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Solid phase synthesis of glutamic acid derivatives via nucleophilic ring opening of *N*-Boc pyroglutamate with heteronucleophiles

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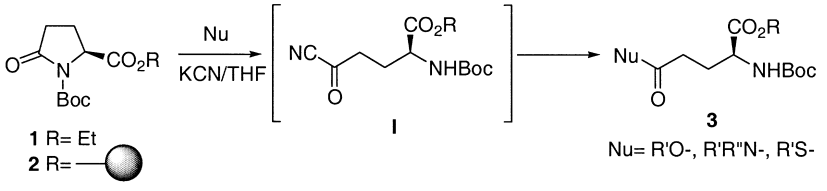
Abstract

A solid phase method for the synthesis of glutamic acid derivatives based on the chemoselective ring opening of *N*-Boc pyroglutamic–Wang resin by heteronucleophiles is described. It allows the preparation of a large number of amides and esters of glutamic acid in a simple procedure with moderate to good yields and excellent purity.

Keywords: amino acids and derivatives; solid phase synthesis.

Ethyl *N*-Boc protected pyroglutamic acid **1** can be recognized as an internal protection of the terminal carboxylic group of glutamic acid, allowing an easy differentiation of the two carbonyl moieties. Thus, **1** undergoes nucleophilic ring opening with a variety of carbon nucleophiles[1–3] giving rise to δ-oxo,α-amino acids, that have been used as an intermediate in several syntheses.[4–6] This reactivity profile has also been extended to heteronucleophiles (Scheme 1), such as alcohols[7–10] amines and thiols,[10] where the heteronucleophile displaces the highly reactive acyl cyanide intermediate **I**, generated under KCN catalyst in THF, producing **3** as mixed diesters, ω-amides and ω-thioesters. These reactions require a large excess of the heteronucleophile (2–6 equiv.), making the purification process difficult.[10] Recently the addition of trimethylsilyldiazomethane has been described.[11]



Scheme 1.

As a way of simplifying and expanding this reaction, we report herein the application of solid phase chemistry, by using the *N*-Boc pyroglutamate bound to Wang resin (**2**), performing this

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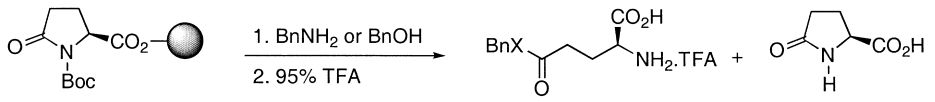
nucleophilic ring opening reaction with alcohols and amines, allowing construction of a large number of glutamic acid derivatives.

The L-pyroglutamic acid was attached to Wang resin through an ester linkage, following a typical coupling procedure (DIC, DMAP, CH_2Cl_2), and *N*-Boc protected under standard conditions (Boc_2O, DMAP, CH_2Cl_2).

In order to study the reaction conditions in solid phase, we performed a set of experiments with benzyl amine and benzyl alcohol, analyzing the influence of the catalyst (KCN), the solvent and reaction time (Table 1). The release of the final compounds from the resin was performed with 95% TFA with concomitant hydrolysis of the *N*-Boc protecting group, obtaining the corresponding glutamic acid derivatives (**3**/**4**) as trifluoroacetate salts.

Table 1
Benzyl amine and benzyl alcohol addition to *N*-Boc pyroglutamic acid–Wang supported resin



2 | **3a**, X= NH; **4a**, X= O | **Pyroglutamic Acid**

Entry	Nucleophile	Equiv.	Solvent	Catalyst	Time (h)	3(4): Pyroglutamic Acid[a]
1	BnOH	100	THF	KCN	60	100 : 0
2	BnOH	100	THF	-	60	0 : 100
3	BnOH	Neat	-	KCN	60	100 : 0
4	BnOH	Neat	-	-	60	0 : 100
5	$BnNH_2$	100	THF	KCN	40[b]	100 : 0
6	$BnNH_2$	100	THF	-	40[b]	100 : 0
7	$BnNH_2$	100	DMSO	-	24	40 : 60
8	$BnNH_2$	100	DMF	-	24	52 :48
9	$BnNH_2$	100	$CHCl_3$		24	36 : 64

[a] Determined by ^{1}H NMR.

[b] When the reaction time was set to 24 h, 70% of **3a** was measured.

