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DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN THE NODAL POSITIONS.

21.* HETEROATOM-PROMOTED LITHIATION OF BENZO[b]-1,4-DIAZABICYCLO[2.2.2]OCTENE AND INTRODUCTION OF SUBSTITUENTS INTO THE ANNELATED BENZENE RING

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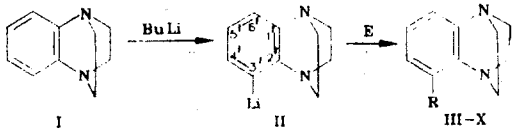
The action of n-butyllithium on benzo[b]-1,4-diazabicyclo[2.2.2]octene leads to lithiation in the 3' position of the aromatic ring. The reaction of this lithium derivative with electrophilic reagents was used to synthesize 3'- and 3',6'-substituted derivatives of benzo[b]-1,4-diazabicyclo[2.2.2]octene.

The reaction of benzo[b]-1,4-diazobicyclo[2.2.2]octene (I) with electrophiles under severe conditions leads to primarily 4'-substituted I [2].

It is known that when substituents that are capable of coordinating with the lithium atom are present in the aromatic ring, lithiation proceeds selectively in the ortho position relative to the substituent [3]. According to the data in [4], prolonged heating of the reaction mixtures is required to accomplish the direct lithiation of aromatic tertiary amines. We have established that treatment of benzodiazabicyclooctene I with n-butyllithium in tetrahydrofuran (THF) leads to 3'-lithiobenzo[b]-1,4-diazabicyclo[2.2.2]octene (II). It follows from the PMR spectra that the reaction is complete after a few minutes at room temperature. During the reaction the symmetrical multiplet of aromatic protons of I centered at 6.99 ppm is gradually converted to two 4'-H and 6'-H doublets at 7.63 and 6.65 ppm (J = 7.0 Hz) and a 5'-H triplet at 6.84 ppm (J = 7.0 Hz), which confirms lithiation in the 3' position. The ease of lithiation of



I II III–X

III R=Br, IV R=I, V R=COOH, VI, R=OH, VII R=$SiMe_3$, VIII R=$B(OH)_2$, IX R=SC_6H_{13}-*n*, X R=CHO

*See [1] for Communication 20.

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I is probably due to the increased C—H acidity of the 3′ position because of the presence of the −I effect and the absence of the +M effect of the nitrogen atoms and the ability of the heteroatoms to coordinate with the lithium atom. The resulting II was used without isolation in reactions involving the exchange of lithium for B-, C-, O-, Si-, S-, Br-, and I-containing substituents by the action of the corresponding electrophilic reagent E.

The corresponding 3′-halo-substituted benzodiazabicyclooctenes III and IV are formed by the action of bromine or iodine on lithium derivative II. Treatment of II with solid carbon dioxide in THF leads to a mixture, from which carboxylic acid V and starting compound I were isolated. A difficult-to-separate mixture consisting primarily of starting heterocycle I and 3′-hydroxybenzo[b]-1,4-diazabicyclo[2.2.2]octene (VI) is formed when dry air is passed into a solution of II in THF. Compound VI can be regarded as an analog of 8-hydroxyquinoline, and complexing properties can be expected for it. As a confirmation of this, we obtained complexes of VI with copper [5].

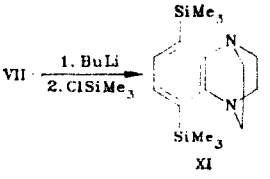
Treatment of lithium derivative II with trimethylchlorosilane leads to 3′-trimethylsilyl derivative VII in high yield. This compound is easily isolated from the reaction mixture owing to its very low solubility in water and its very low volatility.

In the reaction of II with tributyl borate the initial product is probably 3′-dibutyloxyborylbenzo[1′,2′-b]-1,4-diazabicyclo[2.2.2]octene, which is rapidly hydrolyzed to 3′-dihydroxyborylbenzo[1′,2′-b]-1,4-diazabicyclo[2.2.2]octene (VIII) when the reaction mixture is treated with water.

