

A Practical Solid Phase Synthesis of Quinazoline-2, 4-diones

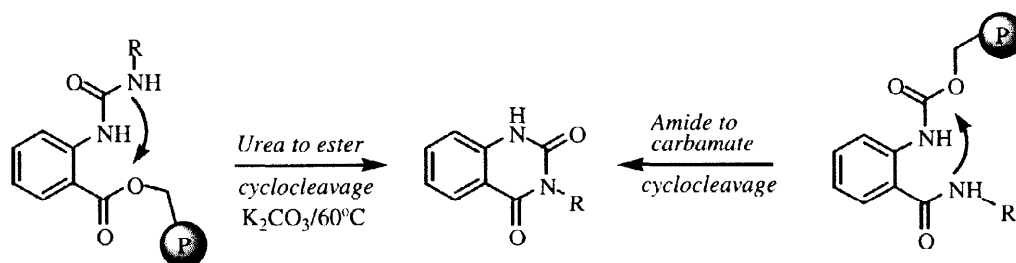
Hui Shao[†], Marcus Colucci, Shaojing Tong, Hesheng Zhang, and Arlindo L. Castelhana*

Cadus Pharmaceutical Corporation
777 Old Saw Mill River Road, Tarrytown, NY 10591

Received 2 July 1998; accepted 17 July 1998

Abstract. We describe a practical solid phase synthesis of quinazoline-2,4-diones using a short-chain, high loading capacity, polyethyleneglycol polystyrene copolymer ("PEG₄-PS" resin). The highlights of this synthesis include efficient acyl azide formation on the solid phase, Curtius rearrangement, and cyclocleavage with K₂CO₃ followed by simple product isolation. © 1998 Elsevier Science Ltd. All rights reserved.

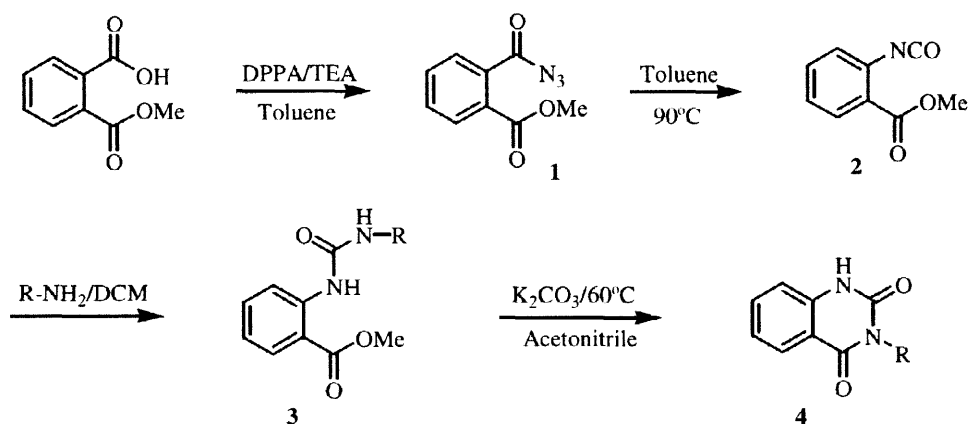
Solid phase organic synthesis is emerging as a powerful tool in the rapid synthesis of small molecule, compound libraries for drug discovery.¹ A common approach is to express molecular diversity on key heterocyclic templates such as benzodiazepines, pyrrolidines, beta-lactams, and 4-thiazolidinediones.¹ The quinazolinodione template appears in a wide range of bioactive molecules that interact with G-protein coupled receptors (GPCRs; adrenergic, serotonergic, dopaminergic, endothelin ET_A), and enzymes (cyclooxygenase, collagenase, aldose reductase, and carbonic anhydrase).² Solid phase library synthesis that incorporates the quinazolinodione template utilize two strategies.³ In each case, starting with anthranilic acids, diversity is added in a combinatorial manner followed by quinazolinodione formation and simultaneous product release from the resin (cyclocleavage) either urea to ester or amide to carbamate-directed, *vis.*,



The cyclocleavage reaction is an elegant and practical approach to build heterocycle systems. We were interested in developing conditions that would induce cyclocleavage at or near room temperature and amenable to robotic handling. Previous syntheses of quinazolinodiones involve harsh conditions (125°C in DMF or KOH in ethanol) or use organic bases (tetramethylguanidine at 60°C), complicating product purification.³ The approach to quinazolinodiones described herein, uses phthalic half-esters as an additional source of anthranilates,⁴ explores the diversity of primary amines, and utilizes a short chain PEG linker for solid phase synthesis and K₂CO₃ to induce cyclocleavage.

