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# One-Pot Synthesis of 2-Substituted Indoles from 2-Aminobenzyl Phosphonium Salts. A Formal Total Synthesis of Arcyriacyanin A

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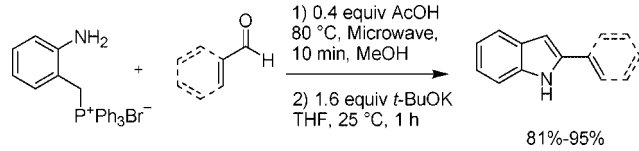
## ABSTRACT




**The reaction of (2-aminobenzyl) triphenylphosphonium bromide with aromatic aldehydes or α,β-unsaturated aldehydes under *microwave-assisted conditions* constitutes a new synthesis of 2-substituted indoles in high yields (81−97%) in a one-pot reaction. The adduct from indole-4-carboxaldehyde was an advanced intermediate in the synthesis of arcyriacyanin A.**

Many 2-aryl and 2-vinylindoles are key subunits of a variety of biologically active molecules.[1] The 2-vinylindole moiety can function as a heterocyclic diene for stereocontrolled annulation of the indole skeleton.[4c] The traditional methods include Fischer indole synthesis, Batcho−Leimgruber synthesis from *o*-nitrotoluenes, Gassman synthesis from *N*-haloanilines, reductive cyclization of *o*-nitrobenzyl ketones, and Madelung cyclization of *N*-acyl-*o*-toluidines.[2] Transition-metal-catalyzed reactions, using palladium or copper, for the direct arylation of indoles and related heterocycles have been widely reported.[3] The Wittig cyclizations of N-acylated 2-aminobenzyl phosphonium salts also provide versatile syntheses of quinolines and 2-aryl or vinylindoles.[4] Despite the fact that these reactions are synthetically useful, they suffer from several disadvantages: (i) high temperatures and long times (above 125 °C and 12 h), (ii) expensive transition-metal catalysts, (iii) multistep and moderate yields as well as high sensitivity to moisture. We report herein a new approach that can successfully afford 2-aryl or vinylindoles in high yields in one pot under very mild conditions.

In an approach to the indoloquinoline alkaloids, we condensed commercially available phosphonium salt **1** with isatin **2** to form imine **3** under the conditions shown in Scheme 1. Treatment of imine **3** with potassium *tert*-butoxide in either THF or toluene provided adduct **5** in around 21% yield.

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(4) (a) Le Corre, M.; Hercouet, A.; Le Stanc, Y.; Le Baron, H. *Tetrahedron* **1985**, *41*, 5313. (b) Mahboobi, S.; Bernauer, K. *Helv. Chim. Acta* **1988**, *71*, 2034. (c) Eitel, M.; Pindur, U. *Synth.* **1989**, *5*, 364. (d) Kuehler, T. C.; Swanson, M.; Christenson, B.; Klintenberg, A.; Lamm, B.; Faegerhag, J.; Gatti, R.; Oelwegaard-Halvarsson, M.; Shcherbuchin, V.; Elebring, T.; Sjoestroem, J. *J. Med. Chem.* **2002**, *45*, 4282. (e) Tao, M.; Park, C. H.; Bihovsky, R.; Wells, G. J.; Husten, J.; Ator, M. A.; Hudkins, R. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 938.

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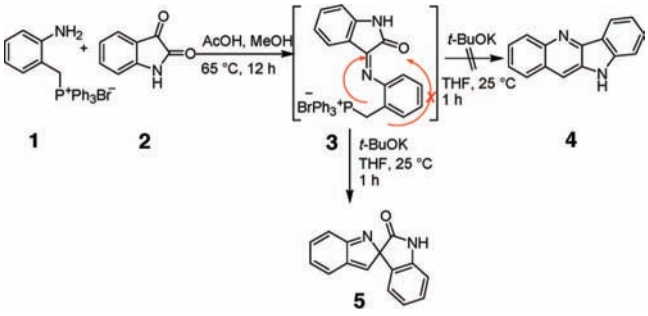
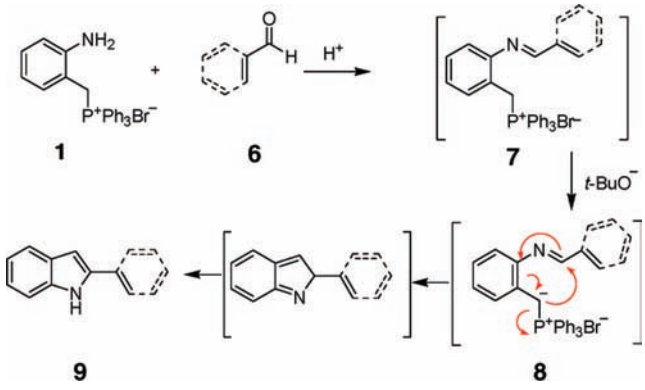
**Scheme 1**




