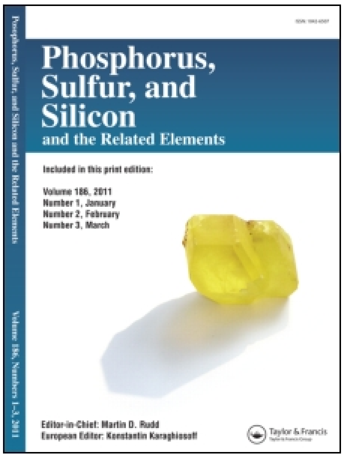

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A FAST AND MILD METHOD FOR NITRATION OF AROMATIC RINGS

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The use of benzyltriphenylphosphonium nitrate ($PhCH_2Ph_3P^+NO_3^-$) *(BTPPN) as a useful reagent for nitration aromatic compounds in the presence of methanesulfonic anhydride under solvent-free conditions is described. This methodology is useful for nitration of activated aromatic rings.*

Keywords: Aromatic compounds; benzyltriphenylphosphonium nitrate; methanesulfonic anhydride; nitration; solvent-free conditions

Conventional methods for the nitration of aromatic rings utilize a mixture of nitric and sulphuric acids or nitronium tetrafluroborate methods.[1] These conditions are incompatible with a range of compounds that are sensitive to oxidizing or strongly acidic conditions. In the case of borane/nitronium salt, HF and BF_3 are liberated.[1] We have been engaged in the synthesis of azido aromatic compounds as photoaffinity ligands.[2] The nitro compounds required for the synthesis of these derivatives were prepared by the conventional nitric-sulphoric acid or nitronium tetraborate methods.[3] We became concerned about the disposal of the large amount of acid waste that resulted, sensitivity of starting material, and low yields of product. To avoid this complication and the associated hazards, we set out to test the nitrating ability of benzyltriphenylphosphonium nitrate under solvent-free conditions in a projected route to develop a simple synthesis of the nitro compound in a relatively short period.

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RESULTS AND DISCUSSION

Heterogeneous reactions that are facilitated by supported reagents on various solid inorganic surfaces have received attention in recent years.[4–6] The advantage of these methods over conventional homogenous reactions is that they provide greater selectivity, enhanced reaction rates, cleaner products, and manipulative simplicity. In connection with our ongoing program to develop environmentally benign methods using solvent-free conditions,[7] herein we report on an extremely convenient method for nitration of a variety of aromatic compounds with BTPPN 1 under solvent-free conditions. The reagent is readily prepared by addition of an aqueous solution of KNO_3 to an aqueous solution of benzyltriphenylphosphonium chloride at room temperature (Scheme 1). The resulting white powder, which can be stored for months without loss of its reactivity, is soluble in polar solvents such as methanol, THF, acetonitrile, acetone, DMF, chloroform, ethyl acetate, and dichloromethane, but insoluble in nonpolar solvents such as carbon tetrachloride, *n*-hexane, and diethyl ether.

$$PhCH_2\,P^+Ph_3Cl^- + KNO_3 \xrightarrow[\text{room temperature 95\%}]{H_2O/20\,\text{min}} \underset{\mathbf{1}}{PhCH_2P^+Ph_3NO_3^-} + KCl$$

SCHEME 1

Here we report on the nitration of activated aromatic compounds to the corresponding nitrobenzene derivatives under solvent-free conditions with reagent **1**. The process in its entirety involves a simple mixing of one molar ratio of aromatic compounds, methanesulfonic anhydride, and reagent **1** in a mortar and grinding the mixture with a pestle for the time specified in Table I at room temperature. This reaction proceeds rapidly and purification of the product is very straightforward.

