SHORT PAPER

J. Chem. Research (S),
2003, 628–629

Intramolecular Wittig reactions. A new synthesis of coumarins and 2-quinolones†

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o-Hydroxybenzaldehydes (**1a-d**) on reaction with chloroacetyl chloride in presence of pyridine followed by addition of triphenyl phosphine and base gave coumarins (**2a-d**). A similar sequence of reactions on *o*-aminoacetophenone/benzophenone (**1e-f**) and methyl anthranilate (**1g**) gave the corresponding 2-quinolones (**2e-g**).

Keywords: intramolecular wittig reactions, coumarins, 2-quinolones

In continuation to our interest in using the Wittig reaction for the synthesis of biologically interesting heterocycles,[1,2] we were interested in synthesis of 4-alkoxy substituted coumarins[3,5] and 2-quinolones.[6] An earlier reported method[7] using intermolecular Wittig reaction failed to provide us these products. This prompted us to envisage an intramolecular Wittig reaction[8] approach (Scheme 1).

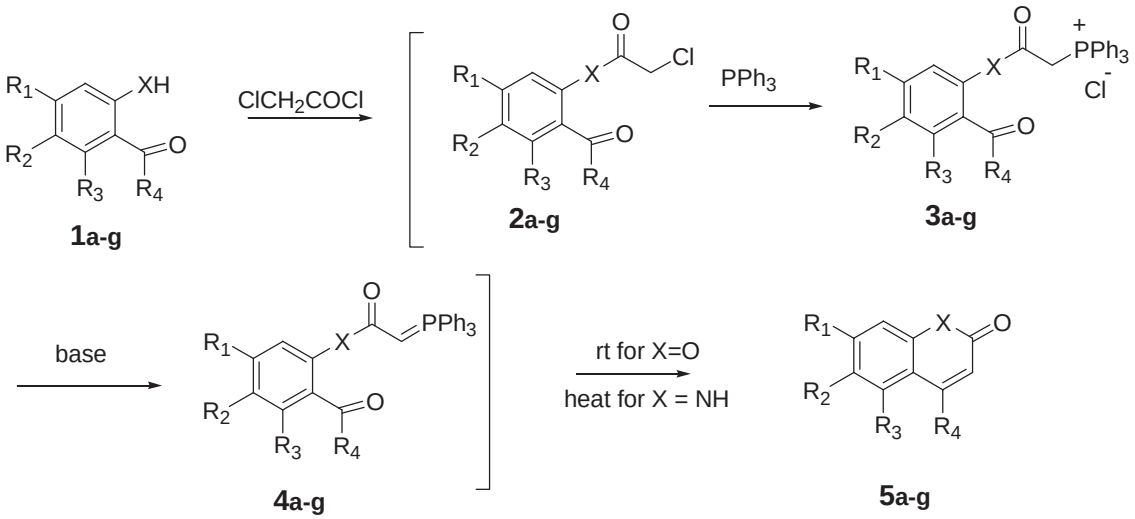
Initially, it was decided to synthesise unsubstituted coumarin, thus salicylaldehyde was reacted sequentially with pyridine, chloroacetyl chloride, and triphenyl phosphine, followed by reaction with triethylamine. The coumarin **5a** was obtained in 30% yield after chromatographic separation. Attempts to improve the yield and isolate the intermediates **2**, **3** and **4** were unsuccessful. Pyridine was chosen as a base for the formation of chloroacetyl derivative **2** as previous attempts to isolate this with triethylamine had resulted in formation of 3-chlorocoumarin.[14] A similar sequence of reactions with 2-hydroxy-4-methoxybenzaldehyde, 2-hydroxy-4-methylbenzaldehyde and 1-hydroxynaphthaldehyde gave the corresponding 7-methoxycoumarin (hernin, **5b**), 7-methylcoumarin (**5c**) and benzocoumarin (**5d**) (Table 1).

Extension of this approach to the synthesis of 4-methoxycoumarins did not succeed. The chloroacetyl derivative of methyl salicylate on treatment with triphenyl phosphine and base resulted in hydrolysis to give back methyl salicylate.

Table 1 Coumarins and 2-quinolones synthesised according to Scheme 1

Product **5**	X	R_1	R_2	R_3	R_4	Yield /%	M.p. /°C	Lit. m.p. /°C
a	O	H	H	H	H	30	68	69[7]
b	O	OMe	H	H	H	27	118	119[10]
c	O	Me	H	H	H	26	118	117–118[7]
d	O	H	-CH=CH-CH=CH-		H	27	116	116–117[9]
e	NH	H	H	H	OMe	49	238	240[9,11]
f	NH	Cl	H	H	Ph	32	260	262[12]
g	NH	H	H	H	Me	29	222	222–224[13]

This Wittig approach was then applied to the synthesis of 4-substituted 2-quinolones (**5e–g**). Thus, methyl anthranilate was converted into its chloroacetyl amide **2e** by the Schotten-Baumann method. The amide **2e** and triphenyl phosphine were refluxed in chloroform to give the salt **3e**, which without isolation was converted into phosphorane **4e** by treatment with a base. The crude phosphorane **4e** was then heated at



Scheme 1

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

180–200 °C to give 4-methoxyquinolone (**5e**) in 90% yield via a non classical Wittig reaction.[15,16] Similar sequence of reactions with *o*-aminobenzophenone (**1f**) and *o*-aminoacetophenone (**1g**) gave the corresponding 7-chloro-4-phenyl-2-quinolone (**5f**) and 4-methyl quinolone (**5g**) (Table 1)

In conclusion, we have demonstrated the usefulness of an intramolecular Wittig reaction in the synthesis of coumarins. Although the desired products are formed in low yield (26–30%), they are obtained in a one-pot process from readily-available materials. Similarly, 2-quinolones unavailable via intermolecular Wittig reactions are obtained in fair yields.

