Pergamon

Tetrahedron Letters, Vol. 37, No. 40, pp. 7319-7322, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01597-3

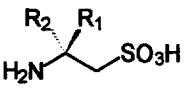
New Methods for the Preparation of 2-Amino-2-methylpropanesulfonic Acid

Daniela Braghiroli and Maria Di Bella*

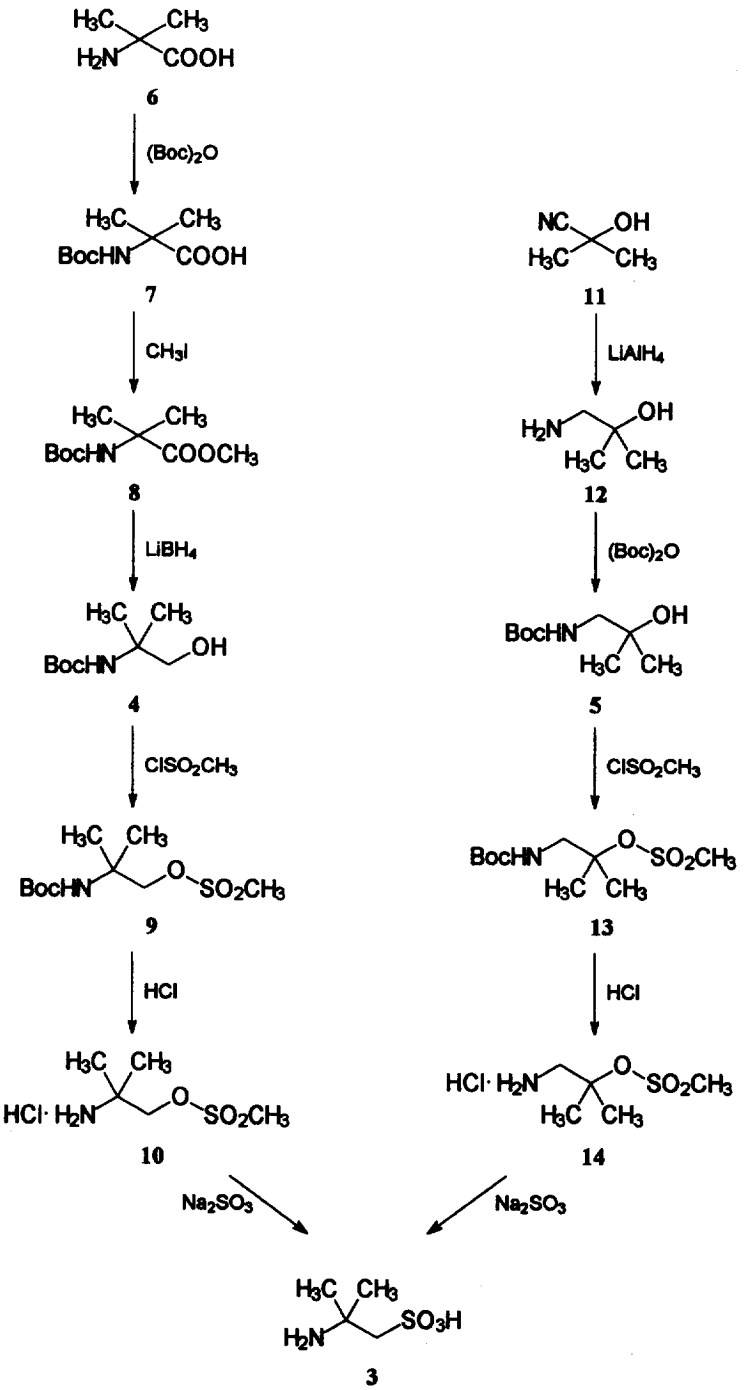
Dipartimento di Scienze Farmaceutiche, University of Modena, Via Campi 183, 41100 Modena, Italy

Abstract: 2-Amino-2-methylpropanesulfonic acid **3** was prepared either from 2-N-[(1,1-dimethylethoxy)carbonyl]amino-2-methyl-1-propanol **4** or from 1-N-[(1,1-dimethyl-ethoxy)carbonyl]amino-2-methyl-2-propanol **5** in good overall yields.

Previous data[1] have shown that 2-aminopropanesulfonic acid **1** mimics, when intracerebroventricularly injected in rat, the hypotensive effect of taurine (2-aminoethanesulfonic acid) **2** and that the effect elicited by the racemate is mainly due to the (S) enantiomer. Therefore an extensive study of the effect of numerous other taurine structural analogs on the biological activities of this important amino acid is carrying out.[2-4] In this program 2-amino-2-methylpropanesulfonic acid **3** seems to be an interesting pharmacological tool. Although reference to this compound does appear in the literature,[5] a detailed synthesis could not be located, hence new synthetic methods to obtain **3** were performed.



