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# Utilization of Fukuyama's sulfonamide protecting group for the synthesis of *N*-substituted α-amino acids and derivatives

Xiaodong Lin, Hilary Dorr and John M. Nuss *

*Chiron Corporation, 4560 Horton Street, Emeryville, CA 94608, USA*

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**Abstract**

A novel and general route for the solid phase synthesis of *N*-substituted α-amino acids has been developed. This synthesis employs Fukuyama's 2-nitrobenzenesulfonamide protecting group for preparation of secondary amines. The versatility of this methodology is demonstrated by the facile synthesis of a trisubstituted diketopiperazine (DKP) skeleton. 

Solid supported organic synthesis has been one of the most intensely investigated areas of organic chemistry, due to its implications in combinatorial chemistry and, in turn, in accelerating the drug discovery process. α-Amino acids continue to be useful chiral building blocks for the synthesis of peptides and small molecule combinatorial libraries. Easy access to *N*-substituted α-amino acids would add even more diversity to this set of chiral building blocks. However, few reports have documented the successful, general synthesis of *N*-substituted α-amino acids directly from amino acid precursors. Perhaps one of the reasons for this difficulty lies in the inability to control mono- and di-*N*-alkylation, particularly on the solid support. Here we wish to report our results describing a general, high yielding method for the synthesis of *N*-substituted α-amino acids on solid support utilizing Fukuyama's sulfonamide technology to protect and activate support bound amines.[1]

To evaluate the generality of the process, polystyrene based Wang and Rink Amide resins were used as starting materials. Our protocol begins with resin bound L-Fmoc-α-amino acids (Scheme 1).[2] Removal of the Fmoc protecting group, followed by sulfonylation under standard conditions, affords 2-nitrobenzenesulfonamides **2**. The subsequent alkylation was achieved using typical Mitsunobu conditions.[3] As summarized in Table 1, the reaction to form **3** was general for both Wang and Rink Amide resins, a number of amino acids and a variety of primary alcohols. Among the examples investigated, amino acids with aliphatic side chains (entries 1–6) and functionalized side chains (entries 7–11) gave the desired products in high yields and purity. Primary alcohols were found to be the most desirable for the Mitsunobu step. The reaction proceeded smoothly with relatively bulky substituents at both the R1 and

* Corresponding author.

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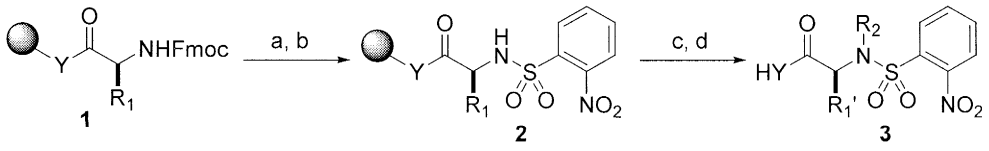
R2 positions (entry 5). Reactions using secondary alcohols resulted in either incomplete conversion or complicated mixture under more forced conditions (heating to 60°C in THF). No detectable racemization occurred during the four-step process.[4]

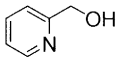
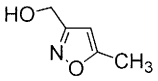
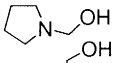
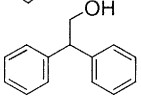



Y = O, PS-Wang resin; Y = NH, PS-Rink Amide resin

a) 20% piperidine in DMF, rt, 30 min.; b) 8 equiv. 2-$NO_2$-$PhSO_2Cl$, 10 equiv. Py., 1 equiv. DMAP, DCM,rt, 6 h; c) 5 equiv. $R_2OH$, 5 equiv. $Ph_3P$, 5 equiv. DIAD, THF, rt, 15 h; d) 90% TFA in $H_2O$, rt, 1 h.

Scheme 1.

