Solid-Phase Synthesis of 3*H*-Quinazolin-4-ones Based on an Aza Wittig-Mediated annulation Strategy

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Abstract: Aza *Wittig*-mediated annulation provides a highly efficient and straightforward strategy for the parallel synthesis of 3*H*-quinazolin-4-ones on solid support. The products were recovered in good yields and exhibited excellent purities.

Combinatorial chemistry and related multiple synthesis technologies toward the synthesis of small organic molecules have recently emerged as powerful tools for lead structure identification. Thus, numerous protocols have already been disclosed for the construction of various heterocyclic and other compound libraries[1-8]. For most of these protocols, the use of solid phase methods has been the technique of choice[9-11].

As a part of our ongoing project devoted toward the development of efficient solid phase methodologies for the combinatorial and parallel synthesis of diverse heterocyclic systems[11,12] we have focused our attention on the benzopyrimidone (quinazoline) nucleus **1**. (Figure 1)

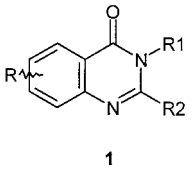

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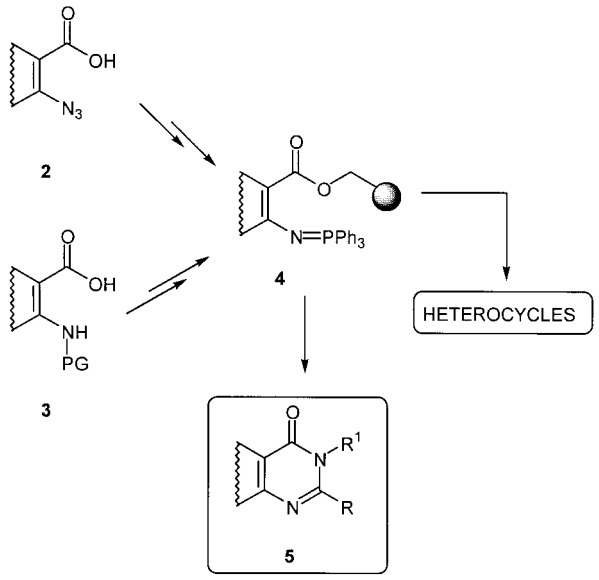
Figure 1

3*H*-Quinazolin-4-ones of type **1** represent an interesting pharmacophore that displays a wide rage of biological properties[13-15]. Therefore, an efficient strategy for the combinatorial and parallel synthesis of this interesting target, that allows the introduction of a high degree of molecular diversity, would be of interest.

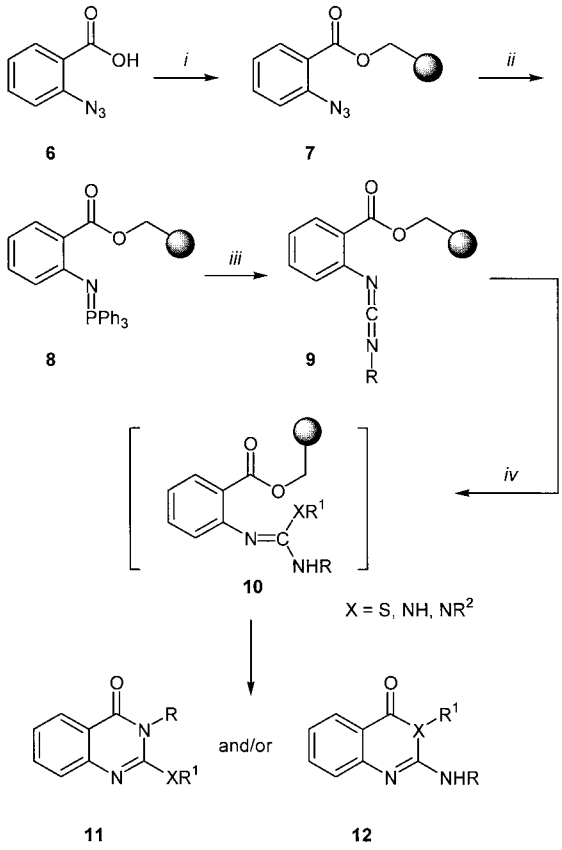
Herein, we report a highly versatile solid phase synthesis of quinazolinones **1**, which efficiently combines the aza *Wittig* reaction with a multidirectional cleavage process. As recent literature has discussed in depth,[16-22] iminophosphoranes have been shown to be useful intermediates in organic synthesis, particularly for the preparation of different heterocyclic systems containing an endocyclic C,N double bond. In these cases, an aza *Wittig*-mediated annulation reaction was involved as the key step. Our working hypothesis began with the idea that a benzoic acid derivative containing an *ortho*-azido **2**, or an *ortho*-amino group **3** would be tethered to the Merrifield resin and would provide the starting point for the formation of the corresponding phosphorylimine derivative **4** *via* a *Kirsanov*[19] or a *Staudinger*[23] reaction respectively.

