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NADIA EL-AASAR
Department of Chemistry, Faculty of Science, Ain Shams University, Abbassia, Cairo, Egypt.

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

NADIA K. EL-AASAR

Department of Chemistry, Faculty of Science, Ain Shams University, Abbassia, Cairo, Egypt.

Abstract

Reactions of 3-substituted-5-(2-aryl-2-oxoethylidene)-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-1*H*-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-thioxo-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 3*H*-5-arylidene-2-oxo/thioxothiazolidin-4-ones and 3-substituted-2-thioxothiazolidin-4-ones have been previously studied[1-3]. Most of these reactions affected the ring cleavage at the 2-oxo/thioxo 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 ^{1}H-NMR spectra of the products **3** and **5a** displayed patterns for the –CH_A-CH_MH_X- 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

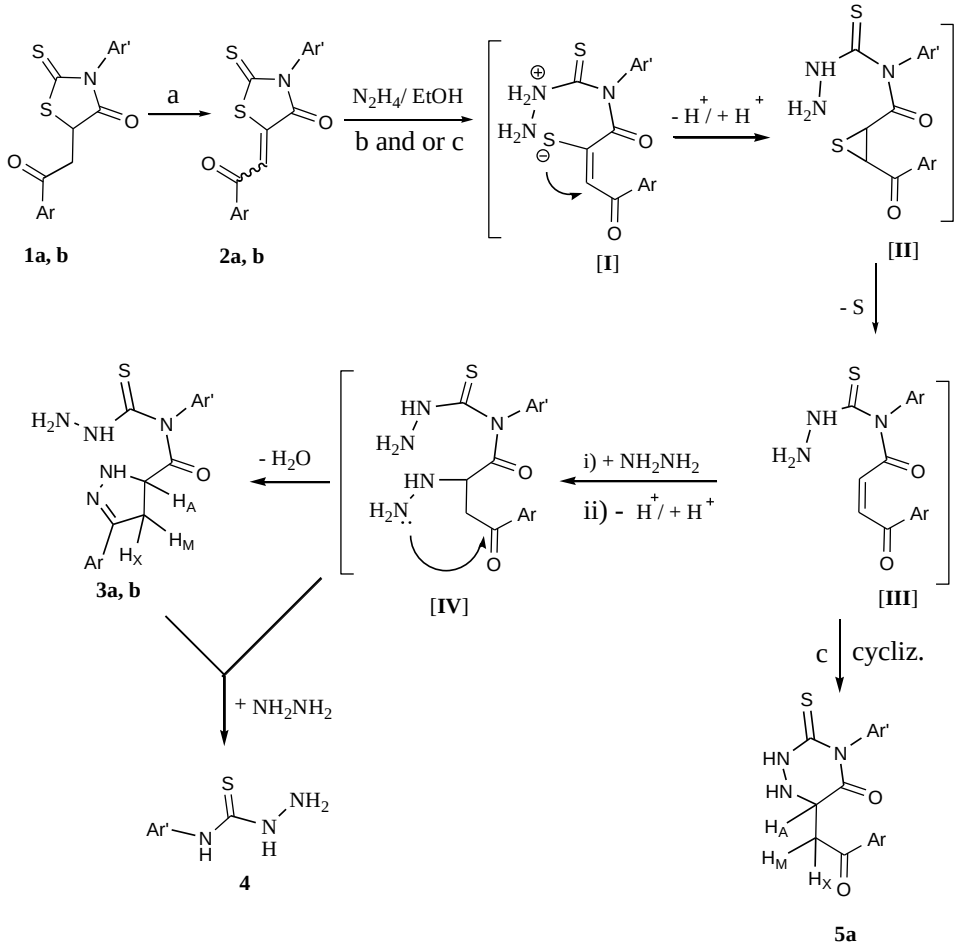
The starting 5-[2-(4-bromophenyl)-2-oxoethyl]-3-(2-methoxyphenyl)-2-thioxo-thiazolidin-4-one **1b** was synthesized from 3-(4-bromobenzoyl)-2-propenoic acid[4] and ammonium 2-methoxyphenyldithiocarbamate, following previously reported methods[5, 6]. Treatment of **1b** with bromine in acetic acid solution 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[5, 6].

