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

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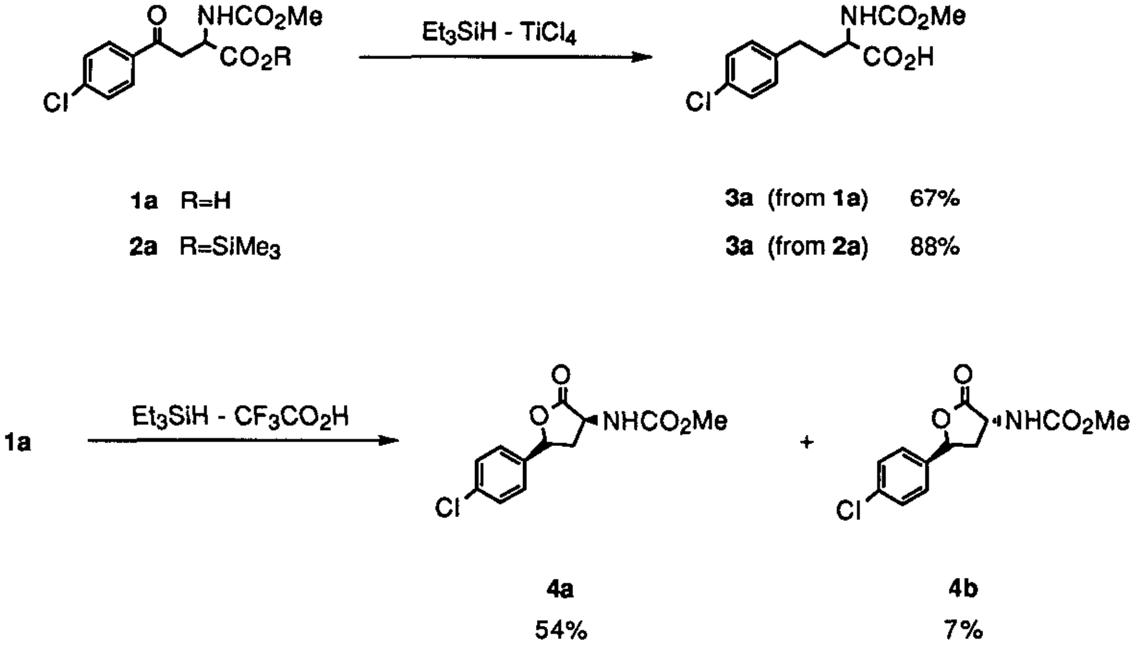
Abstract ---- Several *N*-protected 2-aminobutanoic acids(**3**) with aromatic or heteroaromatic ring at their terminal position were prepared in good yields by reduction of the corresponding ketones(**1**) with triethylsilane (Et_3SiH) in the presence of titanium tetrachloride ($TiCl_4$). The reduction proceeded without racemization and was successfully applied to the synthesis of optically active 2-aminobutanoic acids(**6**).

Reduction of aromatic ketones with Et_3SiH 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, owning 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 Et_3SiH-$TiCl_4$ reduction[3] 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 Et_3SiH and $TiCl_4$ which was found to be more oxophilic Lewis acid than BF_3OEt_2 or CF_3CO_2H. Reduction proceeded smoothly when reduction was carried out using 3.0 molar amounts of Et_3SiH and $TiCl_4$, respectively. The isolated yield of product (**3a**) was, however, a 67%. Hydrogen chloride, generated *in situ*, from carboxylic acid of **1a** and $TiCl_4$,[4] appears to lower the yield of the reaction product (**3a**). Release of hydrogene chloride was hindered by converting the free acid(**1a**) into its trimethylsilyl ester (**2a**). Consequentry, 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 Et_3SiH in boiling CF_3CO_2H gave similar results reported in the literature.[1] Reduction involved cyclization giving a mixture of cis and trans lactones (**4a** and **4b**).[5]



1a R=H

2a R=$SiMe_3$

3a (from **1a**) 67%

3a (from **2a**) 88%

4a 54%

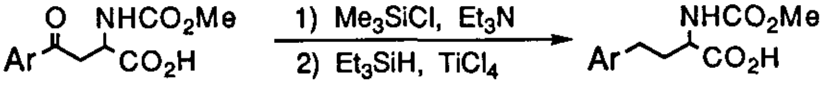
4b 7%

Scheme 1

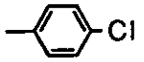
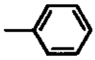
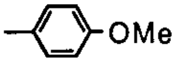
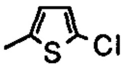
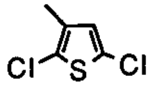
Several examples of the Et_3SiH reduction mediated by $TiCl_4$ are demonstrated in **Table 1**. Besides chlorosubstituted aromatic and heteroaromatic ketones (**1a**,**1d** and **1e**), phenyl and 4-methoxyphenyl ketone (**1b** and **1c**) were readily reduced via trimethylsilyl ester(**2**) into the 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 Et_3SiH-$TiCl_4$ 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 Et_3SiH - $TiCl_4$

