M^{+\bullet}$, 100), 137 (63), 124 (16), 98 (24), 58 (100). Anal. Calcd for $C_7H_6N_2S_2$: C, 46.13; H, 3.32; N, 15.37. Found: C, 45.75; H, 3.08; N, 14.99. The compound is unstable to air and must be stored under nitrogen.

Bis(*N*-methylimidazol-2-yl)methane (8). Powdery malonodiimidoyl diethyl ether dihydrochloride[35] (2.50 g, 10.8 mmol) was added to a solution of (methylamino)acetaldehyde

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dimethyl acetal (2.62 g, 22.0 mmol) in absolute EtOH (18 mL), maintaining the temperature below 10 °C. After stirring for 4 h at room temperature, the solvent was removed to give crude **N^1,N^3-dimethyl-N^1,N^3-bis(2,2-dimethoxyethyl)malonamidine dihydrochloride (27)** as a brown oil (3.50 g, 9.3 mmol, 86.1%), which was used without any further purification in the next step: ^{1}H NMR ($CDCl_3$) δ 8.30 (broad, 4 H), 4.85 (t, 2 H, J = 5.1), 3.35 (s, 12 H), 2.95 (d, 4 H), 2.65 (s, 6 H). A solution of hydrochloride **27** (9.00 g, 23.8 mmol) in 37% HCl (20 mL) was refluxed for 2 h and then made strongly alkaline with 30% aqueous NaOH. The solvent was removed to leave a residue that was submitted to continuous extraction with hexane in a Soxhlet apparatus. The product was obtained as a white precipitate upon concentration of the solution (0.25 g, 1.4 mmol, 5.9%): mp 135−142 °C (lit.[36] mp 143−148 °C); ^{1}H NMR ($CDCl_3$) δ 6.90 (d, 1 H, J = 1.1), 6.80 (d, 1 H), 4.20 (s, 2 H), 3.65 (s, 6 H).

2-(β-Styryl)thiazole (12). A procedure reported in the literature for the preparation of 2-(β-styryl)benzothiazole and 2-(β-styryl)benzoxazole[30] was used. Aqueous 50% NaOH (1 mL) was added dropwise to a solution in DMSO (4 mL) of benzaldehyde (0.53 g, 5.0 mmol) and 2-methylthiazole[37] (0.50 g, 5.0 mmol) (prepared from pure chloroacetaldehyde hydrate).[38] The yellow mixture turned to orange, and the formation of a precipitate was observed. After stirring for 24 h at room temperature, the reaction mixture was poured into H_2O (15 mL) and extracted with diethyl ether (2 × 25 mL). The solvent was removed from the dried extracts to leave a yellowish oil (0.24 g) that was submitted to flash chromatography (CH_2Cl_2−AcOEt, 3:1) on silica gel to provide the product as a yellow solid (30 mg, 0.2 mmol, 4%): mp 55−59 °C (lit.[39] mp 59 °C); ^{1}H NMR ($CDCl_3$) δ 7.81 (d, 1 H, J = 3.4), 7.66−7.17 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 166.70, 142.86, 135.14, 133.81, 128.29, 128.24, 126.47, 120.79, 117.66.

2-(β-Styryl)-*N*-methylimidazole (13). A procedure similar to that used for the synthesis of 2-benzyl-*N*-methylimidazole **(3)** was employed. From (methylamino)acetaldehyde dimethyl acetal (1.67 g, 14.0 mmol) and cinnamimidoyl ethyl ether hydrochloride (2.96 g, 14.0 mmol) (prepared following a general procedure)[33] ***N*-methyl-*N*-(2,2-dimethoxyethyl)cinnamamidine hydrochloride** (1.87 g, 6.6 mmol, 47.1%), mp 180−183 °C, was obtained: ^{1}H NMR ($CDCl_3$) δ 10.1 (broad, 1 H), 9.7 (broad, 1 H), 8.20 (d, 1 H, J = 17.5), 7.65 (m, 2 H), 7.35 (m, 3 H), 6.70 (d, 1 H), 4.50 (t, 1 H, J = 5.1), 3.60 (d, 2 H), 3.50 (s, 3 H), 3.40 (s, 6 H). Anal. Calcd for $C_{14}H_{20}N_2O_2$·HCl: C, 59.05; H, 7.43; N, 9.84. Found: C, 58.97; H, 7.18; N, 9.96. From *N*-methyl-*N*-(2,2-dimethoxyethyl)cinnamamidine hydrochloride (1.83 g, 6.4 mmol) crude product **13** was obtained as an orange solid (0.91 g, 4.9 mmol, 76.6%): mp 70−72 °C (mp 80 °C, hexane); ^{1}H NMR ($CDCl_3$) δ 7.65−7.18 (m, 5 H), 7.60 (d, 1 H, J = 16.5), 7.07 (d, 1 H, J = 1.1), 6.90 (d, 1 H), 6.87 (d, 1 H), 3.75 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 144.90, 136.60, 130.40, 128.63, 128.16, 127.85, 126.67, 122.21, 114.64, 32.22. Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.56; N, 15.20. Found: C, 78.23; H, 6.57; N, 15.21.

2-(β-Styryl)-*N*-methylbenzimidazole (16). A procedure similar to that used for the synthesis of 2-benzyl-*N*-methylbenzimidazole **(6)** was employed. From *N*-methyl-*o*-phenylenediamine[34] (1.16 g, 9.5 mmol) and cinnamimidoyl ethyl ether hydrochloride (2.01 g, 9.5 mmol) the crude product was obtained as a dark oil (1.33 g, 5.7 mmol, 60.0%), which was purified by flash chromatography (CH_2Cl_2−AcOEt, 2:1) on silica gel to provide the pure product as a white solid (0.39 g, 1.7 mmol, 17.9%): mp 114 °C (cyclohexane) (lit.[40] mp 113−114 °C); ^{1}H NMR ($CDCl_3$) δ 7.96 (d, 1 H, J = 15.7), 7.82−7.72 (m, 1 H), 7.60 (dd, 1 H, J = 7.5, J = 1.8), 7.44−7.18 (m, 6 H), 7.10 (d, 1 H), 3.85 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 150.91, 142.77, 136.03, 135.97, 135.82, 128.87, 128.78, 127.43, 122.03, 121.95, 118.43, 114.37, 110.11, 29.55. Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.06; H, 6.02; N, 11.88.

JO951884L

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