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One-Pot Synthesis of New Pyranopyrazoles via Domino Multicomponent Reaction

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Abstract

An active heterocyclic unite building represented by compound 1,3,4-thiadiazole-2,5-dithiole (1) was prepared through the reaction of carbon disulfide and hydrazine hydrate. This unite building was reacted with hydrazine hydrate to afford the corresponding 2,5-dihydrazino -1,3,4-thiadiazole (2) which then undergoes one-pot catalytic-free multicomponent reaction with malononitrile, substituted aldehyde and ethyl acetoacetate to obtained 2,5-di (3-methyl-4-aryl-pyrano [2,3-c] pyrazole-5-amino-6-cyno-1-yl)-1,3,4-thiadiazole (3-9). All prepared compounds were elucidated by available methods represented by M.P, T.L.C, FT-IR and for some compounds ^{1}H.NMR.

Key words: multicomponent reaction, pyrano [2,3-c] pyrazole 1,3,4-thiadiazole, pyrazole, green chemistry.

1. Introduction

Many heterocyclic compounds are very useful and essential for human life , so, many recent reports have confirmed that heterocyclic compound could exhibited numerous biological activities such as anti cancer [1] have also been identified as anti HIV [2]. Pyrano [2,3-c] pyrazoles are an important class of fused heterocyclic compounds involving five and six membered ring , because of pyrazole ring in this compounds found to be associated with various biological activities such as antimicrobial [3] analgesic [4], anticancer [5, 6] inhibiters of human ChK1 kinase [7] [8], molluscicidal [9] biodegradable [10] and HIV [11] , anti infective [12] anti platate and antifungal [13, 14] , antioxidant [15] and also anti inflammatory [16],[17]. Furthermore, some of pyrano pyrazole compounds are commonly used in cosmetics and pigments industry [18, 19]. Recently , pyrano [2,3-c] pyrazole moiety were prepared via multicomponent reaction supported by using of green chemistry techniques represented by microwave irradiation [20] , ultrasonic assistance [21] , grinding [22] and also catalytic electro generation [12] . In view of the great application these compounds possess, a new series of pyrano [2,3-c] pyrazoles represented by compounds 2,5-di(3-methyl-4-aryl-pyrono [2,3-c] pyrazole -5-amino-6-cyno-1-yl)-1,3,4-thiadi azole (3-9) has been prepared in this presentation through one-pot catalytic–free multicompon -ent reaction using grinding technique in solid phase which reduced the reaction times and also gave pure products with high percentage yields and eco-friendly.

2. Experimental

Starting material and solvents were procured from Fluka, BDH and Sigma-Aldrich chemical companies and used without further purification . Melting points (M.P.) were measured on Electrothermal SMP30-Stuart melting point apparatus. ^{1}H-NMR spectra were recorded using Bruker Bio Spin GmbH Spectrophotometer (400 MHz by using TMS as internal standard and using DMSO-d6 as a solvent) in University of Gazi Othman Basha, Turkey, [(s) singlet, (d) doublet, (m) multiplet]. Infrared (FT-IR) spectra were recorded using FT-IR Spectrophotometer, Shimadzu 8400s (Japan). Ultraviolet (U.V) spectra were performed on (Jasco V-630 UV–Vis) Spectrophotometer using methanol as a solvent. The Thin-layer chromatography (TLC) was carried out on an eastman chromatogram sheet (20x20) cm, 13181 silica gel with the fluorescent

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indicator (No. 6060) using solvent system benzene: methanol in the ratio (80:20).

Synthesis of 2,5-dimercabto-1,3,4-thiadiazole(1) [23]:

A solution of carbon disulphide (0.020 mole/15ml) with pyridine (5ml)was added drop wise with stirring to the ethanolic solution of hydrazine hydrate (80%) (0.020mole/5ml) in (5ml) ethanol. The reaction mixture was then heated under reflux for (1hour) , cooled down and left overnight at lab. temp. then poured in crashed-ice water, acidity by hydrochloric acid to remove the excess of pyridine, The resulting product filtered off. followed by washing with water several time and recrystallized from ethanol to afford the compound(1) pale yellow powder with M.P (163-165ºC), Yield (60%).

