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An efficient synthesis of N3,4-diphenyl-5-(4-fluorophenyl)-2-isopropyl-1*H*-3-pyrrolecarboxamide, a key intermediate for atorvastatin synthesis

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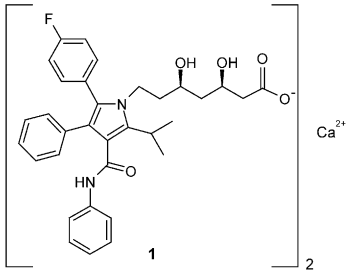
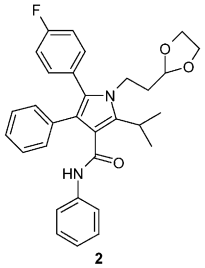
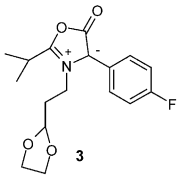
Abstract—An efficient synthesis of N3,4-diphenyl-5-(4-fluorophenyl)-2-isopropyl-1*H*-3-pyrrolecarboxamide, a key intermediate for the synthesis of an effective HMG-CoA reductase inhibitor atorvastatin, is described. The synthesis is based on the 1,3-dipolar cycloaddition reaction of mesoionic munchnone (1,3-oxazolium-5-olate) with N1,3-diphenyl-2-propynamide leading to *N*-benzyl pyrrole, and *N*-debenzylation using sodium in liquid ammonia as key steps.

Atorvastatin (**1**, Lipitor®, Sortis®) is an HMG-CoA reductase inhibitor, which inhibits the action of HMG-CoA reductase and thereby decreases endogenous cholesterol synthesis, leading to a decrease in circulating low-density lipoprotein cholesterol,[1] of great medicinal and commercial importance.[2] Hence, there has been considerable interest in the recent past in the synthesis of atorvastatin **1**.[3,4] Roth and co-workers have synthesized atorvastatin **1** in lactone form using N3,4-diphenyl -1-[2-(1,3-dioxolan-2-yl)ethyl]-5-(4-fluorophenyl)-2-isopropyl-1*H*-3-pyrrolecarboxamide **2** as an intermediate.[5] They have used 1,3-dipolar cycloaddition reaction of mesoionic munchnone (1,3-oxazolium-5-olate) **3** with N1,3-diphenyl-2-propynamide for the synthesis of **2**. But the synthesis of **2** is not economical as the starting material, ethyl 2-bromo-2-(4-fluorophenyl)acetate, is not readily accessible and some of the reagents used are very expensive.







1,3-Dipolar cycloaddition reactions of mesoionic munchnones (1,3-oxazolium-5-olates) derived from cyclodehydration of secondary *N*-acylamino acids with acetylenic dipolarophiles give rise to a mixture of pyrrole regioisomers.[6] The product distribution of regioisomers is highly dependent on substituents.[7] As part of our study on the effect of substituents on the regioselectivity of these reactions, we have studied the 1,3-dipolar

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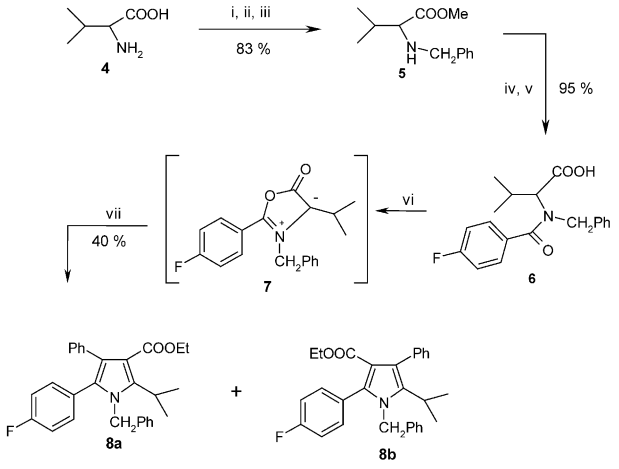
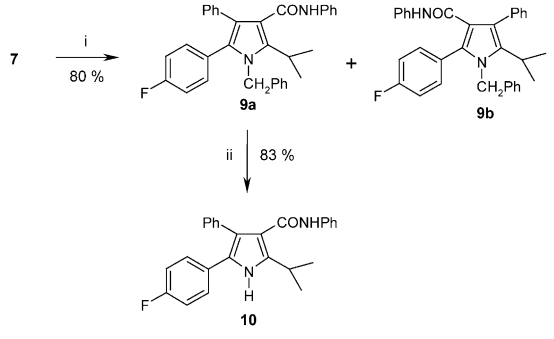
cycloaddition reactions of mesoionic munchnone **7** with ethyl phenylpropiolate and N1,3-diphenyl-2-propynamide.[8] The reaction of **7** with ethyl phenylpropiolate (Scheme 1) is regioselective giving 1:9 ratio of regioisomers **8a** and **8b** (**8a** being the desired isomer). However, we have found that the reaction of **7** with N1,3-diphenyl-2-propynamide is not regioselective giving 1:1 ratio of regioisomers **9a** and **9b** (Scheme 2), thus increasing the yield of **9a**, which is precursor for **10**. Interestingly, the regioisomer **9a** is easily separated from **9b** by crystallization. Hence, this result has led us to synthesize the pyrrole **10** in a convenient and efficient manner (Scheme 2). We also used natural amino acid L-valine which is readily available and inexpensive as the starting material.

