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ON THE CATALYTIC AMIDOCARBONYLATION OF SUBSTITUTED ALLYLIC ALCOHOLS *

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Summary

Substituted allylic alcohols (3-methyl-2-buten-1-ol and 2-methyl-3-buten-2-ol) were isomerized and amidocarbonylated. In addition to the expected product, *N*-acetylleucine, arising from their rearrangement to 3-methylbutanal and subsequent amidocarbonylation (22% yield), we isolated two additional products (28% yield). These were shown by spectroscopic methods and by syntheses, via amidocarbonylations of the respective aldehydes, to be 2-acetamido-5-methylhexanoic acid and 2-acetamido-4-methylhexanoic acid. Their formation is postulated to be the sequential result of (i) dehydration first to form isoprene, (ii) hydroformylation and hydrogenation of isoprene to give 3-methyl-1-pentanal and 4-methyl-1-pentanal, and (iii) aldehyde amidocarbonylation. Treatment of isoprene itself under the same conditions also gave these latter two acetylamino acids.

Introduction

As a continuation of our synthetic work directed toward the preparation of stable isotope labeled amino acids [1,2] we attempted to duplicate the isomerization-amidocarbonylation of allylic alcohols catalyzed by transition metals in the presence of cobalt octacarbonyl. Our specific objective was the synthesis of *N*-acetylleucine from 3-methyl-2-buten-1-ol. This reagent was treated in dioxane with 1 eq. of acetamide, 2 mol% of $Co_2(CO)_8$, 0.2 mol% of $HRh(CO)(PPh_3)_3$, and 100 atm of 1/1 CO/H_2, then agitated in an autoclave at 120°C for 12 h as described in the recent work of Ojima et al. [3,4].

On the basis of ^1H NMR alone, the crystalline product obtained after work-up appeared to be the desired *N*-acetyl amino acid. But, in contrast to published findings [3,4], a more careful examination of this material showed instead that the reaction had produced a mixture of *N*-acetyl amino acids.

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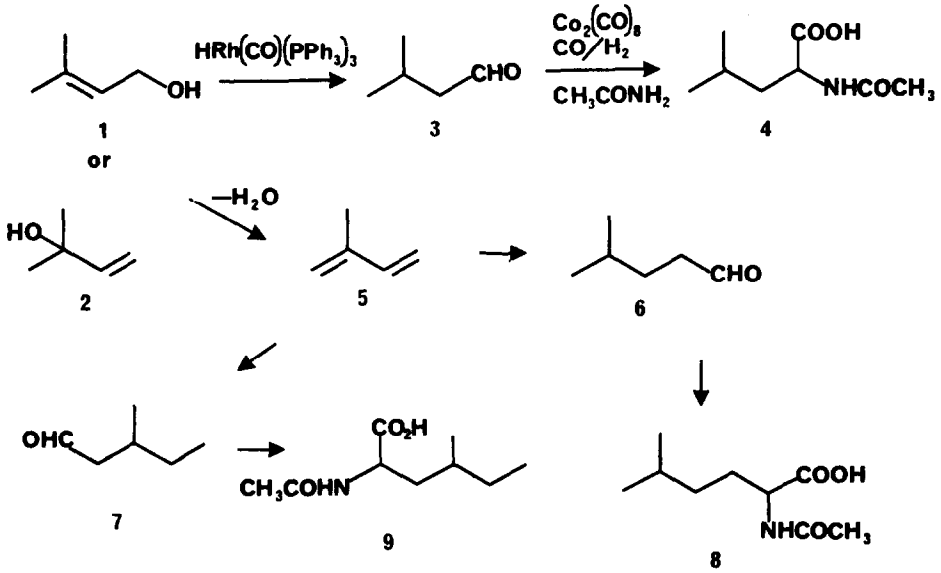
Results and discussion

After esterification of the isolated solids with diazomethane, GLC analysis on a Supelco SP-300 chiral phase column at 120°C revealed that the coupled isomerization-amidocarbonylation reaction actually yielded only 22% *N*-acetylleucine in addition to several unknown materials, inseparable by fractional crystallization and unidentifiable by proton NMR alone. GC/MS analysis [5] of these esters suggested that the major components were one CH_2-unit higher homologs of *N*-acetylleucine. A careful examination of the ^{13}C NMR spectrum of the unfractionated product mixture then permitted identification of three components, consistent with the previously obtained GC/MS fragmentograms. As shown in Scheme 1, they were *N*-acetylleucine (**4**), 2-acetamido-5-methylhexanoic acid (**8**) and 2-acetamido-4-methylhexanoic acid (**9**). The ratio of **8** and **9** was estimated to be 2/1 by ^{13}C NMR and GLC on SP-300.

