Indium Mediated Barbier Reaction of Ninhydrin and Isatin

Ji Hyeon Gong, Ka Young Lee, Ji Suk Son,† and Jae Nyoung Kim*

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Korea
†Acrylate TS&D Center, LG Chemical Ltd., Jeonnam 520-130, Korea
Received October 30, 2002

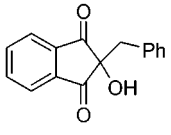
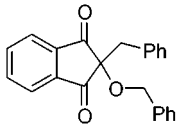
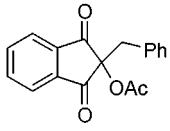
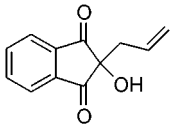
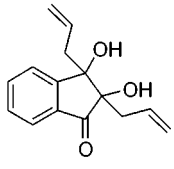
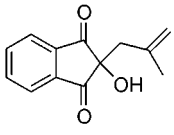
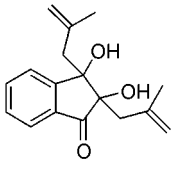
Key Words : Indium, Barbier reaction, Ninhydrin, Isatin

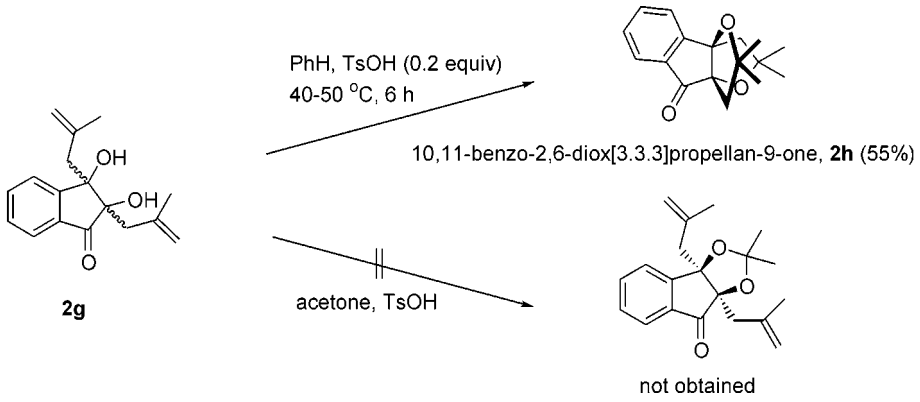
The development of Barbier type of carbon-carbon bond-forming reactions opened a new era in synthetic organic chemistry.[1] Various metals including In,[2] Sn,[3] Zn,[4] Mg,[5] Bi,[6] and Cd[7] have been used. Among them the use of indium in aqueous solution has shown considerable promise in the addition 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 ^{1}H and ^{13}C 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_2O (2 equiv) In (1 equiv) NaI (4 equiv) DMF, rt, 50 min	**2a** (14)	**2b** (18)	 **2c** (10)
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)	

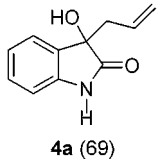
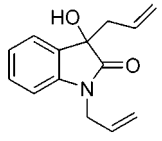
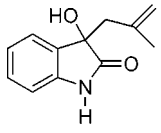
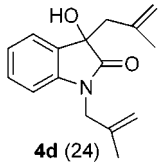
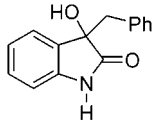
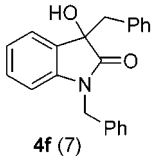
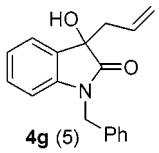
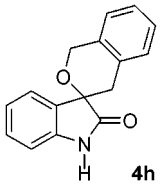


