Pergamon

Tetrahedron Letters, Vol. 37, No. 30, pp. 5277-5280, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01103-3

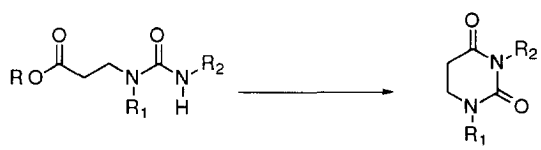
Solid-Phase Synthesis of 5,6-Dihydropyrimidine-2,4-diones

Stephen A. Kolodziej and Bruce C. Hamper*

Ceregen Division of Monsanto Corporation
800 North Lindbergh Blvd., St. Louis, MO 63167

Abstract: A series of 1,3-disubstituted-5,6-dihydropyrimidine-2,4-diones **1** are prepared by solid phase organic chemistry using a cyclization-cleavage strategy from readily available amines and isocyanates. An acrylate ester of Wangs resin is treated with primary amines to afford N-substituted β-aminoesters followed by treatment with isocyanates to afford β-ureido ester **4**. Cyclization-cleavage of the bound ureido ester under acidic conditions gave direct formation of 5,6-dihydropyrimidinedione **1**. Copyright © 1996 Elsevier Science Ltd

Combinatorial synthesis methods, which allow the facile preparation of chemical libraries, are valuable tools for the discovery of new biologically active compounds.[1] The effort to prepare such libraries has led to an unprecedented growth in solid phase organic chemistry (SPOC), particularly for the preparation of small organic molecules.[2] Recent reports have appeared for the preparation of nitrogen heterocyclic compounds by SPOC which are amenable towards production of compound libraries.[3] Related pyrimidinones have been prepared by a solid phase three component Biginelli reaction.[4] The pyrimidinedione ring system is particularly attractive since it is known to be a core structural element of some recently discovered fungicides[5] and herbicides.[6] We required a straightforward method for the preparation of 5,6-dihydropyrimidinediones **1** that could be used to generate combinatorial libraries for our biological testing efforts.

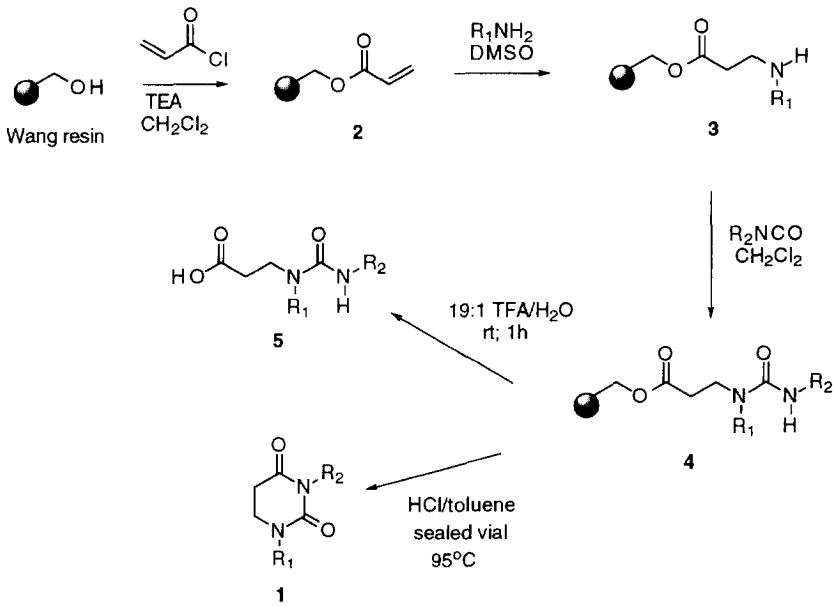


1

Previously reported solution phase approaches to **1** include condensations of ureas with α,β-unsaturated carboxylic acids,[7] and cyclizations of N-β-bromopropionyl ureas, N-acryloyl ureas and β-ureido esters.[8] The cyclization of β-ureido esters is particularly attractive for the development of a SPOC method since cyclization of ester linked intermediate **4** leads to the cleavage and formation of pyrimidinedione **1** (scheme). A similar cyclization-cleavage approach has been reported for the formation of hydantoins from resin bound α-ureido esters and benzodiazepines from resin bound imines.[9] Given that relatively few N-protected β-aminoacids are commercially available and that a variety of substituents on nitrogen were required for library synthesis, a method was developed that allows sequential introduction R_1 and R_2 as amines and isocyanates. Michael addition of a primary amine to acrylate **2** provided N-substituted-β-aminoesters which were treated with isocyanates to obtain the intermediate β-ureido ester. Pyrimidinediones **1** were subsequently obtained by acidic cyclization-cleavage from the resin.

Treatment of Wangs resin with either acryloyl chloride in the presence of triethylamine or acrylic acid and DCC provided acrylate resin **2**. The polymer bound acrylate was characterized by microscopy FTIR,[10] which showed complete disappearance of the hydroxyl OH stretch and the appearance of a C=O stretch at 1725 cm^{-1}.

