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Is water a suitable medium for the Amadori rearrangement?

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Letter to the Editor

Cui et al. (2017), Cui, Duhoranimana, Karangwa, Jia, and Zhang (2018) have published a modification of the standard conditions for the synthesis of Amadori rearrangement products. They report good yields (up to 75%) of xylulose-phenylalanine when the starting materials are heated under mildly alkaline conditions in water containing some sodium sulfite. Water had previously been regarded as an unfavorable solvent since, in the second step of the reaction, a reversible dehydration takes place to form an imine (Mossine & Mawhinney, 2010).

We have made xylulose-phenylalanine following the procedure of Davidek, Kraehenbuehl, Devaud, Robert, and Blank (2005) who used methanol as solvent. Excess xylose was removed as usual with a Dowex 50 column. The ^{13}C NMR spectrum of this product showed residual phenylalanine but also resonances attributable to the four expected isomers of the product (Cui et al., 2017; Zhao et al., 2009). The least cluttered regions of the spectra are those well-removed from the sugar region. There are at least three resonances about 0.4 ppm upfield of the carboxylate resonance at δ 173.9. There are four resonances upfield of the α -carbon resonance of phenylalanine [δ 36.32] at 35.99, 35.73, 35.67, and 35.61. And there are four resonances upfield of the β -carbon resonance of phenylalanine [δ 56.00] at 52.93, 51.82, 49.37, and 48.85. The presence of xylulose-phenylalanine was confirmed by mass spectrometry.

We then examined the report of Cui et al. (2018) under a number of the published conditions, varying the time of heating at 90°C and the pH but always including sulfite. Neither ^1H nor ^{13}C NMR showed the presence of xylulose-phenylalanine. Examination of these samples by mass spectrometry, a much more sensitive technique, shows that xylulose-phenylalanine is indeed formed under Cui's conditions. We confirm that the yields are greater at pH 8 than at pH 6.5. The fact that we cannot detect the product in our NMR scans means that the yields are, at best, no greater than a few percent. The procedure of Cui et al. (2017, 2018) has two stages: in the first, the reaction is carried out at 90°C in water; in the second, the water is removed on a rotary evaporator at 45°C. We looked at these stages separately. Heating in water at 90°C, pH 8, for 30, 60 and 90 min. gave increasingly dark reaction mixtures. When these were examined by mass spectrometry, no trace of xylulose-phenylalanine could be found. ^{13}C NMR likewise showed many new resonances but none attributable to xylulose-phenylalanine. However, when xylose and phenylalanine were dissolved in water, pH 8, and taken to dryness on a rotary evaporator [45°C, 30 min.] there resulted a white solid which mass spectrometry showed to contain xylulose-phenylalanine.

We conclude that the formation of the desired product does not take place in the first stage but only in the second upon removal of much of the water. The yield will clearly be dependent on the time and temperature of the second stage in which water is removed. However, we note that water has been used successfully for the synthesis of xylulose-glycine (Davidek et al., 2005; Hodge & Fisher, 1963). Xylulose-glycine may be an exception as Davidek et al. (2005) did not use water for the synthesis of sixteen other Amadori compounds. An important factor may be the equilibrium constant for imine formation (Hine & Yeh, 1967). Mass spectrometry showed no Amadori product from glucose-6-phosphate and asparagine under Cui's conditions.

The observation that Amadori products are formed when the starting materials are first dissolved in a minimum amount of water and then reaction takes place by heating the syrup is not new (Weygand, 1940; Anet & Reynolds, 1957). Amadori himself heated the starting materials in the absence of solvent (Amadori, 1931). For a review, see Hodge (1955).

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