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Moderate and Efficient One-Pot Multicomponent Strategy to Perform a New Series of Fused 1,2,4-Triazolopyrimidine Derivatives Assisted by Lemon Juice and Grinding Technique

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Abstract

Polyfused heterocyclic compounds have been performed by using lemon juice as active natural acid catalysis through one of the most important and famous reactions represented by the Biginelli reaction as a one-pot multicomponent reaction using only stirring at room temperature (25°C) as moderated circumstances. Substantially, the reaction started firstly by the action of hydrazine carbohydrazide (1) on the isophorone to achieve the corresponding hydrazone (2) in acidic media from glacial acetic acid, which then underwent intercyclization reaction via grinding technique for (20 minutes) with thiourea in basic media from NaOH (10%) to obtain 3-(2-isopheronyl hydrozonyl)-5-amino-1,2,4-triazole (3). Finally, the compound (3) proceeded through a one-pot Biginelli reaction with dimedone and substituted benzaldehyde in the presence of the catalytic amount of lemon juice as a natural acidic catalyst to achieve poly fused 1,2,4-triazole pyrimidine derivatives (4-6) in moderate and selective circumstances.

Keywords: Fused 1,2,4-triazole, Poly fused heterocyclics, Biginelli reaction, Lemon juice, Grinding technique.

Introduction

Multicomponent reactions (MCR_s) are considered one of the most important reactions involving efficient tools in modern chemistry, especially organic synthesis. They have all the features that contribute to an ideal synthesis of high atom efficiency, quick and simple implementation, time and energy saving, and economic and environmentally friendly. The interest in developing the preparation methods and extending the range of polyfused heterocyclic compounds is still very high. Also, it is worth noting that poly-fused heterocyclics have attracted the attention of chemists in earlier decades. Also, one-pot multicomponent reactions have served

as the basis for rapid progress in the chemistry of poly-fused heterocyclics. Relatively, these types of compounds have shown high and distinctive effectiveness in medical, pharmacological, and biological fields; they suppress multi-drug resistance of various microbial[1-3], viral [4,5], fungi[6,7], inflammatory[8,9] , as well as cancer cell[10-12] , antihypertensive [13,14], migraines[15,16], epilepsy in children[17,18] and immunodeficiency (AIDS)[19,20]. In the agricultural field, they act as effective insecticides[21-23]. Furthermore, they act industrially as anti-corrosion materials[24-26]. Due to the all mentioned above, herein in this work, poly fused heterocyclic system have been successfully prepared through three stages, including, firstly, the preparation of hydrazone derivative (2) from the reaction between the hydrazine carbohyrazide (1) and isophorone. The second stage includes converting compound (2) to the corresponding 5-amino-1,2,4-triazole (3) through an inter cyclization reaction with thiourea in basic condition using the grinding technique for (20 minutes). Finally, a one-pot multicomponent reaction among compound (3), dimedone, and substituted benzaldehyde was take place accelerated by natural acid catalysis represented by freshly prepared lemon juice with stirring at the moderate conditions for (2.5hrs.) to perform a supreme new series of poly fused 1,2,4-triazolopyrimidine (4-6) with yield enhancement.

Experimental

Melting points (M.P.) were determined using the SMP30-Stuart melting point apparatus. FT-IR spectra were recorded on a (KBr) disk using a Pye Unicom sp 2000. ^{1}H-NMR spectra were scanned using Bruker Bio Spin GmbH Spectrophotometer (400 MHz) (Turkey) with TMS as the internal standard and d_6- DMSO as the solvent. TLC, glass plates of suitable height (12cm) were used and coated with silica gel 60°A gypsum free using solvents systems such as (methanol: benzene) were used in various proportions (2:8) and (5:5) and ethanol enhanced with iodine vabor to reveal spots and to calculate the disability factor (R_f) for them with determine it's purity.

Synthesis of hydrazine carbohydrazide (1)[27] :

This compound was prepared according to the literature (Dutta and Sarkar ,1981) and it has conformity to the literature in all it's physical constants.

