Monatsh Chem 139, 991–993 (2008)
DOI 10.1007/s00706-008-0876-6
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

A microwave-assisted synthesis of phenanthroperylene quinones as exemplified with hypericin

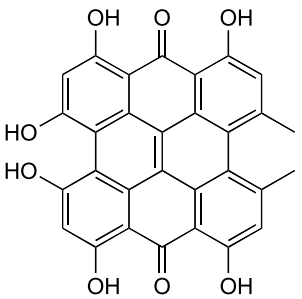
Stefan Aigner, Heinz Falk

Institute of Organic Chemistry, Johannes Kepler University, Linz, Austria

Received 4 December 2007; Accepted 18 December 2007; Published online 18 February 2008

Abstract The synthesis of hypericin, one of the most important phenanthoperylene quinones used in photodynamic therapy, could be highly improved by using either a microwave-assisted dimerization of emodinanthrone, or a mixed dimerization of emodinanthrone with emodin in the presence of potassium *t*-butoxide as the key-step.

Keywords Hypericin; Emodin; Emodinanthrone; Synthesis; Microwave irradiation.



1

Introduction

Hypericin (**1**; 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-phenanthro[1,10,9,8-*opqra*]perylene-7,14-dione) and several of its derivatives are highly potent photosensitizers for photodynamic therapy [1]. The synthesis of this pigment **1** and most of its derivatives is commonly achieved by a dimerization of two precursor ''halves'' [1]. These synthons are either produced by total synthesis or are available as derivatized natural products (*e.g.*, emodin).

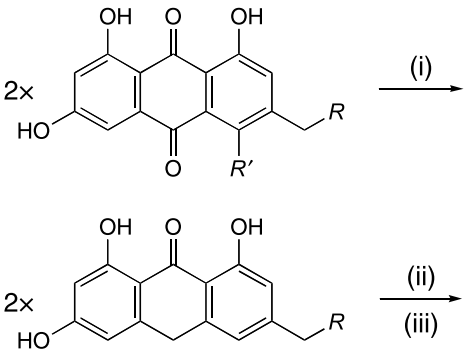
With respect to the chemistry involved in the key dimerization step the coupling can be achieved on three paths: (i) starting from suited bromo substituted anthraquinones (Scheme 1, $R = H$, $R' = Br$) by means of an *Ullmann* coupling [2], (ii) from anthraquinones (Scheme 1, $R' = H$) by reductive dimerization in a strongly alkaline solution using hydroquinone as the reducing agent [3, 4], and (iii) by a biomimetic sequence starting from an anthrone derivative (Scheme 1, R = H or certain substituents) [5–14]. Although the latter methodology as the most suited one has been used several times, it suffers from the rather modest yields that could be achieved. Moreover, only hypericinoid compounds derived from identically substituted ''halves'' are accessible if the rather tedious separations of the otherwise formed isomers should be avoided. Therefore we followed the quest for a more efficient methodology of hypericin synthesis focusing on the dimerization key-step.

Correspondence: Heinz Falk, Institute of Organic Chemistry, Johannes Kepler University, Altenbergerstraße 69, 4040 Linz, Austria, Europe. E-mail: heinz.falk@jku.at

Results and discussion

A recent communication on microwave-assisted condensations yielding sterically overcrowded ethylenes [15] prompted us to investigate this possibility with regard to the formation of the phenanthroperylene

skeleton. For the key-step of dimerization we first pursued the coupling of two identical ''halves'' of emodinanthrone (**2**) as shown in Scheme 2. Interestingly enough, in the presence of potassium *t*-butoxide in *DMF* microwave irradiation for 20 min and usual work-up provided protohypericin (**3**) in 78% yield, and not the sterically congested ethylene derivative. Also, addition of an oxidizing agent was not necessary to achieve the reaction. Obviously, this reaction condition even furthered a regioselective phenol coupling after the initial condensation step.

