Ene-Carbonyl Reductive Coupling for the Synthesis of 3,3-Disubstituted Phthalide, 3-Hydroxyisoindolin-1-one and 3-Hydroxyoxindole Derivatives

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Abstract: An efficient method for the synthesis of three classes of heterocyclic derivatives such as 3,3-disubstituted phthalides, 3-hydroxyisoindolin-1-ones and 3-hydroxyoxindoles, is reported. In the presence of the simple reductive system, zinc (Zn)/ammonia (NH₃) [or zinc-copper (Zn-Cu)/ammonia], a wide range of alkenes including acrylates, acrylonitrile, acrylamide and vinyl sulfoxide underwent reductive coupling with methyl 2-acylbenzoates and subsequent lactonization to provide 3,3-disubstituted phthalides in good to high yields at ambient temperature. In a similar manner, 3-hydroxyisoindolin-1-one and 3-hydroxyoxindole derivatives could also be

Introduction

Phthalides (isobenzofuranones), a class of heterocycles with the framework of a five-membered lactone adjacent to a benzene ring, occur in an abundance of biologically active compounds which are useful for the treatment of several diseases.^[1] There is an array of methods developed in the past few years for the synthesis of 3-substituted phthalides.^[2] Nevertheless, the synthesis of 3,3-disubstituted phthalides is only reported in a few contributions, for example, by the rhodium-catalyzed sequential [2+2+2] cycloaddition with transesterification,^[3a] the allylic alkylation of MBH (Morita-Baylis-Hillman) carbonates with 3phthalides,^[3b] the addition of *ortho*-lithium or Grignard reagents to ketones or carbon dioxide,^[4] the Pd-catalyzed oxyalkynylation reaction of olefins with hypervalent iodine reagents,^[5] the solid-state photoreaction of N,N-disubstituted 2-benzoylbenzamides^[6] and the lanthanide-promoted annulation of dihalides with keto esters.[7]

easily prepared by direct reductive coupling of phthalimides and N-substituted isatins with activated alkenes, respectively. Application of this methodology towards the synthesis of 1-naphthol derivatives on a gram scale is also depicted. Furthermore, the intramolecular phthalimides-ene reductive coupling afforded the respective cyclization products with high diastereoselectivity.

Keywords: ammonia; 3,3-disubstituted phthalides; 3hydroxyisoindolin-1-ones; 3-hydroxyoxindoles; reductive coupling; zinc; zinc-copper

For the synthesis of 3-hydroxyisoindolin-1-ones^[8] and 3-hydroxyoxindoles,^[9,10] several strategies have been reported. However, the reductive coupling of phthalimides with activated alkenes to afford 3-hydroxyisoindolin-1-one derivatives is only scarcely mentioned in literature, with examples such as the intra- and intermolecular reductive coupling of phthalimides with activated alkenes *via* an electroreductive method^[11] or samarium(II) iodide (SmI₂) chemistry.^[12] Moreover, to the best of our knowledge, the synthesis of 3,3-disubstituted phthalides and 3-hydroxyoxindole derivatives *via* ene-carbonyl reductive coupling has never been reported.

As a matter of fact, 3,3-disubstituted phthalide, 3hydroxyisoindolin-1-one, 3-hydroxyoxindole and related structures appear in abundant bioactive molecules, for instance, sinaspirolide,^[13] ansasirolide,^[13] shihunine,^[14] citalopram,^[15] talopram,^[15]corollosporine,^[16] chilenine,^[17] fumadensine,^[18] NU8165,^[19] SM-130686,^[20] arundaphine^[21] and welwitindolinone C^[22] (Figure 1). Thus, the development of a new synthetic strategy to afford these skeletons is in high demand.



Figure 1. Representative 3,3-disubstituted phthalides, 3-hydroxyisoindolin-1-ones, 3-hydroxyoxindoles and related structures.

