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The Unility of the Pummerer Rearrangement Intermediates in the Presence of Lewis Acids—A Short and Practical Synthesis of 4-(2-Di-n-Propylaminoethyl)-7-methoxyindole

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THE UTILITY OF THE PUMMERER REARRANGEMENT INTERMEDIATES IN THE PRESENCE OF LEWIS ACIDS - A SHORT AND PRACTICAL SYNTHESIS OF 4-(2-DI-n-PROPYLAMINOETHYL)-7-METHOXYINDOLE

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Abstract. The interesting compound **5** was prepared by treatment of **3** with Ra-Ni and $LiAlH_4$. In turn, **3**, was obtained in high yield utilizing the trapping of a Pummerer intermediate, under mild Lewis acid conditions.

Back in 1985 we reported a new electrophilic heteroalkylation-homoacylation methodology[1-3]. This, in principle, involves the trapping of a Pummerer rearrangement intermediate, generated *in situ*, from appositely functionalised precursors, by a π-electron system in the presence of a Lewis acid, under very mild reaction conditions.

We have applied this technology effectively on both intermolecular[4-6,8] and intramolecular reactions[7,8].

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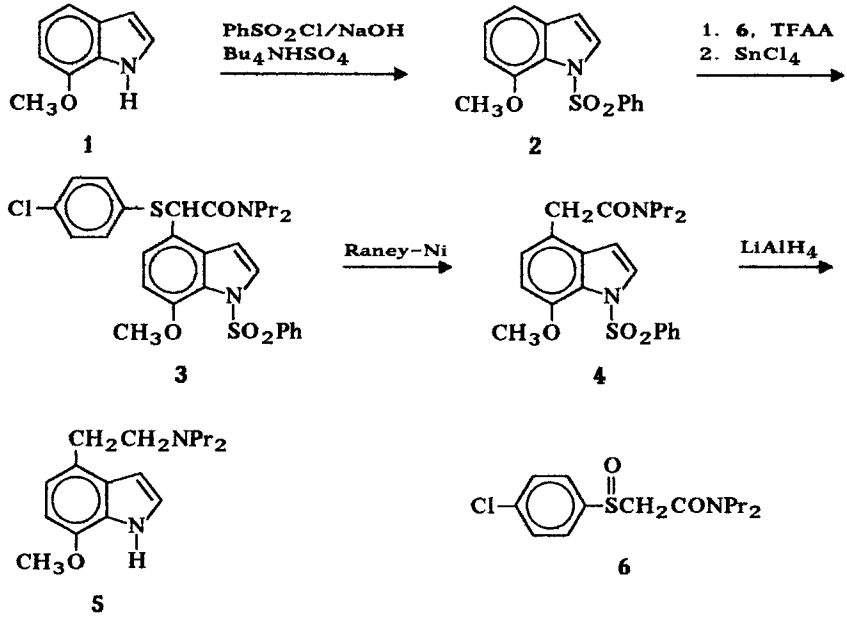
The utility of this heteroalkylation-homoacylation reaction is further manifested due in part to its preference of the site of attack, in comparison with other well known electrophilic substitution reactions such as the Friedel-Crafts alkylation-acylation.

More specifically, whereas in the case of Friedel-Crafts acylation of the substrate, 1-acetyl-7-methoxyindoline, the electrophilic substitution was reported to occur exclusively at C-4 position[9], in the case of applying this methodology on the substrate 1-benzenesulfonyl-7-methoxyindoline, the electrophilic substitution occurs regioselectively at C-5 position instead[5].

Furthermore, it was also reported that, the Friedel-Crafts acylation of 1-benzenesulfonyl-6-methoxyindole occurs exclusively at 3-position, despite the deactivating effect of the 1-benzenesulfonyl group on this position. On the other hand, Friedel-Crafts alkylations of 1-benzenesulfonylindoles at 3-position have met with failure[10].

However, employing the reaction conditions of this methodology on the substrate 1-benzenesulfonyl-7-methoxyindole, the electrophilic attack occurs exclusively at C-4 position.



1 2 3 4 5 6

Thus, having in mind the aforementioned peculiarities of this reaction, we attempted the synthesis of the title compound **5**, with the result to accomplish it in a short (4 steps) and practical way, since a previously reported method seems to be inconvenient due to the multiple step (13 steps) sequence starting from 3-methyl-2-nitrophenol[11].

Specifically, the Pummerer intermediate which was generated from the precursor compound **6** by treatment with $(CF_3CO)_2O$, was trapped by the 1-benzenesulfonyl-7-methoxyindole **2** in the presence of $SnCl_4$ to give compound **3** in 85% yield. Compound **2** was easily prepared from 7-methoxyindole by standard procedures in 84% yield. Raney-Ni removed the p-chlorophenylthio-group from **3** almost quantitatively. The produced amide **4** was converted to the target compound **5** in one step , in 92% yield by treatment with $LiAlH_4$.

