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General combinatorial synthesis of tertiary amines on solid support. A novel conditional release strategy based on traceless linking at nitrogen

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Abstract—A novel solid phase synthesis of tertiary amines involving iodide-induced cleavage of the N–O bond of resin bound alkoxyammonium intermediates is described. The quaternary intermediates were assembled via sequential reductive aminations followed by alkylation. Cleavage from the solid support was induced by iodide ion or base, to afford the target tertiary amines in excellent purity. © 2000 Elsevier Science Ltd. All rights reserved.

Solid phase organic synthesis (SPOS) offers certain advantages compared to traditional solution phase reactions.[1] Solid phase reactions are particularly attractive for combinatorial parallel synthetic work because of the relative ease of isolation and automated purification of the resin bound material after each reaction step. As part of a major effort to identify novel ligands for G-protein coupled receptors via R-SAT™ ultra high throughput screening[2] we needed to develop a general combinatorial approach to tertiary amines. Although amine-containing building blocks may be introduced using a variety of the traditional coupling reactions, greater diversity in the target library requires the combinatorial construction of carbon–nitrogen bonds. Elegant approaches utilising resin bound Michael acceptors for this purpose have been described by Brown et al. and Heinonen et al.[3,4] Unfortunately, the limited availability of secondary amine building blocks as well as potential lability of the linkers and a requirement for basic cleavage conditions present potential drawbacks with these methods.

Important provisos for our approach were (i) to use the nitrogen of the target tertiary amine as the point of attachment to the solid support, (ii) to construct all three carbon–nitrogen bonds via reliable reactions involving readily available building blocks, and, importantly, and (iii) to use a highly robust linking chemistry which, under mild cleavage conditions, would release only fully functionalised material.

Upon surveying the literature for suitable nitrogen–heteroatom linking chemistries, we were particularly intrigued by two papers by Liguori et al.,[5,6] who investigated ring opening reactions of isoxazolidinium salts by a variety of reagents, including bases and, notably, lithium iodide. These reports invited the use of alkoxyammonium intermediates in a solid phase synthesis of amines involving very mild conditional release from the resin. A suitable aminoxy-functionalised resin, allowing extremely robust linking during the sequence, was recently prepared for other purposes by Floyd et al. and Salvino et al.[7,8] We envisaged to introduce building blocks at nitrogen via either alkylation with alkyl halides, or a reductive amination sequence employing carbonyl compounds. Quaternisation of the trisubstituted hydroxylamines with a suitable electrophile would labilise the linking bond in the final step. Since only the quaternised material would be susceptible to iodide-induced release, tertiary amines of high purity should result. Grigg et al. very recently disclosed a related sequence, relying upon base induced cleavage to afford tertiary amines from resin bound alkoxyammonium precursors.[9] This prompted us to report on our preliminary results[10] concerning the solid phase synthesis of tertiary amines.

Preliminary experiments were carried out in solution, but under reaction conditions suitable for immediate adaption to the solid phase.

Keywords: tertiary amines; N–O cleavage; LiI; SmI_2; conditional release; solid phase.

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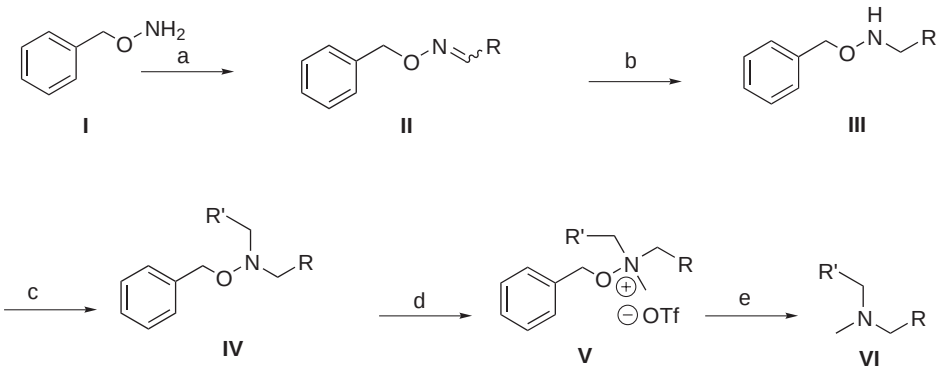


Scheme 1. Solution phase synthesis of tertiary amines via a hydroxylamine anchor. (a) RCHO, HOAc, MeOH, rt, 15 h. (b) BH_3·pyridine, HCl (4 M in dioxane), MeOH, rt, 12 h. (c) R′CHO, PPTS, BH_3·pyridine, THF:MeOH 1:3, rt, 12 h. (d) MeOTf, CH_2Cl_2, rt, 15 h. (e) Cleavage reagent.

