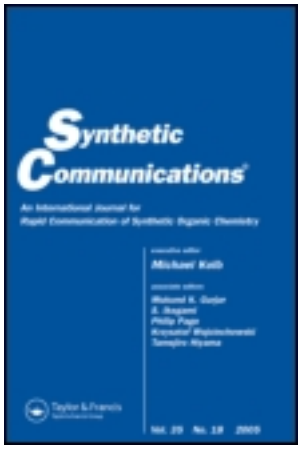

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Synthesis of Substituted Tetrahydrochromenes by the Reactions of α,β-Unsaturated Cyanoesters with Dimedone/1,3-Cyclohexanedione

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SYNTHESIS OF SUBSTITUTED TETRAHYDROCHROMENES BY THE REACTIONS OF α,β-UNSATURATED CYANOESTERS WITH DIMEDONE/1,3-CYCLOHEXANEDIONE

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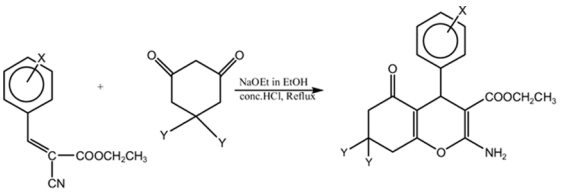
GRAPHICAL ABSTRACT



Y = CH_3/H
X = 4-CH_3, 4-N $(CH_3)_2$, 2-OCH_3, 2-Cl.

Abstract *Ethyl esters of 2-cyano-3-arylacrylic acid* ***1a–d*** *(a = 4-CH_3-C_6H_4-, b = 4-N$(CH_3)_2$-C_6H_4-, c = 2-CH_3O-C_6H_4-, d = 2-Cl-C_6H_4-) reacted with 5,5-dimethyl-1,3-cyclohexanedione (****2p****, Y=CH_3), and* ***1e–g*** *(****e*** *= 4-CH_3-C_6H_4-, ****f*** *= 2-CH_3O-C_6H_4-, ****g*** *= 2-Cl-C_6H_4-) reacted with 1,3-cyclohexanedione (****2q****, Y=H) in the presence of alcoholic sodium ethoxide to give the corresponding ethyl esters of 2-amino-7,7-dimethyl-5-oxo-4-aryl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylic acid* ***4a–d*** *and 2-amino-5-oxo-4-aryl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylic acid* ***4e–g****. The structures of the compounds* ***4a–g*** *were confirmed by their ultraviolet, infrared, ^{1}H NMR, ^{13}C NMR, and mass spectral data and elemental analyses.*

Keywords 4*H*-Chromene; 1,3-cyclohexanedione; 5,5-dimethyl-1,3-cyclohexanedione; α,β-unsaturated cyanoesters

INTRODUCTION

Synthesis of chromenes and its derivatives has been a subject of considerable interest during past decades because of their usefulness as biologically active agents.[1,2] Reports are available for the biological and pharmacological properties of substituted 4*H*-chromenes, such as spasmolytic, diuretic, anti-coagulant, anti-cancer,[3] anti-ancaphylactia,[4] and molluscicidal activity.[5] They are also used

