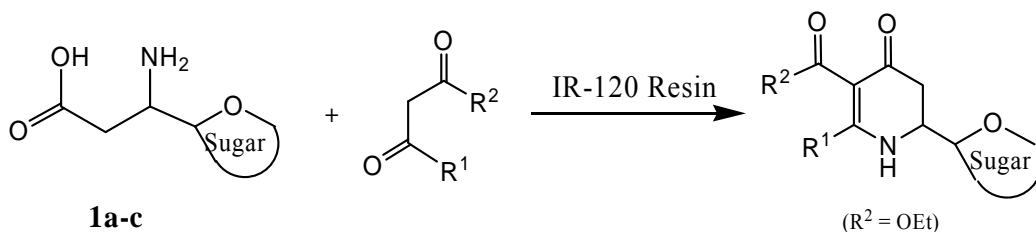


One pot Amberlite IR-120 Catalysed Synthesis of Glycosyl Dihydropyridones#

Vinod K. Tiwari,^{1Ψ} Neetu Tewari,¹ Diksha Katiyar¹ and Rama P. Tripathi^{1*}

¹Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow-226001, INDIA

Abstract: One pot reaction of β-glycosyl amino acids with β-ketoesters in the presence of IR-120 resin and 4Å molecular sieve in refluxing toluene resulted in respective dihydropyridones in fair to good yields.



Key words: β-glycosyl β-amino acid, dihydropyridones, C-Nucleosides, Amberlite IR 120 resin.

Dihydropyridones are useful and interesting building blocks for the synthesis of a large number of heterocyclic compounds of great biological significance.¹⁻² Because of their aminoenone moiety, these can be used in nucleophilic addition (both 1,2 and 1,4 addition), electrophilic substitution and enolate alkylation reactions.³ Earlier reported methods for the synthesis of dihydropyridones till date include the use of organometallics and 1-acyl salts of 4-methoxy pyridine,⁴ conversion of β-aryl-β-amino acids to dihydropyridones,^{5,6} Hetero Diels-Alder reaction of aromatic imines in presence of a chiral catalyst⁷ and a very recent report⁸ of multi step conversion of aryl amino acids into 2,3-dihydropyridones. In continuation of our work on development of biologically active compounds from sugars,⁹ we have also been reported¹⁰ a two-step process, for the synthesis of glycosyl dihydropyridones, which involves Amberlite IR-120 catalysed synthesis of glycosyl enamines followed by NaH mediated cyclisation.

*Corresponding address: E-mail: rpt_56@yahoo.com, Fax No: (0522) 2223938, 2223405.

CDRI communication No. 6470

^{1Ψ} Present address: Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi-221005, India.

Earlier methods for the synthesis of dihydropyridones suffer many drawbacks. In our reported method NaH mediated cyclisation sometimes possess difficulty in isolating the products and the yields of dihydropyridones are also not encouraging. This has led to search an alternative method for their synthesis. We thought if glycosyl amino acids instead of esters are used the resulting enamine having carboxyl substituent would lead to acid catalysed carbocation which would be attacked by electron rich β -carbon of enamine to give dihydropyridone.

Thus condensation of β -glycosyl- β -amino acid **1**^{9e} with ethyl acetoacetate in presence of IR-120 resin and 4Å MS in refluxing toluene resulted in the formation of a mixture of three products over a long reaction period. The products were isolated by column chromatography and were characterized as glycosyl-2, 3-dihydro pyridones **2** and **3** with 5-carbethoxy- and 5-carboxy substituents respectively and a dibasic acid **4**. Since application of phase transfer catalyst (PTC) is known to enhance the rate of such reactions and whence it prompted us to see its effect on the progress of reaction. Thus addition of tetrabutyl ammonium bromide (TBAB) to the above reaction led to reduce the time period to 2 hours and better yields of cyclised dihydropyridones were observed. The same reaction of the above glycosyl amino acid **1** with ethyl butyryl acetate resulted in the formation of three products, the cyclized dihydropyridones with 5-carbethoxy **2**, 5-carboxy substituent **3** and dibasic acid **4**. However, the reaction of glycosyl amino acid **1** and acetyl acetone after several hours of refluxing in toluene with or without TBAB resulted only in the uncyclised enamino monobasic acid **5**, similar to our earlier observation.⁹ Similarly reaction of glycosyl amino acids **6**^{9e} and **7**¹¹ with ethyl acetoacetate and ethyl butyryl acetate in refluxing toluene in presence of molecular sieve resulted in the formation of cyclized dihydropyridones **2** and **3** with carbethoxy and carboxy substituents¹¹ and dibasic acid **4**. Compounds **6** and **7** on similar reaction with acetyl acetone here too gave only uncyclised monobasic acids **5**.