Substituted β-aminoesters **3** were obtained by Michael addition of a six fold excess of the primary amine to the acrylate resin in DMSO. Reactions of unhindered alkyl amines with **2** were complete within 24 h while α-branched amines required longer reaction times or higher temperatures to drive the reaction to completion. Cleavage of **3** with 95% TFA afforded the TFA salts of the N-substituted-β-amino acids.[11] Progress of the reaction of amine **3** with an isocyanate was monitored by the isatin test.[12] The reactions were generally complete in 4 h using a two-fold excess of isocyanate in CH_2Cl_2. FTIR revealed the appearance of a new carbonyl stretch at 1650-1675 cm^{-1} as well as a broad N-H stretch between 3300-3400 cm^{-1} (table). Treatment of **4** with 95% TFA/H_2O yielded β-ureido acids **5**. In some cases, mixtures of **1** and **5** were obtained on reaction with TFA; the ratio dependent on the relative steric bulk of the R_2 group and the resultant ease of post-cleavage cyclization under acid conditions. For **4b** (R_2 = methyl) nearly exclusive formation of the cyclized product **1b** was obtained, whereas for **4c** (R_2 = isopropyl) only the expected urea **5c** is obtained. Resin bound urea **4a** (R_2 = phenyl) afforded a 3:1 mixture of the urea **5a** and pyrimidinedione **1a**.



Consistent cyclization of the ureido esters to pyrimidinediones was acheived by treatment of the resin with acidic solutions at higher temperatures. Treatment of **4a** with a saturated solution of dry HCl in ethanol in a sealed vial at 90-100°C gave **1a** in 60% yield. In an effort to increase the yield, we examined the effect of using solvents with different polymer swelling properties. Reaction of **4a** with 6N HCl at 95°C gave 10% of **1a**, while saturated HCl in toluene gave 95-99% yield of **1a** based on recovered weight and HPLC purity. While the crude products from each run appeared to consist of a single component by reverse phase HPLC, ^1H nmr and mass spectral analysis showed the presence of **1** contaminated by the HCl salt of the corresponding β-amino acid. This side product can be envisioned to arise from loss of isocyanate from **4** followed by acidolysis of the ester link to the resin. It is unlikely to occur from incomplete reaction of **3** with isocyanate since TFA cleavage of **4** did not yield any of the corresponding β-amino acid (by ^1H nmr or MS analysis). These HCl salts were

easily removed from the crude product by filtration through silica using 1:1 ethyl ether/CH_2Cl_2. The isolated yields of **1** (table) after silica filtration were 13-76% for a variety of R_1 and R_2 groups. Yields of cyclized product were generally higher for compounds having an alkyl group in the R_2 position (entries b,c,d,g,h,j) compared to phenyl which can be attributed to the increased nucleophilicity of the urea nitrogen bearing the R_2 group. The low yield obtained for **1e** is due to the relatively high amount of cross-linked product formed on addition of methylamine to two of the bound acrylates **2**. This tertiary amine is uneffected by the isocyanate treatment and either remains bound to the resin or is removed as the HCl salt during silica filtration.

Table.[11,13] Preparation of Polymer Bound β-Ureido Esters **4** and Pyrimidinediones **1**.

entry	R_1	R_2	Loading of **4** (mmole/g)	FTIR of **4** (cm^{-1})	Yield of **1**
a	benzyl	phenyl	0.65	3403, 3334 1730, 1672	46%
b	benzyl	methyl	0.65	3462, 3379 1731, 1653	69%
c	benzyl	iso-propyl	0.68	3436, 3367 1730, 1652	51%
d	benzyl	2-(CH_3)phenyl	0.67	3442, 3342 1730, 1673	44%
e	methyl	phenyl	0.44	3428, 3338 1731, 1678	37%
f	allyl	phenyl	0.65	3403, 3334 1731, 1674	51%
g	allyl	isopropyl	0.67	3436, 3377 1732, 1654	43%
h	isopropyl	isopropyl	0.67	3436, 3367 1729, 1647	63%
i	isobutyl	phenyl	0.65	3443, 3338 1731, 1673	13%
j	isobutyl	isopropyl	0.64	3451, 3368 1731, 1651	76%
k	2-phenylethyl	phenyl	0.63	3396, 3327 1729, 1673	45%
l	$CH_2CH_2CO_2Et$	isopropyl	0.61	3440, 3367 1732, 1654	69%

In summary, we have developed a generally applicable SPOC approach to the synthesis of 1,3-disubstituted-5,6-dihydropyrimidine-2,4-diones **1**. Conjugate addition of a primary amine to the polymer bound α,β-unsaturated ester **2** yielded the N-substituted β-amino ester **3**, which was further treated with an isocyanate to yield the β-ureido ester **4**. Acidolysis of the polymer-ester bond with TFA at room temperature yielded mixtures of the β-ureido ester **5** and cyclized product **1**, while reaction of **4** with saturated HCl-toluene at elevated temperatures in a sealed vial yielded **1** in yields of 13-76%.

