A Platinum Open Access Journal
for Organic Chemistry

Paper

Free to Authors and Readers

DOAJ Seal

Arkivoc **2024** (4) 202412337

Copper(II)-catalyzed oxidation of *N*-substituted isoindolinones to the corresponding phthalimides

Frederick A. Luzzio*, Shramana Ghosh, and Bernard L. Adjei

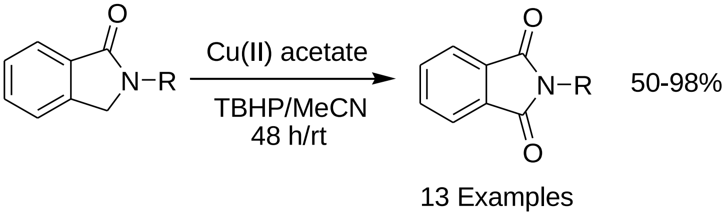
Department of Chemistry, University of Louisville, 2320 South Brook Street, Louisville, KY 40292 USA
Email: faluzz01@louisville.edu

Dedicated with best wishes to Professor R. Alan Aitken

Received 12-05-2024 **Accepted** 02-16-2025 **Published on line** 02-19-2025

Abstract

A series of *N*-substituted isoindolinones were treated with an oxidation system comprised of catalytic copper(II) acetate monohydrate and *tert*-butylhydroperoxide (TBHP) in a non-chlorinated solvent (acetonitrile). As a result of benzylic methylene oxidation, the oxidation system afforded the corresponding phthalimides in isolated yields of 50-98%. Simple isoindolinones responded quite well to the oxidation system and gave the products after a reaction period of 24-48 hours at room temperature. The oxidation was selective for the benzylic (C3) carbon of the isolindolinone as opposed to isolated methylene groups and benzylic methyl groups. Using selected substrates, an analogous oxidation method mediated by Cu(II) oxinate is also detailed.

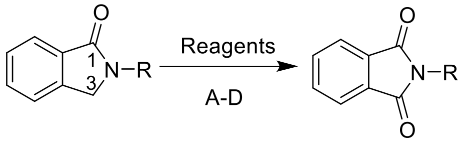


Keywords: Copper(II) acetate, Cu(II)-oxine, isoindolinones, oxidation, phthalimides, selectivity, TBHP

DOI: https://doi.org/10.24820/ark.5550190.p012.337

Introduction

The oxidation of methylene groups α- to nitrogen can result in the formation of amides, imides or even triacylamines depending on the nitrogen substitution.[1,2] In particular the α-methylene oxidation of cyclic amines can give rise to lactams or cyclic imides, functional groups which appear in a great many biologically-active compounds and natural products. In particular, the isoindolinone or otherwise lactam core forms a central scaffold from which a great many therapeutics and naturally-occurring compounds have been derived.[3,4] Previous reports from these laboratories have focused on the oxidation of lactam and hydroxylactam derivatives of isoindolinones to phthalimides.[5-8] Considering the well-established applicability of the phthalimide group, its interconversion between the corresponding lactams and hydroxylactams would be of interest in the protecting group chemistry of nitrogen.[9] While isoindolinones have yet to be proven and accepted as routine protecting groups for nitrogen, their use in unnatural amino acid synthesis has been briefly demonstrated.[5] Catalytic iron(III) salts in conjunction with *tert*-butylhydroperoxide (TBHP) have proven to be useful in the methylene oxidation of isoindolinones to the corresponding phthalimides (Scheme 1).[8]



Reagents:

A. Oxone/KBr (Ref. 5)
B. Cr(VI) (Ref. 6)
C. Fe (III)/TBHP (Ref. 8)
D. Cu(II) This work

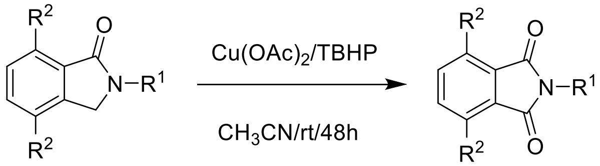
Scheme 1. Oxidative conversions of isoindolinones to phthalimides.

While the catalytic iron/TBHP systems can be harsh to some substrates, the 'eco' friendliness, low expense and ready availability of these systems make them highly desirable for organic synthesis. Recent studies from other laboratories have demonstrated that catalytic copper salts in conjunction with TBHP are effective in oxidizing both benzylic methylenes (C1, C3) of isoindolines to give the corresponding phthalimides.[10] While the majority of oxidations in the copper/TBHP report utilized CuCl as the catalyst, one example listed utilized copper(II) acetate as the oxidant along with TBHP in dichloromethane. Furthermore, both catalytic copper salts and complexes in conjunction with organic peroxides have been demonstrated to be synthetically useful oxidants in the conversion of π-activated methylene groups to carbonyls.[11] Accordingly, it was of interest to study the properties of catalytic copper salts or copper complexes in conjunction with the peroxide oxidant in acetonitrile whereby the employment of dichloromethane or other chlorinated reaction solvents are avoided. The application of catalytic copper(II)/TBHP systems for the oxidation of isoindolinones (lactams) to the corresponding imides is examined in the present report with emphasis on selectivity of the benzylic methylene group (C3). While many metal salts in conjunction with organic peroxides have received attention in the oxidation of isolated or otherwise unactivated methylenes,[12] the work reported herein focused on phthalimide/isoindolinone chemistry. Particular attention was paid to yield, mild reaction conditions and the ease of isolation and purification of the product imides.