Herein, we report a new synthetic method based on $Zn/NH_3^{[23]}$ (or Zn-Cu/NH₃) mediated ene-carbonyl reductive coupling, which provides an efficient and practical route to access 3,3-disubstituted phthalide, 3-hydroxyisoindolin-1-one and 3-hydroxyoxindole skeletons in a highly regio- and chemoselective manner. It is worth noting that all of the reactions were performed under ambient conditions.

Results and Discussion

During the course of an initial investigation, we tested the reaction of methyl 2-benzoylbenzoate (**1a**) (0.20 mmol) with acrylonitrile (**2a**) (0.60 mmol) in the presence of Zn (0.60 mmol)/saturated aqueous NH₄OH solution (0.20 mmol) as the reductive system and CH₃CN (1.20 mL) as the solvent. When the reaction was carried out at ambient temperature, no expected product **3aa** was found. (Table 1, entry 2). At 100 °C, the reaction did not afford any reductive coupling product, instead 3-phenylphthalide **1a'** was observed as a result of the reduction of **1a** (Table 1, entry 3). We then switched to several different reductive coupling systems, SmI₂/HMPA, Ni(cod)₂/Zn and CoI₂(dppe)/Zn, but only the recovery of starting material **1a** was obtained (Table 1, entries 4–6).

When aqueous NH_4OH was replaced with NH_3 (1 atm, balloon pressure) and H_2O (0.4 mmol), we were pleased to find that the desired product **3aa** was obtained in 67% yield (Table 1, entry 7). After addi-

tional screenings of reaction stoichiometry and solvent species, a quantitative yield was achieved by increasing the loading of alkene and Zn to 1.0 mmol (Table 1, entry 8). Interestingly, Zn-Cu/NH₃ as the reductive system was also found to be effective affording 3aa in similar 98% yield (Table 1, entries 15 and 16) and no product was obtained in the absence of H₂O (Table 1, entry 17). Moreover, when NH₃ was replaced by various amine species, such as primary amines (n-butylamine and benzene-1,2-diamine), secondary amine (diphenylamine) and ammonia salts (ammonium acetate and ammonium carbonate), only the recovery of starting material 1a or 3phenylphthalide (1a') was observed (Table 1, entries 18-22). This reveals that gaseous ammonia $[NH_{3(g)}]$ plays a central role for activation of the Znketyl radical to effect the ene-carbonyl reductive coupling.^[23]

Having the optimized reaction conditions in hand, we subsequently explored the scope of the alkenes (Table 2). When methyl acrylate (**2b**) and ethyl acrylate (**2c**) were used as ene-species, both 3,3-disubstituted phthalides (**3ab** and **3ac**) were obtained in high yields (Table 2). However, when *tert*-butyl acrylate (**2d**) and acrylamide (**2e**) were employed, only 26% and 41% yields of the desired products **3ad** and **3ae** were observed.

To our delight, the product yields of **3ad** and **3ae** were greatly improved by replacing zinc dust with the Zn-Cu couple and using DMF as solvent (Scheme 1). In addition, the reductive couplings of **1a** with

Table 1. Optimization studies for the synthesis of 3,3-disubstituted phthalides.^[a]



