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Technical Notes

One-Step Preparation of Some 3-Substituted Anisoles

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Abstract:

A one-step preparation of 3-bromoanisole, 3-chloroanisole, and 3-trifluoromethylanisole from the corresponding 3-substituted nitrobenzenes is carried out by nucleophilic aromatic substitution of the nitro group with sodium or potassium methoxide, employing an effective amount of a phase-transfer catalyst (PTC), in a medium of a nonpolar aprotic solvent, under aerobic conditions, at a temperature of 50−65 °C. The alkali methoxide used can be a pre-prepared solid, or it can be prepared in situ from the alkali hydroxide and methanol. The methoxydenitration proved to be very sensitive to the type of PTC. The effect of the solvent on the reaction is discussed. The targeted anisoles are obtained in yields of more than 80% and purities of greater than 99%.

Introduction

Meta-substituted bromo- and chloroanisoles (**2a**, **2b**) are important intermediates in the pharmaceutical field. In particular, **2a** is used for producing the analgesic drug Tramadol[1] and for preparing the antidepressant Moxifetin hydrogen maleate.[2]

Among the few known methods for preparing **2a** and **2b**, as well as 3-trifluoromethylanisole (**2c**), the most frequently encountered one is that based on the methylation of meta-substituted phenols synthesized by multistep procedures.[3−5] Another method consists of using *m*-anisidines to prepare **2a** and **2b**, via a diazotization reaction.[6]

Results and Discussion

This work presents a convenient one-step preparation of meta-substituted anisoles in high yield and purity (**2a**−**c**), by the nucleophilic substitution of the NO_2^- group in the corresponding meta-substituted nitrobenzene **1** (Scheme 1).

The reactions of *m*-halonitrobenzenes with alkali metal alkoxides have been reported in a small number of publications. A study of the reactivity of halonitrobenzenes, **1a**,**b**, in 2-propanol solutions of potassium 2-propoxide, showed that the only product obtained under anaerobic conditions was 3,3′-dibromo- or dichloroazobenzene (**4a**, **4b**), whereas in the presence of air, both compounds displayed almost insignificant reactivities.[7] Only in rare cases was the nucleophilic displacement of a nitro group meta to an electron-withdrawing group, such as Cl and Br, selective.

Scheme 1

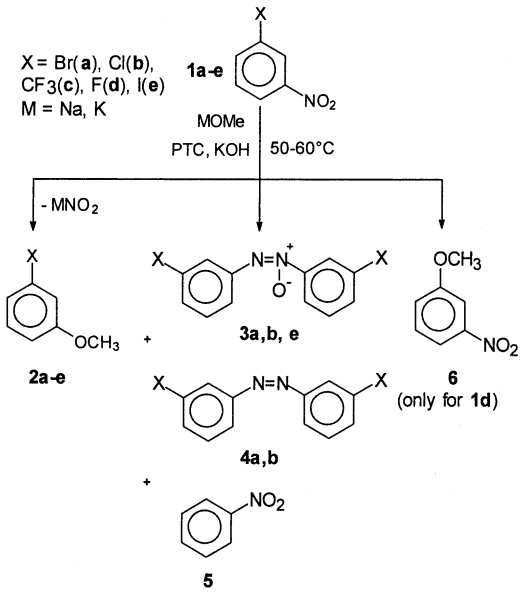

Table 1. **Methoxydenitration of 1a in the Presence of Various PTC[a]**

PTC	methoxylating agent	conversion of nitrobenzene **1a**, %	selectivity for anisole **2a**, %
$Bu_4N^+Br^-$	NaOMe solid	99.5	96.9
$Bu_4N^+Cl^-$	NaOMe solid	98.4	96.0
$Bu_4N^+OH^-$ [b]	NaOMe solid	99.5	96.9
$Bu_4N^+HSO_4^-$	NaOMe solid	95.6	93.4
PEG-1500	NaOMe solid	100	32.2
$Bu_4N^+Br^-$ [c]	NaOMe solid	99.2	85.0
$Bu_4N^+Br^-$	KOMe - in situ	100	97.1
$Bu_3MeN^+Cl^-$	KOMe - in situ	96.8	96.8
$Octyl_4N^+Br^-$	KOMe - in situ	86.6	50.6
$BenzMe_3N^+Br^-$	KOMe - in situ	67.4	10.5
$Et_4N^+Br^-$	KOMe - in situ	56.2	26.8
$Bu_4N^+Br^-$ [c]	KOMe - in situ	98.2	80.0
No PTC	KOMe - in situ	53.7	53.7

[a] All reactions carried out in toluene. [b] Aqueous 40% solution. [c] Anaerobic conditions.

