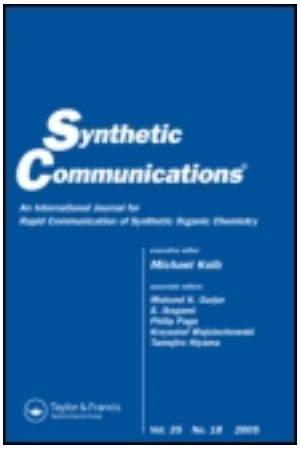

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A Direct and High Yielding Route to 2-(5-Tetrazolyl) Substituted Benzopyran-4-ones: Synthesis of Pranlukast

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A DIRECT AND HIGH YIELDING ROUTE TO 2-(5-TETRAZOLYL) SUBSTITUTED BENZOPYRAN-4-ONES: SYNTHESIS OF PRANLUKAST

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Abstract: A direct and high yielding route to 2-(5-tetrazolyl)benzopyran-4-ones **1**, including pranlukast **1a** is described. This involves the Claisen condensation reaction between the relevant hydroxyacetophenone **2** and the ethyl ester of tetrazole-2-carboxylic acid **5** to give the 1,3-diketone **6**, which is then cyclised to give the desired benzopyran-4-ones **1**.

Benzopyran-4-ones are a class of biologically important compounds, occurring both in nature and as synthetic products designed for the treatment of various diseases. Recent reports describe 2-(5-tetrazolyl)-benzopyran-4-one derivatives as potent leukotriene D4 antagonists,[1] one example being pranlukast **1a**[2] which is currently being developed for the treatment of asthma. The synthetic methodology used to prepare substituted benzopyran-4-ones has been

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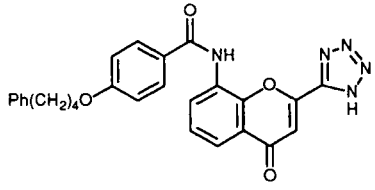
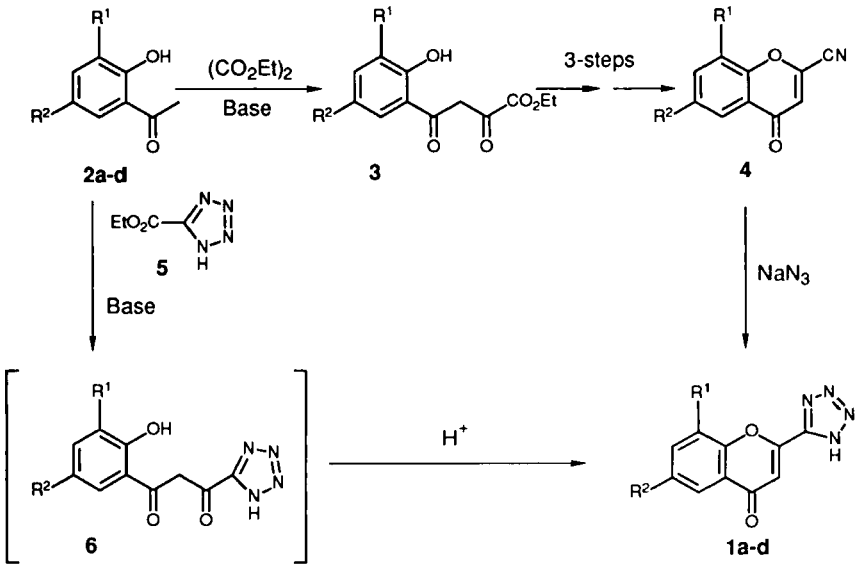
reviewed[3] and often uses 2-hydroxyacetophenone derivatives as starting materials. This includes the Kostanecki-Robinson synthesis,[4] the Baker-Venkataraman rearrangement,[5] and syntheses *via* chalcones[6] and phosphonium salts.[7] Currently only one indirect method is available for preparing 2-(5-tetrazolyl)-benzopyran-4-one derivatives from substituted hydroxyacetophenones and has been exploited in previous syntheses[8] of pranlukast **1a** (Scheme 1). Condensation of the hydroxyacetophenone **2** with diethyl oxalate gives the 1,3-dicarbonyl compound **3** which is converted in three steps to the 2-cyanobenzopyran-4-one **4**. Reaction with sodium azide then forms the tetrazole ring, resulting in a five step synthesis of **1** from **2**. The main drawbacks of this synthesis are the number of steps required, and the use of the hazardous reagent, sodium azide, to form the tetrazole ring in the final step. It was believed that this multi-step sequence could be avoided by employing a more convergent route. To this end, we wish to report a new synthesis utilising the Claisen condensation reaction between hydroxyacetophenone **2** and ethyl *1H*-tetrazole-5-carboxylate[9] **5** which results in the conversion of **2a** to pranlukast **1a** in a high yielding one-pot process. This new synthesis is amenable to the preparation of this compound in large quantities, and also avoids the use of sodium azide in the final step.



