



Synthesis of some new Pyrazoline Carbothioamides and Pyrimidinethiols Derivatives from Bis- α , β -Unsaturated Carbonyl Compounds

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ABSTRACT

In our research, new bis- α , β -unsaturated carbonyl compounds (Z2-Z4) were prepared via Claisen-Schmidt reaction, by the condensation of 2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridine (Z1) with different appropriate benzaldehyde, like (benzaldehyde, m-nitro benzaldehyde and o-chloro benzaldehyde) using 10% aqueous sodium hydroxide as a base.

A simple and efficient method has been applied for the synthesis 2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridine (Z1) by multi components Rudolf-Hantzsch condensation reaction which included heating the starting materials (paraformaldehyde, acetylacetone and ammonium acetate) at 80°C degrees centigrade in aqueous medium. Bis- α , β -unsaturated carbonyl compounds (Z2-Z4) can be considered as useful intermediates leading to the formation of several heterocyclic compounds such as pyrazoline carbothioamide (Z5-Z7) and pyrimidinethiole (Z8-Z10). The titled compounds (Z5-Z7) and (Z8-Z10) were prepared by interacting with thiosemicarbazide in neutral medium, and thiourea in basic medium respectively. These mentioned compounds (Z1-Z10) were characterized by Ferrier Translate-Infrared spectrum (FT-IR) and Ultraviolet spectrum (UV), in addition to some physical properties. Also, all these reactions followed by thin layer chromatography (TLC) technique and calculate the retardation factor (R_f) values.

Keywords: bis- α , β -unsaturated carbonyl compounds, pyrimidinethiole, pyrazol carbothioamide

INTRODUCTION

The 1,4-dihydropyridine derivatives as well as bis- α,β -unsaturated carbonyl compounds are not only useful synthetic intermediates (Hassanien, 2004; Sun *et al.*, 2012; Indumathi *et al.*, 2015), but also exhibit diverse pharmacological activities, such as anti-inflammatory (Abdel-Aziz *et al.*, 2011), (Indumathi *et al.*, 2015), and anti-tumor (Husain *et al.*, 2013), (Jillepalli *et al.*, 2014).

The α,β -unsaturated carbonyl compounds bear very good synthon so that variety of novel heterocycles (e.g., pyrazoline and pyrimidine) (Amira, 2008) with good pharmaceutical activity have synthesized (Munera *et al.*, 2019). Usual synthesis of pyrazoles involves, (i): 1,3-dipolar cycloaddition reactions of nitrile imines to alkenes and alkynes (Prabhashankar *et al.*, 2013) (ii): Cyclocondensation of β -thioalkyl- α,β -unsaturated ketones with hydrazines produced pyrazoles with high regioselectivity (Jin *et al.*, 2011). Earlier an efficient synthesis of substituted pyrazole was reported by an acid catalyzed reaction of α,β -unsaturated ketones with semicarbazide hydrochloride in good yield (Chandrashekar *et al.*, 2016).

Synthesis of pyrimidine derivatives obtained by reaction of α,β -unsaturated carbonyl compounds with different nucleophilic reagents namely, urea, thiourea and guanidine in basic medium under microwave assist or refluxing conditions (Amin *et al.*, 2011; Chintan *et al.*, 2012; Abdel Megid *et al.*, 2013; Christian *et al.*, 2014).

Furthermore, five and six membered rings contain two nitrogen atoms (pyrazoline and pyrimidine) derivatives were found to be extremely significant pharmacophore in many therapeutic agents (Thanushree *et al.*, 2012; Abd El-Sattar *et al.*, 2018).

As mentioned above, we decided to prepare pyrazoline carbothioamide and thiopyrimidine heterocyclic compounds using bis- α,β -unsaturated carbonyl compounds derivatives contain 1,4-dihydropyridine moiety as synthon, in hope to improve the biological activity of the mentioned compounds.

EXPEREMENTAL

Melting points were determined on an electro thermal Stuart melting point SM P30 and were uncorrected. Infrared absorption spectra were recorded on SHIMADZU FTIR-8400S spectrophotometer from college of Science, University of Tikrit. Ultra-Violet spectra obtained via Spectro UV-Vis Auto, UV-2602, from College of Science, University of Mosul.

