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Metal-Free C-Arylation of Nitro Compounds with Diaryliodonium Salts

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Supporting Information Placeholder

ABSTRACT: An efficient, mild and metal-free arylation of nitroalkanes with diaryliodonium salts has been developed, giving easy access to tertiary nitro compounds. The reaction proceeds in high yields without the need for excess reagents, and can be extended to α-arylation of nitroesters. Nitroalkanes were selectively C-arylated in the presence of other easily arylated functional groups, such as phenols and aliphatic alcohols.

Carbon-carbon bond formation belongs to the fundamental transformations in synthetic organic chemistry, and efficient methods to achieve C-C bonds are of high importance. Synthetic strategies towards complex molecules often rely on functional groups that are compatible with a range of conditions. Such groups can hence be introduced at an early stage, and later on be selectively transformed into other interesting functional groups. Nitroalkanes fulfill these criteria and are often key intermediates in total synthesis, due to the plethora of derivatization possibilities (Scheme 1a).2

Scheme 1.

a) Derivatization of nitro compounds

The acidity of nitroalkanes parallels that of stabilized carbonyl compounds, and they are easily functionalized with electrophiles under basic conditions.2−3 While α-arylation of carbonyl compounds has been studied extensively,4 the arylation of nitroalkanes remains largely unexplored. Stoichiometric use of heavy metal reagents based on lead5 or thallium6 generates toxic waste, while reactions with triphenylbismuth reagents7 have poor atom efficiency. Furthermore, the above reagents have only been demonstrated with a limited substrate scope (Scheme 1b). Palladium-catalyzed methodology has mainly focused on arylation of nitromethane and primary nitroalkanes, and requires excess substrate, elevated temperature and expensive ligands (Scheme 1b).9

Hypervalent iodine(III) compounds have recently been demonstrated as efficient reagents for a wide range of transformations.9 Diaryliodonium salts are non-toxic, bench-stable, and readily available electrophilic arylating reagents useful in a range of transformations.10 Although diaryliodonium salts have been applied in α-arylation of carbonyl compounds, the scope remains moderate especially for acyclic systems.11 The arylation of preformed alkali nitronates with diaryliodonium salts was reported in the 1960s with a very limited substrate scope.12

Our research group has focused on the synthesis and applications of diaryliodonium salts in metal-free arylation of oxygen and nitrogen nucleophiles.13 Motivated by the ubiquitous nature of the nitro functional group, we envisioned the use of diaryliodonium salts in C-arylation of nitro compounds under mild and metal-free conditions. We focused on the arylation of secondary nitroalkanes as tertiary nitro compounds are difficult to access with conventional methods and can be converted to highly useful...
Electron-donating groups on the diaryliodonium salts were well tolerated, yielding 3g–j. Aroyl-substituted product 3j could be obtained despite its instability.8b, 15 To our delight, transfer of a pyridyl group could be accomplished to furnish 3k in high yield. This is important as pyridyl moieties are omnipresent in biologically interesting molecules.17 Steric hindrance in the ortho-position of the aryl group Hamperten the reaction, and dimethylidonium triflate gave only traces of product. While an ortho-tolyl group could only be transferred to reach product 3l with difficulty, the corresponding ortho-fluoro substituted product 3m was obtained in excellent yield. Nitroalkanes with varying ring sizes were compatible with this transformation, and both the six- and seven-membered phelylated products 3n,o were isolated in comparable yields to 3a. Various diaryliodonium salts were applied to these nitroalkanes, delivering products 3p–s in high yield, including pyridyl-substituted products 3r and 3s.

The scope could be extended to also include C-C bond formation with acyclic nitroalkanes. These compounds underwent the arylation smoothly with both electron-withdrawing and electron-donating diaryliodonium salts, delivering products 3t–ac in good to excellent yields. Phenylation of 2-nitropropane furnished the product 3t in high yield, but the volatility of 3t lowered the isolated yield. The synthesis of 3y could easily be scaled up, with efficient recovery of the resulting iodoarene.15 Nitroalkanes with longer carbon chains were employed to provide products 3x–3ac. Importantly, acyclic products containing a pyridyl moiety could be obtained both by arylation with a pyridyl moiety (3z) and by arylation of a pyridyl-substituted nitroalkane (3aa and 3ab). Selective C-arylation was observed with 5-nitro-2-heptanol to reach 3ac (vide infra).

Pd-catalyzed arylation of nitromethane and primary nitroalkanes use 2-10 equivalents of nitroalkane.8a-d Under our optimized conditions, the arylation of 1-nitropropane resulted in a mixture of mono- and diarylated products. To our delight, monoarylation proceeded well in the presence of excess nitropropane, delivering compound 4 in up to 76% yield (Scheme 3).

**Scheme 2. C- Arylation of Nitroalkanes**

**Scheme 3. Monoarylation of 1-Nitropropane**

α,α,α-Disubstituted α-amino acids are important structural motifs present in many natural products and antibiotics,18, 19 and the α-arylation of α-amino acid derivatives introduces new structural motifs that can affect binding mode to proteins and receptors.19 We envisioned a complementary method to access such compounds via α-arylation of nitroesters,18 the products of which are easily reduced to the corresponding α-amino acids.18a, 19c Upon arylation of 2-nitroester 5 under the optimized conditions, only trace amounts of product 6 was obtained with recovery of starting material 5 (Scheme 4). Reoptim-
This dummy group could also be employed in transition 
substitution of the reaction with this less reactive nucleophile 
reduced α-aromated product 6a could be obtained in 
good yield with cesium carbonate in toluene at reflux.15
Upon exploring the scope of the reaction, electronically 
and sterically different iodonium salts were employed un-
der the optimized reaction conditions, affording α-aromated 
nitroesters 6. Again, electron-withdrawing as well as elec-
tron-donating aryl groups could be transferred (6b-f). The 
synthesis of α-anisyl nitroester 6e was accomplished in 
good yield upon prolonged reaction time. Also this ary-
lation proved sensitive to ortho-substituents on the aryl 
group, and reaction with dimesityl iodonium triflate only 
afforded trace amounts of product. Pleasingly, transfer of 
an anisyl-fluorophenyl group to nitroester 
was achieved in 73% yield, and a pyridyl moiety was easily incorporated to reach product 6g.

