Pergamon

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Tetrahedron Letters 44 (2003) 7533–7536

TETRAHEDRON LETTERS

Solid-phase synthesis of 2,6- and 2,7-diamino-4(3*H*)-quinazolinones via palladium-catalyzed amination☆

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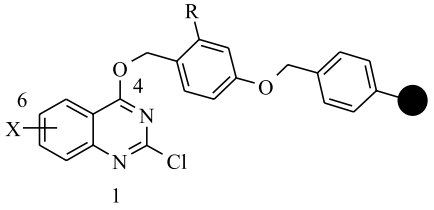
Received 4 June 2003; revised 24 July 2003; accepted 1 August 2003

Abstract—A new procedure for the solid-phase synthesis of 2,6- and 2,7-diamino-4(3*H*)-quinazolinones is described. The method involves coupling of 2,4,6- and 2,4,7-trichloroquinazoline to a solid support via benzyl alcohol type linkers, subsequent displacement of chlorine at C-2 then at the C-6 or C-7 positions by amines (Fig. 1) and the cleavage of the products from the resin. The palladium-catalyzed amination of C-6 and C-7 positions with a representative set of amines in the presence of 2-(di-*t*-butylphosphino)biphenyl (DTBPBP), P(*t*-Bu)$_3$ and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) ligands has been investigated. This method should prove to be a useful tool for constructing combinatorial libraries containing the 4(3*H*)-quinazolinone moiety.

2-Amino-4(3*H*)-quinazolinones have a wide range of biological activity.[1–5] Recently antitumor[6] and anti-HIV[7] activities of quinazolinones have been disclosed as well. These effects make 4(3*H*)-quinazolinones valuable target molecules in drug research. Combinatorial chemistry has proven a highly powerful tool in drug discovery and has become popular among medicinal chemists.[8] This new technique has encouraged chemists to evolve new synthetic approaches suitable for the preparation of combinatorial libraries. Such attempts have led to the development of new, solid-phase strategies in the synthesis of 4(3*H*)-quinazolinone derivatives.[9–14]

In our recent paper a novel general method for the solid-phase synthesis of 4(3*H*)-quinazolinones was described.[15] This approach is based on the coupling of 2,4-dichloroquinazoline derivatives to solid-support at C-4 via a benzyl alcohol type linker. The 2-chloro substituent and a suitable functional group on the benzene ring (X, Fig. 1) provide possibilities for the introduction of diversity elements. This approach is especially useful for the synthesis of 4(3*H*)-quinazolinone libraries which fulfil the following criteria: (1) They cannot be prepared from easily accessible anthranilic acid derivatives. (2) The diversity elements coupled to the core structure are easily accessible in a large number. (3) The advantages of the solid-phase technique are exploitable in the synthesis. The synthesis of 2-amino-6-alkoxy-4(3*H*)-quinazolinones demonstrated in our previous publication,[15] and the preparation of 2,6- and 2,7-diamino-4(3*H*)-quinazolinones which is our current subject fulfil these three criteria.

The goal of the present paper is to demonstrate the feasibility of our approach for the synthesis of 2,6- and 2,7-diamino-4(3*H*)-quinazolinone libraries and to show how the scope of this strategy can be widened by using the appropriate linker. Application of the same 2-amino substituents as used before permits us to compare our



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R = H or MeO, X = suitable functional group

Figure 1. The resin bound form of the core structure for the solid–phase synthesis of 4(3*H*)-quinazolinone derivatives.

Keywords: 4(3*H*)-quinazolinones; solid-phase synthesis; palladium; amination.

☆ Supplementary data associated with this article can be found at doi:10.1016/S0040-4039(03)01876-8

