Imide Arylation with Aryl(TMP)iodonium Tosylates

Souradeep Basu  
*Portland State University*

Alexander H. Sandtorv  
*Portland State University*, sandtorv@pdx.edu

David R. Stuart  
*Portland State University*, dstuart@pdx.edu

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Imide arylation with aryl(TMP)iodonium tosylates
Souradeep Basu, Alexander H. Sandtorv and David R. Stuart*
counter anion, solvent and volume, reaction temperature, and stoichiometry (Table 1). Consistent with an electronically controlled aryl transfer, the trimethoxyphenyl (TMP) auxiliary was superior to mesityl (Mes), phenyl (Ph), and anisyl (An) auxiliaries under several different reaction conditions (Table 1, entries 1-3; 11 and 12; 16 and 17). While the counter anion did

![Scheme 1: Imides as an important scaffold.](image)

![Table 1: Discovery and optimization of reaction conditions.](image)

| Entry | X group | Aux group | Phth. equiv | Solvent | Temp. (°C) | \(^1\)H NMR yield |
|-------|---------|-----------|-------------|---------|------------|-----------------|
| 1     | TFA     | Mes       | 2           | DCE (1 mL) | 70         | 27%             |
| 2     | TFA     | Ph        | 2           | DCE (1 mL) | 70         | 50%             |
| 3     | TFA     | TMP       | 2           | DCE (1 mL) | 70         | 52%             |
| 4     | TFA     | TMP       | 3           | DCE (1 mL) | 80         | 54%             |
| 5     | OTs     | TMP       | 3           | DCE (1 mL) | 80         | 62%             |
| 6     | TFA     | TMP       | 3           | toluene (0.42 mL) | 100 | 50%         |
| 7     | OTf     | TMP       | 3           | toluene (0.42 mL) | 100 | 56%         |
| 8     | OTs     | TMP       | 3           | toluene (0.42 mL) | 100 | 68%         |
| 9     | OTs     | TMP       | 3           | toluene (0.5 mL) | 90          | 64%             |
| 10    | OTs     | TMP       | 3           | toluene (0.5 mL) | 100         | 70%             |
| 11    | OTs     | Ph        | 3           | toluene (0.5 mL) | 100         | 23%             |
| 12    | OTs     | TMP       | 3           | toluene (0.5 mL) | 110         | 62%             |
| 13    | OTs     | TMP       | 1.1         | toluene (0.5 mL) | 100         | 39%             |
| 14    | OTs     | TMP       | 1.1         | toluene (1 mL) | 100         | 28%             |
| 15    | OTs     | TMP       | 1.1         | toluene (1.5 mL) | 100        | 16%             |
| 16    | OTs     | An        | 5           | toluene (0.5 mL) | 100        | 46%             |
| 17    | OTs     | TMP       | 5           | toluene (0.5 mL) | 100        | 75%             |

\(^a\)Conditions: 1 (0.1 mmol, 1 equiv), potassium phthalimide (see table for equivalents), solvent (see table), temperature (see table), 24 hours.
not exert a dramatic influence on the reaction yield, using tosylate (OTs) produced the highest yield in both DCE and toluene as solvent (Table 1, entries 4–8). Given our ability to readily access aryl(TMP)iodonium tosylate salts [12] we continued our optimization with these reagents. We observed a very narrow operating temperature with a maximum yield at 100 °C when toluene was used as solvent (Table 1, entries 9, 10, and 12). We also observed that the reaction yield decreases with dilution (Table 1, entries 13–15). Finally, the yield increases with increasing stoichiometry of phthalimide (Table 1, entries 10, 13, and 17). It is also important to note that under “optimal” conditions (Table 1, entry 17) we did not observe a Phth–TMP adduct. Moreover, we did observe essentially quantitative formation of TMP–I and therefore complete consumption of 1a and high fidelity for aryl transfer selectivity. At this time we are unable to account for the remaining mass balance (∼25%) of the methyl benzoate moiety of 1a. We have employed the conditions of entry 17 (Table 1) as our standard conditions to evaluate the scope of this reaction.

