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Phosphine-Mediated Coupling of Gramines with Aldehydes: A Remarkably Simple Synthesis of 3-Vinylindoles

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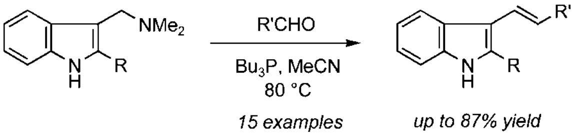
ABSTRACT



A new and practical synthesis of terminally substituted 3-vinylindoles is described involving tributylphosphine-mediated coupling of gramines with aldehydes.

Vinylindoles are valuable synthetic intermediates[1] that are utilized in the synthesis of a number of biologically significant compounds such as indole alkaloids,[2] carbazoles,[3] and carbolines.[4] Currently, there exist a few general methods for the preparation of 3-vinylindoles.[5] The most frequently used strategy involves palladium-catalyzed Heck[6] and Stille[7] coupling reactions of 3-bromoindoles with alkenes and vinyl stannanes, respectively.[8] These methods require protection of the indole nitrogen with an electron-withdrawing group because N-unprotected 3-bromoindoles are notoriously unstable.[9] An alternative strategy toward 3-vinylindoles employs the Wittig reaction of 3-acylindoles with stabilized phosphorus ylides.[10] The reactions of unstabilized phosphoranes, however, required prior protection of the indole nitrogen because of the strongly basic reaction conditions.[11] The synthesis of vinylindoles by reactions of indole-derived phosphoranes with aldehydes has also been developed.[12] This method involved a five-step reaction sequence starting from gramine and also necessitated protection of the indole ring nitrogen. In this paper, we disclose a convenient protection-group-free synthesis of 3-vinylindoles through direct coupling of gramines with carbonyl compounds. This operationally simple and efficient synthetic reaction nicely complements

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(6) (a) Frank, W. C.; Kim, Y. C.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2947−2949. (b) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657−2662. (c) For coupling of 3-indolyl triflates, see: Gribble, G. W.; Conway, S. C. *Synth. Commun.* **1992**, *22*, 2129−2141.

(7) Yokoyama, Y.; Matsumoto, T.; Murakami, Y. *J. Org. Chem.* **1995**, *60*, 1486−1487.

(8) Suzuki couplings of indole-3-boronic acids with vinyl triflates have also been employed: Zheng, Q.; Yang, Y.; Martin, A. R. *Tetrahedron Lett.* **1993**, *34*, 2235−2238.

(9) Piers, K.; Meimaroglou, C.; Jardine, R. V.; Brown, R. K. *Can. J. Chem.* **1963**, *41*, 2399−2401.

(10) (a) Brooks, S.; Sainsbury, M.; Weerasinge, D. K. *Tetrahedron* **1982**, *38*, 3019−3022. (b) Eberle, M. K.; Shapiro, M. J.; Stucki, R. *J. Org. Chem.* **1987**, *52*, 4661−4665. (c) Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, *48*, 1145−1174.

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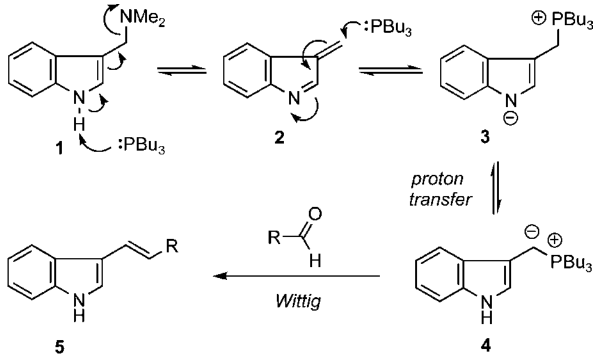
the existing methodology and is a method of choice for the synthesis of vinylindoles from nonenolizable aldehydes.

