A Novel Synthesis of *N*-Arylamides from Nitroarenes via Reductive N-Acylation with Red Phosphorus and Iodine

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Abstract: A series of *N*-arylamides and imides were synthesized via reductive N-acylation of nitroarenes with red phosphorus and carboxylic acids, catalyzed by iodine or iodides; an I^-/I^0 redox cycle was proposed to promote the reaction.

Key words: *N*-arylamide, nitroarene, reductive N-acylation, red phosphorus, iodine

N-Arylamides are widely useful compounds as pharmaceuticals, pesticides, dyes, and intermediates. A widely practical method of amide synthesis is the acylation of primary or secondary amines with an acylating agent, such as acyl chloride, acyl bromide, ester, acyl anhydride, or carboxylic acid, etc.[1] On the other hand, several attempts have been made in order to synthesize amides from nitro compounds, so-called reductive N-acylations. This direct synthesis of amides is an advantageous method of saving a single step, the reduction of nitro compounds to amines. These reductive acylations were attained by employing various reducing agents. Ho[2] used excess molybdenum hexacarbonyl (2.0 equiv) as the reducing agent, giving 46–85% yield of anilides. Nahmed et al.[3] used methyl formate or formic acid as the supply of hydrogen, catalyzed by a ruthenium carbonyl compound $[Ru_3(CO)_{12}]$. Matsuda et al.[4] claimed that reacting nitrobenzene with a large excess of acetic acid at 250 °C gave 97% acetanilide. Kajimoto et al.[5] reduced nitrobenzene at 310 °C with carbon monoxide in acetic acid or propionic acid in the presence of transition-metal-carbonyl catalyst [for example $Ni(CO)_4$] to give anilides in moderate yields. Watanable et al.[6] utilized an alternative catalytic system, $PtCl_2(PPh_3)_2$ combined with tin(IV) chloride for reductive acylation with carbon monoxide. For example, acetanilide was obtained in 91% yield from nitrobenzene at 180 °C and 60 atm of carbon monoxide pressure for four hours. Choudary et al.[7] accomplished a reductive N-acylation of nitroarenes with a stoichiometric amount of sodium iodide, catalyzed by Fe(III)-exchanged montmorillonite.

Here, we wish to report a novel catalytic reductive N-acylation of nitroarenes promoted by red phosphorus and iodine or iodides.

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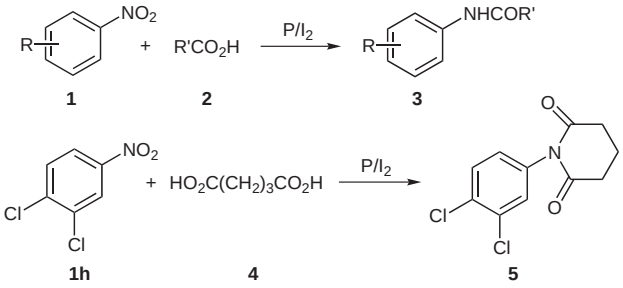
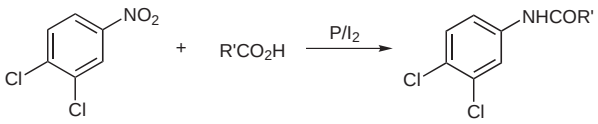
Red phosphorus and iodine had been employed to reduce arylsulfonyl chlorides,[8] where hydroiodic acid was considered as the reducing agent. For example, refluxing with two equivalents of red phosphorus and a catalytic amount of iodine in acetic acid, 2-chloro-4-fluoro-5-nitrobenzenesulfonyl chloride was converted to *S*-(2-chloro-4-fluoro-5-nitrophenyl)ethanethioate. In this reaction, the nitro group was unchanged. Interestingly, however, we found that if four equivalents of red phosphorus were used in the above reaction, besides the chlorosulfonyl group being reduced, the nitro group was also reduced and acylated to form an amide.[9] This result inspired us to investigate the reductive N-acylation of nitroarenes with the red phosphorous/iodine system (Scheme 1).



Scheme 1 Substituents: **1a**: R = H; **1b**: R = 2,3-Me_2; **1c**: R = 2-Cl; **1d**: R = 3-Cl; **1e**: R = 4-Cl; **1f**: R = 4-F; **1g**: R = 2-Cl-4-CF_3; **1h**: R = 3,4-Cl_2. **2a**: R′ = Me; **2b**: R′ = Et; **2c**: R′ = *n*-Pr; **2d**: R′ = *n*-Hex; **2e**: R′ = Ph.

