Highly Efficient Synthesis of Pyrimidines under Microwave-assisted Conditions

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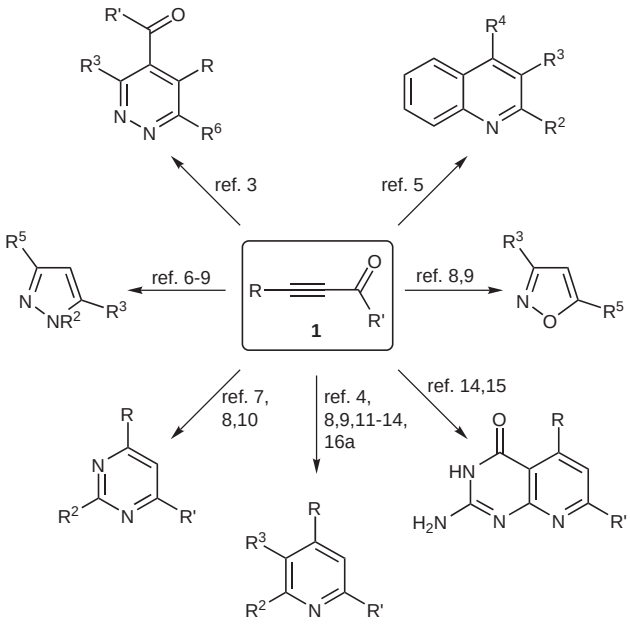
Abstract: Microwave irradiation of an amidine and alkynone in acetonitrile at 120 °C gives 2,4-disubstituted and 2,4,6-trisubstituted pyrimidines in very high yield.

Key words: pyrimidines, microwave synthesis, heterocycles

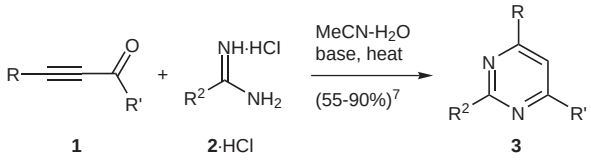
Microwave dielectric heating has emerged as a valuable alternative to conventional conductive heating methods in recent years.[1] With no direct contact between the chemical reactants and the energy source, microwave-assisted chemistry can be more efficient, in terms of the energy used, provide faster heating rates and enable rapid optimisation of synthetic procedures, often with an increase in reaction rate and efficiency. Recent advances in instrumentation, with the introduction of dedicated ovens for organic synthesis that focus microwaves in a monomodal cavity, have increased the popularity and reproducibility of microwave chemistry, increasing the methodology available for the development of new synthetic reactions and optimisation of existing procedures.[2]

Ethynyl ketones **1** are valuable synthetic intermediates for the preparation of a wide range of simple nitrogen-containing heteroaromatic molecules. Pyridazines,[3] pyridines,[4] quinolines,[5] pyrazoles,[6–9] isoxazoles,[8,9] triazoles[9] and pyrimidines[7,8,10] have all been prepared from these intermediates (Scheme 1), the latter used in the facile synthesis of heterocyclic building blocks, biologically active targets and non-proteinogenic amino acids.[10]

We have developed a number of new methods for the synthesis of pyridines[11–14] and pyrido[2,3-*d*]pyrimidines[14,15] using ethynyl ketones. As part of our interest in the development of new procedures in microwave chemistry for the facile synthesis of simple nitrogen-containing heterocycles,[16] we set out to to extend these findings to the preparation of pyrimidines from ethynyl ketones under microwave-assisted conditions. Using traditional heating methods this conversion is effected by heating a solution of an ethynyl ketone **1** and the hydrochloride salt of an amidine **2** in wet acetonitrile in the presence of base to give pyrimidines **3** in good yield (Scheme 2).[7,8,10]

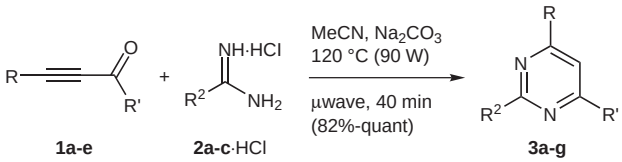


Scheme 1 Ethynyl ketones as synthetic intermediates



Scheme 2 Synthesis of pyrimidines **3** using traditional heating methods

In a new microwave-assisted procedure, a range of readily available alkynones **1a**–**e**[12] and an excess of the hydrochloride salt of either benzamidine **2a**, acetamidine **2b** or guanidine **2c**, was stirred at 120 °C for 40 min in acetonitrile in the presence of sodium carbonate using microwave irradiation at an initial power of 90 W in a self-tunable microwave synthesizer (Scheme 3).[17] After cooling and filtering, pyrimidines **3a**–**g** were obtained in excellent yield,



Scheme 3 Synthesis of pyrimidines **3a**–**g** under microwave-assisted conditions

