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A Novel Dimerization of Ethyl 3-Cyanomethyl-2-indolecarboxylate

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Abstract: Reaction of ethyl 1-benzenesulfonyl-3-bromomethyl-2-indolecarboxylate (3) with KCN in THF resulted in the formation of ethyl 1-benzenesulfonyl-3-cyanomethyl-2-indolecarboxylate (4) and two other dimeric indole derivatives **5** and **6**. The machanism of formation of products **5** and **6** is explained, via the elimination of benzenesulfinate.

3,4-Disubstituted indoles are potential intermediates for many alkaloids and pharmacologically important substances.[1] Many dimeric indoles were isolated from nature and some of them were found to be lead compounds as protein-kinase C (PKC) inhibitors.[2] Efforts have also been made to improve the potency of such compounds, to develop them as chemotherapeutic agents.[3,4] Our interest in this area stems from the fact that the dipeptide of 5-bromotryptophan is the most potent antisickling agent reported to date,[5] and recent computer modeling studies have suggested that indole-derived substances are a potential source of new antisickling agents.[6]

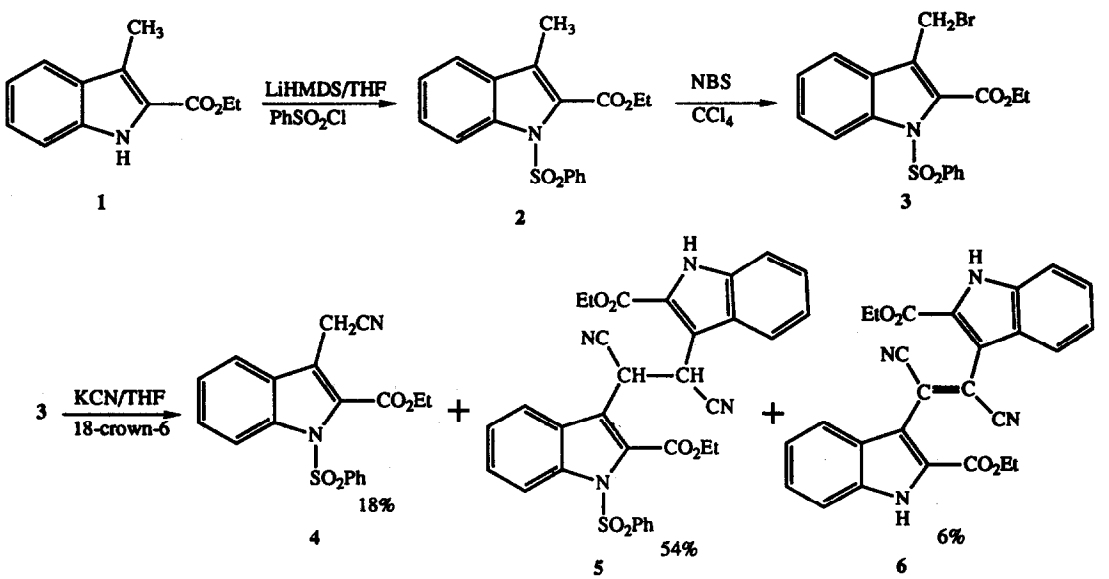
Recently, one of us described the wide application of 3-bromomethylindoles for the preparation of potential intermediates of alkaloids and pharmacologically important substances.[1] Here, we present the synthesis of another useful intermediate, ethyl 1-benzenesulfonyl-3-bromomethyl-2-indolecarboxylate (**3**), and its novel reaction with KCN.

The required ethyl 3-methyl-2-indolecarboxylate (**1**) was prepared by the reaction of phenylhydrazine with 2-ketobutyric acid in ethanol.[7] Initially, when we tried the benzenesulfonylation of **1**, under standard reaction conditions using *n*-BuLi or NaH or dimsyl anion as the base, it either resulted in the complete recovery of the starting material **1** or the formation of a small amount of the expected product, ethyl 1-benzenesulfonyl-3-methyl-2-indolecarboxylate (**2**). Generation of molecule **1** on computer modeling and energy minimization using MMOD calculations[8] showed a strong intramolecular hydrogen bonding of the

indole N-H with the carbonyl oxygen of the 2-CO_2Et group, which explains the difficulty of the N-substitution. However, the sulfonation of **1** was accomplished by using a strong base, lithium hexamethyldisilazide (LiHMDS), in THF followed by treatment with benzenesulfonyl chloride to give the desired product **2** in 94% yield.