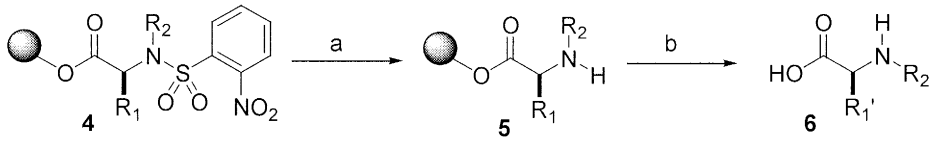
Table 1
Formation of *N*-substituted sulfonamide **3**

| Entry | Resin | $R_1$' Derivative | $R_2OH$ | %Purity[a] | %Yield[b] |
|---|---|---|---|---|---|
| 1 | Wang | Ala | p-Cl-BnOH | 95 | 99 |
| 2 | " | Ala |  | 95 | 92 |
| 3 | " | Ala |  | 95 | 95 |
| 4 | " | Ala |  | 95 | 90 |
| 5 | " | Val |  | 95 | 89 |
| 6 | " | Ile |  | 95 | 90 |
| 7 | " | Trp | p-Cl-BnOH | 98 | 95 |
| 8 | " | Lys | p-Cl-BnOH | 95 | 95 |
| 9 | " | Ser | p-Cl-BnOH | 90 | 90 |
| 10 | " | Asp | p-Cl-BnOH | 99 | 90 |
| 11 | Rink Amide | Tyr | p-Cl-BnOH | 95 | 90 |

a. Purity was determined by HPLC analysis recorded at 220 nm. b. Yields are based upon mass balance of lyophilized product relative to the resin substitution level.

Next, the scope of desulfonylation reaction was examined in detail. To obtain *N*-substituted amino acids, Wang resin bound sulfonamides **4** were subjected to typical Fukuyama desulfonylation conditions (Scheme 2). The results are summarized in Table 2.[5] Overall, anticipated acids **6** were obtained with satisfying yields and purity.

In sharp contrast to the above results, unexpected difficulties were encountered during the removal of the sulfonyl group with Rink Amide resin bound sulfonamides **7** (Scheme 3). A number of reaction conditions were examined[6] and each failed to produce the desired product cleanly. Nevertheless, the



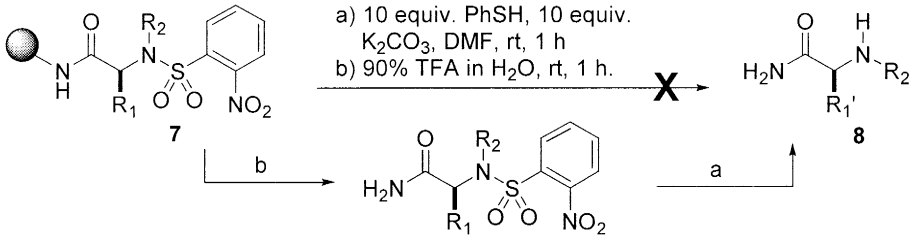

Scheme 2.

Table 2
Desulfonylation of Wang resin bound sulfonamide to amino acid **6**

| Entry | $R_1$' Derivative | $R_2$ | %Purity[a] | %Yield[b] |
|---|---|---|---|---|
| 1 | Phe | 2-Butynyl | 95 | 95 |
| 2 | Val | 2,2-diphenylethyl | 95 | 96 |
| 3 | Trp | p-Cl-benzyl | 98 | 90 |
| 4 | Lys | p-Cl-benzyl | 91 | 90 |
| 5 | Tyr | p-Cl-benzyl | 99 | 95 |
| 6 | Ser | p-Cl-benzyl | 88 | 90 |
| 7 | Asp | p-Cl-benzyl | 99 | 85 |

a. Purity was determined by HPLC analysis recorded at 220 nm. b. Yields are based upon mass balance of lyophilized product relative to the resin substitution level.

