A Novel Preparation of Scalemic N-Methyl-α-amino Acids

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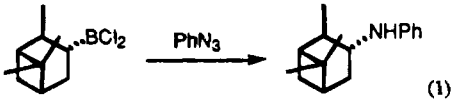
Scalemic *N*-methyl-α-amino acids are present in a variety of natural products such as the dolastatins[1] and the didemnins.[2] These peptides have been studied because of their interesting biological properties.[1-3] Optically active *N*-methyl-α-amino acids have been prepared in various ways.[4] However, each procedure has limitations which include the number of steps needed to prepare the substrate,[4a] the problems of racemization and lack of reactivity associated with an S_N2 reaction,[4b] harsh reaction conditions,[4c] and the instability of acid-sensitive substrates.[4d] In addition, *N*-*tert*-butyl- and *N*-phenyl-α-amino acids cannot be readily synthesized by any of these methods except that of Effenberger's.[4b] The ability to synthesize a variety of scalemic *N*-substituted α-amino acids from a common intermediate would simplify the preparation of such derivatives.

A useful method to prepare secondary amines is the reductive alkylation of organic azides with alkylboranes.[5] Scalemic secondary amines have been formed from optically active dichloroalkylboranes (eq 1).[5c] To our

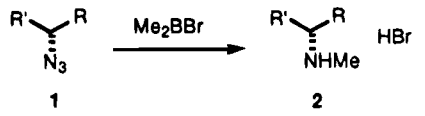


(1)

knowledge, the only reported reductive alkylation of a scalemic azide is an intramolecular reaction with a trialkylborane.[6] We prepared (*S*)-α-methylbenzyl azide, **1a** (98% ee),[7] and treated it with dimethylbromoborane. The reaction proceeded to afford scalemic (*S*)-*N*-methyl-α-methylbenzylamine, **2a**, in 82% yield (Table 1).

Optically active α-azido acid derivatives are readily accessible precursors,[7-9] and we examined the reaction of α-azido acids, esters, and amides **1b–i** with dimethylbromoborane (Table 1). The reductive alkylations were carried out at either 20 or 40 °C in dichloroethane and were complete in less than 2 h. The reactions were quenched with 1 equiv of ethanol, concentrated, and triturated with methylene chloride to yield the HBr salt of the scalemic *N*-methyl-α-amino acid derivatives **2b–i** in good yields.[10] The reactions were initially carried out with racemic material or with each enantiomer so that the optical purity of the products could be determined by chiral HPLC analysis after conversion to an adduct which contained a chromophore.

Table 1. Reductive Alkylation of Scalemic Azides



1 **2**

entry	R	R′	% ee, **1**	*T*, °C	yield (%)	% ee, **2**
a	Me	Ph	98[a]	40	82	98[c]
b	COOEt	Me	98[a]	40		
c	COOH	Me	98[a]	40	89	98[c]
d	CONHBn	Me	98[a]	40	94	98[d]
e	$CH_2(C_6H_4)OMe$	COOH	98[b]	20	92	98[c]
f	Ph	COOH	99[a]	40	68	38[d]
g	Ph	COOH	99[a]	20	99	99[d]
h	*t*-Bu	COOH	99[a]	40	78	96[e]
i	*t*-Bu	CONHBn	99[a]	20	63	99[d]

[a] Percent ee of starting azide as reported in the literature. [b] Percent de of starting azido imide as determined by chiral HPLC. [c] Percent ee of Cbz-*N*-methylamine as determined by chiral HPLC. [d] Percent ee determined by chiral HPLC. [e] Percent ee of NHBn amide determined by chiral HPLC.

The stereoselectivity of the reaction as well as the functional group tolerance were examined. Although the reductive alkylation of ester **1b**[7] with dimethylbromoborane proceeded, there was partial ester cleavage. The use of 2 equiv of borane yielded *N*-methylalanine, but borane complexation to the amino acid made product isolation difficult. This problem was easily overcome by treating acid **1c**, obtained from **1b** by ester hydrolysis, with 1 equiv of dimethylbromoborane to afford scalemic (*R*)-*N*-methylalanine in 89% yield. No epimerization occurred when azido amide, **1d**, was treated with dimethylbromoborane. Unlike the ether deprotection which was observed with β-azido ethers,[11] remotely placed ethers are stable to the reductive alkylation reaction as demonstrated by the reaction of dimethylbromoborane with **1e** which was prepared *via* the Evans oxazolidinone.[8] The resulting (*S*)-*N*,*O*-dimethyltyrosine was formed without racemization.

The reductive alkylation of 2-azidophenylacetic acid was then studied since this substrate is more prone to epimerization. Attempts to prepare the scalemic azide from ethyl mandelate and diphenyl phosphorazidate in the presence of DBU were unsuccessful as racemization occurred, so 2(*S*)-azidophenylacetic acid (99% ee) was prepared as described by Evans.[8] Reaction of 2(*S*)-azidophenylacetic acid, **1f**, with dimethylbromoborane at 40 °C yielded two products, (*S*)-*N*-methylphenylglycine, 38% ee, and phenylglyoxylic acid. Scalemic (*S*)-*N*-methylphenylglycine was successfully prepared in 99% yield

