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Friedel-Crafts Cyclization of 2-(3-Indolythio)propionic Acids. An Unusual Rearrangement Leading to 4-Sulfur-Substituted Tricyclic Indoles

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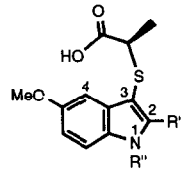
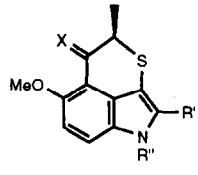
Key Words: Friedel-Crafts acylation; rearrangement; tricyclic-indoles; 4-thio-indoles; thiopyrano-[4,3,2-c,d]indoles

Abstract: *The intramolecular Friedel-Crafts acylation of 2-(3-indolythio)propionic acid 1 has been found to undergo an unprecedented rearrangement to provide a novel tricyclic indole having the sulfur substituted on C-4 rather than on the expected C-3. A mechanism for its formation is proposed. This rearrangement also proceeded with good optical retention when a chiral substrate was used.*

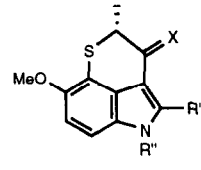
The acid-catalyzed migration of carbon substituents from C-3 to C-2 in the indole systems is a well-studied phenomenon.[1] Recently, three groups[2] reported the first examples of this rearrangement in which the migrating atom is sulfur. Other migration patterns of sulfur-containing groups in indoles such as C-2 to C-3, C-3 to C-1 and C-1 to C-3 migrations have also been documented.[3] However, rearrangement of the sulfur-containing groups from C-3 to C-4 has not been reported. Here we report an unexpected rearrangement of the acid chloride of 2-(3-indolythio)propionic acid **1** that gave, overall, such migration in a Friedel-Crafts cyclization reaction providing the thiopyrano-[4,3,2-c,d]indole **3a** rather than the expected **2a**. Interestingly, this rearrangement and the subsequent Friedel-Crafts cyclization proceeded with retention of optical activity when a chiral substrate was used. This ring system's resemblence to the antibiotic Chuangxinmycin, **4**,[4] makes this rearrangement a potential non-racemic approach to this class of compounds.



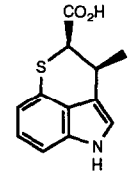
1
R' =$CH_2C(CH_3)_2CH_2CN$
R''= p-$ClC_6H_4CH_2$



2a X=O
2b $X=H_2$



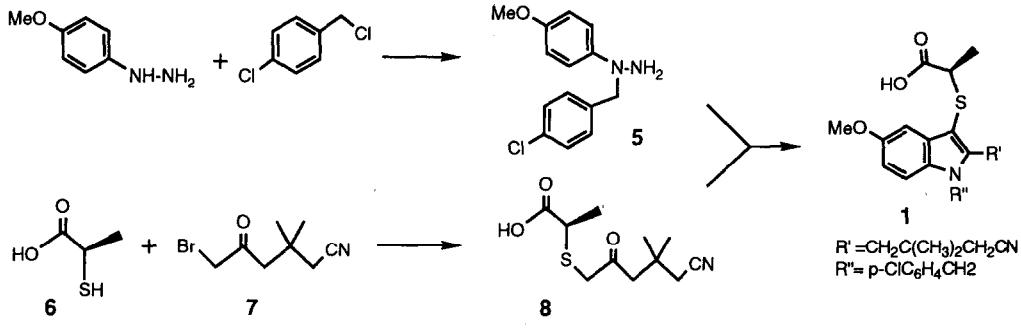
3a X=O
3b $X=H_2$



4

In connection with our indole synthesis program, we were interested in the preparation of enantiomerically pure tricyclic indole **2b**. Since the all-carbon analogue (e.g. Uhle's ketone) has been prepared by Friedel-Crafts cylization of 3-(3-indolyl)propionic acid[5] onto the C-4 position, we envisioned that **2b** could be constructed in a similar fashion using a chiral thiolactic acid derivative **1** followed by a deoxygenation of the resulting tricyclic

