EXTRUSION OF SULFUR IN THE REACTIONS OF HYDRAZINE HYDRATE WITH 5-(2-ARYL-2-OXOETHYLIDENE)-3-(2-METHOXYPHENYL)-2-THIOXOTHIAZOLIDIN-4-ONES

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Abstract

Reactions of 3-substituted-5-(2-arylidene)-2-thioxothiazolidin-4-ones 2a, b with 2.5 equiv. of hydrazine hydrate were carried out with reflux and/or at room temperature. Both of these conditions gave 4-(3-aryl-4,5-dihydro-1H-pyrazole-5-carbonyl)-4-(2-methoxyphenyl)thiosemicarbazides 3a, b and 4-(2-methoxyphenyl) thiosemicarbazide 4. In addition, the 6-(2-oxo-2-phenylethyl)-4-(2-methoxyphenyl)-3-thioxa-1,2,4-triazinan-5-one 5a was obtained from 2a. The successful isolation of sulfur from these reactions was the key to rationalize the above mentioned transformations. The structures of all the products were evidenced by microanalytical and spectral data.

Introduction

Reactions of hydrazine hydrate with the 3H-5-arylidene-2-oxo/thioxothiazolidin-4-ones and 3-substituted-2-thioxothiazolidin-4-ones have been previously studied1-3. Most of these reactions affected the ring cleavage at the 2-oxo/thioso and the 4-oxo groups, forming variety of heterocycles. The recent work deals with the reactions of hydrazine hydrate with the 5-(2-aryl-2-oxoethylidene)-3-(2-methoxyphenyl)-2-thioxothiazolidin-4-ones 2. Owing to the –CO-C≡C-CO- moiety, compound 2 was anticipated to serve in such reactions, for synthesis of pyrazole derivatives. However, the 1H-NMR spectra of the products 3 and 5a displayed patterns for the –CH₂-CH₃-HX- moiety, similar with the respective 5-(2-aryl-2-oxoethyl) precursors 1. Since 2 were not subjected to reducing conditions, the way to these products was not easily rationalized.

Results and discussion

The starting 5-[2-(4-bromophenyl)-2-oxoethyl]-3-(2-methoxyphenyl)-2-thioxothiazolidin-4-one 1b was synthesized from 3-(4-bromobenzoyl)-2-propenoic acid4 and ammonium 2-methoxyphenyldithiocarbamate, following previously reported methods5,6. Treatment of 1b with bromine in acetic acid solution gave the respective 5-[2-(4-bromophenyl)-2-oxoethylidene] derivative 2b. The route of this conversion
has occurred, via two successive steps, involving first bromination at H-5 to provide the respective 5-bromo homologue, then elimination of hydrogen bromide to give 2b. This transformation has previously discussed for preparing other derivatives of this class.

The structure of 1b and 2b were substantiated by microanalytical and spectroscopic data. The IR spectra of 1b and/or 2b exhibited two stretching absorption bands for aroyl and cyclic amide carbonyl groups. The 1H-NMR spectrum of 1b exhibited the expected pattern consistent with the \(-\text{CH}_2\text{CH}_2\text{H}_\text{X}\)-moiety, which has collapsed in the spectrum of 2b into a singlet at 8.15 ppm, corresponding to an olefinic proton, whose integration ratio was 100%, showing that this compound is a pure \((E)\) or \((Z)\)-isomer. The EI-MS of 2b exhibited a correct molecular ion peak \(m/z\) 433, an abundant peaks \(m/z\) 183 and \(m/z\) 165 for the \([4-\text{BrC}_6\text{H}_4\text{CO}]^+\) and \([2-\text{OMeC}_6\text{H}_4\text{NCS}]^+\) fragments and a base peak \(m/z\) 50 for the stable ion radical \([\text{C≡C─CH=CH}]^+\) (Fig 1).

