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Convenient synthesis of bis(indolyl)alkanes and bis(pyrrolyl)alkanes by $Cu(OTf)_2$-catalyzed addition of indole and pyrrole to acetylenic sulfone

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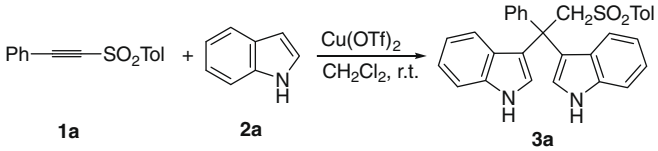
ABSTRACT

Sulfonyl-containing bis(indolyl)alkanes and bis(pyrrolyl)alkanes were synthesized conveniently by $Cu(OTf)_2$-catalyzed double Michael addition of indole and pyrrole to acetylenic sulfone.

Indole derivatives are found abundantly in nature and are well known to possess various biological activities, which are used in antioxidatives and pharmaceuticals.[1] Bis(indolyl)alkanes are present in many biologically active natural products and are known to have applications in research areas such as pharmaceuticals and materials science.[2] Consequently, there is an increasing interest in the synthesis of compounds containing bis(indolyl)alkanes moiety due to their importance and a number of synthetic methods for the synthesis of bis(indolyl)alkanes have been described in the literature. However, the procedures described in the literature to access bis(indolyl)alkanes are mainly focused on the condensation of indole with carbonyl compounds in the presence of a protic acid or a Lewis acid.[3] Syntheses of bis(indolyl)alkanes by the reaction of indoles with alkynes are very rare and these methods suffered from disadvantages such as only terminal alkynes can be used or the use of expensive transition metal (e.g., Au, Pd, or Pt) catalysts is necessary.[4]

Michael additions have attracted much attention as one of the most important carbon–carbon bond-forming reactions in organic synthesis for the reason that Michael additions are atom-efficient procedures and thus are inherently green transformations.[5] Various Lewis acids such as metal halides or metal triflates are used to promote Michael addition reaction.[6] Acetylenic sulfones are very attractive Michael acceptors since the sulfonyl moiety is a strong electron-withdrawing group and can be readily transformed into different substituents by alkylation, by desulfonylation reaction, and by Julia olefination.[7] Therefore, the chemistry of sulfones has been extensively studied and exploited in the organic synthesis for the past several decades. However, to the best of our knowledge, synthesis of bis(indolyl)alkanes or bis(pyrrolyl)alkanes from acetylenic sulfone has not been reported. Recently, we have reported the regio- and stereoselective synthesis of polysubstituted vinyl sulfones by Michael addition of organozinc reagent to acetylenic sulfone.[8] During our ongoing investigations on the application of acetylenic sulfone in organic synthesis, we have found that sulfonyl-containing bis(indolyl)alkanes or bis(pyrrolyl)alkanes can be obtained conveniently from the reaction of indole or pyrrole with acetylenic sulfone. Herein, we wish to report the synthesis of sulfonyl-containing bis(indolyl)alkanes and bis(pyrrolyl)alkanes by $Cu(OTf)_2$-catalyzed double Michael addition of indole or pyrrole to acetylenic sulfone.

Firstly, the Michael addition of indole to (1-phenyl-2-tosyl)ethyne (**1a**) was investigated. Catalysts and reaction solvents were screened. It was found that no reaction happened when indole **2a** (3 equiv) and acetylenic sulfone **1a** (1 equiv) was stirred in CH_2Cl_2 at room temperature. In the presence of 10 mol % $Cu(OTf)_2$, the reaction completed in 10 h and bis(indolyl)alkane **3a** was obtained in



Scheme 1. $Cu(OTf)_2$-catalyzed reaction of **1a** and **2a**.