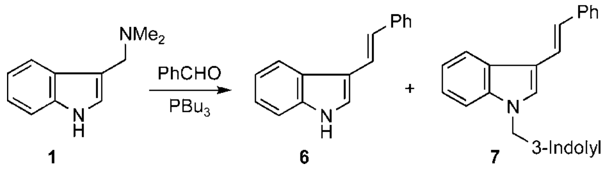
Reactions of gramine (**1**) with bases are known to proceed via elimination of dimethylamine and generation of a highly reactive electrophile **2** (Scheme 1).[13] When tributylphosphine is employed as a base, the conjugate addition reaction of the phosphine to imine **2** restores the aromaticity of the indole and produces zwitterion **3**. Intermediates **2** and **3** were previously implicated in Somei condensations of gramine with active methylene compounds.[14] The formation of intermediate **3** possibly constitutes a storage mechanism for unstable **2**, preventing it from polymerization. We speculated that under the reaction conditions, proton transfer could in principle isomerize **3** to phosphorane **4**. Although the exact pK_a values for conjugate acids of **3** and **4** were unknown, roughly assessed acidities suggested that an appreciable amount of **4** might exist in equilibrium with **3**.[15] We imagined that in the presence of a carbonyl compound, the intermediate phosphorane **4** could be intercepted to directly produce vinylindole **5** by the Wittig reaction.

Scheme 1. Phosphine-Mediated Reaction of Gramine with Aldehydes



With this idea in mind, we began our study by examining the coupling reaction of benzaldehyde with gramine. An excess of gramine was utilized in the initial experiments because of the potential proclivity of **2** to polymerization. To our delight, gentle reflux of an acetonitrile solution of gramine (1.8 equiv, 0.5 M solution), tributylphosphine (1.8 equiv), and benzaldehyde (1.0 equiv) for 2 h produced vinylindole **6** in 46% isolated yield (Table 1, entry 1).

Table 1. Reactions of Gramine with Benzaldehyde



entry	ratio of **1**:PBu_3:PhCHO	time (h)	yield of **6**[a] (%)	ratio of **6**:**7**[b]
1	1.8:1.8:1	2	46	74:26
2	1.8:5.4:1	2	53	82:18
3	1:3:1	2	50	>97:3
4	1:1.5:1	24	73	>97:3
5	1:1.5:1.25	24	78[c]	>97:3
6	1:1.5:1.5	24	84	>97:3

[a] Isolated yields. [b] Determined from ^1H NMR spectra of unpurified reaction mixtures. [c] Determined from ^1H NMR spectrum using 1,4-dimethoxybenzene as an internal standard.

In addition to the desired product, the proton NMR spectrum of the unpurified reaction mixture displayed the presence of unreacted benzaldehyde, a trace amount of *cis*-**6** (<5%), and a significant amount of bisindole byproduct **7**, which displayed a characteristic singlet of methylene protons at 5.44 ppm ($CDCl_3$). The yield of this transformation could be slightly increased by increasing the amount of phosphine (entry 2). Because **7** is presumably a product of reaction of vinylindole **6** with **2**,[16] the formation of **7** could be suppressed by lowering the molar ratio of gramine relative to that of benzaldehyde (entry 3). In addition, we found that an excess of gramine was not required, as an equimolar mixture of gramine and aldehyde produced **6** in a comparable yield. Moreover, when the reaction time was extended to 24 h, the starting aldehyde was completely consumed to afford **6** in a synthetically useful yield of 73% (entry 4). Entries 5 and 6 suggest that in the case of readily available aldehydes, it makes sense to use an excess of the carbonyl compound to further increase the yield of the vinylindole.

Although semistabilized phosphoranes often display poor *E*/*Z*-olefin selectivity in their reactions with aldehydes,[17] the high *E*-selectivity in the formation of **6** is not unexpected and is characteristic of the reactions of phosphoranes derived from trialkylphosphines.[18] Notably, the *E*/*Z*-selectivity strongly depended on the reaction medium. For example, while reactions in acetonitrile proceeded with high *E*-selectivity, significant amounts of *cis*-**6** were produced in reactions carried out in refluxing THF (40%) or ethyl acetate (46%).[19] The yield and selectivity of the coupling reactions were not

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[13] Howe, E. E.; Zambito, A. J.; Snyder, H. R.; Tishler, M. *J. Am. Chem. Soc.* **1945**, *67*, 38−39.

