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Novel Safety-Catch Linker and its Application with a Ugi/De-BOC/Cyclization (UDC) Strategy to access Carboxylic acids, 1,4-Benzodiazepines, Diketopiperazines, Ketopiperazines and Dihydroquinoxalinones

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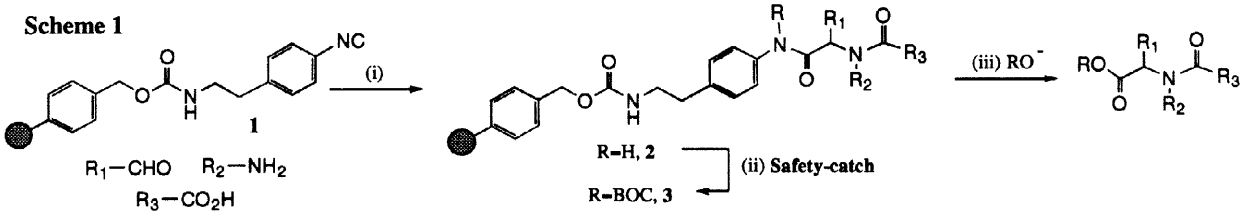
Abstract: This communication reveals the synthesis and application of a novel resin bound isonitrile. The resin is an example of a novel safety-catch linker which upon BOC-activation can be resin cleaved with a variety of nucleophiles. Use of this polymer supported isonitrile in the Ugi multi-component reaction (MCR), followed by resin clipping and cyclization allows access to diverse arrays of 1,4-benzodiazepine-2,5-diones, diketopiperazines and ketopiperazines respectively. The methoxide safety-catch clipping strategy and subsequent solution phase cyclization offers similar advantages to a traceless linker.

Interest in polymeric supported reagents has blossomed in recent years with the emergence of combinatorial chemistry and automated parallel synthesis. Multi-component reactions (MCR's) are especially attractive for automated parallel synthesis and are powerful tools for producing diverse arrays of compounds, often in one step and high yield.[1] Several groups have used polymer supported reagents in combination with the Ugi multi-component reaction[2] giving a resin bound flexible Ugi product. Subsequent multi-step synthetic manipulation has allowed generation of a wide range of constrained derivatives, such as diketopiperazines,[3] imidazoles[4] and pyrroles.[5a] Product diversity with resin bound isonitriles has often been limited however by the clipping strategy, leaving final products containing a similarly positioned carboxylic acid or carboxamide functionality.[5b]

Reports from this laboratory have recently revealed the solution phase synthesis of conformationally constrained Ugi derivatives, employing the Ugi/De-BOC/Cyclization (UDC) strategy in combination with a convertible isonitrile (cyclohexenyl isonitrile)[6] and an internal amino nucleophile to generate diketopiperazines.[7] Final product purity from this solution phase protocol was limited as excess amounts of reagent could not be used to drive the initial Ugi MCR to completion, without dramatically effecting Area % yield (lc/ms - UV 220 nm). Thus to avoid tedious and costly parallel purification of the solution phase products a novel resin bound isonitrile, **1**, deployed as a novel safety-catch linker[8] was developed which would allow for excess reagent use in the Ugi condensation and potential further synthetic manipulation of the initial Ugi product as shown in Scheme 1.

Scheme 1



BOC-activation of the benzamide carbonyl to give **3** (R = BOC) (ie the safety-catch) promotes facile cleavage from the resin with methoxide or hydroxide[9] giving the corresponding methyl esters or carboxylic acids respectively. Multi-gram quantitites of the resin, **1** (IR NC stretch 2121 cm^{-1}), were accessible via modification of the Wang resin in 4 steps as shown

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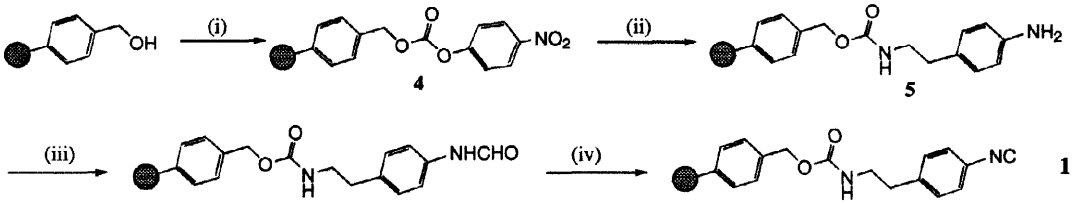
in Scheme 2.[10] Treatment with 4-nitrophenylchloroformate gives the carbonate resin **4**, and nucleophilic displacement allows access to the desired amino resin **5**. Formylation and dehydration affords the isonitrile linker, **1**.

