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STEREOSELECTIVE METHODS FOR THE SYNTHESIS OF 4-BENZOYL-1-BENZOYLAMINO-3-(2-CHLOROPHENYL)-2-CYANO-1-METHYLTHIO-1-BUTENE AND ITS STRUCTURE

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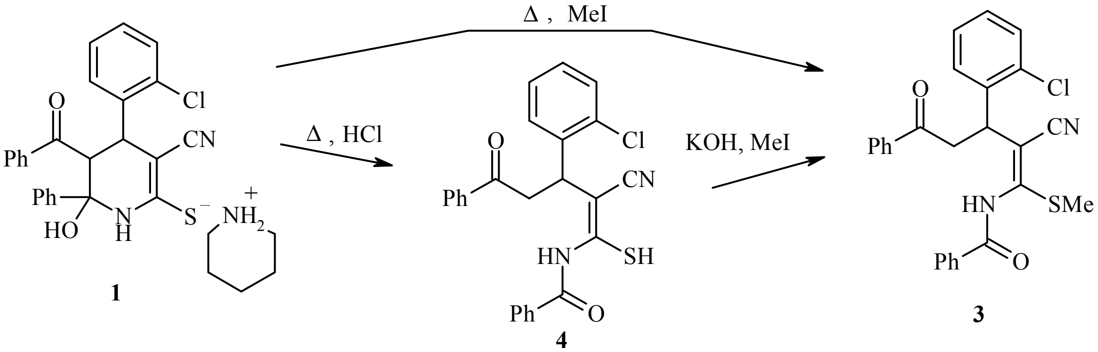
Selective methods were developed for the synthesis of 4-benzoyl-1-benzoylamino-3-(2-chlorophenyl)-2-cyano-1-methylthio-1-butene on the basis of the reaction of N-methylmorpholinium and piperidinium 5-benzoyl-4-(2-chlorophenyl)-3-cyano-6-hydroxy-6-phenyl-1,4,5,6-tetrahydropyridine-2-thiolates with methyl iodide. The structure of the product was established by X-ray crystallographic analysis.

Keywords: 1-butene, tetrahydro-2-pyridinethiolates, methylation, X-ray crystallographic analysis.

Earlier it was shown that the condensation of 2-chlorobenzaldehyde with cyanoacetamide and dibenzoylmethane in the presence of N-methylmorpholine or piperidine leads to the formation of substituted tetrahydropyridine-2-thiolates **1**, **2** [1]. Here it was established that compound **1** was transformed under the reaction conditions into piperidinium 4-benzoyl-1-benzoylamino-3-(2-chlorophenyl)-2-cyano-1-butene-1-thiolate, the methylation of which gave the corresponding 1-methyl-1-butene **3** in the form of a mixture of two conformational isomers.



On boiling the salt **1** with methyl iodide we obtained compound **3** in the form of an individual conformer (Table 1 and Fig. 1).

The geometric parameters of the molecule of **3** are extremely close in value to the corresponding parameters obtained earlier for the S-ethylated isostructural homolog of the molecule **3** [1]. Thus, the difference

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TABLE 1. The Principal Bond Lengths (*d*) and Bond Angles (ω) in the Molecule of Compound **3**

