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Arabian Journal of Chemistry

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ORIGINAL ARTICLE

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

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Received 23 June 2010; accepted 24 June 2010

Available online 27 June 2010

KEYWORDS

2-Ylidene-4-thiazolidinones;
2,5-Diylidene-4-thiazolidi-
nones;
5-(Phenylamino)-1H-
pyrazoles

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 ($\nu_{\max}$ 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)

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Peer review under responsibility of King Saud University.
doi:10.1016/j.arabjc.2010.06.051



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Table 1 Melting points, yields and spectral data of compounds **2a–d**.

Compound, m.p. (°C), yields (%)	IR (cm ⁻¹)	¹ H NMR (ppm) (CDCl ₃)	¹³ C NMR (ppm) (CDCl ₃)
2a^a , 164–166, (50)	3059, 3032 (Ar–H), 2957, 2861 (sp ³), 2214 (CN), 1730 (C=O) _{ester} , 1689 (C=O) _{amide}	7.91 (s, 1H, CH), 7.69–7.32 (m, 10H, arom.), 4.30 (q, 2H, CH ₂), 1.31 (t, 3H, CH ₃)	166.63 (C _{ester}), 165.33 (C _{amidic}), 163.89 (C ₂), 136.22 (CH=C), 134.32, 133.12, 131.30, 130.94, 129.93, 129.42, 128.96 (C _{arom.}), 119.69 (CN), 111.90 (C ₅), 78.58 (C=C ₂), 62.27 (CH ₂), 14.22 (CH ₃)
2b^a , 288–290, (43)	3032 (Ar–H), 2976, 2877 (sp ³), 2214 (CN), 1715 (C=O) _{ester} , 1648 (C=O) _{amide}	7.83 (s, 1H, CH), 7.67–7.32 (m, 10H, arom.), 4.33 (q, 2H, CH ₂), 1.31 (t, 3H, CH ₃)	166.46 (C _{ester}), 165.27 (C _{amidic}), 163.38 (C ₂), 137.21 (CH=C), 134.21, 132.00, 131.36, 129.75, 129.42, 128.92, 128.34 (C _{arom.}), 120.30 (CN), 111.75 (C ₅), 78.88 (C=C ₂), 62.37 (CH ₂), 14.21 (CH ₃)
2c^b , 262–264, (35)	2214 (CN), 1730 (C=O) _{ester} , 1690 (C=O) _{amide}	7.86 (s, 1H, CH), 7.68–7.01 (m, 10H, arom.), 4.33 (q, 2H, CH ₂), 3.89 (s, 3H, OCH ₃), 1.35 (t, 3H, CH ₃)	166.85 (C _{ester}), 165.46 (C _{amidic}), 161.98 (C ₂), 136 (CH=C), 125.85 (C _{arom.}), 116.55 (CN), 111.68 (C ₅), 79.53 (C=C ₂), 55.59 (CH ₂), 31.79 (OCH ₃), 14.25 (CH ₃)
2d^b , 210–212, (32)	3067, 3027 (Ar–H), 2987 (sp ³), 1713 (C=O) _{ester} , 1647 (C=O) _{amide}	7.97 (s, 1H, CH), 7.67–7.28 (m, 10H, arom.), 3.41 (q, 2H, CH ₂), 2.23 (s, 3H, CH ₃), 1.09 (t, 3H, CH ₃)	193.65 (C _{ketone}), 166.89 (C _{ester}), 166.07 (C _{amidic}), 154.03 (C ₂), 135.11 (CH=C), 136.35–122.5 (C _{arom.}), 109.25 (C ₅), 61.56 (OCH ₂), 28.34 (CH ₂) 13.60 (CH ₃)

^a Crystallization solvent: benzene.^b Crystallization solvent: ethanol.**Table 2** Melting points, yields and spectral data of compounds **4a–d**.

Compound, m.p. (°C), yields (%)	IR (cm ⁻¹)	¹ H NMR (ppm) (acetone-d ₆)	¹³ C NMR (ppm) (acetone-d ₆)
4a , 204–206, (57)	3479–3368 (NH ₂), 3307 (2NH), 3027 (Ar–H), 2214 (CN)	10.59 (s, 1H, NH), 7.64 (br, 1H, NH), 7.63–6.77 (m, 5H, Ar), 6.35 (br, 2H, NH ₂)	153.63 (C ₃), 143.42 (C ₅), 129.33, 122.18, 117.32, 120.50 (C _{arom.}), 114.80 (CN), 65.04 (C ₄)
4b , 162–164, (97)	3473–3216 (2NH, NH ₂), 3154 (Ar–H), 2984–2909 (sp ³ -H), 1641 (C=O) _{ester}	8.09 (s, 1H, NH), 7.66–6.7 (m, 5H, Ar) 5.85 (br, 2H, NH ₂), 4.33 (q, 2H, CH ₂), 1.37 (t, 3H, CH ₃)	165.54 (C=O) _{ester} , 142.88, 130.50, 129.02, 117.19 (C _{arom.}), 142.96 (C ₃), 114.53 (C ₅), 83.28 (C ₄), 59.81 (CH ₂), 14.94 (CH ₃)
4c , 144–146, (73)	3402 (NH), 3156 (Ar–H), 2978, 2908 (sp ³ -H), 1664 (C=O)	7.98 (s, 1H, NH), 7.59–6.85 (Ar–H), 4.35 (q, 2H, CH ₂), 4.02–3.5 (OH + H ₂ O), 1.37 (t, 3H, CH ₃)	165.46 (C=O) _{ester} , 151.6 (C ₃), 142.82 (C ₅), 128.68, 21.17, 117.89, 117.19 (C _{arom.}), 82.92 (C ₄), 60.31 (CH ₂), 16.85 (CH ₃)
4d^a , 216–218, (94)	3269, 3208, 2NH, 2954–2805 (sp ³ -H), 1692 (C=O)	10.53 (s, 1H, NH), 9.25 (s, 1H, NH), 7.54–6.81 (Ar–H), 3.42 (s, 2H, CH ₂)	170 (C=O), 152.46 (C ₅), 140.62, 128.63, 120.47, 116.87 (C _{arom.}), 36.89 (CH ₂) (C ₄)

