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Efficient Method for Selective Introduction of Substituents as C(5) of Isoleucine and Other α-Amino Acids

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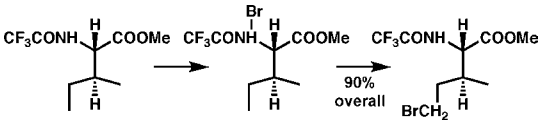
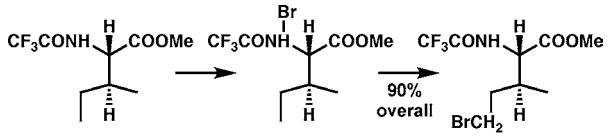
ABSTRACT



A useful process for the position-selective remote bromination of *N*-trifluoroacetyl-α-amino esters is illustrated for the isoleucine case. The 5-bromoisoleucine derivative shown above can be used for the synthesis of many modified amino acids, as described herein.

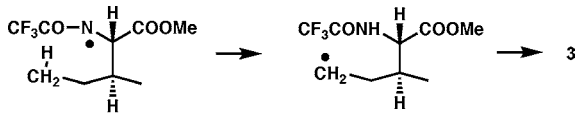
This paper describes an efficient methodology for the synthesis of useful chiral substances from the readily available α-amino acids isoleucine, norleucine, and leucine. Although isoleucine is unique among the 20 genetically coded amino acids in having both a branched carbon chain and two stereocenters, it has not been used as a platform for generating more complex α-amino acids by the selective introduction of new substituents. We envisaged that such α-amino acids with enhanced molecular complexity could be of value in a variety of research applications, including the discovery of new bioactive substances.

The approach that we have taken is based on the use of the α-amino function to effect hydrogen atom abstraction selectively from C(5) of isoleucine to allow subsequent attachment of a reactive group. Specifically, *N*-trifluoroacetylisoleucine methyl ester (**1**) was converted to the *N*-bromo derivative **2** (>97%) using acetyl hypobromite[1] in CCl_4 at 23 °C for 1 h (flask protected from light). When



1 2 3

this solution was exposed to light from a sunlamp at 23 °C, a free radical chain reaction of the Hofmann−Löffler−Freytag type[2,3] occurred rapidly (1 h) to give the 5-bromo derivative **3** in 90% isolated yield. The structure of **3** followed unambiguously from ^{1}H NMR, ^{13}C NMR, infrared, and mass spectral data. No products isomeric with **3** could be detected by careful chromatographic and spectral analysis. The high yield and positional selectivity of the conversion of **1** → **3** stand in contrast to an early study in which the reaction of various α-amino acids in 90% sulfuric acid with chlorine was found to yield mixtures of *β*- and *γ*-chlorinated products.[4] We believe that the electron-withdrawing ability



4 5

of the CF_3CO group renders the intermediate amide radical **4** especially reactive in H atom abstraction to form *δ*-carbon

(1) Duhamel, L.; Plé, G.; Angibaud, P.; Desmurs, J. R. *Synth. Commun.* **1993**, *23*, 2423−2433.

(2) (a) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1960**, *82*, 1657−1668. (b) Hofmann, A. W. *Chem. Ber.* **1883**, *16*, 558−560 and 586−591. (c) Löffler, K.; Freytag, C. *Chem. Ber.* **1909**, *42*, 3421−3426 and 3427−3434. (d) Coleman, G. H.; Goheen, G. E. *J. Am. Chem. Soc.* **1938**, *60*, 730−730. (e) Coleman, G. H.; Nichols, G.; Martens, T. F. *Organic Syntheses*; John Wiley: New York, 1955; Coll. Vol. 3, pp 159−162.

(3) For reviews, see: (a) Cekovic, Z. *J. Serb. Chem. Soc.* **2005**, *70*, 287−318. (b) Neale, R. S. *Synthesis* **1971**, 1−15. (c) Minisci, F. *Synthesis* **1973**, 1−24. (d) Wolff, M. E. *Chem. Rev.* **1963**, *63*, 55−64.

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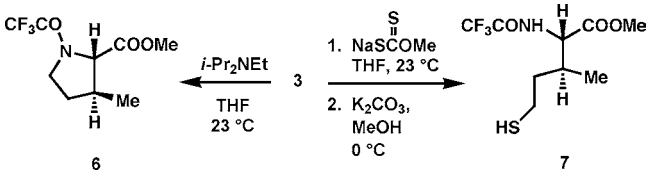
radical **5** (see above) which propagates the chain reaction by intermolecular Br abstraction from **2** to form **3**. The positional selectivity derives from the exceptional favorable stereoelectronics of the transition state for 1,5-H migration.[2a,5,6]

