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Solid-phase synthesis of tertiary methylamines via reductive alkylation–fragmentation using a hydroxylamine linker

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Abstract

The solid-phase synthesis of tertiary methylamines via reductive alkylation–fragmentation employing a hydroxylamine linker is described. The hydroxylamine linker is traceless, robust and versatile, allowing strong organometallic reagents to be used in the synthesis of diverse tertiary methylamines.

Keywords: solid-phase synthesis; tertiary methylamines; traceless hydroxylamine linker.

Solid-phase synthesis has evolved into a powerful tool for the rapid construction of combinatorial libraries of small, drug-like compounds.[1] There is a perceived lack of suitable linkers that are stable to a wide range of reagents required during synthesis, which can be cleaved under mild conditions and which are traceless.[2]

Tertiary amines are an attractive target from a drug discovery perspective, due to their good intestinal absorption, CNS penetration and the potential for involvement of the tertiary nitrogen in ligand binding.[3] REM resin has been used successfully for the synthesis of tertiary amine libraries.[4] However, the ester linkage of the REM resin precludes the use of certain desirable but aggressive reagents, which the more stable vinyl sulfone linker partially addresses.[5]

This letter describes a novel solid-phase strategy for the synthesis of tertiary methylamines utilising resin-bound hydroxylamine as a linker. This linker is inert to a range of aggressive reagents, including Grignard reagents, metal hydride reducing agents and strong acids or bases. The hydroxylamine linker employed in these studies is attached directly to hydroxymethyl polystyrene resin[6] (Scheme 1).

The hydroxylamine linker **1** was Boc-protected and the protected resin **2** alkylated (20 mol equiv. NaH/DMF/RT/16 h) with alkyl halides (40 mol equiv.), giving **3**. The Boc group was

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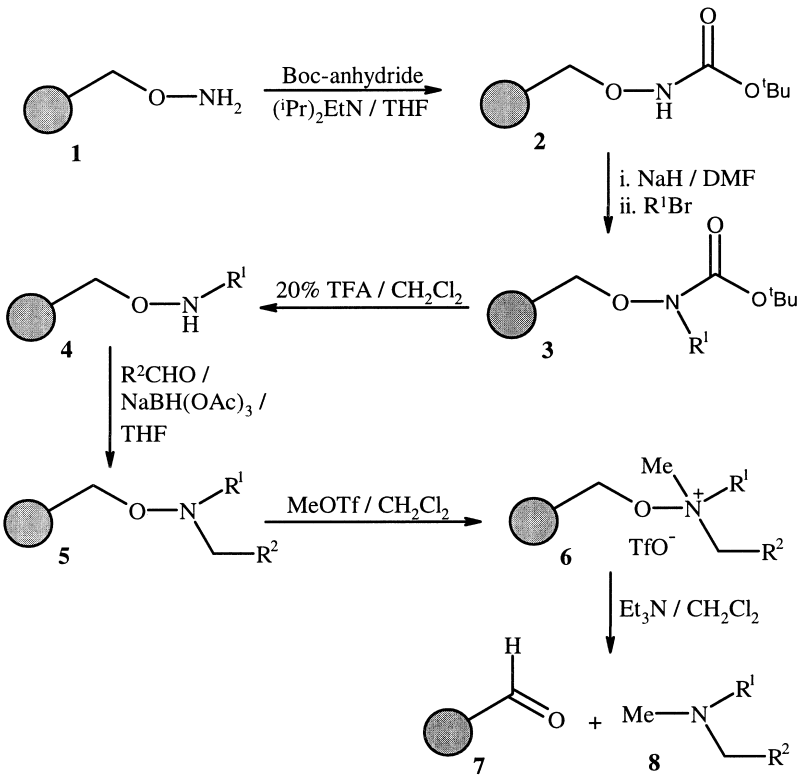


Scheme 1.

removed and the unprotected resin **4** reductively alkylated[7] with a variety of aldehydes (10 mol equiv. R^2CHO/5 mol equiv. $NaBH(OAc)_3$/THF/RT/16 h) to give the resin-bound tertiary hydroxylamines **5**. Extensive solution-phase studies of the quaternisation of tertiary hydroxylamines showed that methyl triflate was the only alkylating agent that gave excellent yields of quaternary salts. Although other triflates prepared in situ via silver triflate/alkyl halide exchange gave quaternary salts in solution (unpublished observations), this methodology proved unsuitable for the solid-phase sequence due to interference from the silver halide precipitate. The possibility that the α-effect might facilitate the quaternisation was not realized and this accords with related observations by other workers.[8]

Alkylation of **5** with methyl triflate (5 mol equiv./CH_2Cl_2/RT/16 h) gave the quaternised resin **6** and base-induced cleavage (5 mol equiv. Et_3N/CH_2Cl_2/RT/16 h) furnished the resin-bound aldehyde **7** and tertiary amines **8** (Table 1). The tertiary amines released from the resin were separated from the excess triethylamine and salts by a simple aqueous sodium bicarbonate wash.

The yields for the six-step reaction sequence are mostly excellent. The purity of the amine released from the resin is high (>99%, Table 1), because only the quaternised material **6** is susceptible to the base-induced cleavage. The reaction sequence was followed by FTIR analysis of the resins **1**–**7**, i.e. the alkylation step **2**→**3** was characterised by Boc carbamate C=O str. shifting from ~1740 to ~1700 cm^{-1} after alkylation. The resin-bound aldehyde **7** was characterised by the appearance of a strong absorption band at 1702 cm^{-1}.

