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β,β-Disubstituted *C*- and *N*-Vinylindoles from One-Step Condensations of Aldehydes and Indole Derivatives

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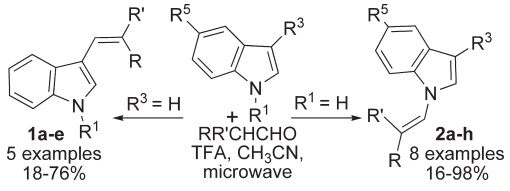

Direct preparation of β,β-disubstituted *C*- and *N*-vinylindoles from condensation of aldehydes on indole derivatives is presented. Heating 1-methyl- and 1-benzylindole **3a**,**b** with alkyl and aryl α-branched aldehydes and TFA in acetonitrile using microwave irradiation furnished 3-vinylindoles **1a**−**e** in 18−76% yields. Under similar conditions, 3-substituted indoles **4a**−**c** provided *N*-vinylindoles **2a**−**h** in 16−98% yields.

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C-Vinylindoles are building blocks for the preparation of biologically active compounds and natural products, such as indole alkaloids,[1] carbazoles,[2] and carbolines.[3] In particular, 3-vinylindoles have served as dienes in regio- and stereocontroled [4 + 2] cycloaddition reactions as entry to polycyclic heterocycles.[4] 3-Vinylindoles are typically prepared by palladium-catalyzed cross-coupling reactions of suitably functionalized indole and alkene precursors, including Heck,[5] oxidative Heck,[6] and Suzuki cross-couplings,[7] as well as by the Wittig reaction employing 3-formylindoles and various ylides.[8] Preparation of *C*-vinylindoles via direct condensation of indole derivatives and carbonyl compounds such as ketones[9] and aldehydes[10] was also reported; however, this route is less common. In principle, almost all of the reports in which the above-mentioned methods were used describe the preparation of *C*-vinylindoles with only one substituent on the olefin at the β position; only a few describe entry to β,β-disubstituted *C*-vinylindoles (Scheme 1).

N-Vinylindoles serve as monomers in radical and cationic polymerizations to produce poly(*N*-vinylindoles),[11] materials that possess semiconducting and photosensitive capabilities.[11c,11d] In spite of their utility, *N*-vinylindoles have been made by few methods, which have been typically limited in scope. For example, they are commonly prepared by the condensation of indole and 2- and 3-methylindole with acetylene[11a,11c] and acetylene derivatives,[12] albeit using harsh conditions. Reports on the preparation of *N*-vinylindoles from condensation of 3-substituted indoles and aldehydes are rare and refer only to dicarbonyl compounds such as malondialdehyde.[13] *N*-Vinylindoles have also been prepared by palladium-catalyzed cross-couplings of lithiated indoles and vinyl bromides[14] and indole derivatives with vinyl triflates.[15] Gold(III)-catalyzed double hydroamination of *O*-alkynylaniline with terminal alkynes,[16] and treatment of magnesium alkylidene carbenoids with *N*-lithiated indole,[17] were also reported to provide *N*-vinylindoles. Current methods, which typically utilize alkynes or alkenes as reagents and involve multiple steps, offer, however, only limited substitution around the double bond and indole ring. To the best of our knowledge, only two preparations of β,β-disubstituted *N*-vinylindoles have been reported requiring two and five synthetic steps with yields in the last step ranging from 18 to 65% (Scheme 1).[15,17]

The effective synthesis of 2-vinylpyrroles was recently achieved by reacting 4-aminopyrrole-2-carboxylates in condensations with aldehydes catalyzed by TFA.[18] Considering their applications in medicinal chemistry and materials science, and limitations for their procurement, *C*- and *N*-vinylindoles were targeted using condensations of

