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Rapid synthesis of α-ketoamides using microwave irradiation–simultaneous cooling method

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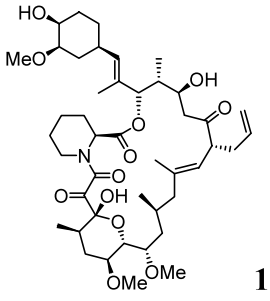
Dedicated to the memory of Professor Arno F. Spatola

Abstract—Microwave-assisted acyl chloride–isonitrile condensation and $CaCO_3$-mediated hydrolysis constitute a one-pot, 2-minute process to prepare α-ketoamides.

The electron-deficient α-carbonyl group of α-ketoamide provides exceptional adducting opportunities to nucleophiles such as the hydroxyl and thiol groups that are abundantly present in the reactive sites of proteolytic enzymes.[1] Because of these enzymes' crucial roles in biochemical pathways, α-ketoamide containing natural products or synthetic agents often deliver profound biological effects. Structurally related microbial products rapamycin and FK-506 (**1**) are two well known instances.[2] Both are potent T-cell activation and proliferation blockers and **1** has been approved for use in organ transplant.[3] Many transition-state protease inhibitors incorporate α-ketoamides into their P_1 sites to affect reversible enzyme modifications. Good examples include thrombin inhibitor cyclotheonamide **2**,[4] calpain inhibitor **3**,[5] and Caspase-3 and 7 inhibitor **4**.[6] Further development of these compounds could lead to therapeutic solutions to stroke, Alzheimer's disease and muscular dystrophy (Fig. 1).

Synthetically, α-ketoamides are prepared mainly by (1) oxidation of the corresponding α-hydroxyamides[7] or α-cyanoketones,[8] and (2) amidation of α-ketoacids.[9] There are also a few less notable protocols including a



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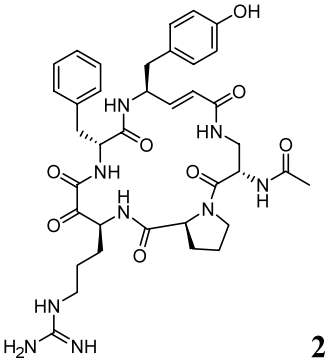

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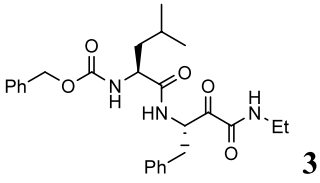

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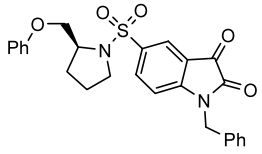

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Figure 1. Biologically active α-ketoamides.

Keywords: microwave synthesis; α-ketoamide; isocyanide chemistry.
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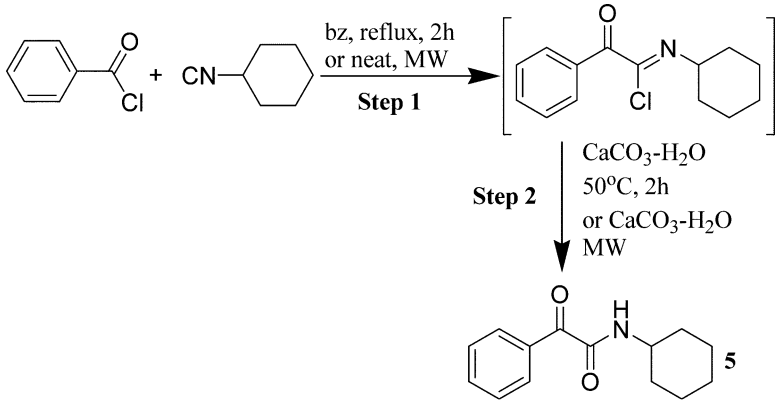
direct synthesis method developed by Ugi in the 1960s.[10] In this protocol, an acyl chloride couples with an isonitrile to form an α-ketoimidoyl chloride intermediate, which is then converted to an α-ketoamide upon hydrolysis (Scheme 1).

