A Stereoselective Preparation of 1,2,7-Triazabicyclo[3.3.0]oct-2-enes

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5-(Alkylamino)methyl-2-pyrazolines react with ketones or aldehydes to give 1,2,7-triazabicyclo-[3.3.0]oct-2-enes in high yields. The reaction gives only one diastereomer with various aldehydes, except for CH_3CHO.

INTRODUCTION

Compounds with polyazabicyclo[3.3.0]octane skeleton are useful for pharmacological and other purposes.[1-8] We reported previously a novel method to prepare 2,3,7-triazabicyclo[3.3.0]oct-2-enes (**1**) and their tautomers, 2,3,7-triazabicyclo[3.3.0]oct-3-enes (**2**), by one-pot multiple-step reaction of allyl azide and alkenes carrying electron-withdrawing groups.[9] In this paper we describe the preparation of 1,2,7-triazabicyclo[3.3.0]oct-2-enes (**3**).

RESULTS AND DISCUSSION

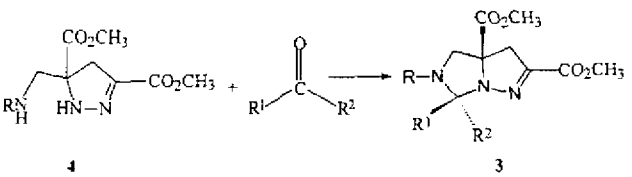
There are precedents of cyclization by forming two C-N bonds from condensation of aldehylde or ketone with an amine and a hydrazono NH.[10,11] Therefore we anticipated 1,2,7-triazabicyclo[3.3.0]oct-2-enes may be prepared from condensation of 5-(alkylamino)methyl-2-pyrazolines (**4**) and aldehyde or ketone. 5-(Alkylamino)methyl-2-pyrazolines (**4**) were obtained conveniently and in high yields from the reaction of alkyl azides with alkenes carrying electron-withdrawing groups in one pot procedure. The reaction was initiated by an intermolecular dipolar cycloaddition to give triazoline, which underwent an isomerization to α-(alkylamino)methyl diazoacetate. Another intermolecular dipolar cycloaddition occurred to give the observed product.[12] When 3,5-dimethoxycarbonyl-5-(propylamino)methyl-2-pyrazoline (**4a**) was allowed to react with acetone, a yellow liquid was obtained (Table 1). The structure of this condensation product is evident from the mass, ^1H and ^{13}C NMR spectral analyses. The ^1H NMR spectrum showed two non-equivalent methylenes with coupling constants of 9.6 and 18.1 Hz, respectively, indicating the presence of imidazolidine and pyrazoline rings. When **3a** is exposed to air for a prolonged time a white solid, which is insoluble in chloroform but soluble in water, is obtained. Hydrolysis of **4a** also gives the same compound. The NMR spectra of this compound are consistent with the structure of 5-hydroxycarbonyl-3-methoxycarbonyl-5-(propylamino)methyl-2-pyrazoline (**5a**). The ester at C-5 of **4a** was hydrolyzed as evidenced by shift of its resonance (at δ_c 173.4) to a downfield (δ_c 179.4) attributable to the carboxylic group in **5a**.

Similarly, the reaction of **4b** and **4c** with acetone also gave **3b** and **3c**, respectively, in high yields.

Since the reaction of propyl azide and methyl acrylate, giving **4a**, would not be interfered with acetone as the solvent, it was anticipated that the reaction of alkyl azide with methyl acrylate using acetone as the solvent could give **3a** directly in one pot. Indeed, **3a** was obtained neatly in a 78% isolated yield. The two-step protocol, by initial preparation of **4a** (80%) and subsequent condensation of **4a** with acetone (88%) gave **3a** in an inferior total yield (70%).

The reactions of other ketones and aldehydes with **4a** were also studied. The reaction of methyl ethyl ketone and **4a** gave **3d** as a mixture of two diastereomers (5:1). How-

Table 1.