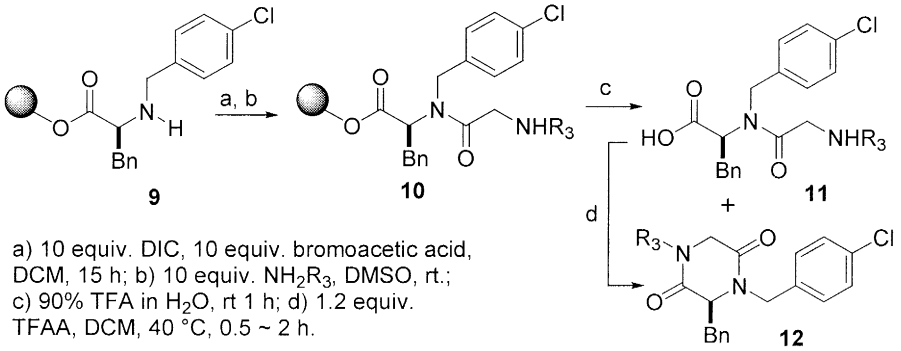
amide analogue **8** ($R_1$=Ala, $R_2$=*p*-Cl-benzyl) was obtained in 60% purified yield from its resin free sulfonamide precursor using Fukuyama's thiophenol/$K_2CO_3$ condition.




Scheme 3.

The versatility of this methodology can be demonstrated by facile syntheses of trisubstituted DKPs **12** using *N*-substituted amino acids **9** (Scheme 4).[7] Thus, acylation of *N*-alkyl amino acid **9** with bromoacetic acid, followed by substitution with primary amines gave compound **10**. Upon cleavage from the resin, dipeptide **11** or a mixture of **11** and DKP **12** were obtained. The results depend highly upon the nature of the amines used. As summarized in Scheme 4, when α-branched primary amines were used in substitution step, the open chain *N*-substituted dipeptides **11** were obtained exclusively with good purity and high yields (entries 1–2). However, as the steric bulkiness of the amine decreased (entry 3), intramolecular cyclization spontaneously occurred during cleavage, affording a mixture of dipeptide **11** and DKP **12**. When benzylamine (entry 4), a β-branched amine, was used, longer reaction time (2 h) led to very poor mass recovery. This presumably arose from intramolecular cyclization of intermediate **10** and/or cleavage of the ester linkage by benzylamine during the substitution step. Shortening the reaction time to 45 min afforded a higher yield of products, as a mixture of **11** and **12**. To convert the dipeptide **11** into DKP **12**, **11** (or a mixture of **11** and **12**) was simply treated with TFAA (1.2 equiv.) in DCM at

40°C for 0.5 to 2 h. Concentration in vacuo followed by lyophilization afforded pure DKP **12** in nearly quantitative yield.[8]




a) 10 equiv. DIC, 10 equiv. bromoacetic acid, DCM, 15 h; b) 10 equiv. $NH_2R_3$, DMSO, rt.; c) 90% TFA in $H_2O$, rt 1 h; d) 1.2 equiv. TFAA, DCM, 40 °C, 0.5 ~ 2 h.

| Entry | $NH_2R_3$ | Substitution Time (h) | %Yield[a] **11 + 12** | Ratio%[b] **11 : 12** | %Purity[c] **12** |
|---|---|---|---|---|---|
| 1 | t-Butylamine | 2 | 95 | 100 : 0 | 100 |
| 2 | Cycloheptamine | 2 | 95 | 100 : 0 | 100 |
| 3 | Cyclopropylamine | 2 | 92 | 37 : 63 | 91 |
| 4 | Benzylamine | 0.75 | 70 | 56 : 44 | 95 |

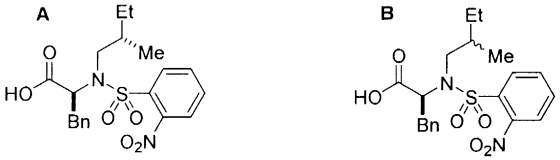
a. Yields are based upon mass balance of lyophilized product relative to the resin substitution level. b. Ratios are determined by LC/MS. c.Purity was determined by HPLC analysis recorded at 220 nm.

Scheme 4.

In summary, we have demonstrated a general and efficient route for the synthesis of important *N*-substituted amino acid building blocks. This route can be further expanded to synthesize heterocycles such as DKPs. This approach allows the incorporation of three diversity elements on the DKP ring, arising from readily available amino acids, primary alcohols and primary amines. Studies toward making a DKP combinatorial library using this strategy are in progress.

