ARTICLE IN PRESS

Tetrahedron xxx (2015) 1-5

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis and cyclisation studies of (*E*)-2-aryl-1-methyl-3styrylquinolin-4(1*H*)-ones

Djenisa H.A. Rocha, Diana C.G.A. Pinto*, Artur M.S. Silva*

Department of Chemistry & QOPNA, University of Aveiro, 3810-193 Aveiro, Portugal

ARTICLE INFO

Article history: Received 16 May 2015 Received in revised form 18 July 2015 Accepted 21 July 2015 Available online xxx

Keywords: (E)-2-Aryl-1-methyl-3-styrylquinolin-4(1H)-ones Benzo[c]acridin-7(12H)-ones 4-Arylfuro[3,2-c]quinolones Heck reaction *N*-methylation

ABSTRACT

The synthesis of (*E*)-2-aryl-1-methyl-3-styrylquinolin-4(1*H*)-ones, through the Heck reaction of 2-aryl-3iodo-1-methyl-quinolin-4(1*H*)-ones with styrene is described. 2-Aryl-3-iodo-1-methyl-2-quinolin-4(1*H*)-ones can be obtained efficiently in a two-step transformation, methylation followed by *in situ* cyclization of *N*-(2-acetylphenyl)benzamides into 2-aryl-1-methylquinolin-4(1*H*)-ones, which underwent selective 3-iodination with iodine and a catalytic amount of Can. Cyclisation studies of (*E*)-2aryl-1-methyl-3-styrylquinolin-4(1*H*)-ones under high temperature or photoinduced electrocyclisation lead to 4-aryl-2-phenylfuro[3,2-c]quinolines and 12-methyl-5-phenylbenzo[c]acridin-7(12*H*)-ones.

© 2015 Elsevier Ltd. All rights reserved.

Tetrahedror

1. Introduction

The nucleus quinolin-4(1H)-one is a well-known nitrogen heterocycle due to its occurrence in a wide range of biological active molecules, namely natural compounds¹ or commercially available synthetic drugs. Although active derivatives are known for more than fifty years, the synthesis and biological assessments are still a hot topic.² For example, in 2010 Mphahlele³ reviewed several synthetic methodologies towards 2-arylquinolin-4(1H)-ones, and also described some natural derivatives widely distributed in the Rutaceae family. The interest in these compounds arises mostly from their broad spectrum as antimicrobial agents. Some are already in the market and other are potential pharmaceuticals acting as promising antitumor agents.⁴ One particular biological assessment showed that 2-arylquinolin-4(1H)-ones can inhibit bacterial DNA-gyrase and mammalian topoisomerase II enzymes, which indicates their potential as antibacterial and antitumor agents, respectively.5

Due to the described biological properties, the research on new and efficient methodologies to obtain 2-arylquinolin-4(1H)-ones is still essential. Recently efficient routes using benzoic acid derivatives⁶ or 2-aminobenzylic alcohol,⁷ as starting materials were

reported. In most of the cases good yields (above 70%) for the final step are reported, but their procedures involve several steps so the overall yield, which is not reported, should be lower. However, Lee et al.^{6a} reported an overall yield of 39%–68% of a 6-step sequence. All the same, other methodologies, with higher yields and fewer steps are desired.

We showed that quinolin-4(1*H*)-ones bearing groups such as 2and 3-styryl can be obtained with efficient methodologies.⁸ Continuing our research in this area, we report the stereoselective synthesis of (*E*)-2-aryl-1-methyl-3-styrylquinolin-4(1*H*)-ones, as well as their transformation into 4-aryl-2-phenylfuro[3,2-*c*] quinolones.

2. Results and discussion

In connection with our previous interest in the synthesis of new 3-styrylquinolin-4(1*H*)-ones⁸ and 3-styrylflavones⁹ we envisaged the synthesis of new 2-aryl-3-styrylquinolin-4(1*H*)-ones through the Heck reaction of 2-aryl-3-iodoquinolin-4(1*H*)-ones **3** and styrene (Scheme 1). Having previously studied the synthesis of 3-iodo-2-styrylquinolin-4(1*H*)-ones,^{8d} we chose to apply the same meth-odology to obtain the desired 2-aryl-3-iodoquinolin-4(1*H*)-ones **3**. *N*-(2-Acetylaryl)benzamides **1a–c** were obtained in excellent yields from the commercially available 2'-aminoacetophenone and benzoyl chlorides. The cyclization into 2-arylquinolin-4(1*H*)-ones **2a–c** was not as easy as described in the literature.³ It was necessary to study the reaction conditions, several combinations of



^{*} Corresponding authors. Tel.: +351 234 401 407; fax: +351 234 370 084 (D.C.G.A.P.); tel.: +351 234 370 714; fax: +351 234 370 084 (A.M.S.S.); e-mail addresses: diana@ua.pt (D.C.G.A. Pinto), artur.silva@ua.pt (A.M.S. Silva).