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Entries	product	R	R^1	R^2	yield
1	**3a**	$CH_3(CH_2)_2$	CH_3	CH_3	88%
2	**3b**	$CH_3(CH_2)_3$	CH_3	CH_3	90%
3	**3c**	$C_6H_5CH_2$	CH_3	CH_3	91%
4	**3d***	$CH_3(CH_2)_2$	CH_3	CH_3CH_2	87%
5	**3e**	$CH_3(CH_2)_2$	H	H	95%
6	**3f***	$CH_3(CH_2)_2$	H	CH_3	90%
7	**3g**	$CH_3(CH_2)_2$	H	$C(CH_3)_3$	88%
8	**3h**	$CH_3(CH_2)_2$	H	$CH(CH_3)_2$	95%
9	**3i**	$CH_3(CH_2)_2$	H	$(CH_2)_2CH_3$	87%
10	**3j**	$CH_3(CH_2)_2$	H	2-naphthyl	80%
11	**3k**	$C_6H_5CH_2$	H	C_6H_5	85%
12	**3l***	$C_6H_5CH_2$	H	CH_3	90%

* The product existed as a mixture of two diastereomers.

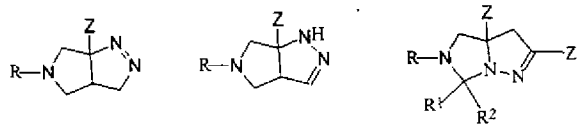
ever, when **4a** was treated with diethyl ketone, methyl isopropyl ketone or acetophenone, no product with 1,2,7-triazabicyclo[3.3.0]oct-2-ene skeleton was obtained; only starting materials were recovered. It seemed that condensation was prevented by a steric hindrance from the alkyl or aryl groups of the ketone.

Formalin reacted with **4a** to give **3e** in a low yield (40%), presumably due to further hydrolysis to carboxylic acid as in that from **4a** to give **5a**. It was anticipated that using paraformaldehyde to replace formalin would solve the hydrolysis problem of **4a** during the condensation reaction. Indeed, the reaction using paraformaldehyde in methanol as the source of the formaldehyde resulted in a 95% yield of **3e**.

Acetaldehyde reacted with **4a** to give two diastereomers of **3f** in a 1:1 ratio and a yield of 90%. However, the reaction of **4a** with other aldehydes carrying more bulky alkyl or aryl substituentes gave only one diastereomer in good yields. A similar trend was observed in the reaction of **4c** with aldehydes.

In order to determine the stereochemistry of these products, an NOE study of **3k** was carried out. Irradiation of $H_{6\beta}$ ($\delta = 2.42$) results in 5% and 9% enhancements for H_8 and the methoxycarbonyl CH_3 at 5-position, respectively. These results indicate that $H_{6\beta}$, H_8, and the $COOCH_3$ at 5-position are on the same face of the pyrroline ring. Therefore, the phenyl substituent at 8-position is trans relative to the methoxycarbonyl group at 5-position. The stereochemistry of other products (**3g-3j**) is believed to be the same as that of **3k** based on NMR spectral analyses.

To account for the reaction and the stereochemistry of the products, the following mechanism is proposed. First, nucleophilic attack from pyrazoline nitrogen to the carbonyl group of the ketone or aldehyde gives aminal **6**. Protonation on the hydroxyl group of **6** followed by dehydration gives iminium **7**. The reaction does not proceed if both R_1 and R_2 are bulky enough to hinder the formation of **7**, such as in the cases with diethyl ketone, methyl isopropyl ketone, and acetophenone. For the cases of methyl ethyl ketone or acetaldehydes with R^1 and R^2 substituents of similar size, both cis and trans isomers of **7** can be formed. Therefore, two diastereomers of final products **3d**, **3f** and **3l** are obtained. However, in the cases of aldehydes with bulky R^2, only the isomer having R^2 trans with respect to the RN group in the intermediate **7** can be formed. The following nucleophilic attack of the nitrogen of RN to the iminyl carbon must occur from the same face as that of the RN group with respect to the pyrazoline ring. Therefore the reaction gives only one stereoisomer with the CO_2CH_3 and R^2 groups in trans relationship.



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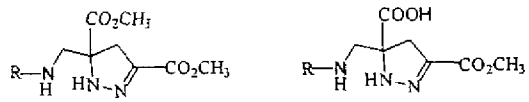

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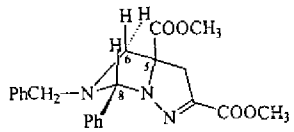
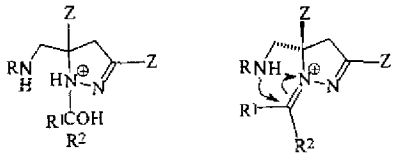


3k



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EXPERIMENTAL SECTION

The ^1H NMR and ^{13}C NMR spectra were determined on a Bruker Ace-200 MHz or a Brucker AM-300 WB FT-NMR spectrometer using TMS and $CDCl_3$ as internal standards. The mass spectra were obtained on a VG-trio 2000 mass spectrometer and a JEOL JMS SX/SX 102A high resolution mass spectrometer. Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected.

