Pergamon

Tetrahedron Letters 42 (2001) 1749–1752

TETRAHEDRON LETTERS

Solid-phase synthesis of 1,3-disubstituted 2-thioxoquinazoline-4-ones using S_NAr reaction

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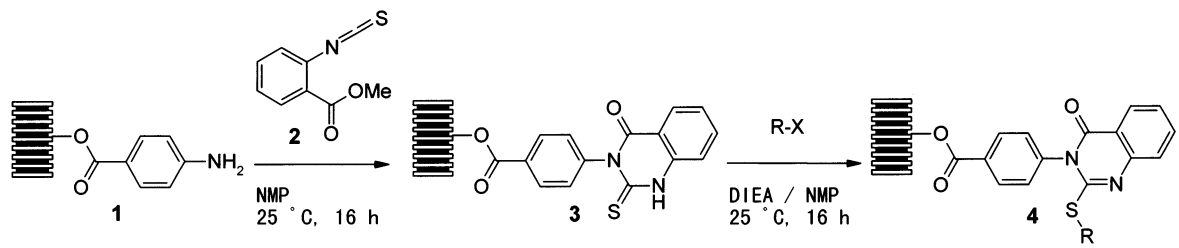
Received 16 November 2000; revised 21 December 2000; accepted 22 December 2000

Abstract—We have developed a solid-phase synthesis of diverse 1,3-disubstituted 2-thioxoquinazoline-4-ones. In this synthesis, the fluorine atom on support-bound 2-fluoro-5-nitrobenzoyl amides was substituted with various primary amines, followed by cyclization with thiocarbonyldiimidazole. Since 1-substitutions can be achieved with primary amines, diverse 1,3-disubstituted 2-thioxoquinazoline-4-ones can be efficiently synthesized using this method. Although solid-phase synthesis of 2-thioxoquinazoline-4-ones using 2-methoxycarbonylphenylisothiocyanate has been reported previously, the introduction of 1-substitutions could not be achieved due to the reactivity of the 2-sulfur atom with alkyl or aryl halide.

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 in particular has been a focus of recent investigations with application toward a variety of drug targets.[2] Among heterocycles we are particularly interested in the synthesis of quinazolines, which have shown a wide range of pharmacological activities.[3] As part of our project to develop efficient synthetic methods for quinazoline derivatives,[4] we have investigated the solid-phase synthesis of 2-thioxoquinazoline-4-ones. Although diverse 2-thioxoquinazoline-4-ones **4** can be obtained using a previous method as shown in Scheme 1,[4] introduction of 1*N*-substitutions on 2-thioxoquinazoline-4-ones **3** was not possible as *S*-substitutions proceed faster than 1*N*-substitutions. Therefore, novel solid-phase chemistry that allows the synthesis of 1,3-disubstituted 2-thioxoquinazoline-4-ones has been developed. Previously, various heterocycles, such as benzimidazoles,[5] benzopiperazinones,[6] macrocycles[7] and 1,4-benzothiazepin-5-ones[8] have been synthesized using fluoronitrobenzoic acid as a key building block. However, to the best of our knowledge, this strategy has not been applied to the solid-phase synthesis of 2-thioxoquinazoline-4-ones. Therefore, we decided to develop the chemistry to synthesize 1,3-disubstituted 2-thioxoquinazoline-4-ones using 2-fluoro-5-nitrobenzoic acid **5** (Scheme 2).

Synphase™ Lanterns bearing 4-aminobenzoic acid ester **1** were prepared as previously described.[4a] Coupling of 2-fluoro-5-nitrobenzoic acid **5** using *N*,*N*′-diisopropylcarbodiimide (DIC)/1-hydroxy-7-azabenzotriazole (HOAt) gave the amide **6** with high purity according to LC-MS analysis after cleavage. Activation of **5** prior to addition of the Lantern was important to prevent



Scheme 1.

Keywords: solid-phase synthesis; 2-thioxoquinazoline-4-one; S_NAr reaction.

