Transition-Metal-Free Oxidative Homocoupling of Aryl, Alkenyl, and Alkynyl Grignard Reagents with TEMPO

Modhu Sudan Maji, Armido Studer*
Institute of Organic Chemistry, NRW Graduate School of Chemistry, Westfälische Wilhelms-University Münster, Corrensstr. 40, 48149 Münster, Germany
Fax +49(251)8336523; E-mail: studer@uni-muenster.de
Received 18 March 2009; revised 3 April 2009

Abstract: Oxidative homocoupling of aryl, alkenyl, and alkynyl Grignard reagents by using commercially available TEMPO as an organic oxidant is described. These coupling reactions occur highly efficiently without the presence of any transition metal.

Key words: Grignard reagents, oxidative homocoupling, alkoxyamine, nitroxide, persistent radicals

Introduction

It is well known that various alkyl organometallic compounds (R-M) react with 2 equivalents of 2,2,6,6-tetramethylpiperidine-N-oxyl radical (TEMPO) to the corresponding alkoxyamines TEMPO-R.1 This has been shown for alkyl-Li, alkyl-Mg, alkyl-Zn, alkyl-Cu, alkyl-Sm, and alkyl-Ti compounds. In these transformations, the given organometallic compound R-M is oxidized with TEMPO to generate the corresponding C-centered radical, which is subsequently trapped by the second equivalent of TEMPO to eventually form an alkoxyamine (Scheme 1).2

Analogous oxidation/trapping reactions of alkenyl-, aryl-, and alkynylorganometallic compounds are highly unlikely, since aryl, alkyl, and alkynyl radicals are destabilized and therefore oxidation of the more stable aryl-, aryl-, and alkynylorganometallic derivatives with TEMPO should not occur. In fact, we recently published that aryl, alkyl, and alkenyl Grignard reagents 1 undergo efficient homocoupling upon oxidation with TEMPO to give 2.3 This is surprising since transition metals are generally necessary to conduct such oxidative coupling reactions.4 There is only one precedence in the literature on a high yielding homocoupling of Grignard reagents by using an organic oxidant as a coupling reagent.5

In this practical synthetic procedure we report on scope and limitations of our recently developed homocoupling reaction of various organometallic compounds with the environmentally benign TEMPO as an oxidant.

Scope and Limitations

First studies were performed with PhMgBr by using 1.08 equivalents of TEMPO in THF as a solvent. At room temperature, the conversion of the reaction was completed within 40 minutes and the targeted product 2a was isolated in 92% yield (Table 1, entry 1). Yield was further improved upon increasing reaction temperature. Hence, under refluxing conditions coupling was completed in five minutes and 2a was isolated in 98% yield (entry 2). All subsequent reactions were therefore carried out in refluxing THF. Changing the halide counter ion of the Grignard reagent did not affect the reaction outcome (98%, entry 3). To study the substrate scope of our newly developed methodology, we performed homocoupling reactions of various aryl Grignard reagents 1 undergo highly efficient homocoupling upon oxidation with TEMPO to give 2.4 There is only one precedence in the

SYNTHESIS 2009, No. 14, pp 2467–2470
Advanced online publication: 29.05.2009
DOI: 10.1055/s-0029-1216859; Art ID: Z04409SS
© Georg Thieme Verlag Stuttgart · New York
received and all Grignard reagents were titrated prior to use.6

Grignard reagents having electron-poor or -rich substituents at the para position underwent smooth transformation to give biphenyls 2b–e in high yields (77–87%, Table 1, entries 4–7). Similar results were obtained with meta-substituted aryl Grignard derivatives (entries 8 and 9) and with mono-ortho-substituted magnesium compounds the corresponding biphenyls 2h and 2i were isolated in good yields (entries 10 and 11). β-Naphthylmagnesium bromide also underwent homocoupling to give 2j in high yield (96%, entry 12). However, the sterically more demanding α-naphthylmagnesium compound was coupled in a low yield and reaction with o,o’-dimethylphenylmagnesium failed (→ 2k, 2l, entries 13 and 14) documenting the limitations of the presented method.

