Stereoselective Addition of Carbamates to Unsaturated Systems by Means of Mercury(II) Nitrate. Synthesis of Saturated Nitrogen-containing Heterocycles

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The aminomercuration of dienes with carbamates and mercury(II) nitrate affords, after in situ demercuration with sodium borohydride, stereoselectively saturated nitrogen-containing heterocycles. Thus, the corresponding amidomercuration-demercuration of 1,4- or 1,5-hexadiene, and diallyl ether gives respectively N-alkoxycarbonyl cis-2,5-dimethylpyrrolidines and trans-3,5-dimethylmorpholines. From 1,5-cyclooctadiene 9-alkoxycarbonyl-9-azabicyclo[3.3.1]- and [4.2.1]-nonanes (molar ratio ca. 1:1) are obtained. By amidomercuration-demercuration of N-allylurethane cis-N,N'-bis(ethoxycarbonyl)-2,5-dimethylpiperazine is obtained. The intermolecular amidomercuration of unsaturated systems results stereochemically opposite to the same aminomercuration process.

Introduction.

In connexion with our studies on mercuration reactions we have employed the tandem aminomercuration-demercuration process of appropriate dienic systems for the synthesis of saturated nitrogen heterocycles. In this way pyrrolidines [1], piperidines [2], morpholines [3], and piperazines [4] were obtained (Scheme I). When N-allylanilines were used as starting unsaturated systems trans-N,N'-diaryl-2,5-dimethylpiperazines [5] were stereoselectively prepared (Scheme I).

On the other hand, the recently discovered addition of amides and related compounds such as urethane or urea to olefins through an amidomercuration process [6]

Scheme I

$[X = (CH_2)_2, (CH_2)_3, CH_2OCH_2, CH_2N(R)CH_2]$
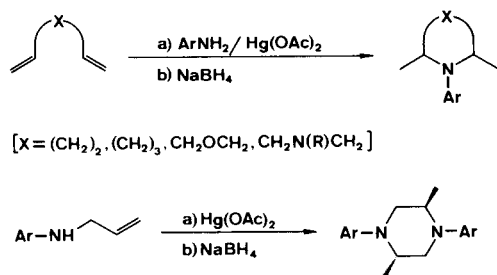
prompted us to use these nucleophilic agents in the above described synthesis of saturated nitrogen heterocycles. We have found that only the carbamates are adecuated nucleophiles for these cyclization reactions by means of an amidomercuration process.

Results and Discussion.

I. Synthesis of cis-N-Alkoxycarbonyl-2,5-dimethylpyrrolidines.

When 1,5-hexadiene was allowed to react with anhyd-

rous mercury(II) nitrate in the presence of N-ethyl or N-methylcarbamate in methylene dichloride followed by in situ demercuration with sodium borohydride in aqueous sodium hydroxide and n-butylamine as co-solvent the corresponding cis-N-alkoxycarbonyl-2,5-dimethylpyrrolidines **1** were obtained (Scheme II and Table I). The cyclization process is of interest due to its high yield, their stereoselectivity, and very available materials [7]. The cis stereochemistry was deduced by study of the ^{1}H- and ^{13}C-nmr data: the protons and carbons of the methyne and methyl groups should appear together in the cis isomer, while in the trans isomer they should appear separately [7,8]. Also, the ^{1}H-nmr chemical shifts for the methyne protons in the cis isomers appears at higher field than for the trans isomers [1,9,10].