## References


1. (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. Applications to solid phase synthesis were reported as we were preparing this manuscript: (b) Seitz, O. *Angew. Chem., Int. Ed.* **1998**, 37, 3109. (c) Mohamed, N.; Bhatt, U.; Just, G. *Tetrahedron Lett.* **1998**, *39*, 8213. (d) Kung, P.-P.; Swayze, E. *Tetrahedron Lett.* **1999**, *40*, 5651.
2. (a) Resin bound α-amimo acids were either purchased from NovaBiochem or prepared by the following procedure. To load amino acids on Wang resin: 4 equiv. DIC, 4 equiv. Fmoc-aa-OH, 2 equiv. DMAP, DCM, rt, 45 min and double coupling. To load amino acids on Rink Amide resin: 4 equiv. Fmoc-aa-OH, 4 equiv. HBTU, 4 equiv. HOBT, 8 equiv. DIEA, NMP, rt, 1.5 h. (b) Functionalized side chains were protected by either *t*Bu (Tyr, Ser, Asp) or Boc (Orn, Lys, Trp). Protecting groups were removed simultaneously upon cleaving compounds off the resin. (c) All reactions were run in a vial using 100 mg of resin in 2 mL solvent with constant agitation.
3. Mitsunobu, O. *Synthesis* **1981**, 1.
4. $^1$H NMR analysis of compounds **A** and **B** showed racemization was <5% (within the limits of detection).




5. Other amino acids such as Met, His(Trt), Arg (Tos), Asn (Trt) and Cys (*t*Bu) resulted in complex mixtures, although the desired compounds **6** were observed.
6. Conditions examined for desulfonylation of **7** include: (a) PhSH/$K_2CO_3$/DMF, rt–40°C, Ref.1. (b) Mercaptaacetic acid/$Et_3N$/DMF/rt–40°C, Ref. 1. (c) LiSPh/DMF/rt–40°C. (d) PhSH/$K_2CO_3$/$CH_3CN$/50°C, Based upon: Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253.
7. DKP formation on solid support with different strategies has been reported: (a) Hulme, C.; Peng, J.; Morton, G.; Salvino, J. M.; Herpin, R.; Labaudiniere, R. *Tetrahedron Lett.* **1998**, *39*, 7227. (b) del Fresno, M.; Alsina, J.; Royo, M.; Barany, G. Albericio, F. *Tetrahedron Lett.* **1998**, *39*, 2639. (c) Smith, R. A.; Bobko, M. A.; Lee, W. *Bioorg. Med. Chem. Lett* **1998**, *8*, 2369. (d) Szardenings, A. K.; Burkoth, T. S. *Tetrahedron* **1997**, *53*, 6573. (e) Kowalski, J.; Lipton, M. A. *Tetrahedron Lett.* **1996**, *37*, 5839. (f) Gordon, D. W.; Steele, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 47.
8. NMR data for **12** ($R_3$=*t*-Bu): $^1$H 7.317–7.050 (m, 9H, aromatic), 5.322, 3.888 (ABq, *J*=14.79 Hz, 2H, NC*H*$_2$Ph-pCl), 4.018 (app. t, 1H, methine), 3.628, 2.312 (ABq, *J*=17.18 Hz, 2H, $NCH_2CO$), 3.206 (dd, *J*=13.74, 3.85 Hz, 1H, PhC*H*$_2$), 3.062 (dd, *J*=13.74, 4.43 Hz, 1H, PhC*H*$_2$), 1.280 (s, 9H, *t*-Bu). $^{13}$C 166.46 (CO), 165.59 (CO), 134.79 (ipso), 134.07 (ipso), 133.97 (ipso), 130.20, 129.85, 129.16, 128.69, 127.80 (aromatic CH), 61.35 (methine), 58.11 (quaternary), 46.21 (Ph*C*$H_2$), 46.14 (Ph*C*$H_2$), 36.83 ($NCH_2O$), 27.74 (Me of *t*-Bu).