Entry	Additive	Solvent	Temp. [°C]	Yield of 3aa ^[a] [%]	Yield of 1a' ^[a] [%]
1	$NH_4Cl (0.20 \text{ mmol})$	CH ₃ CN	r.t.	0	99
2 ^[b]	NH_4OH (0.20 mmol)	CH ₃ CN	r.t.	RSM	
3 ^[b]	$NH_4OH (0.20 \text{ mmol})$	CH ₃ CN	100	0	55
4 ^[b,c]	SmI ₂ (1.00 mmol), HMPA (1.60 mmol), <i>t</i> -BuOH (0.60 mmol)	THF	r.t.	R	SM
5	$Co(dppe)I_2$ (5 mol%), $ZnCl_2$ (0.60 mmol)	CH ₃ CN	r.t.	R	SM
6	Ni(cod) ₂ (5 mol%), ZnCl ₂ (0.60 mmol)	CH ₃ CN	r.t.	R	SM
7	NH_3 (1 atm)	CH ₃ CN	r.t.	67	28
8 ^[d]	NH ₃ (1 atm)	CH ₃ CN	r.t.	99 ^[e]	0
9	NH_3 (1 atm)	THF	r.t.	37	2
10	NH_3 (1 atm)	methanol	r.t.	15	0
11	NH_3 (1 atm)	ethanol	r.t.	21	0
12	NH_3 (1 atm)	ether	r.t.	31	38
13	NH_3 (1 atm)	DCM	r.t.	trace	36
14	NH_3 (1 atm)	toluene	r.t.	trace	23
15 ^[f]	NH ₃ (1 atm)	CH ₃ CN	r.t.	98 ^[e]	0
16 ^[f]	NH ₃ (1 atm)	DMF	r.t.	98 ^[e]	0
17 ^[b]	NH_3 (1 atm)	CH ₃ CN	r.t.	0	10
18	<i>n</i> -butylamine (0.20 mmol)	CH ₃ CN	r.t.	R	SM
19	benzene-1,2-diamine (0.20mmol)	CH ₃ CN	r.t.	R	SM
20	diphenylamine (0.20 mmol)	CH ₃ CN	r.t.	R	SM
21	$NH_4OAc (0.20 \text{ mmol})$	CH ₃ CN	r.t.	0	46
22	$(NH_4)_2CO_3$ (0.20 mmol)	CH ₃ CN	r.t.	0	42

^[a] All the yields mentioned above are NMR yields using mesitylene as the internal standard.

^[b] No water was added.

^[c] The reaction was carried out according to a previously reported procedure.^[24]

^[d] Zn dust (1.0 mmol) and **2a** (1.0 mmol) were used.

^[e] Isolated yield.

[f] Zn dust was replaced with Zn-Cu. HMPA = hexamethylphosphoramide. RSM = recovery of starting material.

a broad range of ene species, *N*-methylacrylamide (**2f**), phenyl vinyl sulfoxide (**2g**), methyl crotonate (**2h**) and α -methylene- γ -butyrolactone (**2i**), using Zn-Cu/NH₃ were also investigated. All of them provided the desired phthalides in moderate yields. Especially, β -substituted acrylate **2h** afforded **3ah** with high diastereoselectivity. Other ene species, such as cinnamates and methacrylates gave the desired products in low yields.

As a control experiment, the Zn-Cu couple was replaced with Cu powder and as a result, only recovery of the starting material was obtained. It is noteworthy that for the reactions of **1a** with **2d-h**, 3-phenylphthalide was observed as the major product under Zn/ NH₃ as reductive system. To verify the preparative utility of the present methodology, we scaled up the model reaction of methyl 2-benzoylbenzoate (**1a**; 7.0 mmol, 1.7 g) with methyl acrylate (**2b**) affording **3ab** (1.8 g) in 88% isolated yield.

As illustrated in Table 3, the scope of the reaction was successfully extended to various methyl 2-acylbenzoate derivatives (1). With the Zn-Cu/NH₃ (or Zn/NH₃) reductive system, a wide range of 3,3-disubstituted phthalide derivatives was prepared in good to moderate yields. The results demonstrated that the R² substituent attached to the keto moiety of 1 including 4-fluorophenyl (1b), 4-chlorophenyl (1c), 4-methoxyphenyl (1d), 2-furan (1h), 3-benzo[b]thiophene (1i), or 3-pyridyl (1j) is well tolerated. Conversely, 2-pyridyl (1k) afforded 3ka only in 17% yield. It is important to mention that the reductive debromination product 3aa was observed when the R² moiety is 4-bromophenyl. Interestingly, the reaction of methyl 9-oxofluorene-1-carboxylate (1l) with 2b gave only the re-



Table 2. Zn/NH_3 (Zn-Cu/NH₃) mediated reductive coupling of methyl 2-benzoylbenzoate **1a** and activated alkenes **2**.^[a,b]



- ^[b] Yields are of isolated products.
- ^[c] Zn-Cu as reducing agent and DMF as solvent.
- ^[d] The diastereomeric ratio was determined by ¹H or ¹³C NMR spectroscopy.

ductive coupling product **3lb** in excellent yield [Scheme 2, Eq. (1)]. Pleasingly, methyl *ortho*-[(me-thoxycarbonyl)carbonyl]benzoate (**1m**) also reacted with **2c** to afford disubstituted phthalide **3mc** in 36% yield [Scheme 2, Eq. (2)].

