Tetrahedron Letters 50 (2009) 2767–2769

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Efficient synthesis and fluorescence properties of highly functionalized 2-aryl-quinazolin-4(3*H*)-ones

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ARTICLE INFO

Article history:
Received 22 January 2009
Revised 16 March 2009
Accepted 18 March 2009
Available online 25 March 2009

Keywords:
Quinazolin-4(3*H*)-one
Heterocycle
HPQ
Fluorophore

ABSTRACT

Three different methodologies for the preparation of highly substituted 2-aryl-quinazolin-4(3*H*)-ones including short and high-yielding reaction sequences are described. The 2-aryl-substituent of most of the target compounds bears three functional groups. The fluorescence properties of these compounds are presented and potential correlations between structure and optical properties are discussed.

Quinazolin-4(3*H*)-ones, especially their 2-alkyl and 2-aryl derivatives, are a class of nitrogen-containing heterocycles of considerable interest, owing to the remarkable diversity of their biological activities.[1] Anticancer,[2] anticonvulsant,[3] antiinflamatory,[4] antidiabetic,[5] and antimalarial[6] effects are only some of their reported characteristics. Additionally, 2-(2′-hydroxyphenyl)-quinazolin-4(3*H*)-one HPQ (**1**) and some of its derivatives have been reported to be highly fluorescent in the solid state.[7,8] Their fluorescence properties arise from excited state intramolecular proton transfer (ESIPT) from the phenol hydroxyl to the imine function (Fig. 1). Such compounds can serve different useful applications, for example, in chemical sensing systems or in fluorogenic probes for biological assays.[7,9]

The construction of the quinazolin-4(3*H*)-one ring system has been achieved via condensation of anthranilic acid derivatives with acid chlorides or other benzoic acid derivatives,[10,11] by the condensation of imidates with anthranilic acid,[12–14] or aza-Wittig reactions of α-azido-substituted aromatic imides.[15] Although some of these methods provide useful strategies for the synthesis of these bicyclic compounds, they often suffer from major drawbacks, such as low yields, too many synthetic steps, and lack of general applicability.[10] Moreover, only few methods have been described for the synthesis of 2-aryl-quinazolin-4(3*H*)-ones with rather reactive functional groups at the 2-aryl ring, such as hydroxyl or amino groups.[7,16,17] In particular, the literature lacks methods for the synthesis of quinazolin-4(3*H*)-ones that tolerate multiple functional groups on the 2-aryl substituent.

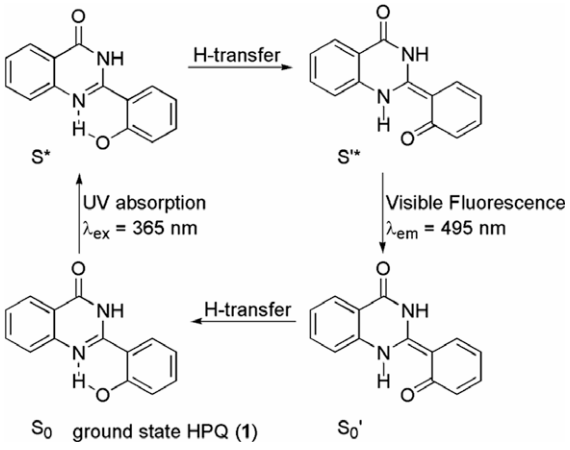

Figure 1. Basic mechanism for excited state intramolecular proton transfer (ESIPT) in HPQ **1**. (S_0: ground state, S'^* excited state, S'_0 and S^*: vibrationally excited forms of S_0 and S'^*, respectively).

Therefore, there is certainly a need for improved concepts that allow further derivatization of the quinazolin-4(3*H*)-one system at the 2-aryl substituent in order to create novel fluorophores or compounds of pharmaceutical potential.

We herein report three rapid and efficient routes to quinazolin-4(3*H*)-ones with a phenol or aniline ring as the 2-substituent, some of which are highly substituted. The fluorescence properties of the synthesized compounds were evaluated, and relationships between the observed fluorescence and the substitution pattern on the 2-aryl ring were deduced.

