NEW APPROACH TO THE SYNTHESIS OF 3-AMINO-1,2-BENZOTHIAZINE 1,1-DIOXIDES

A. G. Nemazanyi, Yu. M. Volovenko,
V. V. Neshchadimenko, and F. S. Babichev

The possibility of obtaining 3-amino-1,2-benzothiazine 1,1-dioxides by nucleophilic substitution of the chlorine atom in 5-nitro-2-chlorobenzenesulfonamides by carbanions generated from substituted acetonitriles was studied.

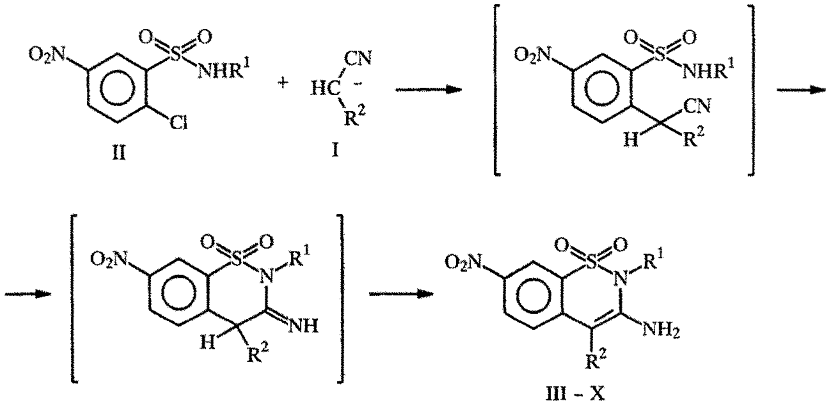
Isomeric benzothiazines and, particularly, 1,2-benzothiazines display a broad spectrum of biological activity [1-3]. Of particular interest in connection with the possibility of their purposeful modification are 3-amino-1,2-benzothiazine 1,1-dioxides. The latter, however, have thus far remained difficult to obtain, and little study has been devoted to them [3].

Continuing our study of nucleophilic substitution in a series of functionally substituted halo arenes [4] we have discovered the possibility of a new approach to the synthesis of 3-amino-1,2-benzothiazine 1,1-dioxides.

The synthesis of 4-substituted 3-amino-7-nitro-2H-1,2-benzothiazine 1,1-dioxides III-X (Table 1) is accomplished by the reaction of substituted acetonitriles I with 5-nitro-2-chlorobenzenesulfonamides II in the presence of alkali metal carbonates (K_2CO_3, Cs_2CO_3).

The formation of the benzothiazine ring can be conceived of as follows: the carbanion generated from the substituted acetonitrile by the action of a base — the alkali metal carbonate — replaces the chlorine atom; this is followed by intramolecular addition of the NH group of the sulfonamide to the cyano group with subsequent isomerization of the molecule.

Characteristic absorption bands of stretching vibrations of a primary amino group at 3280-3425 cm^{-1} are observed in the IR spectra of III-X; the conjugated cyano group in III and IV shows up at 2180 and 2210 cm^{-1}, respectively, while the absorption of a sulfonamido group is observed in the form of an intense band at 1310-1365 cm^{-1}. The UV spectra of products III-X are characterized by the presence of a long-wave maximum at 390-448 nm (log ε 4.10-4.71).



III R^1=H, R^2=CN; IV R^1=CH_3, R^2=CN; V R^1=CH_3, R^2=3,4-$(CH_3O)_2C_6H_3$; VI R^1= 4-pyridyl R^2= 2-pyridyl-2; VII R^1=CH_3, R^2= 1-methyl-2-benzimidazolyl -2; VIII R^1=$CH_2C_6H_5$, R^2= 1-methyl-2-benzimidazolyl -2; IX R^1=C_6H_5, R^2= 1-methyl-2-benzimidazolyl -2; X R^1=C_6H_5, R^2= 2-quinolyl

---

T. G. Shevchenko Kiev State University, Kiev 252601. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 264-266, February, 1992. Original article submitted July 17, 1990.

