An Approach to the Synthesis of 2-Acylchromeno[3,4-*c*]pyrrol-4(2*H*)-one Derivatives via a Sequential Three-Component Reaction

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Abstract: An efficient synthesis of 2-acylchromeno[3,4-*c*]pyrrol-4(2*H*)-one derivatives by a three-component reaction of salicylaldehydes, β-keto esters, and *p*-toluenesulfonylmethyl isocyanide is reported.

Key words: 2-acylchromeno[3,4-*c*]pyrrol-4(2*H*)-one, *p*-toluenesulfonylmethyl isocyanide, salicylaldehyde, [1,3]-acyl shift

Coumarins play important roles in natural products and are widely present in animal and microbial metabolites and also in higher plants such as Rutaceae, Apiaceae, Asteraceae, Leguminosae, and Thymelaeaceae.[1] They exhibit a broad pharmacological profile[2] including anticancer activity,[3] inhibition of platelet aggregation,[4] steroid 5α-reductase,[5] and HIV-1 protease.[6] Coumarins have also been used as insecticides[7] and optical brighteners.[8] Consequently, chromenes and coumarins have attracted considerable attention[9] and a range of methods has been reported for their synthesis including cyclization of salicylaldehydes with enamines,[10] Petasis reaction of salicylaldehydes,[11] palladium-catalyzed oxidative cyclization of aryl-3-butenyl ethers,[12] Baylis–Hillman reactions of salicylaldehyde,[13] and reaction of α,β-unsaturated Fischer carbene complexes of chromium with propargyl ethers.[14]

Toluenesulfonyl methyl isocyanide (TosMIC) is a useful synthon, adding to various unsaturated functional group, such as electron-deficient carbon–carbon double bonds as well as imino, formyl, and thiocarbonyl groups to give pyrroles, imidazoles, 1,3-oxazoles, and 1,3-thiazoles, respectively.[15] Accordingly, and in continuation of our studies on the synthesis of new polycyclic heterocyclic compounds,[16] we decided to investigate the reaction of salicylaldehydes, β-keto esters, and TosMIC in the synthesis of new coumarin derivatives.

To test this new process, we initially explored the reaction of a range of salicylaldehydes **1** and β-keto esters **2** in DMF at room temperature in the presence of piperidine (0.1 mmol) to afforded the expected 3-acetylcoumarins. Then, a solution of TosMIC (1 mmol) and triethylamine (1 mmol) was added to this mixture, and we unexpectedly observed the formation of 2-acylchromeno[3,4-*c*]pyrrol-4(2*H*)-one derivatives **3**, generated through an [1,3]-acyl shift[17] in 62–95% yields (Table 1).

Optimization of the reaction conditions showed that the reaction proceeds with excellent yields when DMF was used at room temperature;[18] whereas at higher temperatures complex mixtures were obtained. When we used triethylamine instead of piperidine for the synthesis of 3-acetylcoumarin, the Knoevenagel condensation did not occur, thus we used piperidine as a catalyst in this step. However, as large amounts of piperidine may lead to side reactions such as Michael addition, we used triethylamine in the second step. We also examined malonic esters instead of β-keto esters, but this failed to afford the desired 2-alkylcarboxylatechromeno[3,4-*c*]pyrrol-4(2*H*)-ones, probably because of the lower electrophilicity of esters in comparison to ketones. Having established the optimal conditions, we then examined the scope of the reaction for the construction of various 2-acylchromeno[3,4-*c*]pyrrol-4(2*H*)-ones, and the results are summarized in Table 1.

The molecular structures of all products **3a**–**j** were elucidated from their spectroscopic analyses as described herein for **3a**. In the IR spectrum of **3a**, two sharp absorption bands at 1730 and 1713 cm^{-1}, three bands at 1598, 1524, and 1462 cm^{-1}, and two absorption bands at 1234 and 1182 cm^{-1} could be related to NCO and CO_2, C=C, and C–O stretching frequencies,. The mass spectrum of **3a** displayed the molecular ion peak at m/z = 227, and also a base peak at m/z = 185, which is in good agreement with the proposed structure and deacylation of the proposed molecule, respectively. The ^{1}H NMR spectrum of **3a** exhibited a sharp singlet signal at δ = 2.71 ppm (CH_3) and