- [a] All reactions were carried out under ammonia atmosphere using 1a (0.20 mmol), 2 (1.00 mmol), H₂O (0.40 mmol) and Zn-Cu (1.00 mmol) in DMF (1.2 mL) at room temperature for 20 h.
- ^[b] Yields are of isolated products.
- ^[c] Zn instead of Zn-Cu and CH₃CN instead of DMF as solvent.
- ^[d] The diastereomeric ratio was determined by ¹H NMR spectroscopy.





Table 3. Results of Zn-Cu/NH₃ mediated reductive coupling

of methyl 2-acylbenzoate derivatives and activated alk-



Scheme 1. Optimization studies for the reductive coupling of methyl 2-benzoylbenzoate (1a) with acrylamide (2e).



Scheme 2. Reductive couplings of 11 with 2b, 1m with 2c and 1a with 4.

When the ene species was switched to methyl propiolate (4), the reductive coupling followed by reduction of the olefin occurred to give **3ab** in 76% yield [Scheme 2, Eq. (3)]. The control experiment showed that no yne-carbonyl reductive coupling product was observed when we reduced the reaction time or the zinc loading.

Due to the fact that phthalimides are effective single electron transfer acceptors,^[11,12] we envisioned that the reductive coupling of carbonyl substrates of phthalimide with activated alkenes could also be achieved by a Zn-NH₃ reductive system; under ketyl radical initiation conditions. Thus, we examined the reaction of *N*-phenylphthalimide (**5a**) and acrylonitrile (**2a**) under Zn-NH₃ conditions (Table 4, entry 1). The starting material was fully converted in a short period, but we observed only a complicated hetero-intermolecular coupling mixture. Fortunately, 3-hydroxyisoindolin-1-one **6aa** was obtained in 35%

yield upon replacing CH_3CN with tetrahydrofuran (THF) as solvent (Table 4, entry 2). After extensive studies, improved yields were obtained by increased loading of Zn to 1.0 mmol and switching the solvent system to dichloromethane (DCM) (Table 4, entry 11).

Having established the optimized reaction conditions, we subsequently explored reactions of different substituted phthalimides with acrylonitrile (**2a**). When R^1 was a methyl (**5b**), benzyl (**5c**), *para*-fluorophenyl (**5d**), *para*-methoxyphenyl (**5e**), 1-phenylethyl (**5f**) or (*IR*)-1-(4-methoxyphenyl)ethyl group (**5j**), the desired products were isolated in good to moderate yields (82–51%, Table 5). Subsequently, the reductive couplings of phthalimides with a broad range of ene species [methyl acrylate (**2b**), acrylamide (**2e**), *N*-methylacrylamide (**2f**) methyl vinyl ketone (**2j**) and vinyl sulfone (**2k**)] were investigated, all of them provided the desired 3-hydroxyisoindolin-1-one derivatives

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Table 4. Optimization studies for the synthesis of 3-hydroxyisoindolin-1-one.^[a]



Entry	Zn [mmol]	Time [h]	Solvent	Yield [%] ^[b]
1	0.6	1	CH ₃ CN	ND
2	0.6	20	THF	35
3 ^[c]	1.0	20	THF	30
4 ^[d]	0.6	16	ether	low
5	0.6	16	toluene	low
6 ^[d]	0.6	16	CH ₂ Cl ₂	70
7 ^[d]	0.6	1	$CH_{2}Cl_{2}$	51
8 ^[d,e]	0.6	1	CH_2Cl_2	RSM
9 ^[f]	0.6	1	CH_2Cl_2	RSM
10 ^[d]	0.6	2	CH_2Cl_2	50
11 ^[d]	1.0	1	CH_2Cl_2	86 (75) ^[g]
12 ^[h]	1.0	24	CH_2Cl_2	trace
13 ^[e,i]	0.6	6	CH_2Cl_2	ND

