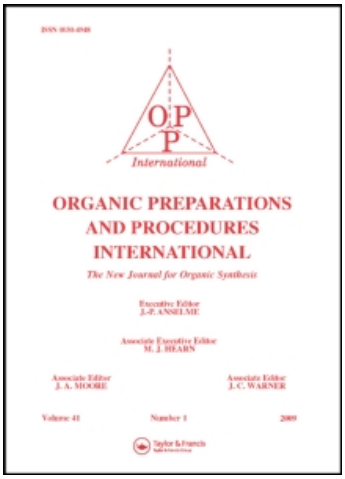


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN IMPROVED SYNTHESIS OF 4,7-DIMETHOXY-1H-INDOLE

H. D. Hollis Showalter[a]; Gerd Pohlmann[ab]
[a] Chemistry Department, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Co., Ann Arbor, MI [b] Goedecke A.G., Freiburg, FR, GERMANY

To cite this Article Showalter, H. D. Hollis and Pohlmann, Gerd(1992) 'AN IMPROVED SYNTHESIS OF 4,7-DIMETHOXY-1H-INDOLE', Organic Preparations and Procedures International, 24: 4, 484 — 488
To link to this Article: DOI: 10.1080/00304949209356232
URL: http://dx.doi.org/10.1080/00304949209356232

Chemistry", Kekule Symposium, Butterworths Scientific Publications, London, 1959, p 35; W. B. DeMore, H. O. Pritchard and N. Davidson, *J. Am. Chem. Soc.*, **81**, 5874 (1959).

8. cf. C. A. Coulson, *Proc. Roy. Soc.*, **A169**, 413 (1939).

9. D. P. Craig, *J. Chem. Soc.*, 3175 (1951); D. P. Craig, "*Non-benzenoid Aromatic Compounds*", D. Ginsburg, Ed., Interscience, New York, 1959, pp 1-42.

10. M. Randic, *J. Am. Chem. Soc.*, **99**, 444 (1977).

11. D. Valentine, N. J. Turro, Jr. and G. S. Hammond, *J. Am. Chem. Soc.*, **86**, 5202 (1964).

12. A. J. Birch and J. M. H. Graves, *Proc. Chem. Soc.*, 282 (1962), A. J. Birch, J. M. H. Graves and J. B. Siddell, *J. Chem. Soc.*, 4234 (1963).

13. P. E. Eaton, *J. Am. Chem. Soc.*, **84**, 2344 (1962) describes the method with 2-cyclopentene-1-one. His results with 2-cyclohexene-1-one have not been published (personal communication).

14. The IR spectrum indicated an approximate composition of 70% of **7** and 30% of **2** and **3** based on the enol ether (1602 cm^{-1}) and carbonyl (1709 cm^{-1}) absorptions.

****

AN IMPROVED SYNTHESIS OF 4,7-DIMETHOXY-1H-INDOLE

Submitted by (03/16/92)

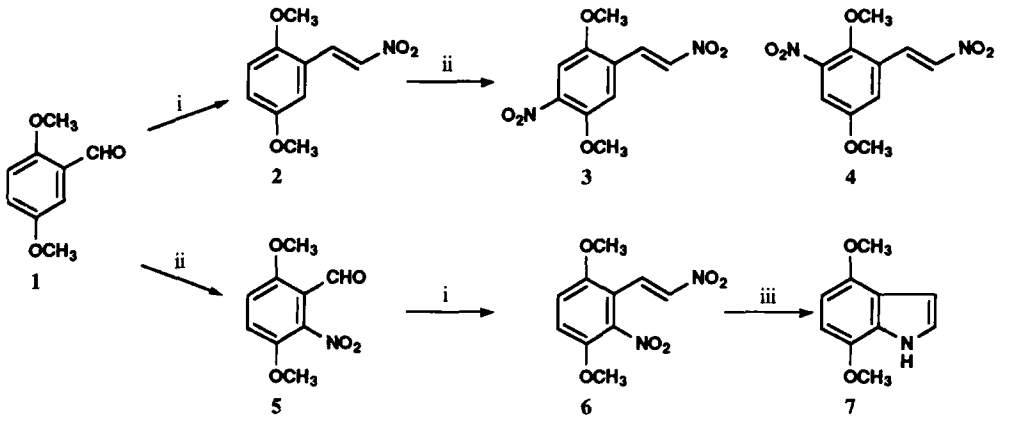
H. D. Hollis Showalter* and Gerd Pohlmann

Chemistry Department, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Co., Ann Arbor, MI 48106 and Goedecke A.G., D-7800 Freiburg, FR GERMANY

As part of a program to design selective inhibitors for various pathways of signal transduction, we required a simple, high-yield synthesis that would provide multigram quantities of 4,7-dimethoxy-1**H**-indole (**7**). The preparation of this compound has been described previously through the reductive cyclization of readily derived (**E**)-1,4-dimethoxy-2-nitro-3-(2-nitroethenyl)benzene (**6**) either with iron in acetic acid[1,2] or *via* transfer hydrogenation.[3] In our hands, neither of these methods was suitable for scale-up operations. We now report a improved sequence to nitrostyrene **6** and its clean conversion to **7** utilizing high pressure hydrogenation over Pearlman's catalyst (10% $Pd(OH)_2/C$).