D.H.A. Rocha et al. / Tetrahedron xxx (2015) 1–5



solvents (THF and *t*-BuOH),[†] bases (NaH and *t*-BuOK),[†] temperature (from 30 °C to 80 °C and also MW irradiation) and different reactions times were tested in order to obtain the products in good vields. The best reaction conditions found for derivative 2a (t-BuOK as base and THF as solvent) were not appropriate for the other derivatives. For instance for derivative 2b t-BuOH was the best solvent and for derivative **2c** NaH was the best base. The next step was the iodination under our previously reported conditions^{8d}, which allowed the synthesis of the desired 2-aryl-3-iodoguinolin-4(1*H*)-ones **3a**–**c** in good yields (Scheme 1). It should be emphasised that as far as we are aware the synthesis of both 2-(4nitrophenyl)quinolin-4(1*H*)-one **2c** and 3-iodo-2-(4-nitrophenyl) quinolin-4(1H)-one **3c** are being reported for the first time, the overall yields (2c, 46% and 3c, 28%) are not extraordinary but the presence of such an electron withdrawing group usually causes some difficulties. The synthesis of the other derivatives **2a**,**b** and **3a,b** was previously reported³ but the overall yields were not indicated and in our conditions were moderate (2a, 48%; 2b, 62%; 3a, 34% and **3b**. 56%).

The characterization of these compounds was mainly done with NMR experiments; most care was taken with the nitro substituted derivatives due to their novelty. The most important features in the ¹H and ¹³C NMR spectra of *N*-(2-acetylaryl)benzamides **1a**–**c** are the resonances of 2-CH₃ protons ($\delta \sim 2.7$ ppm), NH proton (δ 12.7–12.9 ppm), C-1 ($\delta \sim 203$ ppm) and the amide carbonyl carbon (δ 164–166 ppm). In the case of 2-arylquinolin-4(1*H*)-ones **2a**–**c** it can be highlight the resonances of proton H-3 (δ 6.3–6.5 ppm), NH proton (δ 11.6–12.0 ppm), C-3 (δ 107–109 ppm) and C-4 ($\delta \sim$ 177 ppm). Finally, 2-aryl-3-iodoquinolin-4(1*H*)-ones **3a**–**c** present the characteristic resonances of NH proton (δ 12.2–12.5 ppm), C-3 ($\delta \sim 86$ ppm) and C-4 ($\delta \sim$ 174 ppm).

The next consisted in the use of our previous optimal conditions to obtain 2-aryl-3-styrylflavones⁹ hoping to synthesise 2-aryl-3-styrylquinolin-4(1*H*)-ones.^{8b} However, since all the attempts were unfruitful, even using MW as source of energy did not improve the results and only the (*E*)-2-phenyl-3-styrylquinolin-4(1*H*)-one was identified as a minor product in one of our attempts,¹⁰ a different approach was hypothesised.

Previous fruitful results with 2-styrylquinolin-4(1H)-ones^{8d} prompted us to envisage another route involving the synthesis of 2-aryl-3-iodo-1-methylquinolin-4(1H)-ones 7 (Scheme 2). The synthesis of this type of compounds was previously reported³ but using a different approach and again there is no reference to the nitro derivative nor to overall vields. Our methodology involves the synthesis of 2-arvl-1-methylquinolin-4(1H)-ones 4a-c followed by its iodination with iodine in the presence of CAN as catalyst. First we study the synthesis of 2-aryl-1-methylquinolin-4(1H)-ones 4 following two synthetic strategies, the N-methylation of 2arylquinolin-4(1*H*)-ones **2** or the N-methylation and in situ cyclization of N-(2-acetylaryl)benzamides 1. For compounds 4a and 4b both routes produced the desired product as the major one and a by-product was also obtained (compounds **5** or **6** the structure of which were confirmed by NMR spectroscopy) (Scheme 2). In the case of compound **4c** only the methylation and in situ cyclization of *N*-(2-acetylaryl)benzamide **1c** can be used (overall yield of 56%, 6% with the other method).