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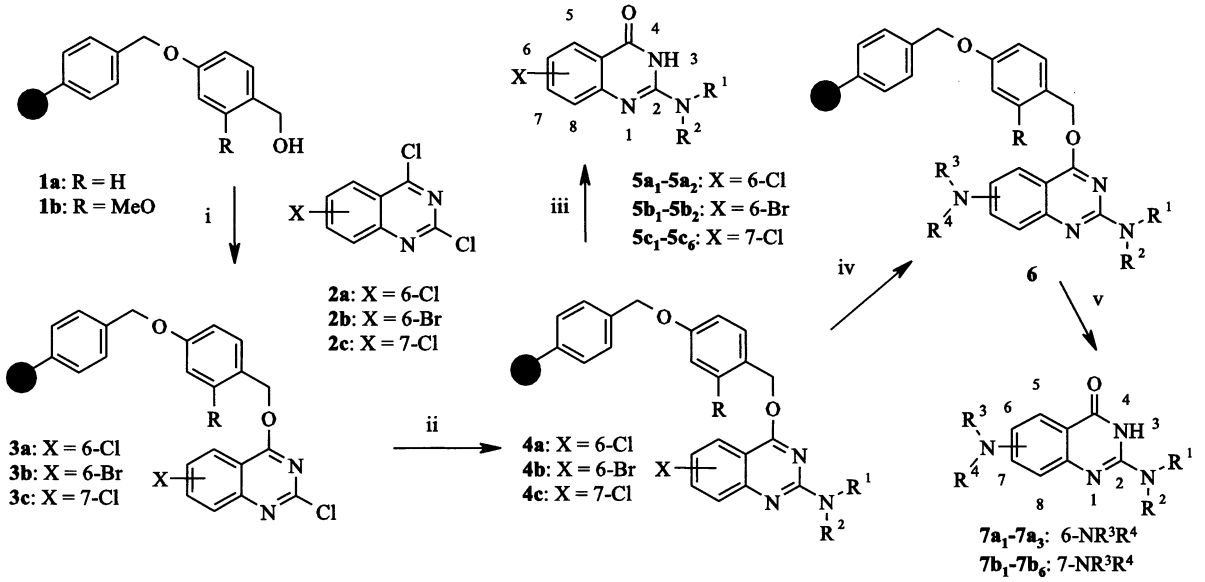
0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01876-8

new and previous results and hereby to study the effect of the substituents at the benzene ring on the aromatic nucleophilic substitution and on the 'cleavage point' of the linker.

The solid-phase synthesis of 2,6- and 2,7-diamino-4(3*H*)-quinazolinones is outlined in Scheme 1. 6- And 7-halo-2,4-dichloroquinazolines[16,17] **2a–c** were tethered to Wang alcohol resin[18] (4-benzyloxybenzyl alcohol, polymer bound) **1a** and 4-(4-hydroxymethyl-3-methoxyphenoxy)benzyl polystyrene[19] **1b**, respectively. The resins were deprotonated with *n*-BuLi at −20°C then **2a–c** were added. Complete conversion of **3a–c** to the resin bound 2-aminoquinazoline derivatives **4a–c** was achieved after treatment with aliphatic primary and secondary amines at 80°C. Amines branched at the α position required higher temperatures (100°C) or longer reaction times (Table 1, entries 9, 10). These compounds were cleaved from the resin with TFA/DCM mixture to give 2-amino-6- and 2-amino-7-halo-4(3*H*)-quinazolinones $\mathbf{5a_1}$–$\mathbf{5c_5}$ in high yield and excellent purity (Table 1, entries 1–10). The yields and purities were practically the same for the two different linkers (Table 1, entries 6–7). Comparing our new results to our previous experiments[15] with 6-hydroxy derivatives, it was observed that with aryl amines neither the 6-hydroxy nor the 7-halo derivatives afforded pure products (entry 11). On the other hand while 6-hydroxy derivatives did not give pure products with primary aliphatic amines the 6- and 7-halo compounds afforded the expected 2-amino-4(3*H*)-quinazolinones in high purity (Table 1, entries 1, 5, 9).

The next step was the introduction of the second amino group into the C-6 and C-7 position via palladium-catalyzed amination.[20] According to our literature survey this reaction has been rarely utilized in the field of solid-phase chemistry[21–24] and has not been used before for the synthesis of aminoquinazolines. To study this reaction and to find general reaction conditions, 6- and 7-halo-2-(piperidin-1-yl) derivatives **4a–c**, (NR^1R^2 = piperidin-1-yl) were chosen as model compounds. Three types of aryl halide–Pd/ligand systems have been investigated: aryl bromide–Pd/BINAP,[25] aryl chloride–Pd/$P(t\mathrm{Bu})_3$[26] and aryl chloride–Pd/DTBPBP.[27] The reactions were carried out at 100°C in xylene using NaO*t*Bu. Our experimental results with the aryl bromide–Pd/BINAP system (Table 1, entries 12–14) were in accordance with the observations made by Wolfe et al.[25] It was shown that the system is effective with primary amines while with certain acyclic secondary amines the yields decrease because of the significant reduction of the bromide. The aryl chloride–Pd/$P(t\mathrm{Bu})_3$ system, in accordance with Hartwig's solution-phase experiments[26] gave the expected 6- and 7-amino compounds in good yield with secondary amines (Table 1, entries 17–20). The amount of reduced side product was in the range of 1–7%. However, with primary amines, even with a fivefold excess of amine, diarylation occurred yielding about 30% of *N*,*N*-diaryl-*N*-alkylamine side product (Table 1, entries 15–16). This side reaction had also been observed in solution-phase experiments. DTBPBP is one of the most recently reported air-stable phosphine ligands.[27] In our case the aryl chloride–Pd/DTBPBP system worked well with primary amines providing only 1–6% of reduced side product (Table 1 entries 21–26). With secondary amines, however, a higher amount of such impurities was produced (Table 1, entries 27, 28) unlike in the case of Pd/$P(t\mathrm{Bu})_3$ (Table 1, entries 18, 19).

