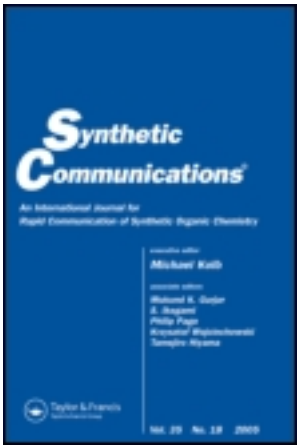

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Efficient Synthesis of 3-Substituted Coumarins

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ABSTRACT

The Mukaiyama's esterification protocol, using 2-chloro-1-methylpyridinium iodide-triethylamine reagent, has been successfully exploited to provide rapid access to a variety of 3-substituted coumarins in satisfactory yields.

Key Words: 3-Substituted coumarins; Synthesis; 2-Chloro-1-methyl-pyridinium iodide/triethylamine reagent; Coumarin laser dye; Mukaiyama esterification protocol.

A number of natural products and synthetic analogs featuring coumarin structural motif display wide-ranging biological properties[1,2] and, in

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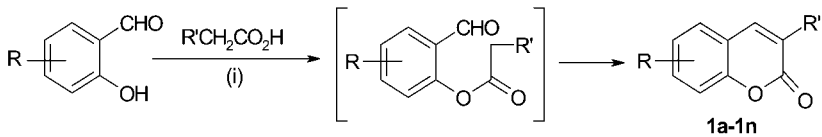
addition, selected coumarins also find applications as luminescent probes,[3] fluorescent brightners,[4] laser dyes,[5] and fluoroionophores.[6] Among the plethora of methods available for coumarin synthesis,[7] viz. lactonizations, Wittig condensations, and transition metal catalyzed reactions, the classical Perkin condensation[8] is perhaps the only direct method known for 3-arylcoumarins. However, from a practical standpoint, the Perkin method suffers from the need to use an excess of acetic anhydride/sodium acetate reagent, harsh conditions, tedious work-up, and unsatisfactory yields. Not surprisingly, many attempts at improving the Perkin method have been described in the literature (For attempts at improving the Perkin method, see Ref.[9a–f]). In particular, the method using $PhPOCl_2/Et_3N$ as the condensing agent[9f] is noteworthy in providing 3-substituted coumarins in appreciable yields.

Herein, we describe a convenient, single-step methodology for 3-substituted coumarins by using Mukaiyama esterification conditions.[10] We envisaged that esterification of appropriate salicaldehyde with arylacetic would be followed by a Claisen-type condensation under catalysis by Et_3N to provide 3-arylcoumarins, as illustrated in Sch. 1.

To check the validity of Sch. 1, we set up a test reaction between salicaldehyde and phenylacetic acid in dry CH_3CN containing 2 equivalents of freshly crystallized 2-chloro-1-methylpyridinium iodide and an excess of triethylamine. The reaction, after refluxing for 2 hr under N_2 was worked-up to provide the desired product, 3-phenylcoumarin in 81% isolated yield. Attempts to effect the reaction in other solvents, i.e., dry THF, dioxan, or DMF or use of less than 2 equivalents of 2-chloro-1-methylpyridinium iodide, resulted in lower yields of 3-phenylcoumarin. The scope of the present methodology was found to be general (Table 1), being equally successful with either electron-rich or electron-deficient substrates, and the yields are also in general quite satisfactory.

The reaction was also successfully executed with phenoxyacetic acid and thiophenoxyacetic acid to afford 3-phenoxy- and 3-thiophenoxycoumarins, respectively (entries 6 and 7, Table 1). In addition, 2-hydroxy-arylketones **1** and **2** also participated in the reaction with phenylacetic acid to give the corresponding coumarins[17] **3** and **4** in acceptable yields (Sch. 2). The



Scheme 1. Reagent and condition: (i) 2 equiv of 2-chloro-1-methylpyridinium iodide/$(C_2H_5)_3N$ in CH_3CN, Δ, N_2.

Table 1. Synthesis of 3-substituted coumarins.

Entry	Product[a]	R	R′	% Yield[b]	Lit.[c]
1	**1a**	H	C_6H_5	81	11
2	**1b**	H	4-$MeOC_6H_4$	78	11
3	**1c**	H	4-$NO_2C_6H_4$	91	11
4	**1d**	H	3,4-$(MeO)_2C_6H_3$	75	9b
5	**1e**	H	2-thienyl	68	9f
6	**1f**	H	-OC_6H_5	25	9f
7	**1g**	H	-SC_6H_5	75	12
8	**1h**	6-NO_2	C_6H_5	89	13
9	**1i**	6-Br	C_6H_5	72	14
10	**1j**	7-NMe_2	C_6H_5	75	15
11	**1k**	7-NEt_2	4-$NO_2C_6H_4$	80	16
12	**1l**	6-NO_2	3,4-$(MeO)_2C_6H_3$	91	–[d]
13	**1m**	6-CHO	3,4-$(MeO)_2C_6H_3$	80	–[d]
14	**1n**	6-NO_2	3-indolyl	63	–[d]

[a]Reactions refluxed for 2 hr, unless mentioned otherwise; for **1c** and **1h**, reflux time is 1 hr, for **1f** reflux time is 8 hr.

