Research Article

Green Synthesis of Triazole Derivatives with Pyrimidine Moiety

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ABSTRACT

A series of 6-methyl-4-aryl-5-(5-phenyl-4H-1,2,4-triazole-3-yl)-3,4,dihydropyrimidin-2(1H)- one/thione(IIIa–g) have been synthesised from Ethyl -6- methyl- 2- oxo/thioxo- 4- substituted phenyl- 1,2,3,4-tetrahydropyrimidine-5- carboxylates (Ia-g) followed by treatment with hydrazine hydrate in ethanol gave different 6-methyl-2-oxo/thioxo-4-substituted phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazides (IIa-g) by means of the microwave irradiation . All steps were synthesised by green procedure with excellent yield. Product obtained characterised by means of the NMR, IR and Mass spectral analysis.

Keywords: Pyrimidines, Carbohydrazides, Triazole, Green synthesis.

INTRODUCTION

Triazole and its derivatives have wide range of the biological activities such as Antibacterial[1-3], Antifungal[4-5], Antitumour[6], Antiinflammatory[7], Antitubercular[8], Hypoglyce-mic[9-10], Antidepressant[11], Anticonvulsant[12], Anticancer[13], Antimalarial[14], Anti-proliferative[15], Analgesic[16]. They also inhibit the formation of granulomata and presence of the nitrogen atom makes triazole derivative as an important class of the medicinal and heterocyclic chemistry, thus there is demand for their synthesis and development of the synthetic procedures which are environmentally friendly. Microwave heating has attracted the attention of chemist in that it makes it possible to shorten the reactions time significantly, and to increase the product yields, which is particularly important in the case of high-temperature processes that take a long time[17]. Microwave radiation (MWR) has been used more and more often in organic synthesis, domestic type of microwave is generally used for the synthesis. Similarly, pyrimidine derivatives are important class of heterocyclic compound due to their therapeutic and pharmacological properties and used as calcium channel blockers and alpha-1α-antogonists. The biological and synthetic significance places this scaffold at a prestigious position in medicinal chemistry research so we have developed an operationally simple, inexpensive, efficient and environmental benign protocol for synthesis. In present work, we have developed rapid and operationally simple method for synthesis of different triazoles with pyrimidine nucleus.

MATERIALS AND METHODS

All chemicals were of synthetic grade (S. D. Fine .Chem. Ltd. Mumbai, India). MP was determined by open capillary method and is uncorrected. Products were recrystalized from ethanol as a solvent. The purity of compounds checked by the TLC on silica gel G plates and was purified by column chromatography on silica gel (60-120 mesh). The microwave used for the synthesis is of the LG-Little Chef MS-192 W. The compounds were characterised by using IR, ^{1}H NMR and Mass spectral analysis. The IR spectra were recorded on Perkin – Elmer spectrum in form of KBr pellet. ^{1}H NMR was recorded in $CDCl_3$ on Perkin Elmer R-32 spectrum using TMS as internal standard. Mass spectrum was recorded on EI-shimadzu GC-MS spectrometer. All the compounds were analysed for C, H and N on Carlo-Erba elemental analyser.

Experimental

Ethyl -6- methyl- 2- oxo/thioxo- 4- substituted phenyl- 1, 2, 3, 4-tetrahydropyrimidine-5- carboxylate (Ia-g)

A mixture of substituted aldehyde (0.01 mol) ethylacetoacetate (0.015 mol), urea /Thiourea (0.01 mol) &concentrated H_2SO_4 (1–5 drops) in absolute ethanol (10 ml) were taken in a borosil beaker (250ml) was zapped inside the microwave oven for a period of 3 -4 min (at 160w) the reaction mixture was then allowed to stand at room temperature and then poured on ice. The product formed was filtered, washed with water, dried & recrystalized from ethanol (table 1).

6-methyl-2-oxo/thioxo-4-substituted phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide (IIa-g)

The compound I (0.01 mol) in ethanol & hydrazine hydrate (0.99%, 0.015 mol) were taken in borosil beaker (250 ml) the reaction mixture zapped inside the microwave oven for a period of 2 -3 min. (at 160w). Then reaction mixture allowed to cool for a while after some time mixture was poured on ice. Product formed filtered, washed with water, dried and recrystalized from ethanol (table 2).

