Organic Chemistry

Stereoselective cyclization of alkyl *N*-phthaloyl-4-bromoglutamates to cyclopropane derivatives

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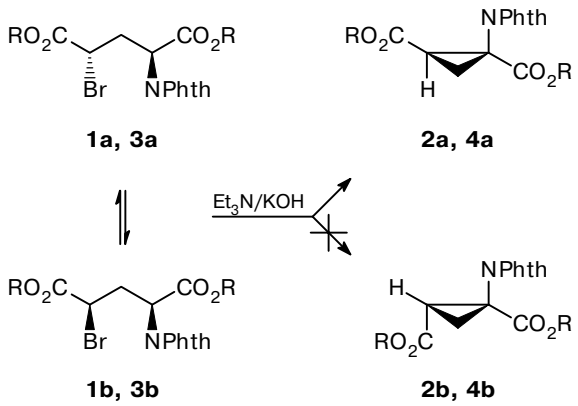
The kinetics of the reactions of alkyl *N*-phthaloyl-4-bromoglutamates with Et_3N and KOH was investigated. The reactions proceed stereospecifically to form alkyl 1-phthalimidocyclopropane-*r*-1,*t*-2-dicarboxylates. In alcohols, the reactions are accompanied by transesterification. The concerted mechanism accounting for the stereospecificity of these reactions is proposed.

Key words: glutamic acid, cyclopropane-1,2-dicarboxylic acid, transesterification, cyclization.

Previously, it has been established[1—4] that the nucleophilic substitution reactions of 4-halogeno derivatives of glutamic acid with aniline derivatives resulting in the replacement of the halogen atom proceed diastereoselectively to form an excess of *threo*-isomers of the products. A model which provides an explanation for the difference in the reactivity of the diastereomers was proposed based on the results of investigation on the influence of the structures of the reagents and the reaction conditions. In addition, the reaction of dimethyl (2*S*,4*RS*)-*N*-phthaloyl-4-bromoglutamate (**1**) with Et_3N in ethanol was demonstrated[5] to afford dimethyl 1-phthalimidocyclopropane-*r*-1,*t*-2-dicarboxylate (**2a**) as the major product (Scheme 1) whose structure was established by X-ray diffraction analysis.

In view of the fact that cyclopropane-containing analogs of glutamic acid are of considerable interest

Scheme 1



R = Me (**1**, **2**), Et (**3**, **4**); Phth is phthaloyl

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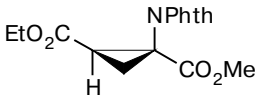
for biological studies[6,7] and with the aim of obtaining additional data on the characteristic features of the nucleophilic substitution of the halogen atom in 4-halogeno derivatives of glutamic acid, we studied the reactions of dimethyl and diethyl (2*S*,4*RS*)-*N*-phthaloyl-4-bromoglutamates (**1** and **3**, respectively) with Et_3N and KOH, which are stronger bases than arylamines.

A mixture of *threo* (**1a**) and *erythro* isomers (**1b**) of dimethyl *N*-phthaloyl-4-bromoglutamate in a ratio of 68 : 32 was refluxed with Et_3N in ethanol. The reaction products were analyzed by ^1H NMR spectroscopy, HPLC, and GLC-mass spectrometry. It appeared that the reaction afforded a mixture of products containing compound **2a** (85.2%) along with diethyl 1-phthalylimidocyclopropane-*r*-1,*t*-2-dicarboxylate (**4a**) (0.2%) and 1-methyl 2-ethyl 1-phthalylimidocyclopropane-*r*-1,*t*-2-dicarboxylate (**5a**) (14.6%). Two last-named compounds were formed due to transesterification. The mixture did not contain compound **2b** isomeric to the major product.