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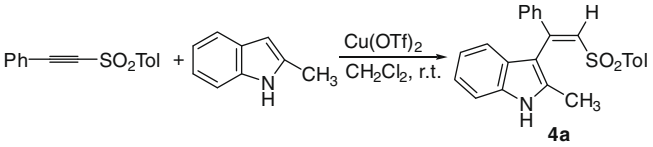
52% yield (Scheme 1). The use of 10 mol % $FeCl_3$ gave the expected product **3a** only in 8% yield along with a recovery of **1a**. Other Lewis acid catalysts, such as $CeCl_3{\cdot}7H_2O$, $ZnCl_2$, $Cu(acac)_2$, and $Cu(OAc)_2$, could not catalyze the reaction. The yield of **3a** was increased to 68% when 20 mol % $Cu(OTf)_2$ was used. Further increasing the amount of catalyst has no apparent effect on the yield. Among the various solvents such as ether, acetonitrile, ethanol, and tetrahydrofuran tested, CH_2Cl_2 was found to be the most effective for this reaction. Therefore, we used 20 mol % $Cu(OTf)_2$ as catalyst in CH_2Cl_2 at room temperature as the standard reaction conditions in the subsequent studies.

The scope and generality of this reaction was investigated under the optimized reaction conditions. The results are complied in Table 1.[9] Table 1 shows that several substituted indoles can react with acetylenic sulfones to give the corresponding bis(indolyl)alkanes **3** in moderate to good yield. Indoles can be unsubstituted indole (Table 1, entries 1, 6 and 11), *N*-ethyl (Table 1, entries 2 and 7), *N*-benzyl (Table 1, entries 3 and 8), 5-bromo (Table 1, entries 4 and 9), or 5-methoxyl-indoles (Table 1, entries 5 and 10). Acetylenic sulfone can be phenyl- or *n*-pentyl-substituted acetylenic sulfone.

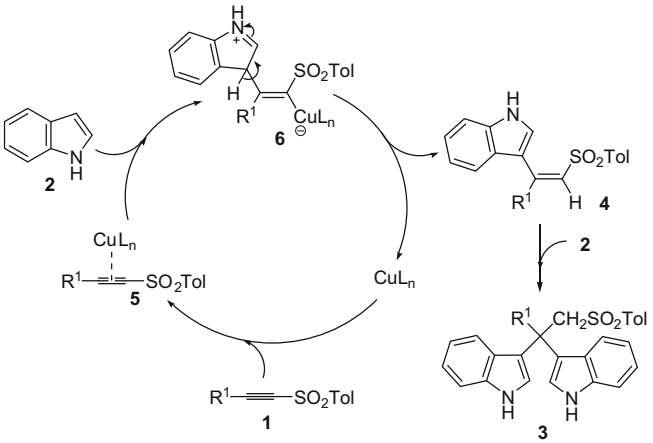
However, only mono-adduct **4a** was obtained in 52% yield and no expected bis(indolyl)alkane was observed when 2-methylindol reacted with (1-phenyl-2-tosyl)ethyne **1a** under standard reaction conditions (Scheme 2). This is probably because of the steric hinderance of the methyl in 2-position which inhibits the second Michael addition. 2-Phenyl and *N*-tosyl indole are inert under the same reaction conditions. This may be attributed to the large steric effect of phenyl and the electron-withdrawing effect of tosyl, respectively.

A plausible catalytic mechanism that explains the formation of product **3** is shown in Scheme 3. The first step of the catalytic cycle is the coordination of Cu(II) catalyst to the triple bond of alkyne **1** to form intermediate **5**. Addition of indole to the β-position of acetylenic sulfone generates vinylcopper intermediate **6**. Proton release followed by protonation of **6** affords indolylalkene **4**. The second Michael addition of indole to the formed **4** leading to bis(indolyl)alkane **3** is considered to proceed in the same way. The indolylalkene **4** as an intermediate of the reaction can be supported by the mono-adduct **4a**, which was obtained by the reaction of 2-methylindol with **1a**.

Bis(pyrrolyl)alkanes derivatives are among the most important fundamental constituents of biologically and physiologically active molecules, such as porphyrins and related macrocycles, hemoglobins, and vitamin B_{12}. Bis(pyrrolyl)alkanes derivatives have been synthesized using a variety of procedures and most of them based



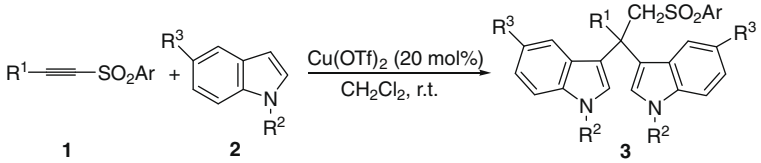
Scheme 2. $Cu(OTf)_2$-catalyzed reaction of **1a** and 2-methylindole.