Preparation of 5-(Alkylamino)methyl-2-pyrazoline (4)

To a solution of sodium azide (3.5 g) dissolved in 25 mL of DMSO, 4.5 mL of alkyl bromide was added. The mixture was stirred for 3 h, and 25 mL of distilled water was added. The mixture was extracted with 100 mL of THF. To the THF extract, 9.5 g of methyl acrylate was added, and the mixture was allowed to stir for 24 h. After evaporation of the solvent, 5-(alkylamino)methyl-2-pyrazoline was obtained in the yields of 80-90%.

3,5-Dimethoxycarbonyl-5-(propylamino)methyl-2-pyrazoline (4a)

This compound was obtained as a colorless liquid. ^1H *NMR* ($CDCl_3$): δ *0.80* (*t*, 3H, $J = 7.0$ Hz, CH_3), 1.38 (m, 2H, CH_2), 2.50 (m, 2H, CH_2), 2.70, 3.01 (AB pattern, 2H, $J =$

12.0 Hz, CH_2), 3.05, 3.09 (AB pattern, 2H, J = 17.7 Hz, CH_2), 3.74 (s, 3H, OCH_3), 3.78 (s, 1H, NH), 3.79 (s, 3H, OCH_3), 6.90 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 11.3 (CH_3), 22.7 (CH_2), 38.4 (CH_2), 51.6 (CH_2), 51.9 (CH_2), 52.6 (CH_3), 54.2 (CH_3), 73.3 (C), 142.0 (C=N), 162.2 (C=O), 173.3 (C=O). MS *m/z* (rel int.): 258 (M^+ + 1, 15), 226 (21), 198 (24), 72 (100).

5-(Butylamino)methyl-3,5-dimethoxycarbonyl-2-pyrazoline (4b)

This compound was obtained as a colorless liquid. ^1H NMR ($CDCl_3$): δ 0.86 (t, 3H, J = 7.0 Hz, CH_3), 1.3-1.8 (m, 4H, CH_2CH_2), 2.55 (t, 2H, J = 7.0 Hz, CH_2), 2.76, 2.99 (AB pattern, 2H, J = 12.0 Hz, CH_2), 3.05, 3.27 (AB pattern, 2H, J = 17.6 Hz, CH_2), 3.74 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.89 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.7 (CH_3), 20.0 (CH_2), 31.9 (CH_2), 38.4 (CH_2), 49.5 (CH_2), 52.0 (CH_2), 52.7 (CH_3), 54.3 (CH_3), 73.3 (C), 142.2 (C=N), 162.3 (C=O), 173.4 (C=O). MS *m/z* (rel int.): 272 (M^+ + 1, 12), 240 (18), 212 (26), 139 (34), 86 (100).

5-(Benzylamino)methyl-3,5-dimethoxycarbonyl-2-pyrazoline (4c)

This compound was obtained as a colorless liquid. ^1H NMR ($CDCl_3$): δ 2.80, 3.01 (AB pattern, 2H, J = 12.0 Hz, CH_2), 3.05, 3.29 (AB pattern, 2H, J = 17.8 Hz, CH_2), 3.72 (s, 3H, OCH_3), 3.78 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 6.90 (s, 1H, NH). 7.2-7.3 (m, 5H, aromatic H). ^{13}C NMR ($CDCl_3$): δ 38.5 (CH_2), 52.1 (CH_2), 52.9 (CH_2), 53.5 (CH_3), 53.6 (CH_3), 73.3 (C), 127.0 (CH), 127.8 (CH), 128.3 (CH), 139.6 (C), 142.5 (C=N), 162.3 (C=O), 173.3 (C=O). MS *m/z* (rel int.): 305 (M^+, 2), 274 (3), 246 (3), 120 (97), 91 (100).

