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# NOVEL APPROACHES TOWARD NINHYDRIN ANALOGS

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***Abstract**: Several new 5-arylninhydrins have been prepared using palladium-catalyzed cross-coupling reactions.*

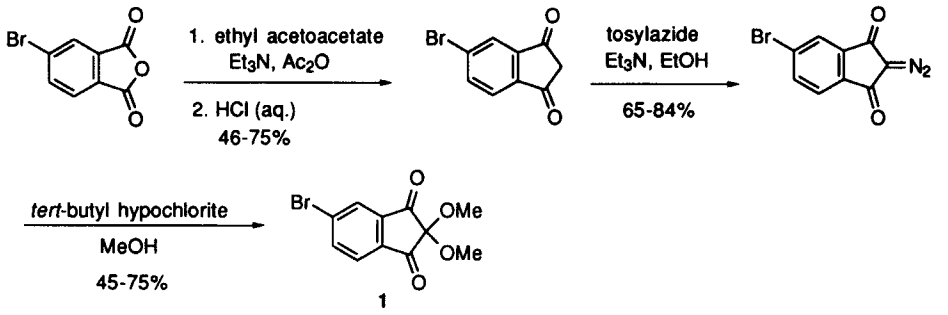
Chemical enhancement of latent fingerprints with ninhydrin or one of its analogs, coupled with post-ninhydrin treatment with metal salts, followed by illumination with an appropriate light source, is still the most practical and affordable technique for the majority of forensic laboratories. To further increase the utility of this technique, chemical modifications of the ninhydrin nucleus are of great importance to improve the chromogenic and luminescent properties of the product resulting from the reaction of ninhydrin or its analogs with amino acids.[1] Until recently, the protocols available to synthesize ninhydrin analogs were inefficient. Our first goal was to develop new and improved ninhydrin derivatives, and efficient synthetic methodology for these compounds. We have improved the syntheses of two very useful ninhydrin analogs: benzo[*f*]ninhydrin,[2] and 5-methoxyninhydrin.[3] Additionally, we have synthesized some novel analogs, among which the sulfur-containing ninhydrins, such as 5-(methylthio)ninhydrin[3] and thieno[2,3-*f*]ninhydrin,[4] have shown exceptional efficiency. As a continuation of these efforts, we targeted novel sulfur-containing analogs and analogs with extended conjugation. We now wish to present the initial results of these studies.

The analogs prepared by our new protocols (**2-15**), their yields and the coupling method employed are shown in the **Table**. All ninhydrins were prepared from 5-bromo-2,2-dimethoxy-1,3-indandione (**1**), shown in **Scheme 1**, by a suitable coupling procedure (A or B, **Scheme 2**). The acetal intermediate (**1**) was synthesized from the known 5-bromo-1,3-indandione[5] using the oxidation protocol reported by Regitz and Adolph (**Scheme 1**).[6,7]

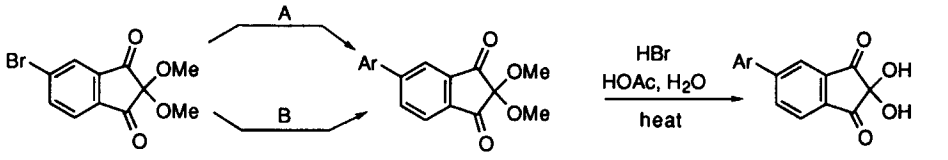
Procedure A (**Scheme 2**) involved the coupling of **1** with a boronic acid in the presence of a palladium catalyst.[8] The boronic acids were prepared by a general procedure involving the formation of a Grignard reagent from a haloarene, followed by reaction with trimethyl borate at -78 °C and subsequent acid hydrolysis.[9-12] Alternatively, several boronic acids were synthesized from the corresponding thienyllithium

derivatives using a similar method.[13-16] A typical procedure for method A is as follows: to a solution of **1** (4.28 g, 15.00 mmol) in benzene (50 mL), was added aqueous 2 M $Na_2CO_3$ (15.0 mL) and a solution of 2-thienylboronic acid[17] (2.88 g. 22.5 mmol) in ethanol (10 mL). After removal of dissolved oxygen, a catalytic amount of tetrakis(triphenylphosphine)palladium (0), $[(C_6H_5)_3P]_4Pd$, (175 mg, 1 mol%) was added. The reaction mixture was heated for 6 h, under a nitrogen atmosphere and protected from light.

