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Research Article

AN EFFICIENT SYNTHESIS OF ETHYL [2-(2H-CHROMENE-3Y1)-4 OXO-1, 3-THIAZOTIDIN-3-YL) ACETATES

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ABSTRACT

*G*lycine ethyl ester hydrochloride salt **(2),** 2H-3-chromene carbaldehydes **(1a-h),** mercapto acetic acid **(3)** and diisopropylethylamine in benzene was heated to reflux with Dean-Stark trap for 18 h to give ethyl [2-(2H-chromene-3y1)-4-oxo-1, 3 -thiazolidin-3y1) acetate **(4a-h)** in good yields.

Keywords*: G*lycine ethyl ester hydrochloride salt, 2H-3-chromene carbaldehydes, diisopropylethylamine, mercapto acetic acid, Dean-Stark trap method.

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, chromones, 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.

METERIAL AND METHODS

General: - Melting points were determined on a Polmon instrument (model no. MP 96).IR spectra were recorded on FT-IR Perkin-Elmer 1605 spectrometer, and ^{1}H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) were recorded on a VarianGemini 200 spectrometer using TMS as internal standard (chemical shifts and ppm). UV spectra were obtained on a Shimadzu UV-visible spectrophotometer (model UV-1601). Mass spectra were recorded on a VG micromass70-70H instrument.

General procedure for the Synthesis of ethyl [2-(2H-chromene-3y1)-4-oxo-1,3-thiazolidin-3-y1)acetates (4a-h):

i) Synthesis of ethyl -2-(2H-chromene-3y1)-4-oxo-1,3-thiazoliclin-3-y1) acetate (4a):

A mixture of glycine ethyl ester hydrochloride salt **(2)** (1.67g, 12nunol), 2H-3-chromenecarbaldehyde **(1a)** (3.84g, 24mmol), mercaptoacetic acid **(3)** (2.5mL, 36mmol) and diisopropylethylamine (2.61mL, 15mmol) in 50mL of benzene was heated to reflux with a Dean-Stark trap for 18 h during which time about 0.5mL of water was collected in the trap. The reaction mixture was cooled to room temperature and diluted with EtOAc. The organic phase was washed with saturated $NaHCO_3$, 1N HC1 and saturated NaCl. The organic solution was dried with $MgSO_4$ and concentrated to give a light brownish oil, which was chromatographed over silica gel (60-120 mesh) by eluting with pet.ether: ethyl acetate (9:1) to afford ethyl [2-(2H-chromene-y1)-4-oxo-1,3-thiazolidin-3-yl]acetate **(4a)** as a colorless oil (semi solid)(2.07g, 65% yield).

IR (KBr): 1673 cm^{-1}(C=O).

UV (MeOH): 349 nm (log ε 4.1), 282 nm (log ε 4.4) and 235 nm (log ε 4.5).

^{1}H NMR ($CDCl_3$) (200 MHz): δ 6.75-7.20(m, H-5`, 6', 7', 8), 6.50(s, H-4), 5.49(s, H-2),

4.83(d, J=13.5Hz, OCH of 2'-OCH_2), 4.57(d, J=13.5Hz, OCH of 2'-OCH_2), 4.40(d,-J=17.3Hz, S-CH), 4.18(q, J=6.7Hz, $COOCH_2CH_3$), 3.64(m, S-CH and N-CH_2), 1.25(t,J=6.7Hz, $COOCH_2CH_3$).

^{13}C NMR ($CDC1_3$) (100.6 MHz): δ 171.9(C=O at C-4), 167.7($COOCH_2CH_3$), 154.1(C-8a), 130.3(C-7'), 128.8(C-3), 127.2(C-5'), 125.6(C-4). 121.7(C-6'), 121.4(C-4'a), 115.9(C-8'), 63.8(C-2'-OCH_2), 63.2(C-2), 61.7($COOCH_2CH_3$), 44.0(N-CH_2), 32.0(S-CH_2), 14.0

($COOCH_2CH_3$).

MS: m/z 319(M^+) (20), 244(35), 175(100), 145(45) and 131(50).

Employing the similar procedure as mentioned for **4a,** compounds **4b-h** were obtained from **1b-h** as semi solids in 60-70% yield.

ii) Ethyl [2-(6-chloro-2H-chromene-3y1)-4-oxo-1, 3-thiazolidin-3-yl]acetate (4b):

Column chromatography elution with pet.ether: ethyl acetate (9:1) gave as a light brown Colored semi solid.

