Ni-NHC-catalyzed Cross-coupling of 2-Methylsulfanylbenzofurans with Alkyl Grignard Reagents

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Abstract: NiCl₂(PPh₃)(IPr) catalyzes cross-coupling reactions of 2-methylsulfanylbenzofurans with alkyl Grignard reagents, which other nickel complexes such as NiCl₂(dppe) failed to achieve. The alkylation is applicable to the synthesis of a couple of protein tyrosine phosphatase inhibitors, 3-(4-biphenylyl)-2-alkylbenzofurans.

Key words: Nickel, Alkylation, Cross-coupling, Sulfide, Homogeneous catalysis

Cross-coupling reactions of organosulfur compounds date back to 1979, when Takei and Wenkert independently reported NiCl₂(PPh₃)₂-catalyzed arylation of aryl or alkenyl sulfides with Grignard reagents. Despite subsequent extensive studies since then, cross-coupling of aryl sulfides still remains in its infancy compared with the mature cross-coupling of aryl halides. The immaturity would be mostly attributable to 1) slow oxidative addition of the ir Sp²-S bonds, 2) reluctant transmetalation due to high affinity between a transition metal and sulfur in an oxidative adduct, and 3) catalyst poisoning by sulfur compounds. New reaction conditions for more efficient and robust cross-coupling of aryl sulfides with a sustainable metal catalyst have thus been awaited.

We have been interested in extended Pummerer reactions of ketene dithioacetal monoxides and recently developed an efficient and modular access to multisubstituted benzofurans through Pummerer annulation (Scheme 1). Since our annulation always leads to formation of 2-methylsulfanyl-substituted benzofurans, transformations of the sulfur moieties should dictate the usefulness of our methodology. Indeed, with state-of-the-art transition metal catalysis, cross-coupling arylation of the products yielded highly fluorescent compounds as well as anticancer agents. Among this line, we report herein that a Ni-NHC (N-heterocyclic carbene) complex is an effective catalyst for cross-coupling alkylation of 2-methylsulfanyl-substituted benzofurans, which was applied to efficient synthesis of protein tyrosine phosphatase (PTP) 1B inhibitors.

Cross-coupling butylation of benzofuran 1a was chosen as a model reaction to probe a potent catalytic system. The results of catalyst optimization are summarized in Table 1. Although nickel phosphine complexes are known to promote cross-coupling of aryl sulfides, the transformation of 1a is not trivial. Attempted butylation with nickel diphosphine complexes resulted in no conversions (entry 1–3). As 1a is regarded as a bulky aryl sulfide due to the neighboring phenyl group, we envisioned a Ni-NHC complex bearing a bulky NHC to be suitable. Indeed, a commercially available nickel complex NiCl₂(PPh₃)(IPr) catalyzed the desired alkylation very smoothly to afford 2a in 95% yield (entry 4). Finally, replacing toluene with THF as a solvent led to quantitative formation of 2a in 30 min (entry 5). In the absence of any catalysts, no reaction took place (entry 6).

Scheme 1 Pummerer annulation/cross-coupling strategy for tailor-made synthesis of benzofurans

Table 1 Optimization of catalyst for alkylation

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>solvent</th>
<th>results (by NMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NiCl₂(PPh₃)₂</td>
<td>toluene</td>
<td>no conversion</td>
</tr>
<tr>
<td>2</td>
<td>NiCl₂(dppe)</td>
<td>toluene</td>
<td>no conversion</td>
</tr>
<tr>
<td>3</td>
<td>NiCl₂(dppp)</td>
<td>toluene</td>
<td>no conversion</td>
</tr>
<tr>
<td>4</td>
<td>NiCl₂(PPh₃)(IPr)</td>
<td>toluene</td>
<td>95% yield of 2a</td>
</tr>
<tr>
<td>5</td>
<td>NiCl₂(PPh₃)(IPr)</td>
<td>THF</td>
<td>&gt;99% yield of 2a</td>
</tr>
<tr>
<td>6</td>
<td>none</td>
<td>THF</td>
<td>no conversion</td>
</tr>
</tbody>
</table>

The scope of the alkylation is summarized in Scheme 2. Electronically biased substituents at the 6 position have virtually no influence on the efficiency of the reaction (2b and 2c). The smallest methyl (2d),
unsaturated 10-undecenyl (2f), and THP-protected 11-hydroxyundecyl (2h) groups were installed easily. Benzylmagnesium chloride was less reactive and required 4 h to reach completion (2e). Trimethylsilylmethylmagnesium chloride was much more reluctant to afford 2g in 24 h even at 50 °C. It is worth noting that 2-methylsulfanylbenzofuran, which has no substituent at the 3 position, totally resisted alkylation with NiCl2(dppe) but underwent very smooth alkylation with NiCl2(PPh3)(IPr) to yield 2i.

Scheme 3 Formal synthesis of PTP inhibitors.

In summary, we have developed highly efficient cross-coupling alkylation of benzofuryl sulfides with a nickel-NHC catalyst and applied it to formal synthesis of PTP 1B inhibitors. Investigations to find efficient transformations of organosulfur compounds with a sustainable transition metal catalyst are underway in our laboratory.

The butylation of 1a is representative. NiCl2(PPh3)(IPr) (11.7 mg, 0.015 mmol) was placed in a dry Schlenk tube equipped with a magnetic stir bar and a rubber septum under argon. A solution of methylsulfanylbenzofuran 1a (120 mg, 0.50 mmol) in THF (5.0 mL) was then added. Butylmagnesium bromide (0.60 M in THF, 0.60 mmol) was then added to the mixture and the resulting mixture was stirred for 30 min at 25 °C. The mixture was filtered through a pad of silica gel with copious washings with CH2Cl2. The filtrate was evaporated to leave a crude oil. 1H NMR analysis of the oil revealed the yield of 2a was quantitative. Silica gel column purification (n-hexane) afforded butylated benzofuran 2a (121 mg, 0.48 mmol) in 97% yield as a colorless oil. 2-Butyl-3-phenylbenzo[b]furan (2a): 1H NMR (600 MHz, CDCl3) δ (ppm) 7.60 (d, 1H, J = 7.8 Hz), 7.54–7.50 (m, 5H), 7.40 (t, 1H, J = 6.6 Hz), 7.30 (t, 1H, J = 6.6 Hz), 7.25 (t, 1H, J = 7.8 Hz), 2.90 (t, 2H, J = 7.8 Hz), 1.81 (quint, 2H, J = 7.2 Hz), 1.44 (sex, 2H, J = 7.2 Hz), 0.95 (t, 3H, J = 7.2 Hz). 13C NMR (150 MHz, CDCl3) δ (ppm) 155.46, 154.18, 133.07, 129.25, 129.06, 128.86, 127.12, 123.66, 122.68,
Acknowledgment

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References

(1) (a) Satisfactory


(8) Ni-NHC catalysts are known to be more effective than Ni-phosphine catalysts for cross-coupling arylation of organosulfur compounds with aryl Grignard reagents. See references 4b, 4g, and 4h.


Short title: Ni-catalyzed desulfanylatve alkylation

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