Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 2389

www.rsc.org/obc

COMMUNICATION

Efficient syntheses of 2,3-disubstituted natural quinazolinones *via* iridium catalysis†

Jie Fang and Jianguang Zhou*

Received 26th December 2011, Accepted 23rd January 2012
DOI: 10.1039/c2ob07178a

Natural products sclerotigenin, pegamine, deoxyvasicinone, mackinazolinone, and rutaecarpine were synthesized. Core quinazolinone structures were constructed *via* Ir catalysis.

Recently we described[1] a one-pot synthesis of 3-unsubstituted quinazolinones *via* Ir-catalyzed hydrogen transfer.[2] This operationally convenient methodology avoided any stoichiometric oxidants under base-free conditions. Many naturally occurring quinazolinones[3] contain 3-substitions (Fig. 1), it is thus our interest to expand the substrate scope using this methodology and explore the synthesis of these natural products.

Initially, we investigated whether 3-substituted quinazolinones could be synthesized starting from 2-amino-*N*-methylbenzamide **2**. Screening of conditions (for details, see the ESI†) established that benzyl alcohol **1** and amide **2** (1 : 1 molar ratio) under the catalysis of $[Cp^*IrCl_2]_2$ (Cp^* = pentamethyl-cyclopentadienyl)[4] gave the best results. As shown in Scheme 1, without acid or base additives, an excellent yield (97%) of product **3** was achieved in a shorter reaction time as compared to its 3-unsubstituted analog (24 h *vs.* 36 h).[1]

The success of this model reaction prompted us to explore the synthesis of 3-aromatic substituted quinazolinones. Methaqualone, for example, is a 3-*o*-tolyl substituted quinazolinone well-known for its sedative–hypnotic effects.[5] Ethanol was employed in our synthesis of this compound (Scheme 2). Because of the low boiling point of ethanol, the conditions of refluxing ethanol and benzamide **4** (1 : 1 molar ratio) in xylene did not give good yield of product (conversion <20%) due to loss of the ethanol. Ethanol was thus applied as solvent in a sealed tube, and methaqualone was isolated in 97% yield under these conditions. Subsequently, *N*-substituted aminobenzamide **6** was employed under the same conditions as **4** to give quinazolinone **7** in 89% yield. The methyl ester group in **6** did not interfere with the quinazolinone formation, testifying to the mildness of our conditions without base. After following known procedures[6] for bromination of **7** to **8**, sclerotigenin **9** was synthesized in the excellent yield of 94% using ammonia in methanol under sealed tube conditions.[7]

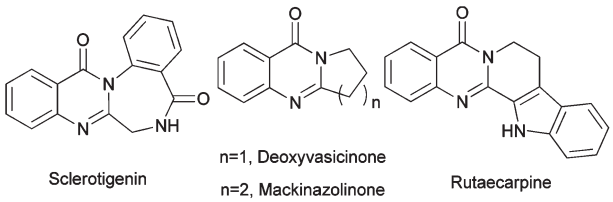
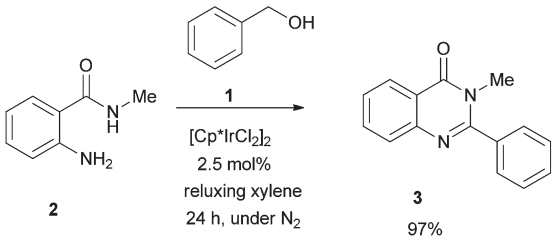


Fig. 1 Naturally occurring quinazolinones.



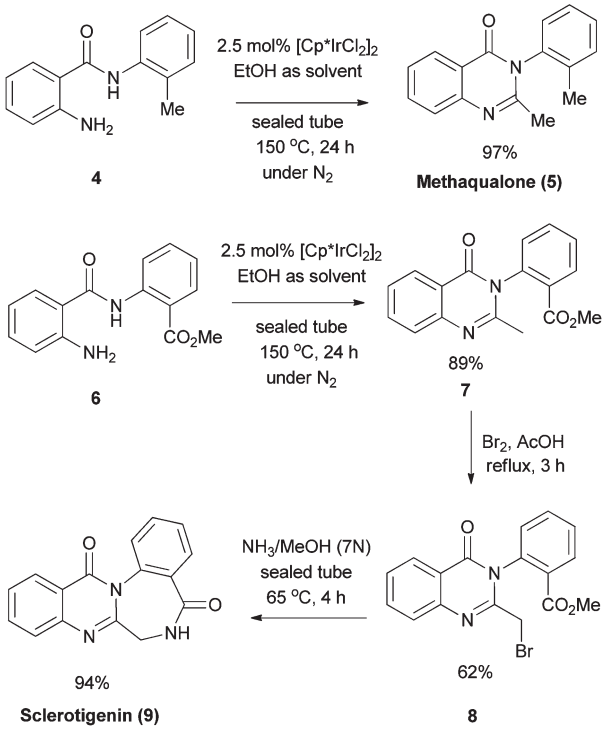
Scheme 1 Synthesis of 3-methyl-2-phenylquinazolin-4(3*H*)-one.

