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Ugi four component condensations using aldehydes with an asymmetric centre at C-2

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Abstract

Epimerisation of an aldehyde possessing a hydrocarbon substituent α to the carbonyl occurs in the Ugi four component condensation whereas, with either a benzyl or TBDMS ether at C-2 the stereochemical integrity is maintained. A deuterium isotope effect is observed and by carrying out the reaction in methanol–OD, deuterium can be introduced efficiently into C-3 of the condensation products. © 2000 Elsevier Science Ltd. All rights reserved.

The Ugi four component condensation reaction (4CC)[1] has been used to good effect in the synthesis of a range of organic compounds including natural products.[2] Armstrong and Keating have increased the utility of the reaction by the design of a 'convertible' isonitrile in which the resultant cyclohexenyl amide condensation product may be readily converted to a range of other functional groups.[3] In addition, Linderman and coworkers have developed an alternative easily hydrolysable isonitrile which can be applied to the asymmetric Ugi reaction.[4] Recently the application of the Ugi reaction to the synthesis of combinatorial libraries has generated much interest since the use of a multicomponent reaction is a good way of generating the diversity required for such libraries.[5]

The vast majority of examples of 4CC reactions involve the use of an aldehyde without an asymmetric centre at C-2. However, early studies by Ugi and coworkers[6] indicate that (*S*)-2-methylbutanal may be used to prepare amino acids with an asymmetric centre at C-3 such as L- and D-isoleucine. In addition, isomers of the antibiotic furanomycin have been prepared via a 4CC reaction of *trans*-aldehyde **1** which gives a 1:1 mixture of **2** and **3** in 55% overall yield (Scheme 1).[7] We now report the results of our investigations on four component condensations using aldehydes with a stereogenic centre at C-2 which have led to an efficient method for the incorporation of deuterium labels at C-3 of the adducts.

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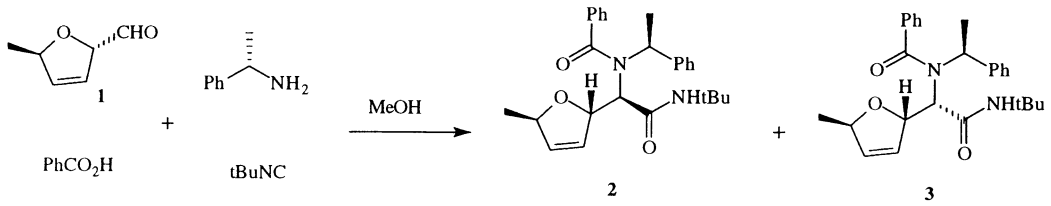
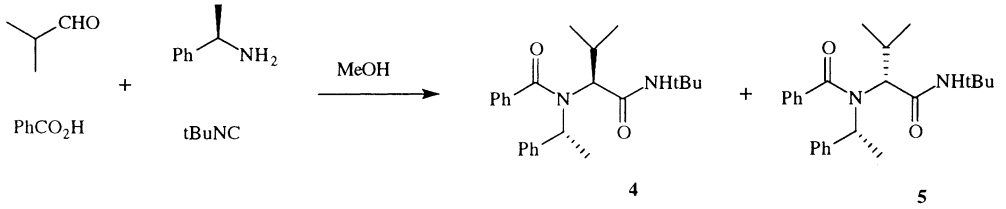


Scheme 1.