Please insert Scheme 1.

To the best of our knowledge this is the first report of IR-120 resin catalysed synthesis of glycosyl dihydropyridones. The method is very simple as it requires only filtration and evaporation of solvent followed by purification by column chromatography.

Please insert Figure 1.

The mechanism proposed for the above condensation reaction involves protonation of the β -keto oxygen and then nucleophilic attack by the amino functionality of β -glycosyl β -amine acids to the same β -keto carbonyl carbon resulting in a tetrahedral intermediate (**III**). The latter may undergoes dehydration yield to formation of β -glycosyl enamine that on further protonation at acid functionality (**IV**) followed by intramolecular nucleophilic attack by the carbanion, to the electrophilic carbonyl carbon species ($+C=O$) and subsequent removal of proton would result in formation of the glycosyl dihydropyridones (**VII**). Their corresponding acids (**IX**) may be results of IR-120 resin catalysed subsequent hydrolysis of **VII** *ie* the removal of C_2H_5OH from that of glycosyl dihydropyridones (**VII**) as shown in *Figure 1*.

Please insert Table 1.

In conclusion we have developed a new, simple and economical method for the synthesis of glycosyl dihydropyridones, which may serve as scaffolds for the stereoselective synthesis of diverse class of compounds of biological significance. The method may be extended to other β - amino acids too.

Acknowledgements

The authors thank the Director of CDRI for his encouragement and ICMR, New Delhi for financial support. Support from Dr. R C Mishra is also acknowledged. We thank RSIC, CDRI staff for spectral data and microanalysis.

References and notes

1. (a) Chen, C; Mc Donald, I.A.; Munoz, B. *Tetrahedron Lett.* **1998**, *39*, 217-220.(b) Coutts, R. T.; Scott, J. R. *Can. J. Pharm. Sci.* **1971**, *6*, 78-85; (c) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 22-243; (d) Yamaguchi, R.; Hata, E.; Matsuki, T.; Kawanisi, M. *J. Org. Chem.* **1987**, *52*, 2094-2096.
2. (a) Grenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277-294. (b) Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445-7447. (c) Rault, S.; Renault, O.; Guillon, J.; Dallemagne, P.; Pfeiffer, B.; Lestage, P.; Lebrun, M.C. EP Patent 1,050,530, **2000**.
3. Cook, A. G. *Enamines*, Marcel Dekker: New York, **1969**.
4. (a) Comins, D. L.; Killpack, M. O.; *J. Am. Chem. Soc.* **1992**, *114*, 10972-10974. (b) Comins, D. L.; Joseph, S.P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719-5.
5. (a) Renault, O.; Guillon, J.; Dallemagne, P.; Rault, S.; *Tetrahedron Lett.* **2000**, *41*, 681-683. (b) Leflemme, N.; Dallemagne, P.; Rault, S. *Tetrahedron Lett.* **2001**, *42*, 8997-8999.
6. Leflemme, N.; Dallemagne, P.; Rault, S. *Synthesis*, **2002**, 1740 and references cited therein.
7. (a) Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 3309-3311. (b) Waldmann, H. *Synthesis* **1994**, 535-551. (c) Badorrey, R.; Cativiela, F.C.; Diaz-de-villegas, M.D.; Galvez, J.A. *Tetrahedron* **2002**, *58*, 341-354.
8. Kumar, A.S.; Haritha, B.; Rao, B.V.; *Tetrahedron Lett.*, **2003**, *44*, 4261-4263.

