Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 9011–9014
Tetrahedron Letters

Tetrabutylammonium hydrogen sulfate catalyzed eco-friendly and efficient synthesis of glycosyl 1,4-dihydropyridines

Neetu Tewari, Namrata Dwivedi and Rama P. Tripathi*

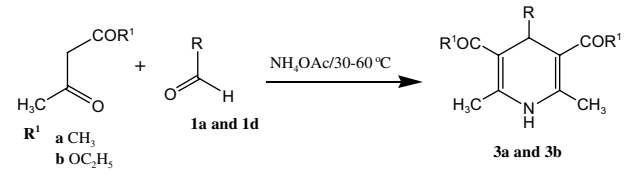
Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow-226001, India

Received 29 July 2004; revised 27 September 2004; accepted 8 October 2004

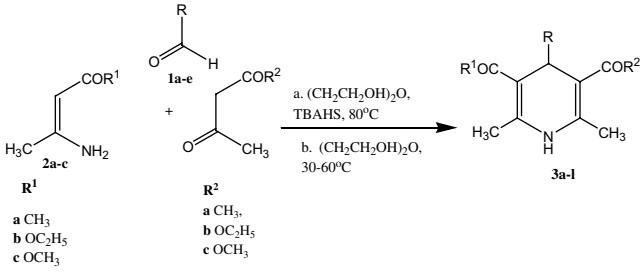
Abstract—An efficient and eco-friendly synthesis of glycosyl 1,4-dihydropyridines has been achieved by a three-component reaction of β-keto esters or ketones, enamines and glycosyl aldehydes in the presence of tetrabutylammonium hydrogen sulfate as catalyst in diethylene glycol.

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^{++} channel blockers and their role as drugs for the treatment of cardiovascular diseases and hypertension.[3] The dihydropyridine skeleton is common in many vasodialator, bronchiodialator, anti-atherosclerotic, antitumor, hepatoprotective and anti-diabetic agents.[4,5] They are also known as neuroprotectants, 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. Alternative strategies for their synthesis involving different catalysts and conditions have been developed but all suffer from one or more drawbacks including low yields, use of costly reagents and drastic reaction conditions. In continuation of our effort to develop new anti-tuberculosis agents[6,7] from sugars and the report of reversal of drug resistance[8,9] and anti-tubercular activity[8,10] in this class of molecule, we were prompted to synthesize several glycosylated dihydropyridines.

The synthesis of sugar-substituted dihydropyridines is of great significance because of their good pharmacokinetic and pharmacodynamic properties and the role of sugars in molecular recognition whereby they can influence drug receptor interaction in a beneficial manner.[11] Dondoni et al.[12] have synthesized glycosyl dihydropyridines using two- or three-component Hantzsch reactions with *C*-glycosylated reagents. Their novel method requires a very high temperature and DMF as solvent with 48 h reflux and the yields are not high in every reaction. Very recently we encountered a solventless approach for the synthesis of 1,4-dihydropyridines published in *Synlett*[13] Encouraged by this report we carried



Scheme 1.



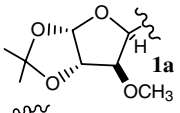
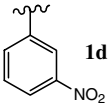
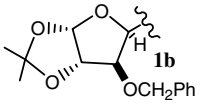
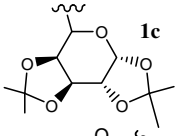
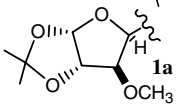
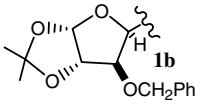
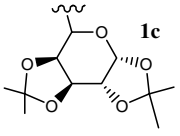
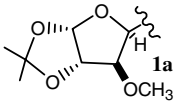
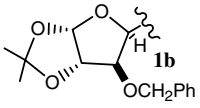
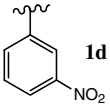
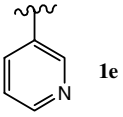
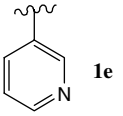
Scheme 2.

