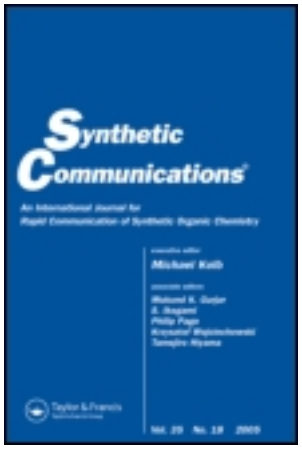

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NITROMETHANE IN POLYPHOSPHORIC ACID—A NEW REAGENT FOR CARBOXYAMIDATION AND CARBOXYLATION OF ACTIVATED AROMATIC COMPOUNDS

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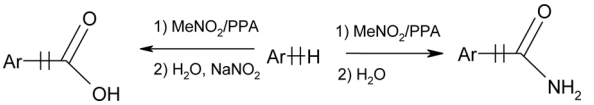
GRAPHICAL ABSTRACT



Abstract *A new method of carboxyamidation of aromatic compounds based on their reaction with nitromethane in polyphosphoric acid has been developed. Upon the hydrolysis of benzamides during the reaction mixture workup, the corresponding benzoic acids can be obtained.*

Keywords Aromatic compounds; carboxyamidation; carboxylation; nitromethane; polyphosphoric acid

INTRODUCTION

Amides are compounds of current industrial interest as intermediates in the production of pharmaceuticals and dyes. For example, lidocaine is a widely used anesthetic.[1]

Amides can be prepared by several well-established procedures including acylation of amines, hydrolyses of nitriles, and rearrangement reactions such as Schmidt and Beckmann procedures.[2]

For synthetic purposes, it is more efficient to start directly from arenes rather than from carboxylic acids, their derivatives, or ketones, thereby bypassing some steps. A direct carboxyamidation procedure has been reported, in which arenes condense with trimethylsilylisocyanate in hydrochloric acid medium.[3a] Some methods of carboxyamidation have been developed with various reagents in Friedel–Crafts conditions.[3b,c]

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Table 1. Synthesis of amides **3a–f**

Entry	R1	R2	R3	R4	Product	Time (h) in PPA	Yield %
1	H	H	OH	H	**3a**	7	46
2	H	H	OMe	H	**3b**	7	71
3	OMe	H	H	OMe	**3c**	5	62
4	H	OMe	OMe	H	**3d**	5	67
5	H	H	Me	H	**3e**	8	48
6	H	OH	OH	H	**3f**	6	49

In the current article, we propose a new, convenient method of carboxyamidation or carboxylation of aromatic compounds, suggesting reagent availability and experimental simplicity based on the usage of nitromethane in polyphosphoric acid (PPA).

RESULTS AND DISCUSSION

The reaction of arenes (**1a–f**) with nitromethane (**2**) in PPA† at 90–95 °C leads to formation of benzamides (**3a–f**) with yields of 46–71% (Table 1, Scheme 1). Arenes containing electron-donating groups such as hydroxy-, alkoxy- or alkyl-participate in this reaction.

We have proposed that nitromethane in PPA medium forms diphosphorylated *aci*-nitromethane **4**, which is used for acylation of arenes **1a–f** by means of a Vilsmeier-type reaction with oximes **5a–f**. Intermediate aldoximes **5a–f** experience dehydration with the formation of nitriles **6a–f**, which hydrolyze in PPA into corresponding amides **3a–f** (Scheme 2).

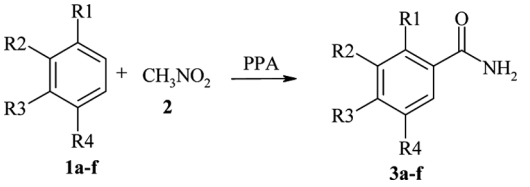
An advantage of the suggested mechanism is the formation of mixed anhydrides of nitronic acids.[5] The existence of monoacyl anhydrides was proved by spectroscopy methods,[5b] a reasoning for diacyl anhydrides had been provided,[5c] and anhydrides obtained from secondary nitroalkanes were isolated.[5d]

It was reported,[6] that arenes can be acylated with sodium salts of nitroalkanes, nitroacetic ester, or nitroacetophenone in trifluoromethanesulfonic acid (TFSA) with formation of corresponding oximes. Intermediate nitriles such as **6b** can be isolated from PPA by distillation. The observed regioselectivity and a lack of *ortho*-products in the cases of toluene, anisole, and phenol probably imply thermodynamic or orbital control in this reaction.

