Available online at www.sciencedirect.com
ScienceDirect
Journal of Pharmaceutical and Biomedical Analysis 46 (2008) 574–576
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Short communication

Impurities of tazarotene: Isolation and structural characterisation

Elisabetta Brenna *, Samuele Frigoli, Giovanni Fronza, Claudio Fuganti, Stefano Serra

Dipartimento di Chimica, Materiali ed Ingegneria Chimica del Politecnico, Istituto CNR per la Chimica del Riconoscimento Molecolare, Politecnico di Milano, Via Mancinelli 7, I-20131 Milano, Italy

Received 25 May 2007; received in revised form 6 November 2007; accepted 8 November 2007
Available online 17 November 2007

Abstract

Two impurities showing structures **5** and **6** were isolated and characterised by means of NMR analysis, during the optimisation of a synthetic procedure to tazarotene. Impurity **5**, *i.e.* ethyl 6-((4,4-dimethyl-4*H*-thiochromen-6-yl)ethynyl)nicotinate, was a by-product of the reduction of the intermediate sulfoxide **7** with PCl_3. Impurity **6**, *i.e.* 1,4-bis(4,4-dimethylthiochroman-6-yl)buta-1,3-diyne, was due to a side reaction of the Sonogashira coupling.

Keywords: Tazarotene; Impurity; Isolation; Structural characterisation

1. Introduction

Tazarotene (**1**) is a member of a new generation of receptor-selective, synthetic retinoids for the topical treatment of mild to moderate plaque psoriasis, acne vulgaris and photoaging [1]. It represents an evolution of dermatology research aimed to the discovery of retinoids that are safer than tretinoin and/or are more effective in skin rejuvenation or treatment of acne and other conditions [2].

The known synthetic method [1] is based on a Sonogashira coupling between 4,4-dimethyl-6-ethynylthiochromane (**2**) and 6-chloronicotinic acid ethyl ester (**3**) (Scheme 1). We have recently optimised a new practical synthetic procedure [3] to tazarotene, in which we took advantage of the beneficial effect of sulfur oxidation state on the activation of the acetylenic coupling of compound **4** with **3**. During this work, we identified impurities **5** and **6** in final tazarotene **1**.

We now wish to report on the elucidation of the chemical structure of these two by-products, which are strictly related to the reactions employed in this specific synthetic path.

2. Experimental

2.1. Mass spectrometry

The ESI spectra were acquired on a Bruker Esquire 3000plus instrument. GC–MS analyses were performed on a HP 6890 gas-chromatograph equipped with a 5973 mass-detector, using a HP-5MS column (30 m × 0.25 mm × 0.25 μm), and helium as the carrier gas. The analyses were performed at a constant flow rate (1 ml/min). The following temperature program was employed: 60° (1 min)/6°/min/150° (1 min)/12°/min/280° (8 min)/5°/min/300 (5 min).

2.2. NMR spectroscopy

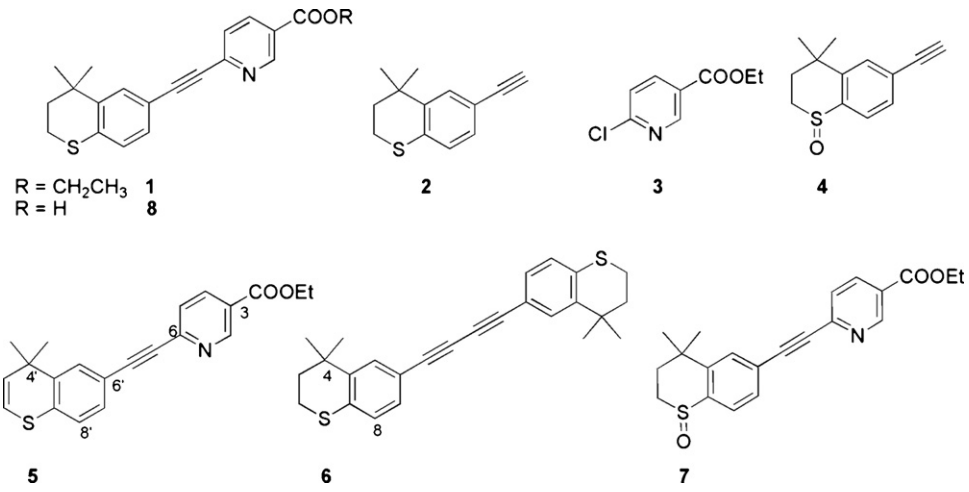
^{1}H and ^{13}C NMR spectra were acquired on a Bruker DMX instrument at 305 K. The hydrogen and carbon chemical shifts are referred to the internal tetramethylsilane (TMS). The coupling constants are expressed in Hz.