Division of the polymer bound iminophosphorane beds **4**, followed by suitable manipulations and a cyclative cleavage process from the resin, would produce various heterocycles. We envisioned that this strategy could be applied efficiently to create compound libraries of diverse fused pyrimidones **5**. (Scheme 1).

To prove the above mentioned hypothesis, easily available *ortho*-azido benzoic acid[24] **6** was selected as a model case. Thus, alkylative esterification of **6**, via the corresponding cesium salt[25], with high loaded *Merrifield* resin (3.4 mmol/g) resulted in polymer-bound *ortho*-azido



Scheme 1



Reagents and Conditions: i: High-loaded Merrifield resin (3.4 mmol/g), Cs_2CO_3, DMF, KI, 80ºC, 8h.; ii: Ph_3P (1 M in THF, r.t., 6 h.; iii: R-N=C=O, CH_2Cl_2, r.t., 8h.; iv: R^1-XH, THF, 50ºC, 4h

Scheme 2

ester **7**. Treatment of **7** with a 5-fold excess PPh_3 in THF at room temperature produced the corresponding iminophosphorane **8** attached to the resin (evolution of N_2 clearly detected). Division of the resin beads and subsequent aza *Wittig* reaction with different isocyanates at room temperature smoothly formed the corresponding reactive carbodiimides **9**. Further division of resin-bound carbodiimides **9** and treatment with different nucleophiles (*e.g.* amines, thiols) led, *via* intramolecular cyclization and simultaneous cleavage from the resin, to quinazolines **10** (together with **11**, when primary, non-sterically hindered amines were used) in good yields and excellent purities. The formation of the polymer-bound compounds was routinely monitored by FT-IR of the resin beds. (Scheme-2, Table 1).

When primary amines were used as the nucleophiles, the product composition **11:12** was strongly influenced by differences in nucleophilicity and/or sterical hindrance of the two adjacent nitrogen atoms of the presumably formed guanidine intermediate **10** (X=NH), (entries ***b*** and **i**, Table 1). When those differences were minimal, both possible compounds of type **11** and type **12** were generally formed in 1:1 ratio (entries ***e***, ***h*** and ***l***, Table 1).

Typical experimental procedure

Polymer-bound ortho-azide ester **7**, obtained by essentially following the experimental procedure described in ref. 25, was swollen with 5ml/mmol of dry THF and treated with 5 equiv. of a 1M soln. of Ph_3P in dry THF. The reaction mixture was vortexed at r.t. under Ar during 6h. (evolution of N_2, clearly detected) and then washed with 5ml/mmol of dry THF (2x), dry toluene (2x), dry CH_2Cl_2 (2x) and pentane (2x), repeating this washing cycle 3 times to give resin **8**, that was dried in high vacuum, divided up and used in the next step. Polymer-bound phosphorylimine **8** was swollen as before, and treated with 5ml/mmol of dry THF and 5 equiv. of the corresponding isocyanate. The heterogeneous reaction mixture was vortexed at r.t. under Ar during 8 h. After washing cycles as above, resin **9** was dried in high vacuum and newly divided. Polymer-bound carbodiimide **9** was treated with 3ml/mmol of dry THF and 1 equiv. of the corresponding nucleophile. The reaction mixture was vortexed at 50ºC during 4h. and then at r.t. overnight liberating compounds **11** and/or **12**, that were analysed by HPLC and isolated by simply evaporating the solvent. Compounds **10** and **11** were characterised by M.S. and ^{1}H-NMR[26].

In summary, we have developed a simple and efficient solid-phase methodology that allows for a rapid synthesis of quinazoline libraries. There is also the possibility of introducing additional functionalities on the aromatic ring, allowing further chemical manipulations compatible with the ester, which is linked to the *Merrifield* resin[27]. The mild reaction conditions and the selective multidirectional cyclization make out of this traceless linker strategy an attractive procedure toward the synthesis of highly functionalized quinazolinones and other heterocycles. Further developments along this line are now in progress and will be published in due course.