5-Hydroxycarbonyl-5-(propylamino)methyl-3-methoxycarbonyl-2-pyrazoline (5a)

This compound was obtained as a white solid, mp 214-215 °C, by adding 1 mL of water to 1 g of 3,5-dimethoxycarbonyl-5-(propylamino)methyl-2-pyrazoline (**4a**) and leaving it to stand for a few days. ^1H NMR (D_2O): δ 0.91 (t, 3H, J = 7.2 Hz, CH_3), 1.65 (m, 2H, CH_2), 3.06 (t, 2H, J = 7.2 Hz, CH_2), 3.07, 3.39 (AB System, 2H, J = 18.0 Hz, CH_2), 3.38 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3). ^{13}C NMR (D_2O): δ 12.8 (CH_3), 21.4 (CH_3), 42.4 (CH_2), 52.8 (CH_2), 54.1 (CH_2), 55.4 (CH_3), 73.1 (C), 145.3 (C=N), 166.3 (C=O), 179.4 (C=O). MS *m/z* (rel int.): 244 (M^+ + 1, 70), 198 (22), 154 (100), 136 (71).

General Procedure for Preparations of 1,2,7-Triazabicyclo[3.3.0]oct-2-enes (3)

To 0.01 mole of 3,5-dimethoxtcarbonyl-5-(alkylamino)methyl-2-pyrazoline (**4**) was added 30 mL of ketones or aldehydes. The mixture was then kept at 100 °C or under reflux for 3 to 7 days. After evaporation of the excess ketones or aldehydes, the pure products were obtained by column chromatography using alumina as the stationary phase and $CHCl_3$:hexane = 1:5 as the eluent.

3,5-Dimethoxycarbonyl-8,8-dimethyl-7-propyl-1,2,7-triazabicyclo[3.3.0]oct-2-ene (3a)

This compound was obtained as a yellow liquid in 88% yield. ^1H NMR ($CDCl_3$): δ 0.82 (t, 3H, J = 7.3 Hz, CH_3), 1.15 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.33-1.47 (m, 2H, CH_2), 2.16-2.45 (m, 2H, CH_2), 2.38, 2.78 (AB system, 2H, J = 9.6 Hz, CH_2), 3.14, 3.26 (AB pattern, 2H, J = 18.1 Hz, CH_2), 3.72 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 11.6 (CH_3), 21.4 (CH_3), 21.9 (CH_2), 22.1 (CH_3), 43.8 (CH_2), 49.4 (CH_2), 52.2 (CH_3), 52.8 (CH_3), 57.0 (CH_2), 73.5 (C), 82.0 (C), 142.6 (C=N), 162.1 (C=O), 173.0 (C=O). MS *m/z* (rel int.): 297 (M^+, 18), 282 (100), 268 (14), 238 (20); HRMS: calcd for $C_{14}H_{23}N_3O_4$: 297.1683, obsd 297.1684.

7-Butyl-3,5-dimethoxycarbonyl-8,8-dimethyl-1,2,7-triazabicyclo[3.3.0]oct-2-ene (3b)

This compound was obtained as a yellow liquid in 90% yield. ^1H NMR ($CDCl_3$): δ 0.77 (t, 3H, J = 7.0 Hz, CH_3), 1.09 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.13-1.33 (m, 4H, CH_2CH_2), 2.17-2.34 (m, 2H, CH_2), 2.73, 3.17 (AB pattern, 2H, J = 9.6 Hz, CH_2), 3.09, 3.19 (AB pattern, 2H, J = 18.1 Hz, CH_2), 3.66 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 13.7 (CH_3), 20.1 (CH_2), 21.1 (CH_3), 22.1 (CH_3), 30.7 (CH_2), 43.7 (CH_2), 47.2 (CH_2), 52.1 (CH_3), 52.7 (CH_3), 57.0 (CH_2), 73.4 (C), 81.9 (C), 142.6 (C=N), 162.0 (C=O), 173.3 (C=O). MS *m/z* (rel int.): 311 (M^+, 26), 296 (68), 268 (17), 252 (24), 84 (100); HRMS: calcd for $C_{15}H_{25}N_3O_4$: 311.1839, obsd 311.1846.

