SHORT PAPER

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Novel one pot synthesis of new pyranopyrimidines using microwaves†

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A novel and one pot synthesis of pyrano[2,3-*d*]pyrimidines from thiobarbituric acids under microwave irradiation using basic alumina is reported.

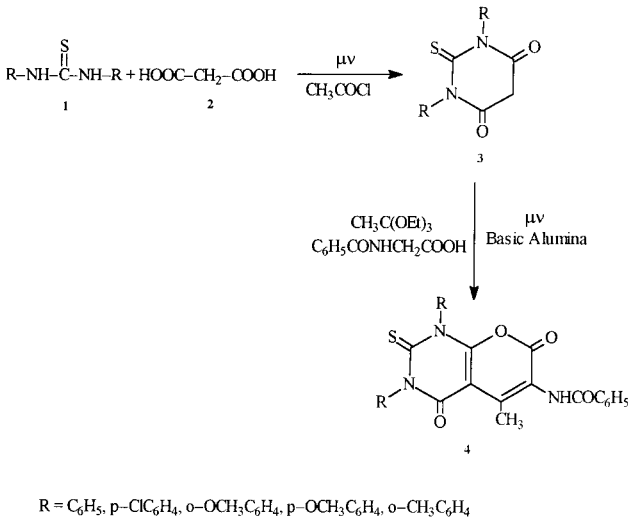
Pyranopyrimidines generate widespread interest due to the diverse biological activities[1,2] associated with them. Moreover they have wide range of synthetic applications, especially as oxidising agents.[3] Although a variety of routes for the synthesis of these compounds is known,[3–5] the majority involve several steps, and often yields are poor. The general approach for their synthesis involves either cyclization of substituted pyrimidines or condensation of specific moieties with it.

In recent years solid supported reagents have gained popularity[6] in organic synthesis because of their enhanced reactivity, selectivity and associated ease of manipulation. During, the course of our experimentation, [7] on organic reactions that are carried by microwave irradiation, experienced a pronounced microwave effect.[7,8] 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 also provide a possibility of upscaling the reactions on preparative scale.

In search of a more efficient synthesis of these compounds, we here report a novel one-step synthesis of functionalized pyrano[2,3-*d*]pyrimidines from thiobarbituric acids, triethylorthoacetate, a versatile reagent,[9] and in view of cleaner methodology, basic alumina as condensing agent. Thus, the reaction of an equimolar amount of 1,3-diarylthiobarbituric acids with hippuric acid and triethylorthoacetate on basic alumina results in cyclocondensation to yield the product 1,3-diaryl-6-benzamido-2,3-dihydro-2-thioxo-5-methyl-4*H*-pyrano[2,3-*d*]pyrimidine-4,7(1*H*)-diones. The structure of the product was characterised by its spectral and analytical data.

The synthesis of 1,3-diarylthiobarbituric acid was also modified to give a better yield and reduced reaction time (Table 1). A mixture of a diaryl thiourea, malonic acid and acetyl chloride was irradiated for few seconds at 750 W to yield the product in 90–95% yield. The spectra and the melting points of the products were in agreement with the literature data.[10]

The usage of basic alumina in microwave for the preparation of pyranopyrimidines not only eliminates the need for external base, but also gives a significant enhancement in yield and reduction in reaction time (Table 1). The approximate temperature attained by the reaction mixture as measured immediately after taking it out from the oven (a domestic microwave oven at 750 W) was 100–120ºC. A reaction with basic alumina using conventional heating in a oil-bath maintained at 110–120ºC was also undertaken, but the reaction took more than five hours to give the required product in about 60–70% yield. This clearly indicates that the combination of microwaves with the solid supported reagent operates by more than simple thermal effects. The use of external base (triethylamine) on the other hand did not give the required product.



R = C_6H_5, p–ClC_6H_4, o–$OCH_3C_6H_4$, p–$OCH_3C_6H_4$, o–$CH_3C_6H_4$

Scheme 1

In conclusion, basic alumina coupled with microwave heating is a better condensation method for the preparation of pyranopyrimidines. It involves easy work up and gives better yields with reduced reaction times. Moreover, on account of the one-step preparation the net yield of the reaction is very much improved.