Synthesis of isopheronyl hydrozone carbohydrazide (2)[28,29] :

Dissolve of equimolar (0.001 mole) of compound (1) and isophorone in (15 ml) methanol with catalytic amounts of glacial acetic acid (3-4 drop) followed by stirring at room temperature (25°C) for (3hrs.) until thick yellowish solid mass separates which then filtered off and washed thoroughly with cold water followed by drying and recrystallized from methanol to affored compound (2) as yellowish powder with, M.P.=208-210°C , Yield=95% , T.L.C (R_f)=0.53.

Table (1): Spectral data for compound (2)

Comp. No.	FT-IR (KBr), *υ (cm^{-1})*						^{1}H-NMR, δ (ppm)
	NH_2	NH	CH_3	C=O	C=N	C=C	
2	3300	3198	asym. 2944 sym.2866	1673	1633	1505	0.95 (S,3CH_3, 12H), 1.79-2.6(m, isopheron-H,4H), 2.18(S,NH_2,2H); 5.91(S,C=CH, 1H); 7.49(s,NH_2NH-C=O,1H),9.27(S,=N-NH-C=O,1H).

Synthesis of 3-(isopheronyl hydrazine)-5-amino-1,2,4-triazole (3)[30]:

In a small ceramic mortar, a mixture of equimolar (0.001 moles) from compound (2) and thiourea with a catalytic amount of (10%) NaOH (3ml) was well ground for (20 minutes). The addition of conc then neutralized the reaction mixture. hydrochloric acid followed by filtration and washed thoroughly with cold water, dried and recrystallized from ethanol to obtain compound (3) as greenish powder, M.P.=119-121 , Yield= 92% , T.L.C(R_f)=0.30

Table (2): Spectral data for compound (3)

Comp. No.	FT-IR (KBr), υ (cm^{-1})					^{1}H-NMR, δ (ppm)
	NH_2	NH	CH_3	C=N	C=C	
3	3353	3203	asym. 2955 sym. 2868	1681	1642	0.92(s,3CH_3, 12H), 1.79-2.18(m, isophoron-H,4H); 3.32(s, NH,2H); 5.96(s, C=CH,1H); 9.32(s, NH-N=,1H); 9.64(s,NH-Triazole,1H).

Synthesis of 3-(2-isopheronylidine hydrozonyl)8,8-dimethyl-5-aryl-5,7,8,9-tetrahydro[1,2,4]-triazolo[3,4,6]quinazolin-6-one(4-6)[31]:

In a round-bottomed flask equipped with a magnetic bar, a mixture of equimolar (0.001 moles) from compound(3), dimedone, and substituted benzaldehyde with catalytic amounts of freshly prepared lemon juice (3ml) was stirred for (2.5hrs.). The formed crude product was then filtered off , washed thoroughly with cold water, and dried, followed by recrystallization from ethanol to perform the compound (4-6) with physical properties and spectral data listed in Tables (4) and (5), respectively.

Table (4): Physical properties for compound (4-6)