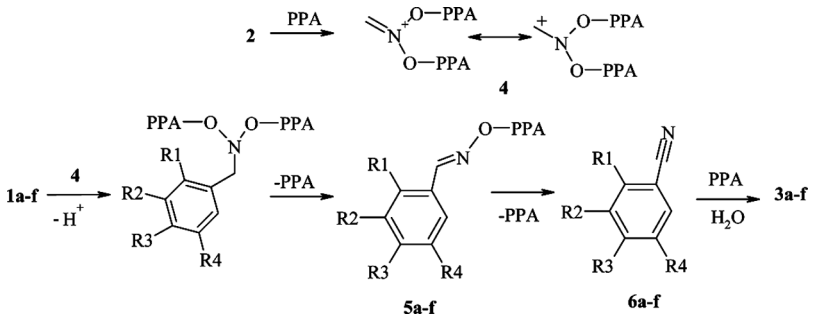
It is well known that amides can undergo hydrolysis down to carboxylic acids upon treatment with sodium nitrite in an acidic medium.[2a,7] On the basis of these works, we have proposed that the investigated reaction may be used for the synthesis of benzoic acids. When a reaction mixture treated with water was cooled down and then sodium nitrite was added, corresponding benzoic acids **6** were formed with 38–64% yields (Scheme 3, Table 2).

In conclusion, it should be noted that the methods described here in allow for relatively easy introduction of carbamoyl and carboxyl groups into activated aromatic compounds.

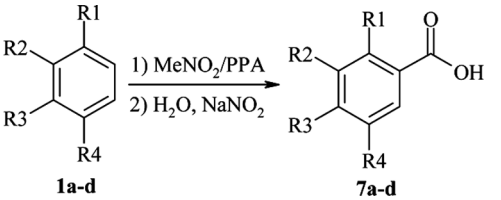
†PPA containing 86% P_2O_5 was used; preparation according to Uhlig.[4]



Scheme 1. Synthesis of amides **3a–f**.



Scheme 2. Mechanism proposed for the reaction of arenes with nitromethane in PPA.



Scheme 3. Direct one-step carboxylation of arenes (**1a–d**).

Table 2. Synthesis of carboxylic acids **7a–d**

Entry	R1	R2	R3	R4	Product	Time (h) in PPA	Yield %
1	H	H	OH	H	**7a**	7	38
2	H	H	OMe	H	**7b**	7	64
3	OMe	H	H	OMe	**7c**	5	58
4	H	OMe	OMe	H	**7d**	5	61

EXPERIMENTAL

Evaporation of solvents was carried out using a rotary evaporator under reduced pressure (2–400 mbar) with a bath temperature of up to 60 °C. Thin-layer chromatography (TLC) was performed on silica-gel plates Silufol UV-254. In general, the course of the reactions was followed by TLC. NMR spectra were obtained on a Bruker AM-300 spectrometer ^{1}H at 300 MHz using $CDCl_3$, acetone-d_6, or dimethylsulfoxide (DMSO-d_6) as solvent. Chemical shifts are expressed in parts

per million (ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard. Infrared (IR) spectra were recorded on a Perkin-Elmer Fourier transform (FT–IR) spectrometer. Melting points of small samples were obtained after recrystallization; solvents are given in parentheses. Microanalyses were carried out on a C,H,N-1 elemental analyzer. Chemicals were obtained from commercial sources, we used without purification, and were of reagent quality or better.

Typical Procedure: Preparation of Benzamides 3a–f

Corresponding aromatic compounds **1a–f** (1 mmol) and nitromethane **2** (0.244 g, 4 mmol) in PPA (3–4 g) were stirred at 90–95 °C for 5–8 h (Table 1). The reaction mixture was poured in cold water (10 mL) with intense stirring. The resulting mixture was extracted by CH_2Cl_2 (10×30 mL). The solution was evaporated under vacuum; the residue was purified by crystallization from water.

