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LETTERS TO THE EDITOR

FEATURES OF THE α-AZOLYL-2-HYDROXY-ACETOPHENONES REACTION WITH CHLOROACETYL CHLORIDE

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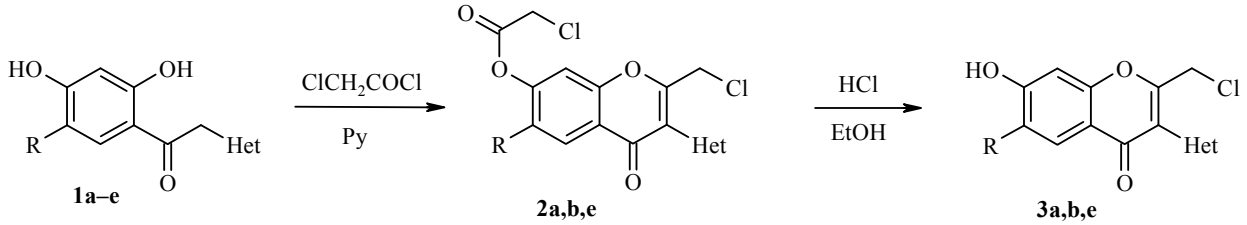
The patent [1] reports the synthesis of 2-chloromethyl-7-hydroxyisoflavones by condensation of α-aryl-2-hydroxyacetophenones with chloroacetic acid anhydride and subsequent acid hydrolysis of the 7-acyloxy group. In our study of the reactivity of α-hetaryl-2-hydroxyacetophenones of type **1** we have shown that chloroacetyl chloride acylation of the derivative with a 5-phenyl-1,3,4-thiadiazol-2-yl substituent gives a 2-chloromethylchromone of type **2** [2], while both the α-(2-pyridyl)- and α-(2-quinolyl) derivatives form the products of subsequent intramolecular cyclization with annelation of indolizine or pyrroloquinoline ring to the chromone ring [3, 4].



1–3 a R = Et, Het = 4-methylthiazol-2-yl, **b** R = Hex, Het = benzothiazol-2-yl, **c** R = Pr, Het = 1-methylbenzimidazol-2-yl, **d** R = Et, Het = 3-isoxazolyl, **e** R = Et, Het = 1-phenylpyrazol-4-yl

In order to define the boundaries of use of this method for synthesis of 2-chloromethyl-3-hetaryl chromones we have introduced acetophenones with 4-methylthiazol-2-yl (**1a**), 2-benzothiazolyl (**1b**), 1-methyl-benzimidazol-2-yl (**1c**), 3-isoxazolyl (**1d**), or 1-phenylpyrazol-4-yl (**1e**) substituents into this reaction. It was found that ketones **1a,b**, treated with excess chloroacetyl chloride and pyridine in dioxane or acetonitrile, give satisfactory yields of the corresponding chloroacetoxy products **2a,b** (even at room temperature) and that these hydrolyze in alcohol in the presence of HCl to the 7-hydroxychromones **3a,b**. By comparison, carrying out the cyclization of ketones **1c** and **1d** was unsuccessful either under mild conditions or upon heating but the ketone **1e** gave the product **3e**, even though in only low yield.

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Hence this method has proved effective in the synthesis of 2-chloromethylchromones only with a sulfur-containing azole substituent in position 3.

^{1}H NMR spectra were recorded on a Varian Mercury 400 spectrometer (400 MHz) using DMSO-d_6 with TMS as internal standard. Melting points were determined on a Boetius type mini observation stage with a VEB Analytic PHMK 0.5 apparatus.

2-Chloromethyl-6-ethyl-3-(4-methyl-1,3-thiazol-2-yl)-4-oxo-4*H*-chromen-7-yl Chloroacetate (2a). Pyridine (1.19 g, 15 mmol) and chloroacetyl chloride (1.69 g, 15 mmol) were added to a solution of compound **1a** (1.38 g, 5 mmol) in acetonitrile (15 ml), held for 24 h at room temperature, and obtained precipitate was filtered off. Yield 44%; mp 147-148ºC (MeCN). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.26 (3H, t, *J* = 7.2, 6-C<u>H</u>$_3$CH$_2$); 2.55 (3H, s, 4'-CH$_3$); 2.70 (2H, q, *J* = 7.2, 6-CH$_3$C<u>H</u>$_2$); 4.68 (2H, s, COCH$_2$Cl); 5.56 (2H, s, 2-CH$_2$Cl); 7.33 (1H, s, H-5'); 7.64 (1H, s, H-8); 8.11 (1H, s, H-5). Found, %: N 3.67; S 7.59. $C_{18}H_{15}Cl_2NO_4S$. Calculated, %: N 3.40; S 7.78.