IR (KBr): 1684 cm^{-1} (C=O).

UV (MeOH): 342 nm (log ε 4.6), 277 nm (log ε 4.3) and 229 nm (log ε 4.2).

^{1}H NMR ($CDCl_3$) (300MHz): δ 6.90-7.24(m, H-5', 7'), 6.79(d, J=8.3Hz, H-8'), 6.38(s, H-4'), 5.39(s, H-2), 4.77(d, J=13.5Hz, OCH of 2'-OCH_2), 4.52(d, J=13.5Hz, OCH of 2'-OCH_2), 4.32(d, J=17.3Hz, S-CH), 4.09(q, J=6.7Hz,, $COOCH_3$), 3.58(m, S-CH and N-CH_2),1.17(t, J=6.7Hz, $COOCH_2CH_3$).

^{13}C NMR ($CDC1_3$) (50.3MHz): δ 172.3(C=O at C-4), 168.2($COOCH_2CH_3$), 154.7(C-8a),

132.5(C-3'), 129.5(C-7'), 128.9(C-4), 122.5(C-4a), 121.9(C-5), 119.0(C-6'), 113.2(C-8'),

64.8(C-2'-OCH_2), 62.1(C-2), 61 .5($COOCH_2CH_3$), 41 .5(N-CH_2), 32.6(S-CH_2), 13.9

($COOCH_2CH_3$).

MS: m/z 354[M+H]$^+$

iii) Ethyl [2-(6-bromo-2H-chrornene-3yl)-4-oxO-1,3-thiazohdin-3-yl]acetate (4c):

Column chromatography elution with pet.ther : ethyl acetate (8.5:1.5) gave as a light brown colored semi solid.

IR (KBr): 1678 cm^{-1}(C=O).

UV (MeOH): 338 nm (log ε 4:1), 281 nm (log ε 4.5) and 246 nm (log ε 4.1).

^{1}H NMR ($CDC1_3$) (300MHz): δ 7.21(m, H-7'), 7.11 (d, J=3.0Hz, H-5'), 6.70(d, J=8.3Hz, H- 8'), 6.42(s, H-4'), 5.46(s, H-2), 4.85(d, J=13.5 Hz, OCH of 2'-OCH_2), 4.59(d, J=13.5Hz,

OCH of 2'-OCH_2), 4.38(d, J=17.3Hz, S-CH), 4.18(q, J=6.7Hz, $COOCH_2CH_3$), 3.66(q, J=6.7Hz, N-CH_2), 3.55(d, J=17.3Hz, S-CH), 1.26(t, J=6.7Hz, $COOCH_2CH_3$).

^{13}C NMR ($CDC1_3$) (100.6MHz): δ 172.3(C=O at C-4), 168.2($COOCH_2CH_3$), 154.8(C-8a),

132.3(C-3'), 130.7(C-7'), 129.8(C-5'), 129.3(C-4'), 124.2(C-4a), 112.6(C-8'), 109.8(C-6'),

64.8(C-2'-OCH_2),62.1(C-2),61.6($COOCH_2CH_3$),41.5(N-CH_2),31.4(S-CH_2), 14.0($COOCH_2CH_3$).

MS: m/z 399$[M+H]^+$.

iv) Ethyl -2-(6-methyl-2H-chromene-3yl)-4-oxo- 1, 3-thiazolidin-3-yl] acetate (4d):

Column chromatography from pet.ether: ethyl acetate (9:1) gave as a colorless semi solid

IR (KBr): 1690 cm^{-1}(C=O).

UV (MeOH): 351 nm (log ε 4.4), 276 nm (log ε 4.3) and 233 nm (log ε 4.1)

^{1}H NMR ($CDC1_3$) (300MHz): δ 6.79-7.16(m, H-5', 7, 8'), 6.48(s, H-4'), 5.37(s, H-2), 4.80(d,J=13.5Hz, OCH of 2'-OCH_2), 4.54(d, J=13.5Hz, OCH of 2'-OCH_2), 4.38(d, J=17.3Hz, S-CH), 4.l0(q, J=6.7Hz, $COOCH_2CH_3$), 3.77(s, 6'-CH_3), 3.52(m, S-CH and N-CH_2), 1.26(t, J=6.7Hz, $COOCH_2CH_3$).