Data

4-Hydroxybenzamide (3a). Mp 160–162 °C. Lit.[8] mp 159–161 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.28 (br. s, 2H, NH_2); 7.03 (d, $J = 8.6$ Hz, 2H, H-3/5); 7.84 (d, $J = 8.6$ Hz, 2H, H-2/6); 9.87 (br. s, 1H, OH). IR (KBr): 3617, 3412 (NH), 1651 (CONH), 1612 (CONH) cm^{-1}. Anal. calcd. for $C_7H_7NO_2$ (%): C, 61.31; H, 5.14; N, 10.21. Found: C, 61.48; H, 5.11; N, 10.15.

4-Methoxybenzamide (3b). Mp 166–167 °C. Lit.[8] mp 165–166 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 3 H, OMe); 5.93 (br. s, 2 H, NH_2); 6.94 (d, $J = 8.7$ Hz, 2 H, H-3/5); 7.79 (d, $J = 8.7$ Hz, 2 H, H-2/6). IR (KBr): 3390, 3170 (NH), 1660 (CONH), 1618 (CONH) cm^{-1}. Anal. calcd. for $C_8H_9NO_2$ (%): C, 63.57; H, 6.00; N, 9.27. Found: C, 63.71; H, 5.93; N, 9.20.

2,5-Dimethoxybenzamide (3c). Mp 141–142 °C. Lit.[9] mp 141–142 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ 3.82 (s, 3 H, OMe); 3.91 (s, 3 H, OMe); 6.41 (br. s, 1 H, NH); 6.92 (d, $J = 9.0$ Hz, 1 H, H-3); 7.01 (dd, $J = 9.0$, 3.1 Hz, 1 H, H-4); 7.75 (d, $J = 3.1$ Hz, 1 H-6); 7.84 (br s, 1 H, NH). IR (KBr): 3386, 3180 (NH), 1664 (CONH), 1619 (CONH) cm^{-1}. Anal. calcd. for $C_9H_{11}NO_3$ (%): C, 59.66; H, 6.12; N, 7.73. Found: C, 59.78; H, 6.08; N, 7.65.

3,4-Dimethoxybenzamide (3d). Mp 162–163 °C. Lit.[10] mp 162.5-163.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.89 (s, 6 H, OMe); 5.94 (br. s, 2 H, NH); 6.87 (d, $J = 8.8$ Hz, 1 H, H-5); 7.37 (dd, $J = 8.8$, 2.5 Hz, 1 H, H-6); 7.44 (d, $J = 2.5$ Hz, 1 H, H-2). IR (KBr): 3386, 3180 (NH), 1664 (CONH), 1619 (CONH) cm^{-1}. Anal. calcd. for $C_9H_{11}NO_3$ (%): C, 59.66; H, 6.12; N, 7.73. Found: C, 59.81; H, 6.03; N, 7.67.

4-Methylbenzamide (3e). Mp 159–160 °C. Lit[8] mp 157–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3 H, Me); 5.80 (br. s, 2 H, NH_2); 7.26 (d, $J = 7.8$ Hz, 2 H, H-3/5); 7.72 (d, $J = 7.8$ Hz, 2 H, H-2/6). IR (KBr): 3341, 3170 (NH), 1670 (CONH), 1612 (CONH) cm^{-1}. Anal. calcd. for C_8H_9NO (%): C, 71.09; H, 6.71; N, 10.36. Found: C, 71.27; H, 6.64; N, 10.29.

3,4-Dihydroxybenzamide (3f). Mp 216–218 °C. Lit.[11] mp 212 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.92 (br. s, 2 H, NH_2); 6.81 (d, $J = 8.1$ Hz, 1 H, H-5); 7.23 (dd, $J = 8.1$, 2.1 Hz, 1 H, H-6); 7.38 (d, $J = 2.1$ Hz, 1 H, H-2). IR (KBr): 3610, 3190 (NH), 1660 (CONH), 1615 (CONH) cm^{-1}. Anal. calcd. for $C_7H_7NO_3$ (%): C, 54.90; H, 4.61; N, 9.15. Found: C, 55.08; H, 5.55; N, 9.02.

