system and the four non-hydrogen atoms attached to it. The results, which are shown in Table II, indicate that for structures 1 and 3 the MINDO/3 structure was significantly poorer than the MNDO or AM1 structures. As the data in Table II indicate, MINDO/3 flattened the geometry about the lactam nitrogen whereas AM1 increased the pyramidality. A comparison between calculated and experimental bond lengths for the 11 bonds which define the ring and the attached groups at positions 7 and 8 for compound 1 reveals correlation coefficients (R^2) of 0.953 for the MINDO/3 structure, 0.979 for the MNDO structure, and 0.949 for the AM1 structure, indicating a slight superiority of the MNDO method in this regard.

Key differences in the accuracy of the methods are revealed, however, in their ability to predict the relative energies of the three isomers. Table III contains the calculated relative heats of formation of these isomers and the experimentally determined relative energies. That is, the energy of the most stable isomer was set to zero and the energies of the others were adjusted accordingly within the same semiempirical method. Comparison between numbers derived from theory and experiment is possible since solvation energies of the various species are likely to be similar and little entropic differences should exist between the fairly rigid isomeric structures. These results demonstrate the clear superiority of AM1 with respect to the energetics of the isomers and the large error that is possible with MINDO/3. The availability of sulfur parameters for AM1 should provide further improvements in the reliability of this method.[17]

Conclusions

The structure of **3b**, the first 3-*exo*-methylene isomer of a cephalosporin to have its structure determined by X-ray crystallography, has been shown to be quite ordinary in terms of the length and orientation of the carbon–carbon double bond. This isomer was determined to lie 4.55 kcal/mol above its cephalosporin isomer, **1b**. Of the three common semiempirical molecular orbital methods, AM1 was found to provide the best agreement with experimentally determined relative energies of cephalosporins and their isomers and is the recommended method for analysis of these compounds, especially for analysis of possible alternate mechanisms.

Experimental Section

X-ray Crystallography. Compound **3b** crystallized in the monoclinic space group $P2_1$ with a unit cell having the dimensions a = 7.228 (4) Å, b = 10.328 (4) Å, c = 15.436 (8) Å, β = 90.415 (5)° and a calculated density of 1.39 g cm^{-3}. A total of 1747 reflections with 2θ less than 116.0° was measured on an automated four-circle diffractometer using monochromatic copper radiation. The structure was solved using the direct methods routine TREF of the SHELXTL program library and was refined by the least-squares method with anisotropic temperature factors for all atoms except hydrogen. All hydrogen atoms were included at calculated positions. The final R factor was 0.074 for 1475 unique observed reflections.

High-performance liquid chromatography (HPLC) was performed on a 25-cm Zorbax C8 column eluted at 1.25 mL/min with 55% acetonitrile and 45% aqueous buffer prepared by raising the pH of 0.3% phosphoric acid to 3 with triethylamine. Detection was by UV at 255 nm. Retention times are 9.34 min for **3b**, 10.45 min for **1b**, and 10.72 min for **2b**. Nuclear magnetic resonance spectra were obtained on a Bruker AC300 at ambient temperatures in dimethyl-d_6 sulfoxide.

***p*-Nitrobenzyl 7-(phenoxyacetamido)-3-methylenecepham-4-carboxylate (3b)** was prepared by a modification of the known reduction of the corresponding sulfoxide.[18] A methylene chloride (1000 mL) solution of *p*-nitrobenzyl 7-(phenoxyacetamido)-3-methylenecepham-4-carboxylate 1β-oxide[19] (103 g, 0.206 mol) was cooled to 0 °C and treated with acetyl bromide (31 mL, 0.309 mol) over a period of 20 min. The solution was warmed to 15 °C over the course of 1 h, and water (250 mL) was added followed by dropwise addition of 5 M NaOH solution to achieve a pH of 6. The layers were separated, and the lower layer was washed with dilute sodium chloride (500 mL). After drying over sodium sulfate, the solution was distilled at atmospheric pressure until the still temperature was 50 °C, whereupon methanol (500 mL) was added and the solution was distilled until the still temperature was 55 °C. Another 250-mL portion of methanol was added, and the slurry was cooled slowly to 0 °C. The product was collected by filtration and rinsed with methanol, and the wetcake was slurried at 80 °C for 1 h in toluene (350 mL). The slurry was cooled to ambient temperature and the product was filtered, rinsed with toluene, and dried in vacuo at 30 °C for 3 days to yield 78.4 g of **3b**. Its NMR spectra was consistent with that reported in the literature,[20] and its purity was 99% by HPLC.

