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Synthesis of C_2-symmetric bis-indolyl sulfones

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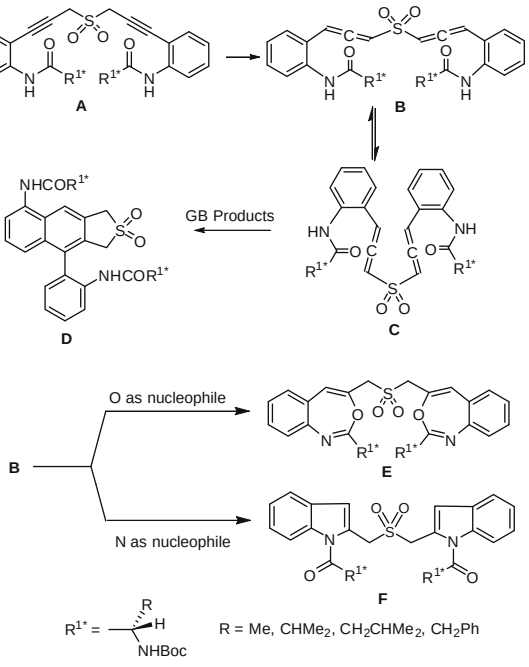
ABSTRACT

A new class of C_2-symmetric bis-indole derivatives with 2,2′-linkage has been synthesized from bis-propargyl sulfones. The method involves treatment of the sulfones with catalytic amount of triethylamine to form the indole derivatives presumably via the intramolecular Michael addition to the intermediate bis-allenic sulfones. Interestingly, the expected Garratt-Braverman pathway was not followed.

Bis-indole derivatives are important targets for drug design.[1] This is mainly because of recent reports of various activities exhibited by various bis-indoles[2,3] as well as their presence in many bioactive natural products.[4] A variety of methods exist for the synthesis of indole systems including bis-indole. The newer methods of indole synthesis mainly include metal-catalyzed intramolecular cyclization to propargylic systems.[5] For the bis-indoles, most of the methods start from indole derivatives itself in which two indole units are joined directly or through a suitable linker.[6] The usual linkage pattern is 3,3′ which are the preferential sites for electrophilic substitution in indoles.[7] Recently, a gold (I)-catalyzed sequential cycloisomerization/bis-addition of *o*-ethynylanilines to 3,3′-bis-(indolyl)methanes has been reported.[8] Simple and efficient ways for constructing bis-indole derivatives with 2,2′-linker are still in demand. While trying to induce a Garratt-Braverman (GB) cyclization[9] to study the stereo-differentiation, if any, during the formation of the atropisomers, we prepared a series of bis-propargyl sulfones of the type **A** with an *ortho* aminoacyl amino acid (Scheme 1). We found that the major pathway followed was isomerization followed by intramolecular addition of the amide nucleophile via the nitrogen to form the indoles in high yields. A close look at the structure of the sulfones reveals an interesting feature: the bis-allenic sulfone obtained via base-induced isomerization of the corresponding propargylic analog can either undergo GB-rearrangement or can be intramolecularly trapped by the nucleophilic amide.

However, in reality, the nucleophilic addition was found to be the only pathway followed which led to the formation of bis-indoles **F** in high yields. Neither the phenyl-substituted naphthalene sulfolenes **D** (GB product) nor any oxazepine derivative **E** could be isolated in these reactions. The method is very general and works with various amino acid derivatives. Herein, we report the results in detail along with a probable explanation for such a preference.

Our first task was to make the starting materials **1a–d**. Thus EDC-mediated coupling of 2-iodo aniline with *N*-Boc amino acids produced the *N*-acyl derivatives. Sonogashira coupling[10] with propargyl alcohol followed by mesylation (mesyl chloride, Et_3N) and bromination (LiBr, THF)[11] gave the bromide. The latter upon treatment with Na_2S in methanol afforded the sulfide which on oxidation with *m*CPBA produced the sulfone (Scheme 2). The simple aryl sulfone **3** was similarly prepared from the intermediate bromide **6a.**



Scheme 1. Possible reaction pathways via the bis-allenic sulfone.