A method was warranted to rapidly prepare structurally diverse α-ketoamides to support our protease-related discovery projects. After careful assessment of the available methodologies, we concluded that Ugi's approach was more practical for our purpose since it could generate products directly from commercially available reagents, whereas others necessitated special starting materials that require additional synthetic efforts. However, in Ugi's method, formation and hydrolysis of the key intermediate α-ketoimidoyl chloride demand two to six hours of heating. These lengthy heating steps compromise reaction throughput and thus ought to be optimized. We decided to quest microwave technology for solutions since it has proved to dramatically accelerate heating-involved reactions.[11]

The approach was examined in a Discovery™ microwave synthesizer (Scheme 1). Solvents were eliminated from the original protocol to reduce environmental impact and reagent cost. Neat benzoyl chloride and cyclohexyl isonitrile were mixed in a microwave reaction tube and irradiated at 60 W for 2 minutes. $CaCO_3$–water suspension was injected and the irradiation continued at 60 W for 2 more minutes. The LC-MS analysis indicated that purity of the crude product was comparable to the original method. Though the yield after purification was found to be less than the one with conventional heating,[12] the total reaction time was reduced from 4 h to 4 minutes!

Because of the short turnover time of microwave synthesis, the reaction conditions were quickly optimized using preparation of **6** as the model reaction (Table 1). When the power of irradiation in step **1** was raised to 100 W, only a black tar-like product was produced, which presumably was caused by overheating (entry b). The overheating effect was relieved and the reaction efficiency recovered when air-cooling was engaged during the course of irradiation (entry c).[13] By applying 100 W irradiation along with air-cooling to both condensation and hydrolysis steps, the yield was improved and the total reaction time was further reduced to 2



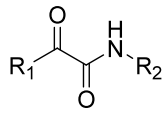
Scheme 1. Preparation of α-ketoamide **5** with different heating methods

Table 1. Optimization of microwave conditions

Entry		a	b	c	d	e	f
Step 1	t_1 (min)[a]	2	1	1	1	1	1
	P_1[b] (W)	60	100	100	100	100	100
	Cooling	Off	Off	On	On	On	On
	T_{1max} °C[c]	149	150	100	100	100	100
Step 2	t_2 (min)[a]	2	2	2	1	1	1
	P_2[b](W)	60	60	60	100	100	100
	Cooling	Off	Off	Off	On	On	On
	T_{2max} °C[c]	195	195	180	125	125	125
Reagent ratio[d]		1	1	1	1	2/3	3/2
%Yield		45	N/A	69	74	70	77

[a] Irradiation time of step 1 or 2.
[b] Wattage of irradiation power.
[c] Maximal temperature during the irradiation.
[d] Molar ratio of benzoyl chloride/cyclohexyl isonitrile.

Table 2. α-Ketoamides prepared by the irradiation-simultaneous cooling method



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Entry	R_1	R_2	%Yield (MW)	%Yield (Ugi)[a]
5	Ph	Cyclohexyl	74	69
6a	Ph	Bn	51	
6b	Ph	*n*-Bu	40	
6c	*p*-Anisoyl	Cyclohexyl	53	
6d	1-Napthyl	Cyclohexyl	64	65
6e	1-Napthyl	*n*-Bu	60	
6f	1-Napthyl	Bn	21	
6g	$PhCH_2CH_2$	Cyclohexyl	60	
6h	$PhCH_2CH_2$	*n*-Bu	51	
6i	$PhCH_2CH_2$	Bn	36	
6j	Ph	1,1,3,3-Tetramethylbutyl	N/A	
6h	Ph	2,5-Dimethylphenyl	N/A	

[a] Yields reported in Ref. 10.

minutes (entry d). It is noteworthy that, this is the first reported instance that demonstrated the practical benefits of microwave irradiation–simultaneous cooling method apart from few scarce mentions.[11a] The alternative acyl chloride–isonitrile ratios were also investigated. Our results suggested that increasing the amount of either reagent did not provide significant benefit to offset the extra reagent cost and purification efforts.

The irradiation–simultaneous cooling method was employed to prepare a series of α-ketoamides listed in Table 2.[14] The final isolation yields of the syntheses were found at least to be comparable to the conventional heating method. Both aromatic and aliphatic acyl chlorides provided good to moderate yields. Sterically hindered or less nucleophilic isonitriles, such as 1,1,3,3-tetramethylbutyl isocyanide and 2,5-dimethylphenyl isocyanide did not perform well, the cause of which is still being investigated.

In summary, a microwave-assisted, rapid synthetic method for α-ketoamides has been developed. The speed of the reaction and a variety of commercially available reagents provide a broad access for this class of compounds. The performance of synthesized ketoamides in protease inhibition assays and their further applications in construction of heterocyclic systems are under active investigation. We will report those results in due course.