Bond	*d*, Å	Angle	ω, deg
$S_{(1)}–C_{(1)}$	1.764(3)	$C_{(1)}–S_{(1)}–C_{(19)}$	103.8(2)
$S_{(1)}–C_{(19)}$	1.772(4)	$C_{(20)}–N_{(1)}–C_{(1)}$	125.0(3)
$O_{(1)}–C_{(5)}$	1.221(3)	$C_{(20)}–N_{(1)}–H_{(1N)}$	119(2)
$O_{(2)}–C_{(20)}$	1.221(4)	$C_{(1)}–N_{(1)}–H_{(1N)}$	115(2)
$N_{(1)}–C_{(20)}$	1.372(4)	$C_{(2)}–C_{(1)}–N_{(1)}$	119.6(3)
$N_{(1)}–C_{(1)}$	1.404(4)	$C_{(2)}–C_{(1)}–S_{(1)}$	119.7(2)
$N_{(1)}–H_{(1N)}$	0.84(3)	$N_{(1)}–C_{(1)}–S_{(1)}$	120.7(3)
$C_{(1)}–C_{(2)}$	1.345(4)	$C_{(1)}–C_{(2)}–C_{(6)}$	118.0(3)
$C_{(2)}–C_{(6)}$	1.437(4)	$C_{(1)}–C_{(2)}–C_{(3)}$	126.2(3)
$C_{(2)}–C_{(3)}$	1.537(4)	$C_{(6)}–C_{(2)}–C_{(3)}$	115.8(3)
$C_{(3)}–C_{(7)}$	1.531(4)	$C_{(7)}–C_{(3)}–C_{(4)}$	112.9(3)
$C_{(3)}–C_{(4)}$	1.536(4)	$C_{(7)}–C_{(3)}–C_{(2)}$	109.1(2)
$C_{(4)}–C_{(5)}$	1.511(4)	$C_{(4)}–C_{(3)}–C_{(2)}$	111.5(2)
$C_{(5)}–C_{(13)}$	1.495(4)	$C_{(5)}–C_{(4)}–C_{(3)}$	113.0(3)
		$O_{(1)}–C_{(5)}–C_{(13)}$	120.7(3)
		$O_{(1)}–C_{(5)}–C_{(4)}$	121.0(3)
		$C_{(13)}–C_{(5)}–C_{(4)}$	118.4(3)
		$O_{(2)}–C_{(20)}–N_{(1)}$	121.3(4)
		$O_{(2)}–C_{(20)}–C_{(21)}$	122.7(3)
		$N_{(1)}–C_{(20)}–C_{(21)}$	116.0(3)

between the lengths of the equivalent bonds in these molecules amounts to only 0.1-0.7 σ (average 2.4 σ), while that between the equivalent bond angles amounts to 0.1-5.0 σ (average 1.6 σ). The two molecules have practically identical conformation; the corresponding torsional angles coincide within 8.5°. In the molecule of **3**

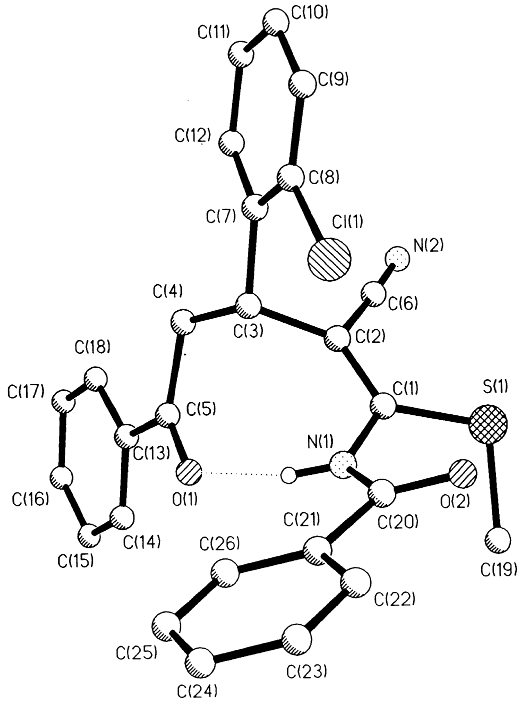
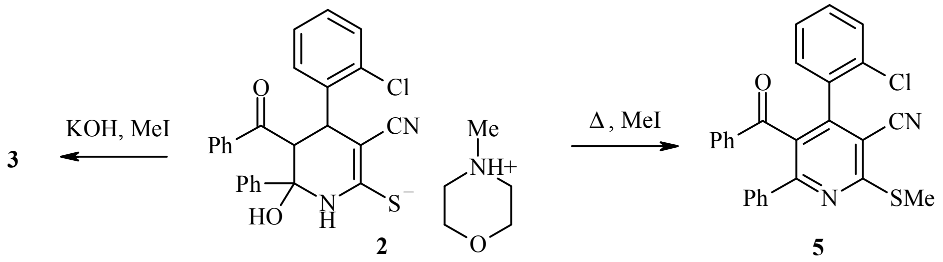


