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Synthesis of an Array of Amides by Aluminium Chloride Assisted Cleavage of Resin-Bound Esters

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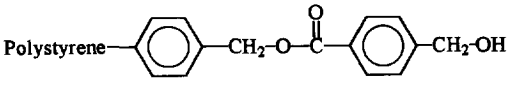
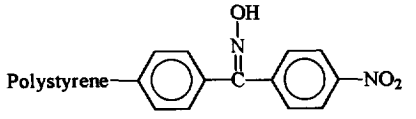
Abstract: A new method for the synthesis of amino amides using Wang or Tentagel-PHB resins is described. The method uses aluminium chloride to promote the conversion of resin-bound benzylic esters to amides under ambient conditions. The reactions were monitored in 'real-time' using ^{13}C gel phase NMR. Copyright © 1996 Elsevier Science Ltd

The solid phase synthesis of organic molecules is an area of much current attention, in particular its application to simultaneous automated synthesis of large numbers of pharmaceutically interesting molecules.[1] We were interested in developing a solid phase method which could be used for the automated synthesis of an array of amides by aminolysis of resin-bound esters.

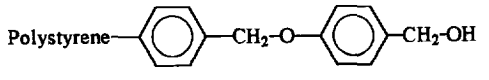
Early work by Sheppard and co-workers demonstrated that a hydroxymethyl benzoic acid (HMB) derivatised resin could be used for the synthesis of C-terminally amidated peptides.[2] The oxime resin originally developed by Kaiser[3] has been used for the production of a range of alkylamides.[4] The ease with which amides are formed from these two resins is also a potential drawback. The susceptibility of these linkers to attack by nucleophiles limits the range of solid phase chemistry which can be performed. Wang resin, being much less labile towards nucleophiles, is more versatile in such cases but cleavage of the resin bound ester by an amine is correspondingly more difficult. A recent publication[5] exploring the aluminium amide promoted aminolysis of resin-bound esters prompts us to report a wider range of potential reagents. We examined reagents known to produce good results for the conversion of esters to amides in solution, including BBr_3[6], $RhCl_3$ and $RuCl_3$[7], $ZrCl_4$ and $AlCl_3$[8], Me_3Al[9] and $[(Me_3Si)_2N]_2Sn$[10].



HMB resin

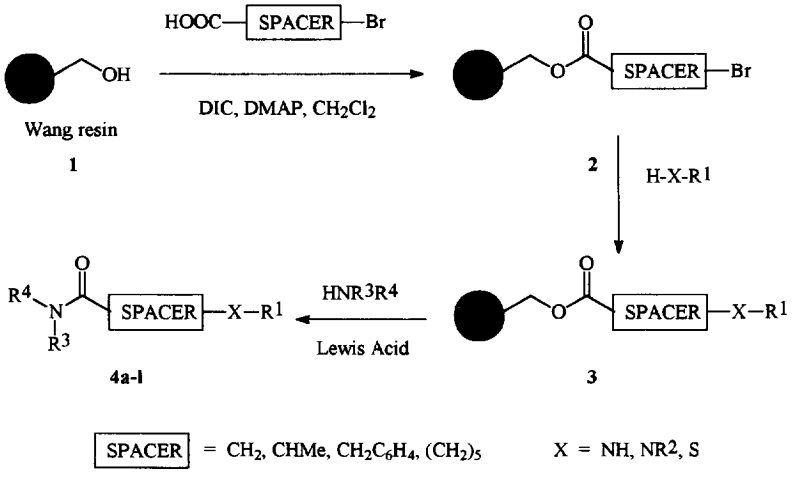


Oxime resin



Wang resin

We were particularly interested in the solid phase synthesis of amine derivatives containing an intervening amide group. Thus, a range of bromoacids were coupled to Wang resin **1**[11] (Scheme 1). The bromoesters **2** were reacted with various primary and secondary amines to gives secondary and tertiary amines respectively **3**, and with 2-dimethylaminoethylmercaptan to give a thioether. In the final cleavage step to give amides **4a-l**, a number of different Lewis acids and a range of amines were investigated.



