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Solid-Phase Synthesis of Diverse Tetrahydro-1,4-Benzodiazepine-2-ones

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Abstract: A general method for the construction of tetrahydro-1,4-benzodiazepine-2-ones on solid-support has been developed utilising a cleavage-conjugate addition protocol as the key step in the design. Using this novel methodology the synthesis of a diverse one hundred and twenty compound library with three points of diversity has been achieved starting from readily available anthranilic esters.
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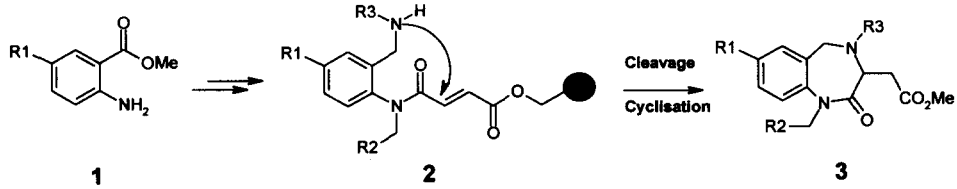
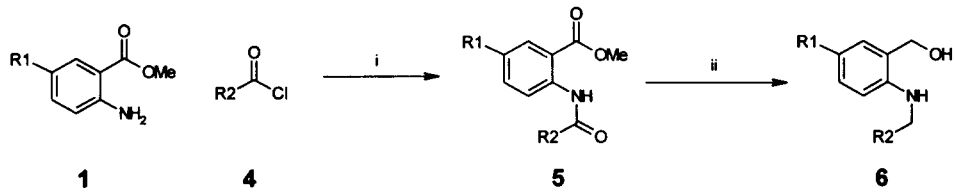
Organic synthesis by solid-phase methods is emerging as a powerful tool for the expeditious generation of structurally diverse molecules suitable as potential drug candidates.[1] Anchoring starting materials on to resin can accelerate the reaction work-up and render the possibility of automation thus allowing for the high throughput of drug-like molecules. These alluring features of solid-phase synthesis have been appreciated in peptide chemistry for decades and recently these methods have been applied to the synthesis of heterocyclic molecules.[2] Thus the solid-phase generation of small heterocyclic libraries for the screening against biological targets has enticed medicinal chemists to this area.

Often the search for new drugs is initiated by the modification of an old drug; this has proven to be a common and reliable route to a new product one such example has been the benzodiazepine[3] class of drug. It is known that 1,4-benzodiazepines display pharmacological activity, including anti-anxiety, sedative, anti-convulsant and tranquillising properties.[4] Thus it is not surprising that the use of benzodiazepines has increased over the last two decades making them one of the most frequently prescribed group of drugs.[5] We felt that this privileged[6] structure was worthy for further study and therefore decided to investigate the as yet unreported[7] solid-phase synthesis of the tetrahydro-1,4-benzodiazepine-2-one class of compounds **3** (Scheme 1).



1 **2** **3**

Scheme 1. The proposed route into the tetrahydro-1,4-benzodiazepine-2-one system.



