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Synthesis of pyrimidines from ketones using microwave irradiation

Sriram Tyagarajan* and Prasun K. Chakravarty

Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA

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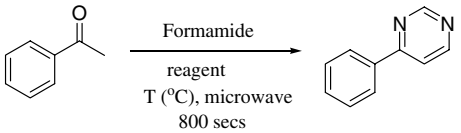
Abstract—A simple, high yielding synthesis of pyrimidines from ketones in the presence of HMDS and formamide is described. Under microwave irradiation, heteroaromatic, aryl, aliphatic, and cyclic ketones cyclized to give pyrimidines in good yields.

Pyrimidine is an important heterocycle with a variety of biological activities. Many methods are available for the synthesis of the pyrimidine ring system. The most common method used involves the reaction of a 1,3-dicarbonyl component with a reagent bearing an N–C–N fragment such as urea,[1] amidine,[2] or guanidine.[3] The use of formamide or an orthoester in combination with ammonia[4] as a potential surrogate N–C–N reagent in the synthesis of pyrimidines has also been reported. A variety of β-dicarbonyl compounds,[4–6] halogenated compounds,[7–9] tris-(formylamino)methanes,[10] 2-amino-2-formyl-malon-aldehyde,[11] and 3-methyl-5-nitro-3*H*-pyrimidin-4-one[12] have been used as synthons for 1,3-dicarbonyl components in the synthesis. Fused pyrimidines have been prepared from *ortho*-aminonitriles[13] and β-aminoesters.[14] In general, most of these methods involve multiple synthetic steps, which often require harsh reaction conditions or reagents that are not readily available, making these methods unsuitable for use in the synthesis of pyrimidine libraries. Thus, there exists a need for a simpler synthesis of pyrimidines that can be accessed under milder conditions from readily available starting materials and that can be automated. Recently, Helland and Lejon[15] have reported the synthesis of 4-phenylpyrimidine in 60% optimized yield from condensation of acetophenone with formamide at 179 °C for 17 h in the presence of cuprous chloride as an oxidant. However, the long reaction time and formation of the corresponding formyl amide, a major side product, limit the usefulness of this variant of Leuckart reaction.[16] Herein, we describe a simple, single step synthesis of pyrimidines using a combination of ketones, formamide and a source of ammonia under microwave irradiation that represents a significant improvement over existing methods of pyrimidine synthesis.

The use of microwave irradiation has become an attractive tool in recent years in organic synthesis.[17,18] In our attempts to develop a simpler synthesis of pyrimidines from readily available stating materials, we discovered that treatment of a mixture of acetophenone and ammonium acetate in formamide under microwave irradiation for 800 s at 215 °C produced 4-phenylpyrimidine in 51% yield (Table 1, entry 1). Since the yield of the resulting pyrimidine was variable and depended on the quality of ammonium acetate used, we decided to substitute ammonium acetate with a mixture of

Table 1. Optimization of pyrimidine formation



Entry	*T* (°C)	Reagent	Conversion[a] (%)
1	215	NH_4OAc	51
2	215	TsOH (cat),[b] HMDS	81
3	215	TsOH,[c] HMDS	89
4	175	TsOH,[c] HMDS	47
5	150	TsOH,[c] HMDS	12

[a] Reactions were run in 3 mL of formamide with 1 equiv of acetophenone and 5 equiv of ammonium acetate or HMDS. The isolated yields of the final product obtained after workup and column chromatography are reported.
[b] 0.1 equiv of TsOH was used.
[c] 1 equiv of TsOH was used.

Keywords: Microwave; Pyrimidines; Ketones; Formamide.
* Corresponding author. Tel.: +1 732 594 6226; fax: +1 732 594 5350; e-mail: sriram_tyagarajan@merck.com

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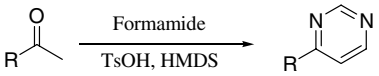
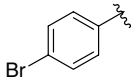
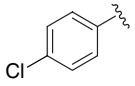
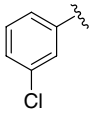
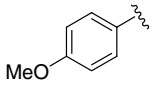
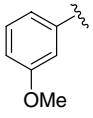
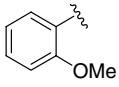
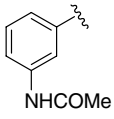
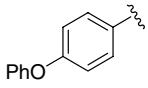
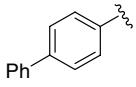
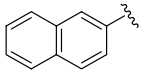
Table 2. Representative pyrimidines



Entry	R	Yield[a]
1		89
2		57
3		66
4		77
5		84
6		77
7		61
8		38
9		38
10		52
11		48
12		45
13		35
14		19
15		23
16		27

[a] Reactions were run in 3 mL of formamide with 1 equiv of acetophenone, 5 equiv of HMDS and 1 equiv TsOH. The isolated yields of the final product obtained after workup and column chromatography are reported.