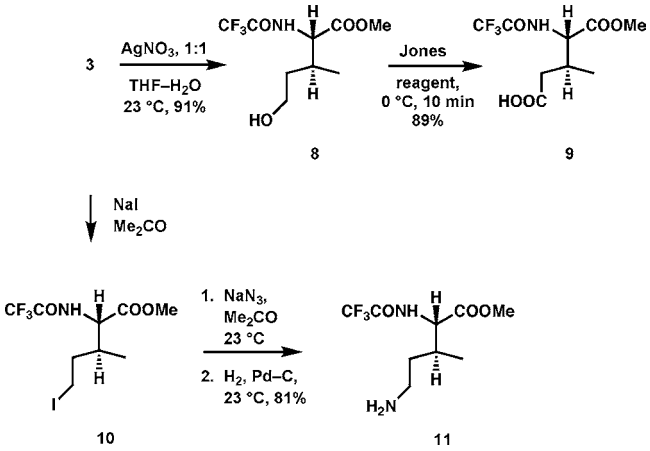
N-Trifluoroacetyl-5-bromoisoleucine methyl ester (**3**) is an excellent starting material for the synthesis of a wide variety of α-amino acid derivatives. For instance, treatment of **3** with 3 equiv of diisopropylethylamine in THF at 23 °C for 8 h results in the formation of *N*-trifluoroacetyl (*S*,*S*)-3-methylproline methyl ester **6** in 90% yield whereas sequential treatment of **3** with CS_2 and NaOMe in THF at 23 °C for 6 h and K_2CO_3 in MeOH at 0 °C for 12 h produces *N*-trifluoro-5-mercaptoisoleucine methyl ester **7**, an interesting homologue of cysteine, in 90% overall yield. In addition, **3** could



6 7

be converted efficiently into *N*-trifluoroacetyl-5-hydroxyisoleucine methyl ester **8** and then into *N*-trifluoroacetyl-(*S*,*S*)-3-methyl glutamic acid methyl ester **9**, as shown in Scheme 1. Also shown in Scheme 1 is the transformation of

Scheme 1. Synthesis of 5-Functionalized Isoleucine Derivatives



8 9 10 11

3 into *N*-trifluoroacetyl-5-aminoisoleucine methyl ester via the iodide **10** in 81% overall yield.

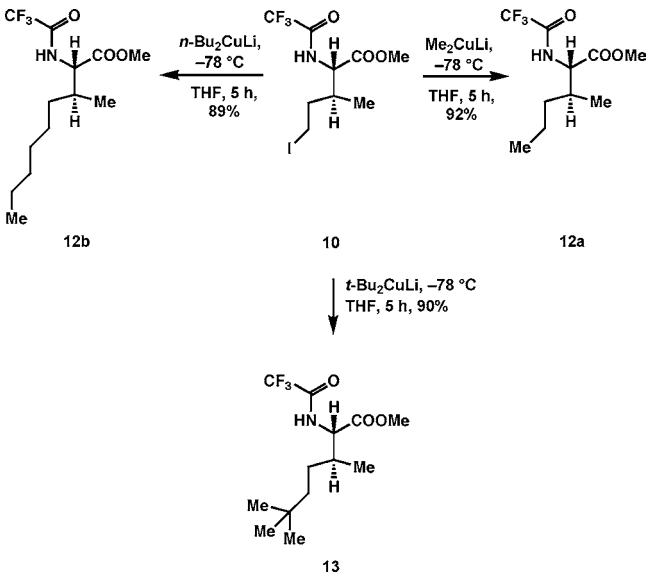
The transformations shown in Scheme 2 illustrate the application of iodide **10** to the synthesis of higher homologues of isoleucine in which the carbon chain has been extended from the C(5) position as the point of attachment.

(4) Kollonitsch, J.; Rosegay, A.; Doldouras, G. *J. Am. Chem. Soc.* **1964**, *86*, 1857−1858.

(5) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1958**, *80*, 2903−2904.

(6) The N···H···C angle for the six-membered transition state corresponding to **4** → **5** of approximately 115° is intermediate between the optimum for anionic N⁻···H−C proton abstraction (ca. 180°) and nitrenium N⁺···H−C hydride abstraction (ca. 90°), in accord with expectations based on orbital interactions.

Scheme 2. Synthesis of 5-Alkylated-*N*-trifluoroacetylisoleucine Methyl Esters

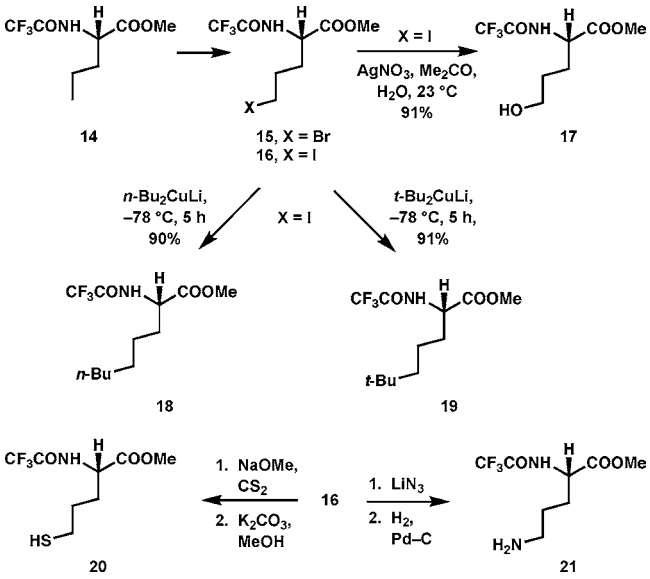


12b 10 12a 13

Very good yields of C−C coupling products were obtained from the reaction of the 5-iodoisoleucine derivative **10** with Me-, *n*-Bu-, and *t*-Bu-cuprate reagents. These carbon-extended higher homologues of isoleucine have considerable potential as probes for research in chemical biology.[7]