Firstly, 3,4-dichloronitrobenzene (**1h**) was selected as a model compound and reacted with two equivalents of red phosphorus and 0.04 equivalents of iodine in various carboxylic acids.[10] The reaction was kept at reflux for six hours for acetic acid and 140 °C for other acids whose boiling points were higher than 140 °C. As shown in Table 1, *N*-arylamides of the tested aliphatic acids, benzoic acid, and dicarboxylic acid were synthesized in moderate to good yields. For aliphatic acids (Table 1, entry 1–4), good conversions and selectivity were obtained. Although the conversion in benzoic acid (Table 1, entry 5) was high, the selectivity was remarkably lower than for aliphatic acids. For glutaric acid (**4**), a dicarboxylic acid, *N*-heterocyclodione (*N*-glutarimide) was obtained (Table 1, entry 6) with high conversion and selectivity.

Table 1 Reductive Acylation of 3,4-Dichloronitrobenzene[a,10]



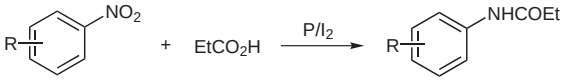
1h **2** **3**

Entry	Products	R′	Conversion (%)[b]	Selectivity (%)[c]
1	**3a**	Me	82.4	96.7
2	**3b**	Et	98.1	97.2
3	**3c**	*n*-Pr	97.8	95.6
4	**3d**	*n*-Hex	87.4	91.2
5	**3e**	Ph	99.3	85.4
6	**5**		94.2	96.9

[a] Reactions carried out at 140 °C, except for **3a** which reacted at 110 °C.
[b] The conversion of 3,4-dichloronitrobenzene.
[c] Analyzed by GC and calculated with area normalization.

Secondly, seven nitroarenes were utilized to investigate the applicability of this reaction.[11] At this time, propionic acid (**2b**) was used as the acylating agent. As shown in Table 2, all nitroarenes were reductively acylated, giving *N*-arylpropionamides with high selectivity.

Table 2 Reductive Acylation of Nitroarenes with Propionic Acid



1 **2b** **3**

Entry	Products	R	Conversion (%)	Selectivity (%)
1	**3f**	H	54.1	98.3
2	**3g**	2,3-Me_2	33.2	90.7
3	**3h**	2-Cl	32.4	97.8
4	**3i**	3-Cl	58.4	98.2
5	**3j**	4-Cl	91.2	99.0
6	**3k**	4-F	48.8	96.7
7	**3l**	2-Cl-4-CF_3	58.3	98.3

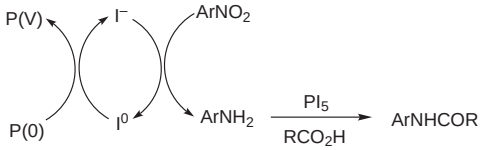
Thirdly, the effects of catalysts were investigated, using the reaction of 3,4-dichlooronitrobenzene (**1h**) with propionic acid (**2b**) to give *N*-(3,4-dichlorophenyl)propionamide (**3b**) as the model reaction.[12] According to the results shown in Table 3, for reductive N-acylation of **1h** with red phosphorus in **2b** the amount of catalyst was an important factor. Both the conversion and selectivity dropped as the amount of iodine decreased. In the absence of iodine (Table 3, entry 1), the conversion was less than 0.5% even with prolonged reaction times of 24 hours; with 0.01 equivalents of iodine (Table 3, entry 2), the conversion and selectivity were 76.1% and 89.4%, respectively. When the amount of iodine was increased to 0.03 equivalents (Table 3, entry 4), **1h** reacted nearly completely in six hours, but the selectivity was only 92.8%. The best selectivity was obtained with 0.04 equivalents of iodine (Table 3, entry 5). Further increasing the amount of iodine (Table 3, entry 6) was not obviously beneficial to the reaction. When iodine was replaced by potassium iodide (Table 3, entry 7), sodium iodide (Table 3, entry 8), or KI_3 (Table 3, entry 9), no obvious change in the conversion and selectivity occurred.

Table 3 Effects of Catalyst on the Reductive Acylation of 3,4-Dichloronitroarenes with Propionic Acid

Entry	Catalyst	Amount (mol)[a]	Conversion (%)	Selectivity (%)
1	none	0	–	–
2	I_2	0.01	76.1	89.4
3	I_2	0.02	96.9	90.8
4	I_2	0.03	99.8	92.8
5	I_2	0.04	100	95.6
6	I_2	0.05	100	95.1
7	KI	0.08	99.4	94.8
8	NaI	0.08	98.9	93.7
9	KI_3	0.03	99.7	95.3

[a] Per mol of dichloronitrobenzene.