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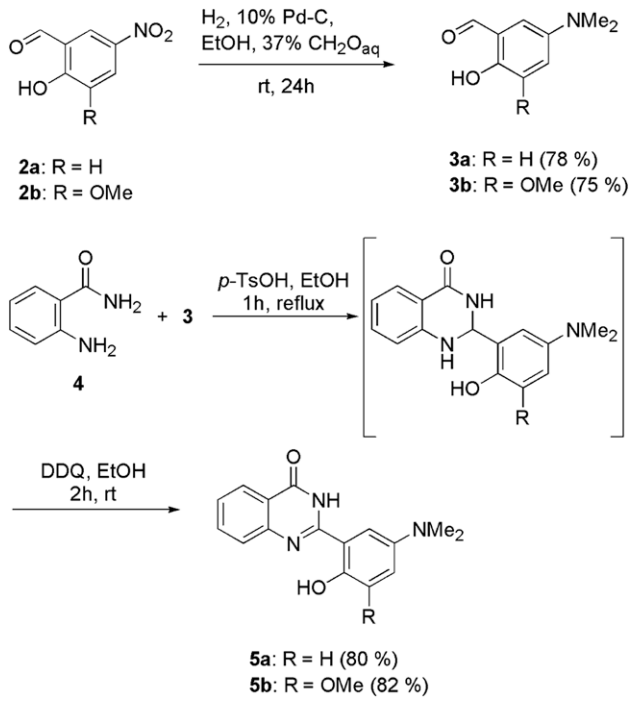
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.03.139

Initially, we synthesized an HPQ derivative with a dimethyl amino group in *para* position to the phenol and another compound with an additional *ortho*-methoxy substituent. Aldehydes **3a**,**b** were prepared from commercial compounds under reductive amination conditions[18], transforming the nitro function of **2a**,**b** into a dimethylamino group in a single one-pot reaction in good yield. This comprises the reduction of the nitro group, and two subsequent reductive amination steps. Subsequently, aldehydes **3a**,**b** were condensed with anthranilamide **4**,[7] followed by in situ oxidation to establish the imine function, furnishing target compounds **5a**,**b** in high yield (Scheme 1).

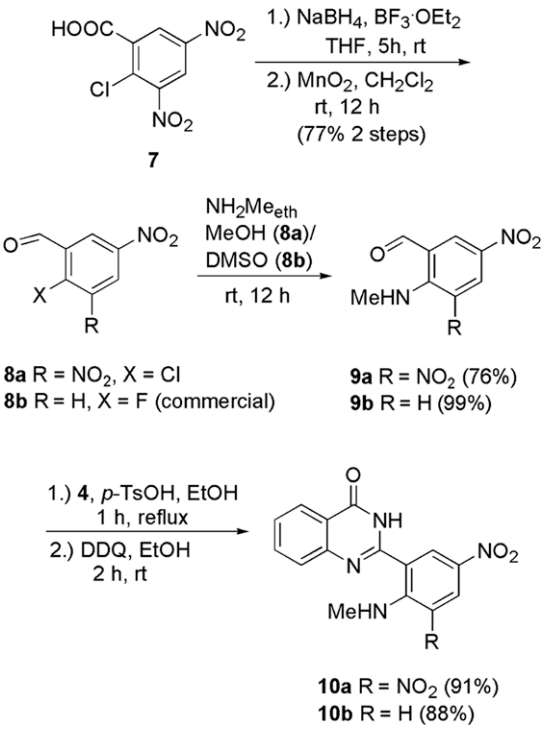
Scheme 2 illustrates the preparation of HPQ derived nitroanilines. The synthesis of aniline **10a** bearing two nitro groups started with acid **7** that was transformed into aldehyde **8a** by reduction and subsequent oxidation of the crude alcohol intermediate.[19] This highly electrophilic species was efficiently converted to **9a** via an S_NAr type reaction.[20] Subsequent condensation of highly substituted aldehyde **9a** with **4,** followed by in situ oxidation gave target compound **10a** in excellent yield. In order to obtain mono-nitro aniline **10b**, commercial fluoroaldehyde **8b** was treated in a similar way than **8a**, quantitatively furnishing aldehyde **9b**.[21] Reaction with **4** yielded target compound **10b**.

Scheme 3 illustrates the synthesis of anilines bearing either an unsubstituted amino group, or an electron-rich (methylation) or an electron-poor (Cbz substitution) one. Aminoalcohols **11a** and **11b** were Cbz-protected[22], followed by oxidation of benzylic alcohols **12** using MnO_2[23] furnishing aldehydes **13**. Reaction with anthranilamide **4**, followed by in situ oxidation with DDQ gave N-Cbz aniline **14**. The protecting group was removed using 5% Pd-C to quantitatively produce free HPQ-derived aniline **15b** and its methylated congener **15a**. It should be noted that use of 10% Pd-C was found to cause partial reduction in the imine function. As in the preparation of **5** and **10**, the preparation of the target compounds was achieved in short syntheses with good to excellent yields.

