Synthesis of 3-Alkoxyindoles *via* Palladium-Catalyzed Intramolecular Cyclization of N-Alkyl *ortho*-Siloxyallylanilines

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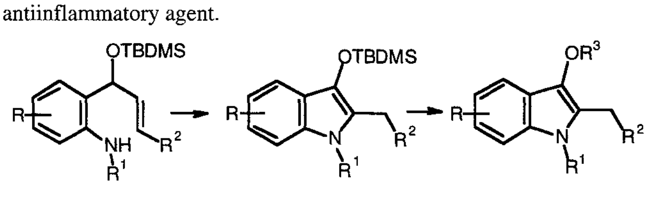
Abstract: Palladium-catalyzed intramolecular cyclization of N-alkyl-*ortho*-siloxyallylaniline leads to the synthesis of N-alkyl-3-siloxyindoles. Treatment of the latter with fluoride followed by *in situ* trapping of the resulting alkoxides with various alkyl halides gives the corresponding N-alkyl-3-alkoxyindoles.

Indoxyl (3-hydroxyindole) derivatives are important natural products. Indican (indoxyl-β-D-glucoside), isolated from various species of *Indigofera* and *Leguminosae*,[1] is the precursor of the blue dye indigo, probably the oldest known coloring agent. Indoxyl derivatives are also found in many pharmaceutical products such as antibacterials,[2] antiasthmatics,[3] antiallergics,[4] antiarthritics,[5] as well as antipsychotics.[6] They are emerging as important pharmacophores. The most general synthesis of indoxyl derivatives is the cyclization of N-(*o*-carboxyphenyl)amino acids to the corresponding stable N,O-diacylindole derivatives.[7] However, alkylation of the anion of indoxyl favors C-alkylation, probably due to the predominance of the keto form of indoxyl.[8] Herein we report an efficient and versatile synthesis of stable indoxyl derivatives based on palladium-catalyzed cyclization of 2-(1-siloxyally)anilines. Removal of the 3-siloxyl protecting group followed by *in situ* trapping of the hydroxyl anion with alkyl halides gives predominantly C-alkylated products (Scheme 1). The method has been applied to the synthesis of N-benzylindol-3-oxyacetic acid, a potential antiinflammatory agent.



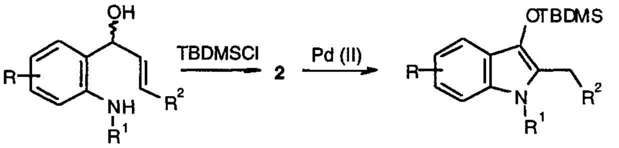
2 3 4

Scheme 1

Palladium-catalyzed intramolecular cyclization of 2-allylaniline derivatives to indoles are well documented,[9] but palladium-assisted cyclization of 2-(1-hydroxyallyl)anilines to indoxyls is not known. Recently we reported the synthesis of various substituted 2-(1-hydroxyallyl)anilines **1** as *o*-quinone methide imine precursors,[10] and we were interested to see if they can also serve as precursors to indoxyl derivatives. Attempts to cyclize these compounds to indoxyls in the presence of various palladium catalysts failed to give any desired products, and only intractable materials were recovered. However, the *t*-butyldimethylsilyloxyl derivatives of these compounds cyclized readily to the corresponding 3-siloxyindoles in the presence of $PdCl_2(CH_3CN)_2$ either stoichiometrically or catalytically.

The starting materials, 2-(1-hydroxyallyl)anilines **1**, were prepared according to our reported procedures.[10] Silylation of the allylic alcohols was selective and was achieved with 1.5 equivalents of *t*-butyldimethylsilyl chloride in dichloromethane in the presence of 1 equivalent each of triethylamine and 4-N,N-dimethylaminopyridine at r.t. over a 24 h period. The results are summarized in Table 1.