These tentative structural assignments were further confirmed through synthesis: (i) 4-methyl-1-pentanol was oxidized with pyridinium chlorochromate to the aldehyde (66% yield) which was then amidocarbonylated using Wakamatsu's procedure [6] (1 eq. of acetamide, 0.1 eq. of cobaltous acetate tetrahydrate, 100 atm of 1/1 CO/H_2, ethyl acetate, and agitated at 120°C for 12 h) to give 2-acetamido-5-methylhexanoic acid (**8**) (50% yield). (ii) 3-methyl-1-pentanol was similarly oxidized and amidocarbonylated to give 2-acetamido-4-methylhexanoic acid (**9**).

The isolation of these homologs of leucine demonstrates that, under the reaction conditions of isomerization-amidocarbonylation [3,4], 3-methyl-2-buten-1-ol (**1**) not only rearranges to 3-methyl-1-butanal (**3**) but also undergoes dehydration to isoprene (**5**) which is then hydroformylated [7] and hydrogenated to give 3-methyl-1-pentanal and 4-methyl-pentanal. These aldehydes in turn were amidocarbonylated to form the *N*-acetyl amino acids **8** and **9** (Scheme 1).



SCHEME 1

Additional evidence for this postulated mechanism was obtained when 2-methyl-3-buten-2-ol (**2**) [8], an isomer of **1**, give the same mixture of products (**4**, **8** and **9**) in 47% yield upon amidocarbonylation under identical conditions to those applied on **1**. Predictably, the dehydration product of both **1** and **2**, isoprene (**5**), gave a mixture of **8** and **9** as the only products (40% yield).

The spectroscopic and gas chromatographic characteristics of compounds **4**, **8** and **9**, when independently synthesized, coincided with the predictions based on analysis of their mixture produced in situ from the allylic alcohol (**1**). Again, we observed that ^{1}H NMR spectroscopy could not differentiate unambiguously between pure **4** and its combination with **8** and **9**. The results of this study, therefore, emphasize the need for caution in documenting the outcome of coupled isomerization-amidocarbonylation [3,4] and also clarify the product distribution in previous reports on hydroformylation of **2** and **5** where the resulting aldehydes were not identified [7,8.]

It is interesting to note also that the amino acid obtained from hydrolysis of **8**, 2-amino-5-methylhexanoic acid, has not been reported as a natural product. The (2*S*, 4*S*) isomer of 2-amino-4-methylhexanoic acid (homoisoleucine) derived from **9**, by contrast, has been isolated from *Serratia marcescens* [9], from *Aesculus californica* [10,11] and characterized extensively in connection with in vitro studies [12] on the substrate specificity of L-isoleucyl-tRNA-synthetase. Judicious use of cobalt carbonylrhodium complex catalyzed amidocarbonylation of allylic alcohol or olefinic synthons may provide a rapid synthetic approach to these novel and potentially important branched-chain amino acids.

Experimental

General. Reagents were obtained from Aldrich Chemical Co., Milwaukee, WI 53233. ^{1}H and ^{13}C NMR were recorded with a IBM NR-80F NMR spectrometer. Mass spectra were recorded with a Varian MAT-44 Mass spectrometer. GC analysis were performed in a Carle AGC-111 instrument.