Synthesis of 2,6-dimethyl- 3,5-diacetyl-1,4-dihydropyridine (Z1) (Abdel-Mohsen *et al.*, 2012):

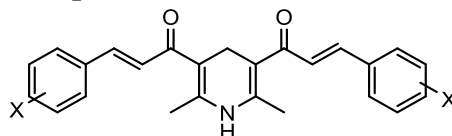
A mixture of paraformaldehyde (4.8gm, 0.16mol), acetylacetone (32gm, 0.32mol), ammonium acetate (18.5gm, 0.24mol) and 25ml water, were freight in dried conical-flask 100ml with a magnetic stirrer bar. The conical flask was closed with calcium chloride tube and the reaction mixture was stirred at 80 ° C for 15min. After finishing the reaction time, unrefined product was isolated upon addition of ice-cold water accompanied with scratching. The precipitate filtered, washed with cold water and recrystallized from methanol to yield 2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridine (Z1) as yellow powder (25.5gm, 41%), mp. (215-216⁰C) published (213-215) (Abdel-Mohsen *et al.*, 2012), $R_f = 0.282$ (petroleum ether-ethyl acetate 1:2).

Synthesis of 1,1'-(2,6-dimethyl-1,4dihydropyridine-3,5-diyl)bis(3-substituted phenyl))prop-2-ene-1-one) (Z2-Z4)(Ghoneim *et al.*, 2020; Yang *et al.*, 2020).

From compound (Z1), dissolve (3gm, 0.015mol) and a proper aldehyde (0.03mol) in 20-30ml methanol, after making sure of solubility, added 5ml of 10% NaOH drop wise with magnetic stirring (color change from yellow to orange), then, reaction was complete in basic medium, either with refluxing for 3-6 hrs. to prepare compound (Z2 and Z4) (method A), or stirring at room temperature for 24 hrs. to prepare compound Z3 (method B), the reaction was followed by TLC technique using ethyl acetate-hexane (40:60). The mixture was poured into ice water, the formed precipitate washed with water, dried and crystallized with methanol to afford amorphous solid of

compounds (Z2-Z4). (Table 1) and Scheme (1) illustrate some physical properties and synthesis of (Z2-Z4) respectively, while the suggest mechanism illustrated in Scheme (2) (Ghoneim *et al.*, 2020).

Table 1: Physical properties of compounds (Z2-Z4)

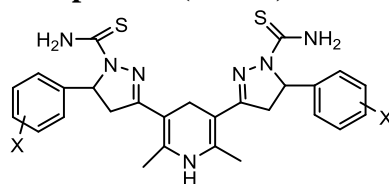


Comp. No.	X	M.P. °C	Yield %	Color	R _f values
Z2	H	150-153	72	yellow	0.235
Z3	Cl	134- 137	80	orange	0.200
Z4	NO ₂	>300	83	brown	

Synthesis of 3,3'-(2,6-dimethyl-1,4-dihydropyridine-3,5-diyl) bis (5-substituted phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide) (Z5-Z7), (Abd El-Karim *et al.*, 2014):

About (0.001mol) of (Z2-Z4) and (0.18gm, 0.002mol) of thiosemicarbazide were dissolved in (15-20) ml DMF. The mixture was refluxed for 8-11 hrs. (the reaction was followed by TLC technique in ethylacetate: n-hexane 40:60). The mixture was allowed to cool, poured into ice water and leaved in fridge overnight. The resulting solid was filtered, washed with water, dried, crystalized with methanol to gives powder compounds(Z5-Z7) (Table 2), Scheme (1) illustrate some physical properties and synthesis of (Z5-Z7). The suggest mechanism illustrated in scheme (3) (Aboelnaga *et al.*, 2020).

