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A NON-CATALYST METHOD FOR THE SYNTHESIS OF BIS-4-ARYL-3, 4-DIHYDROPYRIMIDONES (THIONES) UNDER SOLVENT-FREE CONDITIONS

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Abstract - Three component coupling of an aromatic dialdehyde, a β-keto ester or β-diketone and urea or thiourea (1:2.2:2.5 mol ratios) in one–pot under solvent-free conditions without any catalyst produced the bis-dihydropyrimidones (thiones) in a microwave oven. This is therefore a "green" synthesis of the title compounds under the said conditions.

The synthesis of the bis-dihydropyrimidones is rather rare in the literature.[1] In continuation of our efforts towards the synthesis of novel heterocycles,[2-4] we aimed at the construction of a variety of bis-dihydropyrimidones (thiones) by three component coupling of an aromatic dialdehyde, a β-keto ester or β-diketone and urea or thiourea (1:2.2:2.5 mol ratios) in one–pot under catalyst-free, solvent-less conditions.

Green Chemistry is a rather emerging new field that ensures proactive avenue for the development of future science and technology.[5] To maintain such aspects, solvent-free organic syntheses by employing microwaves have attracted varied interest as ecofriendly methodologies.[6] With this idea in mind, we started with the syntheses of the title compounds, the bis-dihydropyrimidones (thiones), which are otherwise rather difficult to prepare but at the same time possessing immense biological activities[7] by employing solvent-less conditions and even without any catalyst.

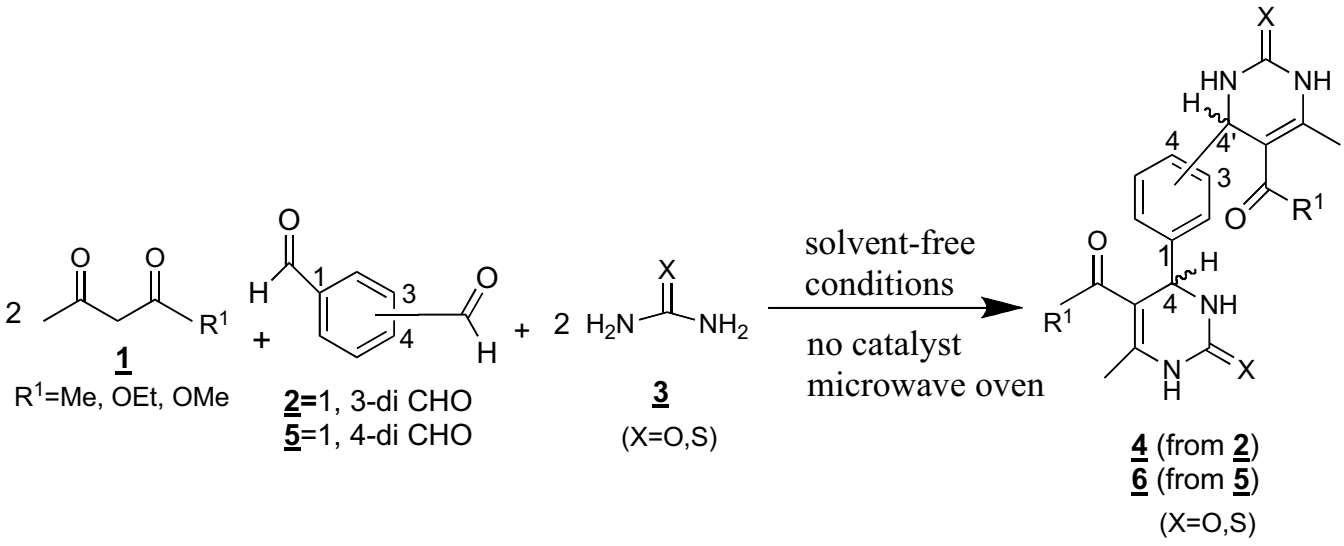
For the initial study, isophthalaldehyde **2** (1 mol) was coupled with ethyl acetoacetate (EAA) (2.2 mole) and urea (2.5 mole) in a microwave oven without using any catalyst and under solvent-free conditions (Scheme 1). Different power and time combinations were employed and the reaction conditions were finally optimized using 720 watt power for 25 minutes (Table 1, entry 4). Use of solvents like DMF or DMSO or EtOH did not further improve the yield.