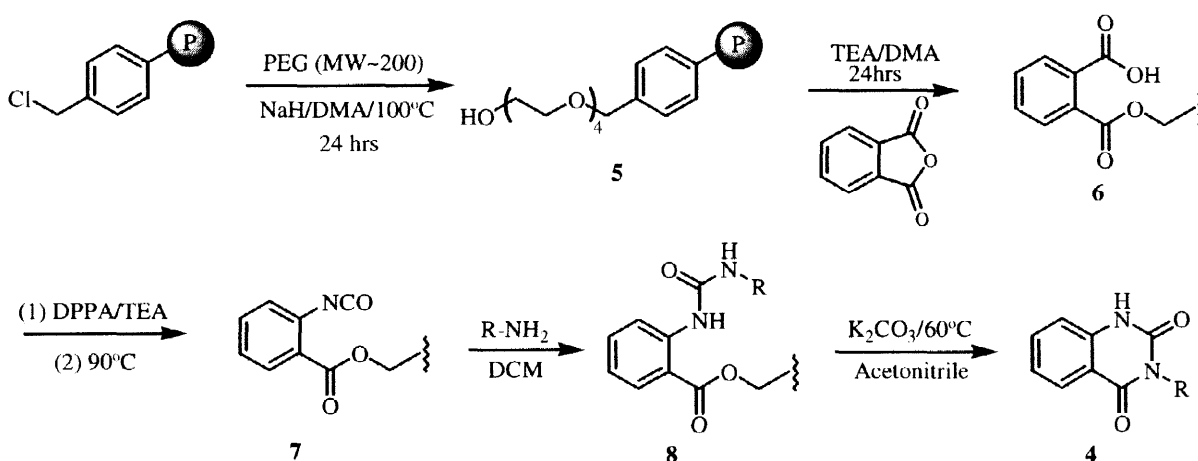
Preliminary synthetic evaluation in solution, involved converting phthalate monomethyl ester to the acyl azide **1** with diphenylphosphoryl azide (DPPA), followed by Curtius rearrangement to give cleanly isocyanate **2** (Scheme 1).⁵ The isocyanate intermediate was transformed into urea **3** in the presence of a primary amine and

the key cyclization step occurred in high yield with powdered K_2CO_3 in toluene, DMF, or acetonitrile at $60^\circ C$, with quinazoline-2,4-dione **4** isolated after simple filtration.



Scheme 1

The development of a suitable linker for solid phase synthesis led us to a graft copolymer of short chain polyethyleneglycol-polystyrene⁶ (~200 Da, approximately 4 units of ethylene glycol; "PEG₄-PS" resin **5**). We find this resin to be a useful and superior solid support than commercial PEG-based resins because of high loading (both hydroxyl terminals of the long PEG chains (>800 Da) tend to react with chloromethylated polystyrene⁶ and the long PEG chains tend to break down under certain reaction conditions contaminating the desired product. As shown in *Scheme 2*, the linker was introduced on Merrifield resin using the sodium salt of PEG (10 equiv.).⁷ The "PEG₄-PS" resin was then acylated with excess phthalic anhydride (4 eq) and triethylamine in N, N-dimethylacetamide (DMA) and the immobilized carboxylic acid was converted to acyl azide using DPPA (4 eq) and TEA in toluene at room temperature over two hours.⁸ The corresponding acyl azide was transformed to isocyanate **7** in toluene at $90^\circ C$ for 4 hours. The conversion of azide to isocyanate was monitored by FT-IR.⁹