- [a] Reaction conditions: 5a (0.20 mmol), 2a (0.60 mmol), H₂O (0.40 mmol) and Zn dust (0.60–1.00 mmol) in solvent (1.5 mL) under an NH₃ atmosphere.
- ^[b] All the yields mentioned above were NMR yields using mesitylene as internal standard.
- ^[c] **2a** (1.0 mmol) was used.
- ^[d] NH₃ was bubbled into the reaction flask with ice bath cooling.
- ^[e] No H₂O was added.
- ^[f] In the absence of $NH_{3(g)}$.
- ^[g] Isolated yield.
- ^[h] $NH_{3(g)}$ was replaced with NH_4Cl .
- ^[i] $NH_{3(g)}$ was replaced with BF_3 THF (RSM=recovery of starting material; ND=no desired product).

(82–22% yields), despite the fact that some products were obtained in unsatisfactory yields. The yields were significantly improved by simply replacing zinc dust with Zn-Cu couple; such as **6da**, **6ea** and **6ab**. However, no expected product was observed when we tested methyl crotonate (**2h**) or α -methylene- γ -butyrolactone (**2i**) as ene species. To identify the preparative utility of the present methodology, we chose to scale up the model reaction of *N*-benzylphthalimide (**5c**; 6.0 mmol, 1.4 g) with acrylonitrile (**2a**). This afforded **6ca** (1.3 g) in 72% isolated yield.

Following the previously reported intramolecular coupling of phthalimides with α , β -unsaturated esters by an electroreductive system^[11] or SmI₂ chemistry,^[12] we envisaged that these Zn-NH₃ conditions could provide an opportunity to achieve the intramolecular reductive coupling reaction (Scheme 3). To examine







Figure 2. X-ray crystal structures of compound 6k.

this, we first applied the standard reaction conditions (as described in Table 5) to phthalimide **5k**. Although the **5k** only gave low conversion, we were glad to observe the expected product **6k** (Figure 2) with high diastereoselectivity. Subsequently, fully conversion was enabled by increasing the loading of H₂O to 6.0 equiv. Next, we tested the intramolecular coupling of phthalimides with an α,β -unsaturated ketone motif (**5l**) and the reaction was also found to be successful by using this set of reaction conditions.

Isatins bear an electron-withdrawing carbonyl group and thus could be a suitable skeleton for the Zn-NH₃ reductive coupling reaction. Thus, we tested the reaction of NH-isatin (1*H*-indole-2,3-dione) with acrylonitrile (**2a**) under the standard reaction conditions. The initial study revealed that NH-isatin was fully consumed within several minutes, but no expected product was observed. Next, an attempt was conducted by modifying NH-isatin into *N*-Boc-isatin, however, the result was unsuccessful because no intermolecular coupling product was generated. Delightedly, when *N*-methylisatin (**7a**) was employed, the 3-hydroxyoxindole derivative **8aa** was afforded in a 76%



Table 5. Results of zinc mediated reductive coupling of phthalimides and activated alkenes. $^{[a,b]}$

[a] All reactions were carried out under an ammonia atmosphere using 5 (0.20 mmol), 2 (0.60 mmol), H₂O (0.40 mmol) and Zn (1.00 mmol) in CH₂Cl₂ (1.5 mL).
 [b] Isolated violds

- ^[c] **5c** (6.0 mmol), **2a** (30.0 mmol), H_2O (12.0 mmol) and Zn (30.0 mmol) in CH_2Cl_2 (45.0 mL) were used.
- ^[d] Zn-Cu instead of Zn.
- ^[e] Zn (0.60 mmol) was used.
- ^[f] H_2O (1.2 mmol) was used.
- ^[g] Zn-Cu conditions achieved the same yield as with Zn dust conditions.
- ^[h] The diastereomeric ratio was determined by ¹H NMR spectroscopy.

