

Solid Phase Synthesis of 1,4-Benzodiazepine-2,5-diones

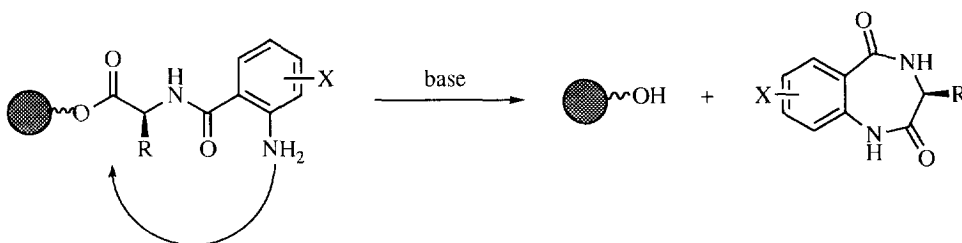
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Abstract. 1,4-benzodiazepine-2,5-diones were synthesized by a simple procedure utilizing polymer supported amino acids and o-nitrobenzoic acids or protected anthranilic acids. Cyclization of the common aminoamide intermediate with concomitant release from the support furnished the desired 1,4-benzodiazepine-2,5-diones. The products were recovered in high yields and exhibited excellent purities. Copyright © 1996 Elsevier Science Ltd

The synthesis of structurally diverse non-peptidic compounds has emerged as an important paradigm in modern drug discovery. With few exceptions solid phase synthesis has been the predominant method of choice for these applications.¹

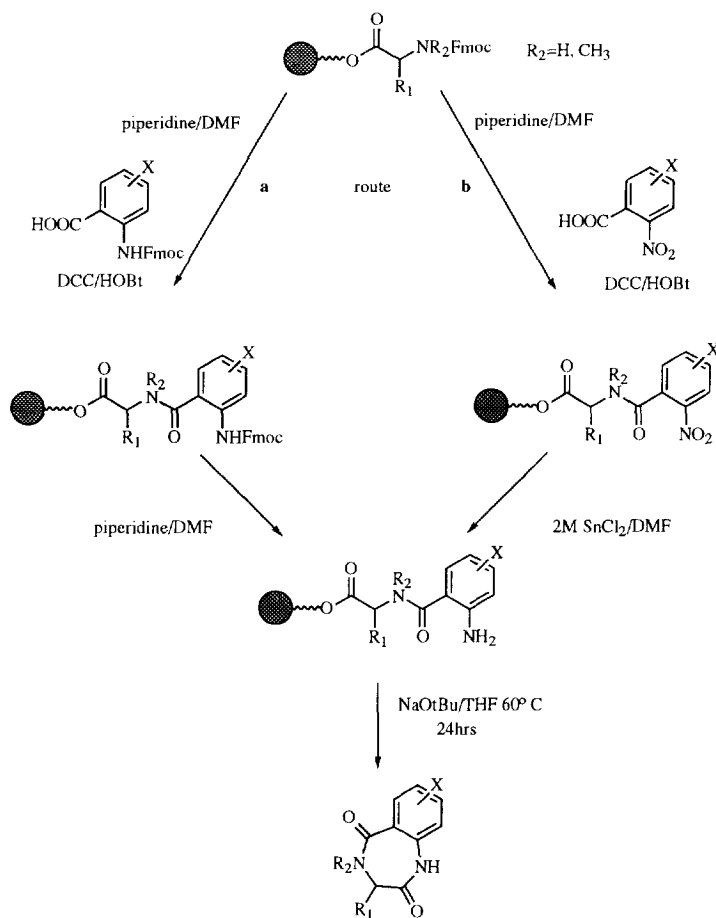
The 1,4-benzodiazepine-2,5-diones represent a versatile pharmacophore with a wide range of pharmaceutical utility which can function as opiate receptor antagonists,² anticonvulsant agents,³ glycoprotein mimics⁴ and cholecystokinin receptor antagonists.⁵ As such the 1,4-benzodiazepine-2,5-diones have been the target of several solid phase synthetic strategies.⁶



Scheme 1.

