

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

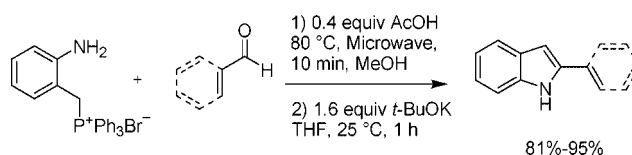
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ABSTRACT



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.

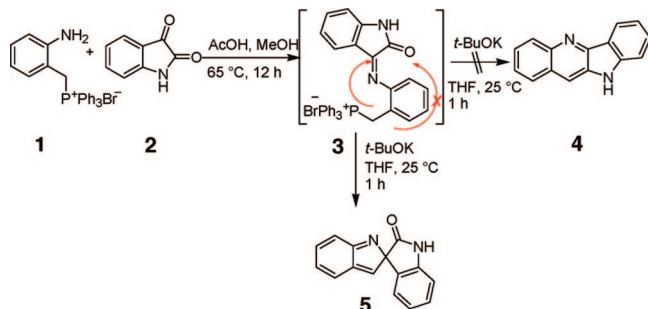
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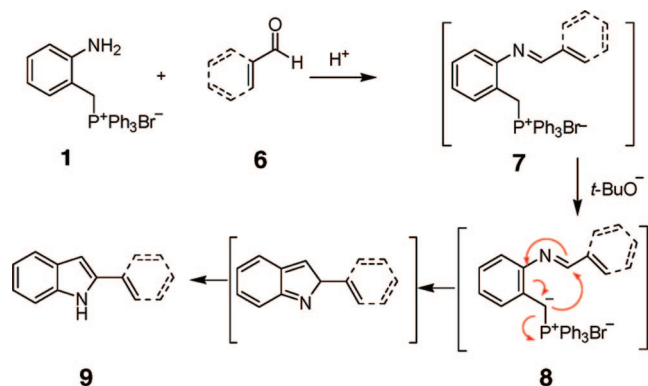
Scheme 1



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 ¹³C 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 methods⁸ 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

Table 1. Reaction 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

conditions the reaction proceeds very efficiently within a few minutes, and the yield also increased from 21% to 87%.

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 α,β -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 α,β -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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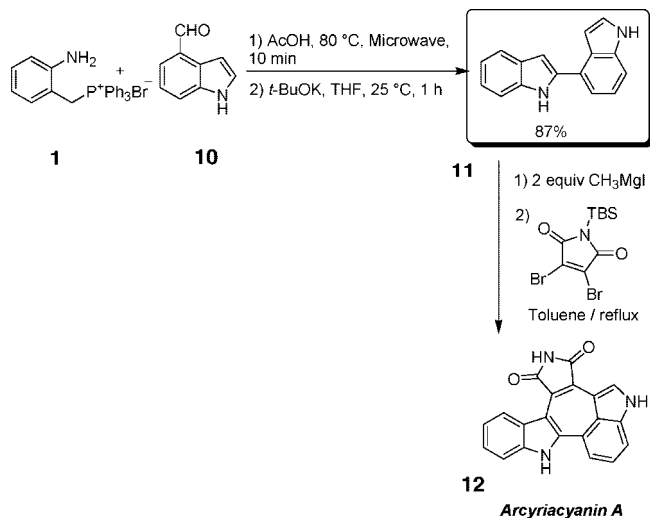
Table 2. Reaction of **1** with Aldehydes to Generate 2-Aryl and 2-Vinyl Indoles^a

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) ^{12h}

^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

Scheme 3



in Scheme 3,¹² the synthesis of compound **11** constitutes a formal *two-step* total synthesis of **12** from commercially available starting materials.

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.

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Supporting Information Available: Detailed synthetic procedures, characterization data, and ¹H NMR, ¹³C 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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