

Indium Mediated Barbier Reaction of Ninhydrin and Isatin

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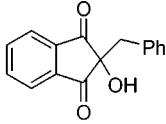
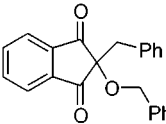
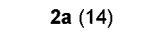
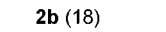
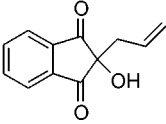
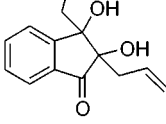
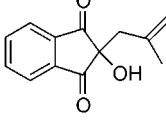
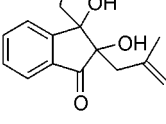
The development of Barbier type of carbon-carbon bond-forming reactions opened a new era in synthetic organic chemistry.¹ Various metals including In,² Sn,³ Zn,⁴ Mg,⁵ Bi,⁶ and Cd⁷ have been used. Among them the use of indium in aqueous solution has shown considerable promise in the addition of allylic halides to the carbonyl groups.² Some fragmental examples on the indium-mediated Barbier reaction of isatin derivatives have been reported.⁸ Although the products derived from the Barbier reaction of isatins or ninhydrins have highly functionalized interesting structures,⁹ the reactions have not been studied systematically.⁸

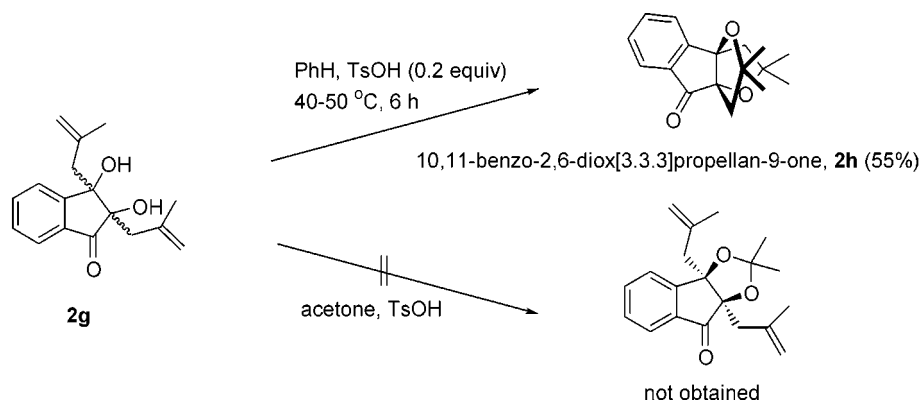
Thus, we intended to examine systematically on the indium mediated Barbier reaction of ninhydrin and isatin with allyl bromide, methallyl bromide and benzyl bromide. The reaction of ninhydrin (**1**) and benzyl bromide occurred at the 2-position of ninhydrin selectively to give **2a** in 39% yield. We used typical experimental conditions for the indium-mediated Barbier reactions: Use of indium metal in

the presence of sodium iodide in *N,N*-dimethylformamide.^{2,8} The use of aqueous tetrahydrofuran as solvent showed slow and incomplete reaction. Without sodium iodide no reaction occurred in most cases. Besides **2a**, *O*-benzylated compound **2b** was also isolated in a similar yield (44%). In the reaction, the intermediate indium alkoxide was quenched with benzyl bromide in the reaction mixture (entry 1) or with additional acetic anhydride (entry 2) to give **2c**. The observation of *O*-benzylated compound **2b** is the first example to the best of our knowledge.¹⁰ For more reactive allyl bromide or methallyl bromide, 1,2-diallylation or 1,2-dimethallylation was observed in appreciable amounts (entries 3 and 4). We could not find any 1,2,3-triallylated compounds.^{8b} The representative results are listed in Table 1.

The stereochemistry of **2g** was the point of interest. The ¹H and ¹³C NMR spectra of **2g** showed it a single compound. Some chemical transformation of **2g** was investigated in order to determine the stereochemistry of **2g** as shown in

Table 1. Indium mediated Barbier reaction of ninhydrin (**1**)

Entry	Conditions	Products (% yield)	
1	benzyl bromide (4 equiv) In (1 equiv) NaI (4 equiv) DMF, rt, 5 min		
		2a (39)	2b (44)
2	benzyl bromide (2 equiv) Ac ₂ O (2 equiv) In (1 equiv) NaI (4 equiv) DMF, rt, 50 min		
		2a (14)	2b (18)
3	allyl bromide (4 equiv) In (1 equiv) NaI (4 equiv) rt, 5 min		
		2d (21)	2e (49)
4	methallyl bromide (3 equiv) In (1 equiv) NaI (3 equiv) DMF, rt, 3 min		
		2f (44)	2g (27)