In summary, $P(t\mathrm{Bu})_3$ proved to be the most suitable ligand for the introduction of secondary aliphatic and aromatic amines in palladium-catalyzed aminations,



Scheme 1. *Reagents and conditions*: (i) 2.2 equiv. *n*-BuLi, −20°C, 5 equiv. **2a–c**, rt, 16 h; (ii) 5 equiv. HNR^1R^2, DMF, 3 h, 80 or 100°C; (iii) 5% (R = MeO) or 20% (R = H) TFA/DCM, 2 h; (iv) 5 equiv. HNR^3R^4, 0.2 equiv. Pd-complex, 5 equiv. NaO*t*Bu, *o*-xylene, 100°C, 24 h; (v) 5% (R = MeO) or 20% (R = H) TFA/DCM, 2 h.

Table 1. The purities and yields of the 2-amino-4(3*H*)-quinazolinones[a]

Entry	Comp.	Precursor	Linker	Ligand[b]	NR^1R^2	NR^3R^4	Purity (%)[c]	Yield (%)[d]
1	**5a$_1$**[e]	**3a**	**1a**	–	2-Phenylethylamino	–	97	84
2	**5a$_2$**[e]	**3a**	**1a**	–	Piperidin-1-yl	–	98	89
3	**5b$_1$**	**3b**	**1a**	–	Bis(*n*-butyl)amino	–	97	91
4	**5b$_2$**	**3b**	**1a**	–	Piperidin-1-yl	–	95	86
5	**5c$_1$**	**3c**	**1a**	–	*n*-Hexylamino	–	96	81
6	**5c$_2$**	**3c**	**1a**	–	Piperidin-1-yl	–	98	82
7	**5c$_2$**	**3c**	**1b**	–	Piperidin-1-yl	–	98	85
8	**5c$_3$**	**3c**	**1a**	–	Bis(*n*-butyl)amino	–	95	78
9	**5c$_4$**	**3c**	**1a**	–	*sec*-Butylamino	–	96[f]	81
10	**5c$_5$**	**3c**	**1a**	–	2-Methylpiperidin-1-yl	–	98[f]	87
11	**5c$_6$**	**3c**	**1a**	–	*N*-Methylphenylamino	–	26	–
12	**7a$_1$**	**3b**	**1b**	BINAP	Piperidin-1-yl	2-Phenylethylamino	81	57
13	**7a$_2$**	**3b**	**1b**	BINAP	Piperidin-1-yl	Bis(*n*-butyl)amino	65	–
14	**7a$_3$**	**3b**	**1b**	BINAP	Piperidin-1-yl	*n*-Hexylamino	76	–
15	**7a$_3$**	**3a**	**1b**	P(*t*-Bu)$_3$	Piperidin-1-yl	*n*-Hexylamino	63	–
16	**7b$_1$**	**3c**	**1b**	P(*t*-Bu)$_3$	Piperidin-1-yl	Benzylamino	43	–
17	**7a$_2$**	**3a**	**1b**	P(*t*-Bu)$_3$	Piperidin-1-yl	Bis(*n*-butyl)amino	83	66
18	**7b$_2$**	**3c**	**1b**	P(*t*-Bu)$_3$	Piperidin-1-yl	Bis(*n*-butyl)amino	85	61
19	**7b$_3$**	**3c**	**1b**	P(*t*-Bu)$_3$	Piperidin-1-yl	*N*-Methylphenylamino	94	65
20	**7b$_4$**	**3c**	**1b**	P(*t*-Bu)$_3$	Piperidin-1-yl	*N*,*N*-Diphenylamino	96	68
21	**7a$_3$**	**3a**	**1b**	DTBPBP	Piperidin-1-yl	*n*-Hexylamino	82	58
22	**7b$_5$**	**3c**	**1b**	DTBPBP	Piperidin-1-yl	*n*-Hexylamino	94	62
23	**7b$_1$**	**3c**	**1b**	DTBPBP	Piperidin-1-yl	Benzylamino	92	63
24	**7b$_1$**	**3c**	**1a**	DTBPBP	Piperidin-1-yl	Benzylamino	86	58
25	**7b$_6$**	**3c**	**1b**	DTBPBP	Piperidin-1-yl	2-Phenylethylamino	96	71
26	**7b$_6$**	**3c**	**1a**	DTBPBP	Piperidin-1-yl	2-Phenylethylamino	82	61
27	**7b$_2$**	**3c**	**1b**	DTBPBP	Piperidin-1-yl	Bis(*n*-butyl)amino	48	-
28	**7b$_3$**	**3c**	**1b**	DTBPBP	Piperidin-1-yl	*N*-Methylphenylamino	37	-