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 ^{1}H-NMR spectrum of **1b** exhibited the expected pattern consistent with the $-CH_A$-CH_MH_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[7, 8]. 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 $[4\text{-}BrC_6H_4CO]^+$ and $[2\text{-}OMeC_6H_4NCS]^+$ fragments and a base peak *m*/*z* 50 for the stable ion radical $[C{\equiv}C{-}CH{=}CH]^+$ (*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-1*H*-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[9], 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 3207and NH at 3128 cm^{-1}. The spectrum did not exhibit ν_{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.



Ar' = 2-$MeOC_6H_4$, Ar = **a;**C_6H_5 , **b;**4-BrC_6H_4

a) Br_2\ AcOH\ ≈ 10 min\ 90°C b)reflux/ 30 min, c)stirring at r. t/ 24h

Scheme 1

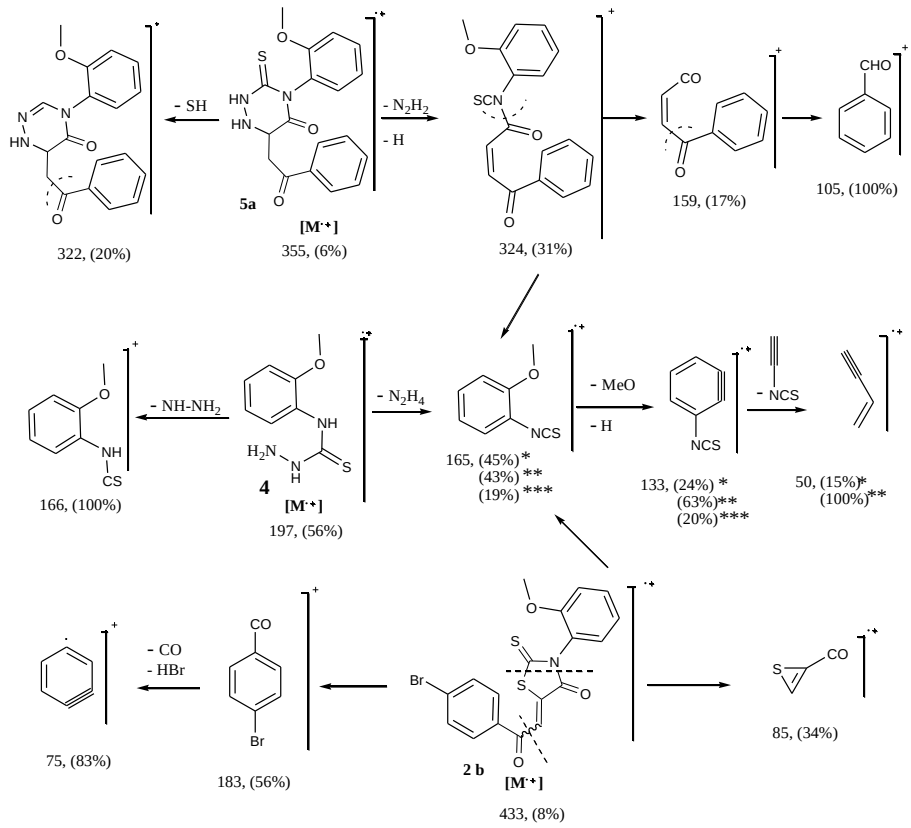
The EI-MS of **3b** (*Fig 2*) showed a low abundant molecular ion peak *m/z* 447, which eliminated the fragment [B]˙ *m/z* 224 to give the base peak $[A]^+$ *m/z* 223 or eliminated [A]˙ to give $[B]^+$. The peak *m/z* 224 was not attributed to the bromo-fragment $[A+H]^{\cdot+}$, since the spectrum did not exhibit $[M^{\cdot+}+2]$ peak for it. The displayed peaks *m/z* 165 and *m/z* 149, corresponding to the $[2\text{-}OMeC_6H_4NCS]^+$ and

$[2\text{-}OMeC_6H_4NCO]^+$ fragments inferred that the $[2\text{-}OMeC_6H_4N\text{-}]^+$ moiety is attached to C=S as well as C=O groups. Also, the existence of the easily removable -NH-NH_2 group was proved by the exhibited peak *m*/*z* 416. In the EI-MS of the thiosemicarbazide **4**, the [M^{+}- NH-NH_2] fragment *m*/*z* 166 represented the base peak (*Fig 1*).