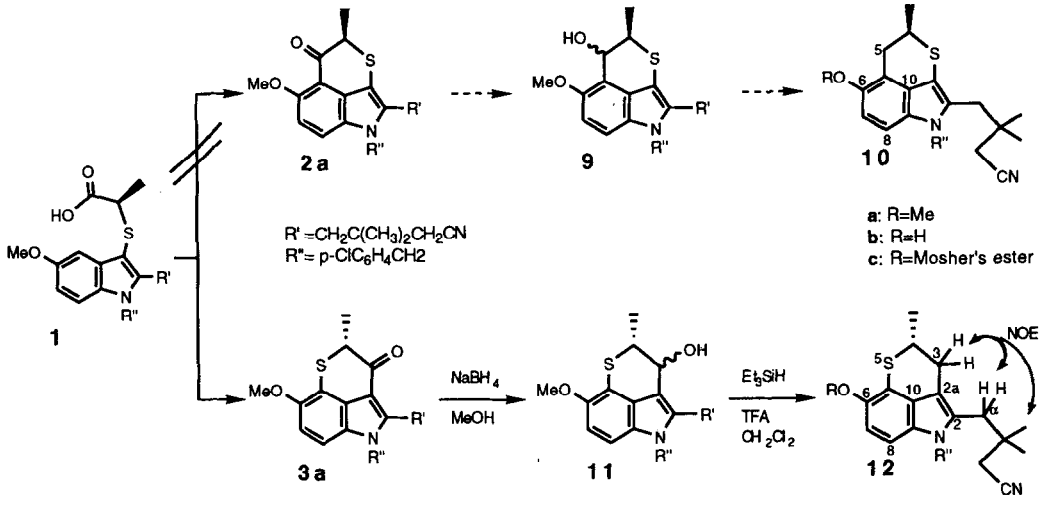
ketone **2a**. Thus the required indole acid **1**[6] was readily prepared by a Fischer indole synthesis in 85% yield with retention of optical activity by the reaction of Nα-(*p*-chlorobenzyl)-*p*-methoxyphenyhydrazine, **5**, chiral keto-acid **8** and 5 eq. of acetic acid in toluene for 2 days at room temperature. Hydrazine **5** was prepared in 74% yield by a selective *p*-chlorobenzylation of the more basic nitrogen in *p*-methoxyphenyhydrazine hydrochloride using two eq. of triethylamine in refluxing toluene for 3 h. The keto-acid **8**[7] was synthesized from (S)-thiolactic acid, **6**[8], and bromoketone **7**[9] with the aid of 2 eq. of Hunig's base in THF at room temperature.



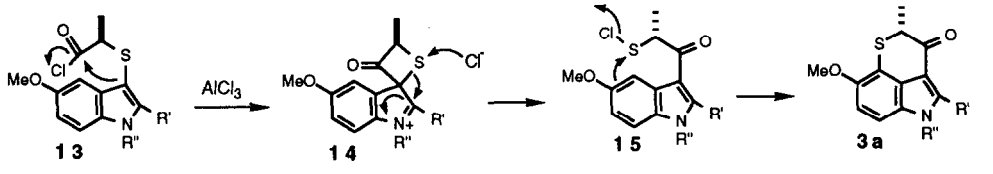
All attempts to effect the ring closure of **1** to **2a** via the mixed anhydride methods (such as TFAA, PPA, trimethylsilyl polyphosphate, and P_2O_5-$MeSO_3H$) gave either no reaction or decomposition of starting material. One possible rationale for such facile decomposition is that decarbonylation of the reactive acylium ion intermediate is a rapid process due to the high electron density of the system stablizing the resulting carbocation. After screening a variety of Lewis acids, the Friedel-Crafts cyclization of **1** was best effected by treating a CH_2Cl_2 solution of the corresponding acid chloride (generated in situ using 1.2 eq. of oxalyl chloride and 5 mol% DMF in CH_2Cl_2) with 3.5 eq. of $AlCl_3$ (1 M solution in nitrobenzene) at 0° C for 3 h. After quenching with 2 N HCl and purification by flash chromatography (EtOAc/Hexane), a 40-50% yield of the apparent tricyclic ketone was obtained. The ^1H NMR was consistent with **2a**, however, it could not differentiate between **2a** and the isomeric product **3a**. Subsequently this ketone was deoxygenated ((a) $NaBH_4$ /MeOH, then (b) the resulting diastereomeric alcohols were reduced with 10 eq. TFA/2 eq. Et_3SiH/ CH_2Cl_2) and demethylated (BBr_3/CH_2Cl_2)). The resulting product was then compared with an authentic racemic sample of **10b**[10] by ^1H-, ^{13}C-NMR, MS, TLC and HPLC. To our surprise, the results indicated that the two compounds were isomeric. Inverse detection long-range ^1H-^{13}C correlation experiments[11] and NOE difference studies were used to identify the material as **12b**.[12] Long-range correlations from the C-3 and C-α methylene protons to C-2 and C-2a (two- and three-bond coupling pathways) were used to establish the opposite orientation of the C-ring. NOE enhancements were observed between the C-3 methylene protons and protons of the *gem*-dimethyl side chain, adding additional support for this rearranged product. Longe-range ^1H-^{13}C connectivity data for authentic (±)**10b** showed correlations from H-8 to C-6 and C-10 (three-bond pathways) and from the C-5 methylene protons to these same carbons, thus confirming the orientation of the C-ring.