Keywords: Glycosyl dihydropyridines; Tetrabutylammonium hydrogen sulfate; 1,4-dihydropyridines; Enamines; Ammonium acetate.
* Corresponding author. Tel.: +91 522 212411 18; fax: +91 522 223405/22393; e-mail: rpt_56@yahoo.com

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.057

out the reaction of glycosyl aldehyde **1a**,[14] acetyl acetone and ammonium acetate under similar conditions to those of Zolfigol and Safaiee,[13] however, a mixture of three products was obtained and completion of the reaction required a long time (Scheme 1). Even using the same substrate, 3-nitrobenzaldehyde **1d** and similar reaction conditions to those reported[13] did not give the same result in our hands. The intermediate enamine **2a** was a major product (Scheme 2). Hence, we decided to use the enamine of the β-keto compound **2a** (obtained by reaction of acetylacetone and ammonium acetate in the presence of IR-120 resin in refluxing toluene[15]) and 1 equiv of the above keto-ester or diketone, instead of using 2 equiv of the keto compound and 1 equiv of

Table 1. Synthesized glycosyl-, aryl- and heteroaryl-1,4-dihydropyridines

Entry	Product	R	R^1	R^2	Time	Isolated yield (%)
1	**3a**	 **1a**	CH_3	CH_3	1.5 h	98[a]
2	**3b**	 **1d**	OCH_2CH_3	OCH_2CH_3	30 min[a], 1 h[b], 2 min[c]	93[a], 60[b], <50[c]
3	**3c**	 **1b**	CH_3	CH_3	2 h	95[a]
4	**3d**	 **1c**	CH_3	CH_3	2.5 h	90[a]
5	**3e**	 **1a**	OCH_2CH_3	OCH_2CH_3	1.5 h	98[a]
6	**3f**	 **1b**	OCH_2CH_3	OCH_2CH_3	1 h	97[a]
7	**3g**	 **1c**	OCH_2CH_3	OCH_2CH_3	1.5 h	90[a]
8	**3h**	 **1a**	CH_3	OCH_3	2 h	95[a]
9	**3i**	 **1b**	CH_3	OCH_3	2 h	95[a]
10	**3j**	 **1d**	CH_3	CH_3	1.5 h	95[a]
11	**3k**	 **1e**	CH_3	CH_3	30 min	95[a]
12	**3l**	 **1e**	OCH_2CH_3	OCH_2CH_3	35 min	90[a]

[a] Present method in the presence of catalyst.
[b] Present method without catalyst.
[c] As reported earlier.[13]

ammonium acetate. Although the formation of side products was reduced, the yield of the reaction was not very encouraging. This led us to think of using some sort of catalyst in a suitable eco-friendly solvent.

Based on our earlier observation that phase transfer catalysts work well in such cyclization reactions,[16] we chose tetrabutylammonium hydrogen sulfate (TBAHS) as the phase transfer catalyst, being acidic in nature, to help in the dehydration and cyclization steps. To our pleasant surprise the desired product **3a** was obtained rapidly in almost quantitative yield (98%) in the reaction of aldehyde **1a**, enamine **2a** and acetylacetone in the presence of TBAHS in diethylene glycol at 80 °C (Scheme 2). The structure of compound **3a** was established on the basis of spectroscopic data and elemental analysis. In the ^{1}H NMR spectrum, H-4 appeared as a doublet at δ 4.27 having a J value of 9.6 Hz. The product **3b** obtained by the method of Zolfigol and Safaiee[13] could be obtained in quantitative yield by our method. To the best of our knowledge this is the first report of glycosyl 1,4-dihydropyridines being synthesized simply by stirring and pouring the reaction mixture into ice-water followed by filtration and subsequent purification of the products.

Similarly, tetrasubstituted 4-glycosyl-1,4-dihydropyridines **3c** and **3d** were synthesized by the reaction of glycosyl aldehydes **1b**[17] and **1c**[18] with enamine **2a** in quantitative yields. Glycosyl aldehydes **1a, 1b** and **1c**, on similar reaction with enamine **2b** and ethyl acetoacetate resulted in the 1,4-dihydropyridines **3e–g**, respectively, with carbethoxy substituents at C-3 and C-5 in very good yields (Table 1).

