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Solid-phase combinatorial synthesis of benzothiazole and 2,3-dihydro-[1,5]-benzothiazepine derivatives

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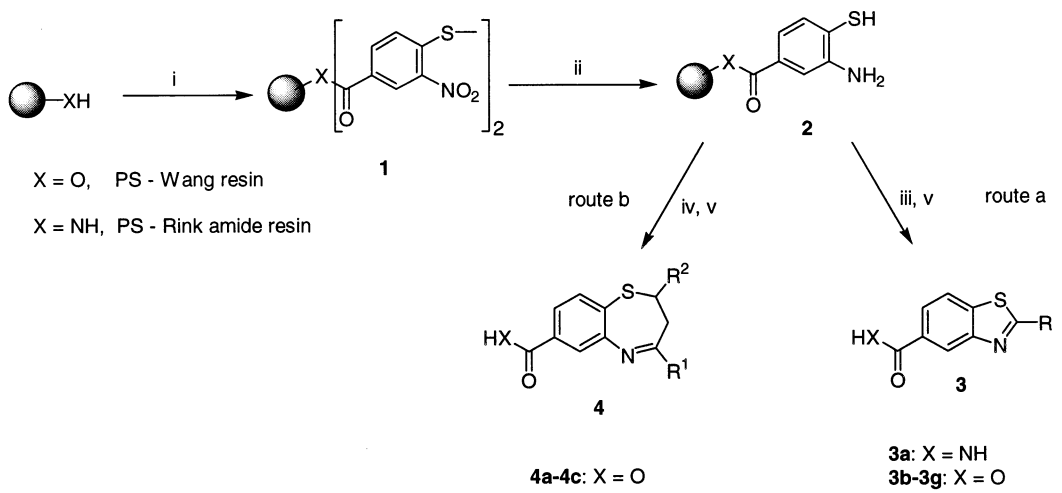
Abstract—Bis-(2-nitro-4-carboxyphenyl) disulfide was loaded on Wang resin and Rink amide resin. The nitro group was reduced to its amine with concomitant cleavage of the disulfide bond using $SnCl_2 \cdot 2H_2O$ to afford **2**. Condensation of an aldehyde and nucleophilic attack on an α,β-unsaturated ketone, followed by TFA cleavage from the resin, gave benzothiazole **3** and 2,3-dihydro-[1,5]-benzothiazepine **4**, respectively.

Heterocycles containing the thiazole moiety are present in many natural products such as bleomycin,[1] epothilone A,[2] lyngbyabellin A[3] and dolastatin 10.[4] Benzothiazole derivatives are important members of this class of compounds as they have been shown to possess antimicrobial properties[5] and have found applications in industry as antioxidants[6] and vulcanization accelerators.[7] Seven-membered ring analogous benzothiazepine derivatives exhibit diverse biological activities as calcium antagonists,[8] angiotensin converting enzyme inhibitors,[9] anticonvulsant and tranquillizing agents,[10] potential anticancer drugs[11,12] and as endogenous natriuretic factors.[13] Following these studies and inspired by the solution-phase strategies developed earlier,[14] a solid-phase combinatorial approach was envisaged (Scheme 1) for the synthesis of benzothiazoles and 2,3-dihydro-[1,5]-benzothiazepine derivatives. To our knowledge, there are no earlier reports on the solid-phase synthesis of these compounds.



Scheme 1. Solid-phase synthesis of benzothiazole and 2,3-dihydro-[1,5]-benzothiazepine. Reagents: (i) bis-(2-nitro-4-carboxyphenyl) disulfide, HOBt, DIC, DMF, rt, 12 h; (ii) $SnCl_2 \cdot 2H_2O$, NaOAc, DMF, rt, 4 h; (iii) RCHO, EtOH, 80°C, 4 h; (iv) $R^1COCH{=}CHR^2$, EtOH, 1% AcOH, 80°C, 12 h; (v) 20% TFA, 1 h.

Keywords: solid-phase synthesis; benzothiazole; 2,3-dihydro-[1,5]-benzothiazepine.

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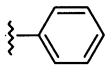
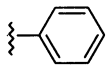
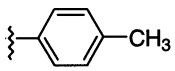
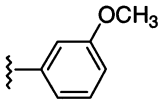
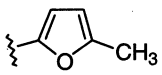
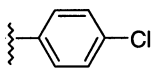
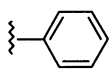
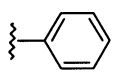
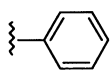
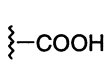
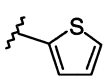
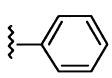
In our synthesis, **1** was obtained by reacting bis-(2-nitro-4-carboxyphenyl) disulfide[15] with Wang resin and Rink amide resin under standard HOBt and DIC coupling conditions. The nitro group was reduced to its amine with concomitant cleavage of the disulfide bond using tin(II) chloride dihydrate to afford **2**. In route A, an aldehyde was condensed with **2** in refluxing ethanol, followed by TFA cleavage and spontaneous oxidation[5,16] to afford benzothiazole **3**. A one step bisnucleophilic attack of **2** on an α,β-unsaturated ketone in the presence of 1% acetic acid and refluxing ethanol yielded **4** (Route B).

The benzothiazoles **3** and 2,3-dihydro-[1,5]-benzothiazepines **4** were characterized after cleavage by ^{1}H NMR and MS. Ten representative examples were randomly selected and their crude yields and purities are summarized in Table 1.

Initially, the condensation of **2** with *p*-tolualdehyde was carried out at room temperature and incomplete condensation was observed. Whilst under reflux condition, the yield for compound **3d** increased greatly from 33 to 74%. Hence, the condensation was performed at reflux for 4 h. Condensation of the immobilized 3-amino-4-

Table 1. The yield and HPLC purity of compounds **3** and **4**

Compound	R	R^1	R^2	HPLC Purity[a]	% Yield[b]
3a		–	–	88	65
3b		–	–	92	89
3c		–	–	100	91
3d		–	–	74	74, 33[c]
3e		–	–	88	49
3f		–	–	64	73
3g		–	–	87	80
4a	–			100[d]	29[d]
4b	–			100[d]	31[d]
4c	–			90[d]	34[d]

[a]HPLC purity at 300 nm with a Hypersil ODS C18 reverse-phase column (2.1 x 200mm).
[b]Crude yield calculated based on theoretical loading of the resins.
[c]Condensation reaction was performed at rt for 4 h.
[d]Purified HPLC purity and yield.

sulfanylbenzoic acid **2** with aliphatic aldehydes gave better yields than with aromatic aldehydes. All electron-donating substituents on the aldehyde, however, led to poorer yields due to the reduced negative charge in the carbonyl group making it less susceptible to nucleophilic attack. Nucleophilic attack of **2** on α,β-unsaturated ketones afforded compounds **4** in greater than 29% yield. It was noted that electron-withdrawing substituents at the 7-position, where the linkage to the resin is, decreased the yield to some extent.[17]

In this paper we have reported a simple and straightforward route to the synthesis of benzothiazoles and 2,3-dihydro-[1,5]-benzothiazepine derivatives. Further work is in progress on the synthesis of 1,4-benzothiazines.

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