9. (a) Khan, A. R.; Tripathi, R. P.; Tiwari, V. K.; Mishra, R. C.; Reddy, V. J. M.; Saxena; J. K. *J. Carb. Chem.* **2002**, *21*, 591-604. (b) Tripathi, R. P.; Tripathi, R.; Tiwari, V. K.; Bala, L.; Sinha, S.; Srivastava, A.; Srivastava, R.; Srivastava, B. S. *Eur. J. Med. Chem*, **2002**, *37*, 773-781. (c) Tripathi, R. P.; Rastogi, S. K.; Kundu, B.; Saxena, J. K.; Reddy, V. J. M.; Srivastava, S.; Chandra, S.; Bhaduri, A. P. *Comb. Chem. Highthroughput Screen.* **2001**, *4*, 237-244 (d) Tewari N.; Mishra, R. C.; Tiwari, V. K.; Tripathi R. P. *SYNLETT*, **2002**, 1779-1781. (e) Mishra, R. C.; Tewari, N.; Arora, K.; Ahmad, R.; Tripathi, R. P.; Tiwari, V. K.; Walter R. D.; Srivastava, A. K.; *Combi Chem & Highthroughput Screening*, **2003**, *6*, 37-50.(f) Mishra, R.C.; Tripathi, R.; Katiyar, D.; Tewari, N.; Singh, D.; Tripathi, R. P. *Bioorg. & Med. Chem.* **2003**, *11*, 5363-5374. (g) N Dwivedi, R C Mishra, R P Tripathi, *Lett. Org. Chem.* **2005**, *2*(5), 450-457.
10. Tewari, N.; Katiyar, D.; Tiwari, V. K.; Tripathi, R. P. *Tetrahedron Lett.* **2003**, *44*, 6639-6642.
11. **General procedure for the synthesis of compounds:** A mixture of β -glycosyl- β -amino acid (**1**, 1.0 gm, 2.96 mmol), ethylacetoacetate (0.46 ml, 2.96 mmol) and amberlite IR-120 resin (0.50 gm) in presence and 4Å MS in anhydrous toluene (20 ml) fitted with Dean- Stark apparatus to remove water formed during reaction, was refluxed under magnetic stirring for 3h. The resin and 4Å MS were filtered and solvent was evaporated. The residue obtained was chromatographed over SiO₂ column using a gradient of chloroform: methanol (98:2) to give compound **2** as colourless oil. Application of TBAB as phase transfer catalyst led to shorter duration of reaction.
12. **Physical data of selected compounds: Entry 4 (2):** Colourless oil, FAB MS: m/z = 432 [M+H]⁺; IR (KBr): ν_{\max} cm⁻¹ 3414, 1720, 1640 and 1540; ¹H NMR (200 MHz, CDCl₃): δ 7.32 (m, 5H, Ar-H), 5.95 (d, J = 3.6 Hz, 1H, H-1'), 5.89 (s, 1H, NH), 4.68 (m, 2H, H-2', OCH_APh), 4.48 (d, J = 11.4 Hz, 1H, OCH_BPh), 4.26 (q, J = 7.4 Hz, 2H, OCH₂CH₃), 4.12 (m, 2H, H-4' and H-6), 3.97 (d, J = 3.1 Hz, 1H, H-3'), 2.38 (m, 2H, H-5), 2.22 (s, 3H, C=CCH₃), 1.50, 1.33 (s, 6H, C(CH₃)₂), 1.28 (t, J = 7.1 Hz, 3H,

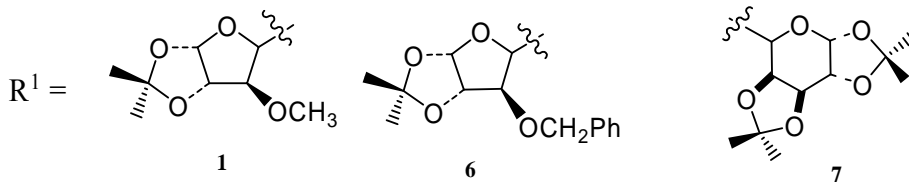
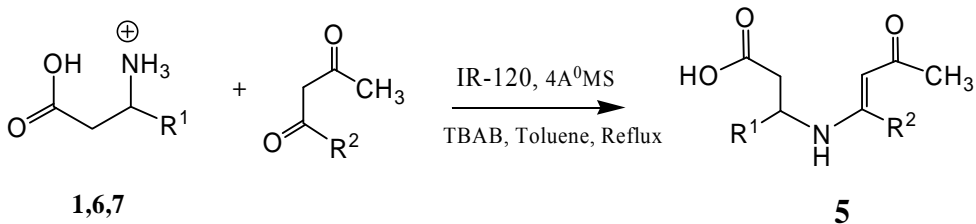
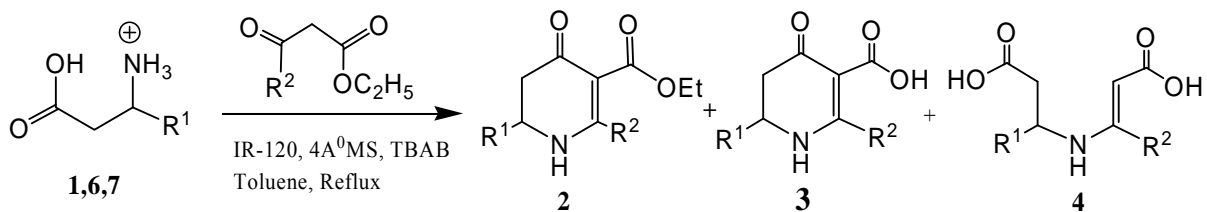
OCH₂CH₃); ¹³C NMR (50 MHz, CDCl₃): δ 187.1 (COCH₂), 167.0 (COOC₂H₅), 165.7 (NC=C), 136.6 (Ar-C), 129.1, 128.9, 128.3 (Ar-CH), 112.6 [$>C(CH_3)_2$], 105.3 (NC=C), 104.2 (C-1'), 82.2 (C-2'), 81.7 (C-4'), 81.0 (C-3'), 72.6 (OCH₂Ph), 60.5 (OCH₂CH₃), 51.6 (C-6), 38.3 (C-5), 27.1 and 26.5 [2 x $>C(CH_3)_2$], 14.7 (OCH₂CH₃).