1: (R) $R_1 = H$ $R_2 = CH_3$
1: (S) $R_1 = CH_3$ $R_2 = H$
2: $R_1 = H$ $R_2 = H$
3: $R_1 = CH_3$ $R_2 = CH_3$


H3C CH3
H2N COOH
6
(Boc)2O
H3C CH3
BocHN COOH
7
CH3I
H3C CH3
BocHN COOCH3
8
LiBH4
H3C CH3
BocHN OH
4
ClSO2CH3
H3C CH3
BocHN O SO2CH3
9
HCl
H3C CH3
HCl· H2N O SO2CH3
10
NC OH
H3C CH3
11
LiAlH4
H2N OH
H3C CH3
12
(Boc)2O
BocHN OH
H3C CH3
5
ClSO2CH3
BocHN O SO2CH3
H3C CH3
13
HCl
HCl· H2N O SO2CH3
H3C CH3
14
Na2SO3
Na2SO3
H3C CH3
H2N SO3H
3

Scheme 1

Compound **3** was prepared either from 2-N-[(1,1-dimethylethoxy)carbonyl]amino-2-methyl-1-propanol **4** or from 1-N-[(1,1-dimethylethoxy)carbonyl]amino-2-methyl-2-propanol **5** according to procedure previously reported for other taurine analogs (Scheme 1).[3,4,6,7]

To obtain **4** the amino group of 2-methylalanine **6** was protected with di-*tert*-butyldicarbonate, $(Boc)_2O$, according to conventional procedure[8] to give N-[(1,1-dimethylethoxy)carbonyl]amino-2-methylalanine **7** in 53.4% yield. Compound **7** was then converted to the corresponding methyl ester **8** in 96.6% yield by treatment with methyl iodide (1.6 eq.) in presence of potassium hydrogen carbonate (2 eq.) in N,N-dimethylformamide at room temperature for 5 hrs. The methyl ester **8** was then reduced with lithium borohydride (2 eq.) in ethanol to give the amino alcohol **4** in 86.7% yield.

The 2-N-[(1,1-dimethylethoxy)carbonyl]amino-2-methylpropanol **4** was mesylated in 85% yield to **9** using methanesulfonyl chloride (1 eq.) in presence of triethylamine (1.1 eq.) in methylene chloride at 0°C for 1 hr. Deprotection of compound **9** with an excess of hydrochloric acid in dioxane provided the corresponding hydrochloride **10** (91.5 % yield), which was treated with aqueous sodium sulfite (1.5 eq.) to give **3** in 76.3% yield.

Compound **5** was prepared by reduction of 2-hydroxyisobutyronitrile (acetone cyanohydrin) **11** to 1-amino-2-methyl-2-propanol **12** (51.5% yield),[9] followed by protection with $(Boc)_2O$ (97.4% yield). After mesylation (74.3% yield) and removal of the protecting group (83.4% yield), the hydrochloride **14** obtained was allowed to react with sodium sulfite to give still **3** in 71.4% yield. This alternative route seems to be more convenient first of all because of the very lower prices of starting materials as well as because of the lower step number. Both reasons overcome notably the somewhat lower yields.

The key step of these syntheses is the reaction of hydrochlorides **10** and **14** with sodium sulfite, namely a nucleophilic substitution in molecules with a group with an unshared pair of electrons β to the leaving group, therefore it is possible to occur either by a simple substitution or by a rearrangement. Under the used reaction conditions hydrochlorides **10** and **14** afforded both only 2-amino-2-methylpropanesulfonic acid **3** in good overall yields.

ACKNOWLEDGMENTS

This work was supported by a grant from MURST, Rome (40%).

REFERENCES AND NOTES

1. Braghiroli D.; Truzzi C.; Brandoli C.; Baraldi M.; Gamberini G.; Di Bella M. *Pharmacol.Res.* **1996**, in press.

2. Braghiroli D.; Di Bella M.; Zanoli P.; Truzzi C.; Baraldi M. *Il Farmaco*, **1990**, 45, 631.
3. Braghiroli D.; Mussati E.; Di Bella M.; Saladini M. *Tetrahedron: Asymmetry* **1996**, 7, 831.
4. Braghiroli D.; Di Bella M. *Tetrahedron: Asymmetry* **1996**, 7, 2145.
5. a) Falk R.A.; Nicolson P.C. Ger. Offen. Patent 2 758 013 , 1978; *Chem. Abstr.* **1978**, 89, 165322g; b) Hoke D.I. U.S. Patent 3 991 079, 1976; *Chem. Abstr.* **1977**, 87, 25813b.
6. Higashiura K.; Morino H.; Matsuura H.; Toyomaki Y.; Ienaga K. *J. Chem. Soc. Perkin Trans. I* **1989**, 1479.
7. All new compounds were fully characterized. Their spectral data and elemental analyses are consistent with the assigned structures.
   Selected data:

   3: m.p. dec. >320°C. ^{1}H NMR (200 MHz, D_2O) δ 1.53 (s, 6H), 3.26 (s, 2H). Anal. Calcd. for $C_4H_{11}NO_3S$: C, 31.36; H, 7.24; N, 9.14. Found: C, 31.39; H, 7.33; N, 9.11.

   10: m.p. 153-4°C. ^{1}H NMR (200 MHz, D_2O) δ 1.45 (s, 6H), 3.31 (s, 3H), 4.72 (s, 2H). Anal. Calcd. for $C_5H_{14}ClNO_3S$: C, 29.48; H, 6.93; N, 6.88. Found: C, 29.19; H, 6.79; N, 6.81.

   14: m.p. 162-3°C. ^{1}H NMR (200 MHz, D_2O) δ 1.72 (s, 6H), 3.37 (s, 2H), 3.61 (s, 3H). Anal. Calcd. for $C_5H_{14}ClNO_3S$: C, 29.48; H, 6.93; N, 6.88. Found: C, 29.16; H, 6.75; N, 6.79.
8. Keller O.; Keller W.E.; van Look G.; Wersin G. *Org. Synt.* **1985**, 63, 160.
9. Kjær A.; Christensen B.W.; Hansen S.E. *Acta Chem. Scand.* **1959**, 13, 144.

(*Received in UK* 20 *June* 1996; *revised* 8 *August* 1996; *accepted* 15 *August* 1996)