J.Serb.Chem.Soc. 68(4–5)383–390(2003)
JSCS – 3053

UDC 66.095.25–936.4+547.78:615.214
Original scientific paper

Regiospecificity in the heterocyclization of β-oxonitriles to 5-substituted 4-oxothiazolidine derivatives*

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(Received 23 December 2002)

Abstract: A study on the regiospecificity of the base-catalyzed reaction of activated β-oxonitriles **1** with diethyl mercaptosuccinate affording the title compounds **3** is reported. Other competitive heterocyclic products, that is 4-oxo-1,3-thiazinanes **4**, derivatives of tetrahydrothiophene **5** and/or thiacyclohexane **6** which on the grounds of mechanistic considerations could be formed, were not observed. Spectroscopic and experimental evidence, together with theoretical considerations, provides a reasonable explanation for the observed regiospecificity.

Keywords: regiospecific, heterocyclization, 4-oxothiazolidines.

Thiazolidinone derivatives are the subject of renowned interest because they have been found to be useful intermediates for the synthesis of various heterocyclic compounds.[1,2] In addition, synthetic and naturally occurring 4-oxothiazolidines attract attention as they show anticonvulsant, sedative-hypnotic and anxiolytic activity.[3,4] A new one-pot cyclization reaction leading to a range of 4-oxothiazolidines **3** from diethyl mercaptobutanedioate and activated nitriles **1** (Scheme 1) was recently reported by us.[5,6]

According to the mechanistic hypothesis shown in Scheme 1, the *in situ* generated intermediate **2** could in turn direct the intramolecular cyclization[7] toward the formation of four possible heterocyclic products, 4-oxothiazolidine derivatives **3**, 4-oxo-1,3-thiazinane derivatives **4**, derivatives of tetrahydrothiophene **5** and/or thiacyclohexane **6**. However, the exclusive formation of 2-alkylidene-4-oxothiazolidine derivatives **3** in moderate yields (24–52 %) is observed without any detectable traces of compounds **4**–**6**. These heterocycles are obtained as pure (*Z*)-diastereomers in ethanol as the solvent. Classified as push-pull alkenes due to the presence of an electron-donating and electron-withdrawing

* Dedicated to Professor Miroslav J. Gašić on the occasion of his 70th birthday.

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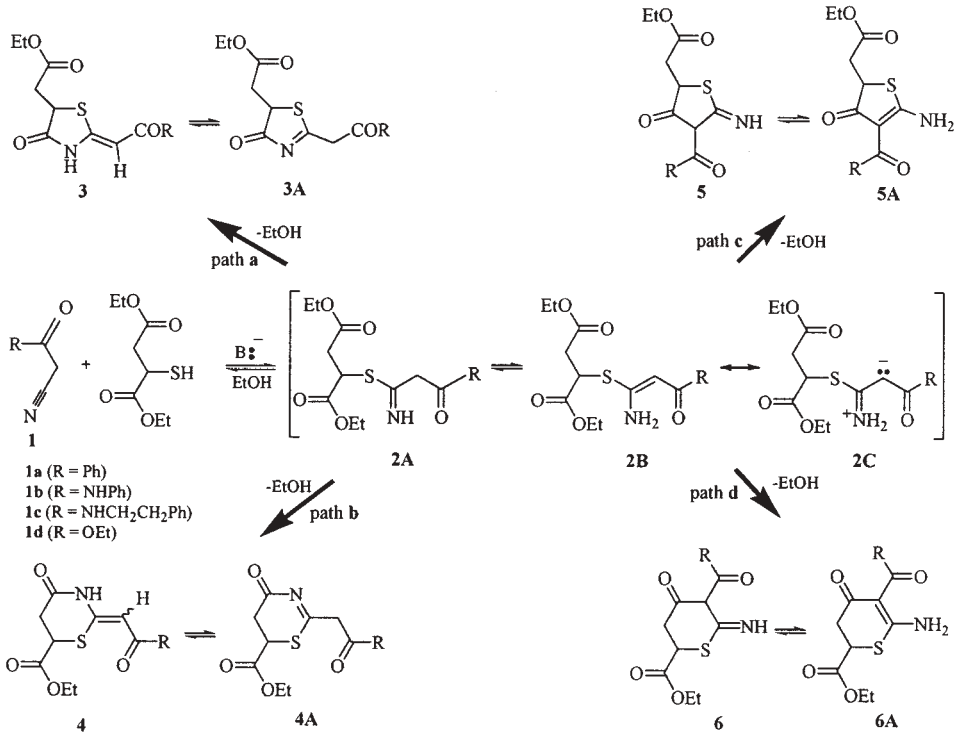


