



Revisiting Amadori and Heyns synthesis: Critical percentage of acyclic form play the trick in addition to catalyst



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ABSTRACT

Amadori and Heyns reaction are landmark reactions of carbohydrate chemistry. Synthesis of simple Amadori and Heyns compounds are complicated by various factors and require tedious column chromatographic or ion chromatographic separations. Herein, we report an improved catalytic method based on classical synthetic method of Amadori and Heyns compounds in light of new understanding of a factor governing the reaction. By utilizing the improved catalytic method, we have accomplished several Amadori compounds of D-tagatose and also numerous other Amadori and Heyns compounds.

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Amadori rearrangement is a cornerstone reaction of carbohydrates that has received meagre interest from mainstream organic chemists [1,2]. It has attracted the major attention from food scientists and biochemists from the perspective of Maillard reaction related to flavours and glycation respectively [3,4]. Amadori reaction allows formation of 1-aminodeoxyketose from aldose and amine/amino acid whereas, Heyns reaction results in the formation of 2-aminodeoxyaldoses from the ketose and amine/amino acid without requirement of protection and deprotection steps [1]. Amadori and Heyns reaction forms the first step of complex Maillard reaction and they are stable intermediates. The classical synthetic method for accomplishing Amadori and Heyns compounds derived from amino acids employ methanol as a solvent with acetic acid as a catalyst and pH regulator and necessitates purification by either column or ion exchange chromatographic techniques [5]. Recently, Lewis acid $ZnCl_2$ has been demonstrated as catalyst for the synthesis of Amadori/Heyns compounds [6–8]. However, it works only in aprotic solvent combination of pyridine and acetic acid and also requires substantial time for completion. We were intrigued by lack of catalytic protocols in polar solvents including methanol-acetic acid for these compounds and also driven by curiosity to understand the factors hindering development of catalytic version of classical synthetic reaction in protic

solvents. Towards this step, we looked carefully in the literature pertaining to mechanism of these rearrangement reactions for critical factors. The Amadori and Heyns reaction has the first step, formation of Schiff base. Subsequently, Schiff base undergoes rearrangement because of presence of α -hydroxy group (probably driven by pH) wherein imine to keto-enol transformation occurs. Further, it has been shown previously that Zn^{2+} drives the rearrangement via formation of complex with Schiff base [6–8]. Keeping this fact, We hypothesized that formation of Schiff base could be having some hindrance which subsequently results in moderate conversion to Amadori/Heyns product that necessitate employment of separation techniques. We further, hypothesized that formation of Schiff base is dictated by the acyclic ratio of the reducing sugar and that is the bottleneck controlling fate of rearrangement reaction leading to only moderate conversion. This hypothesis has some grounds supported by previous observations that reducing sugars consisting of hexoses or ketoses occur as ring structures and only tiny fraction or trace amount occur as acyclic structures and acyclic form is the most reactive form [5,9].

To validate our hypothesis, we carried out reaction of D-glucose with L-valine in MeOH-AcOH combination in presence of $ZnBr_2$. This resulted in majority of the Amadori product N-(1-deoxy-fructos-1-yl)-L-valine but still some starting material was remaining. Then, we did reaction of D-mannose with L-valine under similar conditions and found that, the desired compound N-(1-deoxy-fructos-1-yl)-L-valine had indeed formed and no starting material was

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Table 1
Percentage of acyclic forms of reducing sugars.

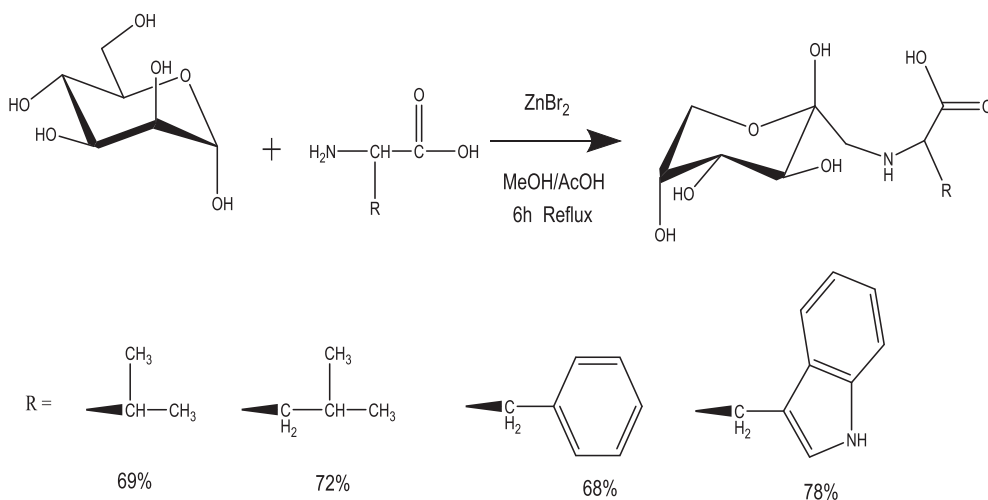
Reducing sugar	Percentage of acyclic form
D-glucose	0.01 [*]
D-mannose	0.026 [*]
D-galactose	0.052 [*]
D-fructose	0.5 [#]
D-xylose	0.075 ⁺

^{*} Ref. [10], # Ref. [11], + Ref. [12].

left behind. The acyclic form of D-mannose occur nearly threefold higher than D-glucose (Table 1).

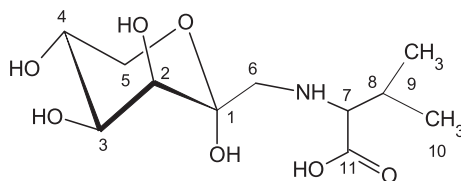
We reasoned that, D-mannose with acyclic form of 0.026% compared to only 0.01% of glucose was driving force for the formation of Schiff base and further with assistance from the Lewis acid catalyst ZnBr₂ lead to the accomplishment of the pure Amadori compound. Enlightened by this new observation, we switched to

D-galactose which has about 0.052% of acyclic form. From the earlier experiments, we anticipated neat reaction and the story turned out to as expected. We observed fast reaction and the reaction time was only about 6 h (Scheme 1). We then set out for the optimization of zinc based Lewis acid catalyst to figure out effect of changing anions of zinc salts on the Amadori synthesis. We expected that in the solvent mixture of MeOH-AcOH, which is relatively polar environment, ZnBr₂ would undergo dissociation to Zn²⁺ and Br⁻ and the catalytic activity is due to solvated Zn²⁺. We expected that reaction may work irrespective of nature of anion. The primary trouble is solubility issues of reaction associated with the presence of different anions which alter the catalytic reaction due to non-availability of catalyst. In this context, we screened several zinc salts as shown in the Table 2, and to our surprise, we found that Zn(OAc)₂ was the best catalyst. We believe that Zn(OAc)₂ with acetate anion is the best choice as solvent mixture has also acetic acid due to this the solubility of Zn(OAc)₂ is much better than other catalyst including ZnBr₂, ZnCl₂ or Zn(OTf)₂. Utilizing Zn(OAc)₂, we accomplished twelve tagatose derivatives



Scheme 1. Amadori compounds derived from D-Mannose.

Table 2
Optimization of catalyst.



Catalyst		Product yield (%)	
ZnBr ₂	Entry		
	Mol%		
	4.44	85	
	0.84	80	
ZnCl ₂	0.44	80	
	0.73	83	
	Zn(OTf) ₂	0.27	80
		5.45	85
Zn(OAc) ₂	2.72	86	
	1.63	84	
	0.81	86	
	0.54	85	

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