Scheme 2. Synthesis of 2-aryl-3-iodo-1-methylquinolin-4(1H)-ones 7.

In addition to the characteristic signals of the 2-arylquinolin-4(1*H*)-one skeleton, the ¹H NMR spectrum of 2-aryl-1-methylquinolin-4(1*H*)-ones **4**, present a singlet at δ 3.61–3.65 ppm due to the *N*-methyl protons and a signal at δ 37.3–37.4 ppm in the ¹³C NMR spectrum due to the methyl carbon resonance.

Compounds **4** having been obtained, the next step was their iodination and 2-aryl-3-iodo-1-methylquinolin-4(1*H*)-ones **7a**–**c** were obtained in excellent yields (above 90%). In this study we proved that the route involving steps (iv) and (v) (Scheme 2), not only has less steps but also gives better overall yields (61%).

Having the 2-aryl-3-iodo-1-methylquinolin-4(1*H*)-ones **7a–c** the next step was their reaction with styrene under Heck reaction conditions and using MW irradiation as source of energy to shorten the reaction time. This methodology proved to be efficient to synthesise (*E*)-2-aryl-1-methyl-3-styrylquinolin-4(1*H*)-ones **8a–c** (Scheme 3).

Our interest in the synthesis of benzoacridone derivatives started with the synthesis of benzo[*b*]acridin-12(7*H*)-ones.¹¹ So, in order to assess the value of (*E*)-2-aryl-1-methyl-3-styrylquinolin-4(1*H*)-ones **8** as synthon for preparation of new benzo[*c*]acridin-7(12*H*)-ones, their electrocyclisation was studied (Scheme 3). To begin we used the established methodology that was efficient for the synthesis of *O*-analogues, benzo[*c*]xanthones, through the photoinduced electrocyclisation of 3-styrylflavones.^{9a} The first conclusions of this study are: i) the reactivity of these aza-

[†] We use the abbreviation t-Bu=C(CH₃)₃ for the t-butyl group.

ARTICLE IN PRESS

D.H.A. Rocha et al. / Tetrahedron xxx (2015) 1-5



Scheme 3. Synthesis and transformation of (*E*)-2-aryl-1-methyl-3-styrylquinolin-4(1*H*)-ones **8**.

analogues is much lower due to the fact that more than one week was necessary to obtain the desired 12-methyl-5-phenylbenzo[c] acridin-7(12H)-ones 9 and their yields were not very good; ii) with the nitro derivative 8c the transformation did not occur. If we take into account the mechanism proposed for the O-analogues electrocyclisation^{9a} it makes sense that the nitro group do not favour the transformation; iii) again the analysis of the expected mechanism^{9a} also explains the lower yield in the case of derivative **8b**, the methoxy group although an electron donating group also favours the ortho/para substitution and in this case it should occur at the meta; iv) a by-product, (Z)-2-aryl-1-methyl-3-styrylquinolin-4(1*H*)-one **10** is obtained in the case of the unsubstituted derivative **8a** (Scheme 3). This result indicates that a syn(E) to syn(Z) isomerization is favoured under the reaction conditions and the electrocyclisation would be favoured if a syn-(E) to anti-(E)isomerization occurs.

Considering that acridones can be obtained through thermal cyclisation^{8d} a solution of (*E*)-2-aryl-1-methyl-3-styrylquinolin-4(1H)-ones 8 was heated to reflux in 1,2,4-trichlorobenzene with a catalytic amount of iodine for several days. The result was not the expected one as new 4-aryl-2-phenylfuro[3,2-c]quinolines 11 were obtained instead of the desired 12-methyl-5-phenylbenzo[c]acridin-7(12H)-ones 9 (Scheme 3). This type of furo[3,2-c]quinolone derivatives were previously obtained from quinolin-4(1H)ones.^{8d,12} As far as we are aware, this is the first report of the synthesis of such derivatives from N-methylated quinolin-4(1H)ones. We suspect that first an electrophilic addition of iodine occurs, followed by demethylation and hydroiodic acid elimination (Scheme 4). To confirm this hypothesis, we tested the reaction using an equimolar amount of iodine and, after two days, the furo [3,2-c]quinolone derivatives 11 were obtained in good to very good yields (above 70%).

