

Insertion of the *o*-Aminophenol Core into Ninhydrin–Phenol Adducts: Migration of Ninhydrin Carbon Leading to *N*-Phenylbenzoate-Substituted Phthalimides

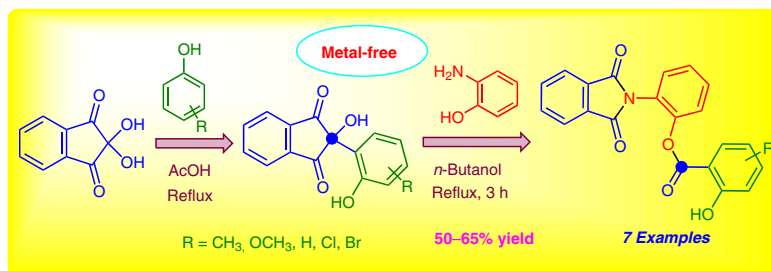
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Abstract An unexpected migration of a ninhydrin carbon bearing a phenolic subunit has been observed when phenolic adducts of ninhydrin reacted with 2-aminophenol in butan-1-ol at the reflux temperature. The products were unambiguously assigned as 2-(1,3-dioxoisindolin-2-yl)phenyl benzoates on the basis of NMR spectroscopy and X-ray crystallographic analysis.

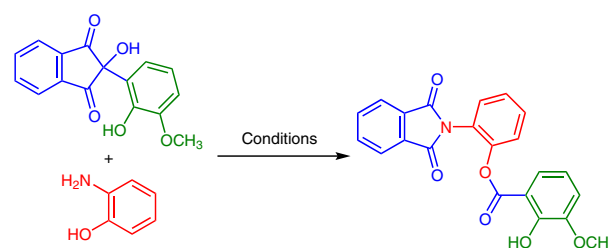
Key words phenols, rearrangement, heterocycles, migration, insertion

Isoindole and its derivatives are found in a variety of naturally occurring alkaloids and pharmaceutical compounds.¹ Among them, *N*-substituted phthalimides [1*H*-isoindole-1,3(2*H*)-diones] have been considered as attractive synthetic targets due to their diverse biological activities² and their applications as functional materials.³ Additionally, phthalimide photochemistry has been applied to chiral synthesis,⁴ as well as in the synthesis of macrocyclic polyethers.⁵ Recently, some substituted phthalimide derivatives have been reported to exhibit color-tunable luminescence.⁶ Therefore, access to *N*-substituted phthalimides remains an important challenge in current organic chemistry.

On the other hand, ninhydrin [2,2-dihydroxy-1*H*-indene-1,3(2*H*)-dione] is a compound with two hydroxy groups attached to the same carbon atom, which is flanked by two carbonyl groups. Adducts of ninhydrin have attracted considerable attention due to their applicability as building blocks in the development of various heterocyclic scaffolds.⁷ We recently reported the synthesis of benzimidazoisindole and benzodiazonine frameworks from ninhy-

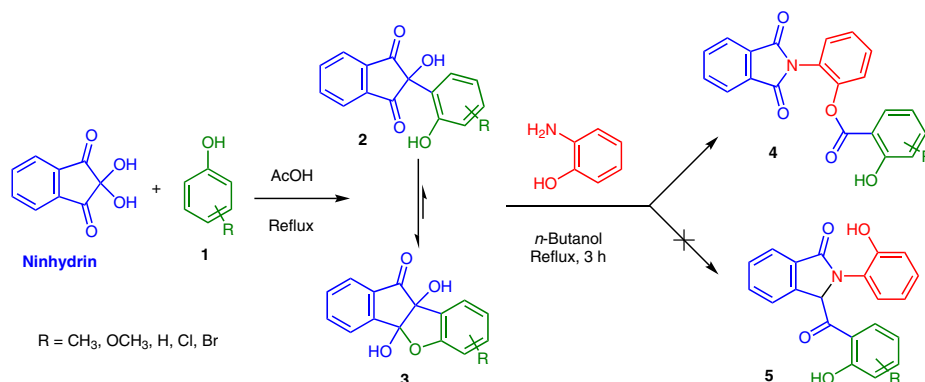
drin–phenol adducts.⁸ Consequently, it was thought of interest to explore the reactivity of ninhydrin adducts towards 2-aminophenol. However, the reaction did not afford the expected 3-(2-hydroxybenzoyl)-2-(2-hydroxyphenyl)isoindolin-1-one **5**,⁹ but instead we observed an insertion of the 2-aminophenol core into the adducts in conjunction with a migration of the ninhydrin carbon to the aminophenol oxygen (Scheme 1). Although several related migration reactions have been documented for different

Table 1 Optimization of the Synthesis of Benzoate **4a**



Entry	Solvent	Temp.	Time (h)	Yield (%)
1	MeOH	r.t. (25 °C)	24	NR ^a
2	EtOH	r.t. (25 °C)	24	NR
3	BuOH	r.t. (25 °C)	24	NR
4	EtOH	reflux	8	NR
5	PrOH	reflux	8	trace
6	BuOH	reflux	3	60
7	MeCN	reflux	8	NR
8	toluene	reflux	8	NR

^a NR = no reaction.