As an example of the replacement of the lithium in the benzene ring of heterocycle I by a sulfur-containing substituent we carried out the reaction of II with di-n-hexyl disulfide and obtained 3′-n-hexylthiobenzo[1′,2′-b]-1,4-diazabicyclo[2.2.2]octene (IX) in the form of a viscous colorless oil.

The reaction of lithium derivative II with N-formylmorpholine and subsequent treatment of the reaction mixture with water lead to 3′-formylbenzo[1′,2′-b]-1,4-diazabicyclo[2.2.2]octene (X).

In all of the investigated reactions 3′-substituted benzo[1′,2′-b]1,4-diazabicyclo[2.2.2]octenes were isolated as the principal products. It is known that dilithiation of the benzene ring is possible when strong activating groupings are present [6]. However, only 3′-monosubstituted VII is formed when I is treated with two equivalents of n-butyllithium with subsequent treatment with trimethylchlorosilane. Retreatment of VII with n-butyllithium and then with trimethylchlorosilane gives 3′,6′-bis(trimethylsilyl)benzo[1′,2′-b]-1,4-diazabicyclo[2.2.2]octene (XI) in high yield.



XI

The similar lithiation of VI and VIII with excess n-butyllithium does not lead to 3′,6′-disubstituted products, probably as a consequence of suppression of the C—H acidity of the 6′ position due to the donor effect of the ionized substituents in the 3′ position. Thus I does not undergo dilithiation, but 3′,6′-substituted derivatives of heterocycle I can be obtained through lithiation of derivatives with substituents in the 3′ position that do not deactivate the 6′ position.

Molecular-ion peaks, as well as $[M - 28]^+$ fragments, which correspond to splitting out of ethylene bridges, are observed in the mass spectra of III-XI.

The absorption at 230-280 nm in the UV spectra of III-XI (see Table 1) is due primarily to the effects of the substituents in the 3′ position, since the absorption in this region is insignificant for unsubstituted I.

In the IR spectra of the benzodiazabicyclooctene derivatives obtained one notes characteristic (for these compounds) vibrations, which show up in the form of intense absorption bands at 2870-2979 and 1044-1056 cm^{-1} (C—H stretching vibrations and skeletal vibrations of the 1,4-diazabicyclo[2.2.2]octane fragment [7]) and at 1416-1474 and 817-838 cm^{-1} (CH_2 deformation vibrations). In addition, less intense signals at 3059-3070 and 760-860 cm^{-1}, which correspond to stretching and deformation vibrations of aromatic ring C—H bonds, are observed in the spectra of all of the compounds. The spectra of V and IX contain intense bands in the region of carbonyl-group absorption (1742 and 1681 cm^{-1}, respectively).

Symmetrical multiplets at 2.5-3.5 ppm, which correspond to eight protons of ethylene bridges, are observed in the PMR spectra of III-XI (see Table 1). The symmetrical character of this signal is disrupted substantially only in the case of V; this is probably associated with the formation of a zwitter-ion structure due to the interaction of the proton of the carboxy group with the nitrogen atom. The signals of aromatic protons in the spectra of III-X correspond to a 1′,2′,3′-trisubstituted benzene ring; the protons in the 4′,5′ and 5′,6′ positions undergo coupling with ortho constants of 2.6-8.4 Hz, while the protons in the 4′,6′ positions undergo coupling with meta constants of 0-1.9 Hz. In the spectrum of XI the signal of the aromatic protons shows up in the form of a singlet at 7.33 ppm. Examination of the character of the ^{13}C—H satellites in the PMR spectrum of XI showed that the constant of spin-spin coupling

TABLE 1. Characteristics of the C-Substituted Benzo[b]-1,4-diazabicyclo[2.2.2]octenes

