Nitroethane in Polyphosphoric Acid: A New Reagent for Acetamidation and Amination of Aromatic Compounds

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Abstract: A new method of acetamidation of aromatic compounds based on their reaction with nitroethane in polyphosphoric acid has been developed. Upon the hydrolysis of acetamides during the reaction mixture workup, the corresponding amines can be obtained.

Key words: aromatic compounds, nitroethane, polyphosphoric acid, acetamidation, amination

Anilides are compounds of current industrial interest as intermediates in the production of pharmaceuticals and dyes. For example, acetaminophen (Paracetamol) is a widely used analgesic and antipyretic as well as older analgesic acetophenetidin; acetoacetanilide serves as dyestuff in the manufacture of pigments.[1]

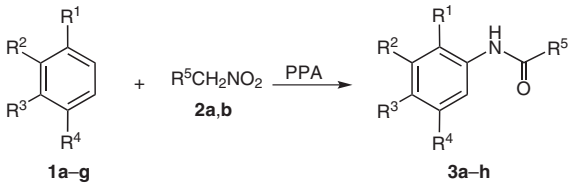
Amides can be prepared by several well-established procedures including acylation of amines, reductive amidation of nitro arenes, and rearrangement reactions such as the Schmidt and Beckmann procedures.[2]

In synthetic purposes it is more efficient to start directly from arenes rather than from amines or ketones, thereby bypassing some steps. A direct arylamidation procedure has been reported, in which arenes can condense with a hydroxamic acid[3a,b] or *N*-tosyloxyphthalimide[3c] but this reaction has a limited scope of applications.

In the current paper we propose a new method of acetamidation or amination of aromatic compounds based on the usage of nitroethane in polyphosphoric acid (PPA).

The reaction of arenes **1a–g** with nitroethane (**2a**) in PPA[4] at 110–110 °C leads to formation of acetanilides **3a–g** with yields of 63–92% (Table 1, Scheme 1). Arenes containing electron-donating groups such as hydroxy-, alkoxy-, alkyl-, as well as benzene itself participates in this reaction.[5] Similarly, a reaction of arenes in PPA proceeds with nitrobutane; the yield for *N*-(4-methoxyphenyl)butyramide (**3g**) is 83%.

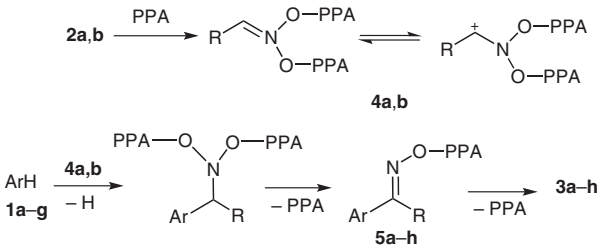
We have proposed that nitroalkanes in PPA medium form diphosphorylated aci-nitroalkanes **4**, which are prone for acylation of arenes **1** by means of a Vilsmeier-type reaction followed by Beckmann rearrangement of intermediate oximes **5** (Scheme 2).



Scheme 1 Synthesis of amides **3a–h**

Table 1 Synthesis of Amides **3a–h**

Entry	R^1	R^2	R^3	R^4	R^5	Product	Time (h) in PPA	Yield (%)
1	H	H	OH	H	Me	**3a**	3.5	77
2	H	H	OMe	H	Me	**3b**	3	92
3	OMe	H	H	OMe	Me	**3c**	3	83
4	H	OMe	OMe	H	Me	**3d**	3	88
5	H	H	H	H	Me	**3e**	5	63
6	H	H	Me	H	Me	**3f**	5	65
7	H	Me	Me	H	Me	**3g**	5	69
8	H	H	OMe	H	Me	**3h**	3	83



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

In favor of the suggested mechanism we can mention the formation of mixed anhydrides of nitronic acids.[6] The existence of monoacyl anhydrides was proved by spectroscopy methods,[6b] a reasoning for diacyl anhydrides had been provided,[6c] and anhydrides obtained from secondary nitroalkanes were isolated.[6d]

It was reported[7] that arenes can be acylated with sodium salts of nitroalkanes, nitroacetic ester, or nitroacetophenone in TFSA with formation of corresponding