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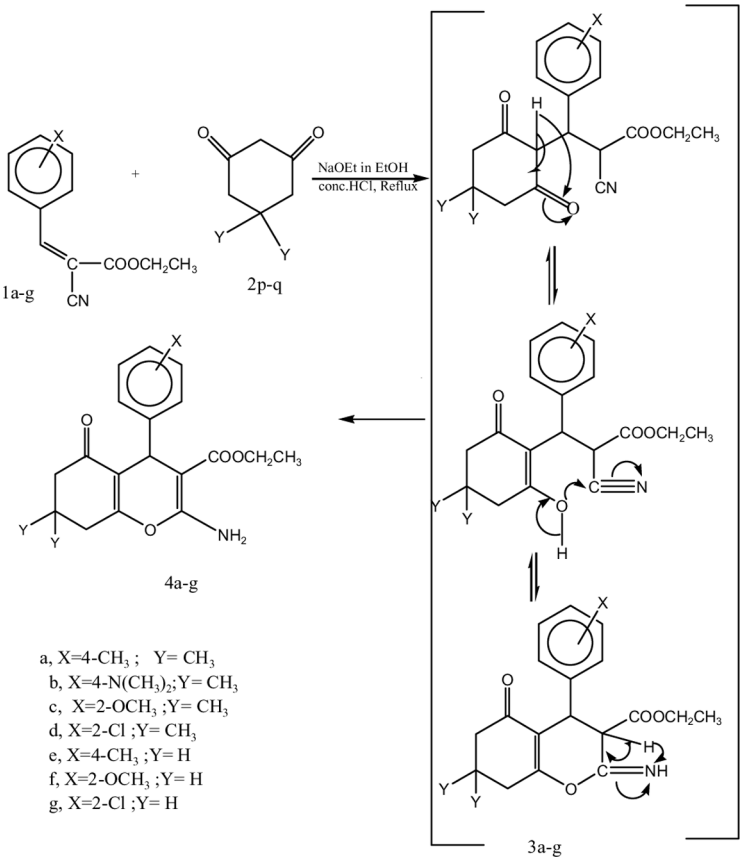
for the treatment of neurodegenerative disease, AIDS-associated dementia, and Down syndrome as well as for schizophrenia and mycolonus. Besides, polysubstituted 4*H*-chromenes constitute the structural unit of many natural products,[6] and 2-amino-4*H*-chromenes are useful as photoactive materials.[7] Thus, several methods have been reported for the synthesis of these compounds.[8–15] However, many of these methods were associated with use of hazardous organic solvents, poor yields of products, and lack of general applicability; particularly, synthesis of substituted 4*H*-chromene was rarely addressed. This prompted us to develop a convenient method for the synthesis of 4-aryl-4*H*-chromene derivatives, and we report herein the synthesis of 4-aryl-4*H*-chromene derivatives via a tandem Knoevenagel and cyclocondensation reaction using sodium ethoxide as catalyst.

α,β-Unsaturated cyanoesters **1a**–**g** were prepared via Knoevenagel condensation of the corresponding aldehydes with ethyl cyanoacetate in the presence of a base catalyst as reported in the literature.[16] Compounds **1a**–**g** were reacted with dimedone/1,3-cyclohexanedione **2p**–**q** in the presence of sodium ethoxide in ethanol to give tetrahydro-4*H*-chromenes **4a**–**g** (Scheme 1). The structures of **4a**–**g** were



Scheme 1. Synthesis of tetrahydro-4H-chromenes **4a**–**g**.

confirmed with the help of their ultraviolet (UV), Infrared (IR), ^{1}H NMR, ^{13}C NMR, mass spectrum, and elemental analyses. The formation of **4a–g** may be explained by the initial formation of 1:1 adduct **3a–g**, which presumably underwent subsequent cyclization.

EXPERIMENTAL

Melting points were determined on an Electrothermal micromelting-point apparatus and uncorrected. The UV spectra were recorded using a Shimadzu UV-160A spectrophotometer. IR spectra were recorded using a Shimadzu IR-470A spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were taken in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard on a Bruker 400-MHz spectrophotometer. Mass spectra were carried out using a Jeol JMS-HX 110A instrument.

General Procedure

A mixture of α,β-unsaturated cyanoester **1a-g** (5 mmol), dimedone/1,3-cyclohexanedione **2p–q** (5 mmol), 5% sodium ethoxide in dry ethanol (1.5 ml), and dry ethanol (25 ml) was refluxed for 12–15 h. The progress of the reaction was followed, and purity of the product was checked by thin-layer chromatographic (TLC) silica-gel plates using $CHCl_3$ as eluting solvent. The reaction mixture was cooled to room temperature, and the volume was reduced by evaporation. It was then neutralized with 0.1 M HCl acid and extracted with ether (3×25 ml). The ether extract was dried over anhydrous Na_2SO_4 and evaporated in a rotary vacuum evaporator. A solid mass was obtained, which was recrystallized from hot ethanol.