5a

A comparative study of the kinetics of the reactions of isomer **1a** and a mixture of stereoisomers **1a** and **1b** with Et_3N in ethanol demonstrated that compound **2a** was formed much more slowly from the *threo* epimer than from a mixture of isomers of compound **1** (Figs. 1 and 2, respectively). After 5 h, the degree of conversion in ethanol at 68 °C was 25 and 68%, respectively. Apparently, compound **2a** formed primarily from *erythro* isomer **1b**, whereas isomer **1a** was initially converted into isomer **1b**. This conversion can proceed both through epimerization at the C(4) atom, as has been mentioned earlier,[8] and through racemization at the C(2) atom under the action of a base. The possibility of racemization of compound **1** at the C(2) atom was confirmed by racemization of dimethyl *meso*-2,4-diphthalimidoglutarate in the presence of bases.[9]

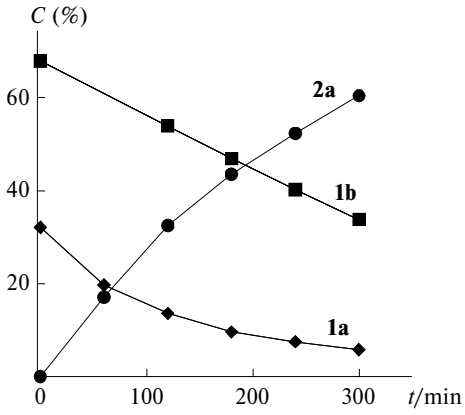


Fig. 1. Kinetics of cyclization of compound **1**.

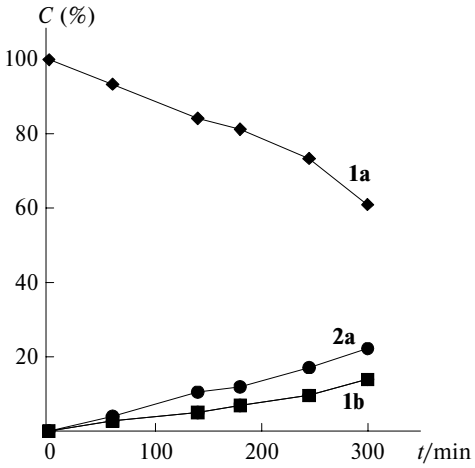


Fig. 2. Kinetics of cyclization of compound **1a**.

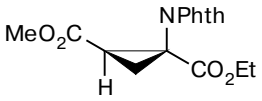
The formation of compound **2a** from a mixture of compounds **1a** and **1b** in ethanol proceeded much more rapidly with the use of stronger bases, in particular, of KOH. However, in the latter case the resulting mixture contained larger amounts of transesterification products along with the major product (Table 1). At the initial stage, compound **5a** was the major transesterification product, whereas compound **4a** became the prevailing product as the reaction time was increased. "Heteroester" **6a** isomeric to compound **5a** was present only in trace amounts. Analogously, the reaction of compound **3** with KOH in methanol gave rise to both compound **4a** and transesterification product **6a**. With the aim of obtaining compounds **2a** and **4a** free of admixtures of transesterification products, we carried out the reactions in DMF or MeCN. The structures of compounds **5a** and **6a** were established based on the data from GLC-mass spectrometry and ^1H NMR spectroscopy using comparison of their spectra with those of compounds **2a** and **4a** for

Table 1. Degrees of conversion and the compositions of the reaction mixtures in the reactions of compounds **1** and **3** with Et_3N and KOH[a]

Compound	Base	Solvent	S^b (%)	C^c (%)		
				2a	**4a**	**5a**
1	Et_3N	DMF	15.1	15.1	—	—
	Et_3N	EtOH	47.7	43.0	—	4.7
	KOH	EtOH	81.4	58.5	3.2	19.7
3	Et_3N	DMF	8.6	—	8.6	—

[a] The initial concentration of the substrate was 0.0325 mol L^{-1}, T = 68 °C, t = 3 h.
[b] Degree of conversion.
[c] The concentrations of the reaction products.

which the assignment of the signals of the ester groups has been made.



6a

Thus, cyclization of esters **1** and **3** was accompanied by transesterification, transesterification at the C(5)-ester group proceeding more rapidly than that at the C(1) atom.