Entry 5 (3): Colourless oil, FAB MS: $m/z = 432 [M+H]^+$, IR (KBr): $\nu_{\max} \text{ cm}^{-1}$ 3405, 1724 and 1660. ¹H NMR (200 MHz, CDCl₃): δ 7.31 (m, 5H, Ar-H), 5.96 (d, $J = 3.6$ Hz, 1H, H-1'), 4.67 (m, 2H, H-2', OCH_APh), 4.47 (d, $J = 11.4$ Hz, 1H, OCH_BPh), 4.07 (m, 1H, H-4'), 3.95 (d, $J = 3.0$ Hz, 1H, H-3'), 3.20 (m, 1H, H-6), 2.39 (m, 4H, H-5, and CH₂CH₂CH₃), 1.56 (m, 2H, CH₂CH₂CH₃), 1.47 and 1.31 [each s, 6H, $>C(CH_3)_2$], 0.87 (t, $J = 7.3$ Hz, 3H, CH₂CH₂CH₃); ¹³C NMR (50 MHz, CDCl₃): δ 206.3 (COCH₂), 174.4 (COOH), 166.1 (NC=C), 136.8 (Ar-C), 128.5, 128.0 (Ar-CH), 112.3 [$>C(CH_3)_2$], 109.9 (NC=C), 104.8 (C-1'), 81.9 (C-2'), 79.4 (C-4'), 77.4 (C-3'), 71.7 (OCH₂Ph), 48.7 (CH₂CH₂CH₃), 45.61 (C-6), 45.2 (C-5), 26.7 and 26.2 [2 x $>C(CH_3)_2$], 16.6 (CH₂CH₂CH₃), 13.4 (CH₂CH₂CH₃).

Entry 8 (3): Colourless oil, FAB MS: $m/z = 394 [M-17]^+$; IR (KBr): $\nu_{\max} \text{ cm}^{-1}$ 3345, 1719 and 1637. ¹H NMR (200 MHz, CDCl₃): δ 5.54 and 5.50 (each d, $J = 3.0$ Hz, 1H, diastereomeric H-1'), 4.61 and 4.58 (dd, $J = 7.6$ & 1.7 Hz, 1H, H-3'), 4.38 (m, 3H, H-2', H-4' and H-5'), 4.09 (m, 1H, H-6), 2.80 (m, 2H, H-5), 2.52 (t, $J = 7.4$ Hz, CH₂CH₂CH₃), 1.60 (m, 2H, CH₂CH₂CH₃), 1.50 and 1.43 [each s, 6H, $>C(CH_3)_2$], 1.31 [s, 6H, [$>C(CH_3)_2$], 0.91 (t, $J = 7.4$ Hz, 3H, CH₂CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 206.1, 205.8 (diastereomeric COCH₂), 175.1, 174.6 (NC=C), 166.1, 165.9 (COOH), 109.3 and 108.7 (C(CH₃)₂), 96.3 (C-1' and NC=C), 71.6 (C-3'), 71.0 (C-2'), 70.8 (C-4'), 66.9 (C-5'), 49.8 (CH₂CH₂CH₃), 47.5 (C-6), 35.2 (C-5), 25.9, 25.0 and 24.2 [2 x $>C(CH_3)_2$], 16.8 (CH₂CH₂CH₃), 13.5 (CH₂CH₂CH₃).

| Entry | Substrates | | Products % yield (% Conversion) | | | | |
|-------|----------------|---|---------------------------------|--------|--------|----|----------|
| | R ¹ | R ² | 2 | 3 | 4 | 5 | Time (h) |
| 1 | 1 | CH ₃ | 15(70) | 15(70) | 70(70) | - | 3 |
| 2 | 1 | <i>n</i> -C ₃ H ₇ | 20(80) | 20(80) | 60(80) | - | 2.5 |
| 3 | 1 | CH ₃ | - | - | - | 80 | 2 |
| 4 | 6 | CH ₃ | 20(75) | 20(75) | 60(75) | - | 3 |
| 5 | 6 | <i>n</i> -C ₃ H ₇ | 25(80) | 20(80) | 55(80) | - | 2.5 |
| 6 | 6 | CH ₃ | - | - | - | 85 | 2 |
| 7 | 7 | CH ₃ | - | 20(70) | 80(70) | - | 3 |
| 8 | 7 | <i>n</i> -C ₃ H ₇ | - | 25(80) | 75(80) | - | 2.5 |
| 9 | 7 | CH ₃ | - | - | - | 85 | 2 |