isolated yield under the standard conditions (Table 6). The *N*-methyl group of **7a** was then replaced with different substituents (phenyl **7b** and benzyl **7c**) and subsequent screening with a variety of ene species under Zn-NH₃ reductive conditions afforded all of the desired products in 84-42% yields without further optimization of the procedure (Table 6). The scope of the reaction was also tested with various substituted isatins **7d–g**. For instance, fluoro-, and chloro-substituted isatins (**7e**, **7g**, **7h**) were well tolerated to afford the

corresponding products in moderate to good yields. Similarly, methoxy-substituted isatin (**7f**) also worked well, furnishing **8fa** in good yield. Furthermore, in analogy to the ene-phthalimide reductive coupling, the Zn-Cu couple also has a directly beneficial influence on the ene-isatin reductive coupling and the result is well documented. To demonstrate the gramscale preparation of a 3-hydroxyoxindole derivative, we chose the reaction of isatin **7h** (1.5 g, 6.0 mmol)

^[b] Isolated yields.



Table 6. Results of zinc mediated reductive coupling of *N*-substituted isatins and activated alkenes^[a,b]

- ^{a]} All reactions were carried out under an ammonia atmosphere using 7 (0.20 mmol), 2 (0.60 mmol), H_2O (0.40 mmol) and Zn (1.00 mmol) in CH_2Cl_2 (1.5 mL).
- ^[b] Isolated yields.
- ^[c] 7c (6.0 mmol), 2a (18.0 mmol), H₂O (12.0 mmol) and Zn (30.0 mmol) in CH_2Cl_2 (45.0 mL) were used.
- ^[d] Zn-Cu instead of Zn.
- ^[e] Zn-Cu conditions achieved the same yield as with Zn dust conditions.

with acrylonitrile **2a**. Gratifyingly, the reaction afforded **8ha** (1.4 g) in 73% isolated yield.

To show the synthetic utility of this methodology, we treated 3,3-disubstituted phthalide **3ab** with sodium hydride in toluene at reflux (Dieckmann condensation), which furnished 1-naphthol^[25] derivative **9**

on a gram scale (Scheme 4). We believe that a series of 1-naphthol derivatives can be prepared through the sequential manipulation. Also, we revealed the extension of this methodology to the synthesis of 3-hydroxyisoindolin-1-one **6ja'** by oxidative cleavage of the N- α -methyl-4-methoxybenzyl group of **6ja** via

(3 equiv.)

CH₃CN, H₂O, r.t.

1 h

Scheme 5. Oxidative removal of the N- α -methyl-4-methoxy-

OMe

ĊN



Scheme 4. Dieckmann condensation to afford a 1-naphthol derivative.

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HO

6ja (0.3 mmol)

benzyl group.

HO

6ja' (68%)

ĊΝ



Scheme 6. A plausible mechanistic pathway for the formation of 3,3-disubstituted phthalide.



Scheme 7. A possible key intermidiate for the formation of 3-hydroxyisoindolin-1-one and 3-hydroxyoxindole.

ceric ammonium nitrate (CAN) oxidation (Scheme 5).^[26]

A possible mechanism for the ene-carbonyl reductive coupling is outlined in Scheme 6. It is proposed that $Zn-Cu/NH_3$ (or Zn/NH_3) initiates a single electron transfer to a carbonyl group to form a Zn-ketyl diradical **I**. Addition of this radical to the alkene sub-



Scheme 8. Control studies.

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strate followed by further reduction gives a five-membered zincacycle **II**. Final protonation and *in situ* lactonization affords the 3,3-disubstituted phthalide 3.^[23,27] Similarly, for the ene-phthalimide and ene-*N*substituted isatin reductive couplings it is proposed that Zn-NH₃ initiates a single electron transfer to a phthalimide or an *N*-substituted isatin to form a Znketyl radical **III** or **III**' (Scheme 7). Addition of this radical to the alkene substrate followed by further reduction gives a five-membered zincacycle **IV** or **IV**', while final protonation affords 3-hydroxyisoindolin-1one and 3-hydroxyoxindole.