Presently, one cannot give the unambiguous answer to the question of whether transesterification proceeds prior to conversions of esters into cyclopropane derivatives or it takes place in the resulting esters of cyclopropanedicarboxylic acid. We only demonstrated that the reaction of compound **2a** with 1 mol.-equiv. of KOH in ethanol afforded "heteroester" **5a** in 20% yield after 6 h, whereas compounds **5a** and **4a** were the only reaction products in a ratio of 1 : 4 after 3 days

Cyclization is accelerated under pressure. Thus the reaction of compound **1** with Et_3N in MeCN performed at 5 kbar and 68 °C for 1 h gave rise to cyclopropane **2a** in 73% yield, whereas the yield of **2a** in the reaction performed at normal pressure under the same conditions was lower than 10%.

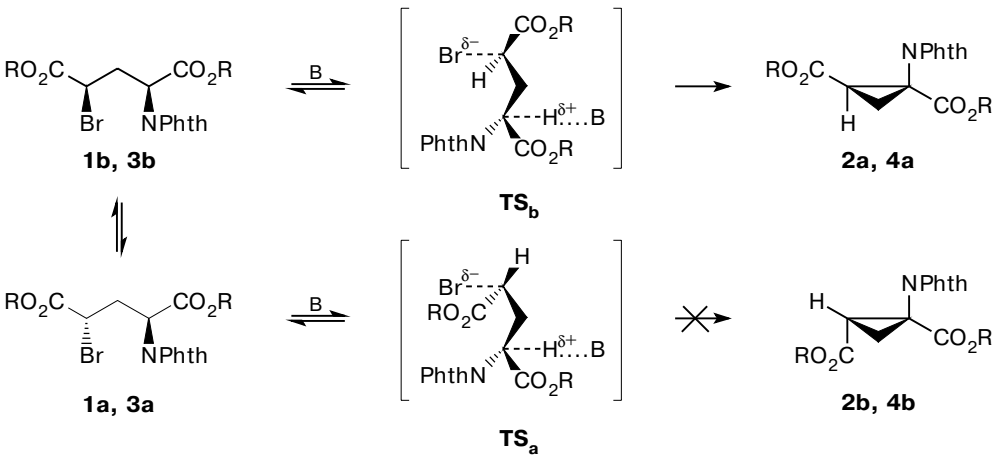
The results of the present study allow the conclusion that cyclization proceeds more rapidly in the case of the *erythro* isomer of halogeno derivatives of glutamic acid, the process is accompanied by racemization, and the reaction is accelerated by either stronger base (KOH) instead of Et_3N or pressure.

These facts agree well with the assumption of concerted elimination of the proton and the halogen atom similar to the E2 mechanism, which begins with the attack of a base on the proton at the C(2) atom. The requirements of the coplanarity of the C(1), C(2), C(3), C(4), and C(5) atoms in the transition state and of the *anti* elimination of the proton and the Br atom have the consequence that the activation energy of the reaction is much higher for the *threo* isomer than for the *erythro* isomer due apparently to the forced eclipsed arrangement of the C(5) atom and the phthalimide group in the transition state from epimer **1a** (**TS_a**) (Scheme 2).

According to the Woodward—Hoffmann rule,[10] the electrocyclic reaction in a system containing no π electrons should be conrotatory. Hence, the C(2)—C(3) and C(3)—C(4) bonds perform a conrotatory motion, isomers **a** are generated from **TS_b**, whereas isomers **b** of compounds **2** and **4** should be generated from **TS_a**. However, the energy of the transition state **TS_a** is substantially higher than that of **TS_b** due to repulsion between the COOR and NPhth groups. As a result, derivatives of 1-phthalimidocyclopropane-1,2-dicarboxylic acid **2b** and **4b** with the *cis* arrangement of the alkoxycarbonyl groups were not generated from the *threo* diastereomers of **1** and **3**, respectively. In the latter case, isomers **1a** (**3a**) were converted into isomers **1b** (**3b**) through epimerization at the C(4) and C(2) atoms followed by conversion into compounds **2a** (**4a**).