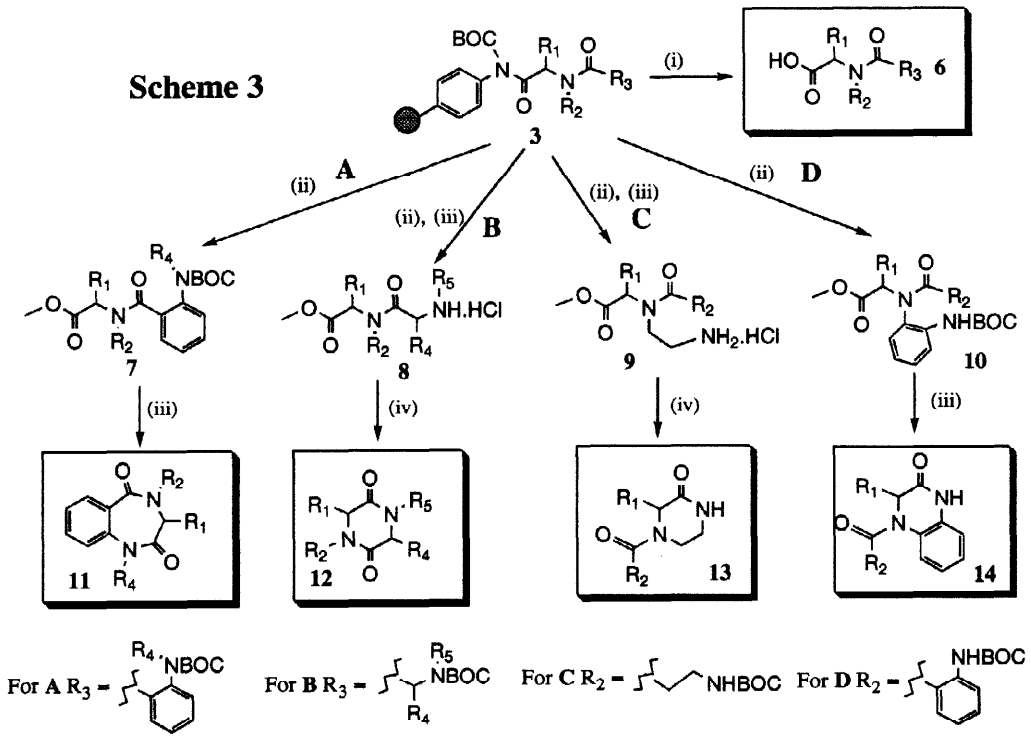
Scheme 2



Reagents and Conditions:- (i) Wang resin, 4-nitrophenylchloroformate (5 equiv.), *n*-methyl morpholine (10 equiv.), THF. (ii) 2-(4 amino phenyl)ethylamine (5 equiv.), DMF. (iii) Formic acid (excess), acetic anhydride (excess), CH_2Cl_2 (iv) Ph_3P (5 equiv.), CCl_4 (5 equiv.), Et_3N (5 equiv.), CH_2Cl_2.

The resin **1** was found to be stable for > 6 months when stored at low temperature and elemental analysis indicated a loading of 0.8mmol/g. The reaction sequences from isonitrile resin to constrained products **11**, **12**, **13**, **14** and **15** are shown in Scheme 3. The resin performed well in the Ugi MCR with a variety of supporting reagents and complete disappearance of the characteristic isonitrile absorption ($2121cm^{-1}$) was normally seen after 2 to 3 days at ambient temperature. Five potential sources of internal amino nucleophiles were investigated, namely *N*-BOC anthranilic acids to give 1,4-benzodiazepine-2,5-diones, **11**, *N*-BOC α-amino acids to give diketopiperazines, **12**, and 2 *N*-BOC diamines to give ketopiperazines, **13** and dihydroquinoxalinones , **14**.