Synthesis of 2,5-dihydrazino-1,3,4-thiadiazole(2) [23]:

An ethanolic solution of (0.018 mole of hydrazine hydrate (80%)with catalytic amount of tri ethylamine(3drops) was added drop wise with stirring to the ethanolic solution of (0.01mole/1.5gm)of compound (1),the reaction mixture was heated under reflux for (6hrs),cooling and poured in crashed-ice water followed by acidity with hydrochloric acid. The resulting precipitate was filtered off and washed thoroughly with water followed by recrystallization from ethanol to afford compound (2), yellowish powder with M.P(195-197ºC) , Yield (58%). FT-IR (KBr,υ cm^{-1}): NH_2 (3210); NH (3124); C=N (1480); C-N (1092), C-S (855).

Synthesis of 2,5-di (3-methyl-4-aryl-pyrono[2,3-c] pyrazole-5-amino-6-cyno-1-yl)-1,3,4-thiadiazole (3-9) [24]:

Malononitrile, ethyl acetoacetate and substituted benzaldehyde (0.002mole) was well grinded with compound (2) (0.001mle/0.146gm) then dissolved in methanol (30ml) followed by reflux for (3hrs).The reaction mixture was cooled and poured into crashed-ice (20ml).The formed solid crude was then filtered off ,washed thoroughly with water then dried and recrystallized from ethanol to afford the compounds (3-9).

2,5-di(3-methyl-4-phenyl-pyrono[2,3-c] pyrazole-5-amino-6-cyno-1-yl)-1,3,4-thiadiazole (3):

M.P (99-101°C), Yield 63%. UV λ_{max} (nm): 315 & 217. FT-IR (KBr) (υ cm^{-1}): 3310 (NH_2), 2926 & 2855 (CH_3), 2205 (CN), 1599 (C=C), 1541(C=N), 1375 &1100 (C-O-C), 760 (C=S). ^{1}H-NMR δ (ppm): $2CH_3$ (s,1.08,6H), $2NH_2$ (s,7.09,4H), 2Ar-H (m,7.09-7.41,10H) , 2H-pyran (s,7.96,2H).

2,5-di(3-methyl-4-(p-chloro phenyl)-pyrono[2,3-c]pyrazole-5-amino-6-cyno-1-yl)-1,3,4-thiadiazole (4):

M.P (129-131°C), Yield 54%. UV λ_{max} (nm): 314 & 226. FT-IR (KBr) (υ cm^{-1}): 3397 (NH_2), 2924 & 2853 (CH_3), 2207 (CN), 1636 (C=C), 1595 (C=N), 1371 &1091 (C-O-C), 761 (C=S), 712(C-Cl).

2,5-di(3-methyl-4-(p-methoxy phenyl)-pyrono[2,3-c]pyrazole-5-amino-6-cyno-1-yl)-1,3,4-thiadiazole (5):

M.P (142-143°C), Yield 71%. UV λ_{max} (nm): 342 & 231. FT-IR (KBr) (υ cm^{-1}): 3389 (NH_2), 2926 & 2843 (CH_3), 2222 (CN),1602 (C=C), 1572 (C=N), 1426 & 1184 (C-O-C acycl.), 1370 & 1172 (C-O-C), 833(C=S). ^{1}H-NMR δ (ppm): $2CH_3$ (s,3.83,6H), $2NH_2$ (S,8.41,4H), $2OCH_3$ (s,3.89,6H), 2H-Ar(AB system) (d-d,7.80-8.01,8H), 2H-pyrane (s,8.64,2H).

2,5-di(3-methyl-4-(p-N,N-dimethyl amino phenyl)-pyrono[2,3-c]pyrazole-5-amino-6-cyno-1-yl)-1,3,4-thiadiazole (6):

M.P (174-175°C), Yield 58%. UV λ_{max} (nm): 336 & 218. FT-IR (KBr) (υ cm^{-1}): 3373 (NH_2), 2922 & 2859 (CH_3), 2209 (CN), 1615 (C=C), 1568 (C=N), 1360 & 1197 (C-O-C), 833 (C=S). ^{1}H-NMR δ (ppm): $2CH_3$ (s,2.50,6H), $4CH_3$ (p-N,N-dimethyl) (s,3.12,12H), $2NH_2$ (s,6.85,2H), 2H-Ar (AB system) (d-d,6.88-7.86,8H), 2H-pyrane (s,8.06,2H).