Thus, conversions of dialkyl *N*-phthaloyl-4-bromoglutamates into derivatives of cyclopropanedicarboxylic acid in the reactions with Et_3N and KOH proceed stereospecifically to afford exclusively the isomer with the *trans* arrangement of the alkoxycarbonyl groups. It should be noted that the reactions in alcohols are accompanied by transesterification, the latter proceeding predominantly at the C(5)-ester group. This fact can be used for the selective blocking—deblocking of the carboxy group at the C(5) atom in the synthesis of peptides of 1-aminocyclopropane-1,2-dicarboxylic acid.

Scheme 2



B = Et_3N, KOH

Experimental

The ^{1}H NMR spectra were recorded on a Tesla BS-567a instrument (100 MHz) in $CDCl_3$ with Me_4Si as the internal standard. The UV spectra were measured on a Specord UV—VIS spectrophotometer in ethanol. The IR spectra were recorded on a Specord IR-75 spectrophotometer in Nujol mulls. HPLC was carried out on a Milikhrom chromatograph using Silasorb-600 as the sorbent (64×2 mm column; detection at 220 nm, 10 : 1 hexane—THF (*A*) and 20 : 1 hexane—propan-2-ol (*B*) systems as the solvents). The rate of elution was 0.20 mL min^{-1}, the partition coefficient was 1.15—1.30. TLC was performed on standard Silufol UV-254 plates using the 5 : 4 : 3 hexane—benzene—acetone system (*C*) as the solvent. The GLC-mass spectrometric analysis was carried out on a Finnigan MAT ITD-700 instrument equipped with an HP 5790A gas chromatograph. The mixtures were separated on an HP-5 quartz capillary column (30 m×0.32 mm, the thickness of the film was 0.52 μm). The column was connected to an ion source of the mass spectrometer through an interface with an open separator. The energy of ionizing electrons was 70 eV (EI). The column thermostat temperature was increased from 100 °C to 280 °C with a delay of 2 min at a rate of 10 °C min^{-1}; the injector and interface temperature was 270 °C; helium was used as the carrier gas, the flow rate was 1 mL min^{-1}. The concentrations of compounds were quantitatively estimated by normalizing the chromatographic peaks, which were recorded with the use of the total ionic current.

Compounds **1a**, **1b**, **3a**, and **3b** were prepared according to known procedures.[8] The retention times of these compounds in the system *A* were 11.0, 9.0, 6.1, and 5.1 min, respectively.

The solvents were purified and dried according to standard procedures.[11] The kinetics of the reactions under high pressure was studied by a procedure reported previously.[4]

Investigation of the kinetics of the reactions of compounds 1 and 3 with Et_3N and KOH (general procedure). A halogeno derivative (0.065 mmol) was dissolved in a solvent (1 mL) and mixed with a solution of KOH or Et_3N (0.065 mmol) in the same solvent (1 mL). Then the first sample was withdrawn for analysis. The resulting mixture was placed in a cell which was tightly closed and kept at 68 °C. Samples were withdrawn every 30 min, dissolved in a 25 : 1 chromatographic system—benzene mixture, and analyzed by HPLC.