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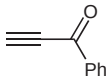
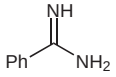
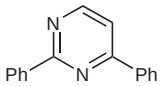
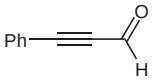
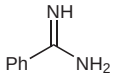
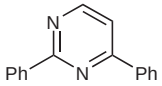
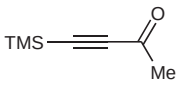
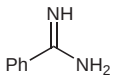
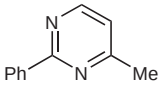
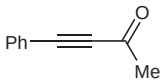
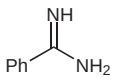
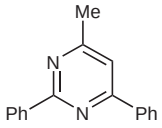
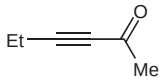
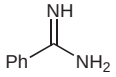
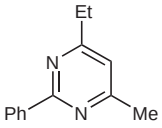
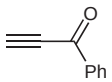
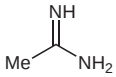
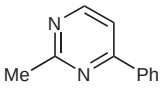
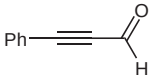
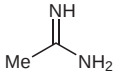
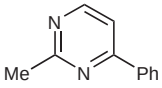
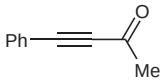
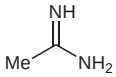
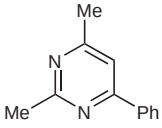
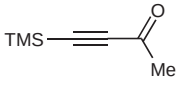
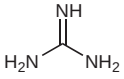
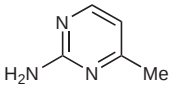
often without any need for further purification.[18] The results from this study were compared with experiments conducted using more traditional heating methods (Table 1). In all cases the microwave-assisted conditions were found to be superior, often generating the pyrimidine product in near quantitative yield. Traditional heating methods not only took longer but also gave a lower yield of product and usually required further purification by column chromatography.

In conclusion, microwave irradiation of an amidine and alkynone using a self-tunable microwave synthesizer provides a facile and extremely efficient method for the rapid synthesis of pyrimidines, often without any need for further purification. This new procedure is much more efficient than other reported conditions using traditional heating methods and so should find application in the synthesis of these heterocyclic building blocks in the future.

Table 1 Comparison of Microwave and Traditional Heating Methods

Entry	Alkynone **1a–d**	Amidine **2a–c**·HCl	Product **3a–g**	Thermal Yield%[a]	Microwave Yield%[b]
1	 **1a**	 **2a**	 **3a**	95	>98
2	 **1b**	 **2a**	 **3a**	78[c]	>98
3	 **1c**	 **2a**	 **3b**	88[c]	>98
4	 **1d**	 **2a**	 **3c**	98[c]	>98
5	 **1e**	 **2a**	 **3d**	91	>98
6	 **1a**	 **2b**	 **3e**	91[c]	97[c]
7	 **1b**	 **2b**	 **3e**	79[c]	91[c]
8	 **1d**	 **2b**	 **3f**	60[c,d]	82[c,d]
9	 **1c**	 **2c**	 **3g**	71	90

[a] Reaction complete after heating at reflux for 2 h in the presence of Na_2CO_3.
[b] Reaction complete after irradiation for 40 min.
[c] Purification by column chromatography on silica, eluting with light petroleum-ether (1:1), was required.
[d] Unreacted alkynone **1** was still present in the crude reaction mixture.

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(17) In a typical experimental procedure, a mixture of 1-phenyl-2-propyn-1-one **1a**[12] (0.13 g, 1.0 mmol), benzamidine hydrochloride salt **2a**·HCl (0.19 g, 1.2 mmol) and sodium carbonate (0.25 g, 2.4 mmol) in acetonitrile (5 ml) was irradiated for 40 min in a self-tunable CEM microwave synthesizer at 120 °C (initial power 90 W) and then allowed to cool. The solution was filtered and evaporated in vacuo to give *2,4-diphenylpyrimidine* **3a** (0.23 g, 99%) as a yellow solid, mp 72–73 °C (lit.[19] mp 71 °C); IR (nujol)/cm^{-1}: 1563; ^{1}H NMR ($CDCl_3$; 400 MHz) δ (ppm) 8.73 (1 H, d, *J* = 4 Hz, 6-H), 8.50 (2 H, m, *o*-PhH), 8.13 (2 H, m, *o*-PhH), 7.49 (1 H, d, *J* = 4 Hz, 5-H), 7.43 (6 H, m, *m*,*p*-PhH); ^{13}C NMR ($CDCl_3$; 100 MHz) δ (ppm) 164.6 (C), 164.0 (C), 157.8 (CH), 137.8 (C), 136.9 (C), 131.1 (CH), 130.8 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 127.3 (CH), 114.6 (CH); *m*/*z* (APcI) 233 (MH^+, 100%).
(18) Compounds demonstrated spectroscopic properties that were in agreement with literature data.
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