Experimental

^{1}H NMR spectra are recorded at 300 MHz in $CDCl_3$ using TMS as an internal standard. IR spectra were obtained on a Shimadzu DR-8031 spectrophotometer.

General procedure for the preparation of coumarins (**5a–d**) *from o-hydroxybenzaldehydes* (**1a–d**): A mixture of *o*-hydroxybenzaldehyde (**1a–d**) **(**1mmol) and dry pyridine (1 mmol) in dry chloroform was stirred at 0 °C. Chloroacetyl chloride (1 mmol) was then added slowly. The resulting mixture was stirred for 2 hours at 0 °C. Triphenyl phosphine (1mmol) was added and the reaction mixture was refluxed for 2 hours. The reaction mixture was allowed to attain room temperature. Triethylamine (3 mmol) was added and the reaction mixture was stirred for one hour. The residue obtained after evaporation of chloroform was chromatographed over silica gel using ethyl acetate : petroleum ether (1 : 9) as an eluent. The initial fractions gave solid materials which were recrystallised from dichloromethane-petroleum ether to furnish the coumarins (**5a–d**).

General procedure for the preparation of 2-quinolones (**5e–g):** Chloroacetyl derivatives (**2e–g**) (1 mmol) and triphenylphosphine (1 mmol) in dry chloroform were heated under reflux for 12 hours. The reaction mixture concentrated under vacuum. Water (20 ml) was added, the aqueous layer washed with ether (3 × 15 ml). This was then neutralised with aqueous sodium hydroxide to a phenolphthalein end point and extracted in chloroform (3 × 25 ml). The chloroform layer was dried over anhydrous sodium sulfate and concentrated to yield phosphoranes **4e–g**. The phosphoranes **4e–g** were heated at 180–200 °C in an oil bath for five hours. Column chromatography using methanol : chloroform (1 : 9) gave white solids which were recrystallised using chloroform – petroleum ether.

^{1}H NMR of phosphonium salt **3e**: δ 3.77 (s, 3H, OCH_3); 5.51 (d, J = 14.1 Hz, 2H, CH_2); 7.09–7.87 (m, 19H, Ar-H). 11.5 (bs, 1H, NH, exchangeable with D_2O).

^{1}H NMR of phosphorane **4e**: δ 3.04 (d, J = 20.4 Hz, CH); 3.82 (s, 3H, OCH_3); 6.72 (t, J = 7.5 Hz, 1H, Ar-H); 7.13–7.91 (m, 17H, Ar-H); 8.6 (d, J = 8.7 Hz, 1H, Ar-H); 11.5 (bs 1H, NH, exchangeable with D_2O).

We thank UGC, New Delhi, for financial assistance and RSIC., Mumbai, for spectral analysis.

Received 19 March 2003; accepted 30 July 2003
Paper 03/1824

References

1 S.G. Tilve, A.S. Tilve and V.G. Desai, *Synth.Commun.*, 1996, **26**, 1921.
2 R.S. Mali, S.G. Tilve and V.G. Desai, *J. Chem. Research* 2000, *(S)*, **8**, *(M)*, 0150.
3 G. Feuer, *Prog. Med. Chem*., 1974, **10**, 85.
4 B.M. Trost and F.D. Toste, *J. Am. Chem. Soc*., 1998, **120**, 9074.
5 R.D.H. Murray, J. Mendez and S.A. Brown, *The Natural Coumarins, Occurrence, Chemistry and Biochemistry*, Wiley, Chichester, 1982.
6 *Rodd's Chemistry of Carbon Compounds*, 2nd edn. Vol. IV, Caffey, F.S. ed., Elsevier Scientific Publishing Company, Amsterdam 1979, 319.
7 R.S. Mali and V.J. Yadav, *Synthesis*, 1977, 464.
8 B.M. Heron, *Heterocycles* 1995, **41**, 2375.
9 H.J. Bestmann, G. Schimid, D. Sandmev, G. Schade and H. Oochsner, *Chem. Ber*., 1985, **118**, 1709.
10 R. Connor and P.L. deBenneville, *J. Am. Chem. Soc*., 1940, **62**, 3067.
11 K. Nickisch, W. Klose, E. Nordhoff and F. Bohlmann, *Chem. Ber*., 1980, **113**, 3086.
12 K. Hino, K. Furukawa, Y. Nagai and H. Uno, *Chem. Pharm. Bull*., 1980, **28**, 2618.
13 L. Knorr, *Justus Liebigs Ann. Chem*., 1886, **236**, 69.
14 R.S. Mali and J.V. Deshpande, *Organic Prep. Proc. Int.*, 1995, **27**, 663.
15 P.J. Murphy, *Chem. Soc. Rev*., 1988, **17**, 1.
16 A.W. Johnson, (ed.) *Ylides and Imines of Phosphorus*, John Wiley & Sons, NewYork, 1993.