



A novel traceless solid phase tertiary amine synthesis based on Merrifield resin

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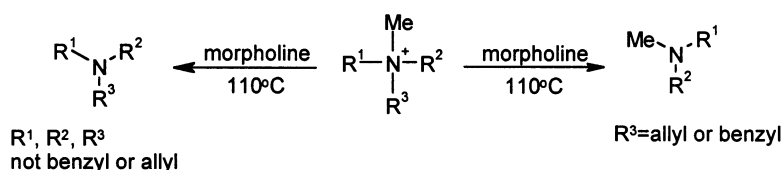
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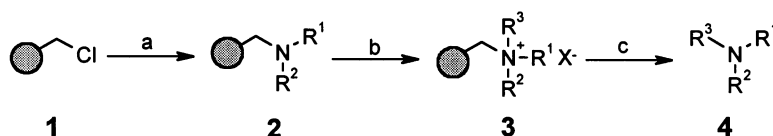
Abstract—Substitution of Merrifield resin by a secondary amine gives a resin-bound tertiary amine which is then quaternised with an alkyl halide to provide a resin-bound quaternary ammonium salt. Cleavage of the ammonium salt with morpholine delivers a tertiary amine in high yield and purity. © 2001 Elsevier Science Ltd. All rights reserved.

Solid phase tertiary amine synthesis has been the subject of several recent publications.^{1–10} In our laboratories we have developed the REM linker^{1,2} for the production of tertiary amines. This methodology is based on an addition–quaternisation–elimination sequence. Michael addition of a secondary amine to the resin-bound α,β -unsaturated ester provides a resin-bound tertiary amine. Quaternisation of the resin-bound tertiary nitrogen with an excess of an alkyl halide gives a resin-bound quaternary ammonium salt, which when treated with a base^{1,6,7} effects a Hofmann elimination and provides the desired tertiary amine in high purity. Although this methodology has been successfully applied to the preparation of libraries for HTS, it has some limitations: firstly, only reactive alkyl

halides, such as methyl iodide, allyl and benzyl bromides, can give a meaningful yield of final product; secondly, the linker itself is not stable under all reaction conditions. Several modifications of this method have been recently published^{3–7} in an attempt to extend the utility of this methodology and to overcome some of these limitations. As part of our effort to develop a reliable method suitable for making novel combinatorial tertiary amine screening libraries, we discovered that, in solution, quaternary ammonium salts can be dequaternised with high selectivity by heating in neat morpholine¹¹ at 110°C. Under these conditions, debenzylation and deallylation are highly favoured over demethylation which itself is much more favoured over the loss of other alkyl groups, such as *n*-butyl and



Scheme 1.

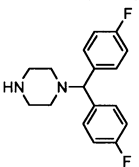
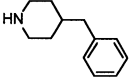


Scheme 2. (a) 3.5 equiv. of $\text{R}^1\text{R}^2\text{NH}$, 1 equiv. of NaI, *N*-methylpyrrolidin-2-one (8–10 ml/g resin), 65 h, 100%; (b) 20 equiv. of R^3X , DMF (8 ml/g resin), 58°C,¹⁵ 60 h, 64–100%; (c) morpholine (8 ml/g resin), 70–110°C, 10–20 h.

Keywords: tertiary amine; traceless linker; solid phase synthesis.

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Table 1. Results from the solid phase tertiary amine synthesis¹⁸

R ¹ R ² NH	R ³ X	Yield ^c of 3	Yield ^d of 4 @70 °C (purity) ^e	Yield ^f of 4 @110 °C (purity) ^e	MWt(MS)
	MeI ^a	100%	94%(>95%)	g	302(303MH ⁺)
	EtI ^b	100%	86%(>95%)	g	316(317MH ⁺)
	n-BuI ^b	93%	74%(>95%)	g	344(345MH ⁺)
	Ph(CH ₂) ₃ Br ^b	64%	31%(>95%)	g	406(407MH ⁺)
	MeI ^a	100%	13%(85%)	83%(85%)	189(190MH ⁺)
	EtI ^b	100%	23%(>95%)	83%(93%)	203(204MH ⁺)
	n-BuI ^b	100%	37%(>95%)	85%(90%)	231(232MH ⁺)
	Ph(CH ₂) ₃ Br ^b	70%	38%(>95%)	g	293(294MH ⁺)

^a Room temperature, 20 equiv. of MeI.^b Heated at 58 °C for 60 hours, 20 equiv. of R³X^c Yields are based on the dried resin weight. In some cases, weight is slightly higher than expected.^d Cleaved at 70 °C for 20 hours.^e Purity by ¹H-NMR and LC-MS, generally only expected product can be detected.^f Cleaved at 110 °C for 10 hours.^g Reaction not attempted

3-phenylpropyl (Scheme 1). This selectivity opened up the possibility for the development of a resin bound approach to tertiary amine synthesis, particularly as benzyl was one of the best leaving groups and could be easily derived from Merrifield resin.

Although several dequaternisation reagents have been reported,¹² we believe that this is the first application of these conditions to solid phase synthesis. In this letter we disclose a novel traceless¹³ methodology for solid phase tertiary amine synthesis which is based on an S_N2–quaternisation–S_N2¹⁴ reaction sequence (Scheme 2).