Results and Discussion

Isoindolinones **1a-1l** (Table 1) were prepared from the corresponding imides through selective reduction of phthalimides using activated zinc metal and acetic acid.[13,14,15] There are countless strategies for the preparation of substituted isoindolinones and many of these utilize both transition metal-catalyzed and non-transition metal-mediated annulation reactions.[16,17] While the annulation reactions focus on the de novo construction of the lactam ring, the lactam substrates utilized in the present study did not require extensive substitution and we deemed the phthalimide reduction method more suitable for our application. The substrates **1a-l** were treated with a mixture of cupric acetate monohydrate (5 mol%) and *tert*-butylhydroperoxide (TBHP, 70%, 10 equivalents) in acetonitrile. The reaction mixtures were entirely homogeneous and took on a clear blue coloration at the start of the reaction while changing to a bluish-green at its conclusion.

Table 1. Oxidation of Isoindolinones (lactams) **1a-l** to Imides 2a-l using Cu(OAc)2/TBHP1,2

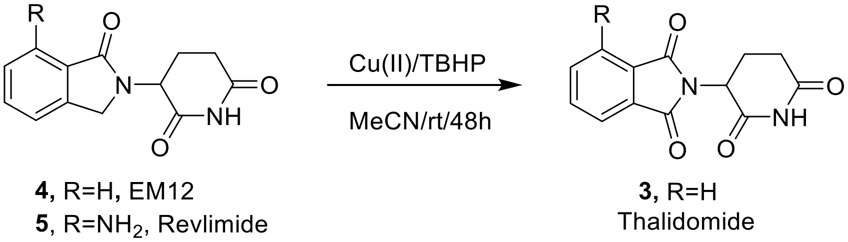


1a-l **2a-l**

Substrate	Product	Yield (%)[3]
1a, R^1=Et, R^2=H	**2a**	85
1b, R^1=*n*-Pr, R^2=H	**2b**	84
1c, R^1=*c*-Pentyl, R^2=H	**2c**	83
1d, R^1=*n*-Pentyl, R^2=H	**2d**	83
1e, R^1=Phenyl, R^2=H	**2e**	65
1f, R^1=*c*-Hexyl, R^2=H	**2f**	60
1g, R^1=$CH_2C_6H_5$, R^2=H	**2g**	67
1h, R^1=C_6H_4-4-F, R^2=H	**3h**	98
1i, R^1=(*S*)-Phenethyl, R^2=H	**2i**	50
1j, R^1=C_6H_4-4-OMe, R^2=H	**2j**	72
1k, R^1=$CH_2C_6H_4$-4-OMe, R^2=H	**2k**	82
1l, R^1=C_6H_4-2,4-difluorophenyl, R^2=Me	**2l**	76

1. Typical oxidations utilized Cu(OAc)2 monohydrate (5 mol%), TBHP (70%, 10 eq)/acetonitrile.
2.Reactions were conducted under nitrogen at room temperature.
3.Yields (%) are of isolated purified product.

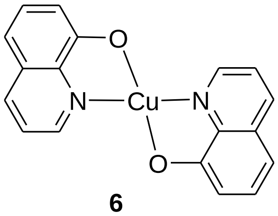
The corresponding product imides (**2a-2l**, Table 1) were obtained in isolated yields of 50-98% after silica gel column chromatography. In cases of substrates bearing one or more benzylic methylenes or benzylic methyl groups (**2g**, **2i**, **2k**, **2l,** Table 1) the oxidation was selective for the methylene α-to the nitrogen of the isoindolinone. Of special interest in the oxidation study were the structures and conversions of isoindolinone substrates **1b** and **1l**. Substrate **1b** (2-propylisoindol-1-one) forms the structural backbone of a class of small-molecule inhibitors of the MDM2-p53 interaction.[18] In certain cancers, the MDM2 (murine double minute) oncoprotein-p53 interaction plays a role in deactivating the tumor suppressor p53, so inhibition of the interaction will reactivate the tumor suppressor which leads to eliminating tumors. In the design of isoindolinone inhibitors of MDM2-p53, scaffolds such as **1b** are further elaborated through placement of aryl groups on C3 of the isoindolinone. As part of an earlier biological profile study, substrate **1l** (Table 1) was derived from imide **2l**, a compound which was of interest as a tumor necrosis factor (TNFα) inhibitor. TNFα is a cytokine which is present during chronic inflammation and is associated with the progression of complications such as autoimmune disorders. In a bioassay of LPS (lipopolysaccharide)-induced TNF-α production in human monocytes, **2l** exhibited <10% inhibition and 74% cell viability at 50μM, which was marginal compared to other phthalimide-derived analogues in the study.[19] There is interest in the interconversion of thalidomide **3** and its isoindolinone analogue known as EM12 (3-(1-oxoisoindolin-2-yl)piperidine-2,6-dione, **4**).[20] During the course of early studies on the teratogenicity of thalidomide, EM12 was found to be a more potent teratogen than thalidomide along with many of its analogues as evidenced by bioassay studies using thalidomide-sensitive species.[21] Furthermore, the isoindolinone core of EM12 formed a conceptual or otherwise structural starting point for the development of the immunomodulatory compound Revlimid **5**.[22] Thus the treatment of **4** with catalytic (5 mol%) copper(II) acetate/with TBHP (10 equiv.) in acetonitrile over a 48 hour period resulted in clean conversion to thalidomide **3** with an isolated yield of 94% (Scheme 2).