2-Amino-7,7-dimethyl-5-oxo-4-(4-methylphenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylic Acid Ethyl Ester, 4a

Yield 92%; white crystalline solid; mp 160–162 °C; R_f value in TLC 0.56 (neat chloroform); IR (KBr) (ν_{max}, cm^{-1}): 3395, 3280 (N-H), 1680, 1650 (C=O), 1610, 1510 (C=C stretching of phenyl), 1350 (C-N stretching), 1270, 1190 (C-O stretching); ^{1}H NMR δ (in ppm): 7.14 (d, $J = 8.0$ Hz, ArH, 2H), 6.99 (d, $J = 8.0$ Hz, ArH, 2H), 6.14 (br s, NH_2, 2H), 4.66 (s, C_4-H, 1H), 4.02 (q, $J = 8.0$ Hz, -C$\underline{H_2}$CH$_3$, 2H), 2.40 (s, methylene protons at C-6, 2H), 2.25 (s, ArC$\underline{H_3}$, 3H), 2.15 (d, $J = 16.40$ Hz, C_8-H, 1Hax), 2.13 (d, $J = 16.40$ Hz, C_8-H, 1Heq), 1.17 (t, $J = 8.0$ Hz, -CH$_2$C$\underline{H_3}$, 3H), 1.08 (s, CH_3 at C-7, 3H), 0.97 (s, another CH_3 at C-7, 3H); ^{13}C NMR δ (in ppm): 196.4 (C=O), 169.1 (C-2), 161.2 (–$\underline{C}$OOCH$_2$CH$_3$), 158.3 (C-9), 142.8, 135.4, 128.5 (2C), 128.0 (2C) (6C-aromatic), 117.0 (C-10), 81.0 (C-3), 59.6 (COO$\underline{C}$H$_2$CH$_3$), 50.8 (C-6), 40.7 (C-8), 33.4 (C-4), 32.2 (C-7), 29.1 ($\underline{C}$H$_3$ at C-7), 27.5 (another $\underline{C}$H$_3$ at C-7), 21.0 (Ar$\underline{C}$H$_3$), 14.2 (COOCH$_2\underline{C}$H$_3$); MS: m/z 355.11 (M^+). Anal. calcd. for $C_{21}H_{25}NO_4$: C, 70.98; H, 7.04; N, 3.94. Found: C, 70.80; H, 7.03; N, 3.91.

2-Amino-4-(4-N,N-Dimethylaminophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylic Acid Ethyl Ester, 4b

Yield 70%; white solid; mp 155–157 °C; R_f value in TLC 0.60 (neat chloroform); IR (KBr) (ν_{max}, cm^{-1}): 3400, 3280 (N-H), 1680, 1640 (C=O), 1610, 1510

(C=C stretching of phenyl), 1350 (C-N stretching), 1275, 1190 (C-O stretching); ^{1}H NMR: δ (in ppm): 7.13 (d, $J = 8.0$ Hz, ArH, 2H), 6.99 (d, $J = 8.0$ Hz, ArH, 2H), 6.21 (s, NH_2, 2H), 4.66 (s, C_4-H, 1H), 4.05 (q, $J = 7.10$ Hz, -C$\underline{H}_2$CH$_3$, 2H), 2.40 (s, methylene protons at C-6, 2H), 2.25 (s, NC$\underline{H}_3$, 6H), 2.23 (d, $J = 13.60$ Hz, C_8-H, 1Hax), 2.17 (d, $J = 13.60$ Hz, C_8-H, 1Heq), 1.16 (t, $J = 7.10$ Hz, -CH$_2$C$\underline{H}_3$, 3H), 1.07 (s, CH_3 at C-7, 3H), 0.96 (s, another CH_3 at C-7, 3H); ^{13}C NMR δ (in ppm): 196.3 (C=O), 169.6 (C-2), 161.2 (C$\underline{C}$OOCH$_2$CH$_3$), 158.3 (C-9), 142.8, 135.3, 128.5 (2C), 128.0 (2C) (6C-aromatic), 117.0 (C-10), 80.7 (C-3), 59.5 (COO$\underline{C}$H$_2$CH$_3$), 50.8 (C-6), 40.6 (C-8), 33.3 (C-4), 32.1 (C-7), 29.0 ($\underline{C}$H$_3$ at C-7), 27.3 (another $\underline{C}$H$_3$ at C-7), 20.9–20.6 [N($\underline{C}$H$_3$)$_2$], 14.1 (COOCH$_2\underline{C}$H$_3$). MS: m/z 384.08 (M^+). Anal. calcd. for $C_{22}H_{28}N_2O_4$: C, 68.75; H, 7.29; N, 3.64. Found: C, 63.95; H, 5.88; N, 3.66.

