Pergamon

Tetrahedron Letters, Vol. 37, No. 27, pp. 4819-4822, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00945-8

Solid Phase Reductive Alkylation of Secondary Amines.

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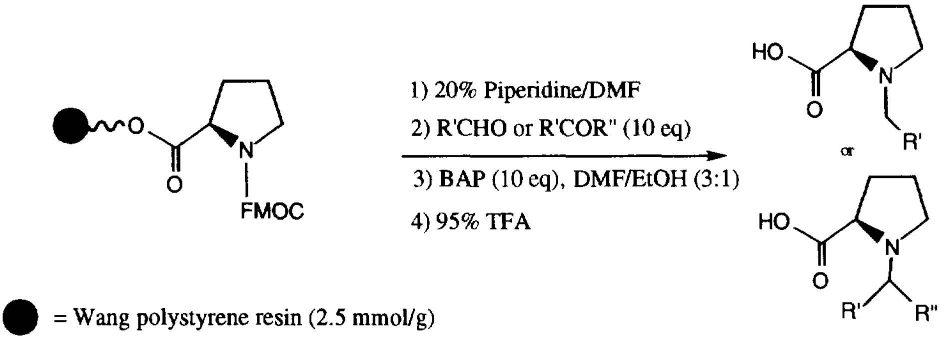
Abstract: *Solid phase reductive alkylation of secondary amines has been carried out in excellent yields using borane-pyridine complex (BAP). Various aldehydes and ketones have been reacted with L-proline substituted on high-capacity Wang Resin.* Copyright © 1996 Elsevier Science Ltd

Recent innovations in solid phase organic synthesis have provided access to libraries of large numbers of structurally diverse compounds.[1] The development of general, high-yielding, novel solid phase reactions is crucial for the synthesis of small molecule libraries.[2]

Reductive alkylation of primary amines on solid phase has become a powerful tool for introducing diversity to small molecule libraries.[3] Reductive alkylation of secondary amines is more challenging, due to the instability of the iminium ion intermediate, and remains problematic in both solution and solid phase chemistry.[4] We have studied a variety of reagents and conditions to mediate this reaction, and herein, we report a novel method for the solid phase reductive alkylation of secondary amines (and primary amines) using Borane-pyridine complex (BAP).[5]

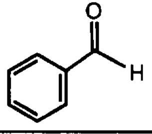
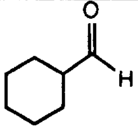
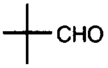
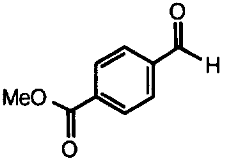
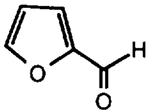
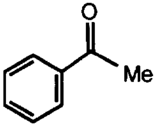
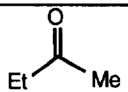
The Borch Reduction, using sodium cyanoborohydride ($NaCNBH_3$) is the most popular method to carry out the reductive alkylation of amines in solution,[6] however poor selectivity of the reagent render it unsuitable for our purposes. Sodium triacetoxyborohydride ($NaBH(OAc)_3$), a milder and more selective reducing agent,[7] was investigated for the *in situ* reduction of the iminium ion on solid phase, but in our hands the yields were dissappointing (<20%). The use of titanium isopropoxide ($Ti(O^iPr)_4$) as a reducing reagent gave clean, high-yielding reactions in solution, however on solid phase (Wang polystyrene resin) the reaction was problematic due to the formation of insoluble titanium dioxide byproduct.[8]



