

L-Ascorbic acid in organic synthesis: A facile synthesis of 4-(butenolide-5-methylidenyl)-1, 4-dihydropyridines[#]

Surendra S. Bisht, Namrata Dwivedi and Rama P. Tripathi*

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow-226001, India

Abstract

An efficient synthesis of 4-(butenolide-5-methylidenyl)-1,4-dihydropyridines has been achieved via a three-component reaction of β -keto esters or ketones, ammonium acetate and vinylic aldehydes from ascorbic acid in the presence of tetrabutylammonium hydrogen sulphate in ethylene glycol.

Keywords: L-Ascorbic acid; 1,4-Dihydropyridines; 4-(Butenolid-5-methylidenyl)-1, 4-dihydropyridines; Tetrabutylammonium hydrogen sulfate; Ammonium acetate.

Since the first report of the Hantzsch synthesis of 1,4-dihydropyridines, a number of strategies have been developed for their synthesis^{1,2} due to their important biochemistry and biological activities. The prominent biological activities associated with 1,4-dihydropyridines are as Ca^{++} channel blockers and as drugs for the treatment of cardiovascular diseases and hypertension.³ The dihydropyridine skeleton is common in many vasodilator, bronchodilator, anti-atherosclerotic, antitumor, hepatoprotective and anti-diabetic agents.^{4,5} They are also known as neuroprotectants, as anti-platelet treatment of aggregators and are important in Alzheimer's disease as antiischemic agents.⁶ Interest in 1,4-dihydropyridines also relates to nicotinamide dinucleotide (NADH), a co-enzyme, and its unique ability to reduce many functional groups in biological systems. Although

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*Correspondence Email: rpt_56@yahoo.com, Fax No.0522-2623405

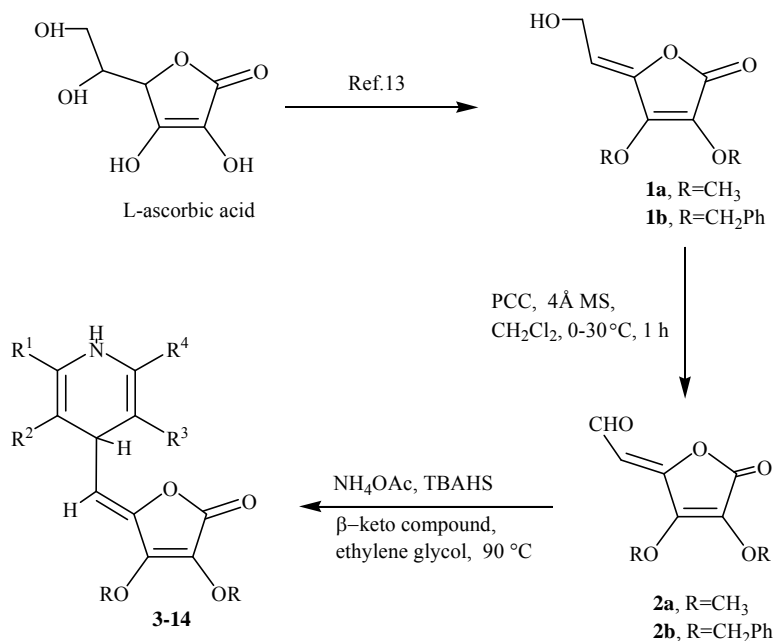
1,4-dihydropyridines with various aromatic, heteroaromatic, aliphatic and sugar substituents at C-4 have been reported,^{1, 7, 8} there is no report of 1,4-dihydropyridines

bearing a (5-ethylidene tetranolactonyl) substituent at C-4. In continuation of our studies towards the development of new anti-tuberculosis agents⁸ from sugars and prompted by reports on the wide range of biological activities, particularly antimicrobial (antitubercular), in butenolides^{9,10} as well as drug resistance reversal¹¹ and anti-tubercular activity¹² in dihydropyridines, we investigated the synthesis of butenolide derivatives of 1,4-dihydropyridines. To the best of our knowledge there is no report where an aldehyde (butenolidyl aldehyde) possessing a number of potentially reactive functional groups has been used as a substrate in the Hantzsch synthesis.