Scheme 1

It was decided to concentrate initially on the synthesis of a single diamine, **4a** (Table 1), in order to compare the propensity for different Lewis acids to effect cleavage from the resin. 6-Bromohexanoic acid was coupled to Wang resin and the bromoester **2** was reacted with piperidine.[11] The resin was then divided into ten equal batches and each was suspended in dichloromethane containing 1 equivalent of the Lewis acid (relative to the loading of the original resin) and 3 or 4 equivalents of the amine. Each suspension was agitated for 18 hours at room temperature. It was found that $AlCl_3$ and $ZrCl_4$ gave superior results compared to the other Lewis acids, the isolated yield of **4a** following solid phase extraction (SPE) being 45% and 52% respectively. In contrast, BBr_3, $RhCl_3$, $RuCl_3$, $SnCl_4$, Me_3Al and $[(Me_3Si)_2N]_2Sn$ produced little or none of the desired amide under the same conditions. The $[(Me_3Si)_2N]_2Sn$ reagent gave a good yield (43%) of **4a** when 5 equivalents of the reagent and 5 equivalents of N-methylpiperazine were used. However, such large excesses of reagents lead to problems with the work-up of the reaction, in particular the removal of excess tin reagent by SPE. For 1g of resin, 1.56g of $[(Me_3Si)_2N]_2Sn$ was necessary, whereas only 0.16g of $AlCl_3$ or 0.28g of $ZrCl_4$ was required. The removal of aluminium or zirconium residues was easily accomplished by SPE. $AlCl_3$ was selected as the reagent of choice for the synthesis of an array of amides. The overall yields and purities of 12 amino amides are given in Table 1.

Carbon-13 gel phase NMR is a useful technique for monitoring the progress of solid phase reactions[12]. In order to monitor the rate of the alkylation reaction in 'real-time', we performed the reaction in deuterated DMF in an NMR tube. It was decided to select compound **4g** for these studies, in view of the commercial availability of ^{13}C labelled bromoacetic acid, and to compare the rate of the reaction on Tentagel-PHB resin

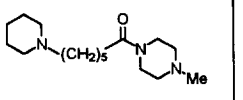
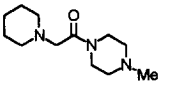
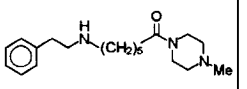
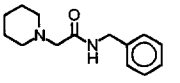
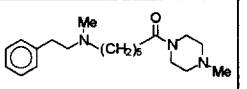
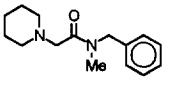
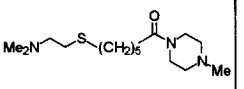
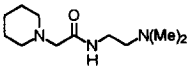
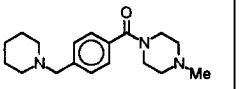
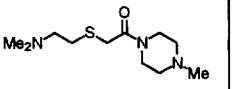
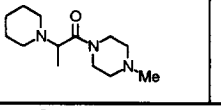
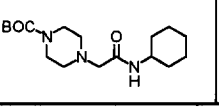
No	Structure	% yield [a]	% purity [b]	No	Structure	% yield [a]	% purity [b]
4a		45[c]	84.3	**4g**		46	95.1
4b		18	89.7	**4h**		62	99.3
4c		65	93.3	**4i**		65	98.0
4d		11	94.2	**4j**		15	98.0
4e		19	85.0	**4k**		74	97.8
4f		54	95.4	**4l**		54[d]	-

Table 1. [a] Overall yields are based on the stated substitution capacity of the Wang resin (0.63mmol/g); [b] Purity was determined by gas chromatography. [c] Solution phase synthesis of (**4a**) afforded a yield of 32.7% based on N-methylpiperazine starting material. [d] Boc deprotection of (**4l**) with 20% TFA in dichloromethane afforded the anti-ulcer drug, N-cyclohexyl-1-piperazineacetamide (Esaprazole) in 28% overall yield (97.1% purity).

with that on Wang resin. Carbon-13 enriched bromoacetic acid (20% $^{13}C_3$) was coupled to Wang resin.[11] Approximately 200mg of the bromoester functionalised resin **2** was loaded into an NMR tube and swollen with d^7-DMF (1.5ml). The labelled methylene resonance at 27.4ppm is clearly visible after just 10 minutes acquisition time (Figure 1). Piperidine (10 equivalents) was then added and the NMR tube was agitated on a rotator for 30 minutes. A second spectrum was recorded which showed that the peak at 27.4ppm was much reduced in intensity (overlapping piperidine resonances also occur in this region) and that a new resonance at 60.3ppm ($^{13}\underline{C}H_2N$) had appeared (Figure 2). This procedure was then repeated using Tentagel-PHB resin. It appears that the alkylation reaction to give **3** proceeds equally rapidly on both types of resin and is essentially complete in under 30 minutes. The 18 hour reaction time allowed previously is unnecessary.