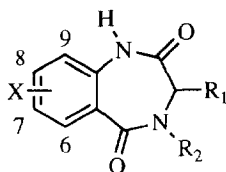
This report describes a short, expedient method allowing maximal diversity in the R and X substituents. Our approach utilizes commercially available Fmoc-amino acid derivatized Wang⁷ resins in combination with o-nitrobenzoic acids or protected o-anthranilic acids. The option of using either synthon within the reaction sequence permits a wider range of aromatic substituents than would otherwise be possible through a single route. The central feature of the strategy is a base promoted cyclization of the amino acid anthranilate intermediate to form and simultaneously release the 1,4-benzodiazepine-2,5-dione (Scheme 1). This ensures that only the desired, cyclized material is released from polymer support. A typical procedure is outlined in

Scheme 2. Fmoc amino acid derivatized Wang resins from commercial sources, or those prepared by published loading procedures were deprotected by two successive 20 minute treatments with 20% piperidine in dimethylformamide. Coupling of the *o*-anthranilic acid⁸ (route a) and *o*-nitrobenzoic acid (route b) synthons



Scheme 2. a) *o*-anthranilic acid route, b) *o*-nitrobenzoic acid route.

was carried out using 2 equivalents of the acid in the presence of diisopropylcarbodiimide in DMF for 2-4 hours and could be monitored in a majority of cases ($R_2=H$) by the ninhydrin test. Fmoc deprotection of the anthranilate intermediate (route a) was again achieved using a 20% piperidine/DMF treatment. Reduction of the *o*-nitro group (route b) by exposure of the resin to 2M $SnCl_2$ in DMF for five hours proceeded in nearly quantitative yield.⁹ Trifluoroacetic acid cleavage of a small sample of resin prior to and following the reduction indicated essentially quantitative conversion (>99% by HPLC analysis) to the amido-anthranilate intermediate.



Cmpd.	Starting Resin	Route	R1	R2	X	%yield	%purity
1	Fmoc-L-Ala	a	CH ₃	H	H	60	81
2	Fmoc-L-Val	a	CH(CH ₃) ₂	H	H	71	98
3	Fmoc-L-Leu	a	CH ₂ CH(CH ₃) ₂	H	H	79	94
4	Fmoc-D-Phe	a	CH ₂ Ph	H	H	64	95
4	Fmoc-D-Phe	b	CH ₂ Ph	H	H	66	99
5	Fmoc-L-MePhe	b	CH ₂ Ph	CH ₃	H	50	97
6	Fmoc-L-MeVal	b	CH(CH ₃) ₂	CH ₃	H	46	88
7	Fmoc-L-MeLeu	b	CH ₂ CH(CH ₃) ₂	CH ₃	H	59	93
8	Fmoc-D-Ala	b	CH ₃	H	7-OCH ₃	45	92
9	Fmoc-D-Ala	b	CH ₃	H	9-OCH ₃	60	95
10	Fmoc-L-Leu	a	CH ₂ CH(CH ₃) ₂	H	7-Br	80	86
11	Fmoc-L-Pro	b	-CH ₂ CH ₂ CH ₂ -		H	79	81

Table 1. Representative examples of 1,4-benzodiazepine-2,5-diones.

A number of cyclization conditions were evaluated, and optimal results were obtained by heating the resin in tetrahydrofuran with two equivalents of sodium-*t*-butoxide at 60 degrees for 24 hours.¹⁰ Substitution of dioxane for tetrahydrofuran and elevation of cyclization temperature to 90 degrees resulted in only a marginal improvement in yield. Conventional workup procedure consisted of filtration and extraction of the resin with EtOAc, washing the organic layer with several volumes of 5% sodium bicarbonate, drying with MgSO₄ and concentrating under reduced pressure. The compounds were characterized by ¹H-NMR and electrospray mass spectrometry.¹¹ Table 1 summarizes purity^{12a} and yield^{12b} data from a set of representative compounds. Both routes produced similar results in terms of these criteria (e.g. compound 4).