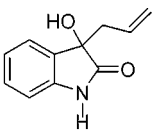
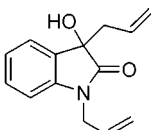
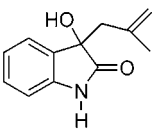
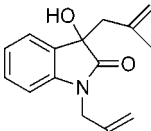
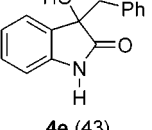
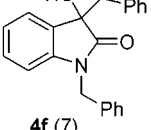
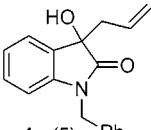
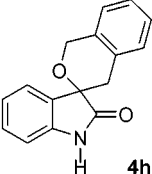
Scheme 1

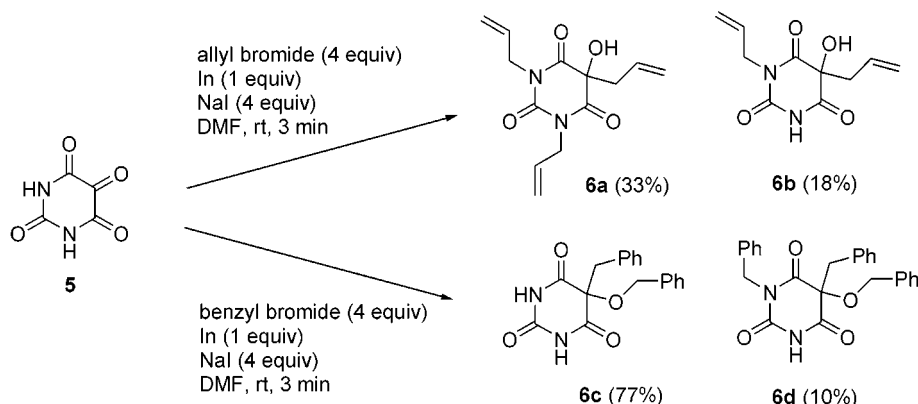
Scheme 1. Acid-catalyzed acetonization did not give the corresponding acetonide. Whereas, acid-catalyzed intramolecular cyclization reaction of **2g** in benzene afforded the tricyclic compound **2h** in 55% yield. From the experiments we could conclude that two hydroxyl groups are *trans* relationships. The diastereoselective formation of *trans*-**2g** could be rationalized as follows. Initial Barbier-type allylation occurred at the 2-position of ninhydrin to give **2f**. The following second Barbier allylation occurred at the 1-position of **2f** in the direction of forming *trans*-form due to the sterically bulkier methallyl moiety.

The Barbier reaction of isatin (**3**) occurred at the 3-

position. High yields of products were observed with allyl bromide and methallyl bromide (entries 1 and 2 in Table 2). It is interesting to note that *N*-allylation or *N*-methallylation were occurred simultaneously to some extent.¹¹ However, the reaction with benzyl bromide showed sluggish reactivity (entry 3).^{4a} The relative reactivity of allyl bromide and benzyl bromide was clearly observed when we used equimolar amounts of both reagents (entry 4). The products **4a**, **4b** and **4g** resulting from the incorporation of allyl bromide were formed. Spiro compounds **4h** could be prepared in low yield (entry 5) by using α,α' -dibromo-*o*-xylene. The representative results are listed in Table 2.

Table 2. Indium mediated Barbier reaction of isatin (**3**)

Entry	Conditions	Products (%)	
1	allyl bromide (4 equiv) Indium (1 equiv) NaI (4 equiv) DMF, rt, 5 min	 4a (69)	 4b (11)
2	methallyl bromide (3 equiv) In (1 equiv) NaI (3 equiv) DMF, rt, 5 min	 4c (65)	 4d (24)
3	benzyl bromide (4 equiv) In (2 equiv) NaI (4 equiv) DMF, rt, 8h	 4e (43)	 4f (7)
4	benzyl bromide (2 equiv) allyl bromide (2 equiv) In (1 equiv) NaI (4 equiv) DMF, rt, 5 min	4a (58) + 4b (5)	 4g (5)
5	α,α' -dibromo- <i>o</i> -xylene (2 equiv) In (2 equiv) NaI (4 equiv) DMF, rt, 6 h	 4h (21)	



Scheme 2

Alloxan (5) reacted similarly to give the highly allylated or benzylated compounds **6a-d** in moderate yields (Scheme 2).

In this paper we disclosed the first systematic indium-mediated Barbier reaction of isatin, ninhydrin and alloxan with some organo-halogen compounds. We are currently undergoing the chemical transformation of the obtained compounds.