The calorimetry was performed with a Mettler RC1 using a 1-L reaction vessel. Compound **3b** (70 g, 145 mmol) was dissolved in 700 mL of methylene chloride at 20 °C, and the heat capacity was measured. Triethylamine (2.2 g, 21.8 mmol) was added rapidly, and the heat load measured. The calorimeter was operated in a nonadiabatic mode, and the heat load was measured according to the following equation where ΔT_j is the differece between the temperature of the jacket fluid and the reaction mixture, ΔT_r is the change in reaction mixture temperature, and ΔT_b is the change in temperature of the base added. The adi-

$$q = UA(\Delta T_j) + mCp(\Delta T_r) + mCp(\Delta T_b)$$

abatic temperature rise was calculated by the software to be 2.1 °C, and the heat of reaction to be 4.71 kcal/mol. The process was repeated on another 70 g of **3b** at 25 °C, giving a calculated adiabatic temperature increase of 1.8 °C and a heat of reaction of 4.38 kcal/mol. The product solution when analyzed immediately by HPLC showed near quantitative conversion to **1b**. After standing several days at ambient temperature, HPLC and NMR[18] indicated a 4:1 mixture of **1b** and **2b**.

Acknowledgment. Dr. D. B. Boyd provided assistance with SYBYL and comments on the manuscript, Mr. J. Niemeier and Mr. D. Creeden performed the calorimetry, and Dr. W. D. Luke reviewed the manuscript and participated in lively discussions.

Supplementary Material Available: Atomic coordinates, equivalent isotropic displacement parameters, bond lengths, bond angles, and anisotropic displacement parameters for compound **3b** (5 pages). Ordering information is given on any current masthead page.

(17) Dewar, M. J. S.; Yuan, Y.-C. submitted to *J. Inorg. Chem.* Thanks to Ms. Yuan for this information.

(18) Hatfield, L. D. US4044002, 1977, example 3.

(19) Kukolja, S.; Lammert, S. R.; Gleissner, M. R. B.; Ellis, A. I. *J. Am. Chem. Soc.* **1976**, *98*, 5040.

(20) Davis, M.; Wu, W.-Y. *Aust. J. Chem.* **1987**, *40*, 1519.

Reactions of Lithiooxazole

John C. Hodges,* William C. Patt, and Cleo J. Connolly

Parke-Davis Pharmaceutical Research Division, Warner-Lambert Co., 2800 Plymouth Rd., Ann Arbor, Michigan 48105

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Recent research in our laboratory has been directed toward the preparation of symmetrical bis(oxazolyl)-methanols, 1–3, as fragments of larger synthetic targets. A simple strategy for their synthesis would involve regioselective generation of isomeric lithiooxazoles and

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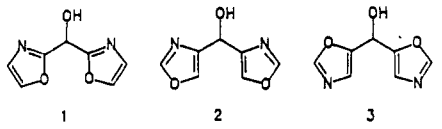


Figure 1. Synthetic targets.