Reactions of the yellow 2a, b with 1.2 equiv. of hydrazine hydrate was performed in boiled ethanol, affording the white products 3 and 4 polluted with ca 30% of 2 unreacted. Thus, the reactions were repeated using 2.5 equiv. of the nucleophile with reflux for 30 min. (method \(i\)) and/or at room temperature for 24h (method \(ii\)). Each of these methods provided 4-(3-aryl-4,5-dihydro-1H-pyrazole-5-carbonyl)-4-(2-methoxyphenyl)-3-thiosemicarbazides 3a, b and 4-(2-methoxyphenyl)-3-thiosemicarbazide 4. In addition, 6-(2-oxo-2-phenylethyl)-4-(2-methoxyphenyl)-3-thioxo-1,2,4-triazinan-5-one 5a was also obtained from 2a, under the conditions of method \(ii\) (Scheme 1). The structure of 4 was confirmed by EI-MS and by matching m.p. with an authentic sample, whereas that of 3 was elucidated based on microanalytical and spectroscopic records.

The IR spectrum of 3b showed a broad absorption band for NH\(_2\) group at 3207 and NH at 3128 cm\(^{-1}\). The spectrum did not exhibit \(\nu_{\text{CO}}\) for the aroyl CO which was present in 2b, whilst an absorption band for CO of cyclic amide was displayed at 1670 cm\(^{-1}\). The \(^1\)H-NMR spectrum in DMSO exhibited two singlet at 9.85, 9.41 ppm for two NH, a broad singlet at 4.36 ppm the for NH\(_2\) group and a singlet for the MeO protons at 3.89 ppm.
The EI-MS of 3b (Fig 2) showed a low abundant molecular ion peak $m/z$ 447, which eliminated the fragment [B] $m/z$ 224 to give the base peak [A]$^+$ $m/z$ 223 or eliminated [A] to give [B]$^+$. The peak $m/z$ 224 was not attributed to the bromo-fragment [A+H]$^+$, since the spectrum did not exhibit [M$^+$+2] peak for it. The displayed peaks $m/z$ 165 and $m/z$ 149, corresponding to the [2-OMeC$_6$H$_4$NCS]$^+$ and

\[ \text{Ar'} = 2-\text{MeOC}_6\text{H}_4, \text{ Ar} = \text{a};\text{C}_6\text{H}_5, \text{ b};4-\text{BrC}_6\text{H}_4 \]

a) Br$_2$\ AcOH $\sim$ 10 min, 90°C  b) reflux/ 30 min,  c) stirring at r. t/ 24h

**Scheme 1**
[2-OMeC₆H₄NCO]^+ fragments inferred that the [2-OMeC₆H₄N-]^+ moiety is attached to C=S as well as C=O groups. Also, the existence of the easily removable -NH-NH₂ group was proved by the exhibited peak m/z 416. In the EI-MS of the thiosemicarbazide 4, the [M^+ - NH-NH₂] fragment m/z 166 represented the base peak (Fig 1).

Formation of 3 was supposed to be achieved by merging of two N₂H₄ molecules with elimination of sulfur atom and water molecule (Scheme 1). This suggestion was supported by the successful isolation of sulfur element on chromatography the oily mother liquors. Extrusion of sulfur from 2, on treatment with N₂H₄ was only attributed to the presence of the ethylenic bond at C-5, since similar 5-(2-aryl-2-oxoethyl) derivatives³ did not extrude sulfur, under the same conditions.

Accordingly, cleavage of 2 has occurred, most likely at the -S—C=S with N₂H₄ molecule (Scheme 1). The thiolate group in [I] attacked the neighboring double bond forming the episulfide¹⁰ [II], which extruded sulfur affording [III]. Addition of N₂H₄ molecule to [III] provided the intermediate [IV] which furnished 3 via a cyclo-condensation process with the aroyl CO group. On the other hand, formation of the thiosemicarbazide 4 is reasonable in terms of the reactions of N₂H₄ with any of the intermediates as well as the product 3 at the —N— CO— group.