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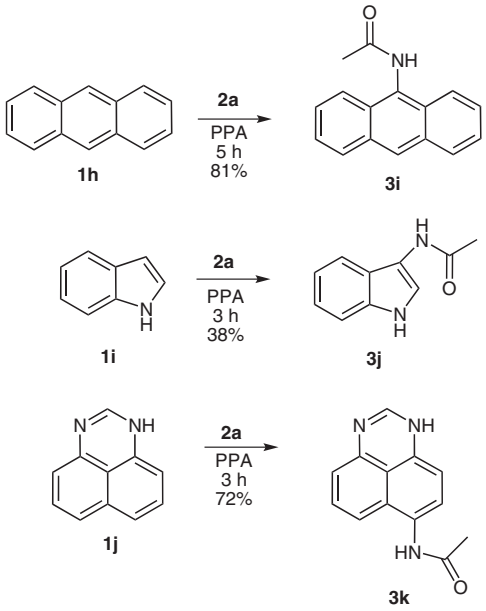
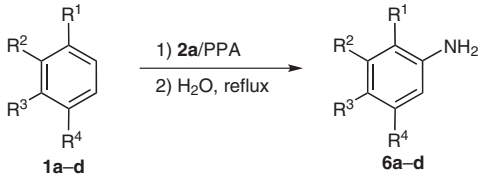
oximes. The observed regioselectivity and a lack of *ortho* products in the case of toluene, anisole, and phenol probably imply a thermodynamic control in this reaction.

Polynuclear aromatics also may be used in the reaction, that is, anthracene forms 9-acetaminoanthracene (**3i**, Scheme 3). The reaction is plausible for electron-donating heterocyclic compounds like perimidine or indole. In the case of indole, a significant amount of tar is formed in the reaction mixture, the yield is low and chromatographic resolution is required (Scheme 3).



Scheme 3 Anthracene, perimidine, and indole acetamidation

The reaction also may be used for the synthesis of anilines: when a reaction mixture treated with water is boiled for 3 hours, corresponding amines **6** are formed[8] with yields of 45–86% (Scheme 4, Table 2).



Scheme 4 Direct one-step amination of arenes

Table 2 Synthesis of Anilines **6a–d**

Entry	R^1	R^2	R^3	R^4	Product	Time (h) in PPA	Yield (%)
1	H	H	OH	H	**6a**	3.5	45
2	H	H	OMe	H	**6b**	3	86
3	OMe	H	H	OMe	**6c**	3	51
4	H	OMe	OMe	H	**6d**	3	61

In conclusion, it should be noted that the described methods herein allow for relatively easy introduction of acetamido and amino groups into the certain range of aromatic compounds.

Acknowledgment

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(5) **Preparation of Compounds 3a–k: General Procedure**
Corresponding aromatic compound **1a–j** (1 mmol) and nitroethane (**2a**) or nitrobutane (**2b**, 1.1 mmol) in PPA (3–4 g) was stirred at 105–110 °C for 3–5 h (Table 1, Scheme 3).[9] Reaction mixture was poured in cold H_2O (10 mL) with intense stirring. The resulting mixture was extracted by CH_2Cl_2 (10 × 30 mL). The solution was evaporated under vacuum, and compounds **3a–i**,**k** were purified by recrystallization. Compound **5j** was purified by flash chromatography on silica gel, eluting with toluene–EtOAc.
***N*-(4-Hydroxyphenyl)acetamide (3a)**
Mp 168–170 °C (H_2O); lit.[10] mp 168–169.5 °C. ^{1}H NMR (300 DMSO-d_6): δ = 1.97 (3 H, s, COMe), 6.67 (2 H, d, *J* = 8.7 Hz, H-3/5), 7.32 (2 H, d, *J* = 8.7 Hz, H-2/6), 9.15 (1 H, br s, OH), 9.66 (1 H, br s, NH). IR (KBr): ν_{max} = 3376, 3185 (OH, NH), 1664 (CONH), 1596 (CONH) cm^{-1}. Anal. Calcd (%) for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.76; H, 5.92; N, 9.21.
***N*-(4-Methoxyphenyl)acetamide (3b)**
Mp 130–132 °C (H_2O); lit.[2d] mp 130–132 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.00 (3 H, s, COMe), 3.70 (3 H, s, OMe), 6.85 (2 H, d, *J* = 9.0 Hz, H-3/5), 7.47 (2 H, d, *J* = 9.0 Hz, H-2/6), 9.79 (1 H, br s, NH). IR (KBr): ν_{max} = 3240 (NH), 1644 (CONH), 1606 (CONH) cm^{-1}. Anal. Calcd (%) for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.56; H, 6.68; N, 8.42.
***N*-(2,5-Dimethoxyphenyl)acetamide (3c)**
Mp 91–92 °C (H_2O); lit.[11] mp 91. ^{1}H NMR (300 MHz, acetone-d_6): δ = 2.11 (3 H, s, COMe), 3.78 (3 H, s, OMe), 3.82 (3 H, s, OMe), 6.48 (1 H, dd, *J* = 8.2, 3.6 Hz, H-4), 6.84 (1 H, d, *J* = 8.2 Hz, H-3), 7.99 (1 H, d, *J* = 3.6 Hz, H-6), 8.89 (1 H, br s, NH). IR (KBr): ν_{max} = 3284 (NH), 1658 (CONH), 1604 (CONH) cm^{-1}. Anal. Calcd (%) for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.69; H, 6.61; N, 7.03.