Two routes to target **7** were explored as shown in the scheme. In the first, condensation of commercially available 2,5-dimethoxybenzaldehyde (**1**) with nitromethane under conditions described by Dallacker and Bernabei[4] proceeded cleanly to give the known nitrostyrene **2**[5,6] in 71% yield. Nitra-

tion of **2** under standard conditions did not give desired **6** but the previously unreported nitrostyrene **3** in 72% yield. The possibility that nitration gave the known isomer **4**[7] instead was ruled out on the



i) CH_3NO_2, NH_4OAc, HOAc ii) HNO_3, HOAc iii) H_2, $Pd(OH)_2/C$, THF-HOAc

basis of comparative melting point and proton NMR data. Synthesis *via* the second path proceeded by reversal of these steps. Hence, nitration of **1** was performed by a modification of the literature procedure[8] to provide the tetrasubstituted benzaldehyde **5** in 58% yield in a process carried out with a considerably simplified work-up. A small amount of isomeric 2,5-dimethoxy-4-nitrobenzaldehyde was isolated from the mother liquor and characterized spectroscopically. Condensation of **5** with nitromethane as described above gave nitrostyrene **6** in 73% yield. Reductive cyclization of **6** with iron in acetic acid as previously described[1,2] or *via* a modified method[9] proceeded satisfactorily on small scale, but was cumbersome and gave low yields upon scale-up. Similarly, attempts to duplicate an efficient reductive cyclization of **6** to **7** *via* transfer hydrogenation as recently reported[3] resulted in only a partial conversion to product in our hands. Based on previous literature procedures for the synthesis of substituted indoles,[10,11] we decided to subject nitrostyrene **6** to reductive cyclization *via* standard conditions of hydrogenation. Hence, atmospheric hydrogenation of **6** over Pearlman's catalyst in 10:1 THF:acetic acid at 50° proceeded with only 30% conversion to an unidentified intermediate. However, when this same reaction was carried out at a pressure of 150 psi hydrogen, a clean conversion took place to give the target indole **7** in 75% yield after a simple silica gel chromatography to remove small amounts of baseline impurity. While the THF:acetic acid medium was chosen for our large-scale runs, we found on one small-scale run that ethyl acetate:acetic acid was equally suitable for this transformation.

In summary, we have developed an operationally simple, medium- to large-scale synthesis of 4,7-dimethoxy-1H-indole in 32% overall yield from commercially available 2,5-dimethoxybenzaldehyde. While we have not generalized this process to other examples, we feel that it has broad applicability for the synthesis of other substituted indoles.

EXPERIMENTAL SECTION

Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Bruker IFS 66 instrument coupled to an Aspect 1000 computer. ^{1}H Nuclear magnetic resonance (^{1}H NMR) spectra were determined at 300 MHz on a Bruker Aspect 3000 instrument. Chemical shifts are reported as ∂ units downfield from internal tetramethylsilane on samples of ca. 1% w/v. Combustion analyses were performed on a Control Equipment Corp CEC 440 Microanalyzer.

(*E*)-1,4-Dimethoxy-2-(2-nitroethenyl)benzene (2).- A mechanically stirred solution of 41.6 g (250 mmol) of 2,5-dimethoxybenzaldehyde (**1**), 65 ml of nitromethane, 32.8 g (425 mmol) of ammonium acetate, and 150 ml of glacial acetic acid was heated at gentle reflux for 0.5 hr. The mixture was maintained at 25° for 3 days, the mixture was diluted with 150 ml of 2-propanol, and the solid was collected. The filtrate was concentrated to near dryness, then diluted with 200 ml of ethyl acetate. The solution was washed twice with water, dried ($MgSO_4$), and concentrated to a solid that was crystallized from hot 2-propanol. The two crops of solid were combined and boiled as a suspension in hot ethanol. The suspension was cooled in ice for 30 min, and the solid was collected, washed with 2-propanol, and dried to leave 37.3 g (71%) of **2** as a yellow-orange solid, mp. 117-119°, lit.[5] mp. 118-119°. The ^{1}H NMR spectrum was the same as previously reported.[5]