2.3. Isolation of the impurities

A column chromatography (silica gel, 0.063–0.2 mm 70–230 mesh) of final tazarotene (hexane/ethyl acetate) gave in order of elution: (i) impurity **6** (2%), (ii) a 6:4 mixture of

* Corresponding author. Tel.: +39 02 23993077; fax: +39 02 23993080.
E-mail address: elisabetta.brenna@polimi.it (E. Brenna).

0731-7085/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2007.11.004



Scheme 1.

impurity **5** and compound **1** (4%), and (iii) pure compound **1** (92%).

*2.3.1. Impurity **5** [ethyl 6-((4,4-dimethyl-4H-thiochromen-6-yl)ethynyl)nicotinate]*

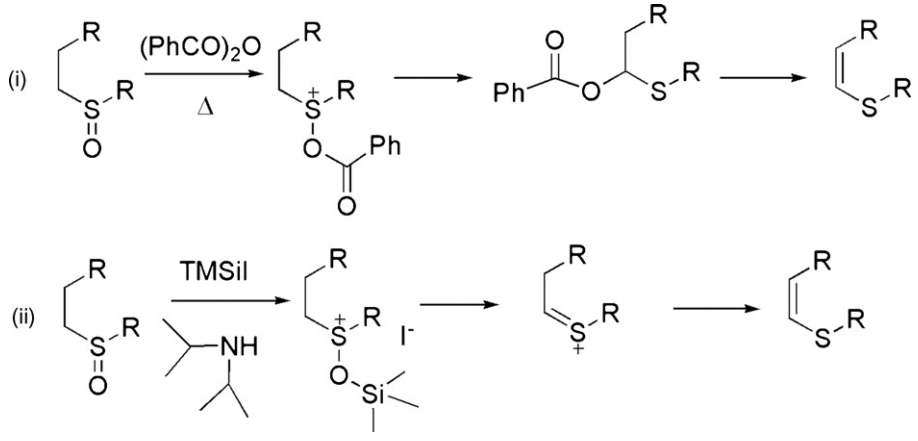
The signals were obtained from the NMR spectra of the 6:4 mixture of impurity **5** and compound **1**, by comparison with the NMR spectra of pure **1**. ^{1}H NMR ($CDCl_3$) δ (ppm): 9.20 (1H, dd, J = 2.2 and 0.9 Hz, H-C(2)), 8.28 (1H, dd, J = 8.2 and 2.2 Hz, H-C(4)), 7.64 (1H, d, J = 1.8 Hz, H-C(5′)), 7.58 (1H, dd, J = 8.2 and 0.9 Hz, H-C(5)), 7.37 (1H, dd, J = 8.1 and 1.8 Hz, H-C(7′)), 7.23 (1H, d, J = 8.1 Hz, H-C(8′)), 6.28 (1H, d, J = 9.5 Hz, H-C(2′)), 5.77 (1H, d, J = 9.5 Hz, H-C(3′)), 4.43 (2H, q, J = 7.2 Hz, OCH_2), 1.42 (3H, t, J = 7.2 Hz, CH_3), 1.41 (6H, s, $2CH_3$-C(4′)); ^{13}C NMR ($CDCl_3$) δ (ppm) 165.1, 151.3, 147.1, 141.0, 137.4, 133.3, 132.4, 129.7, 129.6, 126.6, 126.5, 125.0, 120.0, 116.7, 92.7, 88.7, 61.8, 33.2, 29.0, 14.3. GC/MS t_R = 31.39 min, m/z 349 ($M^{+\bullet}$, 14), 334 (100), 306 (30), 207 (27).

