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Pmc-protected Amino Acid Esters as Substrates in N-alkylamino Acid Synthesis.

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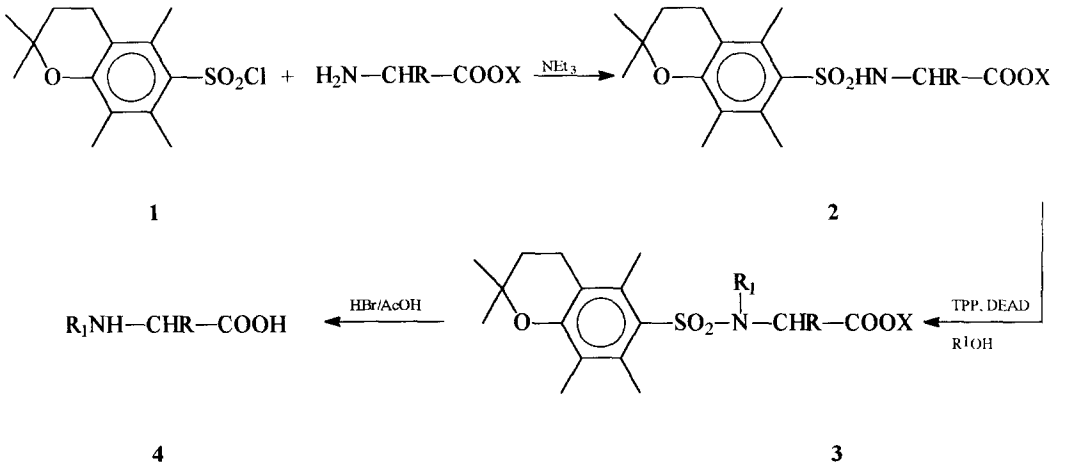
Abstract: N-alkylamino acids may be synthesised via Mitsunobu reaction of N-(2,2,5,7,8-pentamethylchroman-6-sulphonyl-)-amino acid esters with various alcohols and subsequent deprotection. Copyright © 1996 Published by Elsevier Science Ltd

It has been demonstrated[1,2] that N-alkyl p-toluenesulphonamides can be successfully used as acidic components in the Mitsunobu reaction.[3] This reaction was employed in the synthesis of chiral amines[1,2] and N-alkylamino acids[4], but a drawback is the necessity of application of harsh conditions for the tosyl group removal.

In an attempt to find a more convenient protecting group of sulphonamide type we turned our attention to the acid labile 2,2,5,7,8-pentamethylchroman-6-sulphonyl (Pmc) group commonly used for guanidine function protection in arginine derivatives.[5] It was obvious to us that electron donating substituents, which are an essential prerequisite for enhanced acid lability of Pmc-group, cause a reduction of the acidity of Pmc-sulphonamide proton. To check whether the Pmc-group compromises between the contradictory needs for sulphonamide proton acidity adequate for the Mitsunobu reaction (it is usually assumed pK_a must be < 15)[6] and acidic lability sufficient for deprotection we determined acidity of N-methyl-2,2,5,7,8-pentamethylchroman-6-sulphonamide by potentiometric titration[7]. The obtained value (pK_a = 12.05) was only slightly above that obtained for N-methyl-p-toluenesulphonamide (pK_a = 11.69[8]) which prompted us to an attempt of N-alkylamino acid synthesis following the Scheme.

Although Pmc-amino acids could be converted into N-alkyl-Pmc-amino acid esters (X = R_1) in a "one pot" procedure under Mitsunobu conditions, we initially decided to investigate N-alkylation reaction using Pmc-amino acid esters, **2**, obtained from commercially available amino acid esters (X = t-Bu or Bzl) and Pmc-chloride **1** to avoid ester saponification necessary in case X = R_1 and saponification-related possible loss of the chirality of protected N-alkylamino acids. The chosen protecting groups allowed us to remove both protecting groups (Pmc and X) in one acidolytic (HBr/AcOH) step.



To test the conditions of Pmc group removal we subjected the Pmc-amino acid esters to several acidic conditions used in peptide chemistry. The Pmc-sulphonamide group turned out to be stable under the conditions applied for the deprotection of guanidine function.[5] When Pmc-Phe-OtBu was treated with TFA only rapid removal of t-butyl ester occurred. No further changes were detected after overnight reaction. To our disappointment the group also remained intact in HCl/dioxane solution. Finally, we found that the Pmc group is cleaved from the protected amino acids by HBr/AcOH, within several hours. Since Benoiton et al.[9] have reported N-alkylamino acids racemisation occurring under such conditions we added 2% of water to the reaction mixture to reduce the possible loss of the chirality.