^{13}C NMR ($CDC1_3$) (50.3MHz): δ 172.5(C=O at C-4), 168.4($COOCH_2CH_3$), 133.8(C-6'),

150.1(C-8a), 130.1(C-3'), 126.3(C-4'), 122.8(C-4a), 117.0(C-7'.), 114.6(C-5'), 112.2(C-81),

64.6(C-2'-OCH_2), 62.5(C-2), 61 .9($COOCH_2CH_3$), 55.4(C-6'-CH_3), 41 .8(N-CH_2), 31.6(S-CH_2), 14.3($COOCH_2CH_3$).

MS: m/z 350[M+H].

v. Ethyl -2-(2(2-methyl-2H-chromene-3y1)-4-oxo-1,3-thiazoliclin-3-y1) acetate (4e):

Column chromatography elution with pet.ether: ethyl acetate (9:1) gave as a light brown

Colored semi solid.

IR (KBr): 1675 cm^{-1}(C=O).

UV (MeOH): 360 nm (log ε 4.1), 285 nm (log ε 4.4) and 245 nm (log ε 4.5).

^{1}H NMR ($CDCl_3$) (200 MHz): δ 6.75-7.20(m, H-5`, 6', 7', 8), 6.50(s, H-4), 5.49(s, H-2),

4.57(d, J=13.5Hz, 2'-CH_3), 4.40(d,-J=17.3Hz, S-CH), 4.18(q, J=6.7Hz, $COOCH_2CH_3$), 3.64(m, S-CH and N-CH_2), 1.25(t,J=6.7Hz, $COOCH_2CH_3$).

^{13}C NMR ($CDC1_3$) (100.6 MHz): δ 171.9(C=O at C-4), 167.7($COOCH_2CH_3$), 154.1(C-8a), 130.3(C-7'), 128.8(C-3), 127.2(C-5'), 125.6(C-4). 121.7(C-6'), 121.4(C-4'a), 115.9(C-8'), 63.8(C-2'-CH_3), 63.2(C-2), 61.7($COOCH_2CH_3$), 44.0(N-CH_2), 32.0(S-CH_2), 14.0 ($COOCH_2CH_3$).

MS: m/z 333(M^+) (20), 260(35), 159(100).

vi) Ethyl -2-(2(6-chloro-2-methyl-2H-chromene-3y1)-4-oxo-1, 3-thiazolidin-3-yl]acetate (4f).

Column chromatography elution with pet.ether: ethyl acetate (9:1) gave as a light brown

Colored semi solid.

IR (KBr): 2284 cm^{-1} (C=O).

UV (MeOH): 345 nm (log ε 4.6), 275 nm (log ε 4.3) and 300 nm (log ε 4.2).

^{1}H NMR ($CDCl_3$) (300MHz): δ 6.90-7.24(m, H-5', 7'), 6.79(d, J=8.3Hz, H-8'), 6.38(s, H-4'), 5.39(s, H-2), 4.77(d, J=13.5Hz, 2'-CH_3), 4.32(d, J17.3Hz, S-CH), 4.09(q, J=6.7Hz,, $COOCH_3$), 3.58(m, S-CH and N-CH_2), 1.17(t, J=6.7Hz, $COOCH_2CH_3$).

^{13}C NMR ($CDC1_3$) (50.3MHz): δ 174.3(C=O at C-4), 165.2($COOCH_2CH_3$), 155.7(C-8a),

132.5(C-3'), 129.5(C-7'), 128.9(C-4), 127.5(C-4a), 121.9(C-5), 115.2(C-8'), 64.8(C-2'-CH_3), 62.1(C-2), 61 .5($COOCH_2CH_3$), 43 .5(N-CH_2), 32.6(S-CH_2), 14.9 ($COOCH_2CH_3$).

MS: m/z 367 $[M+H]^+$

vii) Ethyl 2-(2-6-bromo-2-methyl2H-chrornene-3yl)-4-oxO-1,3-thiazohdin-3-yl]acetate (4g):

Column chromatography elution with pet.ther : ethyl acetate (8.5:1.5) gave as a light brown colored semi solid.

IR (KBr): 1878 cm^{-1}(C=O).

UV (MeOH): 335 nm (log ε 4:1), 285 nm (log ε 4.5) and 250 nm (log ε 4.1).

^{1}H NMR ($CDC1_3$) (300MHz): 6 7.21(m, H-7'), 7.11 (d, J=3.0Hz, H-5'), 6.75(d, J=8.3Hz, H- 8'), 6.43(s, H-4'), 5.46(s, H-2), 4.59(d, J=13.5Hz, 2'-CH_3), 4.38(d, J=17.3Hz, S-CH), 4.18(q, J=6.7Hz, $COOCH_2CH_3$), 3.66(q, J=6.7Hz, N-CH_2), 3.55(d, J=17.3Hz, S-CH), 1.26(t, J=6.7Hz, $COOCH_2CH_3$).