Scheme 1.

groups bonded to the intervening C=C bond, they undergo facile *Z*/*E* isomerization in nonpolar solvents.[8–10] The details of (*i*) an experimental and spectroscopic study as a useful reference in assisting the characterization of the title compounds **3** and derivatives thereof[11] and (*ii*) the optimized procedure to the regiospecific formation of these 5-substituted 4-oxothiazolidines are reported here.

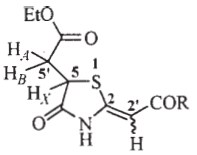
Given the constitutional similarity between the isolated 2-alkylidene-4-oxothiazolidine derivatives **3a**–**d** and the 2-alkylidene-4-oxothiazinane derivatives **4a**–**d** as expected products, the sharp ^{1}H-NMR signal within the range of ≈ 5.50–6.90 ppm and a singlet between ≈ 9–12 ppm for all the examined compounds (Table I), indicates a trisubstituted vinyl group and a lactam proton respectively, regardless of the ring size. These shift values fit either structure **3** or **4**, but rule out the heterocycles **5** and **6** or the tautomers **5A** and **6A** including other possible tautomers as well (not depicted in Scheme 1). By the application of the DEPT technique, the ^{13}C-NMR signal which appears between 93.23–94.94 ppm (Table II) is assigned to a CH fragment linked to carbon atom C(2), whereas the three resonances (≈167–188 ppm) suggest the presence of three carbonyl groups. What is more, the highest ^{13}C-NMR shift value in all the 4-oxothiazolidinones **3a**–**c** is 187.77 ppm which indicates a conjugated keto carbonyl function of the derivative **3a**.

TABLE I. Selected ^{1}H chemical shifts (ppm) of the cyclic derivatives **3a** (R = Ph) and **3d** (R = OEt)

Compound	C(2')H	NH(ring)	C(5')H_A	C(5')H_B	C(5)H_X
(*Z*)-**3a**	6.85 (*s*)	9.88 (*s*)	3.00 (*dd*)	3.15 (*dd*)	4.22 (*dd*)
($CDCl_3$)			J_{AB}=17.5 Hz, J_{AX}=8.2 Hz	J_{AB}=17.5, J_{BX}=4.3 Hz	J_{AX}=8.2 Hz, J_{BX}=4.3 Hz
(*Z*)-**3d**	5.44 (*s*)	11.60 (*s*)	2.95 (*dd*)	3.04 (*dd*)	4.28 (*dd*)
(DMSO-d_6)			J_{AB}=17.6 Hz, J_{AX}=7.8 Hz	J_{AB}=17.6, J_{BX}=4.6 Hz	J_{AX}=7.8 Hz, J_{BX}=4.6 Hz

Once again, the ^{13}C-NMR spectra of **5** (or **5A**) and **6** (or **6A**) are not compatible with these spectral features. Hence, in accordance with this interpretation, the ^{1}H and ^{13}C-NMR spectra (*vide infra*) correspond obviously to either compounds **3** or **4**.

TABLE II. Selected ^{13}C-NMR chemical shifts (ppm) of the cyclic derivatives (*Z*)-**3a**–**3c** in DMSO-d_6



