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Microwave-assisted simple, one-pot, four-component synthesis of 2,4,6-triarylpyrimidines under solvent-free conditions

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Abstract—2,4,6-Triarylpyrimidines are synthesized via a simple, one-pot, four-component reaction between aryl methyl ketones, benzaldehydes, aromatic nitriles, and hydroxylamine under microwave irradiation and solvent-free conditions in good to excellent yields.

Pyrimidines are of chemical and pharmacological interest.[1,2] Compounds containing a pyrimidine ring system have been shown to possess antitumor, antibacterial, antifungal, antimalarial, and anticonvulsant activities.[1–5] Some examples are valuable drugs in the treatment of hyperthyroidism, acute leukemia in children and adult granulocytic leukemia.[1] Furthermore, some pyrimidines are used in polymer and supramolecular chemistry.[6,7] Conjugated molecules which have a pyrimidine core as the key unit have recently received much attention and they are prospective candidates for light-emitting devices[8] and molecular wires.[9]

So far the most common synthetic methods for the preparation of pyrimidine ring systems involve: (i) transformation of another ring and, (ii) cyclizations classified on the basis of the number of ring atoms in each of the components being cyclized: (iia) from six ring atoms, by N1–C2 or N3–C4 bond formation; (iib) by formation of two bonds, from [5+1], [4+2], or [3+3] atom fragments; and (iic) by formation of three bonds, from [2+2+2] or [3+2+1] atom fragments.[1,2,10]

2,4,6-Trisubstituted pyrimidines have been synthesized using various methods and procedures including the reaction of amidines with α,β-unsaturated ketones,[11] dimerization–oxidative fragmentation of aryl-β-arylvinylimines,[12] one-pot condensation of β-dicarbonyl compounds, NH_4OAc and aldehydes,[13] condensation of phenacyldimethylsulfonium salts, aldehydes, and ammonia,[14] reaction of alkynes and nitriles in the presence of TfOH,[15] rearrangement of 2,4,5-trisubstituted imidazolines,[16] one-pot, three-component reaction of aryl halides, terminal propargyl alcohols and amidinium salts based upon a coupling-isomerization–cyclocondensation sequence,[17] arylation of halogenated pyrimidines via a Suzuki coupling reaction,[18] reaction of α,α-dibromo oxime ethers with Grignard reagents,[19] microwave-assisted reaction of amidines and alkynones,[20] and sequential assembly of aryl groups onto a pyrimidine core (2-methylthiopyrimidine).[21] However, in some these methods the reactants such as amidines, unsaturated ketones, aryl-β-arylvinylimines, sulfonium salts, imidazoline derivatives, and dihalo oxime ethers have to be synthesized initially, hence these methods are relatively expensive and time consuming.

Due to the unique properties of pyrimidine derivatives, the development of synthetic methods which enable a facile access to this heterocycle are desirable. As part of our ongoing program to develop efficient methods for the preparation of widely used organic compounds from readily available building blocks, we report a simple, versatile and solvent-free route to 2,4,6-triarylpyrimidines. Thus, aryl methyl ketones **1**, aromatic aldehydes **2**, aromatic nitriles **3**, and hydroxylamine **4** undergo a one-pot, four-component reaction (by the formation of four bonds from [2+1+2+1] atom

Keywords: 2,4,6-Triarylpyrimidines; Four-component reactions; Solvent-free synthesis; Microwave irradiation.
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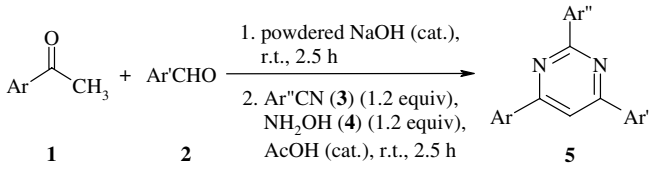
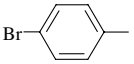
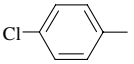
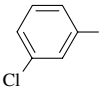
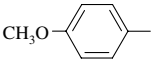
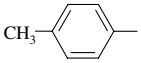
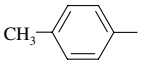
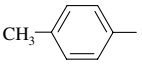
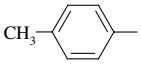
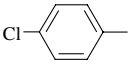
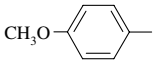
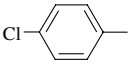
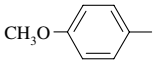
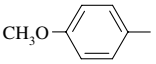
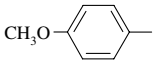
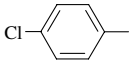
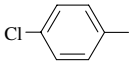
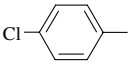
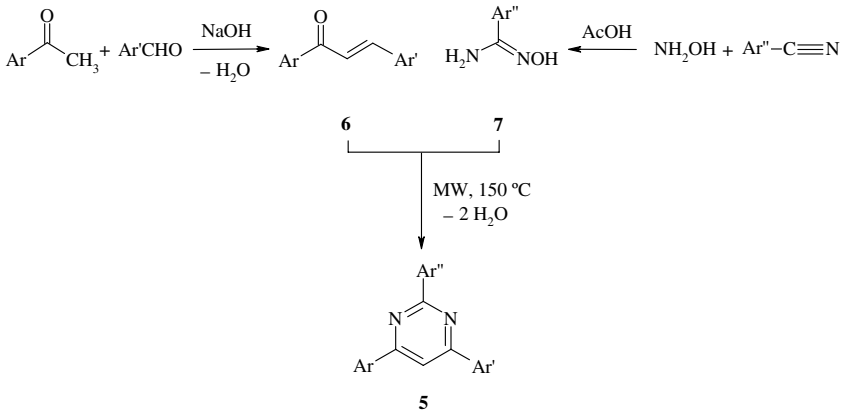
Table 1. Microwave-assisted solvent-free synthesis of 2,4,6-triarylpyrimidines



