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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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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.

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. ^{1}H NMR spectra were recorded on a Bruker avance 300 MHz spectrometer using TMS as an internal reference (chemical shifts in δ, ppm), ^{13}C 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 (ν_{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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Table 1 Melting points, yields and spectral data of compounds **2a**–**d**.

Compound, m.p. (°C), yields (%)	IR (cm^{-1})	^1H 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})	^1H 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_2O), 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, ^{13}C NMR solvent: DMSO-d_6.

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***

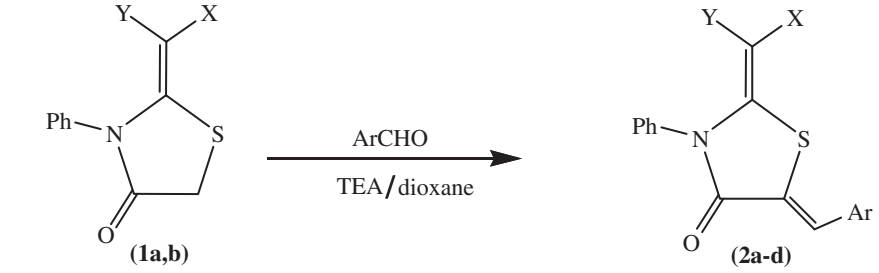
A mixture of compounds **1a–d** (4 mmol) and hydrazine hydrate (20 mmol) was refluxed in dioxane (30 ml) for 3 h, cooled and then poured into ice-cold water. The white solid precipitate was filtered off and recrystallized from benzene. Melting points, yields and spectral data of the synthesized pyrazoles **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, $2NH_2$), 2215 (CN), 1649 (CO). ^{1}H NMR (DMSO-d_6 , δ ppm, 12.32 (br, 1H, NH_2), 9.20 (s, 1H, NH), 6.44 (s, 2H, NH_2–NH), 4.25 (s, 2H, NH_2), 3.63 (s, 2H, CH_2) .^{13}C NMR (DMSO-d_6), δ ppm, 166.65 ($C{=}O)_{amide}$, 154.11 (C_3), 142.30 (C_5), 70.4 (C_4), 33.40 (CH_2). 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



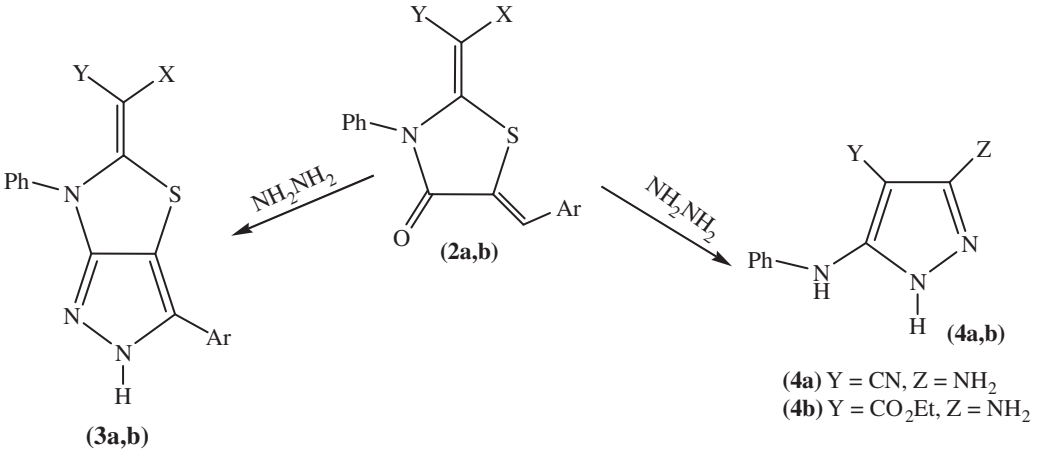
(1a,b)

(1a) X = CN, Y = CO_2Et
(1b) X = $COCH_3$, Y = CO_2Et

(2a-d)

(2a) X = CN, Y= CO_2Et, Ar =Ph
(2b) X = CN, Y = CO_2Et, Ar = p-C_6H_4 Cl
(2c) X = CN, Y = CO_2Et, Ar = p-$C_6H_4OCH_3$
(2d) X = $COCH_3$, Y = CO_2Et, Ar = p-C_6H_4Cl

Scheme 1



(3a,b)

(2a,b)

(4a,b)

