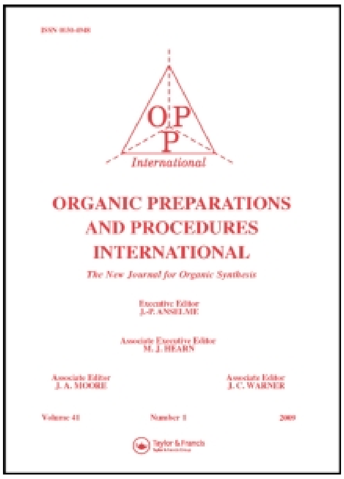

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AN IMPROVED SYNTHESIS OF 3-(2,5-DIMETHOXYBENZYL)PYRROLE

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AN IMPROVED SYNTHESIS OF 3-(2,5-DIMETHOXYBENZYL)PYRROLE

Submitted by (06/22/05)

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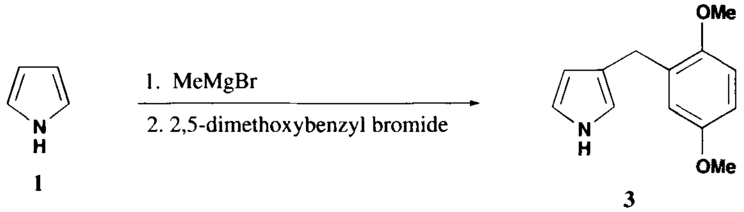
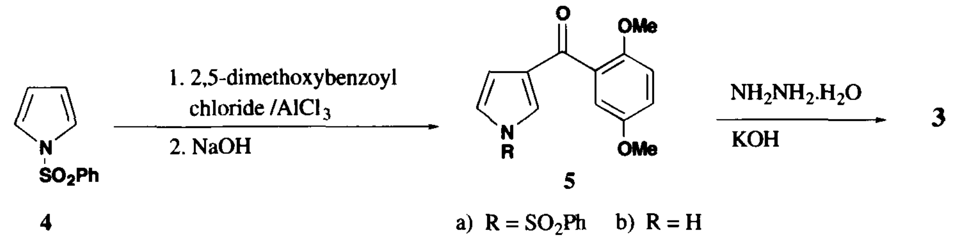
There has been a lot of interest recently in conductive polymers, especially polypyrroles, for their potential in the development of chemical sensor technology.[1,2] Polypyrroles are ideally suited for the design of sensory material because they not only exhibit high conductivity and electroactivity but also their building blocks, *i. e.* pyrrole monomers, can be easily modified by substitution. 3-(2,5-Dimethoxybenzyl)pyrrole[3] (**3**) is an important pyrrole monomer because its polymer can be demethylated to yield a hydroquinone substituted polypyrrole. Despite its simple structure and its importance as a key starting material, no high-yield synthesis of **3** has been described. 3-Alkylpyrroles[4] are normally prepared by the reaction of the pyrryl Grignard reagent with alkyl halides. Recently Foos *et al.*[3] reported the preparation of 3-(2,5-dimethoxybenzyl)pyrrole (**3**) by reaction of pyrrylmagnesium bromide (**1**) with 2,5-dimethoxybenzyl bromide (**2**) in 3% yield. This yield is not only low but extensive chromatography is required to isolate the desired 3-isomer from 1- and 2-substituted pyrroles. Attempts to improve the yield of 3-isomer by altering the order of addition of benzyl bromide or changing the solvent were unsuccessful.



We required gram quantities of **3** as a starting material for the preparation of the polymer for chemical sensor applications. Although it is well known that the 2-position of the pyrrole ring is the most reactive site for electrophilic substitution, aluminium chloride catalyzed acylation of 1-(benzenesulfonyl)pyrrole[5] (**4**) gives 3-acyl derivatives[6,7] regiospecifically. Thus reaction of 1-(benzenesulfonyl)pyrrole (**4**) with 2,5-dimethoxybenzoyl chloride followed by hydrolysis and reduction was investigated.



