Pergamon

Tetrahedron Letters 42 (2001) 5331–5334

TETRAHEDRON LETTERS

Solid-supported synthetic equivalents of 3-formylchromone and chromone

José I. Borrell,[a,*] Jordi Teixidó,[a] Elisabeth Schuler[a] and Enrique Michelotti[b]

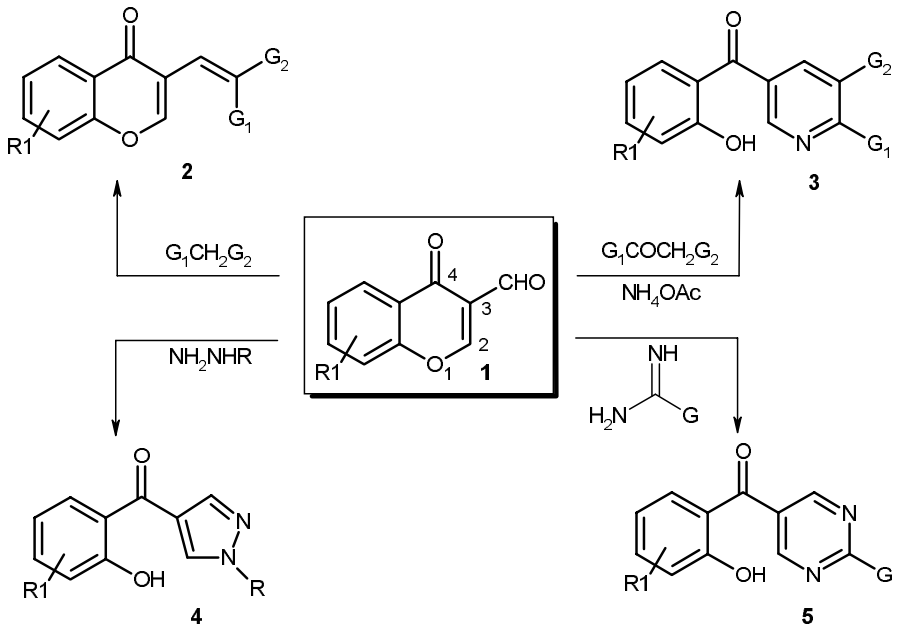
[a]*Grup d'Enginyeria Molecular, Institut Químic de Sarrià, Universitat Ramon Llull, Via Augusta, 390, E-08017 Barcelona, Spain*
[b]*Rohm and Haas Company, 727 Norristown Road, Spring House, PA 19477-0904, USA*

Received 30 March 2001; accepted 11 June 2001

Abstract—Treatment of bound *o*-hydroxyacetophenone **10** under Vilsmeier–Haack reaction conditions yields **11a** or **12b**, synthetic equivalents of 3-formylchromone (**1**) and chromone (**13**) respectively, depending on the resin used as solid support (Merrifield or Wang chloro resin respectively).

3-Formylchromone derivatives (**1**) have been extensively used as versatile solution phase building blocks for the synthesis of a large number of heterocyclic systems (Scheme 1).[1] In contrast, despite their versatility in solution phase chemistry, resin bound chromone derivatives have received no attention.

Several solution phase methods are reported in the literature for the preparation of substituted 3-formylchromones.[2–4] The most convenient method to synthesize **1** uses substituted *o*-hydroxyacetophenones as starting materials which are treated using Vilsmeier–Haack reaction conditions ($POCl_3$ in DMF) to afford the desired 3-formylchromones in good yields.[4]



Scheme 1.

