N-(1-Haloalkyl)pyridinium Salts: Preparation and Use for New Syntheses of Other *N*-(1-Substituted-alkyl)pyridinium Salts, *N*,*N*'-(1-Alkylidene)bisamines, and *N*,*N*'-(1-Alkylidene)bisbenzazoles‡

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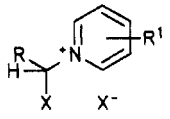
N-(1-Haloalkyl)pyridinium halides, obtained from an aldehyde, a thionyl halide, and pyridine, react readily with nucleophiles to yield *N*-(1-substituted-alkyl)pyridinium salts. *N*-(1-Bromoalkyl)pyridinium bromides react readily with a wide range of nucleophiles to replace either the halogen (by 1 mol) or both halogen and pyridinium (2 mol). They are useful precursors for the preparation of bisbenzazoles and other aminals under neutral and mild conditions.

One of our research groups recently reported the first preparation of *N*-(1-haloalkyl)heteroarylium salts 1 from an aldehyde, thionyl halide, and a heterocycle, in a preliminary communication,[1] and outlined some of their synthetic potential in nucleophilic displacement reactions. We now provide full details of this work and demonstrate that such salts, and more particularly *N*-(1-bromoalkyl)-pyridinium bromides, are highly efficient precursors for a range of *N*-(1-substituted-alkyl)pyridinium salts **2** and, further, for compounds in which both bromine and the pyridinium group have been substituted.



Structure 1

Pyridinium salts with an α-halogen atom in the N-substituent were almost unknown before our work.[2] The few attempted preparations did not proceed in satisfactory yields.[3] Even if a large excess of a dihalomethane is present in the reaction with pyridine, the bispyridinium adduct is formed,[3a] while with other tertiary amines (e.g., trimethylamine, DABCO, etc.) stable α-halogeno ammonium salts are produced. Therefore, the method that we now present is the first useful reaction for the preparation of a wide range of compounds 1.

We find that α-chloro or α-bromo compounds 1 are readily available from the reaction of pyridine and an aldehyde with thionyl chloride or bromide in dichloromethane at −50 °C under a nitrogen atmosphere. The reaction is applicable to both aliphatic and aromatic aldehydes and can be extended to substituted pyridines and other N-heterocycles such as isoquinoline and 1-methylimidazole (see Table I). These novel salts have been characterized microanalytically and by their ^{1}H and ^{13}C NMR spectra (see Table II).

A characteristic feature of these compounds is the relative position of both C and H signals in ^{1}H and ^{13}C NMR spectra, respectively. The range of the C*H* protons between δ 9.5 and 7.7 indicates their acidic character. There is only a weak influence asserted by the α-halogen atom on the chemical shift of the CH signal. Changing the other α-substituent influences the position more strongly. The C*H* signals of compounds with aliphatic chains are observed at a relatively high field whereas the negative σ-effect of aromatic rings causes a shift to lower field (see Table II).

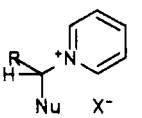
Table I. Preparation of *N*-(1-Haloalkyl)heteroarylium Halides 1a–k[a]

no.	R	X	heterocycle	yield, %	mp, °C
1a	4-MeC_6H_4	Cl	pyridine	83	171–172[b]
1b	4-MeC_6H_4	Cl	4-*tert*-butylpyridine	81	222 dec
1c	4-MeC_6H_4	Cl	3-methylpyridine	86	oil[b]
1d	$(C_6H_5)_2CH$	Cl	pyridine	82	189–190
1e	ethyl	Cl	pyridine	89	94–96[b]
1f	4-MeC_6H_4	Cl	isoquinoline	69	88–90
1g	4-MeC_6H_4	Cl	1-methylimidazole	66	141–142
1h	4-MeC_6H_4	Br	pyridine	92	175–177
1i	ethyl	Br	pyridine	68	80–83
1j	*n*-propyl	Br	pyridine	73	oil[c]
1k	C_6H_5	Br	pyridine	85	oil[c]

[a] Satisfactory analytical data (±0.3 for C, H, N) were obtained. [b] Compounds **1a,c,e** are very hygroscopic, but the corresponding hexachloroantimonates are stable and analyses were made: **1a'**, 92%, mp 127–129 °C; **1c'**, 94%, mp 160–161 °C; **1e'**, 94%, mp 126–127 °C. [c] Compounds **1j** and **1k** were very hygroscopic, and **1j** is unstable: the structures were assigned from spectral data (see Table II).