Scheme 2. Oxidation of EM12 4 to thalidomide **3**.

While the employment of copper salts in conjunction with oxygen or peroxides has been established as synthetically-useful for the preparation of carbonyl compounds, copper coordination complexes such as $Cu(acac)_2$, Cu(II) salen or Cu(II) ethylenediamine have also been evaluated for the oxidation of a wide spectrum of substrates. In contrast, comparatively little attention has been given to the evaluation of the Cu(II) oxine complex [bis(8-quinolinolato)copper(II)] **6** or its analogues as catalysts for the types of oxidative transformations detailed in the present study.[12,23] Copper(II) oxinate, otherwise known as Cu(II)8HQ **6** was prepared by a method described in an early U.S. patent and was isolated as a green-brown powder.[24] Treatment of three selected substrates **1c**, **1e** and **1f** (Table 1) on a 0.05 mmol scale gave the corresponding phthalimide products **2c**, **2e** and **2f** in isolated yields of 76, 99 and 80% respectively (Table 2). Similar to the $Cu(OAc)_2$-mediated reactions, the Cu(II)8HQ reactions were conducted with 5 mole % copper oxine catalyst and TBHP (10 equivalents) in acetonitrile with the exclusion of air.

Table 2. Oxidation of Isoindolinones **1c**, **1e**, **1f** to Imides **2c**, **2e**, **2f** using Cu(II)8HQ1,2



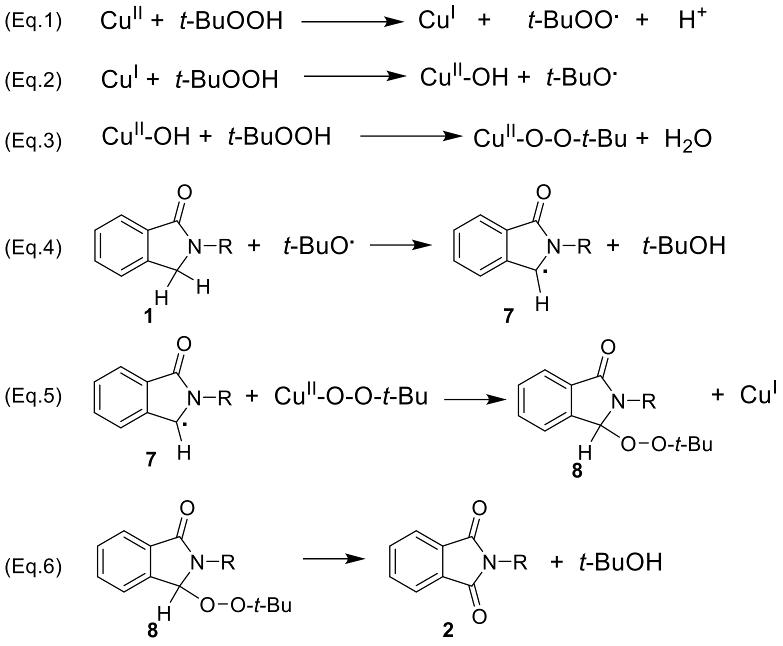
6
Cu(II)8HQ

$$\mathbf{1c, 1e, 1f} \xrightarrow[\text{CH}_3\text{CN/rt/48h}]{\text{Cu(II) 8HQ/TBHP}} \mathbf{2c, 2e, 2f}$$

Substrate	Product	Yield (%)[3]
1c	**2c**	76
1e	**2e**	99
1f	**2f**	80

1.Typical oxidations utilized Cu(II)8HQ (5 mol%), TBHP (70%, 10 eq)/acetonitrile.
2.Reactions were conducted under nitrogen at room temperature.
3.Yields (%) are of isolated purified product.

Plausible mechanistic steps include the interconversion of Cu(II) and Cu(I) as the initiation step (Eq. 1) and the transformation of the *N*-substituted isoindolinone **1** to the corresponding radical **7** (Eq. 4) (Scheme 3). The reactive intermediate **7** in the overall mechanism is derived from that formulated for Cu-mediated benzylic oxidation as proposed by Sasson and co-workers.[11] Specifically, exposure of copper(II) to *tert*-butylhydroperoxide results in the generation of copper(I) with concomitant formation of the *tert*-butylperoxy radical. Copper(I) reacts further with *tert*-butylhydroperoxide to provide the copper(II) species (Cu (II)-OH and the *tert*-butoxy radical (Eq. 2).



