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Solid Phase Synthesis of 2-Aminobutadienes Using a Piperazine Linker

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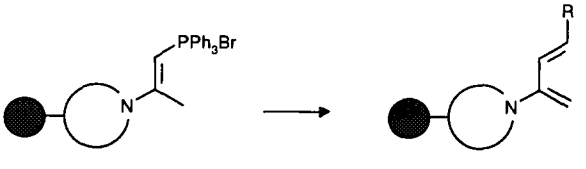
Abstract: A series of resin-bound 4-substituted-2-aminobutadienes have been synthesised *via* Wittig reaction with polymer supported 2–(*N*-piperazino)prop-1-enyl-1-triphenylphosphonium bromide. The use of piperazine provides a readily cleavable enamine linker for attachment of ketones that is compatible with anion chemistry. © 1997 Elsevier Science Ltd.

The potential for rapid lead generation by use of combinatorial libraries has recently prompted intense interest in the development of new solid phase synthetic methodology[1]. As part of our continuing effort to develop new solid phase reactions[2] we decided to examine the synthesis of 2-aminobutadienes[3] as resin-bound activated dienes for use in solid phase [4+2] cycloadditions. 2-Aminobutadienes have been prepared in solution by Wittig reaction of β-enamino phosphonium salts[4] with a wide range of aldehydes in good yields. We considered the efficiency of this chemistry suitable for transfer to solid phase to enable the synthesis of aminobutadienes with a diverse set of substituents at the 4-position (Scheme 1).

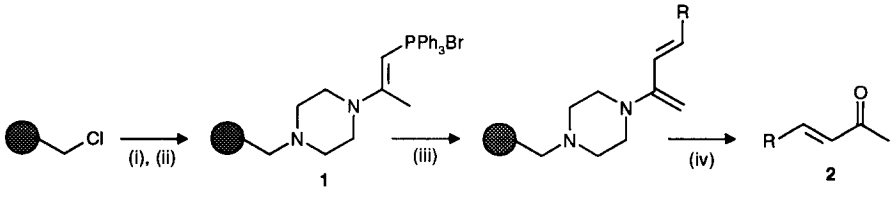
Scheme 1



Attachment of the amine function of the aminobutadiene to the resin has the potential advantage that the amine would have the dual function of linking the ligand to the resin as well as activating the attached ligand to [4+2] cycloaddition chemistry. In addition an enamine would provide a novel solid phase linker which is stable to strong bases but readily cleaved by mild acid treatment to give ketones[5] and is thus attractive not only because of its compatibility with anion chemistry, but its mild cleavage conditions make it suitable for automated synthesis.

Piperazine was selected as the cyclic secondary amine since this provided a convenient attachment to both resin and butadiene, which would not require the use of protecting groups during synthesis because of the site isolation effects of the polymer support. Resin-bound 3-piperazinoprop-1-enyl-1-triphenylphosphonium bromide **1** was synthesised by reaction of Merrifield resin with piperazine, followed by treatment with propargyl triphenylphosphine (Scheme 2). Both reactions could be monitored by elemental analysis which gave consistent results for nitrogen and halide which indicated quantitative conversion, and this Wittig precursor resin **1** was conveniently prepared on a 50 g scale.[6]

Scheme 2



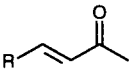
Conditions: (i) Piperazine, dioxane, 70 °C, 16 h; (ii) propargyltriphenylphosphine bromide, CH_2Cl_2, RT, 3 h; (iii) a) KO^{t}Bu, THF, 0 °C, 5 min; b) RCHO, reflux; 16 h; (iv) 3% TFA in CH_2Cl_2 , 10 min.

The Wittig reaction was investigated using a variety of conditions and it was found that hydrolysis was a significant problem unless the resin was dried rigorously. Prolonged storage in a vacuum oven was insufficient, and best results were obtained when the resin was dried by azeotroping with benzene immediately prior to use. We initially investigated the conditions of Barluenga *et al*[4]. using sodium hexamethyldisilazide as base, but obtained cleaner products when potassium *tert*-butoxide was used as reported by Enders *et al*[7]. Thus the dried resin was treated with potassium *tert*-butoxide solution causing the resin immediately to turn a red-orange colour indicating ylide formation. In solution, it is reported that prolonged treatment (3 h) was required for ylide generation, but we found that the ylide was fully formed after 5 minutes and longer reaction resulted in loss of colour and significant hydrolysis. Aldehyde was added to the ylide, after which the mixture was heated under reflux for 3-16 h. Bromine analysis indicated complete reaction and the 2-aminobutadiene products were released as α,β-unsaturated methylketones **2** by treatment with 3% TFA in dichloromethane.

