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Use of the Mitsunobu reaction in the synthesis of orthogonally protected α,β-diaminopropionic acids

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Abstract—Orthogonally protected α,β-diaminopropionic acids have been synthesised in good yields by the reaction of *N*-trityl L-serine esters with N-substituted sulfonamides under Mitsunobu reaction conditions (DEAD, PPh_3, THF). The best isolated yields were obtained when *N*-Boc *p*-toluenesulfonamide was used as the nitrogen nucleophile precursor in the Mitsunobu reaction. Subsequently, the *N*-trityl group was efficiently replaced with the more stable allyloxycarbonyl (alloc) group.

1. Introduction

Interest in the properties of α,β-diamino acids is evidenced by the large number of publications in this area. A recent review has highlighted the wide range of methods for their synthesis and also the myriad of possible biological applications.[1] A number of recent examples, in particular, demonstrate the different approaches to the preparation of these types of compounds. Lee prepared 2,3-diaminopropionates by ring opening of aziridine-2-carboxylates with azide ions and subsequent reduction of the azido group to an amine,[2] while Panda used the Mitsunobu reaction[3] of HN_3 on N-protected L-serine-derived Weinreb amides.[4] The reason for the use of the Weinreb amide derivative was to reduce the acidity of the serine α-hydrogen and thus stop the formation of a dehydroalanine (Dha) by a dehydration reaction. Pedatella prepared orthogonally protected 2,3-diamino acids by treatment of the enolate of N,N-dibenzylated β-amino esters with di-*tert*-butyl azodicarboxylate (DBAD). Subsequent removal of the Boc group and cleavage of the hydrazine gave the 2,3-diamino acids.[5] Nadir prepared 2,3-diamino acids by reaction of *N*-arylsulfonyl aziridines with a chiral isocyanate and subsequent hydrolysis of 2-imidazolidinones.[6]

As part of a program of peptide synthesis, incorporating unusual amino acid residues, we are interested in the synthesis of orthogonally protected α,β-diaminopropionic acids for solid-phase peptide synthesis. We decided to examine the Mitsunobu reaction of L-serine derivatives with nitrogen-based nucleophiles, other than azide, for their synthesis. Our first choice was sulfonamide based nucleophiles (Ts or Ns) because they have appropriate pK_a values. In 1989 Weinreb introduced Ts–NH–Boc in the Mitsunobu reaction for the conversion of alcohols into *N*-Boc *p*-toluenesulfonamides in excellent yields.[7] A survey of the literature shows that the correct choice of nitrogen and/or carboxyl protecting groups is critical to the positive outcome of the Mitsunobu reaction at the hydroxyl group of L-serine derivatives. In many cases, the incorrect choice of protecting group leads to elimination reactions giving Dha compounds, or cyclisations to form aziridines. Cherney and Wang showed that protection of the L-serine nitrogen with a trityl group gives excellent yields of Mitsunobu products, using phthalimide as the nitrogen nucleophile, where the carboxyl group was protected as the methyl ester.[8] The trityl group works in two ways, by sterically preventing cyclisation of the nitrogen to form aziridines, and secondly, by reducing the acidity of the α-hydrogen compared to carbamate protecting groups, thus preventing Dha formation. We prepared *N*-trityl L-serine methyl ester (**2**) in 75% yield from L-serine methyl ester (**1**) using the method of Baldwin (Scheme 1).[9] Subsequent treatment of **2** with the commercially available Weinreb nucleophile Ts–NH–Boc (**3**), under Mitsunobu reaction conditions (diethyl azodicarboxylate (DEAD), PPh_3, THF), gave the orthogonally protected α,β-diaminopropionic acid **4** in 75% isolated yield. Due to the propensity for the trityl group to be easily removed, even on treatment with mild acid, we decided to replace this

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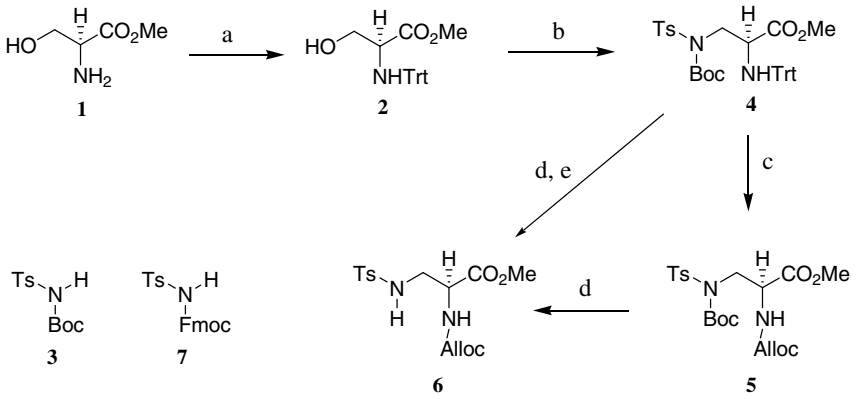


