SELECTFLUOR™ CATALYZED ONE POT SYNTHESIS OF DIHYDROPYRIMIDINONES: AN IMPROVED PROTOCOL FOR THE BIGINELLI REACTION

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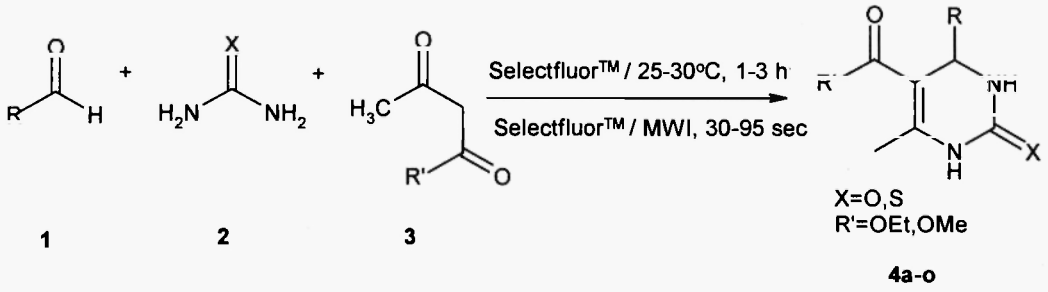
Abstract : A novel one pot condensation of an aldehyde, β-ketoesters and urea / thiourea in acetonitrile has been performed using selectfluor™ in both conventional and microwave irradiation method affording dihydropyrimidinones in excellent yields (80-95%) and short reaction time.
Key words : Biginelli reaction, dihydropyrimidinones, selectfluor™, one-pot condensation, microwave irradiation methods.

Introduction

Dihydropyrimidines-2(*1*H)-ones (DHPMS) are important class of compounds due to their therapeutic and pharmacological properties as calcium channel blockers, antihypertensive agents, α-1-a-antagonists, and neuropeptide Y(NPY) antagonists[1]. Many synthetic methods for preparing the DHPMS compounds under classical reflux[2a-j] or solvent free conditions[3-9] and microwave[10-13] (or) ultrasonic irradiation[14-15] have been reported. In continuation of our work[2d] on Bignelli reaction we developed simple, convenient and efficient catalytic system for the preparation of DHPMS compounds (Scheme-1). Recently, selectfluor™, has been introduced commercially as a user-friendly electrophilic fluorinating agent. Selectfluor™ is readily available at low cost and is easy to handle and retains its activity even in the presence of amines[16]. More recently, selectflour™, has been employed as an efficient Lewis acid catalyst for the one-pot allylation reactions of imines and for the hydrolysis of acetals, dithia-acetals and tetrahydropyranyl ethers[17], However, there are no examples of the use of selectfluor™ as a catalyst for the synthesis of DHPMS compounds. Microwave irradiation is a non-conventional energy source that has been a special interest in organic chemistry in recent years[18]. Some of the interesting features of this method are the rapid reaction rates, simplicity and cleaner reaction conditions[18b d]. Microwave irradiation generates rapid intense heating of polar substance, which results in reduction of reaction time compared to conventional heating, this prompted us to compare and synthesize DHPMS compounds in

conventional and microwave irradiation methods. All the Biginelli adducts were identified by their ^{1}H NMR and mass spectral data.



1 2 3 4a-o

Scheme-1

Experimental

Method A. The Biginelli condensation reaction was carried out at 25-30°C using an aldehyde (1m mol), urea or thiourea (1.5 m mol) and selectfluor™ (0.2 m mol) in acetonitrile (10 ml) for a certain period of time (1-3 h) as required to complete the reaction. The solvent was removed under reduced pressure. The solid thus obtained was filtered and washed with ice-cold water which was recrystallized from ethanol to get pure product with 80-92% yield.

Method B. In microwave irradiation method the above said reactants are charged in 25 ml beaker containing 10 ml acetonitrile, selectfluor™, was placed inside a container filled with silicagel and then inserted into microwave oven. The reaction mass subjected to microwave-irradiation at 300 watt power level for different times (30-95 sec). The solid thus obtained was filtered and washed with ice-cold water which was recrystallized from ethanol to get pure product with 85-95% yield. The results of these experiments are depicted in **Table-1.**

Table-1 : Selectfluor™ catalyzed efficient synthesis of dihydropyrimidin-2(*1*H)-ones

Product	R	R^1	X	Method A		Method B	
				Time (h)	Yield (%)[a]	Time (sec)	Yield (%)[a]
4a[2a]	C_6H_5	OEt	O	1.5	92	45	95
4b[2a]	4-(Cl)-C_6H_4	OEt	O	2.0	83	60	92
4c[2a]	4-(NO_2)-C_6H_4	OEt	O	3.0	87	50	92
4d[2a]	3-(NO_2)-C_6H_4	OEt	O	2.0	86	65	93
4e[aa]	4-(OCH_3)-C_6H_4	OEt	O	1.0	85	60	89
4f[2a]	3-(NO_2)-C_6H_4	OEt	O	2.5	86	95	91
4g[2a]	4-(OH)-C_6H_4	OEt	O	1.5	87	85	88
4h[2b]	4-(OH)-C_6H_4	OEt	S	1.0	88	95	89
4i[2b]	4-(OCH_3)-C_6H_4	OEt	S	2.0	80	80	85
4j[2c]	2-furyl	OEt	O	2.0	87	90	88
4k[2a]	4-(NO_2)-C_6H_4	OMe	O	3.0	82	75	87
4l[2a]	4-(OCH_3)-C_6H_4	OMe	O	1.5	83	60	89
4m[2a]	C_6H_5	OMe	O	2.0	91	30	94
4n[2a]	4-(Cl)-C_6H_4	OMe	O	2.0	90	60	92
4o[2a]	4-(OH)-C_6H_4	OMe	O	2.5	84	55	86

[a]Yields refer to pure solid products, all products were characterized by comparison of their physical and spectral data with those of authentic samples.

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