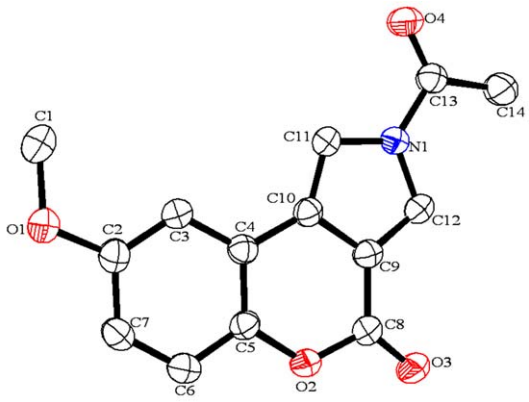

Figure 1 ORTEP diagram of **3d**

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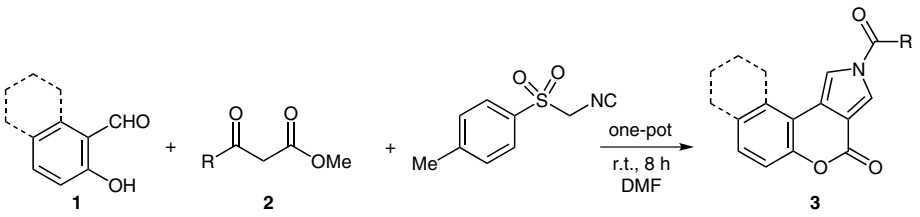
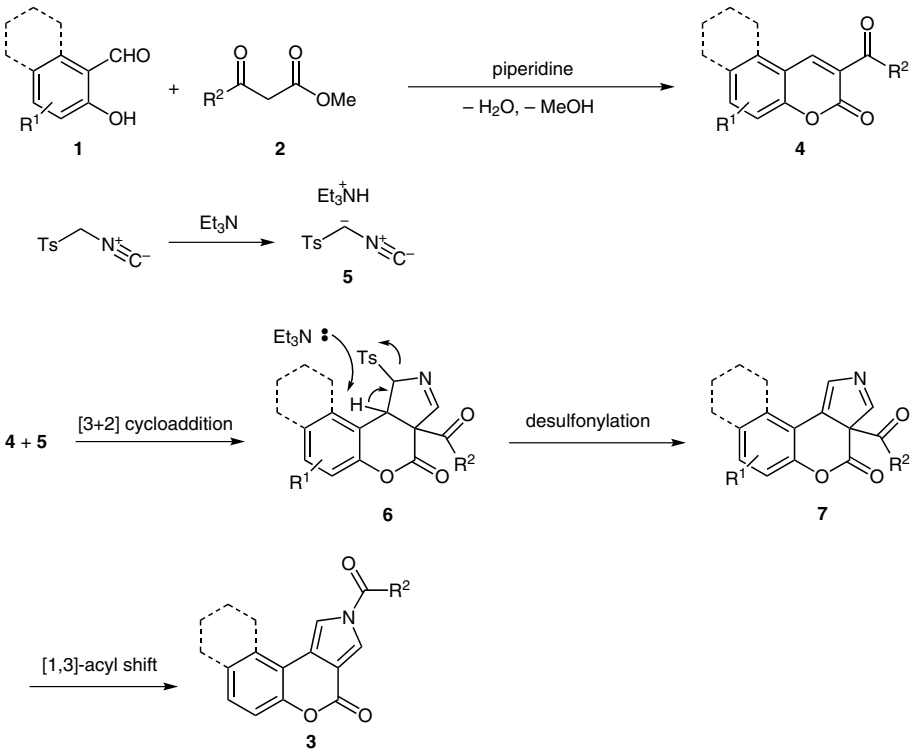
Table 1 One-Pot, Three-Component Synthesis of 2-Acylchromeno[3,4-*c*]pyrrol-4(2*H*)-one Derivatives **3a**–**j**



Entry	Products	Compound **1**	R	Yield (%)
1	**3a**	salicylaldehyde	Me	75
2	**3b**	3-methoxysalicylaldehyde	Me	80
3	**3c**	4-methoxysalicylaldehyde	Me	90
4	**3d**	5-methoxysalicylaldehyde	Me	85
5	**3e**	5-nitrosalicylaldehyde	Me	65
6	**3f**	3,5-dichlorosalicylaldehyde	Me	95
7	**3g**	5-chlorosalicylaldehyde	Me	87
8	**3h**	2-hydroxynaphthalene-1-carbaldehyde	Me	70
9	**3i**	salicylaldehyde	*n*-Pr	65
10	**3j**	3-methoxysalicylaldehyde	*n*-Pr	62

four aromatic protons of the coumarin as two triple doublets at δ = 7.26 and 7.36 ppm and two double doublets at δ = 7.28 and 7.98 ppm. Two protons of the pyrrole ring appeared as two mutually coupled doublets at δ = 8.26 and 8.41 ppm. The ^{1}H-decoupled ^{13}C NMR spectrum of **3a** showed 13 distinct signals in agreement with the suggested structure. The most important peak is related to the NCO group which appeared at δ = 169.1 ppm (see Supporting Information). Final confirmation for the formation of the reaction products was obtained by X-ray crystal structure analysis of compound **3d**. The ORTEP diagram for compound **3d** is shown in Figure 1.



Scheme 1 Proposed mechanism for the formation of **3**

A plausible mechanism for the sequential three-component reaction is proposed in Scheme 1. The formation of the 2-acylchromeno[3,4-*c*]pyrrol-4(2*H*)-one **3** can be explained by initial Knoevenagel condensation between salicylaldehydes **1** and β-keto esters **2** in the presence of piperidine leading to 3-acetylcoumarins **4**.[19] Then, [3+2] cycloaddition of the TosMIC ion pair **5** leads to intermediate **6**. Desulfonylation of **6** under the basic conditons of the reaction leads to intermediate **7** which is converted into 2-acylchromeno[3,4-*c*]pyrrol-4(2*H*)-one **3** by [1,3]-acyl shift. To evaluate this proposed mechanism, 3-acetylcoumarin was synthesized separately and added to the TosMIC ion-pair solution with the same result being observed.

Although acyl shifts are more difficult than hydrogen shifts and usually require forcing conditions, in this case full aromatization of the pyrrole ring and full conjugation of the π-electron system and steric effects led to [1,3]-acyl shift at room temperature.

In summary, we have disclosed a concise approach to the synthesis of *N*-acylchromeno[3,4-*c*]pyrrol-4(2*H*)-one derivatives by the reaction between salicylaldehyde, β-keto esters, and TosMIC through an unexpected acyl shift. A simple workup procedure, mild reaction conditions, lack of side products, and good yields are the main aspects of this method.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(18) To a solution of salicylaldehyde **1** (1 mmol) and β-keto ester **2** (1 mmol) in DMF (2 mL), piperidine (0.1 mmol) was added, and the solution was stirred for 1 h at r.t. Then, Et_3N (1 mmol) and TosMIC (1 mmol) were dissolved in DMF (2 mL) and added to the reaction mixture. Upon completion of the reaction as monitored by TLC (7 h), the mixture was filtered, and the precipitate was washed with EtOH (4 mL) to afford the pure product **3a**–**j**.

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