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BASE CATALYSED ONE POT MULTICOMPONENT SYNTHESIS OF NOVEL 6-(3-NITROPHENYL)-7, 9-DIHYDRO-1H-PURINE-2,8 (3H,6H)-DITHIONEVIA A THREE-COMPONENT BIGINELLI TYPE CONDENSATION DERIVATIVES UNDER MICROWAVE IRRADIATION

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ABSTRACT
An efficient one-pot synthesis of novel 6-(3-nitrophenyl)-7,9-dihydro-1H-purine-2,8 (3H,6H)-dithionevia a three-component Biginelli type condensation of 2- Thiohydantoin, Aldehyde and urea/thiourea in the presence of fused Sodium acetate and acetic acid as a solvent using microwave irradiation was carried out.

KEY WORDS: 2-Thiohydantoin, Urea/Thiourea, Aromatic aldehydes, Biginelli reaction,Microwave irradiation.

INTRODUCTION
The use of microwave irradiation in organic synthesis has become increasingly popular within the pharmaceutical and academic arenas, because it is new enabling technology for drug discovery and development. By taking advantage of his efficient source of energy compound libraries for lead generation and optimization can be assembled in a fraction for time required by classical thermal methods.
In the last decades the MW technique has been intensively used to carry out organic reactions of almost all kinds, and has become a useful non-conventional means of performing organic syntheses.Hence,we found that microwave reactions occur with dramatic decreases in reaction times[I] cleaner reactions with easier workups than observed when using conventional heating and gives better yields. Thus, the use of the MW heating technique has become an essential tool in all areas of synthetic organic chemistry, including solvent-free, and water-mediated reactions[II-VI].Due to this application, the microwave technique were chosen for synthesis.
Multicomponent reactions (MCRs) are one-pot procedures in which almost all atoms of three or more reagents are combined, in order to afford only one product.Ithas several advantages when compared to classical procedures, especially considering atom economy and purification procedures and it emerged as an efficient and powerful tool in modern synthetic

organic chemistry because the synthesis of complex organic molecules from simple and readily available substrates can be achieved in a very fast and efficient manner without the isolation of any intermediate[VII, VIII].

Over the last decade, industrial and academic researchers have made MCRs as powerful strategies for the synthesis of bioactive organic compound[IX-XII].Synthesis of heterocycles compounds by MCRs, such as Biginelli[XIII] or Biginelli like reaction[XIV-XVI] have stimulated great interest due to their wide variety of biological activities, such as antiviral, antitumor, antibacterial, antihypertensive, neuropeptide antagonist and anti-inflammatory properties as well as calcium channel modulating activity[XVII-XXI].In this context, the one-pot cyclocondensation of any active methylene with aromatic aldehydes and thiourea/urea, known as Biginellireaction[XXII],has been one of the most well studied MCRs in recent years.

The reaction affords formation of dihydropyrimidine derivatives as an important substructure of many synthetic[XXIII–XXVI]and natural compounds. In addition, several dihydropyrimidine containing alkaloids are isolated from marine sources which possess bilological and anti-HIV properties[XXVII-XXVIII].To extend the scopes of the Biginelli reaction, many alterations are made to the original high temperature HCl catalyzed condensation of ethylacetoacetate, benzaldehyde, and urea in ethanol[XXIX] by variation of the three components[XXX–XXXV]and the conditions[XXXVI– XL].

Due to their unique physical, chemical, and biological properties,this work involves three component reaction between Thiohydantoin, aldehyde and thiourea/urea in acetic acid as a solvent to obtain a novel product i.e6-(3-nitrophenyl)-7, 9-dihydro-1H-purine-2,8 (3H,6H)-dithionein the presence of fused sodium acetate as a base catalyst by using microwave irradiation.