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Table 2. **Reactions of 1 with sodium or potassium methoxides and sodium ethoxide[a]**

substrate **1**	alkoxylating agent	solvent	reaction time, h	conversion of **1**, %	selectivity for **2** or **7**, %	isolated yield of **2**, %
1a	NaOMe solid	*n*-heptane	3.0	96.4	94	82
1a	KOMe - in situ	*n*-hexane	2.5	100	97	84
1a	NaOMe - in situ	toluene	6	76	71	–
1b	NaOMe solid	cyclohexane	2.5	97.8	95.3	81
1c	NaOMe solid	*n*-hexane	3.0	100	97.2	85
1d	NaOMe solid	toluene	2.5	86	12	–
1e	NaOMe solid	toluene	24	52	85	–
1a	NaOEt solid	*n*-hexane	3.0	89.8	50.5	–
1b	NaOEt solid	toluene	1.5	93.6	63.6	–

[a] All reactions were carried out under aerobic conditions with $Bu_4N^+Br^-$ as a PTC.

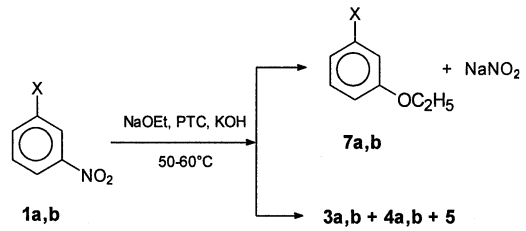
Thus, 3-benzyloxybromo- or chlorobenzenes were obtained in yields close to theoretical by treating **1a**,**b** with benzyl alcohol−potassium hydroxide (KOH) in tetramethylurea, in the presence of a PTC, at 50 °C, for 24 h.[8] However, no information was found in this article, or in other publications, on the reactions between methoxides and meta-substituted nitrobenzenes, **1a**−**e**.

In this work, methoxydenitration is observed in the reaction of **1** with sodium methoxide (NaOMe) or potassium methoxide (KOMe), employing an effective amount of a PTC, selected from quaternary ammonium salts, in the medium of a water-immiscible nonpolar aprotic solvent, such as cyclohexane, hexane, heptane, and toluene. No reaction was observed in dichloromethane. It is generally known that PTC reactions proceed readily in apolar aprotic solvents. It can be assumed that the absence of any reaction in dichloromethane is due to its relatively high polarity in comparison with that of toluene, hexane, or cyclohexane (δ = 8.9, 2.4, 1.9, and 2.0 respectively). [9,10]

The methoxydenitration of **1a**,**b**,**e** is accompanied by radical reactions leading to the formation of byproducts of mainly nitro reduction to the corresponding 3,3′-disubstituted azoxy- and azobenzenes (compounds **3a**,**b**,**e** and **4a**−**b**, respectively), and hydrodehalogenation to nitrobenzene, **5**. Therefore, in a nitrogen atmosphere, the selectivity for anisoles, **2a**,**b**, over byproducts **3**, **4**, and **5**, does not exceed 80−85% (Table 1). To suppress the undesirable radical processes, the methoxydenitration was performed under aerobic conditions. As a result, the selectivity for **2a**,**b** increased to 95−97%.

Two different approaches to using the alkali metal methoxide are suggested. The first approach consists of carrying out the reaction using a pre-prepared solid NaOMe or KOMe, in the presence of an effective amount of KOH. The amount of methoxide used is 1.1−1.4 mol, based on 1 mol of substituted nitrobenzene, **1**. The amount of KOH is 1.5−1.7 mol per 1 mol of **1**. The reaction is carried out at a temperature of 50−55 °C for 2−4 h.

Scheme 2



The second approach to carrying out the methoxydenitration employs KOMe, prepared in situ from methanol and KOH. The amounts of methanol and KOH are 1.2 and 2.2−2.4 mol, respectively, per 1 mol of substituted nitrobenzene, **1**. The reaction is carried out at a temperature of 55−60 °C for about 3 h. It should be noted that NaOMe prepared in situ in the course of the reaction is significantly less reactive than KOMe obtained in a similar way (Table 2).

In both approaches, the amount of PTC employed is in the range of 20−30% w/w, based on the initial substituted nitrobenzene, **1**. The reaction proved to be very sensitive to the type of PTC. As seen from Table 1, tributylmethylammonium chloride and all the tetrabutylammonium salts, regardless of the anion, afforded good results. Neither hydrophilic tetraethylammonium and benzyltrimethylammonium bromides nor lipophilic, but bulky, tetraoctylammonium bromide provided satisfactory results. Use of poly(ethylene glycol) (PEG-1500) as a PTC afforded full consumption of **1a**, but the selectivity for **2a** over byproducts was low.

The anisoles, **2a**−**c**, were isolated in a yield of more than 80% and a purity of more than 99% by fractional distillation of the final reaction mixtures (Table 2).