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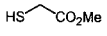
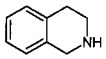
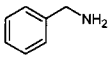
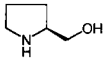
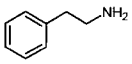
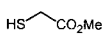
Table 1. Some representative 3*H*-Quinazolin-4-ones synthesized on solid support

Entry	R	R^1-XH	Product	Ratio 10:11[a]	Yield (%)[b]	Calculated MS	Obtained MS[c]	Purity (%)[a]
a	C_3H_7		**11a**	100:0	42	292.36	293.2	98
b	C_3H_7		**11b**	100:0	56	245.33	246.2	100
c	C_3H_7		**11c**	100:0	71	319.41	320.3	97
d	C_3H_7		**11d**	100:0	85	286.38	287.2	98
e	C_3H_7		**11e/12a**	50:50	77	293.37	294.3	96
f	Ph		**11f**	100:0	72	321.38	322.3	97
g	Ph		**11g**	100:0	75	291.36	292.3	97
h	Ph		**11h/12b**	50:50	74	341.42	342.3	93
i	Ph		**11i**	100:0	68	319.41	320.3	95
j	Ph		**11j**	100:0	72	307.36	308.2	99
k	Ph		**11k**	100:0	45	326.38	327.2	90
l	Ph		**11l/12c**	50:50	79	293.37	294.4	92

[a] Determined by HPLC analysis of the crude reaction mixture on a superspher® 60 RP-select column with a gradient 50% MeCN/H2O (with 1% TFA) until 100% MeCN over a period of 20 min.
[b] Based on initial loading of the Merrifield resin.
[c] Chemical ionization mode. $[M+1]^+$ observed.

References and Notes

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1. Obrecht, D.; Villalgordo, J. M. *Solid Supported Combinatorial and Parallel Synthesis of Small Molecular-Weight Compound Libraries*; Organic Chemistry Series; Pergamon: Oxford, 1998.
2. Gallop, M. A.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994,** *37*, 1233.
3. Gordon, E. M.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994,** *37*, 1385.
4. Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996,** *52*, 4527.
5. Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996,** *96*, 555.
6. Balkenhohl, F.; Bussche-Hünnefeld, C. v. d.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed. Engl.* **1996,** *35*, 2288.
7. Special issue on combinatorial chemsitry. *Acc. Chem. Res.* **1996,** *29*, 111.
8. Früchtel, J. S.; Jung, G. *Angew. Chem.* **1996,** *108*, 19.
9. Boger, D. L.; Tarby, C. M.; Meyers, P. L.; Caporale, L. H. *J. Am. Chem. Soc.* **1996,** *118*, 2109.
10. Cheng, S.; Comer, D. D.; Williams, J. P.; Meyers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996,** *118*, 2567.
11. Chucholowsky, A.; Masquelin, T.; Obrecht, D.; Stadlwieser, J.; Villalgordo, J. M. *Chimia* **1996,** *50*, 525.
12. Obrecht, D.; Grieder, A.; Villalgordo, J. M. *Helv. Chim. Acta* **1997,** *80*, 65.
13. Fry, D. W.; Kraker, A. J.; McMichael, A.; Ambroso, L. A.; Nelson, J. M.; Leopold, W. R.; Connors, R. W.; Bridges, A. J. *Science* **1994,** *265*, 1093.
14. Laszlo, S. E. d.; Chang, R. S.; Cheng, T.-B.; Faust, K. A.; Greenlee, W. J.; Kivlighn, S. D.; Lotti, V. J.; O´Malley, S. S.; Schorn, T. W.; Siegl, P. K.; Tran, J.; Zingaro, G. J. *Biorg. Chem. Med. Lett.* **1995,** *5*, 1359.
15. Johne, S. *Pharmazie* **1981,** *36*, 583.
16. Barluenga, J.; Palacios, F. *Org. Prep. Proced. Int.* **1991,** *23*, 1.
17. Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197.
18. Molina, P.; Alajarin, M.; Vidal, A. *Tetrahedron Lett.* **1988,** *29*, 3849.
19. Taylor, E. C.; Patel, M. *J. Heterocyclic Chem.* **1991,** *28*, 1857.
20. Wamhoff, H.; Haffmanns, G. *Chem. Ber.* **1984,** *117*, 585.
21. Wamhoff, H.; Wintersohl, H.; Stölben, S.; Paasch, J.; Nai-Jue, Z.; Fang, G. *Liebigs Ann. Chem* **1990**, 901.
22. Wamhoff, H.; Berressem, R.; Herrmann, S. *Synthesis* **1993**, 107.
23. Staudinger, H.; Hauser, E. *Helv. Chim. Acta* **1921,** *4*, 861.
24. Elshihi, T.; Herrmann, R. *Z. Naturforsch. B* **1986,** *41*, 132.
25. Frennette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994,** *35*, 9177.
26. 250 MHz ^{1}H-NMR ($CDCl_3$) data for compound **11d**: 8.25-8.15 (m, 1*H*, arom.); 7.7-7.6 (m, 1*H*, arom.); 7.55-7.5 (m, 1*H*, arom.); 7.35-7.25 (m, 1*H*, arom.); 4.07 (t, 2*H*); 3.20 (t, 4*H*); 2.60 (t, br., 4*H*); 2.37 (s, 3*H*); 1.85-1.70 (m, 2*H*); 0.90 (t, 3*H*).
27. The use of other solid supports like Tenta-Gel resulted in detriment of yields and purities of the isolated compounds.