Journal of the Chinese Chemical Society, **1997**, *44*, 597-600

Microwave Induced Synthesis of 3,4-Dihydro-2*H*-pyran-2-carboxaldehyde: A Versatile Linker for Solid Phase Combinatorial Library

Hsing-Pang Hsieh (謝興邦), Shui-Tein Chen* (陳水田) and Kung-Tsung Wang* (王光燦)
Institute of Biological Chemistry, Academia Sinica, Taipei, Taiwan 11529, R.O.C.

Procedures for the dimerization of acrolein to form 3,4-dihydro-2*H*-pyran-2-carboxaldehyde by microwave induced synthesis have been developed. Significant rate-enhancement and yield increase were observed. 3,4-Dihydro-2*H*-pyran-2-carboxaldehyde was obtained in 91% yield under microwave irradiation for 5 minutes instead of 39% yield by reacting at 190 °C for 40 min or at 160 °C for 4 hr.

INTRODUCTION

The preparation and screening of combinatorial libraries have become an attractive method for the discovery of pharmaceutical lead compounds over the past few years.[1] In general, the field of combinatorial chemistry focuses primarily on the synthesis of peptide and oligonucleotide libraries, and screening strategies for many pharmaceutical industries.[2] Furthermore, much of the work in developing techniques for solid-phase synthesis of combinatorial libraries has been documented.[3]

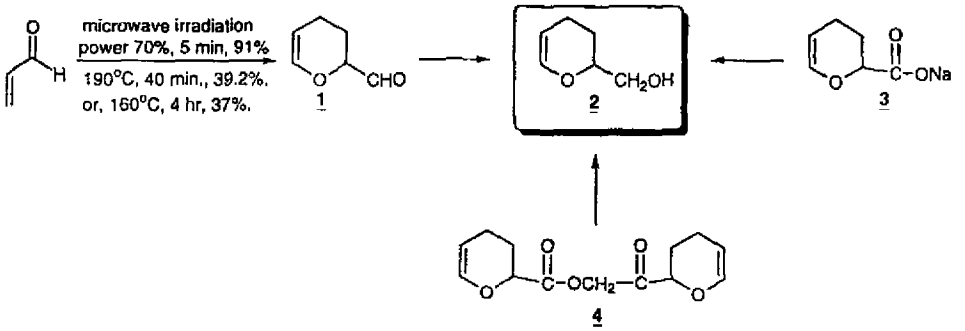
Recently, Ellman and his coworker first developed a dihydropyran (DHP) linker **2** to effectively synthesize aspartic acid protease inhibitors *via* DHP-Merrifield resin bound strategy.[4] They found out that dihydropyran-functionalized resin has high loading levels for primary and secondary as well as functionalized alcohols. More important, the tetrahydropyran (THP) ether linkage is quite stable to both strongly basic and nucleophilic reagents throughout solid phase synthesis conditions. However, since 3,4-dihydro-2*H*-pyran-2-methanol **2** was reported for solid phase synthesis of combinatorial libraries, the 3,4-dihydro-2*H*-pyran-2-carboxaldehyde **1**, 3,4-dihydro-2*H*-pyran-2-carboxylic acid, sodium salt **3**, and 3,4-dihydro-2*H*-pyran-2-yl-methyl 3,4-dihydro-2*H*-pyran-2-carboxylate **4** are all out of supply now.

Much of our ongoing research is focused on developing a series of bifunctional DHP linkers coupled with peptide and non-peptide alcohols for solid phase combinatorial libraries.[5] However, **1** is our original starting material which could be obtained *via* thermal dimerization of acrolein by heating at 190 °C for 40 min[6] or at 160 °C for 4 hr[7] with yields less than 40%. During the last few years, we have introduced a rapid method of microwave heating for the facile preparation of protein and peptide hydrolysates prior to amino acid analysis.[8] Furthermore, we have also applied microwave irradiation to several organic reactions in a continuous-flow process.[9] The rapid heating capability of a microwave oven could lead to a considerable saving in dissolution time and may eventually replace some conventional heating protocols.[10] We describe herein a new method for the preparation of 3,4-dihydro-2*H*-pyran-2-carboxaldehyde **1** by microwave-assisted self-dimerization.