Table 1. Preparation of 3-siloxyindoles



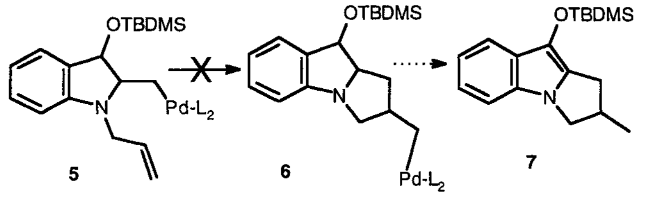
1 3

	R	R¹	R²	Product	Yield (%)[a] Stoichiometric[b]		Catalytic[c]
1a	H	Me	H	**2a**	74	**3a** 93	77
1b	H	Me	Me	**2b**	55	**3b** 55	50[d,e]
1c	H	Me	Ph	**2c**	59	**3c** 76	47[d]
1d	4-OMe	CH_2(4-BrPh)	H	**2d**	84	**3d** ---	84
1e	H		H	**2e**	53	**3e** 54	54[d]

[a]Yields of isolated product; [b]1.5 equiv Pd(II), 8 equiv Et_3N, 25 °C in THF; [c]10-20 nol% Pd(II), 1.5 equiv benzoquinone, 3 equiv K_2CO_3, 25 °C in THF; [d]10 equiv LiCl resent; [e]reaction at 85 °C.

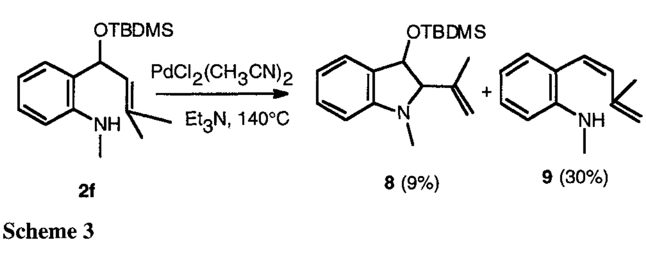
The cyclization of the 2-(1-*t*-butyldimethylsiloxyallyl)anilines **2** under stoichiometric conditions was typically performed with 15 mmol of $PdCl_2(CH_3CN)_2$, 10 mmol of **2**, 80 mmol of triethylamine in 300 ml of THF at r.t. over a period of 24 h. The catalytic reaction was performed using only 10-20 mol% of $PdCl_2(CH_3CN)_2$, 1.5 equivalents of benzoquinone as reoxidant and 3 equivalents of Na_2CO_3 or K_2CO_3, with or without LiCl in THF. Thus 1-(2-methylamino)-phenyl-1-*t*-butyldimethylsiloxy-prop-2-ene **2a** cyclized under stoichiometric conditions to 1,2-dimethyl-3-(*t*-butyldimethylsiloxy)indole **3a** in 93% yield. The same product was obtained in 77% yield under catalytic conditions with 10 mol% palladium at r.t. (Table 1). In contrast to the palladium-catalyzed cyclization of 2-(2-butenyl)aniline,[9] the analogous 1-(2-methylamino)-phenyl-1-*t*-butyldimethylsiloxy-but-2-ene **2b** cyclized under stoichiometric condition to the corresponding indole **3b** in 55% yield, with no trace of any six-membered ring product. However, no reaction was observed when **2b** was treated under the same catalytic conditions as described for **2a**. In the presence of 10 equiv of LiCl,[9] **2b** cyclized at 85°C to give **3b** in 50% yield. The reaction was very slow with 10 mol% of palladium but was completed in 4.5 h when 20 mol% of palladium was used. With compound **2c**, the formation of a six membered ring was expected, since attack of the nitrogen presumably would occur at the more stable benzylic cationic site. However, only the five-membered ring indoxyl derivative **3c** was obtained under both stoichiometric (76%) and catalytic conditions (47%). In contrast to **2b**, compound **2c** cyclized at r.t. under catalytic conditions (in the presence of LiCl) even though it required 120 h for the reaction to go to completion. The N-benzyl derivative **2d** cyclized under catalytic conditions (without LiCl) at r.t. to give the corresponding 3-siloxyindole derivative **3d** in 84% yield.

ortho-Allylacrylanilide has been reported to undergo palladium-catalyzed tandem cyclization to give a bicyclic indole derivative.[9b,9c] The N-allyl compound **2e** was designed to mimic this process (Scheme 2). It was hoped that the the palladium intermediate **5** that formed after the initial cyclization of **2e** would continue to cyclize with the olefin of the allyl substituent to give compound **7**. However, only the monocyclized product **3e** was obtained in 54% yield under both stoichiometric and catalytic conditions (Table 1).