To start, we prepared the butenolidyl aldehydes (**2a** and **2b**) by oxidation of allyl alcohols (**1a** and **1b**),¹³ obtained from L-ascorbic acid, with pyridinium chlorochromate (PCC) in anhydrous dichloromethane. Reaction of (3,4-dimethoxy-5-oxo-5*H*-furan-2-ylidene)acetaldehyde **2a** with acetyl acetone in the presence of ammonium acetate and tetrabutylammonium hydrogensulphate (TBAHS) in ethylene glycol as per our earlier method^{2d} gave 4-(butenolid-5-methylidenyl)-1,4-dihydropyridine **3** in good yield along with several unisolated minor products as observed on TLC after work-up of the reaction. The structure of compound **3** was established on the basis of spectroscopic data and elemental analysis. The MS data and NMR spectra (¹H and ¹³C) were consistent with the structure **3**. In the ¹H NMR spectrum of **3** H-4 appeared as a doublet at δ 4.90 having a *J* value of 10.3 Hz while the olefinic proton of the ethylidene moiety appeared as a doublet at δ 5.12 with a *J* value of 10.4 Hz. The six protons corresponding to the two methoxy groups in the tetranolactone moiety appeared as two singlets at δ 4.10 and δ 3.91 and two singlets at δ 2.32 and δ 2.29 (each six protons) accounted for the six acetyl and six methyl group protons. The exchangeable NH appeared as a broad singlet at δ 5.90.

In the ¹³C NMR spectrum of **3** the two acetyl carbonyls of the dihydropyridine ring appeared at δ 196.4 and the lactone carbonyl carbon occurred at δ 164.5, while C-4 and the olefinic carbon appeared at δ 108.6 and δ 110.0, respectively. It was interesting to note that functionalities other than aldehyde present in the butenolidyl aldehyde were unaffected during the reaction. Similarly reaction of **2a** with other β -keto compounds including methyl acetoacetate, ethyl acetoacetate, ethyl butyrylacetate and cyclohexanone gave the corresponding dihydropyridines in moderate to good yields (Table 1).

In order to determine the steric effects of substituents on the tetranolactone moiety the reaction of (3,4-di-*O*-benzyl-5-oxo-5*H*-furan-2-ylidene)-acetaldehyde **2b** with β -keto compounds and ammonium acetate under the above mentioned reaction conditions afforded the respective products in similar yields (Table 1) indicating that the change in substituent on the tetranolactone moiety did not affect the rate of reaction.



Scheme 1: Synthesis of 4-(butenolide-5-methylidenyl)-1,4-dihydropyridines

Table 1: Synthesis of 4-(butenolide-5-methylidenyl)-1,4-dihydropyridines **3-14**.

Product	R	R ¹	R ²	R ³	R ⁴	Time (h)	% yield ^a
3	CH ₃	CH ₃	COCH ₃	COCH ₃	CH ₃	1.0	70
4	CH ₃	CH ₃	COOCH ₃	COOCH ₃	CH ₃	1.5	60
5	CH ₃	CH ₂ CH ₂ CH ₃	COOC ₂ H ₅	COOC ₂ H ₅	CH ₂ CH ₂ CH ₃	2.0	60
6	CH ₂ Ph	CH ₂ CH ₂ CH ₃	COOCH ₂ CH ₃	COOCH ₂ CH ₃	CH ₂ CH ₂ CH ₃	2.0	75
7	CH ₂ Ph	-CH ₂ CH ₂ CH ₂ CO-		-OCH ₂ CH ₂ CH ₂ -		1.0	70
8	CH ₃	CH ₃	COOC ₂ H ₅	COOC ₂ H ₅	CH ₃	2.0	70
9	CH ₂ Ph	CH ₃	COCH ₃	COCH ₃	CH ₃	1.0	75
10	CH ₂ Ph	CH ₃	COOCH ₃	COOCH ₃	CH ₃	1.3	55
11	CH ₂ Ph	CH ₃	COOC ₂ H ₅	COOC ₂ H ₅	CH ₃	2.0	45
12	CH ₃	-CH ₂ CH ₂ CH ₂ CO-		-OCH ₂ CH ₂ CH ₂ -		1.5	50
13	CH ₃	CH ₃	COCH ₃	COOC ₂ H ₅	CH ₃	1.0	60
14	CH ₃	CH ₃	COCH ₃	-OCH ₂ CH ₂ CH ₂ -		1.0	60

