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Synthesis of the 5-HT_{1D} Receptor Agonist MK-0462 *via* a Pd-catalyzed Coupling Reaction

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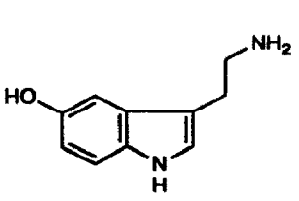
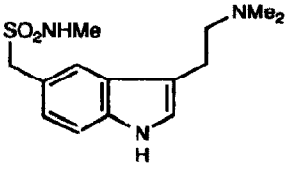
Abstract: Application of a palladium-catalyzed coupling between **3** and **5a** to the synthesis of the novel 5-HT_{1D} receptor agonist MK-0462 (**1**), a potential anti-migraine drug, is described.

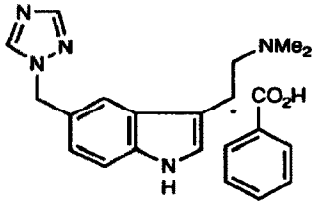
The complex physiological and pathophysiological processes of the neurotransmitter serotonin (5-HT) are becoming increasingly elucidated.[1] In one role it acts as a vasoconstrictor in the brain and, thereby, displays beneficial properties in migraine therapy. Its potential as a pharmaceutical agent, however, is limited due to its rapid metabolism *in vivo*. Over the past few years an extensive effort has been devoted to the development of *N,N*-dialkyltryptamines as 5-HT_{1D} receptor agonists to achieve the desired activity and selectivity for the treatment of migraine. Sumatriptan is the first of this class of drugs to be approved for this purpose.[2] MK-0462, which contains the 1,2,4-triazole heterocycle instead of a sulfonamide, is also a potent 5-HT_{1D} receptor agonist that is undergoing clinical studies.



Serotonin (5-HT)



Sumatriptan

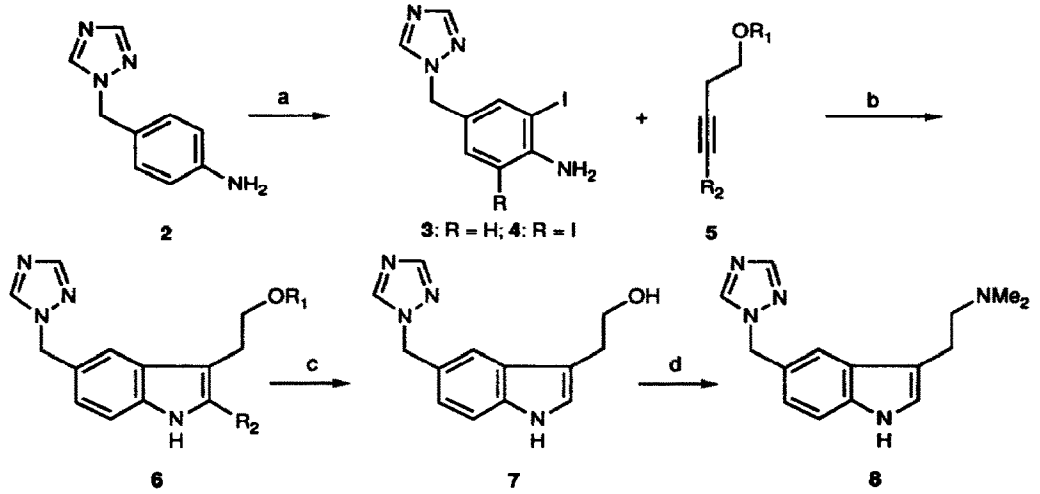


MK-0462 (1)

Recently, we reported a modification of the Fisher indole reaction for the preparation of the *N,N*-dimethyltryptamine framework.[3] Application of this methodology to the synthesis of MK-0462, however, was ineffective and low-yielding due to the instability of the benzyl triazole moiety to the reaction conditions, which leads to polymerization. We now wish to disclose a highly efficient method for the preparation of the *N,N*-dimethyltryptamine, MK-0462 (**1**) via a palladium-catalyzed coupling between the iodoaniline **3** and acetylene **5a**.

