NEW AND EFFICIENT SYNTHESES OF 4-CARBAMOYLQUINUCLIDINE

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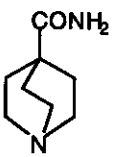
Abstract - Two efficent routes starting from 4-carbamoylpiperidine or 2,2',2"-trichlorotriethylamine were developed for preparing 4-cyanoquinuclidine which was hydrolyzed to give 4-carbamoylquinuclidine, a chemical modifier of cephalosporin antibiotics.

Quinuclidine and its 4-substituted derivatives, which have threefold symmetry, have been prepared mainly from theoretical and pharmacological viewpoints.[1-11] Recently 4-carbamoylquinuclidine (**1**) was found to be a useful chemical modifier for cephalosporin antibiotics. Namely, cephalosporin E-1040, which shows a strong antibiotic activity against pseudomonas bacteria, is a 7-aminocephalosporanic acid derivative having 4-carbamoylquinuclidine moiety.[11]



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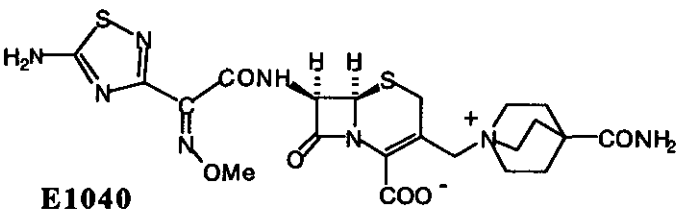
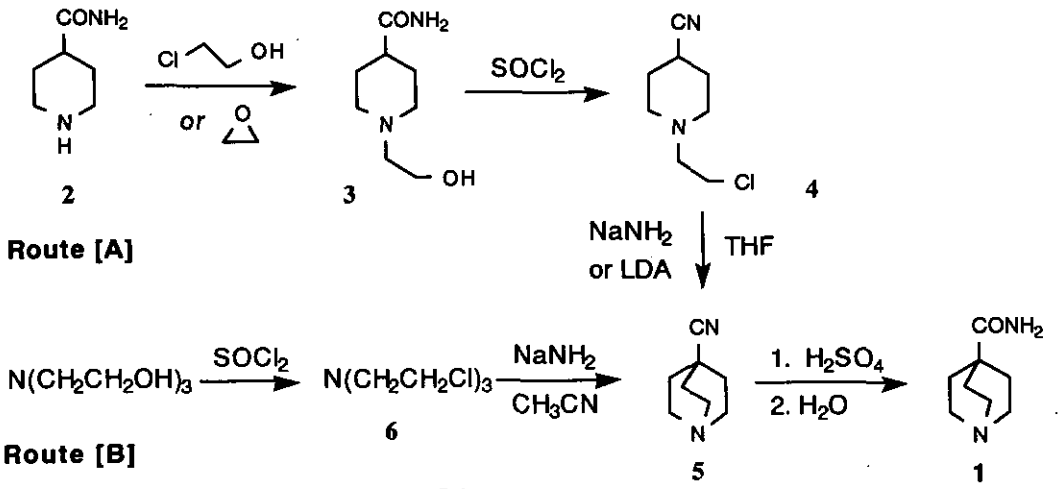


E1040

For the synthesis of 4-substituted quinuclidines, bothersome methods[1-3,5,6] were reported. For instance, 4-carbamoylquinuclidine (**1**) was synthesized in literature by two methods: One utilizes 1-benzyl-4-piperidone as a starting material, which is transformed into **1** through seven steps.[6,10] Other comprises five steps starting from

isonipecotamide.[1,2] Both of these methods are unsatisfactory in viewpoint of yield and manipulation. We initiated investigation to develop efficient syntheses of **1**, which is the subject of the present paper.



Scheme 1

We chose 4-cyanoquinuclidine (**5**) as a synthetic precursor of **1**, and the convenient synthesis of **5** as well as its hydrolysis was investigated. As summarized in Scheme 1, two routes for preparing **5** were examined. The starting material of the first route (Route [A]) is 4-carbamoylpiperidine (**2**), easily obtainable by reduction of isonicotinamide.[5] Transformation of **2** into 4-carbamoyl-1-(2-hydroxyethyl)piperidine (**3**) was achieved by the reaction with 2-chloroethanol or ethylene oxide. A mixture of **2**, potassium carbonate, and 2-chloroethanol in ethanol was refluxed for 3 h to give **3** in 96% yield. Ethylene oxide smoothly reacted with **2** in methanol at room temperature for 3 h and the yield of **3** was 90%.

