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L-Ascorbic acid in organic synthesis: a facile synthesis of 4-(butenolide-5-methylidenyl)-1,4-dihydropyridines☆

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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 sulfate in ethylene glycol.

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^{2+} channel blockers and as drugs for the treatment of cardiovascular diseases and hypertension.[3] The dihydropyridine skeleton is common in many vasodilator, bronchiodilator, anti-atherosclerotic, anti-tumour, 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 anti-ischaemic 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 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 agents[8] from sugars and prompted by the reports on the wide range of biological activities, particularly anti-microbial (anti-tubercular), in butenolides[9,10] as well as drug resistance reversal[11] and anti-tubercular activity[12] 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 the oxidation of allyl alcohols (**1a** and**1b**),[13] obtained from L-ascorbic acid, with pyridinium chlorochromate (PCC) in anhydrous dichloromethane. The reaction of (3,4-dimethoxy-5-oxo-5*H*–furan-2-ylidene)acetaldehyde **2a** with acetylacetone in the presence of ammonium acetate and tetrabutylammonium hydrogensulfate (TBAHS) in ethylene glycol as in our earlier method[2d] gave 4-(butenolide-5-methylidenyl)-1,4-dihydropyridine **3** in a 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 ^{13}C) were consistent with 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.

Keywords: L-Ascorbic acid; 1,4-Dihydropyridines; 4-(Butenolide-5-methylidenyl)-1,4-dihydropyridines; Tetrabutylammonium hydrogen sulfate; Ammonium acetate.
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In the ^{13}C 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, the 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 the substituent on the tetranolactone moiety did not affect the rate of reaction (Scheme 1).

We have also demonstrated that 4-(butenolide-5-methylidenyl)-1,4-dihydropyrdines 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, acetylacetone prepared by our earlier method[14] was reacted with vinylic aldehyde and ethyl acetoacetate and 1,3-cyclohexanedione, separately, in the presence of TBAHS in ethylene glycol at 90 °C.

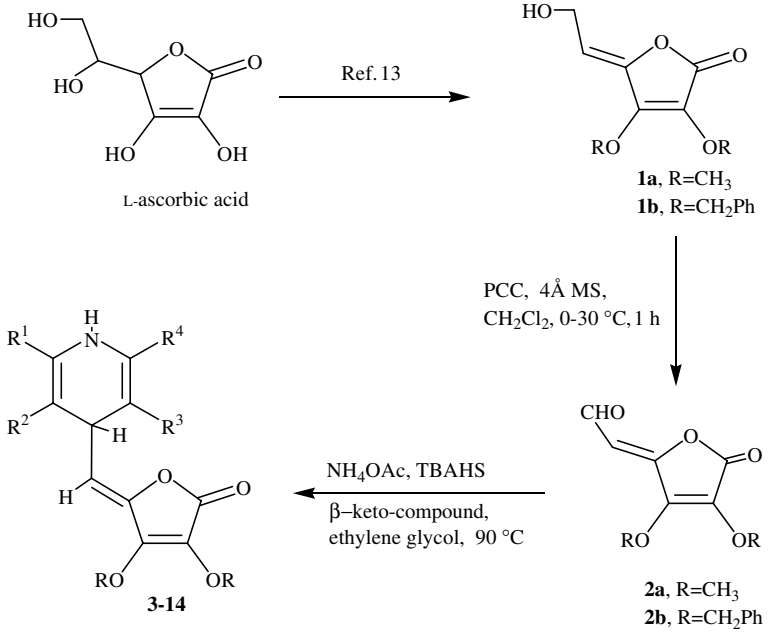
In conclusion we have synthesized a new class of dihydropyridines bearing a 4-(butenolide-5-methylidenyl) moiety at C-4 having the same or different substituents at the 3- and 5-positions using tetrabutylammonium hydrogensulfate (a cheap and easily available phase transfer catalyst) and ethylene glycol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

Typical experimental procedure for the synthesis of dihydropyridines: Compound **3**: A mixture of vinylic alde-

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	$CH_2CH_2CH_3$	$COOC_2H_5$	$COOC_2H_5$	$CH_2CH_2CH_3$	2.0	60
6	CH_2Ph	$CH_2CH_2CH_3$	$COOCH_2CH_3$	$COOCH_2CH_3$	$CH_2CH_2CH_3$	2.0	75
7	CH_2Ph	$-CH_2CH_2CH_2CO-$		$-OCH_2CH_2CH_2-$		1.0	70
8	CH_3	CH_3	$COOC_2H_5$	$COOC_2H_5$	CH_3	2.0	70
9	CH_2Ph	CH_3	$COCH_3$	$COCH_3$	CH_3	1.0	75
10	CH_2Ph	CH_3	$COOCH_3$	$COOCH_3$	CH_3	1.3	55
11	CH_2Ph	CH_3	$COOC_2H_5$	$COOC_2H_5$	CH_3	2.0	45
12	CH_3	$-CH_2CH_2CH_2CO-$		$-OCH_2CH_2CH_2-$		1.5	50
13	CH_3	CH_3	$COCH_3$	$COOC_2H_5$	CH_3	1.0	60
14	CH_3	CH_3	$COCH_3$	$-OCH_2CH_2CH_2-$		1.0	60

[a] Isolated yield.



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

hyde **2a** (0.5 g, 2.71 mmol), ammonium acetate (0.20 g, 2.71 mmol), acetylacetone (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 the 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, $CDCl_3$) δ 5.90 (br s, 1H, NH), 5.12 (d, 1H, $J = 10.4$ Hz, C*H*=CO), 4.90 (d, 1H, $J = 10.3$ Hz, C*H*), 4.10 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 2.32 (s, 6H, COCH_3), 2.29 (s, 6H, CH_3), ^{13}C NMR (50 MHz, $CDCl_3$) 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 $C_{18}H_{21}NO_6$: 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, $CDCl_3$) δ 7.30 (br s, 1H, NH), 5.15 (d, 1H, $J = 9.5$ Hz, C*H*=CO), 4.88 (d, 1H, $J = 9.6$ Hz, C*H*), 4.09 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.66 (s, 6H, OCH_3), 2.37 (s, 6H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): 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 $C_{18}H_{21}NO_8$: 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 data.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.067.

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