Scheme 1 Synthesis of 2-(1,3-dioxoisindolin-2-yl)phenyl benzoates **4**

systems,¹⁰ to the best of our knowledge, migration of the ninhydrin ring carbon bearing a phenol is hitherto unreported. Here, we report an unprecedented synthesis of 2-(1,3-dioxoisindolin-2-yl)phenyl benzoates **4** from 2-aminophenol and ninhydrin-phenol adducts through this rearrangement.

The ninhydrin-phenol adducts, 2-hydroxy-2-(2-hydroxyaryl)-1,3-indanediones **2**, were prepared as reported previously¹¹ by refluxing the corresponding phenols **1** with ninhydrin in glacial acetic acid. The resulting adducts preferentially remain in the cyclic hemiketal form **3**.^{11a,b} In the next step, we treated the ninhydrin-guaiacol adduct **2a** with 2-aminophenol in various solvents. The reaction did not proceed in methanol, ethanol or butan-1-ol at 25 °C (Table 1, entries 1–3), and no reaction occurred refluxing ethanol, even after eight hours (entry 4); however, traces of the product were isolated when the reactants were heated in propan-1-ol (entry 5). When the reaction was carried out in refluxing butan-1-ol, the unexpected rearrangement product 2-(1,3-dioxo-1,3-dihydro-2*H*-isindol-2-yl)phenyl 2-hydroxy-3-methoxybenzoate (**4a**) was isolated in 60%

yield within three hours (entry 6).¹² When the aprotic solvents toluene and acetonitrile were used, the reaction failed to give product **4a** (entries 7 and 8).

Under the optimized conditions, various substituted phenolic adducts **2b–g** gave products **4b–g** (Figure 1). Products **4a–g** were all obtained smoothly as precipitates from the reaction mixture in yields of 50–65%. Notably, simple filtration afforded phthalimide derivatives **4a–g** in a pure form, and no byproducts were detected in the filtrate.

The IR spectrum of compound **4a** exhibited bands at 1720 and 1688 cm⁻¹ for the ester and imide carbonyl groups, respectively. In the ¹H NMR spectrum, the phenolic-OH proton appeared as a singlet at $\delta = 9.89$. Aromatic protons were observed in the range $\delta = 7.94$ – 6.75 . The ¹³C NMR spectrum showed distinct signals in agreement with the proposed structure. The structure of compound **4a** was supported by mass spectrometry, which showed a molecular ion [M + Na]⁺ at $m/z = 412$. The structure of **4a** was finally and unambiguously confirmed by single-crystal X-ray analysis (Figure 2).¹³

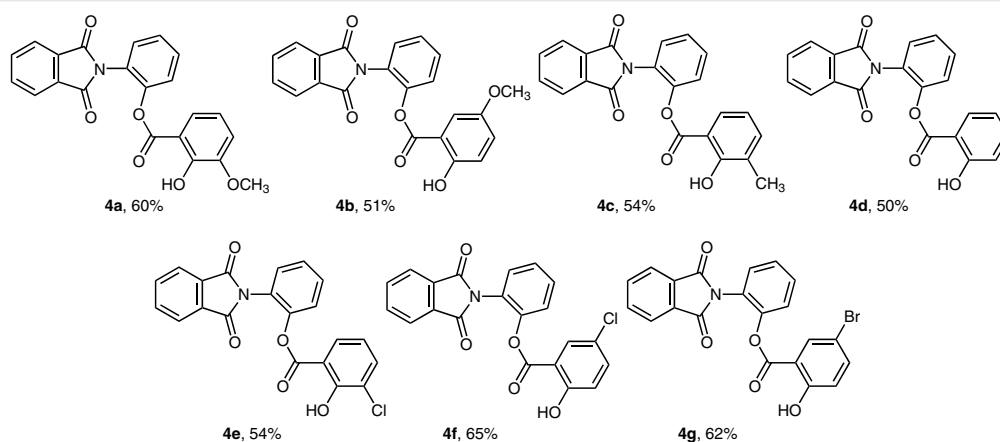


Figure 1 Synthesized 2-(1,3-dioxoisindolin-2-yl)phenyl benzoate derivatives **4a–g**

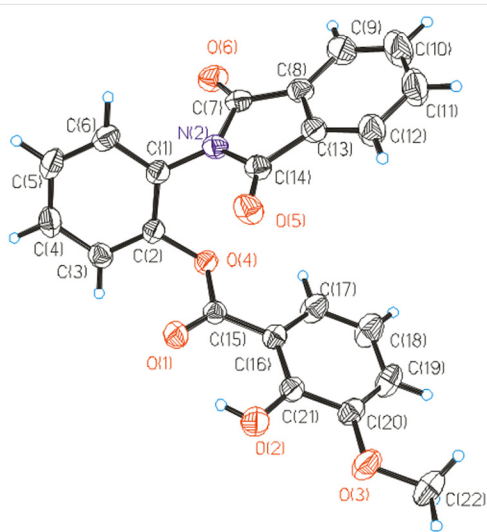


Figure 2 ORTEP view of compound **4a** (40% thermal ellipsoids)