These results indicate that an unexpected rearrangement had taken place. Reflection pointed to the Friedel-Crafts cyclization as the most likely place for this rearrangement to occur. While the reduction (CF_3CO_2H/ Et_3SiH/CH_2Cl_2) was also suspect, since neat trifluoroacetic acid has been reported[2] to induce isomerization of

indol-3-yl sulfides to indol-2-yl sulfides, this notion was dismissed by the demonstration that indole acid **1** was completely inert toward trifluoroacetic acid for 18h at room temperature. In addition, **10b** was inert toward the Lewis acids used in the demethylation steps. It appears reasonable that the rearrangement occurred during the Friedel-Crafts cyclization to give **3a** rather than the expected **2a**.



A reaction mechanism is proposed below. The spiroindolenine intermediate **14** is formed from an intramolecular acylation at C-3. Chloride ion displacement of the sulfur would give the sulfenyl chloride **15**, which in turn undergoes an intramolecular electrophilic substitution at C-4 to give the rearranged tricyclic indolic ketone **3a**. The involvement of such spirocyclic intermediates has been well precedented in the chemistry of tryptamine and related derivatives.[13] Interestingly, the enantiomeric purities of both tricyclic ketone **3a** and the 5-hydroxy indole **12b** were shown to be >90% ee,[14] indicating good stability of the stereogenic center.



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6. **1**: mp 60-65°C; $[\alpha]_D^{22}$ +81.9° (c 1.05, EtOAc); >95% ee based on the HPLC analysis using chiral Supelcosil™ column; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.20 (d, J=2.5 Hz, 1H), 7.18 (d, J=8.4, 2H), 7.04 (d, J=8.8, 1H), 6.80 (dd, J=8.8, 2.5, 1H), 6.68 (d, J=8.4, 2H), 5.36 (s, 2H), 3.86 (s, 3H), 3.57 (q, J=7.1, 1H), 2.96, 2.86 (AB, J=14.6, 2H), 2.35 (s, 2H), 1.40 (d, J=7.1, 3H), 1.13 (s, 6H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 178.5, 155.3, 142.7, 135.4, 133.3, 131.8, 130.9, 129.1, 126.9, 118.3, 113.0, 111.4, 103.0, 100.9, 55.8, 47.5, 45.0, 36.2, 35.3, 31.1, 27.2, 16.7.
7. **8**: $[\alpha]_D^{22}$ +111.0° (c 1.0, EtOAc).
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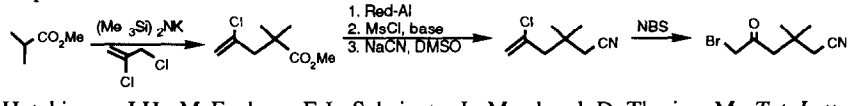
9. Prepared as shown below:



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12. Inverse detection long-range ^{1}H-^{13}C correlation experiments and NOE difference studies were done on **12c**.
13. (a) Ungemach, F.; Cook, J.M. *Heterocycles*, **1978**, *9*, 1089. (b) Ritchie, R.; Sexton, J.E. *J. Chem. Res. (M)*, **1990**, 529.
14. Optical purities of **3a** and **12b** were determined by the ^{1}H NMR analysis using chiral shift reagent Eu(hfc)3 and the Mosher's ester **12c** respectively. **3a**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.27 (d, J=8.4 Hz, 2H), 6.88 (d, J=8.8, 1H), 6.85 (d, J=8.4, 2H), 6.82 (d, J=8.8, 1H), 5.38 (s, 2H), 3.91 (s, 3H), 3.92 (q, J=7.1, 1H), 3.29, 3.16 (AB, J=14.1, 2H), 2.59, 2.50 (AB, J=16.8, 2H), 1.58 (d, J=7.1, 3H), 1.23 (s, 6H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 189.2, 151.0, 142.7, 134.1, 133.9, 130.0, 129.3, 127.3, 127.2, 118.4, 110.5, 110.2, 109.2, 107.9, 56.9, 47.3, 45.0, 36.9, 36.1, 30.2, 27.3, 27.2, 17.8. **12b**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.19 (d, J=8.4, 2H), 6.78 (d, J=8.6, 1H), 6.73 (d, J=8.6, 1H), 6.72 (d, J=8.4, 2H), 5.28 (s, 2H), 4.70 (s, -OH), 3.45 (m, 1H), 3.15 (dd, J=15.4, 3.1, 1H), 2.78 (dd, J=15.4, 9.6, 1H), 2.69 (s, 2H), 2.32 (s, 2H), 1.53 (d, J=6.8, 3H), 1.15 (s, 3H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 144.6, 136.2, 133.2, 131.8, 131.0, 129.0, 127.2, 124.2, 118.3, 112.1, 111.0, 109.9, 106.9, 46.7, 38.6, 36.7, 35.6, 33.1, 30.9, 27.2, 27.1, 20.9.

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