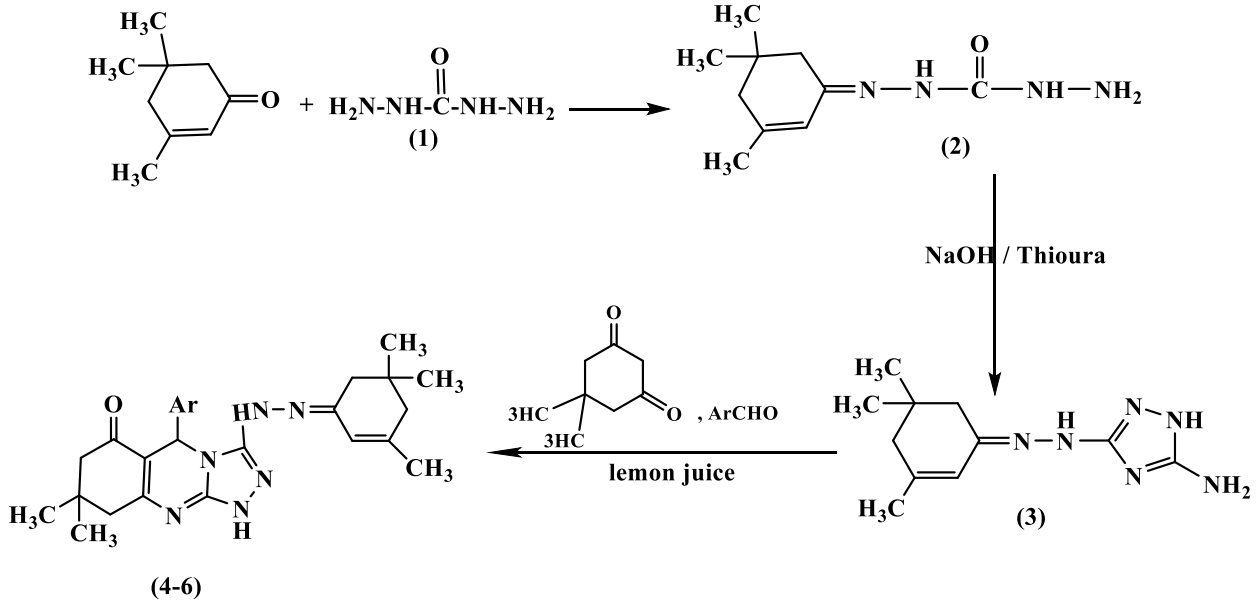
Comp. No.	x	Molecular Formula	M.Wt	M.P. °C	Yield %	Colour	R_f (Benzene:MeOH) 8:2
4	H	$C_{26}H_{31}N_6O$	443	81-82	90	Yellow	0.50
5	p-NO_2	$C_{26}H_{31}O_3N_7$	489	70-71	92	Yellow	0.42
6	p- OCH_3	$C_{27}H_{33}N_6O_2$	473	175-177	91	Greenish yellow	0.62

Table (5): Spectral data for compound (4-6)

Comp. No.	FT-IR (KBr), υ (cm^{-1})						^{1}H-NMR, δ (ppm)
	NH	CH_3	C=O	C=N	C=C	others	
4	3208	asym.2956 sym.2868	1682	1594	1517	–	Isophorone & dimedon H=0.97-2.23(m,23H); C=CH=6.00(s,1H); =N-NH=7.89 (s,1H), triazole-N=7.94 (s,1H) ; aromatic-H=8.3-8.36 (m,6H).
5	3200	asym.2931 sym.2868	1682	1634	1589	NO_2 asym.1512 sym.1342	Isophorone & dimedon-H aliphatic =0.95-2.39(m,23H); OCH_3=3.13(s,1H);-C-CH=4-58(s,1H),-NH-N= =6.94(s,1H); aromatic-H=7.08-7.33(m,6H).
6	3384	asym.2956 sym.2870	1720	1684	1604	C-O-C asym.1229 sym.1071	–