The reaction was also carried out with glycosyl aldehydes **1a** and **1b**, enamine **2c** and acetylacetone resulting in the formation of 4-glycosyl-1,4-dihydropyridines **3h** and **3i** (with different substituents at the 3- and 5-positions), respectively.

That the reaction is equally good with aromatic **1d** and heteroaromatic aldehydes **1e** was evidenced by reaction of enamines **2a** and **2b** with acetylacetone and ethyl acetoacetate separately resulting in very good yields of the 1,4-dihydropyridines **3j**, **3k** and **3l**, respectively. A general method for the synthesis and physical data of prototype compounds are given.[19] A comparative study of the solventless conditions is also given in Table 1.

In conclusion we have developed a novel method using tetrabutylammonium hydrogen sulfate, a cheap and easily available phase transfer catalyst, and diethylene glycol as an eco-friendly solvent for the synthesis of several 4-substituted dihydropyridines having the same or different substitutents at the 3- and 5- positions.

Acknowledgements

This paper is CDRI Communication 6604. N.T. and N.D. are thankful to CSIR New Delhi for a Senior Research Fellowship and a Junior Research Fellowship, respectively. Financial Assistance from ICMR New Delhi in the form of a Project grant BMS-II 58/6/2000 is also acknowledged.

References and notes

1. (a) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1–42; (b) Kill, R. J.; Widdowson, D. A. In *Bioorg. Chem.*; Van Tamelen, E. E., Ed.; Academic: New York, 1978; Series 4, pp 239–275; (c) Kutney, J. P. *Heterocycles* **1977**, *7*, 593–614.
2. Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223–243.
3. (a) Bossert, F.; Meyer, H.; Wehinger, E. *Angew Chem., Int. Ed. Engl.* **1981**, *20*, 762–769; (b) Nakayama, H.; Kasoka, Y. *Heterocycles* **1996**, *42*, 901–909.
4. (a) Saushins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 269–289; (b) Mager, P. P.; Coburn, R. A.; Solo, A. J.; Triggle, D. J.; Rothe, H. *Drug Des. Discov.* **1992**, *8*, 273–289.
5. Manhold, R.; Jablonka, B.; Voigdt, W.; Schoenfinger, K. F.; Schravan, K. *Eur. J. Med. Chem.* **1992**, *27*, 229–235.
6. (a) Klusa, V. *Drugs Future* **1995**, *20*, 135–138; (b) Bretzel, R. G.; Bollen, C. C.; Maeser, E.; Federlin, K. F. *Am. J. Kidney Dis.* **1993**, *21*, 53–64; (c) Boer, R.; Gekker, V. *Drugs Future* **1995**, *20*, 499–509; (d) Bretzel, R. G.; Bollen, C. C.; Maeser, E.; Fedrlin, K. F. *Am. J. Kidney Dis.* **1992**, *17*, 465–468.
7. (a) 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; (b) Tewari, N.; Tiwari, V. K.; Mishra, R. C.; Tripathi, R. P.; Srivastava, A. K.; Ahmad, R.; Srivastava, R.; Srivastava, B. S. *Bioorg. Med. Chem.* **2003**, *11*, 2911–2923.
8. Shah, A.; Gaveriya, H.; Motohashi, N.; Kawase, S. M.; Saito, S.; Sakagami, H.; Satoh, Y.; Solymosi, A.; Walfard, K.; Molnar, J. *Anticanc. Res.* **2000**, *20*, 373–377.
9. Kharkar, P. S.; Desai, B.; Gaveria, H.; Varu, B.; Loria, R.; Maliapara, Y.; Shah, A.; Kulkarni, V. M. *J. Med. Chem.* **2002**, *45*, 4858–4867.
10. Shah, A.; Gaveriya, H.; Motohashi, N.; Kawase, S.; Farkas, S.; Gyorgyi, G.; Molnar, J. *Int. J. Antimicrob. Agents* **2002**, *20*, 227–235.
11. Shah, A.; Vora, V.; Desai, B.; Gaveriya, H. *Heterocycl. Commun.* **2001**, *7*, 481–486.
12. Dondoni, A.; Massi, A.; Minghini, E. *Synlett* **2002**, 89–92.
13. Zolfigol, M. A.; Safaiee, M. *Synlett* **2004**, 827–830.
14. Freudberg, K.; Dum, W.; Hochstetter Von, H. *Ber. Dtsch. Chem. Ges.* **1928**, *61*, 1732–1734.
15. Tewari, N.; Katiyar, D.; Tiwari, V. K.; Tripathi, R. P. *Tetrahedron Lett.* **2003**, *44*, 6639–6642.
16. Tewari, N.; Mishra, R. C.; Tiwari, V. K.; Tripathi, R. P. *Synlett* **2002**, 1779–1782.
17. Wolform, M. L.; Hanessian, S. *J. Org. Chem.* **1962**, *27*, 1800–1804.
18. Katiyar, D.; Mishra, R. C.; Tripathi, R. P. *J. Carbohydr. Chem.* **2004**, *23*, 49–70.
19. *General Procedure*: A mixture of glycosyl aldehyde **1a** (1.0 g, 4.95 mmol), enamine **2a** (0.49 mL, 4.95 mmol), acetylacetone (0.49 mL, 4.95 mmol) and TBAHS (0.2 g) was magnetically stirred at 80 °C in diethylene glycol (2 mL) for 1.5 h. After cooling the reaction mixture it was poured onto crushed ice. The crude product, thus obtained, was purified by column chromatography on silica gel using chloroform:methanol (98:2) as eluent to afford the desired product **3a**. Physical data **3a**: Colourless foam, yield 98%, $[\alpha]_D^{20}$ −120 (c = 0.25, $CHCl_3$), ESMS: m/z = 366 $[M+H]^+$, IR (KBr) 3430, 2827, 1596, 1465,