Scheme II

1a, R = Me
1b, R = Et
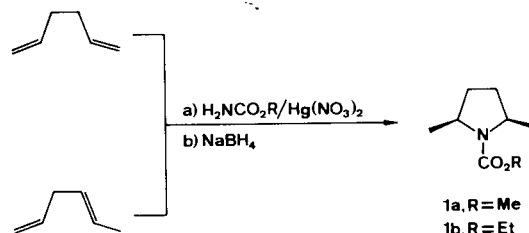
The treatment of 1,4-hexadiene ($\geq 95\%$ E-isomer from ^{13}C-nmr) with anhydrous mercury(II) nitrate and the same carbamates as above, followed by reduction with sodium borohydride leads to the corresponding cis-pyrrolidines **1** (Scheme II and Table I). In this case compounds **2** resulting from a monodesamidomercuration process were also obtained as by-product ($\leq 15\%$) [11]. The stereochemistry observed in the above intermolecular amidomercuration was the same as the obtained in the corresponding sulphonamidomercuration [6b]. However, the aminomercura-

tion reaction of the same dienes affords, after the subsequent reduction, mainly the corresponding *trans* isomers [1]. The possible mechanism to explain the stereoselective amidomercuration of 1,4- and 1,5-hexadiene described in this paper could be similar as proposed in the case of the sulphonamidomercuration [12].

2a, R=Me
2b, R=Et
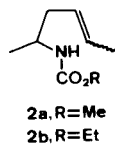
II. Synthesis of *N*-Alkoxycarbonyl-9-azabicyclo[3.3.1]- and [4.2.1]nonanes.

The intermolecular amidomercuration of 1,5-cyclooctadiene with carbamates and anhydrous mercury(II) nitrate and further demercuration with sodium borohydride leads to a mixture of *N*-alcoxycarbonyl-9-azabicyclo[3.3.1]- and [4.2.1]nonanes (isomer ratio *ca.* 1:1) (**3**) and (**4**) respectively [13] (Scheme III and Table I). The isomer ratio was determined by glc analysis as well as by ^{13}C-nmr data. Similar results were also obtained in the corresponding sulphonamidomercuration-demercuration of 1,5-cyclooctadiene [12].

Scheme III

3   **4**

a, R=Me
b, R=Et
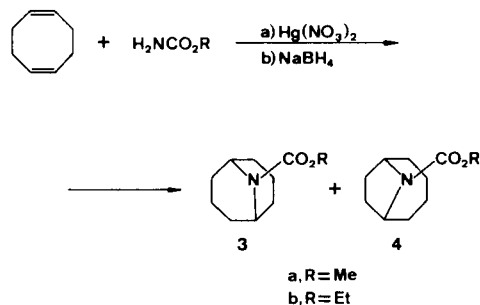
## III. Synthesis of *trans-N*-Alkoxycarbonyl-3,5-dimethylmorpholines.

The reaction of diallyl ether with anhydrous mercury(II) nitrate in the presence of *O*-ethyl or methyl carbamates followed by *in situ* reduction with sodium borohydride in alkaline media yielded *trans-N*-alkoxycarbonyl-3,5-dimethylmorpholines **5** stereoselectively (Scheme IV and Table I). The *trans* stereochemistry for the compounds **5** was deduced from ^{13}C-nmr data by comparison with the two isomers of 3,5-dimethylmorpholine [14] and their *N*-arylanalogues [3]. In this type of heterocycles the chemical shifts of the carbon atoms of the methyl and methyne groups of the *trans* isomer appear at higher fields than those of the *cis*. isomer [15]. The herein described amidomercuration of diallyl ether is more stereoselective than the aminomercuration of this diene [3] since in the last case a mixture of *cis*- and *trans*-3,5-dimethylmorpholines was obtained.

Starting Compound	Carbamate R	Product	Yields % [a] Product	Yields % [a] Hg(0)	Bp Range °C/torr
1,5-Hexadiene	Me	**1a**	96	99	80-3/15
	Et	**1b**	90	99	50-3/0.1
1,4-Hexadiene	Me	**1a** [b]	84	99	82-5/15
	Et	**1b** [c]	85	90	53-6/0.1
1,5-Cyclooctadiene	Me	**3a + 4a** [d]	80	99	120-3/15
	Et	**3b + 4b** [d]	90	98	71-3/0.1 [13]
Diallyl ether	Me	**5a**	48	93	80-3/15
	Et	**5b**	43	91	60-3/0.1
N-Allylurethane [e]	—	**6**	98	99	75-8/0.01

[a] Based on starting unsaturated systems. [b] By-product **2a** (15%) was also obtained. [c] By-product **2b** (8%) was also obtained. [d] Mixture *ca.* 1:1 molar ratio (by glc, Bentone **34** and diisodecyl phtalate). [e] Prepared from allylamine and ethyl chloroformiate [16].

