

**REDUCTION OF AROMATIC KETONES INTO METHYLENES
USING TRIETHYLSILANE AND TITANIUM TETRACHLORIDE.
SYNTHESIS OF 2-AMINO BUTANOIC ACIDS**

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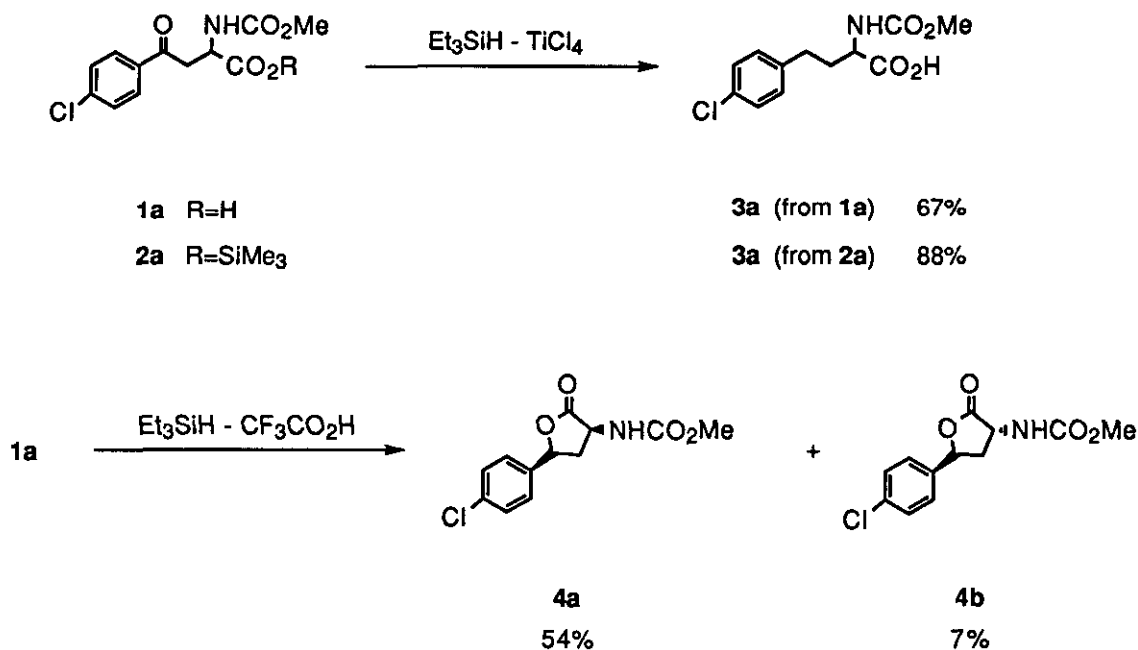
Abstract ---- Several *N*-protected 2-aminobutanoic acids(3) with aromatic or heteroaromatic ring at their terminal position were prepared in good yields by reduction of the corresponding ketones(1) with triethylsilane (Et₃SiH) in the presence of titanium tetrachloride (TiCl₄). The reduction proceeded without racemization and was successfully applied to the synthesis of optically active 2-aminobutanoic acids(6).

Reduction of aromatic ketones with Et₃SiH is an effective method for converting those ketones into methylene analogs. Application to reduction of aromatic ketones(1) bearing amino acid moiety, however, has been restricted, owing to the accompanying undesirable side reactions or a poor yield.¹ In connection with another project in organic synthesis, we required the preparation of several 2-aminobutanoic acids(6)² with halogen substituted aromatic or heteroaromatic ring at their terminal position.

In this communication, we wish to report a practical and general procedure for Et₃SiH-TiCl₄ reduction³ of 1 and its trimethylsilyl ester(2) into *N*-protected 2-aminobutanoic acid(3) without racemization.

In the first place, the reduction of 1a, derived from the Friedel-Crafts acylation of chlorobenzene and *N*-(methoxycarbonyl)aspartic anhydride(5), was examined using Et₃SiH and TiCl₄ which was found to be more oxophilic Lewis acid than BF₃OEt₂ or CF₃CO₂H. Reduction proceeded smoothly when reduction was carried out using 3.0 molar amounts of Et₃SiH and TiCl₄, respectively. The isolated yield of product (3a) was, however, a 67%. Hydrogen chloride, generated *in situ*, from carboxylic acid of 1a and TiCl₄,⁴ appears to lower the yield of the reaction product (3a). Release of hydrogen chloride was hindered by converting the free acid(1a) into its trimethylsilyl ester (2a). Consequently, reduction of 2a gave the desired *N*-protected

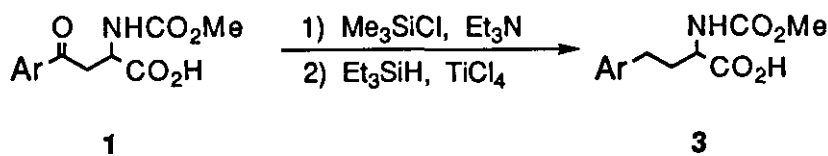
2-aminobutanoic acid(3a) in an excellent yield (Scheme1). On the other hand, reduction of 1a with Et₃SiH in boiling CF₃CO₂H gave similar results reported in the literature.¹ Reduction involved cyclization giving a mixture of cis and trans lactones (4a and 4b).⁵

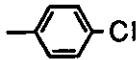

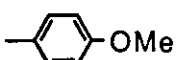
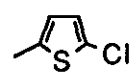
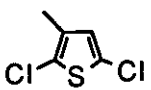


Scheme 1

Several examples of the Et₃SiH reduction mediated by TiCl₄ are demonstrated in Table 1. Besides chlorosubstituted aromatic and heteroaromatic ketones (1a, 1d and 1e), phenyl and 4-methoxyphenyl ketone (1b and 1c) were readily reduced via trimethylsilyl ester(2) into the corresponding 2-methoxycarbonylamino-butanoic acids(3) in high yields.

