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A Novel Linker Strategy for Solid-Phase Synthesis

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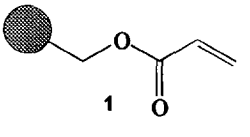
Abstract: The REM resin for solid phase synthesis is described. Its use is illustrated by preparing a small array of tertiary amines using a Hofmann elimination reaction. No functional group is required for linking these compounds onto the resin other than the amine constructed during the synthesis.

The synthesis of non-oligomeric organic compounds using resin-bound synthetic routes is a key component of the emerging technology of combinatorial chemistry.[1-4] One of the current limitations of this approach is the requirement for a "handle" to link small organic molecules onto a polymeric resin. In Merrifield peptide synthesis, for example, a carboxylic acid is linked via an ester group. Recently the range of linkers has increased [3,4] and silicon-based traceless linkers for phenyl rings have been reported.[5,6]

This letter describes a new type of linker and release system for resin-bound synthesis which is based upon the classical Michael addition and Hofmann elimination reactions. We note that Michael addition reactions to resin-bound acrylate ester derivatives have been reported previously[7,8] and that a β-elimination reaction has been used as a cleavage mechanism to liberate carboxylic acids during peptide synthesis.[9,10] One of the fascinations of combinatorial chemistry is the opportunity it offers organic chemists to rediscover new uses for old reactions; the origins of our study can be traced back to 1851 when Hofmann first reported the elimination of quaternary ammonium compounds.[11]

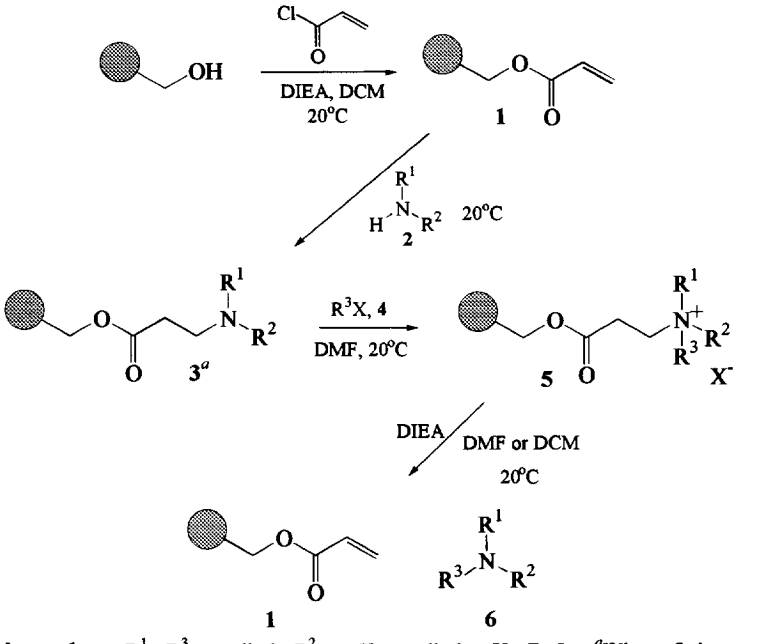


THE *REM* RESIN

= polystyrene resin

Our synthetic route, which is outlined in Scheme 1, utilises hydroxymethyl polystyrene resin derivatised as the acrylate ester **1**. Michael addition of a secondary amine **2** gives the resin-bound tertiary amine **3**. Alternatively, a primary amine **2** gives a resin-bound secondary amine which is converted into the tertiary amine **3** by reductive alkylation. Quaternisation of the tertiary amine **3** with an alkyl halide **4** to give **5** introduces another site of diversity and activates the linker for cleavage by a facile Hofmann elimination reaction. Thus iPr_2NEt (DIEA) at room temperature liberates the tertiary amine **6** into solution and regenerates the resin **1**. Since the resin linker **1** is REgenerated after cleavage of the product and is

functionalised via a Michael reaction, we refer to the resin as the REM resin. This strategy for solid-phase chemistry is exemplified with the synthesis of a small array of tertiary amines using mild experimental conditions.



Scheme 1 R^1, R^3 = alkyl, R^2 = H or alkyl. X=Br,I. [a]Where **3** is a secondary amine (R^2=H), conversion to a tertiary amine is achieved by reductive alkylation on the resin using a suitable aldehyde and $NaBH(OAc)_3$ in 1% acetic acid/DMF for 18 hours at 20°C.

Tables 1 and 2 show some of the amines that have been prepared by this route. The purity of the products is good, presumably because only the desired quaternised amine **5** will be susceptible to the cleavage conditions. Table 1 indicates that the method is compatible with esters, anilines or Boc protected amines. The very low yield (8%) obtained for one of the transformations in Table 2 is thought to be due to poor quaternisation of a resin-bound bisbenzylic tertiary amine.

In summary, we have shown that the Hofmann elimination reaction can be used to prepare tertiary amines via resin-based synthesis utilising mild experimental conditions without recourse to the functional groups usually associated with solid-phase chemistry. A characteristic of this concept is that it requires no linker to the resin other than the functional group constructed during the synthesis. In principle this strategy is applicable to other resins and the Michael reaction could be performed with a variety of nucleophiles.

