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A facile synthesis of *N*-benzyl-4-acetylproline via a tandem cationic aza-Cope rearrangement-Mannich reaction

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Abstract—*N*-Benzyl-4-acetylproline can be prepared from *N*-(2-hydroxy-2-methyl)but-3-enyl-*N*-benzylamine and glyoxylic acid via a tandem cationic aza-Cope rearrangement-Mannich reaction. This reaction represents the first example of such a mechanism being utilised for the synthesis of functionalised proline derivatives. In addition the reaction requires only mild conditions and a good yield of amino acid product is obtained without any need for purification. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

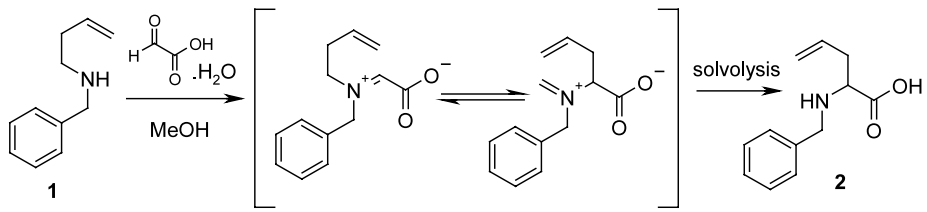
Substituted proline derivatives have been shown to exhibit interesting biological activities, e.g. α-kainic acid and domoic acid, which possess potent neuropharmacological activity.[1] A number of synthetic strategies have been utilised to synthesise substituted proline derivatives, including the cycloaddition of azomethine ylides to olefinic dipolarophiles.[2]

We had identified *N*-benzyl-4-acetylproline as a novel amino acid and interesting synthon for the preparation of pharmaceutically active analogues. We recently reported the synthesis of *N*-benzylallylglycine **2** from *N*-benzylbut-3-enylamine **1** and glyoxylic acid via the tandem aza-Cope rearrangement-iminium ion hydrolysis reaction (Scheme 1).[3] The rearrangement requires a subsequent reaction, in this case an iminium ion hydrolysis, to drive the equilibrium to the desired product.

We hypothesised that a combination of this work and the tandem cationic aza-Cope rearrangement-Mannich cyclisation pioneered by Overman et al. would yield *N*-benzyl-4-acetylproline.[4]

The tandem cationic aza-Cope rearrangement-Mannich cyclisation reaction as reported by Overman et al. proceeds by iminium ion formation of a 2-hydroxy-2-methylbut-3-enylamine **3** with an aldehyde and subsequent 3,3 cationic aza-Cope rearrangement to afford 3-acetylpyrrolidines **4** (Scheme 2). However, in this case a nucleophilic substituent is incorporated into the starting iminium ion. After the 3,3 aza-Cope rearrangement, the nucleophilic substituent is unleashed and irreversibly captures the desired rearranged iminium ion giving 3-acetylpyrrolidine products.

Despite the extensive use of tandem cationic aza-Cope rearrangements, there have been no reports published



Scheme 1. Synthesis of *N*-benzylallylglycine **2**.

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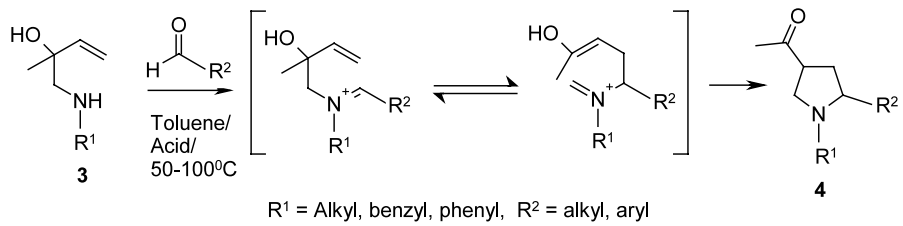


Scheme 2. Synthesis of 3-acetylpyrrolidines **4**.

utilising glyoxylic acid to yield functionalised proline derivatives.[4,5]

In this letter we wish to report the facile synthesis of the novel *N*-benzyl-4-acetylproline **6** from *N*-(2-hydroxy-2-methyl)but-3-enyl-*N*-benzylamine **5** and glyoxylic acid via a tandem cationic aza-Cope rearrangement-Mannich reaction. This method requires only mild conditions and yields pure products without the need for chromatographic techniques.

2. Synthesis

The starting *N*-(2-hydroxy-2-methyl)but-3-enyl-*N*-benzylamine **5** was prepared by heating benzylamine (41 mL, 0.375 mol) and 2-methyl-2-vinyloxirane (7.36 mL, 0.075 mol) at 80°C for 72 h. Chromatography on silica gel gave *N*-(2-hydroxy-2-methyl)but-3-enyl-*N*-benzylamine **5** (12.7 g, 89%) as a clear oil (Scheme 3).[6] *N*-Benzyl-4-acetylproline **6** was prepared by adding glyoxylic acid monohydrate (3.71 g, 0.04 mole) to a stirred solution of *N*-(2-hydroxy-2-methyl)but-3-enyl-*N*-benzylamine (6.99 g, 0.036 mole) in methanol (25 mL). The reaction mixture was stirred for 48 h and the solvent removed under reduced pressure. Addition of ethyl acetate gave a precipitate which was filtered to give *N*-benzyl-4-acetylproline **6** (5.7 g, 64%) as a white solid (Scheme 3).[7] This reaction occurs at room temperature and requires no purification which is in contrast to the work by Overman et al. which required elevated temperatures (50–100°C).[4]

A mixture of two racemic products was expected and it was observed from NMR analysis that a major diastereomer was obtained.[7] The ratio of diastereomeric products varied between 80:20 and 96:4 depending on reaction conditions (note this is a ratio of precipitated products). NOE analysis was used to determine the major and minor diastereomeric products obtained (Fig. 1).