Treatment of L-valine **4** with dry HCl gas in MeOH gave valine methyl ester hydrochloride, which on washing with liquor ammonia solution gave valine methyl ester. This was treated with benzyl bromide and K_2CO_3 in chloroform at room temperature to afford *N*-benzyl-valine methyl ester **5** in 83% overall yield. The reaction of **5** with 4-fluorobenzoyl chloride in the presence of Et_3N, followed by hydrolysis with NaOH in methanol–water (4:1) gave **6** in 95% yield. 1,3-Dipolar cycloaddition reaction[9] of mesoionic munchnone (1,3-oxazolium-5-olate) **7**, derived from cyclodehydration of **6** by using DCC in toluene, with N1,3-diphenyl-2-propynamide gave two pyrrole regioisomers **9a** and **9b** in 1:1 ratio (80% mixture yield). The ratio was determined by ^{1}H NMR signals of $(CH_3)_2CH$– proton appearing at δ 3.27 ppm in **9a** and δ 2.92 ppm in **9b**. The regioisomers **9a** and **9b** were easily separated by crystallization from their mixture using benzene–hexane (1:1) solvent mixture. The resultant **9a** was easily debenzylated[10] to afford **10** in 83% yield by using sodium in liquid ammonia and *t*-BuOH at −78 °C for 10 min.



Scheme 1. Reagents and conditions: (i) dry HCl gas, CH_3OH, reflux, 4 h; (ii) liquor ammonia solution; (iii) benzyl bromide (1.1 equiv), K_2CO_3 (2 equiv), $CHCl_3$, rt, 12 h; (iv) 4-fluorobenzoyl chloride (1.1 equiv), Et_3N (2 equiv), CH_2Cl_2, 0°C to rt, 12 h; (v) NaOH, MeOH–H_2O (4:1), reflux, 3 h; (vi) DCC (1.2 equiv), toluene; (vii) ethyl phenylpropiolate (1 equiv), reflux, 7 h.



Scheme 2. Reagents and conditions: (i) N1,3-diphenyl-2-propynamide (1 equiv), reflux, 7 h; (ii) Na (4 equiv), liquid NH_3, *t*-BuOH (2 equiv), THF, −78 °C, 10 min.

In conclusion, we have developed an efficient and economical route for the synthesis of **10**, a key intermediate for atorvastatin synthesis, by using 1,3-dipolar cycloaddition reaction of mesoionic munchnone (1,3-oxazolium-5-olate) **7** with N1,3-diphenyl-2-propynamide and *N*-debenzylation using sodium in liquid ammonia in the presence of *t*-BuOH at −78 °C, as key steps. Now our efforts are towards the synthesis of atorvastatin **1** via the intermediate **2**.

