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# Synthesis of *N*-vinyl substituted indoles and their acid-catalyzed behavior

Hao Li, Nawong Boonnak, Albert Padwa *

*Department of Chemistry, Emory University, Atlanta, GA 30322, United States*

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Dedicated with admiration and fondness to Harry Wassexman on the occasion of his 90th anniversary

## ABSTRACT

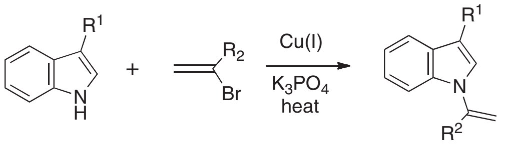
A mild cross-coupling reaction has been used to access several *N*-vinyl substituted indoles. When treated with acid, these unique enamines produce novel dimeric and trimeric products derived from a preferred protonation reaction at the enamine π-bond.

Substituted indoles form the core of numerous natural products and have considerable pharmacological potential.[1,2] Over many years, countless efforts have been devoted to the development of methods that enable the synthesis of functionalized indoles.[3] However, the exploration of new methodologies that allow for rapid introduction of functionality onto the indole skeleton in a single operation still remains an important challenge facing organic chemistry. In this context, transition metal-catalyzed transformations for the synthesis of 2,3-disubstituted indoles, starting from *o*-alkynylanilines or derivatives thereof[4] as well as *o*-haloanilines[5], have been intensively studied. Another effective strategy for the introduction of an alkenyl side chain into the indole skeleton is the palladium-catalyzed oxidative reaction of alkenes via C–H bond cleavage.[6] The vinylation generally occurs at the electron-rich $C_3$ position of the indole ring due to the electrophilic nature of the reaction.[7] In an effort to further expand the diversity of substituents that can be positioned on the indole scaffold, we became interested in accessing indole derivatives substituted at the *N*-position with various alkenyl groups. Such derivatives, in addition to incorporating structural elements that expand the potential for natural product synthesis, also provide an opportunity for manipulating the electronic characteristics of the indole ring itself. Surprisingly, *N*-vinylindoles are not generally represented in the chemical literature[8] and their application as an enamine equivalent in electrophile reactions has not been investigated. In this communication, we report a synthetically useful procedure that allows generation of a variety of *N*-vinylindoles and a study of their acid-promoted electrophilic addition reactions.

N-Vinylation has previously been carried out employing a variety of methods including mercuric acetate/sulfuric acid-catalyzed vinylation of *NH*-heteroaromatics with vinyl acetate,[9a] alkylation with dibromoethane followed by elimination,[9b] palladium(II)-catalyzed vinylation of amides with electron-deficient acrylates,[9c] palladium(0)-catalyzed vinylation with vinyl bromides[9d], and triflates,[9e] and cesium hydroxide-catalyzed addition of alcohols and amine derivatives to alkynes and styrenes.[9f] The drawbacks of these methods are elevated temperatures and a lack of generality and/or substrate scope. We found that by using a *N*-vinylation protocol originally developed by Lam and co-workers[8a] and more recently employed by Xi,[10] we were able to prepare a series of *N*-vinylindoles in good yield. The coupling procedure involved treating a *NH*-indole with various vinyl bromides using a combination of 10 mol % copper(I) iodide and 20 mol % of ethylenediamine as the catalyst in dioxane at 110 °C in the presence of $K_3PO_4$ as the base (Scheme 1).

Enamines are among the most widely used building blocks in organic synthesis.[11] A conventional enamine acts as a nucleophile in a chemical transformation by enlisting its nitrogen lone pair toward nucleophilic attack. We became interested in examining the extent of interaction between the indole nitrogen lone pair of electrons and the enamine double bond present in systems such as **1**. In particular, we recognized that *N*-vinylindoles represent a unique class of enamines that bear a multitude of nucleophilic sites, which could lead to various products (i.e., **2**–**4**) when allowed to react with an electrophile (Scheme 2).