We have assessed the scope of compatible aryl groups under our optimal conditions (Scheme 2). Under electronic control, strong electron-withdrawing groups on the aryl ring lead to high yield of N-aryl phthalimide products (Scheme 2, 2a–d, 66–90% yield). However, the TMP auxiliary also enables the coupling of phthalimide with moderately electron-deficient aryl groups. For instance the p-chlorophenyl moiety (2e) is coupled to phthalimide in moderate yield (42%). Additionally, we have observed that electronic and steric effects operate in concert to couple an o-tolyl (2f) moiety to phthalimide in high yield (67%). In this case, 2,6-disubstituted aryl groups are not required for a sterically controlled coupling. Finally, as an example two polysubstituted aryl groups are introduced in this coupling reaction, which are specifically enabled by the use of an unsymmetrical aryl(TM)iodonium electrophile (Scheme 2, 2g and 2h, 42 and 99% yield, respectively).

The phthalimide moiety is well-recognized as an “NH₃” surrogate, and the products depicted in Scheme 2 may be deprotected to yield aniline derivatives. In a specific example, 1a is reacted under modified conditions to yield 2a. In this one-pot procedure, hydrazine in aqueous ethanol is added directly to the reaction mixture and aniline 3 is isolated in 63% yield from 1a (Scheme 3).

**Scheme 2**: Scope of compatible aryl groups. Conditions: 1 (0.5 mmol, 1 equiv), potassium phthalimide (2.5 mmol, 5 equiv), toluene (2.5 mL), 100 °C, 24 hours. Isolated yields are reported.
We have previously described the coupling of aryl(TMPT)iodonium tosylates with azide nucleophiles [14]. Azide is a notably stronger nucleophile than phthalimide and it is interesting to compare the reaction of these two nucleophiles with 1a under similar conditions (Table 2). The Mayr nucleophilicity constant of azide [15] is 20.5 and high yield (95%) is observed in a reaction with 1a under relatively mild temperature (65 °C) and short reaction time (2 hours, Table 2, entry 1). The Mayr nucleophilicity constant for phthalimide is five-orders of magnitude lower (15.5) [3] and under similar conditions leads to trace product (Table 2, entry 2). In order to obtain a high yield of 2a, albeit lower than given in entry 1, a higher temperature (100 °C) and a longer reaction time (24 hours) are required (Table 2, entry 3). This suggests that the contribution of nucleophilicity (via Mayr nucleophilicity constants) [16] may be useful in developing other coupling reactions with diaryliodonium electrophiles.

**Conclusion**

The coupling of both electron-deficient and sterically encumbered aryl groups with a phthalimide anion is achievable with aryl(TMPT)iodonium tosylate salts. This is an electronically controlled coupling reaction that is enabled by the TMP auxiliary and complementary to the sterically controlled coupling previously reported. We anticipate that this reaction will find use as a starting point for the synthesis of N-aryl imides in a range of applications.

**Supporting Information**

**Supporting Information File 1**

General experimental details, procedures, tabulated spectroscopic data, and $^1$H, $^{13}$C($^1$H), and $^{19}$F NMR spectra of compounds 1g, 2a–i, and 3. [https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-90-S1.pdf]

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**ORCID® iDs**

David R. Stuart - https://orcid.org/0000-0003-3519-9067

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**Scheme 3: One-pot synthesis of anilines.**

| Entry | Nucleophile (Nu) | Mayr nucleophilicity | Temperature (°C) | Time | Yield  |
|-------|------------------|----------------------|------------------|------|--------|
| 1     | azide            | 20.5                 | 65               | 2 hours | 95%    |
| 2     | phthalimide      | 15.5                 | 65               | 2 hours | trace     |
| 3     | phthalimide      | 15.5                 | 100              | 24 hours | 80%     |
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