Although we had expected the product to be compound **4**, an intermediate in the synthesis of cryptolepine,[5] our proton, and carbon NMR spectra did not match the published spectra.[6] After considering its mass spectrum (which showed the mass of **4** plus an oxygen atom) and the $^{13}C$ NMR (which showed a resonance at 99 ppm as the most downfield resonance), we tentatively assigned structure **5**. Compound **5** had been reported,[7] and its major mass spec fragmentation patterns were identical to those in our adduct.

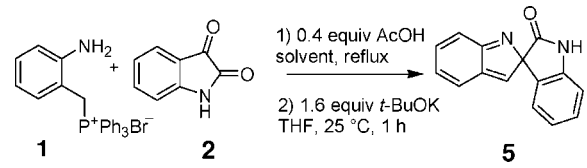
We reasoned that if a spiro compound such as **5** had formed such an intermediate might be employed in a general synthesis of 2-substituted indoles. Since these compounds are intermediates for the synthesis of indole natural products, a one-pot synthesis from commercially available starting materials would be useful. The strategy for the formation of 2-substituted indoles **9** from **1** via **7** and **8** is illustrated in Scheme 2.

**Scheme 2**




It is notable that our initial studies used the traditional methods[8] to form an imine by boiling overnight in methanol or toluene with a catalytic amount of acetic acid with a low yield. Application of microwave energy as a nonconventional activation source in organic syntheses is increasing rapidly, and its benefits have been well documented.[9] Microwave-assisted organic synthesis has proven to be a valuable tool to increase efficiency in the synthesis of heterocyclic compounds.[10] This prompted us to synthesize the 2-unsubstituted indoles under the microwave conditions. The results presented in Table 1 show that under microwave-assisted conditions the reaction proceeds very efficiently within a few minutes, and the yield also increased from 21% to 87%.

**Table 1.** Reation of **1** with Isatin to Generate Compound **5**[a]




| entry | solvent | temperature (°C) | time (h) | yield[b] (%) |
|---|---|---|---|---|
| 1 | methanol | 65 | 12 | 25 |
| 2 | toluene | 111 | 12 | 21 |
| 3[c] | methanol | 80 | 10 min | 87 |

[a] Reaction conditions: phosphonium salt **1** (1 mmol), isatin (1 mmol), AcOH (0.4 mmol), solvent (2 mL). [b] Isolated yield. [c] Microwave assisted

When phosphonium salt **1** was allowed to react with benzaldehyde to form the imine and then potassium *tert*-butoxide was added, 2-phenylindole (**8**) was formed as the only product in 95% yield. In view of this promising result, several aromatic and $\alpha,\beta$-unsaturated aldehydes were reacted with **1**. The results of these experiments are collected in Table 2.

As the results in Table 2 indicate, a wide range of functionalized aldehydes react effectively with phosphonium salt **1**, including a variety of electron-donating and electron-withdrawing substituents, such as aromatic ethers, halides, nitro and aryl groups (entries 2, 3, 4, and 5), and also heterocyclic aldehydes (entries 6 and 7). In addition, the reactions with $\alpha,\beta$-unsaturated aldehydes (entries 8 and 9) also proceed very smoothly and gave high yields under these conditions. Unfortunately, the alkyl aldehydes such as isobutyraldehyde did not form the imine intermediates with phosphonium salt **1** under the same microwave conditions. Adduct **11** is an advanced intermediate in the synthesis of the natural product arcyriacyanin A (**12**).

