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# Modification of the Titanium(IV) Isopropoxide Reductive Amination Reaction: Application to Solid Phase Synthesis

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**Abstract:** Secondary amines are synthesized by a modification of the titanium(IV) isopropoxide reductive amination reaction. The modified procedure was utilized for both solution and solid phase synthesis with excellent purity and yields.

Keywords: Synthesized, reductive amination, titanium(IV) isopropoxide

# INTRODUCTION

As part of a program directed towards the synthesis of ligands for a combinatorial library, we were interested in preparing substituted analogs of the 4-(arylamino)-piperidine ring system. A key step in the synthetic pathway was the reductive amination of an aryl amine and a piperidone derivative. Reductive aminations can be classified into three main categories: Imine preformation,<sup>[1]</sup> Borch-type reductions,<sup>[2]</sup> and titanium(IV) mediated reductions.<sup>[3,4]</sup> The first two reactions work well, provided the intermediate iminium adduct readily forms. In the Borch-type reactions, it is necessary to use an excess of amine to enhance the formation of the iminium intermediate

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as well as to limit over-alkylation. When the iminium adduct is difficult to form or the amine is expensive or difficult to obtain, titanium(IV) reagents were employed to facilitate the reaction. These reactions proceed with equimolar quantities of amine and ketone/aldehyde. Several examples of solid phase reductive aminations using the first two methods are described in the literature.<sup>[5–7]</sup> However, these methods are not ideally suited for weakly nucleophilic, resin-bound amines. Therefore, a solid phase titanium (IV) method would be beneficial.

Of the two reported titanium(IV) reagents, titanium isopropoxide and titanium chloride, titanium(IV) isopropoxide would be expected to be more useful for solid phase applications because titanium(IV) chloride produces hydrochloric acid as a by-product of the reaction. The literature procedure reported by Mattson and colleagues<sup>[4]</sup> describes a reaction carried out in two steps. The first step involves the formation of a titanium complex and/ or iminium species in the absence of a solvent, followed by addition of sodium cyanoborohydride in absolute ethanol. For the titanium(IV) isopropoxide-mediated reaction to be useful in solid phase syntheses, the reaction requires use of an amount of solvent that is sufficient to swell the resin during the complex-forming step.

Solution phase reactions with methyl 4-aminobenzoate and N-benzyl-4piperidone were carried out under the conditions reported by Mattson et al.<sup>[4]</sup> Two main products were formed in approximately a 1:1 mole ratio. The product mixture contained the desired product and a product derived from cyano transfer in an overall yield of 50% (Table 1, entry 2). Performing the reaction with sodium borohydride instead of sodium cyanoborohydride resulted in the formation of the desired product only, in a 52% yield.<sup>[8–10]</sup> This yield is similar to that reported by Mattson et al.<sup>[4]</sup> using aniline and 1-carboethoxy-4-piperidone. Using either chloroform or tetrahydrofuran (THF) as a solvent in the first step of the reaction, followed by evaporative removal of the solvent prior to addition of sodium borohydride (in dry alcohol) resulted in enhanced yields of the desired products. The use of chloroform (Table 1, entry 5) or THF (Table 1, entry 6) as the solvent resulted in purified yields of 77% and 85%, respectively. The THF was determined to be the optimal solvent because of its greater solvating properties.

For the reductive step of the reaction, it is necessary to find a solvent system that will swell the solid support and dissolve the reducing agent. Protic solvents such as alcohols have poor swelling properties with the polystyrene-based resin used in our studies. Therefore, a mixed solvent system was utilized. From a plot of the swelling properties of a varying mixture of THF and methanol, it was determined that an 80:20 ratio of THF to methanol was optimal. The 80:20 mixture of solvents was obtained by adding a solution of sodium borohydride in methanol to the THF solution of the first step of the reaction. This procedure resulted in an 83% yield, which is comparable to the 85% yield obtained when methanol alone is used in the reductive step (Table 1,

