The Eurasia Proceedings of Science, Technology, Engineering & Mathematics (EPSTEM)
ISSN: 2602-3199

The Eurasia Proceedings of Science, Technology, Engineering & Mathematics (EPSTEM), 2019

Volume 7, Pages 141-146

IConTES 2019: International Conference on Technology, Engineering and Science

Synthesis a Series of 2-Pyrazolideno-1,3,4-Thiadiazoline Compounds Derived from Thiocarbohydrazide

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Abstract: A series of some 2-pyrazolideno-1,3,4-Thiadiazoline Compounds [10-15] was prepared under conventional and thermal conditions using an active starting material thiocarbohydrazide [1] as a good precursor. Thiocarbohydrazide [1] was firstly prepared through direct addition reaction between (80%) hydrazine hydrate and carbon disulfide in aqueous media and reflux conditions, then it will be converted to it's hydrazone derivative via condensation reaction with benzophenone in acidic media at room temperature to afford compounds 1-(diphenyl methylene) thiocarbohydrazone [2], and the later one was underwent catalytic intracyclization reaction to give 2-hydrazinyl-5,5-diphenyl-2,5-dihydro-1,3,4-thiadiazoline compound [3] in presence of ferric chloride as a selective catalyst . Finally compound [3] reacted with freshly prepared chalcones (using diffrent substituted benzaldehyde and two types of ketones represented by acetophenone and m-methoxy acetophenono) [4-9] via traditional method to yield the titled compound represented by 1-(5,5-diphenyl-2,5-dihydro-1,3,4-thiadiazol-2yl)-3,5-diaryl-4,5-dihydro pyrazolidine compounds [10-15]. All prepared compounds were illustrated by the available physical and spectral data represented by U.V, FT-IR, H^1-NMR & C^{13}-NMR.

Keywords: Thiocarbohydrazide, Pyrazolidines, 1,3,4-thiadiazolines, Hydrazones

Introduction

Since many decades, active heterocyclic compounds are one of the main topic of interest for the medical chemists as it displays a number of pharmacological activities [(1)]. The most important types are nitrogen and sulfur containing five membered ring which occupied enormous significance in the medical chemistry field. First of all, 1,3,4-thiadiazoles are heterocyclic compounds which perform an important role as anticancer[(2)], while in agricultural field they play an important role as pesticide against rot, mice, and anti insects[(3)]. Additional, these compounds used as anti corrosion of metals in industrial field[(4)].The second important type are pyrazoles a five membered ring with two nitrogen atoms which accepted a great deals of attention especially in medical field[(5)] as anti breast cancer and anti liver cancer[(6)]. wherease in pharmaceutical field they show a wonderful activity as anti inflammatory and anti microbial[(7,8)]. To synthesis these active types of heterocyclic compounds , it must be starting from active materials with wide biological applications, here in this presentation the active starting material is thiocarbohydrazide [1] which have supreme role in heterocyclic synthesis [(9)], so it used to prepared the titled compounds [10-15] through traditional thermal methods.

Method

Melting points (M.P.) were measured on Stuart SMP10.MeltingPoint apparatus and are uncorrected. Proton-Nuclear Magnetic Resonance (^{13}C & ^{1}H-NMR) spectra were recorded using, Bruker DMX-500 NMR Spectrophotometer (300MHz); with TMS as internal standard, and DMSO-d_6 as solvents; Jorden, University of Al-Bayt. [(s) singlet; (d) doublet; (m) multiplet]. Infrared (FT-IR) spectra were recorded as (KBr) disc using a

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Thermo Mattson300 Infrared Spectrophotometer. Ultraviolet (UV) spectra were performed on ShimadzuUV-160Ultraviolet–Vissible Spectrophotometer using methanol as a solvent.

Synthesis of Thiocarbohydrazide [1] [(10)]:

(0.22 mole,13 ml) of carbon disulphide was added drop wise to vigorously stirred solution (0.44 mole, 24 ml) of hydrazine hydrate (85%) in (15 ml) dis. water during (30 minutes). Then the temperature of the reaction was raised to (100-110°C) and the reaction mixture was refluxed for (2 hrs.), then cooled in ice bath to (0° C). The precipitated thiocarbohydrazide was filtered off, washed with ethanol followed by diethyl ether and then air dried. the product thus obtained was recrystallized from minimum amount of hot water. Yield (76%), M.p.(169-170°C). ^{1}H NMR ($CDCl_3$,δ ppm):(s, 3.34, 2H ,1H, NH_2 & NH); FT- IR(cm^{-1}): NH_2 (3306), NH (3274,3203), N-N (1489), C-N (1384) and C=S (1282); U.V DMSO $\lambda_{max\ (nm)}$ (355,272).

