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New synthesis of 3-substituted indoles using lithium trimethylsilyldiazomethane

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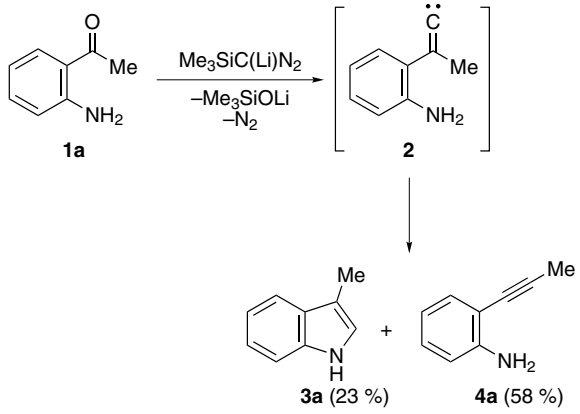
Abstract—Lithium trimethylsilyldiazomethane smoothly reacted with *N*-tosyl-*o*-acylanilines to give 3-substituted indoles in good to high yields.

Indoles have a wide spectrum of biological activities.[1] A large number of methods for the construction of the indole nucleus have been reported.[2] Among them, the base-[3a–c] or Lewis acid-[3d] mediated, and transition-metal-catalyzed[3e–i] cyclization of *o*-ethynylaniline derivatives is one of the most useful methods. However, there is still strong demand for new, versatile, and efficient methods for the construction of the indole nucleus.

We have already demonstrated that the lithium salt of trimethylsilyldiazomethane ($TMSC(Li)N_2$), prepared from trimethylsilyldiazomethane ($TMSCHN_2$) with *n*-butyllithium (*n*-BuLi) or lithium diisopropylamide (LDA), is quite useful as a reagent for generating alkylidene carbenes from carbonyl compounds.[4] For example, $TMSC(Li)N_2$ smoothly reacts with β-amino ketones to give 2-pyrrolines, the intramolecular N–H insertion product, via alkylidene carbene intermediates in good yields.[5] We thought that this reaction would be applicable to the synthesis of 3-substituted indoles if *o*-acylanilines were used as substrates. In fact, treatment of $TMSC(Li)N_2$ with *o*-aminoacetophenone **1a** in THF gave the desired 3-methylindole **3a** in 23% yield, but the major product was *o*-(1-propynyl)aniline **4a**[6] (58%) via the alkylidene carbene intermediate **2** (Scheme 1). However, protection of the amino group of **1a** with tosyl chloride led to a significant improvement of the yield.



Scheme 1.

Thus, we found that *N*-tosyl-*o*-acylanilines **1** smoothly reacted with $TMSC(Li)N_2$ in THF at −78 °C for 1 h and then at room temperature for 1 h to give the corresponding 3-substituted *N*-tosylindoles **3** in good to high yields (Scheme 2).[7] The scope of the new synthesis of 3-substituted *N*-tosylindoles is summarized in Table 1.[8] *N*-tosyl-*o*-acylanilines bearing various R^1 groups such as alkyl, aryl, and heteroaryl groups were smoothly converted to the corresponding 3-substituted *N*-tosylindoles **3** (entries 1 and 5–10). In some cases, the alkynes **4** were also formed as by-products. Analogously, the *N*-methanesulfonyl derivative **1c** afforded the desired indole **3c** in 70% yield (entry 2). In the case of the *N*-Boc derivative **1d**, the product was a mixture of the corresponding **3d** (48%) and the alkyne **4d** (28%) with low selectivity (entry 3). Moreover, although the *N*-acetyl derivative

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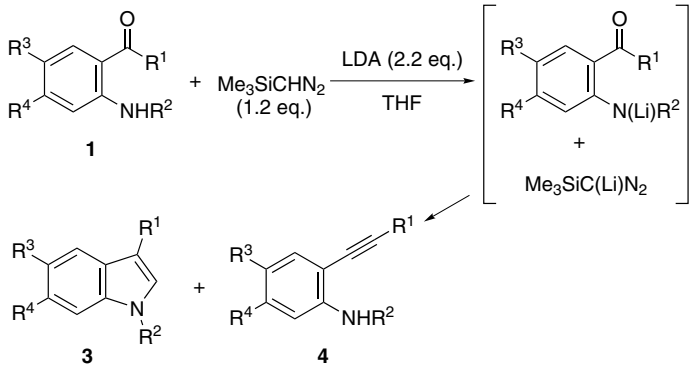

Scheme 2.

