Stereoselective Synthesis of Substituted Piperazines

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The treatment of allylarylamines with mercury(II) acetate in tetrahydrofuran followed by a double decomposition reaction with potassium bromide leads to *trans*-2,5-bis(bromomercuriomethyl)-1,4-diarylpiperazines (**2**). The stereochemistry of the reaction products has been elucidated by an ^{1}H-nmr spectroscopic study of the *trans*-2,5-dimethyl-1,4-diarylpiperazines (**3**) obtained by sodium borohydride reduction of **2** in alkaline media. The course of the reaction strongly depends on the steric demand of the groups attached to either the allylic group or the *ortho*-position in the aromatic ring of the starting amine (**1**).

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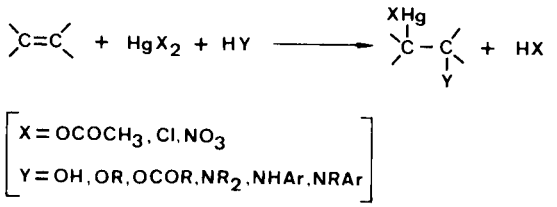
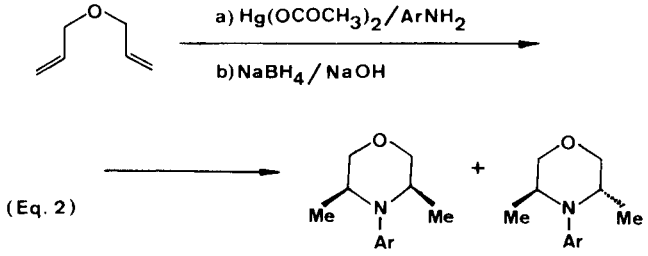
The addition of mercury(II) salts to olefines in a protic media has been extensively studied as a convenient route for the synthesis of β-oxy- and β-amino-substituted organomercurials (1) (Equation 1).



(Eq. 1)

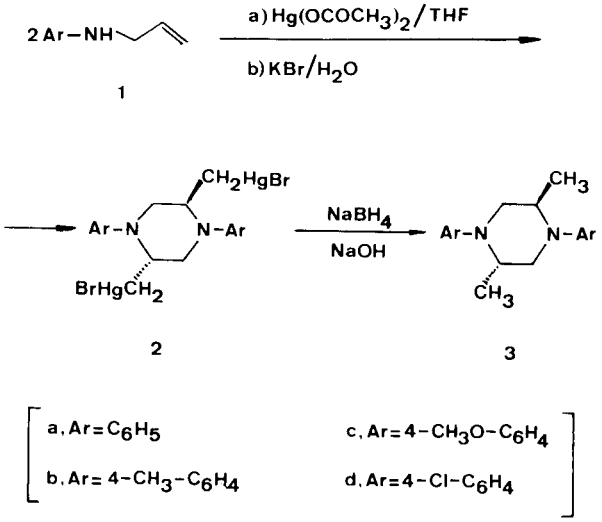
When suitable dienes and primary aromatic amines (2) are used, nitrogen-containing mercurated heterocyclic compounds are obtained through an aminomercuration followed by an intramolecular cyclization reaction (3). Aminomercuration of ω-unsaturated secondary amines (4) yields the same type of heterocyclic compounds as well. Sodium borohydride reduction in alkaline media (5) of mercurated heterocycles affords the corresponding demercurated compounds with good results. The reduction can also be carried out by transmetallation with metals of groups I and II followed by solvolysis (6).

No synthesis of heterocyclic compounds by stereoselective (7) aminomercuration reactions has been reported as yet. Mixtures of all possible stereoisomers (3,4) are always obtained. For instance, the reaction of diallylether with arylamines in the presence of mercury (II) acetate and subsequent reduction, takes place yielding a mixture of *cis*- and *trans*-2,6-dimethyl-*N*-arylmorpholines (3c) (Equation 2).



(Eq. 2)

We have now found a stereoselective aminomercuration reaction with intermolecular cyclization which leads to only one of the two possible stereoisomers. When *N*-allylarylamines **1** are allowed to react with mercury(II) acetate in tetrahydrofuran, *trans*-2,5-bis(bromomercuriomethyl)-1,4-diarylpiperazines **2** are obtained after a double decomposition reaction with potassium bromide (Equation 3).



(Eq. 3)

Reaction rate and yields of the mercuration process are not affected to a noticeable extent by the electronic effects associated with the substitution of various groups for hydrogen in the *para*-position of the starting amine (Table II). However, strong substituent steric effects are observed when different groups are attached to either the allyl residue or the *ortho*-position of the aromatic ring in **1** (8).