Thus, reaction of *O*-benzylhydroxylamine **I** with aldehydes, RCHO (R = Ph, C_6H_{11} or Bn), in methanol containing 5% acetic acid for 15 h uneventfully returned the corresponding oximes **II** in over 80% yield (Scheme 1). Reduction of the oximes **II** proved somewhat difficult. After optimisation, we found that the use of borane–pyridine complex under acidic conditions (HCl, 4 M in dioxane, 12 h) afforded an approximately 70% yield of the *N*-alkylated products **III**. The commonly used reducing agent $NaCNBH_3$ in acetic acid gave considerably lower yields.[11] Subsequent reaction with an aldehyde, R′CHO (R′ = Ph, $CH(CH_3)_2$ or C_6H_{11}), under reductive alkylation conditions (PPTS, BH_3·pyridine, MeOH:THF 3:1, rt, 12 h), gave the corresponding alkoxydialkylamines **IV** in over 60% yield.[12] Importantly, preliminary results from exhaustive alkylation of several alkoxyamine intermediates have indicated that the second alkylation may be achieved equally selectively using an excess of an alkyl halide. Unfortunately, attempted quaternisation under a variety of different alkylation conditions (Table 1) turned out to be very sluggish, and failed to return the desired product with most alkylating agents.

However, the use of an excess of methyl triflate resulted in a good yield of quaternisation product at room temperature (entry 5).[9,13] In addition, activation of methyl iodide using silver triflate gave a similar yield (entry 6). We also noted that the introduction of K_2CO_3 as a base sometimes promoted the methylation reaction, probably by removing any trace of acid. An interesting observation was that combining methyl iodide and K_2CO_3 in DMF (entry 7) returned the product $^tBuC_6H_{11}N^+Me_2I^-$ despite the fact that methyl iodide alone was not a strong enough electrophile to quaternise the alkoxyamines under similar reaction conditions.

As expected, cleavage of the quaternised alkoxy amines could be induced by treatment with base (Table 2, entries 3 and 4). Encouragingly, exposure of the alkoxyammonium intermediate to the much milder reagents lithium iodide (in dioxane or acetonitrile) or samarium diiodide (in THF) also resulted in highly efficient cleavage, delivering tertiary amines of high purity (Table 2, entries 1, 2 and 5).

The reaction conditions which were developed during the successful solution phase sequence turned out to be readily transferred to the solid phase matrix (Scheme 2). In order to facilitate analysis of the efficiency of the individual steps in the polymer bound version of the protocol, building blocks carrying fluorine atoms were favoured initially.[14]

The aminoxy resin **VII** was synthesised from chloromethylated polystyrene (200–400 mesh, 1.19 mequiv. Cl per gram) via *O*-alkylation (K_2CO_3, *N*-hydroxyphthalimide, DMF, 60°C, 15 h), followed by deprotection with methylamine (H_2O:THF 4:6, 12 h, rt). Similarly, applying Mitsunobu conditions on Wang-OH or Argogel-OH resins afforded the desired aminoxy resin after deprotection of the phthalimido moiety.[7,8] Resin **VII** was treated with *p*-fluorobenzaldehyde (5

Table 1. Attempts to quaternise BnON^{i}PrBn (A) and BnON^{i}Pr(C_6H_{11}) (B) under various methylation conditions