Compound	Empirical formula	mp, °C	R_f	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, δ, ppm					Yield, %
					H_{arom} (J, Hz)			$H_{ethylene}$ (sym m)	other signals	
					4′-H*	5′-H	6′-H*			
III	$C_{10}H_{11}BrN_2$	94...96	0,60	212 (4,10), 221 sh (3,99)	7,10 d (3,7)	7,44 dd (5,6; 3,7)	7,08 d (5,6)	2,5...3,3	—	35
IV	$C_{10}H_{11}IN_2$	114...118	0,52	210 (4,21), 228 (4,14)	7,15 dd (8,0; 1,4)	7,00 t(8,0)	7,70 dd (8,0; 1,4)	2,6...3,3	—	56
V	$C_{11}H_{12}N_2O_2$	187...188	0,25	204 (3,64), 229 (3,90), 278 (3,34)	7,43 d** (4,2)	7,84 dd ** (5,4; 4,2)	7,45 d (5,4)	2,5...3,5 asym m	—	30***
VI	$C_{10}H_{12}N_2O$	192...196	0,32	216 (4,22), 270 (3,68)	6,78dd (7,8; 1,1)	7,10 dd (8,4; 7,8)	6,86 dd (8,4; 1,1)	2,6...3,3	7,54 br s (OH)	20***
VII	$C_{11}H_{20}N_2Si$	109...111	0,55	213 (4,09), 266 (2,93)	7,16 d (6,5)	7,32 dd (2,6; 6,5)	7,14 d (2,6)	2,5...3,2	0,29 s ($SiMe_3$)	82
VIII	$C_{10}H_{13}BN_2O_2$	209...215	0,15	220 (3,99), 271 (3,08)	7,29 d (4,5)	7,74t (4,5)	7,29 d (4,5)	2,7...3,4	8,0 br s ($B(OH)_2$)	58***
IX	$C_{16}H_{24}N_2S$	Oil	0,50	212 (4,19), 355 (4,06)	6,94 dd (7,0; 1,9)	7,16 dd (7,0; 8,0)	7,08 dd (8,0; 1,9)	2,6...3,3	0,90 (3H, t); 1,2...1,4 (4H, m); 1,4...1,6 (2H, m); 1,6...1,8 (2H, m); 2,94 (2H,t)	62
X	$C_{11}H_{12}N_2O$	86...87	0,47	208 (4,32), 249 (4,04), 294 (3,30)	7,76 dd (8,0; 1,5)	7,34 t (8,0)	7,45 dd (8,0; 1,5)	2,6...3,4	10,64 s (CHO)	59***
XI	$C_{16}H_{28}N_2Si_2$	140...144	0,95	205 (4,36), 225 (4,33), 231 (4,30), 271 (3,01)	7,33 s		—	2,6...3,1	0,30 s ($SiMe_3$)	70

*The 4′-H and 6′-H signals were assigned arbitrarily.

**From the PMR spectrum in d_6-DMSO.

***Starting I was isolated in 25-50% yield.

(SSC) of the aromatic protons in this compound is 7.0 Hz, which corresponds to a relative ortho orientation of the protons in the aromatic ring.

Thus the direct lithiation of benzodiazabicyclooctene opens up a universal route to the introduction of substituents into the 3′ position.

EXPERIMENTAL

The IR spectra of solutions of the compounds in $CHCl_3$ or of KBr pellets (for the solids) were recorded with a UR-20 spectrometer. The UV spectra of solutions in ethanol were obtained with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Bruker WR-200 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The molecular masses were obtained with a Finnigan MAT-8200 mass spectrometer. The purity of the compounds and the progress of the reactions were monitored by TLC on Silufol UV-254 plates in a chloroform—ethanol (10:1) system, as well as by HPLC in a 0.05 M solution of KH_2PO_4 in 50% methanol with a 2 × 50 mm column packed with Nucleosil-$5C_{18}$ and a Milikhrom chromatograph. Preparative chromatography was carried out on 20 × 30 cm plates with a loose layer of silica gel. The melting points were determined in sealed capillaries.

Benzo[b]-1,4-diazabicyclo[2.2.2]octene (I) was obtained by the method in [8].

3′-Lithiobenzo[1′,2′-b]-1,4-diazabicyclo[2.2.2]octene (II). An 8.8-ml (7.5 mmole) sample of a 0.85 N solution of n-BuLi in hexane was added in an argon atmosphere to a solution of 0.8 g (5 mmole) of I in 20 ml of absolute THF, after which the reaction mixture was maintained for 10 min at 20°C to complete the metallation. The resulting lithium derivative II was used without isolation for the synthesis of the 3′-substituted derivatives of I in all of the subsequent experiments.