6-methyl-4-aryl-5-(5-phenyl-4H-1, 2, 4-triazole-3-yl)-3, 4, dihydropyrimidin- 2(1H) - one/ thione (IIIa-g)

Compound II (0.003 mol) in acetic acid (10 ml) was added a pinch of Ammonium acetate followed by the addition of different aromatic aldehyde (0.003 mol) .Then the mixture was stirred for 24 hrs at Room temperature . The solution was then neutralised with liquid NH_3 solution and the product obtained was filtered washed with H_2O & recrystalized from dioxan - ethanol (table 3).

RESULTS AND DISCUSSION

Various methods have been reported for the synthesis of the triazole derivative which requires high reaction temperature, large reaction time and poor yield .In present work hetero cyclisation reaction proceed with high reaction yield (70-90%) and first two steps completes within (2-3 min) as compare with other methods for 1,2,4 triazole ring. Here new Triazole derivatives with pyrimidine moiety have been reported from corresponding different hydrazide derivatives (IIa-g). Initially, substituted pyrimidine carboxylate I(a-g) were prepared by our earlier reported method i.e. Hanzsch synthesis (Scheme-1) which were treated with hydrazine hydrate in ethanol by microwave irradiation (2-3 min.) to furnish the corresponding substituted carbohydrazides (IIa-g) followed by the stirring for the 24 hrs with aromatic aldehyde and ammonium acetate in glacial acetic acid predicts 6-methyl-4-aryl-5-(5-phenyl-4H-1, 2, 4-triazole-3-yl)-3, 4, dihydropyrimidin-2(1H)-one/ thione (IIIa-g),(Table: III). The newly synthesized compounds **I (a-g), II (a-g) and III (a-g)** were established on the basis of IR, ^{1}H NMR and MASS spectroscopic method. The IR spectra of the compounds(IIa-g) showed absorption band at 1664-1672 cm^{-1} indicates presence of amide group while absence of the absorption band at 1664-1672 in IIIa-g indicating the formation of product. In ^{1}H NMR spectra, a peak observed at 4.53 ppm. due to presence of $-NH_2$ group in IIa-g. While in triazole derivative, absence of peak at 4.53 due to $–NH_2$ proved the structure of the products. The mass spectra of the substituted triazole with pyrimidine derivative were showed molecular ion peak corresponding to their molecular formula. The IIIf compound shows [M+] and [M^+ +2] peak at m/z 380.5(M^+), 382.5(M^++2) showing presence of halogen respectively and peak at 35.5 and 37.5 confirms presence of Chlorine in the ratio 1:3.

SCHEME

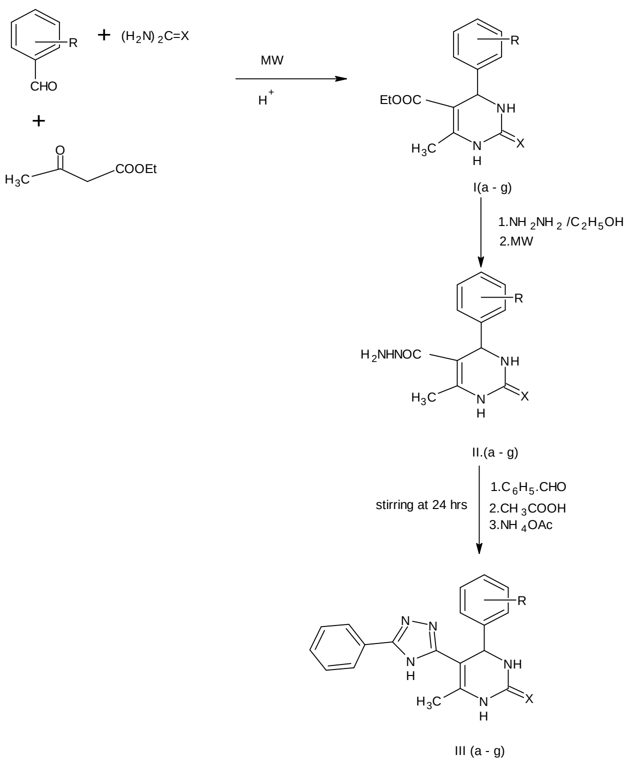

Table 1: Physical & Elemental analysis of the synthesized compound (I a-g)