Sulfonylindole **2** reacted with *N*-bromosuccinimide in the presence of a catalytic amount of benzoyl peroxide to give ethyl 1-benzenesulfonyl-3-bromomethyl-2-indolecarboxylate (**3**) in almost quantitative yield. Compound **3**, on treatment with 1.5 equivalents of KCN in THF under nitrogen in the presence of a catalytic amount of 18-crown-6 at 0 °C, followed by stirring at room temperature for about 24 h, gave ethyl 1-benzenesulfonyl-3-cyanomethyl-2-indolecarboxylate (**4**) in only 18% yield, after careful chromatographic separation. In addition, two other products were also isolated and a thorough spectral and physical characterization of these compounds showed them to have structures **5** and **6** (Scheme **1**).[9] These compounds were obtained in 54% and 6% yields, respectively.

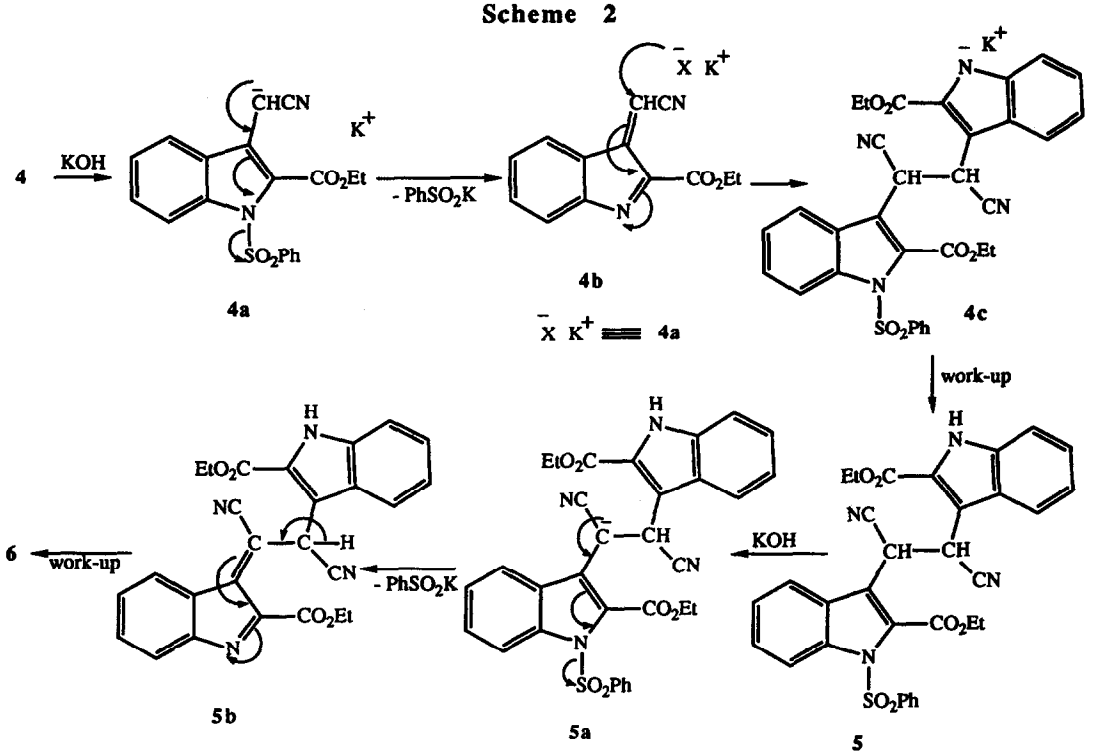
Scheme 1



The formation of **5** can be explained as follows: initially the bromide **3** reacted with KCN to give the desired compound **4**. Then KCN or traces of KOH or K_2CO_3 present in the KCN reagent could generate the anion **4a** by the abstraction of a proton from **4**, which could eliminate a benzenesulfinate to give the intermediate **4b**, as shown in Scheme 2. The intermediate **4b**, in turn could be attacked by another molecule of **4a** to form the intermediate **4c**, which on work-up would give product **5**. This mechanism was supported by the formation of product **6**. Formation of **6** could also be explained by a further elimination of another

benzenesulfinic acid to form the intermediate **5b** and its subsequent isomerization to give product **6**, after work-up.