The electrophilic substitution reaction of 1-(prop-1-en-2-yl)-1*H*-indole (**1a**) with Eschenmoser's salt was initially explored. *N*-Vinylindole **1a** was treated with 1.1 equiv of Eschenmoser's salt in $CH_2Cl_2$ at 40 °C for 1 h and provided a mixture of N-substituted indoles **5**–**7** in a 1:1:2 ratio (Scheme 3, Eq. 1). When the related



**1a**; $R^1$ = H, $R^2$ = Me, 79%
**1b**; $R^1$ = COOMe, $R^2$ = Me, 85%
**1c**; $R^1$ = Me, $R^2$ = Me, 42%
**1d**; $R^1$ = CN, $R^2$ = Me, 98%
**1e**; $R^1$ = COOMe, $R^2$ = Et, 90%

**Scheme 1.** Copper catalyzed cross-coupling of *NH*-indoles with vinyl bromides.

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* Corresponding author. Tel.: +1 404 27 283; fax: +1 404 27 629.
*E-mail address:* chemap@emory.edu (A. Padwa).

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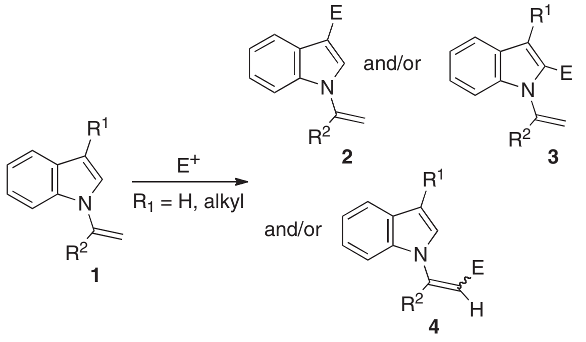
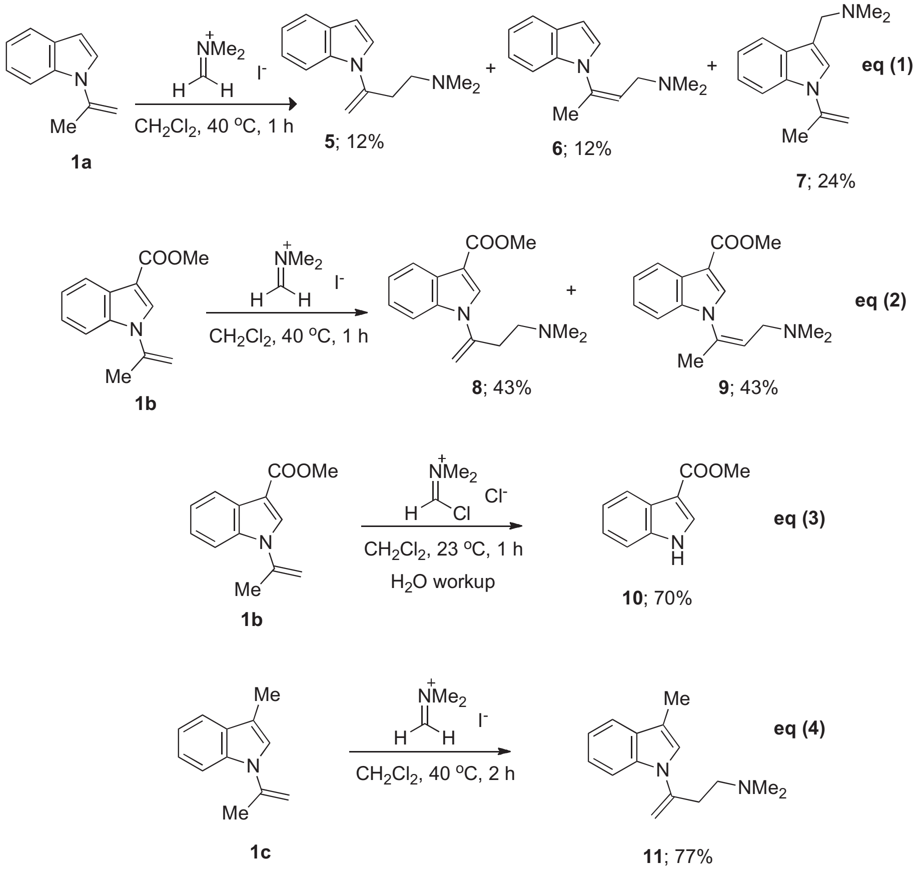