Comp. No.	R	X	MP °C	Yield %	Mol Formula	Elemental Analysis Calc. (Found)%		
						C	H	N
Ia	-H	O	197	86	$C_{14}H_{16}O_3N_2$	64.61 (64.60)	6.15 (6.13)	10.77 (10.76)
Ib	o-OH	O	150	82	$C_{14}H_{16}O_4N_2$	60.87 (60.88)	5.80 (5.78)	10.14 (10.15)
Ic	o-OH	S	120	85	$C_{14}H_{16}O_3N_2S$	57.53 (57.50)	5.48 (5.49)	9.59 (9.55)
Id	p-OCH_3	O	170	88	$C_{15}H_{18}O_4N_2$	62.07 (62.05)	6.2 (6.0)	9.65 (9.66)
Ie	p-OCH_3	S	94	87	$C_{15}H_{18}O_3N_2S$	58.82 (58.80)	5.88 (5.87)	9.15 (9.14)
If	p-Cl	S	70	87	$C_{14}H_{15}O_2N_2ClS$	54.19 (54.20)	4.84 (4.82)	9.03 (9.00)
Ig	p-OH	O	130	88	$C_{14}H_{16}O_4N_2$	60.87 (60.88)	5.80 (5.78)	10.14 (10.12)

Table 2: Physical & Elemental analysis of the synthesized compound (IIa-g)

Comp.No.	R	X	MP °C	Yield %	Mol Formula	Elemental Analysis Calc.(Found)%		
						C	H	N
IIa	-H	O	202	82	$C_{12}H_{14}O_2N_4$	58.54 (58.51)	5.69 (5.70)	22.76 (22.75)
IIb	o-OH	O	190	78	$C_{12}H_{14}O_3N_4$	54.96 (54.96)	5.34 (5.30)	21.37 (21.38)
IIc	o-OH	S	140	85	$C_{12}H_{14}O_2N_4S$	51.80 (51.79)	5.03 (5.01)	20.14 (20.13)
IId	p-OCH_3	O	196	81	$C_{13}H_{16}O_3N_4$	56.52 (56.50)	5.80 (5.79)	20.29 (20.28)
IIe	p-OCH_3	S	130	84	$C_{13}H_{16}O_2N_4S$	53.42 (53.41)	5.48 (5.47)	19.18 (19.17)
IIf	p-Cl	S	150	81	$C_{12}H_{13}ON_4ClS$	48.57 (48.55)	4.38 (4.33)	18.89 (18.90)
IIg	p-OH	O	190	88	$C_{12}H_{14}O_3N_4$	54.96 (54.97)	5.34 (5.32)	21.37 (21.35)

Table 3: Physical & Elemental analysis of the synthesized compound (IIIa-g)

Comp. No.	R	X	MP °C	Yield %	Mol Formula	Elemental Analysis Calc.(Found)%		
						C	H	N
IIIa	-H	O	110	84	$C_{19}H_{16}ON_5$	69 .00 (69.04)	4.85 (4.83)	21.21 (21.20)
IIIb	o-OH	O	230	88	$C_{19}H_{16}O_2N_5$	65.89 (65.90)	4.62 (4.60)	20.23 (20.23)
IIIc	o-OH	S	110	82	$C_{19}H_{16}ON_5S$	62.98 (62.97)	4.41 (4.38)	19.33 (19.35)
IIId	p-OCH_3	O	100	78	$C_{20}H_{18}O_2N_5$	66.66 (66.65)	5.00 (5.08)	19.41 (19.40)
IIIe	p-OCH_3	S	82	86	$C_{20}H_{18}ON_5S$	63.82 (63.80)	4.78 (4.75)	18.61 (18.59)
IIIf	p-Cl	S	130	80	$C_{19}H_{15}N_5Cl$ S	59.12 (59.10)	3.94 (3.93)	18.39 (18.40)
IIIg	p-OH	O	90	84	$C_{19}H_{16}O_2N_5$	65.89 (65.88)	4.62 (4.58)	20.23 (20.20)