3′-Bromobenzo[1′,2′-b]-1,4-diazabicyclo[2.2.2]octene (III). A 1.60-g (10.0 mmole) sample of bromine was added rapidly with stirring and cooling with liquid nitrogen until the reaction mixture began to freeze to a solution of II, after which the mixture was heated to 20°C and evaporated in vacuo. The residue remaining after evaporation of the THF was treated with 10 ml of 20% $NaHSO_3$ solution to remove the excess bromine, after which the mixture was neutralized to pH 7 by the addition of 25% ammonium hydroxide. The reaction product and starting I were extracted with ether (5 × 10 ml), and the extract was dried with $MgSO_4$. The mixture obtained after evaporation of the solvent was separated by preparative TLC with chloroform—methanol (20:1) as the eluent. Workup of the fraction with R_f 0.4-0.5 gave III, which was sublimed in vacuo at 70-80°C (0.2 mm) to give 0.4 g of III in the form of colorless crystals.

3′-Iodobenzo[1′,2′-b]-1,4-diazabicyclo[2.2.2]octene (IV). A solution of II was poured into a solution of 1.40 g (5.5 mmole) of iodine in 100 ml of absolute hexane, after which the reaction mixture was maintained for 30 min at 20°C. The solvent was then removed by evaporation in vacuo, and the crude product was treated with 5 ml of 20% $Na_2S_2O_3$ solution to remove the excess iodine. The solution was made alkaline to pH 9 with Na_2CO_3 and extracted with chloroform (4 × 5 ml), and the extract was dried with $MgSO_4$ and evaporated in vacuo. The solid residue was washed with 20 ml of 25% ammonium hydroxide and removed by filtration. Compound IV was extracted from the mixture with boiling water (5 × 10 ml), the aqueous solution was extracted with chloroform (5 × 10 ml), and the extract was dried with $MgSO_4$. The solvent was evaporated, and the solid residue was sublimed in vacuo at 70-80°C (0.2 mm) and recrystallized from hexane to give 1.3 g of IV in the form of colorless needles.

3′-Carboxybenzo[1′,2′-b]-1,4-diazabicyclo[2.2.2]octene (V). A solution of II was poured into 30 g (680 mmole) of solid dry CO_2, after which the mixture was allowed to stand for 30 min at 20°C and then evaporated. Extraction of the solid residue with boiling hexane (3 × 10 ml) gave 0.22 g of starting I. Water (10 ml) was added to the residue, and the resulting solution was acidified to pH 5 with acetic acid. The reaction product was extracted with chloroform (5 × 10 ml), the extract was dried with $MgSO_4$, and the chloroform was evaporated. The solid residue was recrystallized from toluene and sublimed in vacuo at 140°C (0.2 mm) to give 0.42 g of V in the form of colorless needles.

3′-Hydroxybenzo[1′,2′-b]-1,4-diazabicyclo[2.2.2]octene (VI). Dry air was passed for 1 h into a solution of lithium derivative II, after which the solvent was evaporated in vacuo. Extraction of the solid residue with boiling hexane (5 × 10 ml) gave 0.40 g of I. The solid residue was dried and dissolved in water, the solution was acidified to pH 7 with concentrated HCl, and the reaction product was extracted with chloroform (5 × 10 ml). The extract was dried with $MgSO_4$, and the solvent was evaporated in vacuo to give a mixture, which was separated by preparative TLC in a chloroform—ethanol (5:1) system. Workup of the fraction with R_f 0.4-0.5 gave VI, which was recrystallized from petroleum ether (70-100°C) and sublimed in vacuo at 90°C (0.2 mm) to give 0.17 g of VI.