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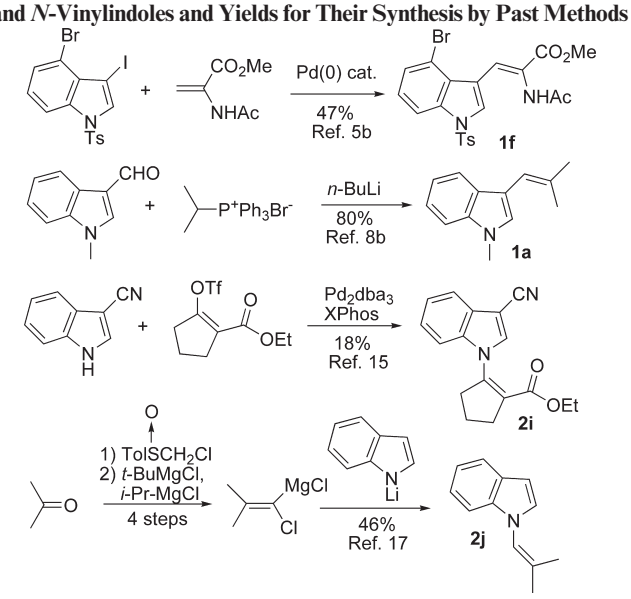
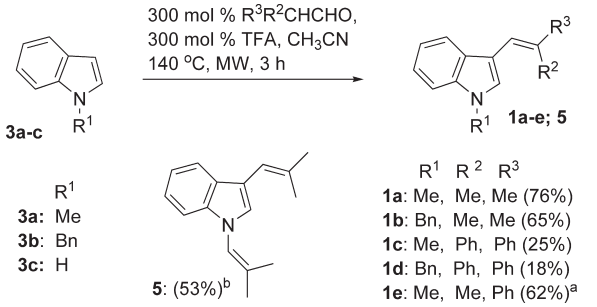
SCHEME 1. Representative Examples of β,β-Disubstituted *C*- and *N*-Vinylindoles and Yields for Their Synthesis by Past Methods



SCHEME 2. Isolated Yields of *C*-Vinylindoles from Microwave Heating of Indole Derivatives and Aldehydes[a,b]



[a] Isolated yields: *E* isomer 53% and *Z* isomer 9%. [b] Performed in neat isobutyraldehyde for 2.5 h.

commercially available indoles and aldehydes in this one-step approach.

Indole was first heated in neat isobutyraldehyde (0.02 M) with TFA (300 mol %) in a sealed tube at 140 °C for 2.5 h using microwave irradiation. 1,3-Divinylindole **5** was isolated as the major product in 53% yield (Scheme 2). Alkenylation on both the N1 and C3 positions was evident from the disappearance of the corresponding protons in the ^{1}H NMR spectrum. 1,3-Divinylindole **5** was similarly the major product in experiments using a decreased amount of TFA (down to 10%), shorter reaction times (down to 1 h), and less aldehyde (110 mol %). 3-*C*- and 1-*N*-vinylindoles were next respectively pursued employing 1- and 3-substituted indoles.

1-Methylindole, isobutyraldehyde, and TFA were heated at 140 °C for 2.5 h using microwave irradiation. Analysis of the crude reaction mixture by LC/MS indicated the formation of both mono- and bis-vinylated derivatives. When the amount of aldehyde was reduced to 300 mol % and toluene was used as the solvent, bisvinylation was avoided and 1-methyl-3-vinylindole **1a** was produced according to the ^{1}H NMR spectrum of the crude reaction mixture; however, **1a** could not be purified from side products that were diminished by replacing toluene with acetonitrile. Heating 1-methyl- and 1-benzylindoles with isobutyraldehyde (300 mol %) and TFA (300 mol %) in CH_3CN for 3 h at 140 °C, followed by chromatography on silica gel, furnished, respectively, 3-vinylindoles **1a** and **1b** in 76% and 65% yields (Scheme 2). Vinylindole **1a** was previously obtained in a comparable yield of 80% by employing a Wittig reaction[8b] (Scheme 1). 1-Phenylsulfonylindole did not react with isobutyraldehyde under our optimized conditions and was recovered, demonstrating the necessity for a nucleophilic pyrrole ring. Vinylindole products were detected by LC/MS and ^{1}H NMR analyses of the condensation products from 1-methylindole with propanal, isovaleryl aldehyde, and phenylacetaldehyde under the same conditions; however, the olefins could not be purified effectively from their complex reaction mixtures. Vinylindoles **1c** and **1d** were also made from condensations of 1-methyl- and 1-benzylindoles with diphenylacetaldehyde, albeit in 25% and 18% yields, due to purification issues with removal of excess aldehyde and an aldehyde derived trimer which coeluted with the products. Attempts to facilitate purification by reducing excess aldehyde to its corresponding alcohol were unsuccessful. 1-Methyl-3-(2-phenylprop-1-enyl)indole **1e** was, however, isolated in a combined yield of 62% by condensation of 1-methylindole with 2-phenylpropionaldehyde. In this case, reduction of excess aldehyde to its corresponding alcohol using $LiBH_4$ proved useful, the *E* (53%) and *Z* (9%) isomers of **1e** were effectively separated by silica gel chromatography. Their structure was determined by NOESY experiments, which showed transfer of magnetization between the protons of the vinylic CH_3 and the indolic proton at position 2 for the *E* isomer, as well as between these protons and the vinylic proton in the case of the *Z* isomer. 1-Methylindole reacted with cyclohexane- and cyclopentanecarboxaldehydes to provide mixtures of the desired 3-vinyl derivative contaminated with a product arising from olefin reduction as ascertained by ^{1}H NMR spectroscopy and LC/MS. The similar retention times of the unsaturated and reduced products hampered isolation of 3-vinyl derivatives by chromatography; however, 3-cylohexyl-1-methylindole **6** was isolated in 21% yield. The vinyl and reduced products ratios were 1:1 and 1:2 for cyclohexane- and cyclopentanecarboxaldehyde, respectively, suggesting ring strain relief may drive reduction. To avoid reduction, variations of the amounts of TFA and aldehyde, the solvent (THF, DMSO), and the acid (TCA) all proved unsuccessful.

