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Base Catalysed One Pot Multicomponent Synthesis of Novel 6-(3-Nitrophenyl)-7, 9-Dihydro-1H-Purine-2, 8 (3H,6H)-Dithione *via* 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)-dithione via 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. 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.

Keywords: Urea/thiourea; Sodium acetate; Organic reactions

INTRODUCTION

Hence we found that microwave reactions occur with dramatic decreases in reaction times 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 synthetic organic chemistry, including solvent-free, and water-mediated reaction. Due to this application, the microwave techniques were chosen for synthesis [1,2]. Multi Component 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. It has 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. Over the last decade, industrial and academic researchers have made MCRs as powerful strategies for the synthesis of bioactive organic compound 9-12. Synthesis of heterocycles compounds by MCRs, such as Biginelli or Biginelli like reaction 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. In this context, the one-pot cyclocondensation of any active methylene with aromatic aldehydes and thiourea/urea, known as Biginelli reaction, has been one of the most well studied MCRs in recent years [3-7].

MATERIALS AND METHODS

The reaction affords formation of dihydropyrimidine derivatives as an important substructure of many synthetic and natural compounds. In addition, several dihydropyrimidine containing alkaloids are isolated from marine sources which possess bilological and anti-HIV properties. 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 ethano l29 by variation of the three components and the conditions. Due to their unique physical, chemical and biological properties.

RESULTS AND DISCUSSION

In this work it involves three component reaction between thiohydantoin, aldehyde and thiourea/urea in acetic acid as a solvent to obtain a novel product i.e. 6-(3-nitrophenyl)-7, 9-dihydro-1H-purine-2, 8 (3H, 6H)-dithione in the presence of fused sodium acetate as a base catalyst by using microwave irradiation [8]. 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 1, Urea/Thiourea 2/2a, and aldehyde 3 were chosen for synthesis under microwave irradiation and its behavior was optimize under a variety of conditions (Table 1).

Table 1: Optimization of solvent for the reaction of Thiohydantoin (3 mmol) Urea/Thiourea (3 mmol), aldehyde (3 mmol), Sodium acetate (20 mol%), under Microwave Irradiation (5 min -20 min).

Entry	Solvent	Time (min)	Yield of product (%)
1	H_2O	12	40
2	EtOH	15	50
3	MeOH	17	52
4	DMF	18	65
5	Acetic Acid	10	93
6	Toluene	19	20
7	DCM	16	24

Recently, microwave irradiation has become a powerful tool in organic synthesis because, 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, Tri Ethyl Amine (TEA), piperidine, imidazole, and pyridine were examined separately as a catalyst in the microwave assisted reaction [9-15]. All the reactions were carried out in a microwave reactor at the power of 200 W. The results are displayed. 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 5). So, sodium acetate was chosen as the catalyst for the reaction (Tables 2 and 3).

Table 2: Effect of catalyst for the synthesis of 4 m under microwave irradiation.

Entry	Catalyst	Time (Min)	Yield (%)
1	Triethylamine	15	70
2	Piperidine	17	68
3	Imidazole	19	69
4	pyridine	23	62
5	Sodium acetate	10	93

Table 3: Characterization table of compound 4 (a-n).

Compound code	R	X	Time (min)	Yield (%)	Melting Point (°C)
4a	H	O	10	93	235-237
4b	4-Cl	O	12	85	269-273
4c	2-Cl	O	15	84	270-272
4d	4-Br	O	14	75	276-279
4e	3-OCH_3	O	12	78	259-263
4f	4-OCH_3	O	16	76	264-265
4g	3-NO_2	O	8	82	280-284
4h	H	S	11	91	240-243

4i	4-Cl	S	13	83	272-274
4j	4-OH	S	15	80	260-263
4k	3-OH	S	18	79	262-264
4l	4-OH-3-OCH_3	S	17	70	250-253
4m	3-NO_2	S	6	93	282-284
4n	4-NO_2	S	9	86	283-285

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 vapoursas visualizing agents. General procedure for the synthesis of tetrahydro-1H-purin-2(3H)-dithione and tetrahydro-1H-purin-2(3H)-one 4(a-n) A mixture of Thiohydantoin (1) (3 mmol), urea/thiourea (2/2a) (3 mmol), substituted (3) aldehyde (3 mmol), in acetic acid (10 ml) and sodium [15-20].

Molecular formula: $C_{11}H_{10}N_4OS$
Molecular weight (gmol^{-1}): 246.29
Melting point (ºC): 235-237
IR (cm^{-1}): 3322 and 3213 (NH), 1610 (C=O), 1258 (C=S).
1H 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).
13C 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 4b

Molecular formula: $C_{11}H_9C_lN_4OS$
Molecular weight (gmol^{-1}): 280.73
Melting point (ºC): 269-273
IR (KBr, cm^{-1}): 3316 and 3207(NH), 1690 (C=O), 1298 (C=S).
1H 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).
13C NMR (500 MHz, DMSO, δ ppm): 62.4, 102.7, 115.7, 126.8, 127.1, 128.9, 144.3, 150.7, 170.5.
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), 1206 (C=S).
1H 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 NMR (500 MHz, DMSO, δ ppm): 59.30, 100.80, 114.91, 125.80, 126.30, 127.60, 145.48, 152.71, 171.51.

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), 1280 (C=S).
1H 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),
13C NMR (500 MHz, DMSO, δ ppm): 60.30, 101.25, 115.48, 125.53, 126.64, 127.33, 144.18, 151.61, 170.41.

CONCLUSION

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. 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. Melting points were measured in open capillaries and are uncorrected. IR spectra were recorded on Bruker FTIR spectrophotometer. 1H-NMR and 13C-NMR spectra were recorded on Bruker FTNMR (500 MHz) spectrophotometer with DMSO-d6 as solvent and TMS as internal standard. Solvent peaks in 1H-NMR and 13C-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.

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