Pergamon

Tetrahedron Letters 41 (2000) 3029–3033

TETRAHEDRON LETTERS

Novel solid-phase synthesis of 1,5-benzothiazepine-4-one derivatives

George C. Morton, Joseph M. Salvino, Richard F. Labaudinière and Timothy F. Herpin *,†

Rhône-Poulenc Rorer Research and Development, 500 Arcola Road, Collegeville, PA 19426, USA

Received 11 January 2000; accepted 24 February 2000

Abstract

A new solid-phase efficient route to 1,5-benzothiazepine-4-one derivatives is reported. The synthesis exploits the variety of halo-nitrobenzene derivatives available and the facile substitution of the benzamide nitrogen. A wide range of derivatives can be obtained in excellent purity.

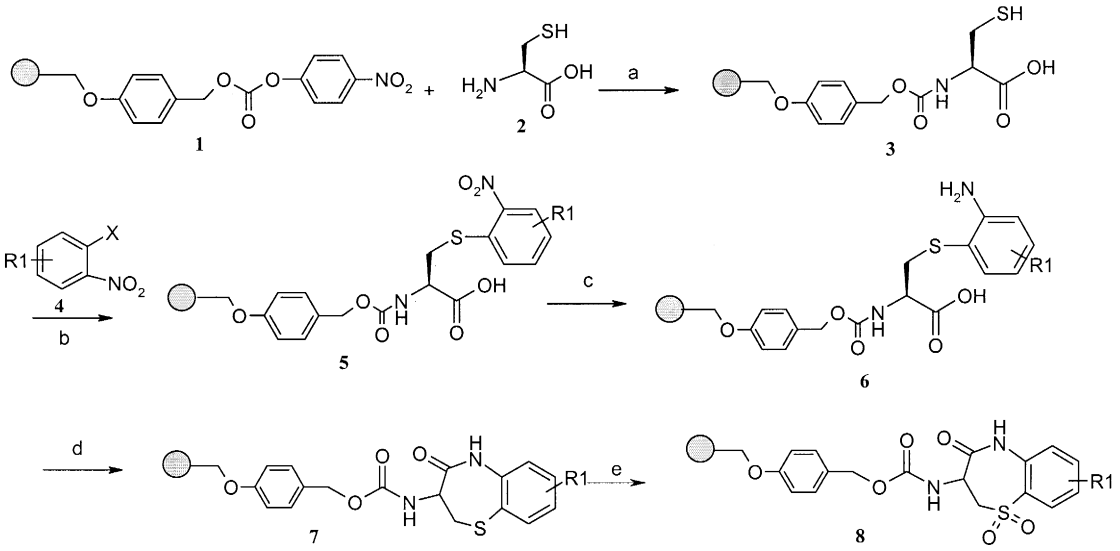
Keywords: benzothiazepine; combinatorial chemistry; solid-phase synthesis.

The synthesis and screening of large combinatorial libraries has become a new paradigm to generate lead compounds in the pharmaceutical industry.[1] Whereas several techniques now exist for the rapid generation of large compound libraries,[2] there are few techniques available to purify large libraries and the compounds are usually screened crude. Developing solution or solid-phase synthetic routes which can provide a wide range of medicinally relevant compounds in high purity has remained a challenge which has been successfully met in several instances.[3,10] We wish to report a novel general solid-phase route to 3-amino-1,5-benzothiazepine-4-one derivatives which allowed the preparation of a wide variety of compounds in high purity. 1,5-Benzothiazepine derivatives are of particular interest for lead discovery because they have been shown to have activity against different families of targets. The 1,5-benzothiazepine scaffold has been used as a constrained dipeptide mimic not only in protease inhibitors such as interleukin-1β-converting enzyme inhibitors,[4] elastase[5] or angiotensin-converting enzyme inhibitors,[6] but also in antagonists of several G-protein-coupled receptors such as the cholecystokinin[7] receptor or the angiotensin II receptor.[8] A solid-phase route to 1,5-benzothiazepine-4-one derivatives has recently been published which uses a carboxamide at the 7-position as a point of attachment to the resin.[9] Our synthetic route, depicted in Scheme 1, uses the 3-amino group as a point of attachment and exploits the wide variety of *ortho*-halo-nitrobenzene derivatives commercially available and the facile substitution of the benzothiazepine amide nitrogen.

* Corresponding author. Tel: 609 818 5417; fax: 609 818 3450; e-mail: timothy.herpin@bms.com (T. F. Herpin)

† Present address: Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, USA.

