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Preparation of amides from acids and resin bound azides: Suppression of intramolecular lactam formation

Zhilian Tang and Jeffrey C. Pelletier*

Wyeth-Ayerst Research, Division of Chemical Sciences, Pearl River, NY 10965

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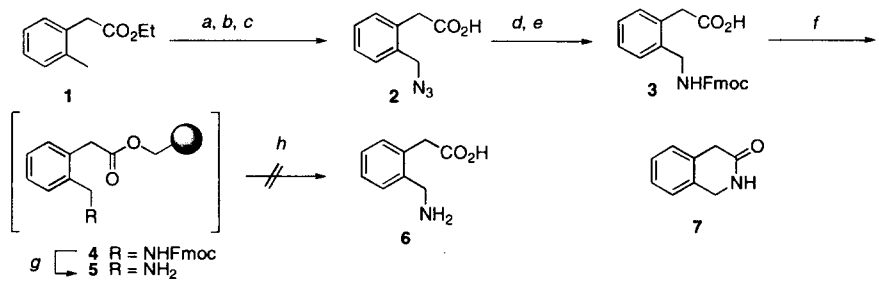
Abstract: A new method for the formation of amides on solid phase has been developed. The procedure involves the reaction between activated acids in solution and resin bound iminophosphoranes generated from the corresponding azides and tributylphosphine. The method is particularly attractive when starting from δ azido acids since amides can form without internal cyclization to the lactam.

The need for rapid and reliable preparation of numerous compounds for biological screening has lead to intense research in combinatorial/parallel synthesis. Much of this effort has focused on the scope and quality of solid phase organic synthesis (SPOS) [1] which owes its genesis to solid phase peptide synthesis and the pioneering work of Merrifield [2]. One of the earliest reactions studied was the formation of amide (peptide) bonds from activated N-protected amino acids and resin bound amines. Although improvements in linkers, reagents, conditions and protecting groups have made this transformation suitable for most instances [3], difficulties remain in cases where resin bound N-protected γ and δ amino acids are deprotected with the intention of further elaborating the resulting amine. The ensuing cyclization/lactam formation leads to cleavage of most, if not all of the intermediate. This is a general problem when substrates are resin bound via ester linkages. For example, when the N-Fmoc protected δ amino acid **3** [4] was prepared from **1** and coupled to polystyrene (crosslinked with 1% divinylbenzene) Wang resin [5] to provide the resin bound substrate **4**, cleavage (50% TFA - DCM, 30 min) following deprotection with 20% piperidine/DMF afforded no detectable product **6** (Scheme 1). MS and HPLC analysis of the deprotection filtrate clearly showed the presence of lactam **7** [6]. The presence of a nucleophilic amine in close proximity to the ester linkage allowed the rapid formation of a stable δ-lactam. Coupling activated acids to the resin bound δ amino acid **5** was preempted by these results and required a different approach.

Scheme 1



a) NBS, Bz_2O_2; *b*) NaN_3, DMF; *c*) LiOH, aq. THF, 51% for 3 steps; *d*) H_2, Pd/C; *e*) FmocCl, 82% for 2 steps; *f*) DIC, Wang resin, DMF; *g*) Piperidine, DMF; *h*) 50% TFA/DCM