1 4 5 6

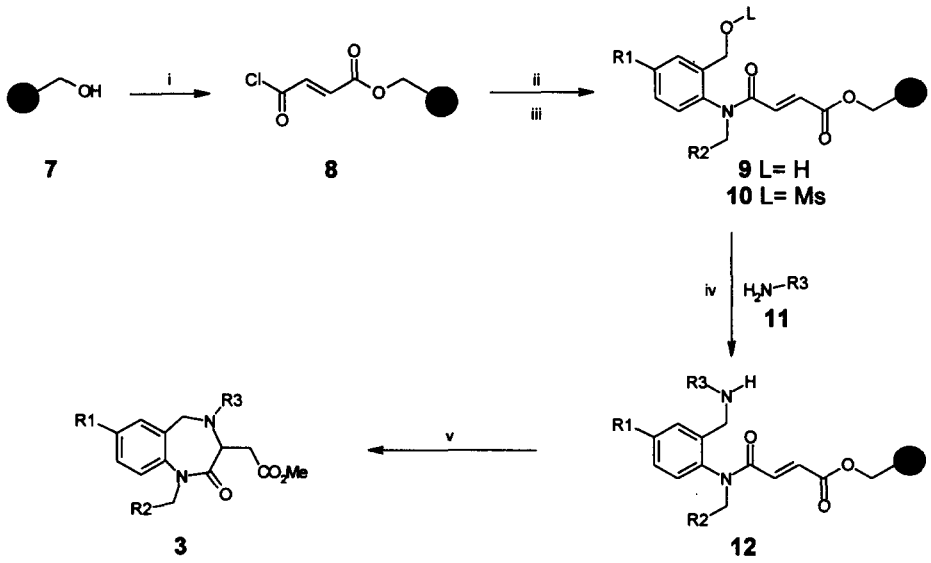
Reagents: i) $NaHCO_3$ (2 eqiuv), THF, R.T., 6h, ii) $LiAlH_4$ (1equiv), THF, 0°C to R.T., 2h.

Scheme 2. Synthesis of the amino alcohol building blocks.

The amino alcohols **6** (Scheme 2) were readily prepared from commercially available anthranilic esters **1** by reaction with acid chlorides **4** ($NaHCO_3$, THF, 6h, R.T.) to afford the amides **5** in excellent yields (>90%). This was followed by lithium aluminium hydride mediated reduction (THF, 2h, R.T.) to furnish the desired building blocks **6** in good yields (>85%).

The solid-phase synthesis (Scheme 3) was initiated by treating Wang resin[8] **7** with fumaryl chloride (5 equiv, THF, 10h, R.T.) to give the resin bound acid chloride **8**.[9] The tethered acid chloride **8** was then reacted with the previously synthesised amino alcohol **6** (4 equiv, DCM, 10h, R.T.); amide formation was monitored using infra-red spectroscopy for the disappearance of the COCl stretch (1770cm^{-1}) and the appearance of the CONHR2 stretch (1640cm^{-1}). A modified literature method[8] was used to convert the hydroxyl group of **9** to the mesylate **10** by exposure of **9** to excess (5 equiv) methanesulphonyl chloride (Et_3N, DCM, 4h, 0°C to R.T.). Introduction of the third point of diversity **R3** was accomplished *via* amine **11** displacement of the resin bound mesylate **10**. This was best achieved in DMF (5 equiv, 10h, R.T.) to produce the advanced intermediate **12**, now ready for a cleavage-conjugate addition protocol, crucial to the strategy. Consequentially, treatment of **12** with sodium methoxide (2 equiv) in a mixed protic solvent medium (THF/MeOH, 4:1*v/v*) resulted in a very efficent cleavage of **12** from solid-support with concomitant 7-*exo-trig* cyclisation[10] (10h, R.T.) to furnish the required tetrahydro-1,4-benzodiazepine-2-one unit **3**. The convenience of this cleavage method is that it allows for the final cyclisation step to be monitored by tlc, from this it was evident that cleavage from resin was occuring first, usually complete within 1h and the conjugate addition requiring longer to reach completion. The products obtained were then filtered through a microtitre plate containing silica gel to supply the final compounds **3** in excellent purity and good overall yield (>72%).

Using this methodology 120 tetrahydro-1,4-benzodiazepine-2-ones have been prepared by reacting 4 anthranilic esters **R1** with 6 acid chlorides **R2** and 5 primary amines **R3**. All 120 compounds produced were analysed using ^{1}H-NMR, MS and tlc these are depicted in figure 1.



Reagents: i) Fumaryl chloride (5 equiv), THF, R.T., 10h, ii) **6** (4 equiv), DCM, R.T., 10h, iii) MsCl (5 equiv), Et_3N (5 equiv), DCM, 0°C to R.T., 4h, iv) **11**, DMF, R.T., 10h, v) NaOMe (2 equiv), THF/MeOH (4:1*v/v*), R.T., 10h.

Scheme 3. Synthesis of a tetrahydro-1,4-benzodiazepine-2-one on solid-support.