^a Isolated yield

We have also demonstrated that 4-(butenolide-5-methylidenyl)-1,4-dihydropyridines with unsymmetrical substituents (**13** and **14**) at the 2,6- and 3,5-positions of the dihydropyridine ring could also be prepared using this method. For this purpose, we used two β -keto compounds in this reaction. The enamine of one of the β -keto compounds, acetyl acetone prepared by our earlier method¹⁴ was reacted with vinylic aldehyde and ethyl acetoacetate and 1,3-cyclohexanedione, separately, in the presence of TBAHS in ethylene glycol at 90°C.

In conclusion we have synthesized a new class of dihydropyridines bearing a 4-(butenolide-5-methylidenyl) moiety at C-4 having the same or different substituents at the 3- and 5-positions using tetrabutylammonium hydrogen sulfate (a cheap and easily available phase transfer catalyst) and ethylene glycol as an eco-friendly solvent.

Typical experimental procedure for the synthesis of dihydropyridines: Compound

3: A mixture of vinylic aldehyde **2a** (0.5g, 2.71 mmol), ammonium acetate (0.20g, 2.71 mmol), acetyl acetone (0.55 mL, 5.42 mmol) and TBAHS (20 mol%) in ethylene glycol (3 mL) was magnetically stirred at 90 °C for 1.5 h. After cooling, the reaction mixture was poured onto crushed ice and the separated solid was filtered and purified by column chromatography on silica gel using ethyl acetate: hexane (4:6) as eluent to afford the desired product **3** as a light yellow foam yield (0.66 g, 70%), R_f =0.3 (ethyl acetate : hexane, 3:6); MS (FAB): m/z 370 ($M+Na$)⁺; IR (neat): ν_{max} 3309 cm^{-1} (OH Stretching); ¹H NMR (200 MHz, CDCl₃) δ 5.90 (bs, 1H, NH), 5.12 (d, 1H, J =10.4 Hz, CH=CO), 4.90 (d, 1H, J =10.3 Hz, CH), 4.10 (s, 3H, OCH₃), 3.91 (s, 3H, OCH₃), 2.32, (s, 6H, COCH₃), 2.29, (s, 6H, CH₃), ¹³C NMR (50 MHz, CDCl₃) δ 196.4 (2C), 164.5, 150.0 (2C), 146.4 (2C), 124.1, 110.0, 108.6 (2C), 60.9, 59.5, 31.8, 19.2 (2C). Anal. Calcd for C₁₈H₂₁NO₆ : C, 62.24; H, 6.09; N, 4.03 %. Found: C, 62.21; H, 6.07; N, 4.01 %..

Compound 4: Light yellow foam, yield (0.58 g, 60%), R_f =0.4 (ethyl acetate : hexane, 4:6); MS (FAB): m/z 380($M+H$)⁺ ; IR (neat): ν_{max} 3433 cm^{-1} (OH Stretching); ¹H NMR (200 MHz, CDCl₃) δ 7.30 (bs, 1H, NH), 5.15 (d, 1H, J = 9.5 Hz, CH=CO), 4.88 (d, 1H, J = 9.6 Hz, CH), 4.09 (s, 3H, OCH₃), 3.91 (s, 3H, OCH₃), 3.66 (s, 6H, OCH₃), 2.37 (s, 6H, CH₃); ¹³C NMR (50 MHz, CDCl₃): 171.0 (2C), 155.0, 148.0 (2C), 144.0 (2C), 116.6, 104.0 (2C), 65.5, 64.2 (2C), 55.9 (2C), 36.1, 23.6 (2C). Anal. Calcd for C₁₈H₂₁NO₈: C, 56.99; H, 5.58; N, 3.69 %. Found: C, 56.97; H, 5.56; N, 3.66%. Experimental details and full characterization data of other compounds is available in supplementary material.

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