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1-Aza-1,3-enynes in Synthesis of Substituted 4*H*-[1,3]thiazino[3,2-*a*]benzimidazol-4-ols

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Abstract—Reaction of *N-tert*-butyl-1-aza-1,3-enynes with symmetrically substituted 2-mercaptobenzimidazoles in water-alcohol solutions afford 4*H*-[1,3]thiazino[3,2-*a*]benzimidazol-4-ols. The structure of compounds obtained was proved by the ^{1}H and ^{13}C NMR spectroscopy and X-ray diffraction data.

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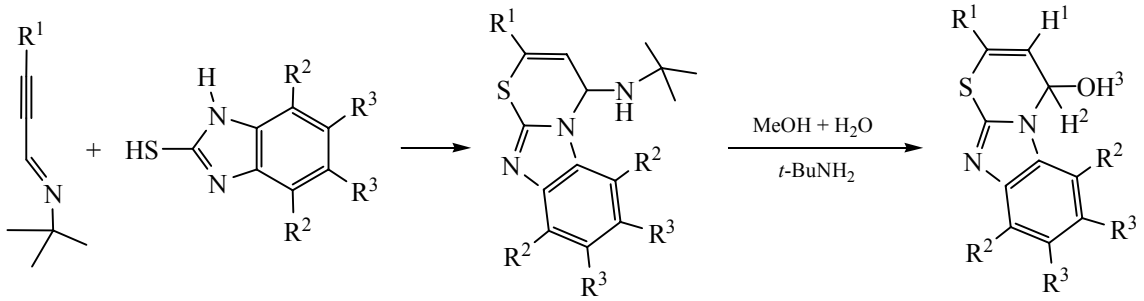
Among the factors determining the steady remaining interest in the 1-aza-1,3-enynes is the wide spectrum of preparative possibilities connected with the presence of conjugated multiple bonds [1–5]. This structural feature makes it possible to use the 1-aza-1,3-enynes for obtaining analogs of natural antibiotics of the thienomycin family and some other pharmaceuticals [1–5], and creates prerequisites for considering the 1-aza-1,3-enynes as convenient syntons for directed synthesis of the polyfunctional molecular materials possessing antipyretic, psychotropic, antiasthmatic, and also pesticidal and antioxidant activities [1–5].

The chemical designing based on the 1-aza-1,3-enynes, i.e., obtaining new compounds from the structural fragments entering into their composition, is attractive mainly with respect to the possibility of carrying out the nucleophilic addition reactions. However, among the reactions of this type the reactions of 1-aza-1,3-enynes with heterocyclic thiols of different structure such as mercaptoazoles, in particular 2-mercaptobenzimidazoles, were insufficiently studied.

We have previously showed that 2-mercaptobenzimidazole can be added to *N-tert*-butyl-1-aza-1,3-enynes to form substituted 4*H*-[1,3]thiazino[3,2-*a*]-benzimidazol-4-ols [6]. In the present work the reaction of *N-tert*-butyl-1-aza-1,3-enynes with some symmetrically substituted 2-mercaptobenzimidazols is studied. The reaction is chemo- and regioselective and make it possible to obtain substituted fused [1,3] thiazin-4-ols **IVa–IVf**:



I **II** **IIIa–IIIf** **IVa–IVf**

a, R^1 = Ph, R^2 = OMe, R^3 = H; **b**, R^1 = Ph, R^2 = H, R^3 = OMe; **c**, R^1 = Ph, R^2 = H, R^3 = Me; **d**, R^1 = *t*-Bu, R^2 = OMe, R^3 = H; **e**, R^1 = *t*-Bu, R^2 = H, R^3 = OMe; **f**, R^1 = *t*-Bu, R^2 = H, R^3 = Me.

