The Synthesis Of Substituted Pyrrolidines By A Samarium (II) Iodide Mediated Ring Closure.

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Abstract: Samarium (II) iodide mediated ring closures have been used to generate a series of 2,3,4-trisubstituted pyrrolidine derivatives.

The usefulness of samarium iodide as a versatile reagent in organic synthesis has been demonstrated by its widespread application¹ for reduction of a variety of functional groups², as well as its mediation of a range of unusual reductive cyclisations³ and intramolecular coupling reactions⁴. The oxophilic samarium(II) species, a potent reducing agent, induces reaction via two sequential one-electron reductions, and the intermediate radicals so formed are capable of undergoing a range of carbon-carbon bond forming reactions. Using this approach, samarium iodide mediated reactions have been used to generate a wide range of carbocycles⁵ and heterocycles⁶. We report the extension of this reaction to the construction of 2,3,4-trisubstituted pyrrolidines (Scheme 1). These are potential precursors for the neurotoxic kainoid group of amino acids⁷.



The required starting materials were prepared in a manner analogous to reported procedures^{8,9}. Ester (1), prepared from L-serine by esterification (MeOH/HCl) and protection (TBDMSCl/Et₃N, cat. DMAP) was converted to unsaturated amine derivatives (2) (Scheme 2 and Table 1) either by reductive amination with the appropriate unsaturated aldehyde (NaBH₄/MeOH) or by alkylation with the corresponding propargylic bromide (in Et₃N, toluene solution), to give the products in yields of 16-54%. Protection of the amine function (phenyl chloroformate, NaHCO₃, EtOAc, H₂O) followed by reduction of the ester (Dibal, toluene, -78° C) cleanly gave the desired aldehydes (3a-g) in good yields, which were generally used without further purification. Reaction of these compounds with an excess of samarium iodide (3-4 equivalents)¹⁰, in the presence of 2 equivalents of t-butanol in a THF/HMPA solvent mixture at 0°C, gave the products (4a-g) as a mixture of diastereomers.

Substrate	Approximate Reaction Time (mins)	Product, [Yield]
(3a) $R=Me_2C=CHCH_2$ -	30	HO $(4a)$ [25%]
		R-C-OPh HO-COSiMe2t-Bu
(3b) $R = p$ -MeOC ₆ H ₄ CH=CHCH ₂ -	30	(4b) $R = p-MeO-$ [43%]
(3c) $R = p - CF_3C_6H_4CH = CHCH_2$	60	(4c) $R = p - CF_{3} - [44\%]$
(3d) $R = p - NO_2C_6H_4CH = CHCH_{2^-}$	-	(4d) $R = p - NO_2 - [0\%]$
(3e) R= H-C≡C-CH ₂ -	15	HO $(4e)$ [70%]
(3f) R= Me-C \equiv C-CH ₂ -	15	HO ^N OPh OSiMe ₂ t-Bu
(3g) R= Me ₃ SiC≡C-CH ₂ -	7	(4f) [60%] Me_3Si HO N OPh $OSiMe_2t-Bu$ (4g) [76%]

Table 1: Reaction of Aldehydes (3) with Samarium (II) Iodide



Reagents: (i) RCH₂Br, Et₃N, toluene; or RCH(O), NaBH₄, MeOH; (ii) PhC(O)Cl, Et₃N (iii) Dibal, -78°C

Scheme 2

Thus, allylic amine (3a) gave isopropyl derivative (4a) in 25% yield, as a mixture of diastereomers at the two new chiral centres. The *p*-methoxycinnamyl and trifluoromethyl derivatives (3b) and (3c) gave the corresponding products (4b) and (4d) in 43% and 44% yields respectively, although the reaction time for the latter compound was longer. However, the *p*-nitro- derivative (3c) gave not the expected cyclised product (4c), but simple reduction of the nitro group. The propargyl derivatives (3e-g) gave especially rapid and efficient ring closures, to give the corresponding alkenes (4e-g) in high yields.

The reaction is also applicable to vinylogous aldehydes. The required starting aldehydes (5a and 5b) were prepared by direct homologation of aldehydes (3a) and (3g) using the Wittig reagent, formylmethylene triphenylphosphorane, and then treated under the standard samarium iodide conditions (Table 2). Substrate (5a) gave product (6a), although only in relatively low yield. However, the prenyl derivative (5b) did not undergo the desired ring closure, giving only products (6b) arising from samarium iodide-induced reduction. The corresponding ester (7), prepared in an analogous manner using carbomethoxymethylene triphenylphosphorane, did not undergo any reaction under these conditions.



Thus, samarium iodide mediated cyclisations provide a convenient entry to highly substituted pyrrolidine ring systems, and a detailed examination of the application of this approach to a range of natural products is in progress.



Table 2: Reaction of Vinylogous Aldehydes with Samarium (II) Iodide

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All new compounds gave satisfactory spectral and mass spectroscopic or elemental analysis data. 0

Prepared by reacting samarium metal with diiodoethane in THF solution, as described in Reference 2. 10.