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Synthesis of some Thiadiazoline Derivatives from 2- Phenyl Chroman-4-one

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ABSTRACT

2-Phenyl chroman-4-one 1(a-g) were synthesized by Pechmann condensation of proper phenol with cinnamic acid using poly phosphoric acid. Reactions of their derivatives with thiosemicarbazide were carried out using two methods, method A, using refluxing ethanol, gave low yield (17-20%). This method was modified to increase the yield using solvent free microwave irradiation technique, (method B), which improved the yield up to (30-40%). The treatment of these thiosemicabazones 2(a-g) with excess acetic anhydrid gave substituted thiadiazoline derivatives 3(a-g). The structure of these compounds was confirmed by IR, UV and NMR spectra in addition to their physical properties. On the other hand, the calculated values of the heat of formation and steric energy were established for compounds 2(a-g) and 3(a-g).

Keywords: 1,3,4-thiadiazoline, chroman-4-one.

تحضير بعض مشتقات الثاياديازولين من فنيل كرومان-4-أون

الملخص

يتضمن البحث تحضير عدد من مركبات 2- فينيل كرومان-4- اون 1(a-g) بواسطة تكاثف بجمان لفينول مناسب مع حامض السينامك وباستخدام متعدد حامض الفسفوريك. فوعلت النواتج مع الثايوسيميكاربازايد باستخدام طريقتين، الطريقة A بالتصعيد بالإيثانول المطلق التي أعطت نسبة ناتج قليلة 17-20% ولزيادة نسبة الناتج تم استخدام تقنية التشعيع بالموجات الدقيقة في الطور الصلب (بدون مذيب) (الطريقة B)، وحققت نسبة ناتج أعلى من 30-40 % من مشتقات الثايوسيمي كاربازون 2(a-g). عوملت المركبات 2(a-g) مع زيادة من انهيدريد الخليك للحصول على عدد من مشتقات الثاياديازولين 3(a-g). شخصت المركبات المحضرة بواسطة أطياف (UV, IR, NMR) فضلا عن خواصها الفيزياوية، كما تم حساب كل من حرارة التكوين وطاقة الإعاقة للمركبات الوسيطة 2(a-g) والنواتج 3(a-g).

INTRODUCTION

Chroman-4-one and their derivatives are used in many organic synthesis. The acid catalyzed condensation of substituted phenol with carboxylic acid such as liglic acid, and crotonic acid gives chroman-4-one derivatives, which underwent ring closure with hydrazine hydrate to form pyrazolines (Ayoub *et al*., 1985).

The reaction of chroman-4-one with aromatic aldehyde in presence of potassium hydrid lead to formation of α,β–unsaturated ketones (Saied, 2000). Such compounds were reacted with hydrazine hydrate under the phase transfer catalysis technique, PTC, to yield pyrazolines derivatives (Hidayet, 2000), while produce pyrimidine derivatives when reacted with urea or thiourea (Raoof, 2005). Also, different aromatic aldehydes and cinnamaldehydes undergo cross-aldol condensation with chroman-4-ones under microwave irradiation to afford 3-arylidene and 3-cinnamylidene derivatives (Mandal *et al.*, 2011).

Chroman-4-one has been used to synthesize various heterocyclic compounds which have a wide range of pharmacological activities, e.g, khellin is a coronary vasodilator (Geissmann *et al.*, 1951) and (Clanrge *et al.*, 1949), and chroman-4-one carboxylic acids are spasmolytic agents (Joshi *et al*., 2006). A series of 3-benzyl chromans were synthesized from 3-benzyl chroman-4-ones and tested against human –rhionvirous activity (Conti *et al*., 2009). The synthetic chromone derivatives also show some important biological activities and used as anti–inflammatory and cytoloxic agents (Mandal *et al.*, 2011).

1,3,4-Thiadiazolines were produced from the oxidation of aldehyde-thiosemicarbazones with NaOH /K_3 [$Fe(CN)_6$] (Kabbe, 1978). Synthesis of 5α-cholestan -3-spiro-(3,4-acetylamino)-Δ^2-1,3,4-thiadiazoline from 5α-cholestan-3-one thiosemicarbazone have also been reported (Pawar *et al*., 2009). On the other hand, 1,3,4-thiadiazolines were obtained from diaryl and aryl-cyclo alkyl ketones, via the corresponding thiosemicarbazones (Martins *et al*., 2000). The reaction of chlorodiazolines with thiourea gives 4-amidion-Δ^2-1,3,4-thiadiazoline (Flowers *et al*., 1979). Another 1,3,4- thiadiazoline derivatives have been prepared by cyclization of thiosemicarbazone under acetylating conditions (Fatondji *et al*., 2011), (Yadong *et al.*, 2006) and (Joshi *et al*., 2006).