Scheme 2



The overall mechanism is also supported by two more observations: firstly, complete analysis of the product mixture did not give any product similar to **5** with both the benzenesulfonyl groups intact or both the benzenesulfonyl groups cleaved. This strongly suggests the elimination of the benzenesulfonyl group as benzenesulfinate, instead of a possible hydrolytic cleavage. Secondly, extension of the reaction time resulted in the formation of more **6**; after 3 days stirring the yield of **6** improved to 35%. This dimerization mechanism was conclusively proved by reacting a pure sample of ethyl 1-benzenesulfonyl-3-cyanomethyl-2-indolecarboxylate (**4**) with KCN or KOH or K_2CO_3 , in three separate experiments, and a catalytic amount of 18-crown-6 in THF and stirring the mixture at room temperature for 24 h, which on work-up, provided products **5** and **6**, in all these experiments.

It is worth noting that such elimination of benzenesulfinate was not observed with 1-benzenesulfonyl-3-bromomethylindole; instead it gave the desired product, 1-benzenesulfonyl-3-cyanomethylindole in 96% yield.[1] Similar elimination of benzenesulfinate was also observed when ethyl 1-benzenesulfonyl-5-methoxy-2-methyl-3-indolecarboxylate was heated with potassium *t*-butoxide, but in poor yield.[10] These results also suggest that activation by a carboxyl group is essential for the elimination of benzenesulfinate.

Preliminary testing of a tetracarboxylic acid derived from compound **5** showed significant antisicking activity. Efforts are currently underway to extend this dimerization reaction to synthesize a variety of useful indole derivatives to screen them for their PKC inhibitory and antisickling activities.

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9. **4**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01 (d, *J* = 7.2 Hz, 1 H), 7.90 (dd, 1 H), 7.63-7.37 (m, 6 H), 7.23 (t, *J* = 7.2 Hz, 1 H), 4.71 (s, 2 H), 4.27 (q, *J* = 7 Hz, 2 H), 1.32 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 137.84, 136.52, 134.02, 133.87, 131.52, 129.02, 128.43, 128.23, 127.35, 127.12, 124.43, 121.17, 115.48, 115.06, 62.41, 52.69, 13.80. CIMS: m/e 369 (MH^+, 100).
5: ^{1}H NMR (DMSO-d_6) δ 12.66 (bs, 1 H, N-H), 7.98 (d, *J* = 7.8 Hz, 1 H), 7.85 (d, *J* = 8.3 Hz, 1 H), 7.73-7.69 (m, 3 H), 7.58-7.48 (m, 3 H), 7.48-7.44 (m, 2 H), 7.35-7.27 (m, 2 H), 6.91 (t, *J* = 7.6 Hz, 1 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 4.36 (s, 2 H), 4.00 (q, *J* = 7.1 Hz, 2 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 1.05 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (DMSO-d_6) δ 160.27, 160.15, 139.90, 137.04, 135.70, 135.65, 134.65, 130.86, 129.62, 128.46, 127.48, 126.49, 125.40, 124.87, 124.24, 123.98, 122.25, 121.28, 119.42, 118.77, 115.42, 114.56, 113.37, 61.99, 61.66, 36.09, 32.66, 14.06, 13.29. CIMS: m/e 595 (MH^+, 18), 550 (26), 549 (71), 394 (51), 343 (21), 342 (100).
6: ^{1}H NMR (DMSO-d_6) δ 12.86 (bs, 1 H, N-H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.66 (d, *J* = 8.0 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 1 H), 7.35 (t, *J* = 7.4 Hz, 1 H), 4.46 (q, *J* = 7 Hz, 2 H), 1.34 (t, *J* = 7 Hz, 3 H). CIMS: m/e 453 (MH^+, 11), 185 (100).
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