Pergamon

Tetrahedron Letters 40 (1999) 6761–6764

TETRAHEDRON LETTERS

New and facile synthesis of 3-styrylflavones

Vladimir Lokshin, Arnault Heynderickx, André Samat,* Gérard Pèpe and Robert Guglielmetti

Université de la Méditerranée, Faculté des Sciences de Luminy, ESA 6114 CNRS Case 901, 13288 Marseille Cedex 9, France

Received 20 May 1999; accepted 1 July 1999

Abstract

A simple synthetic access to 3-styrylflavones is developed through the reaction of 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-diones with phenylacetic aldehydes. The structure of parent compound is confirmed by X-ray analysis.

Keywords: flavones; carbonyl compounds; condensation; cyclisation.

1. Introduction

Chromones (4*H*-1-benzopyran-4-ones) and their 2-phenyl derivatives (flavones), which are an important class of oxygenated heterocycles, have been intensively studied over the years,[1] especially due to their biological and medicinal uses.

The introduction of a styryl group, an original way for structural modifications of these heterocycles, is interesting for two mains reasons. On the one hand, both natural and synthetic 2-styrylchromones exhibit wide biological activities,[2] and on the other hand the styryl group allows preparation of extended polycyclic systems via Diels–Alder reactions.[3]

Nevertheless, although the synthetic approaches to 2- and 3-styrylchromones are relatively well documented,[2,4,5] there is very little information related to 3-styrylflavones. To our knowledge, the only reported synthetic access to these compounds uses a multi-step transformation of the methyl group of a 3-methylflavone.[6]

This work describes a convenient one-step preparation method of 3-styrylflavones starting from simple precursors.

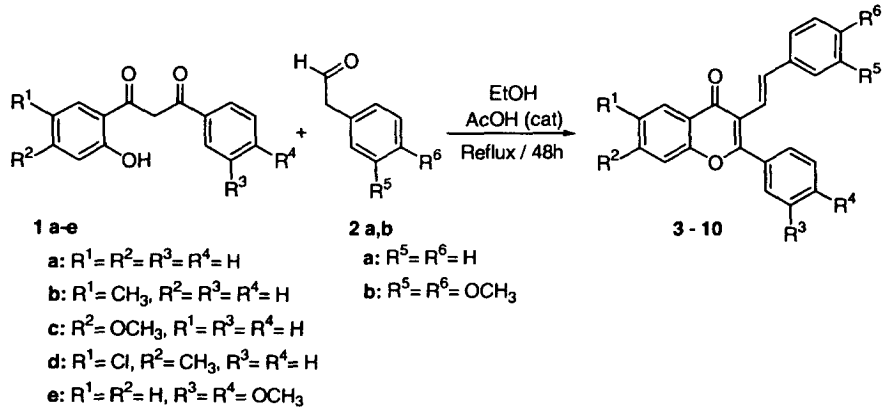
2. Results and discussion

The reaction of 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-diones **1a–e** with phenylacetic aldehydes **2a,b** (Scheme 1) in ethanol, using a catalytic amount of acetic acid, leads to 3-styrylflavones **3–10** (see

* Corresponding author. Tel: (33) 4 91 82 94 05; fax: (33) 4 91 82 93 01; e-mail: samat@chimlum.univ-mrs.fr

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01301-5

Table 1). In a typical experiment, a solution of diketone **1a** (0.25 g, 1.045 mmol), aldehyde **2a** (0.502 g, 4.18 mmol) and glacial acetic acid (0.2 ml) in ethanol (10 ml) is refluxed, till the starting diketone is totally consumed (usually 48 h). The expected styrylflavone **3** is filtered off as a solid after cooling of the reaction mixture. A pure sample is obtained by recrystallisation in ethanol.[7]



1 a-e
a: $R^1 = R^2 = R^3 = R^4 = H$
b: $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$
c: $R^2 = OCH_3$, $R^1 = R^3 = R^4 = H$
d: $R^1 = Cl$, $R^2 = CH_3$, $R^3 = R^4 = H$
e: $R^1 = R^2 = H$, $R^3 = R^4 = OCH_3$

2 a,b
a: $R^5 = R^6 = H$
b: $R^5 = R^6 = OCH_3$

3 - 10

Scheme 1.