The first experiments were performed under the same conditions as described in the homogeneous reaction,[7] but using a large excess of nucleophile (Table 1). The reaction of **2** with benzyl alcohol required the use of KCN as catalyst and a long reaction time (60 h). The solvent did not play a significant role in the reaction since the same quantitative conversion was observed either by using 100 equiv. of alcohol in THF or the alcohol neat (Table 1, entries 1 and 3). As previously reported, KCN is mandatory for reaction. Under the same reaction conditions but in the absence of catalyst (entries 2 and 4), pyroglutamic acid was exclusively obtained. Other bases such as NaH, K_2CO_3, K^+tBuO^- or 2,6-lutidine were also used (without KCN) affording exclusively pyroglutamic acid after release from resin.

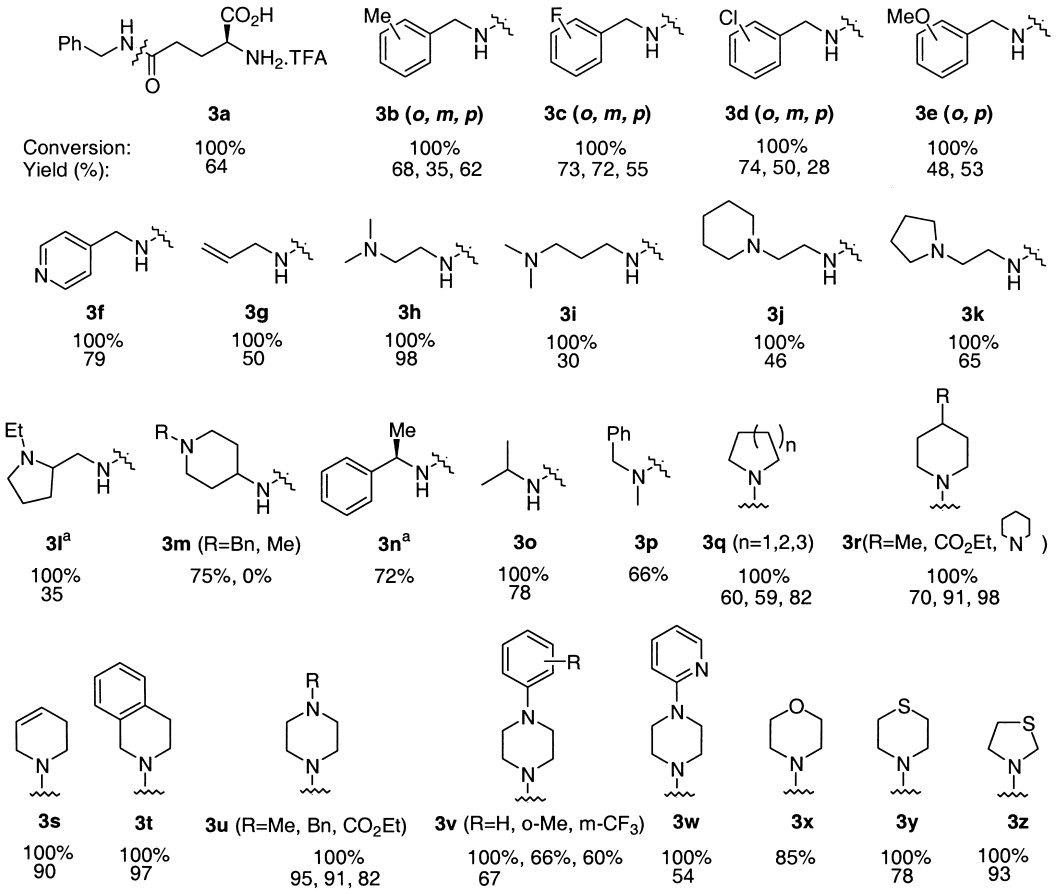
The reaction of **2** with benzyl amine behaved slightly differently. The addition of KCN did not affect the reaction outcome (entry 5 vs 6). This reaction behavior can be explained by the higher nucleophilicity of amines compared with alcohols. The lower nucleophilicity of alcohols requires the addition of KCN, to generate the corresponding acyl cyanide intermediate **I** (Scheme 1), for the nucleophilic displacement to take place.

A complete study of reaction conditions was accomplished with the benzyl amine: different solvents were tested based on its swelling properties (DMSO, DMF, $CHCl_3$, see entries 7–9). Bases such as DIEA, NMM or Et_3N were also used, as solvent or in stoichiometric amount s, producing a significant decrease in **3a** rates (30–35% conversions after 24 h).