On treatment of **3** with thionyl chloride (2.55 equiv.) in acetonitrile, dehydration of the carbamoyl group and substitution of the hydroxyl group with chlorine atom concurrently occurred to form 1-(2-chloroethyl)-4-cyanopiperidine (**4**). In this reaction, acetonitrile was suitably employed as a solvent because of its high solubility of **3** and a high yield (85%) of **4** was attained. Here it is emphasized that the carbamoyl group was protected as a cyano group for the next step. Intramolecular cyclization of **4** to give **5** was achieved by sodium amide (22 °C/5 h) or lithium diisopropylamide (LDA) (-78 °C/1 h) in tetrahydrofuran (THF). The yield of **5** was 67% in both cases. The thus obtained **5** was transformed into the corresponding tosylate salt by treatment with *p*-toluenesulfonic acid because it is an easily handled form of **5**.

Another route leading to **5** (Route [B]) is one-step condensation of acetonitrile with 2,2',2"-trichlorotriethylamine (**6**). This route is extremely effective, but it must be performed very carefully because the amine (**6**) is vesicant and necrotizing irritant .[12] After many efforts, we established the best conditions: A suspension of sodium amide (3.08 equiv. to acetonitrile) in 1,2-dimethoxyethane (DME) was pretreated with a small amount (0.15 mol% to sodium amide) of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) at room temperature for 20 min, and then a DME solution of acetonitrile was dropwise added at a temperature of 30-40 °C. The resulting mixture was further stirred for 1 h to give **5**, which was isolated as its tosylate in 65% yield. The presence of a small amount of HMDS is crucial. In the absence of HMDS, the reaction did not take place at all. The increasing amount of HMDS caused undesired side reaction(s). It is reasonably assumed that HMDS always creates a trace of soluble strong base (sodium hexamethyldisilazide) in the reaction system.

The hydrolysis of **5** was reported in literature.[7] We examined direct hydrolysis of the tosylate salt of **5** . The tosylate was added to 98% sulfuric acid at room temperature and the resulting mixture was stirred at 40 °C for 2 h. Addition of 2-propanol deposited the sulfate of **1**, which was neutralized with potassium hydroxide in a mixture of acetonitrile and methanol at an elevated temperature (70-75 °C) to yield **1** in a free form. Since **1** is very soluble in water, aqueous conditions are unsuitable for hydrolysis of **5**. Other combinations of a solvent and a base such as ammonia/methanol and sodium methoxide/methanol are also applicable to the present neutralization.

In conclusion, two routes of Scheme 1 were developed for the preparation of 4-carbamoylquinuclidine (**1**). The route starting from 2,2',2"-trichlorotriethylamine (**6**) (Route [B]) is straightforward, but special attention should be paid to handling of **6** . Therefore, Route [A] seems to be suitable for a large-scale preparation of **1** .

EXPERIMENTAL

(l) *N-(2-Hydroxyethyl)-4-carbamoylpiperidine (3)*

To a solution of 4-carbamoylpiperidine (**2**) (35.0 g, 0.275 mol) in ethanol (500 ml) were added 2-chloroethanol (26.7 g, 0.33 mol), potassium carbonate (82.0 g, 0.59 mol) and sodium iodide (4.5 g, 30 mmol). The mixture was refluxed for 20 h. Then celite (5 g) was added and the insoluble solid was filtered off. The filtrate was concentrated in vacuo to semisolid state, and the deposited solid was collected by filtration and washed with 2-propanol (50 ml) to give **3** (45.0 g; 96% yield). **3**: colorless crystals; mp 141-142 °C (from ethyl acetate); ir (KBr) 3360, 3160, 1650, 1610 cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.53 (2H, dq, J=3.6 and 12.3 Hz), 1.62 (1H,

diffused d, J=11.2 Hz), 1.90 (2H, dt, J=2 .6 and 11.7 Hz), 2.10 (1H, m), 2,33 (2H, t, J=6.4 Hz), 2.84 (2H, diffused d, J=11.4 Hz), 3.46 (2H, dt, J=5.5 and 6.2 Hz), 4.29 (1H, t, J=5.3 Hz, OH), 6.65 (1H, br s, NH), and 7.15 (1H, br s, NH). Anal. Calcd for $C_8H_{16}N_2O_2$: C,55.15; H, 9.26; N,16.08. Found: C, 55.38; H, 8.99; N, 16.27.