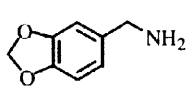
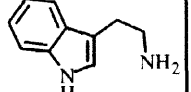
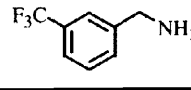
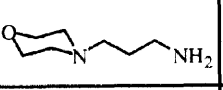
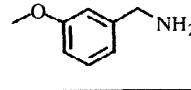
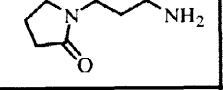
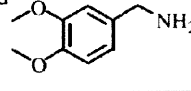
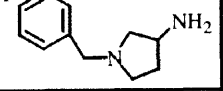
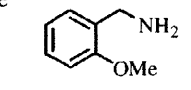
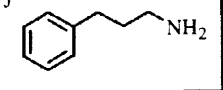
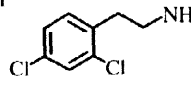
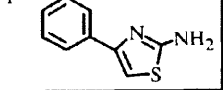


Scheme 2

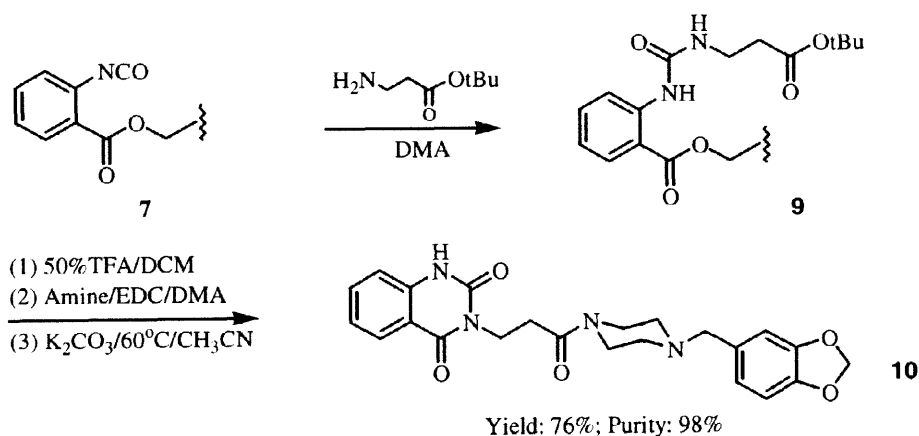
With automated parallel synthesis, the intermediate isocyanate **7** was partitioned and reacted with a set of primary amines (4 eq) to give the corresponding ureas **8**.¹⁰ The quinazolinediones **4** were then generated in acetonitrile in the presence of K_2CO_3 at $60^\circ C$. The cyclization was completed within 24 hours. Methylene

chloride was then added to precipitate trace amounts of K_2CO_3 dissolved in the acetonitrile and the solution of crude product was filtered robotically and concentrated under reduced pressure. Since no organic base was involved in the final step and only the urea intermediate undergoes the cyclocleavage reaction, the products are of excellent purity (> 90%) and isolated in >70% yield (from isocyanate **7**) as shown in Table 1.

Table 1. Examples of cyclocleavage reactions on solid phase

R-NH ₂	Purity (%)	Yield (%)	R-NH ₂	Purity (%)	Yield (%)
	98	76		98	80
	95	75		96	77
	97	80		93	72
	98	72		95	72
	93	73		91	80
	94	77		94	81

While commercial phthalides for solid phase library synthesis are limited, molecular diversity can be extended enormously by using bifunctional amines. For example, as shown in Scheme 3, O-protected β -alanine reacted with isocyanate **7** to give urea **9**. Hydrolysis of the *tert*-butyl ester and coupling of the resulting carboxylic acid with a variety of amines provided **10** and congeners after cyclocleavage.¹¹



Scheme 3

REFERENCES AND NOTES:

† Current address: Bdlg 86/9, Hoffman-La Roche, 340 Kingsland Street, Nutley, NJ 07110

