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Synthesis of 4-(2H-chromene-3yl)-3-phenoxy-1-(4-methoxy/methylphenyl) azetidin-2-ones

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ABSTRACT

*2H-3-Chromeneimine **(1a-h)** react with phenoxyacetylchloride **(2)** at room temperature in a Staudinger reaction to give 4-(2H-chromene-3-yl)-3-phenoxy-1-(4-methylphenyl) azetidin-2-ones (β-lactams) **(3a-h).***

Keywords: 2H-3-chromeneimines, Staudinger reaction, phenoxyacetylchloride, triethylamine.

INTRODUCTION

Natural and synthetic heterocyclic compounds play an important role in both drug discovery and chemical biology. The heterocycles are mainly of the classes of alkaloids, chromenes, flavones, isoflavones etc. The natural heterocyclics are plant secondary metabolites, which protect the plant from attack by pathogens, fungi, bacteria and insects. Several synthetic analogs of these heterocyclics show different bioactivity[1-5]. More than 50% of the drug used in the modern medicine is either derived from synthetic or natural heterocyclic systems.

With a view synthesize new heterocyclic ring fused chromenes and flavones pendent at 3-position.we studied the Staudinger reported the synthesis of a β–lactam by a nonconcerted cycloaddition of diphenylketene with benzylideneaniline[6-10]. Literature shows that methods for the synthesis of azetidin-2-ones (β-lactams) and thiazolidinones.

MATERIALS AND METHODS

Experimental Section (3a-h):
General: - Melting points were determined in a sulfuric acid-bath and are uncorrected. IR spectra were recorded in KBr on a Shimadzu 435 spectrometer, ^{1}H NMR spectra on a Varian

Gemini 200 MHz spectrometer with TMS as an internal standard and mass spectra on a Perkin Elmer Hitachi RDO-62 and MS-30 instrument.

General procedure for the synthesis of 4-(2H-chromene-3yl)-3-phenoxy-1-(4-methylphenyl) azetidin-2-ones (3a-h)

i) 4-(2H-chromene-3y1)-3-phenoxy-1-(4-rnethoxyphenyl)azetidin-2-one(3a):

To a solution of 2H-chromene-3-(4'-methoxyphenyl)imine **(1a)** (2.65g, l0mmol) in dry dichloromethane (25mL) at 0 °C, triethylamine (5.6mL, 40mmol) was added drop wise with constant stirring and then after the addition of triethylamine completed further stirring was continued for about half an hour. Then, phenoxyacetyl chloride **(2)** (1.38mL, 10mmol) in dry dichloromethane (25mL) was added at 0°C for 45 min-and stirred at same temperature for 1 h. Then the ice bath was removed and stirring continued for 18 h at room temperature. Water (25mL) was added and stirring continued for further 30 mn. The organic layer was separated and washed with water (2x50 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave crude solid, which was purified by column chromatography over 60-120 mesh silica gel, elution with pet.ether: ethyl acetate (7:3) gave 4-(2H-chromene-3y1)-3-phenoxy-l-(4-methoxyphenyl) azetidin-2-one **(3a)** (3.1g.78% yield) as a white coloured solid, mp 117 °C. IR (KBr): 1740 cm^{-1} (CO) and 1240 cm^{-1} (C-N). UV (MeOH): 352 nm (log ε 4.4) and 279 nm (log ε 4.7). ^{1}H NMR ($CDC1_3$)(300MHz): δ 7.43(d, J=9.0Hz, H-2",6"), 7.21-7.35(m, H-3",5'"), 6.92-7.19(m, H-5',6,7'; 11-2",6'"), 6.71-6.90(m, H-8'; H-3",5tt; H-4'), 6.61(s, .H-4), 5.46(d. J=5.2Hz, H-3), 4.92(d, J=5.2Hz, H-4), 4.77(AB quartet, J=14.3Hz, 2'-OCH_2), 3.78 (4"-OCH_3); ^{13}C NMR($CDC1_3$)(100.6 MHz): δ 162:2(CO at C-2), 157.2(C-4"), 156.8(C-1'"), 154.0(C- 8'a), 130.7(C-3'), 1298(C-7'), 129.6(C-3'",5 ..), 127.6(C-1"), 126.9(C-5), 126.3(C-4') 122.6(C-4'"), 121.9(C-4'a), 121.5(C-6'), 118.5(C-2",6"), 115.8(C-8'), 115.7(C-3",5"), 114.6(C-2'",6 ...), 81 .8(C-3), 65.4(C-2), 61 .4(C-4), 55.4(C-4"-OCH_3). MS: m/z 400 [M+H] and 306.

