ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 11, pp. 1686–1688. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © K.V. Kudryavtsev, 2008, published in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 11, pp. 1709–1711.

Stereoselective Three-Component One-Stage Synthesis of 2-Pyrrolidinecarboxylic Acid Polyfunctional Derivative

K. V. Kudryavtsev

Moscow State University, Moscow, 119992 Russia
e-mail: kudr@org.chem.msu.ru

Received February 18, 2008

Abstract—A reaction of racemoc methyl 4-oxo-2-phthalimidobutanoate, diethyl aminomalonate, and phenyl vinyl sulfone in the presence AgOAc occurred stereospecifically to form tetrasubstituted pyrrolidine including structural elements of all three initial compounds. The relative stereochemistry of the asymmetrical carbon atoms in the molecule was established by XRD analysis, and it coincided with two stereogenic centers in the left part of kaitocephalin molecule. Therefore the developed three-component process can be recommended for an effective total synthesis of kaitocephalin.

DOI: 10.1134/S1070428008110201

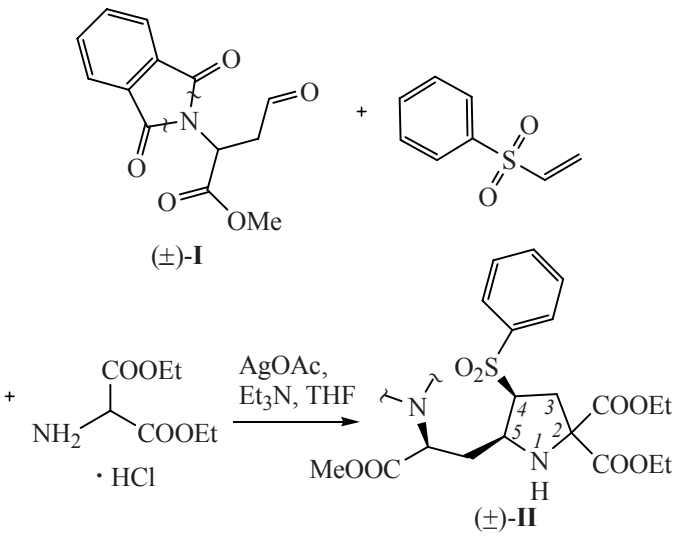
We suggested in [1] an approach to the synthesis of analogs of the natural antagonist of ionotropic glutamate receptors of AMPA-kainate subtype, kaitocephalin [2], based on the 1,3-dipolar cycloaddition of azomethine ylide and vinyl sulfone dipolarophile. The performance of this procedure resulted in the preparation in a low yield of a stereomeric mixture of pyrrolidine derivatives [1]. The low efficiency of this synthesis might be due to the instability of aliphatic aldimine and to the possibility of imine-enamine rearrangement. Recently a three-component method was described for functionalized pyrrolidines from aldehydes, dimethyl aminomalonate, and dipolarophiles occurring through a 1,3-dipolar cycloaddition and providing a possibility to avoid the preparation of iminoester [3].

In this study this method was modified, namely, commercially available diethyl aminomalonate hydrochloride was applied as amine component, the reagents were taken in equimolar amounts, and a tertiary amine was introduced into the reaction. A simple stirring in THF under an inert atmosphere of the racemic methyl 4-oxo-2-phthalimidobutanoate (**I**), phenyl vinyl sulfone, diethyl aminomalonate hydrochloride, triethylamine, and silver acetate led to the formation of tetrasubstituted pyrrolidine **II** as a single stereoisomer (see the Scheme). The spatial structure of compound **II** was unambiguously established by XRD analysis (see the table, Fig. 1). The left part of molecule **II** after desulfonation, removal of protective groups from the amino and carboxy groups and benzoylation of the primary amino group coincides in the structure and stereochemistry with the corresponding fragment of kaitocephalin molecule [4].

