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Efficient solid-phase synthesis of quinazoline-2-thioxo-4-ones with SynPhase™ lanterns

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Abstract

We wish to report the efficient solid-phase synthesis of diverse quinazoline-2-thioxo-4-ones using SynPhase™ lanterns as solid supports. Although target compounds were obtained only with low purity using Wang resin, lanterns derivatized with long chain hydroxymethyl phenoxy linkers successfully gave products with high purity. Furthermore, subsequent reactions of quinazoline-2-thioxo-4-ones with various types of halides gave *S*-alkylated or *S*-arylated products with high purity, showing the usefulness of this chemistry for synthesizing diverse quinazoline-2-thioxo-4-one libraries. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: solid-phase synthesis; quinazolines; isothiocyanates; alkylation; arylation.

Combinatorial chemistry for the synthesis of non-peptide organic compounds has emerged as an important tool for drug discovery.[1] Solid-phase synthesis of substituted heterocyclic compounds has been focussed on in particular, because of their application toward a variety of drug targets. Among various heterocycles, we were particularly interested in the synthesis of quinazolines, which have shown a wide range of pharmacological activities.[2] Although there have been reports of the solid-phase synthesis of quinazolidine-2, 4-diones[3] and quinazolinones,[4] a synthesis strategy to produce a wide range of quinazoline-2-thioxo-4-ones has not been reported.[4b] Here, we report the solid-phase synthesis of diverse quinazoline-2-thioxo-4-ones.

Initially, the synthesis of quinazoline-2-thioxo-4-ones **7** was attempted by reaction of 4-aminobenzoic ester **3** and 2-methoxycarbonyl phenylisothiocyanate **4** on Wang resin[5] (Scheme 1). In contrast to quinazolidine-2,4-dione synthesis using 2-methoxycarbonyl phenylisocyanate,[3b] intermediate **5** smoothly cyclized without subsequent base treatment to give quinazoline-2-thioxo-4-one **6**. However, cleavage of the products with 95% TFA/H_2O gave a mixture of **7** and **8**.

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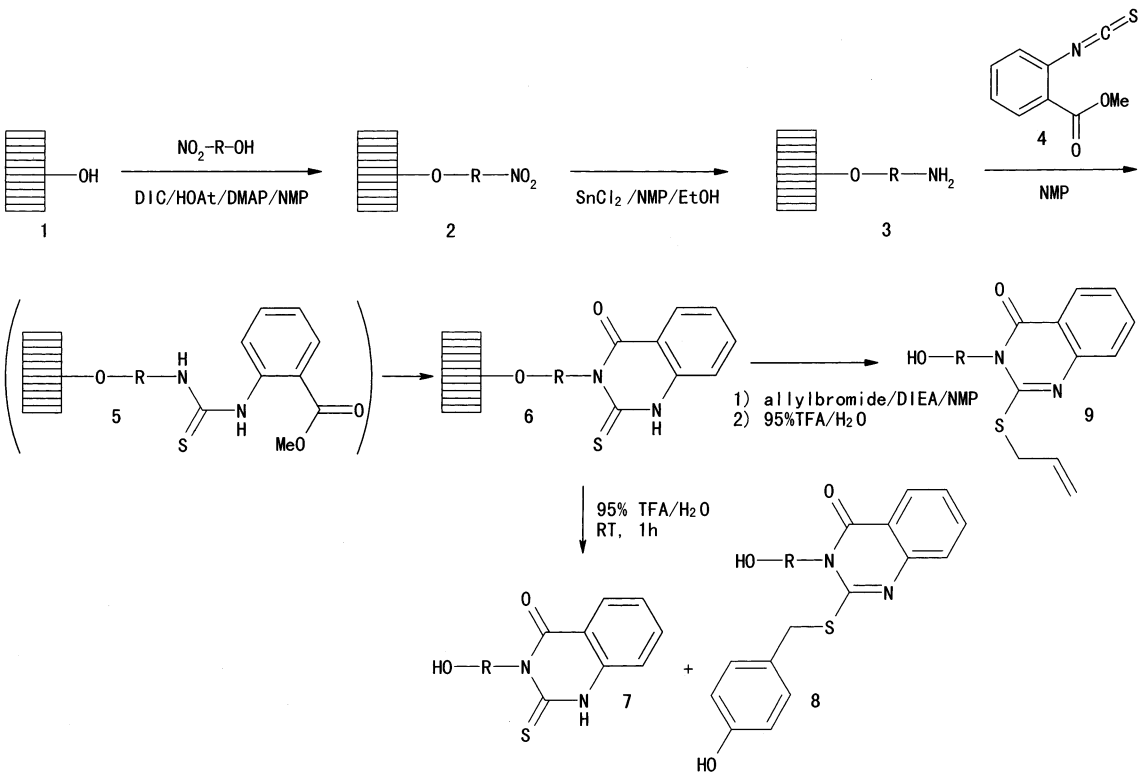
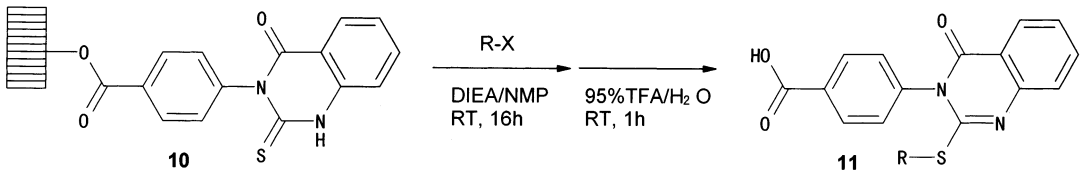