4-methoxybenzonitrile (6b). Anisole **1b** (1.08 g, 10 mmol) and nitromethane **2** (2.44 g, 40 mmol) in PPA (30–35 g) was stirred at 90–95 °C for 7 h. After the reflux, 4-methoxybenzonitrile was distilled from the reaction mixture collecting the fraction with bp 200–260 °C. 4-Methoxybenzonitrile **6b** was purified by crystallization from alcohol with water.

Mp 59–61 °C. Lit.[12] mp 60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (s, 3 H, OMe); 6.96 (d, $J = 8.8$ Hz, 2 H, H-3/5); 7.59 (d, $J = 8.8$ Hz, 2 H, H-2/6). IR (KBr): 2218 (CN) cm^{-1}. Anal. calcd. for C_8H_7NO (%): C, 72.17; H, 5.30; N, 10.52. Found: C, 72.30; H, 5.26; N, 10.52.

Typical Procedure: Preparation of Benzoic Acids 7a–d

Corresponding aromatic compound **1a–d** (1 mmol) and nitromethane **2** (0.244 g, 4 mmol) in PPA (3–4 g) was stirred at 90–95 °C for 5–8 h (Table 2). The reaction mixture was poured in water (30 mL) with intense stirring and then cooled to 0 °C, and sodium nitrite (0.069 g, 1 mmol) was added. The reaction mixture was stirred at this temperature for 15 min, and benzoic acids **7a–d** were precipitated. The resulting mixture was extracted by CH_2Cl_2 (10 × 30 mL). The solution was evaporated under vacuum; the residue was purified by crystallization from water.

Data

4-Hydroxybenzoic acid (7a). Mp 212–214 °C. Lit.[13] mp 211–213 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.84 (d, $J = 8.7$ Hz, 2 H, H-3/5); 7.81 (d, $J = 8.7$ Hz, 2 H, H-2/6); 10.20 (br. s, 1 H, OH); 12.40 (br. s, 2 H, COOH). IR (KBr): 3393 (OH), 1677 (CO) cm^{-1}. Anal. calcd. for $C_7H_6O_3$ (%): C, 60.87; H, 4.38. Found: C, 61.02; H, 4.33.

4-Methoxybenzoic acid (7b). Mp 182–184 °C. Lit.[14] mp 183–184 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.84 (s, 3 H, OMe); 7.04 (d, $J = 8.7$ Hz, 2 H, H-3/5); 7.93 (d, $J = 8.7$ Hz, 2 H, H-2/6); 12.70 (br. s, 2 H, COOH). IR (KBr): 1688 (CO) cm^{-1}. Anal. calcd. for $C_8H_8O_3$ (%): C, 63.15; H, 5.30. Found: C, 63.30; H, 5.24.

2,5-Dimethoxybenzoic acid (7c). Mp 74–76 °C. Lit[13] mp 74–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3 H, OMe); 4.03 (s, 3 H, OMe); 6.97 (d, $J = 9.0$ Hz, 1 H, H-3); 7.12 (dd, $J = 9.0$, 2.5 Hz, 1 H, H-4); 7.68 (d, $J = 2.5$ Hz, 1 H); 11.00 (br. s, 2 H, COOH). IR (KBr): 1664 (CO) cm^{-1}. Anal. calcd. for $C_9H_{10}O_4$ (%): C, 59.34; H, 5.53. Found: C, 59.44; H, 5.48.

3,4-Dimethoxybenzoic acid (7d). Mp 178–179 °C. Lit.[13] mp 176–178 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94 (s, 3 H, OMe); 3.98 (s, 3 H, OMe), 6.93 (d, $J = 8.4$ Hz, 1 H, H-5); 7.61 (d, $J = 1.9$ Hz, 1 H); 7.78 (dd, $J = 8.4$, 1.9 Hz, 1 H, H-4);

8.60 (br. s, 2 H, COOH). IR (KBr): 1677 (CO) cm^{-1}. Anal. calcd. for $C_9H_{10}O_4$ (%): C, 59.34; H, 5.53. Found: C, 59.47; H, 5.47.

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