***N*-(3,4-Dimethoxyphenyl)acetamide (3d)**
Mp 129–131 °C (H_2O); lit.[12] mp 130–131 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.15 (3 H, s, COMe), 3.84 (3 H, s, OMe), 3.86 (3 H, s, OMe), 6.77 (1 H, d, *J* = 8.6 Hz, H-5), 6.89 (1 H, dd, *J* = 8.6, 2.4 Hz, H-6), 7.30 (1 H, d, *J* = 2.4 Hz, H-2), 7.55 (1 H, br s, NH). IR (KBr): ν_{max} = 3276 (NH), 1653 (CONH), 1606 (CONH) cm^{-1}. Anal. Calcd (%) for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.65; H, 6.64; N, 7.09.

***N*-Phenylacetamide (3e)**
Mp 113–115 °C (H_2O); lit.[11] mp 113.5–114.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.04 (3 H, s, COMe), 7.01 (1 H, dt, *J* = 7.5, 1.2 Hz, H-4), 7.28 (2 H, dd, *J* = 8.4, 7.5 Hz, H-3/5), 7.58 (2 H, dd, *J* = 8.4, 1.2 Hz, H-2/6), 9.94 (1 H, br s, NH). IR (KBr): ν_{max} = 3296 (NH), 1662 (CONH), 1600 (CONH) cm^{-1}. Anal. Calcd (%) for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.26; H, 6.63; N, 10.28.

***N*-(4-Methylphenyl)acetamide (3f)**
Mp 147–148 °C (H_2O); lit.[11] mp 147–148.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.01 (3 H, s, COMe), 2.23 (3 H, s, Me), 7.08 (2 H, d, *J* = 8.1 Hz, H-3/5), 7.45 (2 H, d, *J* = 8.1 Hz, H-2/6), 9.84 (1 H, br s, NH). IR (KBr): ν_{max} = 3300 (NH), 1664 (CONH), 1604 (CONH) cm^{-1}. Anal. Calcd (%) for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.65; H, 7.37; N, 9.31.

***N*-(3,4-Dimethylphenyl)acetamide (3g)**
Mp 94–96 °C (H_2O); lit.[13] mp 94–95 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.05 (3 H, s, COMe), 2.26 (6 H, s, Me), 6.97 (1 H, dd, *J* = 8.1, 2.0 Hz, H-6), 7.04 (1 H, d, *J* = 2.0 Hz, H-2), 7.21 (1 H, d, *J* = 8.1 Hz, H-5), 9.73 (1 H, br s, NH). IR (KBr): ν_{max} = 3300 (NH), 1660 (CONH), 1601 (CONH) cm^{-1}. Anal. Calcd (%) for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.72; H, 7.96; N, 8.49.

***N*-(4-Methoxyphenyl)butyramide (3h)**
Mp 88–90 °C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.84 (3 H, t, *J* = 7.5 Hz, Me), 1.61 (2 H, m, CH_2), 2.08 (2 H, t, *J* = 6.7 Hz, CH_2), 3.72 (3 H, s, OMe), 6.82 (2 H, d, *J* = 8.9 Hz, H-3/5), 7.46 (2 H, d, *J* = 8.9 Hz, H-2/6), 9.72 (1 H, br s, NH). IR (KBr): ν_{max} = 3265 (NH), 1656 (CONH), 1604 (CONH) cm^{-1}. Anal. Calcd (%) for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.52; H, 7.77; N, 7.18.