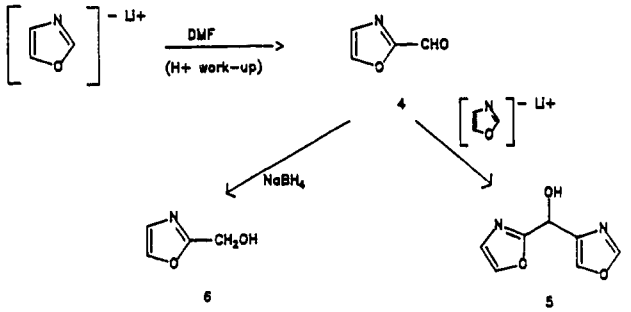


Figure 2. Ambident nucleophilicity of lithiooxazole.

successive addition to a formate equivalent. Of the three targets, **1** appeared to be the most readily accessible based on literature precedents for 2-lithiation of oxazoles. Deuteration experiments[1] have shown H-2 to be the most acidic oxazole proton. Additionally, a number of literature reports also describe 2-lithiation of 4- and 4,5-substituted oxazoles and subsequent reactions.[2] The literature is surprisingly sparse, however, on the lithiation of unsubstituted oxazole and its further use as an organometallic reagent. Two examples in the patent literature give support to the feasibility of such an approach. In the first, 2-(trimethylsilyl)-1,3-oxazole is prepared by treatment of oxazole with *n*-BuLi and TMS-Cl, followed by distillation.[3] The second reports a similar lithiation and subsequent reaction with quinuclidin-3-one to afford 3-hydroxy-3-[2-(1,3-oxazolyl)]quinuclidine.[4] While attempting to prepare **1** we observed both 2- and 4-substitution of lithiooxazole, leading us to a study of the reactions of lithiooxazole with a variety of electrophiles. The results of this study and the syntheses of **1** and **2** are reported in this paper.

Lithiation of oxazole is accomplished by treatment with *n*-BuLi in THF/hexanes at −75 °C. When conducted on a 10-mmol scale at approximately 0.3 M concentration, the metalation reaction is always found to be complete after 20 min at −75 °C. At higher concentrations lithiooxazole precipitates as a colorless solid. The reagent is stable up to room temperature as evidenced by evaporation of solvents and dissolution in D_2O to give 2-deuterio-1,3-oxazole.

Treatment of lithiooxazole with DMF, followed by warming to 23 °C, gives approximately a 50% yield of 1,3-oxazole-2-carboxaldehyde (**4**) upon acidic work up and chromatography (Figure 2). The yield for this step is variable due to the volatility of **4**. TLC of the crude reaction mixture indicates a nearly quantitative reaction, but the product is easily lost during solvent evaporation steps. Reaction of **4** with another equivalent of lithiooxazole

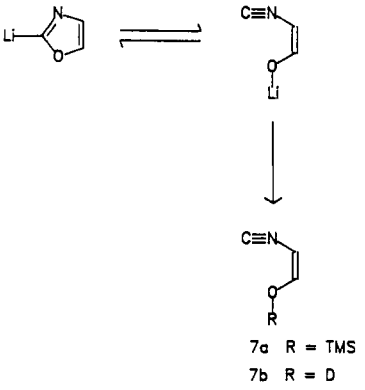


Figure 3. Lithiooxazole ring opening.

affords a single adduct by TLC and NMR analysis of the crude product. Surprisingly, this product is not **1** but rather the unsymmetrical bis(oxazolyl)methanol **5**. The identity of **5** is confirmed by its ^1H NMR spectrum, in which four distinct oxazole proton resonances with consistent chemical shifts are found. Additionally, an NOE is observed between the methyne-H (δ $CDCl_3$ 5.97) and only one oxazole-H that has a chemical shift consistent with a 5-oxazole-H (δ 7.79).

