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# STUDIES ON INORGANIC SOLID SUPPORTS UNDER MICROWAVE IRRADIATION USING SYNTHESIS OF PYRANO[2,3-d]PYRIMIDINES

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## STUDIES ON INORGANIC SOLID SUPPORTS UNDER MICROWAVE IRRADIATION USING SYNTHESIS OF PYRANO[2,3-d]PYRIMIDINES

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#### ABSTRACT

Difference in activity of inorganic solid supports under microwave irradiation, for the synthesis of pyrano[2,3-*d*]pyrimidines is reported.

*Key Words:* Inorganic solid supports; Microwave irradiation; Pyranopyrimidines; Thiobarbituric acids; Chalcone

Pyranopyrimidines have proved to be interesting due to their associated diverse biological activities.<sup>[1-3]</sup> Further their application in organic chemistry, especially as oxidising agents,<sup>[4]</sup> has stimulated the interest of chemists all over the world. Though various methods for their synthesis are known,<sup>[4-6]</sup> the majority are multistep with poor yield and often involves environmentally unacceptable reagents.

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Enhanced reactivity, selectivity and associated ease of manipulation has made solid phase reactions very attractive in organic synthesis. Moreover, the advantages of coupling solid phase synthesis with microwaves are now well established.<sup>[7]</sup> During the course of investigation,<sup>[8]</sup> of organic reactions under microwave irradiation, we have observed that such procedures lead to faster reactions with improved yield. Further, the reactions in dry media condition are specially appealing as they provide an opportunity to work with open vessels, thus avoiding the risk of high pressure development, and offer the possibility of carrying out reactions upto a manufacturing scale.

In the present work, we have made an attempt to provide a milder synthesis of pyranopyrimidines and to study the differential activity of solid supports under microwave irradiation.

Pyrano[2,3-*d*]pyrimidines are known to be prepared by various routes. The most common methodology involves building the pyrano ring on to the pyrimidine ring using the active methylene side. One of the literature procedure<sup>[6]</sup> reporting a general approach of its synthesis, involves condensation of  $\alpha$ , $\beta$ -unsaturated carbonyl compounds with thiobarbituric acids using the noxious P<sub>2</sub>O<sub>5</sub> as condensing agent and glacial acetic acid as solvent. The mechanism involves Michael addition of the carbonyl group to the active methylene of thiobarbituric acid and subsequent cyclization of the Michael adduct so formed, or the concerted addition of mesomeric cations of the  $\alpha$ , $\beta$ -unsaturated carbonyl compounds.

Synthesis of the adduct (3a-f) (Figure A) is generally achieved by refluxing the reactants in methanol in the presence of triethylamine and on further refluxing in glacial acetic acid this is cyclized to give the required product. Single step synthesis have also been achieved by refluxing the reactants in presence of P<sub>2</sub>O<sub>5</sub> and glacial acetic acid. The above methodology is environmentally unacceptable and demands a modification.

Michael addition of chalcone (2) to thiobarbituric acids (1a-f) was attempted on inorganic solid supports under microwave irradiation.



 $R = H, C_6H_5, o-CH_3OC_6H_4, p-CH_3OC_6H_4, o-CH_3C_6H_4, p-CIC_6H_4$ 

Figure A.



 $R = H, C_6H_5, o-CH_3OC_6H_4, p-CH_3OC_6H_4, o-CH_3C_6H_4, p-ClC_6H_4$ 



The best results (Table 1) were seen, when the reactants were adsorbed over basic alumina.<sup>[9a]</sup> In 2–3 min the adduct (**3a–f**) was obtained. On neutral alumina,<sup>[9b]</sup> the reactions do not go to completion and only about 40–60% of the Michael adduct was obtained even after 5 min of irradiation. On the other hand, reaction on acidic alumina<sup>[9c]</sup> resulted in multiple spots along with the reactants, as followed by TLC examination. With Silica Gel<sup>[9d]</sup> also, results similar to acidic alumina were observed. The Michael addition of chalcone to active methylene group of thiobarbituric acid requires basic condition for the abstraction of proton, in line with the preferential formation of the adduct on basic alumina.