Scheme 1. Reagents and conditions: (a) trityl chloride, Et_3N, DCM, rt, 75%; (b) **3**, DEAD, PPh_3, THF, rt, 75%; (c) (i) 5% TFA in $CHCl_3$, (ii) allyl chloroformate, $NaHCO_3$, H_2O, 1,4-dioxane, rt, 30%; (d) 50% TFA in $CHCl_3$, rt; (e) $NaHCO_3$, H_2O, allyl chloroformate, rt.

group with the more stable *N*-allyloxycarbonyl (alloc) protecting group, which also keeps full orthogonality with the other protecting groups present.

Treatment of **4** with 5% TFA in chloroform and subsequent reaction with allyl chloroformate gave the *N*-alloc compound **5** in an isolated yield of only 30%. All attempts to improve the yield of this two-step process were unsuccessful. Removal of the Boc protecting group on the β-nitrogen was efficiently achieved (90% yield) on treatment of **4** with a 50% TFA in chloroform solution to give sulfonamide **6**, which possesses a free sulfonamide N–H for further derivatisation of the β-nitrogen, if required. Thus we have successfully prepared **6**, but in a poor yield of only 27%, from **4**. We were pleased to find that if we treated **4** directly with a 50% TFA in chloroform solution, followed by reaction of the unpurified intermediate amine with allyl chloroformate, we were able to prepare sulfonamide **6** in a much improved isolated yield of 74%.

We were interested in extending the scope of this method in three ways, (i) by changing the groups on the sulfonamide nucleophilic moiety, (ii) by using a different ester of the *N*-trityl L-serine and (iii) using di-*iso*-propyl azodicarboxylate (DIAD) instead of DEAD. Bach reported the use of the Fmoc sulfonamide, Ts–NH–Fmoc (**7**), in the Mitsunobu reaction of alcohols, where the isolated product showed the concomitant loss of the Fmoc group, though the reasons for this result were not discussed.[10] This reaction was of interest to us at it would lead directly to a compound with a free sulfonamide N–H. Thus Fmoc sulfonamide **7** was prepared in good yield, by an adaptation (using fluorenylmethyl alcohol) of Weinreb's synthesis of **3**,[7] and was subjected to reaction with protected serine **4**, under similar Mitsunobu conditions to those used for the Boc derivative; however, none of the desired products were obtained. The two starting materials were re-isolated from the reaction intact. It is known that Fukuyama has performed extensive studies on the use of nitrobenzenesulfonamides in the Mitsunobu reaction,[11] where the presence of the nitro group(s) lowers the pK_a values of the sulfonamides. Thus, we prepared a number of nosyl sulfonamides (**8**–**11**, Fig. 1)[12] in order to examine their usefulness in the Mitsunobu reaction of suitably protected serines. All reactions of these sulfonamides with *N*-trityl L-serine methyl ester **4**, under the Mitsunobu conditions used previously, using either DEAD or DIAD, were unsuccessful, with only starting materials being isolated in each case.

We next studied the effect of using a different carboxylic ester L-serine protecting group instead of the methyl ester. We chose the allyl ester and the required Mitsunobu reaction precursor, *N*-trityl L-serine allyl ester (**12**), was prepared using standard conditions[13] (Scheme 2). Thus *N*-trityl L-serine was prepared in 48% yield starting from serine by treatment with trityl chloride and trichloromethylsilane in DCM. Subsequent allylation of the caesium salt of *N*-trityl L-serine, in DMF, gave allyl ester **12** in 90% isolated yield.

Reaction of **12** with Ts–NH–Boc (**3**), under Mitsunobu reaction conditions (DEAD, PPh_3, THF), again gave an orthogonally protected α,β-diaminopropionic acid (**13**), on this occasion in 72% isolated yield. In this case when the *N*-trityl group was replaced with the *N*-alloc group followed by removal of the Boc group on the sulfonamide, in the two-step method, sulfonamide **15** was isolated, via **14**, in a very poor yield of 19%. Gratifyingly, when the trityl and Boc protecting groups were removed simultaneously, and the intermediate amine was reacted with allyl chloroformate under basic conditions, **15** was obtained in a vastly improved yield of 83%. As before, we examined the use of nosyl sulfonamides **8**–**11** in the Mitsunobu reaction with **12**. In this case the only successful reaction was with the *p*-methoxybenzyl (PMB) substituted *o*-nitrobenzenesulfonamide **11**, where the desired product **16** was obtained in a 51% yield. In all