1-(Benzenesulfonyl)pyrrole (**4**) reacted smoothly with 2,5-dimethoxybenzoyl chloride to give a good yield of 3-benzoylpyrrole **5** along with a small amount of the 2-isomer. This mixture was hydrolyzed to acylpyrrole without purification. The desired 3-isomer (**5a**) could very easily be separated from the 2-isomer by recrystallization from ethyl acetate. The nmr spectrum of **5b** showed a multiplet at δ 6.69 for H4 which is typical of 3-acylpyrroles[6] while in the corresponding 2-acylpyrroles H4 appears at δ 6.33. Wolff-Kishner reduction[8] of 3-(2,5-dimethoxybenzoyl)pyrrole (**5b**) using hydrazine hydrate and potassium hydroxide in ethylene glycol gave the desired benzylpyrrole **3** in excellent yield. The presence of methylene group was readily established by the appearance of a singlet at δ 3.86 in the ^{1}H NMR spectrum and at δ 27.29 in ^{13}C NMR spectrum of the benzylpyrrole **3**. Mass spectrum of the benzylpyrrole showed a molecular ion at 217.

In summary this synthesis of **3** is short and can easily be adapted to the synthesis of other alkyl pyrroles.

EXPERIMENTAL SECTION

Melting points were determined using a Kofler hot stage micromelting point apparatus. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker ACF 300 spectrometer. Infrared spectra were recorded with a Bomem Michelson Series FTIR. Mass spectra were analysed on VG Quattro with source temperature of 200° and 70 eV ionising voltage. UV-Vis spectra were recorded on a Varian Cary 5 Spectrophotometer. Microanalyses were performed by Dr H. P. Pham of the University of New South Wales. All reagents were either laboratory grade or analytical grade reagents and were used as received.

3-(2,5-Dimethoxybenzoyl)pyrrole (5b).- 2,5-Dimethoxybenzoyl chloride (3.07g, 15.3 mmol) (prepared from 2,5-dimethoxybenzoic acid and thionyl chloride) was added dropwise with stirring to a suspension of aluminium chloride (3.71g, 27.8 mmol) in dichloromethane (30 mL). The resulting mixture was stirred for 30 min, then a solution of 1-benzenesulfonylpyrrole (**4**) (2.88g, 13.9 mmol) in dry dichloromethane (20 mL) was added dropwise with stirring. After stirring at room temperature for 3 hrs the complex was hydrolysed with ice and water. The product was extracted into dichloromethane, washed with water, dried and evaporated to give an oily residue. The residue was dissolved in a 50:50 mixture of dioxane (60 mL) and 5N sodium hydroxide (60 mL) and stirred at room temperature overnight. The organic layer was collected and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic phase was washed with water, dried and evaporated to yield an oily residue. Recrystallisation of the crude product from ethyl acetate yielded the 3-benzoyl compound (**5b**) (2.62g, 82%) as light yellow prisms, mp. 156-157°. IR (KBr): 3199, 3077, 2955, 1617, 1603, 1509, 1498, 1226, 1166, 1038, 828, 708 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.75 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.69 (m, 1H, H4), 6.77 (m, 1H, H5), 6.91 (m, 3H, ArH), 7.20 (m, 1H, H2), 8.77 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 55.87, 56.60 ($O\underline{C}H_3$), 109.77, 113.19, 114.34, 116.02, 119.63, 126.53 (Ar$\underline{C}$H), 126.06, 131.39, 150.90, 153.12, 190.60 (Ar$\underline{C}$). MS: *m/z* 231 (88, M$^+$), 123 (18), 80 (45), 66 (37). UV-VIS (MeOH): λ_{max} 203 (ε = 26000), 222 (20000), 251 (12000), 295 nm (7900).