These conditions[8] were examined with a number of aldehydes and the results showed that the chemistry tolerated a wide range of functionality (Table 1). Most substituted benzaldehydes gave clean products except when electron-withdrawing substituents were present. For example, product was not obtained with 4-nitrobenzaldehyde, and that obtained with 4-cyanobenzaldehyde was of only moderate purity. In contrast 3-cyanobenzaldehyde reacted cleanly. Electron-rich substituent groups also performed well. A number of heteroaromatic aldehydes were also examined, and most gave good reaction. However, reaction with aliphatic aldehydes was more variable: clean products were obtained with cyclohexylcarboxaldehyde and pivaldehyde, but only hydrolysis product was obtained with decanal. Changing the solvent to dioxane and elevating the reaction temperature did not alter the reaction outcome,

although it was found that ylide generation was slower in dioxane than THF. In contrast, solution chemistry gave good yields with aliphatic aldehydes, and it is unclear why this reaction is not successful on solid phase. Interestingly, reaction with 2-methyl propionaldehyde gave a mixture of products, possibly due to competing aldol reaction.

Table 1. Cleavage Products From Aminobutadiene Synthesis



Compound	R	Time(h)	Yield (%)	HPLC purity (%)
2a	Ph	16	95	95
2b	4-MeOPh	16	90	83
2c	4-NO_2Ph	16	[a]	-
2d	4-CNPh	16	90	37
2e	3-CNPh	16	64	89
2f	4-FPh	16	87	90
2g	4-^{t}ButylPh	16	85	90
2h	3-Pyridyl	3	84	95
2i	2-Furyl	3	78	70
2j	^{t}Butyl	3	75	75
2k	cyclohexyl	3	78	99
2l	^{n}nonyl	16	[b]	-

[a] complex mixture; [b] hydrolysis product only[9].

The stereochemistry of the 3,4 carbon-carbon double bond in the aminobutadiene was not directly assigned but was inferred to be *E* since only *E* α,β-unsaturated methyl ketones **2** were obtained on cleavage as evidenced by the vinylic proton vicinal coupling constants of *ca.* 16 Hz.[10] This is consistent with the solution synthesis in which only *E* aminobutadienes were obtained.[4,7] It is interesting to note that 2-amino-1,3-butadienes are reported to be unstable liquids,[7] but we found that the resin-bound analogues were stable to prolonged storage in a dry environment.

This chemistry has also been successfully carried out using the Myriad™,[11] automation system, to give products that were indistinguishable from the manually synthesised products, demonstrating that this technology is suitable for the automated synthesis of large numbers of resin-bound 2-aminobutadienes.

In conclusion we have developed conditions for the solid phase synthesis of several 2-aminobutadienes of good purity in moderate to good yields. The use of the piperazine-based enamine linker provides a readily cleavable resin attachment for ketones that is stable to anion chemistry and is an example of a linker that functions as both resin attachment of the ligand and activation of the ligand to further chemistry. This synthesis provides diversely functionalised resin-bound activated butadiene systems for [4+2] cycloadditon reactions which are reported in the following paper.

Acknowledgements

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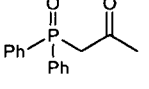
2. Bicknell, A.J. and Hird, N.W. *Bioorganic and Medicinal Chemistry Lett.* **1996**, *6*, 2441.
3. Krohn, K. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1582.
4. Barluenga, J.; Merino, I., Palacios, F. *Tetrahedron Lett* **1990**, *32*, 6713.
5. Ketones have previously been synthesised on solid support by use of a Weinreb amide linker Dinh, T.; Armstrong, R. W. *Tetrahedron Lett* **1996**, *37*, 1161.
6. Procedure: A suspension of Merrifield resin (50 mmol, 1.13 mmol/g) and piperazine (250 mmol) in dioxane (500 ml) was heated to 70 °C for 16 h. The resin was removed by filtration and washed successively with dioxane, dioxane-1N NaOH, dioxane-water, dioxane and methanol then dried under vacuum. The product resin was suspended in anhydrous dichloromethane, then propargyltriphenyl phosphine (150 mmol) was added and the mixture was shaken for 3 h. The resin was then washed with dichloromethane and THF. Elemental analysis of the product gave N 2.10%, Br 5.88% (theoretical N 2.13%, Br 6.07%).
7. Enders, D.; Meyer, O., Raabe, G., Runsink, J. *Synthesis* **1994**, 66.
8. Typical Procedure: resin **1** (0.16 mmol) was suspended in dry benzene (20 ml) in a round bottom flask under argon and 15 ml of solvent was distilled off. The remainder was removed under a gentle stream of argon, then the resin was re-suspended in anhydrous THF and cooled to 0°C . Potassium *tert*-butoxide (2.5eq., 1 M in THF) mixture was added, and the mixture stirred for 5 min resulting in the formation of bright red-orange coloured resin. Aldehyde (10 eq.) was added dropwise and the mixture was refluxed for 16h after which the resin was filtered and washed successively with methanol, THF, dioxane and ether (each 3x10 ml) and dried under high vacuum. The resin was cleaved by suspension in trifluoroacetic acid/ dichloromethane (3:97) for 10 min, followed by washing with dichloromethane.
9. The hydrolysis product after resin cleavage was identified by ^{1}H NMR and MS as:



10. For example **2h** 1-(3-pyridyl)-3-oxo-but-1-ene NMR δ $CDCl_3$ 2.41(3 H, s), 5.5 (1 H, d, J=15.5 Hz), 5.5 (1 H, d, J=15.5 Hz),
11. Myriad^{TM} is a modular robotic synthesiser developed by the Myriad Consortium and The Technology Partnership. The synthesis protocol included *in situ* azeotropic resin drying

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