Scheme 1. Strategy for synthesis of quinazoline-2-thioxo-4-ones on solid supports

Since the Wang resin used in the synthesis possesses a *p*-benzyloxybenzyl ester moiety in its linker, the *p*-hydroxybenzyl cation that was released from the Wang resin in the process of the cleavage alkylated the sulfur atom in the product. Although water molecules in the cleavage solution usually work well for scavenging such cations, the scavenging capability was not sufficient for compounds with moieties highly susceptible to alkylation such as thioureas. Thus, it was necessary to evaluate other types of solid support in order to minimize the *S*-alkylated byproducts. Among several Wang derivatized solid supports[6] that should not generate such *S*-alkylated byproducts **8**, we decided to use SynPhase™ lantern (long-chain HMP),[7] because (1) it possesses stable *p*-hydroxymethylphenoxy valeric amide as a linker, therefore, the generation of *p*-hydroxybenzyl cation would be unlikely, (2) quantification of products is easier than with small particle resin and (3) it is easy to remove insoluble remnants of reagents after reactions. (Because lanterns do not require small mesh filtration for washing.) Several types of polymer-supported amines synthesized from the corresponding nitrobenzenes were converted into quinazoline-2-thioxo-4-ones **7** in excellent purity[8] (Scheme 2, Table 1). In the case of hindered 2-aminocinnamic acid on solid support (entry 4), the cyclization did not occur at all after the thiourea formation. The cyclization proceeded with 20% piperidine/DMF treatment to give the quinazoline-2-thioxo-4-one derivative in high purity. The yields were not high probably because the product was partly captured by benzyl cation on lanterns.



Scheme 2.

Table 1
Synthesis of quinazoline-2-thioxo-4-ones from various aniline derivatives

Entry	NO_2–R–OH	7		9	
		Purity[a] (%)	Yield[b] (%)	Purity[a] (%)	Yield[b] (%)
1	4-Nitrobenzoic acid	>95	35	>95	82
2	4-Nitrocinnamic acid	>95	40	>95	76
3	3-Nitrocinnamic acid	>95	90	>95	97
4[c]	2-Nitrocinnamic acid	86	46	83	76
5[d]	4-Nitrophenol	>95	38	>95	65

[a] Reverse-phase HPLC was carried out using rapid water/acetonitrile (0.04% TFA) linear gradients from 5% organic to 98% organic component over 5 min. Flow: 2 mL/min. Column: Waters Symmetry C_{18} (3.5 μm) 4.6×50 mm. HPLC purities were determined by summation of integrated HPLC peak areas at $(210+3N)$ nm, $N=0$–30.

[b] Crude yields based on the theoretical loading weight of target molecules.

[c] An additional treatment with 20% piperidine/DMF for 30 min was required for cyclization of the thiourea derivative.

[d] Mitsunobu reaction using DIAD/Ph_3P/DCM was used instead of DIC/HOAt treatment.

