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LETTERS

Solid-Phase Synthesis of Substituted Glutamic Acid Derivatives *via* Michael Addition Reactions

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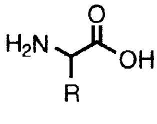
Abstract: The conjugate addition of Michael acceptors to the resin-bound benzophenone imine of glycine leads to a variety of racemic unnatural glutamic acid derivatives. This new approach expands the scope of unnatural amino acid and peptide synthesis (UPS).

Combinatorial chemistry is used to expedite the discovery of biologically active molecules.[1] This if often accomplished by the screening of large numbers of compounds available through solid-phase synthetic techniques. Practical methods have recently been developed for the preparation of resin-bound unnatural α-amino acid derivatives **1** to serve as building blocks in combinatorial chemistry.[2,3] At the same time, we and others have had an interest in the solution-phase synthesis of rare substituted glutamic acid derivatives **2** (Z = CO_2H) because of their important activities on glutamic acid receptors in the central nervous system (CNS).[4]



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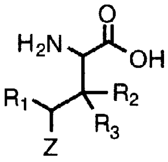

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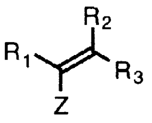

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Herein is reported an efficient and practical method for the solid-phase synthesis of a variety of substituted glutamic acid derivatives via Michael addition reactions. A systematic study of the reaction parameters has allowed the development of highly efficient reaction conditions for the preparation of a variety of compounds **2**.

The benzophenone imine of Wang-resin bound glycine **5** (Scheme) was prepared from commercially available Fmoc-Gly-Wang resin **4** as previously reported.[2] Michael additions of **5** with t-butyl acrylate were examined to establish optimal conditions for typical Michael acceptors. This involved reaction of **5** (1.0 eq) with the Michael acceptor **3** (5.0 eq), using the Schwesinger-type base BEMP (3.0 eq) in NMP at room temperature for 16 h. The resulting resin-bound Michael adduct **6** was

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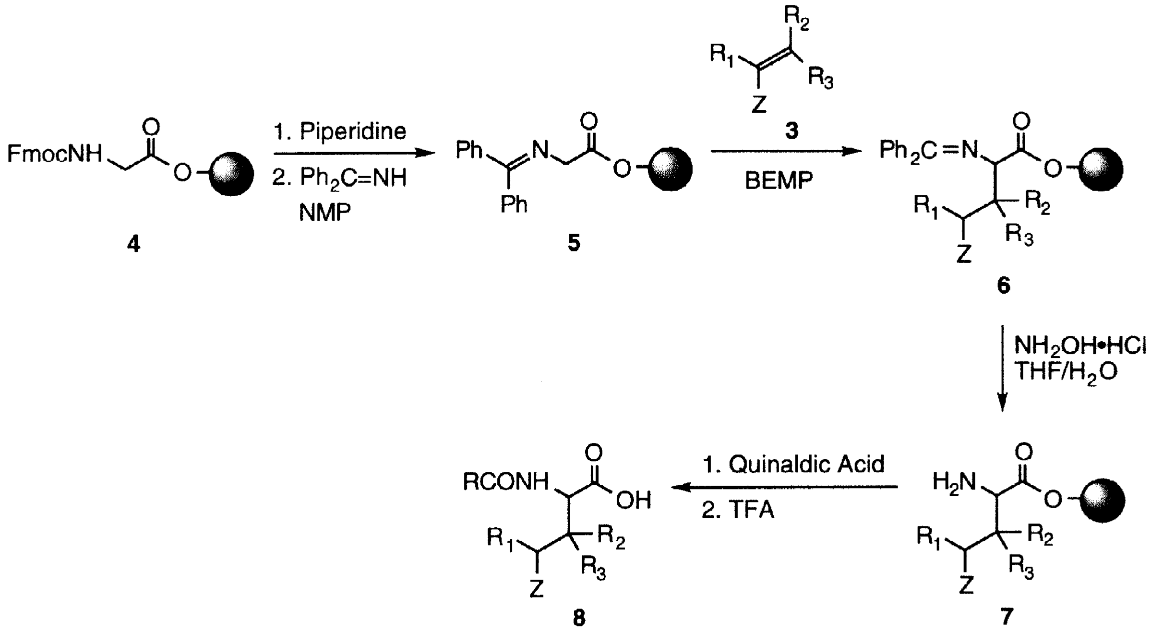
then hydrolyzed with hydroxylamine hydrochloride in THF/H_2O. After filtration and treatment with base, resin-bound **7** was condensed with quinaldic acid to afford a UV active derivative, which was then cleaved from the resin by treatment with TFA. The resulting derivatized product **8** were analyzed by HPLC and LC/MS.[5]