Scheme 3. Plausible mechanism.

on the direct condensation of carbonyl reagents with pyrrole.[4a,10] These processes are often plagued by the inaccessibility of functionalized carbonyl and the formation of undesired side products such as azafulvenes and N-confused dipyrromethanes. Encouraged by the experimental results of the double Michael addition of indole to acetylenic sulfone, we further investigated the reaction of pyrrole with acetylenic sulfone in the similar reaction conditions, hoping to synthesize sulfonyl-containing pyrrole derivatives. The experimental results show that the double Michael addition of pyrrole to acetylenic sulfone proceeded smoothly to give the corresponding bis(pyrrolyl)alkane **7** in moderate to good yields.[11] The results are summarized in Table 2. Acetylenic sulfone can be differently substituted acetylenic sulfone. However, no desired product was obtained in the case of *N*-methyl pyrrole or *N*-tosyl pyrrole. The molecular structure of compound **7a** was confirmed by X-ray diffraction analysis (Fig. 1).[12]

Table 1
$Cu(OTf)_2$-catalyzed Michael addition of indole to acetylenic sulfone

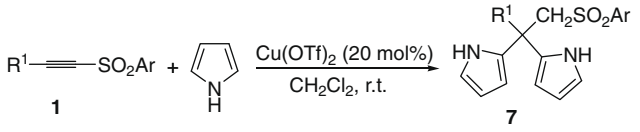


1 2 3

Entry	R^1	Ar	R^2	R^3	Yield[a] (%)
1	C_6H_5	*p*-$CH_3C_6H_4$	H	H	**3a** 68
2	C_6H_5	*p*-$CH_3C_6H_4$	CH_3CH_2	H	**3b** 72
3	C_6H_5	*p*-$CH_3C_6H_4$	$C_6H_5CH_2$	H	**3c** 80
4	C_6H_5	*p*-$CH_3C_6H_4$	H	Br	**3d** 60
5	C_6H_5	*p*-$CH_3C_6H_4$	H	CH_3O	**3e** 62
6	*n*-C_5H_{11}	*p*-$CH_3C_6H_4$	H	H	**3f** 55
7	*n*-C_5H_{11}	*p*-$CH_3C_6H_4$	CH_3CH_2	H	**3g** 65
8	*n*-C_5H_{11}	*p*-$CH_3C_6H_4$	$C_6H_5CH_2$	H	**3h** 74
9	*n*-C_5H_{11}	*p*-$CH_3C_6H_4$	H	Br	**3i** 48
10	*n*-C_5H_{11}	*p*-$CH_3C_6H_4$	H	CH_3O	**3j** 52
11	C_6H_5	*p*-ClC_6H_4	H	H	**3k** 62

[a] Isolated yield based on **1**.

Table 2
Cu(OTf)$_2$-catalyzed Michael addition of pyrrole to acetylenic sulfone



Entry	R^1	Ar	Yield[a] (%)
1	C_6H_5	p-$CH_3C_6H_4$	**7a** 78
2	C_6H_5	C_6H_5	**7b** 80
3	n-C_5H_{11}	p-$CH_3C_6H_4$	**7c** 58
4	p-$CH_3C_6H_4$	C_6H_5	**7d** 75
5	p-$CH_3OC_6H_4$	C_6H_5	**7e** 68
6	C_6H_5	p-ClC_6H_4	**7f** 78

[a] Isolated yield based on **1**.

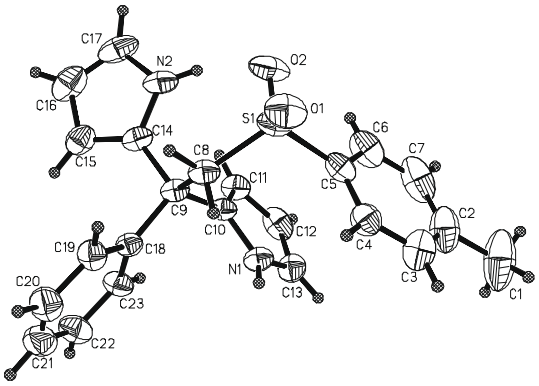


Figure 1. The molecular structure of compound **7a**.