Anal. Calcd. $C_{13}H_{13}NO_3$: C, 67.53; H, 5.63; N, 6.06. Found: C, 67.70; H, 5.88; N, 5.93

3-(2,5-Dimethoxybenzyl)pyrrole (3).- A mixture of 3-(2,5-dimethoxybenzoyl)pyrrole (**5b**) (0.2g, 0.87 mmol), hydrazine hydrate (99%, 0.25 mL), ethylene glycol (10 mL) and KOH (0.07 g, 1.28 mmol) was heated under reflux for 30 min. The water vapour was released after 0.5 hr by removing the stopper while continuously heating the mixture. The mixture was heated under reflux for a further 3 hrs before being left overnight. The reaction mixture was poured into water (30 mL) and ether (30 mL). The aqueous layer was re-extracted with ether (2 x 20 mL), and the combined ether layers were washed with water (2 x 20 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by chromatography on silica using CH_2Cl_2 as eluent to give 3-(2,5-dimethoxybenzyl)pyrrole (**3**)[3] (0.17 g, 90%) as a colorless oil. n_D^{20} = 1.5602. IR (KBr): 3402, 2931, 2832, 1499, 1223, 1179, 1154, 1112, 1049, 802, 762, 712 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.72 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.86 (s, 2H, CH_2), 6.12 (m, 1H, H4), 6.56 (m, 1H, H5), 6.67 (m, 2H, H2 + ArH), 6.74 (d, J 3.1 Hz, ArH), 6.80 (d, J 8.7 Hz, ArH), 8.02 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 27.29 ($\underline{C}H_2$), 55.63, 56.13 ($O\underline{C}H_3$), 109.22, 110.82, 111.32, 115.90, 116.41, 117.76 (Ar$\underline{C}$H), 122.25, 132.30, 151.59, 153.53, (Ar$\underline{C}$). MS: *m/z* 217 (100%, M$^+$), 123 (10), 80 (85), 65 (9). UV-VIS λ_{max} (MeOH): 206 (ε = 98000), 220 (63000), 290 nm (17000).

Anal. Calcd. $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.82; H, 6.74; N, 6.29

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OXIDATION OF VARIOUS ALCOHOLS WITH *IN SITU* GENERATED MONTMORILLONITE K10-SUPPORTED FERRIC NITRATE REAGENT IN AN APROTIC SOLVENT

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(03/21/95)

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Reactions using supported reagents have recently attracted much attention. Indeed, the introduction of a certain agent onto or into an organic polymeric or an inorganic porous or layered support material (henceforth referred to simply as support) not only exerts modified reactivity of the agent and/or specific product selectivity, but considerably simplifies product isolation. Thus, a great variety of supported reagent systems are currently in wide use in organic synthesis.[1] One of the fascinating examples is *Clayfen* (abbreviation for Montmorillonite K10 doped with ferric nitrate, named by Laszlo), which is a versatile reagent for the conversion of various functional groups in a selective fashion.[2] However, there are serious problems in its use, *viz.*, the necessity of meticulous care upon the preparation of *Clayfen* and its relatively rapid deactivation on storage.[2a] Thus, there is a need of exploring a readily accessible technique to extend the utility of this valuable reagent system.

Our recent attempts to bring about oxidations in aprotic solvents have demonstrated that inorganic supports facilitate the reactions appreciably, affording the products in synthetically useful yields and substantiating the specific product selectivities.[3-6] These reactions can be initiated immediately by simple mixing an aprotic solvent, an oxidant, and a support with a substrate without a need to prepare a supported reagent beforehand; however, the oxidizing media are reminiscent of those used for the supported reagents, thereby making product isolation very straightforward. In the course of related work, we were intrigued by the fact that clay minerals serve as highly reactive sites for certain reagents in the oxidation of sulfides to the sulfoxides[6] or the sulfones,[4] which led us to investigate the clay-assisted organic reaction extensively. This article reports an operationally simple Montmorillonite K10-assisted ferric nitrate oxidation of a series of alcohols.