Scheme. UPS Reaction Sequence for Michael Additions to Resin-Bound Glycinates.

In order to determine the reaction scope, we examined a variety of Michael acceptors **3**, bearing different electron-withdrawing groups (Z) and substituents off the double bond. The products of these reactions are shown in the Table. While the typical Michael acceptors (**8a**-**8g**, Table) gave excellent results using the standard conditions,[5] the more reactive Michael acceptors (**8h**-**8j**, model = acrylonitrile, product **8h**) and the less reactive Michael acceptors (**8k**-**8o**, model = ethyl 3-methylacrylate, product **8k**) required further study.

With the more reactive Michael acceptors (**8h**-**8j**, Table) under standard conditions, all the starting material was consumed (except **8i**). However, product purity was only moderate. LC-MS analysis of these samples indicated several impurities consistent with further conjugate addition to the initial Michael adduct. In these cases, the product yields and purity were improved substantially by decreasing the amount of Michael acceptor.[6]

In the case of the less reactive Michael acceptors (**8k**-**8o**, Table), preliminary experiments showed that the use of more Michael acceptor did not substantially increase product yields. From these results we speculated that the rate-determining step, at least in these cases, was the formation of the anion. As predicted, the use of more base in conjunction with more Michael acceptor led to an increase in yield and purity of the product.[7]

The steric requirements of these reactions are important. Products (**8b**, **8f** and **8i**) containing a γ-substituent are available by this methodology. In addition, a variety of products (**8c**-**8f**, **8l**, **8m**) can be obtained with a single substituent in the β-position; however, 3-phenylacrylonitrile (product **8n**) was not an effective Michael acceptor. Finally, reaction of the resin-bound Schiff base with diethyl isopropylidenemalonate, which would yield the highly hindered β,β-disubstituted product **8o**, was not successful.

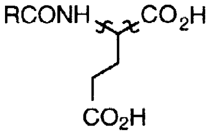
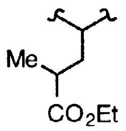
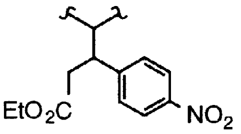
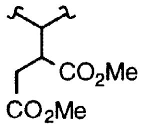
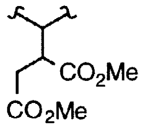
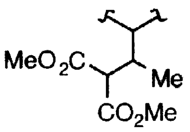
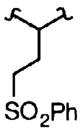
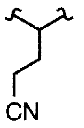
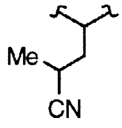
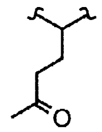
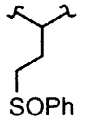
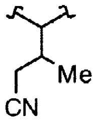
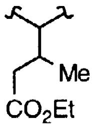
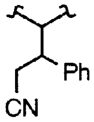
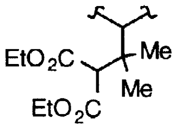
				
8a[a]	**8b**[b]	**8c**[c]	**8d,**[c,d]	**8e**[c,e]
Yield: 66%	61%	88%	71%	74%
Purity: 92%	74%	97%	95%	88%
				
