Synthesis of 1,3,5-triazabicyclo[3.1.0]hexanes containing the fragments of α-amino acids and their esters at the N(3) atom

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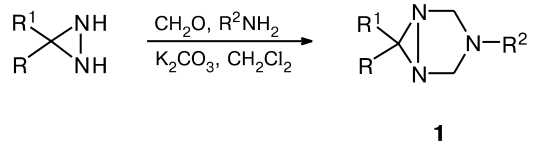
With 3,3-pentamethylene-1,2*H*-diaziridine as an example, it was shown that 3,3-dialkyl-1,2*H*-diaziridines can undergo cyclocondensation with α-amino acids and their esters to give the corresponding N(3)-substituted 1,3,5-triazabicyclo[3.1.0]hexanes, including pure enantiomers.

Key words: 1,2*H*-diaziridines, 1,3,5-triazabicyclo[3.1.0]hexanes, α-amino acids, esters of α-amino acids, cyclocondensation, α-aminomethylation, enantiomers.

The diaziridine ring in bicyclic *cis*-diaziridines (1,5-diaza- and 1,3,5-triazabicyclo[3.1.0]hexanes) is achiral because its plane of symmetry passes through the cyclic C atom and the midpoint of the N—N bond.[1,2] 2,4,6-Trisubstituted 1,3,5-triazabicyclo[3.1.0]hexanes are chiral due to asymmetric C(2) and C(4) atoms.[3,4] Earlier,[5—7] we developed a method for the synthesis of achiral 2,4-unsubstituted 1,3,5-triazabicyclo[3.1.0]hexanes **1** by cyclocondensation of 1,2*H*-diaziridines with formaldehyde and ammonia or primary aliphatic amines in aprotic media in the presence of K_2CO_3 (3—10 days, 20 °C) (Scheme 1). This reaction involves α-aminomethylation of the diaziridine ring at the N atoms, because 1*H*- and 1,2*H*-diaziridines were found earlier[8—10] to enter into the Mannich reaction only as NH acids.

Scheme 1



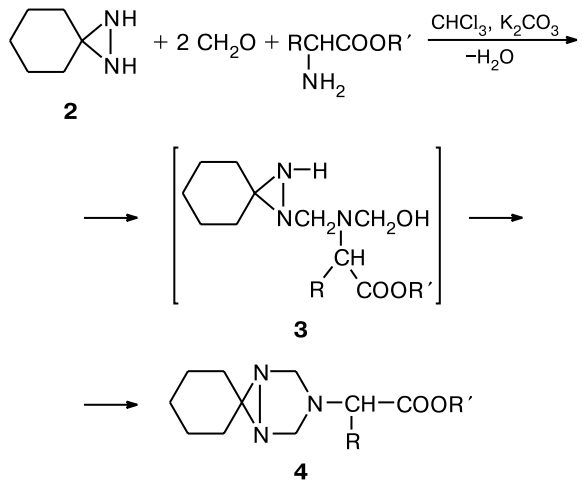
1

R, R^1, R^2, = H, Alk

To introduce an asymmetric center into compounds **1**, the present study is devoted to cyclocondensation of 1,2*H*-diaziridines with formaldehyde and α-amino acids and their esters (including pure (*S*)- or (*R*)-enantiomers). Because diaziridines (including 1,3,5-triazabicyclo[3.1.0]hexane derivatives[11]) are known to be biologically active, introduction of an additional pharmacophoric group can also be of practical value.

The starting diaziridine was 3,3-pentamethylene-1,2*H*-diaziridine **2**, while α-amino acids were represented by glycine, its ethyl ester, and methyl esters of (*S*)-(−)- and (*R*)-(+)-valine. The reactions were carried out in $CHCl_3$ at ~20 °C for five to ten days, with K_2CO_3 as a dehydrant. The reaction completion could be expected to require a longer period of time since the amino group in esters of α-amino acids is less basic (pK_a ~7.5)[12] than ammonia (pK_a 9.21) or primary aliphatic amines (pK_a ~9.8—10.5).[13] However, the reactions of compound **2** with amino acids or their esters were completed within a time comparable

Scheme 2



2

3

4

4a: R = H, R′ = H (isolated as a K^+ salt)
4b: R = H, R′ = Et
***S*-4c:** R = Pr^i, R′ = Me (*S*-isomer)
***R*-4c:** R = Pr^i, R′ = Me (*R*-isomer)

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Table 1. Yields, reaction times, and some physicochemical characteristics of the 1,3,5-triazabicyclo[3.1.0]hexanes **4** obtained

