Utilization of 2-ylidene-4-thiazolidinones in the synthesis of heterocyclic compounds. Part I: Synthesis of pyrazoles

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Abstract 2-Ylidene and 2,5-diylidene-4-thiazolidinones 2a–d were synthesized and converted into pyrazole derivatives 4a–d by reaction with hydrazine hydrate. A mechanism of this novel conversion is suggested.

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1. Introduction

4-Thiazolidinones are topics of numerous reports concerning their synthesis, chemistry and applications (Brown, 1961; Newkome and Nayak, 1979; Srivastava et al., 2002; Koltai et al., 1973; Rao et al., 2004; Paola Vicini et al., 2006; Ravindra Rawal et al., 2005; Blanchet and Jieping, 2004). Nevertheless, transformation of 2-ylidenethiazolidinones into other heterocycles has received less attention. For that, the main goal of this work is to study the utilization of these 4-thiazolidinones in the synthesis of other heterocycles, such as pyrazoles.

2. Experimental

All melting points were determined on a Koffler melting point apparatus and are uncorrected. 1H NMR spectra were recorded on a Bruker avance 300 MHz spectrometer using TMS as an internal reference (chemical shifts in δ, ppm). 13C NMR spectra were recorded on a Bruker avance 75 MHz spectrometer using TMS as an internal reference (chemical shifts in δ, ppm). IR in KBr were obtained on a Bruker FT-IR ISS 25 spectrophotometer (νmax in cm−1) and The Mass spectra were recorded on Shimadzu GCMS-QP 1000 EX (Japan) mass spectrometer at 70 eV.

2.1. Synthesis of 2,5-diylidene-4-thiazolidinones 2a–d

2.1.1. A typical procedure

An equimolar mixture of compounds 1a–d (Farhat et al., 2007) (0.01 mol) and the appropriate aromatic aldehyde (0.01 mol)
<table>
<thead>
<tr>
<th>Compound, m.p. (°C), yields (%)</th>
<th>IR (cm⁻¹)</th>
<th>¹H NMR (ppm) (CDCl₃)</th>
<th>¹³C NMR (ppm) (CDCl₃)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2a</strong>, 164–166, (30)</td>
<td>3059, 3032 (Ar–H), 2957, 2861 (sp³), 2214 (CN), 1730 (C=O)₂ester, 1689 (C=O)amide</td>
<td>7.91 (s, 1H, CH), 7.69–7.32 (m, 10H, arom.), 4.30 (q, 2H, CH₂), 1.31 (t, 3H, CH₃)</td>
<td>166.63 (C₂ester), 165.33 (C=Camide), 163.89 (C₂), 136.22 (CH=C), 134.32, 133.12, 131.30, 130.94, 129.93, 129.42, 128.96 (C₉arom.), 119.69 (CN), 111.90 (C₁), 78.58 (C=C), 62.27 (CH₂), 14.22 (CH₃)</td>
</tr>
<tr>
<td><strong>2b</strong>, 288–290, (43)</td>
<td>3032 (Ar–H), 2976, 2877 (sp³), 2214 (CN), 1715 (C=O)₂ester, 1648 (C=O)amide</td>
<td>7.83 (s, 1H, CH), 7.67–7.32 (m, 10H, arom.), 4.33 (q, 2H, CH₂), 1.31 (t, 3H, CH₃)</td>
<td>166.46 (C₂ester), 165.27 (C=Camide), 163.38 (C₂), 137.21 (CH=C), 134.21, 132.00, 131.36, 129.75, 129.42, 128.92, 128.34 (C₉arom.), 120.30 (CN), 111.75 (C₁), 78.88 (C=C), 62.37 (CH₂), 14.21 (CH₃)</td>
</tr>
<tr>
<td><strong>2c</strong>, 262–264, (35)</td>
<td>2214 (CN), 1730 (C=O)amide</td>
<td>7.86 (s, 1H, CH), 7.68–7.01 (m, 10H, arom.), 4.33 (q, 2H, CH₂), 3.89 (s, 3H, OCH₃), 1.35 (t, 3H, CH₃)</td>
<td>166.85 (C₂ester), 165.46 (C=Camide), 161.98 (C₂), 136 (CH=C), 125.85 (C₉arom.), 116.55 (CN), 111.68 (C₁), 79.53 (C=C), 55.59 (CH₂), 31.79 (OCH₃), 14.25 (CH₃)</td>
</tr>
<tr>
<td><strong>2d</strong>, 210–212, (32)</td>
<td>3067, 3027 (Ar–H), 2987 (sp³), 1713 (C=O)amide</td>
<td>7.97 (s, 1H, CH), 7.67–7.28 (m, 10H, arom.), 3.41 (q, 2H, CH₂), 2.23 (s, 3H, CH₃), 1.09 (t, 3H, CH₃)</td>
<td>193.65 (C₉ketone), 166.89 (C₂ester), 166.07 (C=Camide), 154.03 (C₂), 135.11 (CH=C) 136.35–122.5 (C₉arom.), 109.25 (C₁), 61.56 (OCH₂), 28.34 (CH₂) 13.60 (CH₃)</td>
</tr>
</tbody>
</table>