Cautionary Note: *We caution about the known thermal instability of nitromethane which could lead to a runaway reaction at the temperature used in this preparation. While we never observed an exotherm in any of our runs for the preparation of* **2** *or* **6**, *we advise extreme caution in scale-up operations.*

(*E*)-1,4-Dimethoxy-2-nitro-5-(2-nitroethenyl)benzene (3).- To a 3-necked 500 ml RB flask fitted with a thermometer, a mechanical stirrer, and an addition funnel, was added an ice-cold suspension of 37.3 g (178 mmol) of **2** in 178 ml of glacial acetic acid. The mixture was treated dropwise over 1 hr with 103.3 ml of conc. nitric acid (d = 1.49) while the temperature was maintained at 10-15° during the addition. The cooling bath was removed and the temperature was allowed to rise to 25° over 1 hr. The suspension was poured carefully into ice-cold water and the precipitated solid was collected, washed thoroughly with water, then air dried. The solid was boiled as a suspension in 2-propanol for 10 min, then the mixture was ice-cooled. The solid was collected, washed with 2-propanol, and dried to give 33.2 g (72%) of **3** as an orange solid, mp 193-196°; R_f = 0.18 (SiO_2, 2:1 CH_2Cl_2:cyclohexane). ^{1}H NMR ($CDCl_3$): ∂ 3.98 (s, 6H), 7.18 (s, 1H), 7.49 (s, 1H), 7.92 (d, *J* = 14 Hz, 1H), 8.07 (d, *J* = 14 Hz, 1H); IR (KBr): 1524, 1497, 1344, 1224, 1027, 972 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_2O_6$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.07; H, 3.88; N, 10.92

3,6-Dimethoxy-2-nitrobenzaldehyde (5).- To a 3-necked 500 ml RB flask equipped as above was added an ice-cold suspension of 49.9 g (300 mmol) of 2,5-dimethoxybenzaldehyde (**1**) in 300 ml of glacial acetic acid. The suspension was treated dropwise over a 30 min period with 30 ml of conc. nitric acid (d = 1.49) while the temperature was maintained at 5-10°. The suspension was then warmed to 15° and maintained there for 1.5 hr. The viscous mixture was filtered and the collected solid was washed sparingly with glacial acetic acid, then air dried. The solid was boiled in 200 ml

of ethanol for 15 min, then the mixture was ice-cooled for 1 hr. The solid was collected, washed with 2-propanol, and dried to leave 36.7 g (58%) of **5** as a yellow solid, mp. 161-163°, lit.[8] mp. 164-165°; R_f = 0.10 (SiO_2, 3:2 cyclohexane:ethyl acetate). ^1H NMR ($CDCl_3$): ∂ 3.88 (s, 3H), 3.95 (s 3H), 7.10 (d, *J* = 9.4 Hz, 1H), 7.29 (d, *J* = 9.4 Hz, 1H), 10.38 (s, 1H); IR (KBr): 1694, 1542, 1493, 1282, 1273, 951 cm^{-1}.

Anal. Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 50.94; H, 4.15; N, 6.43

Upon standing at 25°, a small amount of solid crystallized from the ethanol filtrate. This was collected as above to give analytically pure 4-nitro isomer as a solid, mp. 167-168°, lit.[8] mp. 163-165°; R_f = 0.38. ^1H NMR ($CDCl_3$): ∂ 3.98 (s, 6H), 7.45 (s, 1H), 7.55 (s, 1H), 10.48 (s, 1H); IR (KBr): 1699, 1526, 1291, 1223, 1030 cm^{-1}.

(*E*)-1,4-Dimethoxy-2-nitro-3-(2-nitroethenyl)benzene (6).- A mixture of 28.2 g (133 mmol) of aldehyde **5**, 35 ml of nitromethane, 17.7 g (230 mmol) of ammonium acetate, and 70 ml of glacial acetic acid was heated at 80° for 4 hr. 2-Propanol (150 ml) was added to the mixture and heating was continued for 0.5 hr. The suspension was cooled to 25° over a 2 hr period, then the solid was collected, washed with 2-propanol, and dried to leave 24.7 g (73%) of **6** as a yellow solid, mp. 188-190°, lit.[1] mp. 191°; R_f = 0.27 (SiO_2, 2:1 CH_2Cl_2:cyclohexane). ^1H NMR ($CDCl_3$): ∂ 3.90 (s, 3H), 3.98 (s, 3H), 7.04 (d, *J* = 8.5 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 13.5 Hz, 1H), 7.95 (d, *J* = 13.5 Hz, 1H); IR (KBr): 1529, 1511, 1344, 1296, 1280, 967 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_2O_6$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.27; H, 3.93; N, 10.97