pranlukast, **1a**

We have discovered that the reaction between 2-hydroxyacetophenone **2** and the tetrazole ester **5** in NaOMe/THF (reflux) or KO^{t}Bu/DMF (0-10°C) facilitates the rapid formation of the diketone **6**, which if required, may be precipitated by



Scheme 1

quenching the reaction mixture into excess aqueous hydrochloric acid. However, it has been shown that addition of MeOH/hydrochloric acid to the NaOMe/THF reaction mixture containing diketone **6a** affords pranlukast **1a** directly from **2a** in 92% isolated yield in a one-pot process[10] (Scheme 1). The reaction between other 2-hydroxyacetophenone derivatives and tetrazole ester **5** also afforded the corresponding 2-(5-tetrazolyl)-benzopyran-4-one derivatives **1b-d** in high yields (Table). Some examples of direct C-acylation of hydroxyacetophenone derivatives using LDA,[11] LiHMDS[12] and NaH[13] have been reported, although in some cases protection/deprotection steps are required.[11] We have found that for the reaction between hydroxyacetophenones and tetrazole ester **5**, these bases gave inferior results to the described procedure.

Generally, C-acylation of 2-hydroxyacetophenones is achieved by first preparing the isomeric O-acyl derivatives, followed by a base induced Baker-

Table. Conversion of 2-Hydroxyacetophenones **2** to Benzopyran-4-ones **1**

R^1	R^2	Product	Yield %
$Ph(CH_2)_4O$-*p*-C_6H_4CONH	H	**1a**	92
PhCONH	H	**1b**	89
MeCONH	Cl	**1c**	80*
H	H	**1d**	94

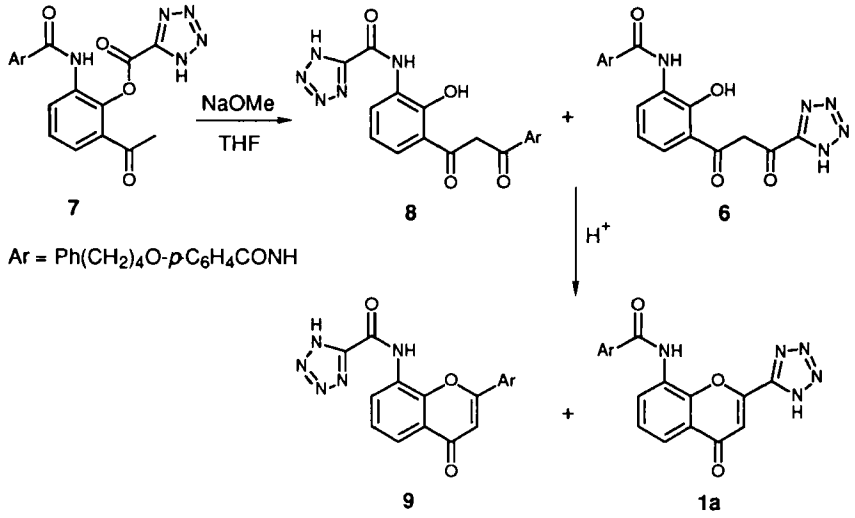
* Note: Hydrolysis of the acetamide group took place during cyclisation to give 8-amino-6-chloro-2-(tetrazol-5-yl)benzopyran-4-one.

Venkataraman rearrangement.[3,5] In an attempt to determine if the Baker-Venkataraman pathway was responsible for the formation of diketone **6**, we prepared the aryl ester **7** and subjected it to the above reaction conditions. As well as forming the expected diketone **6**, we also detected an equal quantity of the isomeric diketone product **8**. Subsequent cyclisation afforded a mixture of **1a** and its regioisomer **9** (Scheme 2). This result suggests that reaction between **2** and **5** (Scheme 1) proceeds *via* direct C-acylation of the methyl ketone.

This is the first example of the synthesis of 2-(5-tetrazolyl) substituted benzopyran-4-ones directly from 2-hydroxyacetophenone derivatives. The chemistry described offers significant advantages over other literature methods as stable, cheap and readily available bulk reagents may be used under conditions amenable to large scale operation. The scope of this procedure is currently under investigation and results will be reported in due course.

Experimental

Melting points are uncorrected and were determined on a Buchi 510 apparatus.



Scheme 2

^{1}H and ^{13}C NMR were recorded on a Jeol GSX400 FT-NMR at 400 MHz and 100 MHz respectively. Mass spectra were obtained using a VG-70-VSEQ double focussing mass spectrometer.

Typical experimental procedures: These procedures use either sodium methoxide or potassium *t*-butoxide as base. The total quantity of base used equates to one equivalent in excess of the theoretical quantity required to deprotonate the tetrazole ring, the amide and phenolic hydroxyl groups present, and to generate both the required enolate anion of the ketone and the enolate of the product diketone.

One pot preparation of 2-(5-tetrazolyl)benzopyran-4-one derivatives. [Reagent and solvent quantities quoted are in relation to the acetophenone substrate.]