2-Amino-4-(2-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylic Acid Ethyl Ester, 4c

Yield 70%; white crystalline solid; mp 153–154 °C; R_f value in TLC 0.69 (neat chloroform); IR (KBr) (ν_{max}, cm^{-1}): 3450, 3400 (N-H), 1690, 1640 (C=O), 1590, 1505 (C=C stretching of phenyl), 1360 (C-N stretching), 1270, 1190 (C-O stretching); ^{1}H NMR δ (in ppm): 7.35 (d, $J = 7.70$ Hz, ArH, 1H), 7.15–7.05 (m, ArH, 1H), 6.88–6.80 (m, ArH, 1H), 6.75 (d, $J = 8.40$ Hz, ArH, 1H), 6.15 (br s, NH_2, 2H), 4.80 (s, C_4-H, 1H), 4.0 (q, $J = 7.80$ Hz, -C$\underline{H}_2$CH$_3$, 2H), 3.75 (s, OC$\underline{H}_3$, 3H), 2.45 (d, $J = 14.20$ Hz, C_6-H, 1Hax), 2.35 (d, $J = 14.20$ Hz, C_6-H, 1Heq), 2.20 (d, $J = 15.40$ Hz, C_8-H, 1Hax), 2.15 (d, $J = 15.40$ Hz, C_8-H, 1Heq), 1.20 (t, $J = 7.80$ Hz, Hz, -CH$_2$C$\underline{H}_3$, 3H), 1.10 (s, CH_3 at C-7, 3H), 0.95 (s, another CH_3 at C-7, 3H); MS: m/z 371.20 (M^+). Anal. calcd. for $C_{21}H_{25}NO_5$: C, 67.92; H, 6.79; N, 3.77. Found: C, 67.73; H, 6.74; N, 3.75.

2-Amino-4-(2-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylic Acid Ethyl Ester, 4d

Yield 60%; white solid powder; mp 162–164 °C; R_f value in TLC 0.70 (neat chloroform); IR (KBr) (ν_{max}, cm^{-1}): 3400, 3300 (N-H), 1680, 1640 (C=O), 1630, 1520 (C=C stretching of phenyl) 1360 (C-N stretching), 1270, 1190 (C-O stretching); ^{1}H NMR δ (in ppm): 7.35 (d, $J = 7.70$ Hz, ArH, 1H), 7.20 (d, $J = 8.20$ Hz, ArH, 1H), 7.18–7.10 (m, ArH, 1H), 7.10–7.02 (m, ArH, 1H), 6.25 (br s, NH_2, 2H), 5.00 (s, C_4-H, 1H), 4.05 (q, $J = 7.40$ Hz, -C$\underline{H}_2$CH$_3$, 2H), 2.45 (s, methylene protons at C-6, 2H), 2.25 (d, $J = 13.80$ Hz, C_8-H, 1Hax), 2.15 (d, $J = 13.80$ Hz, C_8-H, 1Heq), 1.15 (t, $J = 7.40$ Hz, -CH$_2$C$\underline{H}_3$, 3H), 1.10 (s, CH_3 at C-7, 3H), 0.950 (s, another CH_3 at C-7, 3H); MS: m/z 375.15 (M^+). Anal. calcd. for $C_{20}H_{22}NO_4Cl$: C, 64.0; H, 5.87; N, 3.73. Found: C, 63.84; H, 5.92; N, 3.84.