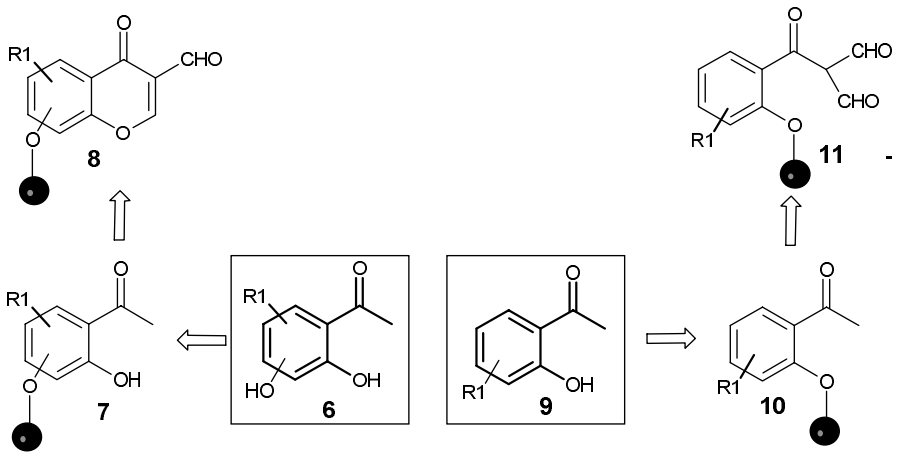
Keywords: solid-phase synthesis; Vilsmeier–Haack reaction; 3-formylchromones; chromones; Merrifield resin; Wang resin.
* Corresponding author. Tel.: +34 932 038 900; fax: +34 932 056 266; e-mail: jibor@iqs.url.es

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00999-6

As a part of our ongoing research in the area of combinatorial chemistry[5] focused on the preparation of random libraries for high throughput screening (HTS), we considered preparing two types of solid-supported 3-formylchromone derivatives (Scheme 2). The first attaches the resin through an ester or ether linkage to a second hydroxy group present in the phenyl ring of an *o*-hydroxyacetophenone **6**, converting the resulting compound **7** to a solid-supported 3-formylchromone **8**. The second, more appealing method, attaches the polymer support directly to the C-2 hydroxy group of a *o*-hydroxyacetophenone **9** leading to **10**, which can be converted to compound **11**, a synthetic equivalent of 3-formylchromone. A search carried out in the Sigma–Aldrich Chemical Directory on CD-ROM (1999 version) showed that the number of dihydroxy substituted acetophenones was rather low but, differently substituted *o*-hydroxyacetophenones were numerous. Consequently, in order to ensure the maximum diversity of a possible combinatorial library to be constructed, we decided to investigate the synthesis of the solid-supported α,α-diformyl-*o*-hydroxyacetophenones **11**. The present paper presents the results obtained in such a study.

The first part of the study was carried out using the Merrifield resin as the solid support and *o*-hydroxyacetophenone **9** (R1 = H) (Scheme 3). Treatment of the resin (1% cross linked, 3.9 mmol/g) in DMA with 3 equiv. of *o*-hydroxyacetophenone (**9**) and 3 equiv. of NaOMe at 80°C for 24 h quantitatively afforded **10a** (R1 = H, Merrifield resin) as established by MAS-NMR. Compound **10a** was then treated under Vilsmeier–Haack reaction conditions varying the amount of $POCl_3$, the temperature and the reaction time (Table 1). Upon cleavage from the polymer with 1:1 TFA/CH_2Cl_2 for 3 h at rt, the resulting crude materials were analyzed by HPLC–MS and ^{1}H NMR.[6] The first chromatograms obtained (entries 1–4) showed a main peak that was assigned to 3-formylchromone **1** on the basis of the MS. However, the ^{1}H NMR spectra showed the presence of both 3-formylchromone (**1**) and chromone (**13**). The ratio between both species was established by using the formyl group signal of **1** (10.40 ppm, s) and the H-C3 signal of **13** (6.53 ppm, d). The latter presumably is formed from the monoformyl derivative **12a** during the Vilsmeier–Haack reaction. It was necessary to increase the temperature to 50°C (Entry 8) to achieve both a total conversion of **10a** and the sole formation of **11a**. However, when the resulting resin was cleaved with 1:1 TFA/CH_2Cl_2 for 3 h at rt, 3-formylchromone (**1**) was obtained in high purity but only in modest yield (25%).[7]

This result prompted us to change Merrifield resin to the Wang chloro resin in order to facilitate the cleavage step. Thus, Wang resin (1% cross linked, 1.13 mmol/g) was converted to the Wang chloro resin by using $SOCl_2$ in CH_2Cl_2. Treatment of this resin in DMA with 3