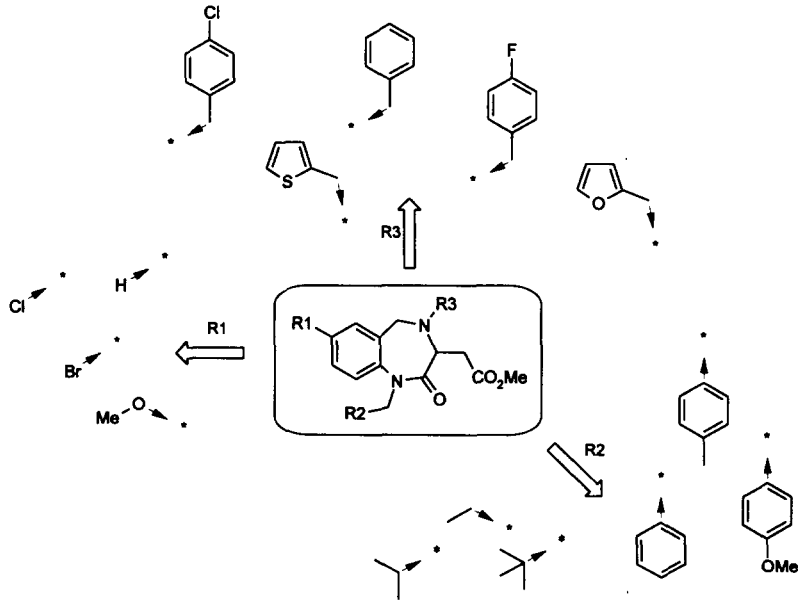


Figure 1. Library of tetrahydro-1,4-benzodiazepine-2-ones.

Typical Experimental Procedure:

To the acid chloride **8** (200mg, 0.20mmol) supported on Wang resin was added dry DCM (5ml), the resin allowed to preswell (30mins) before the addition of the amino alcohol **6** [(170mg, 0.80mmol); R1= H, R2= Ph]. The suspension was stirred for 10h at R.T., filtered and washed in the usual way (DMF then MeOH ↔ DCM), to give the resin bound amide **9**. Next was added methanesulphonyl chloride (114mg, 1.00mmol) as a solution in dry DCM (10ml), followed by the slow addition of Et_3N (100mg, 1.00mmol) as a solution in DCM (5ml), an exothermic reaction ensued and the mixture stirred for 4h at R.T. After this time the suspension was filtered and the resin washed with dry DCM. The resin was then treated with *p*-methoxybenzylamine **11** (107mg, 1.0mmol; R3= *p*-MeO-Ph) in DMF (5ml) and the suspension stirred for 10h at R.T. Then filtered and washed with DMF (20ml), MeOH (3x20ml) and DCM (3x20ml) in succession. Finally treatment with sodium methoxide (100mg, 2.00mmol) in a dry THF/MeOH mixture (5ml, 4:1*v/v*, 10h, R.T.) resulted in cleavage-cyclisation and the filtrate evaporated to give a light brown compound **8** which was filtered through a plug of silica gel using ethyl acetate as eluent to give the product as a yellow oil (14mg, 79%). ^{1}H-NMR [360 MHz, $CDCl_3$] δ 2.3, 3.0 [m (ABX system), 2H, *J* 13.2, 5.7, 2.5Hz, NCH_X-CH_ACH_B], 3.6 (s, 3H, OCH_3), 3.8 (s, 3H, $PhOCH_3$), 3.8 and 4.2 [m, (AB system) 2H, *J* 13, $PhCH_2N$], 5.1 [2H, (AB system), *J* 14.2, $PhCH_2NCO$], 6.8-7.4 (m, 13H, 3xPh).

In conclusion, a solid-phase protocol for the synthesis of functionally diverse tetrahydro-1,4-benzodiazepine-2-ones has been developed with three points of diversity. This has been demonstrated with the expedient synthesis of a library of compounds which can serve as potential lead compounds in the drug discovery process.

Acknowledgements

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References and Notes

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