In the crystal of compound **II** the molecules are joined into endless chains stabilized by hydrogen bonds between one of oxygen atoms of the sulfone group and a hydrogen atom of the secondary amino group (Fig. 2).

The synthetic modifications of polyfunctional pyrrolidine **II** aimed at the preparation of racemic and

Scheme.



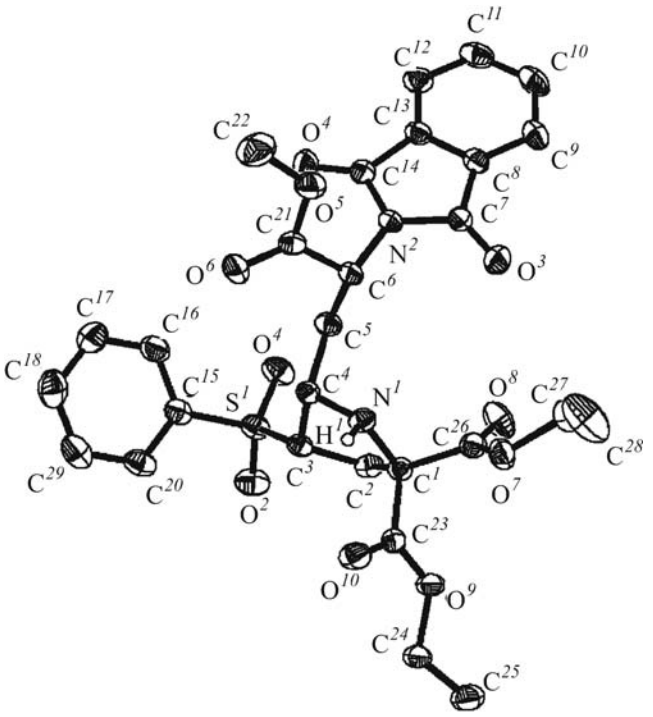


Fig. 1. Structure of compound **II** according to X-ray diffraction analysis.

enantiomerically pure kaitocephalin and its analogs are under active investigation in our laboratory.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker Avance-400 [400 (^{1}H), 100 (^{13}C) MHz] at 298 K in $CDCl_3$ solution using the residual signals of the solvent for internal references. The XRD study of compound **II** was carried out on a diffractometer Enraf-Nonius CAD4 at 293 K.

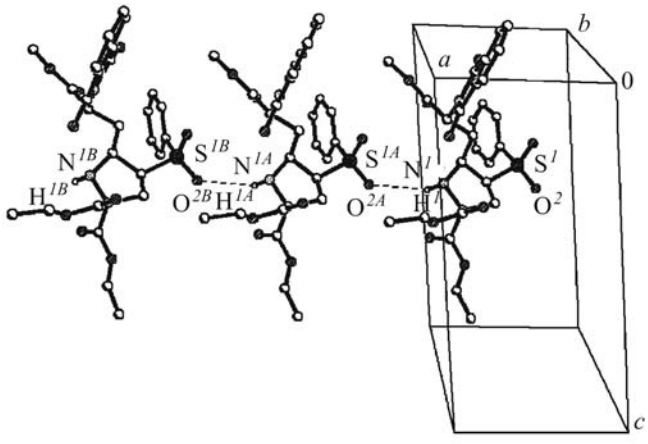


Fig. 2. Intermolecular interactions in the crystal of racemic compound **II**: N^1–H^1 0.86(2), H^1–O^{2A} 2.69(2), N^1–O^{2A} 3.480(2) Å; angle N^1–H^1–O^{2A} 153.5(18)°.