Scheme IV

5a, R=Me
5b, R=Et
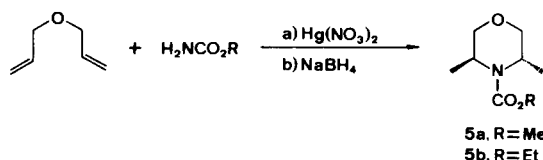
IV. Synthesis of *cis-N,N'*-Bis(ethoxycarbonyl)-2,5-dimethylpiperazine.

The intermolecular mercuration of *N*-allylurethane with anhydrous mercury(II) nitrate in methylene dichloride and further *in situ* demercuration with sodium borohydride in aqueous sodium hydroxide affords the corresponding *N,N'*-disubstituted *cis*-2,5-dimethylpiperazine (**6**) (Scheme V and Table I). The cyclization process is again stereoselective being the *cis*.configuration determinated by comparison of the spectral data of compound **6** with a mixture of the *cis* and *trans* isomers prepared by reaction of a commercially available mixture of *cis*- and *trans*-2,5-dimethylpiperazine with ethyl chloroformiate [16]. We have also found here the opposite stereochemistry by the mercuration of *N*-allylurethane respect to the corresponding

Scheme V

6
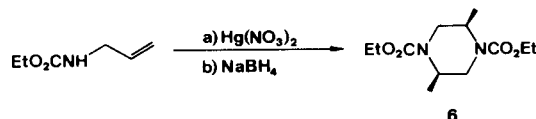
mercuration of *N*-allylanilines [5] that in the last case only the *trans* isomers were obtained.

It must be pointed out that in the amidomercuration reaction reported in this paper, the thermodinamically less stable compounds were formed: *cis*-pyrrolidines or cyclohexanes derivatives doubly substituted in the *e, a* posi-