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References and notes

1. Chong, P. H.; Seeger, J. D. *Pharmacotherapy* **1997**, *17*, 1157.
2. Graul, A.; Castaner, J. *Drugs Future* **1997**, *22*, 956.
3. (a) Brower, P. L.; Butler, D. E.; Deering, C. F.; Le, T. V.; Millar, A.; Nanninga, T. N.; Roth, B. D. *Tetrahedron Lett*. **1992**, *33*, 2279. (b) Baumann, K. L.; Butler, D. E.; Deering, C. F.; Mennen, K. E.; Millar, A.; Nanninga, T. N.; Palmer, C. W.; Roth, B. D. *Tetrahedron Lett*. **1992**, *33*, 2283.
4. Radl, S.; Stach, J.; Hajicek, J. *Tetrahedron Lett*. **2002**, *43*, 2087.
5. Roth, B. D.; Blankley, C. J.; Chucholowski, A. W.; Ferguson, E.; Hoefle, M. L.; Ortwine, D. F.; Newton, R. S.; Sekerke, C. S.; Sliskovic, D. R.; Stratton, C. D.; Wilson, M. *J. Med. Chem*. **1991**, *34*, 357.
6. Padwa, A.; Burgess, E. M.; Gingrich, H. L.; Roush, D. M. *J. Org. Chem*. **1982**, *47*, 786.
7. (a) Coppola, B. P.; Noe, M. C.; Abdon, R. G.; Konsler, R. L. *J. Org. Chem*. **1993**, *58*, 7324. (b) Coppola, B. P.; Noe, M. C.; Schwartz, D. J.; Abdon, R. L., II; Trost, B. M. *Tetrahedron* **1994**, *50*, 93. (c) Coppola, B. P.; Noe, M. C.; Hong, S. S. *Tetrahedron Lett*. **1997**, *38*, 7159.
8. N1,3-diphenyl-2-propynamide was prepared from phenylpropiolic acid and aniline by using DCC and catalytic amount of DMAP in dichloromethane at room temperature in 85% yield.
9. **Procedure for 1,3-dipolar cycloaddition**: A solution of amido acid **6** (300 mg, 0.914 mmol) and N1,3-diphenyl-2-propynamide (223 mg, 1.0 mmol) in toluene (10 mL) was treated with DCC (226 mg, 1.09 mmol) in toluene (6 mL). The resulting yellow mixture was refluxed under nitrogen

for 7 h. After cooling, crystalline dicyclohexyl urea was removed by filtration. The filtrate was poured into saturated aqueous $NaHCO_3$ (15 mL), and the mixture extracted with chloroform (25 mL). The organic layer was dried over Na_2SO_4, and evaporated. Complete removal of dicyclohexyl urea by passing it through a small column of silica gel, benzene as eluent, yielded 355 mg (80%) of mixture of **9a** and **9b** in 1:1 ratio. From the mixture 168 mg (48%) of **9a** was separated out as a white solid by crystallization using benzene–hexane (1:1) solvent mixture. Physical and spectroscopic data for **9a**: mp 218–220 °C; IR (KBr) 3403, 3060–2931, 1664, 1595, 1563, 1527, 1495, 1436, 1309, 1242, 1218, 1154, 845, 753, 737, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–6.81 (m, 20H), 5.08 (s, 2H), 3.27 (septet, $J = 7$ Hz, 1H), 1.40 (d, $J = 7$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166, 164, 161, 143, 138.33, 134.55, 132.93, 130.54, 128.72, 128.39, 127.31, 126.61, 125.48, 123.57, 119.61, 115.31, 115.03, 48.03, 26.65, 21.38.

10. **Procedure for *N*-debenzylation**: A 50 mL three necked flask cooled to −78 °C, was charged with 18 mg (0.8 mmol) of freshly cut sodium metal and 25 mL of liq ammonia. Blue colour started appearing slowly and in 5 min the reaction mixture became blue in colour. 29 mg (0.4 mmol) of *t*-BuOH in 2 mL of THF was added followed by 100 mg (0.2 mmol) of **9a** in 5 mL of THF. The reaction mixture was stirred at −78 °C till the entire blue colour had disappeared. The cooling bath was removed and ammonia was evaporated by using a waterbath. The reaction mixture was then quenched with a minimum amount of aqueous NH_4Cl and extracted with EtOAc. The organic layer was then dried over Na_2SO_4, concentrated and purified by column chromatography (silica gel) to give 68 mg of **2** as a white solid in 83% yield. Physical and spectroscopic data for **10**: mp 208–210 °C; IR (KBr) 3404, 3291, 3059–2870, 1642, 1528, 1438, 1313, 1253, 1192, 752, 692 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (bs, 1H), 7.43–6.96 (m, 15H), 4.11 (septet, $J = 6.9$ Hz, 1H), 1.41 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.67, 165.73, 163.52, 145.3, 144.6, 137.9, 132.19, 131.29, 129.20, 128.64, 127.87, 126.70, 124.65, 123.20, 121.29, 119.13, 118.52, 116.50, 25.95, 22.27.