Heterocycles 21. Reaction of 2-phenyl-thiazol-4-carbaldehyde with 2-bromoaceto phenone

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The condensation reaction of 2-phenyl-thiazol-4-carbaldehyde with 2-bromoaceto phenone was performed in basic catalysis, resulting in a mixture of 2,3-epoxy-1-phenyl-3-(2-phenyl-thiazol-4-yl)-propan-1-one (1), 1-phenyl-3-(2-phenyl-thiazol-4-yl)-prop-2-en-1-one (2), and 2-phenyl-4,5-bis-(2-phenyl-thiazol-4-yl)-3-hydroxyfurane (4). The isolated solids were structurally investigated by spectroscopic methods, i.e. infrared spectroscopy, mass spectrometry and NMR. In solution the dicarboxylic derivative 2 undergoes a tautomeric process, resulting in the enol 2-hydroxy-1-phenyl-3-(2-phenyl-thiazol-4-yl)-prop-2-en-1-one 3. Compounds 3 and 4 were transformed in the corresponding acetyl derivatives 5 and 6, respectively, by reacting them with acetic anhydride. For the furane 4 the single crystal X-ray diffraction structure was determined.

Keywords: condensation reaction, thiazol derivatives, keto – enol tautomerism

In previous papers we described the preparation of some heterochalcones by condensation of thiazol-carbaldehydes and thiazolo[3,2-b][1,2,4]triazol-carbaldehydes with a series of aceto phenones [1–4]. Data related to the reaction of some α-substituted chalcones with nitrogen dinucleophiles, as well as the antifungal and antiprotostar properties of these chalcones were already described [5,6]. The substituents in the α-position with respect to the carbonyl group affect the biological and chemical behaviour of the above mentioned compounds, both by electronic effects and by molecular geometry. These derivatives can be used also as intermediates in synthesis of chiral heterocyclic compounds, due to their tetrahedral stereocenters which appear as a result of the cyclisation reaction.

The synthesis of α-bromochalcones by dehydrobromination of dibromobenzalacetophenone is well known [7,8]. In order to evaluate the biological potential of some α-bromothiazoylhychalcones we tried to prepare such derivatives by condensation of 2-aryl-thiazol-4-carbaldehydes [9] and 2-aryl-thiazolo[3,2-b][1,2,4]triazol-5-carbaldehydes [10], respectively, with 2-bromoaceto phenone. In the presence of potassium hydroxide or other weaker bases, such as sodium hydroxide, sodium carbonate or pyridine, non halogenated reaction products were obtained. Here we report our studies on the condensation reaction between 2-phenyl-thiazol-4-carbaldehyde and 2-bromoaceto phenone.

Experimental part

Melting points are uncorrected. Elemental analysis was performed on a VarioEL analyzer. Infrared spectra were recorded as KBr pellets with a FTTI spectrophotometer Nicolet 210. Mass spectra were recorded on a MAT 311 mass spectrometer with El ion source, at ionization energy of 70 eV with direct inlet probe. 1H and 13C NMR spectra were recorded on a BRUKER DRX 400 instrument operating at 400.13 and 100.61 MHz, respectively with TMS as internal standard. The chemical shifts are reported in δ units (ppm) relative to the residual peak of the deuterated solvent (ref. CDCl3, δ 7.26, δ 174 (4) [M–C6H5–2 CO]+, 147 (4), 105 (100) [benzoyl]+, 77 (20) [M-HCO]+, 246 (21) [M-HCO-S]+, 202 (4) [M-benzoyl]+, 174 (4) [M–C6H5–2 CO]+, 147 (4), 105 (100) [benzoyl]+, 77 (49) [C6H5]+. 1H-NMR, δ (ppm): 4.28 (d, 1H C5-Hepoxy, 3JHH 1.6 Hz), 4.87 (d, 1H, CH-epoxy, 3JHH 1.6 Hz), 7.43 (s, 1H, CH-thiazole), 7.47 (m, 3H C6-H-meta+para), 7.51 (t, 2H CO-C6-H-meta, 3JHH 7.6 Hz), 7.65 (t, 1H CO-C6-H-para, 3JHH 7.6 Hz), 7.98 (m, 2H C6-H-ortho), 8.14 (d, 2H CO-C6-H-ortho, 3JHH 7.2 Hz), 8.16 (d, 2H CO-C6-H-ortho, 3JHH 7.2 Hz), 3C-NMR, δ (ppm): 55.68, 59.06, 118.1, 126.67, 128.45, 128.85, 128.96, 130.44, 133.14, 135.46, 151.88, 169.27, 193.28.