(II) *N-(2-Chloroethyl)-4-cyanopiperidine (4).*

To a suspension of **3** (38.7 g, 0.22 mol) in acetonitrile (390 ml) was dropwise added thionyl chloride (135.3 g, 1.13 mol) below 5 °C under being externally cooled with ice. The mixture was refluxed for 4 h and evaporated under a reduced pressure. After addition of 2-propanol (100 ml), the mixture was refluxed for 10 min and then was cooled to room temperature. The deposited crystals (the HCl salt of **4**) were collected by filtration. Addition of isopropyl ether to the mother liquor afforded the HCl salt of **4** as colorless crystals. The total amount of the HCl salt of **4** was 43.1 g (85% yeild). The HCl salt of **4**: colorless crystals; mp 176-178 °C (from ethanol); ir (KBr) 2456 and 2244 cm^{-1}; ^1H nmr (DMSO-d_6) δ 2.14 (2H, diffused d, J=14.7 Hz), 2.79 (2H, diffused t, J=about 14 Hz), 3.14 (1H, diffused s), 3.21 (1H, diffused s), 3.40 (2H, diffsed s), 3.68 (2H, diffused d, J=12.1 Hz), 4.10 (2H,t, J=6.0 Hz). Anal. Calcd for $C_8H_{13}N_2Cl$+HCl: C, 45.94; H, 6.74; N, 13.39. Found: C, 45.85; H, 6.72; N, 13.43.

(III) *4-Cyanoquinuclidine (5)*

To a suspension of sodium amide (150.9 g, 3.84 mol) and sodium iodide (7.2 g) in 1,2-dimethoxyethane (1500 ml), was added **4** (100.0 g, 0.478 mol), and the resulting mixture was stirred for 24 h at room temperature. Then the reaction mixture was poured into ice-water (2000 ml). After addition of celite (50 g), the insoluble solid was filtered off. Organic layer separated from aqueous layer. The organic layer was dried (potassium carbonate) and evaporated to give **5** (35.2 g) as colorless crystals. The aqueous layer was extracted with chloroform (2000 ml). The extract was washed with a saturated aqueous solution of potassium carbonate and evaporated to give **5** (8.4 g). The total yield was 43.6 g (66.9%). **5**: colorless crystals; mp 133 °C (lit.,[3] mp 135 °C); ir (KBr) 2230 cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.74 (6H, A_2B_2-type t, J=7.7 Hz) and 2.76 (6H, A_2B_2-type t, J=7.7 Hz); ms (70 eV) m/z 137(MH^+). Anal. Calcd for $C_8H_{12}N_2$: C, 70.52; H, 8.88; N, 20.56. Found: C, 70.30; H, 8.77; N, 20.34.

To a solution of **5** (85.0 g, 0.62 mol) in ethanol (200 ml) was added *p*-toluenesulfonic acid hydrate (119.0 g, 0.635 mol), and the mixture was stirred for 1 h at 40 °C. After being cooled with ice-water, the precipitates were collected by filtration and washed with ethanol (30 ml) to give the tosylate of **5** (182.9 g, 95%). The

tosylate of **5**: colorless crystals; mp 220 °C; ir (KBr) 2978, 2585, 1223, 1122, 1038, and 1007 cm^{-1}; ^1H nmr (DMSO-d_6) δ 2.19 (6H, A_2B_2-type t, J=8.1 Hz), 2.29 (3H, s), 3.31 (6H, A_2B_2-type t, J=8.1 Hz), 7.11 (2H, d, J=7.7 Hz), and 7.48 (2H, d, J=8.1 Hz), and 9.52 (1H, s, HO_3S). Anal. Calcd for $C_8H_{12}N_2+C_7H_8O_3S$: C, 58.42; H, 6.54; N, 9.08. Found: C, 58.27; H, 6.57; N, 9.01.