In conclusion, we have developed a novel and straightforward method to synthesize sulfonyl-containing bis(indolyl)alkanes and bis(pyrrolyl)alkanes by double Michael addition of indole or pyrrole to acetylenic sulfone at room temperature in the presence of both moisture and air. This is a convenient, atom-efficient, and green method to synthesis the important indole and pyrrole derivatives. Due to the versatile reactivity of the sulfonyl group, it is predictable that these compounds are potential precursors of differently substituted bis(indolyl)alkanes and bis(pyrrolyl)alkanes.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.093.

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9. *General procedure for the synthesis of compound* **3a***:* Cu(OTf)$_2$ 22 mg (0.06 mmol) was added to a solution of indole (**2a**) 105 mg (0.9 mmol) and (1-phenyl-2-tosyl)ethyne (**1a**) 77 mg (0.3 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was stirred at room temperature. After the reaction was complete (monitored by TLC), the mixture was quenched with a saturated NH_4Cl solution and was extracted with CH_2Cl_2 (3 × 10.0 mL). The organic layer was combined and dried over $MgSO_4$. After filtration and removal of solvent in vacuo, the crude product was purified with flash chromatography (silica gel, petroleum ether–ethyl acetate 5:1 as eluent) to afford product 3-(1-(1*H*-indol-3-yl)-1-phenyl-2-tosylethyl)-1*H*-indole **3a**. White solid, mp 167–168 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (s, 2H), 7.45 (d, J = 7.3 Hz, 2H), 7.31–7.14 (m, 8H), 7.02–6.95 (m, 6H), 6.73–6.69 (m, 3H), 4.77 (s, 2H), 2.20 (s, 3H). ^{13}C NMR (75 MHz, DMSO): δ 144.5, 142.8, 137.8, 135.7, 128.8, 128.3, 128.0, 127.9, 127.6, 126.6, 126.5, 123.3, 123.1, 116.8, 114.1, 111.3, 64.7, 46.8, 21.4. IR (KBr): ν (cm^{-1}) 3398, 1492, 1282, 1138, 1080. HRMS (EI) calcd for $C_{31}H_{26}N_2O_2S$ (M^+): 490.1715, found 490.1718.
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11. *General procedure for the synthesis of compound 3-(1-phenyl-1-(1H-pyrrol-3-yl)-2-tosylethyl)-1H-pyrrole* **7a***:* Compound **7a** was prepared by the similar procedure as described above. White solid, mp 186–187 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.99 (s, 2H), 7.46 (d, J = 7.3 Hz, 2H), 7.22–7.16 (m, 5H), 6.97 (d, J = 6.9 Hz, 2H), 6.76 (s, 2H), 6.10 (m, 2H), 5.66 (s, 2H), 4.47 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.4, 142.6, 138.2, 133.9, 129.8, 128.2, 128.1, 127.5, 127.4, 117.9, 108.6, 107.8, 67.7, 48.4, 21.6. IR (KBr): ν (cm^{-1}) 3437, 1454, 1265, 1134, 1083. HRMS (EI) calcd for $C_{23}H_{22}N_2O_2S$: 390.1402, found 390.1406.
12. X-ray data for **7a** have been deposited at the Cambridge Crystallographic Data Centre, deposition number CCDC 736055. Crystal data for **7a**: $C_{23}H_{22}N_2O_2S$, MW = 390.49, monoclinic, space group $C2/c$, a = 41.797(10), b = 9.486(2), c = 41.828(10) Å; α = 90, β = 166.078(4), γ = 90°. V = 3990.2(16) Å^3, T = 293 K, Z = 8, D_{calcd} = 1.300 g cm^{-1}, μ = 0.183 mm^{-1}, λ = 0.71073 Å; F(0 0 0) 1648, 4588 independent reflections (R_{int} = 0.0553), 16,398 reflections collected; refinement method, full-matrix least-squares on F^2; goodness-of-fit on F^2 = 1.061; Final R indices [$I > 2\sigma(I)$] R_1 = 0.0717, wR_2 = 0.1611.