Reaction of dimethyl *N*-phthaloyl-4-bromoglutamate (1) with Et_3N in ethanol. Compound **1** (3.0 g, 7.8 mmol) was dissolved in anhydrous EtOH (30 mL) with heating and then Et_3N (2.2 mL, 15.8 mmol) was added. The reaction mixture was refluxed for 8 h and cooled. The precipitate that formed was filtered off and the filtrate was concentrated to one-half of the initial volume. The residue was poured into water and kept for ~12 h with cooling. The oil that formed was separated, dissolved in ethyl acetate, and dried with $MgSO_4$. The solvent was evaporated to dryness *in vacuo*. The oil was crystallized from a 4 : 1 heptane—*sec*-butanol mixture and dried over P_2O_5 *in vacuo*. Colorless crystals were obtained in a yield of 1.46 g. According to the data from HPLC and GLC-mass spectrometry, the product contained compounds **2a** (85.2%), **4a** (0.2%), and **5a** (14.6%). MS, *m/z* (I_{rel}(%)), for **2a**: 303 $[M]^+$ (13), 271 $[M - HOCH_3]^+$ (60), 243 $[M - HCO_2CH_3]^+$ (40), 228 $[M - HCO_2CH_3 - CH_3]^+$ (20), 184 $[M - (H + 2\ CO_2CH_3)]^+$ (33), 156 $[M - HNPhth]^+$ (100), 104 $[C_6H_4CO]^+$ (20); for **4a**: 331 $[M]^+$ (7), 285 $[M - (H + OC_2H_5)]^+$ (23), 257 $[M - (H + CO_2C_2H_5)]^+$ (20), 229 $[M - (CO_2C_2H_5 + C_2H_5)]^+$ (24), 200 $[M + H - C_6H_4(CO)_2]^+$ (9), 184 $[M - (H + 2\ HCO_2C_2H_5)]^+ + [M - NPhth]^+$ (58), 132 $[Phth]^+$ (22), 104 (100); for **5a**: 317 $[M]^+$ (8), 285 $[M - (H + OCH_3)]^+$ (26), 272 $[M - OC_2H_5]^+$ (53), 271 $[M - (H + OC_2H_5)]^+$ (49), 257 $[M - (H + CO_2CH_3)]^+$ (9), 244 $[M - CO_2C_2H_5]^+$ (53), 243 $[M - (H + CO_2C_2H_5)]^+$ (22), 228 $[M - (H + CO_2CH_3 + C_2H_5)]^+$ (29), 184 $[M - (CO_2C_2H_5 + H + CO_2CH_3)]^+$ (27), 170 $[M - HNPhth]^+$ (100).

Reaction of compound 1 with KOH in ethanol. Compound **1** (3.0 g, 7.8 mmol) was dissolved in anhydrous EtOH (30 mL) with heating, KOH (0.48 g, 8.6 mmol) was added, and the reaction mixture was refluxed for 40 min. Subsequent workup of the reaction mixture was carried out as described above. According to the data from HPLC and GLC-mass spectrometry, the reaction mixture contained compounds **2a** (82.6%), **5a** (14.2%), and **1** (3.2%).

Reaction of compound 3 with KOH in methanol. Potassium hydroxide (0.32 g, 5.7 mmol) was added to a solution of compound **3** (2.0 g, 4.9 mmol) in anhydrous MeOH (20 mL) and the reaction mixture was refluxed for 2.5 h. Subsequent workup of the mixture was carried out as described above. According to the data from HPLC and GLC-mass spectrometry, the reaction mixture contained compounds **4a** (48%), **6a** (39.7%), **2a** (10%), and **3** (2.3%). MS for **6a**, *m/z* (I_{rel} (%)): 317 $[M]^+$ (7), 285 $[M - (H + OCH_3)]^+$ (6), 271 $[M - (H + OC_2H_5)]^+$ (11), 257 $[M - (H + CO_2CH_3)]^+$ (5), 243 $[M - (H + CO_2C_2H_5)]^+$ (22), 228 $[M - (H + CO_2C_2H_5 + CH_3)]^+$ (26), 184 $[M - (H + CO_2C_2H_5 + CO_2CH_3)]^+$ (20), 170 $[M - HNPhth]^+$ (51), 132 $[Phth]^+$ (20), 104 $[C_6H_4CO]^+$ (100).

