Solid Phase Synthesis of Hydroxy Benzothiazepinones through Cyclative Release under Thermolysis

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Hydroxy benzothiazepinones were synthesized by a simple procedure involving epoxidation of polymer bound cinnamic acids followed by nucleophilic opening of the resulting glycidic ester by *o*-aminothiophenol to afford the intermediate hydroxy anilino-esters which underwent cyclization cleavage on heating in DMF to release the product completely.

Benzothiazepinones are excellent pharmacophores and some of the hydroxy derivatives are marketed as life saving cardiovascular drugs which are utilized for the treatment of supra ventricular arrhythmia e.g., Diltiazem—developed and marketed by a Japanese company—Tanabe Seiyaku[1] is one of the top twenty products[2] in global pharmaceutical market sales in the past two decades, which clearly reflects the significance of benzothiazepinones as therapeutic entities.

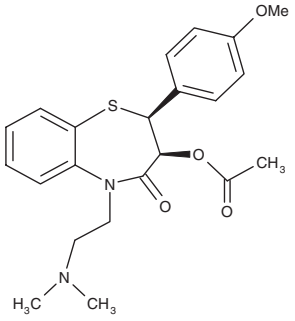
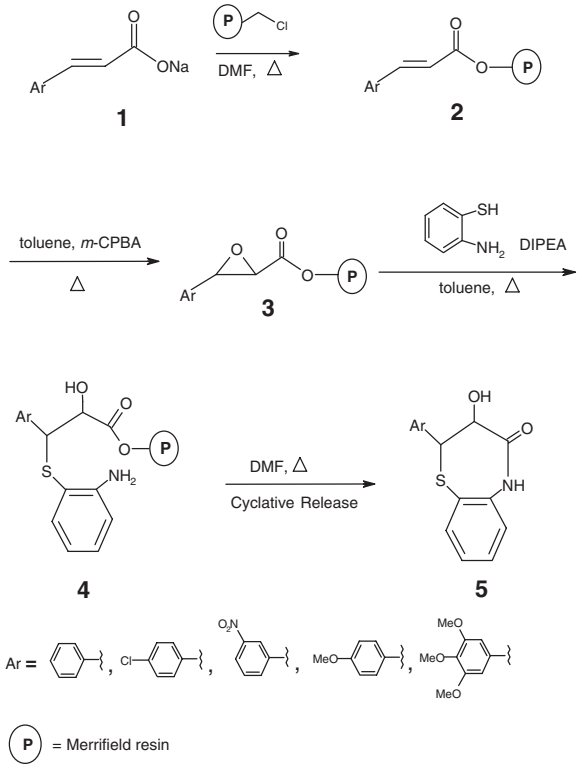


Figure 1. Diltiazem.

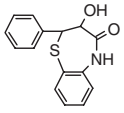
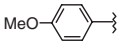
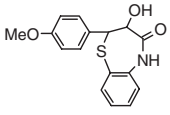
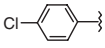
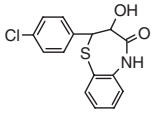
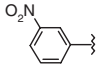
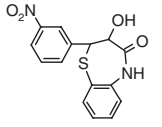
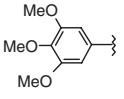
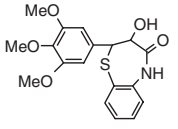
Solid phase synthesis has emerged as an important paradigm for the high throughput screening in modern drug discovery.[3] Of particular interest would be the thermal or base promoted cyclative release technique adopted for the combinatorial synthesis of a variety of therapeutic molecules including benzodiazepinones.[4] Even though a number of solution phase strategies were employed for the synthesis of benzothiazepinones, this has not yet been a target for solid phase synthesis. Our continued efforts towards the development of new solid phase methodologies[5] and their applications to the synthesis of small molecular libraries, prompted us to explore the solid phase synthesis of benzothiazepinones employing a cyclative release strategy.