Fig. 1. A general view of the molecule of **3** with the numbering of the atoms. For simplification the H atoms are not shown (with the exception of $H_{(1N)}$, which participates in the formation of an intramolecular hydrogen bond).

the intramolecular hydrogen bond $O_{(1)}\cdots H_{(1)}–N_{(1)}$ closes the eight-membered ring $O_{(1)}H_{(1)}N_{(1)}C_{(1-5)}$. The geometric parameters of this bond ($O_{(1)}\cdots N_{(1)}$ 2.860(4), $O_{(1)}\cdots H_{(1N)}$ 2.11(3), $N_{(1)}–H_{(1N)}$ 0.84(3) Å, angle $O_{(1)}H_{(1N)}N_{(1)}$ 148(2)°) correspond to a hydrogen bond of medium intensity, while the $O_{(1)}\cdots N_{(1)}$ distance is close to the statistical mean of 2.89 Å for N–H···O bonds [2, 3]. There are no short intermolecular contacts in the crystal of compound **3**. The crystal packing is shown in Fig. 2.



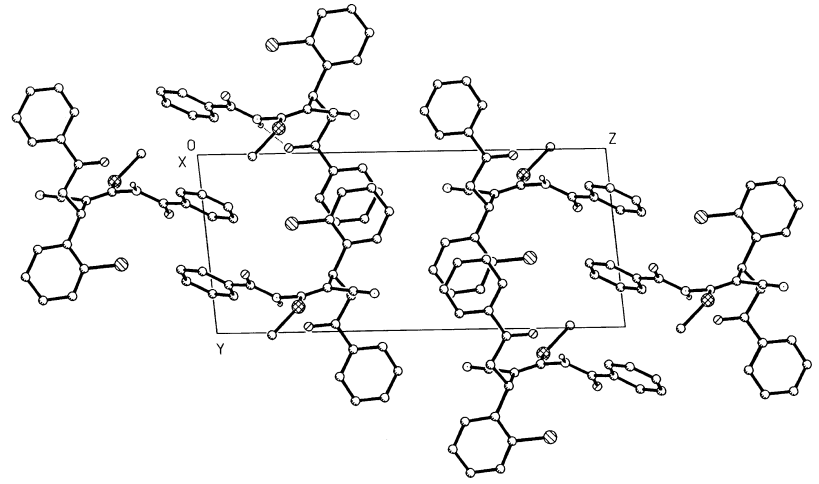


Fig. 2. The crystal packing in compound **3** (*ac* projection).

TABLE 2. The Atomic Coordinates ($\times 10^4$) and Equivalent Temperature Factors U_{eq} (Å × 10^3) in Structure **3**

Atom	*x*	*y*	*z*	U_{eq}
1	2	3	4	5
$Cl_{(1)}$	3117(2)	-6068(1)	2142(1)	98(1)
$S_{(1)}$	6111(1)	-1419(1)	2080(1)	77(1)
$O_{(1)}$	-53(3)	-305(3)	2274(1)	67(1)
$O_{(2)}$	4974(4)	-3278(4)	844(2)	110(1)
$N_{(1)}$	2946(4)	-1943(4)	1566(2)	58(1)
$N_{(2)}$	5082(4)	-2088(3)	3955(2)	72(1)
$C_{(1)}$	3991(4)	-1992(4)	2172(2)	53(1)
$C_{(2)}$	3356(4)	-2446(4)	2832(2)	48(1)
$C_{(3)}$	1644(4)	-3179(4)	2999(2)	49(1)
$C_{(4)}$	299(4)	-1991(4)	3390(2)	54(1)
$C_{(5)}$	-318(4)	-413(4)	2927(2)	51(1)
$C_{(6)}$	4349(4)	-2236(4)	3448(2)	51(1)
$C_{(7)}$	2056(4)	-4877(4)	3422(2)	50(1)
$C_{(8)}$	2745(4)	-6257(4)	3071(2)	60(1)

TABLE 2 (continued)