*2.3.2. Impurity **6** [1,4-bis(4,4-dimethylthiochroman-6-yl)buta-1,3-diyne]*

^{1}H NMR ($CDCl_3$) δ (ppm): 7.51 (2H, d, J = 1.8 Hz, H-C(5)), 7.15 (2H, dd, J = 8.3 and 1.8 Hz, H-C(7)), 7.03 (2H, d, J = 8.3 Hz, H-C(8)), 3.03 (4H, m, CH_2-S), 1.94 (4H, m, CH_2C), 1.31 (12H, s, 4 CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 142.2, 134.5, 130.6, 129.6, 126.6, 117.1, 82.1, 73.5, 37.7, 33.0, 29.9, 23.3. MS (ESI, positive ion): m/z 425 $[M + Na]^+$.

3. Results and discussion

The structures of impurities **5** and **6** were attributed by means of ^{1}H and ^{13}C NMR spectra analysis, and they were further supported by the corresponding mass spectra (GC/MS for compound **5**; ESI-MS for compound **6**). Impurity **5** was formed during the treatment of sulfoxide **7** with PCl_3. The conversion of sulfoxides to α,β-unsaturated sulfide derivatives is a known reaction, which is usually performed either (i) by treatment with benzoic or acetic anhydride [4] or (ii) by reaction with trimethylsilyl iodide and diisopropylamine [5] (Scheme 2). In the first case the reaction is described as a Pummerer rearrangement giving an α-acyloxythioether, followed by the loss of a mole of carboxylic acid, promoted by prolonged heating. In the second case the formation of the vinyl sulfide is consistent with a base mediated deprotonation of the oxysulfonium salt, obtained by silylation of the oxygen atom of the starting sulfoxide. This is the first time that the conversion is obtained by treatment with



Scheme 2.

PCl_3. Sulfoxide **7** and carboxylic acid **8** have been described as a potential impurities of tazarotene [6].

The formation of impurity **6** can be attributed to a side reaction of the Sonogashira coupling. This latter reaction [7] consists of the following steps: oxidative addition of the alkyl halide to the palladium complex, transmetalation of the copper acetylide obtained from the terminal alkyne, and reductive elimination with the formation of the final product. According to this mechanism, the occurrence of halogen–metal exchange could afford the homocoupled derivative **6**.

4. Conclusions

Impurities **5** and **6** are by-products occurring in this specific synthetic approach to tazarotene. Compound **5** is formed during the deoxygenation reaction of sulfoxide **7** with PCl_3, while derivative **6** comes from a side reaction of Sonogashira coupling. They can be present in the impurity profile of tazarotene and they are quite diagnostic of the involvement of these steps in the corresponding synthetic procedure.

References

[1] (a) R.A.S. Chandraratna, U.S. Patent 5,089,509 (1992).;
(b) R.A.S. Chandraratna, U.S. Patent 5,602,130 (1997).
[2] S. Nagpal, R.A.S. Chandraratna, Curr. Pharm. Design 6 (2000) 919–931.
[3] (a) S. Frigoli, C. Fuganti, L. Malpezzi, S. Serra, Org. Proc. Res. Dev. 9 (2005) 646–650;
(b) S. Frigoli, C. Fuganti, S. Serra, F. Pizzocaro, A. Bedeschi, P. Tubertini, Paolo, EP 1700855 (2006).
[4] K. Horner, J. Liebigs, Ann. Chem. 626 (1959) 19–24.
[5] R.D. Miller, D.R. McKean, Tetrahedron Lett. 24 (1983) 2619–2622.
[6] D.B. Pathare, A.S. Jadhav, M.S. Shingare, Chromatographia 66 (2007) 247–250.
[7] R. Chinchilla, C. Nájera, Chem. Rev. 107 (2007) 874–922.