N-Vinylation of 3-methylindole was first tried using the optimized conditions for *C*-vinylation, with heating for 1 h; however, incomplete conversion and side products were detected by analysis of the crude product by ^{1}H NMR spectroscopy and LC/MS. Under optimized conditions using 1000 mol % of aldehyde, 3-methylindole was respectively condensed with isobutyraldehyde, diphenylacetaldehyde, and 2-phenylpropionaldehyde to furnish *N*-vinylindoles **2a**−**c** in 40, 64, and 65% yield, respectively (Scheme 3).

Purification of the latter two products from excess aldehyde was easier than that of their *C*-vinyl isomers because of their increased hydrophobicity. In the case of **2c**, reduction of aldehyde to alcohol, as described for **1e**, also facilitated purification, which provided **2c** as a 6:1 mixture of *E*/*Z* isomers as determined by ^{1}H NMR. NOESY experiments showed transfer of magnetization between the protons of the

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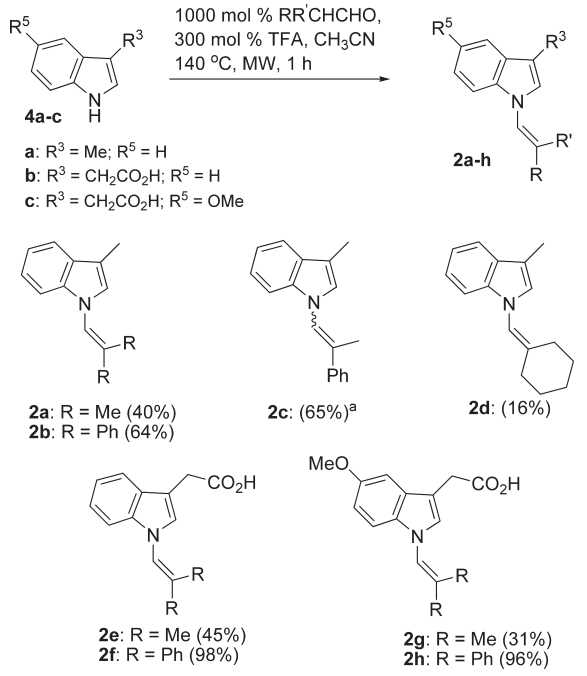
SCHEME 3. Isolated yields of *N*-Vinylindoles from Microwave Heating of Indole Derivatives and Aldehydes[a]



[a] Isolated as a 6:1 mixture of *E*/*Z* isomers.

vinylic CH_3 and the indolic proton at position 2 for the *E* isomer, as well as between these protons and the vinylic proton in the case of the *Z* isomer. 3-Methylindole was similarly treated with cyclohexanecarboxaldehyde to provide the desired *N*-vinyl derivative **2d**, albeit in 16% yield. 3-Methylindole reacted with phenylacetaldehyde and propanal according to ^{1}H NMR and LC/MS analyses; however, vinyl products could not be purified from the reaction mixtures.