Thiadiazoles and their derivatives are compounds possessing a wide spectrum of biological activity. They exhibit anti-inflammatory (Pawar *et al*., 2009), antifunga, (Venkateswalu *et al*., 2005) l and antibacterial activity (Al-Abdullah, 2007).

In view of these observations, we prefer to synthesize new substituted thiadiazolines containing chromanone moiety of anticipated biological importance.

EXPERIMENTAL

Uncorrected melting points were determined using electro thermal Gallen kamp melting apparatus. IR spectra were obtained via Perkin-Elmer 590B spectrophotometer. UV- spectra obtained via Shimadzu UV-160 spectrophotometer, while ^{1}H-NMR spectra were obtained from a Bruker a vance 300-MHz, NMR spectrometer. The chemical shifts are reported in δ values for DMSO-d6 solution using TMS as internal standard, with the use of the following abbreviations:

s, singlet; d, doublet; m, multiplet; br, broad.

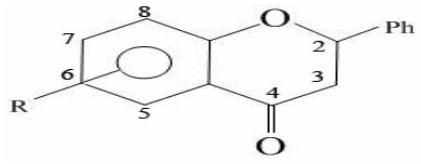
Theoretical calculation:

The geometries of compounds 2(a-g) and 3(a-g) were optimized using PM3 semi-empirical methods to obtain Heat of formation (ΔH_f). Total steric energy (S.E) was computed using molecular mechanic theory 2 (MM2) in the CS-Chem office-version 10.

Synthesis of substituted 2-phenyl chroman-4-one 1 (a-g) (Ayoub *et al.*,1985)

To a mixture of (25 mmole) of the desired phenol and (3.7 gm, 25 mmole) of cinnamic acid, (20-25)g of polyphosphoric acid was added at room temperature. The mixture was stirred and heated on water bath at (75-80)°C for (1-1.5)h. The mixture was then poured on ice bath. The residue was filtered off, washed with cold water, dried and crystallized from ethanol to afford a white amorphous solid of compounds 1(a-g). Table (1) shows some physical properties and spectral data of these compounds.

Table 1: Some physical properties and spectral data for compounds 1(a-g).



Comp. No.1	R	M.P. °C	Yield %	IR, KBr(disc) ν, cm^{-1}, C=O	UV.($CHCl_3$) λ_{max} (nm)	^{1}H –NMR, δ, DMSO				
						H-2	H-3	H-5	H-7	H-8 and ph-H
a	7-NO_2	110-112	40	1689	300					
b	6-NO_2	86-90	52	1685	300	6.5 d (1H)	3.5d (2H)	8.1d (1H)	7.7s (1H)	7.6-6.9m(6H)
c	8-Br	72-73	35	1685	310					
d	6-Br	110-112	79	1637	316					
e	6-Cl	101-102	90	1724	300	6.9 d (1H)	3.3-3.1br (2H)	7.9m (1H)	7.8m (1H)	7.3-7.1m(6H)
f	6,8-$(CH_3)_2$	63-64	80	1705	300					
g	6,7-$(CH_3)_2$	84-86	40	1728	312	4.4 s (1H)	3.3-2.8m (2H)	7.4m (1H)	2-2.3m $H\text{-}C_{7+H\text{-}C6}$ (6H)	7.3-6.8m(6H)

2-phenyl chroman-4-thiosemicarbazone 2(a-g) (Pawar *et al*., 2009)

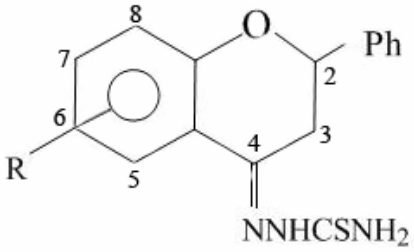
Method A: To a solution of (2.8 mmole) of substituted 2-phenyl chroman-4-one 1(b-c) in absolute ethanol (10 ml), a solution of (2.8 mmole) of thiosemicarbazid in ethanol and few drops of conc. HCl were added with stirring. The reaction mixture was refluxed for (2-5)h on a water bath. After cooling, the solid product was filtered off and crystallized from ethanol to give white product of compounds 2(b-c).