Methyl (*SR*)-4-oxo-2-phthalimidobutanoate (I) was prepared by the procedure previously described for its optically active analog [1, 5] from the DL-methionine methyl ester. Colorless crystals, mp 122–123°C. ^{1}H, NMR spectrum δ, ppm: 3.28 d.d (1H, *J* 18.4, 7.6 Hz), 3.55 d.d (1H, *J* 18.4, 6.0 Hz), 3.74 s (3H, OCH_3), 5.50 d.d (1H, $CHCOOCH_3$, *J* 7.6, 6.0 Hz), 7.74–7.79 m ($2H_{Ar}$), 7.85–7.90 m ($2H_{Ar}$), 9.81 s (1H, CHO).

Diethyl (4*SR*,5*SR*)-4-benzenesulfonyl-5-[(*SR*)-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-2-methoxycarbonylethyl]pyrrolidine-2,2-dicarboxylate (II). In 50 ml of anhydrous THF under inert atmosphere was dissolved 2.33 (8.92 mmol) of compound **I**. Into the reaction mixture was added in succession 1.50 g (8.92 mmol) of phenyl vinyl sulfone, 1.89 g (8.93 mmol) of diethyl

Some bond distances (*d*, Å) and bond angles (ω, deg) in the molecule of diethyl (4*SR*,5*SR*)-4-benzenesulfonyl-5-[(*SR*)-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-2-methoxycarbonylethyl]-pyrrolidine-2,2-dicarboxylate (**II**)

Bond	*d*, Å	Bond	*d*, Å
S^1–C^3	1.784(2)	C^1–C^2	1.542(3)
N^1–C^1	1.469(3)	C^2–C^3	1.525(3)
N^1–C^4	1.472(2)	C^3–C^4	1.540(3)
N^1–H^1	0.86(2)	C^4–C^5	1.533(3)
N^2–C^6	1.464(2)	C^5–C^6	1.523(3)
C^1–C^{26}	1.530(3)	C^{24}–C^{25}	1.484(3)
C^1–C^{23}	1.535(3)	C^{27}–C^{28}	1.464(4)
Angle	ω, deg	Angle	ω, deg
$O^2S^1O^1$	117.96(10)	$C^3C^2C^1$	100.94(16)
$O^2S^1C^{15}$	108.32(10)	$C^2C^3C^4$	103.08(16)
$O^1S^1C^{15}$	108.97(10)	$C^2C^3S^1$	114.69(14)
$O^2S^1C^3$	107.61(10)	$C^4C^3S^1$	119.09(14)
$O^1S^1C^3$	110.91(9)	$N^1C^4C^5$	109.70(16)
$C^1N^1C^4$	109.82(15)	$N^1C^4C^3$	102.27(15)
$C^1N^1H^1$	110.1(14)	$C^5C^4C^3$	114.88(16)
$C^4N^1H^1$	112.8(13)	$C^6C^5C^4$	113.28(17)
$C^7N^2C^6$	124.28(16)	$O^{10}C^{23}O^9$	124.32(17)
$N^1C^1C^{26}$	106.16(15)	$O^{10}C^{23}C^1$	122.55(18)
$N^1C^1C^{23}$	110.07(15)	$O^9C^{23}C^1$	113.08(16)
$C^{26}C^1C^{23}$	111.52(16)	$O^9C^{24}C^{25}$	108.72(18)
$N^1C^1C^2$	106.16(15)	$O^8C^{26}O^7$	124.74(19)
$C^{26}C^1C^2$	113.03(16)	$O^8C^{26}C^1$	125.4(2)
$C^{23}C^1C^2$	109.69(16)	$O^7C^{26}C^1$	109.68(16)