Employing the similar procedure as mentioned for **3a,** compounds **3b-h** were obtained from **1b-h** as solids in 70-85% yield.

ii) 4-(6-Chloro-2H-chromene-3y1)-3-phenoxy-1-(4-methoxyphenyl)azetidin-2-one (3b):

Column chromatography and recrystallisation from chloroform gave white crystals, mp 114 °C.; IR (KBr): 1735 cm^{-1}(C=O) and 1245 cm^{-1}(C-N).; UV (MeOH): 348 nm (log ε 4.1) and 282 nm (log ε 4.5).; ^{1}H NMR ($CDC1_3$+DMSO-d_6) (300MHz): δ 7.41(d, J=9.0Hz, H-2", 6"), 7.27(m, H-3", 5'"), ; 6.99(m, H-5', 7'; H-2", 4'", 6"), 6.83(d, J=9.0Hz, H-3", 5"), 6.68(d, J=8.3Hz, H-8'), 6.56(s, H-4'), 5.59(d, J=5.2Hz, H-3), 5.10(d, J=5.2Hz, H-4), 4.70(AB quartet, J=14.3Hz, 2'-OCH_2), 3.78(4"-OCH_3).; ^{13}C NMR ($CDCl_3$) (100.6 MHz): δ 161.9(C=O at C-2), 157.0(C-4"), 156.7(C-1"), 152.3(C-8'a), 129.8(C-1"), 129.8(C-3", 5"), 129.5(C-3'), 129.2(C-7'), 126.2(C-5'), 125.0(C-4'), 122.6(C-4'a), 122.3(C-4"), 121.9(C-2",6"), 117.0(C-6'), 115.6(C-8'), 114.7(C-3",5"), 114.1(C-2", 6'"), 81.7(C-3), 65.5(C-2'), 61.0(C-4), 55.3(C-4"-OCH_3).; MS: m/z 434 $[M+H]^+$

iii) 4-(6-Bromo-2H-chromene-3y1)-3-phenoxy-1-(4-methoxyphenyl)azetidin-2-one (3c):

Column chromatography and recrystallisation from chloroform gave white colored Solid, mp 147 °C; IR (KBr): 1737 cm^{-1}(C=O) and 1246 cm^{-1}(C-N) UV (MeOH): 355 nm (log ε 4.3) and 267 nm (log ε 4.6). ^{1}H NMR ($CDCl_3$)(300MHz): δ 7.42(d, J=9.0Hz, H-2",6"), 7.25(m, H-7': H-3",5"), 6.99(m, H-5'; H-2"1,6"), 6.83(m, H-3",5"; H-4'), 6.66(d, J=8.3Hz, H-8'), 6.54(s, H-4'), 5.45(d, J=5.2Hz, H-3), 4.92(d, J=5.2Hz, H-4), 4.76(AB quartet, J=14.3Hz, 2'-OCH_2), 3.79(4"-

OCH_3). ^{13}C NMR($CDCl_3$)(100.6 MHz): δ 162.0(C=O at C-2), 157.1(C-4"), 156.9(C-1"), 152.9(C- , 8'a), 132.3(C-7'), 130.5(C-3'), 129.6(C-3",5"), 129.2(C-5'), 129.1(C-1"), 125.0(C-4') 122.7(C-4"), 122.1(C-4'a), 118.5(C-2",6"), 117.6(C-8'), 115.7(C-3",5"), 114.6(C-2",6"), 113.5(C-6'), 81.8(C-3), 65.5(C-2'), 61.1(C-4), 55.1(C-4"-OCH_3).; MS: m/z 479$[M+H]^+$ and 501$[M+Na]^+$.

