Pergamon

Tetrahedron Letters 41 (2000) 6639–6642

TETRAHEDRON LETTERS

Application of Grignard reagents to the synthesis of tertiary methylamines via resin-bound oxyiminium ions

Paul Blaney,[a] Ronald Grigg,[a,*] Zoran Rankovic[b] and Matthew Thoroughgood[a]

[a]*Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Center, School of Chemistry, Leeds University, Leeds LS2 9JT, UK*

[b]*Medicinal Chemistry Department, Organon Laboratories Ltd., Newhouse ML1 5SH, Scotland, UK*

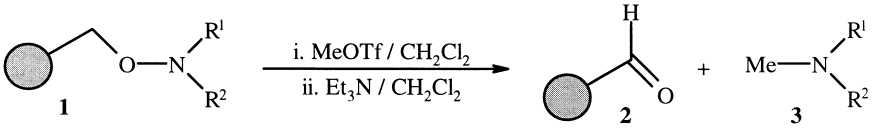
Received 5 June 2000; accepted 29 June 2000

Abstract

The solid-phase synthesis of tertiary methylamines via the nucleophilic displacement of benzotriazole Mannich adducts with Grignard reagents using a hydroxylamine linker is described. The chemistry is exemplified by the synthesis of the MAO inhibitor α-methylpargyline. Also described is the synthesis of the analgesic Tramadol by an alternative one-pot solid-phase Mannich reaction.

Keywords: solid-phase synthesis; oxyiminium; ions; tertiary methylamines; traceless hydroxylamine linker; Grignard reagents; benzotriazole Mannich adducts; α-methylpargyline; Tramadol.

In the preceding communication,[1] we described the use of a traceless hydroxylamine linker for the solid-phase synthesis of tertiary methylamines. Inherent to this protocol is the quaternisation of a resin-bound tertiary hydroxylamine **1**, followed by base-induced cleavage giving resin-bound aldehyde **2** and tertiary amine **3** (Scheme 1).

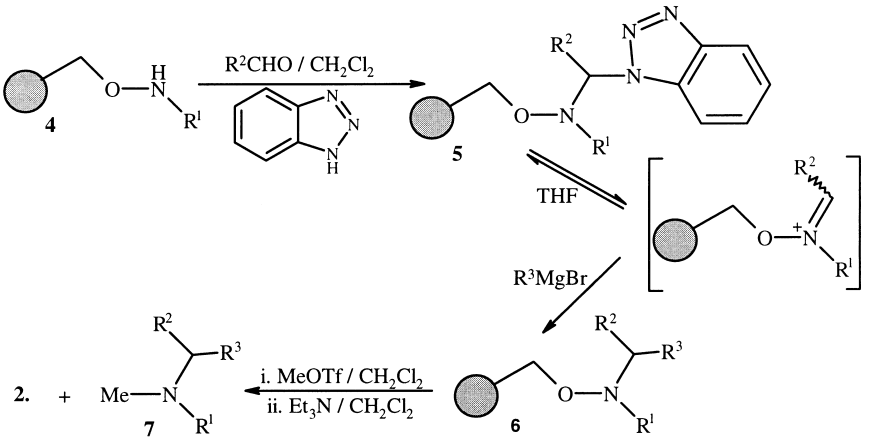


Scheme 1.

* Corresponding author. E-mail: griggs@chemistry.leeds.ac.uk

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01104-7

This letter describes the synthesis of tertiary methylamines using Grignard reagents, which demonstrates the linker's ability to withstand such strong organometallic nucleophiles. A convenient way to demonstrate this (Scheme 2) involves formation of benzotriazole Mannich adducts and subsequent Grignard displacement, a process well documented by Katritzky.[2] The resin-bound secondary hydroxylamine[1] **4** was reacted with an aliphatic or aromatic aldehyde (10 mol equiv. $R^2CHO/CH_2Cl_2/RT/18$ h) in the presence of benzotriazole (10 mol equiv.) to form the resin-bound benzotriazole Mannich adduct **5**. Reaction of **5** with Grignard reagents (10 mol equiv./THF/RT/16 h) occurs via the oxyiminium ion to give the tertiary hydroxylamine resin **6**. Quaternisation of **6** (5 mol equiv. $MeOTf/CH_2Cl_2/RT/16$ h) followed by base-induced cleavage (5 mol equiv. $Et_3N/CH_2Cl_2/RT/16$ h) gives high purity tertiary amines **7** (Table 1) and the resin-bound aldehyde **2**.



