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A simple and efficient one pot biginelli condesation of pyrazolo[3,4-d]pyrimidine-ones/thiones

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ABSTRACT

The synthesis of pyrazolo[5,4-d]pyrimidines from 5-isopropyl-2,4-dihydro-3H-pyrazol-3-one, substituted benzaldehydes and urea or thiourea in ethanol in the presence of catalytic amount of conc. acid as a one pot biginelli reaction involving iminium cation is described. The constitution of the product has been supported by FT-IR, ^{1}H NMR and mass spectral data.

KEYWORDS

Pyrazolo[5,4-d]pyrimidine-ones/thiones;
Antimicrobial activity.

INTRODUCTION

Pyrazolo[3,4-d]pyrimidines constitute a class of naturally occurring fused uracils that possess diverse biological activities[1]. These derivatives[2–5] were found to be selective ligands with antagonist activity for A1 adenosine receptors(A1AR). They may have therapeutical use as cognitive enhancers, antidementia drugs(e.g., for Alzheimer's disease and cerebrovascular dementia), psycostimulants, antidepressant drugs, and ameliorants of cerebral function[6]. Furthermore, a large number of pyrimidine derivatives are reported to exhibit antimyco bacterial[7], antitumor[8], antiviral[9], anticancer[10], anti-inflammatory[11], analgesic[12], antifolate[13], antimicrobial[14], anti-fungal[15], antiproliferative[16] and antihis taminic[17] activities.

To date, several methods have been developed to synthesize pyrazolo[3,4-d] pyrimidines, Yoneda et al.[18a,b] used the cycloaddition of azahexatrienes obtained by the reaction of an arylaldehyde and 6-uracil hydrazone. One disadvantage of this approach is the concomitant arylation of the pyrazole moiety. Earlier, this synthesis compounds was achieved by fusion of 6-uracil hydrazones at 300^{0}C[18c]. In another synthetic method reported[19] required the cycloaddition of an arylhydrazones to 6-chloro-5-nitrouracil, which involved several steps. Further, Kanazawa et al.[20] undertake the synthesis of pyrazolo[3,4-d]pyrimidines by the reaction of 6-benzylidene hydrazonouracils with NBS(N-bromo succinamide), which afforded triazino and pyridazino-uracils in addition to the pyrazolo[3,4-d]pyrimidines. Looking to the above cited literature survey reveals only a few reports on the synthesis of the parent pyrazolo[3,4-d]pyrimidine moiety, which usually requires drastic conditions, long reaction times and complex pathways.

The present research article reports a modified simple synthetic method which utilizes readily available starting material such as substituted benzaldehydes and urea or thiourea with complete regiocontrol reaction. Thus the one-pot reaction involves 5-isopropyl-2,4-dihydro-3H-pyrazol-3-one **(1)**, substituted benzalde-

hydes **(2)** and urea/ thiourea **(3)** in ethanol in the presence of catalytical amount of conc.acid afforded pyrazolo [3,4-d]pyrimidine derivatives **(4a-p)** in good yield.

The present work is explained by considering basic mechanism of multicomponents biginelli reaction. This includes the condensation of substituted benzaldehydes (a) with either urea or thiourea to form hemiaminal (b) with some similarities to the mannich condensation. Hemiaminal (b) undergoes dehydration inpresence of acid catalyst to produce iminium cation (c) as a intermediate. The enamine(iminium cation) (c) generated acts as an elecrophile for the nucleophilic addition of keto enol of pyrazolone with removal of proton to produce (d). The intermediate (d) undergoes intramolecular condensation in presence of acid between oxygen of ketone and amino group of urea or thiourea to give the cyclised targeted product (e).

Completion of the reaction was monitored by TLC. After the completion of the reaction, the pyrazolo[5,4-d]pyrimidines **(4a-j)** were crystallized from ethanol. All new compounds gave satisfactory elemental analyses(C, H,N,S) within ±0.5% of the theoretical values and the structures were in accordance with their spectroscopic data reported in TABLE 1. The structures of the synthesized compounds have been supported by the elemental analyser, FT-IR, ^{1}H NMR and mass spectral data.