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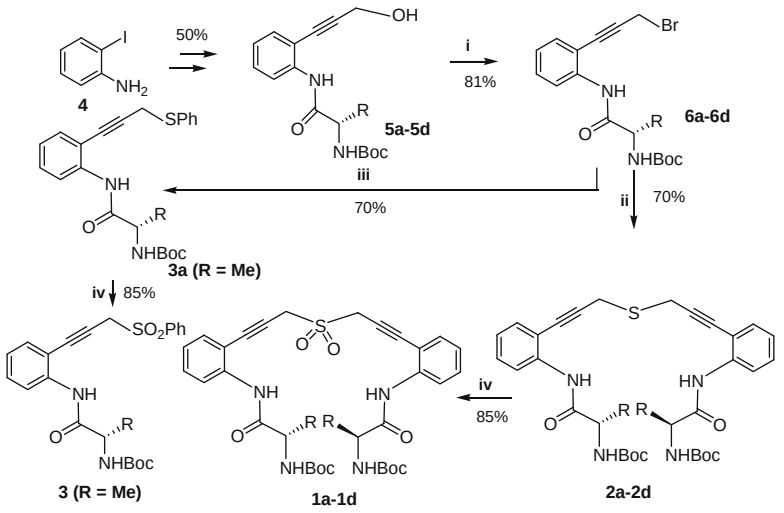


Scheme 2. Synthesis of the target bis-propargyl sulfones. Reagents and conditions: (a) R = Me; (b) R = $CHMe_2$; (c) R = CH_2CHMe_2; (d) R = CH_2Ph; i = MsCl, NEt_3, 0 °C, DCM; LiBr, THF; ii = Na_2S, MeOH; iii = PhSH, NEt_3, DCM; iv = *m*CPBA, DCM.

With the starting bis-propargyl sulfones in hand, the stage was set to check their reactivity under basic conditions. As an initial experiment, the sulfone **1a** was dissolved in $CDCl_3$ in an NMR tube and triethylamine was added and the ^1H NMR was recorded at different time points (Fig. 1). With time, the broad signal for the methylenes in the substrate at $\sim\delta$ 4.4 was slowly replaced by a pair of doublets at δ 4.90 and 5.16 (J = 14.2 Hz) characteristic of an diastereotopic methylene. At the same time, a new singlet started to appear at δ 6.86 which was assigned to the 3 and 3′ hydrogens of indole. The reaction was complete within 2 h. It was repeated on a larger scale in $CHCl_3$ and Et_3N and the product was isolated in a pure form in >95% yield by column chromatography over silica gel using hexane–EtOAc (1:1) as eluent. That the product was not a result of Garratt-Braverman cyclization was apparent from the symmetrical nature of its structure (like appearance of AB pair of doublets, each integrating to 2H and absence of the amide NH signal. The other alternative oxazepine structure, however, could not be ruled out on the basis of NMR or mass spectra.[12] Repeated attempts to obtain single crystal from any of these products failed. The structures were finally confirmed to be the indole derivatives by facile base-mediated deprotection of the acyl groups to form the known free indole derivatives (Scheme 3). Spectral data completely matched with those reported.[7,13]

The generality of this methodology for the synthesis of bis-indole derivatives was demonstrated by carrying out the reaction with various other sulfones. In each case the indole derivatives were obtained in excellent yields. The reaction also works with monopropargyl sulfones **3**. The results are shown in Table 1.