Table 1. Preparation of 3-substituted *N*-tosylindoles

Entry	Substrate	R^1	R^2	R^3	R^4	Conditions	Yield (%)
1[a]	**1b**	Me	Ts	H	H	−78 °C, 1 h→rt, 1 h	81 (**3b**)+8 (**4b**)
2	**1c**	Me	Ms	H	H	−78 °C, 1 h→rt, 2 h	70 (**3c**)+10 (**4c**)
3[b]	**1d**	Me	Boc	H	H	−78 °C, 1 h→rt, 2 h	48 (**3d**)+28 (**4d**)
4[b]	**1e**	Me	Ac	H	H	−78 °C, 1 h→0 °C, 5 h	—[c] (**3e**)+46 (**4e**)
5	**1f**	Me	Ts	–OCH_2O–		−78 °C, 1 h→rt, 1.5 h	78 (**3f**)+nd[d] (**4f**)
6	**1g**	*n*-Bu	Ts	H	H	−78 °C, 1 h→rt, 1 h	68 (**3g**)+29 (**4g**)
7	**1h**	Ph	Ts	H	H	−78 °C, 1 h→rt, 1 h	91 (**3h**)+nd[d] (**4h**)
8	**1i**	Ph	Ts	Cl	H	−78 °C, 1 h→rt, 1 h	87 (**3i**)+nd[d] (**4i**)
9	**1j**	2-Furyl	Ts	H	H	−78 °C, 1 h→rt, 1 h	63 (**3j**)+30 (**4j**)
10	**1k**	2-Pyridyl	Ts	H	H	−78 °C, 1 h→rt, 1 h	64 (**3k**)+nd[d] (**4k**)
11	**1l**	H	Ts	H	H	−78 °C, 1 h→rt, 1 h	85 (**3l**)+nd[d] (**4l**)
12	**1m**	H	Ts	–CH=CHCH=CH–		−78 °C, 1 h→rt, 1 h	79 (**3m**)+nd[d] (**4m**)

[a] **3b** (78%) and **4b** (8%) were obtained when *n*-BuLi was used as a base.
[b] Me_3SiCHN_2 (2 equiv) and *n*-BuLi (2 equiv) were used.
[c] 3-Methylindole **3a** (21 %) was obtained and **3e** could not be detected.
[d] Not detected.

1e also reacted with $TMSC(Li)N_2$ to give the indole **3a** (21%), formed by hydrolysis of the first produced *N*-acetylindole during work-up, the major product was the alkyne **4e** (46%) (entry 4). It is known that hydrogen has a high migratory aptitude for alkylidene carbene rearrangement giving alkynes.[6,9] Interestingly, however, the aldehydes **1l** and **1m** preferentially gave the corresponding indoles **3l** and **3m** in high yields, respectively, and no alkynes could be detected (entries 11 and 12). In these reactions, THF was found to be the reaction solvent of choice. No reaction occurred under the above reaction conditions when Et_2O was used as a solvent because of the poor solubility of substrates. Both LDA and *n*-BuLi could be used as a base. The tosyl group of **3** can be easily removed with 10% aqueous sodium hydroxide in refluxing ethanol to give 3-substituted indoles.[10]

In conclusion, the present method using $TMSCHN_2$ makes possible the efficient conversion of *N*-tosyl-*o*-acylanilines[11] into 3-substituted indoles and will provide added flexibility in indole synthesis.