Major isomer: An NOE correlation was observed between the acetyl CH_3 and hydrogen H^B indicating that the two groups were on the same side of the five-membered ring. Also no NOE correlation was observed between hydrogens H^A and H^B. It was therefore concluded that the major diastereomer had the acid and acetyl groups *trans* to each other.

Minor isomer: An NOE correlation was observed between hydrogens H^A and H^B indicating that these two protons were on the same side of the five-membered ring. Also, no NOE correlation was observed between the acetyl CH_3 and hydrogen H^B. It was therefore concluded that the minor diastereomer had the acid and acetyl groups *cis* to each other.

3. Conclusion

N-Benzyl-4-acetylproline **6** can be prepared from *N*-(2-hydroxy-2-methyl)but-3-enyl-*N*-benzylamine **5** and glyoxylic acid via a tandem cationic aza-Cope rearrangement-Mannich reaction. This reaction requires only mild conditions and a good yield of amino acid product is obtained without any need for purification. The scope of this method is currently being

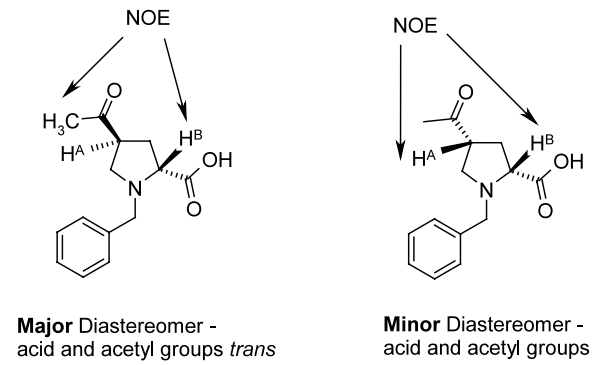
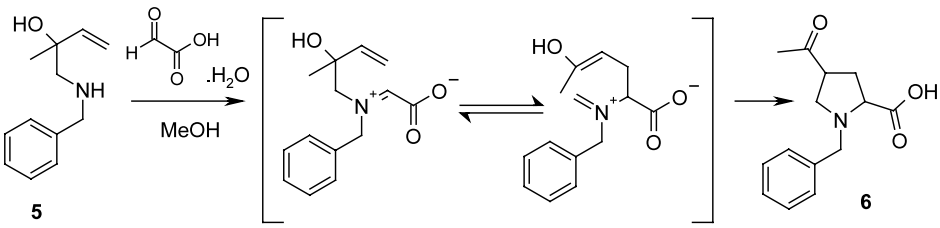


Figure 1. NOE correlations for the major and minor diastereomers.



Scheme 3. Synthesis of *N*-benzyl-4-acetylproline **6**.

extended to other functionalised and chiral hydroxyalkene-amines, and we intend to report the results of these studies in the near future.

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References

1. Johnson, R. L.; Koerner, J. F. *J. Med. Chem.* **1988**, 2057–2066.
2. (a) DeShong, P.; Kell, D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, 2309; (b) DeShong, P.; Kell, D. A. *Tetrahedron Lett.* **1986**, 3979.
3. Bennett, D. J.; Hamilton, N. M. *Tetrahedron Lett.* **2000**, *41*, 7961–7964.
4. Overman, L. E.; Kakimoto, M.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622–6629.
5. Agami, C.; Couty, F.; Lin, J.; Mikaeloff, A.; Poursoulis, M. *Tetrahedron* **1993**, *49*, 4039.
6. *N*-(2-hydroxy-2-methyl)but-3-enyl-*N*-benzylamine **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.22 (m, 5H, Ar-**H**), 5.80 (dd, $J=11$, 16 Hz, 1H, $CH_2C\mathbf{H}C$), 5.31 (d, $J=16$ Hz, 1H, $C\mathbf{H}_2CH$), 5.09 (d, $J=11$ Hz, 1H, $C\mathbf{H}_2CH$), 3.80 (s, 2H, $PhC\mathbf{H}_2N$), 2.71 (d, $J=13$ Hz, 1H, $NC\mathbf{H}_2C$), 2.51 (d, $J=13$ Hz, 1H, $NC\mathbf{H}_2C$), 1.22 (s, 3H, $C\mathbf{H}_3C$). ESI-MS $(M+H)^+$ 192.4.
7. *N*-Benzyl-4-acetylproline **6**. ^{1}H NMR (400 MHz, $CDCl_3$) major isomer (*trans*) δ 7.41–7.23 (m, 5H, Ar-**H**), 4.29 (d, $J=13$ Hz, 1H, $PhC\mathbf{H}_2N$), 3.92 (d, $J=13$ Hz, 1H, $PhC\mathbf{H}_2N$), 3.72–3.64 (m, 1H, $NC\mathbf{H}CH_2$), 3.56–3.42 (m, 1H, $NC\mathbf{H}_2CH$), 3.38–3.23 (m, 1H, $CH_2C\mathbf{H}CH_2$), 3.05 (m, 1H, $NC\mathbf{H}_2CH$), 2.58–2.3 (m, 2H, $CHC\mathbf{H}_2CH$), 2.19 (s, 3H, $C\mathbf{H}_3C$). ESI-MS $(M+H)^+$ 248.2. TOF accurate mass 248.1278.