The range of the C*H* carbon shifts between δ 66.4 and 95.1 is typical of carbons carrying two electronegative substituents. This could be a hint for the observed overall ease of substitution reactions at this center. However, there are no characteristic differences in the δ ^{13}C values caused by the electronic and structural properties of these substituents (R).

Conversion of *N*-(1-Haloalkyl)pyridinium Halides 1a,e,h into Other *N*-(1-Substituted-alkyl)pyridinium Derivatives 2a–i. We have found that a variety of neutral and anionic nucleophiles readily effect such conversions (Table III).



Structure 2

‡ This paper is dedicated to Professor Dr. Ernst Ruch on the occasion of his 70th birthday.

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§ University of Florida.

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Table II. Spectral Data of *N*-(1-Haloalkyl)heteroarylium Halides 1a–k in $CDCl_3$

	^{13}C NMR: δ (ppm)			^{1}H NMR: δ (ppm)		
no.	aromatic carbons	*C*HX	others	aromatic protons	C*H*X	other protons
1a	146.7, 142.0, 140.1, 129.3, 128.6, 127.7, 125.9	76.8	19.7	9.9 (d, 2 H), 8.9 (m, 1 H), 8.4 (m, 2 H), 7.8 (d, 2 H), 7.3 (d, 2 H)	9.2 (s)	2.3 (s)
1b	172.9, 142.9, 141.9, 130.8, 129.8, 127.4, 125.4	77.6	36.7, 29.7, 21.0	10.2 (d, 2 H), 9.0 (m, 1 H), 8.4 (m, 2 H), 7.9 (d, 2 H), 7.3 (d, 2 H)	9.5 (s)	2.4 (s)
1c[a]	150.0, 143.6, 142.6, 141.9, 141.5, 131.5, 130.9, 129.4, 128.5	95.1	21.1, 18.7	9.3 (s, 1 H), 9.2 (m, 1 H), 8.7 (m, 1 H), 8.3 (m, 1 H), 7.7 (d, 2 H), 7.3 (d, 2 H)	8.1 (s) [9.2 (s)][b]	2.7 (s), 2.4 (s)
1d	148.6, 143.8, 139.1, 138.1, 128.8, 128.6, 128.1, 127.7	79.6	57.9	10.1 (d, 2 H), 9.0–7.0 (m, 14 H)		5.8 (d)
1e[a]	149.6, 143.9, 130.1	82.9	10.2, 6.1	9.5 (d, 2 H), 9.0 (m, 1 H), 8.5 (m, 2 H)	7.0 (t) [7.7 (t)][b]	2.7 (dq), 1.1 (t)
1f	150.1, 141.2, 138.1, 137.8, 131.8, 131.5, 130.9, 130.8, 129.8, 127.3, 127.0	78.4	28.4	12.0 (s, 1 H), 9.1–7.1 (m, 10 H)	9.4 (s)	2.3 (s)
1g	139.2, 135.8, 130.6, 128.3, 125.7, 123.3, 119.4	68.5	19.7	11.0 (s, 1 H), 8.0 (d, 1 H), 7.7–7.1 (m, 5 H)	8.4 (s)	4.1 (s, 3 H), 2.3 (s, 3 H)
1h	147.4, 143.3, 141.3, 130.2, 129.8, 128.7, 128.1	67.1	20.8	9.7 (d, 2 H), 8.5 (m, 1 H), 8.1 (m, 2 H), 7.6 (d, 2 H), 6.9 (d, 2 H)	9.0 (s)	2.1 (s)
1i	148.9, 146.3, 127.7	88.0	25.1, 8.6	10.1 (d, 2 H), 9.1 (m, 1 H), 8.5 (m, 2 H)	7.8 (t)	2.8 (dq), 1.2 (t)
1j	147.1, 142.3, 128.3	67.7	40.4, 18.6, 11.9	9.7 (d, 2 H), 8.7 (m, 1 H), 8.4 (m, 2 H)	8.8 (t)	2.8 (q, 2 H), 2.5–0.7 (m, 5 H)
1k	147.1, 142.6, 139.7, 130.2, 128.5, 128.3, 127.9	66.4		9.8 (d, 2 H), 8.8 (m, 1 H), 8.4 (m, 2 H), 7.9 (m, 3 H), 7.4 (d, 2 H)	9.2 (s)	

[a] Spectral data of the corresponding hexachloroantimonates. [b] Value of the corresponding chloride.