We would like to put forward a probable reason for such preference of nucleophilic attack over GB cyclization. Although the final products of both the reactions are the creation of aromatic system, namely indole and naphthalene, the GB cyclization involves a series of steps as shown in Scheme 4. The first step, being likely to be the rate determining step, does not lead to an aromatic system and hence is endothermic. In case of the Michael pathway, the addition of nucleophile is concomitant with the generation of

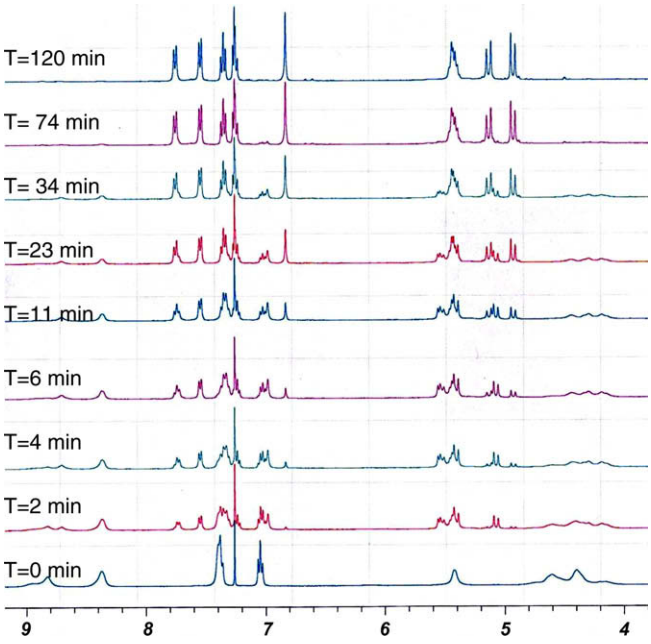
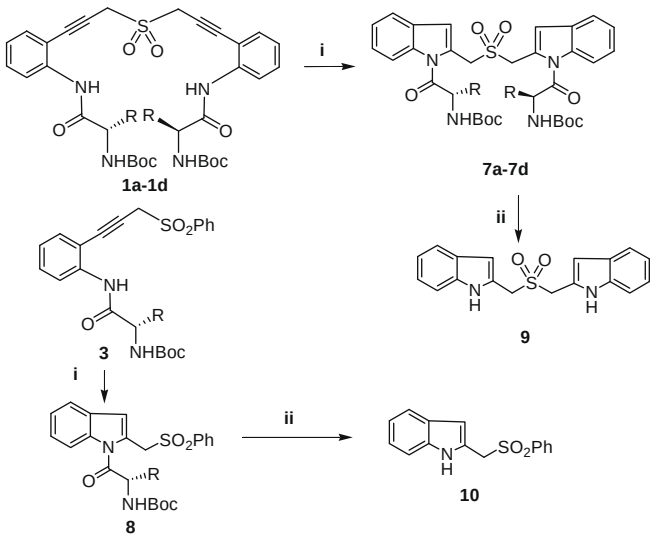


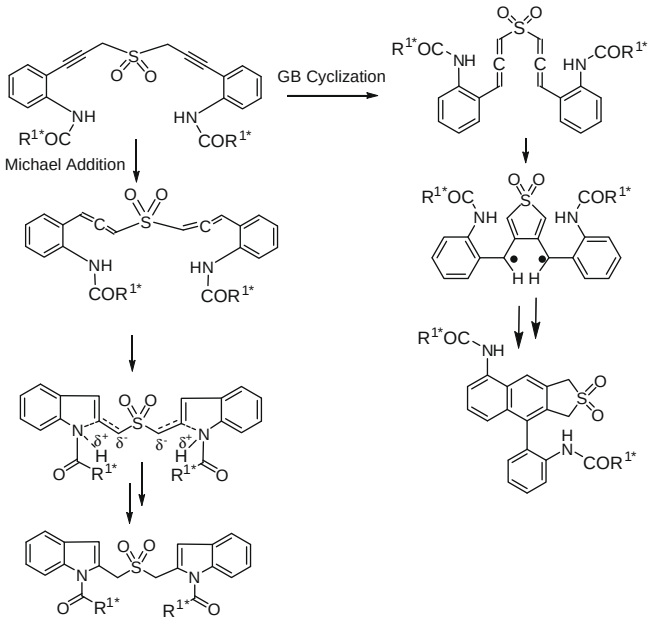
Figure 1. ^1H NMR at different time points upon base treatment of sulfone **1a**.



