Conversion of *N*-Acyl Amino Acids into Imides via Oxidative Decarboxylation Induced by $Ag^+/Cu^{2+}/S_2O_8^{2-}$ in Water

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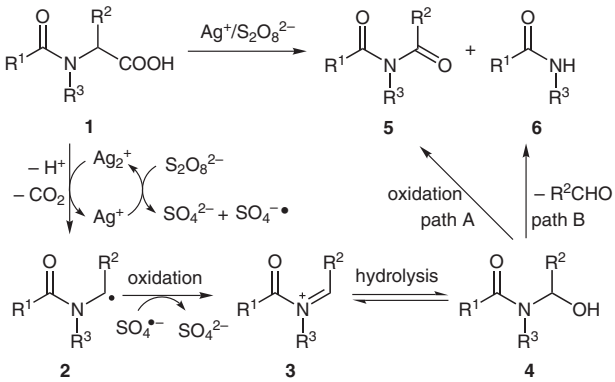
Abstract: *N*-Acyl amino acids can be converted by oxidative decarboxylation induced by $Ag^+/Cu^{2+}/S_2O_8^{2-}$ at room temperature in water into imides in 24–89% yields. Both *N*-benzoylvaline and *N*-benzoylleucine gave *N*-formylbenzamide, which possibly results from oxidative cleavage of an enamide intermediate.

Key words: oxidative decarboxylation, silver, copper, imide, amino acid

Oxidative decarboxylation of amino acids not only has been widely applied in organic synthesis[1] but it also has implications in biological activity.[2] Several methods have been reported for the conversion of *N*-acyl amino acids to imides via oxidative decarboxylation using various oxidants, such as lead tetraacetate,[3a] iodosobenzene,[3b] molecular oxygen,[4a] and *m*-chloroperbenzoic acid.[4b] However, these methods either use stoichiometric amounts of heavy metals, or use expensive reagents, or require an additional step. Recently, Masaki[5] et al. reported that *N*-acyl amino acids can be converted into imides via oxidative photodecarboxylation in the presence of a mesoporous silica, but organic solvents and long reaction times were required. Herein we report a simple method for conversion of *N*-acyl amino acids into imides via oxidative decarboxylation by using persulfate as an oxidant, silver(I) and copper(II) as catalysts ($Ag^+/Cu^{2+}/S_2O_8^{2-}$), and water as solvent.



Scheme 1

Oxidative decarboxylation of *N*-acyl amino acids **1** with stoichiometric persulfate and catalytic silver(I) ($Ag^+/S_2O_8^{2-}$) can form the 1-amidoalkyl radical **2**, which has been applied in the Minisci reaction.[6] The radical **2** is easily oxidized to iminium species **3**, which gives amide **6** and an aldehyde probably via carbinolamide **4** after hydrolysis (Scheme 1, path B).[6c] Our initial work[7] demonstrated that oxidative decarboxylation of *N*-aroylglycine (Scheme 1, $R^2 = R^3 = H$) using $Ag^+/S_2O_8^{2-}$ at 60 °C in a two-phase system (H_2O–$CHCl_3$) could produce imide **5** via an alternative pathway that included oxidation of carbinolamide **4** (path A). However, attempts to extend this reaction to other amino acids failed, for example, *N*-benzoylalanine gave benzamide in 82% yield still via path B. This has driven us to explore this reaction further. After numerous trials, we found that imide **5** could be obtained by increasing the amount of silver(I) and introducing copper(II) as a co-catalyst at room temperature. The results are summarized in Table 1.

As can be seen from Table 1, compound **5b** was obtained in 84% isolated yield when **1b** was treated with three equivalents of ammonium persulfate in the presence of silver nitrate (20 mol%) and copper(II) sulfate (20 mol%) using water as the solvent. This result is in sharp contrast to our previous result, indicating that path B was almost completely suppressed under these reaction conditions. The yield of **5a** from hippuric acid (**1a**) was slightly lower (77%), but higher than that in our initial work (71%).[7a] *N*-Benzoyl-α-phenylglycine (**1c**) gave **5c** in 79% yield, but the replacement of benzoyl with acetyl drastically reduced the yield of **5b** to 32%. For **1c**, the resonance of the PhCO moiety reduces the resonance effect of the amide bond, which results in an increase in the stability of **4** and, therefore, favors path A. On the other hand, for **1d**, the strong resonance of the amide bond may accelerate the hydrolysis of **4** (path B).[7b] Compound **1e**, which is a secondary amide and readily prepared[8] from the condensation of phthalaldehyde with alanine, gave **5e** in the highest yield (89%).