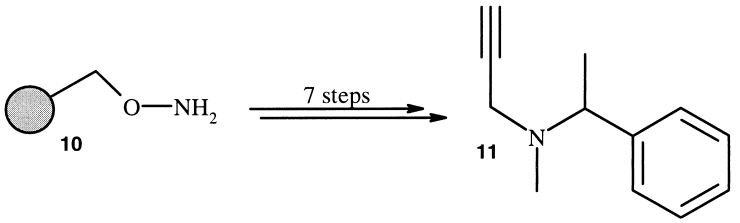
Scheme 2.

Table 1
A selection of aldehydes and Grignard reagents used for the synthesis of tertiary amines

4 R^1 = CH_2Ph			**4 R^1 = CH_2CH_2Ph**		
R^2CHO	**R^3MgX**	**7 (%)[a]**	**R^2CHO**	**R^3MgX**	**7 (%)[a]**
Acetaldehyde	Methyl	72	Acetaldehyde	Methyl	72
Acetaldehyde	Ethyl	70	Acetaldehyde	Ethyl	62
Acetaldehyde	^{i}Propyl	25	Acetaldehyde	^{i}Propyl	18
Acetaldehyde	Phenyl	55	Acetaldehyde	Phenyl	35[b]
Acetaldehyde	*p*-F-Phenyl	28	Acetaldehyde	*p*-F-Phenyl	69
Hexanal	Methyl	65	Hexanal	Methyl	68
Hexanal	Ethyl	47[b]	Hexanal	Ethyl	47[b]
Hexanal	Phenyl	41[b]	Hexanal	Phenyl	51[b]
Hexanal	*p*-F-Phenyl	41[b]	Hexanal	*p*-F-Phenyl	51
Benzaldehyde	Methyl	54[b]	Benzaldehyde	Methyl	56[b]
Benzaldehyde	Ethyl	56	p-F-Benzaldehyde	Ethyl	48[b]

[a]All compounds give satisfactory ^{1}H NMR and mass spectra. Isolated overall yields for 7 steps based on the hydroxylamine resin loading[3] determined by Fmoc quantitation method.[4]
[b]Tertiary amine purity of >99% was determined for randomly selected examples by HPLC and LC-MS.

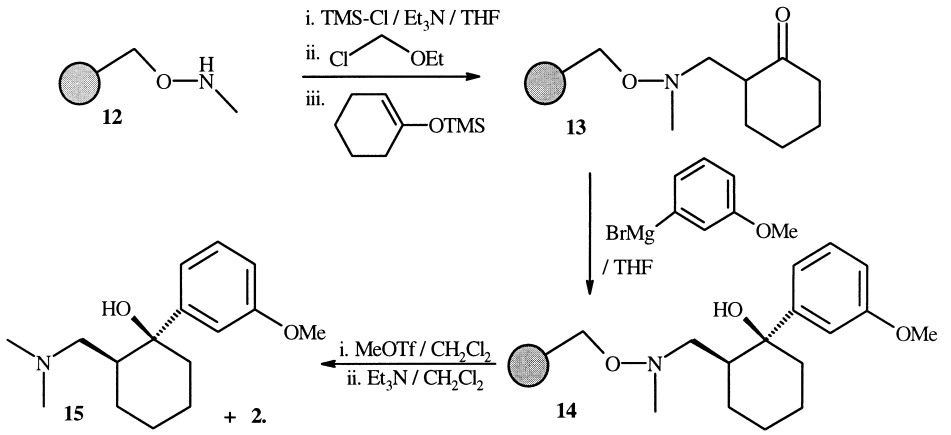
The benzotriazole Mannich base/Grignard reaction protocol allows easy access to tertiary methylamines with branched chain substituents. This is illustrated by the solid-phase synthesis of the racemic MAO inhibitor α-methylpargyline[5] **11** (Scheme 3).



Scheme 3.

Thus, alkylation of Boc-protected **10** with propargyl bromide[1] and subsequent deprotection gave **4** (R^1 = propargyl). The benzotriazole Mannich adduct was formed with acetaldehyde (10 mol equiv. MeCHO/10 mol equiv. benzotriazole/CH_2Cl_2/RT/18 h) to give **5** (R^2 = Me). Reaction of **5** with phenyl magnesium bromide (10 mol equiv./THF/RT/16 h) gave **6** (R^3 = Ph), which was quaternised with methyl triflate (5 mol equiv. MeOTf/CH_2Cl_2/RT/16 h) and cleaved (5 mol equiv. Et_3N/CH_2Cl_2/RT/16 h) to furnish **11** in a 75% overall yield from **10**. The purity of **11** was determined to be >99% by HPLC.