Compound	Yield (%)	M.p. /°C	τ/h [a]	R_f [b]	Found / Calculated (%)			Molecular formula
					C	H	N	
4a	68	79 (decomp.)	240	0	48.42 48.17	7.14 6.47	16.09 16.85	$C_{10}H_{16}KN_3O_2$
4b	75	Oil	120	0.42	61.20 60.23	9.07 8.84	17.22 17.56	$C_{12}H_{21}N_3O_2$
***S*-4c**	77	Oil	192	0.46	62.27 62.89	10.05 9.42	15.59 15.72	$C_{14}H_{25}N_3O_2$
***R*-4c**	65	Oil	192	0.46	62.32 62.89	9.85 9.42	15.61 15.72	$C_{14}H_{25}N_3O_2$

[a] Reaction time.
[b] The eluent for compounds **4a**—**c** is $CHCl_3$: MeOH = 9 : 1.

with that in the synthesis of compounds **1** (TLC data). In all cases, the expected 1,3,5-triazabicyclo[3.1.0]hexanes **4a**—**c** containing the fragments of α-amino acids at the N(3) atom were obtained. Apparently, the cyclization of intermediate **3** is the rate-limiting step in the synthesis of both compounds **1** and **4** (Scheme 2).

Compounds **4b,c** were isolated by column chromatography on SiO_2, while compound **4a** was reprecipitated from anhydrous $CHCl_3$ with diethyl ether. Compound **4a** obtained as a potassium salt is unstable in protic media and when heated.

The yields and some physicochemical characteristics of compounds **4** are given in Table 1; their spectral parameters are presented in Table 2.

As expected, the reactions with methyl esters of (*R*)-(+)-valine and (*S*)-(−)-valine afforded the corresponding enantiomeric 1,3,5-triazabicyclo[3.1.0]hexanes *S*(*R*)-**4c**. These compounds have identical spectral parameters and optical rotation values close in magnitude but opposite in sign.

Experimental

IR spectra were recorded on a UR-20 spectrometer (KBr pellets). NMR spectra were recorded in $CDCl_3$ on Bruker WM-250 (^{1}H, 250 MHz) and Bruker AM-300 spectrometers (^{13}C, 75.5 MHz); the chemical shifts are given on the δ scale with reference to Me_4Si. TLC was carried on Silufol-UV-254

Table 2. Spectroscopic data for the 1,3,5-triazabicyclo[3.1.0]hexanes **4** obtained

Compound	IR ν/cm^{-1}	^{1}H NMR, δ (*J*/Hz)	^{13}C NMR, δ
4a	747, 811, 831, 935, 1076, 1167, 1354, 1372, 1492, 1538, 1596, 1607, 2926, 3100	1.30—2.00 (m, 10 H, 5 CH_{2ring}); 3.10 (br.s, 2 H, NCH_2CO); 3.70 (m, 4 H, 2 NCH_2N)	21.4 (CH_2); 24.7 (CH_2); 25.5 (CH_2), 55.7 ($N\underline{C}H_2CO$); 60.1 (C); 71.5 (NCH_2N); 170.3 (CO)
4b	752, 831, 903, 967, 1116, 1189, 1400, 1475, 1508, 1599, 1654, 1688, 2830, 3125	1.19 (t, 3 H, Me, ^3J = 7.0); 1.35—1.62 (m, 8 H, 5 CH_{2ring}); 2.05—2.10 (m, 2 H, CH_{2ring}); 3.27 (s, 2 H, NCH_2CO); 3.62, 4.05 (AB system, 4 H, 2 NCH_2N, ^2J = 12.4); 4.13 (q, 2 H, $O\underline{C}H_2Me$, ^3J = 7.0)	14.1 (Me); 21.4 (CH_2); 24.8 (CH_2); 25.5 (CH_2); 64.5 ($N\underline{C}H_2CO$); 61.1 ($O\underline{C}H_2C$); 65.1 (C); 67.7 (NCH_2N); 170.7 (CO)
4c	730, 830, 915, 952, 1113, 1160, 1250, 1380, 1580, 1606, 1676, 1699, 2820	0.74 and 0.85 (both d, 3 H each, 2 Me, ^3J = 6.5); 1.29—1.61 (m, 8 H, 5 CH_{2ring}); 1.79 (m, 1 H, $C\underline{H}Me_2$); 1.98—2.07 (m, 2 H, CH_{2ring}); 2.91 (d, 1 H, N—CH, ^3J = 7.3); 3.62 (s, 3 H, OMe); 3.65, 3.81 and 3.77, 3.93 (both signals AB system, 4 H, 2 NCH_2N, ^2J = 12.0)	18.9 ($C\underline{Me}$); 19.9 ($C\underline{Me}$); 24.0 (CH_2); 24.2 (CH_2); 25.5 (CH_2); 25.6 (CH_2); 37.5 ($C\underline{C}H$); 51.0 (OMe); 64.1 (C); 64.3 (NCH_2N); 67.4 (NCH_2N); 68.3 (NCH); 171.5 (CO)

plates; spots were visualized in the vapor of I_2 and, independently, by spraying a solution of diphenylamine in acetone followed by heating of the plate. Melting points were determined on a Gallenkamp Sanyo instrument; optical rotation values were measured in a methanolic solution on a Polamat A instrument.