8f[c]	**8g**	**8h**	**8i**	**8j**
Yield: 68%	74%	71%	68%	62%
Purity: 97%	78%	80%	81%	70%
				
8k[c]	**8l**	**8m**[c]	**8n**[f]	**8o**[f]
Yield: 72%	70%	68%	-	-
Purity: 78%	81%	77%	-	-

Table. Derivatized Glutamate-Type Side-Chains Accessible by Michael Reactions. a. Michael acceptor (MA) was t-butyl acrylate (t-butyl ester removed in resin-cleavage step with TFA); b. Product contained 6% starting material; c. Diastereomers observed by HPLC; d. MA = dimethyl maleate; e. MA = dimethyl fumarate; f. <10% product formed; quinaldoylated starting material was recovered.

In summary, we have developed a new and mild procedure for the solid-phase synthesis of substituted glutamic acids derivatives *via* Michael addition reactions. Further applications of this Michael UPS methodology are being explored.

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5. Experimental procedure for typical Michael acceptors (cases **8a**-**8g**): All reactions were conducted at ambient temperature.

   4 to **5**: Fmoc-Gly-Wang resin **4** (100 mg, 0.054 mmol, 0.54 mmol/g, Novabiochem) was suspended in 30% piperidine/NMP (1-methyl-2-pyrrolidinone) (1.5 mL) and the resulting slurry was mixed by rocking for 30 min. The resin was filtered and washed with NMP (4 x 1.5 mL). Benzophenone imine (0.54 mmol, 10.0 eq) in NMP (1.5 mL) was added to the free amino resin **4** followed by addition of glacial HOAc (0.54 mmol, 10.0 eq) and the suspension was rocked overnight. The resin **5** was filtered and washed with NMP (4 x 1.5 mL).

   5 to **6**: Resin **5**, BEMP (2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine) (3.0 eq), Michael acceptor **3** (5.0 eq), NMP (1.5 mL), 16h. The resin was filtered and washed with NMP (4 x 1.5 mL).

   6 to **7**: Resin **6**, 1N aqueous NH_2OH•HCl/THF (3/7, v/v), 5h. The resin was filtered and washed with THF (4 x 1.5 mL), NMP (4 x 1.5 mL), and then mixed with 1N DIEA (diisopropylethylamine), NMP (1.5 mL) for 30 min. The resin was filtered and washed with NMP (4 x 1.5 mL).

   7 to **8**: Resin **7**, quinaldic acid (10 eq), PyBroP (bromo-tris-pyrrolidino-phosphonium hexafluorophosphate) (10 eq), DIEA (20 eq), overnight. The resin was filtered and washed with NMP, THF, MeOH, CH_2Cl_2 (4 x 1.5 mL each), then the resin was suspended in TFA (95%)/H_2O (5%) and mixed for 3h. The aqueous TFA solution was filtered into a tared vial and the resin was concentrated *in vacuo* to yield crude **8** as a red oil that solidified on standing. Yields of **8** were determined for crude products. Purity of **8** was determined by HPLC using a C18 column (150 x 4.6 mm) with mobile phases consisting of 0.1% (v/v) TFA/H_2O (solvent A) and 0.08% (v/v) TFA/CH_3CN (solvent B) with a gradient of 0-80% B over 20 min at a flow rate of 1 mL/min and detection at 240 nm.
6. Experimental procedure for more reactive Michael acceptors (cases **8h**-**8j**): See note 5 for general conditions.

   5 to **6**: Resin **5**, BEMP (3.0 eq), Michael acceptor (1.0 eq), NMP (1.5 mL), 1h (for **8h** and **8j**). Resin **5**, BEMP (3.0 eq), Michael acceptor (1.5 eq), NMP (1.5 mL), 88h (for **8i**).
7. Experimental procedure for less reactive Michael acceptors (cases **8k**-**8o**): See note 5 for general conditions.

   5 to **6**: Resin **5**, BEMP (10.0 eq), Michael acceptor (10.0 eq), NMP (1.5 mL), 16h.