Acknowledgements

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7. Representative procedure (entry 1 in Table 1): To a solution of LDA, prepared from diisopropylamine (111 mg, 1.1 mmol) and *n*-BuLi (1.59 M in hexane, 0.69 mL, 1.1 mmol) in THF (5 mL), was added dropwise $TMSCHN_2$ (1.61 M in hexane, 0.37 mL, 0.6 mmol) at −78 °C under N_2, and the mixture was stirred at 78 °C for 20 min. A solution of *o*-(*N*-tosylamino)acetophenone (145 mg, 0.5 mmol) in THF (5 mL) was then added to the above mixture at −78 °C. The mixture was stirred at −78 °C for 1 h and then at room temperature for 1 h. After the reaction was quenched with water, the mixture was extracted with AcOEt. The organic extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (Fuji Silysia, PQS 60B, hexane–AcOEt = 15:1) to give **3b** (116 mg, 81%) and **4b** (12 mg, 8%). **3b**: mp 108–109 °C (AcOEt–hexane) (lit.[12] mp 104–106 °C). **4b**: ^1H ($CDCl_3$): δ 2.06 (3H, s), 2.37 (3H, s), 6.94–7.00 (1H, m), 7.17–7.24 (4H, m), 7.53 (1H, d, J = 8 Hz), 7.67 (2H, d, J = 8 Hz). HRMS (EI): Calcd for $C_{16}H_{15}NO_2S$, 285.0823. Found, 285.0816.
8. **3c**: Ref. 13. **4c**: ^1H ($CDCl_3$): δ 2.13 (3H, s), 3.00 (3H, s), 7.02 (1H, br s), 7.06–7.11 (1H, m), 7.27–7.33 (1H, m), 7.40 (1H, d, J = 8 Hz), 7.56 (1H, d, J = 8 Hz). HRMS (EI): Calcd for $C_{10}H_{11}NO_2S$, 209.0510. Found, 209.0513. **3d**: Ref. 14. **4d**: ^1H ($CDCl_3$): δ 1.54 (9H, s), 2.15 (3H, s), 6.89–6.95 (1H, m), 7.22–7.27 (1H, m), 7.32 (1H, d, J = 8 Hz), 8.10 (1H, d, J = 8 Hz). HRMS (EI): Calcd for $C_{14}H_{17}NO_2$, 231.1259. Found, 231.1259. **4e**: ^1H ($CDCl_3$): δ 2.16 (3H, s), 2.23 (3H, s), 6.97–7,03 (1H, m), 7.25–7.31 (1H, m), 7.35 (1H, d, J = 8 Hz), 7.91 (1H, br s), 8.36 (1H, d, J = 8 Hz). HRMS (EI): Calcd for $C_{11}H_{11}NO$, 173.0841. Found, 173.085. **3f**: ^1H ($CDCl_3$): δ 2.15 (3H, s), 2.34 (3H, s), 5.96 (2H, s), 6.78 (1H, s), 7.21 (2H, d, J = 8 Hz), 7.49 (1H, s), 7.70 (2H, d, J = 8 Hz). HRMS (EI): Calcd for $C_{17}H_{15}NO_4S$, 329.0722. Found, 329.0716. **3g**: ^1H ($CDCl_3$): δ 0.93 (3H, t, J = 7 Hz), 1.30–1.44 (2H, m), 1.60–1.71 (2H, m), 2.32 (3H, s), 2.64 (2H, t, J = 8 Hz), 7.18 (2H, d, J = 8 Hz), 7.21–7.29 (3H, m), 7.46 (1H, d, J = 7 Hz), 7.72 (2H, d, J = 8 Hz), 7.97 (1H, d, J = 8 Hz). HRMS (EI): Calcd for $C_{19}H_{21}NO_2S$, 327.1293. Found, 327.1292. **4g**: ^1H ($CDCl_3$): δ 0.93 (3H, t, J = 7 Hz), 1.37–1.63 (4H, m), 2.36 (3H, s), 2.39–2.44 (2H, m), 6.94–7.00 (1H, m), 7.18–7.27 (4H, m), 7.56 (1H, d, J = 8 Hz), 7.65 (2H, d, J = 8 Hz). HRMS (EI): Calcd for $C_{19}H_{21}NO_2S$, 327.1293. Found, 327.1287. **3h**: ^1H ($CDCl_3$): δ 2.34 (3H, s), 7.22 (2H, d, J = 8 Hz), 7.29 (1H, d, J = 8 Hz), 7.33–7.39 (2H, m), 7.43–7.49 (2H, m), 7.60 (2H, d, J = 8 Hz), 7.69 (1H, s), 7.76–7.82 (3H, m), 8.05 (1H, d, J = 8 Hz). HRMS (EI): Calcd for $C_{21}H_{17}NO_2S$, 347.0980. Found, 347.0981. **3i**: ^1H ($CDCl_3$): δ 2.35 (3H, s), 7.23 (2H, d, J = 8 Hz), 7.30–7.40 (2H, m), 7.43–7.49 (2H, m), 7.53–7.57 (2H, m), 7.69–7.72 (2H, m), 7.78 (2H, d, J = 8 Hz), 7.97 (1H, d, J = 9 Hz). HRMS (EI): Calcd for $C_{21}H_{16}ClNO_2S$,381.0590. Found, 381.0617. **3j**: ^1H ($CDCl_3$): δ 2.32 (3H, s), 6.50–6.51 (1H, m), 6.65 (1H, d, J = 3 Hz), 7.21 (2H, d, J = 8 Hz), 7.28–7.39 (2H, m), 7.48 (1H, s), 7.79 (2H, d, J = 8 Hz), 7.86–7.88 (2H, m), 8.03 (1H, d, J = 8 Hz). HRMS (EI): Calcd for $C_{19}H_{15}NO_3S$, 337.0773. Found, 337.0774. **4j**: ^1H ($CDCl_3$): δ 2.35 (3H, s), 6.47 (1H, s), 6.67 (1H, d, J = 3 Hz), 7.04–7.09 (1H, m), 7.17 (2H, d, J = 8 Hz), 7.28–7.36 (2H, m), 7.48 (1H, s), 7.62 (1H, d, J = 8 Hz), 7.67 (2H, d, J = 8 Hz). HRMS (EI): Calcd for $C_{19}H_{15}NO_3S$, 337.0773. Found, 337.0775. **3k**: ^1H ($CDCl_3$): δ 2.32 (3H, s), 7.07 (1H, t, J = 8 Hz), 7.14 (2H, d, J = 8 Hz), 7.29–7.35 (2H, m), 7.41–7.48 (2H, m), 7.60–7.76 (5H, m), 8.65 (1H, d, J = 4 Hz). HRMS (EI): Calcd for $C_{20}H_{16}N_2O_2S$, 348.0932. Found, 348.0926. **3l**: Ref. 15. **3m**: ^1H ($CDCl_3$): δ 2.29 (3H, s), 6.76 (1H, d, J = 4 Hz), 7.17 (2H, d, J = 8 Hz), 7.39–7.48 (2H, m), 7.67 (1H, d, J = 4 Hz), 7.77 (2H, d, J = 8 Hz), 7.88 (1H, d, J = 7 Hz), 7.97–7.99 (2H, m), 8.44 (1H, s). HRMS (EI): Calcd for $C_{19}H_{15}NO_2S$, 321.0823. Found, 321.0822.
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