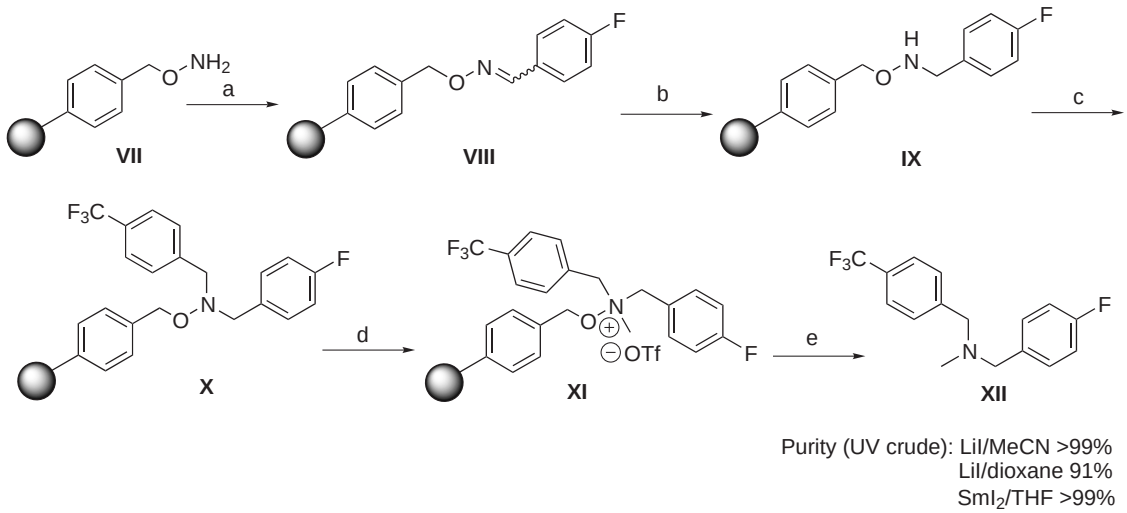
Entry	Substrate	Conditions	Yield (%)
1	A	CH_3I, CH_2Cl_2, rt–50°C	nr
2	A	CH_3I, DMF, 70°C	nr
3	A	$CH_3OSO_2CH_3$, CH_2Cl_2, rt–50°C	nr
4	A	$CH_3OSO_2C_6H_4CH_3$, CH_2Cl_2, rt–50°C	nr
5	A	$CH_3OSO_2CF_3$, CH_2Cl_2, rt	>80
6	A	CH_3I, $AgSO_3CF_3$, CH_2Cl_2, rt	80
7	B	CH_3I, K_2CO_3, DMF, 70°C	–[a]

[a] N–O cleavage occurred to produce $^tBuC_6H_{11}N^+Me_2I^-$ in >80% yield.

Table 2. Release of amine **VI** from **V** (R = Ph, R′ = ^{t}Bu) using various reagents

Entry	Conditions	Purity (%)[a]
1	LiI, dioxane, 70°C	>99
2	LiI, acetonitrile, 70°C	>99
3	K_2CO_3, DMF, 70°C	>90
4	Et_3N, CH_2Cl_2, rt	>99
5	SmI_2, THF, 70°C	89

[a] After ion-exchange chromatography.



Scheme 2. Solid phase synthesis of tertiary amines using a polystyrene based resin with a hydroxylamine linker.[7,8] (a) *p*-F-C_6H_4CHO, HOAc, THF:MeOH 2:1, rt. (b) BH_3·pyridine, HCl (4 M in dioxane), THF:MeOH 1:1, rt. (c) *p*-CF_3-C_6H_4CHO, PPTS, BH_3·pyridine, THF:MeOH 3:1, rt. (d) MeOTf, CH_2Cl_2, rt. (e) LiI in dioxane or acetonitrile, 70°C or SmI_2 in THF, rt.

equiv., THF:MeOH 2:1, 5% HOAc, 15 h) to give resin **VIII**. The oxime was smoothly reduced (BH_3·pyridine, 4 M HCl in dioxane, rt) to give the monoalkylated resin **IX**. A second reductive alkylation with *p*-trifluoromethylbenzaldehyde (PPTS, BH_3·pyridine, MeOH:THF 1:3, rt, 12 h) gave the dialkylated alkoxyamine resin **X**. This resin was treated with an excess of methyl triflate for 15 h at room temperature to give the quaternary salt ready for cleavage. As expected, both LiI and SmI_2 released the desired tertiary amine **XII** with very high purity (Scheme 2). Generally, 100 mg of resin afforded 5–10 mg of amine in a purity of over 90%. Purification by ion-exchange chromatography increased the purity to over 99%. In agreement with the solution phase behaviour, cleavage could be effected also with bases such as triethylamine.