Experimental Section

Typical experimental procedure for the synthesis of 2a and 2b: A mixture of ninhydrin (178 mg, 1 mmol), benzyl bromide (685 mg, 4 mmol), indium powder (115 mg, 1 mmol, Aldrich), and sodium iodide (600 mg, 4 mmol) in DMF (3 mL) was stirred at room temperature for 5 min. The reaction mixture was poured into aqueous HCl solution and extracted with ether. Evaporation of the solvent followed by purification of the product by silica gel column chromatography (hexane/ether, 2 : 1) provided the pure products **2a** and **2b** in 39 and 44% yields, respectively. Selected spectroscopic data of products are as follows. The compounds **2d**,¹² **2f**,¹³ **4a**,⁸ **4e**,¹⁴ and **4f**¹⁵ were known compounds.

2a: 39%; mp 120-122 °C; IR (KBr) 3442, 1741, 1716, 1712 cm⁻¹; ¹H NMR (CDCl₃) δ 3.01 (br s, 1H), 3.23 (s, 2H), 7.01-7.12 (m, 5H), 7.76-7.89 (m, 4H); ¹³C NMR (CDCl₃) δ 42.79, 78.29, 123.63, 127.40, 128.41, 130.04, 132.74, 136.36, 140.65, 199.50.

2b: 44%; mp 172-173 °C; IR (KBr) 1747, 1716 cm⁻¹; ¹H NMR (CDCl₃) δ 3.35 (s, 2H), 4.45 (s, 2H), 6.98-7.00 (m, 5H), 7.27-7.81 (m, 9H); ¹³C NMR (CDCl₃) δ 41.64, 68.91, 84.54, 122.86, 127.04, 128.00, 128.12, 128.16, 128.28, 130.08, 132.92, 136.13, 137.03, 141.21, 200.44.

2c: 10%; yellow oil; IR (KBr) 1738, 1720 cm⁻¹; ¹H NMR (CDCl₃) δ 2.14 (s, 3H), 3.30 (s, 2H), 6.95-7.31 (m, 5H), 7.87-8.01 (m, 4H); Mass (70 eV) *m/z* (rel. intensity) 43 (41), 91 (82), 233 (49), 234 (100), 252 (30), no M⁺.

2d: 21%; mp 65-66 °C; IR (KBr) 3496, 1751, 1720 cm⁻¹; ¹H NMR (CDCl₃) δ 2.61 (d, *J* = 7.5 Hz, 2H), 2.99 (br s, 1H), 5.16-5.24 (m, 2H), 5.65-5.74 (m, 1H), 7.88-8.04 (m, 4H); Mass (70 eV) *m/z* (rel. intensity) 104 (100), 132 (60), 160 (26), 202 (M⁺, 16).

2e: 49%; mp 69-71 °C; IR (KBr) 3489, 3467, 1716 cm⁻¹;

¹H NMR (CDCl₃) δ 2.20-2.31 (m, 2H), 2.59-2.73 (m, 2H), 2.62 (s, 1H), 3.07 (s, 1H), 5.04-5.17 (m, 4H), 5.71-5.79 (m, 2H), 7.47-7.76 (m, 4H); ¹³C NMR (CDCl₃) δ 41.07, 45.61, 80.10, 86.18, 119.77, 120.89, 123.36, 124.80, 129.33, 132.18, 132.44, 132.60, 135.50, 154.29, 203.65.

2f: 44%; mp 112-113 °C; ¹H NMR (CDCl₃) δ 1.61 (s, 3H), 2.64 (s, 2H), 3.26 (br s, 1H), 4.77-4.86 (m, 2H), 7.89-8.02 (m, 4H); ¹³C NMR (CDCl₃) δ 23.67, 44.47, 77.29, 117.73, 123.89, 136.57, 138.40, 140.47, 199.45.

2g: 27%; mp 123-125 °C; ¹H NMR (CDCl₃) δ 1.46 (s, 3H), 1.66 (s, 3H), 2.02 (d, *J* = 11.8 Hz, 1H), 2.07 (d, *J* = 11.8 Hz, 1H), 2.70 (d, *J* = 13.8 Hz, 1H), 2.72 (s, 1H), 2.78 (d, *J* = 13.8 Hz, 1H), 3.27 (s, 1H), 4.58 (s, 1H), 4.68 (s, 1H), 4.89-4.91 (m, 2H), 7.47-7.76 (m, 4H); ¹³C NMR (CDCl₃) δ 24.03, 24.61, 44.68, 48.17, 80.85, 87.67, 115.65, 116.41, 123.25, 125.34, 129.28, 132.47, 134.81, 141.13, 141.19, 153.60, 203.70.