^{13}C NMR ($CDC1_3$) (100.6MHz): δ 175.3(C=O at C-4), 168.2($COOCH_2CH_3$), 155.8(C-8a),

132.3(C-3'), 130.7(C-7'), 129.8(C-5'), 131.3(C-4'), 124.2(C-4a), 112.6(C-8'), 64.8(C-2'-OCH_2), 62.1(C-2), 61 .6($COOCH_2CH_3$), 42 .5(N-CH_2), 31 .4(S-CH_2), 15.0($COOCH_2CH_3$).

MS: m/z 412$[M+H]^+$.

viii) Ethyl 2-(2-2,6-dimethyl-2H-chromene-3yl)-4-oxo- 1, 3-thiazolidin-3-yl] acetate (4h):

Column chromatography from pet.ether: ethyl acetate (9:1) gave as a colorless semi solid

IR (KBr): 1690 cm^{-1}(C=O).

UV (MeOH): 355 nm (log ε 4.4), 275 nm (log ε 4.3) and 245 nm (log ε 4.1)

^{1}H NMR ($CDC1_3$) (300MHz): δ 6.75-7.15(m, H-5', 7, 8'), 6.48(s, H-4'), 5.37(s, H-2), 4.85(d,J=13.5Hz, CH_3), 4.38(d, J=17.3Hz, S-CH),- 4.l0(q, J=6.7Hz, $COOCH_2CH_3$), 3.75(s, 6'-CH_3), 3.55(m, S-CH and N-CH_2), 1.24(t, J=6.7Hz, $COOCH_2CH_3$).

^{13}C NMR ($CDC1_3$) (50.3MHz): δ 175.5(C=O at C-4), 165.4($COOCH_2CH_3$), 135.8(C-6'),

150.1(C-8a), 130.1(C-3'), 126.3(C-4'), 122.8(C-4a), 117.0(C-7'.), 114.6(C-5'), 112.2(C-81),

64.6(C-2'-OCH_2), 62.5(C-2), 61 .9($COOCH_2CH_3$), 55.4(C-6'-OCH_3), 42 .8(N-CH_2), 31.6(S-CH_2), 14.5($COOCH_2CH_3$).

MS: m/z 347[M+H].

RESULT AND DISCUSSIONS

Synthesis of ethyl [2-(2H-chromene-3y1)-4 oxo-1, 3-thiazotidin-3y1) acetates (4a-h)[11-15]

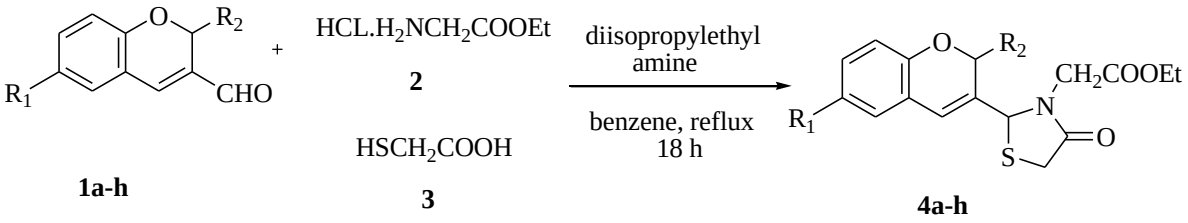
A mixture of glycine ethyl ester hydrochloride salt **(2),** 2H-3-chromene carbaldehydes **(1a-h),** mercapto acetic acid **(3)** and diisopropylethylamine in benzene was heated to reflux with Dean-Star trap for 18 h to give ethyl [2-(2H-chromene-3y1)-4-oxo-1, 3 -thiazolidin-3y1) acetate **(4a).** In the IR spectrum of **4a**, the carbonyl group of thiazolidinone showed absorption at 1673 cm^{-1} Its UV (MeOH) spectrum showed bands at 349 nm (log ε 4.1), 282 nm (log ε 4.4) and 235 nm (log ε 4.5). In the ^{1}H NMR spectrum of **4a** recorded

in $CDCl_3$ (300MHz) H-2 in the new thiazolidinone ring appeared as a singlet at δ 5.49. The CH_2-5 protons are diastereotopic, one H-5 appeared at δ 4.40 as doublet (J=17.3 Hz) and the other H-S overlapped on the N-CH_2 protons appeared as a multiplet at δ 3.64. The chemical shifts and multiplicities of H-2, CH_2-5 suggests that a new thiazolidinone ring formed, which is pendent at C-3 of the chromene. The N-CH_2 protons overlapping with one H-S appeared at δ 3.64 as a multiplet. The OCH_2 of COOEt appeared as a quartet at δ 4.18(J=6.7 Hz) and the CH_3 appeared at δ 1.25 as a triplet (J=6.7Hz).