Furthermore, we investigated the derivatizations of quinazoline-2-thioxo-4-ones **6** using alkyl halides, as the *S*-alkylated byproducts using the Wang resin suggested that such *S*-alkylations could proceed easily on solid supports. After testing several bases (2,6-di-*tert*-butylpyridine, K_2CO_3/18-crown-6, DIEA) and solvents (DCM, NMP), *S*-alkylation with DIEA/NMP was found to give the best results. As shown in Table 1, the products **9** were obtained with excellent purity using allyl bromide. Encouraged by these results, we examined alkylations using various alkylating reagents (Scheme 2, Table 2). The following types of alkylating reagents gave high purity products **11**; allyl bromide type (entries 6, 7), benzyl bromide type (entries 8, 9), alpha-carbonylmethyl bromide type (entries 10, 11), alkyl iodide and bromide types (entries 12, 13, 14). Excellent results were also obtained for the SnAR reactions (entries 15, 16). All the product structures were confirmed by ESI mass spectrometer. Yields of compounds in Table 2 ranged from 78 to 100% based on the theoretical loading weights of target molecules.

Table 2
Alkylation of the quinazoline-2-thioxo-4-one with various alkyl- and arylhalide

Entry	R–X	**11**	
		Purity (%)	Yield (%)
6	Allyl bromide	>95	82
7	Cinnamyl bromide	>95	67
8	2,6-Difluorobenzyl bromide	>95	85
9	2-(Bromomethyl)naphthalene	>95	94
10	Methyl bromoacetate	>95	78
11	4-Methoxyphenacyl bromide	>95	88
12	Iodomethane	>95	95
13	1-Iodo-3-methylbutane	>95	91
14	(2-Bromoethyl)benzene	87	100
15	2,4-Dinitrofluorobenzene	>95	79
16	2-Fluoro-5-nitrobenzaldehyde	92	79

In conclusion, we have successfully developed a strategy for the solid-phase synthesis of quinazoline-2-thioxo-4-ones. Treatment of amines with 2-methoxycarbonylphenyl isothiocyanate usually gave the corresponding quinazoline-2-thioxo-4-ones. In some cases, treatment with base was required for the cyclization. Importantly, careful selection of solid support linkers is critical to avoid *S*-alkylation. Furthermore, the subsequent *S*-alkylations and *S*-arylations of quinazoline-2-thioxo-4-ones were performed with a wide range of reagents to give products with excellent purity.

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5. Wang resin (*p*-benzyloxybenzyl alcohol, 100–200 mesh, loading 0.87 μmol/g) was purchased from Novabiochem (http://www.nova.ch).
6. If compounds were derivatized from, e.g. 4-(bromomethyl)phenoxyethyl polystyrene available from Novabiochem, such byproducts should not be generated.
7. SynPhase™ lanterns are available from Mimotopes (Clayton, Victoria, Australia). The type of Lantern used in this report was SP-PS-D-HMP (long chain hydroxymethyl phenoxy linker), loading 35 μmol/lantern.

8. Representative procedure. The *p*-nitrobenzoic acid bearing SynPhase™ (SP-PS-D-HMP, loading 35 μmol/lantern) was put into 2.5 mL syringes.[9] After reduction of the nitro group with $SnCl_2 \cdot 2H_2O$/NMP/EtOH (1.0 g/2.0 mL/0.1 mL) for 16 h, the lantern was washed with DMF (2 mL×3) and DCM (2 mL×3), and dried under vacuum for 1 h. The amino group was reacted with 2-methoxycarbonyl phenylisothiocyanate/NMP (193 mg/2 mL) at ambient temperature for 16 h, and the lantern was washed with DMF (2 mL×3) and DCM (2 mL×3), and dried under vacuum for 1 h. Additionally, the lantern was reacted with allylbromide/DIEA/NMP (0.5 mmol/174 μL/2 mL) for 16 h and washed with DMF (2 mL×3) and DCM (2 mL×3). The lantern was treated with 95% TFA/H_2O for 1 h and the solution was concentrated with Genevac evaporater.[10] The residue was dissolved with 50% CH_3CN/H_2O and lyophilized to give the product (Table 2, entry 6) in 82% yield based on the theoretical loading weight of the target molecule. ^{1}H NMR (Varian VXR-300S, 300 MHz, $CDCl_3$): δ 3.87 (dd, J=6.9, 0.9 Hz, 2H), 5.16 (d, J=10.2 Hz, 1H), 5.32 (dd, J=17.0, 1.3 Hz, 1H), 5.87–6.10 (m, 1H), 7.26–7.47 (m, 3H), 7.64 (d, J=8.4 Hz, 1H), 7.74–7.80 (m, 1H). MS m/z 339 $(M+1)^+$.
9. Disposable polypropylene/polyethylene syringes are available from Aldrich (Milwaukee, WI).
10. Genevac HT-8 available from Genevac Limited (Farthing road, Ipswich, IP1 5AP, UK).