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Alkylation of the Cyclic Sulfamate of Prolinol. Preparation of Optically Active 2-Alkyl-substituted Pyrrolidines

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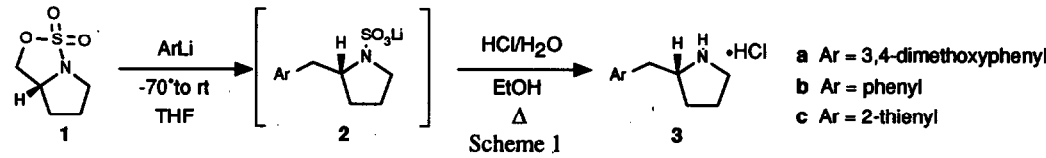
Abstract: Treatment of the cyclic sulfamate of (R)-prolinol (**1**) with aromatic lithium reagents, followed by acidic hydrolysis, gives 2-substituted pyrrolidines **3a-c** in moderate yields.

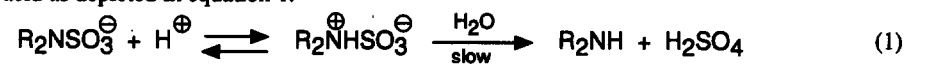
In a recent communication[1] the preparation and chemistry of the cyclic sulfamate of (S)-prolinol (enantiomer of **1**) was described. The observation in that communication that attempts at carrying out substitution reactions on ent-**1** with anionic nucleophiles (including PhLi) proved unsuccessful caught our attention as we had for some time been using essentially that chemistry to prepare the protected catecholamine (R)-**3a**.[2] We describe here the results of our experiments reacting **1** with several organometallic nucleophiles followed by acidic hydrolysis (scheme 1), and offer a potential explanation of how the authors of ref. 1 may have been misled by their results using dialkylamines and methanol as nucleophiles into believing that alkaline hydrolysis would work for anionic nucleophiles.



1 2 3

Scheme 1

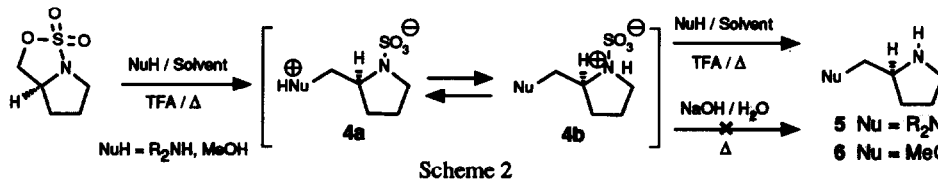
Cyclic sulfamate **1**, which we had prepared essentially as described in ref. 1 (substituting pyridine for triethylamine) was cooled to -70° in THF solution and treated with a 20% excess of the organolithium reagent of interest. The mixture was allowed to warm to room temperature and stir overnight. Evaporation of the solvent gave the sulfamic acid salts **2** as hygroscopic solids.[3] These were dissolved in ethanol and an equivalent volume of 2N hydrochloric acid. Heating under reflux overnight gave complete conversion[4] to the hydrochloride salts of the desired amines, which were isolated in 37.5-61.6% yield.[5] In contrast, when 2N NaOH was substituted for the hydrochloric acid in the case of **2c**, no conversion into **3c** was observed, intermediate **2c** remaining unchanged.[4] This might explain the negative results of Alkers *et al.*[1] who, it is inferred, attempted alkaline hydrolysis[6] of intermediate ent-**2b**, by analogy to all the other experiments described in their communication. Our results are consistent with the literature, which suggests that sulfamic acids are hydrolyzed slowly in acidic media[7] and are stable to dilute aqueous base.[8] Sulfamic acids are strongly acidic (PK_a 1-1.9) and are generally believed to undergo hydrolysis by an A2 mechanism in aqueous acid as depicted in equation 1.[7]



(1)

As our results showed that the intermediate sulfamic acid salts **2** are only hydrolyzed under acidic conditions, one was left to explain the apparently successful basic hydrolysis (treatment with 2N NaOH at 90° for 1 hr) employed in the preparation of the related amines **5** and **6** described in ref. 1 (scheme 2).

It is probable that in the proton-rich reaction mixtures described in ref. 1 (ten equiv. of R_2NH in the case of diamines **5**, and MeOH as solvent in the case of amine **6**, both with added trifluoroacetic acid) the



Scheme 2

initially formed protonated species **4a** is in equilibrium with the sulfamic acid **4b** which is able to solvolyze *in situ* to **5** and **6**, the alkaline hydrolysis step being superfluous. Indeed, at least by tlc[4] comparison with authentic samples, substantial amounts of **5** (R = Et) and **6** are present prior to treatment with aqueous base. In contrast, under the aprotic conditions in which the strongly basic sulfamic acid salts **2** are formed no such solvolysis can occur, and a separate, acid catalyzed hydrolysis is required to obtain the final products.