In the case of *N*-benzoylproline (**1f**), however, compound **5f** was obtained in only 24% yield. Surprisingly, for *N*-benzoylvaline (**1g**), the product was not the expected *N*-isobutyrylbenzamide but **5a** (85%) identified by comparison to the product from **1a** by ^1H NMR, TLC, and IR. *N*-Benzoylleucine (**1h**) also gave **5a** but in a lower yield (60%) upon using four equivalents of persulfate. The reaction seemed to proceed via enamide **7**, which formed

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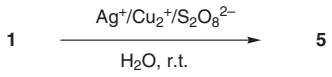
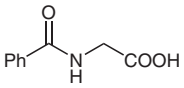
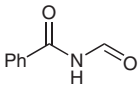
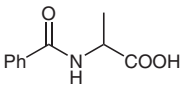
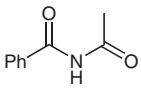
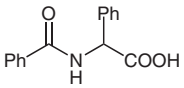
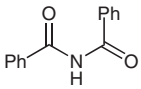
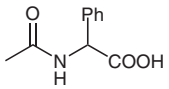
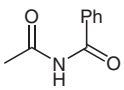
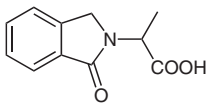
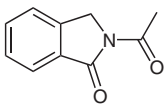
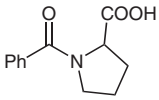
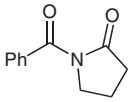
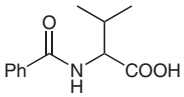
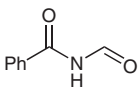
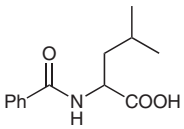
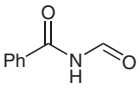
Table 1 Conversion of *N*-Acyl Amino Acids into Imides[a]

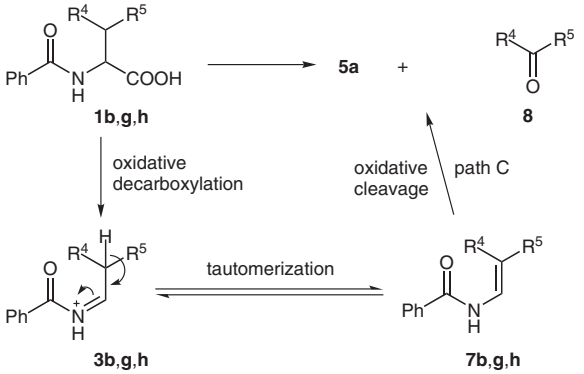


Entry	Substrate **1**		Product **5**		Yield (%)
1	**1a**		**5a**		77
2	**1b**		**5b**		84
3	**1c**		**5c**		79
4	**1d**		**5b**		32
5	**1e**		**5e**		89
6	**1f**		**5f**		24
7	**1g**		**5a**		85
8	**1h**		**5a**		60[b]

[a] Reaction conditions: persulfate (3 equiv), $AgNO_3$ (0.2 equiv), $CuSO_4 \cdot 5\ H_2O$ (0.2 equiv).
[b] Used 4 equiv of persulfate.

from imines **3g**,**h** through tautomerization and gave **5a** after oxidative cleavage (Scheme 2, path C). Needles and Ivanetich[9] isolated *N*-(2-methylpropenyl)acetamide in the oxidative decarboxylation of *N*-acetylvaline with lead tetraacetate in *N*,*N*-dimethylformamide. The ease of the formation of enamide **7** increases with substitution on the carbon–carbon double bond. Therefore, **7b** would be too unstable to form so that **5b** was obtained in high yield still via path A (Scheme 1). Enamide **7g** has one more substituent than **7h**, and therefore forms more readily, which may account for a higher yield of **5a** from **1g** than that from **1h**.

In summary, we have demonstrated that *N*-acyl amino acids can be converted into imides via oxidative decarboxylation induced by $Ag^+/Cu^{2+}/S_2O_8^{2-}$. The reaction was performed at room temperature using catalytic amounts of metals, an inexpensive oxidant, and water as the solvent, hence it provides a simple method to access imides starting from amino acids. Depending on the structure of the



Scheme 2 Proposed mechanism for the formation of **5a** from **1g**,**h**

amino acids, the imides could be formed in two ways: one is oxidation of a carbinolamide intermediate without touching the side chain for glycine, alanine, or α-phenylglycine; another is oxidative cleavage of a possible enamide intermediate with loss of the side chain for valine or leucine to give an *N*-formylimide. This methodology may find applications in peptide modification.

