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## Rapid Solid Phase Synthesis of $\alpha$ -Amino Acids

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### Introduction

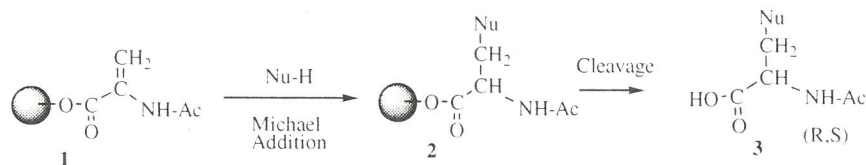
Recently solid phase synthesis of small molecules has emerged as an important tool in drug discovery [1]. Therefore efficient strategies for the development of novel solid phase synthetic methods continue to be of considerable interest in organic synthesis [2].

This report describes solid phase synthesis of  $\alpha$ -amino acids by Michael addition of nucleophilic heterocycles on commercially available 2-acetamidoacrylic acid.

Solid phase synthesis of  $\alpha$ -amino acids has been described by alkylation of resin bound aldimine or ketimine esters of  $\alpha$ -amino acids [3].

We have investigated the following strategy for the synthesis of  $\beta$ -heterocyclic alanines as shown in scheme 1, Wang resin was selected because of an easy acidic cleavage, the starting material was N-protected by an acetyl group, convenient to obtain optically pure  $\alpha$ -amino acids by enzymatic resolution by *Aspergillus genus* acylase [4].

We have previously tested the solution synthesis of  $\beta$ -heterocyclic  $\alpha$ -amino acids using the same strategy but the purification was very tedious because the starting material and the product presented the same solubility.



Scheme 1

### Results and Discussion

Anchoring of N-acetamidoacrylic acid on the Wang resin by activation of the carboxylic acid function was unsuccessful (DCC/DMAP; DCI; BOP); the Mitsunobu reaction turned out to be the method (quantitative yield).

The second step concerning Michael addition of the nucleophile, several experimental conditions were tested and the results are reported in the Table.

Two solvents were used (DMF and  $\text{CH}_3\text{CN}$ );  $\text{CH}_3\text{CN}$  yielded the best results.

The first experiment using 1,2,4-triazole as nucleophile was carried out using  $\text{K}_2\text{CO}_3$  as base according to the experimental conditions described in [9] using 3 equivalents of

nucleophile in the presence of 3 equivalents of base (entry 1) at 50-60°C. Only 7% yield was obtained, the starting material was recovered in the washings.

To optimize these experimental conditions, we chose 1,2,4-triazole because the isolation of the N-acetyl-triazolylalanine was easy. Best yields were obtained at room temperature (entry 3) with 6 equivalents of nucleophile in the presence of 3 equivalents of  $K_2CO_3$  in 2 days. Ultrasonic treatment permitted to reduce reaction time at one day.

Applying the optimized reaction conditions to pyrazole as nucleophile, N-acetyl-pyrazolylalanine was obtained in 54% yield (entry 8). If the nucleophile concentration (175 mM) and the temperature (rt) were decreased the yield was not improved. Only the N-acetyl-dehydroalanine was recovered in 98% yield.

The cleavage was achieved using 20% TFA in DCM.

**Table 1.** Experimental conditions

Entries	Nu-H	Michael addition			Reaction Overall Yield	
		Nu-H (eq.)	Base (eq.)	Nu-H (mM)	Temp <sup>o</sup> C	(%)
1.	1,2,4-Triazole	3	3 $K_2CO_3$	70	50-60	5-10
2.		6	3 $K_2CO_3$	140	50-60	40-42
3.		6	3 $K_2CO_3$	140	25	75-78
4.		6	3 $CS_2CO_3$	140	25	50-54
5.		6	3 $K_2CO_3$	70	25	72-75
6.	Pyrazole	3	3 $K_2CO_3$	70	50-60	2
7.		10	3 $K_2CO_3$	220	50-60	14
8.		15	6 $K_2CO_3$	350	50-60	54

The yields were based on the Wang resin initial loading (0.63 meq/g). The solid support synthesis overall yield was evaluated after cleavage from the resin.

The reaction was monitored by solid gel  $^{13}C$  and  $^1H$  NMR by HRMAS technic on an Avance 400 MHz spectrometer with a HRMAS 4mm probe ( $^1H$ - $^{13}C$ - $^2H$ -gradients). The samples **1** and **2** were swollen in DMF.

A typical procedure is outlined in reference [5].

## References

- Moos, W.H., Green, G.D. and Pavia, M.R. *Annu. Rep. Med.Chem.* 28 (1993) 315.
  - Gordon, E.M., Barrett, R.W., Dower, W.J., Fodor, S.P.A. and Gallop, M.A. *J. Med. Chem.*, 37 (1994) 1385.
- For recent reviews see a) Thompson, L.A. Ellman, J.A. *Chem. Rev.*, 96 (1996) 555. b) Früchtel, J.S., Jung, G. *Angew.Chem.Int.Ed.Engl.*, 35 (1996) 17. c) Hermkens, P.H.H., Ottenheym, H.C.J., and Rees, D.C. *Tetrahedron*, 52 (1996) 4527. d) Hermkens, P.H.H., Ottenheym, H.C.J. and Rees, D.C. *Tetrahedron*, 53 (1997) 5643.
- O'Donnell M.J., Zhou, C.; Scott, W.L. *J. Am. Chem. Soc.*, 118 (1996), 6070. b) O'Donnell M.J., Lugar, C.W., Pottorf, R. S., Zhou, C., Scott, W.L and Cwi, C.L. *Tetrahedron Lett.*, 38 (1997) 7163.
- Rolland-Fulcrand, V., Roumestant, M.L. and Viallefont, Ph., *SYNLETT*, 1998, submitted.
- Barbaste M., Rolland-Fulcrand, V., Roumestant, M.L., Viallefont, Ph. and Martinez J. *Tetrahedron Lett.*, 1998, *in press.*