Table III. Reaction of *N*-(1-Haloalkyl)pyridinium Halides 1 with Nucleophiles[a]

no.	X	salt 1	nucleophile	yield, %	mp, °C
2a	Br	**1h**	F^-	71	132–134
2b	–	**1a**	SO_3^{2-}	46	256
2c	–	**1e**	SO_3^{2-}	25	260
2d	–	**1a**	CS_3^{2-}	37	109–110
2e	2Br	**1h**	PPh_3	95	105–109 dec
2f	2Cl	**1a**	PPh_3	91	106–107[b]
2g	Br	**1h**	phthalimide	86	106–107
2h	Br	**1h**	PhS^-	85	*c*
2i	2Br	**1h**	1-methylimidazole	93	98–99

[a] Satisfactory analytical data (±0.3 for C, H, N) were obtained. [b] Compound is hygroscopic: therefore the corresponding hexachloroantimonate was prepared: yield 88%; mp 125–128 °C. [c] Compound is very hygroscopic: melting point and analysis cannot be obtained.

Thus, sulfite dianion yields *N*-(1-sulfonatoalkyl)pyridinium betaines **2b** and **2c** from **1a** and **1e**. Similar conversions were reported earlier[4] with *N*-[1-(acyloxy)alkyl]pyridinium salts (X = R′COO). The yields obtained with the salts **1a** and **1e** are lower in this case because of the two-phase-reaction system (water/dichloromethane). Under these conditions, a partial hydrolysis of the halides cannot be avoided.

Salt **1a** simply yields the expected betaine **2d** with trithiocarbonate dianion. Such pyridinium betaines have not been reported previously.

Triphenylphosphine and both **1a** and **1h** give the expected bisonium cations **2e** and **2f**. These bisonium salts were characterized by their respective ^1H NMR signals of the C*H* atoms at low field (δ 11.0 and 10.5, respectively). This reflects the expected acidic character of this moiety.

Halogen exchange in **1h** is effected by CsF, sodium thiophenolate, potassium phthalimide, and 1-methylimidazole to produce the 1-fluoroalkyl derivative **2a**, the 1-phenylthio-substituted product **2h**, the 1-phthalimide derivative **2g**, and the bisonium cation **2i**, respectively.

This variety of products characterizes the expected wide range of applicability of **1** in nucleophilic substitution reactions. We suggest that further examples for this reaction mode can be produced easily.

Reaction of *N*-(1-Haloalkyl)pyridinium Halides with N-Nucleophiles. Reaction products of **1** with N-nucleophiles **3** depend strongly on the nature of **3** (Scheme I). The first reaction of **1** with all N-nucleophiles **3** is a simple substitution of the halogen atom to give the mixed bisonium salts **4**. This is the final product for N-heterocycles not containing an NH group: such unsymmetrical bisonium salts as **2i** appear to have been previously unknown, and the symmetrical salts have themselves received little attention.[3a,5]

Spectral data of this bisonium salt **2i** are only slightly different from those of the corresponding phosphonio pyridinium salts mentioned above. Both the ^1H NMR and the ^{13}C NMR signal of the CH moiety (δ 9.2 and 79.6) show a small shift to higher field (see Experimental Section).

The initial products **4** from primary and secondary amines are deprotonated by excess amines to give the corresponding *N*-(1-aminoalkyl)pyridinium salts **5**. These intermediates have never been isolated because of their lability toward nucleophiles (see below).

The *N*-(1-aminoalkyl)pyridinium salts **5** are expected to exist in equilibrium with pyridine and the immonium salt **8** (Scheme II), as shown previously for the analogous equilibria (ionization) of 1-(1-aminoalkyl)benzotriazoles.[6] This behavior is another demonstration of the anomeric effect of the free electron pair on the amino nitrogen atom with the σ* orbital of the exocyclic C–N bond predicted previously by MNDO calculations.[7] The pyridine thus