Scheme 3. Results of base treatment of sulfones. Reagents and conditions: (a) R = Me; (b) R = CHMe; (c) R = CH_2CHMe_2; (d) R = CH_2Ph; i = Et3N, $CHCl_3$, 0.5–2 h; ii = Et_3N, $CHCl_3$, 24 h.

Table 1
Compilation of the results of base treatment of various sulfones

Substrate	Product	Time (min)	Yield (%)	Yield of deprotected indole (%)
1a	**7a**	120	98	95 (for **9**)
1b	**7b**	50	97	95 (for **10**)
1c	**7c**	33	98	
1d	**7d**	81	95	
3	**8**	90	95	



Scheme 4. Mechanism of GB and nucleophilic addition.

the stable indole system and is thought to be exothermic. We believe that it is the endothermicity of the first step in GB cyclization which is responsible for the observed selectivity (Scheme 4).

In conclusion, we have developed a simple method for the preparation of 2,2′-bis-indole derivatives connected via a functional linker involving double Michael-type addition to bis-allenic sulfone, generated in situ from bis-propargyl sulfone. We have also demonstrated that intramolecular nucleophilic addition of amides is more facile than the Garratt-Braverman cyclization pathway which occurs at room temperature in aryl-substituted allenes. Our observation is in line with the reported cleavage of DNA[14] by allenic sulfones via alkylation pathway (Nicolaou[15]).

Acknowledgments

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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.2009.08.001.

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12. *Selected spectral data*: All ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ unless mentioned otherwise.
For **7a**: White solid; yield 98%, mp 130 °C; δ_H 7.78 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 7.6 Hz, 2H), 7.38 (dt, J = 6.4, 1.2 Hz, 2H), 7.30–7.26 (m, 2H), 6.86 (s, 2H), 5.49–5.42 (m, 4H), 5.16 (d, J = 14 Hz, 2H), 4.96 (d, J = 14.4 Hz, 2H), 1.50 (d, J = 6.4 Hz, 6H), 1.46 (s, 18H); δ_C 175.1, 155.3, 135.9, 128.8, 127.1, 125.6, 123.4, 121.5, 115.6, 114.1, 80.2, 53.1, 51.7, 28.3, 18.6; $[\alpha]_D$ −90.5 (c 0.20, $CHCl_3$); MS: m/z = 689.28 [MNa^+], 667.31 [MH^+]; HRMS: calcd for $C_{34}H_{42}N_4O_8S + H^+$ 667.2804; found 667.2799.
For **7b**: White solid; yield 97%, mp 178 °C; δ_H 7.86 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 7.6 Hz, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.28–7.24 (m, 2H), 6.87 (app. d, J = 8.0 Hz, 2H), 5.40–5.38 (m, 4H), 5.17 (dd, J = 22.1, 14.4 2H), 4.98 (dd, J = 22.1, 14.4 Hz, 2H), 2.19 (br s, 2H), 1.46 (s, 18H), 1.01 (app. d, J = 5.2 Hz, 6H), 0.86 (app. d, J = 5.2 Hz, 6H); δ_C 174.1, 156.0, 136.0, 129.1, 127.4, 125.6, 123.6, 121.5, 115.9, 114.3, 80.1, 59.7, 53.6, 31.5, 28.3, 19.7, 16.4; $[\alpha]_D$ −121.32 (c 0.20, $CHCl_3$); MS: m/z = 745.32 [MNa^+], 723.23 [MH^+]; HRMS: calcd for $C_{38}H_{50}N_4O_8S + H^+$ 723.3430; found 723.3427.
For **7c**: White solid; yield 98%, mp 75 °C; δ_H 7.92 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 7.6 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.27–7.24 (m, 2H), 6.84 (app. d, J = 10.0 Hz, 2H), 5.48 (br s, 2H), 5.29–5.12 (m, 4H), 4.84 (dd, J = 27.2, 14.4 Hz, 2H), 1.78–1.75 (m, 2H), 1.45 (s, 18H), 1.33–1.25 (m, 4H), 0.98 (d, J = 6.4 Hz, 6H), 0.87 (d, J = 4.4 Hz, 6H); δ_C 175.7, 155.8, 135.9, 128.9, 127.2, 125.5, 123.5, 121.4, 115.3, 114.2, 80.1, 54.3, 53.0, 41.8, 28.3, 24.8, 23.2, 21.5; $[\alpha]_D$ −28.3 (c 0.20, $CHCl_3$); MS: m/z = 773.36 [MNa^+], 751.06 [MH^+]; HRMS: calcd for $C_{40}H_{54}N_4O_8S + H^+$ 751.3743; found 751.3738.
For **7d**: White solid; yield 95%, mp 125 °C; δ_H 7.88 (d, J = 8.4 Hz, 2H), 7.53 (app. t, J = 6.8 Hz, 2H), 7.36 (app. t, J = 8.0 Hz, 2H), 7.27–7.09 (m, 12H), 6.81 (app. d, J = 4.8 Hz, 2H), 5.68 (b, 2H), 5.37 (app. t, J = 8.0 Hz, 2H), 4.96–4.86 (m, 4H), 3.28–3.21 (m, 2H), 2.96–2.89 (m, 2H), 1.35 (s, 18H); δ_C 174.0, 155.3, 136.0 (2C), 129.4, 128.9, 128.4, 127.0, 126.9, 125.6, 123.6, 121.5, 115.4, 114.3, 80.2, 56.7, 53.1, 39.2, 28.2; $[\alpha]_D$ −30.8 (c 0.20, $CHCl_3$); MS: m/z = 841.31 [MNa^+], 819.25 [MH^+]; HRMS: calcd for $C_{46}H_{50}N_4O_8S + H^+$ 819.3430; found 819.3425.
For **8**: White solid; yield 95%, mp 150 °C; δ_H 7.76 (d, J = 7.6 Hz, 3H), 7.64 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 8.0, 3H), 7.35 (app. t, J = 7.2 Hz, 1H), 7.26–7.23 (m, 1H), 6.57 (s, 1H), 5.46–5.43 (m, 2H), 5.26 (d, J = 14.4 Hz, 1H), 4.89 (d, J = 14 Hz, 1H), 1.52 (d, J = 6.4 Hz, 3H), 1.44 (s, 9H); δ_C 175.0, 155.3, 138.6, 136.0, 133.9, 129.1, 128.7, 128.4, 127.4, 125.6, 123.4, 121.6, 115.6, 114.1, 80.1, 56.2, 51.7, 28.3, 18.9; $[\alpha]_D$ +403.6 (c 0.20, $CHCl_3$); MS: m/z = 465.17 [MNa^+], 443.13 [MH^+]; HRMS: calcd for $C_{23}H_{26}N_2O_5S + H^+$ 443.1642; found 443.1637.