Table 1. Selected bond angles (ω, deg) in the structure of **IVa**

Angle	ω, deg	Angle	ω, deg	Angle	ω, deg
$C^1S^1C^8$	100.96(9)	$C^1N^5C^4$	105.13(16)	$C^9C^{10}C^{11}$	122.23(18)
$C^9O^2C^{19}$	116.65(17)	$C^1N^5C^6$	126.82(16)	$C^{12}C^{11}C^{10}$	121.45(19)
$C^{12}O^3C^{20}$	116.94(17)	$C^4N^5C^6$	126.26(15)	$O^3C^{12}C^{11}$	126.51(19)
$N^2C^1N^5$	114.95(16)	$O^1C^6N^5$	110.56(15)	$O^3C^{12}C^3$	116.40(17)
$N^2C^1S^1$	120.85(14)	$O^1C^6C^7$	111.16(16)	$C^{11}C^{12}C^3$	117.08(19)
$N^5C^1S^1$	124.08(14)	$N^5C^6C^7$	111.14(15)	$C^{14}C^{13}C^{18}$	118.48(18)
$C^1N^2C^3$	103.61(16)	$C^8C^7C^6$	128.49(18)	$C^{14}C^{13}C^8$	120.50(18)
$C^4C^3N^2$	110.50(16)	$C^7C^8C^{13}$	123.79(17)	$C^{18}C^{13}C^8$	121.01(18)
$C^4C^3C^{12}$	120.92(17)	$C^7C^8S^1$	123.67(15)	$C^{13}C^{14}C^{15}$	120.3(2)
$N^2C^3C^{12}$	128.56(18)	$C^{13}C^8S^1$	112.52(14)	$C^{16}C^{15}C^{14}$	120.5(2)
$C^3C^4N^5$	105.81(16)	$O^2C^9C^{10}$	126.63(17)	$C^{17}C^{16}C^{15}$	119.47(19)
$C^3C^4C^9$	122.36(18)	$O^2C^9C^4$	117.43(17)		
$N^5C^4C^9$	131.82(18)	$C^{10}C^9C^4$	115.94(18)		

Table 2. Bond lengths (*d*, Å) in the structure of **IVa**

Bond	*d*, Å	Bond	*d*, Å	Bond	*d*, Å
S^1–C^1	1.7355(18)	N^2–C^3	1.395(2)	C^9–C^{10}	1.377(3)
S^1–C^8	1.7619(19)	C^3–C^4	1.390(3)	C^{10}–C^{11}	1.410(3)
O^1–C^6	1.412(2)	C^3–C^{12}	1.403(3)	C^{11}–C^{12}	1.378(3)
O^2–C^9	1.367(2)	C^4–N^5	1.396(2)	C^{13}–C^{14}	1.395(3)
O^2–C^{19}	1.424(2)	C^4–C^9	1.406(3)	C^{13}–C^{18}	1.393(3)
O^3–C^{12}	1.364(3)	N^5–C^6	1.467(2)	C^{14}–C^{15}	1.392(3)
O^3–C^{20}	1.420(2)	C^6–C^7	1.495(3)	C^{15}–C^{16}	1.384(3)
C^1–N^2	1.316(2)	C^7–C^8	1.333(3)	C^{16}–C^{17}	1.373(3)
C^1–N^5	1.364(2)	C^8–C^{13}	1.487(2)	C^{17}–C^{18}	1.391(3)

The reaction proceeds at room temperature either in not dried methanol or in methanol containing a DMF admixture. The presence of some water and DMF in methanol leads to the hydrolysis of the [1,3]thiazine-4-*tert*-butylamine **IIIa–IIIf** to afford the corresponding [1,3]thiazin-4-ol **IVa–IVf** through *tert*-butylamine elimina-tion. The [1,3]thiazine-4-ols **IVa–IVf** ob-tained are crystalline compounds with high melting points.

