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A Novel Synthesis of *tert*-Leucine *via* a Leuckart Type Reaction

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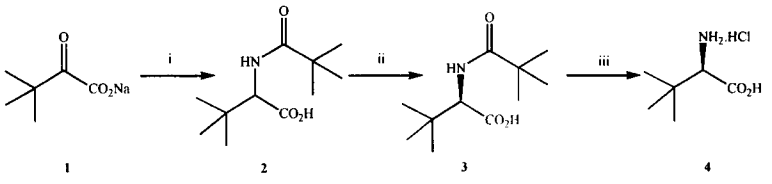
Abstract: An efficient synthesis of racemic *tert*-leucine from trimethylpyruvic acid using a Leuckart type reaction is described. A facile resolution of an intermediate with α-methylbenzylamine allows entry into either (R)-or (S)-*tert*-leucine. © 1997 Elsevier Science Ltd.

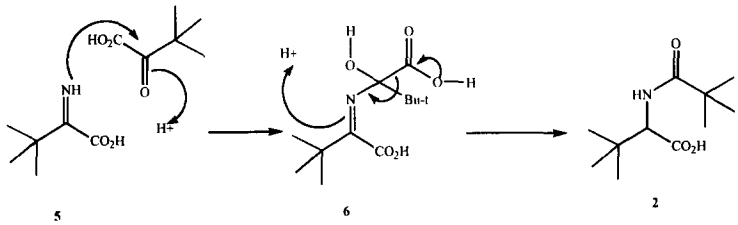
In order to support an approach to (S)-*tert*-leucine based on a dynamic resolution of 2-phenyl-4-*tert*-butyloxazolin-5(4*H*)-one[1] we needed an efficient route to racemic *tert*-leucine and felt that the method of Knoop and Landmann offered the most convenient approach.[2] This route starts with the oxidation of pinacolone to trimethylpyruvic acid which is then converted to the oxime and reduced with zinc/acetic acid to racemic *tert*-leucine in 60% overall yield. Whilst a number of modifications have been made, these methods are characterised by the need for high pressure hydrogenation or the use of enviromentally unfriendly reagents.[3] We were keen to investigate other methods of reduction, in particular the Leuckart reaction,[4] a reaction which does not seem to have been well studied on α-keto acids.[5]

We were surprised to find that treatment of sodium trimethylpyruvate (**1**) with ammonium formate in formic acid at reflux gave a quick and clean conversion to *N*-pivaloyl-*tert*-leucine (**2**) in 73% yield after crystallisation (m.p. 131°C) (scheme 1) (the use of formamide gave a mixture of products). Acid hydrolysis of the pivamide (6N HCl/reflux) proceeded in high yield to complete a novel route to racemic *tert*-leucine.



Scheme 1 i) $HCO_2H/HCO_2NH_4/110°C$ ii) (S)-α–MBA; 2N HCl iii) 6N HCl/Reflux

The facile nature of this process is of note and may be accounted for by the mechanism proposed by Shive and Shive[6] as shown in scheme 2. Thus, the initially formed imine (**5**) reacts with another molecule of the ketoacid to give the intermediate (**6**) which decomposes to the product (**2**) via decarboxylation and proton transfer.



Scheme 2

As a route to racemic *tert*-leucine the main disadvantage is that half of the keto acid ends up as an unwanted protecting group. We sought to exploit this fact in a classical resolution approach to (R)- and (S)-*tert*-leucine, where such approaches typically require extra processing steps to introduce a nitrogen protecting group prior to resolution with a chiral base. An initial resolution screen quickly revealed that the *N*-pivaloyl-*tert*-leucine (**2**) was well resolved with α-methylbenzylamine (MBA). An authentic sample of (S)-*N*-pivaloyl-*tert*-leucine (m.p. 157°C) was prepared by Schotten-Baumen reaction of (S)-*tert*-leucine with pivaloyl chloride. A chiral GC assay showed that (R)-α-MBA gave the (S)-pivamide (30% yield/ 90% d.e.).[7] Resolution with (S)-α-MBA gave the (R)-salt (95% d.e.) in a 27% yield. Cracking of the salt, extraction into ethyl acetate, followed by concentration and crystallisation afforded the (R)-pivamide (**3**) (>99% e.e.) in 85% yield. This represents a 23% overall yield and the process is of note for its operational simplicity. Acid hydrolysis of (**3**) (95% e.e.) afforded (R)-*tert*-leucine hydrochloride (**4**) (93% e.e.) in quantitative yield.

In summary a novel synthesis of *tert*-leucine by way of a Leuckart type reaction has been demonstrated, avoiding the need for a high pressure hydrogenation. The key intermediate, *N*-pivaloyl-*tert*-leucine, has been shown to be well resolved with α-MBA affording a facile preparation of either (R)- or (S)-*tert*-leucine.

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References and Notes

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7. CP Cyclodextrin B, 120°C for 50 min. on methyl ester derivative; retention times (S)-isomer 44.4 min. and (R)-isomer 45.1 min.

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