#### Titanium(IV) Isopropoxide





| Entry<br># | R                                 | Reaction conditions   | Yield                   |
|------------|-----------------------------------|---|-------------------------|
| 1          | 0<br>—С−осн₃                      | <ol> <li>p-TSA, Toluene, Dean-Stark,</li> <li>EtOH, NaBH<sub>4</sub></li> </ol>   | No product <sup>a</sup> |
| 2          | о<br>—Ё–осн₃                      | 1. Ti(O-iPr) <sub>4</sub> , 2. EtOH, NaCNBH <sub>3</sub>  | 50%                     |
| 3          | о<br>—Ё–осн₃                      | 1. Ti(O-iPr) <sub>4</sub> , 2. EtOH, NaBH <sub>4</sub>  | 52%                     |
| 4          | о<br>"<br>—с−осн₃                 | <ol> <li>Ti(O-iPr)<sub>4</sub>, CHCl<sub>3</sub>, 2. Evaporate CHCl<sub>3</sub>,</li> <li>EtOH, NaBH<sub>4</sub></li> </ol> | 82% <sup>b</sup>        |
| 5          | -OCH <sub>2</sub> CH <sub>3</sub> | <ol> <li>Ti(O-iPr)<sub>4</sub>, CHCl<sub>3</sub>, 2. Evaporate CHCl<sub>3</sub>,</li> <li>MeOH, NaBH<sub>4</sub></li> </ol> | 77%                     |
| 6          | -OCH <sub>2</sub> CH <sub>3</sub> | <ol> <li>Ti(O-iPr)<sub>4</sub>, THF, 2. Evaporate THF,</li> <li>MeOH, NaBH<sub>4</sub></li> </ol>                           | 85%                     |
| 7          | -OCH <sub>2</sub> CH <sub>3</sub> | 1. Ti(O-iPr) <sub>4</sub> , THF, 2. 20% MeOH, NaBH <sub>4</sub>   | 83%                     |
| 8          | -OCH <sub>2</sub> CH <sub>3</sub> | 1. Ti(O-iPr) <sub>4</sub> , THF, 2. Na(OAc) <sub>3</sub> BH,<br>AcOH  | 92% <sup>c</sup>        |

<sup>a</sup>No imine formation.

<sup>b</sup>White precipatate formation in step one.

<sup>c</sup>Heterogeneous reaction.

entries 6 and 7). Sodium triacetoxyborohydride has been used in reductive amination reactions without the need to add alcoholic solvents. Entry 8 of the table demonstrates that sodium triacetoxyborohydride could be used in place of sodium borohydride.<sup>[10]</sup> This reaction became heterogeneous upon addition of the reducing agent; nevertheless, it resulted in a 92% yield.

A solid-phase reaction was carried out using benzaldehyde and Merrifield 4-aminobenzoate ester (Scheme 1) under conditions described in entry 7 of Table 1. The product was cleaved from the resin as the methyl ester and determined to have proceeded in a 92% yield based on the loading capacity of the resin.<sup>[11]</sup> Additionally, treatment of Merrifield 4-aminobenzoate ester with N-benzyl-4-piperidone under similar conditions resulted in a 50% isolated yield of product. The product was determined to be the same species listed in Table 1, entries 1–4. Neither solution phase nor solid phase reactions

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Reagents: i) (a) Benzaldehyde, titanium(IV) isopropoxide, THF (b) NaBH<sub>4</sub>, CH<sub>3</sub>OH, ii) NaOCH<sub>3</sub>, THF / CH<sub>3</sub>OH

Scheme 1. Solid phase reductive amination reaction.

without the use of titanium(IV) isopropoxide resulted in product formation (Scheme 1).