Synthesis of thiocarbohydrazone [2] [(11)]:

In round bottomed flask (100ml), benzophenone (0.02 mole,2.4 gm)was dissolved in abs. ethanol (100ml) and a solution of thiocarbohydrazide (0.02mole, 2.21 gm) in HCl (1N, 20ml) was adding drop wise with stirring at room temp. until the appearance of yallow precipitant which filtrate off , washed and recrystallized with abs. ethanol then dried to afford the yellowish hudrazone [2]. M.P. (199-200 °C) ; yield 94% ; ^{1}H NMR ($CDCl_3$,δ ppm):(s, 3.35, 1H,2H, NH-NH_2), (s, 8.5, 1H, =N-NH) and (m, 7.2-7.7, 10H, aromatic); FT- IR(cm^{-1}):3328, 3247, 3269, 1342, 1484 and 1231; U.V DMSO $\lambda_{max\ (nm)}$ (308 &313).

Synthesis of 2,2-diphenyl-5-hydrazino-1,3,4-thiadiazole [3] [(12)]:

The hydrazone[2] (0.0017, 4.59gm) and $FeCl_3$ (0.0005 mole, 0.134 gm) were desolved in abs. ethanol (25 ml), then the reaction mixture refluxed for (1.5 hrs) in water bath then the reaction solvent was concentrated to the half volume and poured onto ice-water. The resulting product was filtered off and recrystallized from abs. ethanol to afford compound [3] with M.P.(120-121 °C); Yield 45%; ^{1}H NMR ($CDCl_3$,δ ppm): (s,3.5 , 1H,2H, NH-NH_2), (s, 7.01,1H,NH), (m, 7.1-7.5, 10H, aromatic); FT- IR(cm^{-1}): 3351, 3328,3261,1539,768; U.V DMSO $\lambda_{max\ (nm)}$ (318 &331).

Synthesis of chalcons [4-9] [(13)]:

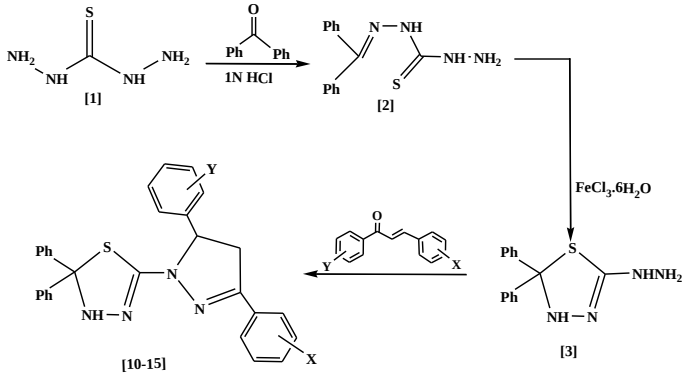
All chalcons were prepared according to the literature method in reference (13) through Claisen-Schmidt condensation and the (Table 1) show all it's physical and spectral data.

Synthesis of 1-(5,5-diphenyl-2,5-dihydro-1,3,4-thiadiazol-2-yl)-3,5-diaryl-4,5-dihydro pyrazoline [10-15] [(14)]:

A mixture of freshly prepared chalcons (4-9) (0.005 mole) and compound (3) (0.005 mole, 1.34 gm) were refluxed for (9- 10 hrs.). After cooling, the reaction mixture poured into ice-water with stirring. The precipitated product was filtered off and washed with cold water then recrystallized from ethanol to affored compounds (10-15). All physical and spectral data were illustrated in Table (2).

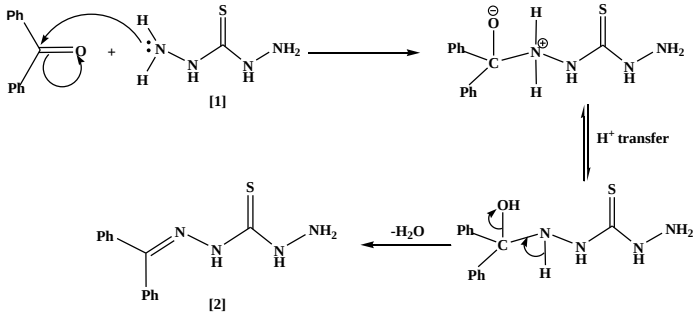
Results and Discussion

Pyrimidines [10-15] has been achieved via traditional methods starting from an active material represented by thiocarbohydrazide [1]. The general synthetic pathway illustrated in (Scheme 1) below:



Scheme (1)
The synthetic pathway of pyrimidines [10-15]

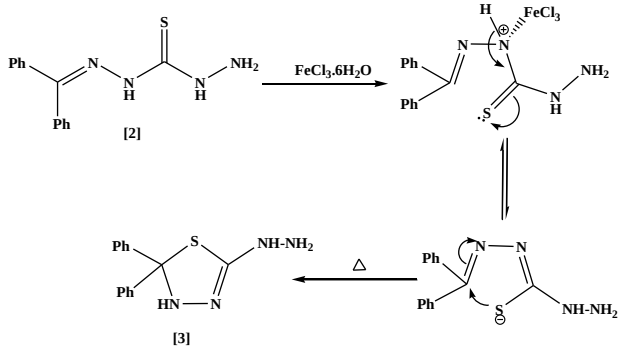
Initially, Thiocarbohydrazide [1] was prepared in aqueous media through direct neucleophilic addition reaction with high percentage yield. Compound [1] characterized by spectral methods represented by ^{1}H-NMR, FT-IR and U.V., as shown in experimental section. this compound was used as a good and an active synthon to prepared the hydrazone compound [2] via condensation reaction with benzophenone. This reaction was activated by few drops of hydrochloric acid (1N) , (Scheme 2).



Scheme (2)

The formation of hydrazone [2] was proved by spectral methods, so, in ^{1}H-NMR spectra it shown shifting (δ, ppm) (s, 3.35, 1H,2H, NH-NH_2), (s, 8.5, 1H, =N-NH) and (m, 7.2-7.7, 10H, aromatic).

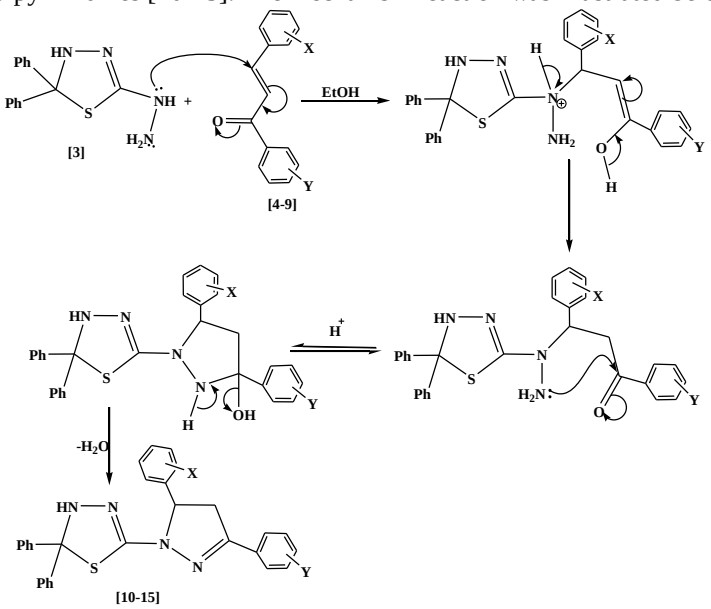
In FT-IR spectra it shown the following stretching absorption bands (cm^{-1}) (3328,3247,3169, 1484, 1342 and 1231) which refer to the functional groups (NH_2, NH, NH=NC, C=N, C=S, and N=N) respectively. While in U.V. spectra it gave two absorption bands at λ_{max} (308 &313 nm) due to the n→π* and π→π* and also due to the increasing of conjugation. The hydrazone [2] underwent intracyclization reaction in presence of catalytic amounts of ferric chloride ($FeCl_3$) to afford 2-hydrazino-1,3,4-thiadiazole [3]. The reaction proceeded easily under thermal conditions as shown in the following (Scheme 3) mechanism[15].



Scheme (3)

Compound [3] was characterized via ^{1}H-NMR spectra which shown shifting (δ, ppm) at (s, 3.35, 2H,1H,NH_2-NH), (s,7.01, 1H, cycl. NH) and (m, 7.1-7.5, 10H, aromatic). FT-IR spectra was used as further identification to proving the right structure, so, it shown the following absorption peaks (cm^{-1}) (3351, 3328, 3261,1531 and 768) refer to the following functional groups respectively (NH_2, cycl. NH, acycl. NH, cycl.C=N and C-S). whereas,

in U.V. spectra it gave absorption bands at λ_{max} (nm) (318 & 331) due to the n→π* and π→π* and also due to the cyclic system. Finally , compound [3] was reacted with different freshly prepared chalcons [4-9], (Table 1), to afford the substituted pyrimidines [10-15]. The mechanism reaction was illustrated below (Scheme 4).