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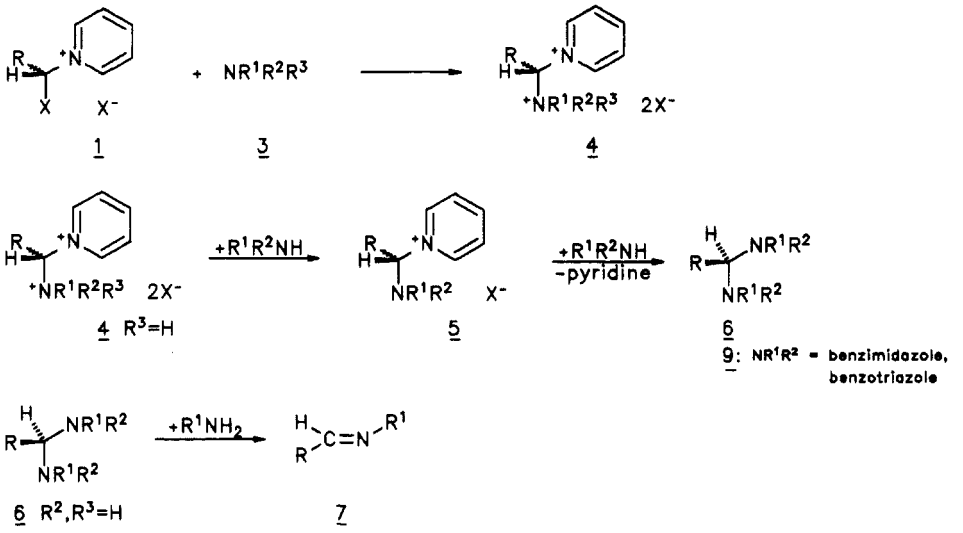
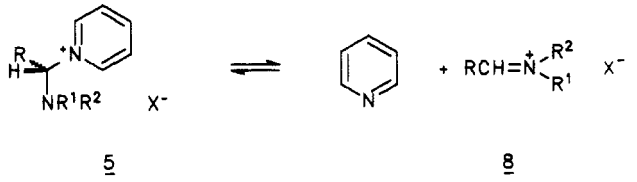
Scheme I



Scheme II



set free is able to compete for unreacted **1** because of its high nucleophilicity, giving the symmetrical bispyridinium salts. Previous preparation of symmetrical **6** required more drastic conditions (boiling under reflux by using a water separator) and long reaction times.[8] The immonium salts **8** derived from primary amines are deprotonated to imines **7**, while salts **8** from secondary amines add a second mole of amine to give aminals **6**. In our experiments we found that diamines **6c** and **6d** can also be obtained in good yields in one-step reactions.

The effect of the free electron pair in the above reactions of amines (Scheme II) is underlined by the behavior of **1** with potassium phthalimide: the first product **4** (Table III, compound **2g**) is stable; the delocalization of the N electron pair into the two C=O groups weakens the anomeric effect so that no further reaction occurs.

Few *N,N'*-(1-alkylidene)bisazoles or -bisbenzazoles have been described in the literature. Most of the publications deal with polyazolylmethanes and were prepared under phase-transfer conditions from the parent heterocycle and dichloromethane.[9] Extension of that method to the preparation of phenylmethane derivatives from benzal chloride has been achieved in the pyrazole series[10] but could not be generalized to other heterocycles.[11] Geminal bisindazolyl or bisbenzotriazolyl compounds were obtained by reaction of the heterocycle with an aldehyde and either zinc chloride as catalyst[9] or thionyl chloride in excess.[12] These methods have, however, not been applied to a wider range of (benz)azoles.

Alternatively, an activation of the carbonyl reagent as an acetal[11] or a ketal[13] seems at present to be the most convenient approach for the preparation of *N,N'*-(1-alkylidene)bisazoles or -bisbenzazoles. However, only the benzaldehyde dimethyl acetal has been reacted with a large variety of (benz)azoles, and the yields reported are moderate to good.[11]

We have found that the activation of the aldehyde reagent by its conversion into a stable *N*-(1-haloalkyl)-pyridinium halide **1** and further reaction without isolation with the sodium salt of a (benz)azole provides a new method for the preparation of *N,N'*-(1-alkylidene)bisbenzazoles **9** under mild conditions. This is illustrated by the synthesis of **9a–d** (Table IV).

Table IV. Reaction of *N*-(1-Haloalkyl)pyridinium Halides 1 with Sodium Salts of (Benz)azoles

no.	R	X	(benz)azole	time, h	yield, %
9a	4-MeC_6H_4	Br	benzimidazole	3	50[a]
9a	4-MeC_6H_4	Cl	benzimidazole	1[b]	43[a]
9b	phenyl	Br	benzimidazole	3	58[a]
9c	4-MeC_6H_4	Br	benzotriazole	0.5[b]	70[c]
9c	4-MeC_6H_4	Cl	benzotriazole	2	62[c]
9d	*n*-C_3H_7	Br	benzotriazole	–	37[c]

[a] Ethyl acetate was used for column chromatography. [b] With longer reaction times, a brown oily residue was obtained. [c] Methylene chloride was used as solvent for chromatography.