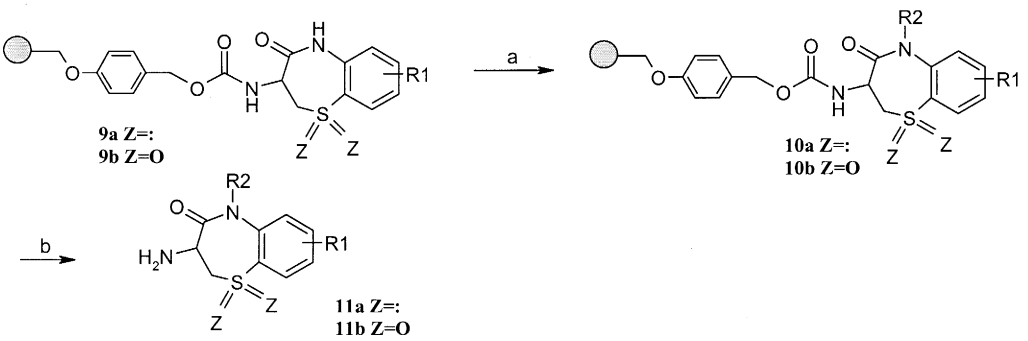
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00341-5



Scheme 1. (a) (1) BSA, DMF, argon, rt; (2) 10% AcOH in DMF; (b) X=Cl, Br or F, DBU, DMF, argon, rt; (c) $SnCl_2 \cdot 2H_2O$, DMF, rt; (d) EDC, NMP, rt; (e) *m*-CPBA, DCM, rt

Cysteine **2** was reacted with the nitrophenyl carbonate derivative of Wang resin **1** by first using bis-(trimethylsilyl)-acetamide[10] (BSA) to dissolve the amino acid (Scheme 1). The thiol **3** was then reacted with a variety of halo-nitrobenzene derivatives **4**. Formation of up to 25% of cystine by dimerization of the resin-bound cysteine was observed during this step. This could be suppressed by using a strictly inert atmosphere and DBU as base. Alternatively, cysteine could be cleanly reduced with tributyl phosphine and further reacted with the halo-nitrobenzene derivative. Reduction of the nitro group with tin-dichloride dihydrate and cyclization with EDC afforded the benzothiazepine derivative **7**. Further diversity could be obtained by oxidation of the sulfide **7** to the sulfone **8** with *m*-CPBA.

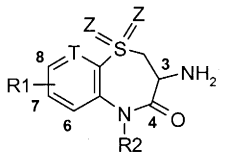
Alkylation of the amide nitrogen could be accomplished with benzamide bases as reported in the solid phase synthesis of benzodiazepine derivatives,[11] but we found that DBU gave cleaner results with a simpler protocol (Scheme 2). Alternatively, the Mitsunobu reaction with alcohols, tributylphosphine and ADDP[12] proceeded cleanly on the sulfone derivative **9b**, but under the same conditions the sulfide **9a** reacted only partially. Cleavage from the resin afforded the benzothiazepine derivatives **11** in high yield and excellent purity (Table 1).



Scheme 2. (a) R2-X (X=Br, Cl), KI, DMF, DBU, rt; (b) 50% TFA–DCM, rt, 1 h

A wide variety of reagents could be incorporated at the two combinatorial positions. Chloro-, bromo-