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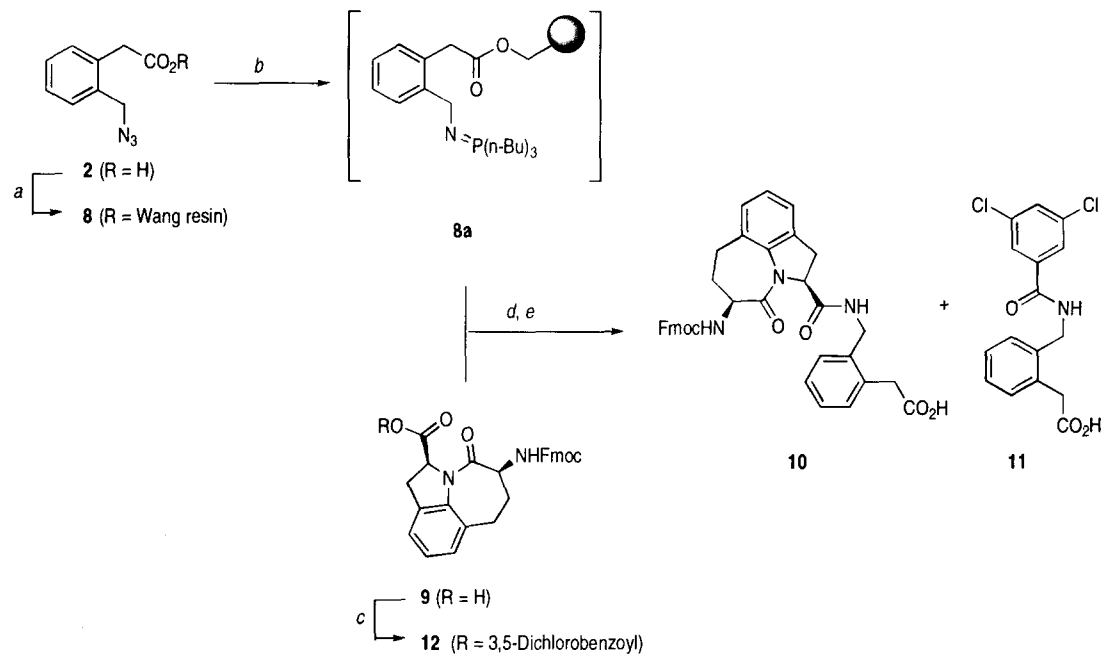
There are reports of carboxylic acids and organic azides reacting to form amides in the presence of phosphines at elevated temperatures [7]. Recent reports describe the transformation taking place at room temperature when the acid is activated [8]. Since the conditions were suitable for solid phase synthesis, attempts were made to prepare resin bound amides utilizing this protocol. Hence, the azido acid **2** was coupled to Wang chloride resin [9] to provide **8** [4] (Scheme 2). Using the reported conditions [8] the N-Fmoc protected amino acid **9** [10] was activated using the Yamaguchi method [8], added to a slurry of **8** in dry acetonitrile and the mixture was treated with tributylphosphine (0.60 M in toluene, 3.0 equivs.) and stirred 14 h. After washing and drying the resin, the product was cleaved (50% TFA-DCM, 30 min) and analyzed. Electrospray MS showed the presence of the desired product **10** as well as product **11** resulting from nucleophilic attack at the other carbonyl of the mixed anhydride **12**. Reversed phase HPLC showed a mixture containing numerous unidentified products. Analysis of the filtrate, however, indicated no formation of the lactam **7**.

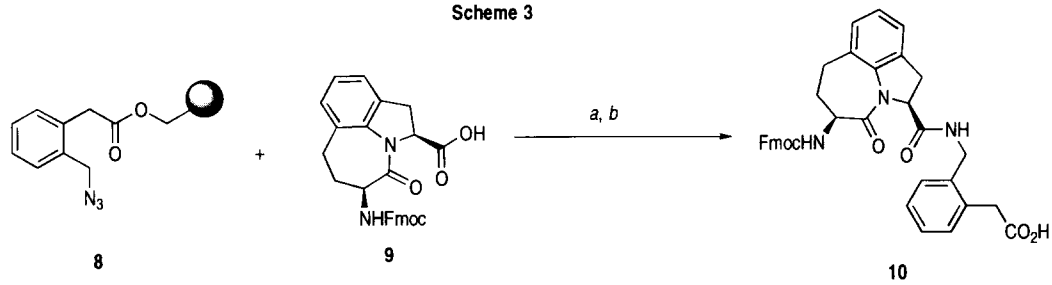
Scheme 2



a) Cs_2CO_3, Chloride Wang resin, DMF, 96%; *b*) $(n\text{-}Bu)_3P$, AcCN; *c*) 3,5-Dichlorobenzoyl chloride, TEA, AcCN; *d*) Combine **8a** and **12**; *e*) 50% TFA/DCM, low overall yield.

The results prompted a survey of reagents and conditions in an effort to improve the yield and purity of the desired products. A satisfactory protocol involved activation of the acid with N-3-(dimethylamino)propyl-N'-ethylcarbodiimide (EDC) and hydroxybenzotriazole (HOBT) in acetonitrile (0 °C) or dioxane (20 °C) with tributylphosphine activation of the azide [11]. The product **10** was obtained in 60% yield [> 80% pure by HPLC] and lactam **7** was not detected (Scheme 3). Results for other acids are in the table. Presumably the reactive intermediate is the iminophosphorane **8a** (Scheme 2). This species would be expected to undergo an intramolecular Staudinger reaction (to provide a resin bound imidate) only at elevated temperatures [12], and after resin cleavage the lactam **7** would be the expected product. At or near ambient temperature, however, amide formation takes precedence. A plausible mechanism for this transformation has been described [8].

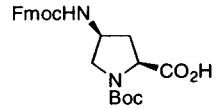
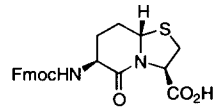
Scheme 3



8 9 10

a) EDC, HOBT, TEA, $(n\text{-}Bu)_3P$, AcCN; *b*) 50% TFA/DCM, 60% overall (>80% pure).

