Microwave Assisted Synthesis of Pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones#

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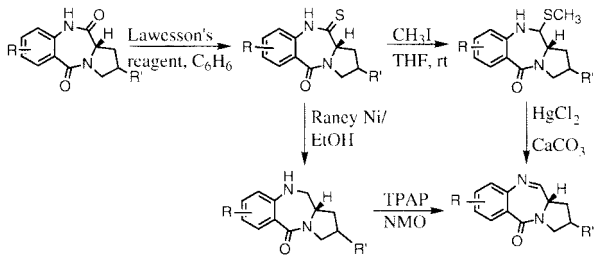
Abstract: In a simple microwave assisted and environmentally benign approach isatoic anhydride reacts readily with proline to afford pyrrolo[2,1-*c*][1,4]benzodiazepines-5,11-diones under solvent-free conditions.

Keywords: imines, dilactams, micro wave energy and cyclocondensation

In recent years there has been considerable interest in ring systems such as pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) that can recognize and bind to specific sequence of DNA.[1,2] These compounds have been obtained naturally from *streptomyces* species and have been synthesised with various structural modifications. Among the well known methods for the synthesis of these compounds imino thioether approach has been extensively employed for the synthesis of some naturally occurring PBD imines or their methyl ethers such as tomaymycin and chicamycin, and as well for the structurally modified synthetic PBDs.[3] In this method pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones have been used as the intermediates. Further, these dilactams are also precursors for the PBD cyclic secondary amines which have been recently employed by us for the preparation of PBD imines through TPAP oxidation method[4] (Scheme 1).

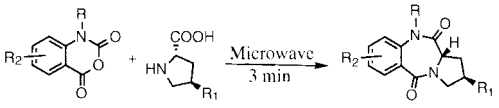


Scheme 1

There are mainly two methods known in the literature for the synthesis of these PBD dilactams. Firstly, one of the method is cyclocondensation of isatoic anhydrides with the corresponding proline in presence of DMF at temperatures ranging from 100 to 110 ^{0}C. Secondly, the other method is reductive cyclization of nitro and azido proline esters.[5a-c] The former method has been extensively utilised in the literature.[5d] Based on this approach another enzymatic process involving condensation of isatoic anhydride with proline in presence of catalase has been developed in this laboratory for the synthesis of PBD dilactams. Though this is performed under mild conditions while it is not suitable for large scale preparations.[5e]

Recently, the use of microwave energy[6] in organic synthesis has received much attention, in view of the mild, clean, convenient and spontaneity of the reaction process in comparison to the conventional solution phase reactions. There is an increasing interest in the use of environmentally benign reagents, conditions and in particular solvent-free procedures. This trend to avoid organic solvents during the organic reactions could lead to cleaner, efficient and economical processes. Microwave irradiation using commercial domestic ovens has recently been employed to accelerate many organic reactions[7] like esterification, etherification, oxidation, hydrolysis, Claisen, Diels-Alder, Reformatsky, Knoevenagel and Bischler-Napieralski reactions. The *in situ* generation of heat is very efficient and can be used to significantly reduce reaction times of numerous synthetically useful organic transformations.[8] Thus microwave assisted organic synthesis as mentioned above has several advantages over conventional processes. Moreover, these processes are energy efficient and generally lead to improved isolated yields of the desired product.

In the present work a microwave assisted process has been successfully developed for the synthesis of the non-covalent DNA-binding agents like pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones (PBD dilactams). Herein, we wish to report an improved solvent free preparation of PBD dilactams employing microwave energy. In this process isatoic anhydride and L-proline have been mixed thoroughly and irradiated for 2-3 min with one min intervals (Scheme 2).



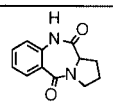
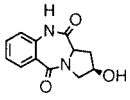
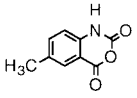
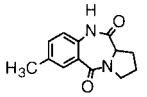
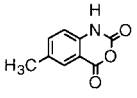
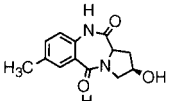
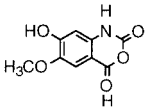
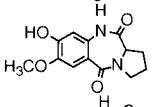
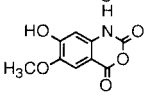
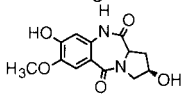
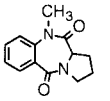
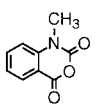
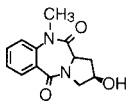
R = H, CH_3; R_1 = H, OH; R_2 = H, CH_3, OH, OCH_3

Scheme 2

In a typical procedure, a mixture of isatoic anhydride (0.163 g, 1.0 mmol) and L-proline (0.115 g, 1.0 mmol) is placed in a test-tube inside the alumina bath (heat sink) and the contents are irradiated in a microwave oven at full

power (600 W) for 3 min (3 x 1 min) with 1 min intervals. The reaction is monitored by TLC (ethyl acetate-hexane 6:4), and the reaction mixture is cooled to room temperature and charged on silicagel pad and eluted with ethyl acetate-hexane (7:3) to afford the PBD dilactam in 87% yield.