1-Phenyl-3-(2-phenyl-thiazol-4-yl)-propan-1-one (1)

2-Benzyl-2-phenyl-thiazol-4-carbaldehyde (0.47 g, 2.5 mmol) and 2-bromoacetophenone (0.49 g, 2.5 mmol) were dissolved in ethanol (7 ml), then a solution of KOH (0.125 g) in water (5 ml) was added, keeping the temperature at 25°C. Subsequently the mixture was stirred at room temperature for 2 h. The formed precipitate was separated by filtration and recrystallized from ethanol. Yield: 45%; M.p. 141-143°C. Elemental analysis: C% 70.34; H% 4.26; N% 4.56; S% 10.43 (calc.); C% 69.90; H% 3.90; N% 4.56; S% 10.53 (found).

IR (cm⁻¹): 1690 (νC=O), 1227, 904, 848 (characteristic for substituted epoxydes). EI MS (m/z, %): 307 (15) [M]+, 278 (20) [M-HCO]+, 246 (21) [M-HCO-S]+, 202 (4) [M-benzoyl]+, 174 (4) [M–C6H5–2 CO]+, 147 (4), 105 (100) [benzoyl]+, 77 (49) [C6H5]+. 1H-NMR, δ (ppm): 4.28 (d, 1H C5-Hepoxy, 3JHH 1.6 Hz), 4.87 (d, 1H, CH-epoxy, 3JHH 1.6 Hz), 7.43 (s, 1H, CH-thiazole), 7.47 (m, 3H C6-H-meta+para), 7.51 (t, 2H CO-C6-H-meta, 3JHH 7.6 Hz), 7.65 (t, 1H CO-C6-H-para, 3JHH 7.6 Hz), 7.98 (m, 2H C6-H-ortho), 8.14 (d, 2H CO-C6-H-ortho, 3JHH 7.2 Hz), 8.16 (d, 2H CO-C6-H-ortho, 3JHH 7.2 Hz), 55.68, 59.06, 118.1, 126.67, 128.45, 128.85, 128.96, 130.44, 133.14, 135.46, 151.88, 169.27, 193.28.

1-Phenyl-3-(2-phenyl-thiazol-4-yl)-propan-1-one (1)

The solution obtained from the filtration of epoxyketone 1 was acidulated with concentrated HCl, when a white precipitate formed. The precipitate was separated by filtration and dissolved in boiling ethanol. From the clear solution, at room temperature compound 2 precipitated as a white solid. Yield: 15% M.p. = 103-105°C; Elemental analysis: C% 70.34; H% 4.26; N% 4.56; S% 10.43 (calc.); C%...
1639 (7.24 (s, 1H, C\textsubscript{H})

142.02, 142.92, 148.04, 148.34, 166.88, 168.04.

129.16, 129.19, 130.33, 130.55, 130.76, 132.41, 133.5, 134.03,

separated by filtration and dried. Yield: 50%; M.p.= 115-

The mixture was boiled for 5 min, then it was left for 24 h

3J\textsubscript{HH} 7.2 Hz), 7.79 (s, 1H, C\textsubscript{H} thiazole), 7.49 (m, 3H, C\textsubscript{H}-meta + para), 7.96 (m, 2H, C\textsubscript{H} ortho).

Alternatively, compound 2 was obtained as following:

to a solution of 2-phenyl-thiazol-carbaldehyde (0.37 g, 2.0

mmol) in ethanol (5 mL) 2-hydroxy-acetophenone (0.28 g, 2 mmol) was added and subsequently a KOH solution

(0.125 g in 0.5 mL water) was added in portions at low

temperature, under stirring. The reaction mixture was

stirred for one hour, then it was diluted with water (20 mL).

