Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 959–962

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Soluble Polymer-Supported Synthesis of Benzodiazepinones

Cheng-Yi Wu and Chung-Ming Sun*

Department of Chemistry, National Dong-Hwa University, Shou-Feng, Hualien 974, Taiwan

Received 16 November 2001; accepted 19 January 2002

Abstract—Soluble polymer-supported synthetic method provides a highly efficient route for the construction of biologically important 1,5-benzodiazepin-2-ones. A library of *N*-substituted benzodiazepinones can be readily assembled utilizing S_NAr reaction, reduction of nitro group and one-pot cyclization following *N*-alkylation as the key step in the synthesis. All reactions in the sequence were performed at room temperature to facilitate the generation of libraries in a parallel fashion. The crude products were obtained in 80–95% yield with 60–96% HPLC purity.

The growing applications of combinatorial chemistry have revolutionized drug discovery programs that increase the chances for the discovery of medicinally interesting compounds. Much of the work in this area has focused on the solid-phase synthesis due to advantages like easy and fast purification to separate excess reagents and side products from the desired compounds, which are attached to the insoluble carrier.[1] It is expected that solid-phase synthesis, using known solution-phase reaction conditions will be useful for the development of efficient methodologies to find novel therapeutics. However, several disadvantages associated with solid-phase chemistry such as heterogeneous reaction condition, reduced rate of reactions, solvation of the bound species and mass transport of reagents were also observed. We have been interested in employing liquid-phase combinatorial technology as a mean of efficiently constructing diverse multifunctional libraries.[2] Polyethylene glycol mono-methyl ether (MeO-PEG-OH) is a quite unique polymer carrier because it is soluble in many organic solvents and selectively precipitated out in various solvents. The progress of the polymer-supported reactions can be easily monitored by using conventional analytical techniques such as ^{1}H NMR, ^{13}C NMR, IR and TLC.

It is well documented that substituted benzodiazepine derivatives are of particular interest for drug discovery since they are known to elicit broad spectrum of biological activity against different families of targets (Fig. 1). Several compounds from this class have been used as a constrained dipeptide mimic in protease inhibitors[3] and as the antagonists of G-protein coupled receptors.[4] Several recent reports described solid-phase synthesis of benzo-fused heterocycles,[5] but to date no liquid-phase synthesis of substituted 1,5-benzodiazepin-2-ones has been explored. Based on our extensive experience with soluble polymer-supported synthesis of benzimidazoles from polymer bound 4-fluoro-3-nitrobenzoic acid **1**,[2a] and stimulation by the known solution-phase protocol,[6] related strategy leading to benzodiazepinones was visualized (Scheme 1). As part of our continuing effort to adapt heterocyclic method to a high-throughput synthesis format, we report here the first soluble polymer-supported synthesis of [6,7]-fused 1,5-benzodiazepin-2-ones (Fig. 1C).

The implementation of our synthetic approach is shown in Scheme 1. For our studies, commercially available MeO-PEG-OH was esterified with 4-fluoro-3-nitro benzoic acid through DCC/DMAP coupling in dichloromethane.[7] This fundamental building block is a useful scaffold for the construction of small heterocyclic libraries. In the first step of the reaction sequence,

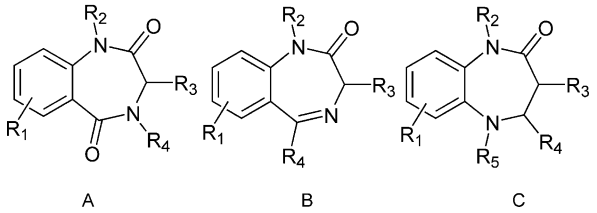


Figure 1. Benzodiazepin skeletons.

*Corresponding author. Tel.: +886-3-866-2500x21215; fax: +886-3-866-3910; e-mail: cmsun@mail.ndhu.edu.tw