General procedure for microwave-assisted synthesis of α-ketoamides: Isocyanide (0.4 mmol) and acyl chloride (0.4 mmol) were added to a 5 mL reaction tube with a stirring bar. The tube was sealed and positioned in the irradiation cavity. The sealed reaction mixture was stirred and irradiated at 100 W while it was cooled by pressurized (20 psi) airflow for 1 minute. To the same reaction tube, a suspension of $CaCO_3$ (24 mg) in acetone (0.8 mL) and water (0.16 mL) was added via a syringe. The mixture was stirred and irradiated at 100 W with air-cooling for 1 min. After ensuring the temperature had dropped and pressure was released, anhydrous K_2CO_3 was added to the reaction tube and the solution filtered. The filtrate was evaporated to dryness and the final product was purified by flash column chromatography with hexane–methylene chloride.

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12. Reaction with neat reagents and conventional heating also provided similar results, but still required total 4 h reaction time.
13. The Discovery™ microwave synthesizer features the option of heating along with spontaneous air-cooling. A similar approach has been mentioned in Chapter 5 of Ref. 11a.
14. The spectroscopic data for selected compounds:
Compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37–8.34 (m, 2H), 7.66–7.61 (dd, 1H, $J_1=7.5$ Hz, $J_2=14.8$ Hz), 7.52–7.47 (dd, 2H, 2H, $J_1=7.8$ Hz, $J_2=15.3$ Hz), 6.99 (s, 1H), 3.93–3.83 (m, 1H), 2.03–1.78 (m, 2H), 1.77–1.64 (m, 3H), 1.51–1.21 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.38, 161.09, 134.60, 134.52, 133.73, 133.68, 131.46, 128.69, 48.70, 32.96, 25.66, 24.99. MS (ESI): m/z 232.26 MH^+.
Compound **6a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41–8.38 (m, 2H), 7.66–7.64 (m, 1H), 7.54–7.49 (m, 2H), 7.42–7.29 (m, 5H), 4.62–4.60 (d, 2H, $J=6.0$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.76, 161.76, 137.34, 134.72, 133.57, 131.51, 129.12, 128.78, 128.17, 128.11, 43.76. MS (ESI): m/z 240.09 MH^+.
Compound **6b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37–8.34 (m, 2H), 7.66–7.61 (m, 1H), 7.52–7.49 (m, 2H), 7.14 (s, 1H), 3.44–3.38 (dd, 2H, $J_1=7.3$ Hz, $J_2=13.1$ Hz), 1.64–1.56 (m, 2H), 1.46–1.38 (m, 2H), 1.00–0.95 (t, 3H, $J=7.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.17, 161.99, 134.59, 133.65, 131.46, 128.80, 128.71, 39.40, 31.57, 20.31, 13.94. MS (ESI): m/z 206.10 MH^+.
Compound **6c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44–8.41 (m, 2H), 6.97–6.94 (m, 2H), 7.06 (s, 1H), 3.90 (s, 3H) 3.88–3.80 (m, 1H), 2.02–1.97 (m, 2H), 1.81–1.63 (m, 3H) 1.49–1.21 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.30, 164.89, 161.61, 134.18, 126.78, 126.74, 114.03, 55.78, 48.61, 32.96, 25.68, 25.00. MS (ESI): m/z 262.10 MH^+.
Compound **6d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60–8.58 (d, 1H, $J=8.4$ Hz), 8.33–8.30 (dd, 1H, $J_1=0.7$ Hz $J_2=6.9$ Hz), 8.10–8.07 (d, 1H, $J=8.0$ Hz), 7.93–7.90 (dd, 1H, $J_1=0.7$ Hz, $J_2=8.0$ Hz), 7.67–7.53 (m, 3H), 7.12–7.10 (d, 1H, $J=7.3$ Hz), 3.99–3.87 (m, 1H), 2.08–2.03 (m, 2H), 1.85–1.78 (m, 2H), 1.71–1.66 (m, 1H), 1.49–1.24 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.14, 161.46, 134.69, 134.10, 133.32, 131.45, 130.08, 128.95, 128.57, 126.75, 125.59, 124.49, 48.99, 33.04, 25.69, 25.02. MS (ESI): m/z 282.26 MH^+.Compound **6g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.22 (m, 5H), 6.87 (s, 1H), 3.81–3.69 (m, 1H), 3.32–3.27 (t, 2H, $J_1=7.0$ Hz, $J_2=14.6$), 2.98–2.93 (t, 2H, $J_1=7.3$ Hz, $J_2=15.0$), 1.94–1.89 (m, 2H), 1.95–1.62 (m, 4H), 1.47–1.16 (m, 5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.96, 159.23, 140.72, 128.74, 128.65, 126.48, 48.57, 38.58, 32.91, 29.41, 25.60, 24.92. MS (ESI): m/z 260.10 MH^+.