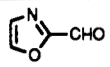
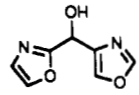
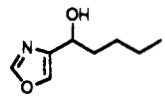
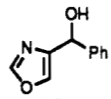
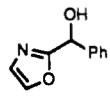
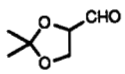
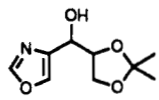
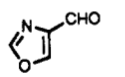
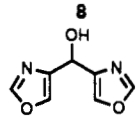
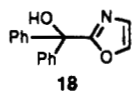
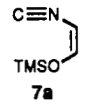
Given the above result, we reexamined **4** by reducing it to the corresponding alcohol, **6**. Chemical shifts of the two oxazole protons are consistent with 2-substitution. The net result is that lithiooxazole reacts to give 2-substitution with DMF whereas 4-substitution is observed with the aldehyde **4**. This ambident nucleophilicity is likely the result of a ring cleavage reaction of lithiooxazole (Figure 3). Such reactions are documented for 4- and 4,5-substituted oxazole derivatives, however only 2- and O-substitutions have been described.[2] The presence of a 4-substituent in these literature examples apparently inhibits further reaction at the 4-position. To further explore the utility of 2- versus 4-substitution of lithiooxazole we examined the reaction with other electrophiles (Table I).

Aldehydes are unique in their reaction with lithiooxazole in that they give nearly exclusively products of 4-substitution. Based on ^1H NMR analysis of the crude reaction products, addition to aldehydes is regiospecific in most cases since there is no evidence of any oxazole-4-H resonances at the expected region of δ ($CDCl_3$) 6.8–7.1 ppm. Benzaldehyde is an exception, giving a 10:1 ratio of 4- to 2-substituted products by NMR.[5] With benzaldehyde there is also a competing reduction which results in the production of benzyl alcohol along with the addition products in approximately equal amounts. This reduction is not observed with other aldehydes.

In order to better understand the reason for the preference of 4-substitution with aldehydes we studied the reaction between lithiooxazole and benzaldehyde in greater detail. A series of temperature-controlled experiments wherein lithiooxazole is first generated at −75 °C, treated with benzaldehyde at −75, −50, −25, and 0 °C and quenched

(1) Brown, D. J.; Ghosh, P. B. *J. Chem. Soc. B* **1969**, 270.
(2) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1987**, *52*, 3413; *Synthesis* **1987**, 693. Dondoni, A.; Dall'occo, T.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Chem. Soc., Chem. Commun.* **1984**, 258. Pridgen, L. N.; Shilcrat, S. C. *Synthesis* **1984**, 1048. Schroder, R.; Schollkopf, U.; Blume, E.; Hoppe, I. *Liebigs Ann. Chem.* **1975**, 533. Jacobi, P. A.; Ueng, S.; Carr, D. *J. Org. Chem.* **1979**, *44*, 2042.
(3) Edwards, P. D.; Lewis, J. J.; Perkins, C. W.; Trainor, D. A.; Wildonger, R. A. Eur. Pat. Appl. 0-291-234-A2, 1988, Example 12.
(4) Baker, R.; Snow, R. J.; Saunders, J.; Showell, G. A. Eur. Pat. Appl. 0-307-141-A2 1988, Example 7.
(5) Compound **4** was reacted with phenylmagnesium bromide to give authentic **13b**, which has an ^1H NMR spectrum identical with the minor component of the previous reaction product.
(6) Dondoni, A. *Phosphorus, Sulfur Silica* **1989**, *43*, 25. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Mastellari, A.; Mastellari, A.; Medici, A.; Negrini, E.; Pedrini, P. *Gazz. Chim. Ital.* **1988**, *118*, 211. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Synthesis* **1988**, 685.
(7) In a typical experiment *n*-butyllithium in hexanes is added dropwise to a −75 °C solution of oxazole in dry THF. After 20 min the electrophile is added, and the cold bath is allowed to gradually warm to 23 °C, stirring a total of 24 h. See the supplementary material for additional details.
(8) Baer, E.; Fischer, H. O. *J. Am. Chem. Soc.* **1948**, *70*, 609.