It was interesting to note that the reaction occurred immediately. In conclusion, this work demonstrate a very simple and efficient method for the synthesis of a well functionalized pyrazolo[3,4-d] pyrimidines of biological importance in excellent yields.

EXPERIMENTAL

Melting points were determined routinely in open capillary tube and are uncorrected. The completion of reaction was routinely checked by TLC on silica gel-G plates of 0.5mm thickness and spots were located by iodine. Elemental analyses of the newly synthesized compounds was carried out on Carlo Erba 1108 analyzer and are found within the range of theoretical value. IR spectra were recorded on Shimadzu-8400 FT-IR spectrometer in KBr(λ in cm^{-1}). ^{1}H NMR spectra were recorded in $CDCl_3$ on a Brucker DRX-300 at 300MHz . EI-MS spectra were recorded on Shimadzu GC-MS QP-2010 by electron Impact method. In all the compounds, the molecular weights were found to be 43m/z less than the molecular ion peak. No particular fragmentation pattern is observed from the spectra.

Preparation of 3-isopropyl-1H-pyrazol-5(4H)-one (1)

A mixture of methyl 4-methyl-3-oxopentanoate (0.01m), and hydrazine hydrate(0.02m) in 1ml methanol stir for 1hrs. After the completion of the reaction a solid material separated was recrystallized from methanol.

Physical data for compound 3-isopropyl-1H-pyrazol-5(4H)-one (1)

Yield 85 %, m.p. 90 ^{0}C Anal. Calcd. for $C_6H_{10}N_2O$; Required: C, 57.12 %; H, 7.99 %; N, 22.21 % Found: C, 56.82 %; H, 8.09 %; N, 21.88 %. PMR δppm (TFA): 1.134(d, 6H, -2CH_3), 2.712(m, 1H, -CH), 10.373(s, 1H, -NH) Mass spectra of compound exhibited molecular ion peak at m/z 126 (M^+).

Preparation of 4,5-dihydro-3-isopropyl-4-(phenyl)-1H-pyrazolo[3,4-d]-pyrimidine-6(7H)-one/thiones (4a-p)

A mixture of the 5-isopropyl-2,4-dihydro-3H-pyrazol-3-one 1(0.01mole), substituted benzaldehydes 2(0.01mole) and urea 3(0.015mole) in ethanol in the presence of catalytic amount of conc. acid were refluxed for several time. After the completion of the reaction the separated solid material was crystallized from ethanol.

The other compounds **(4a-p)** were prepared in a similar manner. The physical data are displayed in TABLE 1.

Physical data for compound 4,5-dihydro-3-isopropyl-4-(4-chloro phenyl)-1H-pyrazolo[3,4-d] pyrimidine-6-(7H)-one (4b)

IR(KBr)ν_{max}cm^{-1} IR: 3439.19(2^0-NH2), 3116.00 (=C-H, SP2), 2870.17(C-H, Aliphatic), 1674.00(C =N),1651.12(C=C), 1089.82(C-N), 1014.59(Ar-Cl). ^{1}H NMR δppm(DMSO-d_6): 1.201(d, 6H, -2CH_3), 2.912(m, 1H, -CH), 5.243(s, 1H –H), 7.121-7.789 (dd, 4H Ar-H), 8.901(m, 3H, -NH). Mass spectra of compound exhibited molecular ion peak at m/z 247 (M^+).