Nmr spectral analysis of product 5. Confirmation of the structure **5** and definitive assignement of the position of substitution on the indole **2**, was obtained by ^1H and ^{13}C NMR spectroscopy.

Thus, in the ^1H-NMR spectrum of 7-methoxyindole **1**, the H-4 signal appears at 7.25 ppm as a doublet with J=8.0 Hz. The signal of the same hydrogen in compound **2** appears at 7.15 ppm as a doublet of doublets with J=7.8 Hz (ortho coupling) and J= 1.4 ppm (meta coupling). Both signals disappeared in the spectra of the substituted products **5** and **4** respectively.

Furthermore, the signal of H-5 in **1**, which appears at 7.014 ppm as triplet with J=7.9 Hz (overlapping with the signal of H-2 at 7.010 ppm) colapsed to a doublet at 6.82 ppm with J=7.8 Hz in the substituted compound **5**. Similarly, the signal of the same H-5 in compound **2** which appeared at 7.10 ppm as a triplet with J=7.8 Hz colapsed to a doubled at 6.98 ppm with J=8.1 Hz in the substituted compound **4**. A N-H proton resonance decoupling reduced the two triplets of H-2 and H-3 of compound **5** to two distinct doublets.

The ^{13}C chemical shifts of 7-methoxyindole in $CDCl_3$ are listed in the table and are in good agreement with those reported in the literature measured in DMSO-d_6 solution, when taking into consideration the parameters of solvation and concentration, and that each carbon atom of

the indole ring behaves in a particular way. The observed two large heteronuclear coupling constants (J_{CH}=183 Hz and J_{CH}=173 Hz) are characteristic of the C-2 and C-3 of indole[12], in comparison to those of the benzene ring moiety of indole, which are confined at a value around 160 Hz (Table).

Table. ^{13}C-NMR Chemical Shifts and Coupling Constants (J_{CH}) of the Ring System of 7-Methoxyindole **1** and 7-Methoxy-DPAI **5**.

	7-methoxyindole **1**			7-methoxy-DPAI **5**		
C atom	δ[12] ppm	δ ppm	$^1J_{CH}$ Hz	δ ppm	SCS ppm	$^1J_{CH}$ Hz
2	124.7	123.7	183	123.8	0.1	183
3	101.5	102.3	173	101.1	-1.2	172
3α	129.2	129.0	—	128.9	-0.1	—
4	112.9	113.2	158	125.4	12.2	—
5	119.3	119.9	159	119.3	-0.6	155
6	101.3	101.5	157	101.7	0.2	156
7	146.2	145.8	—	145.0	-0.8	—
7α	126.1	126.1	—	126.5	0.4	—

The signal of C-4 appears at 113.2 ppm with a J_{CH}=158 Hz. Substitution at this position lead this signal to an *ipso* shift of +12.2 ppm, with concomitant loss of its heteronuclear coupling as well as its intensity. These observations clearly established the site of substitution as can be inferred below.

(1) The loss of about half of its intensity is an indication that the C-4 signal was deprived of nOe enhancement derived from an attached proton; (2) plain methyl substituent-induced chemical shift (SCS) values for the *ipso* carbon in indole itself are reported[13] to be

in the order of 9-10 ppm, which are compared favorably with the above recorded value of 12.2 ppm for the product **5** and (3) a careful examination[13] of the signals of substituted indoles reveals that methyl substituents at C-5, C-6 and C-7 have no important effects on the carbons in the heterocyclic ring of indole, whereas a methyl substituent at C-4 position moves the signal of C-3 upfield by 1.5 ppm. In the case of compound **5**, this effect has the value of 1.2 ppm.

EXPERIMENTAL

7-methoxyindole 1 was prepared in 76% yield from commercial 3-hydroxy-2-nitrotoluene as described previously[5].

^{1}H NMR ($CDCl_3$): δ 3.87 (s, 3H, CH_3O-), 6.49 (m, C3-H), 6.59 (d, 7.7 Hz, C6-H), 7.01 (t, C2-H), 7.01 (t, 7.8 Hz, C5-H), 7.25 (d, 8.0 Hz, C4-H), 8.35 (bs, N-H).

^{13}C NMR ($CDCl_3$): δ 54.7 (CH_3O-), 101.5 (C6), 102.3(C3), 113.2 (C4), 119.9 (C5), 123.7 (C2), 126.1 (C7α), 129.0 (C3α), 145.8 (C7).