Compounds **1b–h** were prepared according to the literature procedure.[8,10] All the products were confirmed by comparison to known compounds (IR, NMR, and TLC).[7,11] ^{1}H NMR spectra were recorded on a MercuPlus 400 NMR spectrometer. IR spectra were recorded on a Thermo Nicolet Avatar 360 IR spectrophotometer. All melting points were measured on a melting point apparatus with microscope and hot stage and were uncorrected. All reactions were carried out under N_2. PE = petroleum ether (bp 60–90 °C). Hippuric acid (**1a**) was purchased from GuangFu Chemical Reagent Company, China. $(NH_4)_2S_2O_8$, $CuSO_4 \cdot 5H_2O$, and silver nitrate were purchased from Kewei Chemical Reagent Company, China. These chemicals were used directly as received. The deionized water, purchased from Water Center of Nankai University, China, was distilled before use.

N-Acetylbenzamide (5b); Typical Procedure

To a round-bottom flask (50 mL), **1b** (77.3 mg, 0.4 mmol), $AgNO_3$ (13.5 mg, 0.08 mmol), $CuSO_4 \cdot 5\ H_2O$ (20.0 mg, 0.08 mmol), and $(NH_4)_2S_2O_8$ (273.8 mg, 1.2 mmol) were added. The flask was covered with a septum and protected under N_2, deionized H_2O (5 mL) was added by syringe after it had been degassed by sparging with N_2. The mixture was stirred at r.t. for 1 h and EtOAc (10 mL) was added and the mixture was filtered. The EtOAc phase was separated from the filtrate and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined extracts were dried (anhyd Na_2SO_4), concentrated under reduced pressure, and separated by preparative TLC (PE–EtOAc, 2:1). *N*-Acetylbenzamide (**5b**) was obtained from **1b** or **1d** in 84% or 32% yields, respectively, as a white solid; mp 109–110 °C (Lit.[11a] 115 °C).

IR (KBr): 1738, 1679 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.30 (s, 3 H, CH_3), 7.44–7.49 (m, 2 H, 3,5-Ar-H), 7.55–7.58 (m, 1 H, 4-Ar-H), 7.85–7.88 (m, 2 H, 2,6-Ar-H), 10.98 (br s, 1 H, NH).

N-Formylbenzamide (5a)

Obtained from **1a**, **1g**, or **1h** (using 4 equiv of persulfate for **1h**) in 77%, 85%, or 60% yields, respectively, as a white solid, preparative TLC (PE–EtOAc, 3:1); mp 109–110 °C (Lit.[3] 109–110 °C).

IR (KBr): 1724, 1670 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.50–7.55 (m, 2 H, 3,5-Ar-H), 7.62–7.65 (m, 1 H, 4-Ar-H), 7.98–8.01 (m, 2 H, 2,6-Ar-H), 9.23 (d, *J* = 8.0 Hz, 1 H, CHO), 11.72 (br s, 1 H, NH);

_N_-Benzoylbenzamide (5c)
Obtained from **1c** in 79% yield as white needles, preparative TLC (CH_2Cl_2–MeOH, 50:1); mp 144–145 °C (Lit.[12a] 144–145 °C).

IR (KBr): 1704 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.47–7.52 (m, 4 H, 3,5-Ar-H), 7.58–7.61 (m, 2 H, 4-Ar-H), 7.87–7.89 (m, 4 H, 2,6-Ar-H), 11.31 (br s, 1 H, NH);

2-Acetyl-2,3-dihydro-1*H*-isoindol-1-one (5e)
Obtained from **1e** in 89% yield as short white needles, preparative TLC (CH_2Cl_2–MeOH, 50:1); mp 120–121 °C.

IR (KBr): 1720, 1686 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.51 (s, 3 H, CH_3), 4.75 (s, 2 H, CH_2), 7.51–7.56 (m, 1 H, 3-Ar-H), 7.62–7.65 (m, 1 H, Ar-5-H), 7.70–7.75 (m, 1 H, 4-Ar-H), 7.79–7.82 (m, 1 H, 2-Ar-H).

1-Benzoylpyrrolidin-2-one (5f)
Obtained from **1f** in 24% yield as a white solid, preparative TLC (PE–EtOAc, 3:1); mp 87–88 °C (Lit.[12b] 89–90 °C)

IR (KBr): 1743, 1664 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.95–2.03 (m, 2 H, CH_2CH_2N), 2.48 (t, *J* = 8.0 Hz, 2 H, COCH_2), 3.76 (t, *J* = 7.2 Hz, 2 H, CH$_2$CH_2N), 7.35–7.39 (m, 2 H, 3,5-Ar-H), 7.45–7.52 (m, 3 H, 2,4,6-Ar-H).

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