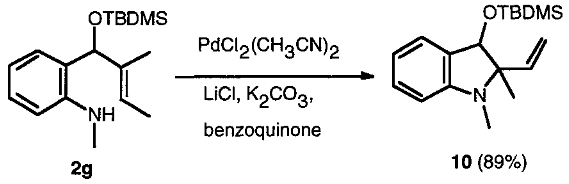


Scheme 2

The effect of a trisubstituted olefin on the palladium-catalyzed cyclization was also studied. Compound **2f** is expected to cyclize to the terminus (tertiary center) of the olefin to give a six-membered ring. No reaction was observed under normal stoichiometric condition. At 140 °C in a sealed tube, compound **2f** gave a 9% yield of 1-methyl-2-(1-methylethenyl)-3-(*t*-butyldimethylsiloxy)indoline **8** and 30% of 1-(2-methylamino)-phenyl-3-methylbuta-1,3-diene **9**, without any six-membered ring product (Scheme 3). For the other trisubstituted olefin **2g**, no reaction occurred at r.t. under normal stoichiometric condition, but at 70 °C only elimination products were observed. In the presence of 10 equivalents of LiCl, however, **2g** cyclized under catalytic conditions at 85 °C to 1,2-dimethyl-2-ethenyl-3-(*t*-butyldimethylsiloxy)-indoline **10** in 89% yield (Scheme 4).



Scheme 3

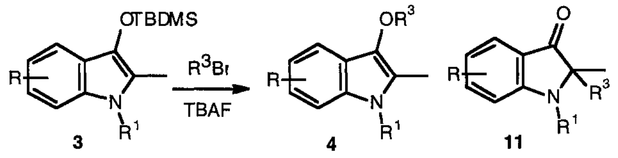


Scheme 4

In connection with our study of N-benzylindol-3-alkanoic acids as potent antiinflammmatory agents,[11] we wished to investigate the analogous 3-oxyalkanoic acid derivatives for their potential antiinflammatory activities. The palladium-catalyzed indoxyl synthesis described above seemed to provide a novel approach to the preparation of such compounds. Alkylation of the anion of indoxyl is known to favor C-alkylation,[8] however, we hoped that in situ trapping of the hydroxyl anion resulting from desilylation of compound **3** would predominantly give the O-alkylated product. When compound **3a** was treated with tetra-*n*-butylammonium fluoride in THF in the presence of methyl bromoacetate, the 3-alkoxy derivative **4a** was isolated in 77% yield with only traces of the corresponding C-alkylated product (Table 2). Similarly, desilylation of compound **3d**, followed by trapping with MeI, or methyl bromoacetate gave the corresponding indoxyl derivatives **4b** and **4c**, in 81% and 90% yield respectively. Compared to the reported synthesis of the desbromo analog of **4c**,[8c] the current method provides a more efficient alternative.

In summary, we have demonstrated that N-alkyl-3-siloxyindoles can be prepared readily from aniline via palladium-catalyzed cyclization of N-alkyl-2-(1-*t*-butyldimethylsiloxyallyl)anilines. The 3-siloxyindoles can be selectively converted to 3-alkoxyindoles and this latter method was applied to the synthesis of a potential antiinflammatory agent.

Table 2. Preparation of 3-alkoxyindoles



	R	R^1	R^3	Products		Yield %	
3a	H	Me	CH_2CO_2Me	**4a**	77	**11a**	trace
3d	4-OMe	CH_2(4-BrPh)	Me	**4b**	81	**11b**	14
3d	4-OMe	CH_2(4-BrPh)	CH_2CO_2Me	**4c**	90	--	--