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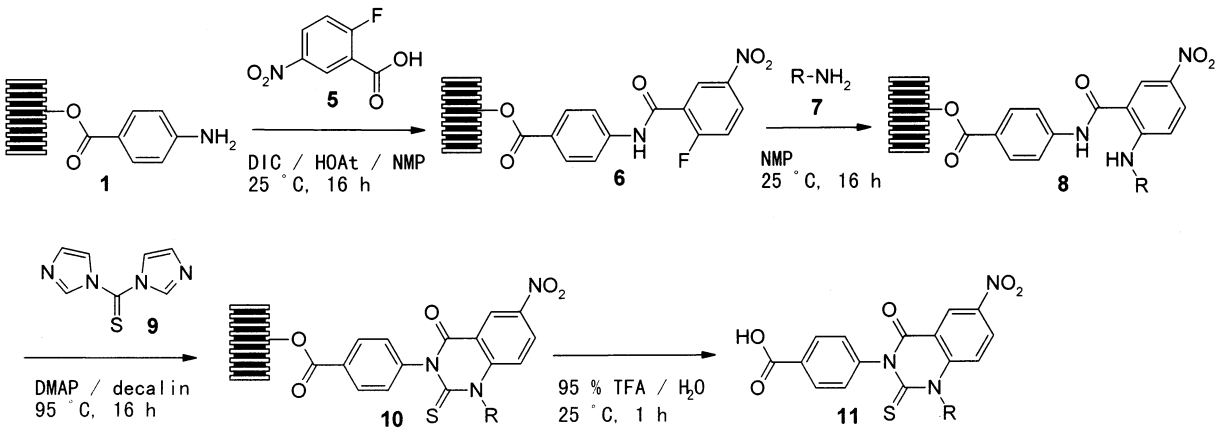
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00008-9

amine **1** from undergoing inadvertent S_NAr reaction with **5**, and from reacting with DIC to give guanidinyl byproduct. S_NAr reaction of **6** with alkyl amines **7** proceeded smoothly at 25°C to give **8** with high purity (entries 1–5 in Table 1). Although a higher temperature (80°C) was required, **8** was also obtained with aryl amines (entries 6 and 7). Next, cyclization of **8** by thiocarbonylation was attempted. Since the electron withdrawing nitro group lowered the nucleophilicity of the substituted aniline function of **8**, the cyclization was expected to be slow. After testing several reagents (thiophosgene, thiocarbonyldiimidazole {TCDI}), solvents (NMP, CH_2Cl_2, dioxane, toluene, decalin[9]) and temperatures (25–95°C), reaction with TCDI in decalin at 95°C was found to give the best result. However, 15% of **8** was not converted into **10** even when R was *n*-propyl. Therefore, thiocarbonylation with various additives such as 1*H*-tetrazole, pyridine, 2,6-lutidine and 4-dimethylaminopyridine (DMAP) was examined to find DMAP as the best additive. Various 1*N*-substituted compounds were synthesized with high purity using this solid-phase protocol[10] (entries 1–7 in Table 1). Several solid-phase bound arylamines were also tested (entries 8–10). Although the 2-thioxoquinazoline-4-one was obtained from 3-aminobenzoic acid ester and 4-aminophenylacetic acid ester with high purity (entries 8 and 9), 4-aminocinnamic acid ester gave a product with lower, but acceptable purity (entry 10). This lower purity was mainly due to the Michael addition of imidazole to cinnamic acid ester.[11] In addition, the nitro group of **10** was reduced to give aryl amine **12** for the third point derivatization (Scheme 3). **12** was reacted with phenylisocyanate and tosyl chloride to give **13** (purity 94%, yield 99%) and **14** (purity 89%, yield 85%), respectively.

All the product structures in this manuscript were confirmed by ^1H NMR and LC–MS (ESI mass spectrometer). Yields of compounds ranged from 59 to 100% (8.7–14.4 mg) based on the theoretical loading weights of target molecules.