Synthesis of 1,3,5-triazabicyclo[3.1.0]hexanes 4a—c (general procedure). A corresponding ester of amino acid or glycine (8.93 mmol) and K_2CO_3 (4.5 g, 44.65 mmol) were added to a solution of 3,3-pentamethylenediaziridine **2** [14] (1 g, 8.93 mmol) in 50 mL of dry $CHCl_3$. The reaction mixture was stirred at ~20 °C for 120—240 h; the course of the reaction was monitored by TLC. After the completion of the reaction, the precipitate was filtered off and washed with anhydrous $CHCl_3$, and the solvent was removed *in vacuo*. Compounds **4b,c** were isolated by column chromatography on SiO_2 (silica gel 40—100 μm, $CHCl_3$: MeOH = 9 : 1), while compound **4a** was reprecipitated with Et_2O from anhydrous $CHCl_3$. Compounds **4a**—**c** were obtained.

{Spiro[cyclohexane-6-(1,3,5-triazabicyclo[3.1.0]hex-3-yl)]}acetic acid, potassium salt (4a). The yield was 1.5 g.

Ethyl {spiro[cyclohexane-6-(1,3,5-triazabicyclo[3.1.0]hex-3-yl)]}acetate (4b). The yield was 1.6 g.

Methyl (2*S*)-(−)-3-methyl-2-{spiro[cyclohexane-6-(1,3,5-triazabicyclo[3.1.0]hex-3-yl)]}butanoate (*S*-4c). The yield was 1.8 g, $[\alpha]^{20}_{546}$ −20.8 (*c* 1.44, MeOH).

Methyl (2*R*)-(+)-3-methyl-2-{spiro[cyclohexane-6-(1,3,5-triazabicyclo[3.1.0]hex-3-yl)]}butanoate (*R*-4c). The yield was 1.55 g, $[\alpha]^{20}_{546}$ +20.4 (*c* 1.44, MeOH).

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References

1. G. V. Shustov, S. N. Denisenko, I. I. Chervin, N. L. Asfandiarov, and R. G. Kostyanovsky, *Tetrahedron*, 1985, **41**, 5719.
2. C. N. Denisenko, G. V. Shustov, I. I. Chervin, and R. G. Kostyanovskii, *Khim. Geterotsikl. Soedin.*, 1985, 1348.
3. P. Rademacher and H. R. Koopman, *Chem. Ber.*, 1975, **108**, 1557.
4. H. R. Koopman and P. Rademacher, *Spectrochim. Acta.*, 1976, **32A**, 157.
5. N. N. Makhova, A. N. Mikhailyuk, A. E. Bova, V. Yu. Petukhova, T. V. Chabina, and L. I. Khmelnitskii, *Mendeleev Commun.*, 1992, 146.
6. N. N. Makhova, A. N. Mikhailyuk, A. E. Bova, T. V. Chabina, and L. I. Khmel´nitskii, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 2091 [*Russ. Chem. Bull.,* 1993, **42**, 2004 (Engl. Transl.)].
7. N. N. Makhova, V. Yu. Petukhova, T. V. Chabina, and L. I. Khmel´nitskii, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1665 [*Russ. Chem. Bull.*, 1993, **42**, 1602 (Engl. Transl.)].
8. G. Paget and C. S. Davis, *J. Med. Chem.,* 1964, **7**, 626.
9. A. A. Dudinskaya, A. E. Bova, L. I. Khmel´nitskii, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1971, 1523 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1971, **20**, 1419 (Engl. Transl.)].
10. O. G. Nabiev, M. A. Shakhgel´diev, I. I. Chervin, and R. G. Kostyanovskii, *Dokl. Akad. Nauk SSSR*, 1985, **284**, 872 [*Dokl. Chem.,* 1985, **284** (Engl. Transl.)].
11. R. G. Kostyanovskii, G. V. Shustov, O. L. Nabiev, S. N. Denisenko, S. A. Sukhanova, and E. F. Lavretskaya, *Khim.-Farm. Zh.*, 1986, **6**, 671 [*Pharm. Chem. J.*, 1986, **6**, 385 (Engl. Transl.)].
12. J. P. Greenstein and M. Winitz, *Chemistry of the Amino Acids*, Wiley, New York, 1961.
13. A. Albert and E. Sergeant, *Ionization Constants of Acids and Bases*, Khimiya, Moscow, 1964.
14. S. R. Paulsen and G. Huck, *Ber.*, 1961, **94**, 968.

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