

Synthesis of 3-Methylindoles from *N*-Aryl-*N*-(3-Triisopropylsilylpropargyl)sulfonamides

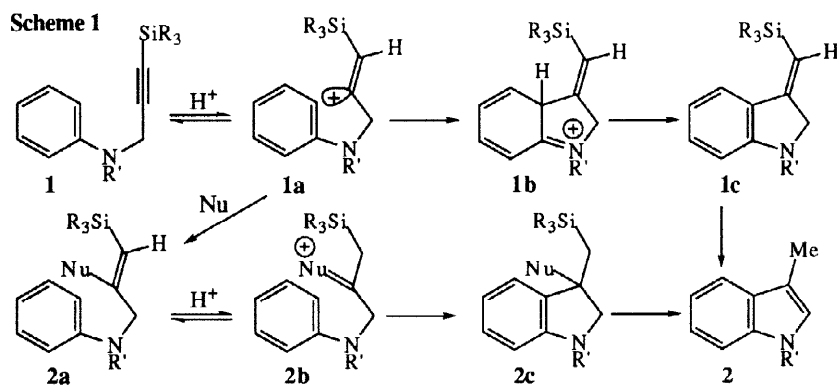
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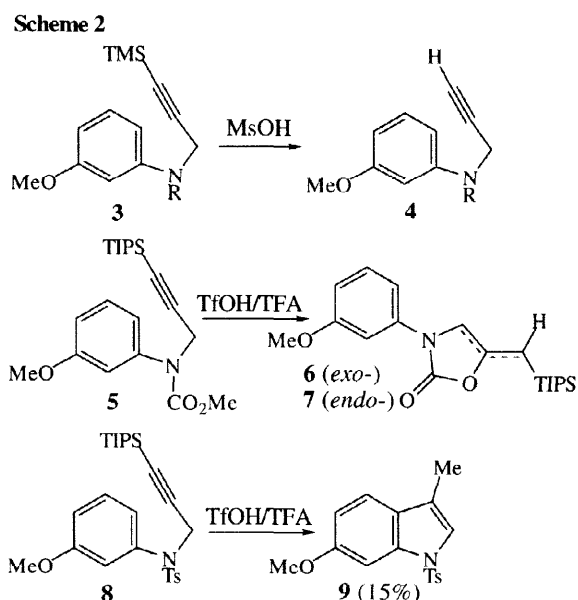
Abstract: Treatment of terminal triisopropylsilyl propargyl anilines with methanesulfonic acid resulted in cyclization to give a 3-methylindole derivative. © 1998 Elsevier Science Ltd. All rights reserved.

Indole alkaloids occupy a central place in natural product chemistry because of their wide range of complex structural variation and frequent potent physiological activity.¹ The indole nucleus is part of the essential amino acid tryptophan, and an unusually large number of drugs with a wide range of biological activities are indole derivatives.² Indeed it would not be an exaggeration to say that indole chemistry has, and still does dominate many aspects of modern synthetic organic, bioorganic and medicinal chemistry. As a consequence of the manifest diversity of indole chemistry there are numerous methods for the synthesis of the indole nucleus.³



Consequently, we considered the reaction sequence depicted in **Scheme 1**.⁴ Protonation of **1** leads to the β -silylvinyl cation **1a**,⁵ which should undergo electrophilic aromatic substitution to give **1b**, provided the aryl ring is sufficiently electron-rich. The *R'* aniline protecting group must prevent ammonium salt formation, which would deactivate **1**, and therefore the conversion of **1a** into **2** would greatly benefit from 3- and 5-electron donating substituents. The arenium ion **1b** should undergo proton loss to give **1c**, which upon protodesilylation and isomerization leads to the 3-methylindole derivative **2**. It is also possible that the vinyl cation **1a** can be intercepted by the solvent to give **2a**, which (depending on the nature of *Nu*) can lead to **2** via **2b** and **2c**, in a reaction process that is very similar to the classical Bischler indole synthesis.⁶ One significant problem with this type of reaction, and one that has been commented upon by Sundberg,⁷ is that the product **2** is