Method B: (2.8 mmole) of substituted 2-phenyl chroman-4-one 1a, 1(d-g) and (2.8 mmole) of thiosemicarbazid was heated for (3-8) min using 360 watt microwave irradiation.

After cooling, the mixture was crystallized from ethanol to give the products 2a and 2(d-g) as a yellow powdered solid.

Table (2) shows some physical properties and spectral data of these compounds.

Table 2: Some physical properties and spectral data for compounds 2(a-g).

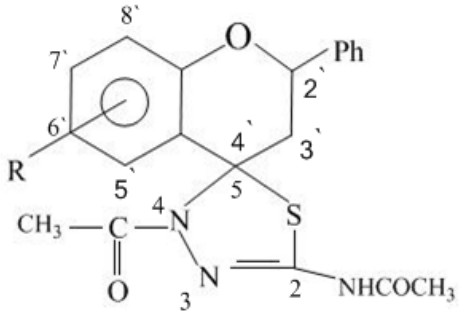


Comp. NO.2	R	M.P °C	Yield %		IR-KBr υ, cm^{-1}		UV (CH Cl_3) λ_{max}(nm)	^{1}H –NMR, δ, DMSO						
			method A	method B	C=N	N-H		H-2	H-3	H-5	H-7	H-8 and ph-H	NH	NH_2
a	7-NO_2	144-48	---	40	1633	3332 3265	326							
b	6-NO_2	166-68	20	---	1635	3364 3263	322	4.8br (1H)	4.5d (2H)	8.5d (1H)	8.1d (1H)	7.9-6-9m(6H)	6.5d (1H)	8.6 s (2H)
c	8-Br	102-104	17	---	1639	3402 3273	320							
d	6-Br	95 decomp.	---	44	1637	3479 3236	320							
e	6-Cl	180 decomp.	---	40	1630	3338 3172	318	6.6d (1H)	3.5-2.9br (2H)	7.9s (1H)	7.6 m	7.0-7.5m(6H)	6.9 m (1H)	8.2 s (2H)
f	6,8-$(CH_3)_2$	90-92	---	35	1633	3413 3265	320							
g	6,7-$(CH_3)_2$	100-102	---	41	1626	3285 3182	325	5.85 (1H)	3.3 s (2H)	7.8 s (1H)	2.4 -2.3 H-C_{7+} H- C6 (6H)	7.8-7.2 m (6H)	7.0 s (1H)	8.3 s (2H)

5-spiro(2`-phenyl-subst.-chroman)-4-acetyl-2-acetylamino-Δ^2-1,3,4-thiadiazolines 3(a-g) (Pawar *et al.*, 2009), (Venkateswalu *et al.*, 2005) and (Joshi *et al.*, 2006)

Compounds 2(a-g)(0.27 mmole) were treated with excess of acetic anhydride (3 ml) and the mixture was refluxed for (6-7)h. The resulting contents were poured over crushed ice. The obtained solid was filtered, dried and crystallized from ethanol to afford the title compounds. Table (3) gives some physical properties and spectral data of these compounds.

Table 3: Some physical and spectral data for compounds 3(a-g).



Comp. NO.3	R	M.P °C	Yield%	IR-KBr υ,cm^{-1}			UV(CH Cl_3) λ_{max}(nm)	^{1}H –NM		
				C=O	C=N	N-H		H_6	H_7	H-2̀
a	7̀ -NO_2	180 decomp.	30	1698 1615	1585	2933	285			
b	6̀ -NO_2	250 decomp.	20	1695 1574	1523	3280	277	1.3s(3H)	3.3s(3H)	4.6s(1H)
c	8̀ -Br	276-78	15	1697 1572	1500	3278	280			
d	6̀ -Br	120 decomp.	25	1699 1624	1617	3175	283			
e	6̀ -Cl	158 decomp.	17	1712 1610	1549	3174	274	2.15 (3H)	2.6s (3H)	4.9s (1H)
f	6̀ ,8̀-$(CH_3)_2$	112-14	15	1720 1620	1604	3087	290			
g	6̀,7̀-$(CH_3)_2$	88-92	20	1698 1655	1612	3175	270	2.3-2.0 d(9H) H_6+H_7+H_6̀ 3.15(3H) H_7̀		4.45 (1H)