Scheme (4)

The structure of compounds [10-15] were also proved by using the spectral methods and the (Table 2) shown their physical and spectral data. The must important proof here is the absence of (NH_2) absorption band at (3351 cm^{-1}) and the appearance of stretching absorption bands at (1624-1659 cm^{-1}) due to the (C=N) functional group in formation pyrazole ring. Moreover, in U.V. spectra they show absorption bands at λ_{max} (nm) (323 - 386) & (307-375) due to the increasing the ring system additionally to the electronic transition represented by n→π* and π→π* respectively. Also, the ^{1}H-NMR spectrum for compound [10] revealed signals for substituted pyrazole at (δ, ppm): (d, 2.5,2H, CH_2) , (t,3.9, 1H, CH), (m, 7.85-7.98, 5H, phenyl) and (m, 8.0-8.2, 4H, p-bromo phenyl). While, the substituent 1,3,4-thiadiazole ring showed the absorption bands at (s, 7.0, 1H, NH) and (m,7.55-7.75, 10H, aromatic). Actually, ^{13}C-NMR was also used to prove the structure of compound [11], so, it gave signals at (δ, ppm): (128.1, phenyl), (123.8, p-bromo phenyl) and (129.3, m-methoxy phenyl) , so, this absorption values were supported the formed structure of compound [11].

Table 1. The physical and spectral data for chalcons [4-9]

Comp. No.	X	Y	M.p. °C	Yield %	FT-IR (KBr) , *υ (cm^{-1})*			*U.V DMf* $\lambda_{max(nm}$
					C=O	C=C	Others	
4	H	p-Br	118-119	92	1656	1607	C-Br 530	320
5	H	p-Cl	110-111	92	1656	1600	C-Cl 688	305
6	H	p-NO_3	163-164	49	1646	1602	NO_2 sym.1385 asym.1504	292
7	m-OMe	p-Br	155-156	96	1656	1593	C-Br 532 C-O-C sym. 1072 asym.1276	244
8	m-OMe	p-Cl	149-150	90	1655	1607	C-Cl 689 C-O-C sym. 1088 asym. 1277	259
9	m-OMe	p-NO_3	124-126	78	1684	1617	NO_2 sym. 1370 asym. 1575 C-O-C sym. 1073 asym.1279	332

Table 2. The physical and spectral data for compounds [10-15]

Comp. No.	X	Y	M.P.°C	Yield %	FT-IR (KBr) , υ (cm^{-1}) N-H cycl.	C=N cycl.	C□C arom.	Others	U.V DMf $\lambda_{max(nm)}$
10	p-Br	H	114-115	66	3328	1658	1583	C-Br 532 C-S 736	319,323
11	p-Br	m-OMe	124-125	69	3328	1659	1583	C-Br 530 C-S 716 C-O-C sym. 1033 asym. 1225	310,380
12	p-Cl	m-OMe	112-113	73	3282	1654	1587	C-Cl 668 C-S 703 C-O-C sym. 1032 asym. 1225	322,386
13	p-Cl	H	215-216	89	3328	1658	1585	C-Cl 669 C-S 707	307,329
14	p-NO_2	H	100-101	80	3327	1624	1584	C-S 703 NO_2 sym. 1345 asym. 1521	375,380
15	p-$N(CH_3)_2$	m-OMe	102-103	91	3209	1645	1576	C-N 1370 C-S 704 C-O-C sym. 1035 asym. 1229	341,391

Conclusion

From the foregoing survey, it seems that thiocarbohydrazide provide a useful and convenient strategy for synthesis of numerous fused heterocyclic compounds containing 1,3,4-thidiazole , so, aseries of some 2-pyrazolideno-1,3,4-Thiadiazoline Compounds was prepared under conventional thermal conditions using thiocarbohydrazide. Thiocarbohydrazide converted to its hydrazonederivatives , and the later underwent catalytic intracyclization reaction to give 2-hydrazinyl-5,5-diphenyl-2,5-dihydro-1,3,4-thiadiazoline compound which reacted with different freshly prepared chalcones to yield the titled compound represented by1-(5,5-diphenyl-2,5-dihydro-1,3,4-thiadiazol-2yl)-3,5-diaryl-4,5-dihydro pyrazolidine compounds.

Recommendations

Thiocarbohydrazid is prepared so easily from hydrazine and carbon disulfide and it is very active in organic synthesis. In this presentation we prepare only one line from thiocarbohydrazide, but we believed that this active unite building will be used to prepare many different active heterocyclics which will show high activity in many different fields

Acknowledgements

The work was supported by department of chemistry, college of science, university of mosul

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