4,5-Dihydro-3-isopropyl-4-(4-fluoro phenyl)-1H-

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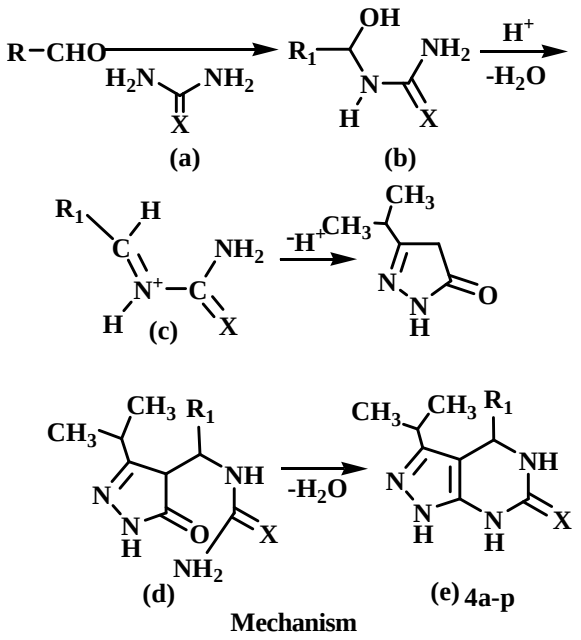
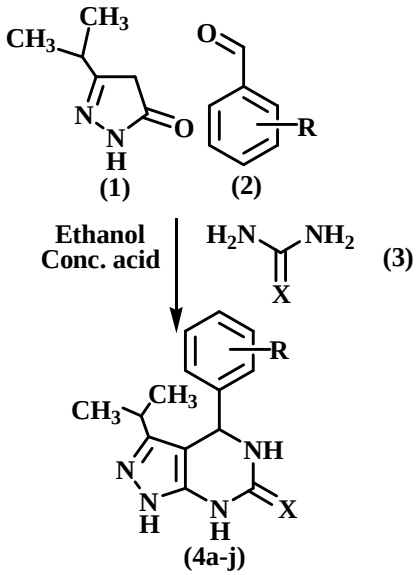
TABLE 1 : Physical and analytical data

Sr.no.	R	X	Molecular formula	m.p.^{O}C	Yield(%)	R_f Value		% of nitrogen calcd. found
						R_f1	R_f2	
4a	C_6H_5	O	$C_{14}H_{16}N_4O$	255	72	0.49	0.45	21.86 / 21.05
4b	4-Cl-C_6H_4	O	$C_{14}H_{15}N_4OCl$	270	78	0.51	0.49	19.27 / 19.81
4c	4-F-C_6H_4	O	$C_{14}H_{15}N_4OF$	260	69	0.52	0.46	20.43 / 20.12
4d	3-NO_2-C_6H_4	O	$C_{14}H_{15}N_5O_3$	291	81	0.41	0.52	23.24 / 23.02
4e	4-OCH_3-C_6H_4	O	$C_{15}H_{18}N_4O_2$	245	75	0.44	0.45	19.57 / 19.11
4f	2-NO_2-C_6H_4	O	$C_{14}H_{15}N_5O_3$	293	85	0.49	0.45	23.24 / 22.86
4g	4-NO_2-C_6H_4	O	$C_{14}H_{15}N_5O_3$	274	82	0.43	0.51	23.24 / 22.91
4h	3-Cl-C_6H_4	O	$C_{14}H_{15}N_4OCl$	292	69	0.54	0.46	19.27 / 18.78
4i	C_6H_5	S	$C_{14}H_{16}N_4S$	289	65	0.41	0.51	20.57 / 19.97
4j	4-Cl-C_6H_4	S	$C_{14}H_{15}N_4SCl$	265	71	0.39	0.52	18.26 / 18.06
4k	4-F-C_6H_4	S	$C_{14}H_{15}N_4SF$	294	69	0.40	0.49	19.30 / 18.93
4l	3-NO_2-C_6H_4	S	$C_{14}H_{15}N_5O_2S$	>300	74	0.44	0.51	22.07 / 21.68
4m	4-OCH_3-C_6H_4	S	$C_{15}H_{18}N_4OS$	274	68	0.46	0.53	18.53 / 18.12
4n	2-NO_2-C_6H_4	S	$C_{14}H_{15}N_5O_2S$	>300	78	0.39	0.48	22.07 / 21.78
4o	4-NO_2-C_6H_4	S	$C_{14}H_{15}N_5O_2S$	284	76	0.49	0.57	22.07 / 21.87
4p	3-Cl-C_6H_4	S	$C_{14}H_{15}N_4SCl$	288	59	0.51	0.59	18.26 / 17.94

TLC Solvent systems for R_f1 & R_f2 are: (1) Hexane : Ethyl acetate : 6.5 : 3.5 (R_f1), (2) Chloroform : Methanol : 9.0 : 1.0 (R_f2).