Table 2: Physical properties of compounds (Z5-Z7)



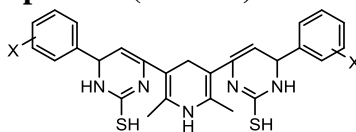
Comp. No.	X	M.P. °C	Time hr.	Yield %	Color	R _f values
Z5	H	161-164	10	76	Yellow	0.210
Z6	Cl	158-160	11	68	Pale Yellow	0.235
Z7	NO ₂	>300	8	52	brown	0.320

Synthesis of 4,4'-(2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)bis(6-substituted phenyl-1,6-dihydropyrimidine-2-thiole)(Z8-Z10),(Abd El-Karim *et al.*, 2014):

To a solution of (Z2-Z4) (0.001mol) and thiourea (0.15gm, 0.002mol) in (15-20) ml DMF, NaOH (10%, 0.5 ml) was added. The reaction was followed by TLC technique using ethylacetate-hexan (40:60), so, the reaction mixture was refluxed for 11hrs., allowed to cool, and the formed precipitate was filtered off, washed with water, dried and finally recrystallized from methanol to

afford compounds (Z8-Z10), (Table 3), Scheme (1) illustrate some physical properties and synthesis of (Z8-Z10). The suggest mechanism illustrated in Scheme (4).

Table 3: Physical properties of compounds (Z8-Z10)



Comp.No.	X	M.P. °C	Yield %	Color	R _f values
Z8	H	262-265	97	white	0.349
Z9	Cl	260 -263	64	white	0.385
Z10*	NO ₂	>300	56	brown	0.315

*Reaction time 15hrs

RESULT AND DISCUSSION

At the beginning, the reaction of formaldehyde, ethyl acetoacetate and ammonium acetate were chosen as a starting material to prepare 1,4-DHP(Z1) via Hantzsch synthesis. IR and UV data gave useful information about the structures of Z1. UV spectra gives λ_{\max} 275nm. IR bands cm^{-1} , 3317 NH, 3051 $\text{CH}_{\text{arom.}}$, 2993,2845 $\text{CH}_{\text{aliph.}}$, 1678 C=O, 1631C=C_{ring}, 1577 C-C_{aliph.} and 1325 C-N, Fig. (1) clarify the IR spectra of Z1.

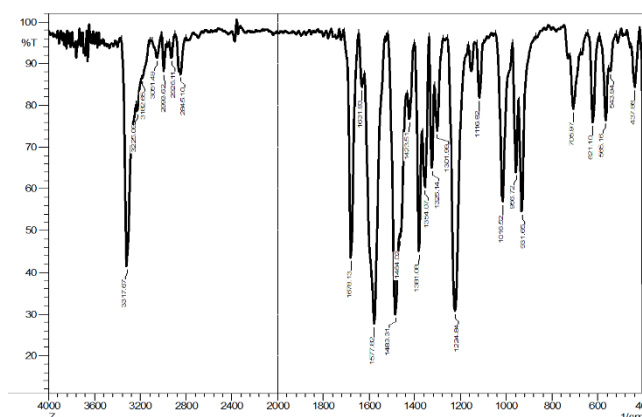


Fig. 1: IR spectra of compound Z1

The synthesis of the starting materials (Z2-Z4) was accomplished according to the Claisen-Schmidt reaction of Z1 with appropriate aromatic aldehydes in presence of base. The characterization compounds (Z2-Z4) based on some physical properties (Table 1) and some spectral data which were given good agreements with the suggested structures. The IR spectral for (Z2-Z4) showed the most useful peaks at 1683cm^{-1} and $(1585-1591)\text{cm}^{-1}$ for C=O and C=C respectively. Other absorption bands were represented in (Table 4), Fig. (2) clarify the IR spectra of Z4. The UV spectral data for (Z2-Z4) showed a red shift in λ_{\max} value (280-306)nm, indicating that these products are more conjugated than starting material Z1(275nm) (Mounera, 2005).

