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KNOEVENAGEL CONDENSATION OF HETEROAROMATIC ALDEHYDES WITH 1-PHENYL-1*H*-PYRAZOL-5(4*H*)-ONES

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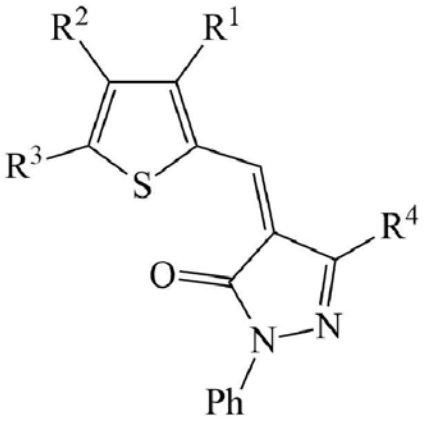
ABSTRACT Thiophene-2-carbaldehydes were condensed with 1-phenyl-1*H*-pyrazol-5(4*H*)-ones by conventional, microwave, ultrasound and grinding method. 2-Chloroquinoline-3-carbaldehydes were subjected to Knoevenagel condensation with 1-(*m*-chlorophenyl)lpyrazolone by conventional method. The structures of all the synthesized compounds were confirmed with the help of spectral and elemental analytical data.



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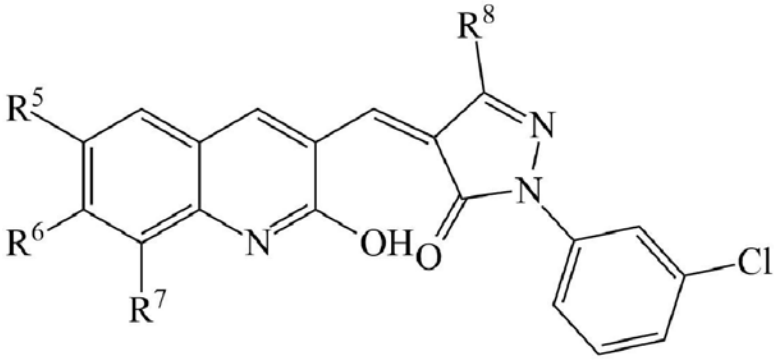

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KEYWORDS Thiophene, Quinoline, Pyrazolone, Knoevenagel condensation

INTRODUCTION

In recent years, green synthetic methods have received considerable attention in the area of organic synthesis. Ultrasonic methods have been considered superior over conventional methods. Many chemical reactions are carried out with mild conditions, short reaction time and high yield under ultrasound irradiation[1]. Sonication can be used for the synthesis of nanoparticles as well as for waste water purification and extraction of plant oil.

Microwave chemistry is the science of applying microwave radiations to chemical reactions[2]. It is time saving, cost effective and environment friendly method. This method is also effectively applicable for phase transfer catalysis[3].

Mechanochemistry is based on grinding, it is solvent free best technique for chemical reactions having green protocol. Avoiding organic solvents during the reactions in synthesis leads to a clean, efficient and green technology

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with increased safety and simplified work-up. Now a days it is mostly preferred by researchers[4-5].

Thiophene is also known as thiofuran. Heterocyclic compounds containing thiophene shows many biological activities like antiallergic[6], anticancer[7] and anti-inflammatory[8]. Raloxifene is a known drug having thiophene moiety and is used to cure Alzheimer's disease.

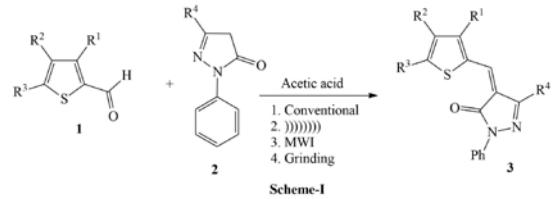
Quinoline or 1-aza-napthalene is heteroaromatic nitrogen containing bicyclic compound. It is associated with various pharmacological activities like antimalarial[9], antitubercular[10], antimycotic[11], anticancer[12] and antimicrobial[13].

Pyrazolone is a derivative of pyrazole having an additional ketonic group. It is a heterocyclic nucleus incorporated in many drugs like ampyrone, phenazone, metamizole and propyphenazone which are potent antipyretics and analgesics[14]. It is an active pharmacophore due to various biological activities associated with it such as antimicrobial[15], antioxidant[16], antidepressant[17], anticonvulsant[17] and antidiabetic[18].