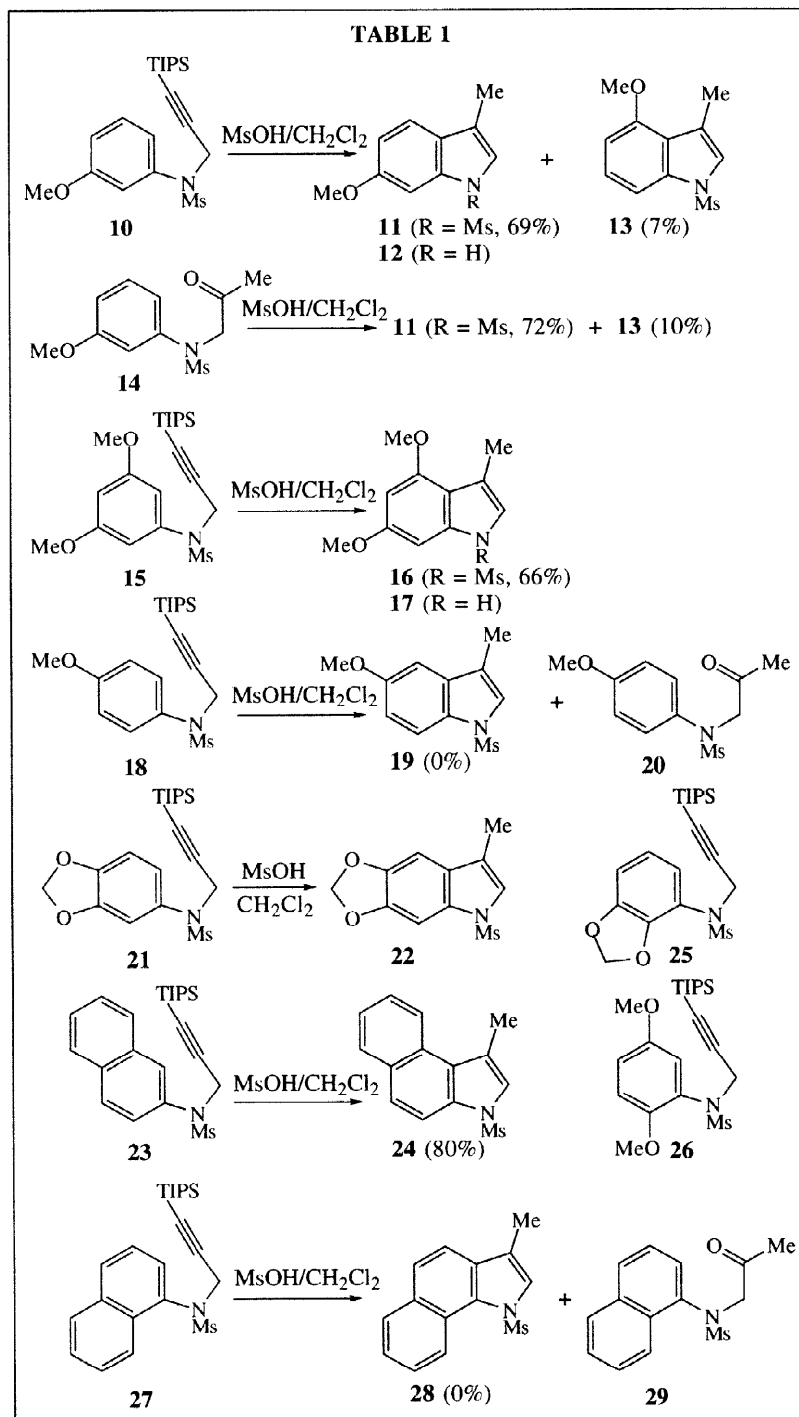
an electron-rich indole and very susceptible to further electrophilic reactions. We hoped that this predictable problem could be overcome by the choice of R'.



With this mechanistic construct in mind we carried out the following preliminary experiments to establish the validity, or otherwise, of this conceptually simple new indole synthesis. The terminal trimethylsilyl acetylene derivative **3** (R' = CO₂Me or Ts) on treatment with a variety of protic acids resulted in clean protodesilylation to give **4** (R' = CO₂Me or Ts), and no further reaction. The more robust triisopropylsilyl (TIPS) provided the first optimistic note. Treatment of **5** with TfOH/TFA/25 °C (12h) gave **6**, which slowly isomerized to **7** (90%), provided the first evidence that the putative vinyl cation intermediate was being formed but is trapped by the carbamate carbonyl group and not the aromatic ring.