The above reaction sequence could be monitored using gel-phase or solid phase IR spectroscopy or, more conveniently, ^{19}F NMR spectroscopy. Resin **VIII** displayed two signals (−109 and −110 ppm, respectively) in the ^{19}F NMR spectrum, assigned as a mixture of *E*- and *Z*-stereoisomers of the oxime (Fig. 1).

After reduction (Scheme 2, step b) a single new resonance appeared at −115 ppm. A trace amount of unreacted oxime could be observed. The second reductive amination (Scheme 2, step c) resulted in the expected two signals (−63 and −115 ppm, respectively) integrating at a ratio of 4:1.

We have prepared a variety of tertiary amines following the general procedure detailed above. For example,

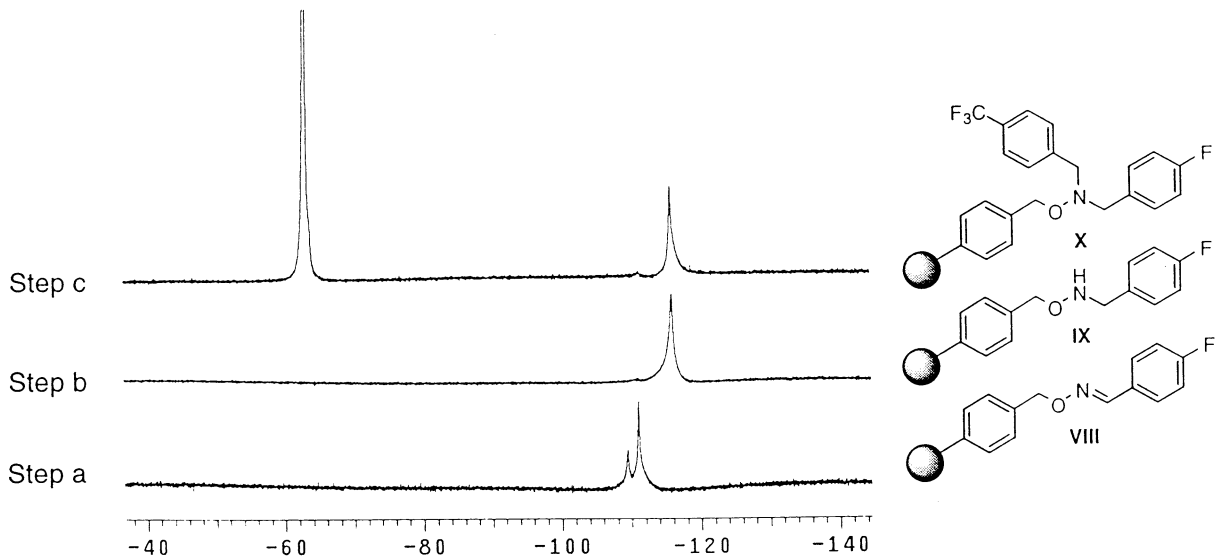


Figure 1. ^{19}F NMR spectra obtained at 376.8 MHz using CCl_3F as an internal standard.

aliphatic aldehydes as well as hindered aryl ketones (e.g. indanone, methylpropanal, etc.) were introduced as building blocks without complications. In our experience, cleavage from 30–50 mg of resin releases appropriate amounts of tertiary amines for HTS purposes. Furthermore, although basic cleavage remains an option, we have observed that the use of lithium iodide in acetonitrile, which is generally preferred because of the neutral reaction medium, tends to deliver products of superior purity. Product isolation can be conveniently performed via simple aqueous extraction and concentration.

In summary, we have developed a general solid phase sequence for the synthesis of quaternary alkoxy amines, and shown that tertiary amines of high purity may be released from the resin using several reagents, including lithium iodide or samarium iodide. We believe that this methodology will provide a useful addition to existing combinatorial strategies for the synthesis of tertiary amines, especially where very mild cleavage conditions are desired. A drawback of the current procedure is the requirement for a very strong alkylating reagent for quaternisation, and further investigations aimed at extending the scope of this step as well as the application of our protocol to the synthesis of focused libraries will be reported in due course.

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