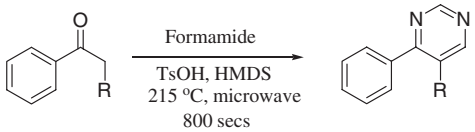
1,1,1,3,3,3,-hexamethyldisilizane (HMDS) and a catalytic amount of *p*-toluenesulfonic acid (TsOH), as an alternative source for ammonia.[19–22] Under these reaction conditions, 4-phenyl pyrimidine was obtained in 81% yield (Table 1, entry 2). Replacing TsOH with catalytic amounts of other acidic reagents such as pyridinium *p*-toluenesulfonate or acetic acid provided similar results (data not shown). The best yield (89%) of 4-phenylpyrimidine[23–25] was obtained when a stoichiometric amount of TsOH was employed in the reaction (Table 1, entry 3). No further improvements in yields were seen with increasing amounts of TsOH. The temperature also played an important role in the outcome of the reaction (Table 1, entries 4 and 5). We observed that 215 °C was the optimal temperature for the reaction and the reaction was generally incomplete at lower temperature.

This synthesis of pyrimidines is applicable to a variety of aromatic, heterocyclic, and aliphatic ketones providing corresponding pyrimidines in varying yields (Table 2). While acetophenone (entry 1) gave the best result, substituted acetophenones also produced corresponding pyrimidines uniformly in good yields. The presence of an electron withdrawing group such as a halogen at the 2-position (entry 5) gave better yield of the product, whereas a halogen substituent at the 4-position of the phenyl ring reduced the product yield (entries 2 and 3). In the case of an electron donating substituent, 4-methoxy acetophenone gave the best yield for the corresponding pyrimidine (entry 6).

The pyrimidines were also obtained in good yields from 4-phenoxy and 4-phenyl acetophenones (entries 10 and 11), and 2-naphthylmethylketone (entry 12). The yields of the corresponding pyrimidines were moderate, when heteroaromatic and aliphatic ketones were used as the starting materials.

Substitution of the methyl group of acetophenone with larger alkyl groups had a dramatic effect on the outcome of pyrimidine synthesis (Table 3). While a simple methyl substituent (entry 2) was well tolerated, a more bulky isopropyl group substitution significantly reduced the product yield (entry 3). Compared to an isopropyl group, a methoxy substituent (entry 4) showed an

Table 3. Representative pyrimidines



Entry	R	Yield (%)[a]
1	H	89
2	Me	80
3	*i*-Pr	16
4	OMe	43
5	Ph	No reaction

[a] Reactions were run in 3 mL of formamide with 1 equiv of acetophenone, 1 equiv of TsOH and 5 equiv of HMDS. The isolated yields of the final product obtained after workup and column chromatography are reported.

improvement in the yield of the corresponding pyrimidine. Not surprisingly, 1,2-diphenylethanone failed to provide any corresponding pyrimidine (entry 5).

In conclusion, we have described a general and simple microwave-assisted synthesis of pyrimidines from acetophenones. In addition to its speed and utilization of readily available starting materials, the reaction is high yielding for a variety of substrates and can be adopted for the synthesis of a library of pyrimidines.

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22. HMDS can be used in reactions at high temperature under microwave condition without having to worry about the pressure generated.
23. Representative experimental procedure: To a solution of acetophenone (150 mg, 1.2 mmol) in 3 mL of formamide, 1,1,1,3,3,3-hexamethyldisilizane (1.31 mL, 6.2 mmol) and *p*-toluenesulfonic acid (237 mg, 1.2 mmol) were added and the solution was subjected to microwave irradiation at 215 °C for 800 s, using Personal Chemistry Smith Optimizer. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic layer was washed sequentially with water and brine, then dried over sodium sulfate, filtered and concentrated in vacuo. Purification of the crude product by column chromatography (hexane/EtOAc; 4:1) yielded 173 mg (89%) of 4-phenylpyrimidine as a white solid. Mp 62–63 °C.[24]
24. The melting point of 4-phenylpyrimidine was identical to the commercially available compound from Aldrich (cat. #P33801).
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