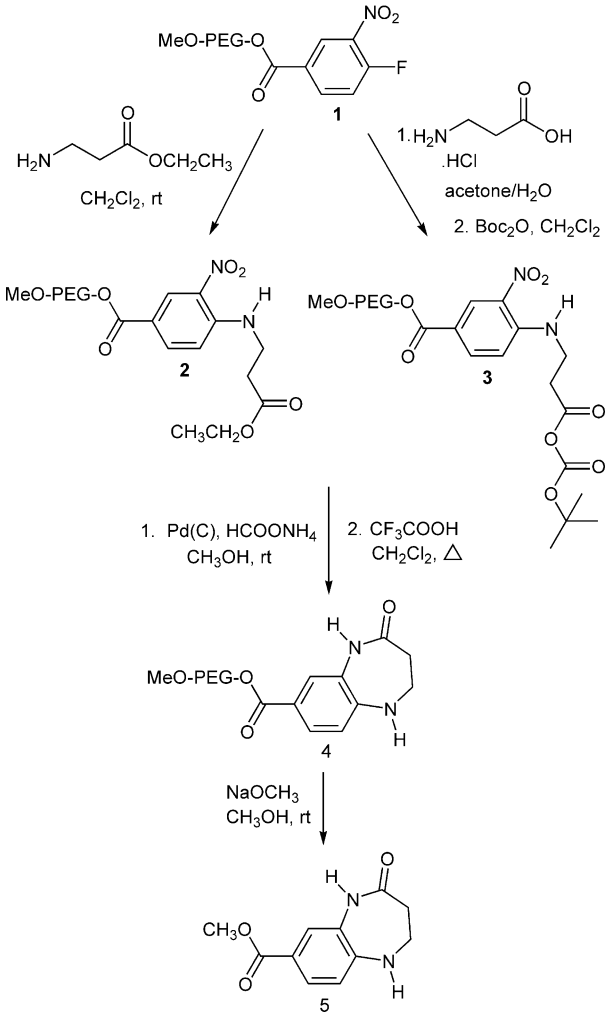
0960-894X/02/$ - see front matter
PII: S0960-894X(02)00058-6

polymer bound 4-fluoro-3-nitro benzoic acid **1** was reacted with β-amino ester in order to construct the basic skeleton of seven-membered benzodiazepinone. For the free β-amino acid, 3:1 (acetone/water) solvent system is required to overcome its poor solubility and to proceed *ipso*-fluoro displacement reaction smoothly at room temperature. We can use regular proton NMR to verify the extent of aromatic substitution without scission product from the support. Subsequent activation of free acid group with di-*tert*-butyl dicarbonate afforded the corresponding aniline **3.** We tried various reducing agents to reduce aromatic nitro group on the support and observed that Zn-NH_4Cl[8] and Pd/C-NH_4COOH[9] reagents reduced nitro group of **2** or **3** to corresponding amine at room temperature in 30 min. Whereas other reducing agents such as Al-NH_4Cl,[10] 2 M $SnCl_2{\cdot}H_2O$[11] failed to reduce immobilized nitro group. Upon completion of reaction the heterogeneous material was removed by filtration and the PEG-bound diamines were purified by precipitation.

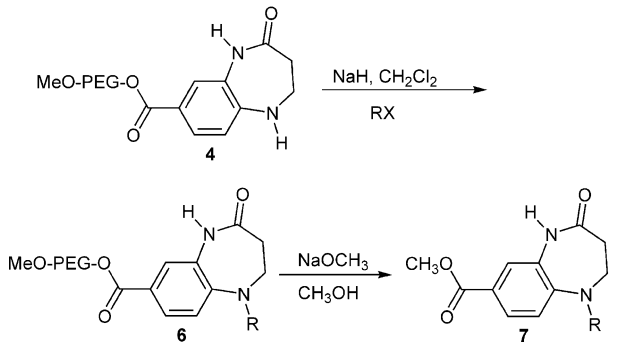
We next turn to evaluate a number of cyclization conditions to achieve the target molecules. Intramolecular cyclization of aniline acid to form seven-membered ring with various coupling reagents was not successful. All attempted ring-closure of **2** or **3** with assistance of bases, heat or use of different solvents was unfruitful and resulted only in the retrieval of the starting material. Even the use of LiHMDS, *n*-BuLi, NaH or sodium *tert*-butoxide in THF did not produce the desired compound, leading primarily to decomposition. Ultimately, intramolecular cyclization of **2** and **3** to **4** was carried out smoothly by heating with trifluoroacetic acid in CH_2Cl_2. It is worth to note that under TFA refluxing condition the O–C=O bond at the polymer attached site survived. Progress of cyclization reaction was easily monitored by regular proton NMR spectroscopy. No trace of uncyclized compound was detected by NMR after overnight reflux. After completion of cyclization, the PEG-bound product **4** was precipitated out selectively by adding diethyl ether to the reaction mixtures. In order to assess the efficiency of cyclization, compound **5** was liberated from the support to confirm the desired structure.[12] Once the preparation of basic skeleton-benzodiazepine **4** has been done on the support, additional diversity was added to N-5 position of the ring. In order to further increase diversity, alkylation of the secondary amine on the benzodiazepinone scaffold was accomplished with sodium hydride in CH_2Cl_2 (Scheme 2). Table 1 outlined the variety of alkyl halides that could be used in the combinatorial step. Aliphatic iodides reacted cleanly and benzyl, allyl bromides gave good crude purity. Functional groups such as ester as well as nitrile were well tolerated.