Activated aromatic compounds **2** were converted to the corresponding nitro aromatic compounds **3** under solvent-free conditions at room temperature in excellent yields in 5–20 min; deactivated aromatic compounds were not converted to nitrobenzene derivatives with reagent **1** in the presence of methanesulfonic anhydride after 60–120 min grinding at room temperature (Scheme 2 and Table I). The reagent does not affect oxidizable groups, such as hydroxyl and amino groups (Table I). After extraction of the nitro aromatic compounds and acidified aqueous layer with aqueous 5% HCl and treatment with a fresh batch of the aqueous KNO_3, the reagent **1** could be recovered in quantitative yield.

TABLE I Nitration of Aromatic Compounds **2** with Reagent **1** to Nitroarens **3** Under Solvent-Free Conditions at Room Temperature [a,b]

Entry	ArH (**2**)	$ArNO_2$ (**3**) (*o:m:p ratio)*	Time (min)	Yield[c] (%)
1	Anisole	Nitroanisole (15:0:85)	5	95
2	Acetanilide	Nitroacetanilide (20:0:80)	10	89
3	3-Methylactanilide	4-Nitro-3-methylactanilide	5	90
4	3-Cloroacetanilide	4-Nitro-3-chloroacetanilide	20	88
5	1,2-Dimethoxybenzene	4-Nitro-1,2-dimethoxybenzene	5	92
6	Toluene	Nitrotluene (40:0:60)	15	98
7	Phenol	Nitrophenol	5	90
8	1,4-Dimethoxybenzene	2-Nitro-1,4-dimethoxybenzene	5	100
9	4-Hydroxybenzaldehyde	2-Nitro-4-hydroxybenzaldehyde	20	85
10	1,3,5-Trimethylbenzene	2-Nitro-1,3,5-trimethylbenzene	20	80
11	Naphthalene	1-Nitronaphthalene	20	99
12	$C_6H_5NO_2$	NR	120	0
13	$4\text{-}MeC_6H_4NO_2$	NR	60	0
14	C_6H_5CHO	NR	120	0
15	C_6H_5COOH	NR	120	0
16	C_6H_5COPh	NR	120	0
17	Benzylalcohol	Nitrobenzylalcohol (18:0:82)	15	83
18	$C_6H_5(CH_2)_2COOH$	$NO_2C_6H_4(CH_2)_2COOH$ (10:0:90)	15	83
19	$C_6H_5(CH_2)_2COOMe$	$NO_2C_6H_4(CH_2)_2COOMe$ (12:0:88)	15	85
20	$C_6H_5CH_2COOH$	$NO_2C_6H_4CH_2COOH$ (15:0:85)	20	80
21	$C_6H_5CH_2COOMe$	$NO_2C_6H_4CH_2COOMe$ (15:0:85)	20	85
22	Cocaine	3-Nitrocoaine	120	10

[a] Confirmed by comparison with authentic samples (IR, TLC, and NMR).
[b] Molar ratio of 1:2 (1:1).
[c] Yield of isolated pure product after purification.

Interestingly, the site of the electrophilic attack by this reagent was found to be identical to the conventional nitric acid or acetyl nitrate-mediated nitration reaction (Table I).

To evaluate the efficiency of this reaction under solvent-free conditions in comparison to the reaction in solution several experiments were performed. We performed the reaction of anisole in several solvents, such as methanol, acetone, ether, dichloromethane, THF, and

$$\underset{\mathbf{1}}{PhCH_2P^+Ph_3NO_3^-} + \underset{\mathbf{2}}{ArH} \xrightarrow[(MeSO_2)_2O]{\text{Solid-State}} PhCH_2P^+Ph_3MeSO_3^-$$

$$+\ MeSO_3H + \underset{\mathbf{3}}{ArNO_2}$$

SCHEME 2

1,4-dioxane. We determined that 1,4-dioxane is the best solvent for this reaction. When anisole was treated with one molar ratio of this reagent, only 30% of anisole was converted to nitroanisole after 24 h stirring at room temperature in the presence of 1 molar ratio of methanesulfonic anhydride. By increasing the amount of the reagent **1** to 2 molar ratios in the presence of 2 molar ratio of methanesulfonic anhydride, the yield of the reaction did not increased. When anisole was treated with a molar ratio of this reagent and allowed to reflux in 1,4-dioxane for 24 h in the presence of 1 molar ratio of methanesulfonic anhydride only 45% of anisole was converted to nitroanisole.