2h: 55%; mp 67-68 °C; ¹H NMR (CDCl₃) δ 0.95 (s, 3H), 1.02 (s, 3H), 1.51 (s, 6H), 2.09 (d, *J* = 14.1 Hz, 1H), 2.21 (d, *J* = 13.5 Hz, 1H), 2.40 (d, *J* = 14.1 Hz, 1H), 2.59 (d, *J* = 13.5 Hz, 1H), 7.48-7.76 (m, 4H); ¹³C NMR (CDCl₃) δ 28.62, 28.98, 46.61, 51.04, 87.16, 87.52, 97.08, 99.09, 123.37, 124.13, 128.56, 132.85, 135.78, 153.98, 202.31; Mass (70 eV) *m/z* (rel. intensity) 104 (38), 132 (33), 197 (28), 239 (23), 257 (100), 272 (M⁺, 39).

4a: 69%; mp 126-127 °C; IR (KBr) 3417, 1720, 1630 cm⁻¹; ¹H NMR (CDCl₃) δ 2.61 (dd, *J* = 13.5 and 8.1 Hz, 1H), 2.75 (dd, *J* = 13.5 and 6.6 Hz, 1H), 3.25 (s, 1H), 5.09 (s, 1H), 5.14 (d, *J* = 6.3 Hz, 1H), 5.60-5.74 (m, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 7.07 (td, *J* = 7.5 and 0.9 Hz, 1H), 7.26 (td, *J* = 7.8 and 1.2 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 8.20 (br s, 1H); ¹³C NMR (CDCl₃) δ 42.74, 76.34, 110.39, 120.47, 123.04, 124.45, 129.63, 130.20, 130.28, 140.27, 180.33; Mass (70 eV) *m/z* (rel. intensity) 92 (9), 148 (100), 149 (10), 189 (M⁺, 6).

4b: 11%; mp 115-116 °C; IR (KBr) 3452, 1693 cm⁻¹; ¹H NMR (CDCl₃) δ 2.64 (dd, *J* = 13.2 and 8.4 Hz, 1H), 2.76 (dd, *J* = 13.2 and 6.4 Hz, 1H), 2.79 (br s, 1H), 4.19 (ddt, *J* = 16.4, 5.3 and 1.5 Hz, 1H), 4.43 (ddt, *J* = 16.4, 5.3 and 1.5 Hz, 1H), 5.08-5.86 (m, 6H), 6.82 (d, *J* = 7.8 Hz, 1H), 7.09 (td, *J* = 7.5 and 1.0 Hz, 1H), 7.29 (td, *J* = 7.8 and 1.0 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H).

4c: 65%; mp 168-170 °C; ¹H NMR (CDCl₃) δ 1.56 (s,

3H), 2.70 (s, 2H), 2.99 (br s, 1H), 4.67 (s, 1H), 4.81 (s, 1H), 6.86 (d, $J = 7.8$ Hz, 1H), 7.07-7.40 (m, 3H), 7.77 (br s, 1H); ^{13}C NMR (CDCl_3 + few drops of $\text{DMSO}-d_6$) δ 23.77, 45.70, 76.37, 109.95, 115.45, 122.07, 124.52, 129.15, 130.68, 139.28, 141.13, 179.85.

4d: 24%; mp 156-157 °C; ^1H NMR (CDCl_3) δ 1.51 (s, 3H), 1.72 (s, 3H), 2.73 (s, 2H), 3.22 (br s, 1H), 4.05 (d, $J = 16.2$ Hz, 1H), 4.38 (d, $J = 16.2$ Hz, 1H), 4.64 (s, 1H), 4.76 (m, 1H), 4.86 (s, 1H), 4.92 (m, 1H), 6.81 (d, $J = 7.8$ Hz, 1H), 7.08-7.43 (m, 3H); ^{13}C NMR (CDCl_3) δ 19.93, 24.05, 45.99, 46.07, 76.33, 109.53, 112.63, 116.36, 122.88, 124.36, 129.64, 129.68, 138.80, 138.90, 143.06, 177.86.

4e: 43%; mp 162-164 °C; IR (KBr) 3340, 1709 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.11 (br s, 1H), 3.13 (d, $J = 13.0$ Hz, 1H), 3.31 (d, $J = 13.0$ Hz, 1H), 6.71 (d, $J = 7.8$ Hz, 1H), 6.97-7.23 (m, 8H), 7.62 (br s, 1H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 43.72, 76.96, 109.65, 121.61, 124.89, 126.70, 127.84, 129.24, 130.41, 131.19, 135.30, 141.90, 179.12.