7-Benzyl-3,5-dimethoxycarbonyl-8,8-dimethyl-1,2,7-triazabicyclo[3.3.0]oct-2-ene (3c)

This compound was obtained as a yellow liquid in 91% yield. ^1H NMR ($CDCl_3$): δ 1.33 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.66, 3.24 (AB pattern, 2H, J = 9.7 Hz, CH_2), 3.10, 3.26 (AB pattern, 2H, J = 18.1 Hz, CH_2), 3.44, 3.67 (AB pattern, 2H, J = 13.2 Hz, CH_2), 3.75 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 7.24-7.29 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$): 21.4 (CH_3), 22.0 (CH_3), 43.1 (CH_2), 51.6 (CH_2), 51.9 (CH_3), 52.4 (CH_3), 56.5 (CH_2), 73.2 (C), 81.6 (C), 126.7 (CH), 127.6 (CH), 127.9 (CH), 138.4 (C), 142.5 (C=N), 161.7 (C=O), 172.8 (C=O). MS *m/z* (rel int.): 345 (M^+, 9), 330 (52), 286 (10), 160 (47), 91 (100); HRMS:

calcd for $C_{18}H_{23}N_3O_4$: 345.1683, obsd 345.1692.

3,5-Dimethoxycarbonyl-8-ethyl-8-methyl-7-propyl-1,2,7-triazabicyclo-[3.3.0]oct-2-ene (3d)

This compound was obtained as a brown liquid in 87% yield. The product existed as a mixture of two diastereomers in a ratio of 5:1 as estimated by ^{1}H NMR spectrum. Separation had been tried unsuccessfully on column chromatography with several solvent systems.

Spectral data for the major component: ^{1}H NMR ($CDCl_3$): δ 0.81 (t, J = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 0.83 (t, J = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 1.12 (s, 3H, CH_3), 1.38 (m, 2H, $CH_2\underline{CH_2}CH_3$), 1.45 (m, 2H, $\underline{CH_2}CH_3$), 2.26 (t, J = 7.3 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 2.52, 3.49 (AX pattern, 2H, J = 9.2 Hz, CH_2), 3.12 (s, 2H, CH_2), 3.67 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 7.7 (CH_3), 11.6 (CH_3), 18.3 (CH_2), 21.6 (CH_2), 28.2 (CH_2), 41.8 (CH_2), 48.5 (CH_2), 51.9 (CH_3), 52.3 (CH_3), 54.8 (CH_2), 73.7 (C), 84.5 (C), 141.9 (C=N), 162.1 (C=O), 172.9 (C=O). MS *m/z* (rel int.): 311 (M^+, 26), 296 (70), 282 (100), 268 (43), 252 (27); HRMS: calcd for $C_{15}H_{25}N_3O_4$: 311.1839, obsd 311.1852.

Spectral data for the minor component: ^{1}H NMR ($CDCl_3$, partial): δ 0.99 (s, 3H, CH_3), 3.01, 3.19 (AX pattern, 2H, J = 18.0 Hz, CH_2), 3.70 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 8.9 (CH_3), 11.7 (CH_3), 16.6 (CH_2), 21.7 (CH_2), 29.7 (CH_2), 45.5 (CH_2), 50.1 (CH_2), 51.9 (CH_3), 52.3 (CH_3), 58.6 (CH_2), 73.6 (C), 84.2 (C), 142.0 (C=N), 162.1 (C=O), 173.7 (C=O).

3,5-Dimethoxycarbonyl-7-propyl-1,2,7-triazabicyclo-[3.3.0]oct-2-ene (3e)

This compound was prepared by the following two methods:

(a) 2 grams of pyrazoline **4a** and 10 mL of formalin were mixed and stirred at room temperature for 1 day. After evaporation of the excess formalin, the crude product was obtained. The pure product was obtained by column chromatography using alumina as the stationary phase and $CHCl_3$:hexane = 1:1 as the eluent. The yield is 40% following this procedure.

(b) The mixture of 4 grams of paraformaldehyde and 2 grams of pyrazoline **4a** dissolved in 30 mL methanol was stirred at room temperature for 1 day in the presence of 1 gram of molecular sieves. After evaporation of the solvent, the crude product was obtained. The pure product was obtained by column chromatography using alumina as the stationary phase and $CHCl_3$:hexane = 1:1 as the eluent. The yield is 95%.