In all cases, no dialkylation products were observed. Following the second addition of excess NaH and alkyl halides, alkylation of the amide nitrogen (N−1) failed. Following solvent washes after precipitation, alkylated benzodiazepinones **6** were subjected to an efficient cleavage from the support with sodium methoxide to provide the desired compounds. Complete cleavage of polymer support was verified by the observation of the upfield shift of α-methylene protons at polymer attached site from δ 4.4 to δ 3.6 ppm in regular ^1H NMR. If the peak of α-methylene protons was still present after NMR checking, the recovered PEG bound products could be resubmitted to the same reaction conditions until complete scission was reached. In most cases, cleavage reactions were done overnight.

The MeO-PEG-OH was removed from the homogeneous solution by precipitation and filtration method



Scheme 1. Synthetic route to the benzodiazepinone scaffold.

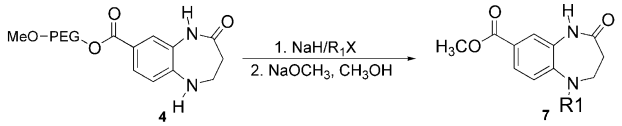


Scheme 2. Alkylation of benzodiazepine.

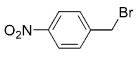
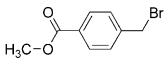
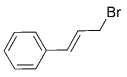
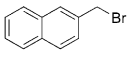
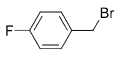
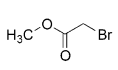
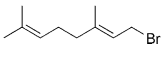
to give the corresponding analytically pure products in 80–95% yield with 60–95% purity as assessed by HPLC. No attempts were made to optimize reaction conditions and all reagents were used directly without any purification. All desired products were characterized by NMR and mass spectrometry. Table 1 data summarized crude yield and purity from the set of representative compounds.[13]

In summary, we have described a novel liquid-phase synthesis of 1,5-benzodiazepin-2-ones from commercially available building blocks. In each step of the reaction sequence, the immobilized intermediates were purified by simple precipitation and washings. All reactions were performed at room temperature to give the desired molecules in high yield and high purity. This synthetic methodology is versatile and produces compounds with known pharmacophoric scaffolds, and is amenable for iterative combinatorial library generation.

Table 1. Alkylation of benzodiazepinone with sodium hydride



4 7

Entry	R_1X	Observed MS	Crude yield[a] (%)	Crude purity[b] (%)
a	CH_3–I	235	95	95
b		277	80	66
c		262	84	73
d		331	89	64
e		355	86	84
f		369	89	96
g		336	89	60
h		361	82	86
i		329	87	84
j		282	89	80
k		259	91	71
l		357	82	84

[a]Determined on weight of crude sample (%).
[b]Purity determined by HPLC analysis (UV detection at $\lambda = 254$ nm) of crude products (%) products show satisfactory ^{1}H NMR and mass data.

Acknowledgements

We thank the general financial support from National Science and Technology Program in Pharmaceuticals and Biotechnology (NSC 90–2323-B-259–001). We also thank Dr. Pravin Bendale for initiating and reviewing this manuscript.

