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A latent aryl hydrazine 'safety-catch' linker compatible with *N*-alkylation

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Abstract

The preparation and use of a latent aryl hydrazine 'safety-catch' linker for solid-phase chemistry, which is compatible with *N*-alkylation, is reported. Its use is exemplified by the preparation of mono-ketopiperazines, whereby release from resin is effected via an intramolecular cyclitive cleavage strategy.

Keywords: solid-phase synthesis; alkylation; hydrazines; cyclisation.

As part of a program to prepare libraries of small heterocycles derived from amino acids via an intramolecular cyclitive cleavage[1] process, we required a 'safety-catch'[2] linker that was compatible with both Mitsunobu *N*-alkylation[3] and stable towards nucleophiles, but which was amenable to activation under mild conditions towards nucleophilic cleavage. Conventional acyl-sulphonamides would be unsuitable for this purpose, since their activation to nucleophilic attack is effected by *N*-alkylation.[4] In addition, the recently reported aryl hydrazine 'safety-catch' linker[5] was found to be incompatible with Mitsunobu *N*-alkylation conditions in our hands, giving rise to multiple products probably derived from alkylation of the linker itself.

However, it was anticipated that this difficulty could be resolved by blocking the reactive hydrazine functionality with a protecting group that could be easily removed prior to oxidative cleavage from the resin (Fig. 1). Herein we report the preparation of a 'latent' aryl hydrazine 'safety-catch' linker which utilises this strategy. Its utility[6] was demonstrated by the preparation of mono-ketopiperazines (MKPs)[7] derived via the cyclitive cleavage of resin-bound dipeptoid precursors which were assembled in situ using Mitsunobu *N*-alkylation chemistry. Notably, using

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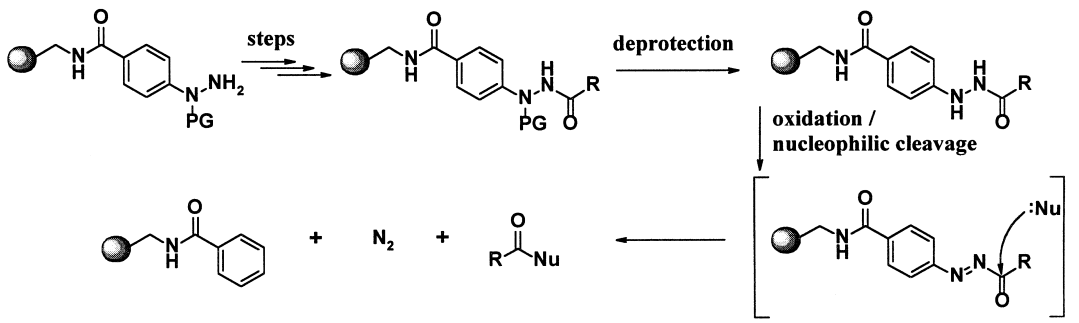
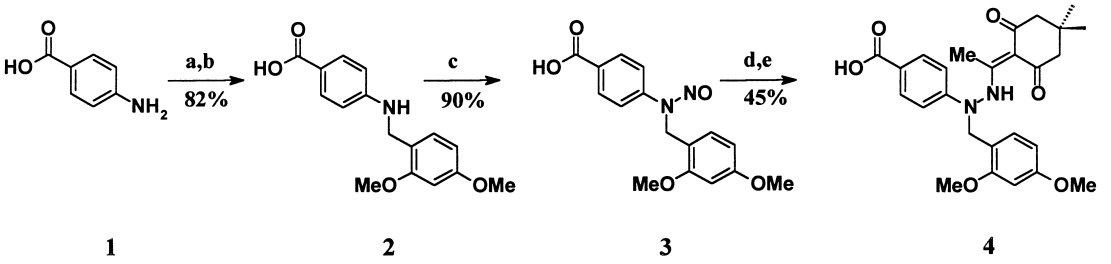


Figure 1. Principle of the latent arylhydrazine 'safety-catch' linker

this strategy it was possible to effect reductive amination of the dipeptoid N-terminus without premature cyclitive cleavage occurring prior to the penultimate oxidative cleavage step. This provides a synthetic route to MKPs bearing four points of diversity on a six-atom scaffold.