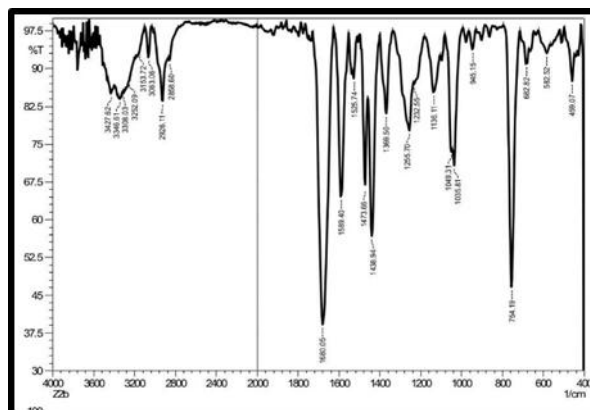


Fig. 2: IR spectra of compound Z4

Bis-dihydro pyrazole carbothioamide (Z5-Z7) were obtained by cyclization of corresponding bis-chalcones (Z2-Z4) in neutral media. Their structures were established by some physical properties Table (2) and IR and UV spectra. The IR of compounds (Z5-Z7) showed stretching vibration of NH & NH₂ groups at (3153-3427) cm⁻¹, C=N bond at (1662-1680) cm⁻¹, C=C bond at (1585-1589) cm⁻¹. Other absorption bands were represented in (Table 5), Fig. (3) clarify the IR spectra of Z6. The UV spectral data for the products (Z5-Z7) showed a blue shift in λ_{max} values (270-280) nm, indicating that these products are less conjugated than starting materials (Z2-Z4) and that the none group was used in the reaction.

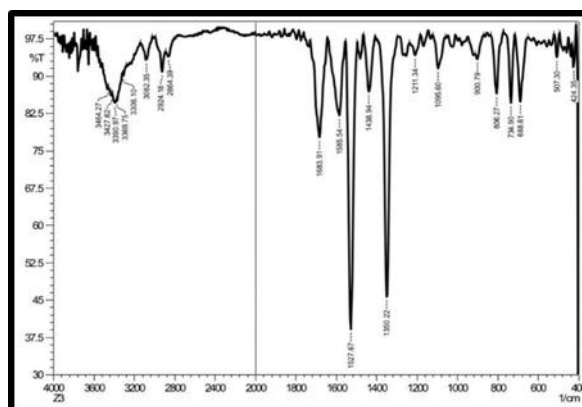


Fig. 3: IR spectra of compound Z6

New pyrimidine thiol derivatives (Z8-Z10) are obtained by the reaction of (Z2-Z4) with thiourea in 10%NaOH. The structures of products confirmed IR and UV spectra. The IR of compounds(Z8-Z10) show the most important absorption bands at: (1602-1618) cm⁻¹ for C=C and (2715-2717) cm⁻¹ for SH (Abd El-Sattar *et al.*, 2018). The final band gives extra support for the presence of the final products as thiol rather than thion form, other absorption bands were represented in (Table 6), Fig. (4) clarify the IR spectra of Z9. The UV spectral data for the products (Z8-Z10) showed a blue shift in λ_{max} values (242-287)nm, indicating that these products are less conjugated than starting materials (Z2-Z4) (Mounera, 2005)¹ and that the none group was used in the reaction.

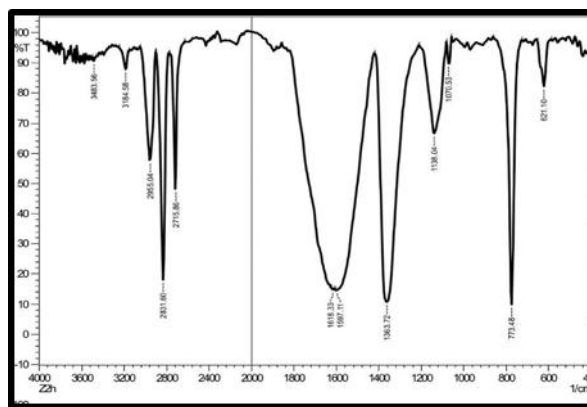
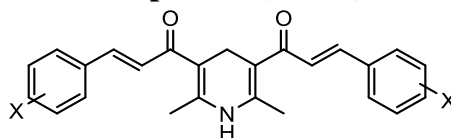


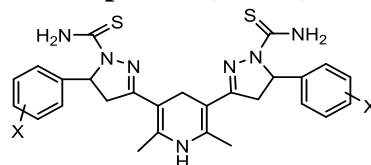
Fig. 4: IR spectra of compound Z9

Table 4: IR and UV spectral data of compounds (Z2-Z4)

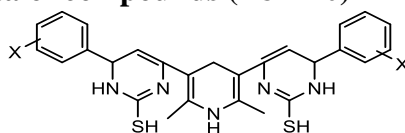


Comp. No.	X	FT-IR(KBr), cm ⁻¹							UV, DMF λ_{\max}
		NH	CH _{arom.}	CH _{aliph.}	C=O	C=C	CC _{arom.}	Others	
Z2	H	3406	3061, 3028	2926, 2858	1683	1585	1535		280
Z3	Cl	3394	3063	2928, 2854	1683	1591	1527	754 C-Cl	306
Z4	NO ₂	3369	3082	2924, 2846	1683	1585	1527	1438 _{asy} m-NO ₂ 1350 _{sym} NO ₂	286