Mechanism



R = Substituted benzaldehydes, R=O,S

Reaction SCHEME

pyrazolo[3,4-d]pyrimidine-6(7H)-one(4c)

IR: 3495.96(2^0–NH_2), 3145.23(=C-H, SP2), 2867.69(C-H, Aliphatic), 1685.15(C=N), 1648.69 (C=C), 1397.89(i-Pr), 1207.85(Ar-F), 1085.26(C-N). ^{1}H NMR δppm (DMSO-d_6): 1.189(d, 6H, -2CH_3), 2.892(m, 1H, -CH), 5.182(s, 1H -H), 7.226-7.981(dd, 4H Ar–H), 9.141(m, 3H, -NH). Mass spectra of compound exhibited molecular ion peak at m/z 231 (M^+).

4,5-Dihydro-3-isopropyl-4-(3-nitro phenyl)-1H-pyrazolo[3,4-d]pyrimidine-6(7H)-one (4l)follows

IR: 3498.99(2^0-NH_2), 140.00(=C-H, SP2), 2865.17(C-H, Aliphatic), 1678.00(C=N), 1649.19 (C=C), 83.61(N=O, Asymmetric), 1396.51(i-Pr), 1087.89(C-N). ^{1}H NMR δppm (DMSO-d_6): 1.161(d, 6H, -2CH_3), 2.722(m, 1H, -CH), 5.286(s, 1H –H), 7.521-7.919(m, 4H Ar-H), 8.201-9.012(m, 3H, -NH). Mass spectra of compound exhibited molecular ion peak at m/z 258 (M^+).

4,5-dihydro-3-isopropyl-4-(4-chloro phenyl)-1H-pyrazolo[3,4-d]pyrimidine-6-(7H)-thione (4j)

IR: 3439.19(2^0-NH_2), 3116.00(=C-H, SP2),

2870.17(C-H, Aliphatic), 1674.00(C=N), 1651.12 (C=C), 1244.13(C=S), 1089.82(C-N), 1014.59 (Ar-Cl). ^{1}H NMR δppm(DMSO-d_6): 1.211(d, 6H, -2CH_3), 2.852(m, 1H, -CH), 5.343(s, 1H -H), 7.323-7.881 (dd, 4H Ar–H), 9.131-10.120(m, 3H, -NH). Mass spectra of compound exhibited molecular ion peak at m/z 263(M^+).

4,5-Dihydro-3-isopropyl-4-(4-fluoro phenyl)-1H-pyrazolo[3,4-d]pyrimidine-6(7H)-thione (4k)

IR: 3495.96(2^0-NH_2), 3145.23 (=C-H, SP2), 2867.69(C-H, Aliphatic), 1685.15(C=N), 1648.69 (C=C), 1397.89(i-Pr), 1207.85(Ar-F), 1275.52 (C=S), 1085.26(C-N). ^{1}H NMR δppm(DMSO-d_6): 1.208 (d, 6H, -2CH_3), 2.789 (m, 1H, -CH), 5.318 (s, 1H –H), 7.126-7.889 (dd, 4H Ar–H), 9.141-9.954 (m, 3H, -NH). Mass spectra of compound exhibited molecular ion peak at m/z 247 (M^+).

4,5-Dihydro-3-isopropyl-4-(4-nitro phenyl)-1H-pyrazolo[3,4-d]pyrimidine-6(7H)-thione (4o)

IR: 3498.99(2^0-NH_{22}), 140.00(=C-H, SP2), 2865.17(C-H, Aliphatic), 1678.00(C=N), 1649.19 (C=C), 83.61 (N=O, Asymmetric), 1396.51(i-Pr), 12843.63(C=S), 1087.89(C-N). ^{1}H NMR δppm (DMSO-d_6) : 1.161(d, 6H, -2CH_3), 2.722(m, 1H, -CH), 5.286(s, 1H -H), 7.521-7.919(dd, 4H Ar-H), 8.201-9.012(m, 3H, –NH). Mass spectra of compound exhibited molecular ion peak at m/z 274 (M^+).

CONCLUSION

It was interesting to note that the reaction occurred immediately. This work demonstrates a very simple and efficient method for the synthesis of a well functionalized pyrazolo[3,4-d]pyrimidines of biological importance in excellent yields.

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