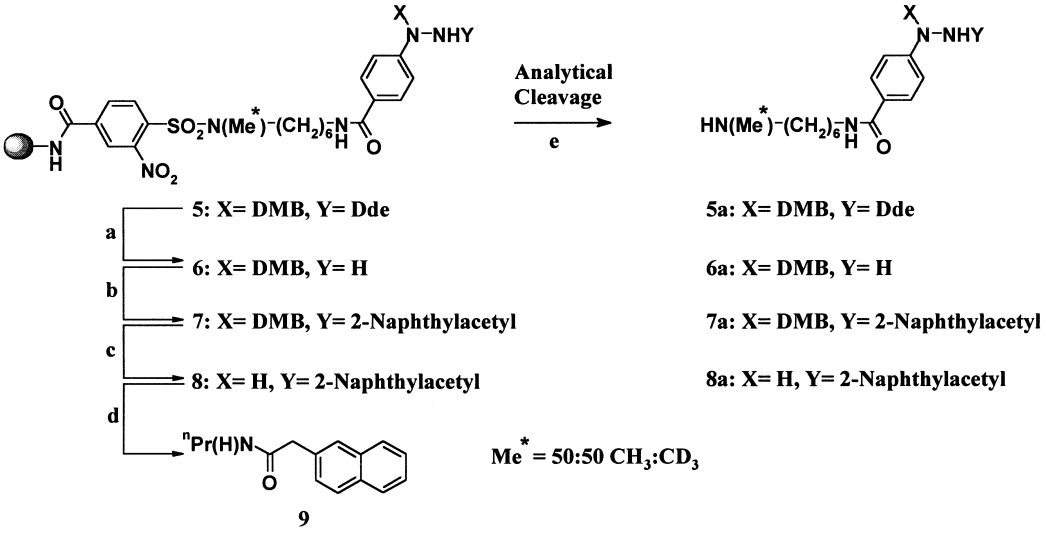
We chose to evaluate 2,4-dimethoxybenzyl[8] (DMB) as the blocking group for the aryl hydrazine, since this *N*-substituent is removable under mildly acidic conditions. Thus, *N*-(2,4-dimethoxybenzyl)-hydrazinobenzoic acid was prepared from 4-aminobenzoic acid by reductive amination with 2,4-dimethoxybenzaldehyde, nitrosation ($NaNO_2$, H_2SO_4) and subsequent zinc-mediated reduction (Scheme 1). The linker was conveniently isolated as the Dde derivative **4**.

To more easily determine its properties, the *N*-(2,4-dimethoxybenzyl)-arylhydrazine (DMBAH) linker **4** was attached to ArgoGel^{TM} amine resin preloaded with the *o*-nitrobenzenesulphonamide linker[9] and a diamine spacer to generate the dual linker system **5**.[10] Selective cleavage of the sulphonamide (DBU, mercaptoethanol) allowed reactions at the DMBAH linker to be conveniently studied by HPLC–MS (10–100 beads) (Scheme 2) by analysis of the products **5a**–**8a**, which contain an amine to enhance ionisation (ES^+) and an isotopic label to aid the interpretation of their mass spectra.



Scheme 1. *Reagents and conditions*: (a) 2,4-dimethoxybenzaldehyde, *p*TsOH, PhMe, reflux, 18 h; (b) $NaBH(OAc)_3$, AcOH, CH_2Cl_2, rt, 72 h; (c) $NaNO_2$, H_2SO_4, EtOH, rt, 18 h; (d) Zn, H_2O, AcOH, 100°C, 6 h; (e) DdeOH, EtOH, reflux, 0.5 h

