Pergamon

Tetrahedron Letters, Vol. 38, No. 10, pp. 1729-1732, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00182-2

A General and Efficient Solid Phase Synthesis of Quinazoline-2,4-diones

Mikhail F. Gordeev,* Hon C. Hui, Eric M. Gordon, and Dinesh V. Patel
Versicor, Inc., 270 East Grand Ave., South San Francisco, CA 94080

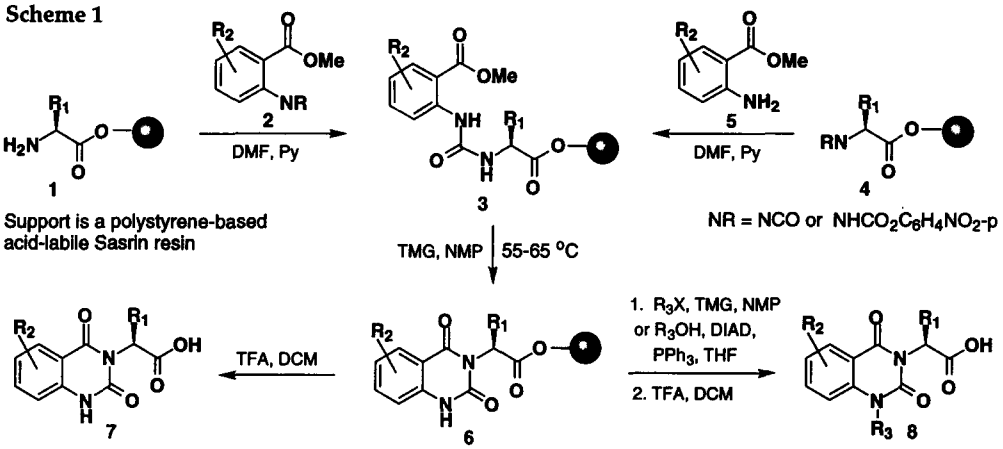
Abstract: *An efficient solid phase synthesis of chiral quinazolinediones is described. Immobilized amino acid based urea derivatives* **3** *undergo a racemization-free heterocyclization upon gentle heating in presence of tetramethylguanidine to afford fused pyrimidine-2,4-diones* **6**, *which are smoothly N^1-alkylated under mild conditions to produce immobilized quinazolinediones* **8**. *The method is amenable to combinatorial synthesis and offers broad scope for structural and chemical diversity, as illustrated by preparation of fused thieno[2,3-d]pyrimidine-2,4-dione* **10** *and hydroxamate pharmacophore bearing quinazolinedione derivative* **11**.

Combinatorial chemistry is a rapidly emerging drug discovery tool, with increasing emphasis on the design and synthesis of libraries of small-sized, non-peptidic molecules.[1] In this context, methodologies for solid phase synthesis (SPS) of drug-like organic entities that were previously synthesized individually *via* solution methods is becoming a critical prerequisite to preparation of corresponding libraries.[2] In this communication, we report a general method for SPS of chiral quinazoline-2,4-diones.[3] Fused pyrimidine-2,4-diones are important heterocyclic pharmacophores: examples include natural purine bases, alkaloids, and pteridines. Benzo derivatives in this series (quinazoline-2,4-diones, QDs) bear ample precedence as potent ligands and inhibitors of receptors and enzymes of pharmaceutical interest.[3,4]

Our SPS of QDs commences with preparation of immobilized ureas **3** obtained *via* acylation of resin bound amino acids **1** with *ortho*-methoxycarbonyl aryl isocyanates or activated carbamates **2**. Alternatively, ureas **3** can also be generated by reaction of anilines **5** with immobilized amino acid-derived isocyanates or activated carbamates **4** (Scheme 1).[5] Initial attempts to achieve heterocyclization of immobilized ureas **3** to QDs **6** using a recently reported solution synthesis protocol[6] (NaOH in water/1,4-dioxane, 50 °C) resulted in ester cleavage and loss of the material from the Sasrin resin.[7] After some experimentation, efficient heterocyclization was achieved by gentle heating of the tethered urea precursor **3** with 5% tetramethylguanidine (TMG) in N-methylpyrrolidine-2-one (NMP) overnight at 55-65 °C.[8] The reaction conditions were optimized using gel-phase ^{13}C NMR. Thus, acylation of Sasrin tethered ^{13}C-2 labeled L-valine **1** (R_1 = iPr) with *ortho*-methoxycarbonyl phenyl isocyanate **2** (R_2 = H, NR = NCO) resulted in an upfield shift of the ^{13}C-2 valine signal from δ 59.0 ppm for the starting amine to δ 57.3 ppm for the corresponding tethered urea **3** in C_6D_6 gel. Next, heterocyclization with 5% TMG in NMP at 60 °C proceeded efficiently to generate the QD **6** (R_1 = iPr, R_2 = H) as evident by the upfield shift of the ^{13}C-2 signal (δ = 58.3 ppm). After cleavage from Sasrin resin[7]