The scope of *N*-vinylation was studied on other 3-substituted indole derivatives. Indole-3-acetic acid and 5-methoxyindole-3-acetic acid were respectively treated with isobutyraldehyde and diphenylacetaldehyde to provide *N*-vinylindoles **2e**−**j** in 31−98% yields, demonstrating tolerance of carboxylic acid functionality. Purification of the diphenylacetaldehyde derivatives **2f** and **2h** from excess aldehyde and trimer was facile due to their relative high polarity. Indole-3-carboxaldehyde and isobutyraldehyde failed to react under the condensation conditions, again indicating the importance of pyrrole electron density for reactivity. Crystals of *N*-vinylindole **2b** were grown from EtOAc and examined by X-ray diffraction. To the best of our knowledge, the crystal structure of **2b** represents the first example of a β,β-branched *N*-vinylindole.[19] The olefin bond length (1.34 Å) was in agreement with the typical ethylene bond length (1.32 Å)[20] and in conjugation with the phenyl rings as ascertained from their connecting bond length (1.49 Å) which corresponded with bond lengths in butadiene and biphenyl (1.48 Å).[20]

(19) The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated deposition no. CCDC 717034.

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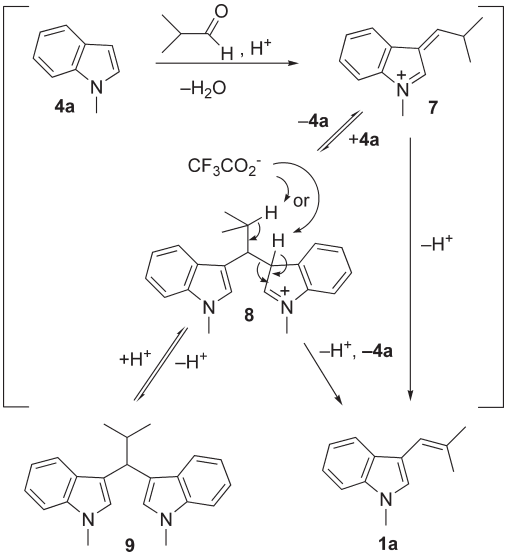
SCHEME 4. Possible Mechanism for 3-Vinylindole Formation



Insight into the mechanism of *C*-vinylation was obtained during optimization studies. Bisindolylalkane **9** formed during production of 3-vinylindole (Scheme 4). On heating 1-methylindole with isobutyraldehyde (300 mol %) and TFA (300 mol %) in toluene at 140 °C for 5, 10, 20, 60, and 120 min, the ^{1}H NMR-determined ratio of 3-vinylindole **1a** and bisindolylalkane **9** changed from 7:3, 8:2, 9:1, 96:4 to 100:0, respectively. Bisindolylalkanes have been reported as typical products of condensations of indoles with aldehydes under various catalytic conditions.[21] This kinetically formed product may arrive from nucleophilic attack of a second indole onto the unsaturated iminium intermediate **7** to provide intermediate **8**, which transforms to **9** by pyrrole proton abstraction and rearomatization (Scheme 4). Intermediate **8** may alternatively eliminate indole to give 3-vinylindole **1a**, which could also be generated directly from intermediate **7**. The amount of TFA was crucial for controlling this equilibrium. Bisindolylalkane **9** was obtained in 72% yield with only a trace amount of **1a** by using 10 mol % of TFA in neat isobutyraldehyde for 10 min. Furthermore, isolation of bisindolylalkane **9** and its retreatment with TFA and heating in toluene for 1 h provided *C*-vinylindole **1a**, bisindolylalkane **9**, and 1-methylindole in a 32:56:12 ratio as determined by ^{1}H NMR analysis. Similarly, temperature played a factor in vinylindole formation. Heating of 1-methylindole, isobutyraldehyde (300 mol %), and TFA (300 mol %) in acetonitrile at reflux for 3 h provided a 43:39:18 mixture of *C*-vinylindole **1a**, bisindolylalkane **9**, and 1-methylindole as ascertained by ^{1}H NMR analysis; similar conditions with microwave heating at 140 °C yielded vinylindole **1a** in 76% yield. Heating the same reagents at lower temperatures of 60 and 110 °C for 3 h under microwave irradiation conditions provided, respectively, bisindolylalkane **9** quantatively and a 1:2.5 mixture of *C*-vinylindole **1a** and bisindolylalkane **9**, as ascertained by ^{1}H NMR analysis, suggesting again the important effect that temperature has on the reaction outcome. Although, in principle, bisindolyl-type products may also be generated in the *N*-vinylation

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reactions, in practice they were not observed. Presumably, the large excess of aldehyde and steric hindrance present prevented this route from occurring. Nor were byproducts arising from other possible mechanisms identified in the *N*-vinylation reactions.