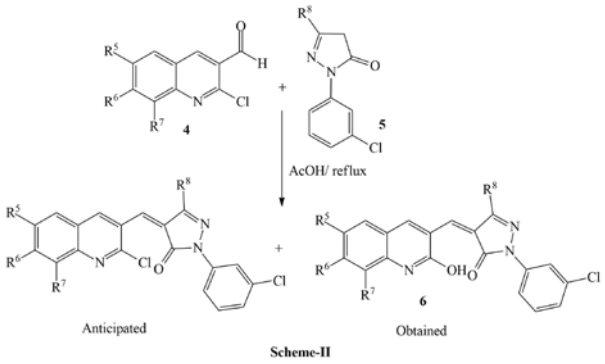
Knoevenagel condensation of aldehyde with active methylene compound is significant and largely used method for carbon-carbon bond formation in synthetic organic chemistry. Many researchers used various catalysts for Knoevenagel condensation like Baker's yeast[19], Al_2O_3[20], CES[21] etc.

RESULTS AND DISCUSSION

The Knoevenagel condensation of heteroaromatic aldehydes (**1a-f**) with 1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2**) was carried out by known literature method[22]. The condensation of compound **1** with compound **2** in acetic acid gives the corresponding(4*Z*)-1-phenyl-4-((thiophen-2-yl)methylene)-1*H*-pyrazol-5(4*H*)-ones **3a-f** (**Scheme I**). IR spectrum of compound **3a** showed a band at 3088 cm^{-1} for Ar-H stretching frequency. The bands at 1668 and 1595 cm^{-1} are due to carbonyl and C=N stretching frequencies respectively. The ^{1}H NMR spectrum of **3a** showed singlet at δ 8.08 due to olefinic proton. The Knoevenagel condensation of compound **4** and **5** in acetic acid gives (*Z*)-1-(3-chlorophenyl)-4-((2-hydroxyquinolin-3-yl)methylene)-1*H*-pyrazol-5(4*H*)-one **6a-j** (**Scheme II**). The IR spectrum of compound **6a** showed bands at 2958 cm^{-1} for aliphatic C-H, 1687 cm^{-1} for carbony l, 1658 cm^{-1} for C=C and 1589 cm^{-1} for C=N stretching frequencies. The ^{1}H NMR spectrum of **6a** showed singlet at δ 10.20 due to olefinic proton and singlet at δ 12.28 due to –OH proton. During this conversion –Cl at second position of quinoline ring is replaced by –OH. This may be due to presence of moisture in acetic acid. Literature survey shows that 2-chloro-3-formyl quinoline get converted into quinolone due to aq. acetic acid[23].



Scheme-I



Scheme-II

EXPERIMENTAL SECTION

Thiophene aldehydes (1a-f) used for condensation were purchased from Sigma-Aldrich chemical company and used without further purification. 2-Chloroquinoline-3-carbaldehydes[24] and substituted 1-phenyl-1*H*-pyrazol-5(4*H*)-ones[25] were prepared by known literature method. Melting points were recorded in open capillaries in liquid paraffin bath and are uncorrected. Microwave irradiation was carried out in Raga's Scientific Microwave System and ultrasonic reaction was carried out in Bio Techno Lab instrument. IR spectra were recorded on *Shimadzu* IR Affinity-1Sfourier transform infrared spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance II 400 MHz NMR spectrometer with DMSO-d_6 as a solvent and TMS as an internal standard. Peak values are shown in δ (ppm). Mass spectra were recorded on Water acquity TQD mass spectrometer.

(4*Z*)-1-Phenyl-4-((thiophen-2-yl)methylene)-1*H*-pyrazol-5(4*H*)-ones, 3a-f:

Conventional method

Equimolar amounts (0.011 mol) of thiophene-2-carbaldehyde (**1**) and substituted pyrazolone (**2**) were taken in glacial acetic acid (4 ml). The reaction mixture was refluxed for 3 hrs. The completion of reaction was checked by TLC. After completion of reaction, contents were allowed to cool and solid obtained was filtered. It was purified by recrystallization from acetic acid to afford pure compound **3**.

Ultrasound method

Equimolar amounts (0.011 mol) of thiophene-2-carbaldehyde (**1**) and substituted pyrazolone (**2**) were taken in minimum amount of glacial acetic acid. The

mixture was subjected to ultrasonic irradiation for 16 min. The completion of reaction was checked by TLC. After completion of reaction, the solid obtained was filtered and purified by recrystallization from acetic acid to get pure compound **3**.