Using this technology, optimal conditions for the removal of the Dde group from the DMBAH linker construct **5**, as well as the loading of the resin **6** with substrate and the removal of the DMB blocking group on the *N*-acylated resin **7** to give **8**, were readily determined. In particular, the DMB blocking group was found to be completely removed from the acylhydrazine **7** upon exposure to 5% TFA/CH_2Cl_2 at 20°C for 15 min. Subsequently, treatment of **8** with *n*-propylamine/$Cu(OAc)_2$ effected complete cleavage of the deprotected DMBAH linker to afford amide **9**



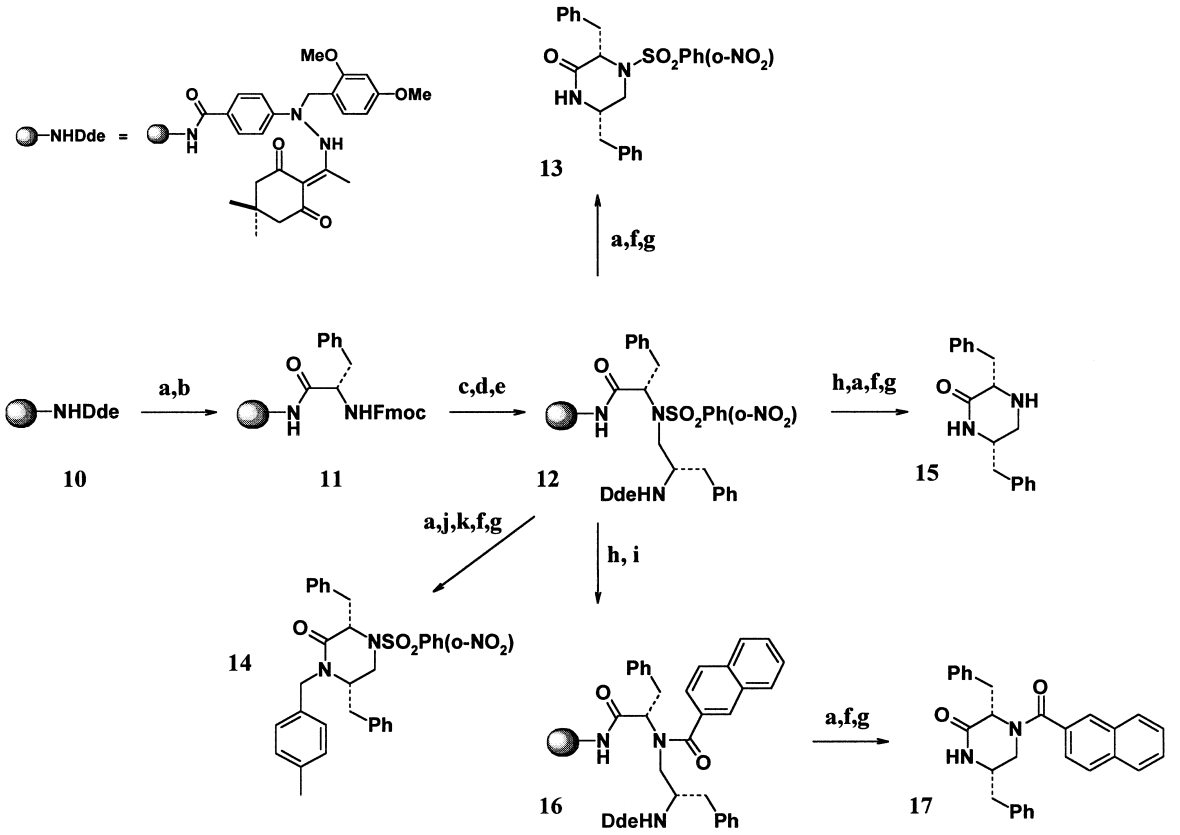
Scheme 2. *Reagents and conditions*: (a) 1:5 $H_2NNH_2{\cdot}xH_2O$:DMF; (b) 2-naphthylacetic acid, DIC, CH_2Cl_2, DMF; (c) 5%TFA/CH_2Cl_2; (d) $Cu(OAc)_2$, *n*-propylamine; (e) mercaptoethanol, DBU, MeCN

(analytical cleavage of the resulting resin showed no trace of residual **8a**). Crucially, these conditions did not affect the DMB-blocked resin **7**, thereby demonstrating the latent 'safety-catch' principle.

