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A facile synthesis of pyrimidin-4-ones

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ABSTRACT

A facile synthesis of 2,6-disubstituted pyrimidin-4-ones and 2,5,6-trisubstituted pyrimidin-4-ones from commercially available materials with application of microwave technology in key steps is described.

Pyrimidin-4-one is an important scaffold in pharmacologically active molecules. Pyrimidin-4-one derivatives are active against various biological targets such as tau protein kinase 1,[1] peroxisome proliferator-activated receptor gamma (PPARγ),[2] angiotensin II receptor,[3] and calcium-sensing receptor (CaSR),[4] thus potentially useful for the treatment of medical conditions such as Alzheimer's disease, obesity, hypertension, and bone and mineral diseases. Despite a number of synthetic approaches that are available in the literature, there remains significant interest in the development of new synthetic methods to prepare pyrimidin-4-ones. During a recent medicinal chemistry program, our attempt to prepare a 2,6-disubstituted pyrimidin-4-one derivative using an imidamide precursor and a 1,3-dicarbonyl, a commonly used method,[5] did not provide satisfactory results. This prompted us to search for an alternative approach. We decided to explore the cyclization reaction of *N*-acyl β-ketoamides as a novel strategy for pyrimidinone synthesis.[6] Herein we report the results of our study.

Scheme 1 depicts the synthesis of 2,6-disubstituted pyrimidin-4-ones (**4**) from Meldrum's acid (**1**) in three steps. Acylated Meldrum's acid (**2**) was prepared according to a literature procedure[7] and used without purification. *N*-Acyl β-ketoamides (**3**) had been reportedly prepared from intermediate **2** under thermal conditions.[8,9] It is now well known that microwaves can accelerate organic reactions thus shortening reaction times.[10] Indeed, *N*-acyl β-ketoamides (**3**) formed rapidly in good yields (55–72% over two steps) upon microwave irradiation. Since the initial attempt on the cyclization of *N*-acyl β-ketoamides (**3**) under thermal conditions required hour-long heating,[11] we decided to perform this transformation also under microwave irradiation. We were pleased to find that this transformation proceeded within 15 min, cleanly and in excellent yields (87–94%). Table 1 summarizes the results.

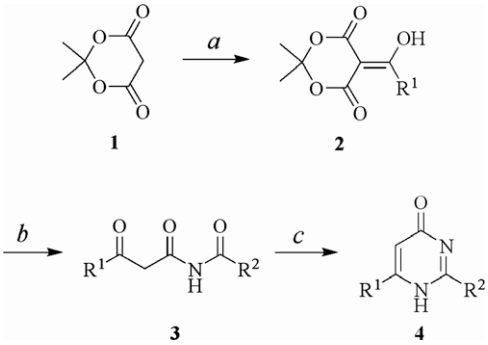
By introducing an alkylation[12] or arylation[13] step prior to the cyclization of *N*-acyl β-ketoamides, we successfully expanded the new methodology to the synthesis of 2,5,6-trisubstituted pyrimidin-4-ones (Scheme 2). Table 2 summarizes these results.

In conclusion, we have described a facile synthesis of both 2,6-disubstituted pyrimidin-4-ones and 2,5,6-trisubstituted pyrimidin-4-ones employing commercially available materials. The

Table 1
Compounds **4** prepared

Compound	R^1	R^2	Yield of **3**[a]	Yield of **4**[b]	Reference[c]
4a	Ph	Ph	55	89	14
4b	Ph	Me	72	88	15
4c	Ph	Et	60	91	16
4d	Ph	*i*-Pr	65	92	17
4e	Me	Ph	68	87	14
4f	Me	*n*-Bu	70	92	18
4g	*n*-Bu	Ph	70	94	14
4h	*n*-Bu	Me	64	93	19
4i	*n*-Bu	4-Pyridyl	56	88	20
4j	*n*-Bu	*n*-Bu	64	93	3

[a] Isolated yield based on **1** (**2** not purified) after purification by column chromatography or preparative thin layer chromatography.
[b] Isolated yield after recrystallization or trituration.
[c] All products are known (prepared by different methods) and their analytical data are consistent with those reported.