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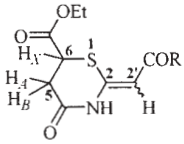
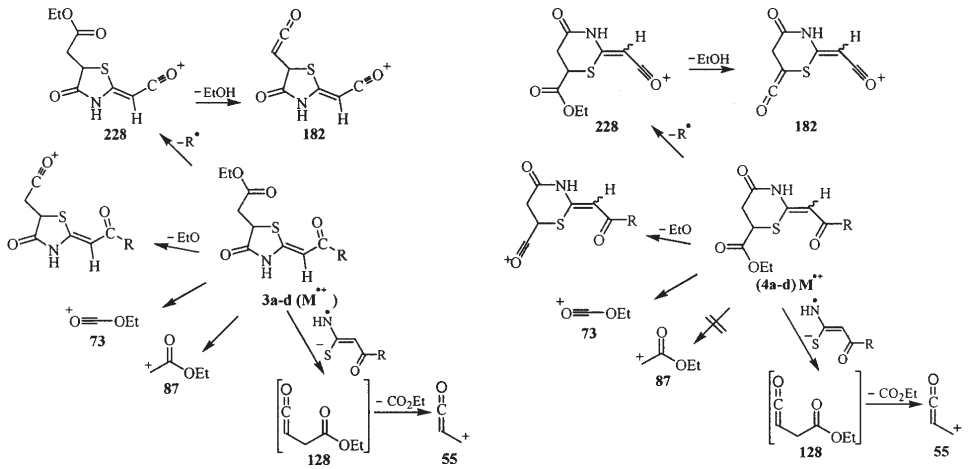


4

3a (R = Ph)
3b (R = NHPh)
3c (R = NHCHCHPh)

Compound	$\underline{C}H_2COO$ (in **3**)	CHS	=CH	C=	$\Delta\delta_{C2,C2'}$	CO_{exo}	CO_{ring}	CO_{ester}
(*Z*)-**3a**	36.40	42.54	94.94	161.56	66.62	187.77	170.72	176.72
(*Z*)-**3b**	37.19	42.44	93.34	153.54	60.20	165.89	170.88	175.68
(*Z*)-**3c**	37.37	42.29	93.23	150.82	57.59	167.05	170.90	175.49



Scheme 2.

Ultimately, the ring size of the resulting heterocyclic products **3** *vs.* the competing six-membered 4-oxo-1,3-thiazinanes **4** was established by a comparative analysis of their mass spectrometric fragmentation patterns (Scheme 2).

The appearance of the strong molecular ions and the most significant peaks at m/z = 228, 128 and 55 in all the spectra can be rationalized by the almost analogous fragmentation processes for compounds of the types **3** and **4**. The examination of the mass spectra of all the products also revealed, as depicted in Fig. 1 for **3a**, the presence of a peak at m/z = 87, corresponding to the fragment with the composition $C_4H_7O_2$. This fragment is obviously formed by the loss of $CH_2COOC_2H_5$ from the molecular ion of the 4-oxothiazolidine-5-acetate derivative **3a**. Therefore, if the isolated heterocycles were the (*Z*)-4-oxo- -1,3-thiazinanes **4**, this fragment would not have been detected.

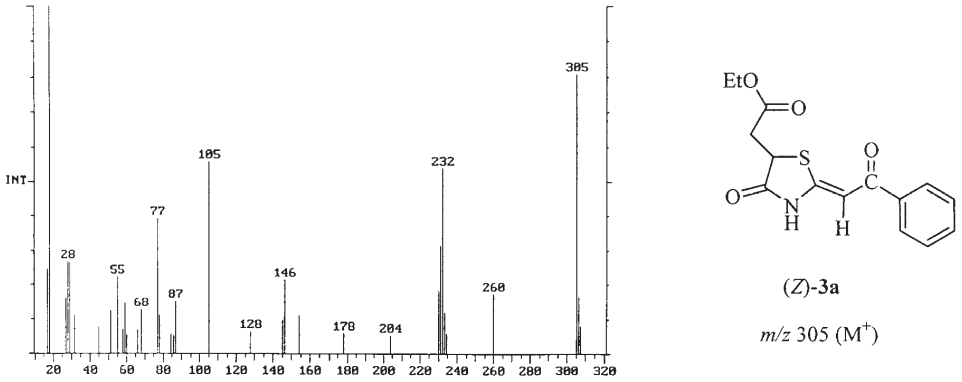
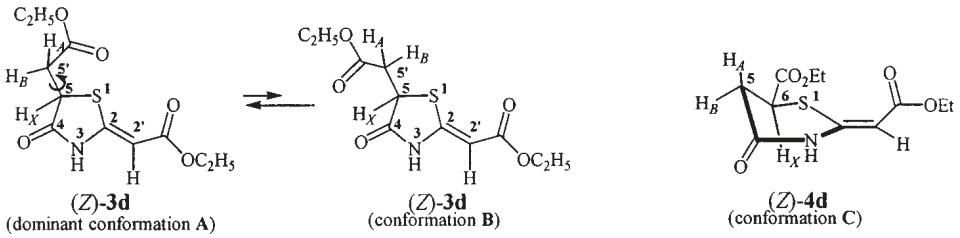


Fig. 1. Mass spectrum of (*Z*)-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (**3a**).