Table 1

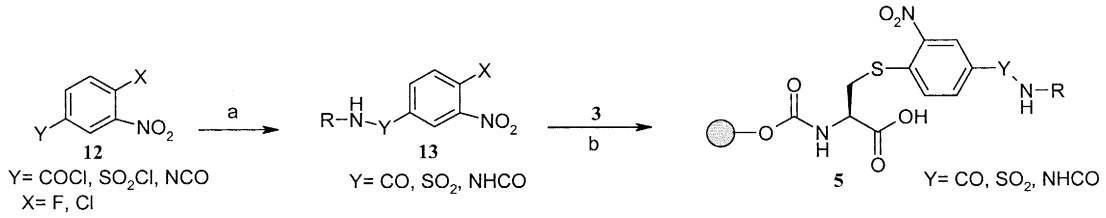


Entry	R1	T	R2	Z	Purity[a]	Yield[b]
1	H	CH	H	-	82	78
2	H	CH	H	O	100	59
3	7-CF_3	CH	CH_2-Ph[c]	-	100	63
4	7-OMe	CH	CH_2-Ph[c]	-	95	68
5	7-C(O)-Ph	CH	CH_2-Ph[c]	-	100	60
6	7-C(O)-(2-methoxymethyl-pyrrolidine)	CH	CH_2-Ph[c]	-	94	61
7	7-NH-C(O)-NH-CH_2-Ph	CH	CH_2-Ph[c]	-	93	65
8	7-C(O)-(2-methoxymethyl-pyrrolidine)	CH	CH_2-Ph[c]	O	67	49
9	7-NH-C(O)-NH-CH_2-Ph	CH	CH_2-Ph[c]	O	94	57
10	8-OMe	N	CH_2-Ph[c]	-	100	58
11	9-Me	CH	CH_2-Ph[c]	-	94	62
12	H	CH	$(CH_2)_3$-Ph[d]	-	100	60
13	H	CH	CH_2-C(O)-$N(Et)_2$[c]	-	83	70
14	H	CH	CH_2-4-fluorophenyl[c]	-	71	53
15	H	CH	CH_2-3-chlorothiophene[c]	-	70	54
16	H	CH	CH_2-3-phenyloxadiazole[c]	-	69	51
17	H	CH	$(CH_2)_2CH_3$[e]	-	89	60
18	H	CH	$(CH_2)_3$-O-CH_2-Ph[d]	-	84	62

a. Purity measured by HPLC/ ELSD (Evaporative Light Scattering Detector); b. Yield based on weight of crude extract from the resin; c. The alkyl-chloride was used for alkylation; d. The alkyl-bromide and potassium iodide were used for alkylation; e. The alkyl iodide was used for alkylation.

and fluoro-nitrobenzene derivatives were reacted with the resin bound cysteine and a wide variety of functional groups were tolerated (Table 1). Halo-nitrobenzene derivatives containing electron withdrawing (entries 3 and 5) or electron donating (entries 4 and 11) groups gave clean reactions, as well as derivatives with *ortho* disubstitution (entry 11). Additional diversity could be obtained by reacting 4-chloro-3-nitrobenzenesulfonyl chloride, 4-chloro-3-nitrobenzoyl chloride or 4-chloro-3-nitrophenylisocyanate with an amine prior to reaction with the resin bound cysteine **3**. These reactions could be done in one pot without isolation of the substituted chloro-nitrobenzene derivative **13** (Scheme 3). Halo-nitrobenzene derivatives substituted with the sulfonamido groups reacted cleanly but the sulfonamide was subsequently alkylated under the conditions to convert **9** to **10**.

Table 1 also outlines the variety of alkyl halides which could be used in the second combinatorial step. Aliphatic iodides and bromides reacted cleanly at room temperature and the reaction with aliphatic chlorides proceeded smoothly with one equivalent of potassium iodide (entries 12 and 17). Benzylic bromides and iodides gave poor conversions presumably because of competing alkylation of DBU, but their corresponding chlorides reacted cleanly. A variety of substituted heterocycles could be introduced (entries 15 and 16), and functional groups such as tertiary amides or ethers were well tolerated (entries 13 and 18). Functional groups such as esters, carboxylic acids or tertiary amines gave side reactions.



Scheme 3. (a) R-NH_2, DCM, DIEA, rt; (b) DBU, DMF, argon, rt

In conclusion, we have developed a general solid-phase route to benzothiazepine derivatives which allows the incorporation of a wide variety of substituents on the benzene ring and on the amide nitrogen. Benzothiazepine-sulfones are also accessible via this route and both alcohols and alkyl halides can serve as a source of diversity for the substitution of its amide nitrogen. All of these compounds offer a third point of diversity in the primary amine which was attached to the resin. Several methods can be envisaged for its clean substitution in solution, such as the tetrafluorophenol resin (TFP-resin), Marshall resin, resin bound EDC or the tosyl resin.[13–17] Their application to the synthesis of large Benzothiazepine and Benzothiazepine sulfone libraries is presently under investigation and will be reported elsewhere.

Typical experimental procedure: BSA (15 equiv.) was added to cysteine (5.0 equiv.) in anhydrous DMF under nitrogen. This reaction was heated to dissolve the cysteine and the 4-nitrophenyl carbonate resin (1.0 equiv.) was added. After stirring overnight at room temperature, the resin was washed with DMF (4×), 10% AcOH in DMF (4×), DMF (4×), THF (3×), DCM (3×) and Et_2O (3×) under a positive pressure of nitrogen. To this cysteine resin was added DBU (10 equiv.) in DMF under nitrogen. The halo-nitrobenzene (10 equiv.) was then added and the reaction was stirred overnight under nitrogen. The resulting sulfide resin was washed with DMF (2×), 10% AcOH in DMF (2×), 20% aqueous THF (2×), THF (2×), DCM (2×), and Et_2O (2×). Tin dichloride dihydrate (10 equiv.) in DMF at 50°C overnight was used to reduce the nitro group. For workup, the reduced resin was washed with DMF (3×), 20% aqueous THF (2×), THF (2×), DCM (2×), and Et_2O (2×). Cyclization to the benzothiazepine was accomplished with EDC (5 equiv.) in NMP overnight. The resulting resin was washed with DMF (1×), aqueous DMF (1×), DMF (1×), aqueous THF (2×), THF (2×), DCM (2×), and Et_2O (2×). MCPBA (12 equiv.) in dichloromethane was used to oxidize the sulfide to the sulfone within 6 h at room temperature. The resin was washed with DCM (2×), aqueous THF (2×), THF (3×) and Et_2O (2×). The alkylations were carried out in DMF with DBU (10 equiv.) and the alkyl halide (10 equiv.) overnight at room temperature. For workup, the resin was washed with DMF (2×), 10% AcOH in DMF (2×), 20% aqueous THF (2×), THF (2×), DCM (2×), and Et_2O (2×). Cleavage with 50% TFA in DCM afforded the desired amino-benzothiazepines.