The new (*E*)-2-aryl-1-methyl-3-styrylquinolin-4(1*H*)-ones **8** were fully characterized and in addition to the signals of the 2-aryl-1-methylquinolin-4(1*H*)-one moiety, it can be observed the presence of an extra aromatic ring and the vinylic system, H- α doublet at δ 6.23–6.47 ppm, H- β doublet at δ 8.15–8.22 ppm, C- α at δ 122.2–123.9 ppm and C- β at δ 130.7–132.4 ppm.

The *syn*-(*E*) stereochemistry depicted in Scheme 3 was confirmed by: i) the vinylic coupling constant ($J \sim 16$ Hz) between



Scheme 4. Proposal mechanism for the synthesis of 4-aryl-2-phenylfuro[3,2-c]quinolines 11.

protons H- α and H- β confirms the (*E*) configuration; ii) the chemical shift of proton H- β ($\delta \sim 8$ ppm) is typical of an intramolecular hydrogen bond with the carbonyl oxygen^{8c} (Fig. 1a); iii) the NOE effect between H- α and H-2',6' observed in the NOESY spectra (Fig. 1a).



Fig. 1. Important NMR features.

The most typical signals in the ¹H and ¹³C NMR spectra of 12methyl-5-phenylbenzo[*c*]acridin-7(12*H*)-ones **9** are: i) the singlet due to proton H-6 at $\delta \sim 8.4$ ppm and the double doublet due to proton H-8 at $\delta \sim 8.6$ ppm, the most deshielded protons owed to the anisotropic and mesomeric effects of the carbonyl group; ii) the singlet due to the *N*-methyl protons at $\delta \sim 4.2$ ppm and the respective carbon signal at δ 45.0 ppm; iii) the signal due to carbon C-7 at $\delta \sim 178$ ppm. The HMBC correlations observed in the spectra (Fig. 1b) not only confirmed the depicted structure but also allowed the assignment of all protons and carbons resonance.

The most typical signals in ¹H and ¹³C NMR spectra of 4-aryl-2phenylfuro[3,2-*c*]quinolines **11** are: i) the singlet due to proton H-3 at $\delta \sim 7.4$ ppm and the signal at δ 101–102 ppm due to the C-3 carbon resonance; ii) the doublets due to protons H-6 at $\delta \sim 8.3$ ppm and H-9 at $\delta \sim 8.4$ ppm, the most deshielded protons owing to the through-space magnetic deshielding effect of the heterocyclic nitrogen and oxygen atoms, respectively; iii) the signal due to carbon C-9b at $\delta \sim 156-157$ ppm. The HMBC correlations observed in the spectra (Fig. 1c) not only confirmed the depicted structure but also allowed the assignment of all protons and carbons resonance.

3. Conclusions

New (*E*)-2-aryl-1-methyl-3-styrylquinolin-4(1*H*)-ones **8** were prepared in good to excellent yields by the Heck reaction of 2-aryl-3-iodo-1-methylquinolin-4(1*H*)-ones **7** with styrene. Novel 4-aryl-

4

D.H.A. Rocha et al. / Tetrahedron xxx (2015) 1–5

2-phenylfuro[3,2-c]quinolines **11** were obtained in excellent yields by an intramolecular cyclization of (*E*)-2-aryl-1-methyl-3-styrylquinolin-4(1*H*)-ones **8**.

2-Aryl-3-iodo-1-methylquinolin-4(1H)-ones **7** were obtained in fair to excellent yields in a straightforward methodology through only three steps: synthesis of *N*-(2-acetylaryl)benzamides **1** followed by their methylation and in situ cyclization, and finally selective iodination at C-3. To the best of our knowledge the synthesis of 2-arylquinolin-4(1H)-ones bearing nitro groups (**4c** and **7c**) are scarcely reported in the literature and our methodology allowed the synthesis in good yields of several new nitro derivatives.