a Crystallization solvent: benzene.
b Crystallization solvent: ethanol.

<table>
<thead>
<tr>
<th>Compound, m.p. (°C), yields (%)</th>
<th>IR (cm⁻¹)</th>
<th>¹H NMR (ppm) (acetone-d₆)</th>
<th>¹³C NMR (ppm) (acetone-d₆)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4a</strong>, 204–206, (57)</td>
<td>3479–3368 (NH₂), 3307 (2NH), 3027 (Ar–H), 2214 (CN)</td>
<td>10.59 (s, 1H, NH), 7.64 (br, 1H, NH), 7.63–6.77 (m, 5H, Ar), 6.35 (br, 2H, NH₂)</td>
<td>153.63 (C₉C), 143.42 (C₂), 129.33, 122.18, 117.32, 120.50 (C₉arom.)</td>
</tr>
<tr>
<td><strong>4b</strong>, 162–164, (97)</td>
<td>3473–3216 (2NH, NH₂), 3154 (Ar–H), 2984–2909 (sp³-H), 1641 (C=O)₂ester</td>
<td>8.09 (s, 1H, NH), 7.66–6.7 (m, 5H, Ar), 5.85 (br, 2H, NH₂), 4.33 (q, 2H, CH₂), 1.37 (t, 3H, CH₃)</td>
<td>165.54 (C₂ester), 142.88, 130.50, 129.02, 117.19 (C₉arom.), 142.96 (C₁), 114.53 (C₂), 83.28 (C₉), 59.81 (CH₂), 14.94 (CH₃)</td>
</tr>
<tr>
<td><strong>4c</strong>, 144–146, (73)</td>
<td>3402 (NH), 3156 (Ar–H), 2978, 2908 (sp³-H), 1664 (C=O)</td>
<td>7.98 (s, 1H, NH), 7.59–6.85 (Ar–H), 4.35 (q, 2H, CH₂), 4.02–3.5 (OH + H₂O), 1.37 (t, 3H, CH₃)</td>
<td>165.46 (C₂ester), 151.6 (C₁), 142.82 (C₂), 128.68, 21.17, 117.89, 117.19 (C₉arom.), 82.92 (C₉), 60.31 (CH₂), 16.85 (CH₃)</td>
</tr>
<tr>
<td><strong>4d</strong>, 216–218, (94)</td>
<td>3269, 3208, 2NH, 2954–2805 (sp³-H), 1692 (C=O)</td>
<td>10.53 (s, 1H, NH), 9.25 (s, 1H, NH), 7.54–6.81 (Ar–H), 3.42 (s, 2H, CH₂)</td>
<td>170 (C=O), 152.46 (C₁), 140.62, 128.63, 120.47, 116.87 (C₉arom.), 36.89 (CH₂) (C₉)</td>
</tr>
</tbody>
</table>

a ¹H NMR, ¹³C NMR solvent: DMSO-d₆.
in dioxane (30 ml) was refluxed for 3 h in the presence of TEA as catalyst. The precipitated solid thus formed was filtered off and recrystallized from the proper solvent. Melting points, yields and spectral data of compounds 2a-d are shown in Table 1.

2.2. Synthesis of 5-aminopyrazoles 4a,b from 2,5-diylidene-4-thiazolidinones 2a,b

A mixture of compound 2a or 2b (4 mmol) and hydrazine hydrate (20 mmol) was refluxed in dioxane (30 ml) for 3 h, cooled and then poured into ice-cold water. The obtained white solid product was filtered off and recrystallized from benzene. Melting points, yields and spectral data of the synthesized pyrazoles 4a-d are shown in Table 2.