Grignard reagents bearing an ester functionality, a cyano substituent, a bromide, or a chloride at the arene ring were studied next (Scheme 2). It is important to note that these magnesium compounds are not accessible by using classical conditions for Grignard generation. These magnesium derivatives were therefore prepared under rather mild conditions according to a procedure developed by Knochel from the corresponding aryl iodides by using i-PrMgCl·LiCl via an I–Mg exchange reaction at –20 °C (Scheme 2). Treatment of these functionalized Grignard reagents with TEMPO at 0 or 20 °C afforded 2m–p in 71–99% yield (Table 2, entries 1–4). Vinylmagnesium compounds could also be homocoupled to the corresponding dienes by TEMPO oxidation as shown for successful transformation of trans-C6H3CH=CHMgCl·LiCl (1q), obtained by I–Mg exchange reaction of the corresponding trans-iodide, to diene 2q. Diene 2q was isolated in 64% yield with excellent stereoselectivity (Scheme 3).

Table 1 Oxidative Homocoupling of ArMgBr with TEMPO

<table>
<thead>
<tr>
<th>Entry</th>
<th>Biaryl</th>
<th>R</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>2a</td>
<td>Ph</td>
<td>20</td>
<td>40</td>
<td>92</td>
</tr>
<tr>
<td>2b</td>
<td>2a</td>
<td>Ph</td>
<td>66</td>
<td>5</td>
<td>98</td>
</tr>
<tr>
<td>3c</td>
<td>2a</td>
<td>Ph</td>
<td>66</td>
<td>5</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>2b</td>
<td>4-MeC6H4</td>
<td>66</td>
<td>20</td>
<td>86</td>
</tr>
<tr>
<td>5b</td>
<td>2c</td>
<td>4-MeOC6H4</td>
<td>66</td>
<td>10</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>2d</td>
<td>4-MeNC6H4</td>
<td>66</td>
<td>15</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>2e</td>
<td>4-FC6H4</td>
<td>66</td>
<td>15</td>
<td>77</td>
</tr>
<tr>
<td>8</td>
<td>2f</td>
<td>3-MeC6H4</td>
<td>66</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>9b</td>
<td>2g</td>
<td>3-MeOC6H4</td>
<td>66</td>
<td>10</td>
<td>87</td>
</tr>
<tr>
<td>10</td>
<td>2h</td>
<td>2-MeC6H4</td>
<td>66</td>
<td>30</td>
<td>81</td>
</tr>
<tr>
<td>11</td>
<td>2i</td>
<td>2-MeOC6H4</td>
<td>66</td>
<td>20</td>
<td>79</td>
</tr>
<tr>
<td>12</td>
<td>2j</td>
<td>β-naphthyl</td>
<td>66</td>
<td>10</td>
<td>96</td>
</tr>
<tr>
<td>13</td>
<td>2k</td>
<td>α-naphthyl</td>
<td>66</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>14</td>
<td>2l</td>
<td>2,6-Me2C6H3</td>
<td>66</td>
<td>60</td>
<td>&lt;2</td>
</tr>
</tbody>
</table>

*Reactions were carried out with TEMPO (1.08 equiv) in THF under different conditions.

* ArylMgBr was used as received from Acros after titration.

* Conducted with PhMgCl·LiCl (Acros).

We also investigated oxidative homocoupling of various alkynylmagnesium compounds (Scheme 4). The required Grignard reagents were prepared by deprotonation of an alkynyl with i-PrMgCl. Oxidative homocoupling with TEMPO in these cases turned out to be slow at room temperature and only a 55% yield of diyne 2r was obtained after three days (Table 3, entry 1). However efficient homocoupling was achieved under refluxing conditions. Hence, aryalkynyl Grignard reagents reacted upon TEMPO treatment under these conditions to the corresponding coupling products 2s–2t (86–94%, entries 2–4). Homocoupling also occurred with alkynylmagnesium derivatives and the product diynes 2u and 2v were isolated in good yields (entries 5 and 6). Under optimized conditions trimethylsilylalkynylmagnesium chloride was transformed to 2w in 65% yield (entry 7). Enynes also underwent homocoupling under these conditions (see entry 8).