[14] Somei, M.; Karasawa, Y.; Kaneko, C. *Heterocycles* **1981**, *16*, 941−949.

[15] Because reactions were planned in a dipolar aprotic solvent (MeCN), the acidity data in DMSO were consulted. The pK_a value of the indole NH is 21.0 according to: Bordwell, F. G.; Drucker, G. E.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 632−635. The pK_a of the conjugate acid of **3** might be slightly lower than that due to the −I and −F effects of the distant phosphonium group. It has been reported that the pK_a value for deprotonation of the benzylic position of benzyltriphenylphosphonium cation is 17.4: Zhang, X.-M.; Bordwell, F. G. *J. Am. Chem. Soc.* **1994**, *116*, 968−972. Assuming the anion-stabilizing effect of the indolyl group is similar to that of phenyl, the pK_a of the conjugate acid of **4** is anticipated to be somewhat higher than 17.4, because tributylphosphonium salts are about 0.5 pK_a units less acidic than their triphenylphosphonium counterparts: Johnson, A. W.; LaCount, R. B. *Tetrahedron* **1960**, *9*, 130−138.

[16] Control experiment demonstrated that warming a solution of **6**, gramine, and PBu_3 in acetonitrile at 80 °C gave rise to **7**.

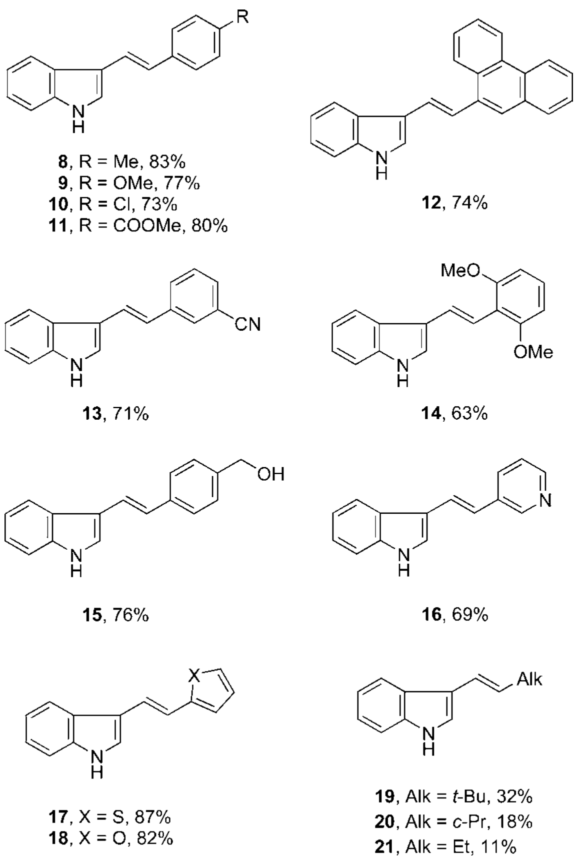
[17] For a review on stereochemical and mechanistic aspects of the Wittig reaction, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.

[18] (a) Meyers, A. I.; Lawson, J. P.; Carver, D. R. *J. Org. Chem.* **1981**, *46*, 3119−3123. (b) Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R.; Whittle, R. R.; Olofson, R. A. *J. Am. Chem. Soc.* **1986**, *108*, 7664−7678. (c) Tamura, R.; Kato, M.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1987**, *52*, 4121−4124.

[19] We thank Dr. P. Ruggiero for performing these experiments.

particularly sensitive to the changes in concentration of reagents. Thus, experiments using both 0.50 and 0.17 M solutions of gramine produced similar results. Finally, the choice of tributylphosphine as a base and nucleophile was crucial to the success of this process. For example, an attempt to use a combination of PPh_3 (1 equiv) and Hunig's base (20 mol %) failed to produce the desired product, while the use of PPh_3 (1 equiv) and DBU (10 mol %) gave rise to only a trace amount of **6**.