The precipitated derivative 2 was separated by filtration

and recrystallized from a 1:1 (v/v) mixture of acetic acid

and water. Yield: 20%. M.p = 103-105\degree C.

\textbf{2-Acetoxy-1-phenyl-3-(2-phenyl-thiazol-4-yl)-propene-1-}

\textbf{C\textsubscript{2}H\textsubscript{4}N\textsubscript{2}O\textsubscript{2}S\textsubscript{2} (4)}

After separation of compound 2, lowering the temperature of the solution to about 15 \degree C a colorless solid

was obtained and separated by filtration. M.p = 187 \degree C,

and water. Yield: 20%. M.p 103-105\degree C.

\textbf{13C-NMR, \delta (ppm)}: 105.64, 115.30, 117.38, 122.96, 125.63, 126.47, 128.52,

109.4, 115.30, 117.38, 122.96, 125.63, 126.47, 128.52,

129.16, 129.19, 130.33, 130.55, 130.76, 132.41, 133.5, 134.03,

142.02, 142.92, 148.04, 148.34, 166.88, 168.04.

\textbf{2-Acetoxy-1-phenyl-3-(2-phenyl-thiazol-4-yl)-propene-1-}

\textbf{4.}

After separation of compound 2, lowering the temperature of the solution to about 15 \degree C a colorless solid

precipitated. Yield: 10%; M.p. = 201-202\degree C; Elemental

analysis: C% 70.27; H% 3.79; N% 5.85; S% 13.40 (calc.); C% 70.24; H% 3.11; N% 5.60; S% 13.01 (found). IR (cm\textsuperscript{-1}): 3400

(ν\textsubscript{C=O}), 1689 (ν\textsubscript{C=O ester}), 1650 (ν\textsubscript{C=C}); 1H-NMR,

δ (ppm): 6.45 (s, 1H CH vinyl), 7.24 (s, 1H, CH thiazole enol), 7.49 (m, 3H, C\textsubscript{H}-meta + para), 7.96 (m, 2H, C\textsubscript{H} ortho).

Yield: 20\%. M.p. 103-105\degree C.

\textbf{Crystal structure determination}

X-ray quality crystals of compound 4 were obtained from a chloroform / n-hexane mixture (1/4 v/v). A colourless block crystal of 4 was mounted on a cryoloop. Data collection and processing was carried out on a Bruker SMART APEX CCD X-ray machine (Babes-Bolyai University, Cluj-Napoca) using graphite-monochromated Mo-K\textsubscript{α} radiation (λ = 0.71073 \AA). Details of the crystal structure determination and refinement for compound 4 are given in table 1.

\textbf{Results and discussion}

The investigation of the condensation reaction between 2-phenyl-thiazol-4-carbaldehyde and 2-bromoaceto-

phenone allowed us to isolate derivatives 1–4, as depicted in scheme 1. The epoxyketone 1 precipitated from the initial reaction mixture, while derivatives 2 and 4 were separated as a mixture of solids after acidulation of the clear solution. From this mixture, the compound 2 and the condensation product 4, respectively, were separated by selective recrystallization. In CDCl\textsubscript{3} solution the dicarbonylic compound 2 undergoes a tautomeric process, resulting in the formation of enol 3. The equilibrium is strongly shifted in favor of the enolic form, as it was suggested by the \textsuperscript{1}H NMR spectrum.