1353 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ = 6.52 (s, 1H, NH), 5.83 (d, J = 3.9 Hz, 1H, H-1′), 4.49 (d, J = 3.9 Hz, 1H, H-2′), 4.27 (d, J = 9.6 Hz, 1H, H-4), 3.80 (dd, J = 3.1, 9.6 Hz, 1H, H-4′), 3.41 (d, J = 3.1 Hz, 1H, H-3′), 3.26 (s, 3H, OCH_3), 2.38 and 2.36 (each s, 6H, 2 × $COCH_3$), 2.30, 2.19 (each s, 6H, 2 × C=CCH_3), 1.35, 1.26 (each s, 6H, $(CH_3)_2C$). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 200.7, 199.2 (C OCH_3), 145.2, 141.6 (N–C=C), 111.5 (N–C=C), 110.0, 109.2 ($C(CH_3)_2$), 105.0 (C-1′), 83.4 (C-2′), 82.4 (C-4′), 80.9 (C-3′), 56.4 (OCH_3), 36.1 (C-4), 30.0, 28.6 ($COCH_3$), 26.9, 26.4 ($C(CH_3)_2$), 20.5, 18.4 (C=CCH_3); Anal. Calcd for $C_{19}H_{27}NO_6 \cdot H_2O$ (383): calcd C, 59.53; H, 7.62; N, 3.65. Found: C, 59.33; H, 7.23; N, 3.60%. **3c**: Colourless foam, yield 95%, $[\alpha]_D^{20}$ −78 (c = 0.15, $CHCl_3$); FAB MS: m/z = 442 $[M+H]^+$, IR (KBr) 3295, 3034, 2946, 1592, 1473, 1353 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ = 7.34 (m, 5H, ArH), 5.85 (d, J = 3.9 Hz, 1H, H-1′), 4.57 (m, 2H, H-4, OCH_APh), 4.35 (d, J = 3.9 Hz, 1H, H-2′), 4.38 (d, J = 11.5 Hz, 1H, OCH_BPh), 3.87 (dd, J = 3.1, 9.5 Hz, 1H, H-4′), 3.69 (d, J = 3.1 Hz, 1H, H-3′), 2.37, 2.35 (each s, 6H, 2 × $COCH_3$), 2.17, 2.09 (each s, 6H, 2 × C=CCH_3), 1.39, 1.32 (each s, 6H, $(CH_3)_2C$), ^{13}C NMR (50 MHz, $CDCl_3$) δ = 201.0, 199.2 ($COCH_3$), 145.0, 141.4 (N–C=C), 137.9 (ArC), 128.7, 128.1, 127.9 (ArCH), 111.6(N–C=C), 110.3, 109.3 ($C(CH_3)_2$), 104.9 (C-1′), 82.3 (C-2′), 82.2 (C-4′), 81.7 (C-3′), 71.3 (OCH_2Ph), 35.9 (C-4), 30.0, 29.1 ($COCH_3$), 27.0, 26.4 ($C(CH_3)_2$), 20.6, 18.5 (C=CCH_3). $C_{25}H_{31}NO_6CH_2CH_2OH$ (486): Anal. Calcd for C, 61.72; H, 7.40; N, 2.88. Found: C, 61.42; H, 7.08; N, 2.79%. **3d**: Colourless foam, yield 90%, $[\alpha]_D^{20}$ −59 (c = 0.11, $CHCl_3$), FABMS: m/z = 422 $(M+H)^+$; IR (Neat) 3284, 2934, 1586, 