Table 1: Dihydropyridones 2, 3 and respectively as shown in Scheme



Scheme 1: Synthesis of Glycosyl Dihydropyridones

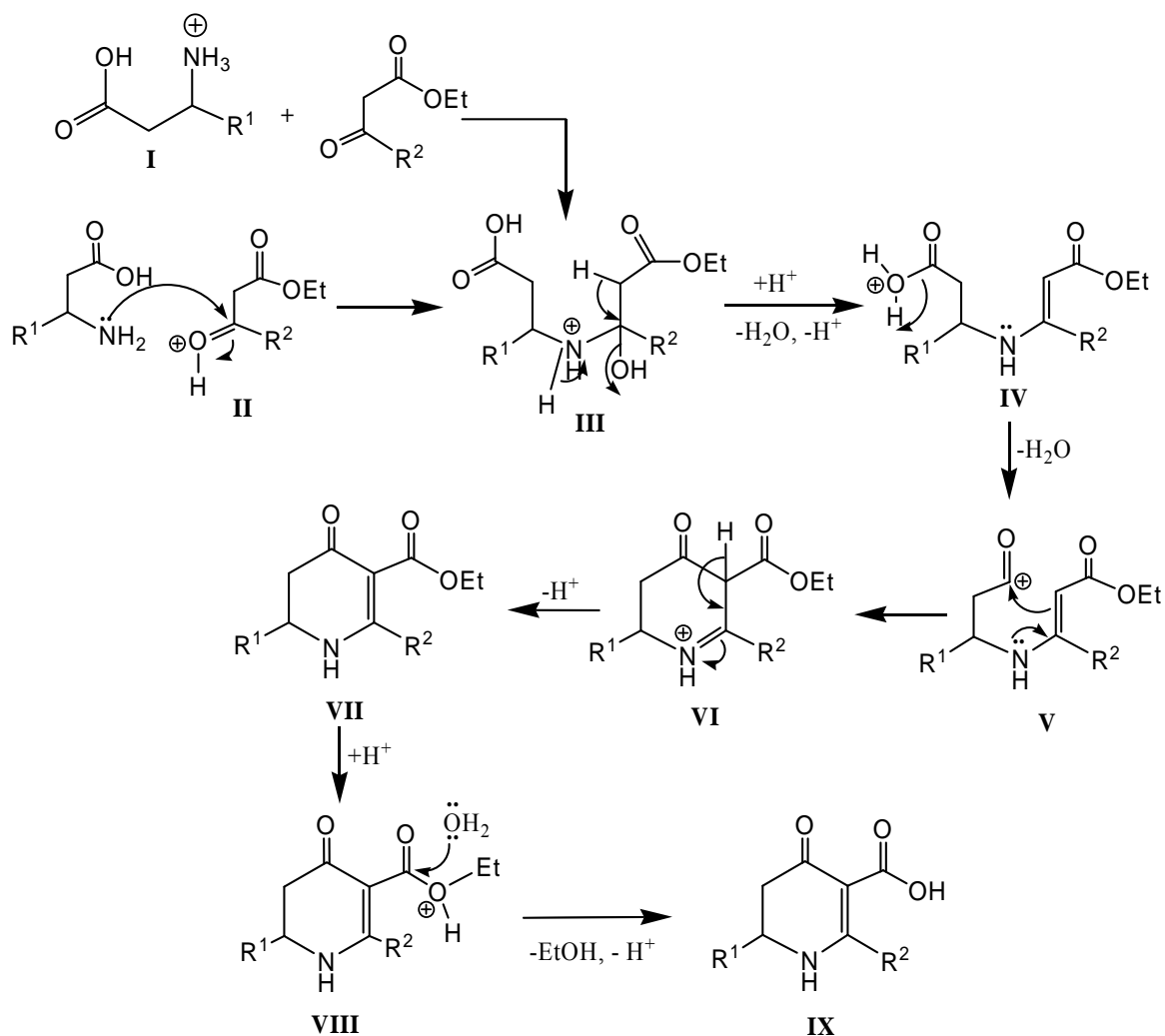


Figure 1: Proposed reaction mechanism