Regioselectivity of the synthesis of 2-pyrazolinylthiazoles by reacting 2-hydrazinothiazoles with unsymmetrical β-diketones

J. Chem. Research (S), 2001, 12–13
J. Chem. Research (M), 2001, 0133–0147

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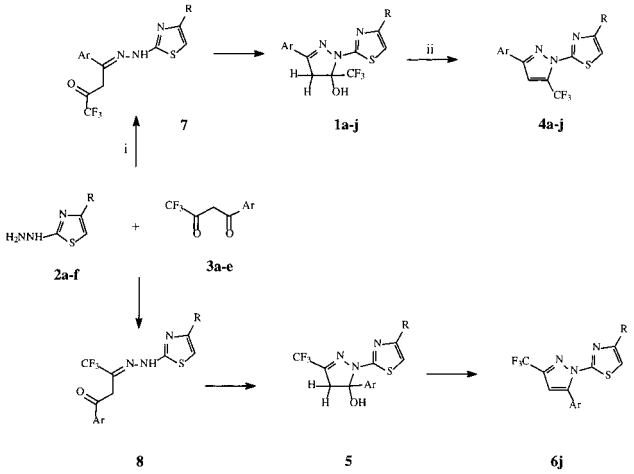
Novel 2-pyrazolinylthiazoles **1** are prepared by reaction of 2-hydrazinothiazoles **2** with 1,3-dicarbonyl compounds of type **3**. The conditions of the aromatization of **1** to 2-(3-aryl-5-trifluoromethylpyrazol-l-yl)thiazoles **4** have been investigated.

Keywords: 2-pyrazolinylthiazoles, 2-hydrazinothiazoles, unsymmetrical β-diketones

Hydrazines are known to react with 1,3-diketones in different ways to form compounds such as hydrazones, pyrazolines and pyrazoles.[2,3] Singh and colleagues[1] based on the ^{1}H NMR spectra made a conclusion on the exclusive formation of compound of type **6** (R = H, Ar =Ph) in the reaction of 2-hydrazinothiazoles **2** (R = H) with diketone **3b** (Ar = Ph). In the reaction of 2-hydrazinothiazoles **2** with 1,3-dicarbonyl compounds **3** one could propose, depending on the relative reactivity of the two carbonyl groups, the formation of two isomeric hydrazones **7** and **8**, which cyclize to the 4,5-dihydropyrazoles **1** and **5**, respectively. Aromatization of **1** and **5** gives the pyrazoles **4** and **6**, respectively (Scheme 1). Data on 2-pyrazolinylthiazoles of type **1** and **5** are only scarcely reported in the literature.[6–8]

We have discovered that the reaction of the 2-hydrazinothiazoles **2a–f** (R = COOEt, aryl substituents) with the unsymmetrical β-diketones **3a–d** (Ar = 2-naphthyl, other aryl substituents) under the literature conditions[3] gave exclusively the dihydropyrazolylthiazoles **1a–l**. Interestingly, the reaction of hydrazine **2a** (R = COOEt) with diketone **3e** (R = 4-EtOC$_6$H$_4$), leads to the formation of a mixture of pyrazoline **1j** and pyrazole **6j** in a ratio of 4:1. Aromatization of compounds **1a–j** to the 2-pyrazolylthiazoles **4a–j** could only be realized under forcing conditions such as boiling an acetic anhydride for extended times (Scheme 1).



Scheme 1 i. EtOH, reflux, 4h ii. Ac_2O, reflux, 4h

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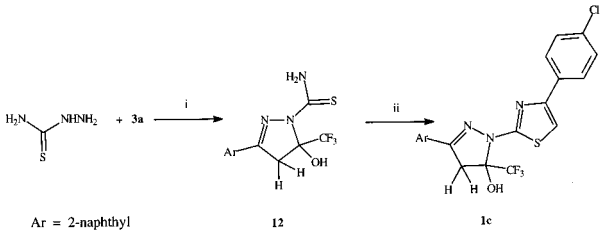
The structures of compounds **1a–j** and **4a–j** were confirmed by spectroscopic methods (Tables 1–4). The exclusive formation of regioisomers **1** and **4** was further supported by comparison with the ^{19}F NMR and ^{1}H NMR spectroscopic data of model compounds.

We have found that 2-(pyrazolinyl)thiazoles **1** could also be prepared in a two step synthesis starting from the readily available thiosemicarbazide (Scheme 3). Thus, reaction of thiosemicarbazide with diketone **3a** affords pyrazoline **12** in high yield. The structure of **12** was confirmed by NMR spectroscopy (see Table 1). Subsequently, reaction of **12** with *p*-chlorophenacyl bromide gave exclusively **1c**.



Scheme 3 I. EtOH,m HCl, reflux ii. 4-chlorophenacyl bromide

Finally, a single crystal X-ray analysis of compound **4i** (R = 4-ClC$_6$H$_4$, Ar = 4-FC$_6$H$_4$) has been carried out (Figure 1) which confirmed the structure of the reaction products of 2-hydrazinothiazoles **2** with diketones **3** as 5-trifluoromethylpyrazoles **4**.

In conclusion, the isolation of the intermediate products in the synthesis of 2-pyrazolylthiazoles by the reaction of 1,3-diketones with 2-hydrazinothiazoles and thiosemicarbazide, respectively, allowed us to make a conclusion about the reaction pathway. Carbony groups of compounds **3** connected to a trifluoromethyl function are less reactive than those connected to an aromatic moiety and therefore direct the reaction of **2** with diketones **3a–d** to give compounds **4**. The introduction of electron donating substituents at the aryl group of diketone **3** decreases the reactivity of ArCO group, which leads to the observation of the minor regioisomer **6j**.

Fig. 1: X-ray structure of **4i**

Table 1. ^{1}H Chemical shifts δ (ppm) and coupling constants (Hz) of **1a–j** and **12** in DMSO-d$_6$

Table 2. ^{1}H Chemical shifts δ (ppm) and coupling constants (Hz) of **4a–j**, **6j**, **9** and **11** in DMSO-d_6

Table 3. ^{19}F Chemical shifts δ (ppm) of the CF_3 group of **1,4a–d** and **f–j**, **9**, **11** and **12** in $CDCl_3$

Table 4. ^{13}C Chemical shifts δ (ppm) of **1c,j** and **4a,c,j** and **6j** in $CDCl_3$

Received 2 July 2000; accepted 15 September 2000
Paper 00/377

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