To exemplify the use of the DMBAH linker **4** in solid-phase synthesis, four representative examples of MKPs were prepared. Thus, the linker **4** was attached to ArgoGel^{TM} amine resin, deprotected and loaded with *N*-Fmoc-phenylalanine to afford the resin **11**. The Fmoc group was removed and the resulting amine was converted into the intermediate *o*-nitrobenzenesulphonamide, which was then *N*-alkylated[3b] with *N*-Dde-phenylalaninol under Mitsunobu conditions in the presence of di-*tert*-butylazodicarboxylate to afford the resin-bound adduct **12** (Scheme 3 and Table 1).

At this stage, several different synthetic protocols could be applied in order to provide MKPs displaying various functionalities. For example, removal of the Dde protecting group with 20% hydrazine hydrate/DMF afforded an intermediate amine, which was treated with 5% TFA/CH_2Cl_2 (RT, 10 min) and then with $Cu(OAc)_2$/pyridine in MeCN to give the MKP **13** in excellent overall yield and purity. Alternatively, the adduct **12** could first be subjected to a reductive amination with 4-methylbenzaldehyde. Deprotection and oxidation then effected cyclitive cleavage to afford the MKP **14**. In another variation the arylsulphonamide could first be removed from **12** (PhSNa, DMF) to give an intermediate secondary amine, which was then either subjected to cyclitive cleavage to afford the amine **15**, or derivatised further prior to cleavage. This latter process was exemplified by the preparation of the carboxamide **16** using 2-naphthoyl chloride as the acylating agent followed by deprotection/oxidation/cyclitive cleavage to afford the MKP **17**.

In conclusion, we have prepared and demonstrated the compatibility and utility of the latent arylhydrazine 'safety-catch' linker (DMBAH) **4** with sulphonylation and Mitsunobu chemistry. Conditions suitable for its deprotection/cleavage have been defined and its use has been exemplified by the preparation of MKPs. Studies to exploit this novel linker in the preparation of other heterocycles of varying ring size and in identifying alternative hydrazine protecting groups will be reported in due course.



Scheme 3. *Reagents and conditions*: (a) 1:5 $H_2NNH_2{\cdot}xH_2O$, DMF; (b) Fmoc-Phe-OH, DIC, CH_2Cl_2, DMF; (c) 20% piperidine, CH_2Cl_2, DMF; (d) *o*-nitrobenzenesulphonyl chloride, DIPEA, CH_2Cl_2; (e) Ph_3P, TBAD, *N*-Dde-phenylalaninol, CH_2Cl_2; (f) 5% TFA/CH_2Cl_2; (g) $Cu(OAc)_2$, pyridine, MeCN; (h) PhSNa, DMF; (i) 2-naphthoyl chloride, DIPEA; CH_2Cl_2; (j) (*p*-Me)PhCHO, TMOF, CH_2Cl_2; (k) Me_4NBH_4, CH_2Cl_2

Table 1
Overall yield and purity of MKPs

Compound	Purity[11]	Isolated yield[12]
13	>90%	65%
14	75%	34%
15	>90%	70%
17	>95%	76%

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6. In principle, linkers based upon simple deactivated esters may be utilised to access MKPs. However, they are prone to nucleophilic cleavage (cf. Fantauzzi, P. P.; Yager, K. M. *Tetrahedron Lett*. ***1998***, *39*, 1291) and, in our case, some hydrazinolytic cleavage from the resin when the N-terminal Dde protecting group was removed prior to oxidative activation would most likely have occurred (in our hands, the Mitsunobu alkylation failed when the alternative acid-labile *N*-BOC or base-labile Fmoc protecting groups were employed). Additionally, in some cases cyclitive cleavage would probably have competed with the reductive amination, limiting the potential to introduce an additional point of diversity into the MKP scaffold.
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11. NMR purity of crude material after removal of copper salts by acidic wash (10% HCl) or sequestation by Chelex® resin.
12. Isolated yield after purification by autopreparative HPLC.