^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

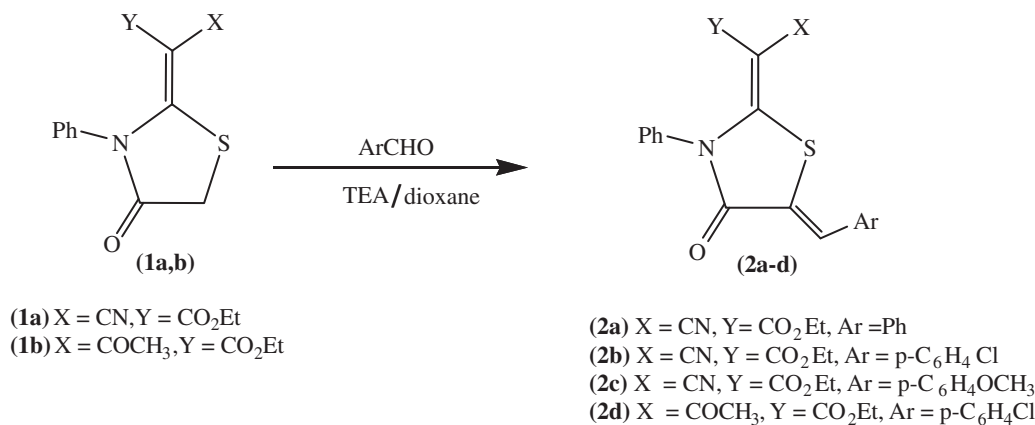
points, yields and spectral data of the synthesized pyrazoles **4a–d** are shown in Table 2.

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

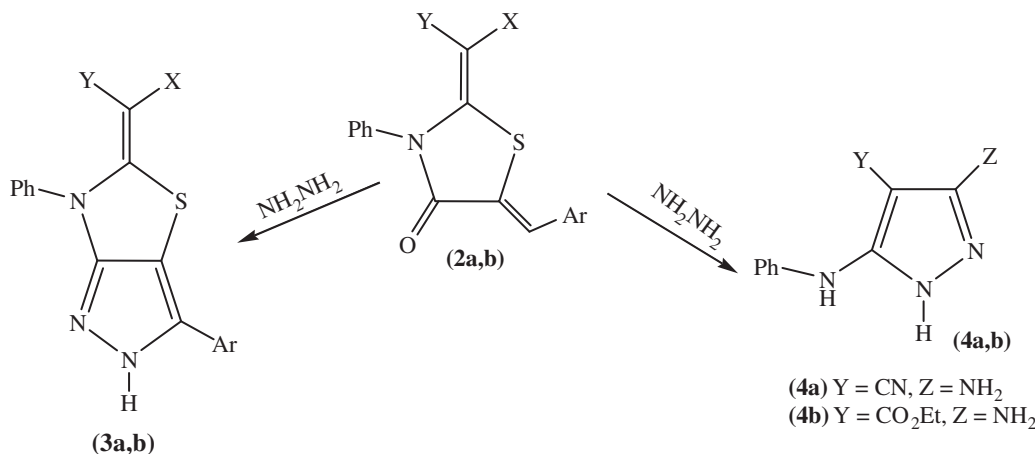
A mixture of compound **1a** (0.004 mol) and hydrazine hydrate (0.02 mol) was stirred at room temperature for 24 h. The precipitated product was filtered off and recrystallized from ethanol to give compound **8**; (MW = 212), m.p. 182–184 °C; yield 50%, IR (cm^{-1}) 3380–3208 (2NH, 2NH₂), 2215 (CN), 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