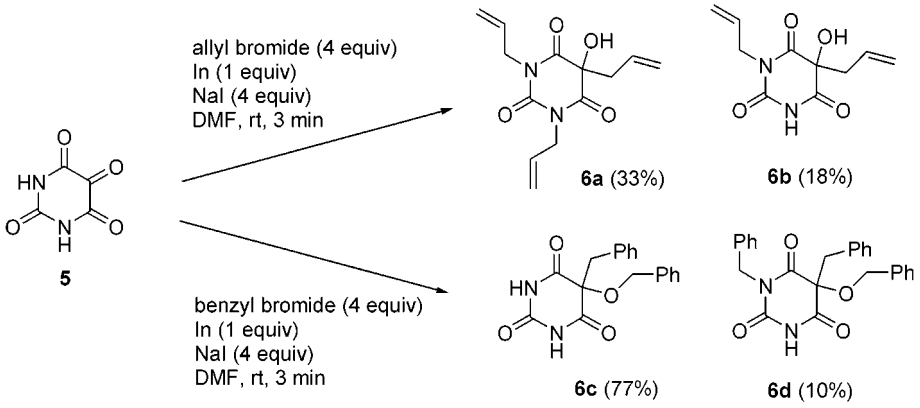
Scheme 1

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 Brabier 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-*o*-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 ($CDCl_3$) δ 3.01 (br s, 1H), 3.23 (s, 2H), 7.01-7.12 (m, 5H), 7.76-7.89 (m, 4H); ^{13}C NMR ($CDCl_3$) 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 ($CDCl_3$) δ 3.35 (s, 2H), 4.45 (s, 2H), 6.98-7.00 (m, 5H), 7.27-7.81 (m, 9H); ^{13}C NMR ($CDCl_3$) 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 ($CDCl_3$) 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 ($CDCl_3$) 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 ($CDCl_3$) 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), 747-7.76 (m, 4H); ^{13}C NMR ($CDCl_3$) 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 ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 ($CDCl_3$) 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 ($CDCl_3$) 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 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; ^{1}H 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}; ^{1}H 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 (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; ^{1}H 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%; ^{1}H 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}; ^{1}H 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%; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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.

References

1. (a) Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831. (b) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643. (c) Li, C.-J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997.
2. (a) Cintas, P. *Synthesis* **1995**, 1087. (b) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (c) Chan, T. H.; Li, C.-J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181. (d) Lee, J. G.; Choi, K. I.; Pae, A. N.; Koh, H. Y.; Kang, Y.; Cho, Y. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1314. (e) Lee, P. H.; Seomoon, D.; Lee, K. *Bull. Korean Chem. Soc.* **2001**, *22*, 1380. (f) Kang, S.-K.; Baik, T.-G.; Jiao, X.-H. *Synth. Commun.* **2002**, *32*, 75. (g) Percy, J. M.; Pintat, S. *Chem. Commun.* **2000**, 607. (h) Pae, A. N.; Cho, Y. S. *Curr. Org. Chem.* **2002**, *6*, 715.
3. (a) Wu, S. H.; Huang, B. Z.; Gao, X. *Synth. Commun.* **1990**, *20*, 1279. (b) Mukaiyama, T.; Harada, T. *Chem. Lett.* **1981**, 1527.
4. (a) Bieber, L. W.; Storch, E. C.; Malvestiti, I.; da Silva, M. F. *Tetrahedron Lett.* **1998**, *39*, 9393. (b) Marton, D.; Stivanello, D.; Tagliavini, G. *J. Org. Chem.* **1996**, *61*, 2731.
5. Bernardon, C.; Deberly, A. *J. Org. Chem.* **1982**, *47*, 463.
6. Katritzky, A. R.; Shobana, N.; Harris, P. A. *Organometallics* **1992**, *11*, 1381.
7. Yi, X.-H.; Meng, Y.; Hua, X.-G.; Li, C.-J. *J. Org. Chem.* **1998**, *63*, 7472.
8. (a) Nair, V.; Jayan, C. N. *Tetrahedron Lett.* **2000**, *41*, 1091. (b) Nair, V.; Jayan, C. N.; Ros, S. *Tetrahedron* **2001**, *57*, 9453.
9. (a) Mendez-Andino, J.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 1263. (b) Balskus, E. P.; Mendez-Andino, J.; Arbit, R. M.; Paquette, L. A. *J. Org. Chem.* **2001**, *66*, 6695. (c) Schmidt, B.; Wildemann, H. *Eur. J. Org. Chem.* **2000**, 3145.
10. 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.
11. The reaction of isatin and allyl bromide (3 equiv) in the presence of NaI (3 equiv) in DMF (50-60 °C, 48 h) gave the *N*-allylisatin in 25% yield.
12. Yalpani, M.; Wilke, G. *Chem. Ber.* **1985**, *118*, 661.
13. Gill, G. B.; Idris, M. S. H.; Kirollos, K. S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2355.
14. Ogata, M.; Matsumoto, H.; Tawara, K. *Eur. J. Med. Chem. Chim. Ther.* **1981**, *16*, 373.
15. (a) Kafka, S.; Klasek, A.; Kosmrlj, J. *J. Org. Chem.* **2001**, *66*, 6394. (b) Munusamy, R.; Dhathathreyan, K. S.; Balasubramanian, K. K.; Venkatachalam, C. S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1154.