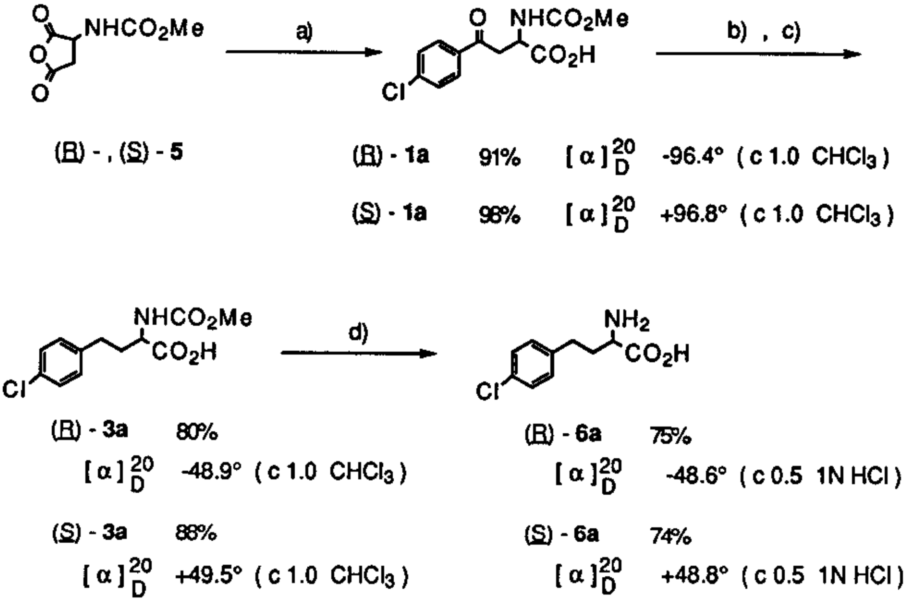


1 3

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 trimethyliodosilane[7] 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 Me_3SiCl(1.2 g, 11 mmol) in THF(5 ml) was added dropwise to a solution of **1a**(2.85 g, 10 mmol) and Et_3N(1.2 g, 11.1 mmol) in THF(20 ml) at 0°C. After removal of the resulting Et_3N•HCl by filtration, the filtrate was evapolated in vacuo to give **2a** quantitatively(3.56 g, 99%). To the solution of **2a** and Et_3SiH(3.35 g, 30.1 mmol) in CH_2Cl_2(20 ml) was added a 1.0 molar solution of $TiCl_4$(5.70 g, 30 mmol) in CH_2Cl_2(30 ml) at room temperture. After 20 h, the reaction mixture was poured into ice-water. The organic layer was extracted with saturated $NaHCO_3$ 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.



(R) - , (S) - 5

(R) - 1a 91% $[\alpha]_D^{20}$ -96.4° (c 1.0 CHCl$_3$)

(S) - 1a 98% $[\alpha]_D^{20}$ +96.8° (c 1.0 CHCl$_3$)

(R) - 3a 80% $[\alpha]_D^{20}$ -48.9° (c 1.0 CHCl$_3$)

(S) - 3a 88% $[\alpha]_D^{20}$ +49.5° (c 1.0 CHCl$_3$)

(R) - 6a 75% $[\alpha]_D^{20}$ -48.6° (c 0.5 1N HCl)

(S) - 6a 74% $[\alpha]_D^{20}$ +48.8° (c 0.5 1N HCl)

a) Chlorobenzene, AlCl$_3$ / ClCH$_2$CH$_2$Cl ; b) Me$_3$SiCl, Et$_3$N ; c) Et$_3$SiH, TiCl$_4$
d) Me$_3$SiI / CHCl$_3$

Scheme 2

REFERENCES AND NOTES

1. J.E.Nordlander, M.J.Payne, F.G.Njoroge, V.M.Vishwanath, G.R.Han, G.D.Laikos, and M.A.Balk, J. Org. Chem., 1985, **50**, 3619.

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.

3. a) Reductive cleavage of acetal, ketal, and bicyclic ketal with Et$_3$SiH-TiCl$_4$ were reported in the literture.[3b,c,d] b) K.Homma and T.Mukaiyama, Heterocycles, 1990, **31**, 443. c) A.Mori, K.Ishihara, and H.Yamamoto, Tetrahedron Lett., 1986, **27**, 987. d) H.Kotsuka, Y.Ushino, I.Kodato, and M.Ochi, Chem.Lett., 1988, 987.

4. R.N.Kapoor, K.C.Pande, and R.C.Mehrotra, J. Indian. Chem. Soc., 1958, **35**, 157. ; K.L.Jaura and P.S.Bajwa, J. Sci. Ind. Research., 1961, **20B**, 391. ; K.L.Jaura, H.S.Banga, and R.L.Kaushik, J. Indian. Chem. Soc., 1962, **39**, 531. ; A.Jacques, and D.Claude, Bull. Soc. Chim. Fr., 1975, 1933.

5. Reduction of ethyl 4-(4-chlorophenyl)-2-(methoxycarbonylamino)-4-oxobutanoate with Et$_3$SiH in boiling CF$_3$CO$_2$H gave ethyl 4-(4-chlorophenyl)-2-(methoxycarbonylamino)butanoate in only 15% yield.

6. Optical purity of the product was determined by hplc analysis.

7. K.Irie, A.Ishida, T.Nakamura, and T.Oh-ishi, Chem.Pharm.Bull., 1984, **32**, 2126.

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