Yellow liquid. ^{1}H NMR ($CDCl_3$): δ 0.82 (t, 3H, J = 7.2 Hz, CH_3), 1.32-1.43 (m, 2H, CH_2), 2.30-2.38 (m, 2H, CH_2), 2.82, 2.93 (AB pattern, 2H, J = 10.0 Hz, CH_2), 3.17, 3.58 (AX pattern, 2H, J = 18.0 Hz, CH_2), 3.54, 4.37 (AX pattern, 2H, J = 8.0 Hz, CH_2), 3.71 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 11.6 (CH_3), 21.8 (CH_2), 43.2 (CH_2), 52.3 (OCH_3), 52.9 (OCH_3), 54.9 (CH_2), 61.7 (CH_2), 74.7 (CH_2), 76.2 (C), 146.5 (CN), 161.5 (CO), 172.1 (CO). MS *m/z* (rel int.): 270 (M^+ + 1, 100), 269 (M^+, 60), 242 (32), 210 (5), 199 (21); HRMS: calcd for $C_{12}H_{20}N_3O_4$ (M^+ + 1): 270.1449, obsd 270.1450.

3,5-Dimethoxycarbonyl-8-methyl-7-propyl-1,2,7-triazabicyclo[3.3.0]oct-2-ene (3f)

There are two isomers in the ratio of 1:1 in the product. Separation had been tried unsuccessfully on column chromatography with several solvent systems. These compounds were obtained as a yellow liquid in 90% yield. ^{1}H NMR ($CDCl_3$) for mixture of 1:1 isomers: δ 0.83 (t, 3H, J = 7.0 Hz, CH_3), 0.85 (t, 3H, J = 7.0 Hz, CH_3), 1.36 (d, 3H, J = 5.8 Hz, CH_3), 1.40-1.48 (m, 4H, two CH_2), 1.51 (d, 3H, J = 6.0 Hz, CH_3), 2.15-2.21 (m, 2H, CH_2), 2.27, 3.62 (AX pattern, 2H, J = 9.0 Hz, CH_2), 2.56-2.60 (m, 2H, CH_2), 2.87, 3.17 (AX pattern, 2H, J = 9.8 Hz, CH_2), 3.00, 3.20 (AX pattern, 2H, J = 18.0 Hz, CH_2), 3.09, 3.14 (AB pattern, 2H, J = 17.6 Hz, CH_2), 3.62 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.74 (q, 1H, J = 5.8 Hz, J = 5.8 Hz, CH), 3.75 (s, 3H, OCH_3), 3.82 (q, 1H, J = 6.0 Hz, CH). ^{13}C NMR ($CDCl_3$) for mixture of 1:1 isomers: δ 11.4, 11.7, 15.4, 18.9, 21.1, 21.2, 39.9, 43.6, 52.1, 52.2, 52.6, 52.8, 53.3, 53.4, 57.4, 61.6, 74.3, 75.1, 79.6, 81.3, 143.1, 145.4, 161.6, 161.7, 172.2, 172.3. MS *m/z* (rel int.): 284 (M^+ + 1, 23), 283 (15), 268 (33), 254 (15), 84 (88), 72 (100).

3,5-Dimethoxycarbonyl-8-tert-butyl-7-propyl-1,2,7-triazabicyclo[3.3.0]oct-2-ene (3g)

This compound was obtained as a yellow liquid in 88% yield. ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 3H, J = 7.3 Hz, CH_3), 0.85 (s, 9H, $C(CH_3)_3$), 1.40 (m, 2H, CH_2), 2.19, 3.87 (AX pattern, 2H, J = 9.2 Hz, CH_2). 2.19 (m, 1H, one of CH_2), 2.70 (m, 1H, one of CH_2), 3.08, 3.15 (AB pattern, 2H, J = 17.7 Hz, CH_2), 3.66 (s, 3H, OCH_3), 3.75 (s, 1H, CH), 3.85 (s, 3H, OCH_3), ^{13}C NMR ($CDCl_3$): δ 11.3 (CH_3), 22.0 (CH_2), 26.1 (CH_3), 36.1 (C), 42.5 (CH_2), 52.4 (OCH_3), 52.5 (OCH_3), 58.6 (CH_2), 58.7 (CH_2), 75.4 (C), 93.1 (CH), 141.6 (CN), 162.1 (CO), 172.4 (CO). MS *m/z* (rel int.): 326 (M^+ + 1, 50), 310 (4), 294 (5), 268 (100); HRMS: calcd for $C_{12}H_{20}N_3O_4$ (M + H): 270.1449, obsd 270.1450.