4f: 7%; mp 177-178 °C; ^1H NMR (CDCl_3) δ 2.98 (s, 1H), 3.27 (d, $J = 12.6$ Hz, 1H), 3.41 (d, $J = 12.6$ Hz, 1H), 4.45 (d, $J = 16.2$ Hz, 1H), 4.99 (d, $J = 16.2$ Hz, 1H), 6.42-7.54 (m, 14H); Mass (70 eV) m/z (rel. intensity) 91 (100), 237 (13), 238 (32), 329 (M^+ , 4).

4g: 5%; ^1H NMR (CDCl_3) δ 2.60-2.84 (m, 2H), 2.93 (s, 1H), 4.73 (d, $J = 15.0$ Hz, 1H), 5.03 (d, $J = 15.0$ Hz, 1H), 5.08-5.26 (m, 2H), 5.57-5.71 (m, 1H), 6.70 (d, $J = 7.8$ Hz, 1H), 7.04-7.34 (m, 7H), 7.40 (dd, $J = 7.4$ and 1.1 Hz, 1H).

4h: 21%; mp 170-172 °C; IR (KBr) 3438, 1742, 1708, 1618 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.88 (d, $J = 16.0$ Hz, 1H), 3.44 (d, $J = 16.0$ Hz, 1H), 5.02 (d, $J = 15.1$ Hz, 1H), 5.21 (d, $J = 15.1$ Hz, 1H), 6.74-7.33 (m, 8H), 8.40 (br s, 1H); ^{13}C NMR (CDCl_3) δ 34.28, 65.17, 76.06, 110.84, 123.11, 124.53, 125.10, 127.16, 127.46, 129.48, 129.79, 130.20, 130.89, 134.50, 140.86, 177.47; Mass (70 eV) m/z (rel. intensity) 104 (100), 194 (49), 233 (85), 251 (M^+ , 42).

6a: 33%; ^1H NMR (CDCl_3) δ 2.67 (d, $J = 7.4$ Hz, 2H), 3.84 (br s, 1H), 4.39 (ddt, $J = 14.5$, 6.5 and 1.2 Hz, 2H), 4.52 (ddt, $J = 14.5$, 6.5 and 1.2 Hz, 2H), 5.13-5.89 (m, 9H); ^{13}C NMR (CDCl_3) δ 44.88, 47.03, 76.22, 120.02, 122.76, 128.49, 131.19, 150.06, 169.72.

6b: 18%; mp 69-70 °C; ^1H NMR (CDCl_3) δ 2.71 (d, $J = 7.5$ Hz, 2H), 4.36 (ddt, $J = 14.6$, 6.5 and 1.2 Hz, 2H), 4.47 (ddt, $J = 14.6$, 6.5 and 1.2 Hz, 2H), 5.17-5.87 (m, 6H); ^{13}C NMR (CDCl_3) δ 44.38, 46.43, 76.45, 120.08, 122.98, 128.30, 130.99, 149.52, 169.84, 170.60.

6c: 77%; mp 142-143 °C; ^1H NMR (CDCl_3) δ 3.46 (s, 2H), 4.50 (s, 2H), 7.12-7.41 (m, 10H), 8.01 (br s, 2H); ^{13}C NMR (CDCl_3) δ 46.77, 70.28, 83.24, 128.84, 128.88, 128.94, 129.03, 129.25, 130.36, 131.38, 136.13, 147.58, 169.02.

6d: 10%; mp 195-197 °C; ^1H NMR (CDCl_3) δ 3.40 (dd, $J = 17.7$ and 12.6 Hz, 2H), 4.43 (dd, $J = 19.5$ and 9.8 Hz, 2H), 4.81 (dd, $J = 48.0$ and 13.9 Hz, 2H), 6.89 (d, $J = 7.3$ Hz, 2H), 7.06 (t, $J = 7.3$ Hz, 2H), 7.18 (t, $J = 7.3$ Hz, 1H), 7.30-7.39 (m, 10H), 7.92 (br s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 45.06, 46.67, 69.73, 82.76, 128.13, 128.22, 128.45, 128.47, 128.63, 128.68, 129.56, 129.83, 131.00, 135.30, 135.88, 148.27, 167.82, 169.11.

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- During the tributylbismuthine-mediated Barbier reaction of carbonyl compounds with allyl bromide, it was known that the *in-situ* generated homoallylic alcohols could be converted into their allylic ethers, see Huang, Y.-Z.; Liao, Y. *Heteroatom Chem.* **1991**, *2*, 297.
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