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A Novel Approach to Furopyrimidinones Using Dry Media

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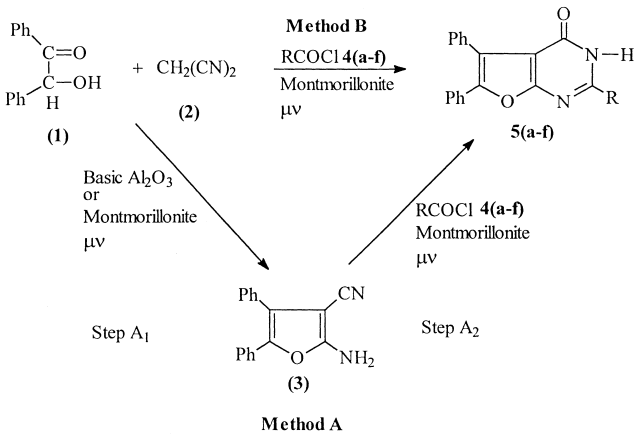
An environmentally benign approach to the synthesis of furopyrimidin-4(3*H*)-one under microwave irradiation (MWI) using an inorganic solid support for catalytic activity as well as an energy-transfer medium is described. The reaction time can be decreased from hours to minutes along with a yield enhancement. In addition, the differential activity of various solid supports was studied for a reaction which enables one to accomplish the one-pot synthesis of the required product via the 2-aminofuran-3-carbonitrile intermediate.

The increasing environmental consciousness throughout the world has triggered a search for new products and processes that are compatible with the environment. Strict legal restrictions on pollution exposure have enforced the application of solvent-less conditions into practice. In this endeavor, inorganic solid supports (alumina, bentonite, zeolite, montmorillonite, etc.) have made a landmark, because reactions can be performed in a "dry media" or under "solvent-free conditions."[1–4] The risk of high-pressure development associated with solution-phase reactions has been circumvented in dry media,[5–6] thus allowing work to be conducted with open vessels. In addition, the use of solid supports[7–8] in conjunction with microwaves[9] leads to a higher yield, a remarkable reaction rate enhancement, and high catalytic activity with the optimum utilisation of energy. This solvent-less approach provides an opportunity to conduct selective organic functional-group transformations more efficiently and expeditiously, thereby increasing the potential of such reactions to be upscaled.[10]

The furo[2,3-*d*]pyrimidine ring system, because of a formal isoelectronic relationship with purine, is specially of biological interest.[11–13] It has numerous pharmacological and agrochemical applications viz. herbicides,[14] antimalarials,[15] antitumour,[16] and antihypertensive[17] drugs, as well as potential radiation protection agents.[18]

In view of the ecofriendly role of dry media using microwaves, the biopotential of furopyrimidines and our ongoing endeavor towards green synthesis, we herein report a facile, rapid, and an environmentally benign synthesis of furopyrimidin-4-ones. Moreover, we studied the behavior of different solid supports under microwaves for the synthesis of the intermediate, 2-aminofuran-3-carbonitrile, and a product, furopyrimidin-4-one, and developed a one-pot synthesis of furopyrimidin-4-one.



where, R = C_6H_5, CH_3, CH_2Cl, 3-C_5H_4N, C_7H_{15}, $C_{11}H_{23}$

Scheme 1.

2-Amino-4,5-diphenylfuran-3-carbonitrile (**3**) upon a reaction with different arenecarbonyl and alkanoyl chlorides (**4a–f**) under MWI[19] in dry media yielded 2-Alkyl/Aryl-5,6-diphenylfuro[2,3-*d*]pyrimidin-4-(3*H*)-one (**5a–f**) (Step A_2) (Scheme 1). Conventionally, a similar cyclization of 2-aminofuran-3-carbonitrile with acyl chlorides to the fused pyrimidin-4-ones, as reported by Yamazaki et al.,[20] is a two-step reaction requiring absolute ethanol and dry HCl. In an attempt to greenify this methodology, the reaction was tried on different solid supports. The best result in terms of the yield and reaction time was obtained with montmorillonite K-10 clay under microwaves, which afforded the required furopyrimidin-4-one in one step from the 2-aminofuran-3-carbonitrile (Table 1). This result may be attributed to the ditopic[21] nature of montmorillonite. The reaction on acidic alumina did not go to completion, even after 15 min of irradiation, indicating that acidic conditions are not sufficient for the formation of furopyrimidin-4-ones (**5a–f**). In the IR spectrum (Table 1), the disappearance of band at 2200 cm^{-1} due to C≡N and the appearance of a band at 1600 cm^{-1} due to C=N and 1650 cm^{-1} due to C=O confirmed the formation of the products (**5a–f**).