Starting *N*-allylarylamines **1** were obtained in high yields by metallation of primary arylamines with phenyllithium (9) and further alkylation with allylbromide (Table I).

Since aminomercurials **2** show very low solubility in common organic solvents, they were reduced with sodium borohydride in neutral or alkaline media in order to study the stereochemistry of the mercuration process. The

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Table I

N-Allylarylamines **1**

Compound No.	Ar	Yield (a) %	B.p. Range °C/15 Torr	Molecular Formula (b)	Analyses % Calcd. / Found C	H	N	^{1}H-Nmr (Carbon Tetrachloride) δ (Multiplicity) NH	CH_2-N	$=CH_2$	$=CH$	Ph	Other
1b (c)	4-CH_3-C_6H_4	77	124-127	$C_{10}H_{13}N$	81.58	8.90	9.51	3.3 (s)	3.6 (d), J = 5 Hz	5.1 (m)	5.8 (m)	6.6 (m)	2.5 (s)
				(147.2)	81.66	8.81	9.46						
1c	4-CH_3O-C_6H_4	82	128-131	$C_{10}H_{13}NO$	73.59	8.03	8.58	3.3 (s)	3.6 (d), J = 5 Hz	5.1 (m)	5.8 (m)	6.5 (m)	3.65 (s)
				(163.2)	73.51	7.94	8.64						
1d	4-Cl-C_6H_4	81	130-132	$C_9H_{10}ClN$	64.48	6.01	8.35	3.6 (s)	3.5 (d), J = 5 Hz	5.1 (m)	5.7 (m)	6.65 (m)	
				(167.6)	64.46	5.94	8.43						

(a) Based on starting arylamines; purity ≥ 95%. (b) Ir spectra were consistent with the proposed structures. (c) *Beilstein*, **12**, 905; II, 493.

Table II

trans-2,5-Bis(bromomercuriomethyl)-1,4-diarylpiperazines (**2**)

Compound No.	Ar	Time (Minutes)	Yield (a) %	M.p. (b) (°C, dec)	Molecular Formula (c)	Analyses % Calcd. / Found Hg	N
2a	C_6H_5	40	97	108-110	$C_{18}H_{20}Br_2Hg_2N_2$	48.61	3.39
					(825.4)	48.15	3.52
2b	4-CH_3-C_6H_4	30	93	126-128	$C_{20}H_{24}Br_2Hg_2N_2$	47.01	3.28
					(853.4)	46.77	3.01
2c	4-CH_3O-C_6H_4	10	98	165-167	$C_{20}H_{24}Br_2Hg_2N_2O_2$	45.35	3.16
					(885.4)	45.06	3.24
2d	4-Cl-C_6H_4	30	87	156-157	$C_{18}H_{18}Br_2Cl_2Hg_2N_2$	44.86	3.13
					(894.2)	44.97	3.02

(a) Based on starting *N*-allylarylamines, **1** (crude). (b) Uncorrected. (c) Ir spectra were consistent with the proposed structures.

Table III

trans-2,5-Dimethyl-1,4-diarylpiperazines **3**

Compound No.	Ar	Time	Yield % Hg(O)	**3** (a)	B.p. Range °C/0.001 Torr	M.p. (b) °C	Molecular Formula (c)	Analyses % Calcd. / Found C	H	N	^{1}H-Nmr (Carbon Tetrachloride) δ (Multiplicity) (d) CH_3-C	CH_2-N	CH-N	Ph	Other
3a	C_6H_5	22 hours	71	78	95-100	—	$C_{18}H_{22}N_2$	81.16	8.32	10.51	1.05 (d)	2.85 (m)	3.5 (m)	7.0 (m)	—
							(266.4)	81.28	8.14	10.50	J = 6Hz	3.25 (m)			
3b	4-CH_3-C_6H_4	1.5 hours	69	76	103-108	—	$C_{20}H_{26}N_2$	81.59	8.90	9.51	1.05 (d)	2.8 (m)	3.45 (m)	6.85 (m)	2.2 (s)
							(294.4)	81.07	8.75	8.81	J = 6Hz	3.15 (m)			
3c	4-CH_3O-C_6H_4	2 days	61	54	108-114	138-140 (e)	$C_{20}H_{26}N_2O_2$	73.59	8.03	8.58	1.05 (d)	2.9 (m)	3.5 (m)	6.9 (m)	3.75 (s)(f)
							(326.4)	73.15	7.89	8.41	J = 6Hz	3.2 (m)			
3d	4-Cl-C_6H_4	17 hours	67	56	110-115	138-139 (e)	$C_{18}H_{20}Cl_2N_2$	64.48	6.01	8.35	1.1 (d)	2.9 (m)	3.6 (m)	7.1 (m)	— (f)
							(335.3)	64.29	6.07	8.30	J = 6Hz	3.3 (m)			