Scheme 1. Reagents and conditions: (a) R^1COCl, pyridine, CH_2Cl_2, 0 °C to room temperature; (b) [27]R^2CONH_2, toluene–$CHCl_3$ (3:1), microwave irradiation, 80 °C, 15–20 min; (c) [28]NH_4OAc, HOAc, microwave irradiation, 120 °C, 15 min.

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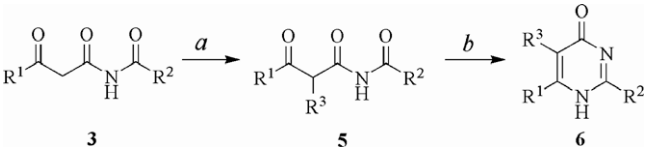
Table 2
Compounds **6** prepared

Compound	R^1	R^2	R^3	Yield of **3**[a]	Yield of **6**[b]	Reference[c]
6a	*n*-Bu	Ph	4-NO_2-benzyl	70	77	21
6b	Ph	Me	Propargyl	72	81	22
6c	Me	2-Thiophenyl	Allyl	68	78	23
6d	Me	2-Cl-phenyl	Me	59	75	24
6e	Me	*n*-Pr	Ph	63	54	25

[a] Isolated yield based on **1** (**2** not purified) after purification by column chromatography or preparative thin layer chromatography.
[b] Isolated yield based on **3** (**5** not purified) after purification by column chromatography or preparative thin layer chromatography.
[c] All products are known (prepared by different methods) and their analytical data are consistent with those reported.



Scheme 2. Reagents and conditions: (a) [29]method A: R^3X (R^3 = alkyl, X = Cl, Br or I), K_2CO_3, acetone, reflux, 2–4 h; method B: R^3X (R^3 = aryl, X = I), CuI, Cs_2CO_3, L-proline, DMSO, microwave irradiation, 100 °C, 30 min; (b) [28]NH_4OAc, HOAc, microwave irradiation, 120 °C, 15 min.

application of microwave technology to key steps led to short reaction times and clean products.[26] We believe that the current methodology will serve as a valuable complement to the existing ones.

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26. Both *N*-acyl β-ketoamides and pyrimidin-4-ones can be obtained under thermal conditions in comparable or slightly lower yields albeit longer reaction times.[9,11]
27. *General procedure for preparation of N-acyl β-ketoamides* (**3**): A mixture of **2** (1 mmol) and amide (1 mmol) in 3:1 toluene/chloroform (3 mL) was irradiated with microwave at 80 °C on a Biotage® Initiator reactor for 15–20 min. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and purified by either flash column chromatography or preparative thin layer chromatography to provide **3**.
28. *General procedure for preparation of pyrimidin-4-ones* (**4** or **6**): A mixture of **3** or **5** (0.5 mmol) and ammonium acetate (5 mmol) in acetic acid (2 mL) was irradiated with microwave at 120 °C on a Biotage® Initiator reactor for 15 min. The reaction mixture was cooled to room temperature, diluted with water, neutralized with sodium bicarbonate, and extracted with dichloromethane (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated to give crude **4** or **6**, which was purified by trituration or recrystallization.
29. *General procedure for preparation of intermediate* **5**. Method A: A mixture of *N*-acyl β-ketoamides **3** (1 equiv), alkyl halide (1 equiv), and potassium carbonate (4 equiv) was heated at reflux in acetone (0.25 M) or stirred at room temperature in *N*,*N*-dimethylformamide (0.25 M) for 2–4 h, quenched with water, and extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated to give crude **5**, which was used in the following step without further purification. Method B: A mixture of **3** (1.0 mmol), aryl iodide (0.5 mmol), copper(I) iodide (0.05 mmol), L-proline (0.1 mmol), and cesium carbonate (2 mmol) in dimethylsulfoxide (2 mL) was degassed and irradiated with microwave at 90 °C on a Biotage® Initiator reactor for 20 min. The reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated to give crude **5**, which was used in the following step without further purification.