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Reaction of the α-azahetaryl-2-hydroxyacetophenones reaction with chloroacetyl chloride

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The reaction of α-azolyl-2-hydroxyacetophenones with chloroacetyl chloride in acetonitrile in the presence of pyridine resulted in 2-chloromethyl-3-azolylchromones, while both the α-(2-pyridyl) and α-(2-quinolyl) derivatives formed the products of the subsequent intramolecular cyclization with annelation of indolizine or pyrroloquinoline ring to the chromone core.

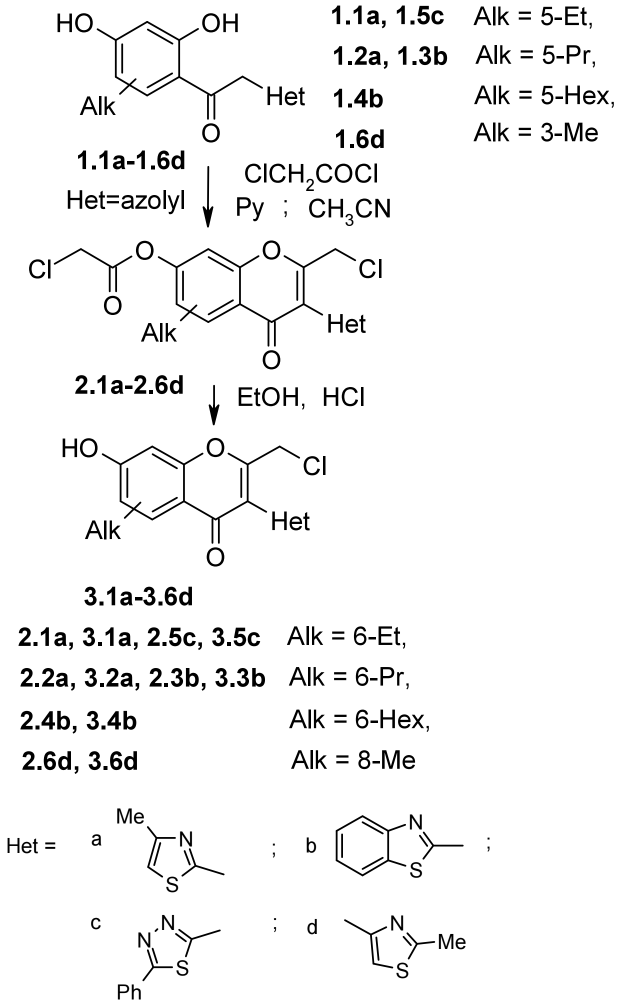
Introduction

Isoflavones are naturally occurring products that possess a wide spectrum of biological activity [1]. 3-Hetarylchromones, heterocyclic analogs of natural isoflavones, are known for their inflammatory, antiviral, anabolic, analeptic, hypoglycemic and hypolipidemic activities [2]. α-Azahetaryl-2-hydroxyacetophenones are the key precursors for the synthesis of 3-azahetarylchromones. We have previously reported that α-azahetaryl-2-hydroxyacetophenones underwent acylation, followed by cyclization with acetic anhydride, trifluoroacetic anhydride and ethoxalyl chloride to give 2-substituted 3-azahetarylchromones [3]. Treatment of α-aryl-2-hydroxyacetophenones with chloroacetic anhydride gave 2-chloromethyl chromones [4].