In summary, we have presented a modified titanium-isopropoxide-based procedure for the reductive amination of weakly nucleophilic amines with ketones and aldehydes. The modified procedure is well suited for solutionphase and solid-phase synthesis, as demonstrated by the reaction of the resin-bound aniline. Work currently is underway to investigate the mechanism of the reaction.

# **EXPERIMENTAL PROCEDURE**

### **General Procedure for Solution Phase Reactions**

A flask containing 1-benzyl-4-piperidone (1.0 ml, 5.3 mmol), p-phenetidine (0.70 mL, 5.3 mmol), and titanium(IV) isopropoxide (1.6 mL, 5.3 mmol) dissolved in 27 mL of dry THF was stirred overnight at room temperature. The resulting solution was cooled to 5°C in an ice bath. Sodium borohydride (0.20 g, 5.3 mmol) dissolved in 7 mL of cold, dry methanol was added to the cooled solution. The mixture was allowed to warm to room temperature and stirred overnight. The solution was transfered to a flask containing methanol (200 mL), and water was added until no more precipitate formed. The mixture was filtered through diatomaceous earth, and the solvent was removed under reduced pressure. The resulting solid was triturated with ethyl acetate and filtered through diatomaceous earth, then the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane:ethyl acetate, 90:10) to afford an oil (1.36 g, 83%). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>),  $\delta$ : 1.25 (t, J = 6.2 Hz, 3H), 1.35-1.65 (m, 2H), 1.90-2.30 (m, 4H), 2.80-3.10 (m, 2H), 3.30-3.50(m, 1H), 3.62 (s, 2H), 3.95 (q, J = 6.2 Hz, 2H), 6.30 (d, J = 8.0 Hz, 2H), 7.22–7.38 (m, 5H), 6.51 (d, J = 8.0 Hz, 2H). Anal. Calcd. For  $C_{20}H_{26}N_2O$ : C, 77.38; H, 8.44; N, 9.03. Found: C, 77.15; H, 8.59; 9.17.

#### Titanium(IV) Isopropoxide

### **General Procedure for Solid Phase Reactions**

A flask containing Merrifield aminobenzoate resin (0.99 g, 1.1 mmol), benzaldehyde (0.20 mL, 2.0 mmol), and titanium(IV) isopropoxide (0.60 mL, 2.0 mmol) in 10 mL of dry THF was shaken overnight at room temperature. The resulting solution was cooled to 5°C in an ice bath. Sodium borohydride (0.08 g, 2.0 mmol) dissolved in 2 mL of cold, dry methanol was added to the cooled solution. The mixture was allowed to warm to room temperature and again shaken overnight. The resin was filtered and washed with methanol  $(2 \times 20 \text{ mL})$ , dichloromethane  $(2 \times 50 \text{ mL})$ , and methanol  $(2 \times 50 \text{ mL})$ ; the resin was dried under reduced pressure. Sodium methoxide (0.11 g, 2.4 mmol) was added to a suspension of the resin in 12 mL of THF/ methanol (10:2) and was shaken at room temperature for 2 days. The resin was filtered and washed with THF (10 mL), and methanol (10 mL), and the filtrate was concentrated under reduced presure. The crude product was purified by flash column chromatography (hexane:ethyl acetate, 80:20) to afford an oil (0.24 g, 92%) that was identical to the product formed from the reductive amination of methyl 4-aminobenzoate and benzaldehyde (Scheme 1), as determined by comparing <sup>1</sup>H NMR spectra. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>), δ: 1.35-1.65 (m, 2H), 1.95-2.28 (m, 4H), 2.80-3.12 (m, 2H), 3.30-3.50 (m, 1H), 3.58 (s, 2H), 3.85 (s, 3H), 6.50 (d, J=8.1 Hz, 2H), 7.22-7.38 (m, 5H), 7.88 (d, J = 8.1 Hz, 2H). Anal. Calcd. For C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: C, 74.04; H, 7.46; N, 8.64. Found: C, 73.92; H, 7.56; 8.69.

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