Apart from the mercapto group, the second nucleophilic center, pyrrole nitrogen atom of 2-mercaptobenzimidazole heterocyclic ring, takes part in the reaction. The heterocyclization occurs via [3+3]-binucleophilic cycloaddition of 2-mercaptobenzimida-zoles to give 1-aza-1,3-enynes. In this case neither the nature of R^1 group at the triple bond of aza-enynes nor the nature of substituents R^2 and R^3 in benzimidazole frame affect the reaction direction and the structure of substances obtained.

In accordance with the published data [2], the addition of azoles to the multiple bond of 1-aza-1,3-enynes proceeds more difficultly than the mercaptans addition [1]. Based on this fact, it is presumable that initially the mercapto-group enters the reaction with aza-enyne, and then the pyrrole nitrogen atom of symmetrically substituted 2-mercaptobenzimidazole, and the elimination of *tert* -butylamine occurs already after the cycloaddition completion.

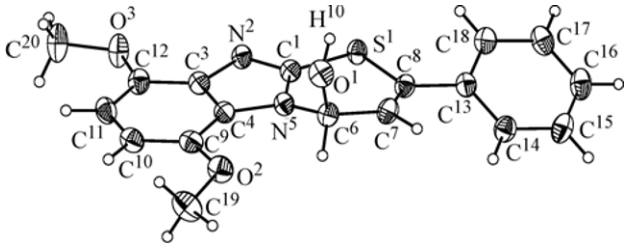


Fig. 1. ORTEP drawing of **IVa** (50% probability *thermal ellipsoids*).

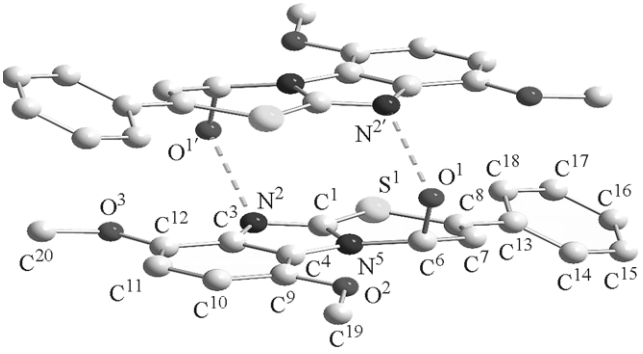


Fig. 2. Intermolecular interactions in the structure of **IVa**.

The structure of compounds **IVa–IVf** was proved by the ^{1}H and ^{13}C NMR spectroscopy. For example, the ^{1}H NMR spectra contain characteristic signals of the protons H^{1} and H^{2} of 1,3-thiazine ring and the hemiacetal hydroxy proton H^{3} at 6.0–7.0 ppm.

According to the X-ray diffraction analysis data compound **IVa** (Fig. 1) crystallized in the monoclinic crystal system, space group *C*2/*c*; unit cell parameters: *a* 19.366(4) Å, *b* 7.9088(16) Å, *c* 20.777(4) Å; α 90°, β 98.52(3)°, γ 90°; *Z* 8, *R* 4.61%. The selected bond lengths and angles are given in Tables 1 and 2, respectively.

Table 3. Crystallographic data of the structure **IVa**

Parameter	Value
Empirical formula	$C_{18}H_{16}N_2O_3S$
Formula weight	340.39
Crystal system	163(2)
Space group	Monoclinic
d_{calc}, g cm^{-3}	*C*2/*c*
Unit cell dimensions	1.437
	a 19.366(4),
	b 7.9088(16),
	c 20.777(4) Å;
	α 90°,
	β 98.52(3)°,
	γ 90°
Volume, Å^3	3147.2(11)
Z	8
Temperature, K	
Crystal habit	Prism
Crystal size, mm^3	0.40×0.20×0.20
Color	Pale brown
R Indicies [$I > 2\sigma(I)$]	*R* 0.0461, R_w 0.1146
R Indicies (all data)	*R* 0.0639, R_w 0.1189

Compound **IVa** in the crystalline state is prone to the formation of unique dimers (Fig. 2), the one-dimensional (1D) constructions formed due to the hydrogen bonding of *head to tail* type. Distance between the planes is ~3.26Å. The shortest bonds are $C^{1}\cdots C^{1A}$ [3.285(3) Å] and $S^{1}\cdots N^{3A}$ [3.418(1) Å].