Scheme 1



Scheme 2

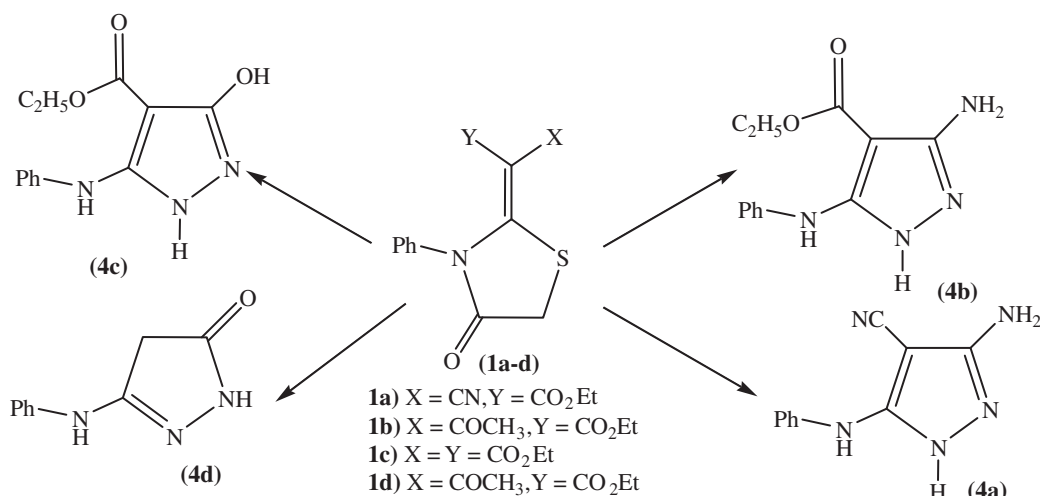
m.p., IR and ^1H NMR to that of the pyrazole **4a**, yield = 93.3%.

3. Results and discussion

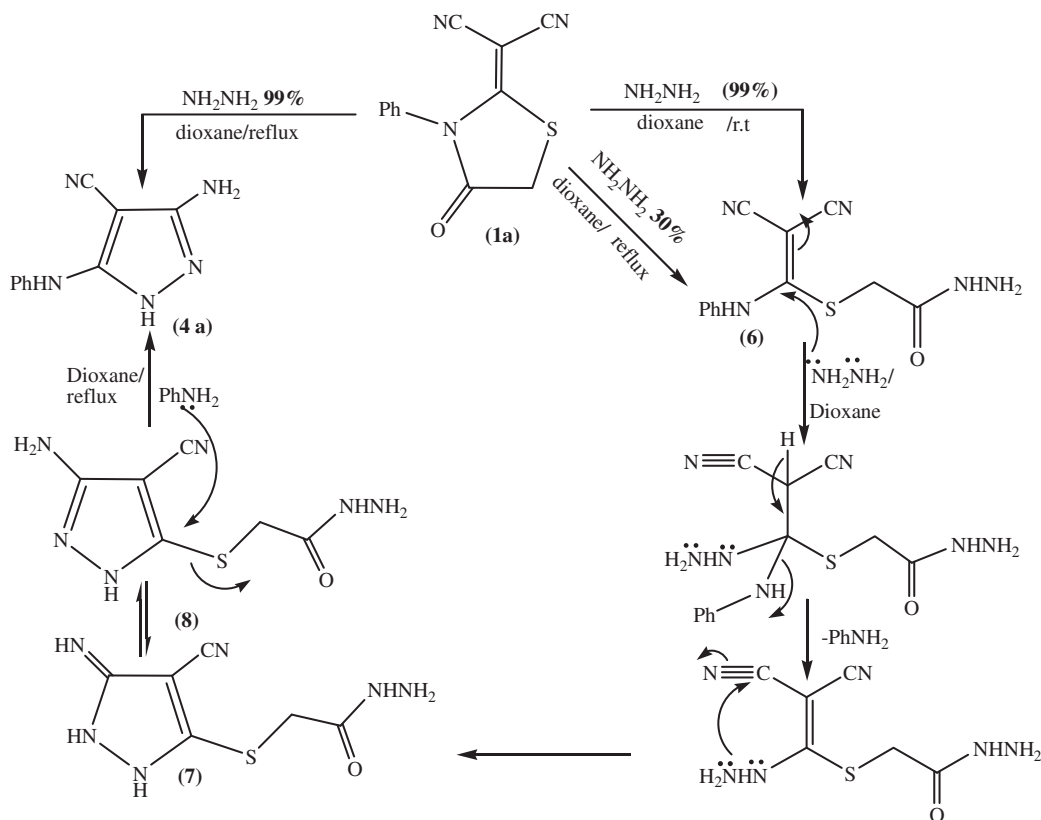
In order to study their use as precursors to other heterocycles, some 2-ylidene and 2,5-diylidene-4-thiazolidinones **1** and **2** were synthesized employing the method recently reported by Farhat et al. (2007) as shown in Scheme 1.

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 C_5 . Instead, pyrazole derivatives **4a,b** were formed as a result of a Michael addition at C_2 , 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



Scheme 3



Scheme 4

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 dicyanomethylenethiazolidin-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 acetohydrazido 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-acetohydrazidopyrazole 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-acetohydrazido derivative **8** which 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-thiazolidenones **1a–d** and 2,5-diylidenes **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.

Acknowledgments

We are grateful to Libyan Petroleum Institute, Advanced Laboratory of Chemical analysis, International Center for Polymer Research, Central Laboratory, Cairo University, Egypt) for recording IR, ¹H NMR, ¹³C NMR and Mass spectra.

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