A Simplified Synthesis of Takemoto’s Catalyst

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Abstract: A facile two-step procedure for the preparation of Takemoto’s catalyst is reported. The thiourea moiety was obtained by condensation of 3,5-bis(trifluoromethyl)aniline with phenyl chlorothioformate and in situ substitution of phenol by trans-1,2-diaminocyclohexane. Subsequent reductive dimethylation using formaldehyde/zinc afforded Takemoto’s catalyst.

Key words: organocatalyst, thiourea, amine, bifunctional

A significant number of C–C couplings, for example, Michael,1,2 Mannich,3 aza-Henry4 reactions, or the alcoholytic dynamic kinetic resolution of azlactones,5 are catalyzed enantioselectively by Takemoto’s bifunctional aminothiourea derivative 5. The original synthesis of the aminothiourea catalyst 5 consists in the addition of the isothiocyanate 7 to N,N-dimethyl-trans-1,2-diaminocyclohexane (6) (Scheme 2).1

The synthesis of the N,N-dimethyl-trans-1,2-diaminocyclohexane building block 6 as reported by Kaik and Gawronski6 is a four-step procedure: As the first step, monoprotection of the diaminocyclohexane 3 is achieved by reaction with phthalic anhydride in the presence of p-toluenesulfonic acid. Deprotonation of the corresponding salt yields the monoprotected diamine. Reductive dimethylation affords the N’-phthaloyl-protected N,N-dimethylamine. Finally, deprotection gives the desymmetrized N,N-dimethylidiamine 6.6

We envisioned an alternative synthesis of Takemoto’s catalyst: If easily accessible and cheap trans-1,2-diaminocyclohexane could be transformed directly to the monothiourea 4, a subsequent dimethylation would yield the fully assembled catalyst 5. A literature survey afforded valuable information regarding the synthesis of monothiourea derivatives of diamines.

It is known that the direct addition of trans-1,2-diaminocyclohexane (3) to the isothiocyanate 7 may lead to the corresponding bis-thiourea derivative.7 To avoid bis-thiourea formation, Moreau et al. used trans-1,2-diaminocyclohexane hydrochloride for additions to iso(thio)cyanates.7 However, addition of trans-1,2-diaminocyclohexane hydrochloride to aromatic isothiocyanates may give the corresponding guanidine derivatives by cyclization and elimination of H2S.7,8 Therefore, the synthesis of the precursor 4 of Takemoto’s catalyst 5 by addition of trans-1,2-diaminocyclohexane hydrochloride to isothiocyanate did not appear practical.

On the other hand, it was known that the urea analogue 9 can be prepared by condensation of 3,5-bis(trifluoromethyl)aniline (1) with 4-nitrophenyl chloroformate (8)
and substitution of the 4-nitrophenol fragment by trans-1,2-diaminocyclohexane (3) (Scheme 3). In our hands, exchange of the chloroformate by its thioanalogue allowed the synthesis of the aminothiourea in a yield of 50%. However, the necessity to synthesize 4-nitrophenyl chlorothioformate by addition of 4-nitrophenol to thiophosgene renders this approach less practical. This disadvantage could be overcome by the use of the commercially available phenyl chlorothioformate (2) in a slightly modified reaction protocol, affording the desired aminothiourea in 50% yield (Scheme 1). Reductive dimethylation with formaldehyde/zinc yields Takemoto’s catalyst 5. In conclusion, an efficient two-step synthesis of Takemoto’s catalyst, using commercially available starting materials has been developed. As the key step, the aminothiourea was prepared by condensation of 3,5-bis(trifluoromethyl)aniline (1) with phenyl chlorothioformate (2), with substitution of phenol by trans-1,2-diaminocyclohexane (3). Reductive dimethylation with formaldehyde/zinc yields Takemoto’s catalyst 5.

Flash chromatography was performed on silica gel (Macherey-Nagel MN-Kieselgel 60, 230–240 mesh). TLC was performed on aluminum backed silica plates (Macherey-Nagel, Polygram© SIL G/UV254), detection by UV fluorescence. Melting points were determined on a Büchi melting point apparatus and are uncorrected. 1H NMR spectra were recorded at 300 MHz on a Bruker DPX 300 instrument; 13C spectra at 75.5 MHz. Chemical shifts (δ) are given in parts per million (ppm) referenced to TMS. High-resolution mass spectra (HR ESI-MS) were recorded on a Finnigan MAT 900 ST spectrometer. IR spectra were recorded on a PerkinElmer Paragon 1000 FT-IR spectrometer using the ATR technique and on a PerkinElmer 1600 Series FT-IR spectrometer. All commercially available chemicals were used without further purification.

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Reducing agent</th>
<th>Time (h)</th>
<th>Solvent</th>
<th>Temp</th>
<th>Yield (%)</th>
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<tbody>
<tr>
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<td></td>
<td>EtO₂C-</td>
<td>72</td>
<td>toluene</td>
<td>60 °C</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>AcOH</td>
<td>Zn</td>
<td>72</td>
<td>dioxane</td>
<td>r.t.</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>NaH₂PO₃</td>
<td>1</td>
<td>dioxane</td>
<td>60 °C</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>HCO₂H</td>
<td>6</td>
<td>HCO₂H</td>
<td>reflux</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>AcOH</td>
<td>NaBH₃CN</td>
<td>2</td>
<td>MeCN</td>
<td>r.t.</td>
<td>32</td>
</tr>
</tbody>
</table>

According to Menche et al., thiourea promotes the reductive methylation of amines with formaldehyde/Hantzsch ester.

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IR (ATR): 2936 (w), 1539 (m), 1472 (m), 1380 (s), 1332 (w), 1269 (s), 1177 (s), 1129 (s), 1100 (w), 964 (m), 881 (m), 846 (w), 754 (m), 700 (m), 675 cm⁻¹ (s).