Table 1: Optimization of reaction conditions for bis-dihydropyrimidone **4** formation in a microwave oven

Entry	Power (watt)	Total time (mins.) (for 5 mins at a stretch with 1 min interval and repeating the process)	Yield % (isolated)
1	360	40	40
2	480	35	50
3	600	30	60
4	720	25	84
5	840	20	70
6	960	15	64

Reagents: isophthalaldehyde **2** (1 mol), EAA (2.2 mole), urea (2.5 mole), no solvent

With the optimized conditions in hand, eight different bis-dihydropyrimidones (thiones) were synthesized using different variations in the three components and the results are depicted in Table 2. All the reactions proceeded in excellent yields.



Scheme 1: Synthesis of bis-4-aryl-3, 4-dihydropyrimidones under solvent-free conditions

Therefore, the advantages of our method are as follows: (a) operational simplicity, being the simplest of the methods available so far (b) absolutely solvent-free reaction procedure, both during the reaction and during work-up (c) environmentally benign technique (d) no hazardous wastes of reagents or solvents (e) very fast and clean reaction (f) rather easy work-up procedure (g) an overall "green" methodology.

Table 2: Synthesis of bis-3,4-dihydropyrimidin-2(1*H*)-ones (thiones) under solvent-free conditions

Entry	R^1	Starting dialdehyde (Product)	X	Total time (mins.) 720 watt.	Yield (%) (isolated)	Mp found (reported)	References
1	OMe	**2** (**4**)	O	20	88	310-312 (309-311)	8
2	OEt	**2** (**4**)	O	25	84	295-297 (296-298)	8
3	OMe	**2** (**4**)	S	15	85	282-283 (280-282)	8
4	Me	**2** (**4**)	O	25	77	308-310 (>300)	1
5	OMe	**5** (**6**)	O	30	73	310-312 (>300)	1
6	OEt	**5** (**6**)	O	28	79	309-311 (>300)	1, 9, 10
7	OMe	**5** (**6**)	S	16	80	308-310 (>300)	1
8	OEt	**5** (**6**)	S	18	84	307-309 (>300)	1, 9

The mechanism of the bis-dihydropyrimidone formation is similar as proposed by Folkers and Johnson[11] for the formation of the dihydropyrimidones. The initial formation of the acylimine intermediate takes place which reacts subsequently with the β-diketone or β-ketoester effectively. Finally, a favourable cyclisation and dehydration path follows to produce the dihydropyrimidone (thione) system. In exactly the similar fashion, the bis-dihydropyrimidones (thiones) are formed.

EXPERIMENTAL

General experimental procedure for bis-dihydropyrimidone (thione) formation:

A mixture of aromatic dialdehyde **2** or **5** (1 mmol), β-keto ester or β-diketone **1** (2.2 mmol), urea or thiourea **3** (2.5 mmol) were mixed thoroughly and then taken in a 5 mL conical flask. It was next placed on a sand bath inside a domestic microwave oven and heated for the specified time as mentioned in Table 2 at power 720 watt. The reactions were monitered by TLC for the absence of the starting dialdehyde. After completion of the reaction, the crude mass was cooled, poured into crushed ice and stirred for further 10 minutes, when the bis-dihydropyrimidones (thiones) precipitated out. They were directly filtered and crystallized from hot aqueous ethanol to obtain the finally pure products without the need for column chromatography. All the products **4** and **6** were characterized by their spectral data.

This reaction generates two new chiral centres (C_4 and $C_{4'}$) and therefore two diastereoisomers either RR (SS) or RS (SR) are possible. The NMR (both ^1H and ^{13}C) data shows the formation of only one diastereoisomer although it is difficult at this stage to say exactly which diastereoisomer is formed. It is therefore best to generalize in the nomenclature as RR / RS. Further, X-ray crystallography of these bis-analogues could not be carried our due to their amorphous nature.

The ^1H NMR data for some representative compounds are given below.

(RR/RS) 4, 4′-(1, 3-phenylene)-bis[5-methoxycarbonyl-3,4-dihydro-6-methyl]-pyrimidin-2(1*H*)-one (Table 2, entry 1): ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.19 (s, 2H, 2×NH), 7.71 (s, 2H, 2×NH), 7.25 (t, J=7.8 Hz, 1H, aromatic C_5-H), 7.20-7.05 (m, 3H, aromatic C_2, C_4 and C_6-H), 5.08 (d, J=3.0 Hz, 2H, C_4-H, $C_{4'}$-H), 3.50 (s, 6H, 2×OCH_3), 2.20 (s, 6H, 2×C_6-CH_3).