[a] All compounds were characterized by MS spectroscopy. The structures of compounds having at least 80% purity were confirmed by ^{1}H NMR spectroscopy. Spectroscopic characterization data are given in the Supplementary Material.
[b] Ratio of BINAP/Pd = 2/1, P(*t*Bu)$_3$/Pd = 1/1, DTBPBP/Pd = 2/1.
[c] The purities and MWs of the crude products were determined by HPLC-MS at 254 nm. All purities reported are the average of at least two runs.
[d] The overall yield was determined by weight based on the loading of **3a**–**c**. The yields refer to compounds purified by flash chromatography.
[e] Known compounds.[28]
[f] Reaction conducted at 100°C.

while DTBPBP proved to be superior in the case of primary aliphatic amines.

The synthesis of diamino-4(3*H*)-quinazolinones was achieved on both linkers. While 2-amino-6-halo-4(3*H*)-quinazolinones and 2-amino-7-halo-4(3*H*)-quinazolinones as well as 2-amino-6-hydroxy-4(3*H*)-quinazolinones and 2-amino-6-alkoxy-4(3*H*)-quinazolinones[15] can be cleaved from **1a** in pure form, the cleavage of 2,6- and 2,7-diamino derivatives from **1a** has resulted in the formation of significant amounts (1–20%) of 4-(4-hydroxybenzyloxy)-2,6(7)-diamino-4(3*H*)-quinazoline impurities. This type of side product was completely eliminated by employing **1b**, a more acid sensitive linker (Table 1, entries 23–24, 25–26).

The solid-phase method developed involves two steps where the issue of regioselectivity should be considered: Due to the presence of three halogens in the quinazoline ring the coupling to the resin as well as the amine substitution steps might, in principle, lead to regioisomers in the route toward the quinazolinone **5a**–**c**. It is well known from the literature that in solution phase the 2,4,6- and 2,4,7-trichloroquinazolines can be selectively substituted with amines.[29] The halogen at position 4 is more reactive than at position 2, while the 6 and 7 positions are considerably less active. Although the same order of selectivity is expected, such investigations with the salts of alcohols in solid-phase synthesis has not been established. One would expect that linking of the starting quinazolines **2a**–**c** to the resin will occur at position 4, thus the 2-amino isomer will be the main product. However, formation of the 4-amino isomer could not be excluded on an a priori basis. This structural question was settled by NMR and HPLC-MS studies. According to HPLC-MS, peaks with a molecular mass equal to the molecular mass of the main product could not be detected among the impurities in either case, indicating considerably high regioselectivity. The structure of the main products (**5a**–**c**) was proved by detailed NMR studies. The following spectroscopic pieces of evidence support the 2-amino-4(3*H*)-quinazolinone structure of compound **5a**–**c**: Firstly, we could not detect NOE interactions between the protons of the amino groups and the aromatic protons of the quinazolinone ring. Secondly, the H-5 proton shows correlation in the PFG-HMBC spectrum with the C-4 carbonyl carbon. Thirdly, due to the *peri* effect of the carbonyl group the H-5 proton resonates considerably

downfield relative to the H-7, H-8 (**5a**,**b**) as well as the H-6, H-8 (**5c**) protons—see Supporting material.

In DMSO-d_6 solution at 30°C at 500 MHz we have observed exchange broadening of the H-8 signal in compounds **5a$_2$**, **5b$_1$**, **5b$_2$**, **5c$_3$**, **7b$_1$**, **7b$_2$**, **7b$_4$** and **7b$_5$** indicating an ongoing N(1)H↔N(3)H tautomerization process that is moderately fast on the NMR chemical shift timescale. Literature data suggest that the 4(3*H*)-quinazolinone tautomer stabilized by amide resonance is preferred over the 4(1*H*)-quinazolinone tautomer.[30] The measured weak NOE interaction between the quinazolinone NH and the H-8 protons indicates that the 4(1*H*)-quinazolinone tautomer is measurably populated under the applied conditions.