**Scheme 1**




**Scheme 2**



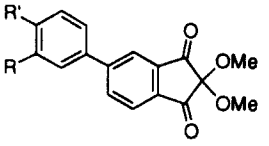
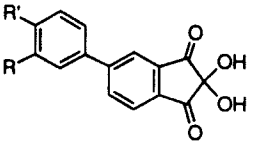
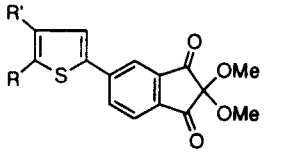
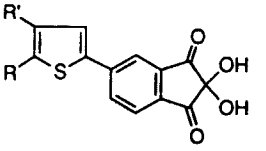
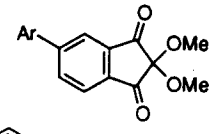
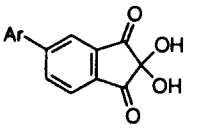
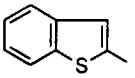
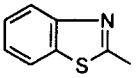
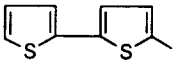
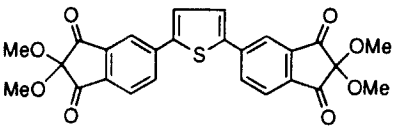
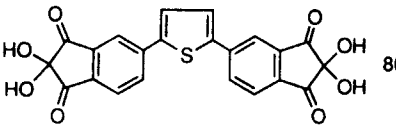

A = $ArB(OH)_2$, 2M $Na_2CO_3$, EtOH, benzene, $Pd(PPh_3)_4$, heat.

B = $ArSnBu_3$, toluene, $Pd(PPh_3)_4$, heat.

It was then poured into water (100 mL) and extracted with methylene chloride (3 x 100 mL). The extracts were washed with brine (50 mL), dried over $Na_2SO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (ether/petroleum ether, 50:50) to afford 4.18 g (96%) of coupled product. A crystalline precipitate, which formed in several of the chromatography fractions, was collected to afford an analytical sample of **7a** (**Table**), mp 133-134 °C. Anal. Calcd for $C_{15}H_{12}O_4S$: C, 62.15; H, 4.20. Found: C, 62.48; H, 4.06.

Procedure B (**Scheme 2**) involved the coupling of **1** with an aryltributylstannane.[18] The organotin reagents were prepared by quenching of the corresponding lithium species with tributyltin chloride.[19-21]The coupling method is illustrated by the following example: to a solution of **1** (4.30 g, 15.0 mmol) in toluene (100 mL) was added 2-(tributylstannyl)benzo[*b*]thiophene (6.35 g, 15.0 mmol) and $[(C_6H_5)_3P]_4Pd$ (350 mg, 2 mol%). The mixture was heated for 6 h, under a nitrogen atmosphere and protected from light. The solvent was evaporated under reduced pressure and the residue was washed with hot hexane. The crude product was purified by silica gel column chromatography (petroleum ether and ether/petroleum ether, 50:50) to afford 3.73 g (73%) of the coupled product as a tan solid. Recrystallization from methanol afforded an analytical sample of **10a** (**Table**), mp 182-183 °C. Anal. Calcd. for $C_{19}H_{14}O_4S$ C, 67.44; H, 4.17. Found: C, 67.81; H. 4.18.

**TABLE**

| 5-Aryl-2,2-dimethoxy-1,3-indandione ( No.) | | Yield, % | Method | 5-Aryininhydrin (No.) | Yield, % |
|---|---|---|---|---|---|
|  | | | |  | |
| R, R' = –H, –H | (2a) | 96 | A | (2) | 54 |
| –OMe, –H | (3a) | 99 | A | (3) | 74 |
| –SMe, –H | (4a) | 95 | A | (4) | 96 |
| –Ph, –H | (5a) | 95 | A | (5) | 41 |
| $-OCH_2O-$ | (6a) | 99 | A | (6) | 80 |
|  | | | |  | |
| R, R' = –H, –H | (7a) | 96 | A | (7) | 86 |
| –Me, –H | (8a) | 47 | A | (8) | 47 |
| –Et, –H | (9a) | 60 | A | (9) | 75 |
| –H, –Me | (10a) | 70 | A | (10) | 44 |
|  | | | |  | |
| Ar =  | (11a) | 73 | B | (11) | 61 |
|  | (12a) | 81 | B | (12) | 29 |
|  | (13a) | 91 | B | (13) | 13 |
|  | (14a) | 55 | A | (14) | 43 |
|  | (15a) | 91 | A |  (15) | 80 |

The coupled products (**2a-15a**) were deprotected as illustrated with **7a**. A vigorously stirred solution of **7a** (1.00 g, 3.47 mmol) in glacial acetic acid (15 mL) was treated with water (15 mL) and 48% HBr (10 mL) to form a fine suspension. The mixture was heated at reflux, and then filtered while hot. The filtrate was poured into 250 mL of cold water to induce precipitation of the product which was collected, washed with water and dried in air to afford 770 mg (86%) of ninhydrin analog **7** (**Table**) as a yellow solid, mp 260-262 °C dec. Anal. Calcd for $C_{13}H_{10}O_4S \cdot H_2O$: C, 56.11; H, 3.62. Found: C, 55.78; H, 3.30.

Preliminary testing of these ninhydrin analogs by forensic experts at the U. S. Secret Service singled out **7** as a superior reagent. To obtain additional quantities of **7** for further testing, the procedures described were followed to prepare 20 g of this reagent. A similar route, using the commercially available 4-chlorophthalic anhydride, provided **7** in comparable yield. We are continuing our efforts to prepare novel ninhydrin analogs and to devise practical commercial syntheses for the most efficacious analogs.

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