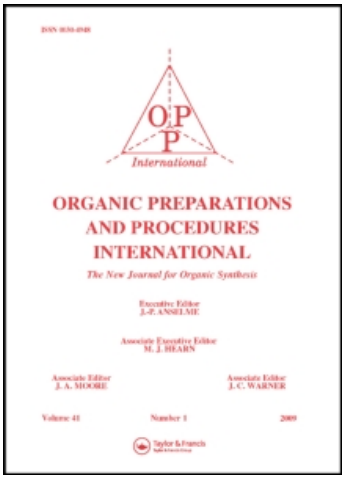

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AN IMPROVED PREPARATION OF 1,2,5-TRIMETHYL-3-NITROPYRROLE. FRIEDEL-CRAFTS ACYLATION WITH 2-FLUOROBENZOYL CHLORIDE

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AN IMPROVED PREPARATION OF 1,2,5-TRIMETHYL-3-NITROPYRROLE. FRIEDEL-CRAFTS ACYLATION WITH 2-FLUOROBENZOYL CHLORIDE

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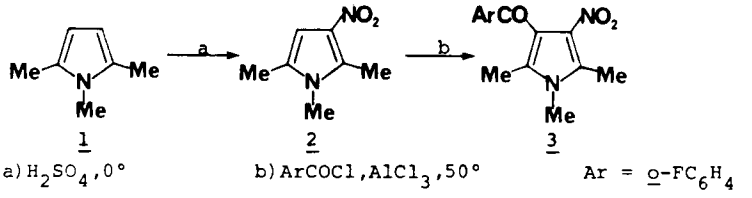
As part of our drug discovery effort, we required a facile synthesis of various substituted phenyl(1,2,5-trimethyl-4-nitropyrrol-3-yl)methanones (3). It is conceivable that compounds of type 3 could be prepared by Friedel-Crafts acylation of 1,2,5-trimethyl-3-nitropyrrole (2). The introduction of the various phenyl moieties in the last step would allow for the use of a common penultimate intermediate 2 and thus facilitate the preparation of a series of congeners.



A search of the literature revealed the difficulty in preparing 2. Attempts to prepare 2 by Friedel-Crafts alkylation of 1,2-dimethyl-3-nitropyrrole with iodomethane and aluminum chloride met with failure.[1] The only successful synthesis was achieved in a very low yield (2.5%) by nitration of 1,2,5-trimethylpyrrole (1) with nitric acid in acetic anhydride followed by "repeated, time consuming chromatography".[1] The same author found that while 1-methylpyrrole is nitrated at 20° with nitric acid in acetic anhydride, 1,2-dimethylpyrrole was readily nitrated under similar conditions at lower temperature (-5°). In this latter case, nitration of the more activated analogue resulted in the formation of several products from addition of one or more nitro groups to the three remaining unsubstituted pyrrole carbons. Therefore it comes as no surprise that while the presence of an additional electron-donating methyl substituent should enhance the nitration rate of 1,[2] it should also increase the tendency for the substrate to undergo undesirable side-reactions.

We now report that 2 can be obtained in 74% yield by modification of the nitration conditions as described in the Experimental Section. Furthermore, the reaction can be carried out on a large scale. The short reaction time (30 min) is crucial as longer reaction times or higher temperatures result in greatly diminished yields. The success of this reaction can be attributed to the use of potassium nitrate which acts as a source of nitric acid when dissolved in sulfuric acid. This method avoids the water content of commercially available nitric acid, resulting in a nitrating system that is considerably less destructive to sensitive substrates.[3] The nitration conditions described in this paper should be applicable to other sensitive heterocycles.

The pyrrole nucleus is known to be highly reactive to electrophilic substitution of the Friedel-Crafts type. The addition of electron-donating alkyl groups at the 2- and 5-positions of the pyrrole nucleus enhances the

reactivity of the 3-position considerably. Several reports in the literature describe the Friedel-Crafts acylation[4] and aroylation[4,5] of 2,5-dialkylpyrroles using $AlCl_3$, $SnCl_4$ or BF_3 as catalysts under relatively mild conditions.

