EFFICIENT MONONITRATION OF INDOLIC COMPOUNDS WITH NITRIC ACID IMPREGNATED ON SILICA GEL

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Abstract- The methoxyindoles (*N*-benzenesulfonyl and 2-carbomethoxy) were mononitrated with nitric acid adsorbed on silica gel *under mild conditions to give mononitroindoles in good chemical yields.*

In connection of our studies on the synthesis of natural products, we planed the use of nitroindoles for the preparation of different precursors of alcaloids.[1] For the synthesis of nitroindoles, the Japp-Klingeman reaction from nitroanilines[2] or the Bergman reaction from nitrotoluenes[3] are not general, and the nitration of indoles often afforded complex mixtures (dinitration, oxidation...).[4] Aromatic nitration by metallic nitrates impregnated on K10 montmorillonite in the presence of acetic acid was known.[5] Recently, Thummel described the nitration of 2,5-dimethoxy-benzaldehyde with silica gel supported nitric acid under ultrasonic agitation.[6]

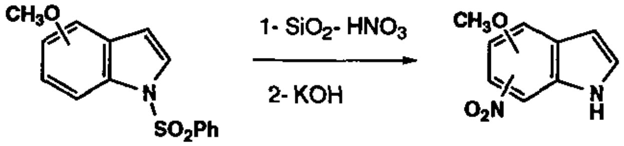
Herein, we show that indolic compounds were mononitrated with nitric acid adsorbed on silica gel[6] in smooth conditions, moderate chemical yields and moderate regiochemistry.

The indolic compound (4-, 5-, 6- or 7-methoxy-*N*-benzenesulfonyl- or 2-carbomethoxyindoles) was dissolved into dichloromethane, silica gel impregnated with nitric acid was added (Indole: SiO_2 = 1 mmol : 600 mg) and the suspension was magnetically stirred at room temperature. The reaction was monitored by tlc; when all the substrate was consumed, the silica gel was filtered off, and washed with 10 ml of dichloromethane. The different isomeric nitro compounds were separated by column chromatography (silica gel, toluene-ethyl acetate 9:1). The characterisation of the methoxy-nitro-*N*-benzenesulfonylindoles was not easy, thus these compounds were hydrolysed under basic conditions, and the regiochemistry of nitration was determined by ^{1}H-nmr, ^{13}C-nmr and HMBC (^{1}H-detected multiple bond heteronuclear multiple-quantum coherence) experiments.[7]

When the methoxyindoles were not substituted with an electron-withdrawing group (*N*-benzenesulfonyl or 2-carbomethoxy), polynitration occurred to afford intractable tars. In our procedure, two nitro-compounds were obtained but a major isomer predominated (70:30 - 94:6). The chemical yields of nitration were moderate (50 - 90%) (see Tables 1 and 2). The methoxynitroindoles can be obtained after hydrolysis of *N*-benzenesulfonyl indoles or by decarboxylation of methoxy-nitro-2-carbomethoxyindoles.

Table 1

1 a: 4-OCH_3
b: 5-OCH_3
c: 6-OCH_3
d: 7-OCH_3



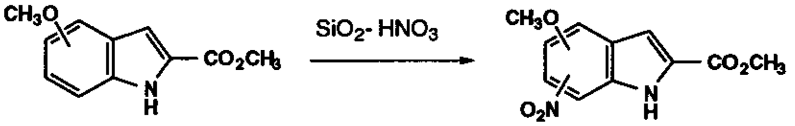
2

Indole	chemical yield (%)*	isomeric ratio
1a	65	7-Nitro:5-Nitro= 90:10
1b	80	4-Nitro:6-Nitro= 93:7
1c	83	3-Nitro:7-Nitro= 94:6
1d	60	4-Nitro:6-Nitro= 70:30

*Yields were calculated in isolated products before hydrolysis and the structures were determined after hydrolysis (^{1}H-nmr, ^{13}C-nmr and HMBC (^{1}H-detected multiple bond heteronuclear multiple-quantum coherence)[7]).

Table 2

3 a: 4-OCH_3
b: 5-OCH_3
c: 6-OCH_3
d: 7-OCH_3



4

Indole	chemical yield (%)	isomeric ratio
3a	77	7-Nitro:5-Nitro=85:15*
3b	83	4-Nitro:6-Nitro=94:6
3c	70	3-Nitro:7-Nitro=81:19
3d	50	4-Nitro:6-Nitro=80:20

*A minute quantity (5%) of 4-methoxy-6-nitroindole was isolated.

In conclusion, the mild nitration of indole compounds with silica gel impregnated with nitric acid afforded mononitrate in good yields.

REFERENCES AND NOTES

1. N. Roué, J. Lévy, and R. Barret, *Synth. Commun.*, 1995, **25**, 681.
2. S. P. Hiremath and S. Siddapa, *J. Indian Chem. Soc*, 1963, **40**, 935; M. Julia and P. Nickel, *Medd. Norsk. Farm. Selsk.*,1966, **28**, 153, (*Chem. Abstr.*, 1967, **66**, 85664e).
3. J. Bergman and P. Sand, *Tetrahedron*, 1990, **46**, 6085; J. Bergman and P. Sand, *Org. Synth.*, 1987, **65**, 146.
4. Indole, Part one- W. J. Houlihan Ed., Wiley-Intersciences, J. Wiley and sons Inc., N. Y., 1972, pp. 78-81; P. Laszlo, *Surfact. Sci. Ser.*, 1991, **38**, 437.
5. A. Cornellis, L. Delaude, A. Gerstmann, and P. Laszlo, *Tetrahedron Lett.*, 1988, **29**, 5657.
6. R. P. Thummel, S. Chirayil, C. Hery, T. L. Liu, and T. L. Wang, *J. Org. Chem.*, 1993, **58**, 1666.
7. A. Bax and M. F. Summers, *J. Am. Chem. Soc.*, 1989, **108**, 2093.
8. Selected physical and spectroscopic data:

2a: yellow cristal, mp: 166-168°C ($CHCl_3$), ^1H-nmr (300 MHz, $CDCl_3$, ppm): δ= 4.05 (s, 3H, OCH_3), 6.55 (d, 1H, ^3J = 9 Hz, 5-H), 6.75 (d, 1H, ^3J = 3 Hz, 3-H), 7.25 (d, 1H, ^3J = 3, 2-H), 8.15 (d, 1H, ^3J = 9 Hz, 6-H), 10.1 (b, 1H, N-H); ^{13}C-nmr (75 MHz, $CDCl_3$, ppm): δ = 55.9 (OCH_3), 100.0 (5-C), 101.2 (3-C), 120.0 (3a-C), 122.6 (6-C), 124.6 (2-

C), 127.7 (7-C), 130.7 (1a-C), 159.9 (4-C). Ms: m/z: 192 ($M^{+\cdot}$, 100%), 162 (24%), 146 (38%), 131 (38%), 103 (44%). HRms: calculated for $C_9H_8N_2O_3$: 192.05349, found: 192.05340. Anal. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N,14.58. Found: C, 56.04; H, 3.88; N,14.29. Uv (CH_3OH): λ_M: 205, 248, 273 nm. Ir (KBr), v: 3420, 3127, 2949, 1624, 1584, 1478, 1323, 1275 cm^{-1}. HMBC experiment had shown three correlations of 4-C with 3-H, 5-H and 6-H.

2b: yellow cristal, mp: 144-146 °C ($CHCl_3$), ^{1}H-nmr (300 MHz, DMSO-d_6, ppm): δ = 3.95 (s, 3H, OCH_3), 6.67 (d, 1H, ^3J = 2 Hz, 3-H) 7.09 (d, 1H, ^3J = 8 Hz, 7-H), 7.61 (d, 1H, ^3J = 2 Hz, 2-H), 7.73 (d, 1H, ^3J = 8 Hz, 6-H); ^{13}C-nmr (75 MHz, DMSO-d_6, ppm): δ = 57.6 (8-C), 100.0 (3-C), 108.5 (6-C), 118.1 (7-C), 122.6 (3a-C), 130.2 (2-C), 130.3 (4-C), 132.1 (1a-C), 148.5 (5-C). Ms: m/z: 192 ($M^{+\cdot}$, 94%), 145 (49%), 119 (51%), 116 (100%). HRms: calculated for $C_9H_8N_2O_3$: 192.05349, found: 192.05273. Anal. Calcd for $C_9H_8N_2O_3$: C,56.25; H, 4.20; N, 14.58. Found: C, 55.90; H, 3.96; N,14.16. Uv (CH_3OH): λ_M: 213, 248 nm. Ir (KBr) v: 3370, 2976, 1510, 1279 cm^{-1}.

2c: yellow cristal, mp: 137-141°C ($CHCl_3$), ^{1}H-nmr (300 MHz, $CDCl_3$, ppm): δ = 3.88 (s, 3H, OCH_3), 6.81 (d, 1H, ^3J = 2 Hz, 7-H), 6.90 (dd, 1H, ^3J=9 Hz, ^4J= 2 Hz, 5-H), 7.39 (s, 1H, 2-H), 7.60 (d, 1H, ^3J = 9 Hz, 4-H), 9.11 (1H, b, 1-H); ^{13}C-nmr (75 MHz, $CDCl_3$, ppm): δ = 49.8 (CH_3O), 94.9 (7-C), 106.0 (4-C), 115.7 (5-C), 121.0 (3a-C), 126.0 (2-C), 138.7 (1a-C), 141.2 (3-C), 161.5 (6-C). Ms: m/z= 192 ($M^{+\cdot}$, 55%), 191 (100%), 134 (56%), 77 (95%). HRms: calculated for $C_9H_8N_2O_3$: 192.05349, found: 192.06177. Anal. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 55.40; H, 3.85; N,14.42. Uv (CH_3OH): λ_M: 207, 230, 260 nm. Ir (KBr), v: 3304, 2926, 1510, 1265 cm^{-1}.

2d: yellow cristal, mp: 175-177 °C ($CHCl_3$), ^{1}H-nmr (300 MHz, $CDCl_3$, ppm): δ= 4.07 (s, 3H, OCH_3), 6.65 (d, 1H, ^3J = 7 Hz), 7.22 (d, 1H, ^3J = 3 Hz, 3-H), 7.41 (d, 1H, ^3J = 3 Hz, 2-H), 8.16 (d, 1H, ^3J = 7 Hz); ^{13}C-nmr (75 MHz, $CDCl_3$, ppm): δ = 56.0 (OCH_3), 100.8 (3-C), 103.6 (6-C), 120.6 (5-C), 123.5 (3a-C), 127.5 (2-C), 134.4 (1a-C), 134.6 (4-C), 154.8 (7-C). Ms: m/z: 192 ($M^{+\cdot}$, 100%), 162 (37%), 146 (18%), 131 (28%). HRms calculated for $C_9H_8N_2O_3$: 192.05349, found: 192.05322. Anal. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.25; H, 4.02; N,14.02. Uv (CH_3OH): λ_M: 209, 231, 244, 269 nm. Ir: (KBr) v: 3370, 3088, 2957, 1630, 1570, 1271, 1096 cm^{-1}.

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