\textbf{Table 1}

\begin{tabular}{|c|c|}
\hline
\textbf{Empirical formula} & \textbf{C\textsubscript{2}H\textsubscript{4}N\textsubscript{2}O\textsubscript{2}S\textsubscript{2} (4)} \\
\hline
\textbf{Formula weight} & 478.56 \\
\textbf{Temperature, K} & 297(2) \\
\textbf{Wavelength, Å} & 0.71073 \\
\textbf{Crystal system} & monoclinic \\
\textbf{Space group} & P2\textsubscript{1} (\textit{n}) \\
\textbf{a (\textdegree}) & 13.8575(12) \\
\textbf{b (\textdegree}) & 11.4711(10) \\
\textbf{c (\textdegree}) & 14.7757(13) \\
\textbf{\beta (\textdegree}) & 90 \\
\textbf{\gamma (\textdegree}) & 90 \\
\textbf{Volume, Å\textsuperscript{3}} & 2294.0(3) \\
\textbf{Z} & 4 \\
\textbf{Density (calculated), g/cm\textsuperscript{3}} & 1.386 \\
\textbf{Absorption coefficient, mm\textsuperscript{-1}} & 0.262 \\
\textbf{F(000)} & 992 \\
\textbf{Crystal size, mm} & 0.39 x 0.26 x 0.06 \\
\textbf{\theta range for data collections (\textdegree}) & 1.83 to 26.37 \\
\textbf{Reflections collected} & 18051 \\
\textbf{Independent reflections} & 4701 (Rint) = 0.0691 \\
\textbf{Goodness-of-fit on F\textsuperscript{2}} & 1.193 \\
\textbf{Final R indices [1=2sigma(I)]} & R1 = 0.0946, wR2 = 0.1766 \\
\textbf{Final R indices (all data)} & R1 = 0.1253, wR2 = 0.1887 \\
\textbf{Largest diff. peak and hole, eÅ\textsuperscript{-3}} & 0.458 and -0.278 \\
\hline
\end{tabular}

The structure was solved by direct methods [11] and refined using SHELX-97 [12]. All of the non-hydrogen atoms were treated anisotropically. All hydrogen atoms were included in idealized positions with isotropic thermal parameters set at 1.2 times that of the carbon or oxygen atoms, respectively, to which they are attached. The drawings were created with the Diamond program [13].
The epoxyketone 1 is formed by an aldolic condensation reaction, when the 2-bromo-acetophenone carbanion, formed under the action of a basic catalyst (NaOH), is added to the aldehydic carbonyl group, leading to an intermediate. Subsequently, an intramolecular nucleophilic substitution of halogen by anionic oxygen takes place (scheme 2). We presume that epoxyketone 1 is able to isomerise partially to the dicarbonylic compound 2, although in the literature only the transformation of epoxyketones into isomeric 1,3-dicarbonylic compounds under the action of BF₃·Et₂O [14] or by heating it in toluene in the presence of small quantities of (Ph₃P)₄Pd and 1,2-bis(diphenylphosphino)ethane [15] are reported.

To explain the formation of derivatives 1 - 3 and to elucidate their structure we performed the condensation reaction between 2-phenyl-thiazol-4-carbaldehyde with 2-hydroxyacetophenone using the same reaction conditions (scheme 3). The same tautomeric process involving the species 2 and 3 was evidenced in this case again by ¹H NMR.

Scheme 1

Scheme 2

Scheme 3

Scheme 4
The presence of the enolic hydroxyl in 3, and of the mobile hydrogen atom in 4 was tested by solubility in basic medium, the reaction with FeCl₃ (red color), as well as by transformation of compounds 3 and 4 in the corresponding acetyl derivatives 5 and 6 by reacting them with acetic anhydride (scheme 4).

The compounds were characterized by IR, NMR and mass spectrometry. In addition, for the derivative 4 the molecular structure was determined by single crystal X-ray diffraction.

The dicarbonylic derivative 2 was detected by ³H-NMR as 10 % component in mixture with the enolic form 3 in CDCl₃ solution. The IR spectrum of 2 is consistent with a dicarbonylic structure. The higher stability of the enolic form towards the dicarboxylic tautomer 2 in solution might be explained by an extended conjugation of the electrons in the C=C bond and the aromatic system. This behaviour is supported also by the low field shifted resonance of the CH=CH proton in the enolic form (δ 6.45 ppm).

The ³H-NMR spectrum of derivative 1 presents characteristic vibrations for the C=O group (1690 cm⁻¹) and for the oxycyclic ring (1227 cm⁻¹), respectively. The ³H-NMR spectrum is consistent with the desired epoxyketone 1. The epoxy protons appear as doublets at 6.42 and 6.47 ppm, respectively. The small value of the coupling constant (3JHH 1.6 Hz) suggests a trans configuration of the oxycyclic ring.