Results and discussion

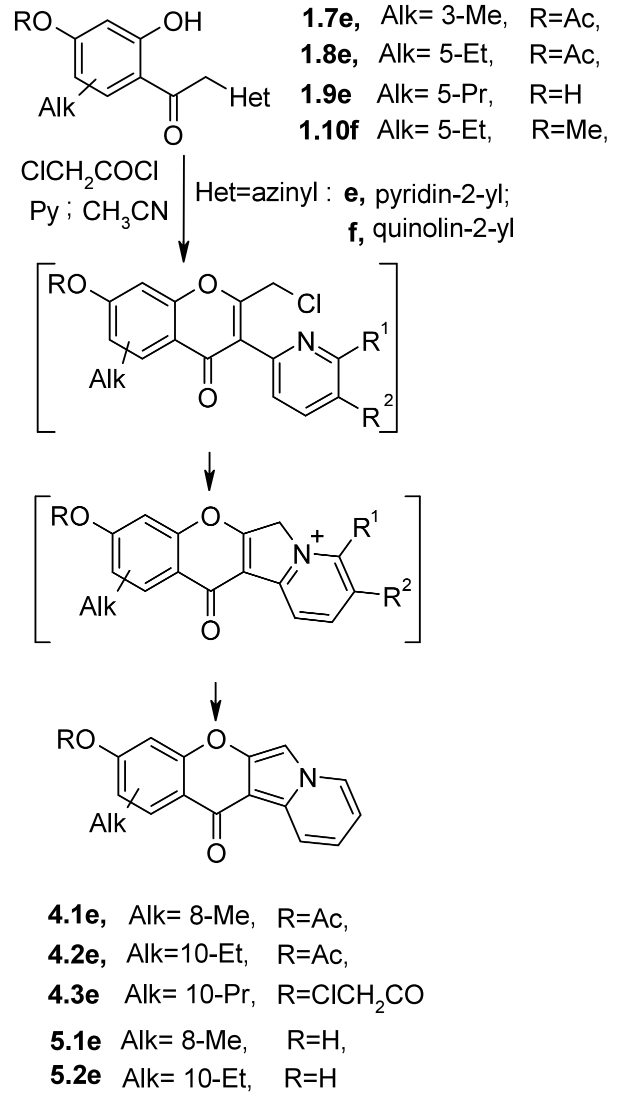
As part of our ongoing interest in the synthesis of the new 3-azahetarylchromones and to extend our earliar work on acylation of α-azahetaryl-2-hydroxyacetophenones, the compounds **1.1a-1.10f** were treated with the excess of chloroacetyl chloride in acetonitrile in the presence of pyridine. Formation of 3-azolyl-7-chloroacetyl-2-chloromethylchromones **2.1a-2.6d** from α-azolyl-2-hydroxyacetophenones **1.1a-1.6d** occurs smoothly in 37-60 % yields. The ^{1}H NMR spectra of products **2.1a-2.6d** revealed the resonances of two methylene groups at 4.65-4.68 ppm ($ClCH_2CO$) and 5.10-5.58 ppm ($2\text{-}ClCH_2$) correspondingly.

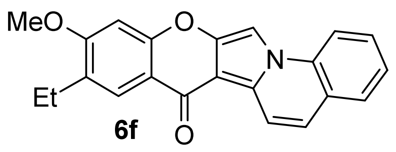
Next we progressed on to elaboration of the hydrolysis of chloroacetates **2.1a-2.6d** to provide 3-azolyl-2-chloromethyl-7-hydroxychromones **3.1a-3.6d.** As expected, the ^{1}H NMR spectra of compounds **3.1a-3.6d** showed disappearance of the signal at 4.65-4.68 ppm of the starting material, while $2\text{-}ClCH_2$ signal remained intact. Finally, a new singlet at 10.77-10.96 ppm was assigned to the 7-OH group.



In contrast with α-azolyl derivatives, both the α-(2-pyridyl) (**1.7e-1.9e**) and α-(2-quinolyl) (**1.10f**) derivatives were found to form the products of the subsequent intramolecular cyclization with annelation of indolizine or pyrroloquinoline ring to the chromone core. This was confirmed by the presence of the characteristic signal of H6 at 7.70-7.80 ppm in the ^{1}H NMR spectra of the products **4.1e-4.3e** and H13 at 7.88 ppm in the spectrum of the product **6f**.