A soft acidic catalyst (acetic acid) has been proved to be more efficient than basic catalysts which were generally used in this kind of condensation reaction. For example, the use of piperidine or 4-dimethylaminopyridine for the preparation of **3** led to the formation of numerous by-products resulting in the autocondensation of the phenylacetic aldehyde. Besides, the use of strong acids has been discarded to avoid the competitive cyclisation of the starting diketones in flavones.

Proton and carbon-13 NMR spectra were in full agreement with the proposed structure.[8,9]

The coupling constant value (J=16.3 Hz) between the ethylenic protons suggests an E-configuration for the styryl double bond. This has been unambiguously confirmed by a radiocrystallographic study[10] (Fig. 1).

Despite the poor or moderate yields (15% to 50%) observed during the preparation of styrylflavones

Table 1
Preparation of 3-styrylflavones

Product	R^1	R^2	R^3	R^4	R^5	R^6	*Yield (%)*[a]	*M.p. (°C)*[b]
3	H	H	H	H	H	H	30	168
4	CH_3	H	H	H	H	H	47	129
5	H	OCH_3	H	H	H	H	15	174
6	Cl	CH_3	H	H	H	H	40	194
7	H	H	OCH_3	OCH_3	H	H	33	154
8	H	H	H	H	OCH_3	OCH_3	50	179
9	Cl	CH_3	H	H	OCH_3	OCH_3	20	183
10	H	H	OCH_3	OCH_3	OCH_3	OCH_3	27	138

[a]Yield of isolated product (not optimised), calculated from the starting diketone.
[b]Melting points are uncorrected.

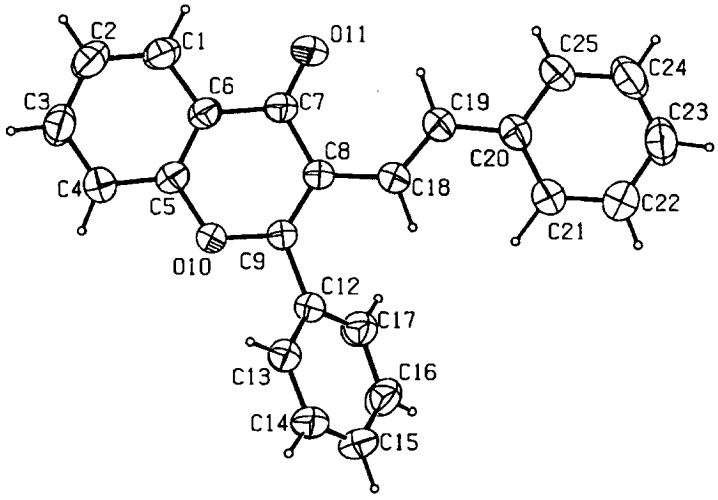
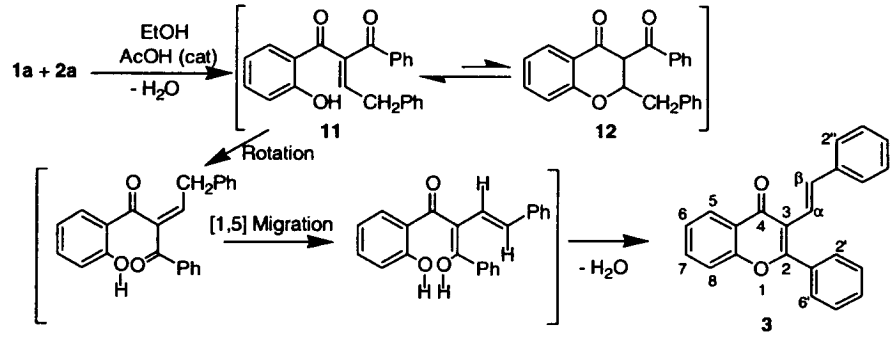


Figure 1. The ORTEP diagram of **3**

3–10 (Table 1), due to the formation of several non-isolated by-products, the simplicity of this method and the easy accessibility of the precursors[11] make this reaction highly attractive.

A possible mechanism for the formation of these 3-styrylflavones is proposed in Scheme 2, taking the preparation of **3** as an example.



Scheme 2.

Contrary to what is observed during the reaction of diketone **1a** with aromatic or heterocyclic aldehydes,[12] the intermediate **11** doesn't lead to the cyclised product **12**, but affords 3-styrylflavone **3**, this reaction being favoured by π conjugation extension through a 1,5-shift of the benzylic proton.