1466, 1363 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.10 (br s, 1H, exchangeable NH), 5.40 (d, J = 5.0 Hz, 1H, H-1′), 4.48 (dd, J = 8.0, 2.2 Hz, 1H, H-3′), 4.23 (d, J = 9.8 Hz, 1H, H-4), 4.18 (d, 1H, J = 5.0 Hz, H-2′), 3.96 (dd, J = 6.6, 1.0 Hz, 1H, H-4′), 3.22 (dd, J = 9.7, 1.0 Hz, 1H, H-5'), 2.19, 2.16 (each s, each 6H, 2 × $COCH_3$ and 2 × C=CCH_3), 1.46, 1.32 (each s, 12H, $(CH_3)_2C$). ^{13}C NMR (50 MHz, $CDCl_3$); δ = 200.9, 199.7 ($COCH_3$), 143.8, 143.6 (N–C=C), 110.0 (N–C=C), 109.5, 109.3, 108.7 ($(CH_3)_2C$), 96.8 (C-1′), 71.3 (C-3′), 71.2 (C-2′), 70.6 (C-4′), 69.4 (C-5′), 36.9 (C-4), 29.8, 29.1 ($COCH_3$), 29.4, 26.1, 25.4, 24.8 ($C(CH_3)_2$), 19.9, 19.2 (C=CCH_3). Anal. Calcd for $C_{22}H_{31}NO_7 \cdot H_2O$ (439): C, 60.13; H, 7.57; N, 3.18. Found: C, 60.00; H, 7.20; N, 3.00%. **3e**: Colourless foam, yield 98%, ESMS: m/z = 448 $[M+Na]^+$, IR (KBr) 3351, 1669, 1489, 1380 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ = 5.81 (d, J = 3.5 Hz, 1H, H-1′), 4.55 (d, J = 7.7 Hz, 1H, H-4), 4.46 (d, J = 3.9 Hz, 1H, H-2′), 4.15 (q, J = 6.9 Hz, 4H, 2 × OCH_2CH_3), 3.89 (dd, J = 3.1, 7.6 Hz, 1H, H-4′), 3.49 (d, J = 3.0 Hz, 1H, H-3′), 3.27 (s, 3H, OCH_3), 2.31, 2.25 (each s, 6H, 2 × C=CCH_3), 1.77 (s, 1H, NH), 1.41, 1.33 (each s, 6H, $(CH_3)_2C$), 1.30 (t, J = 7.3 Hz, 6H, 2 × OCH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) = 168.7, 168.4, (CO), 145.1, 144.9 (N–C=C), 111.3 ($C(CH_3)_2$), 105.0 (C-1′), 101.1, 100.0 (N–C=C), 84.4 (C-2′), 82.5 (C-4′), 81.3(C-3′), 61.7, 60.13 (OCH_2CH_3), 57.2 (OCH_3); 33.7 (C-4); 27.0, 26.5 ($C(CH_3)_2$), 19.6, 19.1 (C=CCH_3), 14.7 (OCH_2CH_3). Anal. Calcd. for $C_{21}H_{31}NO_8 \cdot H_2O$ (443): C, 56.87; H, 7.50; N, 3.16. Found: C, 57.41; H, 7.10; N, 3.15%. **3f**: Colourless foam, yield 97%, $[\alpha]_D^{20}$ +14 (c = 0.13, $CHCl_3$); ESMS: m/z = 524 $[M+Na]^+$, IR (KBr) = 3342, 1596, 1480, 1380 