(4a) Y = CN, Z = NH_2
(4b) Y = CO_2Et, Z = NH_2

Scheme 2

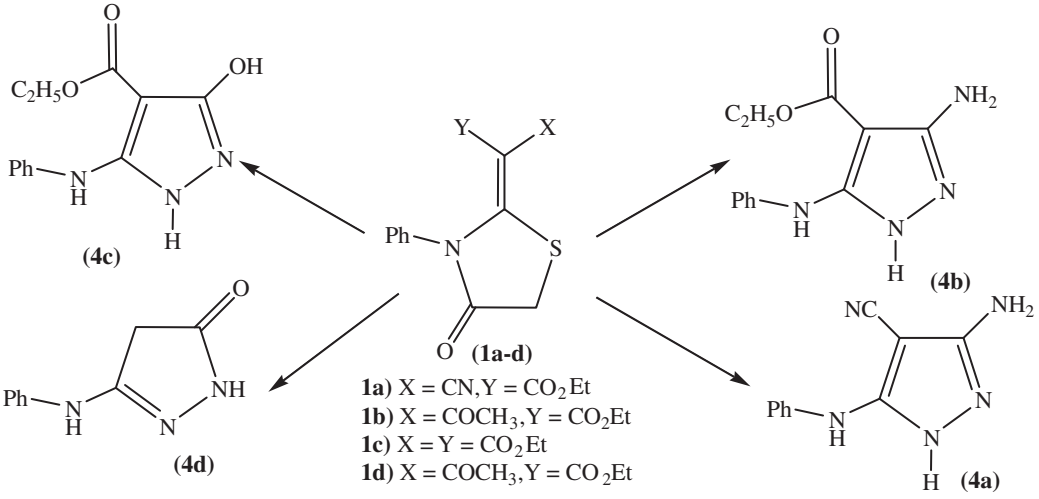
m.p., IR and ^{1}H NMR to that of the pyrazole **4a**, yield = 93.3%.

3. Results and discussion

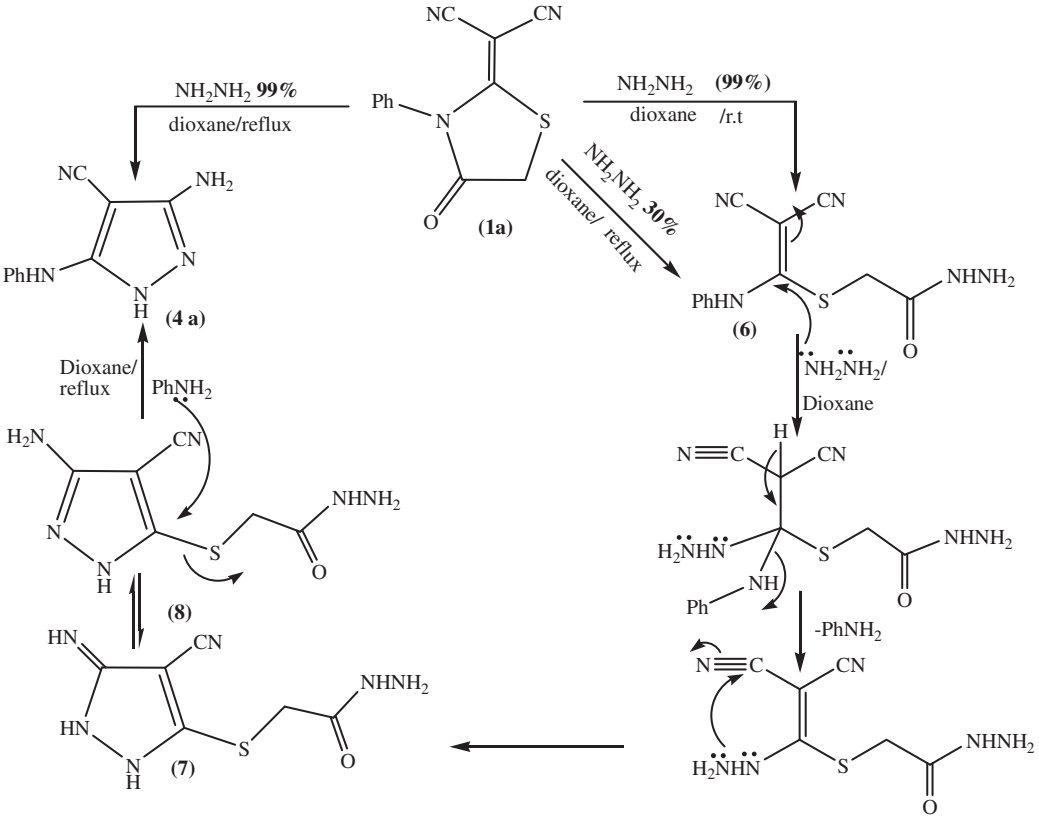
In order to study their use as precursors to other heterocycles, some 2-ylidene and 2,5-diylidene-4-thiazolidinones **1** and **2** were synthesized employing the method recently reported by Farhat et al. (2007) as shown in Scheme 1.

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 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]naphthynidine 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.

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