Formation of **3** was supposed to be achieved by merging of two N_2H_4 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 N_2H_4 was only attributed to the presence of the ethylenic bond at C-5, since similar 5-(2-aryl-2-oxoethyl) derivatives[3] did not extrude sulfur, under the same conditions.

Accordingly, cleavage of **2** has occurred, most likely at the -S─C=S with N_2H_4 molecule (*Scheme 1*). The thiolate group in **[I]** attacked the neighboring double bond forming the episulfide[10] **[II]**, which extruded sulfur affording **[III]**. Addition of N_2H_4 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 N_2H_4 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 N_2H_4 molecule. The ^{1}H-NMR spectrum of **5a** displayed a pattern for the -CH_A-CH_MH_X- 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.

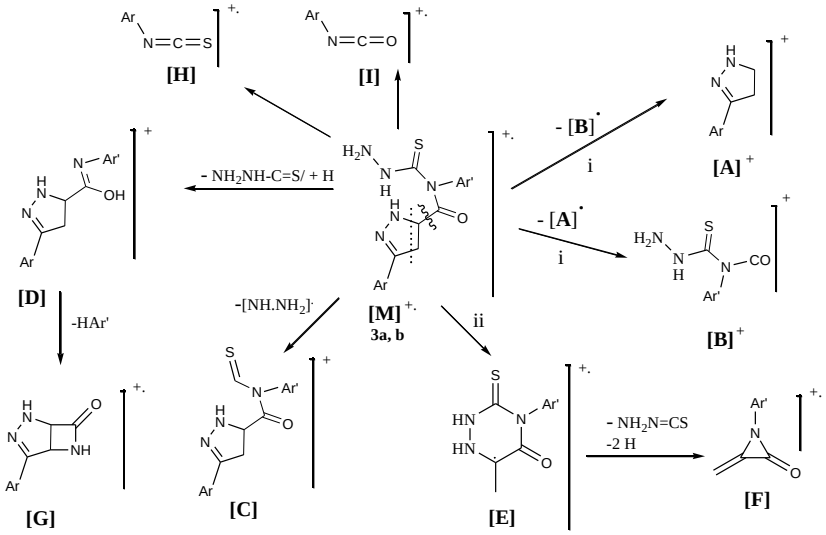


* from **4**, ** from **2b,** *** from **5a**

Fig 1

Consulting the software program (*ChemOffice-2004*)[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 angel with the 5-oxo group is 26.58^o, and 95.33^o, 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$_2$- moiety presented in **3**.



compd.	Fragments m/z(%)									
	$[M]^{+}$	$[A]^{+}$	$[B]^{+}$	$[C]^{+}$	$[D]^{+}$	$[E]^{+}$	$[F]^{+}$	$[G]^{+}$	$[H]^{+}$	$[I]^{+}$
3a	369 (5)	145 (100)	-	338 (21)	295 (9)	-	175 (5)	187 (8)	165 (7)	149 5)
3b	447 (8) 449 (10)*	223 (90) 225 (100)*	224 (20)	416 (16) 418 (18)*	373(15) 275 (13)*	251 (10)	175 (5)	265 (3) 267 (3)*	165 (29)	149 (5)

* $[M^{+}+2]$ peack

Fig 2

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, ϕ = 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 (δ) 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 (2.3g, 10.75 mmol), was added portion wise to a stirred solution of 3-(4-bromobenzoyl)-2-propenoic acid (2.54g, 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-oxoethyl]-3-(2-methoxyphenyl)-2-thioxothiazolidin-4-one (1b)

Yield, 85%; m.p. 183-185^{o}C; IR, ν = 3040 (=CH), 2900, 2920 (C-H), 1750 (C=O aroyl group),1675 (C=O hetero ring) , 830 cm^{-1}; ^{1}H 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 ($C_{18}H_{14}BrNO_3S_2$): C, 49.55; H, 3.23; N, 3.21; found: C, 50.51; H, 3.42; N, 3.04 %.