Table 4: IR, NMR and mass spectral analysis of synthesized compounds (IIIa-IIIg)

Comp.No.	IR (KBr)	NMR($CDCl_3$)	MASS(m/z)
Ia	Vmax **,** 3226.33 (-NH),1718 (>C=O, ester), 1668.98 (>C=O, amido),1640 (>C=C<) cm^{-1}.	δ ,1.25 (3H,t,-CH_3), 2.31 (3H,s,-CH_3), 4.2(2H,q, -CH_2), 5.4(1H,s,-CH), 5.9(1H,s,-NH), 7.2-7.4(5H,m ,Ar-H), 8.4 (1H, s, -NHCO) ppm.	-
Ib	Vmax,3226.30 (-NH),1728(>C=O), 1641(>C=C<),1248 (>C =S), cm^{-1} .	δ ,1.31(3H,t,-CH_3), 2.38(3H,s,-CH_3), 4.52(2H,q,-CH_2), 5.45(1H,s, -CH), 5.83 (1H,s,NH), 7-7.5(5H,m,Ar-H), 8.2 (1H,s, -NHCO) ppm. .	-
Ic	Vmax,3610 (Ar-OH),3226.33 (-NH), 1710.12 (>C=O, ester), 1673.98(>C=O, amido),1640 (>C=C<), Cm^{-1}	δ ,1.28(3H, t, -CH_3), 2.39(3H, s, - CH_3), 4.5(2H,q,-CH_2), 5.51(1H,s,-CH), 5.9(1H,s,-NH), 7.2- 7.5 (4H,m,Ar-H), 8.9(1H,s,-NH), 9.52 (1H,s, Ar- OH). ppm.	-
Id	Vmax, 3610 (Ar-OH), 3226.33 (-NH), 1730 (>C=O) , 1640 (>C=C<), 1240 (>C=S)Cm^{-1}	δ ,1.23(3H, t, -CH_3), 2.48 (3H, s, -CH_3), 4.4 (2H, q, -CH_2), 5.53 (1H,s, -CH), 5.6 (1H, s, -NH), 7-8 (4H, m, Ar-H), 8.5(1H, s, -NH), 9.8(1H, s, Ar- OH)ppm.	-
Ie	Vmax, 3230.33(-NH), 1725 (>C=O), 1650 (>C=C<), 1241 (>C=S) $Cm\text{-}^{1}$	δ ,1.4(3H, t, -CH_3), 2.50(3H, s, -CH_3), 3.5(2H, q, -CH_2), 4.1(3H, s, -OCH_3), 5.52(1H, s, -CH), 5.8(1H, s, NH), 7-8 (4H, m, Ar-H) ,8.23 (1H, s, -NHCO) ppm.	-
If	Vmax, 3210.33(-NH), 1728 (>C=O, ester), 1684 (>C=O, amido),1650 (>C=C<), 780 (-C-Cl) Cm^{-1}	δ ,1.4(3H, t, -CH_3), 2.50(3H, s, -CH_3), 3.5(2H, q, -CH_2), 5.52 (1H, s, -CH), 5.8(1H, s, -NH), 7.1-7.4(4H, m, Ar-H). 8.08 (1H, s, -NHCO),ppm	m/z 294.5(M^+), 296.5(M^++2).
Ig	Vmax, 3225.33(-NH), 1718 (>C=O), 1650 (>C=C<), 1248 (>C=S)Cm^{-1}	δ ,1.43(3H, t, -CH_3), 2.50 (3H, s, -CH_3), 4.5(2H, q, CH_2), 5.53(1H, s, CH), 5.8(1H, s, NH), 7.1-7.4(4H, m, Ar-H). 8.2(1H, s, -NHCO), ppm.	m/z 310,2(M^+)
IIa	Vmax, 3213.33(-$NHNH_2$), 3049 (Ar-H), 1664 (amido, >C=O), 1648 (>C=C<), Cm^{-1}	δ ,2.28(3H, s, -CH_3), 4.2(2H, d, NH_2), 5.50 (1H, s, -CH), 7.1-7.3(5H, m, Ar-H) 7.9(1H, s, NH), 8.4(1H, s, NHCO), ppm.	-