In summary, we have established that the chlorides of aluminium and zirconium are particularly effective reagents for the synthesis of a diverse range of amides using Wang resin. The precise mechanism of action of these reagents in the aminolysis step is unknown. However their ability to act as Lewis acids is probably an important factor. An array of amino amides was prepared by a procedure which involves short reaction times and generally mild conditions and which is appropriate for automated synthesis.

Acknowledgement. We thank the Organon Newhouse analytical chemistry department for providing NMR and GC-MS data and Dr. N. Hone for helpful discussions.

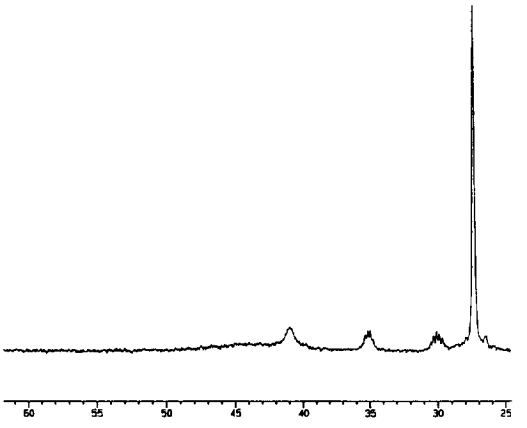


Figure 1

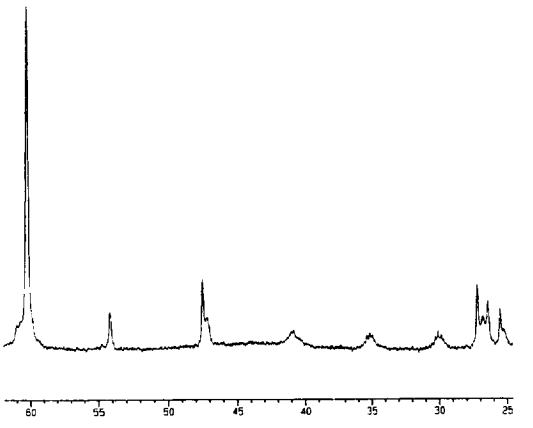


Figure 2

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11 The experimental conditions for the synthesis of (**4a**) are typical for the array. All reactions were performed in Bio-Rad Poly-Prep® columns which were were agitated on a tube rotator. Diisopropylcarbodiimide (0.090g, 0.71mmol) was added dropwise to a solution of 6-bromohexanoic acid (0.138g, 0.71mmol) in dimethylformamide (DMF) (2ml). 4-Dimethylaminopyridine (DMAP) (0.009g, 0.071mmol) was added, and the resulting solution was added to Wang resin (0.20g, 0.126mmol). The mixture was agitated for 18 hours, then the resin was collected by filtration and washed once with DMF (4ml), then twice with dichloromethane (DCM) (4ml) and methanol (4ml) alternately, finally drying under reduced pressure at 50°C. FT-IR confirmed the presence of an ester band at 1730cm^{-1}. The resin-bound ester was suspended in a solution of piperidine (0.121g, 1.42mmol) in DMF (2ml) (for thioethers **4d** and **4k**, 2.84mmol of diisopropylethylamine was added to the reaction mixture along with 1.42mmol of 2-dimethylaminoethylmercaptan hydrochloride) and the mixture was agitated for 18 hours. The resin was collected by filtration and washed with DMF, DCM and methanol as before, then dried. A suspension of $AlCl_3$ (0.019g, 0.142mmol) in DCM (4ml) was stirred at room temperature and N-methylpiperazine (0.056g, 0.564mmol) was added, forming a colourless solution. This solution was added to the resin-bound ester and the mixture was agitated for 18 hours. Thin layer chromatography indicated the presence of the product and excess N-methylpiperazine. Aqueous 1M potassium carbonate solution (0.2ml) was added to the reaction mixture, then the resin was separated by filtration and washed with DCM (4ml). The filtrate and washings were evaporated to dryness under reduced pressure, and the amide was purified by solid phase extraction using an ISOLUTE-XL™ column packed with 500mg of silica. [Eluent: CH_2Cl_2 : CH_3OH : aq.NH_4OH; 90 : 10 : 0.5]. Fractions containing product were evaporated to dryness to give (**4a**) (0.016g). ^{1}H NMR ($CDCl_3$) δ : 3.63 (t, 2H), 3.47 (t, 2H), 2.36 (m, 12H), 2.30 (s, 3H), 1.58 (m, 8H), 1.42 (m, 2H), 1.34 (m, 2H).

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