**Scheme 2.** Reaction of *N*-vinyl indoles with a global electrophile E$^+$.

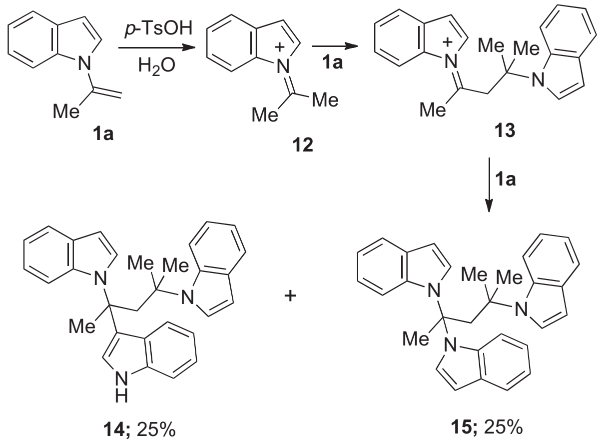
*N*-vinylindole **1b** was exposed to the same reaction conditions, the *N*-substituted indoles **8** and **9** were obtained as a 1:1-mixture in 86% yield (Scheme 3, Eq. 2), thereby indicating that the enamine portion of **1b** was the more nucleophilic site toward electrophilic addition when a methyl carboxylate substituent was incorporated into the 3-position of the indole ring. The electrophilic reaction of *N*-vinylindole **1b** with the more reactive Vilsmeier reagent only afforded the corresponding unmasked indole **10**, formed by C–N bond cleavage upon aqueous workup (Scheme 3, Eq. 3). Of notable interest was the finding that when 3-methyl-1-(prop-1-en-2-yl)-1*H*-indole (**1c**) was allowed to react with Eschenmoser's salt, the N-substituted indole **11** was the only product isolated in 77% yield (Scheme 3, Eq. 4).[12]

In a subsequent study, the behavior of *N*-vinylindoles **1a** and **1b** toward Brønsted or Lewis acid-promoted electrophilic additions was examined. Exposure of *N*-vinylindole **1a** to 1.0 equiv of *p*-toluenesulfonic acid monohydrate ($p$-TsOH·$H_2O$) in $CH_2Cl_2$ at 25 °C for 1 min, afforded a 1:1-mixture of the novel indole trimers **14** and **15** which were isolated in 50% overall yield (Scheme 4). We assume that the formation of indole trimer **14** proceeds via a Brønsted acid-promoted electrophilic addition/Friedel–Crafts reaction cascade. In the first step, protonation of the enamine $\pi$-bond of **1a** by $p$-TsOH·$H_2O$ occurs to give iminium ion **12**. Further reaction of **12** with another equivalent of *N*-vinylindole **1a** leads to a second dimeric iminium ion **13**. Rather than undergoing deprotonation, this iminium ion reacts with 1*H*-indole by either a Friedel–Crafts reaction at the 3-position of the indole ring to give trimer **14** or else reacts with an additional molecule of **1a** at the nitrogen position of the indole to provide aminal **15**. Products **14** and **15** are most likely formed from the free indole, that is, liberated in the reaction by the hydrolysis of intermediate **12** by the water present in $p$-TsOH·$H_2O$. Interestingly, only methyl 1*H*-indole-3-carboxylate (**10**) was isolated in 99% yield when *N*-vinylindole **1b** was submitted to the action of $p$-TsOH·$H_2O$. However, when the *N*-vinylindole **1b** was allowed to react with a milder Lewis acid such as $MgI_2$, the dimeric indole **16** was formed in 63% yield (Scheme 5)[13] and this reaction presumably proceeds via a mechanism related to that outlined in Scheme 4. The exclusive formation of **16** is likely due to the lack of water present in the reaction mixture.

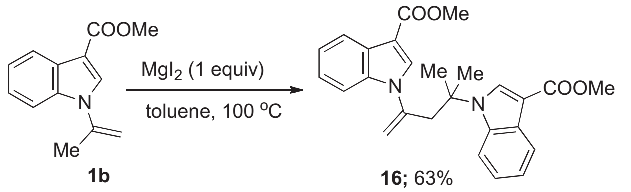
When *N*-vinylindole **1b** was treated with trifluoroacetic acid in the presence of methanol, a near quantitative yield of hemiaminal **17** was obtained. None of the dimeric product **16** could be detected under these experimental conditions. It would appear as though the initially formed iminium ion derived by protonation of the enamine $\pi$-bond is trapped by the nucleophilic solvent before it has a chance to react with the starting indole **1b**. Next, the electrophilic addition of *N*-vinylindole **1b** with isobutyraldehyde was studied using $BF_3$·$OEt_2$ as the Lewis acid (Scheme 6). Unexpectedly, the