Trying to get an insight into the ene-carbonyl reductive coupling reaction, some control experiments were devised by testing hydroxylactam 5c' and 7a' with 2a under Zn-NH₃ conditions, respectively (Scheme 8). In the standard reaction timescale, we could not observe the expected product [Scheme 8, Eqs. (1) and (2)]. However, by extending the reaction time to 22 h, 8aa was obtained in 34% NMR yield via a slowly proceeding 1,4-addition of 7a' with 2a under basic conditions [Scheme 8, Eq. (3)].^[10h] These observations implicate, in the presence of Zn-NH₃, that the phthalimides and N-substituted isatins form the ketyl radical components as key intermediates in-situ, then react with activated alkenes to furnish the expected product rather than proceeding through intermediate 7a'.

Conclusions

In summary, we have established an effective $Zn-NH_3$ (or $Zn-Cu/NH_3$) reductive cross-coupling protocol to generate a series of 3,3-disubstituted phthalides, 3-hydroxyisoindolin-1-ones and 3-hydroxyoxindole derivatives. From a synthetic point of view, this approach is attractive due to the use of cheap and readily available materials in a reaction with an easily manageable and a simple modular procedure. It is worth mentioning that the 3,3-disubstituted phthalide products synthesized in this manner have a broad scope and can be extended for the synthesis of 1-naphthol derivatives *via* the Dieckmann condensation. Furthermore, it discloses a straightforward route to access a series of biologically activated molecules and there is promise in developing intramolecular reductive coupling procedures to afford biologically useful motifs with high diastereoselectivity.

Experimental Section

Typical Procedure for Synthesis of 3,3-Disubstituted Phthalide Derivatives

A glass tube equipped with magnetic stir bar was charged with zinc-copper couple (or zinc dust) (1.00 mmol, 5.0 equiv.), methyl 2-benzoylbenzoate **1** (0.20 mmol, 1.0 equiv.), activated alkene **2** (1.00 mmol, 5.0 equiv.), H₂O (0.40 mmol, 2.0 equiv.) and dry dimethylformamide (or acetonitrile) (1.20 mL) and was then sealed with a rubber septum. The solution was saturated with $NH_{3(g)}$ from a balloon by slow bubbling for 5 min and was stirred at room temperature for 20 h (note: NH_3 should only be handled in a chemical fume hood.). The resulting mixture was diluted with EtOAc, filtered through Celite and the filtrate was then concentrated. Separation on a silica gel column using hexane/EtOAc as eluent gave 3,3-disubstituted phthalide **3**.

Gram-Scale Synthesis of 3,3-Disubstituted Phthalide Derivatives (3ab)

A 100-mL round-bottom flask equipped with a magnetic stir bar was charged with methyl 2-benzoylbenzoate 1a (1.7 g, 7.00 mmol, 1.0 equiv.), zinc dust (2.3 g, 35.0 mmol, 5.0 equiv.), methyl acrylate 2b (3.0 g, 35.0 mmol, 5.0 equiv.), H₂O (0.3 g, 14.0 mmol, 2.0 equiv.) and freshly distilled acetonitrile (35 mL) were then added and the flask was closed with a rubber septum. A long needle was connected to the ammonia gas cylinder via a tygon tubing and then was pierced through the septum. The solution was saturated with NH_{3(g)} by slow bubbling for 20 min and stirred at room temperature for 30 h. The reaction was quenched with saturated aqueous NH₄Cl (25 mL), then extracted with EtOAc ($3 \times$ 15 mL). The combined organic layer was dried over MgSO₄, filtered through Celite and concentrated. Separation on a column of silica gel using hexane/EtOAc as eluent gave **3ab** as a colorless oil; yield: 1.8 g (88%).