Scheme 2 Oxidative homocoupling of functionalized Grignard reagents (for specification of R, see Table 1)

Scheme 3 Oxidative homocoupling of an alkynyl Grignard reagents
In conclusion, we have presented a practical method for highly efficient oxidative homocoupling of various alkyl, alkenyl, and alkylnyl Grignard reagents by using stoichiometric amounts of TEMPO as an organic environmentally benign commercially available oxidant. No transition metals were necessary to perform these C–C bond forming reactions. Various functional groups were tolerated under the applied conditions.

Experiments were easy to perform by using standard argon atmosphere technology in flame-dried glassware using anhyd THF. Most of the starting materials were commercially available and were used as received. Reactions were readily monitored by GC analysis. All compounds reported in this synthetic practical procedure article were known and spectroscopic data of the compounds prepared were in agreement with those reported in the literature.10–15

Biphenyl (2a); Typical Procedure
PhMgBr (2.00 mL, 1.54 mmol, 1.00 equiv) was added to a stirred solution of TEMPO (261 mg, 1.66 mmol, 1.08 equiv) in anhyd THF (3 mL) at r.t. The resulting reaction mixture was refluxed for 5 min. After cooling to r.t., the mixture was partitioned between methyl tert-butyl ether (MTBE, 30 mL) and sat. aq NH4Cl (10 mL). The aqueous layer was extracted with MTBE (2 × 30 mL); the combined organic phases were washed with brine (20 mL), dried (MgSO4), filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel using MTBE–pentane (1:4) as eluent provided 2a (262 mg, 88%) as white crystalline solid. Analytical data were in agreement with those reported in the literature.10

1H NMR (300 MHz, CDCl3): δ = 8.12 (d, J = 8.2 Hz, 4 H), 7.64 (d, J = 8.2 Hz, 4 H), 4.41 (q, J = 7.1 Hz, 4 H), 1.42 (q, J = 7.1 Hz, 6 H).

13C NMR (75 MHz, CDCl3): δ = 165.6 (C), 143.6 (C), 129.6 (CH), 129.5 (C), 126.6 (CH), 60.5 (CH2), 13.8 (CH3).

Diene 2q; Typical Procedure
i-PrMgCl·LiCl in THF (1.76 M, 0.70 mL, 1.23 mmol, 1.14 equiv) was added to a stirred solution of 1q (256 mg, 1.08 mmol, 1.0 equiv) in anhyd THF (0.5 mL) at 30–40 °C. The stirring was continued at that temperature for 16 h. A solution of TEMPO (204 mg, 1.3 mmol, 1.2 equiv) in THF (2.5 mL) was then added. The resulting mixture was refluxed for 25 min. The mixture was then allowed to cool to r.t. and was partitioned between MTBE (30 mL) and sat. aq NH4Cl (10 mL). The aqueous layer was extracted with MTBE (2 × 30 mL); the combined organic phases were washed with brine (20 mL), dried (MgSO4), filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel using pentane as eluent provided 2q (77 mg, 64%). Analytical data were in agreement with those reported in the literature.11

1H NMR (300 MHz, CDCl3): δ = 5.52–5.64 (m, 2 H), 2.05 (q, J = 6.9 Hz, 4 H), 1.29–1.37 (m, 16 H), 0.89 (t, J = 6.6 Hz, 6 H).

13C NMR (75 MHz, CDCl3): δ = 132.4 (CH), 130.4 (CH), 32.6 (CH2), 31.8 (CH2), 29.4 (CH2), 28.9 (CH2), 22.6 (CH2), 14.1 (CH3).

Acknowledgment
A.S. thanks Novartis Pharma AG for financial support (Novartis Young Investigator Award). We thank the NRW Graduate School of Chemistry for providing a scholarship to M.S.M.
References