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 H_2O, air dried and crystallized from dioxane/ toluene to give **2b**.

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

Yield, 90; m.p. 246-248 ^{o}C; IR, ν = 3060 (=CH), 2900, 2920 (C-H), 1753 (CO aroyl group), 1665 (CO hetero ring), 830 cm^{-1}; ^{1}H 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 ($C_{18}H_{12}BrNO_3S_2$): 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 over night 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/ $CHCl_3$ (5: 1: V/V).

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

Yield, (50%, method ***i***; 60%, method ***ii***); m.p. 185-187^{o}C; IR, ν = 3320, 3285 (NH_2, NH), 3050 (=CH), 2937 (C-H), 1683 (C=O), 824 cm^{-1}; ^{1}H NMR: 9.85, 9.40 each (s, 1H, NH), 8.24 (d, *J* = 8.2, 1H, H_{anisyl}), 7.94-7.84 (m, 2H, H_{Ph}), 7.60-7.48 (m, 3H, H_{Ph}), 7.22-7.08 (m, 2H, H_{anisyl}), 6.97 (app.t, *J* = 8.2 1H, H_{anisyl}), 5.26 (dd, *J* = 12.4, 5.0 Hz, 1H, H_A), 4.22 (br.s, 2H, NH_2), 3.78 (dd, *J* = 18.2, 12.4 Hz, 1H, H_M), 3.26 (dd, *J* = 18.2, 5.0 Hz, 1H, H_A), 3.91 (s, 3H, MeO). Anal. calc. for ($C_{18}H_{19}N_5O_2S$): 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-1*H*-pyrazole-5-carbonyl]-4-(2-methoxyphenyl) thiosemicarbazide (3b)

Yield, (50%, method ***i***; 60%, method ***ii***); m.p. 222-224^{o}C; IR, ν = 3207 (NH_2), 3128 (NH), 3050 (=CH), 2937 (C-H), 1670 (C=O), 825 cm^{-1}; ^{1}H NMR: 9.85, 9.41 each (s, 1H, NH), 8.11 (d, *J* = 8.0, Hz, 1H, H_{anisyl}), 7.84, 7.73 each (d, *J* = 8.6 Hz, 2H, H_{aroyl}), 7.19 (app.t, *J* = 8.0 1H, H_{anisyl}), 7.11 (d *J* = 8.0, 1H, H_{anisyl}), 6.96 (app.t, *J* = 8.0 1H, H_{anisyl}), 5.25 (dd, *J* = 12.0, 5.0 Hz, 1H, H_A), 3.89 (s, 3H, MeO), 3.81 (dd, *J* = 18.2, 12.0 Hz, 1H, H_M), 4.36 (br.s, 2H, NH_2), 3.24 (dd, *J* = 18.2, 5.0 Hz, 1H, H_X). Anal. calc. for ($C_{18}H_{18}BrN_5O_2S$): C, 48.22; H, 4.03; N, 15.62; found: C, 46.10; H, 4.13; N, 14.85 %.

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

Yield, (20%, method ***i***; 25%, method ***ii***); m.p. 150-152^{o}C, undepressed on admixture with the sample previously obtained [9].

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^{o}C; IR, ν = 3120 (NH), 3050 (=CH), 2937 (C-H), 1740 (CO aroyl group), 1675 (CO hetero ring), 690, 750 cm^{-1}; ^{1}H NMR: 8.05 (app.t, *J* = 6.8 Hz, 2H, H_{Ph}), 7.76 (br.s, 1H, NH), 7.72 (d, *J* = 7.4 Hz,

1H, H_{anisyl}), 7.60 (d, J = 6.8 Hz, 2H, H_{Ph}), 7.48 (app.t, J = 7.4 Hz, 1H, H_{anisyl}),7.35-7.20 (m, 3H, H_{Ph} + H_{anisyl} + NH), 7.14, (app.t, J = 7.4 Hz, 1H, H_{anisyl}), 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_M), 4.01 (dd, J = 18.2, 10.4 Hz, 1H, H_X) 3.9 (s, 3H, MeO). Anal. calc. for ($C_{18}H_{17}N_3O_3S$): C, 60.83; H, 4.78; N, 11.83; found: C, 58.56; H, 3.69; N, 12.41 %.