iv) 4-(6-Methyl-2H-chromene-3y1)-3-phenoxy- 1 -(4-methoxyphenyl)azetidin-2-one (3d):

Column chromatography and recrystallisation from chloroform gave white colored solid, mp 123 °C IR (KBr): 1734 cm^{-1}(C=O) and 1235 cm^{-1}(C-N); UV (MeOH): 344 nm (log ε 4.2) and 278 nm (log ε 4.3). ^1H NMR ($CDCl_3$)(300MHz): δ 7.39(d, J=9.0Hz, H-2",6t'), 7.22(m, H-3",5'"), 7.00(m, H- 51,8'; H-2",6'"), 6.89(d, J=9.OHz, H-3",5"), 6.72(m, H-7',4"), 6.55(s, H-4'), 5.54(d, J=5.2Hz, H-3), 5.08(d, J=5.2H, H-4), 4.71(AB quartet, J=14.3Hz, 2'-OCH_2), 3.78(s, 4"- OCH_3), 3.72(6'-CH_3). ^{13}C NMR($CDC1_3$+DMSO-d_6)(100.6 MHz): δ 162.2(C=O at C-2), 157.3(C-4"), 156.4(C-1'"), 152.5(C-6'), 149.9(C-8a), 131 6(C-1"), 130.3C-3'",5""), 129.8(C-3'), 126.1(C-4, 125.2(C-4'a), 122.0(C-4'"), 121.5(C-2",6"), 116.7(C-7'), 115.6(C-3",5"), 15.1(C-5') 114.3(C-2'",6""), 112.8(C-8'), 81.9(C-3), 65.5(C-2'), 61.2(C-4), 55 9(C-6'-CH_3), 55 4(C 4"-OCH_3).MS: m/z 413 $[M+H]^+$

v) 4-(2H-Chromene-3y1)-3-phenoxy- 1 -(4-methylphenyl)azetidin-2-one (3e):

Column chromatography and recrystallisation from chloroform gave white solid, mp 141 °C.; IR (KBr): 1736 cm^{-1}(C=N) and 1236 cm^{-1}(C-N).UV (MeOH): 351 nm (log ε 4.3), 269 nm (log ε 4.1). ^1H NMR ($CDCl_3$) (200MHz): δ 7.40(d, J=8.3Hz, H-2", 6"), 7.21-7.33(m, H-3", 5"), 6.92-7.18(m, H-5', 6', 7'; H-3" 5" H-2", 6"), 6.70-6.91(m, H-8`; H-4"), 6.61(s, H-4'), 5.46(d, J=5.2Hz, H-3), 4.95(d, J=5.211z, H-4), 4.75(AB quartet, J=14.3Hz, 2'-OCH_2), 2.33(s, 4"-CH_3).^{13}C NMR($CDC1_3$)(100.6MHz): δ 163 .5(C=O at C-2), 157.0(C-H"), 153.2(C-8'a), 134.7(C-1"), 133.4(C-3'), 129.8(C-7'), 129 8(C-3",5"), 129.6(C-3",5"), 127.6(C-4"), 126.8(C-5'), 126.1(C-4'), 122.6(C-4"), 121.8(C-4'a), 121.5(C-6'), 117.1(C-2", 6"), 116.2(C-8'), 115.8 (C-2", 6"), 81.8(C-3), 65.4(C-2'), 61.2(C-4), 20.9(C-4"-CH_3).MS: m/z 406$[M+Na]^+$ and 384$[M+H]^+$.

vi) 4-(6-Chloro-2H-chromene-3y1)-3-phenoxy-1-(4-methylphenyl)azetidin-2-one (3f):