The intramolecular addition in [III] is a plausible way to the cyclic form 5a. The EI-MS of the white product 5a (Fig 1) showed a molecular ion peak value m/z 355, equals that of the yellow starting 2a. Thus, formation of this product gave further support to the proposed mechanism, since it could only be obtained from 2a by the replacement of sulfur atom by N₂H₄ molecule. The ¹H-NMR spectrum of 5a displayed a pattern for the -CHₓ-CHₓHₓ unity and two doublets of doublet in equal ratios for H-6. The deshielded pattern is supposed to be originated from the form, in which the chiral C-6 attains R configuration. This conformation acquires equatorial H-6, which is deshielded by the 5-oxo- group, compared with the axial counterparts in the S C-6 conformation.
Consulting the software program (ChemOffice-2004)\textsuperscript{11} inferred that, H-6 of the energy optimized R C-6 and S C-6 forms of compound 5 acquires the equatorial configuration in the first form and the axial configuration in the latter, and the dihedral angle with the 5-oxo group is 26.58°, and 95.33°, respectively.

Detection of sulfur, just five min. after reflux inferred that, extrusion of sulfur during these reactions is a very fast process that rapidly occurred before addition of hydrazine to the olefinic bond. Such an addition would result in the elimination of sulfur, as hydrogen sulfide, providing pyrazole derivatives devoid of the –CH-CH\textsubscript{2}– moiety presented in 3.
Experimental

Light petroleum was referred to the fraction b.p. = 60–80°C. 1a and 2a previously were prepared\(^6\). Thin layer chromatography was performed on Merck Kieselgel 60 F\(_{254}\) aluminum packed plates. Chromatography was carried out with silica gel S (SiO\(_2\); 0.63 – 0.1 mm; Riedel-de-Haen; on a column with the following dimensions: l = 17 cm, \(\phi = 1.7\) cm). All melting points are uncorrected. IR Spectra: on a Unicam SP1200 Spectrometer as KBr discs. Spectra of \(^1\)H-NMR (200 MHz) were measured in \(d_6\)-DMSO solution on Varian Gemini spectrometers; chemical shifts (\(\delta\)) are reported in ppm downfield relative to TMS. Mass Spectra: Shimadzu GC-MS-QP 1000X instrument operating at 70 eV.
Synthesis of 1b

Ammonium 2-methoxyphenyldithiocarbamate (2.3 g, 10.75 mmol), was added portion wise to a stirred solution of 3-(4-bromobenzoyl)-2-propenoic acid (2.54 g, 10 mmol) in ethanol (10 ml) and stirred at room temperature for 30 min., then acidified with concentrated hydrochloric acid (1 ml), boiled for 5 min. and left to cool. The precipitated solid was filtered off, washed successively with water, air dried and the crude product was recrystallized from toluene/ light petroleum to give 1b.

5-[2-(4-Bromophenyl)-2-oxoethylidene]-3-(2-methoxyphenyl)-2-thioxothiazolidin-4-one (1b)

Yield, 85%; m.p. 183-185°C; IR, ν = 3040 (=CH), 2900, 2920 (C-H), 1750 (CO aroyl group), 1675 (C=O hetero ring), 830 cm⁻¹; ¹H NMR: 7.85-7.81 (m, 3H, 2H_{aroyl} + 1H_{anisyl}), 7.66 (d, J = 8.0 Hz, 2H, H_{aroyl}), 7.48 (app.t, J = 9.2 Hz, 1H, H_{anisyl}), 7.23 (d, J = 9.2 Hz, 1H, H_{anisyl}), 7.10 (app.t, J = 9.2 1H, H_{anisyl}), 4.80 (dd, J = 9.6, 1.2 Hz, 1H, H_{A}), 4.1 (dd, J = 18.6, 1.2 Hz, 1H, H_{M}), 3.81 (s, 3H, MeO), 3.76 (dd, J = 18.6, 9.6 Hz, 1H, H_{X}). Anal. calc. for (C_{18}H_{14}BrNO_{3}S_{2}): C, 49.58; H, 2.77; N, 3.23; found: C, 48.65; H, 3.07; N, 3.44 %.