Amidocarbonylation

In a 150 ml stainless-steel autoclave was placed 2 g of 3-methyl-2-buten-1-ol, 1.6 g of acetamide, 0.5 g of dicobalt octacarbonyl, 50 mg of $HRh(CO)(PPh_3)_3$ plus 50 ml of 1,4-dioxane. The void space was evacuated and a 1/1 mixture of carbon monoxide/hydrogen was introduced into the autoclave to a pressure of 100 atm at 25°C. The autoclave was heated to 120°C with rocking for 16 h. The pressure rose up to 130 atm and then started to drop after 2 to 3 h. The final pressure was 120 atm at 120°C and 80 atm at 25°C. The gas was vented and the liquid content was evaporated to a syrup. This was taken up in ethyl acetate and was extracted into 10% sodium carbonate solution. The aqueous extract was acidified by hydrochloric acid and the product was extracted into ethyl acetate. Evaporation gave 2.1 g of solid (50% yield). Methyl ester of this product was analyzed by GC (2 meters sp-300 column from Supelco, Bellefonte, PA 16823) to be D,L-pairs of 22% *N*-acetylleucine methyl ester, 52% and 26% two other components. The later two compounds all showed a molecular ion of *m/z* 201, 14 units higher than that of *N*-acetylleucine methyl ester.

NMR spectra were taken in $CDCl_3$ at 80 MHz for ^1H and 20 MHz for ^{13}C with broad band decoupling. The shifts are in δ(ppm) from TMS.

4. ^1H NMR: 0.9 (d, *J* 5 Hz, $(CH_3)_2CH$), 1.5–1.9 (m, CH_2CH), 1.95 (s, CH_3CONH), 4.5 (m, α-CH), 7.2 (d, *J* 6 Hz, N*H*) and 11.0 (s, CO_2H). ^{13}C NMR: 21.1, 21.8 ($(CH_3)_2CH$), 22.2 (CH_3CONH), 24.4 ($(CH_3)_2CH$), 40.6 (CH_2), 50.4 (α-CH), 169.8 (CH_3CONH) and 173.2 (CO_2H).

8. ^1H NMR: 0.9 (d, *J* 5 Hz, $(CH_3)_2CH$), 1.2–2.1 (m, CH_2CH_2CH), 2.0 (s, CH_3CONH), 4.5 (m, α-CH) and 6.4 (bs, NH and CO_2H), ^{13}C NMR: 22.5 ($(CH_3)_2CH$), 23.0 (CH_3CONH), 27.9 ($(CH_3)_2CH$), 30.2, 34.3 (CH_2CH_2), 52.9 (α-CH), 170.9 (CH_3CONH) and 175.1 (CO_2H).

9. ^1H NMR: 0.9–1.0 (m, CH_3CH_2 and CH_3CH), 1.2–2.1 (m, CH_2CHCH_2), 2.0 (s, CH_3CONH), 4.5 (m, α-CH) and 6.1 (bs, NH and CO_2H). ^{13}C NMR (showing two sets of signals for the two diastereomeric pairs): 10.8, 11.1 (CH_3CH_2), 18.6, 19.2 (CH_3CH), 22.9 (CH_3CONH), 28.9, 29.7 (CH_3CH), 31.1 (CH_3CH_2), 39.3 ($CHCH_2CHN$), 50.9, 51.0 (α-CH), 170.5, 171.0 (CH_3CONH) and 176.0 (CO_2H).

A similar procedure was used for 2-methyl-3-buten-2-ol to yield the same kind of mixture (47% yield). When isoprene was used, only **8** and **9** were isolated (40% yield).

*2-Acetamido-5-methylhexanoic acid (**8**)*

A solution of 5 g of 4-methyl-1-pentanol in 250 ml of methylene chloride was treated with 25 g of pyridinium chloro chromate at 25°C for 4 h. The supernatant solution was filtered through 100 g of 200 mesh silica gel and then evaporated to give 3.3 g of oily aldehyde. This was placed in a 300 ml stainless steel autoclave and 2 g of acetamide, 0.1 g of cobaltous acetate tetrahydrate, 100 ml of ethyl acetate was then added. The void space was evacuated and charged up to 100 atm with a 1/1 mixture of carbon monoxide and hydrogen and heated to 120°C for 16 h with rocking. After similar work-up, we obtained 3.7 g of **8** (50% yield).

*2-Acetamido-4-methylhexanoic acid (**9**)*

Using the same procedure and starting with 3-methyl-1-pentanol, we obtained 3.7 g of **9** (50%).

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