Result and Discussion

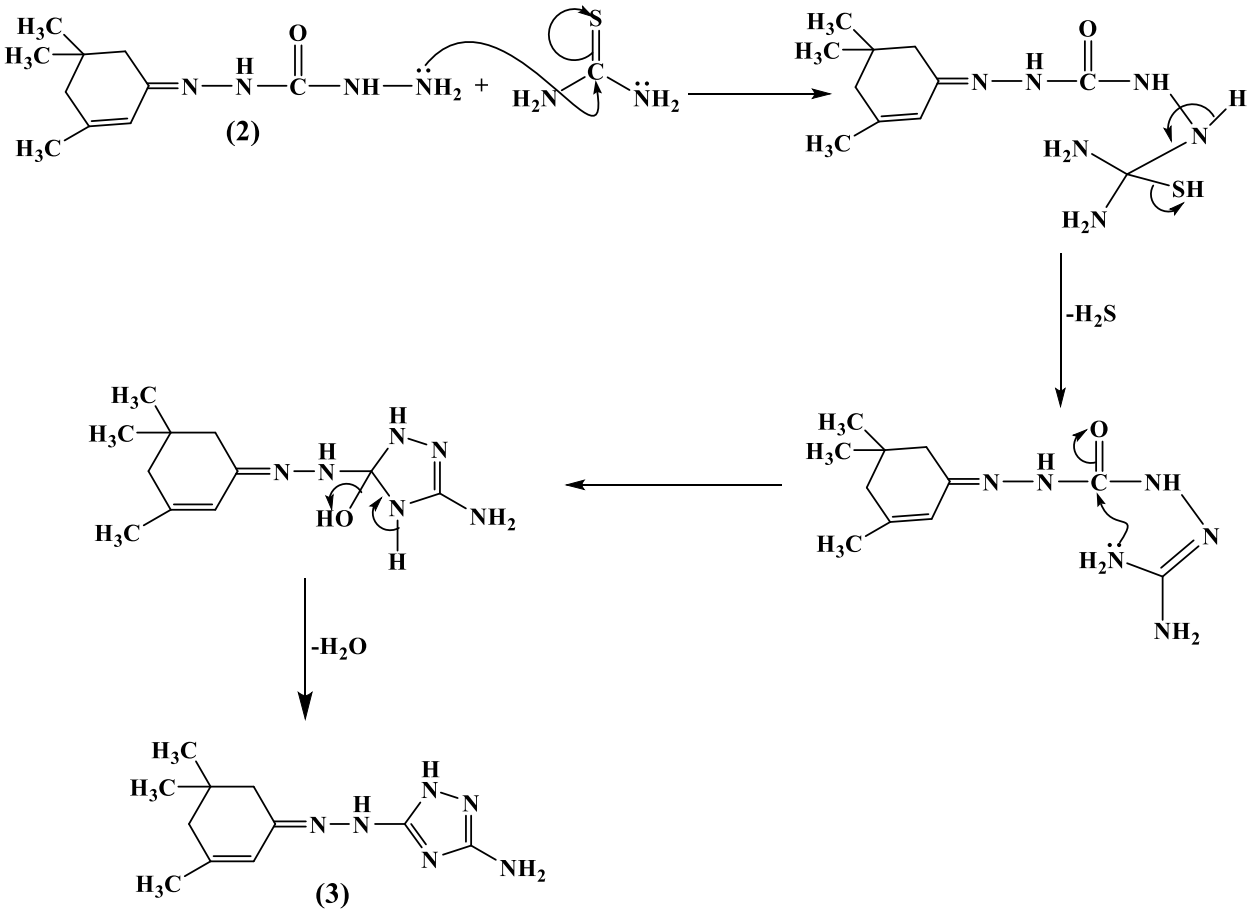
Moderate and efficient strategies have been developed to perform a new series of poly fused 1,2,4-triazoleo pyrimidine derivatives according to the general synthetic pathway described below , Scheme (1):



Scheme (1): Synthesis pathway for compound (1-6)