Synthesis of 2b

Powdered 1b (5 mmol) was dissolved in hot glacial acetic solution (30 ml), left for few min. The stirred solution was treated with (1.0 ml) of bromine dissolved in acetic acid (5 ml). The mixture was gently warmed until HBr gas evolution ceased (ca. 5 min) and left to cool at room temperature. The precipitated solid was filtered off, washed with H₂O, air dried and crystallized from dioxane/ toluene to give 2b.

(E/Z)-5-[2-(4-Bromophenyl)-2-oxoethylidene]-3-(2-methoxyphenyl)-2-thioxothiazolidin-4-one (2b)

Yield, 90%; m.p. 246-248 °C; IR, ν = 3060 (=CH), 2900, 2920 (C-H), 1753 (CO aroyl group), 1665 (CO hetero ring), 830 cm⁻¹; ¹H NMR: 8.18, 7.82 each (d, J = 8.6 Hz, 2H, H_{aroyl}), 8.15 (s, 1H, H_{olefinic}), 7.55, 7.13 each (app.t, J = 7.6 Hz, 1H, H_{anisyl}), 7.40, 7.26 each (d, J = 7.6 Hz, 1H, H_{anisyl}), 3.76 (s, 3H, MeO). Anal. calc. for (C_{18}H_{12}BrNO_{3}S_{2}): C, 49.78; H, 2.77; N, 3.23; found: 48.65; H, 3.0; N, 3.44 %.

Reactions of 2a, b with hydrazine hydrate

A solution of ethanol (50 ml) containing 3 mmol of 2a or 2b and hydrazine hydrate (2.5 mmol) was heated for 30 min. (method i) and/or stirred at room
temperature for 24 h (method ii). The solid product of method i (after cooling) and that of method ii was filtered off, air dried and crystallized from EtOH/dioxan to give 4. After few hours, the mother liquor of 2a from method ii afforded a white precipitate, which was filtered off, dried and crystallized from dioxan to give 5a. The filtrate of 2a (method ii) and the rest of the mother liquors were left overnight to give 3a and 3b. Sulfur element was separated, on chromatography, the residue of 2b method i and method ii, over silica gel with light petroleum/CHCl₃ (5: 1: V/V).

4-(3-Phenyl-4,5-dihydro-1H-pyrazole-5-carbonyl)-4-(2-methoxyphenyl)thiosemicarbazide (3a)

Yield, (50%, method i; 60%, method ii); m.p. 185-187°C; IR, ν = 3320, 3285 (NH₂, NH), 3050 (=CH), 2937 (C-H), 1683 (C=O), 824 cm⁻¹; ¹H NMR: 9.85, 9.40 each (s, 1H, NH), 8.24 (d, J = 8.2, 1H, Hₐₙisyl), 7.94-7.84 (m, 2H, Hₚₐₚ), 7.60-7.48 (m, 3H, Hₚₐₚ), 3.26 (dd, J = 18.2, 5.0 Hz, 1H, Hₐ), 4.22 (br.s, 2H, NH₂), 3.78 (dd, J = 18.2, 12.4 Hz, 1H, Hₘ), 3.91 (s, 3H, MeO). Anal. calc. for (C₁₈H₁₉N₅O₂S): C, 58.52; H, 5.18; N, 18.96; found: C, 55.91; H, 4.57; N, 18.08 %.

4-[3-(4-Bromophenyl)-4,5-dihydro-1H-pyrazole-5-carbonyl]-4-(2-methoxyphenyl)thiosemicarbazide (3b)

Yield, (50%, method i; 60%, method ii); m.p. 222-224°C; IR, ν = 3207 (NH₂), 3128 (NH), 3050 (=CH), 2937 (C-H), 1670 (C=O), 825 cm⁻¹; ¹H NMR: 9.85, 9.41 each (s, 1H, NH), 8.11 (d, J = 8.0 Hz, 1H, Hₐₙisyl), 7.84, 7.73 each (d, J = 8.6 Hz, 2H, Hₚₐₚ), 7.19 (app.t, J = 8.0 1H, Hₐₙisyl), 7.11 (d J = 8.0, 1H, Hₐₙisyl), 6.96 (app.t, J = 8.0 1H, Hₐₙisyl), 5.25 (dd, J = 12.0, 5.0 Hz, 1H, Hₐ), 4.22 (br.s, 2H, NH₂), 3.78 (dd, J = 18.2, 12.0 Hz, 1H, Hₘ), 3.24 (dd, J = 18.2, 5.0 Hz, 1H, Hₐ), 3.91 (s, 3H, MeO). Anal. calc. for (C₁₉H₁₈BrN₅O₂S): C, 58.52; H, 5.18; N, 18.96; found: C, 55.91; H, 4.57; N, 18.08 %.