A plausible mechanism for the reaction, based on our earlier results,⁸ is shown in Scheme 2. In Path a, the eight-membered lactone intermediate **A** is subject to nucleophilic attack by the NH₂ group to give intermediate **B**. Subsequent intramolecular nucleophilic attack on the lactone carbonyl, followed by breaking of the C–O bond, affords the isoindolone core **C**. Alternatively, in Path b, the NH₂ group of the 2-aminophenol attacks either carbonyl of the diketo form **2** to produce intermediate **D**, which is attacked

by NH to generate **C**. Then intermediate **E** (formed by air oxidation) undergoes attack on the carbonyl group by the phenolic–OH group, resulting in the formation of a new C–O bond; subsequent cleavage of the C–C bond affords the rearranged intermediate **F**. Finally, oxidation produces product **4**. However, hemiketal formation might be an important aspect, because the ninhydrin adduct of 1,4-dimethoxybenzene, which exists exclusively in the diketo form,¹⁴ did not lead to product formation when treated with 2-aminophenol. Therefore, **C** is probably formed by Path A. However, none of the intermediates **A** to **F** could be isolated under the reaction conditions.

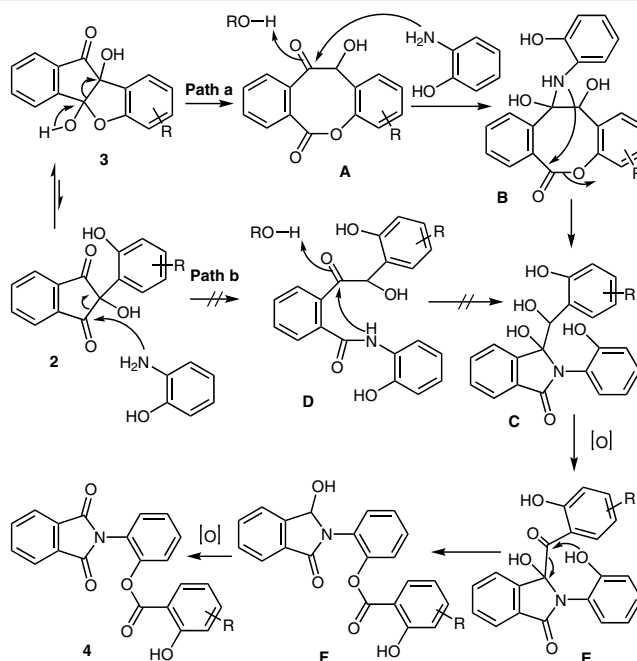
In conclusion, we have observed the migration of the ninhydrin ring carbon to an aminophenol oxygen during the reaction of 2-aminophenol with phenolic adducts of ninhydrin. This migratory insertion reaction proceeds through hemiketal formation. Thus, the novel reactivity of ninhydrin adducts has been expanded.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at <http://doi.org/10.1055/s-0036-1589146>.



Scheme 2 Plausible mechanism for the reaction

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- (12) **2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)phenyl 2-Hydroxybenzoates 4a–g; General Procedure**
The appropriate ninhydrin adduct **2** (1.4 mmol) and 2-aminophenol (2.0 mmol) were added sequentially to BuOH (6 mL), and the mixture was refluxed for 3 h until the reaction was complete (TLC). The mixture was then cooled to r.t. and left overnight. The precipitated product was collected by filtration, washed with cold MeOH, and crystallized from acetone.
2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)phenyl 2-Hydroxy-3-methoxybenzoate (4a)
Light-yellow crystals; yield: 0.33 g (60%); mp 156–157 °C; IR (KBr): 3454, 3208, 1720, 1688 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.89 (s, 1 H), 7.94–7.91 (m, 2 H), 7.88–7.86 (m, 2 H), 7.64–7.58 (m, 3 H), 7.52–7.48 (m, 1 H), 7.24 (d, *J* = 8.0 Hz, 1 H), 7.17 (d, *J* = 7.8 Hz, 1 H), 6.75 (t, *J* = 8.0 Hz, 1 H), 3.76 (s, 3 H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 166.2 (2 C), 165.4, 150.4, 148.3, 146.0, 134.9 (2 C), 131.3 (2 C), 130.1, 129.9, 126.6, 124.1, 123.9, 123.6 (2 C), 120.0, 118.8, 117.3, 112.8, 56.0. MS (ESI): *m/z* = 412 [M + Na]⁺, 279.1, 173.0. Anal. Calcd for C₂₂H₁₅NO₆ (389.37): C, 67.87; H, 3.88; N, 3.60. Found: C, 67.70; H, 3.97; N, 3.45.
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