Scheme 3. Plausible mechanistic steps for the Cu(II)/TBHP-mediated isoindolinone to phthalimide oxidation.

The recombination of copper(II) as CuOH and *tert*-butyl hydroperoxide forms the *tert*-butylperoxy Cu(II) species (Eq. 3). In turn, the *tert*-butoxy radical can then abstract a benzylic hydrogen from the substrate **1** which results in forming the 3-isoindolinoyl radical **7** (Eq. 4). The interception of radical **7** with the *tert*-butylperoxy Cu(II) species gives rise to the 3-*tert*-butylperoxy isoindolinoyl **8** (Eq. 5) which collapses to yield the imide product **2** (Eq. 6).

Conclusions

The development and application of a catalytic copper(II)/TBHP system for the mild and effective oxidation of *N*-substituted isoindolinone-derived lactams is detailed. While catalytic copper-mediated oxidations have been reported to be somewhat selective for π-activated methylene groups as in benzylic oxidation,[12] the isoindolinone scaffold responded with high selectivity to give oxidation at the benzylic methylene α-to nitrogen. The mechanistic steps involve the formation of an isoindolinoyl radical which is mediated by a cascade of reactions starting with the hydroperoxide-initiated conversion of copper(II) to copper(I). The inclusion of a copper complex Cu(II)8HQ in the oxidation of selected isoindolines demonstrated the potential of using Cu co-ordination compounds as opposed to Cu salts as the oxidation catalysts.

Experimental Section

Solvents, reagents, and starting materials were ACS grade and were used as commercially supplied. Deionized water was used for any aqueous washes and in preparing aqueous solutions of brine. Copper(II) acetate monohydrate was reagent grade and used as supplied. Activated zinc for the imide reductions was prepared by the method of Yamamura.[25] Analytical thin-layer chromatography (TLC) utilized 0.25 mm pre-cut glassbacked plates (Merck, Silica Gel 60 F_{254}). Thin-layer chromatograms were visualized during chromatographic, extraction and reactions by rapidly dipping the plates in anisaldehyde/ethanol/sulfuric acid stain or phosphomolybdic acid/ethanol stain and heating. Gravity-column chromatography utilized silica gel 60 (E. Merck 9385-9, 70-23 mesh). Melting points were taken on a Mel-Temp apparatus. Disposal of metal waste was performed in accordance with the National Research Council publication *Prudent Practices in the Laboratory*.[26] Nuclear magnetic resonance (^{1}H and ^{l3}C NMR) spectra were recorded with Varian VNMRS 400 and 700 (^{13}C NMR-100, 175 MHz) and Oxford AS 500 MHz (^{13}C NMR-125 MHz) instruments using $CDCl_3$ and DMSO-d_6 as ^{1}H and ^{13}C NMR solvents. Infrared spectra (Fourier Transform Infrared Spectroscopy, FTIR) were recorded with a Perkin-Elmer Spectrum 100 instrument. High Resolution Mass Spectra (HRMS) were measured at the Indiana University Mass Spectrometry Facility.

Preparation of the Substrate Isoindolinones (lactams) 1a-l (Table 1): The isoindolinone substrates **1a-l** (**Table 1**) were prepared from the corresponding imides by the zinc/acetic acid reduction method of Brewster.[13,14] The scale of the reductions ranged from 250 mg to 1.0 g as shown below. All the substrate lactams with the exception of **1l** (**See Supporting Information**) were known compounds:

2-Ethylisoindolin-1-one (1a): (500 mg scale); Colorless oil (221 mg, 49%); R_f=0.18 (hexanes/EtOAc, 2 :1). The spectral properties of **1a** were consistent with those found in the literature.[27]

2-Propylisoindolin-1-one (1b): (500 mg scale); Colorless oil (196 mg, 43%); R_f=0.2 (hexanes/EtOAc, 2 :1); the spectral data exhibited by **1b** were consistent with those found in the literature.[28]

2-Cyclopentylisoindolin-1-one (1c): (500 mg scale); Yellow oil (291 mg, 63%); R_f=0.24 (hexanes/EtOAc, 2 :1); the spectral data exhibited by **1c** were consistent with those found in the literature.[29]

2-Pentylisoindolin-1-one (1d): (1.0 g scale); Clear yellow oil (440 mg, 47%); R_f=0.28 (hexanes/EtOAc, 2 :1); the spectral data exhibited by **1d** were consistent with those found in the literature.[30]

2-Phenylisoindolin-1-one (1e): (500 mg scale); White solid (207 mg, 45%); Mp. 159-160 ^{o}C [Lit.[31] 156-160 °C]; R_f=0.38 (hexanes/EtOAc, 2 :1); the spectral data exhibited by **1e** were consistent with those found in the literature.