(IV) *Preparation of 4-cyanoquinuclidine (5) from 2,2',2"-trichlorotriethylamine (6).*

To a suspension of sodium amide (30.4 g, 0.78 mol) in 1,2-dimethoxyethane (180 ml) was added 1,1,1,3,3,3-hexamethyldisilazane (2.9 g, 1.2 mmol), and the mixture was stirred for 20 min at room temperture. Then a solution of acetonitrile (10.4 g, 0.25 mol) and **6** (40.0 g, 0.253 mol) in 1,2-dimethoxyethane (120 ml) was dropwise added at 30-40 °C. The reaction mixture was further stirred for 1 h and poured into ice-water (90 ml). The organic layer was separated and the aqueous layer was extracted with chloroform (150 ml x 2). The combined organic layers were dried (magnesium sulfate) and evaporated. Then *p*-toluenesulfonic acid hydrate (37.2 g, 0.19 mol) in methanol (40 ml) was added. After addition of ethanol (300 ml), the deposited precipitate was collected by filtration and dried to give the tosylate of **5** (39.2 g, 65% yield).

(V) *4-Carbamoylquinuclidine (1).*

The tosylate (18.0 g, 58 mmol) of **5** was added into 98% sulfuric acid (30.0 g, 0.30 mol) at room temperature, and the reaction mixture was stirred for 2 h at 40 °C. Then the reaction mixture was dropwise added to 2-propanol (150 ml) at 5 °C to deposit the sulfate of **1** (14.2 g, 94%) which was isolated by filtration, washed with 2-propanol, and dried. The sulfate of **1**: colorless crystals; mp 204-205 °C (from methanol); ir (KBr) 3360, 3182, 2925, 2793, 2649, 1664, 1662 cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.92 (6H, A_2B_2-type t, J=8.1 Hz), 3.26 (6H, A_2B_2-type t, J=8.1 Hz), 7.07 (1H, br s, HN), 7.25 (1H, br s, HN), 9.43 (2H, br s, H_2SO_4) Anal. Calcd for $C_8H_{14}N_2O+H_2SO_4$: C, 38.03; H, 6.34; N, 11.10. Found: C, 37.97; H, 6.25; N, 11.08.

To a solution of potassium hydroxide (6.0 g, 0.10 mol) in methanol (6 ml) and acetonitrile (12 ml) was added the sulfate of **1** (14.2 g, 54.9 mmol) together with acetonitrile (180 ml). The mixture was refluxed for 1 h at 70-75 °C. After addition of celite (5 g), the hot solution was subjected to filtration. The filtrate was evaporated until the volume became 70 ml, and the deposited precipitate was collected by filtration and washed with acetonitrile to give **1** (6.09 g, 72%) as colorless crystals: mp 234-235 °C (from acetonitrile) (lit.,[8] mp 222-224 °C); ir (KBr) 3225, 3125, 1686, and 1645 cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.51 (6H, A_2B_2-type t, J=7.7 Hz), 2.71 (6H, A_2B_2-type t, J=7.7 Hz), 6.71 (1H, br s, HN), and 6.87 (1H, br s, HN); ms (70eV) m/z 155 (MH^+); Anal. Calcd for $C_8H_{14}N_2O$: C, 62.30; H, 9.15; N, 18.16. Found: C, 62.32; H, 9.25; N, 18.06.

REFERENCES

1 C. A. Grob and E. Renk, *Helv. Chim. Acta*, 1954, **37**, 1672 .

2 C. A. Grob and E. Renk, *Helv. Chim. Acta*, 1954, **37**, 1681.

3 T. D. Perrine, *J. Org. Chem.*, 1957, **22**. 1484.

4 C. A. Grob, R. M. Hoegerle, and M. Ohta, *Helv. Chim. Acta*, 1962, **45**, 1823.

5 H. P. Fischer and C. A. Grob, *Helv. Chim. Acta*, 1968, **51**, 153.

6 W. Eckhardt, C. A. Grob, and W. D. Treffert, *Helv. Chim. Acta*, 1972, **55**, 2432.

7 C. A. Grob, W. Simon, and W. D. Treffert, *Helv. Chim. Acta*, 1972, **55**, 2439.

8 B. Stephenson, G. Solladie, and H. S. Mosher, *J. Am. Chem. Soc.*, 1972, **94**, 4184.

9 J. Palecek and J. Hlavaty, *Coll. Czech. Chem. Comm.*, 1973, **38**, 1985 (*Chem. Abstr.*, 1973, **79**, 145795d)

10 E. Ceppl and C. A. Grob, *Helv. Chim. Acta*, 1974, **57**,2332.

11 N. Watanabe, K. Katsu, M. Moriyama, and K. Kitoh, *Antimicrob. Agents Chemother.*, 1988, **32**, 693.

12 Merck Index 11th edition, No. 9560, 1989.

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