While the presence of the nitro group in our system would be expected to diminish the reactivity, the activating 2,5-dimethyl substituents might be expected to balance any deactivation. This hypothesis proved to be correct as 2 was acylated with 2-fluorobenzoyl chloride in the presence of $AlCl_3$ as catalyst at 50° for 3 hrs to afford a 61% yield of 3.[6]

EXPERIMENTAL SECTION

All melting points were obtained on a Thomas Hoover Capillary melting point apparatus and are uncorrected. NMR spectra were recorded with a Varian EM-390 spectrometer using TMS as the internal reference standard and deuterochloroform as solvent. Purity was determined by microanalysis and by tlc using 0.25 mm silica gel-G as the stationary phase. IR spectra were recorded with a Nicolet XS-20 FT-IR spectrometer using KBr pellets.

1,2,5-Trimethyl-3-nitropyrrole (2).- To 200 ml of concentrated H_2SO_4 cooled to 0°, was added 40 g (0.37 mol) of 1 (Aldrich) dropwise over a 15 min. period while the reaction temperature was maintained under 20°. When the addition was complete, the solution was cooled to 0° and KNO_3 (40.8 g, 0.40 mol) was added portionwise over 0.5 hr, at such a rate that the reaction temperature remained below 20°. The mixture was stirred at 25° for 0.5 hr after which tlc showed complete conversion to the desired product; R_f (silica, dichloromethane) 0.35. It was then poured onto 500 g of ice and extracted with diethyl ether (3x500 ml), and dichloromethane (4x500 ml). The combined organic extracts were washed with saturated aq. $NaHCO_3$, dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford crude 2. Flash chromatography over silica (dichloromethane) gave 41.8 g (73%) of pure 2, mp. 107-109°.

NMR: δ 6.41 (s, 1H, pyrrole); 3.43 (s, 3H, N-CH_3); 2.58 (s, 3H, 2-CH_3); 2.18 (s, 3H, 5-CH_3). IR(KBr): 1539, 1456, 1404, 1333, 1304 cm^{-1}.

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17

Found: C, 54.46; H, 6.61; N, 18.38

(2-Fluorophenyl)(1,2,5-trimethyl-4-nitropyrrol)-3-yl)methanone (3).- To 5.0 g (32 mmol) of 2 dissolved in toluene (100 ml) was added 2-fluorobenzoyl chloride (5.04 g, 28 mmol). The reaction mixture was cooled to 0° and $AlCl_3$ (4.4 g, 33 mmol) added in portions over a 10 min. period. The resulting mixture was heated at 55° for 3.5 hrs, cooled to ambient temperature, carefully poured onto ice (150 g), and extracted with dichloromethane (2x100 ml) and diethyl ether (2x100 ml). The combined organic extracts were dried over anhydrous K_2CO_3 and evaporated in vacuo to afford a dark brown oil. Purification was accomplished by flash column chromatography over silica (1:1 ethyl acetate-hexane as eluent; R_f = 0.28) to give 4.7 g (61%) of 3 as a yellow solid, mp. 117-117.5°. NMR: δ 7.75-7.0 (m, 4H, aromatic); 3.52 (s, 3H, N-CH_3); 2.59 (s, 3H, CH_3); 2.31 (s, 3H, CH_3); 2.31 (s, 3H, CH_3). IR(KBr): 1653, 1612, 1546, 1454, 1427, 1337, 1281 cm^{-1}.

Anal. Calcd. for $C_{14}H_{13}N_2O_3F$: C, 60.87; H, 4.74; N, 10.14

Found: C, 60.89; H, 4.65; N, 10.20

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6. It is interesting to note that under the reaction conditions described (1.0 molar equivalent of acylating reagent), no appreciable amount of product resulting from the Friedel-Crafts acylation of the solvent (toluene) was observed.

A SIMPLE SYNTHESIS OF SOME NOVEL OXIME ETHERS†

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The reaction of 4-benzoyl-5-phenylfuran-2,3-dione (1) with phenylhydrazones or phenylhydrazine leads to pyrazolecarboxylic acids.[1] The use of oximes instead of phenylhydrazones would be expected to give the corresponding isoxazolecarboxylic acids. Surprisingly however, the oximes 2 add to 1 to yield the 1:1 adducts which were identified as oxime ethers (3) containing an acetal group; oxime ethers of this type had not been described previously.[2,3] The formation of these oxime ethers may be viewed as occurring *via* a Michael addition to 1; a very similar attack of phenylhydrazine on 1 was discussed in a previous paper.[1] There are only a few known examples of the synthesis of oxime ethers *via* Michael addition of oximes to activated olefins.[3]