0009-3122/92/2802-0220$12.50

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	mp, °C	PMR spectrum, δ, ppm				IR spectrum, ν, cm⁻¹		Yield, %*
			8-H, d	6-H, dd	5-H, d	NH_2, br.s	SO	NH_2	
III	$C_8H_6N_4O_4S$	>300	8,20	8,07	7,12	7,52	1310	3425	62
IV	$C_{10}H_8N_4O_4S$	295	8,45	8,37	7,53	8,40	1365	3280	78
V	$C_{17}H_{17}N_3O_6S$	250	8,33	8,07	7,11	6,57	1360	3290	67
VI	$C_{18}H_{13}N_5O_4S$	249	8,46	8,37	—**	8,95	1325	3270	66
VII	$C_{17}H_{15}N_5O_4S$	247	8,44	8,21	7,07	7,77	1325	3280	64
VIII	$C_{23}H_{19}N_5O_4S$	229	8,45	8,19	7,71	7,74	1340	3380	72
IX	$C_{22}H_{17}N_5O_4S$	231	8,53	8,21	7,67	7,83	1330	3240	74
X	$C_{23}H_{16}N_4O_4S$	213	8,37	8,04	7,69	8,53	1335	3380	65

---

*The compounds were recrystallized: III and VI from o-xylene, IV and X from 2-propanol, VII and IX from nitromethane, V from toluene, and VIII from dioxane.

**The signal was covered by signals of the aromatic ring protons.

The structures of the compounds obtained are confirmed by the PMR spectra. Thus the protons of an amino group are observed in the form of a broad singlet at 6.57-8.95 ppm (2H), which vanishes on treatment of the sample with D_2O. The extreme value of this range (6.57 ppm) is related to V and is explained by the effect of the π-electron ring currents of a phenyl substituent in the 4 position of the molecule. In turn, the weak-field shift of the signal of the protons of the amino group (8.95 ppm, VI) is due to the significant deshielding effect of the pyridine rings in the 2 and 4 positions of the benzothiazine ring. The benzothiazine ring is characterized by the weakest-field signal — a doublet at 8.20-8.53 ppm (J = 1.5 Hz) — from the proton in the 8 position of the molecule. The unusual value of its chemical shift is due to the deshielding effect of the nitro and sulfo groups, which are in direct proximity to it. Signals of the protons in the 6 and 5 positions of the III-X molecules are observed at 8.04-8.37 ppm (dd, J = 8.74 Hz, J = 1.45 Hz) and 7.07-7.71 ppm (d, J = 8.7 Hz), respectively.

Thus we propose a preparative method for the synthesis of the previously unknown 3-amino-7-nitro-2H-1,2-benzothiazine 1,1-dioxides that opens up extensive synthetic possibilities.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with as Pay Unicam SP3-300 spectrometer. The electronic spectra of solutions in 2-propanol were obtained with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in DMSO-D_6 were recorded with a Bruker WP-100 spectrometer with tetramethylsilane (TMS) as the internal standard. The progress of the reactions and the individuality of the synthesized compounds were monitored by means of TLC on Silufol UV-254 plates with development in UV light; the eluent was chloroform—methanol (9:1).

The results of elementary analysis for N and S were in agreement with the calculated values.

5-Nitro-2-chlorobenzenesulfonamides II. These compounds were obtained by treatment of 5-nitro-2-chlorobenzenesulfonyl chloride with the corresponding amines [5].

3-Amino-7-nitro-2H-1,2-benzothiazine 1,1-Dioxides III-X. A 0.01-mole sample of the corresponding substituted acetonitrile I and 0.01 mole of freshly calcined and finely ground potassium carbonate were added to a solution of 0.01 mole of the corresponding II in 70 ml of dry DMF, and the mixture was refluxed for 1.5 h. The solvent was removed in vacuo, the residue was treated with 100 ml of water, and the aqueous mixture was acidified to pH 7 with acetic acid. The resulting precipitate was removed by filtration, washed with water, dried, and crystallized from an appropriate solvent.