RESULTS AND DISCUSSIONS

Using a household microwave oven to irradiate a sus-

Scheme I



pension containing acrolein (1.0 gr.), H_2O (3%), acetaldehyde (5%), and hydroquinone (0.05%) in sealed Teflon tubes (volume of 5 mL) for 3-5 minutes at 50% of full power, the yield of 1 increased to 91% without the formation of any colored byproducts. When a similar acrolein suspension was heated at 190 °C for 40 minutes or 160 °C for 4 hours,[6-7] a deep-brown-colored byproduct appeared in reaction solution with large amounts of starting acrolein. Fig. 1 shows the chromatograms of the reaction mixtures analyzed by gc. Aliquotes were taken out and diluted with methanol before being injected to gc. Fig 1a, 1b, 1c, and 1d correspond to starting material, under microwave irradiation for 4 min, under microwave irradiation for 5 min, and 160 °C for 4 hours, respectively.

This is the first report of microwave assisted Hetero-Diels-Alder dimerization of acrolein. The side reaction that resulted in a brown colored reaction solution is dependent on the reaction time and temperature. The rapid transfer of heat *via* microwave irradiation shortened the reaction time and subsequently reduced the possibility of side reaction. In conclusion, the microwave-irradiation procedure not only shortens the reaction time but also increases the yield of product. In addition, the simple reaction protocol of a microwave reactor provides an advantage over the application of the current commercial linker for the solid phase combinatorial library.

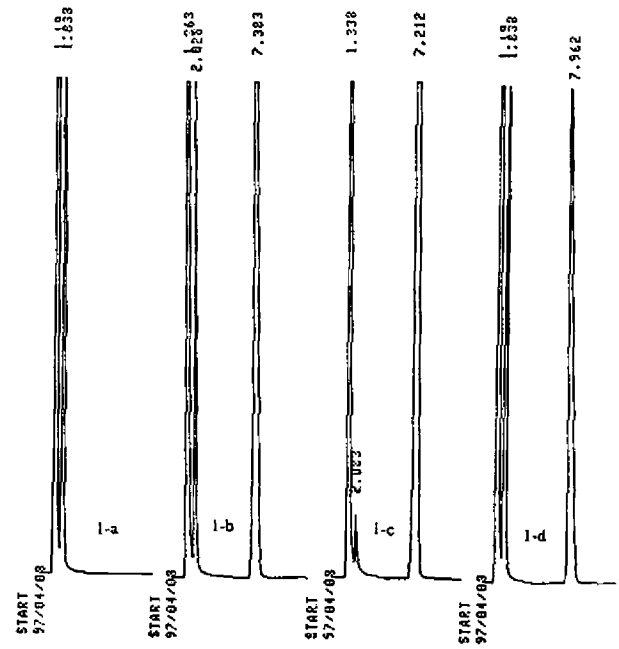


Fig. 1. The analysis of the reaction products by gc use a 10% of SE 30 coated silica-column, with injector at 120 °C, column at 60 °C, FID detector at 150 °C. Fig. 1-a: starting material, (MeOH, 1.1 min, acrolein, 1.9 min); Fig. 1-b: microwave irradiation for 4 min (1, 7.3 min, 57%); Fig. 1-c: microwave irradiation for 5 min (1, 7.2 min, 91%); Fig. 1-d: reaction at 160 °C for 4 hours (acrolein, 1.8 min, 45%; 1, 7.9 min, 47%).