We have converted *N*-trifluoroacetylnorleucine methyl ester (**14**) to the 5-bromo and 5-iodo derivatives (**15** and **16**) in a manner completely analogous to that for the synthesis of **3** from **1**, as shown in Scheme 3. Using the iodo derivative

Scheme 3. Transformations of *N*-Trifluoroacetyl Norleucine Methyl Ester



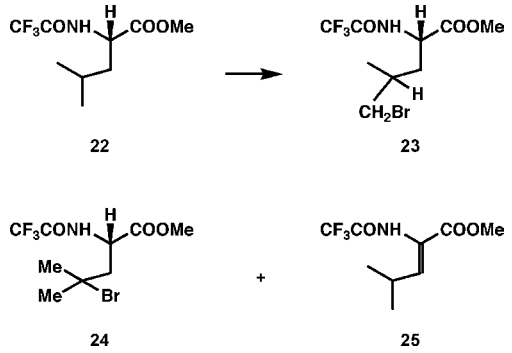
14 15, X = Br 16, X = I 17 18 19 20 21

16, we prepared the corresponding alcohol **17** by hydrolysis, and the *n*-butyl (**18**) and *tert*-butyl (**19**) homologues were

synthesized by coupling with the appropriate dialkyl cuprate reagents as outlined in Scheme 3.

When *N*-trifluoroacetylleucine methyl ester (**22**) was N-brominated and exposed to light at 23 °C for 1 h, it was transformed into a diastereomeric mixture of 5-bromo derivatives **23** (diastereomeric ratio, 1.5:1). In contrast to this intramolecular pathway, the reaction of **22** with *N*-bromosuccinimide gave no **23** but instead a mixture of the 4-bromo derivative **24** (80% yield) and the α,*β*-unsaturated ester **25** (10% yield), possibly formed via an initial bromination at C(2) (Scheme 4). Finally, the prototype reaction of

Scheme 4. Intermolecular and Intramolecular Bromination of *N*-Trifluoroacetylleucine Methyl Ester



22 23 24 25

26 → **27** was studied. As expected, conversion of **26** to the *N*-bromo derivative and the light-initiated radical chain reaction produced *N*-trifluoroacetyl-4-bromo-butylamine (**27**) in 91% isolated yield.

$$\underset{\mathbf{26}}{CF_3CONH(CH_2)_3CH_3} \xrightarrow{91\%} \underset{\mathbf{27}}{CF_3CONH(CH_2)_3CH_2Br}$$

We have also examined other modifications of the intramolecular N-halogenation reaction described in this article. First, with regard to the acyl group on nitrogen, as we had anticipated, *N*-trifluoroacetyl is the most useful.[8] For instance, *N*-*t*-butoxycarbonyl (Boc) derivatives undergo slower and less efficient N-bromination and intramolecular C-bromination reactions, resulting in significantly lower conversions and yields of product. Thus, our experience leads us to the view that *N*-trifluoroacetyl derivatives are optimum, in accord with theoretical expectations.[8]

It has also been found that the use of *N*-chloroamides in these intramolecular halogenations is problematic because of the resistance of these compounds[9] to photoinduced radical chain reactions.

The position-selective intramolecular bromination process described herein provides efficient and convenient synthetic access to many interesting nonnatural α-amino acids. We believe that this chemistry can be applied not only to the synthesis of new bioactive compounds but also for bioorganic research. For instance, the 5-bromoisoleucine derivative **3** provides a greatly shortened route to *N*-methyl (2*S*,3*S*)-5-hydroxyisoleucine derivatives and simplifies the synthesis of halipeptins A and B.[10]

Supporting Information Available: Experimental procedures and characterization data for the new compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) See, for example: Hartman, M. C. T.; Josephson, K.; Szostak, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 4356−4361.

(8) Recent theoretical analyses of C−H abstraction reactions by free radicals indicate that the barrier heights for these processes are lowered in proportion to the electron deficiency (or electron affinity) of the abstracting radical. See: Donahue, N. M.; Clarke, J. S.; Anderson, J. G. *J. Phys. Chem. A* **1998**, *102*, 3923−3933. As far as we are aware, this paper describes the first synthetic application and support of this theoretical proposal.

(9) *N*-Chloroamides can be readily prepared by the trichloroisocyanuric method. See: De Luca, L.; Giacomelli, G.; Nieddu, G. *Synlett* **2005**, 223−226.

(10) See: Hara, S.; Makino, K.; Hamada, Y. *Tetrahedron* **2004**, *60*, 8031−8035.