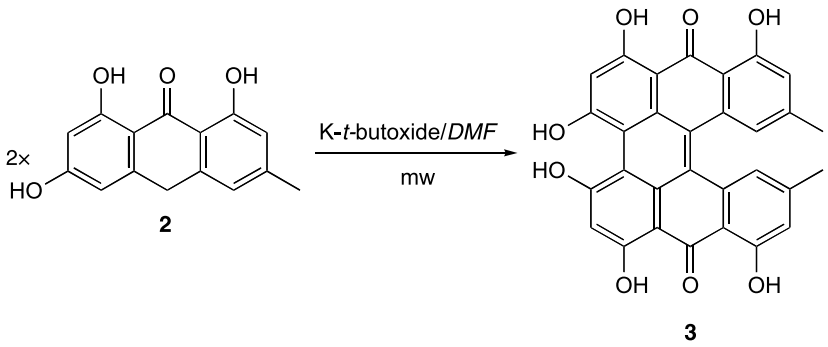


Scheme 1

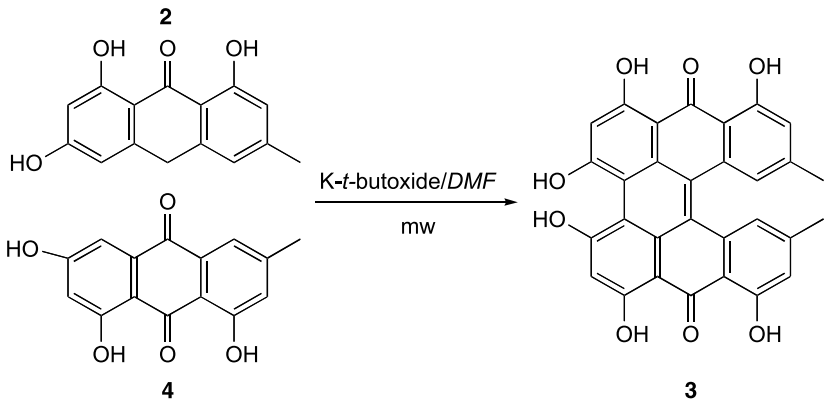
The formed protohypericin (**3**) could then be photocyclized in the usual way [8] with 95% yield of hypericin (**1**) providing an overall yield of **1** starting from **2** of 74%, a value that is superior to the yield (≈50%) on the route established before.

Because a mixed dimerization step could open the way to unsymmetrically substituted hypericin derivatives, such a mixed coupling between emodinanthrone (**2**) and emodin (**4**) – see Scheme 3 – was also tried. Thus, in the presence of potassium *t*-butoxide in *DMF* microwave irradiation for 20 min afforded a mixture of **2** and **4**. Again, this single reaction proceeded regioselectively in a 72% yield of **3**. The latter could be converted to **1** by photocyclization with an overall yield of 68%. That the described reaction was the result of microwave assistance was proven by heating the corresponding reaction mixtures at 130°C for 9.5 h providing **3** in yields of only 20 and 13% when the symmetrical and the unsymmetrical educts were used.

In conclusion, we present a novel microwave-assisted preparation of hypericin (**1**) by either dimerization of identical ''halves'' (anthrones) or mixed ''halves'' (anthrone + quinone) *via* the correspond-



Scheme 2



Scheme 3

ing protohypericin (**3**) in overall yields superior to the hitherto described synthesis. The latter methodology has also the potential to prepare unsymmetrical hypericin derivatives.

Experimental

Microwave assisted syntheses were performed on a MLS-ETHOS 1600 microwave unit with Terminal 320 from MLS-Milestone with temperature monitoring and control. The identities of hypericin (**1**) and protohypericin (**3**) were proven by comparison of their mp (*Kofler* microscope, Reichert), ^{1}H NMR (Bruker Avance DPX, 200 MHz, *DMSO*-d_6), IR (Bruker Tensor 27, KBr), MS (Thermofinnigan LCQ Deca XP Plus), and UV-Vis data (Varian Cary 100 Bio, ethanol) with those of authentical samples [16]. Emodin (**4**) and emodinanthrone (**2**) were prepared according to Refs. [8, 9].