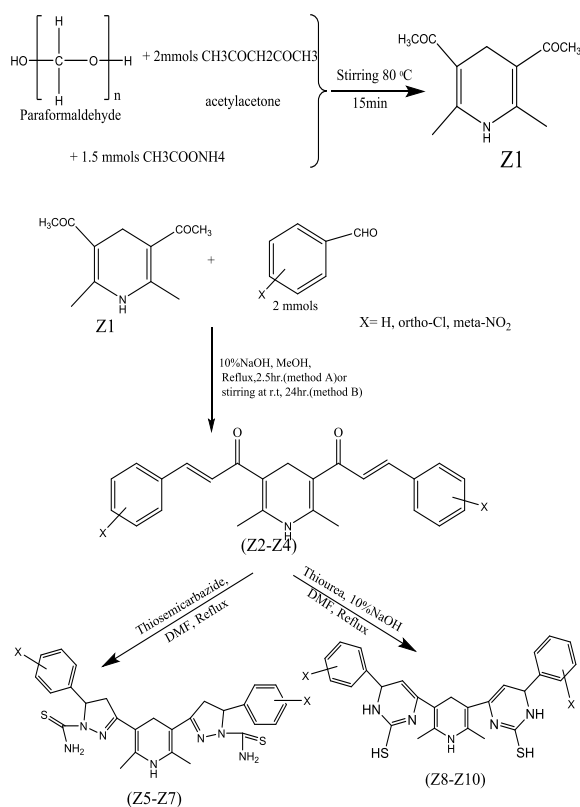
Table 5: IR and UV spectral data of compounds(Z5-Z7)



Comp. No.	X	FT-IR(KBr), cm ⁻¹							UV, DMF λ_{\max}
		NH&NH ₂	CH _{arom.}	CH _{aliph.}	C=N	C=C	C=S	Others	
Z5	H	3427-3182	3061, 3026	2926, 2854	1680	1585	1369		271
Z6	Cl	3427-3153	3063,	2926, 2858	1680	1589	1369	754 C-Cl	281
Z7	NO ₂	3348-3230	3074	2926, 2862	1662	1585	1370	1527asym.NO ₂ 1348sym.NO ₂	270

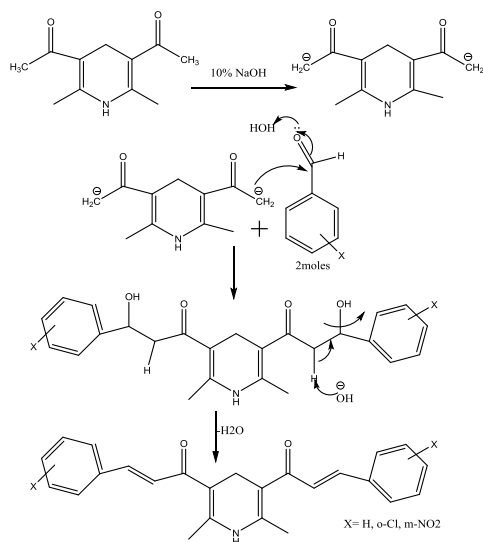
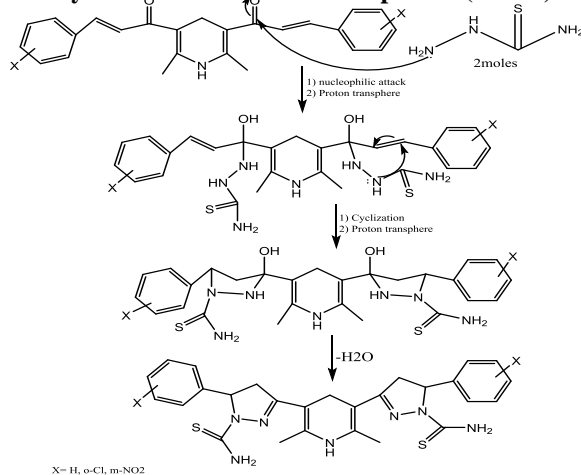
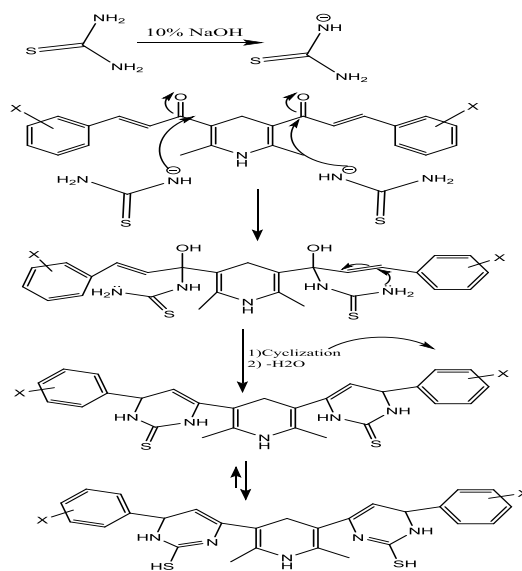
Table 6: IR and UV spectral data of compounds (Z8-Z10)