4,7-Dimethoxy-1H-indole (7).- To a 5-L autoclave was added a mixture of 65.6 g (258 mmol) of **6**, 10 g of 10% palladium hydroxide on carbon (50% water), 2.5 liters of THF, and 42 ml of glacial acetic acid. The autoclave was pressurized to 150 psi with hydrogen, then heated at 50°. After 1.5 hr, the theoretical uptake of hydrogen had taken place. The autoclave was cooled, 1 g of additional catalyst was added, and the mixture was further hydrogenated for 1 hr under the same conditions. The cooled mixture was filtered through Celite, then concentrated to an oily residue that was diluted with CH_2Cl_2. The solution was washed sequentially with water and 5% aq $NaHCO_3$, dried ($MgSO_4$), then loaded onto a flash SiO_2 column (20 x 7 cm). After adsorption of material onto the column, it was eluted with 2.5 liters of CH_2Cl_2 to strip off the product. Product fractions were combined and concentrated to leave a solid residue that was triturated in 100 ml of hot 2-propanol to give 29 g (63%) of **7**, mp. 124-126°, lit.[1] mp. 131°; R_f = 0.41 (SiO_2, 2:1 cyclohexane:ethyl acetate). The mother liquor was concentrated to leave a crude solid that was dissolved in minimal 2:1 CH_2Cl_2:cyclohexane. This was purified over flash SiO_2 eluting first with 500 ml of 3:2 then 250 ml of 4:1 CH_2Cl_2:cyclohexane. Product fractions were combined and processed as above to leave 5.35 g (12%) of a second crop, mp. 124-126°. ^1H NMR ($CDCl_3$): 3.90 (s, 3H), 3.91 (s, 3H), 6.37 (d, *J* = 8.0 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 6.61-6.65 (m, 1H), 7.05-7.08 (m, 1H), 8.41 broad s, 1H, exchanges with D_2O): IR (KBr): 3367, 1526, 1264, 1087, 976 cm^{-1}.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.68; H, 6.24; N, 7.89

REFERENCES

1. G. Rodighiero, G. Malesani and U. Gomasiero, *Gazz. Chim. Ital.*, **91**, 742 (1961).

2. A. S. Ijaz, J. Parrick and A. Yahya, *J. Chem. Res.(S)*, 116 (1990).

3. S. Rajeswari, K. J. Drost and M. P. Cava, *Heterocycles*, **29**, 415 (1989).

4. F. Dallacker and D. Bernabei, *Monatsh. Chem.*, **98**, 785 (1967).

5. A. C. Cheng and N. Castagnoli, Jr., *J. Med. Chem.*, **27**, 513 (1984).

6. W. K. Anderson, T. T. Dabrah and M. D. Houston, *J. Org. Chem.*, **52**, 2945 (1987).

7. G. Malesani, F. Galiano, M. G. Ferlin and S. Masiero, *J. Heterocycl. Chem.*, **17**, 563 (1980).

8. C. A. Howe, A. Howe, C. R. Hamel, H. W. Gibson and R. R. Flynn, *J. Chem. Soc.*, 795 (1965).

9. A. K. Sinhababu and R. T. Borchardt, *J. Org. Chem.*, **48**, 3347 (1983).

10. C. F. Huebner, H. A. Troxell and D. C. Schroeder, *J. Am. Chem. Soc.*, **75**, 5887 (1953).

11. A. Kalir, D. Balderman, H. Edery and G. Porath, *Israel J. Chem.*, **5**, 129 (1967).

****

LARGE-SCALE PREPARATION OF THE SULFUR-TRANSFER REAGENT 3H-1,2-BENZODITHIOL-3-ONE 1,1-DIOXIDE

Submitted by (03/02/92) J. B. Regan, L. R. Phillips and S. L. Beaucage*

Division of Biochemistry and Biophysics
Center for Biologics Evaluation and Research
Food and Drug Administration
8800 Rockville Pike, Bethesda, MD 20892

The thiosulfonate 3H-1,2-benzodithiol-3-one 1,1-dioxide (**4**) is a powerful sulfur-transfer reagent for the synthesis of oligodeoxyribonucleoside phosphorothioates *via* the phosphoramidite approach.[1] These oligonucleotide analogues exhibited antiviral activity in cell cultures[2] and have been effective in the control of gene expression by inhibiting the translation of specific messenger RNAs.[3]

A detailed concentration study revealed that the sulfurization of oligonucleotidic phosphite triesters can be effected consistently to near quantitative yields, within 30 s, with a 0.05 M solution of