Hydrolysis of compounds **4.1e**, **4.2e** with 5 % NaOH afforded the 9-OH derivatives **5.1e**, **5.2e**.





6f

Conclusion

In conclusion we have reported that the resultant structures in reaction of α-azahetaryl-2-hydroxyacetophenone with chloroacetyl chloride relied upon the structure of heterocycle in starting material.

Experimental part

Reaction progress and identity of obtained compounds were monitored by TLC on Merc 60 F_{254} silica gel plates using $CHCl_3$-MeOH (9:1) system. NMR spectra were recorded on Mercury-400 spectrometer (spectrometer frequency for ^1H: 400 MHz) from DMSO-d_6 and $CDCl_3$ solns. The TMS signal was used as an internal standart. Elemental analyses for C, H, and N were performed using Perkin-Elmer C, H, N Analyser.

Compounds **2.1a, 2.2a**, **2.4b**, **2.5c**, **3.1a**, **3.2a** and **3.4b** were synthesized according to a procedure reported in the literature [5-7].

3-Azolyl-2-chloromethyl-4-oxo-4*H*-7-chromen-yl 2-chloroacetates (2.3b, 2.6d). General procedure

Pyridine (1.22 mL, 15 mmol) and chloroacetyl chloride (1.20 mL, 15 mmol) were added to a solution of compound **1.3b** or **1.6d** (5 mmol) in acetonitrile (15 mL), held for 24 h at room temperature, and obtained precipitate was filtered off and washed with water.

3-(1,3-Benzothiazol-2-yl)-2-chloromethyl-4-oxo-6-propyl-4*H*-7-chromenyl 2-chloroacetate (2.3b)

Yellow solid; yield: 1.39 g (60 %); mp 158 °C. ^1H NMR (DMSO-d$_6$): δ=0.98 (t, $^3J_{HH}$ =7.2 Hz, 3H, CH_3), 1.66 (m, 2H, CH_2), 2.68 (t, $^3J_{HH}$ =7.2 Hz, 2H, CH_2), 4.65 (s, 2H, $ClCH_2CO$), 5.58 (s, 2H, CH_2Cl), 7.46 (t, $^3J_{HH}$ =7.2 Hz, 1H, H6’), 7.53 (t, $^3J_{HH}$ =7.2 Hz, 1H, H5’), 7.67 (s, 1H, H8), 8.07 (d, $^3J_{HH}$=8.4 Hz, 1H, H7’), 8.09 (d, $^3J_{HH}$=8.4 Hz, 1H, H4’), 8.13 (s, 1H, H5).

Anal. Calcd for $C_{22}H_{17}Cl_2NO_4S$: C, 57.15; H, 3.71; Cl, 15.34; N, 3.03; S, 6.93. Found: C, 57.41; H, 3.87; Cl, 15.46; N, 2.76; S, 7.11.

2-Chloromethyl-8-methyl-3-(2-methyl-1,3-thiazol-4-yl)-4-oxo-4*H*-7-chromenyl 2-chloroacetate (2.6d)

Colorless solid; yield: 0.73 g (37%); mp 195 °C ^1H NMR (DMSO-d$_6$): δ=2.37 (s, 3H, 8-CH_3), 2.76 (s, 3H, 2’-CH_3), 4.68 (s, 2H, $ClCH_2CO$), 5.10 (s, 2H, CH_2Cl), 7.29 (d, $^3J_{HH}$=8.4 Hz, 1H, H6), 7.94 (s, 1H, H5’), 8.02 (d, $^3J_{HH}$ =8.4 Hz, 1H, H5).

Anal. Calcd for $C_{17}H_{13}Cl_2NO_4S$: C, 51.27; H, 3.29; Cl, 17.80; N, 3.52; S, 8.05. Found: C, 51.49; H, 3.42; Cl, 17.92; N, 3.20; S, 8.23.