Typical Procedure for Synthesis of 3-Hydroxyisoindolin-1-one Derivatives

A glass tube equipped with magnetic stir bar was charged with zinc dust (or zinc-copper couple) (1.00 mmol, 5.0 equiv.), phthalimide **5** (0.20 mmol, 1.0 equiv.), activated alkene **2** (0.60 mmol, 3.0 equiv.), H_2O (0.40 mmol, 2.0 equiv.) and dry dichloromethane (1.50 mL) and was then sealed with a rubber septum. $NH_{3(g)}$ was bubbled into the reaction flask cooled with an ice bath for 0.5 min, then the reaction was allowed to warm to room temperature with continued stirring 1.0–8.0 h. The resulting mixture was diluted with EtOAc, filtered through Celite and the filtrate was then concentrated. Separation on a silica gel column using EtOAc/hexane as eluent gave the 3-hydroxyisoindolin-1-one **6**.

Typical Procedure for Synthesis of 3-Hydroxyoxindole Derivatives

A glass tube equipped with magnetic stir bar was charged with zinc dust (or zinc-copper couple) (1.00 mmol, 5.0 equiv.), *N*-substituted isatin **7** (0.20 mmol, 1.0 equiv.), activated alkene **2** (0.60 mmol, 3.0 equiv.), H₂O (0.40 mmol, 2.0 equiv.) and dry dichloromethane (1.50 mL) and was then sealed with a rubber septum. NH_{3(g)} was bubbled into the reaction flask cooled with an ice bath for 0.5 min, then the reaction was allowed to warm to room temperature with continued stirring for 0.5–5.0 h. The resulting mixture was diluted with EtOAc, filtered through Celite and the filtrate was then concentrated. Separation on a silica gel column using EtOAc/hexane as eluent gave the 3-hydroxyoxindole **8**.

Gram-Scale Synthesis of 3-Hydroxyisoindolin-1-one Derivative 6ca

A 100-mL round-bottom flask equipped with magnetic stir bar was charged with methyl N-benzylphthalimide 5c (1.4 g, 6.0 mmol, 1.0 equiv.), zinc dust (2.0 g, 30.0 mmol, 5.0 equiv.), acrylonitrile **2a** (2.0 mL, 30.0 mmol, 5.0 equiv.), H_2O (0.2 mL, 12.0 mmol, 2.0 equiv.) and freshly distilled dichloromethane (45 mL) were then added and the flask was closed with a rubber septum. A long needle was connected to ammonia gas cylinder via a tygon tubing and then was pierced through the septum. The solution was saturated with $NH_{3(g)}$ by slow bubbling for 5 min and stirred at room temperature for 8 h. Then an needle (23G) was pierced through septum for the relaxation of excess $\ensuremath{\text{NH}}_{3(g)}$ and the reaction was quenched with saturated aqueous NH₄Cl (25 mL). Following extraction with dichloromethane $(3 \times 15 \text{ mL})$, the combined organic layer was dried over MgSO₄, filtered through Celite and concentrated. Separation on a column of silica gel using EtOAc/hexane as eluent gave 6ca as a yellow solid; yield: 1.3 g (72%).

Gram-Scale Synthesis of 3-Hydroxyisoindolin-1-one Derivative 8ha

Prepared in a similar manner to the gram-scale synthesis of 3-hydroxyisoindolin-1-one derivative **6ca**, using isatin **7h** (1.5 g, 6.0 mmol, 1.0 equiv.), zinc dust (2.0 g, 30.0 mmol, 5.0 equiv.), acrylonitrile **2a** (1.2 mL, 18.0 mmol, 3.0 equiv.), H₂O (0.2 mL, 12.0 mmol, 2.0 equiv.), dry dichloromethane (45.0 mL) and NH_{3(g)}. The reaction was completed in 1 h and the 3-hydroxyisoindolin-1-one derivative **8ha** was obtained; yield: 1.4 g (73%).

X-Ray Crystallography

CCDC 955498 (**3be**), CCDC 955499 (**3db**), CCDC 957413 (**3mc**), CCDC 967403 (**6k**; Figure 2), CCDC 967404 (**6l**) and CCDC 969282 (**8ab**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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