In summary we have developed a simple, easily automated procedure permitting introduction of a diverse array of substituents into both the aromatic and heterocyclic portions of the 1,4-benzodiazepine-2,5-dione skeleton. Additionally, the cyclative release feature of this approach results in a significant enhancement of final compound purity.

Acknowledgment

We thank Dr. Theodore Jones and Dr. Lawrence Melvin for their support and critical review of the manuscript, Mr. Michael Curtis for the synthesis of Fmoc protected anthranilic acids and Prof. Marvin H. Caruthers of The University of Colorado for valuable discussions and insights.

References and Notes

- Several excellent reviews highlighting advances in combinatorial chemistry have been published recently. These include a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. b) Special issue on combinatorial chemistry, *Acc. Chem. Res.*, **1996**, *29*, 111. c) Fruchtel, J. S.; Jung, G. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17. For solution-phase approaches to combinatorial chemistry see: Cheng, S.; Comer, D. D.; Williams, J. P.; Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 2567.
- Carabateas, P. M.; Harris, L. S. *J. Med. Chem.* **1966**, *9*, 6.
- Cho, N. S.; Song, K. Y.; Parkanyi, C. *J. Heterocycl. Chem.* **1989**, *26*, 1897.
- McDowel, R. S.; Blackburn, B. K.; Gadek, T. R.; McGee, L. R.; Rawson, T.; Reynolds, M. E.; Robarge, K. D.; Somers, T. C.; Thorsett, E. D.; Tischler, M.; Webb, R. R., II; Venuti, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 5077.
- Aquino, C. J.; Dezube, M.; Sugg, E. E.; Sherrill, R. G.; Willson, T. M.; Szewczyk, J. R. *Int. Pat. Appl.* WO 9528399.
- a) Boojamra, C. G.; Burow, K. M.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 5742. b) Goff, D. A.; Zuckermann, R. N. *J. Org. Chem.* **1995**, *60*, 5744. For an approach to this heterocycle using a novel "resin capture" strategy see: Keating, T. A.; Armstrong, R. W.; *J. Am. Chem. Soc.* **1996**, *118*, 257.
- Wang, S. S. *J. Am. Chem. Soc.* **1973**, *95*, 1328.
- Fmoc-anthranilic acid is commercially available from Advanced ChemTech (Louisville, KY), additional derivatives were prepared from the appropriate anthranilic acid and Fmoc-chloride.
- Meyers, H. V.; Dilley, G. J.; Durgin, T. L.; Powers, S. T.; Winsinger, N. A.; Zhu, H.; Pavia, M. R. *Molecular Diversity*, **1995**, *1*, 13.
- Analysis by chiral chromatography (Phenomenex Chirex column, 3.2 x 250mm, 60:35:5 hexane /dichloromethane /ethanol elution mixture with integration of peak areas at 254nm) revealed partial racemization under these reaction conditions. For example, cmpds. **2** and **3** exhibited enantiomeric excess values of 77% and 56% respectively.
- Selected compounds were purified by flash chromatography: silica gel, ethyl acetate/hexane. Cmpd **4**: ¹H-NMR (400MHz), DMSO-d₆) δ 10.40 (s, 1H), 8.49 (d, 1H, J=6Hz), 7.66 (d, 1H, J=6Hz), 7.51(dd, J=8Hz, J= 1.5Hz), 7.32-7.17 (m, 6H), 7.1 (d, 1H, J= 7.5Hz), 3.90 (ddd, 1H, J=5.5Hz, J=5Hz, J=5Hz), 3.14 (dd, 1H, J= 14Hz, J=5.5Hz), 2.86 (dd, 1H, J= 14Hz, J=5Hz). Electrospray mass spectral characterization: 267 [MH⁺], calc. : 266.
- a) Analysis was carried out by HPLC (Vydac C₁₈ column, 4.6 x 250mm, 0-50% acetonitrile/water containing 0.1% TFA with integration of peak areas at 220nm.) b) yields were calculated from the weight of crude material and the initial loading level of starting Wang resin.

(Received in USA 30 July 1996; revised 6 September 1996; accepted 10 September 1996)