Acknowledgements

Prof. A. Da Silva (Universidade de Aveiro, Portugal) and Prof. G. Duménil (Université de la Méditerranée, Marseille) are sincerely thanked for helpful discussions and suggestions.

References

1. (a) *Chromenes, Chromanones, and Chromones*; Ellis, G. P., Ed.; John Wiley: New York, 1977. (b) *The Flavonoids*; Harborne, J. B.; Mabry, T. L.; Mabry, H., Eds.; Chapman and Hall: London, 1975. (c) *The Flavonoids—Advances in Research since 1980*; Harborne, J. B., Ed.; Chapman and Hall: London, 1988. (d) *The Flavonoids—Advances in Research*

since 1986; Harborne, J. B., Ed.; Chapman and Hall: London, 1994. (e) Dauzonne, D.; Folleas, B.; Martinez, L.; Chabot, G. G. *Eur. J. Med. Chem.* **1997**, *32*, 71–82.
2. Price, W. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *Heterocycles* **1993**, *36*(11), 2601–2612, and references cited therein.
3. (a) Ghosh, C. K.; Ghosh, C. *Indian J. Chem.* **1997**, *36B*, 968–980. (b) Silva, A. M. S.; Pinto, D. C. G. A.; Tavares, H. R.; Cavaleiro, J. A. S.; Jimeno, M. L.; Elguero, J. *Eur. J. Org. Chem.* **1998**, 2031–2038. (c) Silva, A. M. S.; Silva, A. M. G.; Tome, A. C.; Cavaleiro, J. A. S. *J. Eur. J. Org. Chem.* **1999**, 135–139.
4. Reddy, B. P.; Krupadanam, G. L. D. *J. Heterocyclic Chem.* **1996**, *33*, 1561–1565, and references cited therein.
5. Silva, A. M. S.; Cavaleiro, J. A. S.; Elguero, J. *Liebigs. Ann.* **1997**, 2065–2068, and references cited therein.
6. Goyal, S.; Parthasarathy, M. R. *Indian J. Chem.* **1992**, *31B*, 391–395.
7. Compounds **5**, **9** and **10** were purified by silica gel column chromatography.
8. Spectral data for compound **3**: ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 6.83 (1H, d, *J*=16.3 Hz, α-H); 7.19–7.57 (10H, m, Ar); 7.68 (1H, ddd, *J*=7.5, 7.5 and 1.5 Hz, 7-H); 7.74 (2H, m, 2′-H and 6′-H); 8.03 (1H, d, *J*=16.3 Hz, β-H); 8.32 (1H, d, *J*=8.0 Hz, 5-H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δ ppm): 117.9 (s); 118.1 (d); 120.4 (d); 123.8 (s); 125.4 (d); 126.5 (d); 126.8 (d); 127.8 (d); 128.8 (d); 130.1 (d); 131.0 (d); 133.5 (s); 133.7 (d); 134.7 (d); 138.5 (s); 155.7 (s); 163.3 (s); 177.7 (s).
9. Satisfactory microanalyses were obtained for all new compounds.
10. Crystal data for **3** ($C_{23}H_{16}O_2$) Mr=324.36, triclinic, *a*=8.248(1), *b*=9.884(1), *c*=10.550(1) Å, α=90.6(1), β=107.9(1), γ=97.1(1), *V*=811.1(2) Å^3, space group P_{-1}, *Z*=2, D_c=1.328 Mg.m^{-3}, *F*(000)=340, μ=0.084 mm^{-1}, *T*=293(2) K, θ=0°–30°, $-11<h<11$, $-13<k<13$, $0<l<14$, reflections collected 3951, independent reflections 3951 (full-matrix least-squares on F^2). Atomic co-ordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.
11. The 1,3-diketones **1a**, **1b**, **1d** and the aldehyde **2a** were commercially available from Aldrich®.
12. (a) Huffmann, K. R.; Kuhn, C. E.; Zweig, A. *J. Am. Chem. Soc.* **1970**, *92*, 599–605. (b) Cummings, R. T.; Dizio, J. P.; Krafft, G. A. *Tetrahedron Lett.* **1988**, *29*, 69–72.