(a) Based on mercury (O) precipitated; purity ≥ 95% by glc. (b) Uncorrected. (c)Ir spectra were consistent with the proposed structures. (d) The proton assignment was supported by a dnmr experiment. (e) White crystals (hexane). (f) In deuteriochloroform.

sodium borohydride reduction of **2**, which does not affect the stereochemistry of the aminomercuration products, affords exclusively *trans*-2,5-dimethyl-1,4-diarylpiperazines **3** (10) (Table III).

The ^{1}H-nmr spectra of the obtained piperazines **3** clearly show their *trans*-stereochemistry based on the found values for chemical shifts (see nmr data, Table III) and J_{H-H} coupling constants (Table IV). The observed values

Table IV

J_{H-H} Coupling Constants in Hz for Obtained Piperazines **3**

Compound No.	$J_{H_1-H_2}$	$J_{H_1-H_3}$	$J_{H_2-H_3}$
3a	3.5	6.5	12.0
3b	3.5	6.0	12.0
3c	3.5	6.0	12.0
3d	3.5	6.5	12.0

of the coupling constants $J_{H_1\text{-}H_2}$= 3.5, $J_{H_1\text{-}H_3}$= 6.0-6.5 and $J_{H_2\text{-}H_3}$= 12 Hz entirely correlate with those for a general model compound: $J_{H_1\text{-}H_2}$= 2-3, $J_{H_1\text{-}H_3}$= 5-10 and $J_{H_2\text{-}H_3}$= 12-15 Hz (11). The equivalency of both sets of protons H_1, H_2 and H_3 as well as the excellent agreement of their observed ^{1}H-nmr spectral pattern with that of a computed ABX spectra (12) also corroborates the proposed *trans*-structure for **3** (Figure 1).

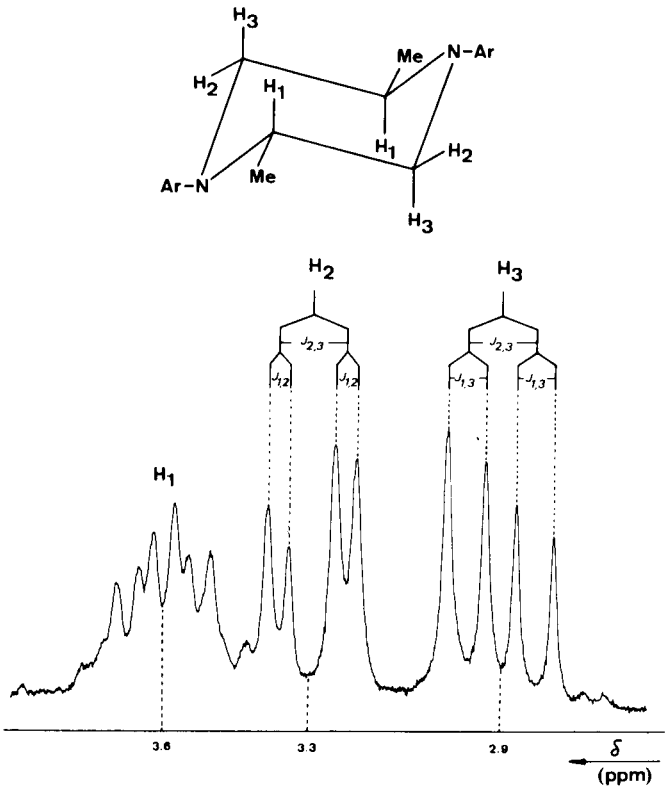

Figure 1. ^{1}H-Nmr absorption pattern for H_1, H_2 and H_3 in 3d.

Stereochemical requirements of the transition state would account for the observed selectivity in the course of the cyclization process. Once a first addition reaction has taken place, two molecular models for the transition state (with the bulky $CH_3COOHgCH_2$ in equatorial position in a chair conformation) can be depicted for the nitrogen *trans*-attack on the mercurinium ion, since two different mercurinium ions can arise. It can be shown that the transition state which leads to the obtained *trans*-piperazine bears the mercurinium ion in equatorial position (A). However, the *cis*-piperazine, which is never observed, would result from a less stable transition state carring the mercurinium ion in axial position (B) (Figure 2).