3-Azolyl-2-chloromethyl-7-hydroxy-4*H*-chromen-4-ones (3.3b, 3.5c, 3.6d). General procedure. A solution of compound **2.3b, 2.5c** or **2.6d,** (3 mmol) in a mixture of EtOH (50 mL) and 37% HCl (1 mL) was refluxed for 1.5 h, then set aside overnight at room temperature, filtered off and washed with ethanol and water.

3-(1,3-Benzothiazol-2-yl)-2-chloromethyl-7-hydroxy-6-propyl-4*H*-4-chromenone (3.3b)

Yellow solid; yield: 1.11 g (96 %); mp 305 °C. ^1H NMR (DMSO-d$_6$): δ=1.00 (t, $^3J_{HH}$ =7.2 Hz, 3H, CH_3), 1.67 (m, 2H, CH_2), 2.65 (t, $^3J_{HH}$ =7.2 Hz, 2H, CH_2), 5.56 (s, 2H, CH_2Cl), 6.95 (s, 1H, H8), 7.43 (t, $^3J_{HH}$ =7.6 Hz, 1H, H6’), 7.51 (t, $^3J_{HH}$ =7.6 Hz, 1H, H5’), 7.86 (s, 1H, H5), 8.04 (d, $^3J_{HH}$ =8.0 Hz, 1H, H7’), 8.07 (d, $^3J_{HH}$ =8.0 Hz, 1H, H4’), 10.89 (s, 1H, OH).

Anal. Calcd for $C_{20}H_{16}ClNO_3S$: C, 62.26; H, 4.18; Cl, 9.19; N, 3.63; S, 8.31. Found: C, 62.48; H, 4.43; Cl, 8.99; N, 3.33; S, 8.54.

2-Chloromethyl-6-ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-4*H*-4-chromenone (3.5c)

Colorless solid; yield: 1.19 g (99 %); mp 236 °C ^1H NMR (DMSO-d$_6$): δ=1.28 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3), 2.71 (q, $^3J_{HH}$=7.2 Hz,, 2H, CH_2), 5.49 (s, 2H, CH_2Cl), 6.98 (s, 1H, H8), 7.55 (m, 3H, H3’, H4’, H5’), 7.89 (s, 1H, H5), 8.07 (m, 2H, H2’, H6’),10.96 (s, 1H, OH).

Anal. Calcd for $C_{20}H_{15}ClN_2O_3S$: C, 60.23; H, 3.79; Cl, 8.89; N, 7.02; S, 8.04. Found: C, 60.45; H, 3.86 Cl, 9.00; N, 6.89; S, 7.79.

2-Chloromethyl-7-hydroxy-8-methyl-3-(2-methyl-1,3-thiazol-4-yl)-4*H*-7-chromenone (3.6d)

Colorless solid; yield: 0.95 g (98 %); mp 240 °C
^1H NMR (DMSO-d_6): δ=2.30 (s, 3H, 8-CH_3), 2.79 (s, 3H, 2'-CH_3), 5.02 (s, 2H, CH_2Cl), 7.02 (d, $^3J_{HH}$=8.8 Hz, 1H, H6), 7.78 (d, $^3J_{HH}$=8.8 Hz, 1H, H5), 7.91 (s, 1H, H5'), 10.77 (s, 1H, OH).
Anal. Calcd for $C_{15}H_{12}ClNO_3S$: C, 55.99; H, 3.76; Cl, 11.02; N, 4.35; S, 9.96. Found: C, 55.73; H, 3.85; Cl, 11.00; N, 4.60; S, 9.79.

12-Oxo-12*H*-chromeno[3,2-a]indolizin-9-yl acetates (4.1e, 4.2e). General procedure

Pyridine (1.6 ml, 20 mmol) and chloroacetyl chloride (0.88 g, 11 mmol) were added to a solution of compound **1.7e** or **1.8e** (10 mmol) in acetonitrile (15 mL). The reaction mixture was refluxed for 20 min and then was cooled to room temperature. The resultant precipitate was filtered off and recrystallized from *o*-xylene.