We believe that the effect of methanesulfonic anhydride is to react with the nitrate ion to produce methanesulfonyl nitrate. This reactive intermediate then reacts with the aromatic ring to produce the corresponding nitro aromatic compounds. We also tried the nitration of anisole with KNO_3 or NH_4NO_3 in the presence methanesulfonic anhydride under solvent-free conditions instead to the benzyltriphenylphosphonium nitrate, the yield of product after 60 min was only 10%. It is possible that the soft phosphonium cation is required to form a weakly associated The methanesulfonic anhydride reacted with this weakly associated ion of nitrate anion to produce methanesulfonyl nitrate and that for potassium and ammonium nitrate would not work.

In summary, we report here the preparation of benzyltriphenylphosphonium nitrate **1** as a mild, inexpensive, and selective nitration reagent. This reagent is easily prepared from low-cost and commercially available starting materials, and could be stored at room temperature for months without losing its activity. The reagent is soluble in polar solvents and slightly soluble in nonpolar solvents. This reagent is an efficient and novel reagent for nitration of activated aromatic compounds to the corresponding nitrobenzene derivatives in the presence of other oxidizable functional groups under solvent-free conditions.

EXPERIMENTAL

General

All yields refer to isolated products after purification by column chromatography. Products were characterized by comparison with authentic samples (IR and ^{1}H-NMR spectra, TLC, melting and boiling points). All ^{1}H-NMR spectra were recorded at 300 MHz in $CDCl_3$ relative to TMS. All reactions were carried out under solvent-free conditions at room temperature.

Preparation of Benzyltriphenylphosphonium Nitrate 1 (BTPPN)

A solution of benzyltriphenylphosphonium chloride (19.0 g, 49 mmol) in 100 ml of water was prepared, and then KNO_3 (4.95 g, 49 mmol) in water (100 ml) was added dropwise to the above solution and stirred for 1 h at room temperature. The resulting precipitate was filtered and washed with cooled, distilled water (50 ml), and dried in a desiccator under vacuum over calcium chloride to afford a white powder (19.92 g, 98% yield), which decomposed at 181–182°C to a dark-brown material. ^{1}H-NMR: δ 7.93–6.87 (m, 20 H), 4.7(d, J = 25.6 Hz, $\underline{\text{CH2}}$-P). ^{13}C-NMR: δ 135.28, 135.25, 134.32, 134.24, 131.o7, 131.03, 130.19, 130.09, 128.99, 128.97, 128.69, 128.66, 127.45, 127.43, 118.01, 117.36, 29.68 (d, J = 193 Hz, $\underline{\text{C}}$-P). IR (KBr): 1298, 1269, 1098, 1060, 700, 658, 590 cm^{-1}. Anal Calcd for $C_{25}H_{22}NO_3P$: C, 72.29; H, 5.30; N, 3.37%. Found: C, 72.50; H, 5.34; N, 3.31%.

Nitration of 1,4-Dimethoxybezene with Reagent (1) to 2-Nitro-1,4-dimethoxybenzene

A mixture of 1,4-dimethoxybezene (1 mmol, 0.14 g), reagent (**1**) (1 mmol, 0.42 g), and methanesulfonic anhydride (1 mmol, 0.17 g) in a mortar was ground with a pestle for the time specified in Table I until a deep-yellow color appeared. When TLC (hexane:EtOAc 70:30) showed complete disappearance of 1,4-dimethoxybezene, the mixture was extracted with CH_2Cl_2 and washed with aqueous HCl (10%). Evaporation of the solvent gave 2-nitro-1,4-dimethoxybenzene. The yield was 0.18 g (100%) of crystalline yellow solid.

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