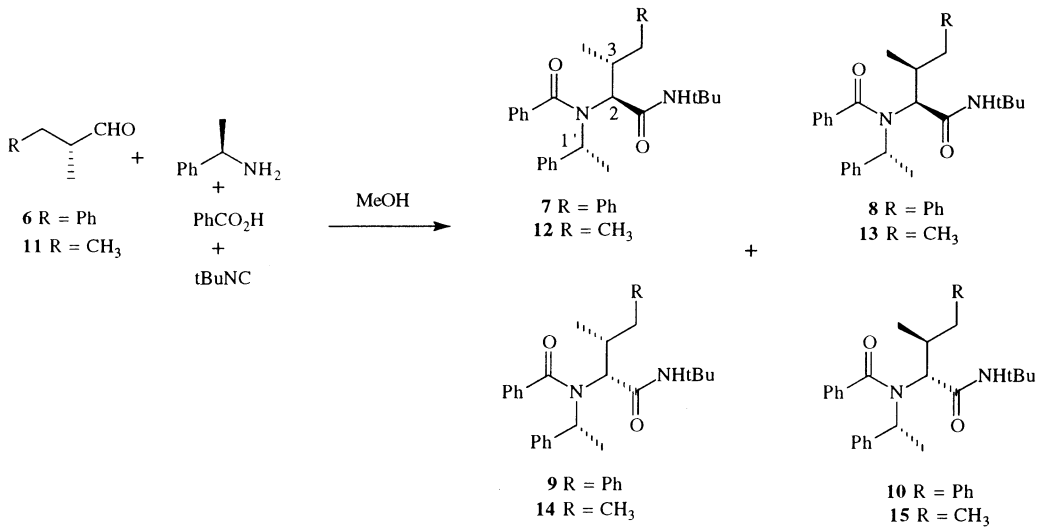
It has been shown that the stereochemical outcome of the Ugi reaction may be affected by temperature, solvent, and concentration. Consequently, in our studies, we maintained a standard set of conditions using (*R*)-α-methylbenzylamine, benzoic acid and *tert*-butyl isocyanide in methanol at room temperature and simply varied the aldehyde component. In a control experiment,[8] isobutylaldehyde gave two products which were readily separated by flash chromatography (Scheme 2). The less polar product (obtained in 28% yield) was assigned as the *R*,*S*-diastereomer **4** from its ^{1}H NMR spectrum[9] and the more polar product, isolated in 71% yield, was the *R*,*R*-diastereomer **5**. To confirm the stereochemistry at C-2, the minor product **4** was converted to L-valine by hydrogenolysis of the α-methylbenzyl group and acid catalysed hydrolysis of the amides, giving L-valine with $[\alpha]_D$+29.4 (*c* 2, 6M HCl) in good agreement with the literature value.[10]



Scheme 2.

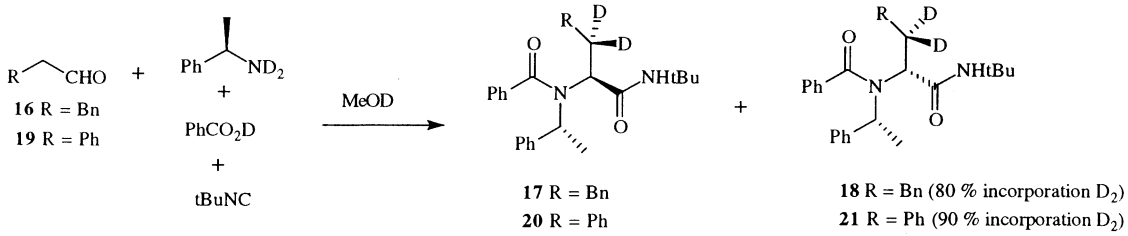
Having reproduced conditions for the four component condensation, next the fate of an asymmetric centre at C-2 of an aldehyde was investigated. (*R*)-2-Methyl-3-phenylpropanal **6** was prepared using Evans' valine derived oxazolidinone[11] and, when used in the Ugi reaction, four products were formed in 86% overall yield as shown in Scheme 3. Purification by flash chromatography gave a mixture of the (2*S*,3*R*)- and (2*S*,3*S*)-diastereomers **7** and **8** followed by the (2*R*,3*R*)- and (2*R*,3*S*)-adducts **9** and **10** which co-eluted. These pairs of diastereomers were separated by normal phase HPLC giving a ratio of ca. 2:8:5:6 of diastereomers (least to more polar).

In contrast to the results of Ugi and coworkers,[6] the formation of the four products **7**–**10** indicates that the stereochemical integrity at C-2 of the aldehyde (C-3 in the adducts) has been lost during the four component condensation. One obvious difference between the two reactions was the aldehyde: we used (*R*)-2-methyl-3-phenylpropanal **6** whereas in the earlier studies (*R*)-2-methylbutanal **11** was used as a precursor to L- and D-isoleucine. We repeated the reaction with (*R*)-2-methylbutanal and again four products were obtained in a ratio 2:8:5:6 (least polar to most polar) and in 72% overall yield (Scheme 3). Purification by flash chromatography gave a crystalline mixture of the (2*S*,3*R*)- and (2*S*,3*S*)-diastereomers **12** and **13** followed by the (2*R*,3*R*)- and (2*R*,3*S*)-adducts **14** and **15** also as a crystalline solid. These products could be further purified by normal phase HPLC.



