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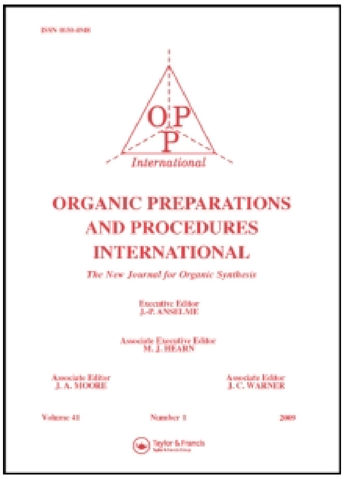

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A HIGH YIELD, SELECTIVE SYNTHESIS OF 1,3,5-TRIMETHOXYBENZENE

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A HIGH YIELD, SELECTIVE SYNTHESIS OF 1,3,5-TRIMETHOXYBENZENE

Submitted by (03/01/02)

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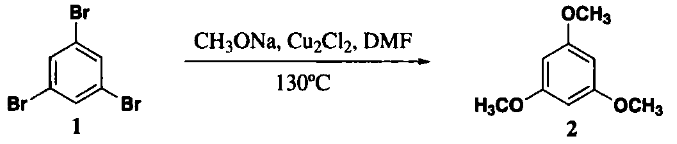
Methods for the introduction of methoxy substituents into aryl rings are important because of the use of methoxy compounds as intermediates for the synthesis of pharmaceutical products. Thus, 1,3,5-trimethoxybenzene (**2**) has been utilized extensively to prepare vasodilator agent buflomedil,[1,2] other novel drugs[3-5] and new compounds.[6,7] Moreover, the demethylation of methyl aryl ethers is an effective approach for the preparation of other phenolic compounds, *e.g.* the demethylation of **2** provides a direct route to phloroglucinol.[8,9] Although the direct preparations of **2** from 1,3,5-tribromobenzene (**1**) by displacement of bromide by methoxide have been reported, both the copper (I)-methyl formate catalyzed system[10] and the copper (II)-carbon dioxide-catalyzed system[11] are undesirable owing to the long reaction time and lower yields (81%[10] and 65%[11]) and selectivity. In general, aromatic nucleophilic substitution provides a useful route to many functionalized aromatic compounds. However, the lack of selectivity and the use of solvents such as hexamethylphorous triamide (HMPT), dimethylformamide (DMF) and pyridines and of copper-catalysts characterize the methoxylation of non-activated aryl bromides.[12] Under ambient pressure, it is difficult to raise the reflux temperature as a result of the release of "solvent cage bonded" methanol from sodium methoxide during methoxylation.[13] The low reflux temperature and the low sodium methoxide concentration retard the progress of the methoxylation of non-activated aryl bromides. We report herein an improved procedure for the preparation of **2**.



Compound **1** was heated with an excess of solid sodium methoxide in the presence of cuprous chloride[14] in DMF in an autoclave at 130° for 6 h. After removal of the solvent, the brown residue was extracted with toluene to afford crystalline **2** in 86-91% yields. Neither the starting material nor by-products such as 3,5-dibromoanisole and 5-bromo-1,3-dimethoxybenzene were detected by GC/MS, indicating **1** was completely converted to **2**. It should be noted that under the condition of atmospheric reflux (maximum temperature is *ca.* 110°) small amounts of 3,5-dibromoanisole (< 1%) and 5-bromo-1,3-dimethoxybenzene (< 2%) were detected by GC/MS analysis even though the starting material was completely consumed. The direct, high yield and selective synthesis of **2** directly from inexpensive and commercially available **1** makes this procedure the better choice for the preparation of **2**.

EXPERIMENTAL SECTION

Mps were determined in capillaries on a domestic melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker ARX-300 spectrometer with TMS as the internal standard. Chemical shifts are expressed in parts per million (δ, ppm). FTIR spectra were obtained on a Nicolet Magna IR-560 spectrometer as neat films. GC/MS analysis was carried out using HP 6890 gas chromatograph equipped with HP 5973 detector and *m/z* values are given with relative intensities in parentheses. DMF was dried over $MgSO_4$ prior to use. Microanalysis was performed on a PE 240-C element analysis instrument.

1,3,5-Trimethoxybenzene (2).- Into a 500 mL stainless steel autoclave, 1,3,5-tribromobenzene (50 g, 0.159 mol) was suspended in DMF (150 mL) and solid sodium methoxide was added [solid sodium methoxide was freshly prepared by reaction of sodium (28 g, 1.217 mol) with methanol (110 mL), followed by distillation of excess methanol to dryness], followed by the addition of cuprous chloride (5 g, 0.05 mol freshly prepared according to reference[14]). After air was displaced with N_2, the autoclave was heated to 130° for 6 h. After being cooled to room temperature, the reaction mixture was transferred to a round-bottomed flask. DMF was evaporated in *vacuo* below 60° and the residue was extracted with toluene (100 mL x 3). The organic extract was washed with 0.1 N sulfuric acid (40 mL) to pH 5-6 to remove salts and bases. It was dried and evaporated to dryness to give a pale yellow solid. Recrystallization from hexane gave

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24.3 g (91%) of **2** as a white solid, mp 51.5-53°, *lit.*[10] 50-51.5°. IR (KBr): 3080, 3005, 2945, 2850, 1385, 1260, 720 cm^{-1}. ^1H NMR: δ 3.72 (s, 9H, OCH_3), 6.05 (d, 3H, ArH). MS (*m/z*): 168 (100% M^+), 139 (86%), 125 (22%), 109 (20%).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.31; H, 7.10

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