Further studies of orientation effects in the Pechmann synthesis of coumarins

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Alan G. Osborne*, Steven J. Andrews and Rachel Mower

Department of Biological Sciences, University of Essex, Wivenhoe Park, Colchester, Essex CO3 4SQ, UK

The proportion of 5-/7- substituted coumarins formed in the Pechmann synthesis from *meta*-substituted phenols and malic acid and ethyl acetoacetate under a variety of reaction conditions, with product analysis by ^{1}H and ^{13}C NMR spectroscopy, is reported.

Keywords: Pechmann synthesis, coumarins

We have previously reported[1] an initial investigation of orientation effects in the Pechmann synthesis[2,3] of coumarins which was confined to a study of alkylphenols **1a** and **1j** (see Table 1) and subsequently extended[6] to *meta*-methoxyphenol **1d**. In the present work an investigation of varying reaction conditions with a series of *meta*-substituted phenols has been performed.

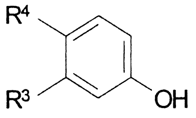
Four reaction procedures were investigated. Method A involved the mixing of the phenol **1** (P), malic acid **9** (M) and sulphuric acid (S) at the outset. In methods B - D, two of the components were mixed initially with the third (S, P and M respectively) added portionwise once the appropriate reaction temperature (85, 115 or 130°C) had been attained. The results are shown in Table 3.

The reaction with malic acid **9** is best performed between 80 and 130°C with the reagents mixed at the outset, the stepwise addition of either the phenol or sulphuric acid had only a minimal effect on the isomer ratio. The proportion of **2d** (see Table 2) increased with temperature to a maximum of 10%. However, when **9** was added portionwise dealkylation[7,14] occurred leading to the formation of **3e**. With *meta*-chlorophenol **1f**, the proportion of **2f** decreased with temperature. A 'reversed' steric effect[20] leading to a transient intermediate is proposed to explain this unexpected trend.

For the study which involved the influence of the *meta*-substituent on the reaction, method B was used with **9** whilst the ethylacetoacetate reactions were performed on the steam bath at *ca* 80°C. The results are shown in Table 4.

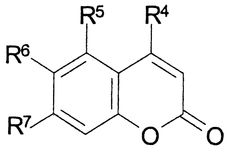
The proportion of the 5-isomer decreased with the increasing bulk of the alkyl group and was zero for **1c**. With electron donating groups (*e.g.* OMe, OH) about 10% of the 5-isomer was obtained, however, secondary reactions[18,21] at the reactive sites made isomer ratios difficult to establish. The reaction failed with electron withdrawing groups, *e.g.* **1g**. Reactions with ethyl acetoacetate gave the 4,7-isomers only.

Table 1 List of phenols



	R^3	R^4
1a	CH_3	H
1b	C_2H_5	H
1c	CMe_3	H
1d	OCH_3	H
1e	OH	H
1f	Cl	H
1g	NO_2	H
1h	NH_2	H
1j	CH_3	CH_3

Table 2 List of coumarins



	X
2 $R^5 = X, R^4 = R^6 = R^7 = H$	a CH_3
3 $R^7 = X, R^4 = R^5 = R^6 = H$	b C_2H_5
4 $R^5 = X, R^4 = CH_3, R^6 = R^7 = H$	c CMe_3
5 $R^7 = X, R^4 = CH_3, R^5 = R^6 = H$	d OCH_3
6 $R^5 = R^6 = CH_3, R^4 = R^7 = H$	e OH
7 $R^6 = R^7 = CH_3, R^4 = R^5 = H$	f Cl
8 $R^4 = R^6 = R^7 = CH_3, R^5 = H$	g NO_2
	h NH_2

Table 3 Variation of reaction conditions in the Pechmann reaction with malic acid

Reactant	Expt no.	Method[a]	Temp/°C	Isomer ratio (product composition)/%[b,c]		
				2d	3d	3e
1d	1	A (-)	85	4	96	
	2	A	115	6	94	
	3	A	130	6	94	
	4	B (S)	85	4	96	
	5[d]	B	115	6	94	
	6[d]	B	130	8	92	
	7	C (P)	85	3	97	
	8	C	115	6	94	
	9	C	130	10	90	
	10	D (M)	85	2	98	
				2	*95*	*3*
	11	D	115	3	97	
				3	*91*	*6*
	12	D	130	7	93	
				6	*80*	*14*
				2f	3f	Yield (%)
1f	13	A	85	14	86	4[e]
	14	A	130	2	98	36

[a] Reagent added portionwise shown in parentheses. M = malic acid (**9**), P = phenol (**1**), S = sulphuric acid.
[b] By ^{1}H NMR spectroscopy.
[c] Product composition % values (in *italics*) include **3e**
[d] Ratio **2d** : **3d** = 8 : 92, see ref. 6.
[e] Lit.[5] yield 3%.

Products were identified by ^{1}H and ^{13}C NMR spectroscopy. Use of the *peri*-deshielding effect[1] to definitively identify the H-4 signals in the 5-substituted compounds was a valuable assignment aid. Detection of the quaternary carbon resonances in the low abundance 5-isomers was only possible after sample concentration by fractional crystallisation.

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* To receive any correspondence.

Table 4 Orientation effects in the Pechmann reaction with malic acid and ethylacetoacetate

	Isomer ratio (%)		
Phenol reactant	Malic acid		Ethylacetoacetate[a]
1a	2a (12)	3a (88)[b]	5a (100)[b]
1b	2b (3)	3b (97)	5b (100)
1c	2c (0)	3c (100)	5c (100)
1d	2d (8)	3d (92)[c]	5d (100)[d]
1e		3e [e]	5e (100)[f]
1f	2f (2)	3f (98)[g]	5f (100)[h]
1g	2g (-)	3g (-)[h]	5g (-)[h]
1j	6 (9)	7 (91)[b]	8 (100)[b]

[a] No 5-isomers (series 4) detected;
[b] Data ex ref. 1;
[c] Data ex ref. 6, see also Table 3;
[d] See also ref. 17;
[e] Isomer in excess;
[f] See also ref. 18;
[g] Ratio 2f : 3f = 14 : 86 at 85°, see Table 3;
[h] See also ref. 5.

Techniques used : ^{1}H and ^{13}C NMR spectroscopy

Schemes : 3

Tables : 8

Tables 5 and 6 : ^{1}H and ^{13}C NMR spectra of coumarins

Table 7 : Synthesis of coumarins

Table 8 : Elemental analyses of coumarins

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