4-(2-Methoxyphenyl)-3-thiosemicarbazide (4)

Yield, (20%, method i; 25%, method ii); m.p. 150-152°C, undepressed on admixture with the sample previously obtained⁹.

6-(2-Oxo-2-phenylethyl)-4-(2-methoxyphenyl)-3-thioxo-1,2,4-triazinan-5-one(5a)

Yield, (20% from 2a; method ii); m.p. 276-278°C; IR, ν = 3120 (NH), 3050 (=CH), 2937 (C-H), 1740 (CO aroyl group), 1675 (CO hetero ring), 690, 750 cm⁻¹; ¹H NMR: 8.05 (app.t, J = 6.8 Hz, 2H, Hₚₐₚ), 7.76 (br.s, 1H, NH), 7.72 (d, J = 7.4 Hz,
1H, H_{anisy}), 7.60 (d, J = 6.8 Hz, 2H, H_{Ph}), 7.48 (app.t, J = 7.4 Hz, 1H, H_{anisy}), 7.35-7.20 (m, 3H, H_{Ph} + H_{anisy} + NH), 7.14, (app.t, J = 7.4 Hz, 1H, H_{anisy}), 5.06, 5.01 each (dd, J = 10.4, 5.0 Hz, 50% H, H_A) for R C-6, and S C-6, 4.24 (dd, J = 18.2, 5.0 Hz, 1H, H_B), 4.01 (dd, J = 18.2, 10.4 Hz, 1H, H_X) 3.9 (s, 3H, MeO). Anal. calc. for (C_{18}H_{17}N_{3}O_{3}S): C, 60.83; H, 4.78; N, 11.83; found: C, 58.56; H, 3.69; N, 12.41 %.

References

الخروج عنصر الكبريت من تفاعلات الهيدرازين هيدرات مع مشتقات
5-(2-أرييل-2-اوكسو أيثيليدين)-3-(2-ميثوكسي فينيل)-2-ثيوكسبثيازوليدين
1-اون

تفاعلات مشتقات 5-(2-أرييل-2-اوكساوايثيليدين)-3-(2-ميثوكسي فينيل)-2-
ثيوكسبثيازوليدين (2) مع 2.5 مكافئ من الهيدرازين هيدرات تم اجراؤها بالتسخين لمدة
نصف الساعه كما تم اجراؤها أيضاً في درجة حراره الغرفة لمدة 24 ساعه وقد أدى كل من
هذه الظروف بالذات 1-اون 4-(2-ميثوكسي فينيل)-3-ثيوسيميكاريبيثيد (3) و4-(2-ميثوكسي فينيل)-3-
ثيوسيميكاريبيثيد (4) في كل حاله. هنا قد تم تكوين 6-(2-فيينيل-2-اوكساوايثيل)-4-
(2-ميثوكسي فينيل)-3-ثيوكسو-1,2,4,5-تربازين-5-اون (5a) من المركب a عند اجراء
التفاعل في درجة حراره الغرفة. وقد امكننا فصل عنصر الكبريت من هذه التفاعلات. الأمر
الذي استطعنا بواسطة تقسيم جميع التحولات السابقة.حيث يتكون 3 من 2 باضافه جزيئ
من الهيدرازين وخروج جزء ماء وذرء الكبريت. كما ان تكوين المركب (5a) يدعم هذه
الميكانيكيه المقترحة التي أدت الى تكون هذا النتيج. وقد تم اثبات جميع هذه
المركبات الناتجه باستخدام أنواع التحاليل الطيفية المختلفة.