Scheme 1

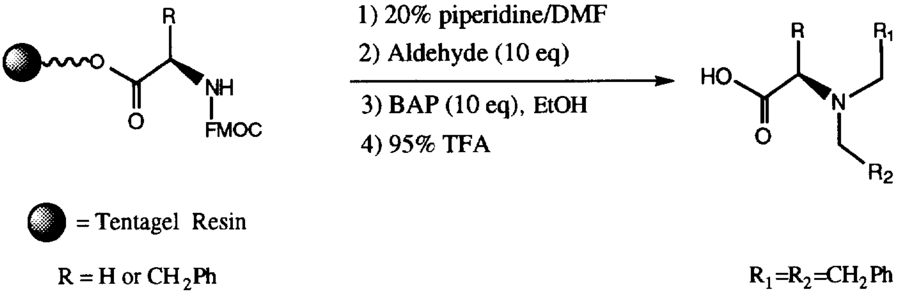
BAP was found to be an excellent reagent for the *in situ* reduction of the iminium ion on solid phase. Assorted aromatic and aliphatic aldehydes and ketones (Table 1) were reacted with L-proline in solution and on a high-capacity Wang-modified polystyrene resin (Scheme 1).[9] Reactions in solution were carried out in a polar protic solvent (EtOH).[10] However, due to poor swelling of polystyrene resins in polar protic solvents, several mixed systems were investigated. The best solvent system found for the solid phase reductive alkylation was DMF/EtOH (3:1).[11] Percentage purity of compounds was determined by HPLC using a SEDEX 55 Evaporative Light Scattering Detector. This method provides a purity analysis based on the actual mass of compound present rather than the absorbance which can be misleading due to the often large differences in extinction coefficients.

Table 1. Reductive alkylation of L-proline in solution and solid phase using borane-pyridine complex.

substrate	solution^{b}		solid phase^{d}	
	% yield^{a}	% purity^{c}	% yield^{e}	% purity^{c}
	95	>95	95	>95
	95	>95	95	>95
	95	>95	95	>95
	95	>95	95	>95
	95	>95	95	67
	95	>95	95	80
	95	60	<1	-
	95	>95	95	90

(a) Crude yield based on mass. (b) All products were characterised by ^{1}H NMR spectroscopy and MALDI-TOF MS. (c) % Purity determined by C-18 reverse-phase HPLC, monitored at 254 nm and using SEDEX Evaporative Light Scattering Detector. (d) All products characterised by MALDI-TOF MS and C-18 reverse-phase HPLC, monitored at 254 nm and using SEDEX Evaporative Light Scattering Detector. (e) Calculation of yields on solid phase were based on initial loading of resin.

The use of Tentagel resin (TGA, Novabiochem), which is compatible with a wide range of solvents, permitted the BAP reduction to be performed in a single solvent system (Scheme 2).



Scheme 2

Reductive alkylation of amino acids using BAP with a two fold excess of aldehyde (benzaldehyde) gave predominantly the dialkylated product in quantitative yields in solution and on solid phase.

In conclusion: conventional solid phase methods of reductive alkylation of primary amines allows access to a large number of secondary amines. The BAP procedure is an excellent method for the reductive alkylation of secondary amines. By combining the two protocols together, ie. reductive alkylation of primary amines using conventional methods to generate the secondary amine followed by reductive alkylation using the BAP procedure, an extra diversity element can be incorporated into the synthesis of small molecule libraries. We are currently investigating the synthesis of small molecule libraries using the BAP protocol.

Acknowledgements. We thank Zeneca for collaborative support and studentships to NMK and VA, and the Royal Society for the University Research Fellowship to SB.

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8. TiO_2 could be removed after the reaction by washing successively with either aq. alkali metal-bisulphate or aq. citric acid, however, it's buildup inhibits the reaction.
9. High capacity (3.5 meq.) chloromethyl polystyrene (Polymerlabs) was converted to the Wang resin by reaction with 4-hydroxybenzyl alcohol (3 eq.) and sodium methoxide (3 eq.) under argon for 3 days in a shaker/water bath at 50 °C. The proline derivative was formed by shaking the Wang resin with Fmoc-proline (2 eq.) for 15 minutes at room temperature, followed by the successive addition of pyridine (3.3 eq.) and 2,6-dichlorobenzoyl chloride (2 eq.) and stirring overnight under argon at room temperature. Unreacted sites were capped with benzoyl chloride.
10. No reduction of acid functionality was observed when using borane-pyridine complex.
11. **General Procedure for Reductive Alkylation on Solid Phase.** Anhydrous solvents were used throughout the experiment. Fmoc-Pro-Wang Resin was deblocked using 20% Piperidine/DMF. Deblocked resin was washed thoroughly with DMF followed by DMF/EtOH (3:1). Resin was allowed to swell in DMF/EtOH (3:1) and treated with aldehyde/ketone (10 eq.) and BAP (10 eq.). The reaction mixture was shaken for 4 days under argon at 25 °C. The resin was washed with DMF/EtOH, CH_2Cl_2 and MeOH then dried under vacuum and finally cleaved using 95% TFA.

(*Received in UK* 1 *May* 1996; *accepted* 17 *May* 1996)