Acknowledgement: We thank Dr. A. Brown for determining the substitution level of the hydroxymethyl polystyrene resin.

Table 1. Synthesis of tertiary amines from secondary amines by the route shown in Scheme 1.[12]

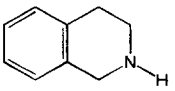
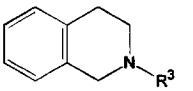
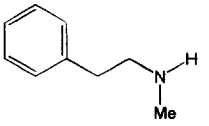
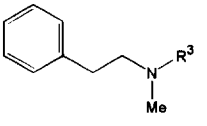
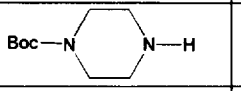
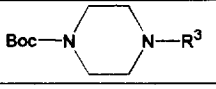
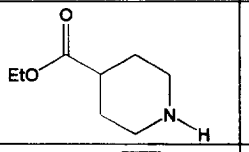
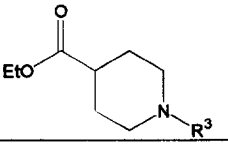
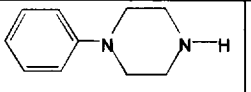
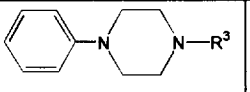
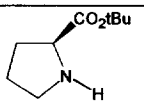
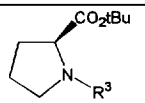
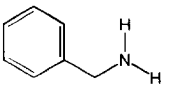
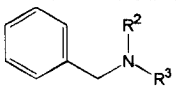
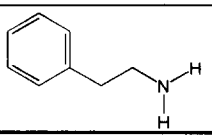
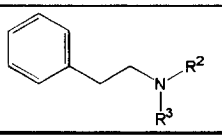
Starting Amine **2**	Product **6**[a]	R^3	Yield[b]
		methyl n-butyl allyl *p*-nitrobenzyl CH_2CO_2Et	63 56[c] 88 63 73
		allyl *p*-nitrobenzyl	81 69
		allyl	84
		allyl *p*-nitrobenzyl	78 64
		allyl *p*-nitrobenzyl	75 47
		*p*-nitrobenzyl	48

Table 2. Synthesis of tertiary amines from primary amines by the route shown in Scheme 1.

Starting Amine **2**	Product **6**[a]	R^2	R^3	Yield[b]
		methyl *p*-nitrobenzyl n-butyl	*p*-nitrobenzyl methyl *p*-nitrobenzyl	86 8 25
		*p*-nitrobenzyl	methyl	75

[a] All compounds gave satisfactory 400MHz ^{1}H NMR spectra and the correct molecular ion by GC-MS. The purity of the final products is greater than 90% as determined by gas chromatography. [b] % yields for 3 or 4 steps based on the resin substitution level determined by the Fmoc quantitation method.[13]
[c] Cleavage of N-butyl-tetrahydroisoquinoline occurred during the quaternisation step.

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12 All tertiary amine products gave satisfactory 400 MHz ^{1}H nmr spectra and GC-MS. A typical experimental procedure is as follows: hydroxymethyl polystyrene resin (1g; 0.58mmol) [Bachem California; 0.58mmol/g] was added to a 10ml polypropylene tube [Biorad 'Poly-Prep' Column]. Anhydrous dichloromethane (7ml) and diisopropylethylamine (866µl; 5mmol) were added, followed by acryloyl chloride (404µl; 5 mmol). The vessel was then placed on a tube rotator [Stuart Scientific Blood Tube Rotator SB1] and agitated for four hours at 20°C. The resin was washed with DCM (3x3ml) and methanol (2x3ml) and was dried in vacuo. A portion of the resin (0.3g; 0.17mmol) was swollen with a mixture of DMF (4ml) and 1,2,3,4-tetrahydroisoquinoline (376µl; 3mmol). The tube was agitated on the rotator for 18 hours at 20°C. The resin was washed with DMF (3x2ml), DCM (3x2ml) and methanol (2x2ml) and dried in vacuo. The resin was suspended in a solution of allyl bromide (130µl; 1.5mmol) in DMF (4ml) and was agitated on the rotator for 18 hours at 20°C. The resin was washed with DMF (3x2ml), DCM (3x2ml) and methanol (2x2ml) and dried in vacuo. A suspension of the resin in DMF (4ml) containing DIEA (106µl; 0.6mmol) was agitated on the rotator for 18 hours at 20°C. The resin was washed (3x2ml DMF, 3x2ml DCM, 2x2ml CH_3OH) and the filtrate was evaporated. The resulting white solid was partitioned between ethyl acetate (2ml) and 5% aqueous sodium carbonate (2ml). The organic layer was removed and the aqueous layer washed with ethyl acetate (2x1ml). The combined organic washings were dried (K_2CO_3) and evaporated. A trace amount of baseline material was removed using an ISOLUTE™-XL solid phase extraction column, containing 500 mg silica (Eluent: 40% Et_20 in heptane). A colourless gum was obtained (29.4mg; 97% overall yield).

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