1 **2** **5**

5	Ar	Ar′	Ar″	% Yield[a]	Mp °C[b] (lit.)
a				90	185–186 (184–185)[19]
b				89	235–237 (237)[20]
c				93	219–221 (219–220)[17]
d				93	172–174
e				95	129–131 (128)[20]
f				94	149–151 (148–150)[13]
g				86	173–174 (176–177)[13]
h				92	171–173 (174–175)[17]
i				87	139–141
j				92	134–136 (135–138)[13]
k				87	135–137 (132–136)[13]
l				89	160–161
m				91	195–197
n				89	209–210 (212–213)[22]
o				91	153–155 (154–155)[14]
p				86	130–133 (132–133)[12a]
q				90	153–155 (153–154)[12a]

[a] Isolated yields.
[b] Recrystallized from absolute EtOH.



Scheme 1.

fragments) under solvent-free conditions and microwave irradiation to produce 2,4,6-triarylpyrimidines **5a–q** in 86–95% yields (Table 1).

The reactions were carried out by first mixing the ketone and the aldehyde, in the presence of powdered sodium hydroxide at room temperature. After a few hours and nearly complete conversion to the corresponding chalcone, **6**, as indicated by TLC monitoring, the nitrile, hydroxylamine and acetic acid (catalytic amount, but more than the amount of NaOH used)[23] were added to the reaction mixture and stirring continued for further 2.5 h.[24] The nitrile and hydroxylamine are converted in situ to the corresponding amidoxime, **7**. Next, the reaction mixture was irradiated in a microwave oven[25] at 150 °C for 3 min. ^{1}H NMR analysis of the reaction mixtures clearly indicated the formation of pyrimidine derivatives **5** (Scheme 1). After optimization, treatment of the in situ prepared chalcones with 1.2 equiv each of the nitrile and hydroxylamine afforded the corresponding 2,4,6-triarylpyrimidines in 86–95% yields (Table 1).

The structures of the isolated products were confirmed by comparison of their mps and their spectral data (high-field ^{1}H and ^{13}C NMR spectra) with those of authentic samples.[26]

In conclusion, we have developed a microwave-assisted, simple, one-pot, four-component and solventless procedure for the preparation of 2,4,6-triarylpyrimidines of potential synthetic and pharmacological interest. The use of commercial materials, and the one-pot and solvent-free conditions are the main advantages of this method. This method appears to have a broad scope with respect to variation in substitution at the pyrimidine 2-, 4-, and 6-positions.