(RR/RS)4,4′-(1,3-phenylene)-bis[5-methoxycarbonyl-3,4-dihydro-6-methyl]-pyrimidin-2(1*H*)-thione (Table 2, entry 3): ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.39 (s, 2H, 2×NH), 9.60 (s, 2H, 2×NH), 7.31 (t, J=7.8 Hz, 1H, aromatic C_5-H), 7.11 (d, J=7.8 Hz, 2H, aromatic C_4, C_6-H), 7.02 (s, 1H, aromatic C_2-H), 5.10 (d, J=3.3 Hz, 2H, C_4-H, $C_{4'}$-H), 3.54 (s, 6H, 2×-OCH_3), 2.30 (s, 6H, 2×-CH_3).

(RR/RS) 4, 4′-(1, 4-phenylene)-bis[5-methoxycarbonyl-3,4-dihydro-6-methyl]-pyrimidin-2(1*H*)-one (Table 2, entry 5): ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.20 (s, 2H, 2×NH), 7.71 (s, 2H, 2×NH), 7.20 (s,4H, ArH), 5.10 (s, 2H, C_4-H, $C_{4'}$-H), 3.52 (s, 6H, 2×OCH_3), 2.20 (s, 6H, 2×C_6-CH_3).

(RR/RS)4,4′-(1,4-phenylene)-bis[5-methoxycarbonyl-3,4-dihydro-6-methyl]-pyrimidin-2(1H)-thione (Table 2, entry 7): ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.36 (s, 2H, 2×NH), 9.67 (s, 2H, 2×NH), 7.20 (s, 4H, ArH), 5.11 (s, 2H, C_4-H, $C_{4'}$-H), 3.57 (s, 6H, OCH_3), 2.26 (s, 6H, CH_3).

We therefore report here a “green” synthesis of the bis-dihydropyrimidones (thiones) in a microwave-oven without using any catalyst under solvent-free conditions in excellent yields of products. This methodology will be of immense importance to both academia and industry in the near future.

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REFERENCES

1. S.-J. Tu, X.-T. Zhu, F. Fang, X.-J Zhang, S.-L. Zhu, T.-J. Li, D.-Q. Shi, X.-S. Wang, and S.-J. Ji, *Chin. J. Chem.*, 2005, **23**, 596.
2. C. Mukhopadhyay and A. Datta, *Heterocycles*, 2007, **71**, 1837.
3. C. Mukhopadhyay, A. Datta, and B. K. Banik, *Heterocycles*, 2007, **71**, 181.
4. C. Mukhopadhyay and P. K. Tapaswi, *Tetrahedron Lett.*, 2008, **49**, 6237.
5. C. O. Kinen, L. I. Rossi, and R. H. de Rossi, *Green Chemistry*, 2009, **11**, 223.
6. (a) K. Tanaka, *Solvent-free Organic Synthesis*, Wiley-VCH, 2003; (b) C. O. Kappe, *Acc. Chem. Res.*, 2000, **33**, 879.
7. (a) C. O. Kappe, *Eur. J. Med. Chem.*, 2000, **35**, 1043; (b) R. M. Shaker, A. F. Mahmoud, and F. F. Abdel-Latif, *Phosphorus, Sulfur and Silicon and the Related Elements*, 2000, **160**, 207; (c) S.-J. Tu, F. Fang, S. Zhu, T. Li, X.-J. Zhang, and Q. Zhuang, *Synlett*, 2004, **3**, 537.
8. C. Mukhopadhyay and A. Datta, *J. Heterocycl. Chem.*, 2009, (in press).
9. S.-J. Tu, C. Miao, F. Fang, F. Youjian, T. Li, Q. Zhuang, X.-J. Zhang, S. Zhu, and D. Shi, *Bioorg. And Med. Chem. Lett.*, 2004, **14**, 1533.
10. B. Liang, X. Wang, J.-X. Wang, and Z. Du, *Tetrahedron*, 2007, **63**, 1981.
11. K. Folkers and T. B. Johnson, *J. Am. Chem. Soc.*, 1933, **55**, 3784.