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12. Typical procedure for the stoichiometric palladium-assisted cyclization reaction: To a degassed solution of bis(acetonitrile)-palladium (II) chloride (15 mmol) in THF (250 ml) was added under nitrogen, a degassed solution of **2a** (10 mmol) and triethylamine (80 mmol) in THF (50 ml). The mixture was stirred at r.t. for 22 h. THF was evaporated under vacuum, the reaction mixture was dissolved in Et_2O and passed over a short pad of neutral alumina. The crude material, after evaporation of solvent, was distilled, to give 2.56g (93%) of **3a** as a solid; mp 80-82 °C; ^{1}H NMR (300 MHz, CD_3COCD_3); δ 0.18 (s, 6H, Si(C$\underline{H}_3$)$_2$), 1.10 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 2.35 (s, 3H, C$\underline{H}_3$-C=), 3.61 (s, 3H, N-methyl), 6.94 (m, 1H), 7.05 (m, 1H), 7.25 (d, 1H, J=7.8 Hz), 7.40 (d, 1H, J=7.8 Hz); ^{13}C NMR (100.6 MHz, CD_3COCD_3); δ -4.1, 9.2, 18.6, 26.1, 29.7, 109.3, 117.4, 118.7, 121.1, 122.2, 122.8, 130.8, 134.7; Anal. calcd. for $C_{16}H_{25}NOSi$: C 69.77, H 9.16, N 5.09; found: C 70.20, H 9.18, N 5.02.

13. Typical procedure for the catalytic palladium-assisted cyclization reaction: To a degassed suspension of K_2CO_3 (414 mg, 3 mmol), benzoquinone (162 mg, 1.5 mmol), bis(acetonitrile)palladium (II) chloride (52 mg, 0.2 mmol) in THF (10 ml) was added under nitrogen, a degassed solution of **2c** (462 mg, 10 mmol) in THF (5 ml). The mixture was stirred at r.t. for 22 h. THF was evaporated under vaccum, the reaction mixture was dissolved in Et_2O and chromatographed on silica gel to give 389 mg of **3d** (84%). ^{1}H NMR (400 MHz, CD_3COCD_3); δ 0.18 (s, 6H), 1.09 (s, 9H), 2.27 (s, 3H), 3.78 (s, 3H, OMe), 5.30 (s, 2H, C$\underline{H}_2$Ph), 6.68 (dd, 1H, J = 8.8, 2.5 Hz), 6.87 (d, 1H), 6.93 (d, 1H, J = 2.4 Hz), 7.15 (d, 1H, J = 8.8 Hz), 7.44 (dd, 2H, J = 6.6, 1.8 Hz); ^{13}C NMR (100.6 MHz, CD_3COCD_3); δ 0.2, 5.8, 13.5, 22.9, 30.4, 50.4, 59.8, 104.0, 114.9, 115.7, 125.2, 127.0, 127.8, 133.0, 134.1, 135.7, 136.5, 143.5, 158.7. Anal. calcd. for $C_{23}H_{30}BrNO_2Si$: C 59.99, H 6.57, N 3.04; found: C 59.89, H 6.73, N 2.99.

14. Typical procedure for the preparation of 3-alkoxy indoles: To a degassed solution of **3d** (100 mg, 0.22 mmol) and methyl bromoacetate (83 mg, 0.54 mmol) in THF (3 mL) was added a solution of n-Bu_4NF (0.33mmol) in THF (1M). The mixture was stirred at r.t. for 22h. Aqueous NH_4Cl was added, the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to an oil. Chromatography on silica gel (eluted with 15% EtOAc/Hexane) gave 88 mg of **4c** (90%). ^{1}H NMR (400 MHz, CD_3COCD_3); δ 2.34 (s, 3H), 3.71 (s, 3H), 3.80 (s, 3H), 4.68 (s, 2H), 5.32 (s, 2H), 6.69 (dd, 1H, J = 8.8, 2.5 Hz), 6.92 (d, 1H, J = 8.5 Hz), 7.10 (d, 2H, J = 2.4 Hz), 7.18 (d, 1H, J = 8.8 Hz), 7.45 (d, 2H, J = 8.4 Hz). ^{13}C NMR (100.6 MHz, CD_3COCD_3); δ 5.7, 13.2, 50.4, 55.9, 60.0, 75.5, 103.8, 115.2, 115.9, 125.3, 125.9, 130.9, 133.2, 134.0, 136.5, 139.9, 143.2. 159.1, 174.9. Anal. calcd. for $C_{20}H_{20}BrNO_4$: C 57.43, H 4.82, N 3.35; found: C 57.01, H 4.98, N 3.23.