Table

Entry	RCO_2H	Conditions[a]	Yield[b,c]	Purity[d]
1		A	69	82
2		A	100	79
3	FmocGly	B	92	80
4	FmocAla	B	82	80
5	Benzoic acid	B	100	91
6	Propionic Acid	B	86	82

a) A: EDC, HOBT, $(n\text{-}Bu)_3P$, AcCN, 0 °C then 50% TFA/DCM; B: EDC, HOBT, $(n\text{-}Bu)_3P$, 1,4-Dioxane, 20 °C.
b) Compounds exhibited satisfactory MS and NMR.
c) Yields are based on Wang resin manufacturers loading capacity.
d) C18 Column, 2-98% aq. Acetonitrile [0.1% TFA], 15 min.

In summary, a new method for the formation of amides on solid supports has been devised. The procedure involves the treatment of resin bound azides and activated carboxylic acids with tributylphosphine. Amines are unlikely intermediates in this reaction since the formation of lactams from internal cyclization and cleavage is detected under typical deprotection conditions of standard resin bound N-Fmoc δ amino acids but not under the new protocol described here. The technique has been shown to produce amides in good yields/purities and it should supplement existing methods where problems from cyclization and internal resin cleavage lead to low product yields.

Acknowledgement: The authors thank John Ellingboe for helpful suggestions.

References and Notes

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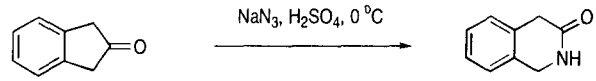
[4] Solution phase product yields are based on purified material. Characterization was performed using ESMS, CHN, ^{1}H & ^{13}C-NMR and IR analyses. Solid phase yields are based on gravimetric analysis and comparison to the manufacturers suggested loading levels.
[5] Wang SS. J. Am. Chem. Soc. 1973; 95: 1328-1333.
[6] Lactam **7** was prepared independently from the following route and used as a standard for comparison purposes:



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[8] Bosch I, Romea P, Urpi F, Vilarrasa J. Tetrahedron Lett. 1993; 34: 4671-4674.
[9] Collini MD, Ellingboe JW. Tetrahedron Lett. 1997; 38: 7963-7966.
[10] Acid **9** and the starting acids from entries 1 & 2 in the table are available commercially from Neosystem Laboratoire, Strasbourg, FR.
[11] A solution of the acid **2** (1.9 g, 9.9 mmol) in ethanol (30 mL) was treated with a solution of cesium carbonate (1.6 g, 5.0 mmol) in water (3 mL). After stirring for 30 minutes the solvents were evaporated to leave a white solid. The cesium salt of **2** was dissolved in DMF (30 mL), added to Wang chloride resin (3.0 g, 1.1 mmol/g loading, 3.3 mmol) that had been previously swelled for 5 minutes in DMF and the mixture was shaken for 18 h. The solvent was drained and resin **8** was washed (DMF; 50% aq. DMF, 4X; DMF, 3X; MeOH; DCM, 3X) and dried (Hi-Vac, 16 h.). IR 2091 cm^{-1}. Loading = 0.97 mmol/g.
To a suspension of acid **9** (44 mg, 94 μmol) and HOBT (13 mg, 94 μmol) in anhydrous acetonitrile (0.50 mL) at 0 °C under nitrogen atmosphere was added EDC (18 mg, 94 μmol). After stirring for 10 minutes the solution was treated with resin **8** (50 mg, 0.97 mmol/g, 47 μmol) followed by a toluene solution of tributylphosphine (0.60 M, 0.12 mL, 71 μmol). The mixture was stirred 18 h then diluted with DMF (2 mL), transferred to a solid phase reaction vessel, drained, washed (DMF, 3X; MeOH; DCM, 3X) and dried (Hi-Vac, 2 h). The product resin was shaken with 50% TFA-DCM for 30 minutes, filtered, washed and evaporated to dryness to leave **10** (18 mg, 60%) as a colorless gum. Reversed phase HPLC (see table note c) indicated a single major product (80.8%). Positive mode Electrospray MS, 616 (M+H). ^{1}H-NMR (DMSO-d_6) δ 8.40 (t, 1H, J = 3.3 Hz), 7.90 (d, 2H, J = 7.4), 7.80-7.65 (m, 3H), 7.43-6.90 (m, 10H), 5.05 (d, 2H, J = 8.5), 4.39-4.13 (m, 3H), 3.63 (s, 2H), 3.46 (dd, 1H, J = 28 Hz, J = 11.6), 3.07-2.89 (m, 3H), 2.23-2.05 (m, 2H), 1.38 (bs, 1H), 0.88 (t, 1H, J = 3.5 Hz).
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