Cyclization of the Michael adduct (3a-f) to the required product (4a-f) (Figure B) was achieved on both acidic alumina and montmorillonite,<sup>[9e]</sup> in approximately same irradiation time (Table 1), though the yields were marginally better in montmorillonite as compared to acidic alumina. The above observation is consistent with requirement of acidic condition for the cyclization of these compound.

When adsorbed over montmorillonite the reactants gave the required product (**4a–f**) (Figure C) directly without detection of intermediate adduct. This can be explained by the fact that clay behaves like a ditopic catalyst<sup>[10]</sup> containing both acidic and basic sites. Moreover unlike the two step mechanism involving Michael adduct and its cyclization, its mechanism may involve the formation of mesomeric cation as reported by Ahluwalia et al.<sup>[6]</sup> On the other hand, single step reaction is not observed with other inorganic solid supports. Acidic alumina and silica gel resulted in multiple spots on TLC examination, which corresponded to both the intermediate adduct and final product in addition to uncharacterized byproducts. On basic alumina, the reaction lead to the intermediate adduct (**3a–f**) only. Even on prolonged irradiation, the cyclization of the adduct to the required product (**4a–f**) was not observed. These further supports the original



 $R = H, C_6H_5, o-CH_3OC_6H_4, p-CH_3OC_6H_4, o-CH_3C_6H_4, p-ClC_6H_4$ 

Figure C.

mechanism of the reaction involving base catalyzed Michael addition followed by acid catalyzed cyclization.

For comparison, these solid supported reactions were carried out by conventional heating in oil bath, under similar reaction conditions of temperature. Heating on basic alumina for about 4h gave the adduct with 60-70% yields and on monomorillonite the required product was obtained in 5–6h of heating with only 50% yield.

In conclusion, the experiment clearly showed the versatility of the inorganic solid supports under microwave irradiation, for preparation of bioactive compounds, avoiding the noxious reagents originally used.

### **EXPERIMENTAL SECTION**

The microwave reactor is a multimode, domestic oven (Padmini Essentia, Model Brownie, 2450 MHz). For TLC analysis, silica gel coated Al plates (Merck) were employed. Melting points were determined by means of a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra (KBr pellets) were recorded on a Perkin-Elmer spectrophotometer model 599. <sup>1</sup>H NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz) instrument using TMS as internal standard. Elemental analysis were performed by means of a Heraeus CHN rapid analyser; their results agreed satisfactorily with the calculated values. The melting point and the spectral data of the known compounds (**3–4a,b,c,e,f**) were in close agreement with those reported.<sup>[6]</sup>

The approximate bulk temperature (approx.  $90-120^{\circ}$ C, 750 W) of the reaction was monitored by inserting the thermometer into the reaction vessel, immediately after taking out from microwave oven.

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			Method A		Mothod D
		(Basic Alumina) <sup>a</sup>	Time (min)	)/Yield (%)	(Montmorillonite) <sup>c</sup>
Compound No.	R	Time/Yield (min)/(%)	Acidic Alumina <sup>b</sup>	Montmorillonite <sup>b</sup>	Time/Yield (min)/(%)
(3, 4)a	Н	2.1/85	2.5/82	2.5/84	3.5/90
(3, 4)b	$C_6H_5$	2.2/87	2.4/84	2.3/89	3.3/92
(3, 4)c	o-H <sub>3</sub> COC <sub>6</sub> H <sub>4</sub>	1.5/88	2.4/85	2.4/89	3.2/92
(3, 4)d	$p-H_3COC_6H_4$	2.2/83	2.5/80	2.4/84	3.5/90
(3, 4)e	o-H <sub>3</sub> CC <sub>6</sub> H <sub>4</sub>	2.0/86	2.3/85	2.3/86	3.3/93
(3, 4)f	p-ClC <sub>6</sub> H <sub>4</sub>	2.3/87	2.5/86	2.4/86	3.5/92
<sup>a</sup> For Figure A	A (Michael addition).				

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Table 1.

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<sup>b</sup>For Figure B (Cyclization of adduct). <sup>c</sup>For Figure C (Single step synthesis).