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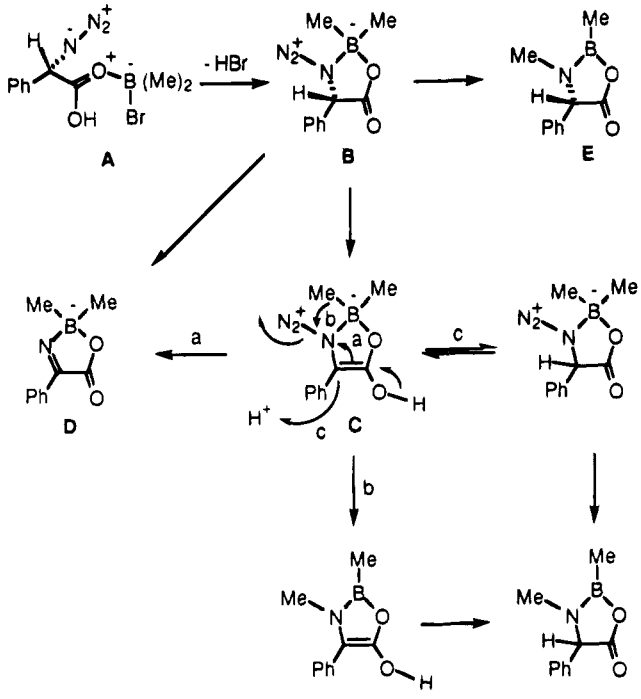
(10) Experimental procedure for the preparation of (*S*)-*N*-methylphenylglycine: Acid **1f** (120 mg, 0.68 mmol) was dissolved in 1,2-dichloroethane (8 mL) under nitrogen. This solution was added dropwise to a 0.3 M dichloroethane solution of dimethylbromoborane (66 μL, 0.68 mmol) under nitrogen at room temperature. There was immediate evolution of nitrogen, and the solution turned light yellow. TLC indicated that the reaction was complete after 1 h, so ethanol (40 μL, 0.68 mmol) was added. The HBr salt of (*S*)-*N*-methylphenylglycine (165 mg, 99%) was isolated by filtration.

(11) Carboni, B.; Vaultier, M.; Carrié, R. *Tetrahedron* **1987**, *43*, 1799.

0022-3263/95/1960-4986$09.00/0

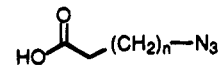
Scheme 1



merely by conducting the reductive alkylation at room temperature. The epimerization and formation of phenylglyoxylic acid that occurred in the reductive alkylation of **1f** at 40 °C indicated there may be initial complexation of the borane to the carbonyl, **A**, followed by intramolecular reaction with the azide to give **B** (Scheme 1). Racemization occurs with **1f** because of the acidity of the α proton leading to the corresponding boron enolate, **C**. This enolate can give rise to either imine **D**, *via* a, or epimerized *N*-methyl phenylglycine, *via* b and/or c. Alternatively, formation of **D** by loss of N_2 and the α proton from **B** would also yield phenylglyoxylic acid. Lowering the reaction temperature causes the reductive alkylation to be preferred over enolization, yielding a scalemic product, **E**.

In order to probe the steric constraints of the reductive alkylation reaction, α-azido acid, **1h**, was prepared.[8] Brown has observed that the rate of reductive alkylation of alkyl azides depends on the sterics of both reacting partners but has not employed azides as sterically hindered as **1h** and **1i**.[12] The reaction of **1h** with dimethylbromoborane was complete in 2 h at 40 °C to afford (*S*)-*N*-methyl *tert*-butylglycine (96% ee) in 78% yield. The reductive alkylation of the amide **1i** proceeded at 20 °C without epimerization although small amounts of benzyl-*tert*-butylglyoxyl amide were formed.

The facile reductive alkylation of **1h** and **1i** is intriguing and lends support to the complexation proposal. Interestingly, treatment of a 1:1 mixture of **1a** and **1h** with 1 equiv of dimethylbromoborane affords (*S*)-*N*-methyl-*tert*-butylglycine as well as unreacted **1a**. The complexation phenomenon was probed by treating dimethylbromoborane with 3-azidopropanoic acid, **3**, 4-azidobutyric acid, **4**, and 5-azidovaleric acid, **5**. The reduc-



3 n = 1
4 n = 2
5 n = 3

tive alkylation of **3** and **4** was complete at room temperature in 1 h to yield the corresponding *N*-methylamino acids while the reaction with **5** was incomplete even after 18 h. This indicates that the rate of reaction is influenced by boron complexation to the carbonyl and shows that 5-, 6-, and 7-membered ring intermediates form readily.

It is possible to form a variety of scalemic *N*-methyl-α-amino acids, including phenyl- and *tert*-butylglycine, from the readily accessible α-azido acids by reductive alkylation. Acids, amides, and remotely placed ethers are stable to the reaction conditions while esters are cleaved. The reaction is facilitated by complexation of the borane to the carbonyl so that haloboranes react with azido acid derivatives in preference to simple alkyl azides. We are in the process of further delineating the scope of this reaction in addition to preparing other *N*-substituted α-amino acids from α-azido acid derivatives.

Acknowledgment. We are grateful to Alfred J. Mical, Andrew M. Blum, Kenneth G. Lynam, and Kathy A. Rathgeb for the chiral HPLC analyses.

Supporting Information Available: General experimental procedures are available for all compounds with procedures and complete characterization data for all new compounds (11 pages).

JO950860B

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