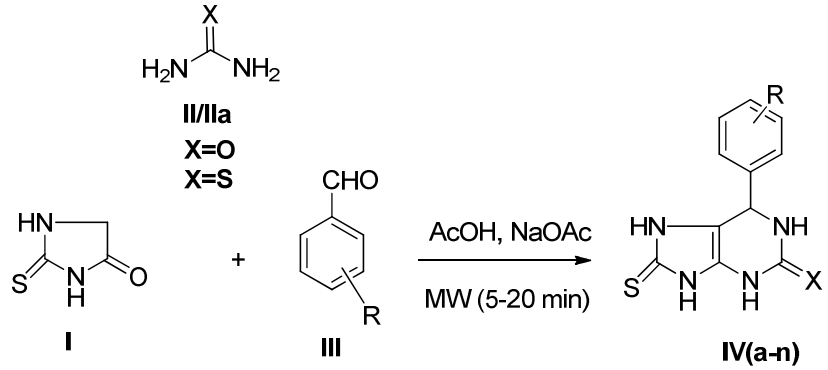
EXPERIMENTAL SECTION

Unless and otherwise noted, all Chemicals used were of commercial grade and they were used without any further purification. All reactions were monitored by thin layer chromatography using aluminium sheets precoated with silica gel 60 F254 (Merck) using either UV light or iodine vapours as visualizing agents.

*General procedure for the synthesis of tetrahydro-1H-purin-2(3H)-dithione and tetrahydro-1H-purin-2(3H)-one***IV(a-n)**

A mixture ofThiohydantoin**(1)** (3 mmol), urea/thiourea**(II/IIa)** (3 mmol), substituted **(III)**aldehyde (3 mmol), in acetic acid (10ml) and sodium acetate (20mol%) were irradiated in microwave for 5-10min.The reaction was monitored by TLC. Upon completion, the reaction mass was cooled to room temperature. The solid thus obtained, was filtered, washed with hot water and recrystallized from alcohol to afford pure compound.

Scheme 1: Synthetic route of the titled compounds 4(a-n)



RESULTS AND DISCUSSION

Melting points were measured in open capillaries and are uncorrected. IR spectra was recorded on Bruker FTIR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker FTNMR (500MHz) spectrophotometer with DMSO-d_6 as solvent and TMS as internal standard. Solvent peaks in ^{1}H-NMR and ^{13}C-NMR spectra have been removed in tracing. The chemical shifts in parts per million (δ) are reported downfield from TMS (0 ppm). The abbreviations s, d, t, q, m and dd refer to singlet, doublet, triplet, quartet, multiplet and doublet of doublet respectively.

*6-phenyl-8-thioxo-6,7,8,9-tetrahydro-1H-purin-2(3H)-one**IVa***

Molecular Formula: $C_{11}H_{10}N_4OS$

Molecular Weight (gmol-1): 246.29

Melting Point (ºC):235-237

IR (KBr, cm-1):3322 and 3213(NH),1610 (C=O),1550(C=C), 1258 (C=S).

^{1}H NMR (500 MHz, DMSO, δ ppm): 5.22 (s, 1H, CH), 7.20-7.53 (m, 5H, Ar-H), 7.89 (s, 2H, 2NH), 10.58 (s, 2H, 2NH).

^{13}C NMR (500 MHz, DMSO, δ ppm): 62.2, 101.5, 115.9, 126.7, 127.2, 128.2, 143.3, 150.2, 170.8.

*6-(4-chlorophenyl)-8-thioxo-6,7,8,9-tetrahydro-1H-purin-2(3H)-one**IVb***

Molecular Formula: $C_{11}H_9ClN_4OS$

Molecular Weight (gmol-1): 280.73

Melting Point (ºC):269-273

IR (KBr, cm-1):3316 and 3207(NH), 1690 (C=O),1603(C=C), 1298 (C=S).

^{1}H NMR (500 MHz, DMSO, δ ppm): 6.22 (s, 1H, CH),7.89-8.10 (m, 4H, Ar-H),8.89 (s, 2H, 2NH), 11.58 (s, 2H, 2NH).

^{13}C NMR (500 MHz, DMSO, δ ppm): 62.4, 102.7, 115.7, 126.8, 127.1, 128.9, 144.3, 150.7, 170.5.

*6-phenyl-7,9-dihydro-1H-purine-2,8(3H,6H)-dithione**IVh***

Molecular Formula: $C_{11}H_{10}N_4S$

Molecular Weight (gmol-1): 262.35

Melting Point (ºC):240-243

IR (KBr, cm-1):3255 and 3305(NH),1580(C=C), 1206 (C=S).