Table II

Analytical and Spectral Data for Compounds 1, 3a + 4a, 5, and 6

Compound No.	Molecular Formula	Analyses % Calcd./Found			IR (neat) ν C=O cm^{-1}	¹H-NMR (carbon tetrachloride) [a] δ ppm	¹³C-NMR (carbon tetrachloride) [a] δ ppm
1a	$C_8H_{15}NO_2$ (157.2)	61.12 60.94	9.62 9.65	8.91 8.96	1700	1.2 (d, 6H, J = 6 Hz, 2 × CH₃C), 1.4-2.2 (m, 4H, 2 × CH₂), 3.6 (s, 3H, CH₃O), 3.85 (m, 2H, 2 × CH)	21.6 (q, CH₃C), 31.5 (t, CH₂), 51.2 (q, CH₃O), 54.0 (d, CH), 154.7 (s, C=O)
1b	$C_9H_{17}NO_2$ (171.2)	63.13 63.02	10.01 9.90	8.18 8.15	1700	1.2 (d, 6H, J = 6 Hz, 2 × CH₃CH), 1.25 (t, 3H, J = 6 Hz, CH₃CH₂), 1.4-2.1 (m, 4H, 2 × CH₂CH), 3.75-4.3 (m with q at 4.05, 4H, J = 6 Hz, 2 × CH + CH₂O)	14.4 (q, CH₃CH₂), 21.7 (q, CH₃CH), 31.5 (t, CH₂C), 54.0 (d, CH), 60.2 (t, CH₂O), 157.6 (s, C=O)
3a + 4a	$C_{10}H_{17}NO_2$ (183.3)	65.54 65.40	9.35 9.30	7.64 7.58	1710	1.1-2.2 (m, 12H, 6 × CH₂), 3.6 (s, 3H, CH₃O), 4.1 (m, 2H, 2 × CH)	20.0, 24.0, 29.0, 29.4, 29.9, 31.0, 33.1, 34.4 (t, CH₂), 45.6, 46.4, 54.9, 55.4 (d, CH), 51.2, 51.4 (q, CH₃O), 153.6, 154.3 (s, C=O)
5a	$C_8H_{15}NO_3$ (173.2)	55.47 55.35	8.73 8.66	8.09 8.00	1720	1.25 (d, 6H, J = 6 Hz, 2 × CH₃C), 3.2-4.0 (m with s at 3.65, 9H, 2 × CH + CH₃O + 2 × CH₂)	19.3 (q, CH₃C), 46.1 (d, CH), 51.2 (q, CH₃O), 70.5 (t, CH₂), 157.9 (s, C=O)
5b	$C_9H_{17}NO_3$ (187.3)	57.73 57.63	9.15 9.04	7.48 7.41	1700	1.15 (d, 6H, J = 6 Hz, 2 × CH₃CH), 1.2 (t, 3H, J = 6 Hz, CH₃CH₂), 3.2-4.2 (m with q at 3.6, 8H, J = 6 Hz, 2 × CH + 2 × CH₂O + CH₂CH₃)	14.4 (q, CH₃CH₂), 19.5 (q, CH₃CH), 46.1 (d, CH), 60.8 (t, CH₂CH₃), 70.7 (t, CH₂O), 157.4 (s, C=O)
6	$C_{12}H_{22}N_2O_4$ (258.3)	55.80 55.71	8.59 8.52	10.85 10.73	1720	1.10, 1.14 (2d, 6H, J = 6 Hz, 2 × CH₃CH), 1.25 (t, 6H, J = 6 Hz, 2 × CH₃CH₂), 2.5-4.3 (m, with 2q at 4.05 and 4.07, 10H, J = 6 Hz, 2 × CH₂N + 2 × CH + 2 × CH₂O)	14.5 (q, CH₃CH₂), 16.6 (q, CH₃CH), 42.6 (t, CH₂N), 49.5 (d, CH), 60.7 (t, CH₂O), 154.8 (s, C=O)

[a] With a deuterium oxide capillary.

tions. These results are opposite to those observed for the aminomercuration reaction [1-5]. This behaviour suggests different reaction pathways for both reactions since the nitrogen substrate-mercury salt complex is much less dissociated for the amides than for the amines [12,17]. We must conclude that, under the reaction conditions reported by us, the amidomercuration is kinetically controlled while the already reported aminomercuration is thermodynamically controlled.

under normal pressure. The residue was distilled in vacuo to yield products 1, 3 + 4, and 5. Data for these compounds are given in Tables I and II.

In the case of compound 6, anhydrous mercury(II) nitrate (4.87 g, 15 mmoles) was added to a solution of N-allylurethane (2.0 g, purity 96%, 15 mmoles) in methylene dichloride (30 ml). The reaction was carried out as above. Data for compound 6 are given in Tables I and II.

EXPERIMENTAL

General Procedure for Amidomercuration-Demercuration of Dienes.

Anhydrous mercury(II) nitrate (Fluka, 20 mmoles) was added to a solution of diene (10 mmoles) and the carbamate (50 mmoles) in methylene dichloride (30 ml). The mixture was stirred under reflux for 24 hours. After the solution was cooled to 0° and then 10% aqueous sodium hydroxide (40 ml), n-butylamine (10 ml), and finally a solution of sodium borohydride (20 mmoles) in 10% sodium hydroxide (10 ml) were added. When the mercury(0) was precipitated the reaction mixture was saturated with sodium chloride and extracted with methylene dichloride (2 × 20 ml). The organic layer was dried (sodium sulfate) and the solvents distilled off

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