Experimental Section

General. Melting points were determined on a hot-stage microscope and are uncorrected. ^1H NMR spectra were recorded on a Varian XL (200 MHz, FT mode) spectrometer and a JEOL JNM-PMX (60 MHz) instrument with TMS as internal standard. ^{13}C NMR spectra were recorded on Varian XL 200 (50 MHz), JEOL JNM-PS 100 (25 MHz), and JEOL JNM-GX 400 FT (100 MHz) instruments referenced to δ $CDCl_3$ = 77.0, δ DMSO-d_6 = 39.5, or δ acetone-d_6 = 29.8. Elemental analyses were carried out under the supervision of Dr. R. W. King (University of Florida) on a Carbo Erba 110 G elemental analyzer and of Dr. A. Haag (Universität Erlangen-Nürnberg) on a HERAEUS CHN-MIK-ROMAR elemental analyzer.

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Materials. Aliphatic and aromatic aldehydes were purchased from Aldrich Chemical Co. and were distilled before use. Amines were bought from Fisher Scientific Co. and were dried and distilled before use. Thionyl halides were from Aldrich and were used as received.

Benzazoles were purchased from Aldrich and were kept under vacuum before use. Solvents and reagents (from Fisher) were purified according to standard procedures and dried before use.

***N*-(1-Haloalkyl)pyridinium halides 1** were prepared according to the procedure reported in the literature.[1]

***N*-(1-Haloalkyl)pyridinium Hexachloroantimonates 1a',c',e'.** The salts 1 were prepared as above and were treated at −50 °C with the equivalent amount of antimony(V) chloride (data: see Tables I and II).

***N*-(1-Substituted-alkyl)pyridinium Halides 2a,e–i. General Procedure.** To a solution of the corresponding 1 (5 mmol) in dry chloroform (30 mL) was added nucleophile (5 mmol) (Table III) at 0 °C. After 1 h, the reaction mixture was treated with ethyl ether (60 mL) and the resulting solid was washed a few times with ether and dried under vacuum to give **2a,e–i** (Table III).

***N*-[Fluoro(4-methylphenyl)methyl]pyridinium bromide (2a)**: ^{1}H NMR ($CDCl_3$) δ 9.8 (d, 2 H, H_2,H_6-pyridine), 8.9 (d, 1 H, CH, $^2J_{HF}$ = 47 Hz), 8.8 (m, 1 H, H_4-pyridine), 8.4 (m, 2 H, H_3,H_5-pyridine), 7.8 (d, 2 H, benzene ring), 7.3 (d, 2 H, benzene ring), 2.3 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 147.6, 143.5, 130.3, 129.9, 129.5, 128.8, 128.2, 67.2, 20.9.

***N*-[(Triphenylphosphonio)(4-methylphenyl)methyl]pyridinium dibromide (2e)**: ^{1}H NMR ($CDCl_3$) δ 10.5 (d, 1 H, CH, $^2J_{PH}$ = 14 Hz), 10.0 (d, 2 H, H_2,H_6-pyridine), 9.0 (m, 1 H, H_4-pyridine), 8.5 (m, 2 H, H_3,H_5-pyridine), 8.2–7.6 (m, 17 H, aromatic protons), 7.3 (d, 2 H, aromatic protons), 2.3 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 147.7, 145.2, 145.1, 142.9, 136.3, 135.0, 134.8, 131.2, 131.1, 131.0, 124.3, 114.2, 113.3, 21.1.

***N*-[(Triphenylphosphonio)(4-methylphenyl)methyl]pyridinium dichloride (2f)**: ^{1}H NMR ($CDCl_3$) δ 11.0 (d, 1 H, CH, $^2J_{PH}$ = 14 Hz), 10.2 (d, 2 H, H_2,H_6-pyridine), 9.0–7.0 (m, 22 H, aromatic protons), 2.3 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) (of corresponding hexachloroantimonate) δ 150.2, 143.9, 137.6, 137.5, 137.4, 136.3, 136.0, 132.2, 131.7, 131.0, 125.5, 116.8, 116.7, 113.4, 89.2, 6.3.