3-(1,3-Benzothiazol-2-yl)-2-chloromethyl-6-(*n*-hexyl)-4-oxo-4*H*-chromen-7-yl Chloroacetate (2b). Prepared similarly to product **2a** from compound **1b**. Yield 54%; mp 132ºC (MeCN). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.89 (3H, t, *J* = 7.2, CH$_3$); 1.30-1.36 (6H, m, (CH$_2$)$_3$); 1.58-1.62 (2H, m, C<u>H</u>$_2$(CH$_2$)$_3$CH$_3$); 2.68 (2H, t, *J* = 7.2, C<u>H</u>$_2$(CH$_2$)$_4$CH$_3$); 4.66 (2H, s, COCH$_2$Cl); 5.58 (2H, s, 2-CH$_2$Cl); 7.46 (1H, t, *J* = 8.0, H-6'); 7.53 (1H, t, *J* = 8.0, H-5'); 7.68 (1H, s, H-8); 8.06-8.11 (3H, m, H-5,4',7'). Found, %: N 2.60; S 6.33. $C_{25}H_{23}Cl_2NO_4S$. Calculated, %: N 2.78; S 6.36.

2-Chloromethyl-6-ethyl-7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-4*H*-chromen-4-one (3a). A solution of compound **2a** (1.23 g, 3 mmol) was refluxed in a mixture of EtOH (50 ml) and 37% HCl (1 ml) for 1.5 h, held for 24 h at room temperature, and filtered off. Yield 88%; mp 213ºC (decomp.) (EtOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, t, *J* = 7.2, 6-C<u>H</u>$_3$CH$_2$); 2.57 (3H, s, 4'-CH$_3$); 2.67 (2H, q, *J* = 7.2, 6-CH$_3$C<u>H</u>$_2$); 5.51 (2H, s, 2-CH$_2$Cl); 6.92 (1H, s, H-5'); 7.27 (1H, s, H-8); 7.83 (1H, s, H-5); 10.90 (1H, s, OH). Found, %: N 3.99; S 9.47. $C_{16}H_{14}ClNO_3S$. Calculated, %: N 4.17; S 9.55.

3-(1,3-Benzothiazol-2-yl)-2-chloromethyl-6-(*n*-hexyl)-7-hydroxy-4*H*-chromen-4-one (3b). Prepared from compound **2b** similarly to product **3a**. Yield 94%; mp 188ºC (decomp.) (EtOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.90 (3H, t, *J* = 7.2, CH$_3$); 1.34 (6H, m, (CH$_2$)$_3$); 1.61 (2H, m, C<u>H</u>$_2$(CH$_2$)$_3$CH$_3$); 2.63 (2H, t, *J* = 7.2, C<u>H</u>$_2$(CH$_2$)$_4$CH$_3$); 5.55 (2H, s, 2-CH$_2$Cl); 6.94 (1H, s, H-8); 7.41 (1H, t, *J* = 8.0, H-6'); 7.50 (1H, t, *J* = 8.0, H-5'); 7.84 (1H, s, H-5); 8.03 (1H, d, *J* = 8.0, H-4'); 8.06 (1H, d, *J* = 8.0, H-7'); 10.87 (1H, s, OH). Found, %: N 3.33; S 7.33. $C_{23}H_{22}ClNO_3S$. Calculated, %; N 3.27; S 7.49.

2-Chloromethyl-6-ethyl-7-hydroxy-3-(1-phenylpyrazol-4-yl)-4*H*-chromen-4-one (3e). Triethylamine (0.5 g, 5 mmol) and chloroacetyl chloride (0.56 g, 5 mmol) were added to a solution of 5-ethyl-2,4-dihydroxy-α-(1-phenylpyrazol-4-yl)acetophenone (**1e)** (0.41 g, 1.2 mmol) in acetonitrile (5 ml), refluxed for 1.5 h, and treated with water. The oil formed was separated, refluxed in ethanol, and the precipitate formed was filtered off. Yield 6%; mp 273ºC (EtOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.23 (3H, t, *J* = 7.2, 6-C<u>H</u>$_3$CH$_2$); 2.67 (2H, q, *J* = 7.2, 6-CH$_3$C<u>H</u>$_2$); 4.73 (2H, s, 2-CH$_2$Cl); 6.86 (1H, s, H-8); 7.30 (1H, t, *J* = 7.6, H-4"); 7.49 (2H, t, *J* = 7.6, H-3",5"); 7.75 (1H, s, H-5'); 7.84 (1H, s, H-5); 7.85 (2H, d, *J* = 7.6, H-2",6"); 8.54 (1H, s, H-3'); 10.69 (1H, s, OH). Found, %: N 7.20. $C_{21}H_{17}ClN_2O_3$. Calculated, %: N 7.36.

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