The *N*-tosyl protected derivative **8** was exposed to TfOH/TFA to give **9**, albeit in low yield. The mass balance of the reaction consisted of a blue insoluble material. Attempts to improve the yield by using a variety of different acids [TFA (no reaction), TfOH (gave **9** in low yield), MsOH/CH₂Cl₂ (**9**, 10%), Nafion/PhH (no reaction)] did not improve the situation. It was suspected that the origin of the low yield was destruction of **9** under the reaction conditions as alluded to earlier, and was confirmed when **9** was treated with MsOH/CH₂Cl₂ to give a blue-purple insoluble mixture. The bulk of the material had lost the Ts group and undergone acid catalyzed oligomerization. The more acid stable *N*-Ms derivative **10** was exposed to MsOH/CH₂Cl₂/25 °C (12h) to give **11** (69%) and the isomer **13** (7%), **TABLE 1**. Deprotection of **11** gave the known indole **12**.⁸ As a control experiment **4** (R = Ms) was converted into the methylketone **14** [Hg(OAc)₂/THF/H₃O⁺], and exposed to cyclization reaction conditions to give **11** and **13** in almost the same ratio and yield as was obtained from **10**. Attempts to detect **14** (tlc and ¹H NMR) in the conversion of **10** into **11** and **13** were not successful, and **10** did not react with Hg(OAc)₂/THF/H₃O⁺ to give **14**. Consequently, it appears unlikely that **14** is an intermediate, but it cannot be rigorously excluded.

Application of these reaction conditions to **15** gave **16** (66%), whose structure was confirmed by deprotection to give **17**.⁹ The *p*-methoxy derivative **18** did not form the corresponding indole **19** under these reaction conditions, and the only isolated product was the ketone **20** which did not undergo cyclization to give **19**. The methylenedioxy derivative **21** was converted into **22**¹⁰ in modest yield, whereas the isomeric derivative **25** did not produce the corresponding indole under the same conditions. Similarly, **26** did not cyclize. The β -naphthylamine derivative **23** cyclized to give **24** in good yield, whereas the α -naphthylamine isomer **27** did not cyclize to give **28**, but rather underwent protodesilylation to the terminal acetylene, and hydration to the derived methyl ketone **29**.



Representative Experimental procedure. Methanesulfonic acid (1.0 mL, 15 mmol) was added to a stirred solution of **10**¹¹ (200 mg, 0.51 mmol) in dichloromethane (1 mL) at 21 °C, and mixture was stirred at for 12 h. The reaction was quenched with saturated aqueous NaHCO₃ (5 mL), extracted into dichloromethane (2x5 mL), and dried (MgSO₄). The extract was evaporated *in vacuo* and the residue purified by chromatography over silica gel eluting with 15% Et₂O/hexanes to give **11** (84 mg, 69%) as a colorless oil IR (film) 2934, 1616 cm⁻¹.

^1H NMR (CDCl_3 , 300 MHz) δ 7.43 (1H, d, $J = 2.2$ Hz), 7.41 (1H, d, $J = 8.9$ Hz), 7.08 (1H, apparent t, $J = 1.4$ Hz), 6.94 (1H, dd, $J = 8.9, 2.2$ Hz), 3.88 (3H, s), 3.00 (3H, s), 2.25 (3H, s). ^{13}C NMR (CDCl_3 , 75 MHz) δ 158.2, 136.3, 125.5, 121.6, 120.2, 118.7, 112.4, 97.5, 55.8, 39.8, 9.7. HRMS (CI^+) calcd for $\text{C}_{11}\text{H}_{14}\text{NO}_3\text{S}$, 240.0694 (MH^+). Found 240.0687. Also the isomeric 4-methoxyindole derivative **13** (8 mg, 7%) was isolated. ^1H NMR (CDCl_3 , 300 MHz) 7.49 (1H, d, $J = 8.2$ Hz), 7.25 (1H, t, $J = 8.2$ Hz), 7.04 (1H, d, $J = 0.6$ Hz), 6.70 (1H, d, $J = 8.2$ Hz), 3.91 (3H, s), 3.01 (3H, s), 2.42 (3H, s). Treatment of **11** with $\text{KOH}/\text{MeOH}/\text{H}_2\text{O}/\text{reflux}$ 2 h gave **12**, m.p. 122-124 °C (Lit.⁸ m.p. 125 °C).

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11. Compounds **10**, **14**, **15**, **18**, **21**, **23**, **25-27** were made from the ArNHMs derivative by treatment with $\text{NaH}/\text{DMF}/\text{propargyl bromide}$, followed by $\text{LDA}/\text{THF}/\text{TIPSCl}$ at -78 °C.