Having established the conditions for the synthesis of vinylindoles, we investigated the reactions of gramine with other aldehydes. Benzaldehydes bearing electron-donating or electron-withdrawing substituents are excellent substrates in this coupling reaction, as outlined in Figure 1. The synthesis of **14** from the sterically hindered 2,6-dimethoxybenzaldehyde and **15** from an unprotected 4-hydroxymethylbenzaldehyde is noteworthy. In addition, vinylindoles from the electron-deficient (**16**) and electron-excessive (**17**, **18**) heteroaromatic aldehydes were produced in good to excellent yields. While the parent vinylindole (**5**, R = H) is an extremely unstable compound,[3a,20] products **8**−**18** are fairly robust and can be handled without special precautions. However, alkyl-substituted vinylindoles (**19**−**21**) displayed diminished stability.[21] Reaction of pivalaldehyde with gramine produced **19** in 32% yield in addition to 15% of the bisindole byproduct similar to **7**. The sterically less hindered and more sensitive olefin **20** was isolated in 18% yield from reaction of cyclopropanecarbaldehyde after quick chromatographic purification over silica gel. Finally, the reaction of gramine with propanal was even more complicated and gave rise to vinylindole **21** in 11% isolated yield. This is presumably due to the potential of enolizable aldehydes to participate in various side reactions such as base-catalyzed condensations or α-alkylation by **2**.



8, R = Me, 83%
9, R = OMe, 77%
10, R = Cl, 73%
11, R = COOMe, 80%

12, 74%

13, 71%

14, 63%

15, 76%

16, 69%

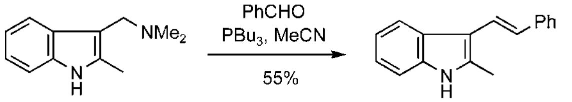
17, X = S, 87%
18, X = O, 82%

19, Alk = *t*-Bu, 32%
20, Alk = *c*-Pr, 18%
21, Alk = Et, 11%

Figure 1. Products of PBu_3-mediated coupling reactions of gramine with aldehydes. Reactions were run on a 1 mmol scale at 0.5 M concentration of aldehyde and gramine in MeCN (80 °C, 24 h) using 1.5 equiv of PBu_3. All yields are isolated. An excess (5 equiv) of aldehyde was used in production of **19** and **21**. Compound **20** was produced using an excess (1.5 equiv) of aldehyde and isolated as a 71:29 mixture of *E*- and *Z*-isomers. Compound **21** was isolated as an 86:14 mixture of *E*- and *Z*-isomers.

The reaction also allows for variations in the gramine structure. Substituted gramines can be readily prepared by Mannich reactions of indoles with formalin and dimethylamine and are convenient starting materials for the synthesis of indole derivatives.[22] We investigated a coupling reaction of benzaldehyde with gramine **22**,[23] which bears a methyl group in proximity to the reaction center. We were pleased to find that this reaction proceeded uneventfully under the standard reaction conditions to furnish a 55% isolated yield of alkene **23** (Scheme 2).

Scheme 2. Coupling of 2-Methylgramine with Benzaldehyde



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In summary, we developed a useful synthesis of 3-vinylindoles by direct coupling of gramines with aldehydes. This method is operationally convenient, does not require protection of the indole nitrogen, and is tolerant of a number of functional groups. In addition, the method utilizes inexpensive reagents and does not involve transition metal catalysts or strongly basic reaction conditions. We expect that this methodology will find wide application for the synthesis of various indole derivatives.

Acknowledgment. We thank the University of Rochester for support of this work.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Pindur, U.; Kim, M.-H.; Eitel, M. *Tetrahedron Lett.* **1990**, *31*, 1551−1552.

(21) Limited stability of these compounds was noted by others, for example: Liu, J.-T.; Jang, Y.-J.; Shih, Y.-K.; Hu, S.-R.; Chu, C.-M.; Yao, C.-F. *J. Org. Chem.* **2001**, *66*, 6021−6028.

(22) Brehm, W. J.; Lindwall, H. G. *J. Org. Chem.* **1950**, *15*, 685−687.

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