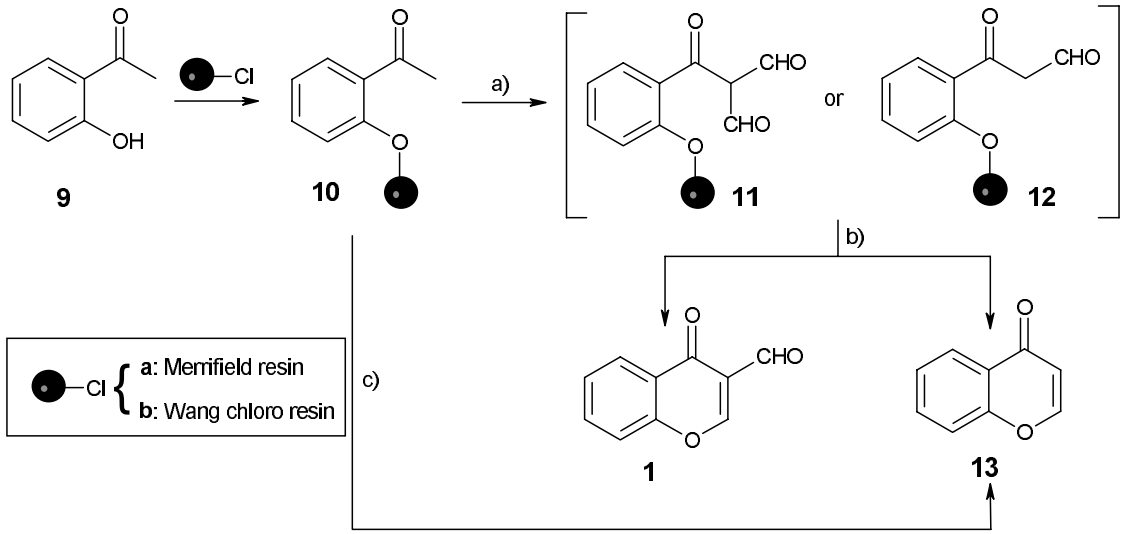


Scheme 2.

Table 1. Vilsmeier–Haack reaction of **10a**

Entry	$POCl_3$ (equiv.)	T (°C)	t (h)	Conversion[a] (%)	**1**:**13** ratio[b] (%)
1	4.0	25	24	44	–
2	4.0	25	48	84	–
3	4.0	25	72	90	42:58
4	4.0	25	96	92	52:48
5	8.0	25	96	97	–
6	30.0	25	48	100	77:23
7	30.0	25	96	100	87:13
8	4.0	50	24	100	100:0
9	4.0	100	48	Decomp.	–

[a] Determined by HPLC–MS.
[b] Determined by ^{1}H NMR.



Scheme 3. (a) $POCl_3$, DMF; (b) 1:1 TFA:CH_2Cl_2; (c) HCOOEt, HNa, 1:1 DMA:THF then (b).

equiv. of *o*-hydroxyacetophenone and 3 equiv. of NaOMe at 80°C overnight quantitatively afforded **10b** (R1 = H, Wang resin) as established by MAS-NMR. Compound **10b** was then treated under Vilsmeier–Haack reaction conditions varying the amount of $POCl_3$, the temperature and the reaction time as above. Surprisingly, in all the experiments carried out, after the cleavage step with 1:1 TFA/CH_2Cl_2 for 1 h at rt, chromone **13** was formed as the major product even though large excesses of $POCl_3$ (2–20 equiv.) were used, even in the optimal conditions found (10 equiv, of $POCl_3$, 50°C, 3 h) a mixture of **13** and **1** in a 94:6 ratio was obtained.[8] The monoformylated intermediate **12b** appears to be selectively formed. Consequently, we decided to obtain the monoformyl derivative **12b** by using a different strategy. Thus, the treatment of **10b** with ethyl formate (15 equiv.) and NaH (20 equiv.) in 1:1 DMA/THF afforded **12b** in high yield.[9] No further work was carried out to explain the different behavior of **10** in the Vilsmeier–Haack reaction between the use of the Merrifield and the Wang chloro resin as solid support.

In conclusion, we have developed procedures for the synthesis of the solid-supported synthetic equivalents of substitued 3-formylchromones and chromones. An application of such methodology to the production of heterocyclic libraries will be reported in due course.