2-Cyclohexylisoindolin-1-one (1f): (1.0 g scale); White solid (305 mg, 33%); Mp. 80-82 ^{o}C [Lit.[32] 78-82 ^{o}C]; R_f=0.26 (hexanes/EtOAc, 2 :1); the spectral data exhibited by **1f** were consistent with those found in the literature.

2-Benzylisoindolin-1-one (1g): (1.0 g scale); Pale yellow solid (506 mg, 54%); Mp. 83-84 ^{o}C [Lit.[33] 85-86 ^{o}C]; R_f=0.22 (hexanes/EtOAc, 2 :1); the spectral data exhibited by **1g** were consistent with those found in the literature.

2-(4-Fluorophenyl)isoindolin-1-one (1h): (500 mg scale); White solid (295 mg/65%); Mp. 169-172 ^{o}C [Lit.[33] 170-171 ^{o}C]; R_f=0.36 (hexanes/EtOAc, 2 :1); the spectral data exhibited by **1h** were consistent with those found in the literature.

(*S*)-2-(1-Phenylethyl)isoindolin-1-one (1i): (1.0 g scale); White solid (256 mg, 27%); Mp. 140-142 ^{o}C [Lit.[34] 144-145 ^{o}C]; R_f=0.24 (hexanes/EtOAc, 2 :1) the spectral data exhibited by **1i** were consistent with those found in the literature.

2-(4-Methoxyphenyl)isoindolin-1-one (1j): (500 mg scale); White solid (248 mg, 52%); Mp. 131-134 ^{o}C [Lit.[35] 130-134 ^{o}C]; R_f=0.23 (hexanes/EtOAc, 2 :1); the spectral data exhibited by **1j** were consistent with those found in the literature.

2-(4-Methoxybenzyl)isoindolin-1-one (1k): (500 mg scale); White solid (303 mg, 63%); Mp. 89-91 ^{o}C [Lit.[36] 87-90 ^{o}C]; R_f=.16 (hexanes/EtOAc, 2 :1); the spectral data exhibited by **1k** were consistent with those found in the literature.

2-(2,4-Difluorophenyl)-4,7-dimethylisoindolin-1-one (1l): Activated zinc powder (680mg, 12 equiv.) was added to a solution of 2-(2,4-fluorophenyl)-4,7-dimethylisoindole-1,3-dione **2l** (250 mg, 0.87 mmol) and glacial acetic acid (3.0 mL). The mixture was heated at reflux while stirring (4h) followed by filtering the hot mixture on a sintered glass funnel with suction. The filter cake was washed with small (2 mL) portions of glacial acetic acid and to the combined filtrates was added saturated aqueous $NaHCO_3$ (30 mL). The solution was extracted with dichloromethane (3X30mL) and the combined extract was washed with aqueous $NaHCO_3$ (15 mL), water (15 mL) and finally brine (15 mL). The organic phase was then dried over anhydrous sodium sulfate followed by removal of the drying agent by filtration and concentration under vacuum. The residue was applied to a gravity silica gel column (hexanes/EtOAc, 2:1) and the product **1l** was obtained as a white solid (71.3 mg, 30%). Mp. 101-102 °C, R_f=0.5 (hexanes/EtOAc, 2 :1); FTIR (neat): 3055, 3018, 1683, 1505, 1387, 1262 cm^{-1}; ^1H NMR (700MHz, $CDCl_3$), ppm δ: 7.57-7.54 (m, 1H), 7.25 (t, J = 4.2Hz, 1H), 7.16 (d, J = 8.4Hz, 1H), 6.96-6.93 (m, 2H), 4.67 (s, 2H), 2.70 (s, 3H), 2.309 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): ppm: 169.10, 162.43, 159.95, 158.79, 156.27, 140.74, 135.58, 132.48, 130.32, 129.40, 128.25, 122.51, 111.53, 104.86, 50.81, 16.92 HRMS: (ESI): *m/z* $[M+Na]^+$ Calcd. For $C_{16}H_{13}F_2NO$ 273.0965, Found: 273.0966.

Oxidation of Isoindolinones 1a-1l to Phthalimides 2a-2l (Table 1); General Procedure:

To a stirred solution of lactam (**1a-1l**, 50mg, 10-25mmol) in acetonitrile (3 mL) was added cupric acetate monohydrate (5 mol%) followed by *tert*-butylhydroperoxide (70%, 10 equiv). The resulting blue homogenous mixture was stirred under nitrogen for 24-48 h. The reaction mixture was concentrated under reduced pressure, the dark residue was taken up in dichloromethane and applied directly to a gravity silica gel column. Elution of the column with hexanes/EtOAc (4 :1) gave the pure product phthalimides (**2a-l, Table 1**).

2-Ethylisoindoline-1,3-dione (Table 1, 2a): White solid (55 mg, 85%); Mp. 73-76 °C [Lit.[27] 75.1-76.2 °C]; R_f=0.23 (hexanes/EtOAc, 4 :1).