Scheme 4. α-Arylation of Nitroesters

Table 1. Chemoselectivity Trends

<table>
<thead>
<tr>
<th>entry</th>
<th>salt 2</th>
<th>1H-NMR ratio</th>
<th>major product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>20:1</td>
<td>3b</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>4.5:1</td>
<td>3c</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>9:1</td>
<td>6g</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>6:1</td>
<td>3a</td>
<td>79d</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>20:1</td>
<td>6a</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>3:3:1</td>
<td>3j</td>
<td>51d</td>
</tr>
</tbody>
</table>

*a Reaction conditions: 5 (0.2 mmol) and C6H5CO2 were stirred in anhydrous toluene (1 mL) for 10 min at rt before addition of 2 and anhydrous toluene (0.5 mL). The resulting mixture was stirred for 1 h at rt followed by 6 h at 110 °C. 
bBF3 as counterion. Reaction time 16 h.

The use of unsymmetric diaryliodonium salts (Ar1 ≠ Ar2) is desirable, due to their straightforward synthesis and the possibility to use an inexpensive aryl iodide as “dummy” ligand. High chemoselectivity, i.e. selective transfer of Ar1 over Ar2, is necessary to ensure high yields of the desired products and to avoid isolation problems. We have recent-
ly reported a detailed study on chemoselectivity trends for arylation of N-, O-, and C-centered nucleophiles under metal-free conditions.20 Based on those results, electronic or ortho-substituted aryl moieties could be good 
dummy groups for the C-arylation of nitrile oxides.

As expected, the more electron-deficient aryl group was 
transferred to nitrocyclopetane, delivering products 3b and 
3c with moderate to excellent selectively (Table 1, 
entries 1-2). The anisyl moiety proved to be a good dummy 
ligand for chemoselective transfer of a pyridyl group 
(6g, entry 3). The observed sensitivity to ortho-
substituents could be exploited with aryl(mesityl)iodonium 
_salts, selectively providing products 3a and 6a (entries 
4,5). This dummy group could also be employed in trans-
fer of other aryl groups.15 This chemoselectivity is opposite to 
the commonly encountered “ortho-effect”,21 and has been termed an “anti-ortho effect”20. We subsequently set 
out to compare the electronic and steric effects using an 
aryl(cis-tolyl)iodonium salt, which resulted in preferential 
transfer of the more electron-rich aryl group to give 3j 
(entry 6). This is a unique example of the “anti-ortho effect” 
overriding the electronic effect in a metal-free arylation with 
diaryliodonium salts.22,23

Scheme 5. Competition Experiments

Table 1. Chemoselectivity Trends

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*a Conditions according to Schemes 2, 4. b Ratio of arylated products (Ar1 vs. Ar2) in the crude reaction mixture. c Isolated yield of major product. d Isolated as a mixture. e 1H-NMR yield with internal standard.

Competition experiments were performed to investigate 
the compatibility of the reaction with other functional 
groups. As mentioned above, selective C-arylation to 3ac 
was observed with 5-nitro-2-heptanol (Scheme 5a), de-
spite the known reactivity of aliphatic alcohols at room 
temperature.13c The addition of a benzyl alcohol to the 
reaction was well tolerated, delivering product 3a in good 
yield (Scheme 5b).13d

Scheme 5. Competition Experiments
and conditions. The reaction is proposed to proceed by a reactivity of alcohols and phenols is excellent, despite the well-known electron richness and electron-deficient iodonium salts.  The arylation of nitroalkanes and nitroesters. The reaction either by normal ligand coupling (A) or via a [2,3]-rearrangement (B).

Scheme 6. Proposed Mechanism

In conclusion, we have demonstrated an efficient, straightforward, and metal-free approach for the C-arylation of nitroalkanes and nitroesters. The reaction entails equimolar amounts of reagents, gives high yields and can be easily up-scaled with recovery of the formed iodoarene. Electron-rich and electron-deficient iodonium salts are equally compatible, and the reaction proceeds smoothly with cyclic as well as acyclic nitroalkanes. The arylations can be chemoselectively performed using either an anisyl or a mesityl dummy group, and provides a strong "anti-ortho" effect that overrides the electronic preference.

The functional group tolerance towards aliphatic alcohols and phenols is excellent, despite the well-known, high reactivity of alcohols with diaryliodonium salts under mild conditions. The reaction is proposed to proceed by a ligand-coupling pathway via two possible intermediates.

**ASSOCIATED CONTENT**

**Supporting Information**

Experimental details and spectral data for novel compounds, as well as NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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**Author Contributions**

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**REFERENCES**


(15) See the Supporting Information for details.

(16) The diaryliodonium salts were synthesized according to: 

(17) Pyridine and its derivatives are commonly found in nature, in agricultural products and in pharmaceuticals. New methods to access pyridyl containing molecules are therefore in high demand. See Baumann, M.; Baxendale, I. R. Beilstein J. Org. Chem. 2013, 9, 2265-2319.


(22) This type of chemoselectivity is common under metal-catalyzed conditions.

