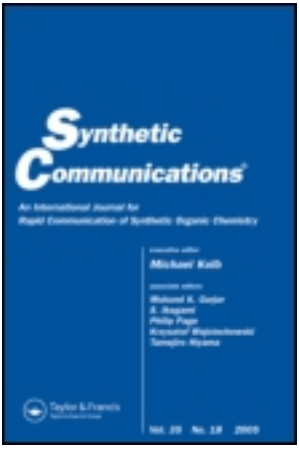

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A CONVENIENT ONE-POT SYNTHESIS OF 4-HYDROXYCOUMARIN, 4-HYDROXYTHIOCOUMARIN, AND 4-HYDROXYQUINOLIN-2(1H)-ONE

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A CONVENIENT ONE-POT SYNTHESIS OF 4-HYDROXYCOUMARIN, 4-HYDROXYTHIOCOUMARIN, AND 4-HYDROXYQUINOLIN-2(1*H*)-ONE

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ABSTRACT

An improved one-pot synthesis of 4-hydroxycoumarin, 4-hydroxythiocoumarin, and 4-hydroxyquinolin-2(1*H*)-one from 2-hydroxyacetophenone, 2-mercaptoacetophenone, and 2-aminoacetophenone, respectively, is described. The synthetic strategies involve the acylation and internal ring cyclization. This method is readily amenable to large-scale synthesis of 4-hydroxycoumarin, 4-hydroxythiocoumarin, and 4-hydroxyquinolin-2(1*H*)-one derivatives in high yields.

4-Hydroxycoumarin, 4-hydroxythiocoumarin, and 4-hydroxyquinolone derivatives are naturally occurring biologically active compounds,[1,2] useful intermediates for many industrial products such as dye stuffs,[3,4] herbicides,[5–7] and anticancer agents.[8] Recent reports show 4-hydroxyquinolone derivatives, i.e., 4-hydroxy-3-arylquinolin-2(1*H*)-one and

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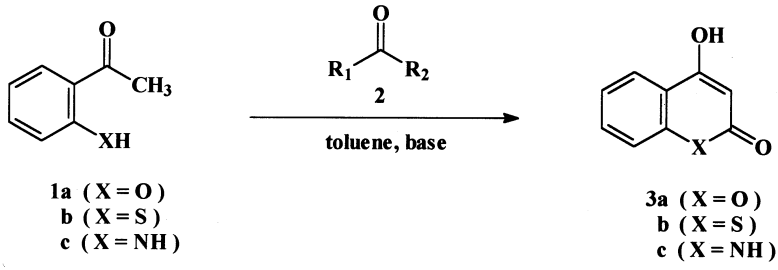
4-hydroxy-3-nitroquinolin-2(1*H*)-one, are selective glycine site antagonists related to several central nervous system disorders including stroke, epilepsy, schizophrenia, Parkinson's disease, and Alzheimer's disease.[9–14]



Scheme.

As part of our synthetic program[16] directed toward the synthesis of 4-hydroxycoumarin derivatives, we have recently reported[17] an efficient method for the preparation of 4-hydroxycoumarin and 4-hydroxythiocoumarin. As an extension to our previous work, we found a convenient one-pot synthesis of 4-hydroxycoumarin, 4-hydroxythiocoumarin, and 4-hydroxyquinolin-2(1*H*)-one, reacting 2-hydroxyacetophenone, 2-mercaptoacetophenone, and 2-aminoacetophenone with acylating agents such as phosgene, dimethylcarbonate, or diethylcarbonate in the presence of stoichiometric amount of base (Scheme). An evaluation of several acylating agents was undertaken and the results of those experiments are shown in the Table. In this reaction, we found that sodium hydride was the most effective base among sodium ethoxide, sodium hydride, freshly prepared sodium 3-aminopropylamide (NAPA), and potassium 3-aminopropylamide (KAPA).

In summary, an efficient one-pot synthesis of 4-hydroxycoumarin (3a), 4-hydroxythiocoumarin (3b), and 4-hydroxyquinolin-2(1*H*)-one (3c) has been developed. This procedure seems to be amenable to large-scale application.

EXPERIMENTAL

Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of air and moisture. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates from EM reagents and visualized with

Table. Reaction of 2-Hydroxyacetophenone, 2-Mercaptoacetophenone, or 2-Aminoacetophenone with Acylating Reagent

Compound	X	2(R1 = R2)	Base	Yield (%)[a]	Product
1a	O	Cl	NaOEt	66	**3a**
			NaH	69	
		OMe	NaOEt	71	
			NaH	84	
			NAPA[b]	60	
			KAPA[c]	55	
		OEt	NaOEt	80	
			NaH	85	
			NAPA	51	
			KAPA	63	
1b	S	Cl	NaOEt	62	**3b**
			NaH	66	
		OMe	NaOEt	74	
			NaH	81	
			NAPA	61	
			KAPA	58	
		OEt	NaOEt	81	
			NaH	86	
			NAPA	55	
			KAPA	62	
1c	NH	Cl	NaOEt	61	**3c**
			NaH	65	
		OMe	NaOEt	76	
			NaH	79	
		OEt	NaOEt	76	
			NaH	81	