1-benzenesulfonyl-7-methoxyindole 2. To a well-stirred solution of 7-methoxyindole **1** (3.69 g, 25 mmol) in CH_2Cl_2 (100 ml), cooled in a water bath (5-10°C), powedered sodium hydroxide (4.0 g, 100 mmol) and tetrabutylammonium hydrogen sulfate (0.17g, 0.5 mmol) were added, followed by a solution of benzenesulfonyl chloride (13.2 g, 75 mmol) in 50 ml CH_2Cl_2. The reaction mixture was stirred at this temperature for 4 h. Then it was filtered, concentrated in vacuo, and purified in a column of silica gel using toluene-hexane 60:40. The product was obtained as a colorless viscous liquid that crystallized on standing, yield 6.0 g (84%). It was recrystallized from CH_2Cl_2-hexane to colorless crystals, m.p. 89-90°C.

^{1}H NMR ($CDCl_3$): 3.62 (s, 3H, CH_3O-), 6.64 (d, 3.7 Hz, C3-H), 6.66 (dd, 7.4/1.3 Hz, C6-H), 7.10 (t, 7.6 Hz, C5-H), 7.15 (dd, 7.8/1.4 Hz, C4-H), 7.42-7.55 (m, 3H, $PhSO_2$-), 7.81-7.84 (m, 2H, $PhSO_2$-), 7.83 (d, 3.9 Hz, C2-H).

N,N-Di-n-propyl-(1-benzenesulfonyl-7-methoxy-4-indolyl)-(p-chlorophenylthio)-acetamide 3. To an ice-cold solution of N,N-di-n-propyl-p-chlorobenzenesulfinyl-acetamide[5] **6** (3.32 g, 11 mmol), in dry CH_2Cl_2

(50 ml) under argon was added dropwise through a syringe trifluoroacetic anhydride (1.6 ml, 11 mmol). The solution was stirred at this temperature for 20 min, then 1-benzenesulfonyl-7-methoxyindole **2** was added (2.87 g, 10 mmol), followed by a dropwise addition of tin tetrachloride (1.2 ml, 10 mmol). The color of the solution turned immediately to dark green.

After stirring for an additional 30 min at $0^{o}C$, the reaction mixture was poured into water, the organic phase was separated, dried over Na_2SO_4 and filtered through a bed of silica. Removal of the solvent afforded a liquid residue, which was chromatographed on silica. The column was first eluted with CH_2Cl_2–hexane 50:50 and finally with CH_2Cl_2 to yield the product **3** as a light pink syrup (4.85 g, 85%).

^1H NMR ($CDCl_3$): 0.65–0.82 (2t, 6H, $-N(CH_2CH_2CH_3)_2$), 1.1–1.6 (m, 4H, $-N(CH_2CH_2CH_3)_2$), 2.9–3.5 (m, 4H, $-N(CH_2CH_2CH_3)_2$), 3.63 (s, 3H, CH_3O-), 5.26 (s, 1H, C4α-H), 6.57 (d, 8.3 Hz, C6-H), 6.62 (d, 3.8 Hz, C3-H), 7.07 (d, 8.3 Hz, C5-H), 7.06–7.14 (m, 4H, $-SC_6H_4Cl$), 7.48–7.59 (m, 3H, $PhSO_2-$). 7.80 (d, 3.6 Hz, C2-H), 7.80–7.83 (m, 2H, $PhSO_2-$).

N,N-Di-n-propyl-(1-benzenesulfonyl-7-methoxy-4-indolyl)-acetamide 4. To a vigorously stirred solution of **3** (2.85 g, 5 mmol) in ethyl acetate (50 ml) a sufficient quantity (*ca* 1 teaspoonful) of Raney-Ni was added under argon. The suspension was stirred at room temperature until TLC indicated that the reaction was complete (1–2 h). The stirring was stopped, the solution was decanted and the catalyst was washed twice with warm ethyl acetate. The product was dried over Na_2SO_4, filtered through a silica bed, concentrated and dried in vacuo to yield 2.05 g (96%) of **4** as a colorless syrup.

^1H NMR ($CDCl_3$): 0.78–0.91 (m, 6H, $-N(CH_2CH_2CH_3)_2$), 1.43–1.60 (m, 4H, $-N(CH_2CH_2CH_3)_2$), 3.15–3.30 (2t, 4H, $-N(CH_2CH_2CH_3)_2$), 3.57 (s, 3H, CH_3O-), 3.82 (s, 2H, C4α-H_2), 6.60 (d, 8.1 Hz, C6-H), 6.75 (d, 3.8 Hz, C3-H), 6.98 (d, 8.1 Hz, C5-H), 7.40–7.52 (m, 3H, $PhSO_2-$), 7.79–7.82 (m, 2H, $PhSO_2-$), 7.84 (d, 3.8 Hz, C2-H),

4-(2-Di-n-propylaminoethyl)-7-methoxy-indole 5. To a suspension of $LiAlH_4$ (5.7 g, 150 mmol) in 50 ml dry THF under argon was added a solution of **4** (2.14 g, 5.0 mmol) in 10 ml THF and the

reaction mixture was stirred under reflux for 3 h. The excess hydride was destroyed under cooling by dropwise addition of saturated NaCl solution, untill a heavy sandy precipitate settled. The supernatant liquid was decanted and the precipitate washed twice with ether.