IIb	Vmax , 3220.33(-$NHNH_2$), 3049 (Ar-H), 1670 (amido, >C=O), 1650 (>C=C<), 1244 (>C=S). $Cm\text{-}^{1}$	δ ,2.3(3H, s, -CH_3), 4.27(2H, d, -NH_2), 5.53 (1H, s, -CH), 7.1-7.3(5H, m, Ar-H) 7.5(1H, s, -NH), 8.3(1H, s, -NHCO) ppm.	-
IIc	Vmax , 3332 (Ar-OH) , 3223 (-$NHNH_2$), 3049 (Ar-H), 1670(amido->C=O),1654 (>C=C<), $Cm\text{-}^{1}$	δ ,2.40(3H, s, -CH_3), 4.3(2H, d, -NH_2), 5.47(1H, s, Ar-OH), 5.51(1H, s, -CH), 6.6(1H, s, -NH), 7.1-7.3(4H, m, Ar-H). 7.8(1H, s, NH), 8.3(1H, s,-NHCO), ppm.	-
IId	Vmax, 3432 (-OH), 3231.27 (-$NHNH_2$), 3050(Ar-H), 1672 (amido->C=O), 1653(>C=C<), 1240 (>C=S). $Cm\text{-}^{1}$	δ ,2.39(3H, s, -CH_3), 4.28(2H, d,-NH_2), 5.5(1H, s, Ar-OH), 5.53(1H, s,-CH), 6.67(1H, s, -NH), 7.1-7.3(4H, m, Ar-H). 7.82(1H, s, NH), 8.34(1H, s,-NHCO), ppm.	-
IIe	Vmax, 3332(-$NHNH_2$), 3049(Ar-H), 1668 (amido,>C=O), 1604 (>C=C<), 1242 (>C=S). $Cm\text{-}^{1}$	δ ,2.34(3H, s, -CH_3),4.3(2H, s, -NH_2), 4.48(3H, s, OCH_3), 5.45(1H, s, -CH), 5.82(1H, s, NH), 7.1-7.3(4H, m, Ar-H), 7.8(1H,s,NH),8.13(1H,s,-CONH), ppm	-
IIf	Vmax, 3330.33(-NH), 3049(Ar-H), 1672 (amido-C=O), 1615 (>C=C<), 838 (C-Cl) $Cm\text{-}^{1}$	δ,2.31(3H, s, -CH_3), 4.62(2H, d, -NH_2), 5.50(1H,s,CH), 5.76(1H, s, -NH), 7.1-7.3(4H,m, Ar-H). 7.7(1H, s,-NH), 7.9(1H, s, -NHCO), ppm.	m/z 280.5(M^+), 282.5(M^++2).
IIg	Vmax ,3430.33(-NH), 3049 (Ar-H), 1648 (amido-C=O), 1634 (>C=C<), 1258 (>C=S) $Cm\text{-}^{1}$	δ ,2.35(3H, s, -CH_3), 4.66(2H, d, -NH_2), 5.53(1H, s, -CH), 5.76(1H, s, -NH), 7.1-7.3(4H,m, Ar-H). 7.8(1H, s, -NH), 8.23(1H, s, -NHCO), ppm.	m/z 296.5(M^+)
IIIa	Vmax, 3233(-NH), 1627 (>C=C<), 1698.33(>C=O), 1604 (>C=N), 1270(C-O-C), 1062(N-N), 1070 (- C-O) $Cm\text{-}^{1}$.	δ ,2.3(s,3H,-CH_3), 5.2(s,1H,-CH), 5.6 (s,1H,-NH), 7.2-7.3 (m,10H, Ar-H) , 8.3(s,1H,-NH), 10(s,1H,-CONH) ppm.	m/z 331.3.(M^+)
IIIb	Vmax ,3233(-NH),1604(>C=N) ,1527(>C=C<), 1062(N-N), 1070 (>C-O),1269 (C-O-C),$Cm\text{-}^{1}$	δ ,2.3(s,3H, -CH_3), 5.48(s,1H,-CH), 5.56(s,1H,-NH),7.2-7.3 (m,9H,Ar-H), 8.4(s,1H,-NH), 8.7(s,1H,Ar-OH), 9.5(s,1H,-CONH) ppm. .	m/z 346.7(M^+)