3,5-Dimethoxycarbonyl-7-propyl-8-isopropyl-1,2,7-triazabicyclo[3.3.0]oct-2-ene (3h)

This compound was obtained as a yellow liquid in

95% yield. ^{1}H NMR ($CDCl_3$): δ 0.77 (d, 3H, J = 6.8 Hz, CH_3), 0.81 (t, 3H, J = 7.2 Hz, CH_3), 0.90 (d, 3H, J = 6.8 Hz, CH_3), 1.36-1.45 (m, 2H, CH_2), 1.75 (m, 1H, CH), 2.17 (m, 1H, one of CH_2), 2.20, 3.73 (AX pattern, 2H, J = 9.3 Hz, CH_2), 2.56 (m, 1H, one of CH_2), 3.14 (s, 2H, CH_2), 3.60 (d, 1H, J = 4.2 Hz, CH), 3.72 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 11.5 (CH_3), 15.6 (CH_3), 19.2 (CH_3), 21.7 (CH_2), 30.0 (CH), 40.9 (CH_2), 52.5 (OCH_3), 52.6 (OCH_3), 55.0 (CH_2), 57.1 (CH_2), 75.5 (C), 90.1 (C), 142.7 (CN), 162.1 (CO), 172.5 (CO). MS *m/z* (rel int.): 312 (M^+ + 1, 100), 280 (10), 268 (95).

3,5-Dimethoxycarbonyl-7-propyl-8-propyl-1,2,7-triazabicyclo[3.3.0]oct-2-ene (3i)

This compound was obtained as a yellow liquid in 87% yield. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, J = 7.4 Hz, CH_3), 0.92 (t, 3H, J = 7.0 Hz, CH_3), 1.40-1.60 (m, 6H, three CH_2), 2.26 (m, 1H, one of CH_2), 2.27, 3.64 (AX pattern, 2H, J = 9.1 Hz, CH_2), 2.60 (m, 1H, one of CH_2), 3.12, 3.18 (AB pattern, 2H, J = 17.0 Hz, CH_2), 3.74 (s, 3H, OCH_3), 3.80 (m, 1H, CH), 3.82 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 11.4 (CH_3), 14.1 (CH_3), 17.7 (CH_2), 21.5 (CH_2), 35.0 (CH_2), 40.5 (CH_2), 52.3 (CH_3), 52.6 (OCH_3), 54.1 (CH_2), 57.4 (CH_2), 75.5 (C), 85.2 (C), 142.9 (CN), 161.9 (CO), 172.4 (CO). MS *m/z* (rel int.): 312 (M^+ + 1, 100), 296 (5), 280 (11), 268 (40), 199 (44).

3,5-Dimethoxycarbonyl-8-(2-naphthyl)-7-propyl-1,2,7-triazabicyclo[3.3.0]oct-2-ene (3j)

This compound was obtained as a yellow liquid in 80% yield. ^{1}H NMR ($CDCl_3$): δ 0.80 (s, 3H, CH_3), 1.46 (m, 2H, CH_2), 2.56 (m, 2H, CH_2), 2.62, 4.09 (AB pattern, 2H, J 9.0 Hz, CH_2), 3.15, 3.30 (AB pattern, 2H, J = 17.7 Hz, CH_2), 3.51 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.47 (s, 1H, CH), 7.4-7.9 (m, 7H, aromatic). ^{13}C NMR ($CDCl_3$): δ 11.5 (CH_3), 22.6 (CH_2), 40.7 (CH_2), 52.6 (OCH_3), 52.6 (OCH_3), 54.6 (CH_2), 57.3 (CH_2), 76.0 (C), 84.7 (C), 123.6 (CH), 124.3 (CH), 125.1 (CH), 125.7 (CH), 126.1 (CH), 126.3 (CH), 128.5 (CH), 129.0 (C), 132.1 (C), 134.3 (C), 143.6 (CN), 162.0 (CO), 172.3 (CO).