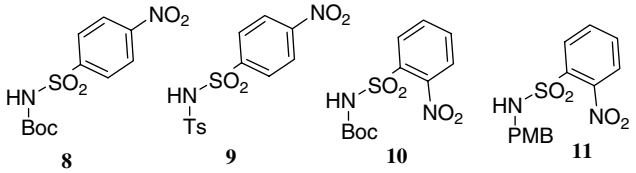
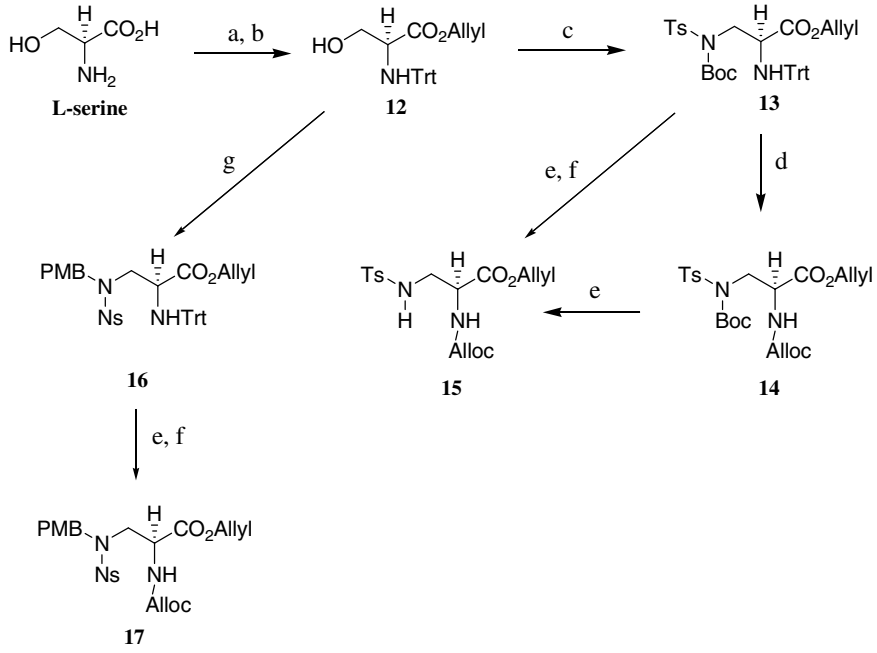


Figure 1. Nosyl sulfonamide derivatives prepared.[9,10]



Scheme 2. Reagents and conditions: (a) trityl chloride, trichloromethylsilane, Et_3N, DCM, rt, 48%; (b) (i) Cs_2CO_3, MeOH; (ii) allyl bromide, DMF, rt, 90%; (c) **3**, DEAD, PPh_3, THF, rt, 72%; (d) (i) 5% TFA in $CHCl_3$, (ii) allyl chloroformate, $NaHCO_3$, H_2O, 1,4-dioxane, rt, 19% from **13**; (e) 50% TFA in $CHCl_3$, rt; (f) allyl chloroformate, $NaHCO_3$, H_2O, rt; (g) **11**, DEAD, PPh_3, THF, rt, 51%.

other reactions only the starting materials were re-isolated. As before, **16** was efficiently converted to the *N*-alloc protected compound **17** (Scheme 2).

In conclusion, we have prepared orthogonally protected α,β-diaminopropionic acids in good yields from protected L-serines using the Mitsunobu reaction of sulfonamide-derived nitrogen nucleophiles. Currently we are studying the chemistry of these compounds, for example, the clean removal of the individual protecting groups, and their incorporation into peptide structures using solid-phase peptide synthesis. We are also examining further functionalisation reactions of N–H sulfonamide compounds **6** and **15**. The results of these studies will be reported in due course.