8-Methyl-12-oxo-12*H*-chromeno[3,2-a]indolizin-9-yl acetate (4.1e)

Green solid; yield: 2.46 g (80 %); mp 265 °C
^1H NMR (DMSO-d_6): δ=2.33 (s, 3H, CH_3), 2.37 (s, 3H, CH_3CO), 7.05 (d, $^3J_{HH}$=7.6 Hz, 1H, H10), 7.07 (t, $^3J_{HH}$=7.6 Hz, 1H, H3), 7.32 (t, $^3J_{HH}$ =7.6 Hz, 1H, H2), 7.74 (s, 1H, H6), 8.07 (d, $^3J_{HH}$=8.4 Hz, 1H, H11), 8.25 (d, $^3J_{HH}$ =8.4 Hz,1H, H1), 8.61 (d, $^3J_{HH}$ =6.4 Hz, 1H, H4).
Anal. Calcd for $C_{18}H_{13}NO_4$: N, 4.56. Found: N, 4.45.

10-Ethyl-12-oxo-12*H*-chromeno[3,2-a]indolizin-9-yl acetate (4.2e)

Green solid; yield: 1.99 g (62 %); mp 202 °C
^1H NMR (DMSO-d_6): δ=1.25 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3), 2.37 (s, 3H, CH_3CO), 2.65 (q, $^3J_{HH}$=7.2 Hz, 2H, CH_2), 7.08 (t, $^3J_{HH}$=7.6 Hz, 1H, H3), 7.33 (t, $^3J_{HH}$ =7.6 Hz, 1H, H2), 7.40 (s, 1H, H8), 7.70 (s, 1H, H6), 8.08 (s, 1H, H11), 8.25 (d, $^3J_{HH}$ =8.4 Hz, 1H, H1), 8.60 (d, $^3J_{HH}$ =6.4 Hz, 1H, H4).
Anal. Calcd for $C_{19}H_{15}NO_4$: N, 4.36. Found: N, 4.21.

12-Oxo-10-propyl-12*H*-chromeno[3,2-a]-indolizin-9-yl 2-chloroacetate (4.3e) was obtained from comp. **1.9e** (2.71 g, 10 mmol) and chloroacetyl chloride (1.75 mL, 22 mmol) according to a procedure for comp. **4.1e**.
Green solid; yield: 0.25 g (68 %); mp 278 °C
^1H NMR (DMSO-d_6): δ=0.92 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3), 1.66 (m, 2H, CH_2), 2.62 (t, $^3J_{HH}$=7.2 Hz, 2H, CH_2), 4.62 (s, 2H, $ClCH_2CO$), 7.07 (t, $^3J_{HH}$=7.6 Hz, 1H, H3), 7.33 (t, $^3J_{HH}$ =7.6 Hz, 1H, H2), 7.40 (s, 1H, H8), 7.74 (s, 1H, H6), 8.08 (s, 1H, H11), 8.28 (d, $^3J_{HH}$ =8.0 Hz,1H, H1), 8.62 (d, $^3J_{HH}$ =5.6 Hz, 1H, H4).
Anal. Calcd for $C_{20}H_{16}ClNO_4$: Cl, 9.59; N, 3.79. Found: Cl, 9.59; N, 3.84.

9-Hydroxy-12*H*-chromeno[3,2-a]indolizin-12-ones (5.1e, 5.2e). General procedure

A mixture of the corresponding acetates **4.1e** or **4,2e** (5 mmol) in 50 mL of EtOH and 5% water solution of NaOH (4 mL, 5 mmol) was refluxed for 1 h, diluted with water (100 mL), refluxed for 5-10 min, neutralized with HCl to pH 7 and the resultant precipitate was filtered off and recrystallized from DMF.