- For recent reviews on solid phase organic synthesis, see: (a) Balkenhohl, F.; von dem Bussche-Hunnefeld; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288. (b) Thompson, L.A.; Ellman, J.A. *Chem. Rev.* **1996**, *96*, 555. (c) Special issue, *Acc. Chem. Res.* **1996**, *29*.
- For recent examples, see: (a) Russo, J. *Med. Chem.* **1991**, *34*, 1850. (b) 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. (c) Zgombick, 1995, *Eur. J. Pharmacol. Mol. Pharmacol. Sect.* **1995**, *291*, 9. (d) Kotani, T.; Nagaki, Y.; Ishii, A.; Konishi, Y. *J. Med. Chem.* **1997**, *40*, 684. Recently, 3,6-substituted quinazolinones were described as fibrinogen receptor antagonists, see: Liverton, N. J.; Armstrong, D. J.; Claremon, D. A.; Remy, D. C.; Baldwin, J. J.; Lynch, R. J.; Zhang, G.; Gould, R. J. *Bioorg. & Med. Chem. Lett.* **1998**, *8*, 483.
- (a) Buckman, B.O.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 4439. (b) Smith, A.; Thomson, C.G.; Leeson, P.D. *Bioorg. & Med. Chem. Lett.* **1996**, *6*, 1483. (c) Gouilleux, L.; Fehrentz, J.A.; Winternitz, F.; Martinez, J. *Tetrahedron Lett.* **1996**, *37*, 7031. (d) Gordeev, M.F.; Hui, H.C.; Gordon, E.M.; Patel, D.V. *Tetrahedron Lett.* **1997**, *38*, 1729.
- Canone, P.; Akssira, M.; Dahdouh, A.; Kasmi, H.; Boumzebrra, M. *Heterocycles* **1993**, *36*, 1305.
- (a) Bonjouklian, R.; Ruden, R.A. *J. Org. Chem.* **1977**, *42*, 2095. (b) Chantegrel, B.; Gelin, R.A. *Synthesis* **1981**, 315.
- Bayer, E. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 113. As far as we can ascertain, this resin has not been exploited for solid phase organic synthesis.
- The graft copolymer of short-chain PEG-PS was made in 75 gram scale: To a stirred solution of polyethylene glycol (300 gram, 1.50 mole) in DMA (500 ml) was added sodium hydride (30 gram, 60% in mineral oil) slowly at 0°C. Merrifield resin (75 gram, 2.0-2.5mmol/g, 1% cross-linked chloromethylated styrene/divinylbenzene copolymer) was then added under N₂. The resulting slurry was stirred at 100°C for 24 hours. The resin was subsequently washed with 2 X 1:1 DMF-H₂O, 2 X DMF, 3 X 5% HCl/ H₂O, 3 X H₂O, 2 X MeOH, 3 X DCM, and dried over high vacuum overnight. The substitution on the resin was over 96% determined by element analysis of chlorine composition, and the loading capacity is as high as 1.8mmol/g based on the weight increase of polymer.
- We found the use of DPPA on the solid phase more efficient than the traditional combination of activated acids and NaN₃.⁴
- When the acyl azide was formed, the corresponding absorption peak (2135 cm⁻¹) was observed in diffuse reflectance analysis of FT-IR. After the Curtius rearrangement occurred, a new peak of aromatic isocyanate (2260 cm⁻¹) was observed.
- The isocyanate on "PEG₄ resin" was prepared on a large scale in a peptide synthesis vessel. This resin (80mg to each well) was transferred to 96-well reaction block in ACT 496 synthesiser. The resin was suspended in DMA (2 ml) with the primary amine (50 mg in each well) for 4 hours, then washed and mixed with pre-grounded K₂CO₃ powder (50 mg to each well) in acetonitrile (1.5 ml) for cyclization at 60°C for 24 hours. DCM (1ml) was added to each well at room temperature and the resulting solution was collected by filtration under pressure. The crude product was obtained after concentration and analyzed by LC-MS directly. The yields were calculated based on the nitrogen composition of isocyanate on resin by element analysis. For example, compound **4l**, ¹H-NMR (200MHz), δ 7.05 (m, 1H), 7.25 (m, 1H), 7.50 (m, 6H), 7.70 (s, 1H), 7.90 (m, 1H), 8.15 (m, 1H); LC-MS, [M+H]=322.40, purity is 94% based on LC trace.
- We have also used the "PEG₄-PS" resin and the K₂CO₃ cyclocleavage conditions to build an hydantoin library at room temperature, see also: (a) Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 6090. (b) Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937.