Scheme 3.

Our results demonstrate that an aldehyde with an asymmetric centre α to the carbonyl group and hydrocarbon side-chains e.g. **6** and **11** can undergo epimerisation in the four component condensation. These observations are not too surprising as the acidic reaction conditions might be expected to induce isomerisation via either an enol or an intermediate enamine. Indeed this proposed tautomerism can be turned to our advantage to incorporate deuterium into a range of compounds for use as mass spectral internal standards. Thus (*R*)-2-methyl-3-phenylpropanal **6** was reacted with (*R*)-α-methylbenzylamine-ND_2, benzoic acid-OD and *tert*-butyl isocyanide in methanol–OD giving the four adducts **7**–**10** with >80% incorporation of deuterium at C-3. This exchange process is quite general and when the reaction was repeated using hydrocinnamaldehyde **16** or phenylacetaldehyde **19** the deuterated adducts (**17**/**18** and **20**/**21**) were isolated with a high incorporation of deuterium (Scheme 4).

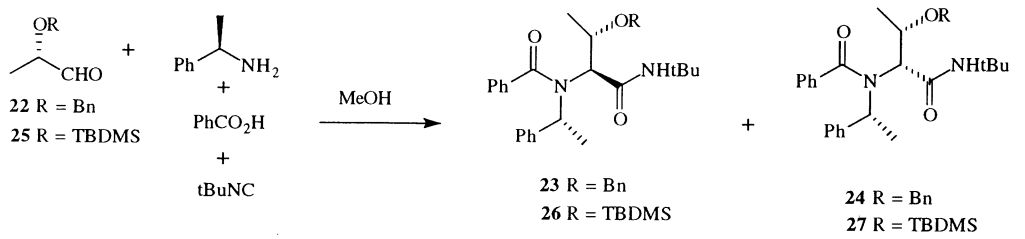


Scheme 4.

Interestingly when the reaction was repeated using a 2-deuterated aldehyde component such as [2-D]-(*R*)-2-methyl-3-phenylpropanal (with 90% incorporation of deuterium) in the presence of protio reagents and solvent, the adducts retained 50% incorporation of deuterium. The mechanism of the four component condensation is complex but this result indicates that deuterium at C-2 of the aldehyde induces a deuterium isotope effect such that enol or enamine formation is less favourable. Using [2,2-D_2]-hydrocinnamaldehyde in the 4CC reaction with protio reagents and solvent, adducts **17** and **18** were isolated, retaining >80% incorporation of deuterium at C-3, whereas in the case of [2,2-D_2]-phenyacetaldehyde in which the α-protons

(deuterons) would be more acidic, a higher degree of exchange was apparent and the products **20** and **21** retained only 30% incorporation of deuterium.

Substituents other than a hydrocarbon α to the carbonyl would also effect the acidity of the α-proton and may reduce the propensity for epimerisation at this site, and to investigate this (*S*)-2-benzyloxypropanal **22** was prepared from methyl (*S*)-lactate. Reaction of **22** with (*R*)-α-methylbenzylamine, benzoic acid and *tert*-butyl isocycanide in methanol gave a 1:2 mixture of just two products **23** and **24**, which were separated by flash chromatography (Scheme 5). Similarly, on repeating the reaction with (*S*)-*tert*butyldimethylsilyloxypropanal **25** only two products **26** and **27** were obtained confirming that no isomerisation had occurred. These results, combined with the example shown in Scheme 1, reveal that the stereochemical integrity of an α-oxygenated aldehyde is maintained during the Ugi reaction and therefore has potential for the synthesis of a range of β-hydroxy-α-amino acids such as threonine and *allo*threonine as well as 3-oxygenated unnatural amino acids.



Scheme 5.

Acknowledgements

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