The solid phase route starts with high loading Merrifield resin **1**. Substitution of the resin-bound benzylic chlorine by a secondary amine using sodium iodide as catalyst afforded a resin-bound tertiary amine **2**. Quaternisation of this resin-bound tertiary nitrogen with an alkyl halide in DMF gave the resin-bound quaternary ammonium salt **3**. Although the quaternisation with methyl iodide

proceeded smoothly, other alkyl iodides were slow at room temperature. The almost quantitative yield can only be achieved with heating at 55–60°C for up to 60 hours. Under these conditions, less reactive alkyl halides, such as 3-phenylpropyl bromide, also give a useful yield (64–70%). Attempts to increase the yield of the quaternisation step by raising the temperature to 100°C were found to be detrimental and led to slow dequaternisation and premature cleavage off the resin.¹⁶ The desired dequaternisation and cleavage of the resin-bound quaternary ammonium salt with morpholine¹⁷ at 110°C proceeded very smoothly and delivered the desired tertiary amine **4** in high purity and very good overall yield (Table 1). When a lower temperature (70°C) was used for the dequaternisation reaction, it was found that the reaction generally requires much longer reaction times.¹⁸

To demonstrate further the usefulness of this methodology, a 3D library of compounds was synthesised in

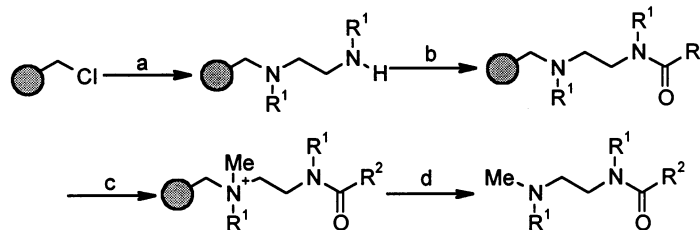
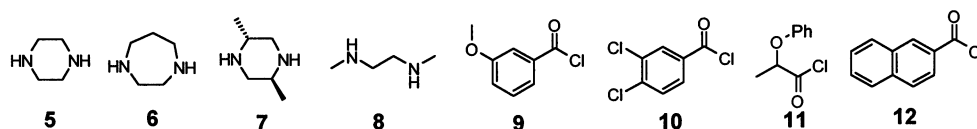
**Scheme 3.** (a) 10 equiv. of bisamines, 1 equiv. of NaI, DMF (5 ml/kan), 60 h; (b) 5 equiv. of R²COCl, DCM/pyridine (5:1) (5 ml/kan), rt, 5 h; (c) 20 equiv. of MeI, rt, 60 h; (d) morpholine (4 ml/kan), 100°C, 10 h.**Figure 1.** Building blocks.

Table 2. Results from 3D library

	Bisamines (R ¹)	R ² COCl	Yield (%)	Purity ^a (%)	MWt ^b (MS)
1	5	9	80	90	234 (235 MH ⁺)
2	5	10	52	>95	273 (273 MH ⁺)
3	5	11	70	90	248 (249 MH ⁺)
4	5	12	75	>95	254 (255 MH ⁺)
5	6	10	77	>95	287 (287 MH ⁺)
6	7	10	6	90	301 (301 MH ⁺)
7	8	10	59	>95	275 (275 MH ⁺)

^a Yields are based on purified product by prep-HPLC; purity determined by LC–MS.

^b Atomic mass of chlorine was taken as 35.5.

IRORITM macrokans using the chemistry depicted in Scheme 3. Four bisamines, four acyl chlorides and one alkyl halide (Fig. 1) were combined to give a library of 16 compounds. A representative sample of the results are shown in Table 2.

In conclusion, a novel traceless solid phase tertiary amine synthesis based on Merrifield resin has been developed. This method should offer a much more versatile stable linker that permits a wider range of functional group transformations to be effected on the resin. We are currently searching for a high throughput cleavage method. One possibility is to use a nucleophilic counter-ion such as hydroxide or fluoride in an assisted solvent free thermal cleavage. The findings from these studies will be reported in due course.

Acknowledgements

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- This can be regarded as a *safety catch* method.
- Quaternisation is also an S_N2 reaction. The dequaternisation might be more complicated than a simple S_N2 reaction. For Ph₃P as reagent see: Deady, L. W.; Korytsky, O. L. *Tetrahedron Lett.* **1979**, 5, 451–452.
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- Choosing morpholine for this reaction is due to its ideal resin swelling property.
- All tertiary amine products gave satisfactory 400 MHz ¹H NMR spectra and LC–MS. A typical experimental procedure is as follows: Merrifield resin (5 g; 9.55 mmol, Polymer Laboratories; 1.91 mmol/g) was added to a 100 ml conical flask. *N*-Methylpyrrolidin-2-one (50 ml) and sodium iodide (1.5 g; 10 mmol) were added, followed by 1-bis(4-fluorophenyl)methylpiperazine (10 g; 34.7 mmol). The flask was shaken at rt on an orbital shaker for 65 h. The resin was cross-washed with MeOH (5×100 ml), water (5×100 ml), *N*-methylmorpholine (10% in DCM, 3×100 ml), DCM (5×100 ml), ether (100 ml) and was dried in vacuo (7.4 g; 100%; equivalent to 1.29 mmol/g). A portion of the resin (1.0 g; 1.29 mmol) was swollen with a mixture of DMF (7 ml) and *n*-butyl iodide (3 ml; 26 mmol) and was heated with slow stirring at 58°C for 60 h. The resin was cross-washed with MeOH (5×10 ml), DCM (5×10 ml) and ether (10 ml) and dried in vacuo (1.221 g, calculated yield: 1.237 g; 93%; equivalent to 0.99 mmol/g). A portion of the resin (0.5 g; 0.49 mmol) was swollen with morpholine (4 ml), and heated at 70°C for 20 h. The resin was washed with MeOH (2×3 ml) and the filtrate was evaporated. The resulting solid was partitioned between DCM (2 ml) and 5% aqueous sodium carbonate (2 ml). The organic layer was removed and the aqueous layer washed with DCM (2×2 ml). The combined organic washings were dried and evaporated to give 125 mg of product (74% for cleavage step; 69% overall yield based on Merrifield resin; >95% purity).