Table 1 Reaction time and yield for thiobarbituric acid **3** and pyrano[2,3-*d*]pyrimidines **4**

Compound no.	R	Time/s	Yield[a]/%
3a	C_6H_5	55	90
3b	*p*-ClC_6H_4	65	93
3c	*o*-$CH_3OC_6H_4$	60	95
3d	*p*-$CH_3OC_6H_4$	60	90
3e	*o*-$CH_3C_6H_4$	45	92
4a	C_6H_5	55	95
4b	*p*-ClC_6H_4	65	95
4c	*o*-$CH_3OC_6H_4$	55	92
4d	*p*-$CH_3OC_6H_4$	60	94
4e	*o*-$CH_3C_6H_4$	55	95

[a]Yield of crude product (5 to 10% loss on recrystallization).

Experimental

Preparation of diarylthiobarbituric acids **(3a–e)***:* Diarylthiourea (0.01 mol), malonic acid (0.01 mol) and 5–6 ml of acetyl chloride were taken in an Erlenmeyer flask, capped with a funnel, and irradiated for 30–60 seconds. On completion of the reaction, as monitored by TLC, the mixture was poured into ice-cold water. The solid obtained was filtered and recrystallized from acetic acid.

Preparation of pyrano[2,3-d]pyrimidines **(4a-e):** The mixture of thiobarbituric acid (0.01 mol), hippuric acid (0.01 mol) and triethyl orthoacetate (0.01 mol) were taken in a beaker, dissolved in ethanol (5 ml), and adsorbed on basic alumina (20 g). The adsorbed material was air-dried at room temperature, placed in the alumina bath[11] and

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irradiated for about a minute. On completion of the reaction, as monitored by TLC at 30-second intervals, the product was eluted with acetone (3 × 10 ml). Evaporating the acetone under reduced pressure gave the product which was recrystallized from chloroform-methanol (1: 1).

6-Benzamido-2,3-dihydro–5-methyl-1,3-diphenyl-2-thioxo-4H-pyrano[2,3-d]pyrimidine-4,7(1H)-dione **4a***:* m.p. 296–298; ^{1}H NMR ($CDCl_3$): δ 2.8 (s, 3H, CH_3), 7.2–7.9 (m, 15H, Ar–H), 8.7 (brs, 1H, NH); IR (KBr) *ν*/cm^{-1} 1720, 1685, 1640. Anal. calcd for $C_{27}H_{19}N_3O_4S$: C 67.35, H 3.95, N 8.73%. Found: C 67.37, H 3.96, N 8.74%.

1,3-Di-(p-chlorophenyl) compound **4b***:* m.p. >300; ^{1}H NMR ($CDCl_3$): δ 2.8 (s, 3H, CH_3), 7.3–7.8 (m, 13H, Ar–H), 8.8 (brs, 1H, NH); IR (KBr) *ν*/cm^{-1} 1720, 1685, 1645. Anal. calcd for $C_{27}H_{17}Cl_2N_3O_4S$: C 59.02, H 3.10, N 7.65%. Found: C 59.00, H 3.00, N 7.66%.

1,3-Di-(o-methoxyphenyl) compound **4c***:* m.p. 285–286; ^{1}H NMR ($CDCl_3$): δ 2.7 (s, 3H, CH_3), 3.8 (s, 6H, 2 × -OCH_3), 7.2–7.3 (m, 13H, Ar–H), 8.8 (brs, 1H, NH); IR (KBr) *ν*/cm^{-1} 1725, 1685, 1635. Anal. calcd for $C_{29}H_{23}N_3O_6S$: C 64.33, H 4.25, N 7.76%. Found:C 64.31, H 4.26, N 7.78%.

1,3-Di-(p-methoxyphenyl) compound **4d**: m.p. 265–267; ^{1}H NMR ($CDCl_3$): δ 2.8 (s, 3H, CH_3), 3.9 (s,6H, 2 × –OCH_3), 7.1–7.7 (m, 13H, Ar–H), 8.8 (brs, 1H, NH); IR (KBr) *ν*/cm^{-1} 1725, 1685, 1630. Anal. calcd for $C_{29}H_{23}N_3O_6S$: C 64.33, H 4.25, N 7.76%. Found: C 64.31, H 4.24, N 7.75%.

1,3-Di-(o-tolyl) compound **4e***:* m.p. 255–257; ^{1}H NMR ($CDCl_3$):δ 2.3 (s, 6H, 2 × CH_3), 2.8 (s, 3H, Ar–CH_3), 7.2–7.8 (m, 13H, Ar–H), 9.0 (brs, 1H, NH); IR (KBr) *ν*/cm^{-1} 1720, 1685, 1630. Anal. calcd for $C_{29}H_{23}N_3O_4S$: C 68.37, H 4.52, N 8.25%. Found: C 68.35, H 4.51, N 8.26%.

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