3′-Trimethylsilylbenzo[1′,2′-b]-1,4-diazabicyclo[2.2.2]octene (VII). A 0.81-g (7.5 mmole) sample of trimethylchlorosilane was added rapidly with stirring to a solution of II, after which the reaction mixture was maintained for 30 min at 20°C. The solvent was evaporated in vacuo, and the crude product was dissolved in 10-15

ml of acetone. The acetone solution was poured into water (30-40 ml), and the curdy precipitate was removed by filtration. The reaction product was dried and sublimed in vacuo at 90°C (0.2 mm) to give 1.05 g of VII.

3'-Dihydroxyborylbenzo[1',2'-b]-1,4-diazabicyclo[2.2.2]octene (VIII). A 0.96-g (7.0 mmole) sample of tributyl borate was added rapidly with stirring and cooling with liquid nitrogen until the reaction mixture began to freeze to a solution of II, after which the mixture was maintained for 30 min at 20°C and then evaporated. Extraction of the solid residue with boiling hexane (5 × 10 ml) gave 0.25 g of starting I. The residue was dried and dissolved in water, and the aqueous solution was acidified to pH 7 with concentrated HCl. The reaction product was extracted with chloroform (5 × 10 ml), and the extract was dried with $MgSO_4$. The solvent was evaporated in vacuo, and the solid residue was recrystallized from toluene to give 0.50 g of VIII.

3'-n-Hexylthiobenzo[1',2'-b]-1,4-diazabicyclo[2.2.2]octene (IX). A 1.76-g (7.1 mmole) sample of di-n-hexyl disulfide was added rapidly with stirring and cooling with liquid nitrogen until the reaction mixture began to freeze to a solution of II, after which the reaction mixture was maintained for 30 min at 20°C and then evaporated. The crude reaction product (an oil) was treated with a solution of 0.6 g of KOH in 40 ml of water, the mixture was extracted with hexane (5 × 10 ml), and the extract was dried with $MgSO_4$. The solvent was removed in vacuo, and the residue was dissolved in 20 ml of 10% HCl. The aqueous solution was washed with hexane (3 × 20 ml), evaporated in vacuo to half its original volume, and made alkaline to pH 8-9 with 25% ammonium hydroxide, during which an oil was liberated. The mixture was extracted with hexane (5 × 10 ml), and the extract was dried with $MgSO_4$ and evaporated in vacuo. The reaction product was sublimed in vacuo at 160°C (0.2 mm) to give 0.85 g of IX in the form of an oil.

3'-Formylbenzo[1',2'-b]-1,4-diazabicyclo[2.2.2]octene (X). A 0.86-g (7.5 mmole) sample of N-formylmorpholine was added rapidly with stirring and cooling with liquid nitrogen until the reaction mixture began to freeze to a solution of II, after which the reaction mixture was maintained for 30 min at 20°C and then evaporated. The starting I (0.20 g) was extracted with boiling hexane (3 × 10 ml), and the solid residue was dried and dissolved in water. The aqueous solution was acidified to pH 7 with concentrated HCl, and the solution was refluxed with activated charcoal for 2-3 min and filtered. The reaction product was extracted with chloroform (5 × 10 ml), and the extract was dried with $MgSO_4$. The solid residue remaining after evaporation of the solvent in vacuo was recrystallized from hexane to give 0.55 g of X in the form of light-yellow needles.

3',6'-Bis(trimethylsilyl)benzo[1',2'-b]-1,4-diazabicyclo[2.2.2]octene (XI). A 0.81-g (7.5 mmole) sample of trimethylchlorosilane was added rapidly with stirring to a solution of II, after which the reaction mixture was maintained for 30 min at 20°C. It was then treated with 11 ml (9.4 mmole) of a 0.85 N solution of n-BuLi in hexane, and the mixture was allowed to stand for 1 h. A 2.1-g (19.6 mmole) sample of trimethylchlorosilane was added, and the mixture was again allowed to stand for 30 min and then evaporated in vacuo. To remove admixed VII the reaction product was dissolved in 20 ml of toluene, 5 ml of 30% H_2O_2 was added to the solution, and the mixture was refluxed with a Dean—Stark adapter for 2 h. The toluene was then evaporated in vacuo, and the residue was recrystallized from ethanol to give 1.07 g of XI in the form of long colorless needles.

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