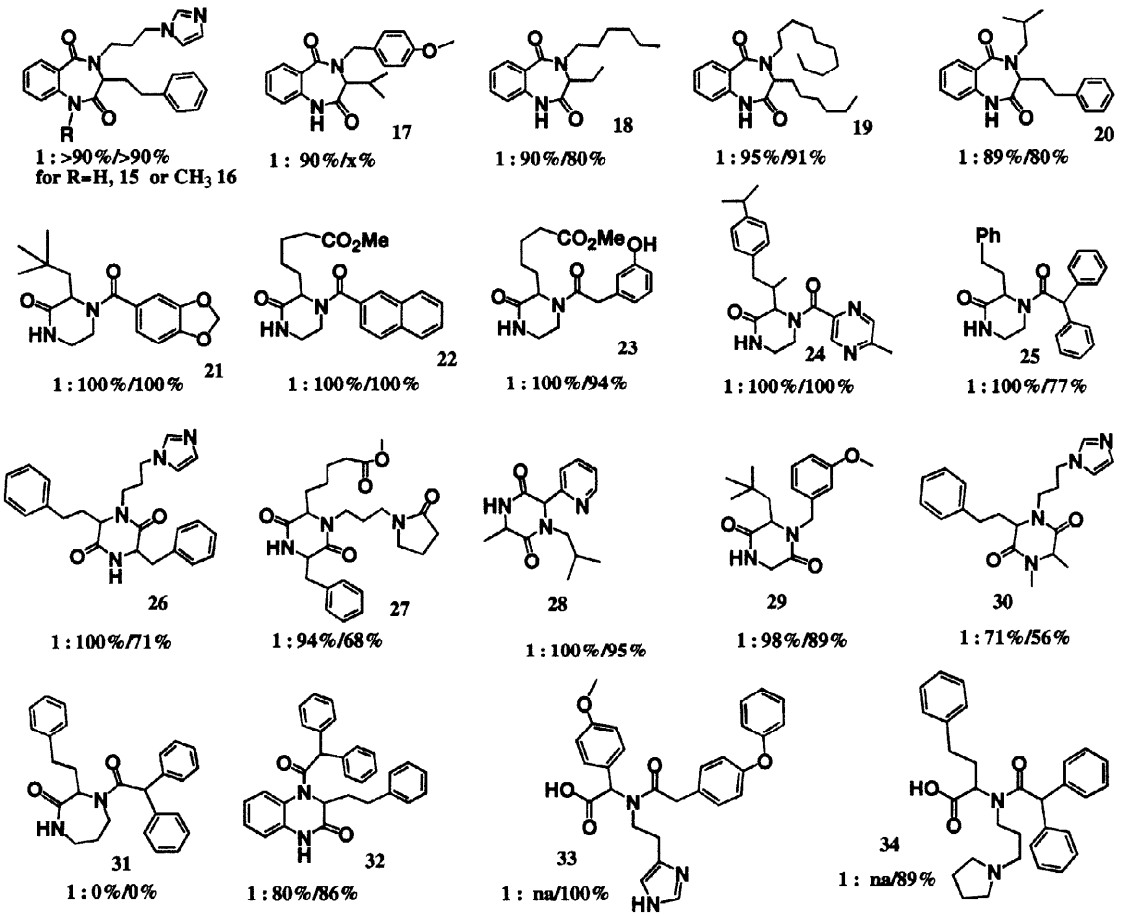
Scheme 3



Reagents & Conditions :- (i) LiOH, 5% H_2O_2/H_2O/THF (ii) NaOMe, MeOH:THF, 1:1. (iii) 10%AcCl/MeOH (iv) 5% Et_2NH in DCE or basic DOWEX.

Reports of the biological utility of compounds containing these core templates are widespread, including applications as antagonists of the platelet glycoprotein IIb-IIIa,[11] anti-convulsant agents,[12] serine protease inhibitors,[13] and CNS agents.[14]

BOC-activation of the benzamide carbonyl to give **3** (R = BOC) promoted facile cleavage from the resin with methoxide[9] giving the corresponding methyl esters. (Note - Lc/ms evaluation of these products also revealed the existence of the analogous di *N*-BOC products). Resin clipping with LiOH also allowed access to a series of carboxylic acids, **6**. Deprotection of the internal amino nucleophile with a 10% solution of AcCl in MeOH and evaporation at 65°C[15] affords products **11** and **14** respectively. Only partial cyclization of the methyl esters **8** and **9** was detected. Cyclization was thus facilitated by base treatment (either a 5% solution of diethylamine in DCE or DOWEX 1 x 8-50 ion-exchange resin[16]) and evaporation giving structures **12** and **13**, respectively. Examples of some of the products are presented, **15** to **34**, along with lc/ms A% purities (**1**, Phenyl isonitrile resin ELSD A%/UV A%).[17]



It is clear from the above examples that high purity (A%) biologically relevant constrained templates are accessible utilising the resin bound isonitrile **1** in the Ugi MCR as a safety-catch linker. The methoxide safety-catch clipping strategy and subsequent solution phase cyclization offers similar advantages to a traceless linker[18] in that no constant functionality derived from clipping remains at the end of the synthetic protocol. A variety of 1,4-benzodiazepine-2,5-diones (**15** to **20**), ketopiperazines (**21** to **25**) and diketopiperazines (**26** to **30**) were all prepared in high purity with the resin. Difficulty was encountered with the 7-membered ring ketopiperazine, **31**, where the final cyclization could not be forced under the above conditions. In excess of 1000 carboxylic acids have currently been produced via hydroxide clipping, with **33** and **34** being representative examples obtained in high A% yield. Diverse side-chain

functionality was compatible with the synthetic process and readily available from the legions of purchasable aldehydes, primary amines and carboxylic acids. With the current ease of automation of polymer supported reagents for parallel synthesis it is expected that the methodology described herein will allow rapid access to highly pure, diverse and large combinatorial arrays based around the above templates.

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