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23. The best results were obtained when the catalytic amount of acetic acid added during the second stage of the reaction was greater than that of the NaOH employed in the first stage.
24. We were concerned regarding the reaction between chalcones and hydroxylamine. However, when a mixture of 1,3-diphenyl-2-propen-1-one, **6**: $Ar = Ar' = C_6H_5$, and hydroxylamine was stirred at 25 °C, the chalcone was recovered almost unchanged after 5 h.
25. The reactions were performed using a microwave oven (ETHOS 1600, Milestone) with a power of 600 W specially designed for organic synthesis.
26. The procedure for the preparation of 2,4,6-triphenylpyrimidine (**5a**) is described as an example. A mixture of acetophenone (0.48 g, 4 mmol), benzaldehyde (0.42 g, 4 mmol), and powdered NaOH (0.01 g, 0.25 mmol) was stirred at 25 °C for 2.5 h. After a nearly complete conversion to the corresponding chalcone, as indicated by TLC monitoring, benzonitrile (0.49 g, 4.8 mmol), 50% hydroxylamine (0.32 g, 4.8 mmol), and acetic acid (a catalytic amount, but greater than 0.25 mmol) were added to the reaction mixture and stirring continued at 25 °C for a further 2.5 h. The reaction was then irradiated in a microwave oven at 150 °C for 3 min. Aqueous work-up and purification by column chromatography (4:1 *n*-hexane–EtOAc as the eluent, Merck silica gel 60 mesh) afforded 2,4,6-triphenylpyrimidine **5a** in a 90% yield. The selected data for 2,4,6-triarylpyrimidines; **5d**: Colorless crystals. MS, *m*/*z* (%): 344 (M^+ ^{37}Cl, 29), 342 (M^+ ^{35}Cl, 100), 265 (6), 126 (7), 103 (10), 98 (11), 77 (9), 50 (4). Anal. Calcd for $C_{22}H_{15}ClN_2$ (342.83): C, 77.08; H, 4.41; N, 8.17. Found: C, 77.2; H, 4.5; N, 8.1. ^1H NMR (500.1 MHz, $CDCl_3$): δ 7.44–7.49 (2H, m, 2CH), 7.52–7.58 (6H, m, 6CH), 8.02 (1H, s, CH), 8.26 (4H, dd, $J = 7.8$ and 2.0 Hz, 4CH), 8.60 (1H, d, $J = 6.8$ Hz, CH), 8.69 (1H, br s, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 110.70, 126.57, 127.26, 128.47, 128.94, 129.67, 130.54, and 130.91 (8CH), 134.55, 137.21, and 139.97 (3C), 163.20 and 164.86 (2C–N). Compound **5i**: Colorless crystals. MS, *m*/*z* (%): 234 (3), 191 (3), 132 (100), 118 (16). Anal. Calcd for $C_{23}H_{17}ClN_2O$ (372.85): C, 74.09; H, 4.60; N, 7.51. Found: C, 74.1; H, 4.7; N, 7.5. ^1H NMR (500.1 MHz, $CDCl_3$): δ 3.84 (3H, s, OCH_3), 7.00 (2H, d, $J = 8.4$ Hz, 2CH), 7.46 (2H, d, $J = 8.2$ Hz, 2CH), 7.50–7.53 (3H, m, 3CH), 7.79 (1H, s, CH), 8.15 (2H, d, $J = 8.4$ Hz, 2CH), 8.18 (2H, dd, $J = 7.9$ and 1.5 Hz, 2CH), 8.59 (2H, d, $J = 8.2$ Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 55.28 (OCH_3), 109.21, 114.09, 127.10, 128.44, 128.62, and 128.74 (6CH) 129.50 (C), 129.69 and 130.61 (2CH), 136.51, 136.71, and 137.32 (3C), 161.87 (C–O), 163.07, 163.93, and 164.18 (3C–N). Compound **5l**: Colorless crystals. MS, *m*/*z* (%): 344 (M^+ ^{37}Cl, 1), 342 (M^+ ^{35}Cl, 3), 238 (8), 204 (7), 136 (83), 103 (100), 77 (99), 63 (19), 51 (78). Anal. Calcd for $C_{22}H_{15}ClN_2$ (342.83): C, 77.08; H, 4.41; N, 8.17. Found: C, 77.1; H, 4.5; N, 7.9. ^1H NMR (500.1 MHz, $CDCl_3$): δ 7.49 (2H, d, $J = 8.3$ Hz, 2CH), 7.50–7.55 (6H, m, 6CH), 7.95 (1H, s, CH), 8.22 (2H, d, $J = 8.3$ Hz, 2CH), 8.27 (2H, dd, $J = 7.8$ and 2.0 Hz, 2CH), 8.69 (2H, dd, $J = 7.9$ and 1.6 Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 109.78, 127.23, 128.43, 128.45, 128.48, 128.87, 129.05, 130.71, and 130.84 (9CH) 135.83, 136.91, 137.27, and 137.94 (4C), 163.31, 164.44, and 164.79 (3C–N). Compound **5m**: Colorless crystals. MS, *m*/*z* (%): 377 (M^+ ^{37}Cl, 1), 375 (M^+ ^{35}Cl, 5), 277 (2), 238 (10), 204 (8), 163 (5), 137 (100), 102 (8), 51 (44). Anal. Calcd for $C_{22}H_{14}Cl_2N_2$ (377.27): C, 70.04; H, 3.74; N, 7.43. Found: C, 69.9; H, 3.8; N, 7.2. ^1H NMR (500.1 MHz, $CDCl_3$): δ 7.49 (2H, d, $J = 8.4$ Hz, 2CH), 7.52 (2H, d, $J = 8.4$ Hz, 2CH), 7.53–7.56 (3H, m, 3CH), 7.96 (1H, s, CH), 8.21 (2H, d, $J = 8.4$ Hz, 2CH), 8.25 (2H, d, $J = 7.6$ Hz, 2CH), 8.63 (2H, d, $J = 8.4$ Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 110.03, 127.24, 128.49, 128.65, 128.95, 129.15, 129.78, and 130.99 (8CH), 135.70, 136.42, 136.93, 137.12, and 137.13 (5C), 163.51, 163.57, and 164.98 (3C–N).