***N*-[Phthalimido(4-methylphenyl)methyl]pyridinium bromide (2g)**: ^{1}H NMR ($CDCl_3$) δ 9.5 (d, 2 H, H_2,H_6-pyridine), 8.9 (m, 1 H, H_4-pyridine), 8.8 (s, 1 H, CH), 8.4 (m, 2 H, H_3,H_5-pyridine), 7.9 (s, 4 H, aromatic protons), 7.4 (q, 4 H, benzene ring), 2.3 (s, 3 H CH_3); ^{13}C NMR ($CDCl_3$) δ 165.4, 147.1, 143.9, 134.5, 129.8, 129.1, 128.7, 127.4, 126.6, 126.2, 123.3, 74.2, 20.2.

***N*-[(4-Methylphenyl)(phenylthio)methyl]pyridinium bromide (2h)**: ^{1}H NMR ($CDCl_3$) δ 9.7 (d, 2 H, H_2,H_6-pyridine), 9.6 (s, 1 H, CH), 8.9–7.0 (m, 12 H), 2.2 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 145.9, 142.7, 140.6, 132.9, 130.3, 129.8, 129.4, 129.2, 128.4, 127.8, 127.3, 77.4, 20.8.

***N*-[(1-Methylimidazolo)(4-methylphenyl)methyl]pyridinium dibromide (2i)**: ^{1}H NMR (DMSO) δ 9.7–9.5 (m, 3 H, aromatic protons), 9.4 (s, 1 H, CH), 8.9 (m, 1 H, H_4-pyridine), 8.5–8.1 (m, 4 H, aromatic protons), 7.4 (s, 4 H, benzene ring), 3.9 (s, 3 H, NCH_3), 2.3 (s, 3 H, CH_3); ^{13}C NMR (DMSO) δ 148.8, 143.6, 141.4, 139.1, 130.2, 129.0, 127.9, 127.2, 125.4, 121.5, 79.6, 36.5, 20.8.

***N*-(1-Substituted-alkyl)pyridinium Betaines 2b–d. General Procedure.** To a solution of the corresponding 1 (5 mmol) in dry dichloromethane (30 mL) was added nucleophile (5 mmol) (Table III) dissolved in water (20 mL). After 1 h, the resulting solid was filtered off, washed a few times with water and then a few times with ether, and dried under vacuum to yield **2b–d** (Table III).

***N*-[Sulfonato(4-methylphenyl)methyl]pyridinium betaine (2b)**: ^{1}H NMR (DMSO) δ 9.4 (d, 2 H, H_2,H_6-pyridine), 8.7–7.2 (m, 7 H, aromatic protons), 7.0 (s, 1 H, CH), 2.3 (s, 3 H, CH_3); ^{13}C NMR (DMSO) δ 146.3, 144.4, 139.2, 129.9, 129.5, 129.3, 127.7, 83.2, 20.7.

***N*-(1-Sulfonatopropyl)pyridinium betaine (2c)**: ^{1}H NMR (D_2O) δ 9.0 (d, 2 H, H_2,H_6-pyridine), 8.7 (m, 1 H, H_4-pyridine), 8.2 (m, 2 H, H_3,H_5-pyridine), 5.6 (t, 1 H, CH), 2.5 (m, 2 H, CH_2), 1.0 (t, 3 H, CH_3); ^{13}C NMR (D_2O) δ 149.2, 145.7, 129.9, 86.1, 24.4, 10.6.

***N*-[Trithiocarbonato(4-methylphenyl)methyl]pyridinium betaine (2d)**: ^{1}H NMR (DMSO) δ 9.7 (d, 2 H, H_2,H_6-pyridine), 8.8–7.0 (m, 8 H, CH and aromatic protons), 2.3 (s, 3 H, CH_3); ^{13}C NMR (DMSO) δ 146.8, 143.5, 142.4, 139.8, 132.5, 129.9, 128.1, 127.0, 79.0, 20.7.

Bisaminals 6 and Imines 7. General Procedure. To a solution of **1h** (5 mmol) in dry chloroform (30 mL) was added the corresponding amine (15 mmol) at 0 °C. The reaction mixture was stirred for an additional 4 h. Solvent was evaporated, and a solid residue was treated with ethyl ether (50 mL). The salts were filtered off, the solution was evaporated, and the corresponding amines **6a,b** and imines **7a–c** were purified by recrystallization.

Bis(piperidino)(4-methylphenyl)methane (6a): yield 47.6%; mp 43–44 °C (acetone); ^{1}H NMR ($CDCl_3$) δ 7.1 (s, 4 H, benzene ring), 3.5 (s, 1 H, CH), 2.6–2.2 (m, 11 H), 1.7–1.3 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 136.3, 133.2, 128.5, 127.9, 89.5, 50.2, 26.3, 25.4, 21.1. Anal. Calcd for $C_{18}H_{28}N_2$: C, 79.33; H, 10.37; N, 10.30. Found: C, 79.19; H, 10.36; N, 10.12.

