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The Synthesis of 3,5-Di- and 3,5,5-Trisubstituted-1,3-oxazolidines from Primary Amines and Carbonyl Compounds

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Abstract: A variety of 3,5-substituted 1,3-oxazolidines are synthesized from primary amines by a novel, two step sequence.

1,3-Oxazolidines are useful synthetic intermediates as equivalents of iminium ions,[1a,b] or of imines,[2] and as chiral auxiliaries.[3a,b] They are usually prepared from β-hydroxy amines by a [4+1] ring synthesis,[4a,b] although a few examples were reported from the [3+2] cycloaddition of azomethine ylides and carbonyl compounds (mostly benzaldehyde),[5a-e] and in other ways.[5f] The present work describes a related [3+2] ring synthesis of 1,3-oxazolidines from readily available starting materials.

N,N-Bis(benzotriazolylmethyl)alkyl amines (**2**)[6a] and *N,N*-Bis(sulphonylmethyl)alkyl amines (**3**)[6b] are easily prepared from primary amines (**1**) following literature procedures. *N,N*-Bis(benzotriazolylmethyl)phenyl amine (**2a**) reacted with 3-pentanone in the presence of samarium diiodide in THF-HMPA to give oxazolidine **4a** as the major product (30% by GC/MS) (Scheme). Under the same conditions, the use of *N,N*-bis(tosylmethyl)benzylamine **3a** as the starting material resulted in 90% isolated yield of oxazolidine **4a**. Similarly, reactions of **3a,c** with the appropriate carbonyl compounds gave oxazolidines **4b-e,g-i** in 39-81% isolated yields.[7] Compound **4f** was obtained from **2b** since **3b** could not be prepared.[6b]

When amine **3a** was first treated with samarium diiodide in THF-HMPA (10:1) for 5 min (during which time the purple color dissipated) and then quenched with 3-pentanone, only piperazine **5** was isolated in 65% yield. This result demonstrated that the formation and the further reaction of the reactive intermediate (whether it be a non-stabilized α-aminocarbanion or azomethine ylide) is very fast, and the preparation of 1,3-oxazolidines needs to be carried out in one step. When amine **3a** was reacted with SmI_2/THF-HMPA in the presence of *trans*-stilbene, pyrrolidine **6** was isolated in 81%. This result may suggest an azomethine ylide intermediate (**8**)[8], but it is still insufficient to exclude a non-stabilized α-aminocarbanion (**7**) intermediate. In order to understand the real reactive intermediate involved in this reaction, more experimental work is underway and will be reported in due course.

Stabilized α-aminocarbanions are important and well investigated reactive synthetic intermediates.[9a,b] Non-stabilized α-aminocarbanions have thus found less use largely due to the lack of appropriate methods for their generation.[10a,b] Recently we described novel methodologies which provide easy access from *N*-(α-aminoalkyl)benzotriazoles or *N*-(sulphonylmethyl)amines to a variety of substituted α-aminocarbanions and reported their capture by various electrophiles.[11a,b] We have now shown that this technique can be applied to allow a two step preparation of 1,3-oxazolidines from primary amines.

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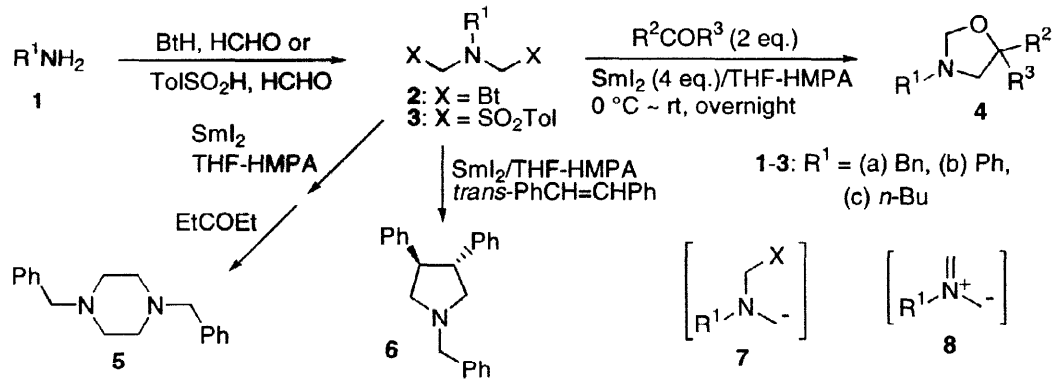

4	a	b	c	d	e	f	g	h	i
R^1	Bn	Bn	Bn	Bn	Bn	Ph	*n*-Bu	*n*-Bu	*n*-Bu
R^2	Et	$-(CH_2)_5-$	*i*-Pr	Pr	*t*-Bu	Et	Et	*t*-Bu	Me
R^3	Et		H	Me	H	Et	Et	H	Pr
yield (%)	90	43	39	81	68	38	54	73	64

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7. Compounds **4a-i** were all isolated as oils which gave satisfactory C-13 and proton NMR spectra. **4f** and **4h** were further characterization by HRMS, all other gave satisfactory CHN elemental analysis (± 0.4%).
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