with 1% TFA in DCM, the crude product **7a** was isolated in ca. 90% yield, and found to be 95% pure by HPLC analysis, in agreement with ^1H and ^{13}C NMR and ESI MS data. Similar sequence of transformations was repeated using different amino acid **1** and isocyanate or activated carbamate **2** building blocks (BBs) to generate a diverse collection of QDs.[9] The crude compounds **7** were typically isolated in high yields with HPLC purity of 90-98% (Table 1).

Scheme 1



Alkylation of immobilized N^1-unsubstituted QDs **6** can be accomplished under mild reaction conditions (alkyl halides R_3X in the presence of TMG in NMP, r.t., overnight; or Mitsunobu-type reaction with alcohols R_3OH in presence of diisopropyl azodicarboxylate and Ph_3P in THF, r.t., overnight) to produce the corresponding N^1-substituted products **8** in high yield and purity (Scheme 1, Table 1). These simple procedures compare favourably with earlier SP alkylations of QDs[3b] and structurally related 1,4-benzodiazepine-2-ones[10] which employ lithium oxazolidinone as a base under strictly anhydrous conditions. Thus, structurally and chemically diverse alkylating reagents can be successfully used for modifications at the N^1 position of the pyrimidine-2,4-dione heterocycle (Table 1). Incorporation of hydrophobic as well as hydrophilic functionalities is readily achieved by employing alkylating agents with appropriately protected functionalities (acidic, basic, amide, ester, alcohol, etc.). In general, this SPS route well tolerates variations around the QD template, and enables the preparation of diverse heterocyclic derivatives.

Since the SPS employs a strong base TMG (pK_a for the conjugated acid of ca. 13.6) under thermal conditions during the cyclization step, the potential for racemization of amino acid derived chiral center cannot be ruled out. To investigate this, Sasrin resin immobilized dipeptide H-L-Phe-L-Ala-Sasrin was converted to the corresponding QD **9a**. To our satisfaction, a single product was obtained, and no additional diastereomer was detected by HPLC and ^1H NMR analysis.[11]

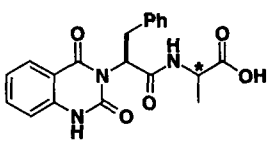
The new SPS method for QDs has been successfully extended to preparation of heterocyclic ring fused pyrimidine-2,4-diones by employing heterocyclic amino esters in place of the anthranilic acid derivatives, as demonstrated by the synthesis of thieno[2,3-d]pyrimidine-2,4-dione **10** from Sasrin resin immobilized L-alanine and *para*-nitrophenyl carbamate derivative of methyl 3-aminothiophene-2-carboxylate.