[a]Isolated yields; [b]Sodium 3-aminopropylamide[15]; [c]Potassium 3-aminopropylamide.[15]

254-nm UV light or ceric sulfate-ammoniummolybdate-sulfuric acid spray. Flash chromatography was carried out on silica gel 60 (E. M. Merck, particle size 0.040 ~ 0.063 mm, 230 ~ 400 mesh ASTM). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker DPX 300 at 300 MHz and 76 MHz, respectively. The chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane, and *J*-values were in hertz. IR spectra were obtained on a Jasco FT/IR-300E spectrometer. Mass spectra were recorded on a Shimadzu-LKB 900 GC/MS system. All m.p. were uncorrected. When necessary, chemicals were purified according to the reported procedure.[18]

General Procedure for the Preparation of 4-Hydroxycoumarin (3a)

To a stirred suspension at room temperature sodium hydride (60% in mineral oil, 60 mmol) in anhydrous toluene (30 mL) was added dropwise a solution of 2-hydroxyacetophenone (12 mmol) and acylating reagent (18 mmol) in anhydrous toluene (6 mL). The reaction mixture was heated at 100°C for 3 h. After cooling, the solvent was evaporated and the residue was treated with water (10 mL). The resulting solid was filtered, washed with water, and then recrystallized from methanol or ethanol to give 4-hydroxycoumarin as a pale yellow crystal. $R_f = 0.30$ (ethyl acetate, neat); m.p. 211° ~ 213°C (*lit*. m.p. 205.1°C[19] and 206°C[20]); IR (ν_{max}, KBr) 3387–2583, 1658, 1599, 1323 cm^{-1}; ^1H NMR DMSO-d_6) δ 12.48 (br s, 1H), 7.82 (d, $J = 7.20$, 1H), 7.67~7.58 (m, 1H), 7.38~7.30 (m, 2H), 5.88 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 169.26, 164.97, 156.02, 134.76, 126.15, 125.53, 118.47, 118.20, 92.72; MS (m/e) 162 (M^+).

General Procedure for the Preparation of 4-Hydroxythiocoumarin (3b)

To a stirred suspension at room temperature of sodium hydride (60% in mineral oil, 50 mmol) in anhydrous toluene (25 mL) was added dropwise a solution of 2-mercaptoacetophenone (10 mmol) and acylating reagent (15 mmol) in anhydrous toluene (5 mL). The reaction mixture was heated at 100°C for 3 h. After cooling, the solvent was evaporated and the residue was treated with water (8 mL). The resulting solid was filtered, washed with water, and then recrystallized from methanol or ethanol to give 4-hydroxythiocoumarin as a pale yellow crystal. $R_f = 0.33$ (ethyl acetate, neat); m.p. 209°~210°C (*lit*.[21] m.p. 207°C); IR (ν_{max}, KBr) 3061–2550, 1519, 1265; ^1H NMR ($CDCl_3$) δ 12.46 (br s, 1H), 8.32 (d, $J = 7.83$ Hz, 1H), 7.83~7.63 (m, 3H), 6.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 182.45, 166.93, 136.88, 131.48, 126.84, 126.38, 126.09, 123.79, 103.26; MS (m/e) 178 (M^+), 150, 136 (base peak), 108, 69.

General Procedure for the Preparation of 4-Hydroxyquinolin-2(1*H*)-one (3c)

To a stirred suspensions at room temperature of sodium hydride (60% in mineral oil, 125 mmol) in anhydrous toluene (60 mL) was added dropwise a solution of 2-aminoacetophenone (50 mmol) and acylating reagent (75 mmol) in anhydrous toluene (20 mL). The reaction mixture

was heated at 100°C for 2 h. After cooling, the solvent was evaporated and the residue was treated with water (26 mL). The resulting solid was filtered, washed with water, and then recrystallized from methanol or ethanol to give 4-hydroxyquinolin-2(1*H*)-one as a pale yellow crystal. $R_f = 0.33$ (10% methanol in chloroform); m.p. 320°C (dec, *lit.*[22] m.p. >320°C); IR (ν_{max}, KBr) 3276, 2867, 1647, 1559, 1261; ^{1}H NMR (DMSO-d_6) δ 13.42 (br s, 1H), 10.27 (br s, 1H), 8.73 (d, $J = 8.44$ Hz, 1H), 7.76~7.32 (m, 3H), 6.33 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 162.46, 160.80, 155.52, 138.09, 130.47, 125.70, 119.03, 115.41, 87.67; MS (m/e) 161 (M^+), 133, 105, 91, 43 (base peak).

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