EXPERIMENTAL SECTION

General

Nuclear magnetic resonance spectra were acquired on Bruker AM-400 spectrometer at 302K. All NMR samples were prepared in $CDCl_3$. Chemical Shift (δ) are expressed as parts per million (ppm) relative to $\delta(CDCl_3) = 7.24$ ppm for ^1H NMR. A G.C. (Chinese Gas Chromatography, TAIWAN) equipped with FID detector, and Ranian integrater with 10% SE-30 column was used for the analysis. All solvents are ACS reagent grade or HPLC grade from ALPS Chem Co. (TAIWAN). Acrolein was purchased from Fluka Chem. Co. (Switzerland); acetaldehyde was obtained from Aldrich Chem. Co. (USA); hydroquinone was acquired from TCI Chem. Co. (Japan); and sodium tripolyphosphate was bought from Hanawa Chem. Co. (Japan). We ordered the custom-made thick-walled telfon vials (6 mm in thickness) from a local glass-plastic shop according to the design as shown in Fig. 2. Previous experience with pyrex tubes as vials in the reaction indicated that the high pressure and temperature readily induced in the sealed tubes by the microwave oven easily caused explosion of the reaction tubes inside the microwave oven. Each teflon vial can contain up to 5 mL of reaction solution and is equipped with a silicon septum and a cap made of the same teflon material. The microwave oven used was a commercially produced cooking apparatus without any modification (Tatung microwave

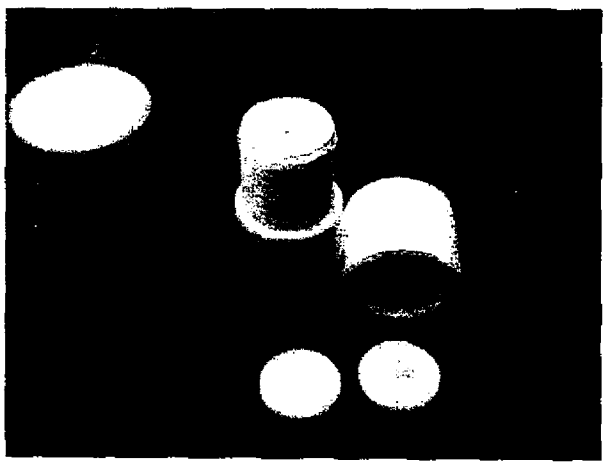


Fig. 2. Telfon vials used for microwave irradiation reactions.

oven TMO-110, Tatung Co., Taipei, Taiwan). The total power of the microwave was 650 W with nine power settings, the lowest of which was 72 W. In this study, 20% to 70% full power was used.

Conventional Preparation of 3,4-Dihydro-2*H*-pyran-2-carboxaldehyde 1

Method A: The compound **1** was prepared by a procedure in the literature.[6] Redistilled acrolein (20 g), 3% H_2O, 5% acetaldehyde, and 0.05% hydroquinone were heated with 0.1% sodium tripolyphosphate at 190 °C for 40 min in a stainless-steel autoclave with a magnetically operated stirrer. After reaction time was finished, the reaction mixture was transfered to a 100 mL round-bottom flask. It underwent simple distillation to remove unreacted acrolein and then fractional distillation at reduced pressure to obtain the desired compound **1** (7.5 g, 38%). bp 52-53 °C/17 mm. ^{1}H NMR ($CDCl_3$): δ 9.68 (1H, s, CHO), δ 6.47 (1H, d, 6.2 Hz), δ 4.75 (1H, octuplet), δ 4.27 (1H, triplet + doublet), δ 2.03-1.93 (4H, m).

Method B: The reaction condition was following Crombie's procedure.[7] Redistilled acrolein (29.5 g), benzene (35 mL), and hydroquinone (0.4 g) were placed in a stainless-steel autoclave (250 mL) fitted with a magnetically operated stirrer. The temperature was raised rapidly to 160 °C and kept just above this figure for 4 hr. After reaction time was over, the reaction mixtures were first subjected to simple distillation to remove unreacted acrolein and then to fractional distillation at reduced pressure to obtain the desired compound **1** (10 g, 34%).