Table I. Reaction of Lithiooxazole with Various Electrophiles[7]

electrophile	product	yield,[a] %	^{1}H NMR, δ ppm	mp,[c] °C
$HCON(CH_3)_2$	 **4**	50	($CDCl_3$) 9.81 (s, 1 H, CHO), 7.93 (s, 1 H, H-5), 7.48 (s, 1 H, H-4)	oil
4	 **5**	65	($CDCl_3$) 7.91 (s, 1 H, H-2), 7.79 (s, 1 H, H-5), 7.68 (s, 1 H, H-5′), 7.14 (s, 1 H, H-4′), 5.97 (s, 1 H, CH), 4.41 (br, 1 H, OH)	57–59
n-C_4H_9CHO	 **12**	28	($CDCl_3$) 7.85 (s, 1 H, H-2), 7.57 (s, 1 H, H-5), 4.68 (q, 1 H, CH), 1.83 (m, 2 H, CH_2), 1.38 (m, 4 H, CH_2CH_2), 0.90 (t, 3 H, CH_3)	oil
PhCHO	 **13a**	20[b]	($CDCl_3$) major 7.83 (s, 1 H, H-2), 7.37 (m, 6 H, PhH + H-5), 5.78 (s, 1 H, CH), 3.43 (br 1 H, OH)	oil
	 **13b**	2	minor 7.60 (s, 0.1 H, H-5), 7.37 (m, 0.5 H, PhH), 7.07 (s, 0.1 H, H-4), 5.89 (s, 0.1 H, CH), 4.08 (br, 0.1 H, OH)	
 **14**	 **8**	65[d]	($CDCl_3$) 7.87 (s, 1 H, H-2), 7.70 (s, 1 H, H-5), 5.0–3.5 (m, 4 H, HCO × 4), 3.05 (br, 1 H, OH), 1.5–1.3 (m, 6 H, Me)	oil
 **10**	 **2**	62	($CDCl_3$) 7.90 (s, 2 H, H-2 + H-2′), 7.70 (s, 2 H, H-5 + H-5M), 5.85 (s, 1 H, CH), 4.15 (br, 1 H, OH)	65–67
D_2O	 **15**	90[e]	(D_2O) 8.23 (s, 0.1 H, H-2), 7.96 (s, 1 H, H-5), 7.27 (s, 1 H, H-4)	oil
PhCOPh	 **18**	73	($CDCl_3$) 7.59 (s, 1 H, H-5), 7.32 (m, 10 H, PhH), 6.89 (s, 1 H, H-4), 5.19 (s, 1 H, OH)	100–102
$^1/_2(HCO_2C_2H_5)$	**5**	22	same as above	
TMSCl	 **7a**	93	($CDCl_3$) 6.30 (br d, 1 H, C=CHOTMS), 5.05 (d, 1 H, C=CHNC), 0.20 (s, 9 H, TMS)	oil
n-C_4H_9I	no reaction			
$PhCH_2Br$	no reaction			
$(C_2H_5O)_2CO$	no reaction			

[a] Isolated yield, unoptimized. [b] $PhCH_2OH$ formed in 34% yield. [c] Solids have satisfactory C, H, N analyses. Oils are >90% pure by ^{1}H NMR analysis. [d] Mixture of diastereomers. [e] NMR yield.

after 30 min at the desired temperature were performed. The results from these experiments were compared to one where the reaction mixture was allowed to warm gradually to room temperature overnight. The resulting product distribution indicates a temperature dependence on the product ratio. Compound **13a** is the major addition product regardless of temperature, but the benzyl alcohol side product only appears in the 0 °C, and the gradually warmed reactions. In the first four cases the amount of unreacted aldehyde decreases relative to **13a** as the reaction temperature increases but the longer and warmer reaction conditions of the gradual warming procedure are needed to consume all of the benzaldehyde. Compound **13b** is not detectable by NMR in any of the first four crude products; however, it is seen upon warming to room temperature. This suggests that the regioselective 4-substitution observed with aldehydes is related to their ability to react with the lithium enolate form at lower temperatures, followed by recyclization to the oxazole, whereas higher temperatures give rise to reaction with the 2-lithio form.