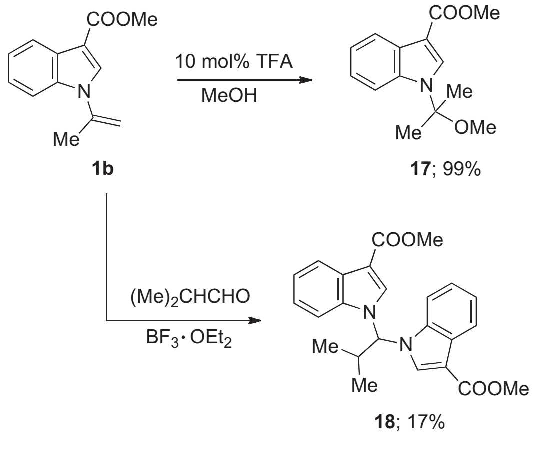
**Scheme 3.** Electrophilic reaction of *N*-vinylindole **1b** with the Vilsmeier reagent.



**Scheme 4.** Lewis acid-promoted electrophilic addition of *N*-vinylindole **1a** with acid.



**Scheme 5.** Lewis acid-promoted electrophilic addition of *N*-vinylindole **1b** with $MgI_2$.



**Scheme 6.** Electrophilic addition of *N*-vinylindole **1b** with isobutyraldehyde.

only product that could be isolated from this reaction in 17% yield corresponded to aminal **18**. In this case, the decomposition of **1b** to *NH*-indole **10** takes place at a faster rate than addition of the enamine onto the carbonyl group of the aldehyde. Once formed, *NH*-indole **10** then reacts with isobutyraldehyde on the nitrogen atom of the indole to give the observed product.[14]

In conclusion, we have developed a mild cross-coupling reaction of *NH*-indoles with vinyl bromides using Cu(I) catalysis to give a variety of *N*-vinyl substituted indoles in good yield. When treated with acid, these unique enamines produce novel dimeric and trimeric products derived from a preferred protonation reaction at the enamine π-bond.

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12. *Typical procedure for electrophilic substitution of N-vinylindoles*: To a round-bottomed flask charged with *N*-vinylindole **1c** (35 mg, 0.2 mmol) in $CH_2Cl_2$ (2 mL) was added Eschenmoser's salt (1.1 equiv, 41 mg, 0.22 mmol) at room temperature. The reaction mixture was heated to 40 °C for 2 h and the reaction progress was monitored by TLC. At the end of the reaction, a saturated aqueous $NaHCO_3$ solution (2 mL) was added. The reaction mixture was extracted with $CH_2Cl_2$ and the combined organic layer was washed with water, brine, and dried over anhydrous $MgSO_4$. The organic phase was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (10% MeOH in $CH_2Cl_2$) to give 35 mg (77%) of **11** as a colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.21 (s, 6H), 2.32 (s, 3H), 2.34 (t, $J = 7.6$ Hz, 2H), 2.74 (t, $J = 7.6$ Hz, 2H), 5.11 (s, 1H), 5.16 (s, 1H), 6.99 (s, 1H), 7.13 (t, $J = 8.0$ Hz, 1H), 7.21 (t, $J = 7.6$ Hz, 1H), and 7.55 (br t, $J = 8.8$ Hz, 2H).
13. *Synthesis of indole dimer* **16**: To a flame dried glass microwave tube charged with *N*-vinylindole **1b** (43 mg, 0.2 mmol) in toluene (2 mL) was added $MgI_2$ (1.0 equiv, 56 mg, 0.2 mmol) at room temperature under an argon atmosphere. The microwave reaction vial was sealed with a septum cap and was heated to 100 °C for 19 h under microwave irradiation. The reaction mixture was cooled to room temperature and filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure and was purified by silica gel column chromatography (33% ethyl acetate in hexanes) to give 27 mg (63%) of **16** as a colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.66 (s, 6H), 3.41 (s, 2H), 3.87 (s, 6H), 4.86 (s, 1H), 5.16 (s, 1H), 7.15 (t, $J = 7.2$ Hz, 1H), 7.19 (d, $J = 7.2$ Hz, 1H), 7.21–7.24 (m, 2H), 7.26–7.29 (m, 1H), 7.48 (s, 1H), 7.53 (d, $J = 8.0$ Hz, 1H), 7.65 (s, 1H), 8.03–8.05 (m, 1H), 8.10 (d, $J = 7.6$ Hz, 1H).
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