Dimethyl 1-phthalimidocyclopropane-*r*-1,*t*-2-dicarboxylate (2a). Distilled Et_3N (3.9 mL, 28 mmol) was added to a solution of compound **1** (5.36 g, 13.9 mmol) in hot MeCN (80 mL). The reaction mixture was refluxed for 8 h and cooled. The precipitate that formed was filtered off. The filtrate was concentrated to one-half of the initial volume, poured into water, and kept at 0 °C for ~12 h. The oil that formed was dissolved in ethyl acetate and dried with anhydrous $MgSO_4$. The solvent was distilled off *in vacuo*. The residue was crystallized from a 4 : 1 heptane—*sec*-butanol mixture and dried over P_2O_5 *in vacuo*. Compound **2a** was obtained as colorless crystals in a yield of 2.49 g (58.9%), m.p. 83.5—85.5 °C, R_f 0.68 in the system *C*. Found (%): C, 59.63; H, 4.56; N, 4.93. $C_{15}H_{13}NO_6$. Calculated (%): C, 59.41; H, 4.29; N, 4.62. IR, ν/cm^{-1}: 1787 (C=O); 1720 (COO); 1610, 720 (arom). UV, λ_{max}/nm: 220, 295.5 (phthaloyl group). ^{1}H NMR, δ: 2.19 (dd, 2 H, CH_2 in the ring); 2.93 (dd, 1 H, CH in the ring); 3.65 (s, 3 H, C(2)$OOCH_3$); 3.69 (s, 3 H, C(1)$OOCH_3$); 7.79 (m, 4 H, Ar).

Diethyl 1-phthalimidocyclopropane-*r*-1,*t*-2-dicarboxylate (4a). Triethylamine (1.36 mL, 9.8 mmol) was added to a solution of compound **3** (2.0 g, 4.9 mmol) in anhydrous MeCN (20 mL). The reaction mixture was refluxed for 6 h, cooled, concentrated to one-half of the initial volume, and poured into water. The oil that precipitated on cooling was dissolved in chloroform, dried with anhydrous $MgSO_4$, and concentrated *in vacuo*. Compound **4a** was obtained as an oil in a yield of 1.62 g (98%). UV, λ_{max}/nm: 220, 295.5 (phthaloyl group). ^{1}H NMR, δ: 1.17 (m, 6 H, 2 CH_3 of ester groups); 2.17 (dd, 2 H, CH_2 in the ring); 2.91 (dd, 1 H, CH in the ring); 4.14 (m, 4 H, CH_2 of ester groups); 7.79 (m, 4 H, Ar).

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References

1. I. A. Nizova, V. P. Krasnov, O. V. Korotovskikh, and L. V. Alekseeva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 2781 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 2545 (Engl. Transl.)].
2. V. P. Krasnov and M. A. Koroleva, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 652 [*Russ. Chem. Bull.*, 1995, **44**, 631 (Engl. Transl.)].
3. V. P. Krasnov, M. A. Koroleva, N. G. Evstigneeva, and I. A. Nizova, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 656 [*Russ. Chem. Bull.*, 1995, **44**, 635 (Engl. Transl.)].
4. V. P. Krasnov, M. A. Koroleva, and G. L. Rusinov, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 583 [*Russ. Chem. Bull.*, 1996, **45**, 543 (Engl. Transl.)].
5. V. Kh. Kravtsov, V. N. Biyushkin, T. I. Malinovskii, V. P. Krasnov, and T. V. Matveeva, *Dokl. Akad. Nauk SSSR,* 1990, **311**, 622 [*Dokl. Chem.*, 1990 (Engl. Transl.)].
6. G. Büchi, J. Botkin, G. C. M. Lee, and K. Yakushijin, *J. Am. Chem. Soc.*, 1985, 5555.
7. I. Sagnar, A. Sasaki, and A. Chiaroni, *Tetrahedron Lett.*, 1995, 3149.
8. V. P. Krasnov, I. M. Bukrina, E. A. Zhdanova, M. I. Kodess, and M. A. Korolyova, *Synthesis*, 1994, 961.
9. V. P. Krasnov, E. A. Zhdanova, M. A. Koroleva, I. M. Bukrina, M. I. Kodess, V. Kh. Kravtsov, and V. N. Biyushkin, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 333 [*Russ. Chem. Bull.*, 1997, **46**, 319 (Engl. Transl.)].
10. R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Weinheim, 1970.
11. A. G. Gordon and R. A. Ford, *The Chemist's Companion*, J. Wiley and Sons, New York—London—Sydney—Toronto, 1972.

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