References

1. V. N. ARTEMOV, S. M. BARANOVA, N. A. KOVACH, O. P. SHVAIKA, *Odkl. Akad. Nauk SSSR*, 211, 1369, 1973; *Chem. Abst.*, 80, 3422b 1974.
2. A. R. A. RAOUF, M. T. OMAR, M. M. El-ATTAL, *Acta Chim. Acad. Sci. Hung*., 87, 187, 1975; *Chem. Abst*., 84, 74185 1976.
3. N. K. EL-AASAR, K. F. SAIED, *J. Sulfur Chemistry* 29, 43, 2008.
4. D. PAPA, E. SCHWENK, F. VILLANI, E. KLINGSBERG, *J. Am. Chem. Soc.*, 70, 3356, 1948.
5. J. KINUGAWA, H. NAGASE, *Takeda Chemical Industries, Ltd. Japan*. 11, 342, 1964 ('66), *Chem. Abst*. 65, 13717e, 1966
6. M. T. OMAR, M. E. SHABAN, N. K. EL-AASAR, K. F. SAIED, *Helv. Chim. Acta*., 91, 1461, 2008.
7. N. BAUMANN, M.-T. SUNG, E. F. ULLMAN, *J. Am. Chem. Soc.*, 90, 4157, 1968.
8. G. DESIMONI, A. GAMBA, P. P. RIGHETTI, G. TACCONI, *Gazz. Chim. Ital.*, 102, 491, 1972.
9. E. FROMM, M. SOFFNER, M. FREY, *Ann.* 434, 285, 1923; *Chem. Abst.*, 18, 378, 1942.
10. W. SCHROTH, S. DUNGER, F. BILLIG, R. SPITZNER, R. HERZSCHUH, A. VOGT, T. JENDE, G. ISRAEL, J. BARCHE, D. STROHL, D. SIELE, J. *Tetrahedron*, 52, 120, 1996.
11. ChemOffice Ultra 2004 (CambridgeSoft, Inc.): Chemical & Biological Publishing, Modeling, And Database Software.

خروج عنصر الكبريت من تفاعلات الهيدرازين هيدرات مع مشتقات 5-(2-اريل-2-اوكسو ايثيليدين)-3-(2-ميثوكسي فينيل)-2-ثيوكسوثيازوليدين-4-اون

تفاعلات مشتقات 5-(2-اريل-2-اوكسوايثيليدين)-3-(2-ميثوكسي-فينيل)-2-ثيوكسوثيازوليدين (2) مع 2,5 مكافئ من الهيدرازين هيدرات تم اجراؤها بالتسخين لمده نصف الساعه كما تم اجراؤها ايضا في درجه حراره الغرفه لمده 24 ساعه وقد ادى كل من هذه الظروف بكرم نيوكت ىلا 4 -(3-اريل-5,4-داي هيدروبيرازول-5-كربونيل)-4-(2-ميثوكسى فينيل)- 3-ثيوسيميكاربازيد (3) و4-(2-ميثوكسى فينيل)- 3-ثيوسيميكاربزيد (4) فى كل حاله. هذاوقد تم تكوين 6-(2-فينيل-2-اوكسوايثيل)-4-(2ميثوكسي فينيل)-3-ثيوكسو-4,2,1-ترايازين-5-اون (5a) من المركب 2a عند اجراء التفاعل فى درجه حراره الغرفه. وقد امكننا فصل عنصر الكبريت من هذه التفاعلات, الامر الذى استطعنا بواسطته تفسير جميع التحولات السابقه.حيث يتكون 3 من 2 باضافه جزيئين من الهيدرازين وخروج جزئ ماء وذره كبريت. كما ان تكوين المركب(5a) يدعم هذه الميكانيكيه المقترحه التى ادت الىتكوين هذه النواتج. وقد تم اثبات جميع هذه المركبات الناتجة باستخدام أنواع التحاليل الطيفية المختلفة.