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ = 5.82 (d, J = 3.8 Hz, 1H, H-1′), 4.72 (d, J = 7.9 Hz, 1H, H-4), 4.59 (d, J = 11.9 Hz, 1H, OCH_APh), 4.53 (d, J = 13.0 Hz, 1H, OCH_BPh), 4.45 (d, J = 3.8 Hz, 1H, H-2′), 4.12 (q, J = 7.0 Hz, 4H, 2 × OCH_2CH_3); 4.00 (dd, J = 3.0, 8.0 Hz, 1H, H-4′), 3.78 (d, J = 3.0 Hz, 1H, H-3′), 2.29, 2.17 (each s, 6H, 2 × C=C–CH_3), 1.54, 1.42 (each s, 6H, $(CH_3)_2C$), 1.13 (t, J = 7.08 Hz, 6H, 2 × OCH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 168.7, 168.4 (COO); 145.1, 144.8 (N–C=C); 138.7 (Ar-C); 128.5, 127.7, 127.2 (ArCH); 111.4 ($(CH_3)_2C$); 105.0 (C-1′); 100.94, 100.67 (N–C=C); 82.7 (C-2′); 82.5 (C-4′); 82.0 (C-3′); 71.4 (OCH_2Ph); 60.1, 59.9 (OCH_2CH_3); 33.4 (C-4); 27.1, 26.6 ($C(CH_3)_2$), 19.8, 19.2 (C=CCH_3); 14.7, 14.6 (OCH_2CH_3). Anal. Calcd. for $C_{27}H_{35}NO_8$ (501): C, 64.65; H, 7.03; N, 2.79. Found: C, 64.43; H, 7.03; N, 2.44%. **3h**: Colourless foam, yield 95%, $[\alpha]_D^{20}$ −121 (c = 0.18, $CHCl_3$); ESMS m/z = 382 $[M+H]^+$, IR (KBr) 3319, 1677, 1610, 1482, 1379 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ = 5.85 (d, J = 3.9 Hz, 1H, H-1′), 4.47 (d, J = 3.9 Hz, 1H, H-2′), 4.42 (d, J = 9.5 Hz, 1H, H-4), 3.81 (dd, J = 3.1, 9.5 Hz, 1H, H-4′), 3.72 (s, 3H, $COOCH_3$), 3.40 (d, J = 3.3 Hz, 1H, H-3′), 3.24 (s, 3H, OCH_3), 2.38, 2.36 (each s, 6H, C=CCH_3), 2.18 (s, 3H, $COCH_3$), 1.62 (s, 1H, NH), 1.39, 1.26 (each s, 6H, $(CH_3)_2C$). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 200.8 (CO), 168.1 (COO), 145.1 (NC=$COCH_3$), 144.3 (N–C=$COOCH_3$), 110.8 ($C(CH_3)_2$), 109.5, 109.0 (NC=CH_3), 104.6 (C-1′), 100.2 (NC=C), 83.5, 83.1 (C-2′), 81.9, 81.6 (C-4′), 80.5, 80.2 (C-3′), 56.8, 55.9 ($COOCH_3$), 51.1 (OCH_3), 35.5, 34.5 (C-4), 30.8, 29.6 ($COCH_3$), 26.4, 25.8 ($C(CH_3)_2$), 19.3, 18.4 (C=CCH_3). Anal. Calcd. for $C_{19}H_{27}NO_7$ (381): C, 59.83; H, 7.14; N, 3.67. Found: C, 59.96; H, 7.24; N, 3.62%.