aminomalonate hydrochloride, 2.23 g (13.36 mmol) of AgOAc, and 2.90 ml (2.11 g, 20.81 mmol) of Et_3N. The mixture was stirred in the dark at room temperature under inert atmosphere for 24 h. The reaction mixture was filtered through Celite, the filtrate was evaporated in a vacuum, and the residue was recrystallized from EtOAc. Yield 3.14 g (60%). Colorless crystals, mp 153–154°C. ^{1}H NMR spectrum, δ, ppm: 1.16 t (3H, CH_2CH_3, *J* 7.0 Hz), 1.28 t (3H, CH_2CH_3, *J* 7.0 Hz), 2.43–2.51 m (1H, H^3), 2.57 d.d (1H, CH_2CH, *J* 15.0, 7.8 Hz), 2.89 d.d (1H, CH_2CH, *J* 15.0, 6.0 Hz), 3.12–3.19 m (1H, H^3), 3.28 br.s (1H, NH), 3.60–3.72 m (2H, H^5, H^4), 3.74 s (3H, OCH_3), 4.12 q (2H, CH_2CH_3, *J* 7.0 Hz), 4.18–4.34 m (2H, CH_2CH_3), 5.37 d.d (1H, $CHCOOCH_3$, *J* 9.0, 6.0 Hz), 7.59–7.63 m (2H, $PhSO_2$), 7.67–7.71 m (1H, $PhSO_2$), 7.74–7.77 m ($2H_{Ar}$), 7.85–7.88 m ($2H_{Ar}$), 7.94 d (2H, $PhSO_2$, *J* 7.6 Hz). ^{13}C NMR spectrum, δ, ppm: 13.84, 14.01, 30.34, 34.84, 49.72, 52.85, 59.77, 62.41, 62.51, 64.94, 71.28, 123.60 (2C), 128.44 (2C), 129.44 (2C), 131.91, 133.98, 134.21 (2C), 139.05, 167.54 (2C), 169.20, 169.30, 171.09. Found, %: C 57.50; H 5.16; N 4.69. $C_{28}H_{30}N_2O_{10}S$. Calculated, %: C 57.33; H 5.15; N 4.78.

Crystals of compound **II** ($C_{28}H_{30}N_2O_{10}S$, *M* 586.60) triclinic, space group *P*-1, *a* 7.627(2), *b* 12.185(3), *c* 15.028(3) Å, α 97.54(2), β 96.25(2), γ 95.78(2)°, *V* 1366.9(6) Å^3, *Z* 2, d_{calc} 1.425 g/cm^3, CuK_α-radiation (λ 0.71073 Å, grqaphite monochromator), *F*(000) 616. The intensity of 6533 reflections (5084 among them independent, R_{int} 0.0191) were measured using ω-scanning in the range $2.03 < \theta < 25.47°$ ($-9 \le h \le 9$, $-14 \le k \le 14$, $-3 \le l \le 18$). The structure was solved by the direct method [6]. All nonhydrogen atoms were refined in a full-matrix anisotropic mean-least squares method by F^2 (SHELXL-97 [7]). The final values of divergence factors were R_1 0.0339, wR_2 0.0811 for 3182 reflections with $I > 2\sigma(I)$. The complete crystallographic parameters are available from the author.

The study was carried out under a financial support of the Russian Foundation for Basic Research (grant no. 08-04-01800-a). The author is grateful to N.V. Nukolova for the participation in the synthesis of compound **II**.

REFERENCES

1. Kudryavtsev, K.V., Nukolova, N.V., Kokoreva, O.V., and Smolin, E.S., *Zh. Org. Khim.,* 2006, vol. 42, p. 424.
2. Shinya, K., Kim, J.-S., Furihata, K., Hayakawa, Y., and Seto, H., *Tetrahedron Lett*., 1997, vol. 38, p. 7079.
3. Garner, P. and Kaniskan, H.U., *J. Org. Chem.,* 2005, vol. 70, p. 10868.
4. Kawasaki, M., Shinada, T., Hamada, M., and Ohfune, Y., *Org. Lett.,* 2005, vol. 7, p. 4165.
5. Meffre, P., Durand, P., and Le Goffic, F., *Org. Synth.,* 1999, vol. 76, p. 123.
6. Sheldrick, G.M., *Acta Cryst.,* 1990, vol. A46, p. 467.
7. *SHELXL-97, Program for the Refinement of Crystal Structures*, University of Gottingen, 1997.