Reaction of **1** with n-butyllithium/hexane, phenylmagnesium chloride, or phenylmagnesium chloride/-CuCN (-70° to room temperature) gave complex mixtures of products on acidic hydrolysis. Reaction of **1** with phenyllithium at 0° gave **3b** on acidic hydrolysis, but in lower yield than the low temperature reaction. Thus, although this alkylation reaction is preparatively useful, yields are moderate and the reaction is sensitive to the nature of the organometallic nucleophile and the reaction conditions.

References and Notes

Contribution No. 851 from the Institute of Organic Chemistry, Syntex Research.

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3 These were not characterized except for **2b** which gave a base peak at m/e = 240 ($C_{11}H_{14}NO_3S$) and a 2M+Li peak at m/e 487 in its negative ion mass spectrum.

4 As judged by silica gel tlc developed with 30/70/1 MeOH/CH_2Cl_2/conc. NH_4OH.

5 Typical procedure: To 0.81 g (3.76 mmole) 4-bromoveratrole in 4.5 ml dry THF under N_2 at -70° was added 2.26 ml 1.63M n-butyllithium in hexane (3.68 mmole) over 40 min. After wash in of the base with 1.5 ml dry THF the white slurry was stirred at -70° for 1 hr. Cyclic sulfamate **1** (0.5 g, 3.06 mmole) dissolved in 2.0 ml dry THF was added over 8 min. The mixture was allowed to warm to room temperature and stir overnight. The solvent was evaporated at 40° to give a beige foam which was refluxed overnight in 6 ml of 2N hydrochloric acid (an equivalent volume of ethanol was added in the case of the less soluble salts **2b** and **2c**). The reflux condenser was replaced with a short-path distillation head to allow removal of veratrole by steam distillation. Water was added to make up for the distillate and the mixture stirred while cooling. The resulting precipitate (mostly bi-vetatrole) was filtered and the aqueous phase was washed with toluene, basified with 50% NaOH solution, and extracted with methylene chloride. The extract was dried over sodium sulfate and evaporated to an oil. Preparation of the hydrochloride salt in isopropanol and crystallization after the addition of diethyl ether gave 0.43 g **3a** (54.5%) as a beige solid. Recrystallization from methyl-t-butyl ether/isopropanol gave an analytical sample: mp 133-135°; $[\alpha]_D$ -35.9° (c=1.203, MeOH); ^1H nmr ($CDCl_3$): δ 6.80 (s, 3H, aromatic), 3.88 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.77 (bs, 1H, CHN), 3.38 (bs, 2H, CH_2N), 3.35 (dd, 1H, J=5.3, 13.7 Hz, $ArCH_2$), 2.96 (dd, 1H, J=9.8, 13.7 Hz, $ArCH_2$), 2.15-1.62 (m, 4H, CH_2); ^{13}C nmr ($CDCl_3$): δ 149.1, 148.1, 128.8, 121.1, 112.2, 111.4, 61.32, 56.04, 55.88, 44.72, 37.75, 29.92, 23.33. For **3b**: (37.5%) mp 109-111° (acetone); $[\alpha]_D$ -33.6° (c=1.07, MeOH); ^1H nmr ($CDCl_3$): δ 7.3 (m, 5H, aromatic), 3.78 (bs, 1H, CHN), 3.5-3.23 (bm, 2H, CH_2N), 3.44 (dd, 1H, J=5.1, 13.4 Hz, $ArCH_2$), 3.01 (dd, 1H, J=10.1, 13.4 Hz, $ArCH_2$), 2.18-1.62 (m, 4H, CH_2); ^{13}C nmr ($CDCl_3$): δ 136.4, 129.0, 128.8, 127.1, 61.34, 44.65, 38.04, 29.84, 23.27. For **3c**: (61.6%) mp 119.5-121.5° (methyl-t-butyl ether/isopropanol); $[\alpha]_D$ -34.1° (c=1.047, MeOH); ^1H nmr ($CDCl_3$): δ 7.2 (m, 1H, thiophene), 6.95 (m, 2H, thiophene), 3.81 (m, 1H, CHN), 3.60 (dd, 1H, J=5.6, 14.7 Hz, $ArCH_2$), 3.38 (m, 2H, CH_2N), 3.28 (dd, 1H, J=9.5, 14.7 Hz, $ArCH_2$), 2.20-1.75 (m, 4H, CH_2); ^{13}C nmr ($CDCl_3$): δ 138.2, 127.2, 126.6, 124.8, 61.11, 44.93, 32.32, 30.12, 23.35.

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