A preliminary mechanism was proposed in Scheme 2. Since KI and NaI showed the same catalytic effects (Table 3, entries 7–9) as iodine in this reaction, there must exist an I^-/I^0 redox cycle in the reaction. During this redox cycle, the nitro group was reduced to an amino group and phosphorus was oxidized from P(0) to P(V); PI_5 was a possible intermediate, which promoted the acylation of the amino group with a carboxylic acid. Further research is going on to disclose the reaction mechanism.



Scheme 2 A preliminary hypothesis

As the reducing agent in the reaction, each phosphorus atom contributed 5 electrons. Considering its atomic weight was 31, the reducing equivalent of phosphorus was only 6.2, which was much more atom economical than other literature reported[2–7] reducing agents (metal-carbonyl compounds, formic acid, acetic acid, carbon monoxide, sodium iodide, etc.). In addition, red phosphorus was readily available, inexpensive, and suitable to industrial scale application.

In summary, the reductive N-acylation of nitroarenes promoted by P/I_2 was a useful method for the synthesis of *N*-arylamides. It has several advantages such as atom economy, readily available and inexpensive raw materials, and relatively mild reaction conditions.

Acknowledgment

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(9) ***S*-(5-Acetylamino-2-chloro-4-fluorophenyl)ethanethioate**: To a solution of 2-chloro-4-fluoro-5-nitrobenzenesulfonyl chloride (0.55 g, 2.0 mmol) in AcOH (5 mL) was added red phosphorus (0.25 g, 8.0 mmol) and I_2 (5.0 mg, 0.04 mmol). The mixture was stirred and heated to reflux at 110 °C for 6 h. After cooling to r.t., the mixture was filtered. The filtrate was poured into ice-water and extracted with EtOAc (3 ×10 mL). The extracts were combined and dried over anhyd Na_2SO_4. After evaporating the solvent 0.49 g (94%) the desired product was obtained; mp 143–145 °C. IR (KBr): 3315, 3143, 3096, 1705, 1676, 1599, 1521, 1472, 1371, 1103, 957, 881, 706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.55 (1 H, d, *J* = 7.6 Hz), 7.43 (1 H, s), 7.28 (1 H, d, *J* = 10.8 Hz), 2.45 (3 H, s), 2.20 (3 H, s). MS (70 eV): *m*/*z* = 261 (M^+), 219 ($M^+ – CH_2CO$), 177 (219 – CH_2CO), 142 (177 – Cl).
(10) **General Procedure.** A 50-mL three-necked flask was charged with 3,4-dichloronitrobenzene (**1h**, 1.92 g, 10 mmol), red phosphorus (0.62 g, 20 mmol), I_2 (0.1 g, 0.4 mmol), and an organic acid (**2a**–**e** or **4a**, 40 mmol). The mixture was stirred at 140 °C (110 °C for AcOH) for 6 h. After cooling to r.t., the mixture was decanted onto ice-water and extracted with EtOAc (3 ×10 mL). The extracts were combined and dried over anhyd Na_2SO_4. The solvent was evaporated to give product **3a**–**e** and **5**.
3a: Mp 110–113 °C. IR (KBr): 3297, 3181, 1669, 1592, 1528, 1470, 1379, 812 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (s, 1 H), 7.31–7.38 (m, 3 H), 2.18 (s, 3 H). MS (70 eV): *m*/*z* = 203 (M^+), 161.
3b: Mp 86–88 °C. IR (KBr): 3304, 3097, 1667, 1588, 1522, 1466, 1380, 815 cm^{-1}. ^{1} H NMR (400 MHz, $CDCl_3$): δ = 7.77 (s, 1 H), 7.26–7.35 (m, 3 H), 2.39 (q, 2 H, *J* = 7.2 Hz), 1.24 (t, 3 H, *J* = 7.2 Hz). MS (70 eV): *m*/*z* = 217 (M^+), 161.