4. Experimental section

4.1. General information

Melting points were determined on a BUCHI Melting point B-545 apparatus and are uncorrected. ¹H and ¹³C NMR spectra were recorded on Bruker Avance III 300, Avance III HD 500, and Bruker Avance III HD 700 [300.13 MHz (¹H), 75.47 MHz (¹³C); 500.13 MHz (¹H), 125.76 MHz (¹³C); 700.13 MHz (¹H), 176,05 MHz (¹³C)] spectrometers with TMS as internal reference and with CDCl3 or DMSO d_6 as solvent. Chemical shifts (δ) are reported in parts per million values and coupling constants (J) in Hertz. Unequivocal ¹H assignments were made using 2D NOESY experiments (mixing time of 800 ms), while ¹³C assignments were made on the basis of 2D gHSQC (1 H/ 13 C) and gHMBC (delays for one bond and long-range J_{Cl} H couplings were optimized for 145 and 7 Hz, respectively) experiments. Positive-ion ESI mass spectra were acquired using a O-TOF 2 instrument [Nitrogen was used as nebulizer gas and argon as collision gas. The needle voltage was set at 3000 V, with the ion source at 80 °C and desolvation temperature at 150 °C. Cone voltage was 35 V]. High resolution mass spectra (HRMS-ESI⁺) were measure in a microTOF (focus) mass spectrometer. Ions were generated using an Apolloll (ESI) source. Ionization was achieved by electrospray, using a voltage of 4500 V applied to the needle and a counter voltage between 100 and 150 V applied to the capillary. Elemental analyses were obtained with LECO 932 CHNS analyser. Preparative thin layer chromatography was carried out with Silica gel 60 GF254 (Merck KGaA) and column chromatography using Silica gel 0.060-0.020 mm 60A (Acros Organics). All other chemicals and solvents were obtained from commercial sources and used as received or dried using standard procedures.

4.2. General procedure for the synthesis of (*E*)-2-aryl-1-methyl-3-styrylquinolin-4(1*H*)-ones 8a–c

A mixture of the appropriate 2-aryl-3-iodo-1-methylquinolin-4-(1*H*)-one **7a**–**c** (0.10 mmol), Ph₃P (3 mg, 0.010 mmol), Et₃N (13.9 μ L, 0.10 mmol), tetrakis(triphenylphosphine)palladium(0) (5.8 mg, 0.005 mmol) and styrene (48.4 μ L, 0.42 mmol) in NMP (7 mL) was heated under microwave irradiation in an Ethos SYNTH microwave (Milestone Inc.) [2 min at 500 W until 100 °C and hold at 100 °C for 30 min] After that period, the reaction mixture was poured into ice (20 g) and water (40 mL) and extracted with diethyl ether (3×10 mL). The organic layer was washed with water (3×30 mL), dried over anhydrous sodium sulfate and evaporated. The residue was purified by thin layer chromatography using a (6:4) mixture of dichloromethane/light petroleum as eluent. (*E*)-2-Aryl-1-methyl-3-styrylquinolin-4(1*H*)-ones **8a**–**c** were obtained in good to very good yields [**8a** 29 mg (85%), **8b** 21 mg (57%), **8c** 27 mg (70%)].

4.2.1. Spectral data of a selected compound, (*E*)-1-methyl-2-(4-nitrophenyl)-3-styrylquinolin-4(1H)-one (**8c**). ¹H NMR (300.13 MHz, CDCl₃): δ 3.49 (s, 3H, NC<u>H</u>₃), 6.23 (d, 1H, H- α , J 16.0 Hz), 7.13–7.24

(m, 5H, H-2",3",4",5",6"), 7.49 (t, 1H, H-6, *J* 7.5 Hz), 7.50 (d, 1H, H-8, *J* 8.1 Hz), 7.62 (d, 2H, H-2',6', *J* 8.6 Hz), 7.72 (t, 1H, H-7, *J* 7.5 Hz), 8.15 (d, 1H, H-β, *J* 16.0 Hz), 8.47 (d, 2H, H-3',5', *J* 8.6 Hz), 8.60 (d, 1H, H-5, *J* 8.1 Hz) ppm. ¹³C NMR (75.47 MHz, CDCl₃): δ 37.9 (NCH₃), 115.6 (C-8), 117.7 (C-3), 122.2 (C-α), 124.2 (C-6), 124.5 (C-3',5'), 126.1 (C-2'',6''), 126.5 (C-4a), 127.2 (C-5), 127.3(C-4''), 128.5 (C-3'',5''), 130.6 (C-2',6'), 132.4 (C-β), 132.43 (C-7), 138.5 (C-1''), 140.1 (C-8a), 141.4 (C-1'), 148.3 (C-4'), 149.8 (C-2), 176.4 (C-4) ppm. ESI⁺-MS *m/z* (%): 383.1 [M+H]⁺ (100). Anal. Calcd for C₂₄H₁₈N₂O₃: C, 75.38%; H, 4.74%; N, 7.33%. Found: C, 75.13%; H, 4.89%; N, 7.34%.