Microwave-induced Synthesis of 3,4-Dihydro-2*H*-pyran-2-carboxaldehyde 1

The reaction vessel was charged with 2~3 mL of the reaction solution (prepared by method A or method B) and the vial was covered with a silicon septa, flushed with nitrogen gas for about 1 minute. Then, the vials were placed in the center of the microwave oven and irradiated for 5 minutes at a setting 50% of full power. The resulting solution was diluted with methanol and analysized by GC using a SE-30 column. For preparative scale reaction, a mixture (~30 mL, containing acrolein [25 g], 3% H_2O, 5% acetaldehyde, 0.05% hydroquinone and 0.1% sodium tripolyphosphate) of the reaction solution was divided into ten parts. Each part of the solution was irradiated for the same reaction period, and the resulting solution was pooled together. The solution was subjected to fractional distillation at reduced pressure to obtain the desired compound **1** (22.75 g, 91%,). The physical properties of the microwave irradiation product were identical the one synthesized by the conventional method as described above.

ACKNOWLEDGMENT

Support for this research provided by the National Science Council, Taiwan, is gratefully acknowledged.

Received July 30, 1997.

Key Words

Microwave irradiation; 3,4-Dihydro-2*H*-pyran-2-carboxaldehyde; Solid phase linker; Combinatorial library.

REFERENCES

1. (a) Lowe, G. *Chem. Soc. Rev.* **1995**, *24*, 309. (b) Enger, B. J.; Cardno, M.; Bradley, M. *J. Chem. Soc. Chem. Commun.* **1995**, 2163. (c) Furka, A. *Drug Develop. Res.* **1995**, *36*, 1. (d) Lyttle, M. H. *Drug Develop. Res.* **1995**, *35*, 230.
2. Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555.
3. (a) Wipe, P.; Cunningham, A. *Tetrahedron Lett.* **1995**, *36*, 7819. (b) Dankwardt, S. M.; Newman, S. R.; Krstenansky, J. L. *Tetrahedron Lett.* **1995**, *36*, 4923. (c) Goff, D. A.; Zuckermann, R. N. *J. Org. Chem.* **1995**, *60*, 5744. (d) Boojamra, C. G.; Burow, K. M.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 5742.
4. (a) Thompson, L. A.; Ellman, J. A. *Tetrahedron Lett.* **1994**, *35*, 9333. (b) Kick, E. K.; Ellman, J. A. *J. Med. Chem.* **1995**, *38*, 1427.
5. Hsieh, H.-P.; Wu, Y.-T.; Chen, S.-T.; Wang, K.-T. unpublished results.
6. Shiraishi, T.; Ichimura, K.; Haga, T. *Chem. Abstr.* **1975**, *82*, 156072d.
7. Crombie, L.; Gold, J.; Happer, S. H.; Stokes, B. J. *J. Chem. Soc.* **1956**, 136.
8. (a) Chen, S.-T.; Chiou, S.-H.; Chu, Y.-H.; Wang, K.-T. *Int. J. Peptide Protein Res.* **1987**, *30*, 572. (b) Yu, H.-M.; Chen, S.-T; Chiou, S.-H.; Wang, K.-T. *J. Chromatogr.* **1988**, *456*, 357. (c) Chiou, S.-H.; Wang, K.-T. *J. Chromatogr.* **1989**, *491*, 424. (d) Yu, H.-M.; Chen, S.-T.; Chiou, S.-H.; Wang, K.-T. *J. Org. Chem.* **1992**, *57*, 4781. (e) Yu, H.-M.; Chen, S.-T.; Suree, P.; Nuansri, R.;

Wang, K.-T. *J. Org. Chem.* **1996**, *61*, 9608.
9. Chen, S.-T.; Chiou, S.-H.; Wang, K.-T. *J. Chem. Soc. Chem. Commun.* **1990**, 807.
10. (a) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (b) Stuerga, D.; Gaillard, P. *Tetrahedron* **1996**, *52*, 5505.