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SYNTHESIS OF SUBSTITUTED 2,5-DIAZABICYCLO[2.2.1]HEPTANES

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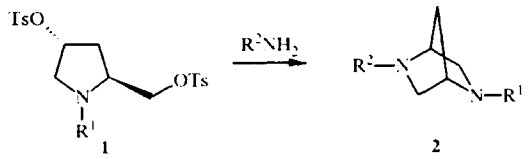
A new method is proposed for the synthesis of substituted 2,5-diazabicyclo[2.2.1]heptanes from 1-(tert-butoxycarbonyl)-4-tosyloxy-2-(tosyloxymethyl)pyrrolidine. ^{1}H NMR spectroscopy indicated multiple conformations of 2-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptanes in solution.

Keywords: diazabicycloheptanes, pyrrolidine derivatives.

Syntheses have already been reported for 2,5-diazabicyclo[2.2.1]heptanes from N-protected ditosylate of hydroxyprolinol **1** [1-4].

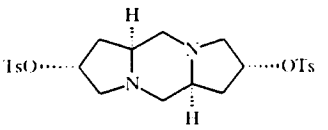


1 **2**

R^1 = Ts, COOBu-*t*; R^2 = H, Me, CH_2Ph

Product **2a** is the most interesting for the synthesis of a variety of 2,5-disubstituted 2,5-diazabicyclo[2.2.1]heptanes **2** (R^1 = CO_2Bu-*t*, R^2 = CH_2Ph). The two protective groups may be readily removed under different conditions, which permits consecutive modification of the molecule at the two nitrogen atoms.

The synthesis of **2a** was first described by Bhattacharya et al. [2]. Heating a mixture of pyrrolidine **1a** (R^1 = CO_2Bu-*t*) and benzylamine and subsequent distillation gave diazabicycloheptane **2a** in 79% yield. Our repeated attempts to repeat this synthesis were unsuccessful. Precise repetition of the procedure using even carefully dried reagents leads to the formation of diazabicyclo[2.2.1]heptane **2a** in yields of only 10-30%. We also used dicyclohexylamine and sodium hydride as the base but this did not lead to an increased yield of desired product **2a**. In all cases, the major reaction product was a compound assigned "dimeric" structure **3** on the basis of its spectrum.



3

Product **3** may be formed by removal of the *tert*-butoxycarbonyl protective group and dimerization of reactive intermediate **1b** (R^1 = H). Thus, according to our data, under vigorous conditions suitable for the cyclization of N-tosyl derivative **1c** (R^1 = Ts) [1], **1a** first loses a protective group and dimerizes. A high yield of

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TABLE 1. Chemical Shifts of the ^{1}H NMR Signals of 2,5-Diazabicyclo[2.2.1]heptanes **2**

N	R^1	R^2	Solvent	1-H, 4-H		3-H, 6-H				7-H	
2a	COOBu-t	CH_2Ph	$CDCl_3$ [2]	4.08	3.37	3.03	3.40	2.46	2.81	1.78	1.59
			DMSO-d_6	4.14	3.40	3.05	3.36	2.41	2.74	1.78	1.59
				4.20		3.12		2.45	2.78		1.65
2b	COOBu-*t*	Me	$CDCl_3$	4.20	3.33	3.10	3.45	2.45	2.81	1.83	1.65
				4.35	3.36		3.55	2.49	2.92		1.70
2c*	H	Me	CD_3OD	4.62	4.55	3.4-4.0				2.62	2.30

* Dihydrochloride.

diazabicycloheptane **2a** was obtained with a significant lowering of the reaction temperature and resultant increase in reaction time. Carrying out the reaction in benzene at 40-45°C for 45 days gave **2a** in 78% yield. The melting point of this product was about 20°C higher than reported by Bhattacharya [2].

The reaction of pyrrolidine **1a** with methylamine led to a similar result. Methylamine proved more reactive than benzylamine and this synthesis was complete after 30 days at 40°C. Diazabicycloheptane **2b** (R^1 = CO_2Bu-*t*, R^2 = Me) was isolated as an oil. Acidic hydrolysis of **2b** gave a reported compound, **2c** (R^1 = H, R^2 = Me).