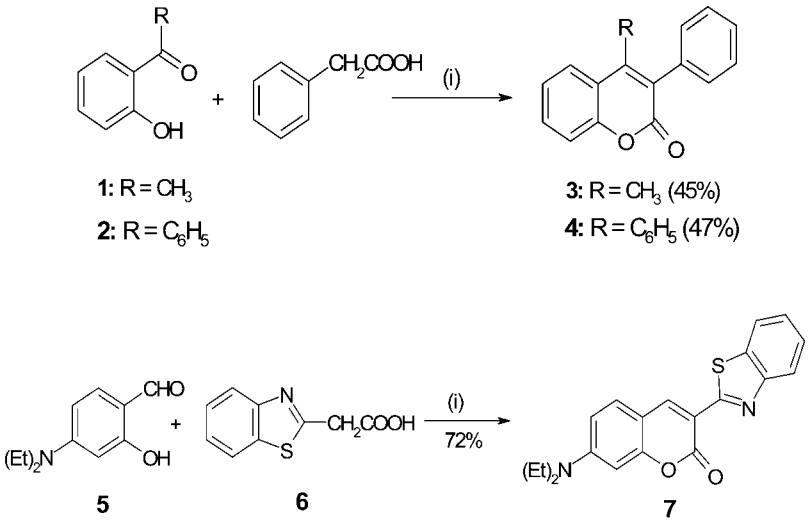
[b]All yields are isolated yields.

[c]Physical and spectral data agree with those reported in the literature.

[d]Selected characterizations of unknown coumarins: Product **1l**; mp 262°C–63°C. IR (KBr): 1740, 1612, 1522, 1350, 1245, 1100, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 6H), 7.08 (d, 1H, $J = 8$ Hz), 7.34–7.38 (m, 2H), 7.64 (d, 1H, $J = 8$ Hz), 8.4 (dd, 1H, $J = 8$ and 1.5 Hz), 8.42 (s, 1H), 8.74 (s, 1H); Anal. Calcd. for $C_{17}H_{13}NO_6$: C, 62.38; H, 3.97; N, 4.28. Found: C, 62.70; H, 4.25; N, 4.47. Product **1m**; mp 165°C–167°C. IR (KBr): 1738, 1697, 1609, 1521, 1360, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 6H), 6.7 (d, 1H, $J = 8.5$ Hz), 7.15–7.3 (m, 2H), 7.66 (s, 1H), 7.7–7.85 (m, 2H), 7.9 (s, 1H), 9.9 (s, 1H); Anal. Calcd. for $C_{18}H_{14}O_5$: C, 69.67; H, 4.51. Found: C, 69.89; H, 4.33. Product **1n**; mp 300°C–304°C; IR (KBr): 3325, 1710, 1505, 1435, 1340, 1250, 1070, 970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.05 (bs, 1H), 7.15–7.30 (m, 2H), 7.5 (d, 1H, $J = 8$ Hz), 7.63 (d, 1H, $J = 8$ Hz), 8.20 (d, 1H, $J = 7$ Hz), 8.25 (s, 1H), 8.32 (d, 1H, $J = 7$ Hz), 8.60 (s, 1H), 8.95 (s, 1H); Anal. Calcd. for $C_{17}H_{10}N_2O_4$: C, 66.66; H, 3.26; N, 9.15. Found: C, 66.49; H, 3.47; N, 9.41.

present procedure has also been successfully extended toward the synthesis of a commercially important laser dye **7**[18] in good yield by reacting 5-diethylamino salicaldehyde **5** with 2-benzothiazolylacetic acid **6**.

In conclusion, we have described a new application of the Mukaiyama esterification protocol as an efficient, metal-free alternative to the classical Perkin condensation to provide rapid entry into a variety of 3-substituted



Scheme 2. Reagent and condition: (i) 2-chloro-1-methylpyridinium iodide/$(C_2H_5)_3N$ in CH_3CN, Δ/N_2.

coumarin systems. Unlike other Perkin modifications,[9] the present method obviates the need to prepare unstable arylacetic chloride/anhydride or the application of corrosive $PhPOCl_2$ as the condensing agent.[9f] Thus, given the ever-rising importance of coumarins in diverse fields, the reported method appears to be an attractive approach toward these molecules.

TYPICAL PROCEDURE

To a solution of freshly crystallized 2-chloro-1-methylpyridinium iodide (4.0 mmol) in dry CH_3CN (distilled over P_2O_5; 20 mL) were added phenylacetic acid (2.2 mmol), salicaldehyde (2.0 mmol), and triethylamine (5 mmol). The reaction was gently refluxed under N_2 for 2 hr. The reaction mixture was concentrated under reduced pressure and the semi-solid residue was treated with diluted hydrochloric acid. The solid product obtained was filtered, dried, and purified by a short SiO_2 column chromatography (elution with petroleum ether-$CHCl_3$ 2 : 1) to give 3-phenyl-coumarin (**1a**) as a colorless solid in 81% yield, mp 140°C–142°C (Lit.[9a] mp 142°C).

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