***N*-(9-Anthracenyl)acetamide (3i)**
Mp 276–278 °C (EtOH); lit.[14] mp 277 °C. For spectral data, see ref. 15.

***N*-(3-Indolyl)acetamide (3j)**
Mp 162–163 °C (EtOH–H_2O); lit.[15] mp 162–163 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ = 2.17 (3 H, s, COMe), 7.01 (1 H, m, ArH), 7.12 (1 H, m, ArH), 7.38 (1 H, d, *J* = 8.3 Hz, ArH), 7.74 (1 H, d, *J* = 8.1 Hz, ArH), 7.89 (1 H, d, *J* = 2.4 Hz, ArH), 9.32 (1 H, br s, NH), 10.06 (1 H, br s, NH). IR (KBr): ν_{max} = 3306 (NH), 1661 (CONH), 1603 (CONH) cm^{-1}. Anal. Calcd (%) for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.12; H, 5.71; N, 15.99.

6 (7)-Acetoaminoperimidine (3k)
Mp 225–226 °C (EtOAc); lit.[16] mp 225–226 °C. For spectral data, see ref. 17.

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(8) **Preparation of Compounds 6a–d: General Procedure**
Corresponding aromatic compound **3a**–**d** (1 mmol) and nitroethane (**2a**, 0.083 g, 1.1 mmol) in PPA (3–4 g) was stirred at 105–110 °C for 3–5 h (Table 1). Reaction mixture was poured in H_2O (30 mL) with intense stirring, then boiled under reflux for 2 h. The resulting mixture was extracted by CH_2Cl_2 (3 × 50 mL). The aqueous layer was made alkaline with ammonia to pH 8–9, the precipitate after cooling (crystals or oil) was extracted by CH_2Cl_2 (10 × 30 mL). The solution was evaporated under vacuum and purified by crystallization (compounds **6a**,**b** were purified by their hydrochlorides' crystallization from ethanol).

4-Aminophenol (6a)
Mp 188–190 °C (alcohol–H_2O); lit.[17] mp 187–190 °C. Anal. Calcd (%) for C_6H_7NO: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.23; H, 6.44; N, 12.76 (HCl); mp 303–305 °C (alcohol; with sublimation). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.87 (d, *J* = 8.9 Hz, 2 H, H-3/5), 7.21 (d, *J* = 8.9 Hz, 2 H, H-2/6), 9.88 (br s, 1 H, OH); 10.19 (br s, 3 H, NH_3).

4-Anisidine (6b)
Mp 57–59 °C; lit.[18] mp 56–59 °C. Anal. Calcd (%) for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.44; H, 7.30; N, 11.31 (HCl); mp 217–220 °C (alcohol; with sublimation). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.71 (s, 3 H, Me), 7.0 (d, *J* = 8.8 Hz, 2 H, H-3/5), 7.35 (d, *J* = 8.8 Hz, 2 H, H-2/6), 10.44 (br s, 3 H, NH_3).

2,5-Dimethoxyaniline (6c)
Mp 80–81 °C (PE); lit.[19] mp 80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.71 (s, 3 H, OMe), 3.76 (br s, 2 H, NH_2), 3.78 (s, 3 H, OMe), 6.24 (dd, *J* = 8.7, 2.8 Hz, 1 H, H-4), 6.31 (d, *J* = 2.8 Hz, 1 H, H-6), 6.67 (d, *J* = 8.7 Hz, 1 H, H-3). Anal. Calcd (%) for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.90; H, 7.18; N, 9.05.

3,4-Dimethoxyaniline (6d)
Mp 85–87 °C (PE); lit.[20] mp 86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.44 (br s, 2 H, NH_2), 3.79 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 6.15 (d, *J* = 2.1 Hz, 1 H, H-2), 6.31 (dd, *J* = 6.0, 2.1 Hz 1 H, H-6), 6.70 (d, *J* = 6.0 Hz, 1 H, H-5). Anal. Calcd (%) for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.86; H, 7.19; N, 9.02.

(9) A reaction with benzene and toluene was carried out in a sealed tube.

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