The ³H-NMR data for the mixture of species 2 and 3 are consistent with a keto-enolic tautomeration. The presence of two singlets at δ 4.32 and 6.45 ppm, respectively, can be assigned to protons from CH₂ and CH groups from the two tautomeric forms in CDCl₃ solution, while the singlet resonance from δ 11.04 ppm may be assigned to the enol proton. From the ratio of the intensities of the CH and CH₂ resonances, respectively, we were able to establish the proportion of enol form in the mixture as being 90 %. The IR spectrum shows three absorption bands at 1708 and 1639 cm⁻¹, assigned to the valence vibrations for the C=O group (1690 cm⁻¹) and for the epoxy protons in the ³H-NMR spectrum of 1 (δH₃ 1.6 Hz) suggests a trans configuration of the oxycyclic ring.

In the liter of compound 5 the vibration bands characteristic for both the ether and the ketone carbonyl (1765 and 1689 cm⁻¹) were observed, as well as the valence vibration of the C=C group (1650 cm⁻¹).

In the ¹H-NMR spectrum of 5 the resonance corresponding to the vinylic proton (δ 7.19 ppm) is low field shifted in comparison with the vinylic proton resonance in the non-acetylated derivative 3 (δ 6.45 ppm).

The ¹³C NMR spectra revealed the expected number of resonances for the described derivatives.

The mass spectra (EI) of the title compounds present the molecular peaks with medium to high intensities and the fragmentation behaviour is in accordance with the proposed structures, i.e.:

- for the epoxyketone 1 are present fragments resulted from elimination of CO (m/z 279) and formyl groups (m/z 278), as well as peaks corresponding to the benzoyl group (m/z 105);
- for the dicarbonylic derivative 2 the molecular peak (m/z 307) confirms the isomerism relation with the epoxyketone 1. Other peaks appear due both to the lability of the CO-CO bond or to the stabilization of the two acyl groups by conjugation, as well as due to elimination of CO. The peak at m/z 174 (M - benzoyl - CO) supports a 1,2-dicarbonylic structure;

- in case of the derivative 4, the molecular peak (m/z 478) is accompanied by fragmentation of either the furanic (m/z 345) or the thiazol (m/z 242) ring.

Taking into consideration the utility of epoxyketones as intermediates in organic synthesis [14], we prepared derivative 1 also from the chalcone 7 using among the large variety of synthesis methods [16-20] the oxidation with hydrogen peroxide in basic medium (scheme 5).

Crystal and molecular structure of 2-phenyl-4,5-bis-(2-phenyl-thiazol-4-yl)-3-hydroxy-furane (4).

The ORTEP-like diagram of 4 with the atom numbering scheme is shown in figure 1, while selected bond lengths and angles are given in table 2.

Compound 4 crystallizes in the monoclinic P2(1)/n space group. The whole molecule is almost planar, both the aromaticity and the intramolecular N...H, O...H and S...H hydrogen bonding (fig. 1 table 2) contributing to the planarity.

The maximum deviation of the non-hydrogen atoms from the mean plane O1/C25/C26/C27/C28 being 0.42 - 0.75 Å for the phenyl ring C10 - C15, while all other non hydrogen atoms have deviations in the range 0.02 - 0.21 Å with respect to the same plane. However, the deviations are much higher than in 5-(furan-2-yl)-1,3,4-oxadiazole-2(3H)-thione (0.005 Å) [21], for which a planar geometry was established. The dihedral angles between the furan and the thiazole rings, respectively, are: P1/P2 7.35°, P1/P2 2.24°, P2/P3 0°. The fragment P1/C1-C15 is deviated below the P1, P2 and P3 planes, with the phenyl rings are P1/C1-C6 4.05°, P2/C10-C15 2.58° and P3/C19-C24 6.65°, respectively. The fragment P2/C10-C15 is deviated below the considered mean plane P3, while the fragment P1/C1-C6 is deviated above this plane. For other furan based derivatives with isolated rings, i.e. 4-(4-chlorophenyl)-3-(furan-2-yl)-1H-1,2,4-triazole-5(4H)-thione [22], 2-(1H-benzimidazol-1-yl)-1-(2-furyl)-3-phenylpropan-1-one [23], 3-(2-furyl)-4-(4-methoxyphenyl)-1H-1,2,4-triazole-5(4H)-thione [24] angular structures were also found, with dihedral angles between the rings ranging from 34.1 to 87.4°. π-π stacking interactions are formed between the
Table 2