Bis(morpholino)(4-methylphenyl)methane (6b): yield 57.5%; mp 88 °C (acetone) (lit.[14] an oil was obtained); ^{1}H NMR ($CDCl_3$) δ 7.1 (s, 4 H, benzene ring), 3.8–3.5 (m, 9 H), 2.6–2.3 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 137.3, 131.0, 128.7, 128.4, 88.9, 67.2, 49.6, 21.1. Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.52; H, 8.76; N, 10.13. Found: C, 69.59; H, 8.68; N, 10.07.

***N*,*N*'-Bis[(4-methylphenyl)methylene]-1,2-diaminoethane (7a)**: yield 45.5%; mp 127–128 °C (acetone) (lit.[15] 127–132 dec); ^{1}H NMR ($CDCl_3$) δ 8.2 (s, 2 H, vinyl CH), 7.6 (dd, 4 H), 7.1 (dd, 4 H), 3.9 (s, 4 H), 2.3 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 162.4, 140.7, 133.5, 129.1, 127.9, 61.6, 21.4.

***N*-[(4-Methylphenyl)methylene]cyclohexylamine (7b)**: yield 43.8%; bp_{14} 101 °C (lit.[16] bp 312 °C); ^{1}H NMR ($CDCl_3$) δ 8.3 (s, 1 H, vinyl CH), 7.7 (dd, 2 H), 7.2 (dd, 2 H), 2.3 (s, 3 H), 2.3–1.2 (m, 11 H, cyclohexyl); ^{13}C NMR ($CDCl_3$) δ 158.2, 140.3, 133.9, 129.0, 127.9, 69.9, 34.3, 25.5, 24.7, 21.3.

***N*-[(4-Methylphenyl)methylene]aniline (7c)**: yield 65.6%; mp 49.0–51.5 °C (lit.[17] mp 46.5–48 °C).

***N*,*N*'-(1-Alkylidene)bisbenzazoles 9a–c and -bisamines 6c,d. General Procedure.** To a solution of a pyridinium salt prepared from thionyl halide (5 mmol), dry pyridine (5 mmol), and the corresponding aldehyde (5 mmol) in 15 mL of dry methylene chloride was added the sodium salt of the corresponding benzazole (10 mmol) or the amine (15 mmol) at −50 °C under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature and then was stirred according to the time given in Table IV for bisbenzazoles and 1 h for bisamines. The solids were removed by filtration, the solution was evaporated, and the residue was washed with the mixture petroleum ether/benzene (1:1) (2 × 10 mL), dried, chromatographed (in the case of benzimidazole and benzotriazole derivatives **9a–d**), and then recrystallized. Their analytical data and ^{1}H and ^{13}C NMR spectra confirmed that structures previously assigned.[17,18]

Bis(morpholino)phenylmethane (6c): yield 40%; mp 97.0–98.5 °C (lit.[17] mp 101.0–101.5 °C); ^{13}C NMR ($CDCl_3$) δ 134.1, 128.8, 127.7 (two peaks), 89.1, 67.1, 49.1.

Bis(piperidino)phenylmethane (6d): yield 52%; mp 80–81 °C (lit.[18] mp 81.0–81.5 °C); ^{13}C NMR ($CDCl_3$) δ 136.9, 129.2, 127.6, 90.4, 50.8, 26.9, 26.0.

Bis(benzimidazolo)(4-methylphenyl)methane (9a): mp 198.0–199.5 °C (benzene); ^{1}H NMR ($CDCl_3$) δ 7.97 (s, 1 H, CH), 7.81 (d, 2 H), 7.73 (d, 2 H, *J* = 8.0 Hz), 7.25–7.01 (m, 10 H), 2.31 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 143.6, 140.9, 140.2, 132.5, 129.9, 126.6, 123.6, 122.9, 120.5, 109.7, 67.9, 20.8. Anal. Calcd for $C_{22}H_{18}N_4$: C, 78.08; H, 5.36; N, 16.55. Found: C, 78.43; H, 5.37; N, 16.68.