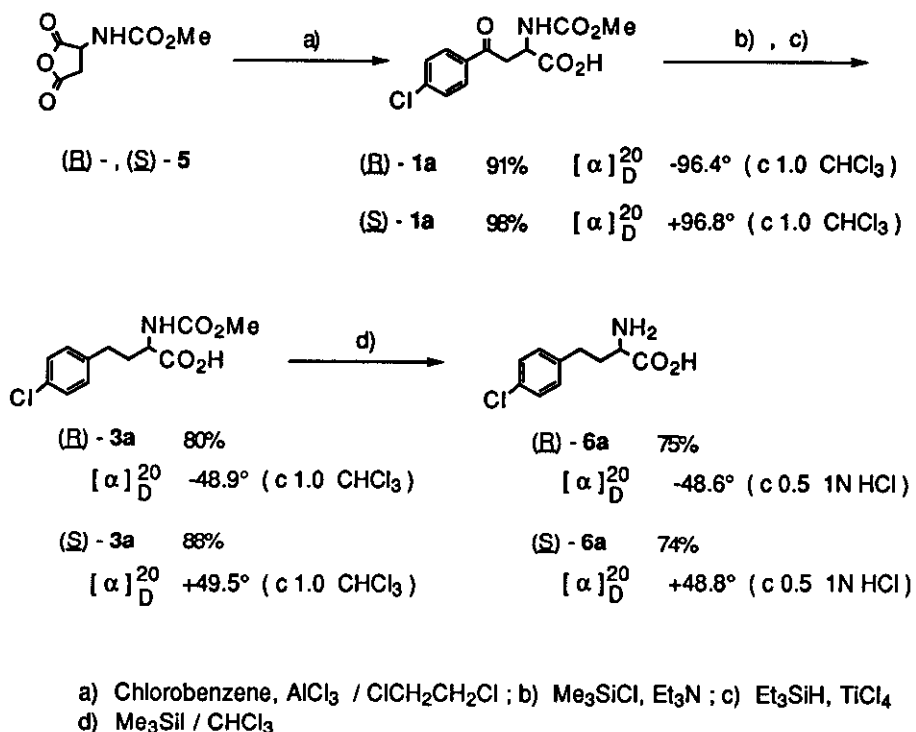
The present reduction was successfully applied to the synthesis of optically active 2-aminobutanoic acid(6a). The reduction of (2R)-4-(4-chlorophenyl)-2-(methoxycarbonylamino)-4-oxobutanoic acid ((R)-1a) with Et₃SiH-TiCl₄ proceeded without racemization to give (2R)-4-(4-chlorophenyl)-2-(methoxycarbonylamino)butanoic acid((R)-3a) in 80% (99%ee) yield.⁶

Table 1. Reduction of aromatic ketones with Et₃SiH - TiCl₄

entry	Ar	Product No.	Yield (%)
1		3a	88
2		3b	95
3		3c	83
4		3d	94
5		3e	85

Removal of *N*-protecting group with trimethylsilylamine⁷ afforded (*2R*)-4-(4-chlorophenyl)-2-aminobutanoic acid(*R*)-**6a** in 75% (99%*ee*) yield.⁶ In a similar manner, (*2S*)-isomer(*S*)-**6a** was obtained in 64% (99%*ee*)⁶ overall yield from (*S*)-**1a** (Scheme 2).

Following is a typical procedure for reduction of **1a**: A solution of Me₃SiCl(1.2 g, 11 mmol) in THF(5 ml) was added dropwise to a solution of **1a**(2.85 g, 10 mmol) and Et₃N(1.2 g, 11.1 mmol) in THF(20 ml) at 0°C. After removal of the resulting Et₃N•HCl by filtration, the filtrate was evaporated in vacuo to give **2a** quantitatively(3.56 g, 99%). To the solution of **2a** and Et₃SiH(3.35 g, 30.1 mmol) in CH₂Cl₂(20 ml) was added a 1.0 molar solution of TiCl₄(5.70 g, 30 mmol) in CH₂Cl₂(30 ml) at room temperature. After 20 h, the reaction mixture was poured into ice-water. The organic layer was extracted with saturated NaHCO₃ solution. The aqueous solution was acidified with 10% HCl solution, and then was extracted with AcOEt. Evaporation of the AcOEt and recrystallization of the residue gave 2.38 g(88%) of **3a**, mp 114-115°C.



Scheme 2

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2. a) 2-Aminobutanoic acids (Homoamino acids) are useful precursors for 2-aminotetraline derivatives with potent dopamine agonistic activities.^{1,2b,c} b) D.G.Melillo, R.D.Larsen, D.J.Mathre, W.F.Shukis, A.W.Wood, and J.R.Colleluori, *J. Org. Chem.*, 1987, **52**, 5143. c) A.D.Baxter, P.J.Murray, and R.J.K.Taylor, *Tetrahedron Lett.*, 1992, **33**, 2331.
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6. Optical purity of the product was determined by hplc analysis.
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