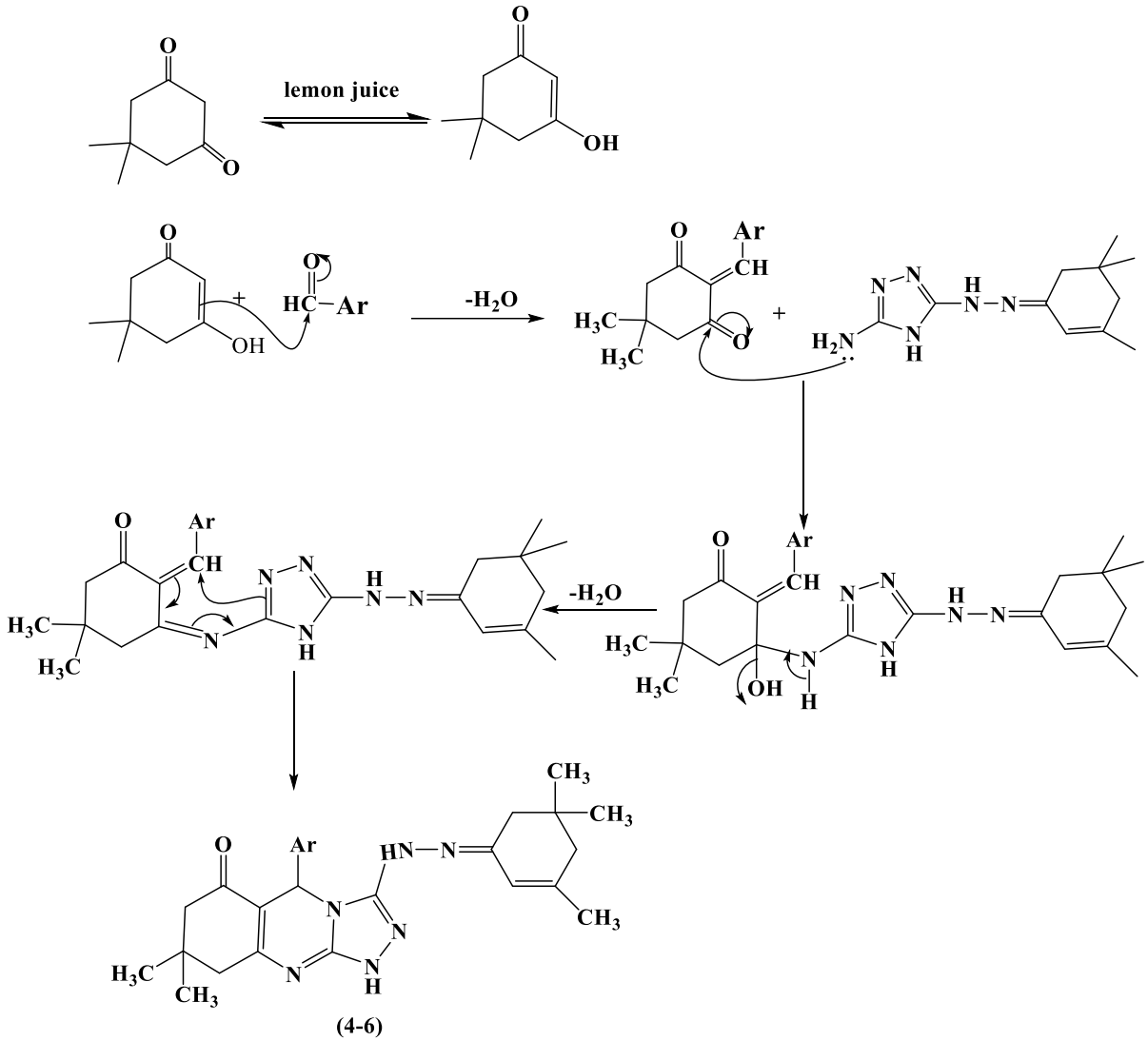
According to Scheme (1), the hydrazine carbohydrazide (1) poly is a key intermediate in the overall preparation method. Also, it was under a condensation reaction with isophorone losing one molecule of water in acidic media to give the corresponding hydrazine (2), which was then identified throng the spectroscopic method that showed characteristic absorption bands listed in

the experimental part. Actually, it was given in 1H-NMR spectroscopy (3) main peak at ẟ ppm :5.96,7.49 and 9.27 refer to the (C=CH, -NH-C=O and =N-NH) respectively, which prove the right sequencing of the active groups. After proving the exact suggested product structure formula, the compound (2) reacted directly with thiourea via an unexpected inter cyclization reaction in basic media which was accelerated by grinding technique as shown in the following Scheme mechanism (2) to afford the compound 5-amino-1,2,4-triazole (3) after losing two molecules of water (H_2O)and hydrogen sulfide (H_2S) respectively[32] :



Scheme (2) : Synthetic mechanism of compound (3)

The absence of a C=O stretching vibrational band in FT-IR with the remaining stretching vibration band of the primary amino group gave initial support for the suggested structure. Besides that , 1H-NMR spectroscopy shows the disappearance of the three main sequence peaks mentioned previously and appearing of NH-triazole proton at δ ppm =9.64 (s,NH,1H); the peak fully conforms with the expected structure. Finally, compound (3) underwent a one-pot Biginelli reaction with each dimedone and substituted benzaldehyde as described in Scheme (3)[33]:



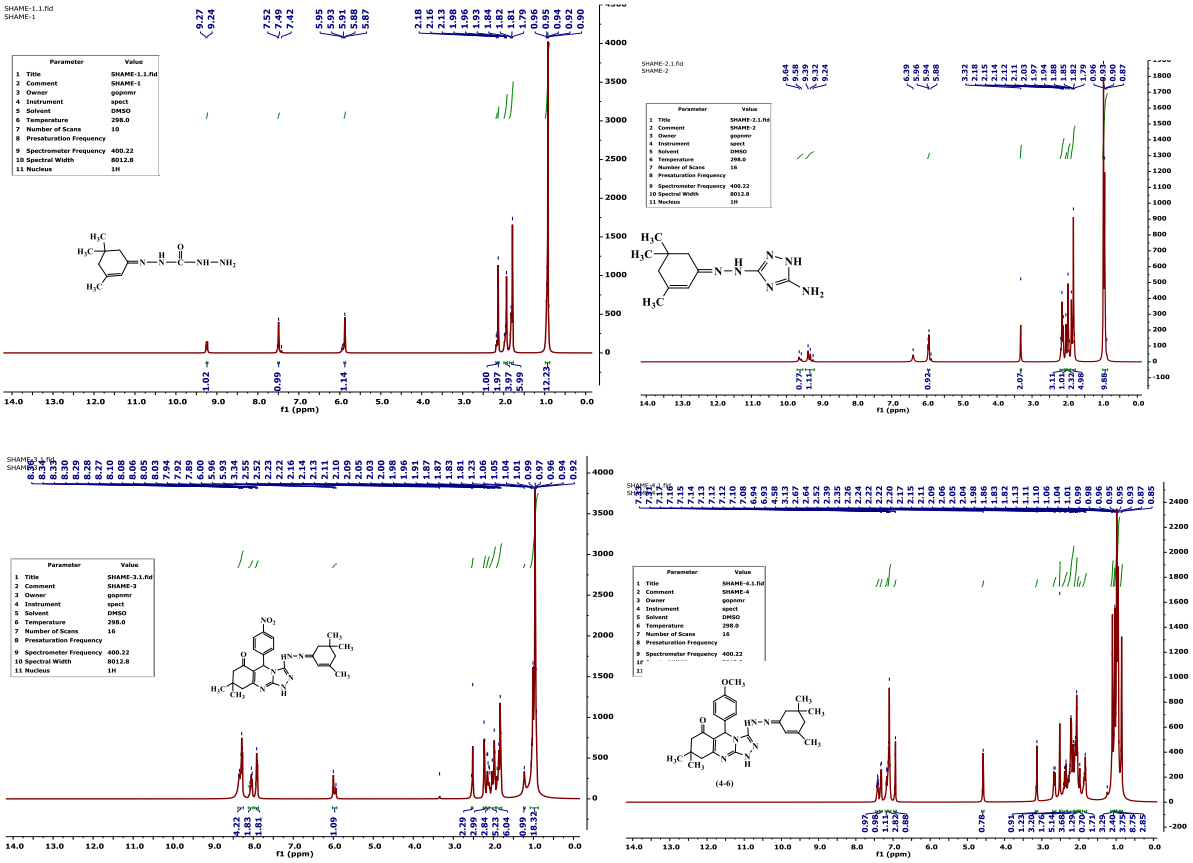
Scheme (3) : Synthetic mechanism of compounds (4-6).

The mechanism shows a direct sequence addition reaction accelerated by lemon juice in moderate conditions with an acceptable percentage yield. The structure of these compounds (4-6) was proven via FT-IR and ^{1}H-NMR spectroscopy Table (5). The most important evidence about the right suggested product structure is the absence of a primary amino peak and the appearance of aromatic protons in its right and exact area, in addition to all absorption bands and peaks listed in Table (5) that agreed with the suggested structures.

Conclusion

Moderate and efficient reaction circumstances were used in this work to perform a new poly fused 1,2,4-triazole system while reducing the reaction time, economical, environmentally, and friendly with yield enhancement via using natural lemon juice as acid catalysis. Beside that, 5-

amino-1,2,4-triazole was prepared directly through one-pot intercyclization reaction with thiourea with yield enhancement.



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