References

1. Sabitha, G. *Aldrichim. Acta* **1996**, *29*, 15–25 and references cited therein.
2. Becket, G. J. P.; Ellis, G. P. *Tetrahedron Lett.* **1976**, 719–720.
3. Klutchko, S.; Cohen, M. P.; Shavel, Jr., J.; von Strandtmann, M. *J. Heterocyclic Chem.* **1974**, *11*, 183–188.
4. (a) Nohara, A.; Umetani, T.; Sanno, Y. *Tetrahedron Lett.* **1973**, 1995–1998; (b) Nohara, A.; Umetani, T.; Sanno, Y. *Tetrahedron* **1974**, *30*, 3553–3561; (c) Klutchko, S.; Kminsky, D.; von Strandtmann, M. US Patent 4,098,799, 1978; *Chem. Abstr.* **1979**, *90*, 22813c.
5. See, for instance: Obrecht, D.; Villalgordo, J. M. Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries; Pergamon, 1998.
6. The isolated yields were calculated based on Merrifield and Wang resin substitution levels. The purity was determined based on area of peak corresponding to the correct molecular weight by a C18 reverse phase HPLC column (Monochrom, 5 μ, 5–95% CH_3CN/H_2O containing 0.1% acetic acid), monitored by UV detection at 220 and 254 nm.
7. Merrifield resin (100 mg, 0.39 mmol) was suspended in DMA (1 ml) and treated with NaOMe (3 equiv) and *O*-hydroxyacetophenone (3 equiv.). The mixture was heated at 70–80°C overnight. Resin **10a** thus obtained was filtered, washed extensively with DMA, MeOH:HAcO 1:1, MeOH and CH_2Cl_2 and dried under vacuum. Resin **10a** (138 mg, 0.39 mmol) was suspended in DMF (1 ml), cooled in a salt ice bath and $POCl_3$ (0.13 ml, 1.56 mmol, 4 equiv) was added. The bath was removed and the reaction was stirred at 50°C for 48 h. Ice–water (1 ml) was carefully added to the reaction mixture. Resin **11a** was filtered, washed with H_2O:MeOH 1:1, MeOH and CH_2Cl_2 and dried under vacuum to a constant weight (157 mg). The resin **11a** (100 mg) was treated with TFA:CH_2Cl_2 (1 ml) at room temperature with stirring for 3 h. The resulting solution was concentrated in vacuo to yield 20 mg of a crude material, which was purified by preparative HPLC to yield 13 mg (0.07 mmol, 25%) of 3-formylchromone **1**.
8. Wang resin (100 mg, 0.17 mmol) was converted in Wang chloro resin by two sequential treatments with thionyl chloride (5 equiv) in CH_2Cl_2 (1 ml) with stirring at 0–5°C for 45 min followed by overnight stirring at rt. This resin (103 mg, 0.17 mmol) was treated as above [DMA (1 ml), NaOMe (3 equiv), **9** (3 equiv), 70–80°C overnight] to yield resin **10b**. Resin **10b** (117 mg, 0.17 mmol) was converted to resin **12b** [DMF (1 ml), $POCl_3$ (0.14 ml, 1.56 mmol, 10 equiv), 48 h rt]. Resin **12b** [100 mg (0.087 mmol)] was treated with TFA:CH_2Cl_2 (1 ml) at room temperature with stirring for 1 h to yield 12 mg of a crude material, which

was purified by SPE (Alltech Silica, part. no. 209362, 1:3 AcOEt:hexane) to yield 6 mg (0.06 mmol, 50%) of chromone **13**.

9. Resin **10b** (100 mg, 0.15 mmol) was suspended in DMA:THF 1:1 (1 ml) and NaH (132 mg, 3 mmol, 20 equiv., 60% dispersion in mineral oil) was added followed by ethyl formate (0.2 ml, 2.25 mmol, 15 equiv.). The mixture was stirred at room temperature for 3 h. Resin **12b** was filtered, washed with HAcO:MeOH 1:1, MeOH and CH_2Cl_2 and dried under vacuum (92% purity by HPLC).