Microwave method

Equimolar amounts(0.011 mol) of thiophene-2-carbaldehyde (**1**)and substituted pyrazolone (**2**) were dissolved in glacial acetic acid (2 ml). The mixture was subjected to microwave irradiation at 300 W for 6 min. The completion of reaction was checked by TLC. After completion of reaction, it was cooled to room temperature. Solid obtained was filtered and purified by recrystallization from acetic acid to get pure compound **3**.

Grinding method

Equimolar amounts of thiophene-2-carbaldehyde (**1**), substituted pyrazolone (**2**) (0.011 mol) and 2 gm of citric acid were taken in mortar and the whole reaction mixture was ground with the help of pestle for 8 min. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured over ice cold water, the solid obtained was filtered, dried and purified by recrystallization from acetic acid to get pure compound **3**.

3a: IR: 3088 (=C-H), 1668 (C=O), 1593 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.05 (t, 3H, CH_3), 1.77 (m, 2H, CH_2), 2.69 (t, 2H, CH_2), 7.18 (t, 1H, Ar-H), 7.42 (t, 2H, Ar-H), 7.94 (d, 2H, Ar-H), 8.08 (s, 1H, Ar-H), 8.18 (s, 1H, =CH), 8.25 (d, 1H, Ar-H); MS: *m/z* (M+1), 375. Ana.Calcd: C, 54.41; H, 4.03; N, 7.46. Found: C, 54.43; H, 4.06; N, 7.49%.

3b: IR: 3086 (=C-H), 1666 (C=O), 1595 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.31 (t, 1H, Ar-H), 7.49 (t, 2H, Ar-H), 7.86 (d, 2H, Ar-H), 8.10 (d, 1H, Ar-H), 8.19 (s, 1H, =CH), 8.27(s, 1H, Ar-H); MS: *m/z* (M+1), 401. Ana. Calcd: C, 44.91; H, 2.01; N, 6.98. Found: C, 44.95; H, 2.03; N, 6.99%.

3c: IR: 3085 (=C-H), 1665 (C=O), 1592 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.08 (t, 3H, CH_3), 1.79 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.65 (t, 2H, CH_2), 7.12 (d, 1H, Ar-H), 7.16 (t, 1H, Ar-H), 7.40 (t, 2H, Ar-H), 7.54 (d, 1H, Ar-H), 7.88 (d, 2H, Ar-H), 8.16 (s, 1H, =CH), 8.27 (d, 1H, Ar-H); MS: *m/z* (M+1), 311. Ana.Calcd: C, 69.65; H, 5.84; N, 9.02: Found: C, 69.67; H, 5.87; N, 9.07%.

3d: IR: 3083 (=C-H), 1667 (C=O), 1596 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.38 (s, 3H, CH_3), 7.16 (d, 1H, Ar-H), 7.29 (t, 1H, Ar-H), 7.45 (t, 2H, Ar-H), 7.58 (d, 1H, Ar-H), 7.84 (d, 2H, Ar-H), 8.18 (s, 1H, =CH); MS: *m/z*(M+1), 337. Ana. Calcd: C, 57.14; H, 3.30; N, 8.33. Found: C, 57.18; H, 3.33; N, 8.35%.

Table-1 Physical data of synthesized compounds 3

Compd	R^1	R^2	R^3	R^4	M.P. (°C)	Conventional method Yield (%)	Ultrasound method Yield (%)	Microwave method Yield (%)	Grinding method Yield (%)
3a	H	Br	H	Propyl	218	64	85	70	85
3b	H	Br	H	CF_3	210	62	82	69	79
3c	CH_3	H	H	Propyl	220	59	79	72	82
3d	CH_3	H	H	CF_3	198	66	84	66	86
3e	H	H	NO_2	Propyl	216	62	76	68	83
3f	H	H	NO_2	CF_3	222	60	86	75	88

Table-2 Physical data of synthesized compounds 6

Compd	R^5	R^6	R^7	R^8	M. P. (°C)	Yield (%)
6a	H	H	H	propyl	298	52
6b	H	F	H	propyl	306	58
6c	OCH_3	H	H	propyl	304	55
6d	H	CH_3	H	propyl	304	54
6e	H	H	CH_3	propyl	286	56
6f	H	H	H	CF_3	298	58
6g	H	F	H	CF_3	296	55
6h	OCH_3	H	H	CF_3	298	59
6i	H	CH_3	H	CF_3	294	57
6j	H	H	CH_3	CF_3	288	53

3e: IR: 3084 (=C-H), 1669 (C=O), 1598 (C=N), 1540 (NO_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.09 (t, 3H, CH_3), 1.75 (m, 2H, CH_2), 2.71 (t, 2H, CH_2), 7.19 (t, 1H, Ar-H), 7.46 (t, 2H, Ar-H), 7.58 (d, 1H, Ar-H), 7.69 (d, 1H, Ar-H), 7.95(d, 2H, Ar-H), 8.20 (s, 1H, =CH); MS: *m/z* (M+1), 342. Ana. Calcd: C, 59.81; H, 4.43; N, 12.31. Found: C, 59.83; H, 4.47; N, 12.32%.