References and Notes

1. (a) Franzén, R. G. *J. Comb. Chem.* **2000**, *2*, 196. (b) Hall, D. G.; Manku, S.; Wang, F. *J. Comb. Chem.* **2001**, *3*, 1. (c) Dolle, R. E. *J. Comb. Chem.* **2000**, *2*, 383. (d) Kurth, M. J.; Sammelson, R. E. *Chem. Rev.* **2001**, *101*, 137.
2. (a) For review, see: Sun, C. M. *Comb. Chem. High Throughput Screening* **1999**, *2,* 299. Wentworth, P., Jr.; Janda, K. D. *Chem. Commun.* **1999**, 1017. (b) Pan, P. C.; Sun, C. M. *Tetrahedron Lett.* **1998**, *39*, 9505. (c) Shey, J. Y.; Sun, C. M. *Synlett* **1998**, 1423. (d) Shey, J. Y.; Sun, C. M. *J. Comb. Chem.* **1999**, *1* (5), 361. (e) Chi, Y. C.; Sun, C. M. *Synlett* **2000**, 591.
3. (a) Skiles, J. W.; Sorcek, R.; Jacober, S.; Miao, C.; Mui, P. W.; McNeil, D.; Rosenthal, A. S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 773. (b) Slade, J.; Stanton, J. J.; Ben-David, D.; Mazzenga, G. *J. Med. Chem.* **1985**, *28*, 1517.
4. Castro, J. L.; Broughton, H. B.; Russell, M. G.; Rathbone, D.; Watt, A. P.; Ball, R. G.; Chapman, K. L.; Patel, S.; Smith, A. J.; Marshall, G. R.; Matassa, V. G. *J. Med. Chem.* **1997**, *40*, 2491.
5. (a) Mayer, J. P.; Zhang, J.; Bjergarde, K.; Lenz, D. M.; Gaudino, J. J. *Tetrahedron Lett.* **1996**, *37*, 8081. (b) Schwarz, M. K.; Tumelty, D.; Gallop, M. A. *Tetrahedron Lett.* **1998**, *39*, 8397. (c) Lee, J.; Gauthier, D.; Rivero, R. A. *J. Org. Chem.* **1999**, *64*, 3060. (d) Schwarz, M. K.; Tumelty, D.; Gallop, M. A. *J. Org. Chem.* **1999**, *64*, 2219. (e) Nefzi, A.; Ong, N. A.; Giulianotti, M. A.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron Lett.* **1999**, *40*, 4939. (f) Morton, G. C.; Salvaino, J. M.; Labaudiniere, R. F.; Herpin, T. F. *Tetrahedron Lett.* **2000**, *41*, 3029.
6. Karp, G. M. *J. Org. Chem.* **1999**, *64*, 8156.
7. (a) Phillips, G. B.; Wei, G. P. *Tetrahedron Lett.* **1996**, *37*, 4887. (b) Pan, P. C.; Sun, C. M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1537.
8. Morita, S.; Kitano, K.; Matsubara, J.; Ohtani, T.; Kawano, Y.; Otsubo, K.; Uchida, M. *Tetrahedron* **1998**, *54*, 4811.
9. Ram, S.; Ehrenkaufer, R. E. *Tetrahedron Lett.* **1984**, *25*, 3415.
10. Pasaha, M. A.; Nagaraja, D. *Tetrahedron Lett.* **1999**, *40*, 7855.
11. (a) Meyer, H. V.; Dilley, G. J.; Durgin, T. L.; Powers, T. S.; Winssinger, N. A.; Zhu, H.; Pavia, M. R. *Mol. Div.* **1995**, *1*, 13. (b) Goff, D. A.; Zuckermann, R. N. *J. Org. Chem.* **1995**, *60*, 744.
12. Analytical data for compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (dd, $J = 8.4$, 1.8 Hz, 1H), 7.88 (d, $J = 1.8$ Hz, 1H), 6.64 (d, $J = 8.4$ Hz, 1H), 3.86 (s, 3H), 3.70–3.67 (m, 2H), 2.79–29.76 (m, 2H).
13. To the 510 mg (97 μmol) of immobilized *o*-fluoronitrobenzene **1**, β-alanine ethyl ester (15 mg), 5 mL dichloromethane and 3 equiv triethylamine (21 mg) was added. The reaction mixture was refluxed in CH_2Cl_2 for 8 h. After completion of reaction, cold diethyl ether (20 mL) was added to precipitate out PEG-bound compounds. The precipitate was dried under vacuo to yield cyclized compound **4** quantitatively. A typical procedure for the synthesis of **7d** was as follows: 500 mg (96 μmol) of immobilized benzodiazepinon **4**, benzyl bromide (17 mg) and NaH (7 mg, 290 μmol) were stirred in 5 mL CH_2Cl_2 for 3 h. After completion of reaction, cold

diethyl ether (20 mL) was added to precipitate out PEG-bound alkylated compound **6d**. The precipitate was dried under vacuo to yield desired compound quantitatively. Finally the resulted **6d** was liberated from the support by treatment with NaOMe/MeOH to provide the target molecule **7d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, $J = 1.9$ Hz, 1H), 7.67 (dd, $J = 8.3$, 1.9 Hz, 1H), 7.23 (m, 4H), 7.19 (m, 1H), 6.76 (d, $J = 8.3$ Hz, 1H), 5.11 (s, 2H), 3.86 (m, 2H), 3.84 (s, 3H), 2.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 166.8, 145.5, 137.7, 132.8, 128.8, 128.6, 127.5, 127.4, 126.0, 123.6, 121.2, 52.4, 52.1, 50.1, 34.1; mass spectrum (FAB) m/z 331 (MH^+).