Column chromatography and recrystallisation from chloroform gave white solid, mp 97 °C.; IR (KBr): 1740 cm^{-1} (C=O) and 1231 cm^{-1}(C-N); UV (MeOH): 340 nm (log ε 4.6) and 265 nm (log ε 4.2); ^1H NMR ($CDC1_3$+DMSO-d_6)(300MHz): δ 7.22-7.53(m, H-2",6"; H-3",5"), 6.91-7.19(m, H-51,7'; H-3",5"; H-2",4'",6'"), 6.70(d, J=8.3Hz, H-8'), 6.52(s, 14-4'), 5.46(d, 3=5.2Hz, H- 3), 4.94(d, J=5.2Hz, H-4), 4.75(AB quartet, J=14.3Hz, 2'-OCH_2), 2.33(4"-CH_3).; ^{13}C NMR ($CDC1_3$) (100.6 MHz): δ 162.2(C=O at C-2), 156.9(C-1'"), 152.3(C-8'a), 134.8(C-134 1(C-4"), 129.8(C-3", 5"), 129.5(C-7'), 129.5(C-7), 5"), 129.2(C-3'), 126.3(C-4'), 124.9(C-5'), 122.7(C-4'a), 120.1(C-4'"), 117.0(C-6'), 116.9(C-2'",6'"), 115.6(C-8'), 114.7(C-2", 6"), 81.7(C- 3), 65.5(C-2'), 60.9(C-4), 20.9(C-4"-CH_3).; MS: m/z 440$[M+Na]^+$ and 418$[M+H]^+$

vii) 4-(6-Bromo-2H-chrornene-3y1)-3-phenoxy-1-(4-methylphenyl) azetidin-2-one (3g):

Column chromatography and recrystallisation from chloroform gave white solid, mp 148 ºC; IR (KBr): 1740 cm^{-1}(C=O) and 1227 cm^{-1}(C-N).; UV (MeOH): 346 nm (log ε 4.1), 279 nm (log ε 4.3) and 254 nm (log ε 4.7).; ^1H NMR ($CDCl_3$) (300MHz): δ 6.82-7.43(m, H-5', 7': H-2", 3",5",6": H-2", 3 ",4`,5",6"), 6.65(d, J=8.3Hz, H-8'), 6.51(s, 14-4'), 5.46(d, J=5.2Hz, H-3), 4.93(d, J=5.2Hz, H-4), 4.74(AB quartet, J=14.3Hz, 2'-OCH_2), 2.32(4"-CH_3).; ^{13}C NMR ($CDC1_3$)

(100.6 MHz): δ 162.4(C=O at C-2), 157.0(C-1''), 152.9(C-8'a), 134.9(C-1''), 134.6(C-4''), 132.2(C-7'), 129.9(C-3'',5'') 129.6(C-3''',5'''), 129.2(C-5'), 128.9(C-3), 124.9(C4'), 123.6(C-4a), 122.7(C-4''), 117.5(C-8'), 117.0(C-2''', 6'''), 1 15.6(C-2'',6''), 113.5(C-6'), 81 .6(C-3), 65.5(C-2'); 60.8(C-4), 20.9(C-4''-CH_3)-; Ms: m/z 463$[M+H]^+$.

viii) 4-(6-Methyl-2H-chromene-3y1)-3-phenoxy- 1-(4-methylphenyl)azetidin-2-one (3h):