2,5-di(3-methyl-4-(2,4-dichloro phenyl)-pyrono[2,3-c]pyrazole-5-amino-6-cyno-1-yl)-1,3,4-thiadiazole (7):

M.P (205-207°C), Yield 72%, T.L.C (R_f):0.733, UV λ_{max} (nm): 313&221. FT-IR (KBr) (υ cm^{-1}): 3372(NH_2),2926&2865 (CH_3), 2219(CN),1616 (C=C), 1586 (C=N), 1385&1101(C-O-C), 860(C=S), 822 (C-Cl).

2,5-di(3-methyl-4-(2,3-dimethoxy phenyl)-pyrono[2,3-c]pyrazole-5-amino-6-cyno-1-yl)-1,3,4-thiadiazole (8):

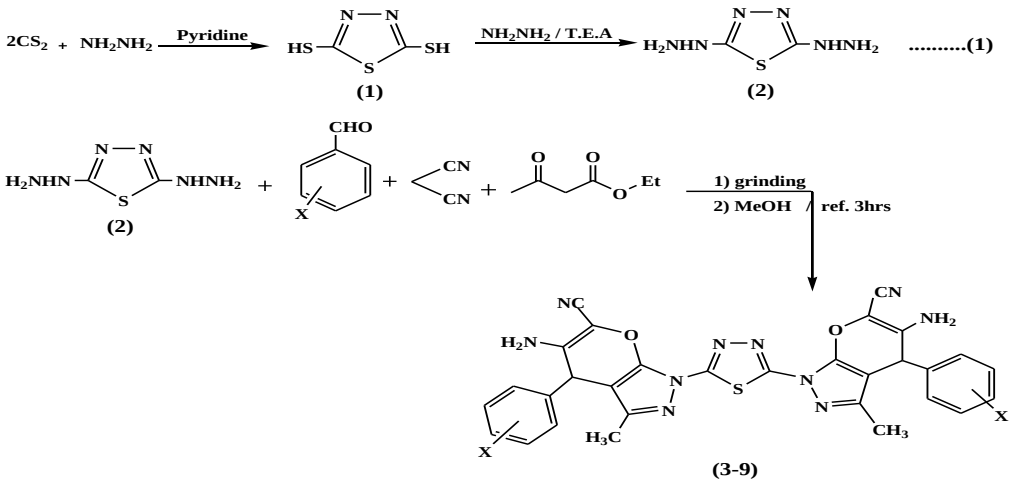
M.P (82-84°C), Yield 50%. UV λ_{max} (nm): 318 & 220. FT-IR (KBr) (υ cm^{-1}): 3399 (NH_2), 2938 & 2837 (CH_3), 2226 (CN),1634 (C=C), 1588 (C=N), 1425 & 1172(C-O-C acycl.), 1383 & 1150 (C-O-C), 789 (C=S).

2,5-di(3-methyl-4-(p-hydroxy phenyl)-pyrono[2,3-c]pyrazole-5-amino-6-cyno-1-yl)-1,3,4-thiadiazole (9):

M.P (73-75°C), Yield 67%. UV λ_{max} (nm): 329 & 227. FT-IR (KBr) (υ cm^{-1}): 3339 (OH), 3306 (NH_2), 2980 & 2932(CH_3), 2210 (CN), 1681 (C=C), 1606(C=N), 1381 &1167 (C-O-C), 835 (C=S).