Table 1. Solid Phase Synthesis of Quinazoline-2,4-diones **7**and **8**

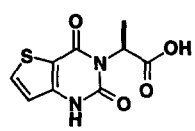
Compd. #	R_1[a]	R_2[b]	R_3[c]	HPLC purity, %[d]
7a	i-Pr (^{13}C)[e]	H	H	95 (91)[f]
7b	i-Bu	7-MeO_2C	H	93
7c	$MeSCH_2CH_2$	H	H	92
7d	p-$HOC_6H_4CH_2$	H	H	97
7e	$H_2NCH_2(CH_2)_4$	H	H	98
7f	(Indol-3-yl)CH_2	H	H	92
7g	$HOOCCH_2CH_2$	6,7,8-$(MeO)_3$	H	97
7h	$H_2NOCCH_2CH_2$	H	H	90
7i	$PhCH_2$	H	H	97 (88)[g]
8a	H_2NOCCH_2	H	Me	91
8b	$PhCH_2$	H	p-$(MeOC_6H_4)CH_2$	94 (90)[h]
8c	$PhCH_2$	H	H_2NCOCH_2	93
8d	$PhCH_2$	H	HO_2CCH_2	93
8e	$PhCH_2$	6-Cl	(c-C_3H_5)CH_2	98
8f	$PhCH_2$	6-Cl	o-$NCC_6H_4CH_2$	91
8g	$PhCH_2$	6-Cl	$HO(CH_2)_3$	79
8h	$PhCH_2$	6-Cl	(Morpholin-4-yl)CH_2CH_2	84
8i	$PhCH_2$	6,7,8-$(MeO)_3$	(Pyrrolidin-1-yl)CH_2CH_2	90
8j	$PhCH_2$	7-MeO_2C	PhO_2CCH_2	85

[a]All QDs were made with L-amino acids. Side chains[9] were deprotected with 5% TES - 40% in DCM. [b]QDs **7a,c-f,h-d** were made with isocyanate, and other QDs - from anthranilic acid - derived Pnp - carbamates. [c]Alkylating reagents R_3X: R_3I in syntheses of **8a,c**; R_3Br for **8d,e**; R_3Cl in other cases; $tBuO_2CCH_2Br$ used in the synthesis of **8d**. QDs **8h,i** made in DMSO with $Bu_4N^+I^-$. [d]Crude products, detection at 220 nm. [e]Prepared from ^{13}C-2 labeled Val. [f]Purity for QD made via tethered Pnp-carbamate. [g]Purity for QD made via tethered isocyanate. [h]Purity for QD made from (p-$MeOC_6H_4)CH_2OH$ via Mitsunobu reaction.

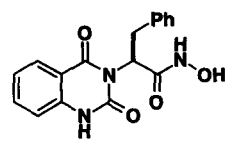
Our interest in the discovery of novel metallo-enzyme inhibitors prompted us to investigate synthetic routes for preparation of QDs bearing a hydroxamic acid pharmacophore. Thus, Fmoc-L-Phe-OH was coupled (HOBt, DIC, NMP) to immobilzed alkoxyamine reagent (H_2N-O-Sasrin) prepared *via* Mitsunobu coupling of N-hydroxyphthalimide to the Sasrin alcohol resin with subsequent deprotection with methylhydrazine in THF,[12] and subjected to the usual conditions for QD formation. The crude product was purified by preparative TLC to afford the expected QD hydroxamate **11** in 60% yield.[13]



9a (* S)
9b (* R)



10



11

This strategy of incorporating desired pharmacophoric groups onto heterocyclic scaffolds using functionalized polymeric supports should find general use in the preparation of focused libraries for lead development and structure activity relationship studies.

In conclusion, an efficient and general solid phase synthesis of quinazoline-2,4-diones has been developed. The novel method allows for introduction of the high degree of chemical and structural diversity onto the heterocyclic scaffold. The general synthetic route has been extended to preparation of other fused pyrimidine-2,4-diones, and to preparation of quinazoline-2,4-diones bearing a hydroxamate pharmacophoric group.

Notes and References:

1. See, e.g., reviews: (a) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385; (b) Gordon, E. M. *Current Opinion in Biotechnology*. **1995**, *6*, 624; (c) Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*; 144; (d) Patel, D. V.; Gordon, E. M. *Drug Discovery Today*. **1996**, 134; (e) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555; (f) Hermkens, P. P. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron.* **1996**, *52*, 4527; (g) Patel, D. V.; Gordon, E. M. *Drug Discovery Today*. **1996**, *1*, 134; (g) Gordeev, M. F.; Patel, D. V. In: Combinatorial Chemistry and Molecular Diversity in Drug Discovery. Eds. E. M. Gordon and J. F. Kerwin. **1996**, in press.
2. SPS offers unsurpassed advantages in comparison with traditional solution phase methodologies, such as high chemical efficiencies resulting from application of excess reagents, easy split-pool manipulations, and biological testing of nanomolar amounts of materials both in immobilized and solution phase formats.
3. Recently, two different SPS of quinazoline-2,4-diones were reported: a) Smith, A. L.; Thomson, C. G.; Leeson, P. D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1483; b) Buckman, B. O.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 4439. Both of these routes require immobilizations of anthranlic acids derivatives. The method in the first reference is limited to preparation of 7-hydroxyquinazoline-2,4-diones resulting from use of the phenolic group as a site of immobilization, whereas the second synthesis employs relatively harsh thermal conditions (125 °C, 16 h) potentially incompatible with labile building blocks and functional groups (such as dipeptides, hydroxamates, etc.), and does not allow for preparation of polymer bound QDs due to the heterocyclization mode involving cyclization at the linker ester group with simultaneous release of quinazoline-2,4-diones from the resin. No SPS of chiral quinazoline-2,4-dione amino acid derivatives has been previously reported.
4. MDL Drug Data Registry database, by MDL Informations Systems, Inc., San Leandro, U.S.A.
5. While immobilized isocyanates can be easily generated from tethered amino acids with triphosgene or phosgene in toluene in excess of base (2,6-lutidine, 0 °C to r.t., 2 h), amino acid-derived p-nitrophenyl carbamates are generally preferred reagents due to their relative hydrolytic stability and ease of handling in the air. For previous application of the tethered activated carbamates in SPS of ureas, see also Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1994**, *35*, 4055.
6. Cannonne, P.; Akssira, M.; Dahdouh, A.; Kasmi, H.; Boumzebra, M. *Heterocycles.* **1993**, *36*, 1305.
7. Polystyrene-based 2-methoxy-4-alkoxybenzyl alcohol resin: Mergler, M.; Tanner, R.; Gosteli, J.; Grogg, P. *Terahedron Lett.* **1988**, *29*, 4005.
8. The SPS of QDs was conveniently performed using the CombiChem oven (by Stovall Life Sci., Inc).
9. The SPS allows one to employ a large number of commercially available immobilized amino acids. Thus, the following side-chain protected amino acids pre-loaded on Sasrin resins were smoothly converted into respective QDs: Tyr(tBu), Lys(Boc), Trp(Boc), His(Trt), Glu(tBu), Asn(Trt), Gln(Trt).
10. Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997.
11. Additional experiments with TMG over extended periods of time gave similar results. Notably, isomeric to the compound **9a** QD, **9b** analogously prepared from L-Phe-D-Ala-Sasrin resin was readily distingusihed from the product **9a** by ^{1}H NMR data. Analytical data for the compound **9a:** MS (m/z): 382.1 $[M+H]^+$. ^{1}H NMR in CD_3OD (δ, ppm): 1.33 (d, J = 7.5 Hz, 3 H), 3.40-3.60 (m, 2 H), 4.48 (m, 1 H), 5.82 (m, 1 H), 7.00-7.20 (m, 7 H), 7.58 (m, 1 H), 7.90 (dd, J = 7.8 and 1.2 Hz, 1 H). ^{1}H NMR data for the diastereomer **9b** in CD_3OD (δ, ppm): 1.43 (d, J = 7.2 Hz, 3 H), 3.48-3.60 (m, 2 H), 4.49 (m, 1 H), 5.83 (m, 1 H), 7.00-7.20 (m, 7 H), 7.58 (m, 1 H), 7.89 (dd, J = 8.1 and 1.5 Hz, 1 H).
12. While this manuscript was in preparation, a similar solid phase approach to hydroxamates appeared in the literature: Floyd, C. D.; Lewis, C. N.; Patel, S. R.; Whittaker, M. *Tetrahedron Lett.* **1996**, *37*, 8045.
13. Analytical data for QD **11:** MS (m/z): 326.0 $[M+H]^+$. ^{1}H NMR in CD_3OD (δ, ppm): 3.72 (m, 2 H), 6.02 (m, 1 H), 7.20-7.38 (m, 7 H), 7.78 (dd, J = 8.1 and 3.9 Hz, 1 H), 8.04 (d, J = 8.1 Hz, 1 H).

(*Received in USA* 6 *December* 1996; *revised* 21 *January* 1997; *accepted* 22 *January* 1997)