One-step approaches to *C*- and *N*-vinylindoles were respectively developed by acid-catalyzed condensations of alkyl and aryl α-branched aldehydes and indole derivatives. Complementing existing methods, which typically rely on multiple steps, these approaches delivered effectively β,β-disubstituted vinylindole products in one step from commercially available starting materials, expanding the diversity of vinylindole products. Considering the utility of *C*- and *N*-vinylindoles, these reactions offer novel means for furthering their investigations in medicinal chemistry and materials science, respectively.

Experimental Section

Representative Procedure for *C*-Vinylindole Formation: Preparation of 1-Benzyl-3-(2-methylprop-1-enyl)-1*H*-indole (1b). A solution of 1-benzylindole **3b** (0.364 mmol) in acetonitrile (17.84 mL) was placed in a 10−20 mL microwave (MW) flask and was treated with isobutyraldehyde (1.092 mmol, 300 mol %) and 300 mol % of TFA (0.273 mmol, 84 μL). The mixture (0.02 M) was flushed with argon, and the flask was immediately capped and heated to 140 °C using microwave irradiation for 3 h. The crude reaction mixture was diluted with EtOAc and was washed with a saturated solution of $NaHCO_3$. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness to provide a residue that was purified by triethylamine-pretreated silica chromatography using 1% Et_2O in hexanes to furnish 3-vinylindole **1b** as a yellow oil (61.0 mg, 65%): R_f 0.33 (1% EtOAc in hexanes); IR ($CHCl_3$) 3019, 2977, 2931, 1702, 1604, 1523, 1468, 1424, 1335, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (qd, J = 7.7 Hz, J = 0.8 Hz, 1H), 7.38−7.10 (m, 9H), 6.48 (qd, J = 1.2 Hz, J = 1.4 Hz, 1H), 5.36 (s, 2H), 2.03 (d, J = 1.2 Hz, 3H), 1.97 (d, J = 0.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 136.8, 133.5, 129.6, 129.2, 129.1, 128.4, 127.5, 126.9, 122.9, 120.2, 116.5, 114.7, 110.4, 50.9, 27.7, 21.3; HRMS (m/z) calcd for $C_{19}H_{20}N$ $(M + H)^+$ 262.1590, found 262.1586.

Representative Procedure for *N*-Vinylindole Formation: Preparation of 2-(1-(2,2-Diphenylvinyl)-1*H*-indol-3-yl)acetic Acid (2f). A solution of indole **4b** (0.364 mmol) in acetonitrile (17.84 mL) was placed in a 10−20 mL microwave (MW) flask, treated with diphenylacetaldehyde (3.64 mmol, 1000 mol %) and TFA (0.273 mmol, 84 μL, 300 mol %), and flushed with argon. The flask was immediately capped and heated to 140 °C using microwave irradiation for 1 h. The crude reaction mixture was evaporated to dryness and purified by silica chromatography using a gradient of 10−50% EtOAc in hexanes to provide 3-vinylindole **2f** as a beige solid (125.7 mg, 98%): mp 174−175 °C; R_f 0.36 (30% EtOAc in hexanes); IR (KBr) 3052, 2518, 2255, 1948, 1715, 1632, 1494, 1460, 1365, 1231 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.30 (br s, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.59 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.38−7.32 (m, 8H), 7.20−7.12 (m, 4H), 6.59 (s, 1H), 3.46 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3, 140.7, 138.3, 136.4, 129.8, 129.7, 129.0, 128.6, 128.4, 127.9, 127.6, 127.4, 125.3, 122.5, 121.5, 120.5, 119.0, 110.7, 110.6, 30.6; HRMS (m/z) calcd for $C_{24}H_{20}NO_2$ $(M + H)^+$ 354.1489, found 354.1486.

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Supporting Information Available: General experimental methods, copies of ^1H NMR and ^{13}C NMR spectra of compounds **1**, **2**, **5**, **6**, and **9**, selected NOESY correlations expansions for **1e** (*E*), **1e** (*Z*), **2c** (*E*), and **2c** (*Z*), and X-ray structure data of compound **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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