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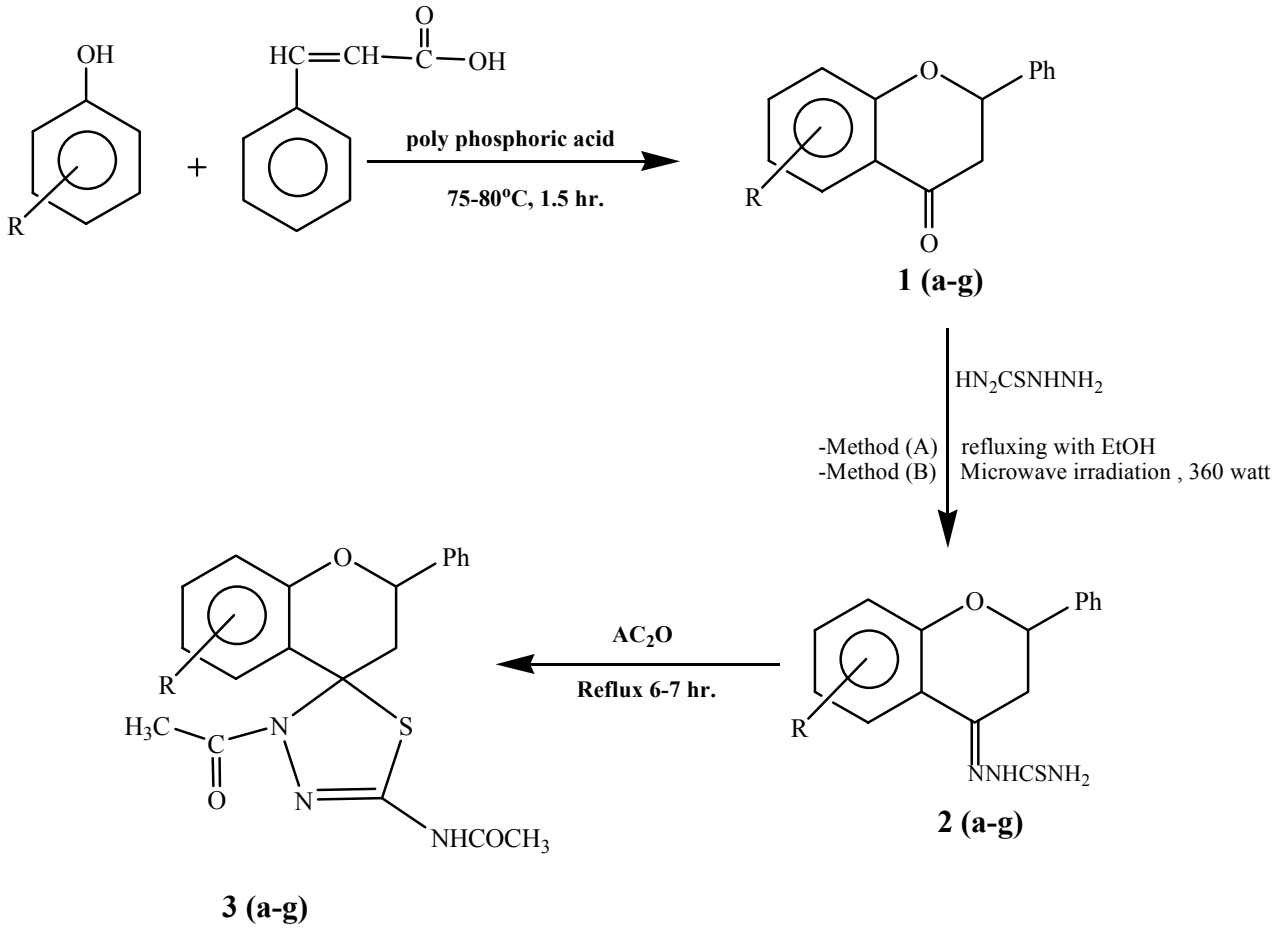
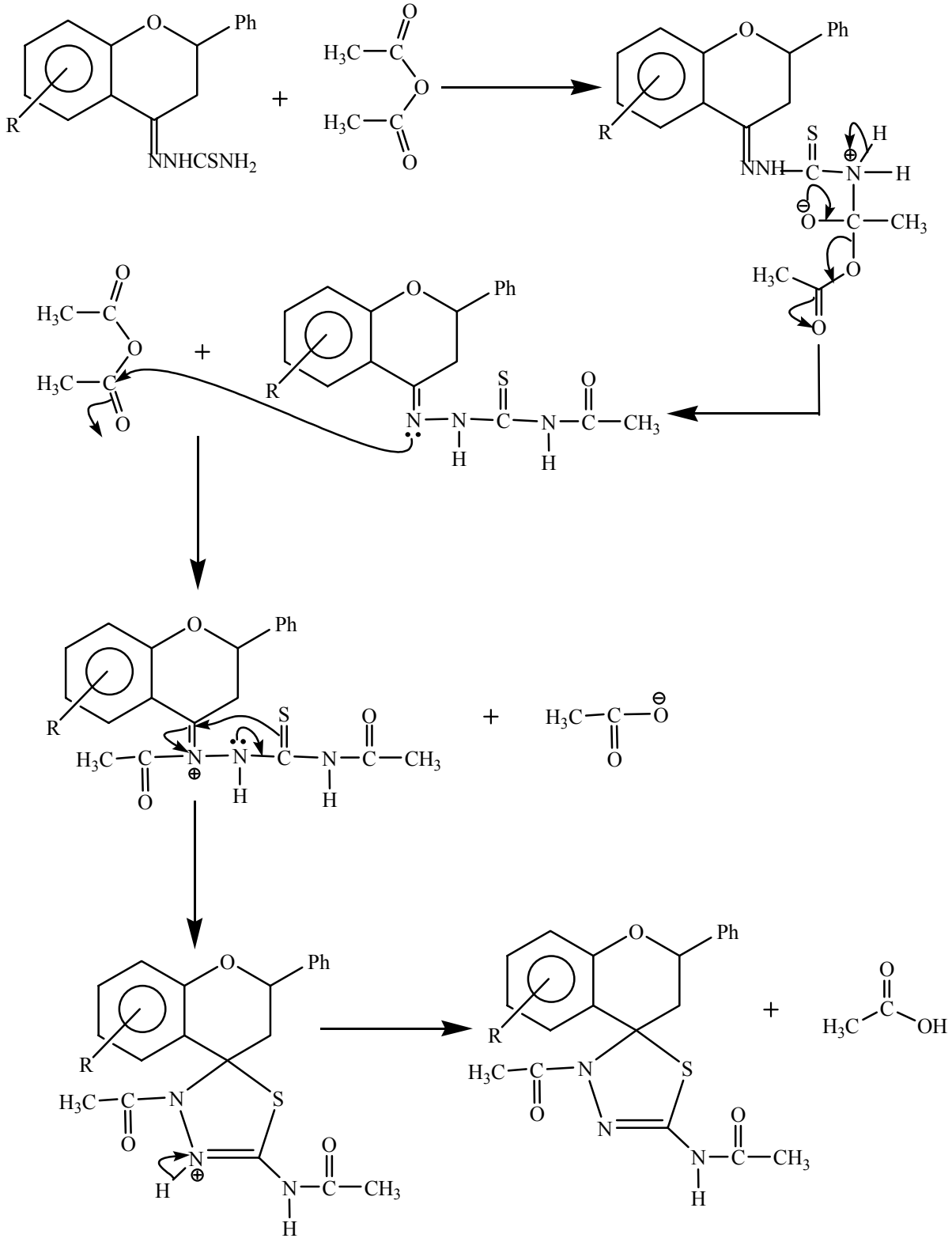
The prepared 4-chromanone derivatives 1(a-g) were considered as a principle nucleus for the synthesis of many important heterocyclic compounds through their reactions with different compounds (Ayoub *et al*., 1985) and (Pawar *et al*., 2009).