2. Typical procedure for Mitsunobu reaction, exemplified by the synthesis of 13

To a solution of *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide **3** (0.16 g, 0.68 mmol) in dry THF (3 ml) was added PPh_3 (0.34 g, 1.4 mmol), followed by the addition of **12** (0.16 g, 0.46 mmol) and DEAD (0.19 g, 1.2 mmol). The resulting mixture was allowed to stir at room temperature, under a nitrogen atmosphere, for 10 h. The solvent was removed in vacuo giving an orange oil, which was purified by flash column chromatography on silica gel, in petroleum ether/ethyl acetate (10:1), to give a white solid (0.30 g, 72%). Mp: 143–145 °C. R_f: 0.80, petroleum ether–ethyl acetate (2:1). IR (KBr) cm^{-1}: 3433, 3066, 2924, 1734, 1595, 1234, 1139. ^1H NMR ($CDCl_3$, 300.4 MHz) δ ppm, 7.77 (d, 2H, $J = 12.3$ Hz, *ortho* tosyl), 7.54 (d, 6H, $J = 12.9$ Hz, *ortho* trityl), 7.27–7.23 (d, 2H, $J = 12.3$ Hz, *meta* tosyl and m, 9H, *para* and *meta* trityl), 5.56 (m, 1H, vinyl CH), 5.11 (m, 2H, vinyl CH_2), 4.24 (dd, 1H, $J = 8.4$ and 8.6 Hz, allyl CH_2), 4.11 (m, 1H, allyl CH_2), 3.92 (dd, 1H, $J = 5.3$ and 6.0 Hz, α-CH), 3.80 (m, 2H, β-CH_2), 2.86 (d, 1H, $J = 11.1$ Hz, NH), 2.37 (s, 3H, tosyl CH_3), 1.25 (s, 9H, *t*-butyl). ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ ppm, 172.6 (ester C=O), 150.8 (Boc C=O), 145.7 (*ipso* trityl), 144.1 (*para* tosyl), 137.4 (*ipso* tosyl), 131.8 (vinyl CH), 129.2 (*meta* trityl), 128.8 (*meta* tosyl), 128.1 (*ortho* trityl), 127.8 (*ortho* tosyl), 126.4 (*para* trityl), 118.3 (vinyl CH_2), 84.4 (C_q *t*-butyl), 70.9 (allyl CH_2), 65.9 ($C(Ph)_3$), 56.0 (α-CH), 50.4 (β-CH_2), 27.8 (CH_3 *t*-butyl), 21.6 (CH_3 tosyl). Mass Spec: expected [M+1] 641.2685, observed [M+1] 641.2690.

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References and notes

1. Viso, A.; Fernandez de la Partilla, R.; Garcia, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167.
2. Kim, Y.; Ha, H.-J.; Han, K.; Ko, S.; Yun, H.; Yoon, H.; Kim, M.; Lee, W. *Tetrahedron Lett.* **2005**, *46*, 4407.
3. Mitsunobu, O. *Synthesis* **1981**, 1.
4. Panda, G.; Rao, N. V. *Synlett* **2004**, 714.
5. Capone, S.; Guaragna, A.; Palumbo, G.; Pedatella, S. *Tetrahedron* **2005**, *61*, 6575.
6. Nadir, U.; Krishna, R.; Singh, A. *Tetrahedron Lett.* **2005**, *46*, 479.
7. Henry, J.; Marcin, L.; McIntosh, M.; Scola, P.; Harris, P. D., Jr.; Weinreb, S. *Tetrahedron Lett.* **1989**, *30*, 5709.
8. Cherney, R.; Wang, L. *J. Org. Chem.* **1996**, *61*, 2544.

9. Baldwin, J.; Spivey, A.; Schofield, C.; Sweeney, J. *Tetrahedron* **1993**, *49*, 6309.
10. Bach, T.; Kather, K. *J. Org. Chem.* **1996**, *61*, 7642.
11. Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353.
12. Compounds **8** and **10** were prepared according to Kurosawa, W.; Kan, T.; Fukuyama, T.; Cheung, M.; Kan, T. *Synlett* **1999**, 1301, and compound **9** was prepared by an adaptation of this method. Compounds **11a** and **11b** were prepared according to the method of Kurosawa, W.; Kan, T.; Fukuyama, T. *Org. Synth.* **2002**, *79*, 186. Note: Analytical data for **9**: Mp: 121–122 °C. R_f: 0.69, methanol–chloroform (1:2). IR (KBr) cm^{-1}: 3308, 3021, 1540, 1364, 1158. ^1H NMR ($CDCl_3$, 300.4 MHz) δ ppm, 8.05 (d, 2H, $J = 8.9$ Hz, *ortho* nosyl), 7.83 (d, 2H, $J = 8.9$ Hz, *meta* nosyl), 7.54 (d, 2H, $J = 8.2$ Hz, *ortho* tosyl), 7.03 (d, 2H, $J = 7.8$ Hz, *meta* tosyl), 2.31 (s, 3H, tosyl). ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ ppm, 149.1 (*para* nosyl), 143.3 (*ipso* nosyl), 141.8 (*para* tosyl), 139.3 (*ipso* tosyl), 129.5 (*meta* tosyl), 128.6 (*ortho* nosyl), 127.9 (*ortho* tosyl), 123.1 (*meta* nosyl), 21.4 (–CH_3, tosyl).
13. Mustapa, M. F. M.; Harris, R.; Bulic-Subanovic, N.; Elliott, S.; Bregant, S.; Groussier, M.; Mould, J.; Schultz, D.; Chubb, N.; Gaffney, P.; Driscoll, P.; Tabor, A. *J. Org. Chem.* **2003**, *68*, 8185.