1H NMR (300 MHz, DMSO-d₆); δ = 8.30 (s, 2 H), 7.68 (s, 1 H), 4.06 (br s, 1 H), 2.76 (s, 1 H), 2.04–1.92 (m, 2 H), 1.66 (s, 2 H), 1.23 (s, 4 H). The NH protons could not be detected.

13C NMR (75.5 MHz, DMSO-d₆); δ = 180.9, 142.6, 130.50 (q, JCF = 21.9 Hz), 124.4 (q, JCF = 271.3 Hz), 122.1, 116.2, 58.5, 54.0, 33.2, 31.2, 24.7, 24.5.

HRMS (ESI): m/z [M + H]+ calcd for C₁₇H₂₂F₆N₃S [M + H]+: 386.1125; found: 386.113 (± 0.0015).

1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(1R,2R)-2-(dimethylamino)cyclohexyl]thiourea (5, Takemoto’s Catalyst)

Table 1, Entry 1: A mixture of the aminothiourea (110 mg, 285 µmol, 1.00 equiv) in toluene (1.5 mL) and aq formaldehyde (37%, 55.0 µL, 0.60 equiv) was stirred under reflux for 6 h. The solvent was removed under reduced pressure and the residue was dissolved in CH₂Cl₂ (2 mL). The product 5 was obtained as an off-white crystalline solid (32.0 mg, 27%).

Table 1, Entry 2: 10 Zn powder (102 mg, 1.56 mmol, 4.00 equiv), AcOH (180 µL, 187 mg, 3.12 mmol, 80.0 equiv) and aq formaldehyde (37%, 95.0 µL, 1.17 mmol, 3.00 equiv) were added to a solution of the aminothiourea (1450 mg, 389 µmol, 1.00 equiv) in dioxane (0.5 mL), and the resulting mixture was stirred for 72 h at r.t. Aq NH₃ (500 µL) was added, the aqueous phase was extracted with CH₂Cl₂ (2 × 1 mL) and the combined organic extracts were dried (MgSO₄). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (CHCl₃–MeOH, 7:1). The product 5 was obtained as an off-white crystalline solid (117 mg, 73%).

Table 1, Entry 3: Aq Na₂HPO₃ solution (2 M, 1.4 mL, 2.85 mmol, 10.0 equiv) and aq formaldehyde (37%, 231 L, 3.38 mmol, 10.0 equiv) were added to a solution of the aminothiourea (110 mg, 285 µmol, 1.00 equiv) in dioxane (1.4 mL). The resulting mixture was stirred for 1 h at 60 °C. The pH was adjusted to 8 by the addition of aq NaOH (2 M) and the reaction mixture was extracted with CH₂Cl₂ (3 × 3 mL). The organic layer was dried (MgSO₄), the solvent was evaporated, and the residue was purified by flash chromatography (CHCl₃–MeOH, 7:1). The product 5 was obtained as an off-white crystalline solid (80.0 mg, 68%).

Table 1, Entry 4: A mixture of the aminothiourea (431 mg, 812 µmol, 1.00 equiv), formic acid (337 µL, 8.94 mmol, 11.0 equiv) and aq formaldehyde (37%, 149 µL, 1.79 mmol, 2.20 equiv) was stirred under reflux for 6 h. The solvent was removed under reduced pressure and the residue was dissolved in CH₂Cl₂ (500 µL) and washed with sat. aq NaHCO₃ (500 µL). The organic layer was dried (MgSO₄), the solvent was evaporated, and the residue was purified by flash chromatography (CHCl₃–MeOH, 7:1). The product 5 was obtained as an off-white crystalline solid (15.0 mg, 4%).

Table 1, Entry 5: Aq formaldehyde (37%, 252 µL, 3.38 mmol, 5.00 equiv) was added to a solution of the aminothiourea (260 mg, 675 µmol, 1.00 equiv) in MeCN (5 mL), and the resulting mixture was stirred for 15 min at r.t. NaBH₄CN (85.0 mg, 1.35 mmol, 2.00 equiv) was then added, followed 15 min later by AcOH (85.0 µL, 1.35 mmol, 2.00 equiv). After stirring for 2 h at r.t., the mixture was diluted with a CHCl₃–MeOH mixture (98:2, 10 mL) and washed with 1 N aq NaOH solution (12 mL). The aqueous layer was extracted with CHCl₃ (3 × 6 mL), the combined organic layers were dried (MgSO₄), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (CHCl₃–MeOH, 7:1). The product 5 was obtained as an off-white crystalline solid (90.0 mg, 32%). mp 110–111 °C (Lit. mp 111–113 °C).

IR (ATR): 3302 (w), 2939 (w), 2860 (w), 2215 (w), 1617 (m), 1538 (s), 1471 (s), 1381 (s), 1272 (s), 1170 (s), 1127 (s), 1061 (m), 1040 (m), 993 (w), 963 (w), 907 (m), 883 (m), 847 (m), 730 (s), 696 (s), 679 cm⁻¹ (s).

1H NMR (300 MHz, CDCl₃); δ = 7.97 (s, 2 H), 7.52 (s, 1 H), 4.28 (br s, 1 H), 2.90 (br s, 1 H), 2.48 (s, 6 H), 2.40 (s, 1 H), 1.96–1.71 (m, 3 H), 1.38–1.19 (m, 4 H). The NH protons could not be detected.

13C NMR (75.5 MHz, CDCl₃); δ = 180.5, 140.6, 131.8 (q, JCF = 33.6 Hz), 123.1 (q, JCF = 272.8 Hz), 122.2, 116.7, 67.2, 53.9, 39.8, 32.4, 24.4, 24.2, 22.2.


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References

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