The structure assignment regarding the ring size in the isolated heterocycles **3a–d** appears to be further supported by the analysis of the coupling constants of the diastereotopic CH_AH_B protons as shown explicitly for the (*Z*)-isomer **3d** (Table I).[12] Therefore, the methylene protons have different chemical shift values, *i.e.*, H_A = 2.95 ppm, and H_B = 3.04 ppm, and the spectrum exhibits an ABX spin-coupling system with a significant geminal coupling ($^2J_{AB}$ = 17.6 Hz). The third proton H_X with a chemical shift value of 4.28 ppm is split differently to the vicinal methylene protons H_A and H_B ($^3J_{AX}$ = 7.8 Hz; $^3J_{BX}$ = 4.6 Hz). The splitting pattern for each proton consists of a doublet of doublets. The unequal vicinal couplings $^3J_{AX}$ and $^3J_{BX}$ reflect hindered rotation around C(5)–C(5') due to steric reasons. In addition, the value of H_AH_X coupling constant strongly suggests a five-membered heteroaliphatic ring. In the case of a six-membered ring in the conformation **C** of the hypothetical 4-oxo-1,3-thiazinane derivative (*Z*)-**4d**, having nearly antiperiplanar protons H_A and H_X, the value of $^3J_{AX}$ should be higher (≈11–13 Hz for neighboring diaxial protons in the cyclohexane derivatives). Two conformers **A** and **B** are considered for (*Z*)-**3d**. The dominant conformation **A** is relatively devoid of steric congestion. In the less stable rotamer **B**, as seen by an inspection of the Dreiding models, the ester group at C(5') experiences an unfavorable interaction with the lactam carbonyl. Such a destabilization can be avoided by the rotation around the C(5)–C(5') bond, leading to the dominant

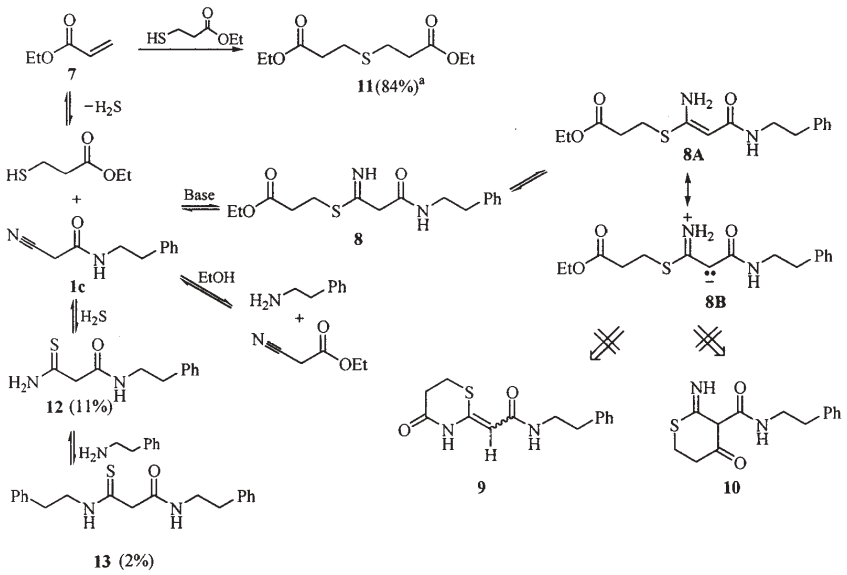
rotamer **A**. The X-ray analysis of derivative **3d** proved the *Z*-configuration of the double bond and indicated that the NH hydrogen is involved in an intermolecular hydrogen bond to the C(4) carbonyl oxygen of an adjacent molecule.[13]