To a stirred suspension of hydroxyacetophenone **2** and sodium methoxide in dry THF (typically 7-10 ml/g) is added a solution of ethyl 1*H*-tetrazole-5-carboxylate

5 (1.3 mole equivalents) in dry THF (typically 5-10 ml/g). The resulting mixture is heated at reflux for two hours. Methanol (typically 7-10 ml/g) containing conc. hydrochloric acid (10 equivalents) is added to the mixture at reflux and heating is continued for a further two hours. The product is filtered, suspended in water, re-isolated and dried (70-100°C). The following compounds were prepared using this procedure:

Pranlukast hemihydrate 1a (92%), m.pt. 232-233° (decomp); ^{1}H NMR (400 MHz, DMSO-d_6:$CDCl_3$ 1:1) δ 1.83 (4H, m, CH_2CH_2), 2.70 (2H, t, $ArCH_2$), 4.08 (2H, t, CH_2O), 7.02 (2H, d, Ar-H), 7.17 (1H, t, Ar-H), 7.19 (1H, s, C(3)H), 7.21 (2H, t, Ar-H), 7.27 (2H, t, Ar-H), 7.47 (1H, t, Ar-H), 7.87 (1H, dd, Ar-H), 7.98 (2H, d, Ar-H), 8.57 (1H, dd, Ar-H), 9.67 (1H, s, NH); ^{13}C NMR (100 MHz, d_6-DMSO:$CDCl_3$ 1:1) δ_c 176.0 (quat), 165.4 (quat), 161.6 (quat), 152.0 (quat), 150.5 (quat), 146.5 (quat), 141.5 (quat), 129.6, 128.1, 127.9, 127.8 (quat), 126.5, 126.1 (quat), 125.3, 125.1, 123.9 (quat), 119.5, 113.7, 110.5, 67.5, 34.9, 28.1, 27.3; Found C, 66.38; H, 4.74; N, 14.12. $C_{27}H_{23}N_5O_4$. $0.5H_2O$ requires C, 66.11; H, 4.93; N, 14.28.

2-(5-Tetrazolyl)benzopyran-4-one 1d (94%), m.pt. 262° (decomp) (Lit[14] 270-271°C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.08 (1H, s, C(3)H), 7.55 (1H, t, Ar-H), 7.75 (1H, d, Ar-H), 7.90 (1H, t, Ar-H), 8.08 (1H, d, Ar-H); ^{13}C NMR (100 MHz, d_6-DMSO) δ_c 176.3 (quat), 155.5 (quat), 153.0 (quat), 151.6 (quat), 134.9, 126.0, 125.0, 123.7 (quat), 118.4, 110.5, HRMS: Found 214.0493, $C_{10}H_6N_4O_2$ requires 214.0491.

Preparation of 2-(5-tetrazolyl)benzopyran-4-one derivatives *via* isolated diketone intermediates 6. To a stirred solution of the hydroxyacetophenone and ethyl 1*H*-tetrazole-5-carboxylate **5** (1.3 mole equivalents) in dry DMF (typically 3 - 10 ml/g) at 0°C is added a solution of potassium *t*-butoxide (6 equivalents) in

dry DMF (typically 5 - 10 ml/g) while maintaining the reaction temperature at 0-5°C. After stirring for one hour at this temperature, the reaction mixture is quenched into water (concentration 30-50 ml/g) containing hydrochloric acid (10 equivalents). The diketone is filtered under vacuum and washed with water. The damp diketone is suspended in methanol (typically 15 - 20 ml/g) containing conc. hydrochloric acid (4 mole equivalents) and the mixture is heated at reflux for two to three hours. The 2-(5-tetrazolyl)benzopyran-4-one is filtered under vacuum, washed with methanol and dried (70-100°C). This procedure has been used to prepare the following compounds:

8-Benzamido-2-(5-tetrazolyl)benzopyran-4-one 1 b (89%), m.pt. 270-271°C (decomp); ^{1}H NMR (400 MHz, DMSO- d_6) δ 7.14 (1H, s, C(3)H), 7.56-7.61 (3H, m, Ar-H and C(6)H), 7.66 (1H, tt, Ar-H), 8.07 (2H, dt, Ar-H), 8.28 (1H, dd, C(5)H), 10.16 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 176.2 (quat), 165.9 (quat), 153.2 (quat), 151.8 (quat), 148.6 (quat), 134.2 (quat), 132.0 , 129.5, 128.5, 128.1 (quat), 127.9, 125.6, 124.3 (quat), 121.0, 110.4 (quat), HRMS: found 334.094, $C_{17}H_{11}N_5O_3$ requires 334.094 (MH^+).

8-Amino-6-chloro-2-(5-tetrazolyl)benzopyran-4-one 1c (80%), m.pt. 286-288°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.06 (1H, d, C(7)H), 7.08-7.09 (2H, m, C(3)H and C(5)H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 175.6 (quat), 151.0 (quat), 142.4 (quat), 140.4 (quat), 140.4 (quat), 130.9 (quat), 125.1 (quat), 115.8, 109.5, 108.6; HRMS: found 263.020; $C_{10}H_6ClN_5O_2$ requires 263.021 (MH^+ for the ^{35}Cl isotope).

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