3f: IR: 3087 (=C-H), 1665 (C=O), 1594 (C=N), 1538 (NO_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.35 (t, 1H, Ar-H), 7.54 (t, 2H, Ar-H), 7.60 (d, 1H, Ar-H), 7.63 (d, 1H,Ar-H), 7.75 (d, 1H, Ar-H), 7.89 (d, 2H, Ar-H), 8.19 (s, 1H, =C-H); MS: *m/z* (M+1), 368. Ana. Calcd: C, 49.05; H, 2.20; N, 11.44. Found: C, 49.08; H, 2.23; N, 11.46%.

(*Z*)-1-(3-Chlorophenyl)-4-((2-hydroxyquinolin-3-yl)methylene)-1*H*-pyrazol-5(4*H*)-ones, 6a-j:

Equimolar amounts (0.011 mol) of 2-chloroquinoline-3-carbaldehyde (**4**) and substituted pyrazolone (**5**) were taken in glacial acetic acid (4 ml). The reaction mixture was refluxed for 6 hrs. The completion of reaction was checked by TLC. After completion of reaction, contents were allowed to cool and solid obtained was filtered. It was purified by recrystallization from acetic acid to afford pure compound **6**.

6a: IR: 2958 (=C-H), 1687 (C=O), 1658 (C=C), 1589 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.07 (t, 3H, CH_3), 1.83-1.86 (m, 2H, CH_2), 2.72 (t, 2H, CH_2), 7.23-7.20 (m, 2H, Ar-H), 7.30 (d, 1H, Ar-H), 7.40 (t, 1H, Ar-H), 7.60 (t, 1H, Ar-H), 7.7 (dd, 1H, Ar-H), 7.90 (dd, 1H, Ar-H), 8.05 (t, 1H, Ar-H), 8.09 (s, 1H, Ar-H), 10.2 (s, 1H, =CH), 12.28 (s, 1H, -OH); MS: *m/z* (M+1), 392. Ana. Calcd: C, 67.43; H, 4.63; N, 10.72. Found: C, 67.44; H, 4.65; N, 10.76%.

6b: IR: 2956 (=C-H), 1685 (C=O), 1654 (C=C), 1587 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.09 (t, 3H, CH_3), 1.81-1.85 (m, 2H, CH_2), 2.70 (t, 2H, CH_2), 7.21-7.24 (m, 2H, Ar-H), 7.33 (d, 1H, Ar-H), 7.42-7.46 (m, 3H, Ar-H), 8.07 (t, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 10.25 (s, 1H, =CH), 12.26 (s, 1H, -OH); MS: *m/z* (M+1), 410. Ana. Calcd: C, 64.47; H, 4.18; N, 10.25. Found: C, 64.50; H, 4.23; N, 10.27%.

6c: IR: 2955 (=C-H), 1688 (C=O), 1656 (C=C), 1586 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.09 (t, 3H, CH_3), 1.80-1.83 (m, 2H, CH_2), 2.70 (t, 2H, CH_2), 3.83 (s, 3H, OCH_3), 7.23-7.26 (m, 2H, Ar-H), 7.38 (d, 1H, Ar-H), 7.59 (dd, 1H, Ar-H), 7.74 (d, 1H, Ar-H), 7.80 (d, 1H, Ar-H), 8.04 (t, 1H, Ar-H), 8.07 (s, 1H, Ar-H), 10.22 (s, 1H, =CH), 12.30 (s, 1H, -OH); MS: *m/z* (M+1), 422. Ana. Calcd: C, 65.48; H, 4.78; N, 9.96. Found: C, 65.49; H, 4.80; N, 9.98%.

