Synthesis of Indoles via Diethylzinc-Mediated Intramolecular Hydroamination Reactions of Alkynyl Sulfonamides

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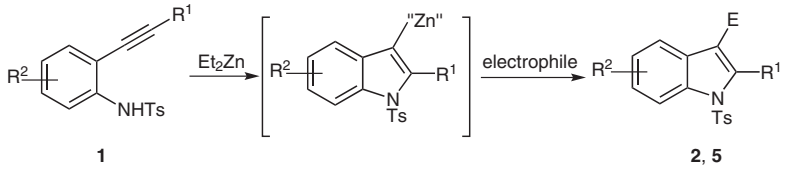
Abstract: A series of indole derivatives were synthesized through the intramolecular hydroamination of alkynyl sulfonamides using 20 mol% of diethylzinc as the catalyst. A tandem cyclization–nucleophilic addition reaction was also possible to afford C2,C3-disubstituted indoles using 120 mol% of diethylzinc.

Key words: diethylzinc, intramolecular hydroamination, alkynyl sulfonamides, cyclizations, tandem reactions



1 2, 5

Scheme 1

Introduction

The synthesis of nitrogen-containing heterocycles such as indoles has been one of the most active areas in organic chemistry due to their extensive existence in a great number of biologically active compounds.[1] Among the numerous methods for the preparation of these azaheterocycles,[2] the intramolecular hydroamination reaction represents a highly atom-economic way and many kinds of catalysts have been developed for this transformation.[3] Recently, as a continuation of their pioneering work in zinc-mediated cyclization of 2-ynylphenol or -aniline, Nakamura and coworkers have developed a novel tandem cyclization/nucleophilic addition procedure of *N*-benzyl-protected alkynylanilines with electrophiles to form indole derivatives mediated by one equivalent of *n*-BuLi, $ZnCl_2$, $[Pd_2(dba)_3]$ (cat.) or *n*-BuLi, $ZnCl_2$, CuCN·2LiCl.[4]

Our group has demonstrated that the use of alkynyl sulfonamides bearing a more acidic NH permits the use of diethylzinc instead of the more basic *n*-butyllithium.[5] The use of this weaker base allows for the generation of a sufficiently nucleophilic nitrogen anion for cyclization, while conceding for a broader functional group tolerance. Moreover, a catalytic amount of diethylzinc was found to be able to catalyze the cyclization reaction and when an excess of diethylzinc was used, the resulting indole zinc salt intermediate could undergo reactions with acid chloride or halides to form C2,C3-disubstituted indoles. Notably, the choice of sulfonyl groups as the protecting group was crucial to effect such a cyclization process and the use of unprotected primary amine or acyl-protected substrates all failed in this transformation.[5]

Scope and Limitations

Firstly, a series of 4-substituted 2-ethynyl-*N*-tosylanilines were prepared and studied in the cyclization reaction with 20 mol% of diethylzinc in toluene (Scheme 1, Table 1). In general, both the substrates with electron-withdrawing or electron-donating groups could provide the desired indole derivative products in excellent yields, while a shorter reaction time was observed for the electron-withdrawing ones (Table 1, entries 3–7). It was found that both halogen and nitro group were well tolerated in the reaction. In addition, compounds with alkyl and functionalized alkyl substituents on the acetylene terminal (R^1) were also tested under similar reaction conditions and the corresponding indole products could also be obtained in high yields (Table 1, entries 8–11). Unfortunately, when the substituent was TMS, the cyclization was inhibited completely, affording only the deprotected aniline **1i** after 24 hours (**1l**/**1i** = 6:1) (Table 1, entry 12). [6]