Column chromatography and recrystallisation from chloroform gave white solid, mp127 °C; IR (KBr): 1734 cm^{-1} (C=O) and 1227 cm^{-1}(C-N) UV (MeOH) 338 nm (log ε 4.4) and 266 nm (log ε 4.2).^{1}H NMR ($CDC1_3$) (300MHz): δ 7.51(d, J=8.3Hz, H-2'', 6''), 7.25(m, H-3'', 5''), 6.92-7.20(m, H-5',7'; H-3'',5'', H-2''',6'''), 6.73(m, H-8',4''), 6.57(s, H-4), 5.49(d, J=5.2Hz, H-3), 4.95(d, J=5.2Hz, H-4), 4.76(AB qurtet, J=14.3Hz, 2'-OCH_2), 3.71(s, 6'-CH_3), 2.33(s, 4''. CH_3).^{13}C NMR ($CDCl_3$) (50.3 MHz): δ 162.4(C=O at C-2), 156.1(C-1''), 152.8(C-61), 149.7(C 8'a), 134.9(C-1''), 1 34.2(C-4''), 131.1(C-3'', 5''), 129.8(C-3''', 5''), 1 29.0(C-3'), 126.2(C-4), 123.6(C-4'a), 122.4(C-4''),' 116.0(C-2''',6'''), 115.2(C-T). 114.9(C -5), 1 14.2(C-2'',6''), 112.8(C-8'), 81 .5(C-3), 65 .3(C-2'), 61 .4(C-4), 55 .7(C-6'-CH_3), 20.6(C-4''-CH_3).; MS: m/z 397$[M+H]^+$.

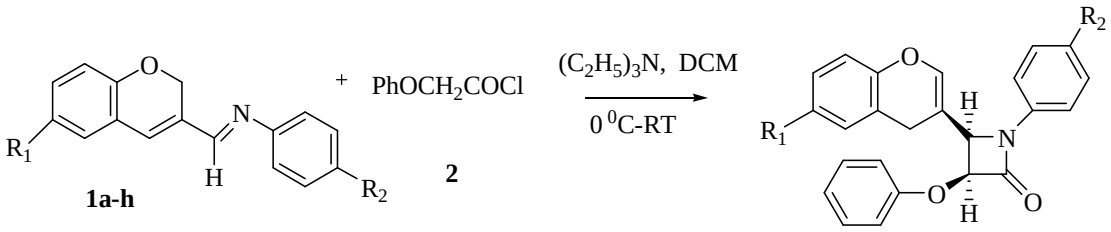
RESULTS AND DISCUSSION

Synthesis of 4-(2H-chromene-3yl)-3-phenoxy-1-(4-methylphenyl) azetidin-2-ones (3a-h)[11-15]

Equimolar amount of 2H-3-chromeneimines**(1a),** phenoxyacetylchloride**(2)** and triethylamine in CH_2Cl_2 at 0 ºC to room temperature in a Staudinger reaction to give 4-(2H-chromene-3yl)-3-phenoxy-1-(4-methylphenyl) azetidin-2-ones (β-lactams) **(3a-h**). In the IR spectrum of 4-(2H-chromene-3y1)-3-phenoxy-1-(4-methoxyphenyl) azetidin-2-one **(3a),** the β-lactam ring C=O absorption is observed at 1740 cm^{-1} and C- N observed at 1240 cm^{-1}. Its UV (MeOH) spectrum of **3a** showed bands at 352 nm (log ε 4.4) and 279 nm (log ε 4.7). In its ^{1}H NMR of **3a** the signals due to the β-lactam ring system H-3 appeared at δ 5.46 as a doublet (J=5.2 and H-4 appeared as a doublet (J=5.2 Hz) at δ 4.92. The methylene protons of 2H-3-chromene ring at C-2' appeared at δ 4.77 as AB quartet (J=14.3 Hz). These three values are that the new lactam ring is pendent at C-3 of the chromene. The other ^{1}H NMR signals are H-4' appeared as a singlet at δ 6.61, the H-8',H-3'',5'',H-4''' protons appeared as a multiplet at δ 6.71-6.90, the H-5,6',7', H-2''',6'' protons appeared at δ 6.92-7.19 as a multiplet and H-3''',5''' appeared at δ 7.21-7.35. H-2'', 6'' appeared as a doublet at δ 7.43 (J=9.0Hz). The β-lactam H-3 and H-4 appeared as a doublets at δ 5.46 and 4.92 with J=5.2 Hz. .The ^{13}C NMR ($CDC1_3$) of **3a** showed the signals due to the β-lactam ring carbons as follows: δ 61.4(C-4), 81.8(C-3) and 162.2(C0 at C-2). The carbon signal assignments due to 21-1-3-chromene moiety are δ 65.4(C-2'), 130.7(C-3'), 126.3(C-4'), 121.9(C-4'a), 126.9(C-5'), 121.5(C-6'), 129.8(C-7'), 115.8(C-3') and 154.0(C-8'a). The carbon signals of the 1-(4''-methoxyphenyl) ring are δ 127.6(C-1''), 118.5(C-2'', 6'').