To verify the unexpected 100 % regioselectivity of the base-catalyzed heterocyclization of β-oxonitriles **1** with diethyl mercaptosuccinate affording the 5-substituted-4-oxothiazolidine derivatives **3** (Scheme 1, path **a**), a reaction involving the cyano derivative **1c** and ethyl 3-mercaptopropanoate was attempted (Scheme 3). If the adduct **8** was formed in the first step of an addition-cyclization reaction sequence, then intramolecular cyclization in two different ways should give the 4-oxo-4H-1,3-thiazinane derivative **9** and/or **10**. Despite many attempts to carry out this reaction under various conditions in order to obtain the expected cyclic compounds, only simple acyclic products **11**–**13** and hydrolysis products of precursor **1c** were isolated (Scheme 3), accompanied by unreacted nitrile in 40 % yield. The cyclization ability, interestingly, was completely suppressed at the expense of the much faster side reactions. Nevertheless, in a similar study, Satzinger[14] reported the formation of tetrahydro-1,3-thiazinane derivatives of the type **9**. Our results demonstrate that the five-membered cyclization products **3a**–**d** were the result of intramolecular cyclization of the intermediates **2a**–**d** which underwent cyclization only by path **a** (Scheme 1) under kinetic control. This is in accordance with the lower cyclization ability of intermediates **2a**–**d** to give the six-membered heterocycles **4a**–**d** *via* path **b**.

Finally, our attention was turned to improve the low to modest yields (24–52 %) of the purified 4-thiazolidinone derivatives **3a**–**d**. Initial attempts toward the conversion of β-oxonitriles **1a**–**d** to **3a**–**d** (Scheme 1) involved treatment of the corresponding nitrile with diethyl mercaptosuccinate in a 1:1 molar ratio, in boiling ethanol. Employing the model substance **1c**, the reaction gave, as depicted in Scheme 4, the cyclization product **3c** in 24 % yield, along with products **12**, **14** and **15** of the secondary processes.

After extensive experimentation, it was found that the use of a large molar excess of diethyl mercaptosuccinate relative to the nitrile derivative **1c** (mole ratio **1a**/mercapto derivative 1.73/1.00) improved the yield of the cyclization product to 60 %. Under these conditions, better yields (60–89 %) were also obtained with activated nitriles **1b**–**1d** (Table III). Possible explanation of the role of the mercapto derivative for the increased yields is that the increased concentration secures at the same time a sufficient quantity of mercaptodiester for the concurrent secondary reactions and heterocyclization.



Conditions: reaction conducted on a 4.26 mmol scale in dry ethanol (5.5 mL);
mole ratio**1c**/ester: 1; reflux time: 11h; catalyst: anh K_2CO_3;
the structures of byproducts 11-13 are fully confirmed on the basis of spectroscopic data.
*relative to mercapto ester.

Scheme 3.

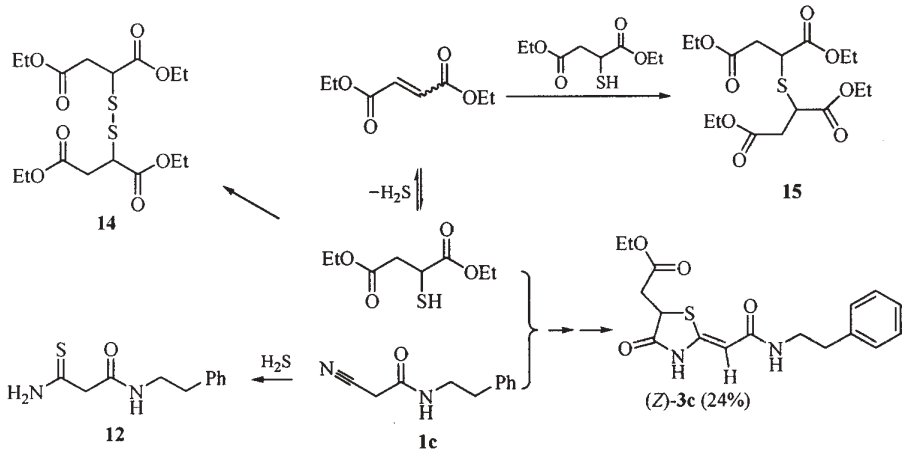
TABLE III. Mole ratio effect on yields of cyclization products **3a–d** according to Scheme 1