4.3. General procedure for the synthesis of 4-aryl-2-phenylfuro[3,2-c]quinolines 11a-c

A mixture of the appropriate (*E*)-2-aryl-1-methyl-3styrylquinolin-4(1*H*)-one **8a**–**c** (0.05 mmol) and an equimolar amount of iodine (12.7 mg) in 1,2,4-trichlorobenzene (3 mL) was stirred under reflux during 2 days. After that period, the reaction mixture was poured into a silica gel column and eluted with light petroleum to remove the excess of iodine and the 1,2,4trichlorobenzene. Upon changing the eluent to dichloromethane and then to a mixture of dichloromethane/ethyl acetate (9:1) compounds **11a–c**, 2,4-diarylfuro[3,2-*c*]quinolines, were obtained in good to very good yields [**11a** 16 mg (92%), **11b** 13 mg (72%), **11c** 15 mg (80%)].

4.3.1. Spectral data of a selected compound, 4-(4-Methoxyphenyl)-2-phenylfuro[3,2-c]quinoline (**11b**). ¹H NMR (300.13 MHz, CDCl₃): δ 3.93 (s, 3H, 4'-OC<u>H₃</u>), 7.14 (d, 2H, H-3',5', J 8.7 Hz), 7.39 (s, 1H, H-3), 7.38–7.43 (m, 1H, H-4"), 7.48–7.53 (m, 2H, H-3",5"), 7.62 (br dd, 1H, H-8, J 7.0 and 8.0 Hz), 7.71 (br dd, 1H, H-7, J 7.0 and 8.0 Hz), 7.96–7.99 (m, 2H, H-2",6"), 8.09 (d, 2H, H-2',6', J 8.7 Hz), 8.25 (d, 1H, H-6, J 8.0 Hz), 8.37 (d, 1H, H-9, J 8.0 Hz) ppm. ¹³C NMR (75.47 MHz, CDCl₃): δ 55.5 (4'-O<u>C</u>H₃), 101.7 (C-3), 114.3 (C-3',5'), 116.1 (C-9a), 119.9 (C-9), 120.1 (C-3a), 124.9 (C-2",6"), 126.3 (C-8), 128.4 (C-7), 128.9 (C-4"), 129.0 (C-3",5"), 129.7 (C-6), 129.9 (C-1'), 130.2 (C-2',6'), 132.2 (C-1"), 145.7 (C-5a), 153.2 (C-4), 156.1 (C-2), 156.2 (C-9b), 160.7 (C-4') ppm. ESI⁺-MS *m/z* (%): 352.1 [M+H]⁺ (100). EI-HRMS: calcd for (C₂₄H₁₇NO₂) 351.1259; found 351.1257.

Acknowledgements

Thanks are due to FCT/MEC for the financial support to the QOPNA research Unit (FCT UID/QUI/00062/2013), through national founds and where applicable co-financed by the FEDER, within the PT2020 Partnership Agreement, and also to the Portuguese NMR Network. D.H.A. Rocha also thanks FCT for her PhD grant (SFRH/BD/ 68991/2010).

Supplementary data

Supplementary data (Detailed experimental procedures, characterization data for all products and representative ¹H, ¹³C NMR spectra.) related to this article can be found at http://dx.doi.org/ 10.1016/j.tet.2015.07.058.

References and notes

- e.g., (a) Zhu, F.; Chen, G. Y.; Wu, J. S.; Pan, J. H. Nat. Prod. Res. 2013, 27, 1960–1964; (b) Jadulco, R. C.; Pond, C. D.; Van Wagoner, R. M.; Koch, M.; Gideon, O. G.; Matainaho, T. K.; Piskaut, P.; Barrows, L. R. J. Nat. Prod. 2014, 77, 183–187.
- e.g. (a) Gomez, C.; Ponien, P.; Serradji, N.; Lamouri, A.; Pantel, A.; Capton, E.; Jarlier, V.; Anquetin, G.; Aubry, A. *Bioorg. Med. Chem.* 2013, *21*, 948–956; (b) Vandekerckhove, S.; Desmet, T.; Tran, H. G.; de Kock, C.; Smith, P. J.; Chibale, K.; D'hooghe, M. *Bioorg. Med. Chem. Lett.* 2014, *24*, 1214–1217.
 Mphahlele, M. J. J. *Heterocycl. Chem.* 2010, *47*, 1–14.