TMS-Cl also reacts with the ring-opened form of lithiooxazole to give the enol ether **7a**, which is isolable in crude form upon distillation. Compound **7a** may subsequently be rearranged to **11** by distillation from KOH.[6] Similarly, D_2O probably quenches the lithium enolate at oxygen to give **7b**, which cyclizes to give **15**.

Products of 2-substitution were seen with DMF, benzophenone, and ethyl formate. In each of these cases NMR spectra of the crude products show no evidence of oxazole-2-H resonances at the expected region of δ ($CDCl_3$) 7.8–8.0 ppm, indicating regiospecific 2-substitution. Less reactive than aldehydes or TMS-Cl, these other electrophiles require warmer temperatures for a reaction to occur and hence give 2-substituted products. Interestingly iodobutane, benzyl bromide, and ethyl carbonate are found to be unreactive toward lithiooxazole, even after prolonged periods at room temperature. Unreacted electrophile is recovered in high yield in all three cases.

Preparation of **2** is accomplished by the route shown in Figure 4. Lithiooxazole is treated with glyceraldehyde acetonide to give a 53% yield of 8 as a mixture of dia-

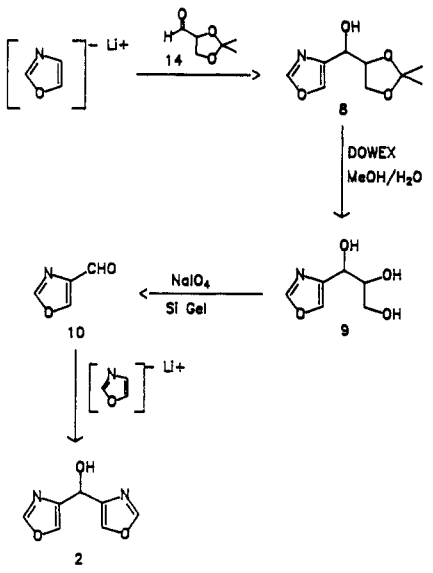


Figure 4. Symmetrical bis(oxazolyl)methanol 2.

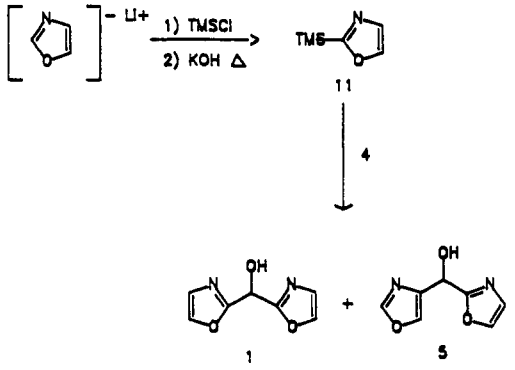


Figure 5. Bis(oxazolyl)methanols 1 and 5.

stereomers. Hydrolysis of the acetonide group is accomplished using Dowex 50 in moist methanol to give a quantitative yield of triol **9**. Oxidative cleavage of **9** using a heterogeneous reagent formed by adsorption of aqueous $NaIO_4$ onto silica gel affords 1,3-oxazole-4-carboxaldehyde (**10**) as a solid in 70% yield after chromatography. Treatment of **10** with 1.3 equiv of lithiooxazole gives **2** in 62% isolated yield.

A low-yielding preparation of **1** is shown in Figure 5. Excess 2-(trimethylsilyl)-1,3-oxazole (**11**) and 1,3-oxazole-2-carboxaldehyde (**4**) are heated neat at 70 °C for 90 min to afford a mixture of **1** and **5** (ca. 1:1, 21% combined yield), which are separable by chromatography. In this sense 2-(trimethylsilyl)-1,3-oxazole behaves as both 2- and 4-lithiooxazole synthons with aldehydes. This is in contrast with literature precedents for thiazole and substituted oxazoles where reaction of 2-TMS derivatives with aldehydes give high-yielding and regiospecific reactions, affording only 2-substituted products.[2,4,6]

