Molbank **2008**, M565 http://www.mdpi.org/molbank/

Synthesis of New β-enaminones of Isoquinolines with 5,5-dimethyl-cyclohexanedione

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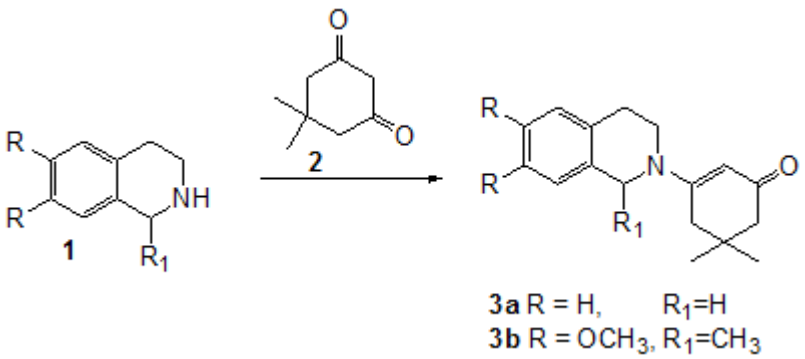
Received: 3 August 2007 / Accepted: 23 January 2008 / Published: 25 March 2008

Keywords: enaminones, dimedone, isoquinoline

Introduction

Enaminones are chemical compounds incorporating an amino group linked through a C=C to carbonyl group. They are versatile synthetic intermediates that combine the ambident electrophilicity of enones with the ambident nucleophilicity of enamines. They are typical push-pull systems in which the amine group pushes and the carbonyl pulls electron density. The carbonyl group, conjugated with the enamine moiety, gives this system enough stability to be easily prepared, isolated and stored under atmospheric conditions at room temperature [1]. Enaminones are known to possess a variety of medicinal properties including anticonvulsant, antimalarial, antiinflamatory, and cardiovascular effects [2-6].
Even though numerous synthesis of enaminones have been reported, the most common way for their preparation remains the condensation between an amine and a 1,3-dicarbonyl compound [7]. In our previous work [8] we obtained β-enaminones of primary amines by stirring the reaction mixture overnight at room temperature or at reflux temperature in dichloroethane for 3h.
Now we wish to report the synthesis of new enaminones of secondary amines, as 1,2,3,4-tetrahydroisoquinoline and 1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with 5,5-dimethyl-cyclohexanedione (dimedone). Enaminones of this type are more difficult to obtain than enaminones of primary amines. The enaminones of 1,2,3,4-tetrahydroisoquinolines and dimedone were obtained by refluxing equimolar amounts of the reagents for 3h in toluene using Dean-Stark trap to remove the water formed during the reaction.



After completion of the reaction the solvent was removed by distillation. Enaminones were purified by column chromatography on silica gel 60 (Merck, 0.063-0.2mm) using n-hexane:Et_2O=1:1 and Et_2O as eluent.

3-(3,4-Dihydro-1H-isoquinolin-2-yl)-5,5-dimethyl-cyclohex-2-enone (3a)

Melting Point: 103-105°C, 82% yield,

IR (KBr, cm^{-1}): 1588; 1562
^{1}H-NMR(600 MHz, $CDCl_3$): 7.24-7.21(m,2H), 7.19-7.17(m,1H), 7.15-7.12(m,1H), 5.35(s,1H), 4.48(s,2H), 3.59(t,2H,J=5.9), 2.93(t,2H,J=5.9), 2.39(s,2H), 2.20(s,2H), 1.11(s,6H); ^{13}C-NMR(150.9, $CDCl_3$): 196.8, 163.0, 134.7, 132.8, 128.2, 127.2, 126.7, 126.4, 98.3, 49.4, 48.6, 44.4, 41.2, 33.0, 28.8.
Anal. Calcd for $C_{17}H_{21}NO$: C 79.96, H 8.29, N 5.49. Found: C 80.08, H 8.32, N 5.53.

3-(6,7-Dimethoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-5,5-dimethyl-cyclohex-2-enone (3b)

Melting Point: 197-200°C, 80% yield,
IR (KBr, cm^{-1}): 1548; 1520
^{1}H-NMR(600 MHz, $CDCl_3$): 6.63(s,1H), 6.57(s,1H), 5.36(s,1H), 4.86(q,1H,J=6.5), 3.88(s,6H), 3.74-3.81(m,1H), 3.45-3.40(m,1H), 2.94-2.89(m,1H), 2.78(dt,1H,J=15.7,3.8), 2.43(d,1H,J=15.9), 2.29(d,1H,J=15.9), 2.22(d,1H,J=16.2), 2.16(d,1H,J=16.2), 1.50(d,3H,J=6.6), 1.13(s,3H), 1.08(s,3H);
^{13}C-NMR(150.9, $CDCl_3$): 196.6, 162.0, 147.9, 147.8, 129.9, 129.8, 111.2, 109.4, 97.8, 56.1, 55.9, 52.8, 49.4, 41.0, 40.7, 30.1, 27.6.
Anal. Calcd for $C_{20}H_{27}NO_3$: C 72.92, H 8.26, N 4.25. Found: C 73.13, H 8.39, N 4.38.

Acknowledgment

The authors acknowledge financial support from the Fund for scientific research of the Plovdiv University.

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