Bis(benzimidazolo)phenylmethane (9b): mp 188.0–191.5 °C (benzene/hexane); ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1 H, CH), 7.84 (dd, 2 H), 7.71 (dd, 2 H, *J* = 7.2 Hz), 7.44–7.15 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 143.8, 140.9, 133.0, 132.7, 130.3, 129.4, 126.8, 123.9, 123.2,

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120.8, 109.7, 68.5. Anal. Calcd for $C_{21}H_{16}N_4$: C, 77.76; H, 4.97; N, 17.27. Found: C, 77.81; H, 4.96; N, 17.22.

Bis(benzotriazolo)(4-methylphenyl)methane (9c): mp 182.5-184.0 °C (lit.[12] mp 183-185 °C); ^{13}C NMR ($CDCl_3$) δ 146.2, 140.0, 132.4, 129.9, 129.7, 128.4, 126.9, 124.7, 120.1, 110.8, 72.4, 21.1.

Bis(benzotriazolo)-*n*-propylmethane (9d): mp 109-111 °C (lit.[12] mp 107-108 °C); ^{13}C NMR ($CDCl_3$) δ 131.2, 128.1, 124.7, 110.5, 72.2, 40.9, 20.7, 14.3 (one carbon is not observed).

Bis(phenylthio)(4-methylphenyl)methane (10). To a solution of **1a** or **1h** (1 mmol) in dry acetonitrile (5 mL) was added sodium thiophenolate (2 mmol) at -30 °C under nitrogen. The reaction was completed within 15 min, and the solid was filtered off as soon as possible. The solution was evaported, and product was recrystallized from petroleum ether to yield **10** (50%): mp 72-73 °C (lit.[19] oil was obtained); ^1H NMR ($CDCl_3$) δ 7.54-6.80 (m, 14 H), 5.40 (s, 1 H, CH), 2.32 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 137.7, 136.6, 134.7, 132.2, 129.1, 128.7, 127.7, 127.6, 60.1, 21.1. Anal. Calcd for $C_{20}H_{18}S_2$: C, 74.49; H, 5.63. Found: C, 74.14; H, 5.58.

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Electrophilic Olefin Heterocyclization in Organic Synthesis.[1] Stereoselective Synthesis of 4,5-Disubstituted γ-Lactams by Iodine-Induced Lactam Formation of γ,δ-Unsaturated Thioimidates

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Iodine-induced lactamization of γ,δ-unsaturated thioimidates proceeds regioselectively to provide γ-lactams. The iodolactamization with allylic substituents brings about 1,2-asymmetric induction, which depends on the allyl groups. Transformation of the *cis*-4-hydroxy-5-(iodomethyl)pyrrolidin-2-one (**24a**) among these highly functionalized γ-lactams into several biologically active compounds is described. In addition, the conversion of an optically active form of **24a** is discussed.

Electrophile-mediated additions to olefins are among the most fundamental and versatile tools in organic synthesis.[2] Recent experimental and theoretical studies have contributed significantly to the understanding of the origin of the stereoselectivity observed during the electrophilic addition to chiral alkenes.[3] The stereoselective synthesis of functionalized 4-6-membered heterocyclic ring systems by such oxidative additions (electrophilic olefin heterocyclization) has been especially notable. Most of these examples, however, are confined to the cyclization with oxygen nucleophiles as exemplified by halogenolactonization and -etherification. We found that γ,δ-unsaturated thioimidates underwent regioselective iodine-induced cyclization based on diastereoselective intramolecular addition of an amino nucleophile to afford γ-lactams, and we developed approaches to the stereoselective formation of 4,5-disubstituted pyrrolidin-2-ones from β-substituted γ,δ-unsaturated thioimidates via 1,2-asymmetric induction (allylic chiral induction).[4,5] In this paper we describe the experimental details for the iodine-induced lactamization method and the synthesis of biologically active compounds with further manipulation of the resulting iodolactams containing functional groups.

Results and Discussion

Iodine-Induced Lactamization of γ,δ-Unsaturated Thioimidates. The iodolactamization of *N*-benzyl γ,δ-unsaturated thioimidate **2a**, prepared from the corresponding secondary thioamide **1a** by methylation with methyl iodide in the presence of potassium carbonate, can be performed by using iodine in tetrahydrofuran (THF) at 5 °C to give γ-lactam **3a** in 72% overall yield from **1a**. The use of other solvents (CH_2Cl_2 and acetonitrile) resulted in low yields (20-35%). Thioimidates **2b-d** and **4** bearing substituents at the olefin underwent regio- and diastereoselective iodine-induced cyclization to provide γ-lactams **3b-d** and **5** as single isomers, respectively (see Table I).[6]

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