Resin bound (*E*)-cinnamic acids were prepared through condensation of the sodium salts of various substituted *trans*-cinnamic acids with the Merrifield resin in DMF at 70–80 °C. The initial loading level was determined by gain of weight after the first condensation and also by cleaving a known quantity of the loaded resin by treatment with TFMSA and analyzing the residue quantitatively. The resin bound cinnamic acids were subjected to epoxidation by treatment with *m*-CPBA at 90 °C. The procedure followed was in analogy with literature methods for the epoxidation of less reactive internal olefins.[6] The resin bound glycidic ester was treated with *o*-aminothiophenol at 80 °C in dry toluene in the presence of a catalytic amount of DIPEA to give the desired amino alcohol. IR (on resin) and ^{1}H NMR spectra of the residue obtained after cleavage of compound **4** confirmed the formation of glycidic esters and the successive opening. Epoxy ring opening was regioselective as found in solution phase synthesis. Furthermore, by varying the substitution on the aromatic ring of the *o*-aminothiophenol, molecular diversity on the benzothiazepinone nucleus can be achieved at this point. It is pertinent to mention here that the 8-chloro derivative known as Clentiazem is also a powerful calcium channel blocker, which was also developed by the discoverers of Diltiazem. The cyclization was effected merely by heating the resin bound compound in DMF at 140–150 °C under nitrogen, which completely released the product. We were able to synthesize a number of benzothiazepinone derivatives employing the above strategy[7] and the purity of the final products could be determined by GC analysis of the residue obtained after cyclative cleavage. As Diltiazem and the other derivatives belonging to this family are marketed in optically pure form which could be achieved either through resolution of the mercapto-acid intermediate as a chiral amine salt or through di-



Scheme 1.

Table 1. Solid phase synthesis of hydroxybenzothiazepinones

Entry	Ar	Product(**5**)	Yield (Purity)/%[a,b]
a			70(72)
b			76(78)
c			75(73)
d			72(77)
e			80(75)

a. Overall yield calculated based on initial loading level.
b. Purity based on the GC analysis of the crude product (after release).

astereoselective synthesis via asymmetric epoxidation using chiral dioxiranes.[8] Currently, efforts are underway to prepare the optically active hydroxy glycidic esters on solid phase.

In conclusion, we present in this paper a solid phase synthesis of hydroxy benzothiazepinones employing a cyclative release technique. The strategy can be conveniently adapted to various commercially available *o*-aminothiophenols and is found to be general with regard to various substituted cinnamic acids to afford an array of substituted hydroxy benzothiazepinones of biological importance.

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References and Notes

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7 The sodium salt of (*E*)-4-methoxycinnamic acid **1**, (1 g, 8.0 mmol) was heated with Merrifield Resin (0.1 g, 0.8 mmol/g, Advanced ChemTech, USA, 100–200 mesh) in DMF at 70–80 °C for 24 h at the end of which the resin was filtered and washed with DMF, DCM, and MeOH alternatively and dried under vacuum to afford the resin bound cinnamic acid ester **2**: FTIR (KBr): 1733 cm^{-1}. Weight gain after condensation and also GC analysis of the residue obtained after cleavage revealed almost quantitative loading (0.8 mmol/g). The resultant resin **2** was treated with *m*-CPBA (300 mg, 1.7 mmol) in toluene and heated (90 °C) for 4 days under nitrogen. The resin was filtered, washed (DMF, DCM, and MeOH) and dried under vacuum to get polymer bound glycidic ester **3**: FTIR (KBr): 1728 cm^{-1}. Resin bound compound **3** (R^1 = MeO–C_6H_4) was heated with *o*-aminothiophenol (0.33 g, 3.0 mmol) and catalytic quantity of DIPEA (0.1 mmol) in toluene (80 °C) for 12 h under nitrogen followed by filtration, washing with DCM and MeOH and drying to afford anilino ester **4**: FTIR (KBr): 1725 cm^{-1}. Resin bound anilino ester **4** on heating in DMF at 140–150 °C for 12 h under nitrogen released the product **5** completely into the solution. The resin was removed by filtration and the filtrate was evaporated under reduced pressure (residue, GC, 78%), followed by purification by preparative thin layer chromatography to afford 18.3 mg of benzothiazepinone **5b** as amorphous white solid. Yield (overall): 76%, IR (KBr): 1704 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 3.21–3.25 (br d, 1H, OH), 3.80 (s, 3H, OCH_3), 4.33–4.40 (t, 1H, J = 7.0, C<u>H</u>OH), 5.0–5.04 (d, 1H, J = 7.0 Hz, S-C<u>H</u>) and aromatic protons at 6.82–6.86 (d, 2H, J = 8.8 Hz), 7.1–7.2 (m, 2H), 7.3–7.32 (d, 1H, J = 1.6), 7.40–7.44 (d, 2H, J = 8.8 Hz), 7.57–7.60 (d, 1H, J = 7.6 Hz) & 10.2 (br, s, 1H, N<u>H</u>). EIMS m/z: 283 ($M^+ - H_2O$, 100%), 301 (M^+, 31%).

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