In conclusion, solid-phase chemistry that allows the synthesis of 1,3*N*-disubstituted 2-thioxoquinazoline-4-ones was developed using the S_NAr reaction as the key reaction step. The approach is important for exploring quinazoline analogues as drug targets, as this chemistry can provide diverse 1,3-disubstituted 2-thioxoquinazoline-4-ones that could not be synthesized with the previously reported methods.[4a]



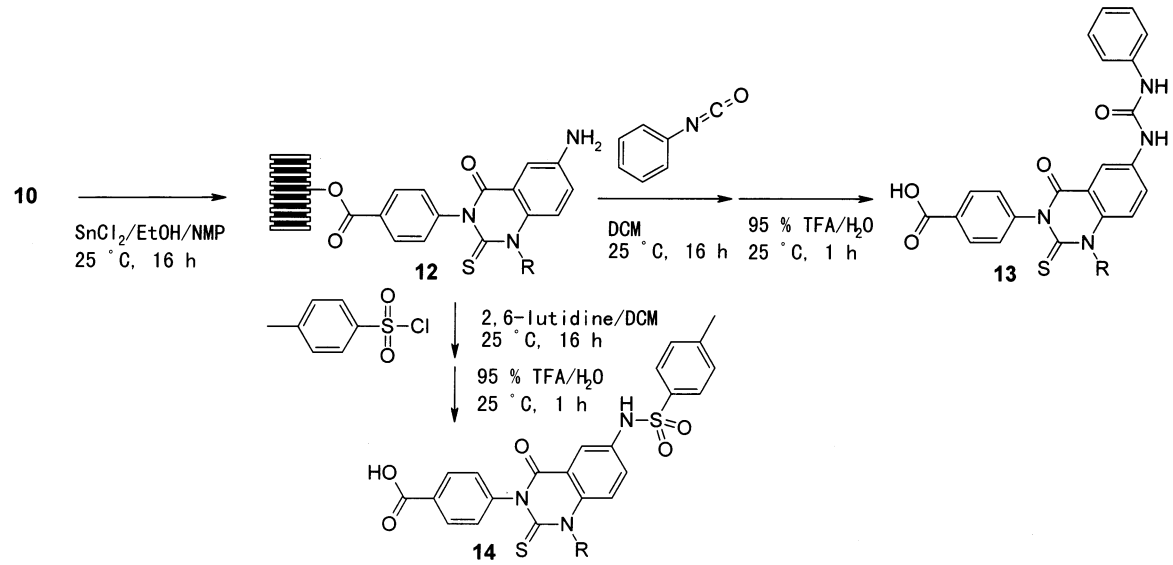
Scheme 2.

Table 1. Various 1,3-disubstituted 2-thioxoquinazoline-4-ones synthesized according to Scheme 2

Entry	Solid-supported amine **1**	Amine **7**	**11**	
			Purity[a] (%)	Yield[b] (%)
1	4-Aminobenzoic acid	*n*-Propylamine	>95	99
2	4-Aminobenzoic acid	Isopropylamine	83	100
3	4-Aminobenzoic acid	Cyclopropylamine	>95	91
4	4-Aminobenzoic acid	Cyclobutylamine	>95	83
5	4-Aminobenzoic acid	Cyclopentylamine	>95	100
6	4-Aminobenzoic acid	Aniline	>95	59
7	4-Aminobenzoic acid	3,4,5-Trimethoxyaniline	>95	65
8	3-Aminobenzoic acid	*n*-Propylamine	>95	85
9	4-Aminophenylacetic acid	*n*-Propylamine	85	86
10	4-Aminocinnamic acid	*n*-Propylamine	68	104

[a] Reverse-phase HPLC was carried out using 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+3*N*) nm, $N=0$–30.

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



Scheme 3.

Acknowledgements

We would like to thank Andrew Bray, at Mimotopes Pty Ltd, for improving this manuscript.