2-Amino-4-(4-methylphenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylic Acid Ethyl Ester, 4e

Yield 55%; white crystalline solid; mp 168–169 °C; R_f value in TLC 0.75 (neat chloroform); IR (KBr) (ν_{max}, cm^{-1}): 3400, 3000 (N-H), 1680, 1640 (C=O), 1520 (C=C stretching of phenyl), 1360 (C-N stretching), 1280, 1210 (C-O stretching);

^{1}H NMR δ (in ppm): 7.15 (d, $J = 8.50$ Hz, ArH, 2H), 7.00 (d, $J = 8.0$, ArH, 2H), 6.15 (br s, NH_2, 2H), 4.70 (s, C_4-H, 1H), 4.00 (q, $J = 7.80$ Hz, -C$\underline{H}_2$CH$_3$, 2H), 2.60–2.50 (m, methylene protons at C-6, 2H), 2.40–2.30 (m, methylene protons at C-8, 2H), 2.30 (s, ArC$\underline{H}_3$, 3H), 2.10–1.90 (m, methylene protons at C-7, 2H), 1.15 (t, $J = 7.80$ Hz, -CH$_2$C$\underline{H}_3$, 3H) ; MS: m/z 327.20 (M^+). Anal. calcd. for $C_{19}H_{21}NO_4$: C, 69.72; H, 6.42; N, 4.28. Found: C, 69.62; H, 6.50; N, 4.15.

2-Amino-4-(2-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylic Acid Ethyl Ester, 4f

Yield 50%; white crystalline solid; mp 208–210 °C; R_f value in TLC 0.72 (neat chloroform); IR (KBr) (ν_{max}, cm^{-1}): 3350, 3200 (N-H), 1710, 1640 (C=O), 1590, 1505 (C=C stretching of phenyl), 1390 (C-N stretching), 1280, 1210 (C-O stretching); ^{1}H NMR δ (in ppm): 7.35 (d, $J = 7.70$ Hz, ArH, 1H), 7.18–7.10 (m, ArH, 1H), 6.88–6.80 (m, ArH, 1H), 6.75 (d, $J = 8.60$ Hz, ArH, 1H), 6.15 (br s, NH_2, 2H), 4.80 (s, C_4-H, 1H), 4.05 (q, $J = 7.80$ Hz, -C$\underline{H}_2$CH$_3$, 2H), 3.80 (s, OC$\underline{H}_3$, 3H), 2.58–2.50 (m, methylene protons at C-6, 2H), 2.35–2.27 (m, methylene protons at C-8, 2H), 2.05–1.85 (m, methylene protons at C-7, 2H), 1.15 (t, $J = 7.80$ Hz, -CH$_2$C$\underline{H}_3$, 3H); MS: m/z 343.20 (M^+). Anal. calcd. for $C_{19}H_{21}NO_5$: C, 66.47; H, 6.12; N, 4.08. Found: C, 65.84; H, 6.11; N, 4.15.

2-Amino-4-(2-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylic Acid Ethyl Ester, 4g

Yield 60%; white crystalline solid; mp 222–224 °C; R_f value in TLC 0.64 (neat chloroform); IR (KBr) (ν_{max}, cm^{-1}): 3400, 3000 (N-H), 1680, 1640 (C=O), 1610, 1500 (C=C stretching of phenyl), 1360 (C-N stretching), 1250, 1210 (C-O stretching); ^{1}H NMR δ (in ppm): 7.35 (d, $J = 7.70$ Hz, ArH, 1H), 7.20 (d, $J = 7.70$ Hz, ArH, 1H), 7.15–7.10 (m, ArH, 1H), 7.10–7.0 (m, ArH, 1H), 6.25 (br s, NH_2, 2H), 5.00 (s, C_4-H, 1H), 4.00 (q, $J = 7.80$ Hz, -C$\underline{H}_2$CH$_3$, 2H), 2.65–2.50 (m, methylene protons at C-6, 2H), 2.35–2.28 (m, methylene protons at C-8, 2H), 2.10–1.90 (m, methylene protons at C-8, 2H), 1.15 (t, $J = 7.80$ Hz, -CH$_2$C$\underline{H}_3$, 3H). MS: m/z 347.14 (M^+). Anal. calcd. for $C_{18}H_{18}NO_4Cl$: C, 62.16; H, 5.18; N, 4.03. Found: C, 62.19; H, 5.19; N, 4.07.

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