Comp. No.	X	FT-IR(KBr), cm-1								UV, DMF λ_{max}
		NH	CH _{ar} om	CH _{aliph}	C=N	C=C	CC _{arom}	SH	Others	
Z8	H	3186	3056	2955, 2831	1681	1606	1550, 1465	2715		242
Z9	Cl	3338	3064	2955. 2831	1663	1618	1597	2715	773 C-Cl	287
Z10	NO ₂	3429	3086	2926, 2831	1668	1602	1527	2717	1438 _{asy} m NO ₂ 1340 _{sym} NO ₂	256



Scheme 1

Scheme 1: Synthesis of compounds (Z1-Z10)

**Scheme 2: Synthesis mechanism of compounds (Z2-Z4)****Scheme 3: Synthesis mechanism of compounds (Z5-Z7)****Scheme 4: Synthesis mechanism of compounds (Z8-Z10)**

CONCLUSION

Twin α , β -unsaturated carbonyl compounds contain 1,4-dihydro pyridine moiety were synthesized in our work in good yields. These compounds are very good intermediates for synthesis of some new heterocyclic derivatives. Physical and chemical properties of these compounds were established.

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تشديد بعض مشتقات البايرازولين ثايوكارباميد والبرمدين ثايول الجديدة من مركبات الفأ، بيتا-كاربونيل غير المشبعة الثنائية

الملخص

يتضمن البحث تحضير سلسلة من مركبات ثنائية الكربونيل الفأ، بيتا-غير المشبعة (Z2-Z4) بتفاعل كلينز-شميدت بتكاتف المادة الأولية 5,3-ثنائي اسيتيل 4,1-ثنائي هيدروبريدين (Z1) مع مكافئين من الالديهيدات الأروماتية المختلفة (بنزالديهيد، اور ثو-كلورو بنزالديهيد و ميتا-نترو بنزالديهيد) باستعمال (10%) هيدروكسيد الصوديوم المائي كقاعدة. المركب (Z1) ابتداء حضر بتفاعل رودلف. هانتس متعدد المكونات من خلال تسخين المواد الأولية (بارا فورمالديهيد، اسيتيل اسيتون و خلات الأمونيوم) عند 80 درجة مئوية وفي وسط مائي.

مركبات ثنائية الكربونيل الفأ، بيتا-غير المشبعة (Z2-Z4) تعتبر مركبات وسطية مهمة لتحضير عدد من المركبات الحلقية غير المتجانسة حيث تم تحويلها الى بايرازولين كاربو ثايواميد (Z5-Z7) و برميدين ثايول (Z8-Z10) من خلال تفاعلها مع الثايوسيميكاربازايد في محيط متعادل والثايويوريا في محيط قاعدي على التوالي. تم تشخيص المركبات المحضرة بالاعتماد على الطرق الطيفية طيف الأشعة تحت الحمراء وطيف الأشعة فوق البنفسجية (FT- IR, UV) وبعض الخواص الفيزيائية. من ناحية اخرى تم متابعة تفاعلات المركبات المشار إليها أعلاه بتقنية كروماتوغرافيا الطبقة الرقيقة (TLC) وحساب قيم عامل الاستبقاء (R_f) .

الكلمات الدالة: مركبات الكربونيل-فأ، بيتا-غير المشبعة الثنائية، برمدين ثايول، بايرازول كاربو ثايواميد.