Table 1 gives the chemical shifts of the signals of the ring protons in diazabicycloheptanes **2**. The form of the spectrum of **2a** is solvent-dependent. One set of signals is found in deuterochloroform [2], while two sets of signals are seen for most of the protons in DMSO. In our opinion, this discrepancy is related to the existence of two rotamers due to hindered rotation about the amide CO–N bond. The conformer ratio is about 1:1. Similar behavior was found in the spectrum of diazabicycloheptane **2b** taken in deuterochloroform. The ratio of the sets of signals was also 1:1.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker DPX-300 spectrometer. Thin-layer chromatography on Silufol plates was used to monitor the reaction course and product purity. Enantiomerically pure pyrrolidine **1a** obtained from *L*-hydroxyproline was used. The synthetic method was described by Portoghese [1] and Bhattacharya [2].

2-*tert*-Butoxycarbonyl-5-benzyl-2,5-diazabicyclo[2.2.1]heptane (2a). A solution of pyrrolidine **1a** (4.00 g, 7.6 mmol) and benzylamine (2.44 g, 22.8 mmol) in dry benzene (75 ml) was maintained for 45 days at 40-45°C. In order to complete the reaction, the mixture was heated at reflux for 15 h. After cooling, benzylamine tosylate was filtered off and the filtrate was evaporated. The product was extracted from the oil obtained using five 20-ml portions of boiling hexane. Hexane was evaporated to give **2a** (1.71 g, 5.9 mmol, 78%); mp 72-75°C (52-57°C [2]).

Reaction of Pyrrolidine 1a with Benzylamine in the Presence of Sodium Hydride. A mixture of pyrrolidine **1a** (0.53 g, 1 mmol), benzylamine (1.15 g, 1.4 mmol), and sodium hydride (0.1 g, 40 mmol) was heated at reflux in dry toluene (8 ml) for 8 h. After cooling, the precipitate was filtered off and the filtrate was evaporated. The oily product was extracted with three 10-ml portions of boiling hexane. Evaporation of hexane gave **2a** (0.09 g, 0.3 mmol, 30%). The solid residue after extraction with hexane was washed with ether to give dimer **3** (0.11 g, 0.2 mmol, 40%); mp 106-109°C. ^{1}H NMR spectrum in $CDCl_3$: 1.68 (2H, 1-H, 6-H); 2.33 (2H, 1'-H, 6'-H); 2.50 (6H, Me); 3.19 (2-H, 3-H, 8-H); 3.94 (2H, 3'-H, 8'-H); 4.12 (2H, 5a-H, 10a-H); 4.19 (2H, 5-H, 10-H); 4.53 (2H, 5'-H, 10'-H); 5.18 (2H, 2-H, 7-H); 7.40 (3H, Ar–H); 7.80 ppm (4H, Ar–H). $J_{1,1'}$ = 14 Hz, $J_{5,5'}$ = 14 Hz, $J_{10,10'}$ = 9 Hz, $J_{1,2}$ = 6 Hz, $J_{1,10a}$ = 8 Hz, $J_{1',10a}$ = 5 Hz, $J_{2,3}$ = 6 Hz, $J_{10,10a}$ = 2 Hz, $J_{10',10a}$ = 8 Hz. The other coupling constants are small and could not be determined from the spectrum.

2-*tert*-Butoxycarbonyl-5-methyl-2,5-diazabicyclo[2.2.1]heptane (2b). A solution of pyrrolidine **1a** (7.9 g, 15.0 mmol) in toluene (100 ml) and methylamine (2 g, 65 mmol) in methanol (15 ml) was stirred. The reaction mixture was maintained at 40°C for 30 days and cooled. Methylamine tosylate was filtered off. The filtrate was evaporated to dryness and dissolved in ether (10 ml). A small amount of residue insoluble in ether was filtered off. Ether was evaporated to give **2b** (2.9 g, 13.7 mmol, 90%) as an oil.

2-Methyl-2,5-diazabicyclo[2.2.1]heptane Dihydrochloride (2c). A sample of concentrated hydrochloric acid (5 ml) was added to a solution of **2b** (2.8 g, 13.2 mmol) in methanol (20 ml) and the mixture was maintained for 48 h at 20°C. The solvent was evaporated and the residue was recrystallized from 2-propanol to give dihydrochloride **2c** (1.8 g, 9.7 mmol, 73%); mp 260-270°C (dec.) (264°C (dec.) [4]). Mass spectrum: M^+: 112.

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