3c: Mp 69–71 °C. IR (KBr): 3310, 3098, 2961, 1671, 1589, 1522, 1466, 1382, 818 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.77 (s, 1 H), 7.34–7.38 (m, 3 H), 2.33 (t, 2 H, *J* = 7.2 Hz), 1.69–1.78 (m, 2 H), 0.98 (t, 3 H, *J* = 7.2 Hz). MS (70 eV): *m*/*z* = 231 (M^+), 161.
3d: Oil. IR (KBr): 3309, 2928, 1666, 1590, 1522, 1470, 1382, 815 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (s, 1 H), 7.57 (s, 1 H), 7.32–7.34 (m, 2 H), 2.34 (t, 2 H, *J* = 7.2 Hz), 1.68–1.73 (m, 2 H), 1.29–1.34 (m, 6 H), 0.88 (t, 3 H, *J* = 6.4 Hz). MS (70 eV): *m*/*z* = 273 (M^+), 161.
3e: Mp 134–136 °C. IR (KBr): 3298, 1652, 1582, 1511, 1381, 813, 714 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (s, 1 H), 7.84–7.90 (m, 3 H), 7.41–7.60 (m, 5 H). MS (70 eV): *m*/*z* = 265 (M^+), 105.
5: Mp 182–184 °C. IR (KBr): 3086, 2961, 1729, 1684, 1468, 1365, 1256, 1135, 832, 760 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, 1 H, *J* = 8.4 Hz), 7.26 (s, 1 H), 6.97 (d, 1 H, *J* = 8.4 Hz), 2.82 (t, 4 H, *J* = 6.4 Hz), 2.11 (dd, 2 H, *J* = 6.4, 6.4 Hz). MS (70 eV): *m*/*z* = 257 (M^+), 229, 187, 161.
(11) Following the same procedure described above, **1h** was replaced by nitroarenes **1a**–**g**, and propionic acid (**2b**) was employed to give **3f**–**l**.
3f: Mp 84–86 °C. IR (KBr): 3255, 1666, 1603, 1541, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.64 (m, 2 H), 7.30–7.32 (m, 2 H), 7.21 (s, 1 H), 7.08– 7.12 (m, 1 H), 2.43 (q, 2 H, *J* = 7.2 Hz), 1.26 (t, 2 H, *J* = 7.2 Hz). MS (70 eV): *m*/*z* = 149 (M^+), 93.
3g: Mp 79–81 °C. IR (KBr): 3280, 2935, 1659, 1529, 1457, 782, 720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (s, 1 H), 6.85–7.11 (m, 3 H), 2.45 (q, 2 H, *J* = 7.2 Hz), 2.33 (s, 3 H), 2.29 (s, 3 H), 1.26 (t, 2 H, *J* = 7.2 Hz). MS (70 eV): *m*/*z* = 177 (M^+), 121, 106.
3h: Mp 91–93 °C. IR (KBr): 3288, 3032, 1664, 1587, 1526, 1285, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.40–8.42 (m, 1 H), 7.64 (s, 1 H), 7.36–7.37 (m, 1 H), 7.26 –7.29 (m, 1 H), 7.02–7.05 (m, 1 H), 2.48 (q, 2 H, *J* = 7.2 Hz), 1.28 (t, 2 H, *J* = 7.2 Hz). MS (70 eV): *m*/*z* = 183 (M^+), 148, 127.
3i: Mp 74–75 °C. IR (KBr): 3248, 2977, 1668, 1596, 1532, 1415, 1307, 879, 774 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 (s, 1 H), 7.50–7.52 (m, 1 H), 7.36–7.42 (m, 1 H), 7.20–7.26 (m, 1 H), 7.06–7.08 (m, 1 H), 2.39 (q, 2 H, *J* = 7.2 Hz), 1.24 (t, 3 H, *J* = 7.2 Hz). MS (70 eV): *m*/*z* = 183 (M^+), 127.
3j: Mp 123–124 °C. IR (KBr): 3299, 2976, 1666, 1605, 1542, 1492, 823 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, 2 H, *J* = 8.0 Hz), 7.28 (d, 2 H, *J* = 8.0 Hz), 7.14 (s, 1 H), 2.39 (q, 2 H, *J* = 7.4 Hz), 1.25 (t, 3 H, *J* = 7.4 Hz). MS (70 eV): *m*/*z* = 183 (M^+), 127.
3k: Mp 105–107 °C. IR (KBr): 3272, 3089, 1663, 1556, 1507, 1212, 830 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.48 (m, 2 H), 7.22 (s, 1 H), 6.99–7.02 (m, 2 H), 2.37 (q, 2 H, *J* = 7.2 Hz), 1.24 (t, 3 H, *J* = 7.2 Hz). MS (70 eV): *m*/*z* = 167 (M^+), 111.
3l: Mp 75–77 °C. IR (KBr): 3270, 2987, 1670, 1532, 1424, 1333, 1121, 820 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.80 (s, 1 H), 7.72 (s, 1 H), 7.49 (d, 1 H, *J* = 8.0 Hz), 7.29 (d, 2 H, *J* = 8.0 Hz), 2.50 (q, 2 H, *J* = 7.4 Hz), 1.29 (t, 3 H, *J* = 7.4 Hz). MS (70 eV): *m*/*z* = 251 (M^+), 195.
(12) Compound **3b** was synthesized by the same procedure as described above, except the amount of catalyst and composition were changed.