Next, we were attracted to the synthesis of biologically important quinazolinones with more complex structures. Deoxyvasicinone[8] and mackinazolinone,[9] for example, are quinazolinones fused with pyrrolidine and piperidine, respectively, with antimicrobial, anti-inflammatory and anti-depressant activities. The syntheses of deoxyvasicinone[10] and mackinazolinone[10c,11] have been widely explored. We were interested in the application of our methodology to the synthesis of 2-substituted quinazolinone intermediates with an alcohol appendage, such as pegamine, the subsequent ring closure of which using Mitsunobu conditions[12] would form the fused ring systems in these natural products. Pegamine itself is a natural product isolated from *Peganum harmala* and exhibits cytotoxic activity.[13]

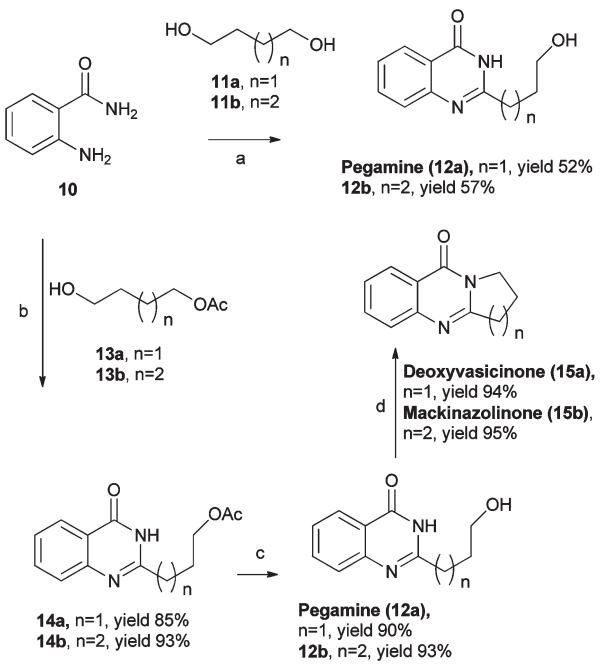
The protocols of synthesis are shown in Scheme 3. The reactions of 2-aminobenzamide (**10**) with unprotected diols **11a** and **11b** furnished quinazolinones **12a** (pegamine) and **12b**, although with fair yields (**12a**: 52%, **12b**: 57%) under our optimized conditions. A number of mono-protected alcohols of **11a** and **11b** were thus tested in the quinazolinone formation reactions. Among all the protected monoalcohols, *e.g.*, with THP, tosyl,

Chemical and Analytical Development, Suzhou Novartis Pharma Technology Co. Ltd, Changshu, Jiangsu, China, 215537. E-mail: jianguang.zhou@novartis.com

†Electronic supplementary information (ESI) available: Experimental procedures and compound characterization data. See DOI: 10.1039/c2ob07178a



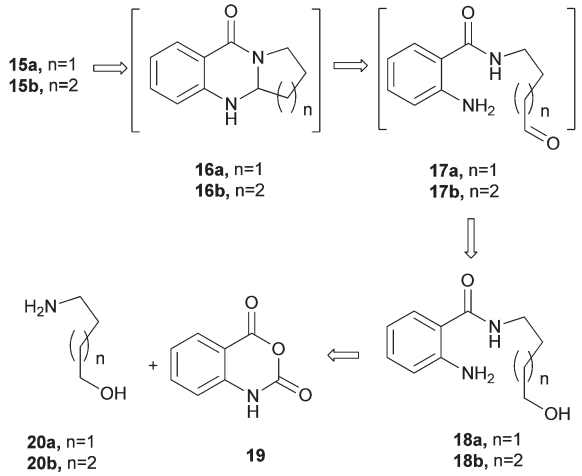
Scheme 2 Synthesis of methaqualone and sclerotigenin.



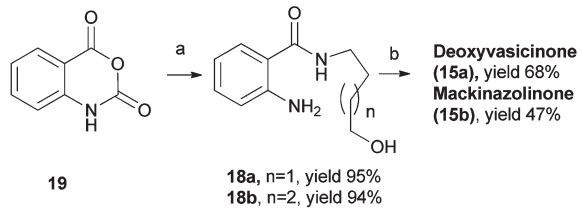
(a) 2.5 mol% $[Cp^*IrCl_2]_2$, refluxing xylene under N_2, 22 h (b) 2.5 mol% $[Cp^*IrCl_2]_2$, refluxing xylene under N_2, 48 h (c) K_2CO_3, methanol/H_2O (4:1), r.t., 4 h (d) DEAD, PPh_3, r.t., 3 h

Scheme 3 Syntheses of deoxyvasicinone and mackinazolinone.

and acetyl protection, **13a** and **13b** stood out as the best substrates, giving **14a** and **14b** in 85% and 93% yield, respectively. Notably, the acetyl group survived this process under heating, again demonstrating the mildness of the base-free conditions of



Scheme 4 Retrosynthesis of **15a** and **15b** *via* an intramolecular Ir-catalysed oxidative cyclization as key step.