The pooled ethereal solution was dried over Na_2SO_4 and concentrated. It was chromatographed on a column packed with basic alumina using CH_2Cl_2-hexane 1:1 as solvent. The product was obtained as a colorless syrup, yield 1.26 g (92%).

^1H NMR ($CDCl_3$): 0.91 (t, 6H, $-N(CH_2CH_2CH_3)_2$), 1.53 (m, 4H, $-N(CH_2CH_2CH_3)_2$), 2.52 (m, 4H, $-N(CH_2CH_2CH_3)_2$), 2.8-3.0 (m, 4H, C4-CH_2CH_2-), 3.91 (s, 3H, CH_3O-), 6.53 (t, 2.6 Hz, C3-H), 6.54 (d, 7.8 Hz, C6-H), 6.82 (d, 7.8 Hz, C5-H), 7.13 (t, 2.6 Hz, C2-H), 8.5 (br s, NH).

^{13}C NMR ($CDCl_3$): δ 12.3 ($-N(C-C-C)_2$), 20.4 ($-N(C-C-C)_2$), 30.4 ($-N(C-C-C)_2$), 55.2-55.4 (C4-C-C-), 56.4 (CH_3O-), 101.1 (C3), 101.7(C6), 119.5 (C5), 123.8 (C2), 125.4(C4), 126.5 (C7α), 128.9 (C3α), 145.0 (C7).

MS (chem. ion.) m/z 274 (M+).

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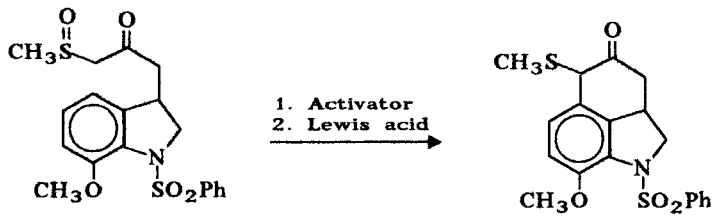
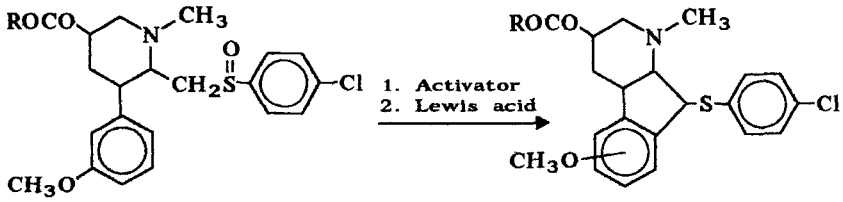
REFERENCES AND NOTES

1. Stamos, I.K., *Tetrah. Lett.*, 1985, **26**(4), 477.
2. Idem, *ibid.*, 1985, **26**(23), 2787.
3. Idem, *ibid.*, 1986, **27**(51), 6261.
4. Reference 1, Note 21.
5. Gourdoupis, C.G. and Stamos, I.K., *Synth. Comm.*, 1993, in press.
6. Gourdoupis, C.G., Kotzamani, H.K. and Stamos, I.K., preceeding paper and notes cited therein.

7. Reference 1, Note 21a, (*cf.* Ref. 6, Note 2), i.e.



oxime m.p. 198-200°C



three stereoisomers

8. For further applications of this methodology see: (a) Veeraragaran, S., Jostmeyer, S., Myers, J. and Wiley, J.C. Jr, *J. Org. Chem.*, 1987, **52**(7), 1355; (b) Mori, I., Bartlett, P.A. and Heathcock, C.H., *J. Org. Chem.*, 1990, **55**(24), 5967; (c) Amat, M. and Bosch, J., *J. Org. Chem.*, 1992, **57**(21), 5793.
9. Troxler, F., Harnisch, A., Bormann, G., Seemann, F. and Szabo, L., *Helv. Chim. Acta*, 1968, **51**(7), 1616.
10. Ketcha, D.M. and Gribble, G.W., *J. Org. Chem.*, 1985, **50**(26), 5451.
11. Cannon, J.G. Lukszo, J. and Max, G.A., *J. Heterocyclic Chem.*, 1983, **20**(1), 149.
12. Ernst, L. and Kang, S., *J. Chem. Res.*, **1981**, (S) 259; (M) 3019.
13. Frasser, R.R., Passannanti, S. and Piozzi, F. *Can. J. Chem.*, **1976**, 2915.

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