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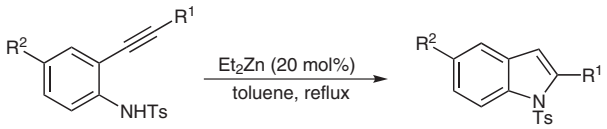
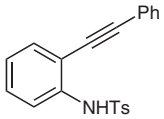
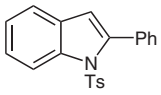
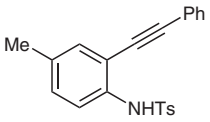
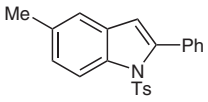
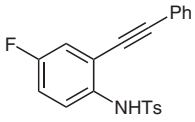
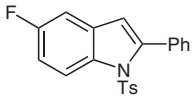
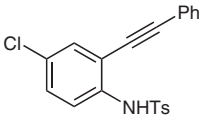
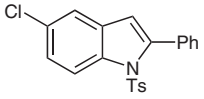
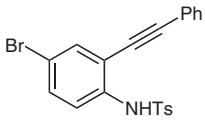
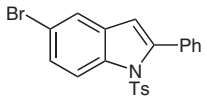
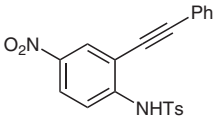
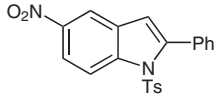
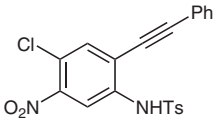
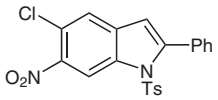
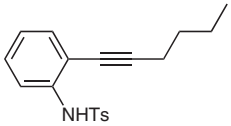
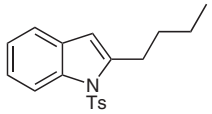
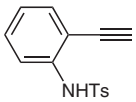
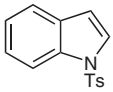
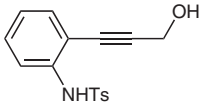
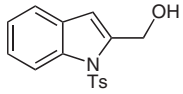
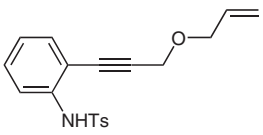
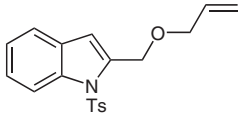
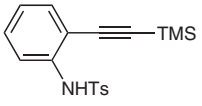
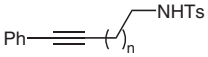
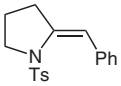
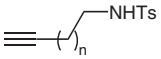
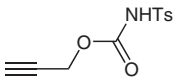
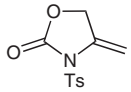
Table 1 Cyclization of a Series of 2-Ethynyl-*N*-Sulfonylanilines[a]



Entry	Substrate	Product	Time (h)	Yield (%)[b]
1	**1a** 	**2a** 	3	98
2	**1b** 	**2b** 	4	90
3	**1c** 	**2c** 	2.5	93
4	**1d** 	**2d** 	2.5	92
5	**1e** 	**2e** 	2.5	92
6	**1f** 	**2f** 	2	94
7	**1g** 	**2g** 	2	93
8	**1h** 	**2h** 	3	95
9	**1i** 	**2i** 	3	97
10	**1j** 	**2j** 	3	98
11	**1k** 	**2k** 	3	82
12	**1l** 	–[c] **1l** + **1i** (6:1)[d]	3 24	–

[a] Reaction conditions: amines (0.3 mmol), Et_2Zn (0.06 mmol), toluene (6 mL).
[b] Yields of isolated products after flash chromatography.
[c] Unreacted **1l** was recovered.
[d] The ratio of **1l** to **1i** was determined by ^1H NMR spectroscopic analysis.

Table 2 Cyclization of Aliphatic Alkynyl Amines[a]

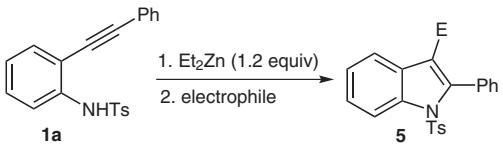
Entry	Substrate		Catalyst loading (mol%)	Product	Time (h)	Yield (%)[b]
1		**3a** n = 1	120	–[c]	12	–[c]
2		**3b** n = 2	120		12	63[d]
3		**3c** n = 1	20		3	93
4		**3d** n = 2	120	–[e]	12	–[e]
5		**3e**	20		3	95

[a] Reaction conditions: amines (0.3 mmol), Et_2Zn (as indicated in Table 2), toluene (6 mL).
[b] Yield of isolated products after flash chromatography.
[c] Compound **3a** was recovered.
[d] Recovered **3b** = 33%.
[e] Recovered **3d** = 89%.

Next, a series of *N*-tosyl-protected aliphatic aminoalkynes were also investigated under similar reaction conditions to further evaluate the substrate scope (Table 2). It was found that the results were highly susceptible to the structural variations of the substrates. Although the δ-alkynylamine **3b** and 2-propynyl *N*-tosylcarbamate (**3e**) underwent the 5-*exo*-dig cyclization smoothly to give the corresponding cyclized products (Table 2, entries 2 and 5), alkyne **3c** was transformed to 2,3-dihydropyrrole in high yields through a 5-*endo*-dig cyclization favored by Baldwin rules (Table 2, entry 3).[7] Disappointingly, substrates **3a** and **3d** with different alkyl chain length failed to cyclize even under prolonged reaction time in the presence of 1.2 equivalents of diethylzinc (Table 2, entries 1 and 4).

Subsequently, it was found that when substrate **1a** was treated with 120 mol% of diethylzinc and the reaction was quenched with D_2O, 96.8% deuterium incorporation at the C3 position of indole was observed, which was in support of the existence of a reactive zinc salt intermediate that could serve as a useful intermediate to synthesize polyfunctional indoles.[8] After completion of the cyclization step, several acid chlorides were introduced into the reaction system to give the desired 3-acylindoles in good yields (Scheme 1, Table 3, entries 1–6). In addition, 3-

Table 3 Tandem Cyclization–Nucleophilic Addition[a]