The reactivity of the substituted nitrobenzene, **1e**, towards methoxides turned out to be considerably lower than that of **1a**−**c** (Table 2). Even with a 4-fold molar excess of NaOMe, the conversion of **1e** was below 85%. In the case of nitrobenzene, **1d**, methoxydefluorination prevailed over methoxydenitration. The main reaction product was *m*-nitroanisole, **6**, and not the targeted anisole, **2d** (Table 2).

We also attempted the preparation of 3-halophenetoles, **7a**,**b**, by a similar route (Scheme 2). For this purpose, **1a**,**b** were reacted with solid sodium ethoxide (NaOEt) under the same conditions as used for the reactions with methoxide. The reactions with NaOEt were characterized by a low selectivity for the phenetoles, **7a**,**b** (Table 2), while the side

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reactions giving **3a**,**b**, **4a**,**b**, and **5** become commensurate with the main reaction. Such a difference between the reactions of the same substrates with NaOMe and NaOEt can be explained by the much greater readiness of the ethoxy group to participate in the reduction processes.

In conclusion, the one-step synthesis of 3-bromo-, 3-chloro-, and 3-trifluoromethylanisoles (**2a**−**c**) reported herein is simple and expeditious and affords the target products in high yields and purities.

Batch preparations of 3-bromoanisole, **2a**, were successfully performed using KOMe prepared in situ from methanol and KOH. For economic reasons, the use of KOMe is preferable to the use of expensive and explosive solid NaOMe.

Experimental Section

General. All chemicals were purchased from Fluka and Aldrich Chemical Co. Mass spectra were obtained on a Hewlett-Packard 5890 spectrometer. ^{1}H NMR spectra were recorded on a Varian Unity Plus 500 MHz instrument using tetramethylsilane as an internal standard.

Representative Procedure for the Preparation of 3-Chloroanisole, 2b, Using Solid Sodium Methoxide. The reaction is carried out with the forced passage of air through the reaction solution. To a solution of 3-chloronitrobenzene, **1b**, (47.3 g, 0.3 mol) in toluene (60 mL) are added at room temperature NaOMe powder (19.4 g, 0.36 mol), solid KOH powder (33.6 g, 0.51 mol), and tetrabutylammonium bromide (12.3 g, 0.038 mol). The heterogeneous mixture is stirred vigorously at 50 °C for 2 h. The mixture is then cooled and washed with water to remove inorganic compounds, followed by phase separation. The organic phase is washed with aqueous HCl solution to remove tetrabutylammonium bromide and products of its decomposition remaining after the washing with water. The organic phase is distilled under vacuum to afford a final pure anisole, **2b**, (88 °C, 18 mmHg) as a colourless, clear liquid (35.9 g, 84%).

The same procedure is employed when the solid NaOMe is replaced by solid KOMe.

Representative Procedure for the Preparation of 3-Bromoanisole, 2a, Using Potassium Methoxide Prepared in Situ. The reaction is carried out with the forced passage of air through the reaction solution. A heterogeneous mixture of cyclohexane (210 mL), methanol (38.4 g, 1.2 mol), solid KOH (158.1 g, 2.4 mol), and tetrabutylammonium chloride (50.5 g, 0.18 mol) is stirred vigorously at 55 °C for about 5 min. A solution of 3-bromonitrobenzene, **1a**, (202 g, 1 mol) in cyclohexane (110 mL) is added dropwise at 55 °C over 0.5 h. The heterogeneous reaction mixture is stirred at 60 °C for 2.5 h. The mixture is treated in a manner similar to that described above for anisole, **2b**. The organic phase is distilled to afford a final pure anisole, **2a**, (92−93 °C, 14 mmHg) as a colorless, clear liquid (155 g, 83%).

The products, **2a**−**c**, were identified by ^{1}H NMR and mass spectroscopy. All the spectral data obtained were compared with those of authentic samples. The anisoles, **2d**,**e**, the byproducts, **3a**,**b**,**e**, **4a**,**b**, **5**, **6**, as well as the phenetols, **7a**,**b**, were identified by mass spectroscopy.

Scale-Up Batch. Batch preparations of 3-bromoanisole, **2a**, in toluene using KOMe prepared in situ and tetrabutyammonium bromide as a catalyst, were performed in a 250-L reactor under the conditions described in the Experimental Section for the laboratory synthesis of **2a.** The toluene was repeatedly recycled. The average isolated yield of **2a** was 85%, based on **1a**. The hazardous, aqueous waste containing potassium nitrite (7−10% w/w) underwent a special treatment based on the reduction of nitrites to nitrogen by urea or sulfamic acid. This waste treatment is rapid, environmentally acceptable, and inexpensive.

Acknowledgment

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Supporting Information Available

^{1}H NMR spectra of **2a**−**c**, mass spectra of **2a**−**e**, **3a**,**b**,**e**, **4a**,**b**, **5**, **6**, and of 3-bromo- and 3-chlorophenetols, **7a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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