In summary, we have developed a new solid phase method for the synthesis of combinatorial libraries of 2,6- and 2,7-diamino-4(3*H*)-quinazolinones. The route features the use of an *o*-methoxybenzylalcohol linker and palladium complexes supported by new phosphine ligands as well as the use of a huge number of commercially available building blocks. The library obtained was characterized by HPLC-MS and NMR spectroscopy.

References

1. Hess, H. J.; Cronin, T. H.; Scriabine, A. *J. Med. Chem.* **1968**, *11*, 130–136.
2. Gauss, W.; Kabbe, H. J.; Paulus, W.; Rosslenbroich, H. J.; Brandes, W. 1984, Ger. Offen. DE 341080, Chem. Abstr. 104. P 64209y.
3. Mannschreck, A.; Koller, H.; Stuhler, G.; Davies, M. A. *Eur. J. Med. Chem.* **1984**, *19*, 381–383.
4. Nobuo, O.; Toshihiko, Y.; Takayuki, A.; Eiichi, K.; Hideo, K.; Yasuo, I. *Chem. Pharm. Bull.* **1988**, *36*, 2955–2967.
5. Kung, P.-P.; Casper, M. D.; Cook, K. L.; Wilson-Lingardo, L. *J. Med. Chem.* **1999**, *42*, 4705–4713.
6. Xia, Y.; Yang, Z.-Y.; Hour, M.-J.; Kuo, S.-C.; Xia, P.; Bastow, K. F.; Nakanishi, Y.; Nampoothiri, P.; Hackl, T.; Hamel, E.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1193–1196.
7. De Clercq, E. *Curr. Med. Chem.* **2001**, *8*, 1543–1572.
8. Dolle, R. E. *J. Comb. Chem.* **2002**, *4*, 369–418.
9. Majer, J. P.; Lewis, G. S.; Curtis, M. J.; Zhang, J. *Tetrahedron Lett.* **1997**, *38*, 8445–8452.
10. Villalgordo, J. M.; Obrecht, D.; Chucholowsky, A. *Synlett* **1998**, 1405–1407.
11. Gopalsamy, A.; Yang, H. *J. Comb. Chem.* **2000**, *2*, 378–381.
12. Yang, R.-Y.; Kaplan, A. *Tetrahedron Lett.* **2000**, *41*, 7005–7008.
13. Keserwani, A. P.; Srivasta, G. K.; Rastogi, S. K.; Kundu, B. *Tetrahedron Lett.* **2002**, *43*, 5579–5581.
14. O'Mahony, D. J. R.; Krchnak, V. *Tetrahedron Lett.* **2002**, *43*, 939–942.
15. Wéber, C.; Bielik, A.; Szendrei, I. Gy.; Greiner, I. *Tetrahedron Lett.* **2002**, *43*, 2971–2974.
16. Lee, S. J.; Konishi, Y.; Yu, D. T.; Miskowski, T. A.; Riviello, C. M. *J. Med. Chem.* **1995**, *38*, 3547–3557.
17. Volzhina, O. N.; Medvedev, B. A.; Kazakov, A. A.; Zhikhareva, G. P. *Pharm. Chem. J.* **1987**, *21*, 478–483.
18. Wang resin was purchased from Novabiochem. Catalog Number: 01-64-0014. 4-Benyzloxybenyzl alcohol resin. Grain size: 100–200 mesh. Substitution: 0.78 mmol/g. The polymer matrix is copoly(styrene–1% DVB).
19. 4-Hydroxy-2-methoxybenzyl alcohol (polymer-bound) was purchased from Aldrich. Catalog Number: 54,073-0. Grain size: 50–90 mesh. Substitution: 0.4 mmol/g. The polymer matrix is copoly(styrene–1% DVB).
20. Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, 125–146.
21. Willoughby, C. A.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 7181–7184.
22. Ward, Y. D.; Farina, V. *Tetrahedron Lett.* **1996**, *37*, 6993–6996.
23. Ding, S.; Gray, N. S.; Wu, X.; Ding, Q.; Schultz, P. G. *J. Am. Chem. Soc.* **2002**, *124*, 1594–1596.
24. Guillier, F.; Roussel, P.; Moser, H.; Kane, P.; Bradley, M. *Eur. J. Chem.* **1999**, *5*, 3450–3458.
25. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157.
26. Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575–5580.
27. Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158–1174.
28. Seth, M.; Khanna, N. M. *Indian J. Chem. Sect. B* **1976**, *14B*, 536–540.
29. Elslager, E. F.; Hess, C.; Johnson, J.; Ortwine, D.; Chu, V.; Werbel, L. M. *J. Med. Chem.* **1981**, *24*, 127–140.
30. Hagiwara, Y.; Kurjhara, M.; Yoda, N. *Tetrahedron* **1969**, *25*, 783–792.