On the basis of the X-ray analysis data of compound **IVa**, it is possible to assume that compounds **IVb–IVf** containing the structural fragment of 4*H*-[1,3]-thiazino[3,2-*a*]benzimidazol-4-ol are also inclined to the formation of similar dimers, in which the individual molecular blocks are associated with each other by means of hydrogen bonds.

Thus, we can conclude that the reaction of *N*-*tert*-butyl-1-aza-1,3-enynes with symmetrically substituted 2-mercaptobenzimidazoles makes it possible to create purposefully 4*H*-[1,3]thiazino[3,2-*a*]benzimidazol-4-ols derivatives **IVa–IVf** through one-pot method in yields of 80–85%. not isolating the intermediately generated a 4*H*-[1,3]thiazino[3,2-*a*]benzimidazole-4-*tert*-butylamine **IIIa–IIIf.**

The crystal data of 6,9-dimethoxy-2-phenyl-4*H*-[1,3]-thiazino[3,2-*a*]benzimidazol-4-ols **IVa** are deposited at Cambridge Crystallographic Data Center, UK, and the CCDC reference number is 757744.

EXPERIMENTAL

The solvents and reagents of analytical grade were used. The ^{1}H and ^{13}C NMR spectra were registered in DMSO-d_6 on a Varian XL-300 instrument operating at 300.13 (^{1}H) and 75.45 MHz (^{13}C). The X-ray diffraction analysis was performed on a four-circle automatic diffractometer Syntex $P2_1$.

6,9-Dimethoxy-2-phenyl-4*H*-[1,3]thiazino[3,2-*a*]-benzimidazol-4-ol (IVa). To a solution of 0.01 mol of

ethynal *tert*-butylimine in 50 ml of methanol was added at stirring 0.01 mol of a solution of symmetrically substituted 2-mercaptobenzimidazole in 10 ml of DMF. After 2 h the mixture was concentrated. The residue was dissolved in 50 ml of ethanol, mixed with 5 ml of water, and refluxed for 1–2 min. After cooling the fine-crystalline precipitate appears. To obtain single crystals for X-ray analysis methanol was used as solvent. Yield 85%, mp 188°C. ^{1}H NMR spectrum, δ, ppm: 3.94 s (6H), 6.43 d (1H, $^3J_{HH}$ 5.82 Hz), 6.52 d (1H, $^3J_{HH}$ 7.99 Hz), 6.57–6.63 m (2H), 6.93–6.98 m (1H), 7.45–7.49 m (3H), 7.60-7.63 m (2H). ^{13}C NMR spectrum, δ_C, ppm: 55.93, 73.80, 103.47, 104.12, 116.54, 123.47, 126.08, 128.78, 129.30, 130.61, 134.71, 136.06, 141.13, 142.90, 144.20. Found, %: C 63.4; N 8.3. $C_{18}H_{16}N_2O_3S$. Calculated, %: C 63.5; N 8.2.

The important crystal data of compound **II** are given in Table 3.

Compounds **IVb–IVf** were prepared similarly.

7,8-Dimethoxy-2-phenyl-4*H*-[1,3]thiazino[3,2-*a*]-benzimidazol-4-ol (IVb). Yield 85%, mp 245°C. ^{1}H NMR spectrum, δ, ppm: 3.85 s (3H), 3.89 s (3H), 6.36 d (1H, $^3J_{HH}$ 4.36 Hz), 6.56–6.60 m (1H), 7.02 d (1H, $^3J_{HH}$ 9.45 Hz), 7.07 s (1H), 7.25 s (1H), 7.44–7.47 m (3H), 7.61–7.63 m (2H). ^{13}C NMR spectrum, δ_C, ppm: 56.04, 73.35, 94.96, 100.75, 116.52, 126.14, 127.03, 129.05, 129.60, 130.10, 136.09, 136.40, 140.73, 146.22, 146.74. Found, %: C 63.6; N 8.1. $C_{18}H_{16}N_2O_3S$. Calculated, %: C 63.5; N 8.2.

