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

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Received: The date will be inserted once the manuscript is accepted.

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.1 Despite subsequent extensive studies since then,2–4 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 rather strong C(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 reactions5 of ketene dithioacetal monoxides6,7 and recently developed an efficient and modular access to multisubstituted benzofurans through Pummerer annulation6e–g (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 compounds6e–g as well as anticancer agents.6e8 Along this line, we report herein that a Ni-NHC (N-heterocyclic carbene) complex is an effective catalyst for cross-coupling alkylation8 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,1,2a–e 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.9,10 Indeed, a commercially available nickel complex NiCl2(PPh3)(IPr)11 [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] 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).

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)</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 2 Scope of alkylation.

A series of 3-(4-biphenylyl)-2-alkylbenzofurans are attracting significant attention since they serve as potent inhibitors of PTP 1B.12 In the previous report, each alkylbenzofuran in the library was prepared via a lengthy linear route. Advantageously, our approach to 2-alkylbenzofurans has proved to be more efficient for the synthesis of 3-(4-biphenylyl)-2-alkylbenzofurans bearing variety in the alkyl chain. Ketene dithioacetal monoxide 3 was prepared through the Knoevenagel condensation in one step according to the literature procedure.7a Phenol underwent the Pummerer annulation6g with 3 by means of trifluoroacetic anhydride to afford 2-methylsulfanylbenzofuran 4 in 61% yield. The following cross-coupling butylation and benzylolation were successful, yielding intermediates 5a and 5b, respectively, in a diversity-oriented fashion. Benzofurans 5a and 5b are key intermediates that should undergo demethylolation as the last step to yield potent PTP 1B inhibitors 6.12

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, 1.0 mL, 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-phenylbenzob[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

This work was supported by Grants-in-Aid from MEXT (Nos.: 21078007, 22106721 “Reaction Integration” and 25107002 “Science of Atomic Layers”) and from JSPS (Nos.: 24685007 (Young Scientists (A)) and 26620081 (Exploratory Research)). A.B. and K.M. acknowledge JSPS for financial support. V.G. thanks the University of Rennes for the student exchange program.

References


(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 desulfanyllative alkylation

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