2.3. Synthesis of 5-aminopyrazoles 4a–d from 2-ylidene-3-phenyl-4-thiazolidinones 1a–d

A mixture of compounds 1a–d (4 mmol) and hydrazine hydrate (20 mmol) was refluxed in dioxane (30 ml) for 3 h, cooled and then poured into ice-cold water. The white solid precipitate was filtered off and recrystallized from benzene. Melting points, yields and spectral data of the synthesized pyrazoles 4a–d are shown in Table 2.

2.4. Synthesis of 2-(3-amino-4-cyano-1H-pyrazol-5-yl)thioacetohydrazide (8)

A mixture of compound 1a (0.004 mol) and hydrazine hydrate (0.02 mol) was stirred at room temperature for 24 h. The precipitated product was filtered off and recrystallized from ethanol to give compound 8; (MW = 212), m.p. 182–184 °C; yield 50%, IR (cm⁻¹) 3380–3208 (2NH, 2NH₂), 2215 (CN), 1649 (CO). ¹H NMR (DMSO-d₆, δ ppm, 12.32 (br, 1H, NH₂), 9.20 (s, 1H, NH), 6.44 (s, 2H, NH₂–NH), 4.25 (s, 2H, NH₂), 3.63 (s, 2H, CH₂). ¹³C NMR (DMSO-d₆), δ ppm, 166.65 (C=O)amide, 154.11 (C₃), 142.30 (C₅), 70.4 (C₄), 33.40 (CH₂). MS (m/z), M⁺ = 212.

2.5. Conversion of compound 8 into the pyrazole 4a

A mixture of compound 8 (2 mmol) and aniline (3 mmol) in dioxane (10 ml) was refluxed for 3 h, cooled and poured into ice-cold water (50 ml) to give a white precipitate. Crystallization of this solid afforded a compound which has identical
m.p., IR and $^1$H NMR to that of the pyrazole 4a, yield = 93.3%.

3. Results and discussion

In order to study their use as precursors to other heterocycles, some 2-ylidene and 2,5-diylidene-4-thiazolidinones 1 and 2 were synthesized employing the method recently reported by Farhat et al. (2007) as shown in Scheme 1.

In an attempt to prepare some fused pyrazolothiazoles 3a,b, 2,5-diylidene-4-thiazolidinones 2a,b were treated with hydrazine hydrate. However, this reaction failed to produce the expected pyrazolothiazoles 3a,b as to be anticipated by a Michael addition on the ylidene double bond at C5. Instead, pyrazole derivatives 4a,b were formed as a result of a Michael addition at C2, as shown in Scheme 2.

These and other pyrazoles 4a–d were prepared by a similar treatment to 2-ylidene-3-phenyl-4-thiazolidinones 1a–d with...
hydrazine hydrate at refluxing temperature, as shown in Scheme 3.

The structures of these \( N \)-unsubstituted pyrazoles 4a–d were elucidated by spectroscopic analysis.

A suggested mechanism for the reaction of the dicyanomethylene-thiazolidin-4-one derivative 1a with hydrazine in the formation of pyrazole 4a is presented as an example of such transformation into pyrazoles and shown in Scheme 4.

The first step of this reaction involves a nucleophilic attack by hydrazine nitrogen at the amidic carbonyl carbon, which causes ring opening and formation of the acetoxyrazido derivative 6. This derivative reacted further with hydrazine in a Michael addition fashion followed by elimination of NH-phenyl group as aniline and ring closure caused by nucleophilic attack by the hydrazino group at the cyano group to form the S-acetoxyrazidopyrazole compound 7. The final step of this postulated mechanism is the nucleophilic attack by aniline and breaking of C–S bond to give the final pyrazole compound 4a. This mechanism is supported by the spectral data of the intermediates 6 and 7. The fact that the S-acetoxyrazido derivative 8 was isolated during the reaction and then converted into 5-anilinopyrazole derivative 4a by treatment with aniline at elevated temperature provides an added proof for this mechanism. As far as we know only one article reported the conversion thiazolo[3,2-\( a \)]-3-aza[1,8]naphthyridine system into pyrazole derivatives, but involving a different route (El-Hag Ali, 2003).

4. Conclusion

Several pyrazole derivatives 4a–d were synthesized by novel ring transformations of 2-ylidene-4-thiazolidinones 1a–d and 2,5-diylidenedes 2a,b. Nevertheless, syntheses of pyrazoles 4a, 4b and 4d were previously reported (Mukaiyama et al., 2007; Verma et al., 2008; Missio et al., 1996). A mechanism of such transformations was suggested.

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References