References

1. Reviews: (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555; (b) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385.
2. (a) Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937; (b) Hanessian, S.; Yang, R. Y. *Tetrahedron Lett.* **1996**, *37*, 5835; (c) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997; (d) Buckman, B. O.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 4439; (e) Gouilleux, L.; Fehrentz, J.-A.; Winternitz, F.; Martinez, J. *Tetrahedron Lett.* **1996**, *37*, 7031; (f) Shao, H.; Colucci, M.; Tong, S.; Zhang, H.; Castelhano, A. L. *Tetrahedron Lett.* **1998**, *39*, 7235.
3. (a) de Laszlo, S. E.; Quagliato, C. S.; Greenlee, W. J.; Patchett, A. A.; Chang, R. S. L.; Lotti, V. J.; Chen, T.-B.; Scheck, S. A.; Faust, K. A.; Kivlighn, S. S.; Schorn, T. S.; Zingaro, G. J.; Siegl, P. K. S. *J. Med. Chem.* **1993**, *36*, 3207–3210; (b) Hutchinson, J. H.; Cook, J. J.; Brashear, K. M.; Breslin, M. J.; Glass, J. D.; Gould, R. J.; Halczenko, W.; Holahan, M. A.; Lynch, R. J.; Sitko, G. R.; Stranieri, M. T.; Hartman, G. D. *J. Med. Chem.* **1996**, *39*, 4583.
4. (a) Makino, S.; Suzuki, N.; Nakanishi, E.; Tsuji, T. *Tetrahderon Lett.* **2000**, *41*, 8333; (b) Makino, S.; Suzuki, N.; Nakanishi, E.; Tsuji, T. *Synlett* **2000**, 1670.
5. Phillips, G. B.; Wei, G. P. *Tetrahedron Lett.* **1996**, *37*, 4887.
6. Morales, G. A.; Corbett, J. W.; DeGrado, W. F. *J. Org. Chem.* **1998**, *63*, 1172.
7. Kiselyov, A. S.; Eisenberg, S.; Luo, Y. *Tetrahedron* **1998**, *54*, 10635.
8. Nefzi, A.; Ong, N. A.; Giulianotti, M. A.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron Lett.* **1999**, *40*, 4939.
9. Due to the high boiling point (189–191°C), decalin is not used as often in solution phase chemistry as lower boiling point non-polar solvents such as toluene. However, we believe decalin is a useful solvent for solid-phase chemistry as it can be easily removed by filtration and washing.
10. Representative procedure. The 4-aminobenzoic acid ester bearing SynPhase™ Lantern (SP-PS-D-HMP, loading 35 μmol/lantern)[12] was placed into a 2.5 mL syringe.[13] After 2-fluoro-5-nitrobenzoic acid (1.0 mmol) was activated with DIC/HOAt/NMP (0.5 mmol/1.0 mmol/2 mL) at 25°C for 1 h, this solution was added to the lantern and the syringe was shaken for 16 h. The lantern was washed with dry DMF (2 mL×3) and dry CH_2Cl_2 (2 mL×3), and dried under vacuum for 1 h. After *n*-propylamine/NMP (200 μL/1.0 mL) was added to the lantern, the lantern was shaken for 3 h and washed with DMF (2 mL×3) and CH_2Cl_2 (2 mL×3). Then, the lanterns were placed into 4 mL glass vials capped with Teflon sheet. To the lantern was added TCDI/DMAP/decalin (100 mg/100 mg/2.0 mL) and the mixture was heated to 95°C using a Flex-Chem Incubator[14] with gentle shaking for 16 h. The lantern was washed with DMF (2 mL×3) and CH_2Cl_2 (2 mL×3), and dried under vacuum for 1 h. The lantern was treated with 95% TFA/H_2O for 1 h and the solution was concentrated with Genevac evaporator.[15] The residue was dissolved with 50% CH_3CN/H_2O and lyophilized to give the product (13.4 mg, entry 1 in Table 1) in 99% yield based on the theoretical loading weight of the target molecule. ^1H NMR (Varian VXR-300S, 300 MHz, $CDCl_3$): δ 1.11 (d, $J=7.2$ Hz, 2H), 1.14 (d, $J=7.5$ Hz, 2H), 1.86–2.01 (m, 3H), 7.33 (d, $J=8.1$ Hz, 2H), 7.49 (d, $J=9.0$ Hz, 1H), 8.29 (d, $J=8.4$ Hz, 2H), 8.61 (dd, $J=2.7$, 9.6 Hz, 1H), 9.10 (d, $J=2.7$ Hz, 1H). MS m/z 386 $(M+1)^+$.
11. Treatment with 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) could

cause β-eliminations to remove imidazole, however, the purity was decreased due to unknown byproducts.

12. SynPhase™ Lanterns are available from Mimotopes (Clayton, Victoria, Australia). The type of lantern used in this communication was SP-PS-D-HMP (long chain hydroxymethyl phenoxy linker), loading 35 μmol/lantern.
13. Disposable polypropylene/polyethylene syringes are available from Aldrich (Milwaukee, WI).
14. FlexChem rotating oven, Model 404, http://www.robsci.com
15. Genevac HT-8 available from Genevac Limited (Farthing Road, Ipswich, IP1 5AP, UK).