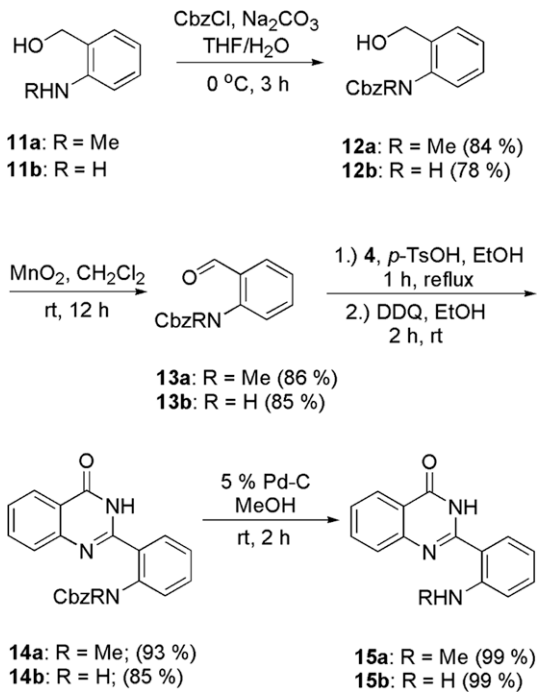
Table 1 summarizes the fluorescence properties of the synthesized compounds in the solid state. This table also includes data of HPQ **1** which was used as reference, and of its analog **16** (MeO-HPQ)[7] bearing a methoxy group *para* to the phenolic hydroxyl. As is the case for the parent fluorophore HPQ, these compounds are fluorescent only in the solid state, but not in solution. It is generally assumed that solvation of the phenol or aniline function precludes an intramolecular hydrogen bond and thus ESIPT. Among the new molecules, aniline **14b** was found to be highly fluorescent, being in the same range as HPQ **1**, and that of its methoxy derivative **16**. But



Scheme 1. Synthesis of phenolic quinazolin-4(3*H*)-ones.



Scheme 2. Synthesis of quinazolin-4(3*H*)-ones with nitroanilines at the 2-position.



Scheme 3. Synthesis of quinazolin-4(3*H*)-ones with N-substituted anilines at the 2-position.

Table 1
Fluorescence properties of HPQ and the synthesized analogs

Entry	Compound	$\lambda_{ex,max}$ (nm)	$\lambda_{em,max}$ (nm)	Relative fluorescence intensity a.u.
1	**1**	365	495	1.00 ± 0.06
2	**16**	365	550	0.96 ± 0.05
3	**15b**	280	460	0.08 ± 0.004
4	**15a**	280	460	0.09 ± 0.005
5	**14b**	365	525	0.89 ± 0.06
6	**5a,b**	S[a]	S[a]	<0.0001
7	**10a,b**	S[a]	S[a]	<0.0001

[a] S = screening of all possible wavelengths between λ = 250 and λ = 850 nm.

also anilines **15a** and **15b** showed good fluorescence intensities that were still four orders of magnitude higher than the one of compounds **5** and **10**. In addition, fluorophores **14b**, **15a**, and **15b** exhibit large Stokes shifts ($\geqslant$160 nm), which are useful for the design of fluorescence-based sensing systems of high sensitivity. For example, a large Stokes shift can circumvent the problem of tissue background fluorescence in in vivo tests.[9]

In attempting to correlate the structure with the fluorescence properties, one finds among the phenols that lack of substitution or introduction of an *ortho*-methoxy group is favorable, while a *para*-amino group appears to be detrimental to fluorescence (**1** vs **16** vs **5a**,**b**).

In case of the anilines, molecules with electron-withdrawing nitro groups in *ortho* or *para* position of the aryl ring displayed negligible fluorescence (**10a**,**b**). On the other hand, simple anilines showed an increase in fluorescence intensity by four orders of magnitude (**15a**,**b** vs **10a**,**b**). Alkyl substitution of the aniline nitrogen appeared to have no significant impact (**15a** vs **15b**). On the other hand, introduction of an electron-withdrawing Cbz substituent into the amino group further increases the fluorescence intensity by one order of magnitude (**14b** vs **15a**, **15b**). Similar observations were reported in related compounds where the aniline nitrogen was part of an amide or sulfonamide unit.[24]

In conclusion, we have established efficient routes to novel phenol and aniline derivatives of the quinazolin-4(3*H*)-one system. The condensation of aldehydes with anthranilamide proved to be tolerant to multiple substitution patterns, furnishing target compounds that are highly functionalized on the 2-aryl ring. In particular, three of the synthesized compounds showed good to high fluorescence intensities and large Stokes shifts and might thus find applications in chemical sensor systems or enzyme assays. Moreover, the correlations between the substitution pattern on the 2-aryl ring and the fluorescence properties made in this study will help to direct our future work in the development of novel fluorophores based on this system. Beyond these advantages, the synthetic procedures established in this study may prove useful in the access to new derivatives of the quinazolin-4(3*H*)-one core that are of interest in pharmaceutical research.

