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Synthesis of 3,4,5-Trisubstituted Cyclohexanones by Cycloaddition To Solid Phase 2-Aminobutadienes

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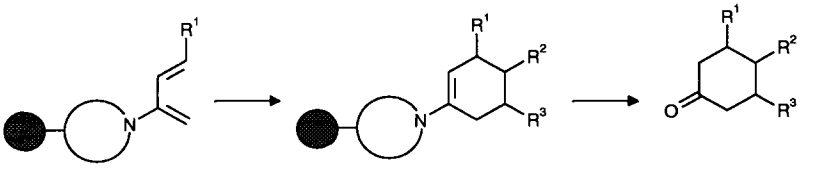
Abstract: [4+2] Cycloaddition of maleimides and nitrostyrenes to resin bound 4-substituted-2-aminobutadienes gives, after cleavage, 3,4,5-trisubstituted cyclohexanones in moderate to good yields and high purities. The reaction occurs under mild conditions and has been automated on the ACT 496 synthesiser. © 1997 Elsevier Science Ltd.

The Diels Alder reaction is the most synthetically useful method for constructing six membered ring systems[1] and offers wide scope in the synthesis of templates for combinatorial libraries. In particular a [4+2] cycloaddition strategy offers the possibility of the synthesis of rigid three-dimensional cores with diverse substituents attached by directionally constrained carbon-carbon bond linkages, in contrast to the decorated monomer concept in which the linkages to the core are often *via* flexible multi-atom groups. The construction of large libraries with reduced flexibility is attractive to explore features of selectivity and specificity when screened against therapeutic targets. To date there are few examples of solid phase Diels Alder reactions.[2,3] Often the conditions required for unactivated systems can be harsh requiring catalysis and high temperature or pressures, which may be unsuitable for polystyrene based resins. Thus our attention focused on activated systems and we were intrigued by the recent work using highly activated 2-aminobutadienes,[4] which were shown to undergo reaction with a variety of dienophiles under mild conditions. Chiral aminobutadienes are currently showing promise as new reagents for diastereoselective Diels Alder reactions.[5,6,7]

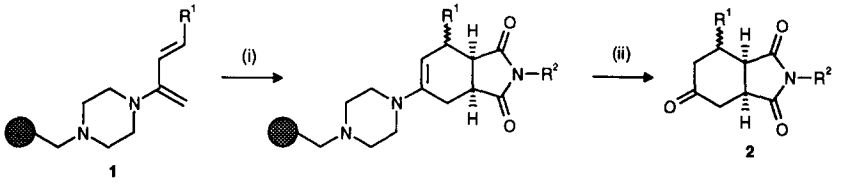
Scheme 1



In the previous paper we described the synthesis of resin-bound 2-aminobutadienes and now we report on their [4+2] cycloaddition reactions to generate 3,4,5-trisubstituted cyclohexanones (Scheme 1).

We first examined reactions with N-substituted maleimides to give azabicyclo[3,6]nonanes which we found to occur under very mild conditions[8] to give high quality products. The yields and purities of the cycloadduct were independent of the nature of the maleimide and selected examples are shown in Table 1.

Table 1. Reaction of Aminobutadienes with Maleimides

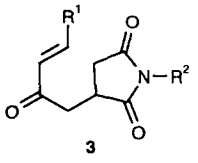


1 2

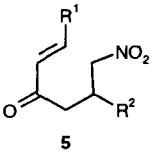
Conditions: (i) N-R^2-Maleimide, THF, 4-8h; (ii) 3% TFA in CH_2Cl_2 , 10 min.

Co-mpound	R1	R2	Method	Yield[9] (%)	HPLC[10] (%)
2a	Ph	Me	manual	87	69
2b	Ph	4-BrPh	manual	81	93
2c	Ph	4-MeCOPh	manual	75	88
2d	4-FPh	4-BrPh	manual	58	91
2e	4-MeOPh	Ph	manual	53	90
2f	^{t}Bu	(4-MeO_2CPh)CH_2	ACT 496	38	95
2g	4-FPh	4-BrPh	ACT 496	37	86
2h	4-MeOPh	4-EtPh	ACT 496	43	88

In solution, reaction is reported[5] to give exclusively the *endo* cycloaddition product with N-phenyl maleimide, and thus a single, racemic product would be expected by concerted cycloaddition to *E*-butadiene. However in all cases an approximately equimolar mixture of diastereomers was obtained (as determined by NMR and HPLC), which may be explained by a non-concerted cycloaddition mechanism due to the enamine character of the aminobutadiene. It is known that [4+2] cycloadditions with aminobutadienes can proceed *via* a step-wise process,[11] and this conclusion is supported by our observation that shorter reaction times gave a product that contained small amounts of a by-product tentatively identified as the open chain enamine addition product **3**. The possibility that attachment of the aminobutadiene to the solid support has an effect on the cycloaddition mechanism is under investigation.