1	2	3	4	5
$C_{(9)}$	3201(5)	-7788(4)	3435(2)	73(1)
$C_{(10)}$	2960(5)	-7990(4)	4169(2)	76(1)
$C_{(11)}$	2278(5)	-6658(5)	4535(2)	71(1)
$C_{(12)}$	1834(4)	-5129(4)	4161(2)	61(1)
$C_{(13)}$	-1261(4)	1015(4)	3288(2)	52(1)
$C_{(14)}$	-1627(5)	2520(4)	2884(2)	71(1)
$C_{(15)}$	-2471(5)	3881(5)	3205(3)	83(1)
$C_{(16)}$	-2953(5)	3730(5)	3914(3)	80(1)
$C_{(17)}$	-2623(5)	2250(5)	4318(2)	77(1)
$C(_{18)}$	-1767(4)	891(4)	4005(2)	64(1)
$C_{(19)}$	5943(6)	136(5)	1345(2)	93(1)
$C_{(20)}$	3459(5)	-2675(5)	945(2)	71(1)
$C_{(21)}$	2054(5)	-2706(4)	414(2)	66(1)
$C_{(22)}$	2530(6)	-3472(5)	-197(2)	89(1)
$C_{(23)}$	1317(9)	-3591(7)	-704(2)	112(2)
$C_{(24)}$	-378(9)	-2934(7)	-610(3)	122(2)
$C_{(25)}$	-889(7)	-2217(8)	-7(3)	146(2)
$C_{(26)}$	321(6)	-2078(7)	503(3)	118(2)
$H_{(1N)}$	1879(46)	-1601(42)	1636(18)	70(12)

When the enethiolate **1** was boiled in ethanol and the obtained solution was acidified with hydrochloric acid the thione **4** was obtained in the form of a single diastereomer. Its alkylation with methyl iodide took place regiospecifically, and the above-mentioned conformer of compound **3** was formed. The latter was also obtained by the reaction of the salt **2** with methyl iodide in the presence of potassium hydroxide according to the usual procedure [1].

It should be noted that opening of the tetrahydropyridine ring is not observed during methylation of the thiolate **2** in boiling ethanol, but the corresponding substituted pyridine **5** is formed as a result of dehydration and dehydrogenation.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker AM300 instrument (300 MHz) with TMS as internal standard. The IR spectra were obtained in Vaseline oil on an IKS-29 spectrophotometer. Elemental analysis was performed on a Perkin-Elmer C,H,N analyzer. The reactions and the individuality of the substances were monitored by TLC on Silufol UV-254 plates in the 3:5 acetone–hexane system. The melting points were determined on a Kofler bench.

The X-ray crystallographic analysis of a single crystal of compound **3** was conducted at room temperature on an automatic Enraf-Nonius CAD-4 diffractometer (λMoKα radiation, graphite monochromator, ratio of scan rates $\omega/2\theta$ 1.2, θ_{max} 24°, spherical segment $0 \leq h \leq 8$, $-9 \leq k \leq 9$, $-21 \leq l \leq 21$). To determine the unit cell parameters and the crystal orientation matrix of compound **3** with linear dimensions 0.24 × 0.27 × 0.44 mm we used 22 reflections with $12 < \theta < 13°$. In all, 3947 reflections were collected, of which 3589 were unique (*R* factor 0.022). The crystals of compound **3** were triclinic, $a = 7.726(1)$, $b = 8.199(2)$, $c = 18.598(4)$ Å; $\alpha = 84.51(2)$, $\beta = 88.05(1)$, $\gamma = 82.02°$; $V = 1161.1(5)$ Å^3; $Z = 2$; $d_{calc} = 1.32$ g/cm^3; $\mu = 0.280$ mm^{-1}, $F(000)$ 480; space group *P*1 (No. 2). The structure was interpreted by the direct method and refined by least-squares treatment in full-matrix approximation using SHELXS and SHELXL93 software [4,5]. In the refinement we used 2273 reflections with $I > 2\sigma(I)$ (293 refined parameters, number of reflections per parameter 7.76, weighting scheme $\omega = 1/[\sigma^2(F_o^2) + (0.0483P)^2 + 0.3121P]$, where $P = (F_o^2 + 2F_c^2)/3$, ratio of maximum/mean shift to error in the last cycle 0.004/0.000). A correction was made for anomalous scattering, and no corrections were made for absorption. All the hydrogen atoms were revealed objectively from an electron density difference synthesis. However, they were all (with the exception of the $H_{(1N)}$ atom, which was refined isotropically) included in the calculation with fixed temperature and position parameters. The final convergence factors were $R_1(F) = 0.0511$ and $R_w(F^2) = 0.1059$, $GOF = 1.013$. The residual electron density from the Fourier difference series was 0.18 and -0.20 e/Å^3. The coordinates of the atoms are given in Table 2.