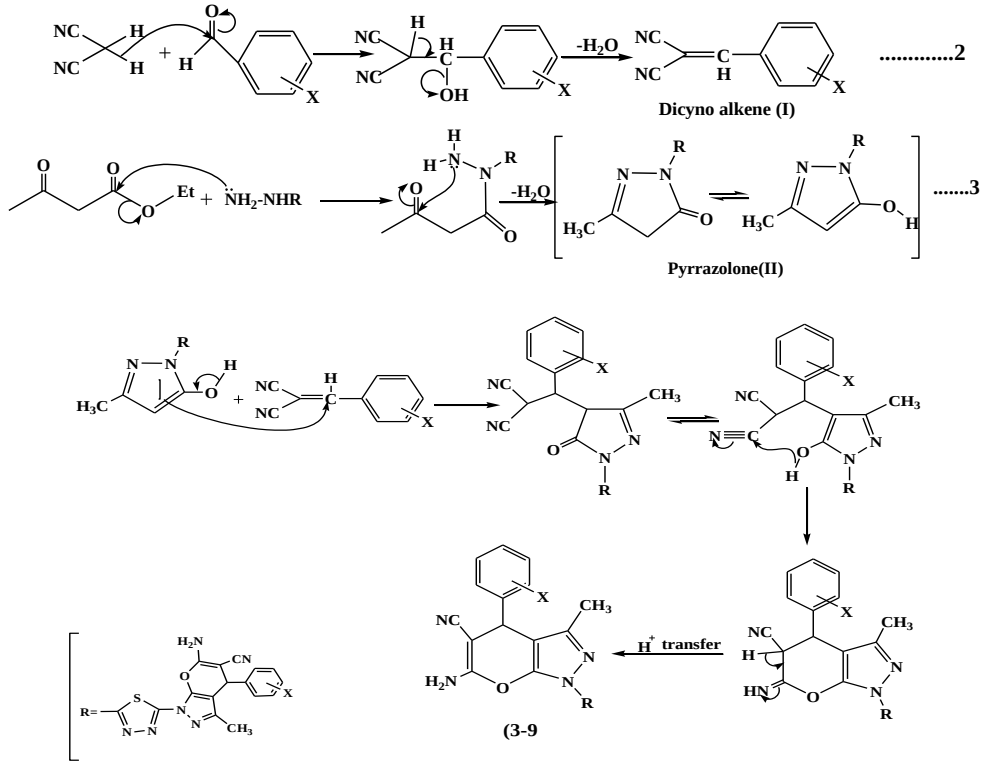
3. Results and Discussion

In this work pyrano [2,3-c] pyrazole moiety (3-9) were prepared according to the following synthetic path way:



Scheme (1): synthesis of compounds (1-9)

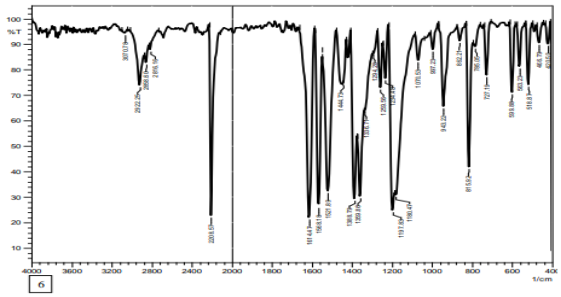
The reaction has occurred through knovenagel intermediate between aryl aldehyde and malononitrile to form di cyano alkene (I) in catalyst–free condition in protic solvent which then undergoes Michael addition with pyrrazolone (II) (synthezied from the condensation reaction between hydrazine moity and ethyl acetoacetate) then subsequently the intramolecular cyclization reaction was take place to obtained the di pyrano [2,3-c] pyrazoles in acceptant yield without using any type of catalyst Scheme (2). [25] [26] :

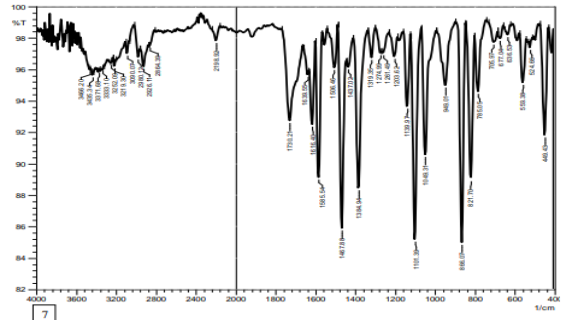


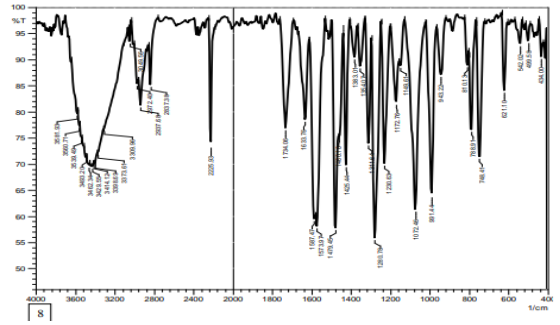
Scheme (2): the formation mechanism of compounds (3-9)