Larock et al. have shown that coupling of an iodoaniline species with an internal acetylene using palladium catalysis gives 2,3-disubstituted indoles in good-to-excellent yields.[4] Three other applications of this methodology have been demonstrated in the syntheses of hetero-condensed pyrroles,[5a] tryptophans[5b] and homotryptophol[5c]. However, the application of palladium-catalyzed coupling methodology to the synthesis of the *N,N*-dimethyltryptamine has not been reported previously. We have found that the tryptophol precursor can be prepared by the coupling of 3-iodo-4-aminobenzyltriazole **3** with a suitably protected butynol derivative **5** (Scheme 1).

Scheme 1[a]



2 **3**: R = H; **4**: R = I **5** **6** **7** **8**

[a]Reaction Conditions: a) ICl, $CaCO_3$, MeOH-H_2O; b) 2 mol% $Pd(OAc)_2$, Na_2CO_3, DMF, 100 °C; c) MeOH-HCl; d) i. MsCl, Et_3N, THF; ii. 40% $HNMe_2$

The synthesis of MK-462 began with the preparation of iodoaniline **3**. 4-Aminobenzyltriazole **2** is available in 3 steps and >90% overall yield from 4-nitrobenzyl bromide and 4-amino-1,2,4-triazole using a modified literature procedure.[6,7] Reaction of **2** with iodine monochloride in the presence of $CaCO_3$ in aqueous methanol furnishes iodoaniline **3** in 91% yield; some over-iodination occurs to provide 1-3% of diiodoaniline **4**. The over-iodination is not difficult to control since it occurs much more slowly; for example, treatment of iodoaniline **3** with one equivalent of ICl only affords 30% of **4**. Using excess ICl (5 equiv) under prolonged aging at room temperature the diiodoaniline **4** may be prepared from **3** in 75% yield.

The coupling reaction between iodoaniline **3** and various derivatives of 3-butyn-1-ol was studied (Table 1). In order to prevent coupling at the terminal carbon of the acetylene, silyl protection was used.[4] The silyl groups were incorporated by formation of the dianion with BuLi followed by quenching with two equivalents of the silyl chloride. In the case of the TBS-protected alkyne the *bis*-silylation did not go to completion; rather, a 1:1 mixture of **5d** and **5e** resulted. Alternative *O*-protection could then be carried out by selective hydrolysis of the *O*-silyl group; for example, **5a** was converted to **5b** in quantitative yield using dilute HCl in aqueous methanol . The hydroxy group of **5c** could then be protected with the TBDMS or THP group to afford the alkynes **5f** and **5g**, respectively, in quantitative yields.

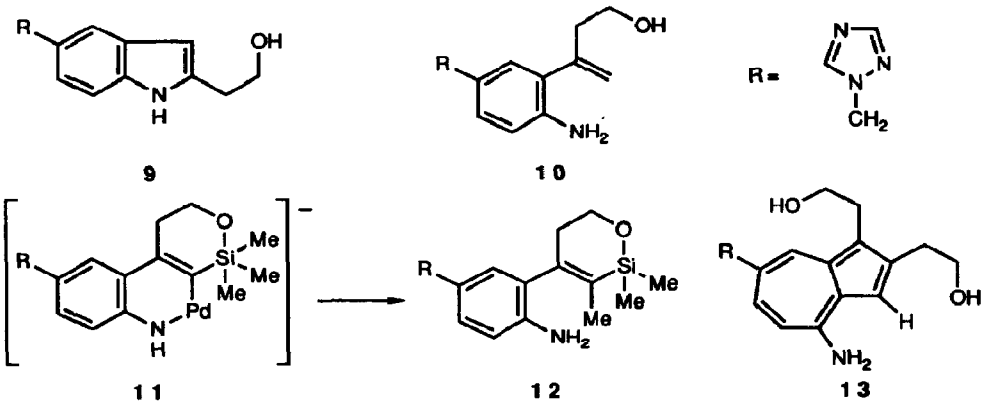
Table 1. Effect of Butynol Protection on Yield of Coupling[a]