Compound V was obtained by using Cs_2CO_3.

LITERATURE CITED

1. P. D. Hammen, H. Berke, J. Bordner, C. Andew, and Joseph G. Lombardino Braisner, *J. Heterocycl. Chem.*, **26**, 11 (1989).
2. E. Sianessi, Paolo Da Re, J. Setnicar, E. Massarani, and S. A. Recordati, *Chem. Abstr.*, **78**, 159,641s (1973).
3. E. Sianessi, J. Setnicar, E. Massarani, and S. A. Recordati, German Offen. No. 2,022,694; *Chem. Abstr.*, **74**, 141,829 (1971).
4. A. G. Nemazanyi, Yu. M. Volovenko, T. A. Silaeva, and F. S. Babichev, *Dokl. Akad. Nauk Ukr. SSR, Ser. B*, No. 12, 36 (1989).
5. A. R. Goldfarb, *J. Am. Chem. Soc.*, **65**, 738 (1943).

CONDENSED SYSTEMS BASED ON 4-AMINO-3-MERCAPTO-1,2,4-TRIAZOLE

N. N. Kolos, V. D. Orlov,
E. K. Slobodina, E. Yu. Yur'eva,
S. P. Korshunov, and Zyong van Tué

1,2,4-Triazolo[3,4-b]-1,3,4-thiadiazines, hydrazones, and β-thio adducts were obtained by reactions of 4-amino-3-mercapto-1,2,4-triazole with ω-bromoacetophenones, aldehydes, and α,β-unsaturated ketones. Conditions that promote the cyclocondensation of the β-thio adducts to the previously undescribed 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepines were found. The chemical and spectral properties of the compounds obtained are discussed.

The aim of this research was to investigate the reactivity of 4-amino-3-mercapto-1,2,4-triazole (I) with respect to aromatic ketones and aldehydes. Only the reactions of 5-substituted I with phenacyl bromide [1] and β-bromo-γ-keto esters [2], which lead to the formation of triazolo[3,4-b]-1,3,4-thiadiazines, have been described in the literature.

The reaction of I with 4-R-ω-bromoacetophenones IIa-g proceeds without a catalyst by refluxing alcohol solutions for from 10-15 min (in the case of IIa-e) to 1-1.5 h (IIf, g). The resulting IIIa-g were identified by means of their spectral characteristics (Table 1) as 5-aryl-6H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines (which is also in agreement with the results of elementary analysis for nitrogen and sulfur). Thus bands of stretching vibrations of azomethine (1582-1628 cm^{-1}) and methylene (2903-2923 cm^{-1}) groups are observed in their IR spectra. The long-wave absorption band in the UV spectra of triazolothiadiazines IIIa-f lies at 281-308 nm. It undergoes an appreciable bathochromic shift when electron-donor substituents R (IIIb, c) are introduced; this, in turn, reflects the π-deficient character of the triazole ring. (See scheme at the top of the next page.)

The development of a band at 352 nm and the pronounced high-frequency shift of the $\nu_{C=N}$ band in the spectra of IIIg (see Table 1) provide unambiguous evidence for the presence of a rather strong intramolecular hydrogen bond in its molecule. The PMR spectra of solutions of IIIa-f in $CDCl_3$ contain singlets of the protons of a methylene group and of a methylidyne proton of a triazole ring, as well as a multiplet of aromatic protons at 8.17-8.50 ppm.

The question of the manifestation of imine—enamine tautomerism often arises in the study of 1,4-thiazine derivatives [3]. From the set of spectral data obtained it follows unequivocally that IIIa-g exist exclusively in the 6H-tautomeric form; the intensity of the signal of the proton of the CH_2 group in the PMR spectra did not change even when solutions of IIIa, e were allowed to stand for 2-3 days.

A. M. Gor'kii Kharkov State University, Kharkov 310077. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 267-272, February, 1992. Original article submitted January 26, 1990; revision submitted April 25, 1990.

0009-3122/92/2802-0222$12.50