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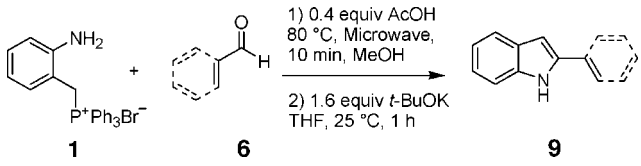
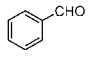
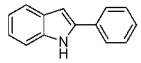
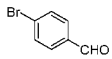
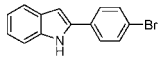
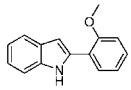
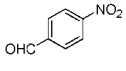
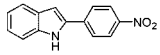
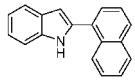
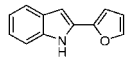
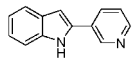
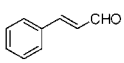
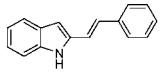
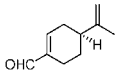
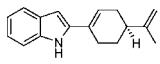
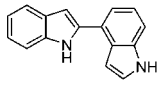
(11) (ai) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S *J. Am. Chem. Soc.* **2006**, *128*, 4972. (aii) Bedford, R. B.; Betham, M. *J. Org. Chem.* **2006**, *71*, 9403. (bi) So, C. M.; Lau, C. P.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 2795. (bii) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843. (c) Le Corre, M.; Hercouet, A.; Le Stanc, Y.; Le Baron, H. *Tetrahedron* **1985**, *41*, 5313. (d) Huffman, J. W. *J. Org. Chem.* **1962**, *27*, 503. (e) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synth.* **2004**, *4*, 610.

**Table 2.** Reaction of **1** with Aldehydes to Generate 2-Aryl and 2-Vinyl Indoles[a]



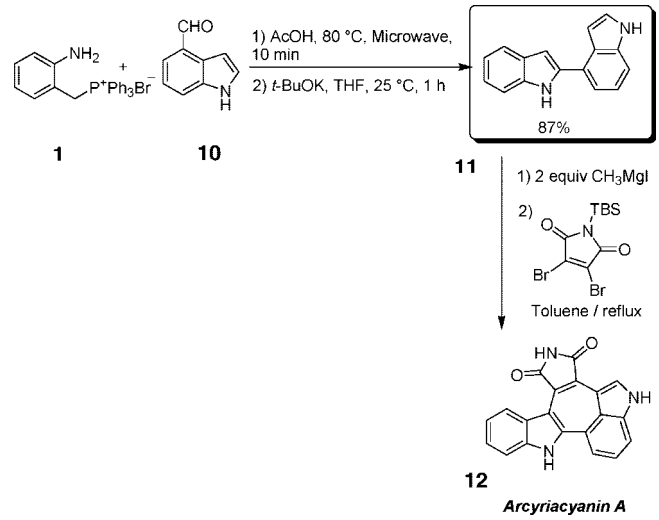

**1** **6** **9**

| entry | 6 | product | yield[b] (%) | melting point (°C) (Lit. mp) |
|---|---|---|---|---|
| 1 |  |  | 95 | 188-190 (188-189)[11a] |
| 2 |  |  | 95 | 211-213 (208-212)[11a] |
| 3 |  |  | 81 | 82.5-83 (83)[11b] |
| 4 |  |  | 86 | 248-250 (249-251)[11c] |
| 5 |  |  | 93 | 97-99 (99-102)[11a] |
| 6 |  |  | 86 | 120-123 |
| 7 |  |  | 85 | 175-176 (170-175)[11d] |
| 8 |  |  | 97 | 202-204 (197-199)[11c] |
| 9 |  |  | 83 | 164-165 |
| 10 |  |  | 87 | 202-203 (199-202)[12b] |

[a] Reaction conditions: (i) phosphonium salt **1** (1 mmol), aldehydes (1 mmol), AcOH (0.4 mmol), methanol (2 mL); (ii) *t*-BuOK (1.6 mmol), THF (2 mL). [b] Isolated yield.

Arcyriacyanin A, a pigment of the slime mold of *Arcyria obvelata Onsberg*, is an effective inhibitor of protein kinase C and protein tyrosine kinase.[13] Since compound **11** has been transformed into **12** with 3,4-dibromomaleimide as shown in Scheme 3,[12] the synthesis of compound **11** constitutes a formal *two-step* total synthesis of **12** from commercially available starting materials.

**Scheme 3**




In conclusion, we have established a new method for the preparation of 2-aryl and 2-vinyl indoles from commercially available starting materials. These reactions proceed under very mild conditions (often at room temperature) and remarkably short times (less than 2 h) in one pot with high yields (81−97%). The adduct from indole-4-carboxaldehyde was an advanced intermediate in the synthesis of arcyriacyanin A, which can be synthesized in two steps in 35% overall yield.

**Acknowledgment.** We thank the Iowa State University Department of Chemistry for support of this work.

**Supporting Information Available:** Detailed synthetic procedures, characterization data, and $^1$H NMR, $^{13}$C NMR, and HRMS spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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