*Dimerization of emodinanthrone (**2**)*

A mixture of 512 mg emodinanthrone (**2**) (2 mmol), 38 mg K-*t*-butoxide (0.34 mmol), and 1 cm^3 *DMF* was irradiated in the microwave unit at 150 W under *Ar* ($t = 130$°C) for 20 min. After melting within the first few minutes the mixture gently boiled under reflux. After cooling the mixture was quenched with deionized H_2O and acidified with 2 *N* HCl. The residue was centrifuged and dried (P_2O_5) overnight. The precipitate was dissolved in $CHCl_3$/*Me*OH 4/1 and purified by chromatography over silica to yield 393 mg protohypericin (**3**) (78%).

In a conventional run 1 mmol **2** and 36 mg K-*t*-butoxide in 0.5 cm^3 *DMF* were heated to 130°C for 9.5 h yielding 20% **3**.

*Mixed dimerization of emodin (**4**) and emodinanthrone (**2**)*

A mixture of 256 mg emodinanthrone (**2**) (1 mmol), 270 mg emodin (**4**) (1 mmol), 38 mg K-*t*-butoxide (0.34 mmol), and 1 cm^3 *DMF* was irradiated in the microwave unit at 150 W under *Ar* ($t = 130$°C) for 20 min. After melting within the first few minutes the mixture gently boiled under reflux. After cooling the mixture was quenched with deionized H_2O and acidified with 2 *N* HCl. The residue was centrifuged and dried (P_2O_5) overnight. The precipitate was dissolved in $CHCl_3$/*Me*OH 4/1 and purified by chromatography over silica to yield 365 mg protohypericin (**3**) (72%).

In a conventional run 0.5 mmol **2** 0.5 mmol **4**, and 36 mg K-*t*-butoxide in 0.5 cm^3 *DMF* were heated to 130°C for 9.5 h yielding 13% **3**.

The protohypericin (**3**) obtained on both ways was then photocyclized in the usual way [9] with 95% yield.

References

1. For reviews see: Falk H (1999) Angew Chem 111:3306; Angew Chem Int Ed Engl 38:3116; Waser M, Falk H (2007) Curr Org Chem 11:547
2. Brockmann H, Kluge F, Muxfeldt H (1957) Chem Ber 90:2302
3. Spitzner D (1977) Amgew Chem 89:55; Angew Chem Int Ed Engl 16:46
4. Rodewald G, Arnold R, Griesler J, Steglich W (1977) Ang Chem 89:56; Ang Chem Int Ed Engl 16:46
5. Brockmann H, Eggers H (1955) Angew Chem 67:706
6. Banks HJ, Cameron DW, Raverty WD (1976) Aust J Chem 29:1509
7. Mazur Y, Bock H, Lavie D (1991) CA 2,029,993, Chem Abstr 116:6343z
8. Falk H, Meyer J, Oberreiter M (1993) Monatsh Chem 124:339
9. Falk H, Schoppel G (1992) Monatsh Chem 123:931
10. Gruszeka-Kowalik E, Zalkow LH (2000) Org Prep Proced Int 32:57
11. Waser M, Falk H (2006) Eur J Org Chem:1200
12. Lackner B, Etzlstorfer C, Falk H (2004) Monatsh Chem 135:1157
13. Waser M, Lackner B, Zuschrader J, Müller N, Falk H (2005) Tetrahedron Lett 46:2377
14. Lackner B, Bretterbauer K, Schwarzinger C, Falk H (2005) Monatsh Chem 136:2067
15. Villemin D, Hachemi M, Hammadi M (2003) J Chem Res (S):260
16. Falk H, Schmitzberger W (1992) Monatsh Chem 123:731