The derivatives1(a-g) were prepared via Pechmann condensation of the proper phenols with cinnamic acid using polyphosphoric acid as shown in scheme (1). The proposed mechanism of the conversion 2(a-g) derivatives to 3(a-g) derivatives was summarized in scheme (2):



Scheme (1)

RESULTS AND DISCUSSION



Scheme (2)

The IR spectra of the 4-chromanones 1 (a-g) showed a strong absorption bands at about (1637-1728 cm^{-1}) which belong to the bond stretching of the carbonyl group of the chromanon (Ayoub *et al*., 1985). The UV spectra of these compounds showed a maximum absorption (λ_{max}) at (300-316 nm) The ^{1}H-N.M.R. spectra of compounds 1(b, e, g) were in agreement with the suggested structures. The H-2 in these compounds appeared at δ (4.6-6.9) ppm (Ayoub *et al*., 1985). Other proton bands are represented in Table (1).

Reactions of 4-chromanone derivatives 1(a-g) with thiosemicarbazide gave thiosemicarbazones 2(a-g). The IR spectra showed absorption band of C=N bond stretching at (1626-1639 cm^{-1}) specific for thiosemicarbazons (Pawar *et al*., 2009), and broad bands at (3236-3338 cm^{-1}) corresponding to the N-H bond stretching. The absence of absorption band carbonyl group frequency give a good indication about the formation of these compounds, Table (2). The UV spectra for products 2(a-g) showed λ_{max} at (318-326 nm) due to the presence of the conjugation system that caused a bathochromic shift. The^{1}H-NMR spectrum in DMSO showed the prensence of two proton bands, NH and NH_2 at 7.0-6.5 ppm and (8.2-8.6) ppm respectively (Pawar *et al*., 2009). Other proton chemical shifts are represented in table (2).

Acetylation of thiosemicarbazones 2(a-g) by acetic anhydride gave thiodiazolines derivatives 3(a-g) (scheme 1), (Venkateswarlu *et al*., 2005) and (Pawar *et al*., 2009). The main IR absorption bands of these products include stretching vibrations of two C=O and C=N bonds at (1695- 1720 cm^{-1}),(1572-1655 cm-1) and (1500-1617 cm^{-1}) respectively (Pawar *et al*., 2009), in addition to a broad absorption at (2933-3280 cm^{-1}) corresponding to N-H bond stretching. The absence of conjugation was confirmed by decreasing the absorption wave lengths in UV spectra of these compounds to (270-290 nm) i.e hypsochromic shift. The^{1}H- NMR spectra of compounds 3(b, e) showed the presence of CH_3 protons of the acetyl groups at 1.3 and 2.15 ppm for H_6 protons and 3.3 and 2.6 ppm for H_7 protons, other proton bands appeared at 12.3 ppm belong to NH proton (Pawar *et al*., 2009). Compound 3g shows chemical shifts at 2.3 – 2 ppm equivalent to nine protons belonging to the protons of the three methyl groups(H_6,H_7 and H_6). It also shows another chemical shifts at 3.15 ppm equivalent to three protons belonging to the protons of fourth CH_3 group(H_7). The chemical shift of the NH proton appeared at 7.3 ppm (Pandeya *et al*., 2009). The other proton chemical shifts are represented in Table (3).

In order to estimate the effect of converting the semicarbazone derivatives 2(a-g) to the thiadiazoline derivatives 3(a-g), we employ quantum chemical calculations to calculate the heat of formation of these compounds as shown in Table (4).

From the results, we can see that there is a large decrease in the heat of formation values of compounds 3(a-g), which mean that these compounds are more stable (less active) compared with the intermediate 2(a-g). On the other hand, the values of total steric energy (shown in Table 4) were increased when compound 2(a-g) converted to compounds 3(a-g) due to the formation of more bulky thiadiazoline molecules compared to the thiosemicarbazone molecules.

Table 4: The calculated heat of formation and steric energy values for compounds 2(a-g) and 3(a-g)

Compd. NO.	Heat of formation kcal/mole	Steric energy kcal /mole
2a	97.1714	4.9520
2b	71.8405	4.8148
2c	90.7184	0.0654
2d	88.900	-0.5439
2e	74.6117	-04485
2f	64.4567	-3.7653
2g	63.6407	-0.7056
3a	-11.0294	10.0020
3b	12.9206	9.3124
3c	5.4776	17.0567
3d	4.7641	16.4330
3e	-10.2778	16.8841
3f	-17.4988	14.4327
3g	-17.8751	16.5216

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