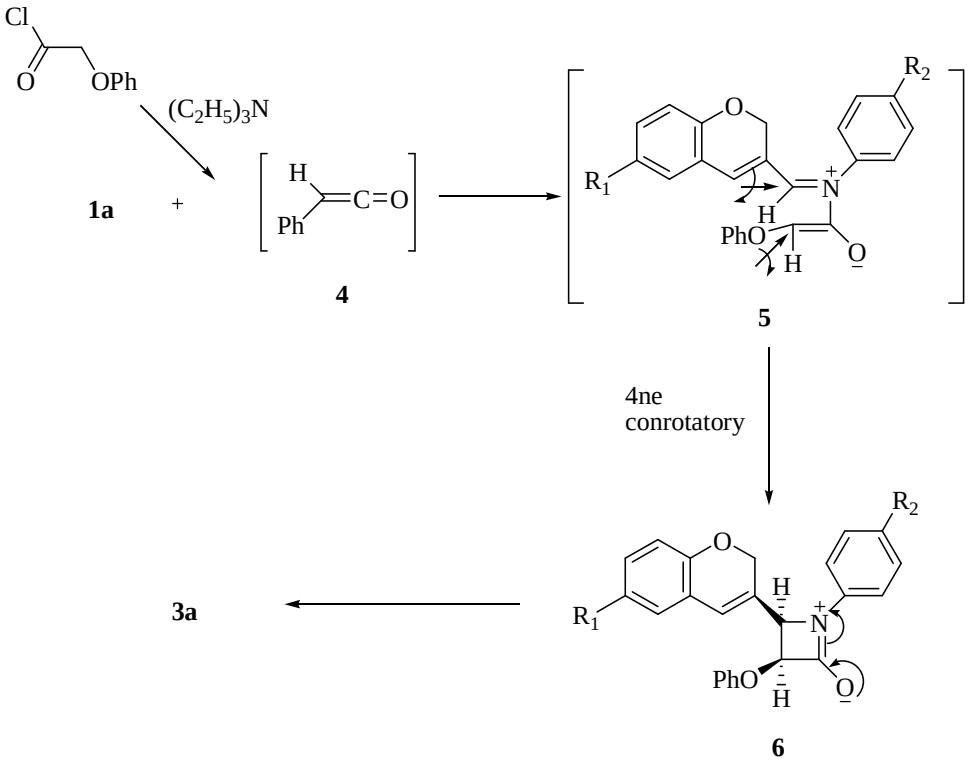
The mechanic pathway of **(1a-3a)** is shown in (**scheme-2**). Staudinger reaction is stepwise in nature, instead of a concerted (although asynchronous) [2+2] cycloaddition. The first step of the reaction consists of a nucleophilic attack of the imine nitrogen to the sp-hybridized carbon atom of the ketene **(5)** (which generated in situ from phenoxyacetyl chloride **(2)** in the presence of Et_3N) to give Zwitterionic intermediate **(6).** This intermediate **6** on conrotatorythermal electrocyclisation

Scheme-1



1,3 **a** = R_1 = H, R_2 = OCH_3 **e** = R_1 = H, R_2 = CH_3
b = R_1 = Cl R_2 = OCH_3 **f** = R_1 = Cl R_2 = CH_3
c = R_1 = Br R_2 = OCH_3 **g** = R_1 = Br R_2 = C H_3
d = R_1 =CH_3 R_2 = OCH_3 **h** = R_1 =CH_3 R_2 =CH_3

Scheme-2



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