^{1}H NMR (500 MHz, DMSO, δ ppm): 6.70 (s, 1H, CH),7.12-7.58 (m, 5H, Ar-H),7.92 (s, 2H, 2NH), 10.21 (s, 2H, 2NH),

^{13}C NMR (500 MHz, DMSO, δ ppm): 59.30, 100.80, 114.91, 125.80, 126.30, 127.60, 145.48, 152.71, 171.51.

6-(3-nitrophenyl)-7, 9-dihydro-1H-purine-2,8 (3H,6H)-dithione***IVm***

Molecular Formula: $C_{11}H_9N_50_2S_2$

Molecular Weight (gmol-1): 307.35

Melting Point (ºC):282-284

IR (KBr, cm-1):3148 and 3241(NH),1580(C=C), 1280 (C=S).

^{1}H NMR (500 MHz, DMSO, δ ppm): 6.53 (s, 1H, CH), 7.10-7.60 (m, 4H, Ar-H), 8.10 (s, 2H, 2NH), 11.31 (s, 2H, 2NH),

^{13}C NMR (500 MHz, DMSO, δ ppm): 60.30, 101.25, 115.48, 125.53, 126.64, 127.33, 144.18, 151.61, 170.41.

To exploit simple and suitable conditions for synthesis of 6-(3-nitrophenyl)-7, 9-dihydro-1H-purine-2,8 (3H,6H)-dithione, the reaction of 2-Thiohydantoin **I** , Urea/Thiourea **II/IIa**, and

aldehyde **III** were chosen for synthesis under microwave irradiation and its behavior was optimize under a variety of conditions (**Table No. 1.)**

Table No. 1. Optimization of solvent for the reaction ofThiohydantoin(3mmol) Urea/Thiourea(3mmol), aldehyde(3mmol), Sodium acetate (20 mol%), under Microwave Irradiation (5-20min)

Entry	Solvent	Time(min)	Yield of product(%)
i	H_2O	12	40
ii	EtOH	15	50
iii	MeOH	17	52
iv	DMF	18	65
v	**Acetic Acid**	**10**	**93**
vi	Toluene	19	20
vii	DCM	16	24

Recently, microwave irradiation has become a powerful tool in organic synthesisbecause,the high heating efficiency giving remarkable rate enhancement and dramatic reduction in reaction time. As a continuation of our efforts in this work we decided to try the different and easily available catalyst, sodium acetate, triethylamine (TEA), piperidine, imidazole, and pyridine were examined separately as a catalyst in the microwave assisted reaction as shown in (**Table no 2**).All the reactions were carried out in a microwave reactor at the power of 200 W. The results are displayed in **(Table no 3).**Interestingly, in all the reactions, we got a single product with high yield and shortest reaction time was observed in the case of sodium acetate (entry v). So, sodium acetatewas chosen as the catalyst for the reaction.

Table no 2. Effect of catalyst for the synthesis of IVm under microwave irradiation

Entry	Catalyst	Time(Min)	Yield (%)
i	Triethylamine	15	70
ii	Piperidine	17	68
iii	Imidazole	19	69
iv	pyridine	23	62
v	**Sodium acetate**	**10**	**93**

Table No. 3: Characterization table of compoundIV(a-n)

Compound code	R	X	Time (min)	Yield (%)	Melting Point (°C)
IVa	H	O	10	93	235-237

IVb	4-Cl	O	12	85	269-273
IVc	2-Cl	O	15	84	270-272
IVd	4-Br	O	14	75	276-279
IVe	3-OCH_3	O	12	78	259-263
IVf	4-OCH_3	O	16	76	264-265
IVg	3-NO_2	O	08	82	280-284
IVh	H	S	11	91	240-243
IVi	4-Cl	S	13	83	272-274
IVj	4-OH	S	15	80	260-263
IVk	3-OH	S	18	79	262-264
IVl	4-OH-3-OCH_3	S	17	70	250-253
IVm	3-NO_2	S	06	93	282-284
IVn	4-NO_2	S	09	86	283-285

(Microwave energy in watt for reaction purpose is 210)

CONCLUSIONS

1. Microwave assisted synthesis of pyrimidines using base as a catalyst offers several advantages over the conventional heating methods such as shorter reaction times, excellent yields and simple experimental workup procedures.
2. The mildness of the method together with ease of operation should largely extend the scope of microwave assisted synthesis which is safe, environmentally friendly and inexpensive for the three component Biginelli reaction.

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