2-Propylisoindoline-1,3-dione (Table 1, 2b): White solid (45 mg, 84%); Mp. 65-66 °C [Lit.[37] 63-65 °C]; R_f=0.31 (hexanes/EtOAc, 4 :1).

2-Cyclopentylisoindoline-1,3-dione (Table 1, 2c): White solid (43 mg, 83%); Mp. 98-100 °C [Lit.[38] 99-100 °C]; R_f=0.55 (hexanes/EtOAc, 4 :1).

2-Pentylisoindoline-1,3-dione (Table 1, 2d): Oil (44 mg, 83%); R_f=0.39 (hexanes/EtOAc, 4 :1). The spectral data exhibited by **2d** was consistent with that previously reported.[39]

2-Phenylisoindoline-1,3-dione (Table 1, 2e): White solid (34 mg, 65%); Mp. 215-217 °C [Lit.[40] 216-218 °C]; R_f=0.28, (hexanes/EtOAc, 4 :1).

2-Cyclohexylisoindoline-1,3-dione (Table 1, 2f): White solid (31 mg, 60%); Mp. 168-170 °C [Lit.[41] 169-172 °C]; R_f=0.37 (hexanes/EtOAc, 4 :1).

2-Benzylisoindoline-1,3-dione (Table 1, 2g): White solid (35 mg, 67%); Mp. 112-115 °C [Lit.[41] 111-113 °C]; R_f=0.35, (hexanes/EtOAc, 4 :1).

2-(4-Fluorophenyl)isoindoline-1,3-dione (Table 1, 2h): White solid (51 mg, 98%); Mp. 181-183 °C [Lit.[41] 181-182 °C]; R_f=0.22 (hexanes/EtOAc, 4 :1).

(*S*)-2-(1-Phenylethyl)isoindoline-1,3-dione (Table 1, 2i): White solid (26 mg, 50%); R_f=0.45 (hexanes/EtOAc, 4 :1). The spectral data for **2i** was consistent with that previously reported.[42]

2-(Methoxyphenyl)isoindoline-1,3-dione (Table 1, 2j): White solid (37 mg, 72%); Mp. 159-162 °C [Lit.[41] 160-163 °C]; R_f=0.19 (hexanes/EtOAc, 4 :1).

2-(4-Methoxybenzyl)isoindoline-1,3-dione (Table 1, 2k): White solid (43 mg, 82%); Mp. 128-130 °C [Lit.[43] 127-129 °C]; R_f=0.48 (hexanes/EtOAc, 4 :1) .

2-(2,4-Difluorophenyl)-4,7-dimethylisoindoline-1,3-dione (Table 1, 2l): White solid (39 mg, 76%); Mp. 135-137 °C; R_f=0.32 (hexanes/EtOAc, 4 :1). A reference sample was prepared by the method described by

Gütschow (Ref. 15): Mp. 135-136 °C [Lit.[19], 212-212.5 °C]. Despite the marked difference in melting point, the spectral data of **2l** prepared in these laboratories was consistent with that previously reported.[19]

Oxidation of 3-(1-oxoisoindolin-2-yl)piperidine-2,6-dione (EM12) 4 to Thalidomide 3:

To a stirred solution of 3-(1-oxoisoindolin-2-yl)piperidine-2,6-dione **4** (50.0 mg, 20mmol) in dry acetonitrile (3 mL) was added $Cu(OAc)_2 \cdot H_2O$ (1.9 mg, 0.1mmol, 5 mol %). The resulting blue mixture was stirred under nitrogen while monitoring by TLC (CH_2Cl_2/Me_2CO, 5 :1). The reaction mixture turned in color to yellow over a reaction period of 24h. The reaction mixture was concentrated under vacuum, diluted with CH_2Cl_2 and passed through a short silica gel column eluting with CH_2Cl_2/Me_2CO. Removal of the solvent gave an off-white solid (49 mg, 94%) which had the spectral properties of thalidomide **3** as previously reported.[6]

***Bis*(8-quinolinolato)copper (II) (Cu(II)8HQ) (6)**: Cupric acetate monohydrate (0.67 mg, 0.34 mmol) was added to a solution of 8-hydroxyquinoline (100 mg, 0.68 mmol) in acetonitrile (5 mL) while stirring under nitrogen. Stirring under nitrogen was continued for 24 h whereby the pale yellow mixture had changed to a green-brown suspension. The solid material was collected by suction filtration and dried under high vacuum (76 mg, 63%). The copper (II) oxine complex could be stored up to three months with no loss of activity.

Oxidation of Isoindolinones 1c, 1e, 1f to Phthalimides 2c, 2e, 2f using the copper(II) oxine (Cu(II)8HQ) catalyst 6: To a solution of substrate lactam (Table 1) **1c**, **1e** or **1f** (10 mg, 0.45-0.5 mmol) and acetonitrile (3 mL) was added copper oxine (Cu(II)8HQ) catalyst **6** (5 mol %) followed by TBHP (70%) while stirring under nitrogen. The resulting pale yellow reaction mixture was stirred under nitrogen (48 h). The reaction mixture was concentrated, the residue then taken up in dichloromethane and applied to a silica gel column. Column elution (hexanes/EtOAc, 4:1) gave **2c** (8.1 mg, 76%), **2e** (10.5 mg, 99%) or **2f** (8.5 mg, 80%). The physical and spectral properties of the imide products were consistent with those listed in the literature.[38,40,41]

Acknowledgements

Support of S.G. and B.L.A. by University of Louisville Graduate Student Teaching Assistantships are acknowledged. A University Fellowship awarded to S.G. for the years 2021-2023 is acknowledged.