4-Benzoyl-1-benzoylamino-3-(2-chlorophenyl)-2-cyano-1-methylthio-1-butene (3). A. A mixture of the salt **1** (2.66 g, 5 mmol) and methyl iodide (0.31 ml, 5 mmol) in 80% ethanol (15 ml) was boiled for 30 min. After 12 h the precipitate was filtered off, washed with ethanol and hexane, and dried. Yield of compound **3** 1.27 g (55%).

B. To a suspension of the thiol **4** (2.24 g, 5 mmol) in ethanol (15 ml), while stirring, we added 10% aqueous potassium hydroxide solution (2.8 ml, 5 mmol) and after 5 min methyl iodide (0.31 ml, 5 mmol). After 5 h the precipitate was filtered off, washed with ethanol, and dried. Yield of compound **3** 1.43 g (62%).

C. Compound **3** was obtained with a yield of 2.03 g (88%) by the method in [1], using a 10% solution of potassium hydroxide and methyl iodide (0.31 ml, 5 mmol); mp 153-155°C. IR spectrum, ν, cm^{-1}: 3289 (NH); 2207 (CN); 1687, 1710 (2CO). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.31 (3H, s, SMe); 3.81 (2H, m, $C_{(4)}H_2$); 4.84 (1H, dd, $^3J = 5.2$, $^3J = 8.8$, $C_{(3)}H$); 7.23-7.68 and 7.90-8.07 (14H, both m, H arom.); 10.35 (1H, br. s, NH). Found, %: C 67.91; H 4.43; N 6.21. $C_{26}H_{21}ClN_2O_2S$. Calculated, %: C 67.74; H 4.59; N 6.08.

4-Benzoyl-1-benzoylamino-3-(2-chlorophenyl)-2-cyano-1-butene-1-thiol (4). A solution of the salt **1** (2.66 g, 5 mmol) in ethanol (15 ml) was boiled for 30 min, and after cooling it was diluted with 10% hydrochloric acid. After 12 h the precipitated thiol **4** was filtered off and washed with ethanol and hexane. Yield 1.18 g (53%); mp 249-251°C. IR spectrum, ν, cm^{-1}: 3480 (NH); 2190 (CN); 1650 (2CO). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.23-2.41 (2H, m, $C_{(4)}H_2$); 4.82 (1H, dd, $^3J = 4.6$, $^3J = 7.8$, $C_{(3)}H$); 7.15-7.66 and 8.16 (14H, both m, H arom.); 12.36 (1H, br. s, NH). Found, %: C 67.33; H 4.25; N 6.42. $C_{25}H_{19}ClN_2O_2S$. Calculated, %: C 67.18; H 4.28; N 6.27.

5-Benzoyl-4-(2-chlorophenyl)-3-cyano-2-methylthio-6-phenylpyridine (5). A mixture of the salt **2** (2.74 g, 5 mmol) and methyl iodide (0.31 ml, 5 mmol) in 80% ethanol (15 ml) was boiled for 1 h. After 12 h the precipitated cyanopyridine **5** was filtered off and washed with ethanol and hexane. Yield 1.48 g (67%); mp 213-215°C. IR spectrum, ν, cm^{-1}: 2220 (CN); 1667 (CO). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.76 (3H, s, SMe); 7.33-7.57 (14H, m, H arom.). Found, %: C 71.03; H 3.81; N 6.54. $C_{26}H_{17}ClN_2OS$. Calculated, %: C 70.82; H 3.89; N 6.35.

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