6d: IR: 2957 (=C-H), 1687 (C=O), 1657 (C=C), 1589 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.08 (t, 3H, CH_3), 1.82-1.86 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.73 (t, 2H, CH_2), 7.22-7.28 (m, 2H, Ar-H), 7.32 (d, 1H, Ar-H), 7.61 (dd, 1H, Ar-H), 7.69 (d, 1H, Ar-H), 7.81 (d, 1H, Ar-H), 8.03 (t, 1H, Ar-H), 8.09 (s, 1H, Ar-H), 10.24 (s, 1H, =CH), 12.29 (s, 1H, -OH); MS: *m/z* (M+1), 406. Ana. Calcd: C, 68.06; H, 4.97; N, 10.35. Found: C, 68.07; H, 4.99; N, 10.37%.

6e: IR: 2959 (=C-H), 1684 (C=O), 1653 (C=C), 1586 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.06 (t, 3H, CH_3), 1.85-1.89 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.68 (t, 2H, CH_2), 7.85 (d, 1H, Ar-H), 7.72 (d, 1H, Ar-H), 7.63 (dd, 1H, Ar-H), 7.30 (d, 1H, Ar-H), 7.20-7.24 (m, 2H, Ar-H), 8.06 (t, 1H, Ar-H), 8.08 (s, 1H, Ar-H), 10.23 (s, 1H, =CH), 12.27 (s, 1H, -OH); MS: *m/z* (M+1), 406. Ana. Calcd: C, 68.06; H, 4.97; N, 10.35. Found: C, 68.09; H, 4.98; N, 10.39%.

6f: IR: 2961 (=C-H), 1681 (C=O), 1652 (C=C), 1591 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.24-7.28 (m, 2H, Ar-H), 7.38 (d, 1H, Ar-H), 7.46 (t, 1H, Ar-H), 7.58 (t, 1H, Ar-H), 7.76 (dd, 1H, Ar-H), 7.94 (dd, 1H, Ar-H), 8.01 (t, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 10.28 (s, 1H, =CH), 12.29 (s, 1H, -OH); MS: *m/z* (M+1), 418. Ana. Calcd: C, 57.50; H, 2.65; N, 10.06. Found: C, 57.55; H, 2.68; N, 10.07%.

6g: IR: 2960 (=C-H), 1687 (C=O), 1659 (C=C), 1589 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.22-7.29 (m, 2H, Ar-H), 7.34 (d, 1H, Ar-H), 7.41-7.48 (m, 3H, Ar-H), 8.06 (t, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 10.27 (s, 1H, =CH), 12.31 (s, 1H, -OH); MS: *m/z* (M+1), 436. Ana. Calcd: C, 55.13; H, 2.31; N, 9.64. Found: C, 55.16; H, 2.34; N, 9.68%.

6h: IR: 2952 (=C-H), 1682 (C=O), 1651 (C=C), 1582 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.81 (s, 3H, OCH_3), 7.22-7.25 (m, 2H, Ar-H), 7.37 (d, 1H, Ar-H), 7.62 (dd, 1H, Ar-H), 7.73 (d, 1H, Ar-H), 7.92 (d, 1H, Ar-H), 8.02 (t, 1H, Ar-H), 8.12 (s, 1H, Ar-H), 10.19 (s, 1H, =CH), 12.26 (s, 1H, -OH); MS: *m/z* (M+1), 448. Ana. Calcd: C, 56.33; H, 2.93; N, 9.38. Found: C, 56.37; H, 2.98; N, 9.39%.

6i: IR: 2958 (=C-H), 1688 (C=O), 1655 (C=C), 1584 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.25-7.29 (m, 2H, Ar-H), 7.36 (d, 1H, Ar-H), 7.63 (dd, 1H, Ar-H), 7.75 (d, 1H, Ar-H), 7.91 (d, 1H, Ar-H), 8.04 (t, 1H, Ar-H), 8.06 (s, 1H, Ar-H), 10.23 (s, 1H, =CH), 12.25 (s, 1H, -OH); MS: *m/z* (M+1), 432. Ana. Calcd: C, 58.41; H, 3.03; N, 9.73. Found: C, 58.43; H, 3.08; N, 9.78%.

6j: IR: 2951 (=C-H), 1685 (C=O), 1658 (C=C), 1590 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.34 (s, 3H, CH_3), 7.20-7.21 (m, 2H, Ar-H), 7.29 (d, 1H, Ar-H), 7.60 (dd, 1H, Ar-H), 7.68 (d, 1H, Ar-H), 7.88 (d, 1H, Ar-H), 8.00 (t, 1H, Ar-H), 8.07 (s, 1H, Ar-H), 10.25 (s, 1H, =CH), 12.28 (s, 1H, -OH); MS: *m/z* (M+1), 432. Ana. Calcd: C, 58.41; H, 3.03; N, 9.73. Found: C, 58.45; H, 3.05; N, 9.74%.

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