Entry	Acetylenes		Yields of Indoles
1	**5a**	R_1, R_2 = $SiEt_3$	**6a** + **6b** (80%)
2	**5b**	R_1 = H, R_2 = $SiEt_3$	**6b** (74%)
3	**5c**	R_1 = H, R_2 = $SiMe_3$	**6c** (56%)
4	**5d**	R_1, R_2 = TBDMS	**6d** (78%)
5	**5e**	R_1 = H, R_2 = TBDMS	**6e** (60%)
6	**5f**	R_1 = TBDMS, R_2 = TMS	**6f** (77%)
7	**5g**	R_1 = THP, R_2 = TMS	**6g** (79%)

[a]Conditions: 2 mol% $Pd(OAc)_2$, Na_2CO_3, DMF, 100 °C; Ratio of **3**/**5** = 1:1.05-1.2

The simplest derivative **5c** coupled with iodoaniline **3** to afford the 2-TMS-indole **6c** in 56% yield.[8] The regioisomer **9** (5%) was also formed. Several other impurities were identified in this reaction (Chart 1): styrene **10**, formed from reductive removal of Pd and desilylation; cyclic siloxane **12**, presumably formed through a hypervalent silicon species **11** followed by a methyl migration; and the deep-lavender compound, azulene **13**, derived from the incorporation of two side chain moieties.[9] The lability of the TMS group was believed to be responsible for these byproducts and the low yield. The more stable TES and TBDMS groups on the alkyne gave indoles **6a** and **6b**, respectively, in higher yields (Entry 1 and 4). Although the more stable *C*-protection gave better results, the bulky TBDMS butyne coupled considerably slower; therefore, TES was the preferred protecting group.

Chart 1



Protection of the hydroxy group also played an important role in the coupling. For instance, coupling of **3** with **5f** and **5g** gave **6f** (77%) and **6g** (79%), respectively, without forming the cyclic siloxane **12** as with **5c**. The *bis*-TBDMS-protected butynol **5d** provided an 18% higher yield than the unprotected-alcohol form **5e**. The reaction of **3** with **5a** gave a 3:1 mixture of indoles **6a** and **6b** in 80% combined yield (Entry 1); the formation of **6b** was due to the partial *O*-desilylation which occured under the reaction conditions. Although TMS protection on the alkyne provided acceptable yields with protection of the alcohol as the TBDMS or THP ethers, a number of highly colored impurities, one of which was the azulene **13**, was generated in the coupling reactions (Entry 6 and 7). The *bis*-TES butynol was chosen for the synthesis of MK-0462 because it offered a suitable rate of coupling and stability.

Desilylation of the combined indoles **6a** and **6b** in MeOH-HCl afforded tryptophol **7**[10] in 70-80% overall yield after work-up and crystallization (Scheme 1). Although desilylation of 2-silylated-indoles with excess $AlCl_3$ in dichloromethane has been reported,[4] MeOH-HCl is more practical. Conversion of **3** and **5a** to **7** was carried out directly without isolation of **6**. In the crystallization of **7** the regioisomer **9** (6%) was removed in the mother liquor. While the regiochemistry is controlled by the silyl group, it is only slightly dependent on the bulkiness of the silyl group. For example, the ratio of the regiochemistry for the coupling of **5c** (TMS), **5b** (TES) and **5e** (TBDMS) is within the range of 92:8-94:6.[11] The bulkiness of the silyl group is more likely to affect the reaction kinetics.

Conversion of tryptophol **7** to MK-0462 (**1**) was straightforward. Thus, the formation of mesylate from tryptophol **7** followed by the dimethylamine displacement afforded MK-0462 free base **8**[10] in 79% yield. The mesylate was prone to polymerization from intermolecular alkylation by the triazole; therefore, the mesylate was treated directly with 40% dimethylamine. The isolated tryptamine was then purified by addition of a solution of benzoic acid in isopropyl acetate-isopropyl alcohol to the free base in isopropyl alcohol to afford the MK-0462 as a benzoate salt in 95% yield.