Supplementary Material

^{1}H and ^{13}C NMR Spectra for new compound 2-(2,4-Difluorophenyl)-4,7-dimethylisoindolin-1-one (**1l**).

References

1. Luzzio, F. A. in *Science of Synthesis* "21.2 Product Class 2: Triacylamines, Imides (Diacylamines), and related Compounds" Thieme 2005, 21, 259.
https://doi.org/10.1055/sos-SD-021-00215
2. Patil, P. C. in *Imides-Medicinal, Agricultural Applications and Natural Products Chemistry* Luzzio, F. A. Ed.; Smith, M. B. Series Ed. Developments in Organic Chemistry, Elsevier, **2019**; pp 29-64.
https://doi.org/10.1016/B978-0-12-815675-9.00010-2
3. Kushwaha, N.; Kaushik, D. *J. Appl. Pharm. Sci.* **2016**, *6*, 159-171.
https://doi.org/10.7324/JAPS.2016.60330

4. Jha, M.; Youssef, D.; Sheey, H.; Jha, A. *Organics*, **2025**, *6*, 3-18. https://doi.org/10.3390/org6010003
5. Patil, P. C.; Luzzio, F. A.; Ronnebaum, J. M. *Tetrahedron Lett.* **2017**, *58*, 3730-3733. https://doi.org/10.1016/j.tetlet.201708.032
6. Luzzio, F. A.; Zacherl, D. P. *Tetrahedron Lett.* **1999**, *40*, 2087-2090. https://doi.org/10.1016/S0040-4039(99)00152-5
7. Adjei, B. L.; Luzzio, F. A. *Molecules* **2022**, *27*, 548. https://doi.org/10.3390/molecules27020548
8. Adjei, B. L.; Luzzio, F. A. *Tetrahedron* **2023**, *149*, 133739. https://doi.org/10.1016/j.tet.2023.133739
9. Wuts, P.G.M. *Greene's Protective Groups in Organic Synthesis.* 5th Ed. New York, John Wiley & Sons; 2014. https://doi.org/10:1002/9781118905074
10. Yan, X.; Fang, K.; Liu, H.; Xi, C. *Chem. Commun.* **2013**, *49*, 10650-10652. https://doi.org/10.1039/C3CC45869E
11. Rothenberg, G.; Feldberg, L.; Wiener, H.; Sasson, Y. *J. Chem. Soc. Perkin Trans 2* **1998**, 2429-2434. https://doi.org/10.1039/A805324C
12. Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234-6458. https://doi.org/10.1021/cr300527g
13. Brewster, J. H. ; Fusco, A. M. ; Carosino, L. E. ; Corman, B. G. *J. Org. Chem.* **1963**, *28*, 498-501. https://doi.org/10.1021/jo01037a056
14. Brewster, J. H.; Fusco, A. M. *J. Org. Chem.* **1963**, 28, 501-503. https://doi.org/10.1021/jo01037a057
15. Yuan, X.; Zhang, M; Kang, C.; Guo, H.; Qiu, X.; Gao, L. *Synth. Commun.* **2006**, *36*, 435-444. https://doi.org/10.1080/00397910500383485
16. Savela, R.; Méndez-Gálvez, C. *Chem. Eur. J.* **2021**, *27*, 5344-5378. https://doi.org/10.1002/chem.202004375
17. Samanta, S.; Ali, S. A.; Bera, A.; Giri, S.; Samanta, K. *New J. Chem.* **2022**, *46*, 7780. https://doi.org/10.1039/d2nj00475e
18. Luzzio, F. A.; Dempster, R. K. *Tetrahedron Lett.* **2011**, *52*, 4992-4995. https://doi.org/10.1016/j.tetlet.2011.07.076
19. Gütschow, M.; Hecker, T; Thiele, A.; Hauschildt, S.; Eger, K. *Bioorg. Med. Chem.* **2001**, *9*, 1059-1065. https://doi.org/10.1016/S0968-0896(00)00323-0
20. Luzzio, F. A.; Mayorov, A. V.; Ng, S. S. W.; Kruger, E. A.; Figg, W. D. *J. Med. Chem.* **2003**, *46*, 3793-3799. https://doi.org/10.1021/jm020079d
21. Schmahl, H. J.; Dencker, L.; Plum, C.; Chahoud, I.; Nau, N. *Arch Toxicol.* **1996**, *70*, 749-56. https://doi.org/10.1007/s002040050336
22. Luzzio, F. A. in *Imides-Medicinal, Agricultural Applications and Natural Products Chemistry* Luzzio, F. A. Ed.; Smith, M. B. Series Ed. *Developments in Organic Chemistry*, Elsevier, **2019**; pp 367-429. https://doi.org/10.1016/B978-0-12-815675-9.00010-2.
23. Summers, K. L.; Pushie, M. J.; Sopasis, G. J.; James, A. K.; Dolgova, N. V.; Sokaras, D.; Kroll, T.; Harris, H. H.; Pickering, I. J. George, G. N. *Inorg. Chem.* **2020**, *59*, 13858-13874. https://doi.org/10.1021/acs.inorgchem.0c01356
24. Taylor, G. E. US Patent 2,678,314, 1954, *Chem. Abstr.* 1954, 49, p39609.
25. Yamamura, S.; Toda, M.; Hirata, Y. *Organic Syntheses* **1973**, Vol. 53, 86-90.