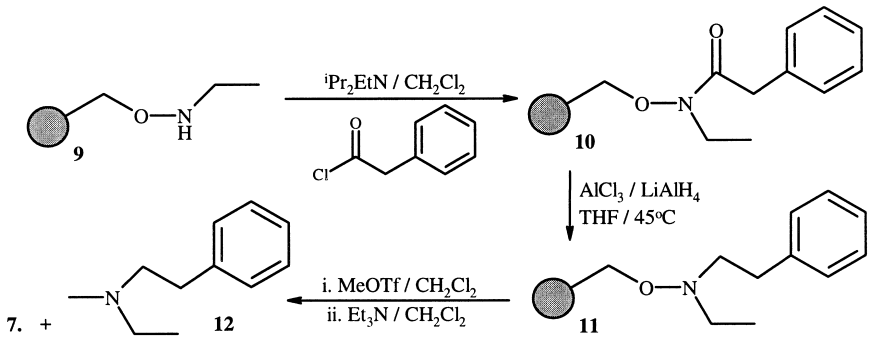
To establish whether the hydroxylamine linker was more robust than REM resin[4] with respect to strong reducing agents, we synthesised **9** by alkylation of **2** with ethyl bromide (Scheme 1) and

Table 1
Solid-phase synthesis of tertiary amines **8** (Scheme 1)

Entry	R^1	R^2	Aldehyde or Ketone	**8** (%)[a]
a.	$PhCH_2$	Me	Acetaldehyde	73
b.	$PhCH_2$	n-C_5H_{11}	Hexanal	80
c.	$PhCH_2$	Ph	Benzaldehyde	61[c]
d.	$PhCH_2CH_2$	Me	Acetaldehyde	76[c]
e.	$PhCH_2CH_2$	n-C_5H_{11}	Hexanal	74[c]
f.	$PhCH_2CH_2$	$(\text{-}CH_2CH_2\text{-})CH$	Cyclopropanecarboxaldehyde	77
g.	$PhCH_2CH_2$	$(\text{-}[CH_2]_5\text{-})CH$	Cyclohexanecarboxaldehyde[b]	51
h.	$PhCH_2CH_2$	2-MeO-PhCH=CH	2-Methoxycinnamaldehyde[b]	34
i.	$PhCH_2CH_2$	$(CH_3)_2CH$	Isobutyraldehyde	45[c]
j.	$PhCH_2CH_2$	$PhCH_2CH_2$	Hydrocinnamaldehyde	60[c]
k.	$PhCH_2CH_2$	Ph	Benzaldehyde	54[c]
l.	$PhCH_2CH_2$	4-MeO-Ph	4-Methoxybenzaldehyde	67[c]
m.	$PhCH_2CH_2$	4-F-Ph	4-Fluorobenzaldehyde	73
n.	$PhCH_2CH_2$	Thiophene	Thiophene-2-carboxaldehyde	64[c]
o.	$PhCH_2CH_2$	$\text{-}(CH_2)_5\text{-}$	Cyclopentanone[b]	56

[a]All compounds give satisfactory ^{1}H NMR and mass spectra. Isolated overall yields for 6 steps based on the hydroxylamine resin **1** loading,[9] determined by the Fmoc quantitation method.[10]
[b]Reductive alkylation reaction done in 1,2-dichloroethane solvent as opposed to THF
[c]Tertiary amine purity of >99% was determined for randomly selected examples by HPLC and LC-MS.

subsequent Boc deprotection. Acylation of **9** (Scheme 2) with phenylacetyl chloride gave resin-bound hydroxymate **10**. Solution-phase studies indicated that the best conditions for the reduction were a 1:1 mixture of aluminium trichloride and lithium aluminium hydride[11] in THF at 45°C. Using lithium aluminium hydride alone resulted in partial N–O bond cleavage.



Scheme 2.

Applying these conditions to the solid-phase synthesis (20 mol equiv. $AlCl_3$/20 mol equiv. $LiAlH_4$/45°C/45 min; followed by addition of resin **10**/45°C/4 h) gave tertiary hydroxylamine resin **11**, which was quaternised and cleaved, yielding the resin-bound aldehyde **7**, plus the tertiary amine **12** in a yield of 56%. A direct comparison of the two routes for the synthesis of **12** is shown in Table 2. The somewhat lower yield in the hydroxymate reduction pathway is the result of Hunig base-induced fragmentation during the conversion of **9** to **10** (Scheme 2), releasing the secondary amide and resin-bound aldehyde **7**. This was observed in solution-phase

Table 2
Comparison of yields for synthesis of **12**

Method	Yield of **12** (%)
Reductive alkylation[a]	76
Hydroxymate reduction	56

[a]Entry **d**, Table 1

experiments, and the FTIR spectrum of **11** indicated the presence of a small amount of aldehyde carbonyl (1702 cm^{-1}) in addition to the expected hydroxymate carbonyl (1670 cm^{-1}). The N–O bond remained intact during the reduction, according to solution-phase experiments.

In order to establish the stability of the hydroxylamine towards strong acids, resin **11** was agitated overnight in a 95% TFA/dichloromethane solution and, after a base wash, subjected to quaternisation and cleavage. The tertiary amine **12** was obtained with no drop in yield, indicating the linker's stability to strong acidic conditions.

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