In summary, a new synthesis of MK-0462 (**1**) featuring a palladium-catalyzed coupling of iodoaniline **3** and *bis*-TES-butynol **5a** to form the indole ring has been developed into an efficient process amenable to scale up that requires no chromatographic purifications.

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8. (a) **5c** was purchased from Farchan Laboratories. (b) $Pd(OAc)_2$ was purchased from Johnson-Matthey.
9. The structure of **13** was fully elucidated by NMR experiments such as HMBC (1H-13C long-range correlation), NOE and SELJRES and NOE difference studies: ^{1}H NMR(400.08 MHz) δ 8.09(br d, J=2.0, 1H), 7.98(s, 1H), 7.94(s, 1H), 7.27(dd, *J* =11.2, 2.0, 1H), 6.95(s, 1H), 6.55(d, *J* =11.2, 1H), 5.35(s, 2H), 5.11(br s, 2H), 3.90(t, *J* =7.4, 2H), 3.71(t, *J* =7.8, 2H), 3.18(t, *J* =7.8, 2H), 3.08(t, 7.4, 2H), 0.90 (s, 9H), 0.86(s, 9H), 0.04(s, 6H), -0.02(s, 6H); ^{13}C NMR(100.61 MHz) d 152.0, 150.1, 142.6, 142.5, 136.1, 133.8, 133.4, 126.7 121.1, 120.2, 113.9, 111.4, 64.6, 64.0, 58.3, 32.7, 29.4 25.9_9, 25.9_7, 18.4_0, 18.3_6, -5.2_7, -5.3_0; Anal. Calcd for $C_{29}H_{48}N_4O_2Si_2$: C, 64.4; H, 8.94; N, 10.35. Found: C, 63.9; H, 8.78; N, 10.35.
10. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR and elemental analysis. Selective data (^{1}H NMR at 250 MHz, ^{13}C NMR at 62.5 MHz):
Tryptophol **7**: mp 131-132 °C; ^{1}H NMR (DMSO-d_6) δ 2.81 (t, *J* = 7.4 Hz, 2H), 3.63 (dt, *J* = 7.4, 5.3 Hz, 2H), 4.65 (t, *J* = 5.3 Hz, 1H), 5.43 (s, 2H), 7.00 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.15 (d, *J* = 2.0 Hz, 1H), 7.51 (s, 1H), 7.94 (s, 1H), 8.62 (s, 1H), 10.85 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 151.3, 143.6, 135.7, 127.3, 125.8, 123.6, 121.1, 118.3, 111.7, 111.4, 61.5, 53.0, 28.7; Anal. Calcd for $C_{13}H_{14}N_4O$: C, 64.44; H, 5.82; N, 23.12. Found: C, 64.38; H, 5.85; N, 23.28.
Tryptamine **8**: mp 120-121 °C; ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 6H), 2.63 (m, 2H), 2.93 (m, 2H), 5.43 (s, 2H), 7.05 (m, 2H), 7.31 (d, J = 8.3 Hz, 1H), 7.56 (s, 1H), 7.97 (s, 1H), 7.99 (s, 1H), 8.49 (s, 1H); ^{13}C NMR ($CDCl_3$) 151.7, 142.8, 136.4, 127.7, 124.5, 123.1, 121.9, 119.1, 113.9, 112.0, 60.2, 54.6, 45.3, 23.5; Anal. Calcd for $C_{15}H_{19}N_5$: C, 66.89; H, 7.11; N, 26.00. Found: C, 66.89; H, 7.20; N, 26.04.
11. Coupling of iodoaniline **3** with *tert*-butyldimethylsilyl 5,5-dimethyl-3-hexyn-1-ol ether (*tert*-butyl protected alkyne) also gives a 96:4 mixture of two *tert*-butyldimethylsilyl tryptophol ethers in 60% yield.

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