7,8-Dimethyl-2-phenyl-4*H*-[1,3]thiazino[3,2-*a*]-benzimidazol-4-ol (IVc). Yield 80%, mp 210°C. ^{1}H NMR spectrum, δ, ppm: 2.37 s (3H), 2.40 s (3H), 6.38 d (1H, $^3J_{HH}$ 5.08 Hz), 6.53-6.57 m (1H), 6.95 d (1H, $^3J_{HH}$ 9.45 Hz), 7.30 s (1H), 7.25 s (1H), 7.44–7.47 m (4H), 7.61–7.63 m (2H). ^{13}C NMR spectrum, δ_C, ppm: 20.03, 73.40, 111.10, 116.52, 117.65, 118.43, 124.47, 126.06, 127.25, 127.62, 128.80, 129.34, 130.13, 130.70, 131.75, 136.14, 141.15, 142.37. Found, %: C 70.5; N 9.4. $C_{18}H_{16}N_2OS$. Calculated, %: C 70.1; N 9.1.

6,9-Dimethoxy-2-*tret*-butyl-4*H*-[1,3]thiazino[3,2-*a*]benzimidazol-4-ol (IVd). Yield 85%, mp 146°C. ^{1}H NMR spectrum, δ, ppm: 1.32 s (9H), 3.94 s (6H), 6.43 d (1H, $^3J_{HH}$ 5.82 Hz), 6.52 d (1H, $^3J_{HH}$ 7.99 Hz), 6.57–6.63 m (2H), 6.93–6.98 m (1H). ^{13}C NMR spectrum, δ_C, ppm: 29.22, 36.43, 55.90, 73.47, 103.18, 104.09, 112.96, 123.71, 134.79, 141.07, 141.82, 143.82, 144.14. Found, %: C 60.5; N 8.3. $C_{16}H_{20}\cdot N_2O_3S$. Calculated, %: C 60.0; N 8.7.

7,8-Dimethoxy-2-*tret*-butyl-4*H*-[1,3]thiazino[3,2-*a*]benzimidazol-4-ol (IVe). Yield 85%, mp 226°C. ^{1}H NMR spectrum, δ, ppm: 1.32 s (9H), 3.91 s (3H), 3.93 s (3H), 6.04 d (1H, $^3J_{HH}$ 5.81 Hz), 6.22 d (1H, $^3J_{HH}$ 7.26 Hz), 6.53–6.59 m (2H), 6.77–6.81 m (1H). ^{13}C NMR spectrum, δ_C, ppm: 29.32, 36.55, 55.74, 55.93, 73.07, 94.80, 100.62, 126.94, 136.40, 141.23, 145.92, 146.50. Found, %: C 59.7; N 8.4. $C_{16}H_{20}N_2O_3S$. Calculated, %: C 59.9; N 8.7.

7,8-Dimethyl-2-*tert*-butyl-4*H*-[1,3]thiazino[3,2-*a*]-benzimidazol-4-ol (IVf). Yield 80%, mp 188°C. ^{1}H NMR spectrum, δ, ppm: 1.33 s (9H), 2.35 s (3H), 2.38 s (3H), 5.96 d (1H, $^3J_{HH}$ 4.36 Hz), 6.32–6.37 m (1H), 6.69 d (1H, $^3J_{HH}$ 8.72 Hz), 7.25 s (1H), 7.37 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 19.97, 29.30, 73.12, 110.86, 112.56, 117.57, 129.54, 130.26, 131.78, 141.07, 141.42, 143.12. Found, %: C 66.4; N 9.3. $C_{16}H_{20}N_2OS$. Calculated, %: C 66.6; N 9.7.

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