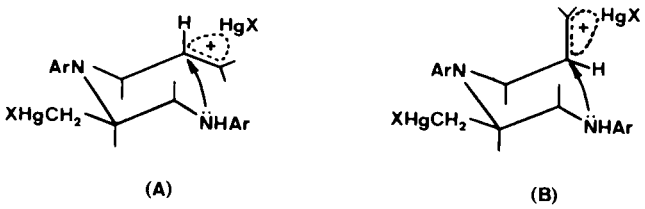

Figure 2

EXPERIMENTAL

General.

GC analyses were performed in a Varian Aerograph 2800 instrument equipped with a OV-101 Chromosorb column. Ir spectra were recorded in a Pye-Unicam SP-1000 spectrometer. Nmr spectra were recorded in a Varian EM-390 spectrometer and tetramethylsilane was used as internal reference. Elemental analyses of **1** and **3** were carried out with a Perkin-Elmer 240 Elemental Analyzer. Nitrogen in **2** was determined by Kjeldahl's method (13) and mercury by gravimetric analysis (13).

N-Allylarylamines **1**.

N-Allylaniline **1a** is commercially available (Aldrich, purity 97%). *N*-Allylamines **1** were synthesized according to the following general procedure.

An ethereal solution of 200 mmoles of arylamine under argon was placed in a flask equipped with a reflux condenser. To this was added dropwise, a 1.0*N* ethereal solution of phenyllithium (150 ml., 150 mmoles) over a period of 30 minutes. Allyl bromide (13.0 ml., 150 mmoles) was then added dropwise in 30 minutes and the mixture was allowed to react overnight at room temperature. The reaction was hydrolyzed with water, extracted with ether, the ethereal layer was dried over anhydrous sodium sulfate and then evaporated *in vacuo*. The residue was distilled at 15 torr with a 25 cm Vigreux column to give the product.

trans-2,5-Bis(bromomercuriomethyl)-1,4-diarylpiperazines **2**. General Procedure.

To a stirred tetrahydrofuran solution (100 ml.) of freshly distilled **1** (60 mmoles) were added mercury (II) acetate (19.1 g., 60 mmoles). Reactions were continued until no yellow precipitate of mercury (II) oxide was observed when a sample was treated with 3*N* potassium hydroxide. Tetrahydrofuran was evaporated *in vacuo* and the remaining oil was dissolved in a mixture of methanol/water (200/50 ml.). Addition of potassium bromide (11.5 g., 100 mmoles) leads to the precipitation of a yellow-brown solid which was washed with water, methanol and ether, dried, and then characterized as **2**. These aminomercurials could not be recrystallized.

Reduction of **2**. *trans*-2,5-Dimethyl-1,4-diarylpiperazines **3**. General Procedure.

To a stirred suspension of **2** (20 mmoles) in a mixture of aniline (20 ml.), tetrahydrofuran (50 ml.) and 0.5*N* sodium hydroxide (100 ml.), was added a solution of sodium borohydride (1.5 g., 39.7 mmoles) in 2.5*N* sodium hydroxide (20 ml.). The reaction was continued until no further precipitate of mercury (0) was noticeable. The reaction mixture was extracted with ether, the ethereal layer was washed with water, dried with anhydrous sodium sulfate and then evaporated *in vacuo* (0.1 torr). The residual oil was distilled at 0.001 torr to yield **3**. Solid products were further purified by recrystallization from hexane.

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(8) Mercuration in the presence of *N*-methallylaniline, *cis*- or *trans*-*N*-crotylaniline, *N*-(2-cyclohexenyl)aniline, *N*-allyl-*o*-toluidine and *N*-allyl-*o*-anisidine was unsuccessful. Mercuration of the aromatic ring was exclusively observed.

(9) For a review on N-H metallation and further alkylation see: Houben-Weyl, "Mettalorganische Verbindungen Li, Na, K, Rb, Cs, Cu, Ag, Au", Band 13/1, G. Thieme Verlag, Stuttgart, 1970, p. 250.

(10) A double deaminomercuration reaction to give the starting amine **1** takes place when **2** is reduced by lithium/aniline at 0°.

(11)R. M. Silverstein, G. C. Bassler and T. C. Morril, "Spectrometric Identification of Organic Compounds", Wiley, New York, N. Y., 1974, chapter 4.

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(14) Similar yields in **3** were obtained when the sodium borohydride reduction was carried out in a mixture of aniline, tetrahydrofuran and water (see reference 3c) instead of 0.5*N* sodium hydroxide.