Acknowledgments. The authors would like to thank Dr. E. Cortez for obtaining microscopy FT-IR spectra and Dr. Ron Smith for obtaining LC-MS data.

References and Notes

1. Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144-154.

2. Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96(1)*, 555-600; Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135-73.

3. For example: Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937-940 (hydantoins); Zhang, C.; Moran, E. J.; Woiwode, T. F.; Short, K. M.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 751-54 and Sarshar, S.; Siev, D.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 835-38 (imidazoles); Marzinzik, A. L.; Felder, E. R. *Tetrahedron Lett.* **1996**, *37*, 1003-06 (pyrazoles and isoxazoles); Gordeev, M. F.; Patel, D. V.; Gordon, E. M. *J. Org. Chem.* **1996**, *61*, 924-28 (pyridines), Goff, D. A.; Zuckermann, R. N. *J. Org. Chem.* **1995**, *60(18)*, 5748-9 and Meutermans, W. D. F.; Alewood, P. F. *Tetrahedron Lett.* **1995**, *36*, 7709-12 (isoquinolines); Ruhland, B. ; Bhandari, A. ; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253-4 (beta-lactams).

4. Wipf, P; Cunningham, A. *Tetrahedron Lett.* **1995**, *36*, 7819-22.

5. Ishii, T.; Motoyoshi, M. Japanese Patent 63-290867, **1988**.

6. Wright, T. R.; Fuerst, E. P.; Ogg, A. G., Jr.; Nandihalli, U. B.; Lee, H. J. *Weed Science* **1995**, *43(1)*, 47-54.

7. Fuchikami, T.; Yamanouchi, A.; Ojima, Iwao *Synthesis* **1985**, 766-768.

8. Johnson, H.W.Jr.; Lovins, R.E.; Reintjes, M. *J. Org. Chem.* **1959**, *24*, 1391-1392; Gabel, N.W.; Binkley, S.B. *J. Org. Chem.* **1958**, *23*, 643-645; Press, J.B.; Russell, R.K.; McNally, J.J.; Rampulla, R.A.; Falotico, R.; Scott, C.; Moore, J.B.; Offord, S.J.; Tobia, J. *Eur. J. Med. Chem.* **1991**, *26*, 807-813.

9. DeWitt, S.H.; Kiely, J.S.; Stankovic, C.J.; Schroeder, M.C.; Cody, D.M.R.; Pavia, M.R. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 6909-6913.

10. Yan, B.; Kumaravel, G.; Anjaria, H.; Wu, A.; Petter, R. C.; Jewell, C. F.; Wareing, J. R. *J. Org. Chem.* **1995**, *60*, 5736-5738.

11. Reactions of polymer bound materials were monitored by microscopy FTIR and elemental analysis of nitrogen. Loadings of **3** and **4** were determined by elemental analysis of nitrogen. Yield of **1** was based on the weight recovery and the loading of **3**. The cleavage products were also characterized by nmr, HPLC (detection at 220 nm, C18, gradient water-acetonitrile), LC-MS and mass spectral analysis.

12. Kaiser, E.; Bossinger, C.D.; Colescott, R.L.; Olser, D.D. *Analyt. Chemica Acta* **1980**, *118*, 149.

13. Solid phase synthesis of **1a**. In a dry vessel was added 0.5 g of Wang's resin (0.88 meq/g) in 4 mL of CH_2Cl_2. The slurry was treated twice with 200 μL of Et_3N followed by 100 μL of acryloyl chloride and allowed to stir for 2h at room temperature. After filtration, the resin was washed three times with each of the following solvents; CH_2Cl_2, MeOH, DMF, MeOH, DMSO. The resultant resin **2** was treated with 2 mL of DMSO and 0.28 g (2.6 mmole) of benzylamine and allowed to stir for 24 h. Washing three times each with DMSO, MeOH and CH_2Cl_2 afforded after filtration and air drying 0.54 g (0.74 meq/g) of resin **3a**. The resin (0.42 g, 0.31 mmole) was treated with 3 mL of CH_2Cl_2 followed by 0.10 g (0.8 mmole) of phenyl isocyanate at room temperature for 4 h and washed three times each with CH_2Cl_2, MeOH, CH_2Cl_2, and diethyl ether to afford **4a**. Polymer bound β-ureido ester **4a** was placed in a glass vial with 4 mL of a satr' solution of HCl in toluene, capped and heated to 95°C for 4 h. After cooling, the resin was filtered, washed three times with MeOH and CH_2Cl_2, and the combined filtrates concentrated. The crude product was purified by silica chromatography (1:1, diethyl ether- CH_2Cl_2) to afford 39.7 mg (46%) of **3a**: ^{1}H nmr ($CDCl_3$) δ 2.89 (t, 2H, 6.8 Hz), 3.50 (t, 2H, 6.8 Hz), 4.73 (s, 2H), 7.25-7.54 (m, 10H).

(*Received in USA* 17 *April* 1996; *revised* 15 *May* 1996; *accepted* 16 *May* 1996)