9-Hydroxy-8-methyl-12*H*-chromeno[3,2-a]indolizin-12-one (5.1e)

Yellow solid; yield: 1.13 g (86 %); mp 218 °C
^1H NMR (DMSO-d_6): δ=2.30 (s, 3H, CH_3), 7.10 (d, $^3J_{HH}$=8.4 Hz, 1H, H10), 7.30 (t, $^3J_{HH}$=7.6 Hz,

1H, H3), 7.70 (s, 1H, H6), 7.73 (t, $^3J_{HH}$ =7.6 Hz, 1H, H2), 8.08 (d, $^3J_{HH}$=8.4 Hz, 1H, H11), 8.25 (d, $^3J_{HH}$ =7.6 Hz,1H, H1), 8.60 (d, $^3J_{HH}$ =6.4 Hz, 1H, H4), 10.40 (s, 1H, OH).

Anal. Calcd for $C_{16}H_{11}NO_3$: N, 5.28. Found: N, 5.09.

10-Ethyl-9-hydroxy-12*H*-chromeno[3,2-a]indolizin-12-one (5.2e)

Yellow solid; yield: 1.00 g (72 %); mp 217 °C
^{1}H NMR (DMSO-d$_6$): δ=1.25 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3), 2.65 (q, $^3J_{HH}$=7.2 Hz, 2H, CH_2), 6.88 (s, 1H, H8), 7.35 (t, $^3J_{HH}$=7.6 Hz, 1H, H3), 7.73 (t, $^3J_{HH}$ =7.6 Hz, 1H, H2), 7.80 (s, 1H, H6), 8.09 (s, 1H, H11), 8.25 (d, $^3J_{HH}$ =8.4 Hz,1H, H1), 8.59 (d, $^3J_{HH}$ =6.4 Hz, 1H, H4), 10.41 (s, 1H, OH).

Anal. Calcd for $C_{17}H_{13}NO_3$: N, 5.02. Found: N, 5.00.

9-Ethyl-10-methoxy-7*H*-chromeno[3',2':3,4]-pyrrolo[1,2-a]quinolin-7-one (6f)

Method **A**. Product **6f** was obtained from compound **1.10f** (0.48 g, 1.5 mmol), pyridine (0.3 mL, 3.7 mmol) and chloroacetyl chloride (0.13 mL, 1.65 mmol) in CH_3CN (11 mL) according to a procedure for compound **4.1e**.

Method **B**. Product **6f** was obtained from compound **1.10f** (0.64 g, 2 mmol), pyridine (0.3 mL, 3.7 mmol) and chloroacetic anhydride (0.88 g, 10 mmol) in CH_3CN (10 mL). The reaction mixture was refluxed for 5-10 min, poured onto water (100 mL) and the resultant precipitate was filtered off and washed with EtOH.

Yellow solid; yield: 0.27 g (52 %, method **A**), 0.5 g (74 %, method **B**); mp 301-302 °C
^{1}H NMR (CDCl$_3$): δ=1.26 (t, $^3J_{HH}$ =7.2 Hz, 3H, CH_3), 2.72 (q, $^3J_{HH}$ =7.2 Hz, 2H, CH_2), 3.94 (s, 3H, CH_3O), 6.84 (s, 1H, H11), 7.47 (t, $^3J_{HH}$=7.6 Hz, 1H, H2), 7.51 (d, $^3J_{HH}$ =8.4 Hz, 1H, H4), 7.65 (t, $^3J_{HH}$ =7.6 Hz, 1H, H3), 7.82 (d, $^3J_{HH}$ =7.6 Hz, 1H, H1), 7.88 (s, 1H, H13), 8.13 (s, 1H, H8), 7.96 (d, $^3J_{HH}$ =8.8 Hz, 1H, H5), 8.37 (d, $^3J_{HH}$ =8.8 Hz, 1H, H6).

Anal. Calcd for $C_{22}H_{17}NO_3$: N, 4.08. Found: N, 4.01.

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