In summary, the equilibrium between 2-lithiooxazole and the ring-opened lithium enolate provides the basis for the ambident nucleophilicity observed for "lithiooxazole". Highly reactive, oxophilic electrophiles such as TMS-Cl and D_2O react at oxygen, aldehydes react at the 4-position, and most other weaker electrophiles either react at the 2-position or do not react. In all instances high regioselectivity is observed, i.e. mixtures of 0-, 2- and 4-substituted products are typically not found. The unusual preference for 4-substitution seen with aldehydes appears to be related to their low oxophilicity and their ability to react at lower temperatures. The fact that traces of the 2-substituted product, **13b**, are seen when benzaldehyde is allowed to react with lithiooxazole at room temperature is supportive of this regioselectivity hypothesis. By reacting 2-(trimethylsilyl)-1,3-oxazole with aldehydes it is possible to alter the regioselectivity of addition, affording low yields of both 4- and 2-substituted products. The isomeric bis(oxazolyl)methanols, **1**, **2** and **5**, may be prepared from "lithiooxazole" by three different strategies.

Registry No. **1**, 130551-89-2; **2**, 130551-90-5; **4**, 65373-52-6; **5**, 130551-91-6; **6**, 130551-92-7; **7a**, 130551-93-8; **8** (isomer 1), 130551-94-9; **8** (isomer 2), 130551-95-0; **9**, 130551-96-1; **10**, 118994-84-6; **11**, 120629-79-0; **12**, 130551-97-2; **13a**, 130551-98-3; **13b**, 130552-00-0; **14**, 5736-03-8; **15**, 67245-00-5; **16**, 130551-99-4; BuCHO, 110-62-3; PhCHO, 100-52-7; PhCOPh, 119-61-9; HCO_2Et, 109-94-4; TMSCl, 75-77-4; BuI, 542-69-8; $PhCH_2Br$, 100-39-0; $(EtO)_2CO$, 105-58-8; $HCONMe_2$, 68-12-2; oxazole, 288-42-6.

Supplementary Material Available: Experimental details for representative reactions, spectral data, analytical data, and ^1H NMR spectra of new compounds (25 pages). Ordering information is given on any current masthead page.

Synthesis of Secondary Amines by Rhodium Catalyzed Hydrogenation of Nitriles

Amalia Galán,† Javier de Mendoza,*,† Pilar Prados,† Javier Rojo,† and Antonio M. Echavarren*,‡

Departamento de Química, C-I, Universidad Autónoma de Madrid, Cantoblanco, 28049-Madrid, Spain, and Instituto de Química Orgánica, CSIC, Juan de la Cierva 3, 28006-Madrid, Spain

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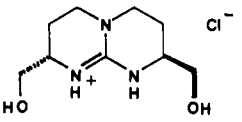
We recently reported the preparation of the first example of a C_2 symmetric, chiral guanidine **1** and its enantiomer starting from L- or D-asparagine, respectively.[1] These chiral guanidines complex aromatic carboxylate anions[2] and phosphate containing guests.[3,4] The high



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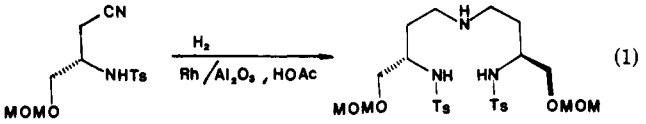
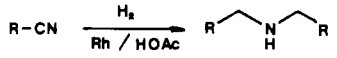
efficiency of the reported syntheses relied on the one-step assemblage of a protected triamine dimer by a rhodium-catalyzed hydrogenation of nitrile **2** (eq 1).



(1)

As part of a broader program aimed at developing chiral anion receptors based on guanidine subunits, we examined the generality of this secondary amine synthesis for the preparation of the key synthetic intermediates (eq 2).



(2)

The catalytic hydrogenation of nitriles is usually complicated by the formation of mixtures of primary, secondary, and tertiary amines.[5] The composition of the reduction products depends markedly on the nature of the

† Universidad Autónoma de Madrid.
‡ Instituto de Química Orgánica, CSIC.

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