1a **5**

Entry	Electrophile	Product	Time (h)[b]	Yield (%)[c]
1	acryloyl chloride	**5a**	2	85
2	PhCOCl	**5b**	2	90
3	2-furoyl chloride	**5c**	2	86
4	EtCOCl	**5d**	2	89
5	cyclopropanecarboxylic acid chloride	**5e**	2	88
6	pivaloyl chloride	**5f**	2	90
7	NBS	**5g**	1	65

[a] All reactions were performed in refluxing toluene for 3 h with amines (0.3 mmol) and Et_2Zn (0.36 mmol), then the reaction systems were cooled to r.t. and the corresponding acid chloride (0.36 mmol) was added.
[b] Reaction time of sequent nucleophilic addition reaction.
[c] Isolated yield after flash chromatography.

bromo-2-phenylindole derivative **5g** could also be obtained with NBS as the electrophile in moderate yield (Table 3, entry 7). Control experiments demonstrated that **2a**, the isolated cyclized product of **1a**, failed to react with benzoyl chloride to give the acylated product **5b** in the absence or presence of diethylzinc at room temperature. Thus these acylation transformations may only be explained by a tandem cyclization–nucleophilic process. The method thus provides a new entry into the present methods[9] of introducing substitution at the C3-position of indoles.

In summary, we have developed a novel and efficient procedure for the intramolecular hydroamination of alkynyl sulfonamides to form nitrogen-containing heterocycles and a tandem cyclization–nucleophilic addition reaction of 2-phenylethynyl sulfonamide with electrophiles to give the corresponding C2,C3-disubstituted indoles in high yields mediated by diethylzinc.

Procedures

^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively) with TMS as an internal standard. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. IR spectra (KBr) were recorded on a PerkinElmer PE 1759 FT-IR spectrometer in the range of 400–4000 cm^{-1}. MS spectra were measured using the EI (70 eV) or ESI method of ionization. Melting points are uncorrected. Petroleum ether (PE) used had bp range 60–90 °C.

5-Chloro-6-nitro-2-phenyl-1-(toluene-4-sulfonyl)indole (2h); Typical Procedure

Et_2Zn (0.06 mmol, 1.0 M in hexanes) was added to a solution of sulfonamide **1h** (128 mg, 0.3 mmol) in anhyd toluene (6 mL). The mixture was stirred at reflux for 2 h, cooled to r.t., and quenched with aq sat. NH_4Cl (2 mL). The mixture was extracted with Et_2O (3 × 25 mL), and the combined Et_2O layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. Purification of the crude product by silica gel column chromatography (8% EtOAc in PE) afforded **2h** (119 mg, 93%) as a yellow solid; mp 174–175 °C; R_f = 0.52 (EtOAc–PE, 10:90).

IR (KBr): 2925, 1738, 1527, 1448, 1380, 1177, 1089, 661, 582 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.92 (s, 1 H), 7.60–7.44 (m, 6 H), 7.26–7.09 (m, 4 H), 6.54 (s, 1 H), 2.33 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.8, 137.5, 137.0, 135.9, 134.4, 129.7, 129.1, 127.3, 126.9, 126.4, 124.6, 123.4, 120.9, 117.4, 114.4, 111.0, 21.6.

MS (ESI): *m*/*z* = 427.0 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{15}ClN_2O_4S$: C, 59.09; H, 3.54; N, 6.56. Found: C, 59.24; H, 3.59; N, 6.40.

Phenyl[2-phenyl-1-(toluene-4-sulfonyl)indol-3-yl]methanone (5b); Typical Procedure

Et_2Zn (0.36 mmol) was added to a solution of **1a** (104 mg, 0.3 mmol) in anhyd toluene (6 mL). The mixture was stirred at reflux for 3 h. At the end of the reaction, the mixture was cooled to r.t. and anhyd benzoyl chloride (51 mg, 0.36 mmol) was added. At the end of the nucleophilic addition reaction, the mixture was quenched with aq sat. NH_4Cl (2 mL). The mixture was extracted with Et_2O (3 × 25 mL), the combined Et_2O layers were dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude product by silica gel column chromatography (10% EtOAc in PE) afforded **5b** as a white solid; yield: 122 mg (90%); mp 194–195 °C; R_f = 0.44 (EtOAc–PE, 10:90).

IR (KBr): 3074, 2919, 1701, 1442, 1361, 1254, 1172, 1084, 751, 710, 581 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98–7.95 (m, 2 H), 7.78–7.75 (m, 1 H), 7.42–7.40 (m, 3 H), 7.32–7.26 (m, 6 H), 7.13–7.07 (m, 6 H), 2.09 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7, 144.8, 138.7, 136.2, 134.3, 132.8, 132.6, 131.5, 131.3, 130.1, 129.2, 129.1, 129.0, 128.8, 128.7, 128.1, 127.6, 123.7, 122.1, 95.1, 85.4, 21.4.

MS (ESI): *m*/*z* = 452.2 $[M + H]^+$.

Anal. Calcd for $C_{28}H_{21}NO_3S$: C, 74.48; H, 4.69; N, 3.10. Found: C, 74.57; H, 4.88; N, 2.95.

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