https://doi.org/10.15227/orgsyn.053.0086

26. *National Research Council 2011. Prudent Practices in the Laboratory: Handling and Management of Chemical Hazards*, Washington, DC: The National Academies Press. https://doi.org/10.17226/12654
27. Ding, G.; Li, C.; Shen, Y.; Lu, B.; Zhang, Z.; Xie, X. *Adv. Synth. Catal.* **2016**, *358*, 1241-1250. https://doi.org/10.1002/adsc.201501093
28. Wang, S.; Huang, H.; Bruneau, C.; Fischmeister, C. *Catal. Sci. Technol.* **2019**. https://doi.org/10.1039/C9CY01019J
29. Jeffrey, J. L.; Bartlett, E. S.; Sarpong, R. *Angew. Chem. Int. Ed.* **2013**, *52*, 1-5. https://doi.org/10.1002/anie.201209591
30. Gao, J.; Feng, L.; Ma, R.; Su, B-J; Alenad, A. M.; Liu, Y.; Beller, M.; Jagadeesh, R. V. *Chem. Catalysis*, **2022**, *2*, 178-194. https://doi.org/10.1016/j.checat.2021.12.009
31. Aganda, K. C. C.; Hong, B.; Lee, A. *Adv. Synth. Catal.* **2019**, *311*, 1124. https://doi.org/10.1002/adsc.201801301
32. Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*,10692-10705. https://doi.org/10.1021/ja103081n
33. Zou, Z.; Cai, W.; Chen, W.; Zou, C.; Li, Y.; Wu, H.; Chen, L.; Hu, J.; Li, Y.; Huang, Y. *J. Org. Chem.* **2021**, *86*, 15777-15784. https://doi.org/10.1021/acs.joc.1c01845
34. Thapa, P.; Corral, E.; Sardar, S.; Pierce, B. S.; Jr. Foss, F.W. *J. Org. Chem.* **2019**, *84*, 1025-1034. https://doi.org/10.1021/acs.joc.8b01920
35. Ordóñez, M.; Tibhe, G. D.; Zamudio-Medina, A.; Viveros-Ceballos, J. L. *Synthesis*, **2012**, *44*, 564-574. https://doi.org/10.1055/s-0031-1289680
36. Takahashi, I.; Nishiwaki, Y.; Saitoh, K.; Matsunaga, T.; Arakate, A.; Morita, T.; Hosoi, S. *Heterocycles*, **2019**, *99*, 222-237. https://doi.org/10.3987/com-18-s(f)14
37. Khalafi-Nezad, A.; Zare, A.; Parhami, A.; Hasaninejad, A.; Zare, A. R. M. *J. Iran. Chem. Soc.* **2008** (Suppl.), *5*, S40-S46. https://doi.org/10.1007/BF03246487
38. Bollinger, F. W.; Hayes, F. N.; Siegel, S. *J. Am. Chem. Soc.* **1953**, *75*, 1729-1730. https://doi.org/10.1021/ja01103a503
39. Milan, M.; Carboni, G.; Salamone, M.; Costas, M.; Bietti, M. *ACS Catal.* **2017**, *7*, 5903-5911. https://doi.org/10.1021/acscatal.7b02151
40. Zhang, M.; Zhang, H.-J.; Ruang, W.; Wen T.-B.; *Eur. J. Org. Chem.* **2015**, 1099. https://doi.org./10.1002/ejoc.201500908
41. Wang, Y.; Zhou, Y.; Lei, M.; Hou, J.; Jin, Q.; Gao, D.; Wu, W. *Tetrahedron* **2019**, *75*, 1180-1185. https://doi.org/10.1016/j.tet.2019.01.023
42. Hoang, T. T.; Nguyen, H. T. H.; Le, T. T.; Truong, T.; Phan, N. T. S. *Tetrahedron* **2016**, *72*, 8241-8251. http://dx.doi.org/10.1016/j.tet.2016.10.059
43. Wu, X.; Ding, G.; Yang, L.; Lu, W.; Li, W.; Zhang, Z.; Lie, X. *Org. Lett.* **2018**, *20*, 5610-5613. https://doi.org/10.1021/acs.orglett.8b02287