Table 1. Microwave assisted cyclocondensation of isatoic anhydride with L-proline

Entry	Starting materials	Product	Reaction time (min)	Yield (%)[a]
1			3	81
2			3	80
3			2	92
4			2	90
5			3	82
6			3	80
7			2	90
8			2	86

[a]Isolated yield

In conclusion, microwave assisted synthesis of pyrrolo[2,1-*c*][1,4]-sbenzodiazepine-5,11-diones proceeds in less than 3 min under mild, clean and efficient conditions. This condensation reaction which affords giving quantitative yields under solvent-free conditions is a practical alternative approach to the earlier reported methods.

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References and Notes

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(1) (a) Thurston, D.E. "Advances in the study of pyrrolo[2,1-*c*]-[1,4]benzodiazepine (PBD) Antitumour Antibiotics" in the 'Molecular Aspects of Anticancer Drug DNA Interaction', Neidle, S. Waring, M.J. Eds.; Macmillan, 1993, vol.1, pp. 54-88. (b) Hurley, L.H. and Needham-Van Devanter, D.R. *Acc. Chem. Res*. **1986**, *19*, 230 (c) Hurley, L.H. *J. Med. Chem*. **1989**, *32*, 2027.

(2) (a). Hartley, J.A.; Souhami, R.L. "DNA Sequence Specificity of Anticancer Agents", in Cancer Chemotherapy. (b). Frontiers in Pharmacology and Therapeutics Series, Hickman, J.A.,Tritton, T. Eds., Blackwell Scientific Ltd., 1993, pp 251-280.

(3) (a) Kaneko, T.; Wong, H.and Doyle, T.W. *Tetrahedron Lett*. **1983**, *24*, 5165. (b) Thuston, D.E. and Bose, D.S. *Chem. Rev.*, **1994**, *94*, 433. (c) Kamal, A.; Reddy, B.S.P.; Reddy, B.S.N. *Tetrahedron Lett*. **1996**, *37*, 2281. (d) Jones G.B.; Davey, C.L.; Jenkins, T.C.; Kamal, A.; Kneale, G.; Neidle, S.; Webster, G.D.; Thurston, D.E. *Anticancer Drug Design* **1990**, *5*, 249.

(4) (a) Kamal. A.; Howard, P.W.; Reddy, B.S.N.; Reddy, B.S.P.; Thurston, D.E. *Tetrahedron* **1997**, *53*, 3223. (b) Kamal, A.; Rao, M.V.; Reddy, B.S.N. *Khim. Geter. Soed.* (*Chem. Het. Comp.*) **1998**, 1588.

(5) (a) Kamal, A.; Reddy, B.S.P.; Reddy, B.S.N. *Tetrahedron Lett*., **1996**, *37*, 6803. (b) Kamal, A.; Reddy, B.S.N.; Reddy, B.S.P. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 1825. (c) Kamal, A.; Reddy, B.S.N. *Chem. Lett*. **1998**, 593. (d) Kamal, A.; Reddy, B.S.P.; Thurston, D.E. *Bioorg. Med. Chem. Let*. **1993**, *3*, 743. (e) Kamal, A. *J. Org. Chem*. **1991**, *56*, 2237.

(6) (a) Caddick. S. *Tetrahedron* **1998**, *51*, 10403. (b) Loupy. A.; Petit, A.; Hamelin. J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213. (c) Galema, S. A. *Chem. Soc. Rev*. **1997**, *26*, 233. (d) Abramovitch, R. A. *Org. Prep. Proced. Int*. **1991**, 685.

(7) Sluerga, D.; Gaillard. P, *Tetrahedron* **1996**, *52*, 5505.

(8) (a) Varma, R.S.; Dahiya, R.; Saini, K.R. *Tetrahedron Lett*. **1997**, *38*, 7029. (b) Varma, R.S.; Dahiya, R.; Saini, K.R. *Tetrahedron Lett*., **1997**, *38*, 8819. (c) Reddy, A.C.S.; Rao, P.S.; Venkataratnam, R.V. *Tetrahedron Lett.* **1996**, *37*, 2845. (d) Bougrin, K.; Bennoni. A.K.; Tetouani, S.F.; Soufiaoui, M. *Tetrahedron Lett*. **1994**, *35*, 377. (e) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Valdisera, L.; Laberga, L.; Rousell, J. *Tetrahedron Lett*. **1986**, *27*, 279. (f) Bogdal, D.; Pielichowski, J.; Boron, A. *Synlett* **1996**, 873.

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