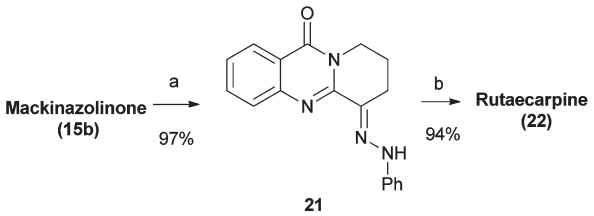
(a) **20a**, or **20b**, 1,4-dioxane, r.t., 6 h (b) **18a** in xylene (0.125 M) under N_2, 2.5 mol% $[Cp^*IrCl_2]_2$, 10 mol% TfOH, reflux, 24 h; **18b** in xylene (0.125 M) under N_2, 5 mol% $[Cp^*IrCl_2]_2$, 20 mol% TfOH, reflux, 36 h

Scheme 5 Ir-catalysed intramolecular oxidative cyclization in the syntheses of **15a** and **15b**.

the Ir-catalysed quinazolinone synthesis. After deprotection of the acetyl group under the conditions of K_2CO_3 in a mixture of methanol–H_2O at room temperature, **12a** and **12b** were obtained in high yield (**12a**: 90%, **12b**: 93%). Further transformations of these 2-substituted quinazolinones with an alcohol appendage, following the known procedure[10d] of an intramolecular Mitsunobu reaction, provided natural products deoxyvasicinone and mackinazolinone in excellent yields (**15a**: 94%, **15b**: 95%).

Although all of our previous examples of quinazolinone syntheses involved intermolecular reactions between primary alcohols and *o*-aminobenzamides, the syntheses of **15a** and **15b** offered us the possibility of an intramolecular version of Ir-catalysed cyclization reactions. As shown in Scheme 4, we anticipated that intermediates such as **18a** and **18b** with both alcohol and aminobenzamide functional groups combined within one molecule, would undergo hydrogen transfer events (alcohol **18** to aldehyde **17**, intramolecular cyclizations to aminal intermediates **16** followed by dehydrogenation) to produce our final desired products **15a** and **15b**.

Thus, intermediates **18a** and **18b** were readily obtained by reaction of compound **19** with either unprotected 1,4-amino alcohol **20a** or 1,5-amino alcohol **20b** in 95% and 94% yield, respectively, as shown in Scheme 5. For the key intramolecular oxidative cyclisation reaction, the conditions using **18a** in



(a) aniline, 30% HCl, $NaNO_2$, AcOH, -5 to 5 °C, 5 h (b) PPA, 180 °C, 1 h.

Scheme 6 Synthesis of rutaecarpine.

refluxing xylene (concentration = 0.5 M) under $[Cp^*IrCl_2]_2$ catalysis (2.5 mol%) only afforded product **15a** in 35% yield. We observed several byproducts resulting from intermolecular reactions under these conditions. We reasoned that acid additives would accelerate the intramolecular cyclizations from **17a** to **16a** and thus increase the yield of **15a**. Another factor to inhibit the intermolecular byproduct formations will be the more dilute concentration of **18a**. Among the acid additives (AcOH, TfOH, H_2SO_4 and TFA), and concentrations of **18a** in xylene (0.25 M, 0.125 M, 0.062 M and 0.031 M) screened, the combination of 10 mol% of TfOH with **18a** concentration of 0.125 M in refluxing xylene gave the best yield of **15a** (68%). Under similar unoptimized reaction conditions, the analog **15b** was obtained in lower yield of 47% even with a higher catalyst loading (5 mol%).

Both deoxyvasicinone **15a**[14] and mackinazolinone **15b**[11b] have been utilized for the synthesis of rutaecarpine **22**. As an example, a literature procedure was followed to transform mackinazolinone (**15b**) to rutaecarpine.[11b] As shown in Scheme 6, compound **15b** reacted with diazonium salt of aniline generated *in situ* to give the corresponding hydrazone **21** in 97% yield. Further Fisher-indole synthesis from **21** led to rutaecarpine (**22**) smoothly in 94% yield.