To further demonstrate the linker's versatility, the analgesic (±)-Tramadol[6] **15** was synthesised as shown in Scheme 4.



Scheme 4.

Resin **12** was made by methylation with methyl iodide.[1] Attempts to form **13** using Katritzky's benzotriazole Mannich intermediate via displacement with lithium enolates[7] failed. Schroth[8] has reported the synthesis of iminium ions by reaction of *N*-trimethysilyl-tertiary amines with chloromethyl ethers. As far as the authors are aware, this methodology has not been used to form oxyiminium ions. The *N*-TMS protection of **12**, oxyiminium ion generation and subsequent Mannich reaction with the silyl enol ether of cyclohexanone[9] was performed in one pot.[10] This approach was adopted due to the reported instability of *N*-TMS-protected hydroxylamines[11] and

also the potential instability of the resin-bound oxyiminium ion. The resin-bound ketone **13** was reacted with 3-methoxyphenyl magnesium bromide[12] (10 mol equiv. Grignard/THF/RT/16 h) to give tertiary alcohol **14**. The resin-bound alcohol **14** was quaternised (5 mol equiv. MeOTf/CH_2Cl_2/RT/16 h) and cleaved (5 mol equiv. Et_3N/CH_2Cl_2/RT/16 h) to give Tramadol **15**[13] as a 96:4 mixture (HPLC) of *cis*:*trans* isomers in an overall yield of 57%.

This represents, as far as the authors are aware, the first solid-phase Mannich reactions involving hydroxylamine substrates. It also successfully demonstrates the viability of resin-bound oxyiminium ions, the versatility of the resin and its ability to support the synthesis of more complex materials of medicinal value.

Acknowledgements

We thank Leeds University and Organon Laboratories for support.

References

1. Blaney, P.; Grigg, R.; Rankovic, Z.; Thoroughgood, M. *Tetrahedron Lett*., **2000**, *41*, 6635–6638 and references cited therein.
2. Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev*. **1998**, *98*, 409–548. Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683–2732.
3. Initial hydroxylamine resin loading determined as 0.65 g $mmol^{-1}$.
4. Ramage, R.; Stewart, A. S. J. *J. Chem. Soc*., *Perkin Trans. 1* **1993**, 1947–1952.
5. Robinson, J. B.; Bocchinfuso, R.; Khalil, A. *J. Pharm. Pharmacol*. **1995**, *47*, 324–328.
6. Dayer, P.; Desmules, J.; Collart, L. *Drugs* **1997**, *53*, 18–24.
7. Katritzky, A. R.; Harris, P. A. *Tetrahedron* **1990**, *46*, 987–996.
8. Jahn, U.; Schroth, W. *Tetrahedron Lett*. **1993**, *34*, 5863–5866.
9. Caputo, R.; Ferreri, C.; Mastroianni, D.; Palumbo, G.; Wenkert, E. *Synth. Commun*. **1992**, *22*, 2305–2312.
10. Typical experimental procedure for the one-pot Mannich reaction for the formation of **13**: Trimethylsilyl chloride (0.14 ml, 1.11 mmol) and triethylamine (0.15 ml, 1.11 mmol) were added to a suspension of resin **12** (0.25 g, 0.222 mmol) in dry THF (10 ml) under nitrogen. The suspension was agitated for 3 h, after which chloromethyl ethyl ether (0.21 ml, 2.22 mmol) was added and agitation was continued for a further 2 h. Finally, 1-cyclohexenyloxy-trimethylsilane (0.86 ml, 4.44 mmol) was added and the agitation continued for 16 h. The resin was filtered and washed thoroughly twice with the series of solvents CH_2Cl_2, DMF and MeOH, and then twice with the series of solvents CH_2Cl_2 and MeOH. The resin was air dried (5 min) then dried in a vacuum desiccator to afford **13** (0.26 g) as a yellow resin. FTIR ν_{max} (cm^{-1}): 3082–3023 ($C–H_{str}$, sp^2), 2950–2860 ($C–H_{str}$, sp^3), 1700 ($C=O_{str}$, ketone), 1600 and 1490 ($C=C_{str}$, aromatic).
11. Smrekar, O.; Wannagat, U. *Monatsh. Chem*. **1969**, *100*, 760–765.
12. Ireland, R. E.; Thaisrivongs, S.; Dussault, P. H. *J. Am. Chem. Soc*. **1988**, *110*, 5768–5779.
13. Physical data (^1H NMR, mass spectrum) were identical to those of a commercial sample.