For **9**: White crystalline solid; yield 95%, mp 220–222 °C; δ_H (MeOH-d_4) 7.56 (dd, J = 8.0, 0.8 Hz, 2H), 7.37 (dd, J = 8.0, 0.8 Hz, 2H), 7.14 (dt, J = 7.2, 1.2 Hz, 2H), 7.04 (dt, J = 6.8, 0.8 Hz, 2H), 6.61 (s, 2H), 4.60 (s, 4H); δ_C (MeOH-d_4) 137.2, 128.0,124.6, 121.7, 119.8, 119.1, 110.7, 104.3, 50.8; MS: m/z = 347.07 [MNa^+], 325.01 [MH^+]; HRMS: calcd for $C_{18}H_{16}N_2O_2S + H^+$ 325.1012; found 325.1008.
For **10**: Yellow solid; yield 95%, mp 191–192 °C; δ_H 8.80 (br s, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.49–7.39 (m, 4H), 7.22 (t, J = 7.6 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.14 (s, 1H), 4.54 (s, 2H); δ_C 137.3, 136.8, 134.0, 129.0, 128.3, 127.5, 124.4, 122.9, 120.6, 120.1, 111.1, 105.6, 56.2; MS: m/z = 294.07 [MNa^+], 272.17 [MH^+]; HRMS: calcd for $C_{15}H_{13}NO_2S + H^+$ 272.0746; found 272.0743.

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