Conclusions

We expanded our substrate scope and synthesized 2,3-disubstituted quinazolinones *via* Ir-catalyzed oxidative cyclisations between primary alcohols and *N*-substituted *o*-aminobenzamides. This reaction utilized an air and water stable Ir catalyst under base-free conditions and without stoichiometric external oxidants. Good functional group tolerance was demonstrated in the successful syntheses of natural products sclerotigenin, pegamine, deoxyvasicinone and mackinazolinone. An intramolecular version of this reaction was investigated in the synthesis of deoxyvasicinone and mackinazolinone and showed that TfOH is a good additive to promote the intramolecular reaction. Further utilization of mackinazolinone in the synthesis of rutaecarpine was demonstrated in an efficient manner.

Notes and references

1 J. Zhou and J. Fang, *J. Org. Chem.*, 2011, **76**, 7730. For a subsequent related report using Ru: A. J. A. Watson, A. C. Maxwell and J. M. J. Williams, *Org. Biomol. Chem.*, 2012, **10**, 240.

2 For recent reviews: (*a*) K. Fujita and R. Yamaguchi, *Synlett*, 2005, **4**, 560; (*b*) T. D. Nixon, M. K. Whittlesey and J. M. J. Williams, *Dalton Trans.*, 2009, 753; (*c*) M. J. Krische, *Angew. Chem., Int. Ed.*, 2009, **48**, 34; (*d*) G. E. Debereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681; (*e*) T. Suzuki, *Chem. Rev.*, 2011, **111**, 1825; (*f*) J. Choi, A. H. R. MacArthur, M. Brookhart and A. S. Goldman, *Chem. Rev.*, 2011, **111**, 1761.

3 (*a*) S. B. Mhaske and N. P. Argade, *Tetrahedron*, 2006, **62**, 9787; (*b*) For a recent review on quinazoline alkaloids: M. P. Joseph, *Nat. Prod. Rep.*, 2008, **25**, 166.

4 K. Fujita, S. Furukawa and R. Yamaguchi, *J. Organomet. Chem.*, 2002, **649**, 289.

5 A. H. Amin, D. R. Mehta and S. S. Samarth, *Prog. Drug Res.*, 1970, **14**, 218.

6 D. R. Harrison, P. D. Kennewell and J. B. Taylor, *J. Heterocycl. Chem.*, 1977, **14**, 1191.

7 A low yield of 38% was reported for the same transformation: A. Witt and J. Bergman, *J. Heterocycl. Chem.*, 2002, **39**, 351.

8 (*a*) A. H. Amin and D. R. Mehta, *Nature*, 1959, **183**, 1317; (*b*) D. R. Mehta, J. S. Naravane and R. M. Desai, *J. Org. Chem.*, 1963, **28**, 445; (*c*) M. P. Jain, S. K. Koul, K. L. Dhar and C. K. Atal, *Phytochemistry*, 1980, **19**, 1880; (*d*) A. Al-Shamma, S. Drake, D. L. Flynn, L. A. Mitscher, Y. H. Park, G. S. R. Rao, A. Simpson, J. K. Swayze, T. Veysoglu and S. T. S. Wu, *J. Nat. Prod.*, 1981, **44**, 745.

9 (*a*) S. R. Johns and J. A. Lamberton, *Chem. Commun. (London)*, 1965, 267; (*b*) J. S. Fitzgerald, S. R. Johns, J. A. Lamberton and A. H. Redcliffe, *Aust. J. Chem.*, 1966, **19**, 151.

10 For examples: (*a*) A. V. Lygin and A. de Meijere, *Org. Lett.*, 2009, **11**, 389; (*b*) C. Zhang, C. K. De, R. Mal and D. Seidel, *J. Am. Chem. Soc.*, 2008, **130**, 416; (*c*) J.-F. Liu, P. Ye, K. Sprague, K. Sargent, D. Yohannes, C. M. Baldino, C. J. Wilson and S.-C. Ng, *Org. Lett.*, 2005, **7**, 3363; (*d*) S. B. Mhaske and N. P. Argade, *J. Org. Chem.*, 2001, **66**, 9038.

11 For examples: (*a*) S. B. Mhaske and N. P. Argade, *Tetrahedron*, 2004, **60**, 3417; (*b*) J. Kokosi, I. Hermecz, G. Szasz and Z. Meszaros, *Tetrahedron Lett.*, 1981, **22**, 4861; (*c*) T. Kametani, T. Higa, C. V. Loc, M. Ihara, M. Koizumi and K. Fukumoto, *J. Am. Chem. Soc.*, 1976, **98**, 6186.

12 O. Mitsunobu, *Synthesis*, 1981, 1.

13 Z. Z. Ma, Y. Hano, T. Nomura and Y. J. Chen, *Heterocycles*, 1999, **51**, 1883.

14 J. Kokosi, G. Szasz and I. Hermecz, *Tetrahedron Lett.*, 1992, **33**, 2995.