Several attempts were performed under sonication reaction conditions but no significant improvements in conversion rates were found.

Finally, in order to establish the scope and limitations of the reaction, we constructed a small library of glutamic acid derivatives with some commercially available amines and alcohols.[†] Results are shown in Table 2 (amines) and Table 3 (alcohols).

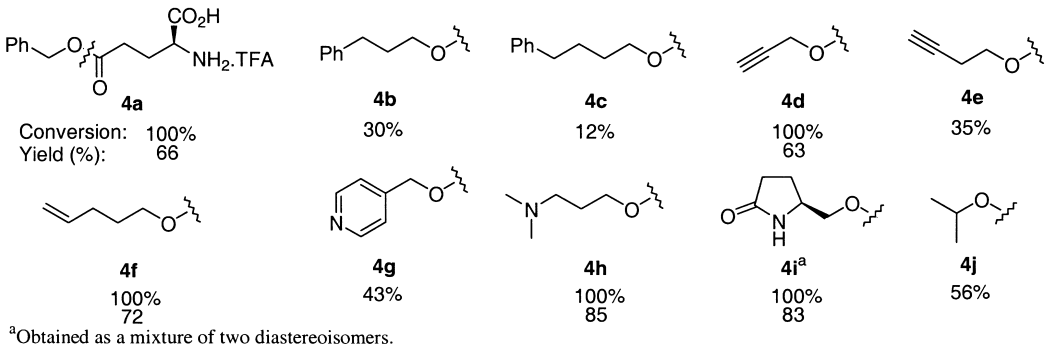
Table 2
Amide derivatives from glutamic acid



[a] Obtained as a mixture of two diastereoisomers.

[†] *Experimental procedure:* Preparation of **3** or **4**. *N*-Boc PyroGlu-Wang resin **2** (100 mg, 0.08 mmol) was suspended in THF (1.5 mL) and the corresponding amine or alcohol was added (100 equiv.). For the reactions with alcohols, KCN (0.1 equiv.) was also added. The resulting slurry was mixed by rocking for a period from 40 h to 5 days. The resin was filtered and washed with THF (4×2 mL), and then alternate with DCM and MeOH (4×2 mL each). Then, the resin was suspended in 95% TFA/H_2O and mixed for 2.5 h. The TFA solution was filtered into a tared vial and solvent removed in vacuo to yield **3** or **4** in a purity >95% in all cases (^{1}H NMR).

Table 3
Ester derivatives from glutamic acid



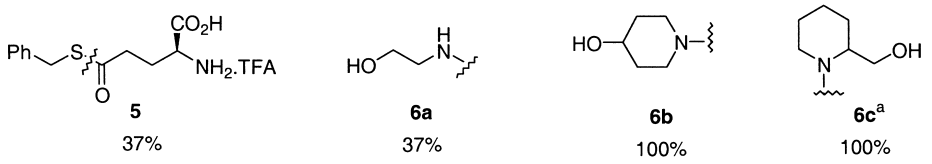
[a]Obtained as a mixture of two diastereoisomers.

Most of the primary and cyclic secondary amines provided 100% conversions (**3a**–**3l**, **3q**–**3t**); α-branched primary amines gave lower conversion rates (**3m** and **3n**).‡ Heterocyclic amines also provided very good conversion rates (**3u**–**3z**) while lower conversions were obtained with acyclic secondary amines (**3p**).‡ The anilines did not react at all, even using catalysts such as KCN or $AlCl_3$.[12]

In the case of alcohols total conversions were obtained for some reactive alcohols (**4a**, **4d**, **4f**, **4h**, **4i**), however lower reaction rates were observed when compared with amines.

Finally, a thiol and three examples of aminoalcohols were studied (see Table 4).

Table 4
Thiol and aminoalcohol addition



[a]Obtained as a mixture of two diastereoisomers.

Reaction with benzyl thiol (in the presence of catalytic KCN) afforded 37% conversion to **5** after 160 h. Aminoalcohols (**6b**, **6c**) reacted through the amino group without KCN, affording total conversions after 136 h. Primary aminoalcohols as well as some α-amino acids studied did not react.

In summary, solid phase conditions for the construction of small libraries of glutamic acid derivatives have been developed based on a chemoselective nucleophilic attack of hetero-nucleophiles on polymer-supported *N*-Boc pyroglutamic acid under mild neutral conditions.

‡ These low yields were observed when the reactions were performed under the usual conditions (without KCN; see above for amines).

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