The classical Gewald[22] method for the synthesis of the intermediate, 2-aminofuran-3-carbonitrile (**3**), involving the reaction of acyloins with CH- acidic nitriles under alkaline conditions in DMF, is time consuming and gives a relatively low yield. The synthesis was thus modified[23] by using basic alumina/montmorillonite under MWI (Step A_1) (Scheme 1), giving an improved yield with a large reduction of the reaction time. Montmorillonite gave an 85% yield, but basic alumina gave a relatively better yield (90%) for a shorter irradiation time. This is attributed to the requirement of basic conditions for the abstraction of a proton by the active methylene group.

Further, the formation of both the precursor, 2-aminofuran-3-carbonitrile, and the final cyclized product, furopyrimidin-4(3*H*)-one, on montmorillonite prompted us to attempt a one-pot synthesis of the final product from the reactants: benzoin (**1**), malononitrile (**2**) and acyl chloride (**4a–f**) (Method B)[24] (Scheme 1). This one-pot synthesis minimizes the yield loss, and energy loss, and limits the necessity of hazardous solvents.[25]

Table 1. Physical and Spectroscopic Data of Compounds (**5a–f**)

Compd No.	R	Method A[a] time/yield (min) (%)	Method B[b] time/yield (min) (%)	MP/°C (Recrystallization solvent)	Spectroscopic data[c] IR (ν_{max}/cm^{-1}) NH	C=N	C=O	^{1}H NMR/δ(CDCl$_3$, DMSO-d_6, 60 MHz)
5a	C_6H_5	4.5/78	9/82	94–96 (pet. ether)	3385	1602	1663	7.4–7.9 and 8.2–8.0 (m, 16H, 3 × Ph and NH)
5b	CH_3	4.0/70	8/74	342–346[26] (DMF)	3318	1592	1616	1.3 (s, 3H, CH_3), 7.3–7.6 (m, 11H, 2 × Ph and NH)
5c	CH_2Cl	10.0/75	14/80	167–170 (benzene–EtOH)	3360	1611	1661	3.8 (s, 2H, CH_2), 7.3–8.0 (m, 11H, 2 × Ph and NH)
5d	C_7H_{15}	6.5/72	11/73	275–277 (hexane–benzene)	3343	1598	1650	0.90 (t, 3H, CH_3), 2.3–2.8 (m, 10H, CH_2), 3.1–3.4 (t, 2H, CH_2), 7.2–7.8 (m, 11H, 2 × Ph and NH)
5e	$C_{11}H_{23}$	8.0/80	12/81	80–83 (hexane)	3279	1591	1611	0.88 (t, 3H, CH_3), 2.2–2.7 (m, 16H, CH_2), 3–3.3 (t, 2H, CH_2), 7.5–8.3 (m, 11H, 2 × Ph and NH)
5f	3-C_5H_4N	7.5/82	13.0/85	248–250 (benzene–hexane)	3393	1600	1654	7.5–7.9 and 8.1–8.3 (m, 15H, 2 × Ph, NH and nicotinyl)

a) (Step A_2). b) Total time for one pot synthesis ($4 + x$) min, 4 min is the time required for the synthesis of the intermediate **3** over montmorillonite. "x" is the additional time required for the synthesis of furopyrimidin-4(3*H*)-one, **5a–f** from intermediate, **3**. c) All the compounds gave satisfactory CHN analysis.

The above-mentioned solid supported reactions (basic alumina/montmorillonite) were performed conventionally in an oil bath under similar conditions. Heating in an oil bath (maintained at ~110–120 °C) for about 4 h gave the intermediate with 30% and 35% yields on montmorillonite and basic alumina, respectively. The final cyclized product was obtained within 6 hours of heating with a 25% yield.

In conclusion, the proposed methodology provides an easier, practically convenient and environmentally benign one-pot synthesis of bioactive furopyrimidin-4-one under much milder reaction conditions. The procedure clearly highlights the versatility of solid supports, especially when coupled with microwaves.

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23 To the solution of **1** (0.01 mol) and **2** (0.01 mol) in ethanol (~10 mL) added basic alumina (20 g)/montomorillonite (15 g) with constant stirring. The mixture was air dried at room temperature, placed in an alumina bath and subjected to MWI for 1.3 min/4 min respectively.

24 To the solution of **1** (0.01 mol) and **2** (0.01 mol) in ethanol (~10 mL) added montmorillonite K-10 clay (15 g) with constant stirring, air dried. Then placed in an alumina bath and subjected to MWI for 4 min. Upon formation of the intermediate (**3**) as observed by TLC, the solution of acyl chloride in ethanol was added to the same solid support with stirring, air dried and further subjected to MWI (approx. bulk temperature reached ~100–120 °C).

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