Acknowledgments

This work was supported by the French Research Ministry and the CNRS. Michael Waibel acknowledges a European Doctoral Fellowship from the Research Ministry.

Supplementary data

Experimental details for the synthesis and the characterization data for all compounds are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.139.

References and notes

1. For a review see: Eguchi, S. *Top. Heterocycl. Chem.* **2006**, *6*, 113–156.
2. Bavetsias, V.; Skelton, L. A.; Yafai, F.; Mitchell, F.; Wilson, S. C.; Allan, B.; Jackman, A. L. *J. Med. Chem.* **2002**, *45*, 3692–3702.
3. Wolfe, J. F.; Rathman, T. L.; Sleevi, M. C.; Campbell, J. A.; Greenwood, T. D. *J. Med. Chem.* **1990**, *33*, 161–166.
4. Ozaki, K.-I.; Yamada, Y.; Oine, T.; Ishizuka, T.; Iwasawa, Y. *J. Med. Chem.* **1985**, *28*, 568–576.
5. DeRuiter, J.; Brubaker, A. N.; Millen, J.; Riley, T. N. *J. Med. Chem.* **1986**, *29*, 627–629.
6. Dempcy, R. O.; Skibo, E. B. *Biochemistry* **1991**, *30*, 8480–8487.
7. Zhang, X. B.; Cheng, G.; Zhang, W. J.; Shen, G. L.; Yu, R. Q. *Talanta* **2007**, *71*, 171–177.
8. Williams, D. L.; Heller, A. *J. Phys. Chem.* **1970**, *74*, 4473–4480.
9. Waibel, M.; Zhang, X. B.; Hasserodt, J. *Synthesis* **2009**, 315–324. and references cited therein.
10. For a review see: Connoly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153–10202.
11. Kikelj, D.. In *Science of Synthesis*; Thieme: Germany, 2004; Vol. 16, pp 573–749.
12. Ried, W.; Sinharay, A. *Chem. Ber.* **1963**, *96*, 3306–3311.
13. Hennequin, L. F.; Boyle, F. T.; Wardleworth, J. M.; Marsham, P. R.; Kimbell, R.; Jackman, A. L. *J. Med. Chem.* **1996**, *39*, 695–704.
14. Connolly, D. J.; Guiry, P. J. *Synlett* **2001**, *11*, 1707–1710.
15. Takeuchi, H.; Hagiwara, S.; Eguchi, S. *Tetrahedron* **1989**, *45*, 6375–6386.
16. Petridou-Fischer, J.; Papadopoulos, E. P. *J. Heterocycl. Chem.* **1983**, *20*, 1159–1167.
17. Luo, H.-Y.; Zhang, X.-B.; He, C.-L.; Shen, G.-L.; Yu, R.-Q. *Spectrochim. Acta, Part A* **2008**, *70*, 337–342.
18. Ando, M.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2433–2434.
19. Rosenström, U.; Sköld, C.; Plouffe, B.; Beaudry, H.; Lindeberg, G.; Botros, M.; Nyberg, F.; Wolf, G.; Karlen, A.; Gallo-Payet, N.; Hallberg, A. *J. Med. Chem.* **2005**, *48*, 4009–4224.
20. Yang, Y.; Babiak, P.; Reymond, J.-L. *Org. Biomol. Chem.* **2006**, *4*, 1746–1754.
21. Wilshire, J. F. K. *Aust. J. Chem.* **1982**, *35*, 2497–2504.
22. Dei, S.; Bellucci, C.; Buccioni, M.; Ferraroni, M.; Gualtieri, F.; Guandalini, L.; Manetti, D.; Matucci, R.; Romanelli, M. N.; Scapecchi, S.; Teodori, E. *Bioorg. Med. Chem.* **2003**, *11*, 3153–3164.
23. Le Sann, C.; Baron, A.; Mann, J.; van den Berg, H.; Gunaratnam, M.; Neidle, S. *Org. Biomol. Chem.* **2006**, *4*, 1305–1312.
24. Haugland, R. P.; Steinberg, T. H.; Patton, W. P.; Diwu, Z. Patent US20020137068, 2002.