7-Benzyl-3,5-dimethoxycarbonyl-8-phenyl-1,2,7-triazabicyclo[3.3.0]oct-2-ene (3k)

This compound was obtained as a yellow liquid in 85% yield. ^{1}H NMR ($CDCl_3$): δ 2.42, 3.79 (AB pattern, 2H, J= 9.5 Hz, CH_2), 3.21 (s, 2H, CH_2), 3.34, 3.92 (AX pattern, 2H, J = 13.6 Hz, CH_2), 3.76 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.72 (s, 1H, CH), 7.20-7.70 (m, 10H, aromatic). ^{13}C NMR ($CDCl_3$): δ 40.0 (CH_2), 52.5 (OCH_3), 52.8 (OCH_3), 54.9 (CH_2), 57.3 (CH_2), 75.5 (C), 87.1 (CH), 127.3 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.8 (C), 129.7 (C), 137.3 (C), 138.4 (C), 144.1 (CN), 162 (CO), 172 (CO). MS *m/z* (rel int.): 393 (M^+, 5), 334 (24), 207 (78), 91 (100).

7-Benzyl-3,5-dimethoxycarbonyl-8-methyl-1,2,7-triazabicyclo[3.3.0]oct-2-ene (3l)

There are two isomers in the ratio of 3:1 in the product. Separation had been tried unsuccessfully on column chromatography with several solvent systems. These compounds were obtained as a yellow liquid in 90% yield.

Major compound: ^{1}H NMR ($CDCl_3$): δ 1.42 (d, 3H, J = 5.8 Hz, CH_3), 2.25 (d, 1H, J = 9.2 Hz, one of CH_2), 3.08 (2H, s, CH_2), 3.33, 3.90 (AX pattern, 2H, J = 13.6 Hz, CH_2), 3.44 (d, 1H, J = 9.2 Hz, one of CH_2), 3.97 (q, 1H, J = 5.8 Hz, CH), 3.73 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 7.72-7.75 (m, 5H, aromatic H). ^{13}C NMR ($CDCl_3$): δ 18.9, 39.8, 52.3, 55.2, 57.4, 75.1, 80.7, 127.0, 128.2, 128.4, 137.4, 143.3, 161.8, 172.3.

Minor compound: ^{1}H NMR ($CDCl_3$): δ 1.54 (d, 3H, J = 6.0 Hz, CH_3), 2.7, 2.85 (2H, AB pattern, J = 10.1 Hz, CH_2), 3.04, 3.51 (d, 2H, J = 18.3 Hz, CH_2), 3.17, 3.90 (d, 2H, J = 12.9 Hz, CH_2), 3.87 (q, 1H, J = 6.0 Hz, CH), 3.72 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 7.72-7.75 (m, 5H, aromatic H). ^{13}C NMR ($CDCl_3$): δ 15.6, 43.4, 52.3, 55.5, 61.4, 74.3, 79.4, 127.1, 128.1, 128.4, 137.7, 143.3, 161.8, 172.3.

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Key Words

1,2,7-Triazabicyclo[3.3.0]oct-2-ene; Stereoselective reaction.

REFERENCES

1. Khalaf, A. A.; El-Shafei, A. K.; El-Sayed, A. M. *J. Heterocyclic Chem.* **1982**, *19*, 609.
2. Krapcho, J.; Turk, C. *J. Med. Chem.* **1979**, *22*, 207.
3. Druey, J.; Schmidt, P.; Eichenberger, K. *U.S. Pat.* **1961**, 2989537 (*Chem. Abstr.* **1961**, *55*, 25990).
4. Koppes, W. M.; Chaykovsky, M.; Adolph, H. G.; Gilardi, R. D.; George, C. F. *J. Org. Chem.* **1987**, *52*, 1113.

5. Nielsen, A. T.; Nissan, R. A.; Chafin, A. P.; Gilardi, R. D.; George, C. F. *J. Org. Chem.* **1992**, *57*, 6756.
6. Molina, P.; Lorenzo, A.; Aller, E. *Synthesis* **1989**, 843.
7. Zvilichovsky, G.; David, M. *Synthesis* **1986**, 239.
8. Meguro, K.; Kuwada, Y. *Heterocycles* **1974**, *2*, 335.
9. Yang, C. H.; Shen, H. J. *Tetrahedron Lett.* **1993**, *34*, 4051.
10. Kassab, N. A. E.; Alla, S. O. A.; Ead, H. A. R. Z. *Naturforsch. Teil B*, **1976**, *31*, 853.
11. Daboun, H. A.; Abdel-Aziz, M. A. *Heterocycles* **1982**, *19*, 1375.
12. Broeckt, W.; Overbergh, N.; Samyn, C.; Smets, G.; L'Abbe, G. *Tetrahedron* **1971**, *27*, 3527.