References

1. Patel, D. V. In *Annu. Rep. Comb. Chem. Mol. Diversity*; Moos, W. H.; Pavia, M. R.; Ellington, A. D.; Kay, B. K., Eds. Application of Combinatorial Technology to Drug Discovery. ESCOM: Leiden, 1997; Vol. 1, pp. 3–5.
2. (a) Sarshar, S., Mjalli, A. M. M. In *Annu. Rep. Comb. Chem. Mol. Diversity*; Moos, W. H.; Pavia, M. R.; Ellington, A. D.; Kay, B. K., Eds. Techniques for Single Compound Synthesis. ESCOM: Leiden, 1997; Vol. 1, pp. 3–5; (b) Xiao, X.-y.; Nova, M. P. In *Combinatorial Chemistry Synthesis and Application*; Wilson, S. R.; Czarnik, A. W., Eds. Radiofrequency and Additional Techniques for the Structure Elucidation of Synthetic Combinatorial Libraries. John Wiley & Sons: New York, 1997; pp. 135–152.
3. Bilodeau, M. T.; Cunningham, A. M. *J. Org. Chem*. **1998**, *63*, 2800.
4. Golec, J. M. C.; Lauffer, D. J.; Livingston, D. J.; Mullican, M. D.; Nyce, P. L.; Robidoux. A. L. C.; Wannamaker, M. W. Inhibitors of Inteleukin-1β Converting Enzyme. PCT intl Appl. WO 9824804, 11 June 1998.

5. Skiles, J. W.; Sorcek, R.; Jacober, S.; Miao, C.; Mui, P. W.; McNeil, D.; Rosenthal, A. S. *Bioorg. Med. Chem. Lett*. **1993**, *3*, 773.
6. Angiotensin converting enzyme inhibitors: 1,5-benzothiazepine derivatives: Slade, J.; Stanton, J. J.; Ben-David, D.; Mazzenga, G. J. *Med. Chem*. **1985**, *28*, 1517.
7. Nagel, A. New Benzothiazepine and Benzoxazepine Derivatives as Cholecystokinin Receptor Antagonists for Treating Pain, Gastrointestinal Disorders and Central Nervous System Disorders. WO 9401421-A1, 20 January 1994.
8. Buhlmayer, P.; Furet, P. New Benzazepinone Derivative are Angiotensin II Antagonists — Used to Treat Hypertension, Thrombosis, Atherosclerosis, Diabetes, Cancer, Cerebral Ischemia, etc. WO 9413651-A1, 23 June 1994.
9. Schwarz, M. K.; Tumelty, D.; Gallop, M. A. *J. Org. Chem*. **1999**, *64*, 2219.
10. Dressma, B. A., Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett*. **1996**, *37*, 937.
11. Boojamra, C. G.; Burrow, K. M.; Thompson, L. A.; Ellman, J. A. *J. Org. Chem*. **1997**, *62*, 1240.
12. Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett*. **1993**, *34*, 1639.
13. Salvino, J. M.; Kumar, V.; Orton, E.; Airey, J. A.; Kiesow, T. A.; Crawford, K.; Mathew, R.; Krolikowski, P.; Drew, M.; Engers, D.; Krolikowski, D.; Herpin, T.; Gardyan, M.; McGeehan, G.; Labaudiniere, R. *J. Org. Chem*. **2000**, in press.
14. Breitenbucher, J. G.; Johnson, C. R.; Haight, M.; Phelan, J. C. *Tetrahedron Lett*. **1998**, *39*, 1295
15. Desai, M. C.; Stephens Stramiello, L. M. *Tetrahedron Lett*. **1993**, *34*, 7685.
16. Iuliana, P. E.; Deprez, B. P.; Tartar, A. L. *J. Org. Chem*. **1997**, *62*, 2594.
17. Rueter, J. K.; Nortey, S. O.; Baxter, E. W.; Leo, G. C.; Reitz, A. B. *Tetrahedron Lett*. **1998**, *39*, 975.