Nitrile **1**	Diester/**1** (mole ratio)	Rxn. time (h)	Product	Yield[a] (%)
1b	1.00	5	**3b**	24
1b	1.72	5	**3b**	89
1c	1.00	7.5	**3c**	40
1c	1.73	5	**3c**	60
1d	1.00	7	**3d**	70
1d	1.54	7	**3d**	80

[a]Crude product

EXPERIMENTAL

Melting points were determined on a Micro-Heiztisch Boetius PHMK apparatus and Büchi apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer 1725X and are reported as wave numbers (cm^{-1}). Samples for IR spectral measurements were prepared as KBr disks. The NMR spectra were obtained using a Varian Gemini 2000 instrument (^1H at 200 MHz, ^{13}C at 50.3 MHz). The chemical shifts are reported in parts per million (ppm) on the δ scale from TMS as an internal standard in the specified solvents. Low-resolution mass spectra were recorded using a Finnigan MAT 8230 BE spectrometer. Isobutane was used as the ionizing gas for the chemical ionization (CI) mass spectra. The UV spectra were measured on a Beckman DU-50 spectrophotometer. Analytical thin-layer chromatography (TLC) was carried out on Kieselgel G nach Stahl, and the spots were visualized by iodine. Column chromatography was



Scheme 4.

carried out on SiO_2 (silica gel 60Å, 12-26, ICN Biomedicals). Elemental analyses were performed at the microanalysis laboratory at the Department of Chemistry, University of Belgrade.

General procedure A for the preparation of 4-oxothiazolidine derivatives **3a**–**d**[5]

To a stirred suspension of activated β-oxonitrile **1a**–**d** (3 mmol) (Scheme 1) and diethyl mercaptosuccinate (≈ 0–1 % molar excess) in 5–10 ml of ethanol, a catalytic amount of K_2CO_3 was added (reagents for the starting compounds **1** were obtained by standard procedure). **CAUTION**: *All reactions involving mercapto ester, due to the unpleasant odor, should be carried out under a well-ventilated fume cupboard.* The mixture was brought to reflux and the reaction mixture was stirred for 3–7.5 h. The mixture was cooled down to rt and the precipitated product was collected by filtration, washed with ethanol and recrystallized from 96 % ethanol to provide the final product **3a**–**d** in 24–52 % yield. Alternatively the filtered solution was concentrated under reduced pressure and the residue was chromatographed (toluene/ethyl acetate, 1:0 →10:1, v/v) affording the desired cyclic product. The structural assignments of all the isolated products were made on the basis of spectroscopic data (IR, ^{1}H and ^{13}C-NMR, MS, UV) and elemental analysis.[5]

General procedure B. The above procedure was adopted with the modification that a large excess of diethyl mercaptosuccinate (1.7 mmol) relative to the β-oxonitrile **1** (1 mmol) was used, which improved the yield of the cyclization products to 60–89 % (Table III).

*By-product characterization in the heterocyclization of cyano-*N*-(2-phenylethyl)ethanamide* **(1c)**