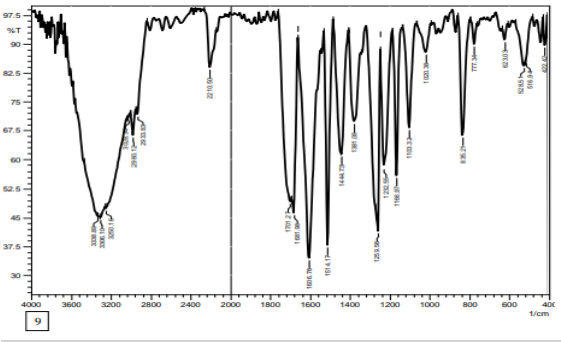
The resulting products were identified by spectral data, mixed melting point and thin layer chromatography (T.L.C). In FT-IR, these compounds show stretching vibration bands for NH_2 group at (3399-3306) cm^{-1} whereas the CH_3 functional group show an absorption bands in two modes asymmetric and symmetric at (2938-2924) cm^{-1} and (2933-2843) cm^{-1} respectively . These absorption bands came in agreement with the suggested structure in addition to the absorption bands for (C-O-C) in pyran ring which appeared at two mode too, asymmetric and symmetric which supported the formation structure.

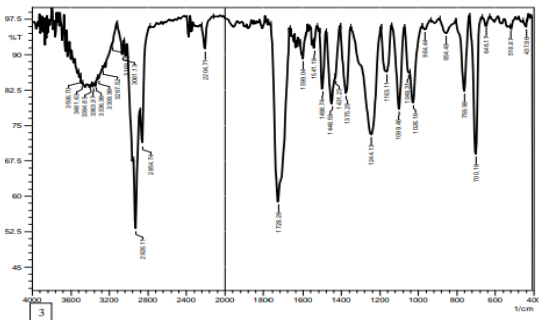
The U.V spectroscopy show absorption band at λ_{max} (nm) (314-342) and (218-231) due to the $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$. On the other hand, in ^{1}H-NMR spectroscopy for compounds (3,5 and 6) shown spectra that came in agreement with the suggested structure, so, they gave clear peaks for NH_2 group near the aromatic area due to the pyrano ring and the conjugation between the amino and cyano groups, and also compounds (5 and 6) gave the AB aromatic system in addition to the other absorption peaks that given in experimental part.