IIIc	Vmax ,3312 (>C-OH), 3233 (-NH), 1698.33 (>C=O), 1527 (>C=C<), 1604 (>C=N), 1269 (C-O-C), 1062(N-N), 1070 (-C-O), Cm^{-1} .	δ ,2.48(3H, s, -CH_3), 5.70(1H, s, CH), 5.88(1H, s, -NH), 6.4(1H, s, -NH), 7.1-8.2(9H, m, Ar-H). 8.8(1H, s, -NHCO), ppm.	m/z 362.1 (M^+)
IIId	Vmax ,3314 (**-**C-OH),3213(-NH), 1528 (>C=C<), 1600 (-C=N), 1270(C-O-C), 1242 (>C=S), 1062(N-N), 1072 (C-O)Cm^{-1}.	δ,2.42(3H,s,-CH_3), 5.69(1H,s,-CH), 5.81(1H, s, -OH), 598(1H, s, -NH), 6.38(1H, s, -NH), 7.1-8.2(9H, m, Ar-H). 8.78(1H, s,-NHCO) ppm.	m/z 359.9(M^+)
IIIe	Vmax, 3233(-NH), 1604 (>C=N-), 1520(>C=C<), 1269(C-O-C), 1242 (>C=S), 1062 (N-N), 1070 (C-O) Cm^{-1}.	δ, 2.45(3H, s,-CH_3), 4.6(3H, s, -OCH_3) , 5.65(1H, s, CH), 5.84(1H, s,-NH), 6.4(1H, s, -NH), 7.1-8.3 (9H, m, Ar-H). 8.7(1H, s,-NHCO) ppm .	m/z 377.5(M^+)
IIIf	Vmax ,3233(-NH), 1698.33 (>C=O), 1604 (>C=N), 1062(N-N), 1527(>C=C<), 1352(-C-N), 1041.47(C-O-C), 780 (C-Cl). Cm^{-1}.	δ,2.48(3H, s, CH_3), 4.61(3H,s,-OCH_3), 5.56(1H, s, -CH), 5.91(1H, s, -NH), 6.3(1H, s, -NH), 7.1-8.2 (9H, m, Ar-H), 8.7 (1H, s, -NHCO) ppm.	m/z 380.5(M^+), 382.5(M^++2).
IIIg	Vmax ,3213(-NH), 1698.33 (>C=O), 1604 (-C=N), 1527(>C=C<), 1270 (C-O-C), 1240(>C=S), 1070(C-O), 1062 (N-N) Cm^{-1}.	δ,2.3(s,3H, -CH_3), 5.48(s,1H,CH), 5.5 (s,1H,-NH). 7.2-7.3(m, 9H, Ar-H), 8.3(s, 1H,-NH), 8.5(s, 1H, Ar-OH), 9.1(s, 1H,-CONH)ppm.	m/z 346 (M^+)

CONCLUSION

We have developed an operationally simple, inexpensive, efficient and environmental friendly green protocol for synthesis of triazole with pyrimidine moiety. Synthesized products were in good yield which thus highlights the need for future work in pharmaceutical area.

The merits of the current protocol are:

1. Yields are excellent.
2. Required short reaction time.
3. Easy workup synthesis and operable on large scale.
4. Use of hazardous chemicals avoided.

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