3



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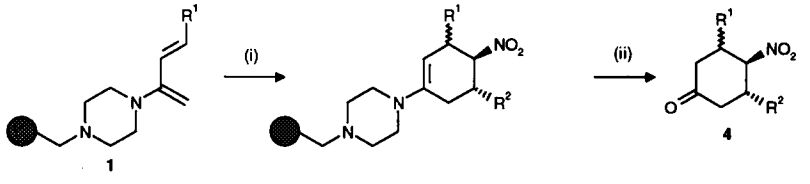
The conditions established for manual synthesis were then optimised for automated synthesis using the Advanced ChemTech 496 Multiple Organic Synthesisier. For efficient use of automation the minimum

conditions necessary for reaction, both in time and reagent excess, were investigated to maximise throughput and to conserve stocks of maleimides. The product yields on the robot were slighly lower than obtained by manual synthesis, possibly due to incomplete washing during the cleavage process. However, the products were of identical purity to manual synthesis but in general longer reaction times were required for complete reaction. For example, in some cases the 4 h reaction product contained significant amounts of uncyclised material **3**. Thus generic conditions were developed,[12] and several hundred compounds were synthesised on the ACT 496 at the rate of 100 compounds per day. It is interesting to note that the mildness of the cleavage conditions of the enamine linker allows the synthesis of compounds with acid labile groups. This is illustrated by the synthesis of **2f**, which contained no evidence of the hydrolysis product (R^2 = (4-$HO_2CPh)CH_2$).

Table 2. Reaction of Aminobutadienes with Nitrostyrenes



Conditions: (i) *trans*-2-R^2-nitrostyrene, THF, 2 h. ii) 3% TFA in CH_2Cl_2 , 10 min.

Compound	R1	R2	Method	Yield[9] (%)	HPLC[10] (%)
4a	4-MeOPh	Ph	manual	45	94
4b	4-MeOPh	4-NO_2Ph	manual	54	87
4c	4-BrPh	Ph	manual	63	90
4d	4-FPh	4-BrPh	manual	58	91
4e	3-Pyr	4-MeOPh	ACT 496	52	98
4f	4-BrPh	3-CF_3Ph	ACT 496	31	91
4g	4-BrPh	Ph	ACT 496	33	88

We next examined reaction of **1** with nitrostyrenes (see Table 2), and found that reaction proceeded more rapidly[13] than with maleimides to give 4-nitrocyclohexanones of high purity. As with maleimide cycloaddition, the nitrostyrene cycloadduct was composed of a mixture of diastereomers and in some cases there was evidence of some uncylised material **5**. As with the previous cycloaddition, the minimum conditions were also developed for synthesis on the ACT 496,[14] enabling rapid synthesis of cyclohexanone libraries as described above.

In conclusion, we have developed conditions for the solid phase synthesis of several 3,4,5-trisubstituted cyclohexanones which provides libraries of diversely functionalised rigid templates. This synthesis illustrated the use of a linker which both activates the ligand to [4+2] cycloaddition and results in

a product that is readily cleaved from the support. The mildness of the reaction and cleavage conditions make this process well suited to automated synthesis for the construction of large array libraries.

Acknowledgements
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8. Typical Procedure: To aminobutadiene resin (0.16 mmol, dried in vacuo) suspended in dry THF (10 mL) in a round bottom flask under argon was added *N*-phenyl maleimide (1.6 mmol) and the mixture shaken for 4 h. The resin was removed by filtration and washed with 3x10 mL THF, toluene and dioxane followed by 1x10 mL diethyl ether. The resin was treated with 3% TFA/dichloromethane for 10 minutes, washed with dichloromethane and evaporated to give the product. **2a** ^{1}H NMR δ ($CDCl_3$): 2.41-3.10(m,4H), 2.88,2.89(2xs,3H), 3.50-3.65(m,2.5H), 3.88(dt,*J*13.1,4.3H,0.5H), 7.21-7.40(m,5H); EI-MS: M^+ 257.
9. Yields were calculated based on the loading of the Merrifield resin used to synthesise the aminobutadienes.
10. HPLC was carried out using Beckman System Gold, Hypersil 3μ C18 10cm column, gradient 0% to 100% acetonitrile in 0.1%TFA/water over 40min, flow rate 0.5ml/min, and monitoring at 220nm.
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12. Typical Procedure: The resin in the reaction block was pre-swelled by washing with 3x1 mL THF and then 1 mL of 0.4 M solution of maleimides in dry THF was added. The block was agitated at 500 rpm for 8 h, emptied, and then washed with 3x1 mL THF and 1x1 mL dichloromethane. With the cleavage block attached, 1 mL of 3% TFA solution in dichloromethane was added and the block shaken for 10 min and then emptied. The resin was washed with a further 1 mL dichloromethane and the combined filtrate was evaporated on a Zymark Turbovap to give products as lightly coloured oils.
13. As 8 except reaction was complete after 2 h. **4a** ^{1}H NMR δ ($CDCl_3$): 2.60-2.90(m,3H), 3.01(dd,*J*5.5,16.2Hz,0.5H), 3.24(dd,*J*9.6,16.0Hz,0.5H), 3.78,3.79(2xs,3H), 3.40-3.90(m,2H), 5.17(t,*J*11.2Hz 0.5H), 5.27(dd,*J*4.8,7.3Hz,0.5H), 6.82-6.95(m,2H), 7.11-7.40(m,7H); EI-MS: M^+ 325.
14. As 12 except reaction time was 4 h.

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