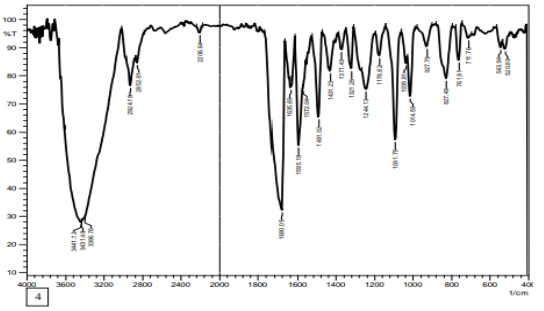


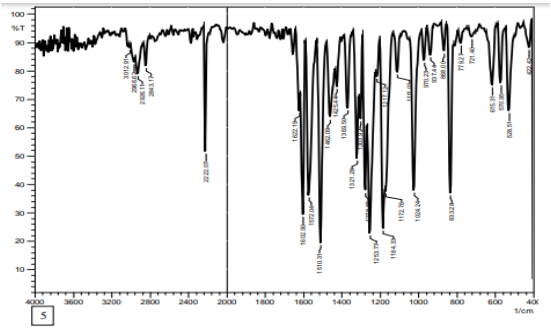


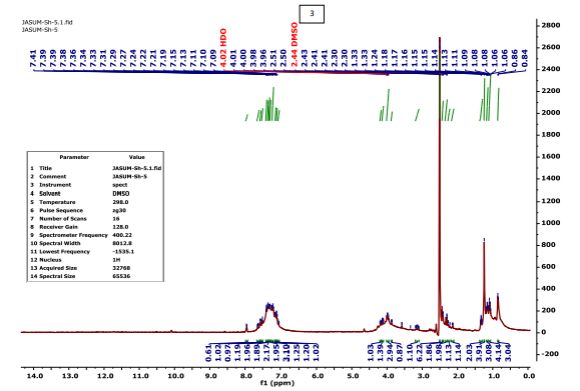


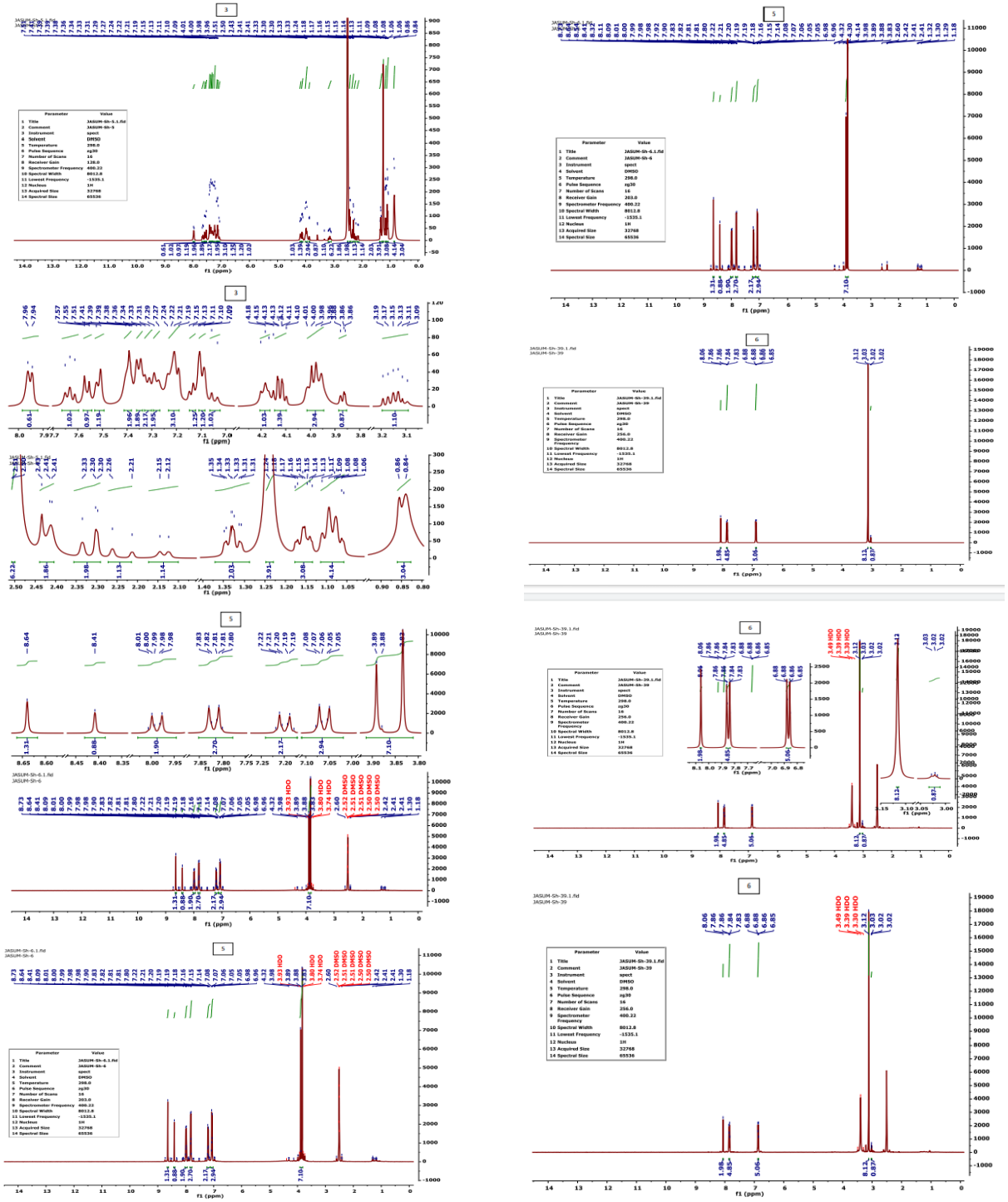












4. Conclusions

In this work, it was found that free catalytic domeno multicomponent reaction was very useful to prepare the pyrano [2,3-c]pyrazole derivatives with high purity and an agreement percentage yields, especially when it prepared from very active and simple starting material represented by compound 1,3,4-thiadiazol-2,5-dithiol. We expect that these compounds will show wide applications in biological ,agricultural and industrial fields due to the variety of heterocyclic rings in its structures.

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