An efficient synthesis of N3,4-diphenyl-5-(4-fluorophenyl)-2-isopropyl-1H-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-1H-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 mesionic 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, Lipitor1, Sortis1) 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-1H-3-pyrrolecarboxamide 2 as an intermediate.5 They have used 1,3-dipolar cycloaddition reaction of mesionic munchnone (1,3-oxazolium-5-olate) 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 mesionic 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...
cycloaddition reactions of mesoionic munchnone 7 with ethyl phenylpropiolate and N1,3-diphenyl-2-propynamide. 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$_2$CO$_3$ 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 DCC in toluene, with N1,3-diphenyl-2-propynamide (226 mg, 1.09 mmol) in toluene (6 mL) was treated with DCC (226 mg, 1.09 mmol) in toluene (10 mL) was refluxed under nitrogen atmosphere in 85% yield. The resulting yellow mixture was refluxed under nitrogen for 12 h. This was treated with sodium in liquid ammonia in the presence of t-BuOH at —78 °C for 10 min. The resultant 9a was easily debenzylated with NaOH, followed by hydrolysis with NaOH in methanol-water (4:1) gave 6 in 95% yield. 1,3-Dipolar cycloaddition reaction 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$_3$)$_2$CH- proton appearing at d 3.27 ppm in 9a and d 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 to afford 10 in 83% yield by using sodium in liquid ammonia and t-BuOH at —78 °C for 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**

8. N1,3-diphenyl-2-propynamide was prepared from phenylpropionic 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 7h. After cooling, crystalline dicyclohexyl urea was removed by filtration. The filtrate was poured into saturated aqueous NaHCO$_3$ (15mL), and the mixture extracted with chloroform (25mL). The organic layer was dried over Na$_2$SO$_4$, and evaporated. Complete removal of dicyclohexyl urea by passing it through a small column of silica gel, benzene as eluent, yielded 355mg (80%) of mixture of 9a and 9b in 1:1 ratio. From the mixture 168mg (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$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.36-6.81 (m, 20H), 5.08 (s, 2H), 3.27 (septet, J=7Hz, 1H), 1.40 (d, J=7Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 166, 164, 161, 144, 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 50mL three necked flask cooled to — 78 °C, was charged with 18mg (0.8mmol) of freshly cut sodium metal and 25mL of liq ammonia. Blue colour started appearing slowly and in 5min the reaction mixture became blue in colour. 29mg (0.4mmol) of t-BuOH in 2mL of THF was added followed by 100mg (0.2mmol) of 9a in 5mL 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$_4$Cl and extracted with EtOAc. The organic layer was then dried over Na$_2$SO$_4$, 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$^{-1}$. $^1$H NMR (300MHz, CDCl$_3$) δ 8.34 (bs, 1H), 7.43-6.96 (m, 15H), 4.11 (septet, J=6.9Hz, 1H), 1.41 (d, J=6.9Hz, 6H); $^{13}$C NMR (75MHz, 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.