In the ^{13}C NMR spectrum ($CDC1_3$) (100.6 MHz) of ethyl [2-(2H-chromene-3y1)-4-oxo-1, 3-thiazolidin-3y1) acetate **(4a),** the carbon signal assignments due to the thiazolidinone ring are as follows: the C-4 carbonyl resonated at δ171.9, C-2 at δ 63.2and C-5 at δ 32.0. The N-CH_2 appeared at δ 44.0, the OCH_2 and CH_3 of the ester group appeared at δ 61.7 and 14.0. The carbon signal assignments in the 2H-3-chromene moiety are as follows: δ 63.8(C-2'), 128.8(C-3'), 125.6(C-4`), 121.4(C-4'a), 127.2(C-5'), 121.7(C- 6'), 130.3(C-7'), I15.9(C-8') and 154.1(C-8'a).

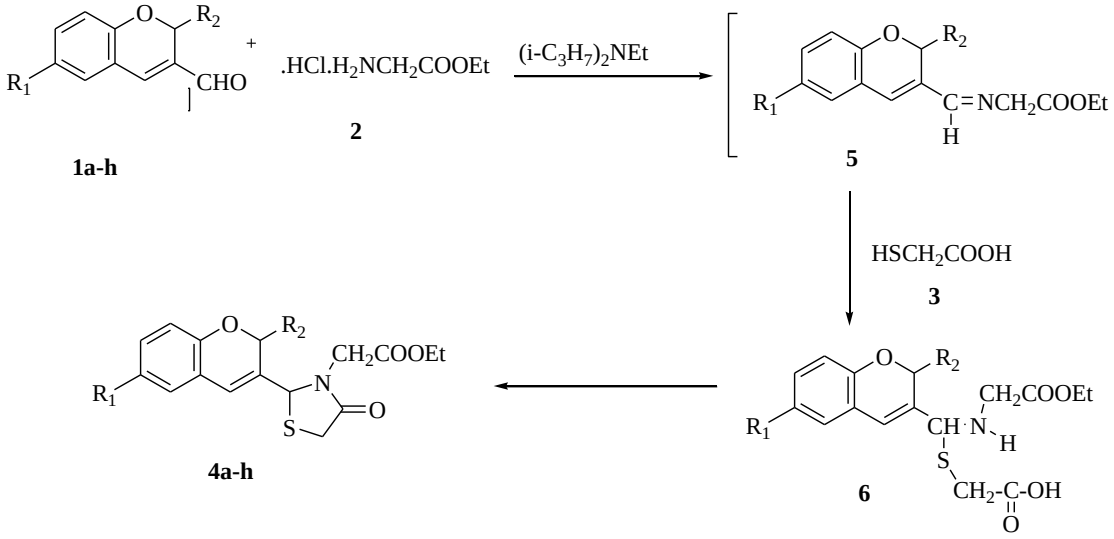
In the EI mass spectrum of **4a** the molecular ion appeared at ring 319 and the other ions observed at m/z 244 (33), 175(100) and 131(50).

The mechanic pathway of **1a-4a** first step is the formation of imines **(5a-h)** by the reaction of aldehydes **(4a- h)** with glycine ethyl ester hydrochloride salt **(2)** in the presence of diisopropylethylamine (base). Nucleophilic attack of the SR of mercaptoacetic acid **(3)** on the imine carbon gives an intermediate **6a-h**. Base catalyzed cyclization of **6a-h** by the elimination of water gives rise to thiazolidinones **(4a-h)** (Scheme-2).



1, 4 **a** = R_1 = H, R_2 = H; **b** = R_1 = Cl R_2 = H; **c** = R_1 = Br R_2 = H; **d** = R_1 = CH_3 R_2 = H; **e** = R_1 = H, R_2 = CH_3; **f** = R_1 = Cl R_2 = CH_3; **g** = R_1 = Br R_2 = CH_3; **h** = R_1 = CH_3 R_2 = CH_3

Scheme 1



Scheme 2

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