<table>
<thead>
<tr>
<th>SELECTED INTERATOMIC DISTANCES (Å) AND ANGLES (°) IN 4</th>
</tr>
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<tbody>
<tr>
<td>C7-N1 1.305(5) C16-N2 1.738(4)</td>
</tr>
<tr>
<td>C8-N1 1.383(5) C18-N2 1.700(4)</td>
</tr>
<tr>
<td>C7-S1 1.718(4) C25-O1 1.378(5)</td>
</tr>
<tr>
<td>C9-S1 1.709(4) C28-O1 1.366(4)</td>
</tr>
<tr>
<td>C16-N2 1.305(5) C26-O2 1.350(5)</td>
</tr>
<tr>
<td>C17-N2 1.375(5)</td>
</tr>
<tr>
<td>N1...H6 2.56  O1...H18 2.48</td>
</tr>
<tr>
<td>N1...H2A 1.93  O2...H20 2.44</td>
</tr>
<tr>
<td>N2...H9  2.26  Cg1 - Cg1' 3.51</td>
</tr>
<tr>
<td>N2...H11 2.57  Cg2 - Cg2' 3.39</td>
</tr>
<tr>
<td>S1...H2  2.76  N2...Cg3 3.39</td>
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<tr>
<td>S2...H15 2.72</td>
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<tr>
<td>C7-N1-C8 112.0(3) C16-N2-C17 111.2(3)</td>
</tr>
<tr>
<td>C7-S1-C9 90.03(19) C16-S2-C18 89.4(2)</td>
</tr>
<tr>
<td>C25-O1-C28 107.4(3) C26-O2-H2A 109.5</td>
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<tr>
<td>C7-N1...H6 77.18 C16-S2...H15 68.74</td>
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<tr>
<td>H6...N1...H2A 68.58 C28-O1...H18 84.96</td>
</tr>
<tr>
<td>C7-S1...H2 68.65 C26-O2...H20 92.63</td>
</tr>
</tbody>
</table>

* Symmetry equivalent positions 1-x, 1-y, 2-z are given by “prime”.

* Symmetry equivalent positions 1-x, 2-y, 2-z are given by “second”.

**Table 2**

SELECTED INTERATOMIC DISTANCES (Å) AND ANGLES (°) IN 4

**Fig. 2.** Polymeric associations based on π-π and η-arene-N interactions in the crystal of 4

Conclusions

Our studies on the condensation reaction of 2-phenylthiazol-4-carbaldehyde with 2-bromoacetophenone in basic catalysis revealed the formation of a mixture of nonhalogenated derivatives, i.e. the isomers 2,3-epoxy-1-phenyl-3-(2-phenyl-thiazol-4-yl)-propan-1-one (1), 1-phenyl-3-(2-phenyl-thiazol-4-yl)-propane-1,2-dione (2), its enolic tautomer 2-hydroxy-1-phenyl-3-(2-phenyl-thiazol-4-yl)-prop-2-en-1-one (3) and 2-phenyl-4,5-bis-(2-phenyl-thiazol-4-yl)-3-hydroxy-furane (4). The formation of the tautomeric species 2 and 3 is supported by spectroscopic evidences (NMR and IR spectroscopy). The species 3 and 4 containing mobile hydrogen atoms were transformed in the corresponding acetyl derivatives 5 and 6, respectively, by reacting them with acetic anhydride.
Supplementary material

Crystallographic data for the structural analysis of compound 4 have been deposited with the Cambridge Crystallographic Data Centre CCDC No. 663512. Copies of the information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

Acknowledgements: This work was financially supported by the Romanian Ministry of Education and Research, grant CEx no. 11-55/2006.

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Manuscript received: 20.08.2008