Following a similar general heterocyclization of **1c** (1.126 g, 5.5 mmol) employing the slight molar exess of diethyl mercaptosuccinate, the reaction mixture was left overnight, whereby a small amount of cyclic product **3c** (0.115 g) precipitated. The filtered solution was concentrated and silica gel chromatography (toluene/ethyl acetate 7:3, v/v) provided the following compounds: N-*(2-phenylethyl)-2-thiocarbamoylethanamide* (**12**) (0.082 g) as a white solid, mp 88 – 9 ºC; IR (KBr) ν_{max}/cm^{-1} 3333, 3282, 2931, 1660, 1648, 1618, 1561, 1497, 1432, 1199, 1155, 1030, 737, 696 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.72 (2H, *t*, *J* = 7.3 Hz, CH_2Ph), 3.24–3.35 (2H, *m*, NCH_2, *J*(CH_2CH_2) = 7.3 Hz, *J*($NHCH_2$) = 5.5 Hz), 3.44 (2H, *s*, $CSCH_2CO$), 7.16–7.34 (5H, *m*, aromatic), 8.17 (1H, *t*, NH, *J* = 5.5 Hz), 9.31 (1H, *br s*, SCNHH), 9.61 (1H, *br s*, SCNHH); ^{13}C-NMR (DMSO-d_6): δ 35.78 (CH_2Ph), NCH_2 not visible, 47.00 (NCH_2), 52.29 ($CSCH_2CO$), 126.92 (*p*-Ph), 129.14 (*o*-Ph), 129.49 (*m*-Ph), 140.18 (C_1–Ph), 167.40 (CO), 200.88 (CS); MS (CI) *m*/*z* 223 (M+1); MS (EI) *m*/*z* (rel. intensity) 222 (M^+, 21), 131 (8), 120 (13), 118 (100), 105 (21), 104 (43), 103 (15), 102 (48), 101 (65), 91 (34), 77 (16), 75 (9), 60 (17), 59 (8), 43 (23), 30 (41); *tetraethyl thiodisuccinate* (**14**) (0.477 g, 46 % of the starting diethyl mercaptosuccinate) as a pale yellow oil. IR (film) ν_{max}/cm^{-1} 3453, 2984, 1734, 1467, 1447, 1260, 1028, 796, 730, 689, 645 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.71 (2H, *t*, *J* = 7.4 Hz, CH_2Ph), 2.88

(2H, *t*, *J* = 7.5 Hz, CH_2Ph), CH_2NH overlapped by H_2O from DMSO, 3.50 (2H, *s*, $CSCH_2CO$), 3.62–3.77 (2H, *m*, $NHCH_2$), 7.16–7.35 (10H, *m*, aromatic), 8.16 (1H, *t*, *J* = 5.6 Hz), 10.26 (1H, *br t*, NH); ^{13}C-NMR (DMSO-d_6): δ 33.16 (CH_2Ph), 35.18 (CH_2Ph), 40.66 (NCH_2), 47.00 (NCH_2), 51.94 ($CSCH_2CO$), 126.36 (*p*-Ph), 126.53 (*p*-Ph), 128.57 (*o*-Ph), 128.66 (*o*-Ph), 128.88 (*m*-Ph), 128.91 (*m*-Ph), 139.20 (C_1–Ph), 139.60 (C_1–Ph), 167.02 (CO), 195.80 (CS); MS (CI) 327 (M+1); MS (EI) *m/z* (rel. intensity) 326 (M^+, 16) 293 (4), 235 (39), 222 (6), 206 (12), 164 (4), 163 (2), 148 (3), 120 (22), 118 (100), 105 (85), 104 (92), 91 (22), 77 (23), 59 (19), 43 (12); *tetraethyl-2,2'-dithiodisuccinate* (**15**) (small amount in the mixture with tetraethyl thiodisuccinate (**14**)). In addition to these products, pure cyclic compound **3c** (0.264 g), a mixture of **3c** and the starting nitrile **1c** (0.385 g) and pure unreacted nitrile (0.125 g) were also isolated.

Acknowledgment: This work was supported in part by the Ministry of Science, Republic of Serbia.

ИЗВОД

РЕГИОСПЕЦИФИЧНОСТ У ХЕТЕРОЦИКЛИЗАЦИЈИ β-ОКСОНИТРИЛА ДО 5-СУПСТИТУИСАНИХ 4-ОКСОТИАЗОЛИДИНСКИХ ДЕРИВАТА

РАДЕ МАРКОВИЋ,[1,2] ЗДРАВКО ЏАМБАСКИ,[2] МИЛОВАН СТОЈАНОВИЋ,[2] PETER STEEL[3] и МАРИЈА БАРАНАЦ[1,2]

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Проучавана је региоспецифичност базно-катализоване реакције активираних β-оксонитрила **1** са диетил-естром меркаптоћилибарне киселине у којој се граде у наслову наведена једињења **3**. Могући хетероциклични производи, 4-оксо-1,3-тиазини **4**, деривати тетрахидротиофена **5** и/или тијациклохексана **6**, који могу бити награђени на основу механистичког разматрања, нису детектовани. Спектроскопски и експериментални докази са теоријским образложењем дају прихватљиво објашњење за уочену региоспецифичност.

(Примљено 23. децембра 2002)

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