Please cite this article in press as: Rocha, D. H.A.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.07.058

ARTICLE IN PRESS

D.H.A. Rocha et al. / Tetrahedron xxx (2015) 1-5

- 4. e.g., (a) Hadjeri, M.; Peiller, E.-L.; Beney, C.; Deka, N.; Lawson, M. A.; Dumontet, C.; Boumendjel, A. J. Med. Chem. 2004, 47, 4964–4970; (b) Huang, S.-M.; Cheng, Y.-Y.; Chen, M.-H.; Huang, C.-H.; Huang, L.-J.; Hsu, M.-H.; Kuo, S.-C.; Lee, K.-H. Bioorg. Med. Chem. Lett. 2013, 23, 699–701; (c) Cheng, Y.-Y.; Liu, C.-Y.; Tsai, M.-T.; Lin, H.-Y.; Yang, J.-S.; Wu, T.-S.; Kuo, S.-C.; Huang, L.-J.; Lee, K.-H. Bioorg. Med. Chem. Lett. **2013**, 23, 5223–5227.
- Sui, Z.; Nguyen, V. N.; Altom, J.; Fernandez, J.; Hilliard, J. J.; Bernstein, J. I.; Barrett, J. F.; Ohemeng, K. A. Eur. J. Med. Chem. 1999, 34, 381–387.
- (a) Song, Y. J.; Choi, J. S.; Lee, J. I. *Bull. Korean Chem. Soc.* **2013**, *34*, 3117–3120; (b) Dhiman, R.; Sharma, S.; Singh, G.; Nepali, K.; Bedi, P. M. S. *Arch. Pharm. Chem.* 6 Life Sci. 2013, 346, 7–16.
- Life Sci. 2015, 340, 7–16.
 Seppänen, O.; Muuronen, M.; Helaja, J. Eur. J. Org. Chem. 2014, 4044–4052.
 (a) Almeida, A. I. S.; Silva, V. L. M.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S. Synlett 2008, 2593–2596; (b) Almeida, A. I. S.; Silva, A. M. S.; Cavaleiro, J. A. S. Synlett 2010, 462–466; (c) Seixas, R. S. G. R.; Silva, A. M. S.; Alkorta, I.; Eiguero, J. Monatsh. Chem. 2011, 142, 731–742; (d) Silva, V. L. M.; Silva, A. M. S. Tetrahedron 2014, 70, 5310–5320.
- 9. (a) Rocha, D. H. A.; Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S.; Patonay, T. Synlett **2012**, 559–564; (b) Rocha, D. H. A.; Pinto, D. C. G. A.; Silva, A. M. S. Synlett **2013**, 2683–2686.
- 10. (E)-2-Phenyl-3-styrylquinolin-4(1H)-one: Mp 245-247 °C, yellow solid. ¹H MR (300.13 MHz, CDCl₃): δ (-7.8 (d, 1H, H-α, *J* 16.2 Hz), 7.10–7.24 (m, 5H, H-2",3",4",5",6"), 7.34 (br dd, 1H, H-6, *J* 7.0 and 8.1 Hz), 7.46–7.49 (m, 3H, H-8, H-2,6'), 7:52–7:61 (m, H, H-7, H-3',4',5'), and 6:112, 7:40 7:40 (H, H-7, J 16:2 Hz), 8:39 (d, 1H, H-5, J 8:1 (d, 1H, H-6, J 16:2 Hz), 8:39 (d, 1H, H-5, J 8:1 Hz), 9:23 (s, 1H, NH) ppm. ¹³C NMR (75:47 MHz, CDCl₃): δ 116.0 (C-3), 117.3 (C-8), 122.5 (C-a), 123.9 (C-6), 125.3 (C-4), 126.2 (C-3",5"), 126.6 (C-5), 126.8 (C-4"), 128.4 (C-2",6"), 128.9 (C-2',6'), 129.2 (C-3',5'), 130.0 (C-4'), 131.4 (C-β), 131.8 (C-7), 135.1 (C-1'), 138.1 (C-8a), 139.1 (C-1"), 149.2 (C-2), 177.6 (C-4) ppm. ESI⁺-MS m/z (%): 324.1 [M+H]⁺ (100).
- 11. Seixas, R. S. G. R.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S. Synlett 2008, 3193-3197.
- 12. Venkataraman, S.; Barange, D. K.; Pal, M. Tetrahedron Lett. 2006, 47, 7317–7322.