#### General Procedure for the Synthesis of Pyrano[2,3-d]pyrimidines

## Method A

Synthesis of Michael adduct: Equimolar (0.01 mole) amount of thiobarbituric acid (1a–f) and chalcone (2) dissolved in methanol were taken in a beaker and adsorbed over the basic alumina (20 g). The reaction mixture was air dried, kept in an alumina bath and irradiated in the microwave oven. On completion of reaction as monitored by TLC examination (after every 30 s), the product was eluted using methanol ( $4 \times 5 \text{ mL}$ ). Removal of the solvent gave the adduct, which was recrystallized using methanol.

**Cyclization of the adduct:** The Michael adduct dissolved in methanol was absorbed over acidic alumina (20 g) or montmorillonite (15 g), air dried and irradiated in an alumina bath. On completion of reaction, the product was eluted in methanol. Evaporating the solvent gave the required product which was recrystallized from chloroform : methanol mixture.

#### Method B

Equimolar (0.01 mole) amount of thiobarbituric acids (1a-f) and chalcone (2) in methanol (5 mL), were adsorbed over the montmorillonite (15 g), and air dried at room temperature. The adsorbed reactants taken in a beaker were kept in an alumina bath and irradiated in the microwave oven. On completion of reaction as monitored by TLC examination (after every 30 s), product was eluted using methanol (4 × 5 mL). Product obtained on removal of solvent was recrystallized using chloroform:methanol mixture.

**3a:** M.p. 298–300°C (300–301°C).<sup>[6]</sup> **3b**: m.p. 230–232°C (230–231°C).<sup>[6]</sup> **3c**: m.p. 190–191°C (190–191°C).<sup>[6]</sup> **3d**: m.p. 198–200°C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$ : 3.50 (m, 1H, H-1'), 3.85 (s, 6H, 2 × OCH<sub>3</sub>), 4.20–4.75 (m, 3H, CH<sub>2</sub>-2' and H-5), 6.90–8.10 (m, 18H, Ar-H). Anal. Calcd. for C<sub>33</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>S: C, 70.21; H, 4.96; N, 4.96. Found: C, 70.18; H, 4.93; N, 4.94. **3e**: m.p. 191–193°C (191–191°C).<sup>[6]</sup> **3f**: m.p. 240–242°C (240–241°C).<sup>[6]</sup>

4.94. **3e**: m.p. 191–193°C (191–191°C).<sup>[6]</sup> **3f**: m.p. 240–242°C (240–241°C).<sup>[6]</sup> **4a**: M.p. 290–292°C (290–291°C).<sup>[6]</sup> **4b**: m.p. 209–211°C (210–211°C).<sup>[6]</sup> **4c**: m.p. 221–222°C (220–221°C).<sup>[6]</sup> **4d**: m.p. 230–232°C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$ : 4.10 (s, 6H, 2 × OCH<sub>3</sub>), 4.90 (d, J = 5 Hz, 1H, H-5), 6.12 (d, J = 5 Hz, 1H, H-6), 7.10–8.00 (m, 18H, Ar-H). Anal. Calcd. for C<sub>33</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>S: C, 72.53; H, 4.76; N, 5.13. Found: C, 72.50; H, 4.74; N, 5.10. **4e**: m.p. 198–200°C (198–199°C).<sup>[6]</sup> **4f**: m.p. 179–181°C (180–181°C).<sup>[6]</sup>

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- (a) Aluminium oxide, activated, basic, Brockmann I: Aldrich Catalogue No. 19, 944-3; ~150 mesh, 58 Å, surface area; 155 m<sup>2</sup>/g; (b) Aluminium oxide, activated, neutral, Brockmann I: Aldrich Catalogue No. 19, 997-4; ~150 mesh, 58 Å, surface area; 155 m<sup>2</sup>/g; (c) Aluminium oxide,

activated, acidic, Brockmann I: Aldrich Catalogue No. 19, 996-6; ~150 mesh, 58 Å, surface area;  $155 \text{ m}^2/\text{g}$ ; (d) Silica gel, Merch: Aldrich Catalogue No. 24, 217-9; 35–70 mesh, 40 Å, surface area;  $675 \text{ m}^2/\text{g}$ ; (e) Montmorillonite K 10: K-catalyst, 69866 Fluka, Surface;  $200 \pm 20 \text{ m}^2/\text{g}$ .

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