The Mitsunobu reaction (**2** $\rightarrow$**3**) with MeOH was complete within an hour. The use of BuOH as an alkylating agent required an additional equivalent of triphenylphosphine (TPP), ethyl (DEAD) or isopropyl (DIAD) azodicarboxylate and the alcohol and isopropanol (R_1 = iPr) required the use of 4-5 equivalents of the chemicals for completion. These results indicate that the alkylation of Pmc-sulphonamides is highly influenced by the bulkiness of the substrate alcohol. The possibility of selective alkylation of diamino acids was also tested. Thus, Pmc-Lys(Z)-OtBu, **2g,** was converted into the corresponding N-α-methyl derivative, **3g,** within an hour using 2 equivalents of the reagents. An attempt at alkylation of Boc-Lys(Pmc)-OtBu with MeOH was only partially successful since 8-fold excess of the reagents gave only 33% of the alkylated product (by HPLC analysis). Incomplete alkylation obviously results from the fact that the acidity of N-ε proton in the substrate is lower (higher basicity of ε-NH_2 group) in comparison to N-α-Pmc-derivatives of lysine. Despite the fact that the Mitsunobu reaction does not involve the only chiral centre of the substrates, we checked whether the reaction conditions does not influence the optical purity of the products by comparison of the $[\alpha]_D$ of the known product with the highest optical rotation. Correspondence between the $[\alpha]_D$ value of MePheOH obtained ($[\alpha]_D$ = +49.1^{O} ,c = 1, 1N NaOH) and the value reported in the literature[10] ($[\alpha]_D$ = +49.3^{O}) assured us that the methodology proposed is safe as far as the optical purity is concerned.

A typical procedure of N-alkylamino acid synthesis consists of three following stages: synthesis of Pmc-amino acid esters, N-alkylation under Mitsunobu conditions, and deprotection.

An amino acid ester salt was dissolved in DCM and 2.1 equivalents of triethylamine were added immediately followed by 1.1 equivalents of Pmc chloride. The reaction mixture was magnetically stirred at room temperature overnight. The solvent was evaporated and the residue was dissolved in ethyl acetate and washed with water, 1M HCl, water, 1M $NaHCO_3$ and water. The organic phase was dried over magnesium sulphate and evaporated. The oily residue was used without further purification in the N-alkylation step.

Pmc-amino acid ester was dissolved in dry THF (2ml per 1 mmol) and an appropriate alcohol (2 eq), TPP (2 eq) and (2 eq) DEAD were added. The reaction was monitored by HPLC until the substrate peak disappeared. Most often, no significant changes were observed after 1 hour. If the reaction was not complete further portions of the reagents were added. The THF was then evaporated and the residue was dissolved in diethyl ether. In most cases a precipitate consisting of triphenylphosphine oxide and alkyl hydrazinedicarboxylate appeared which was removed by filtration. The solvent was evaporated and the crude Pmc-N-alkylamino acid ester was dissolved in 33%HBr/AcOH containing 2% of water and left for 2-5 hours until the removal of protecting groups was achieved. The solvents were evaporated, the residue dissolved in water and washed several times with ethyl ether. The aqueous phase was then evaporated, the residue redissolved in MeOH and the pH adjusted to 5 using triethylamine. The product was filtered off and recrystallised from a suitable solvent. In the case of the better soluble N-alkyl alanines ion-exchanger Dowex 50x8 in H^+ form had to be employed for their isolation. The yields of N-alkylamino acids as well as their chromatographic characteristics are given in the Table.

Table.

entry	R	R^1	excess* of reagents used	X	Yield 2→4(%)	ret. time of 2**	ret. time of 3**
a	Bzl	Me	2	t-Bu	63	17.4	19.5
b	Bzl	i-Pr	5	t-Bu	51	17.4	21.4
c	Bzl	Bu	3	t-Bu	65	17.4	22.9
d	Me	Me	2	Bzl	54	13.5	15.9
e	Me	i-Pr	4	Bzl	45	13.5	17.2
f	Me	Bu	3	Bzl	51	13.5	19.5
g	$-(CH_2)_4NHZ$	Me	2	t-Bu	58	16.4	18.5

* the final number of equivalents of the alcohol, TPP and DEAD used

** HPLC was run on Varian 5500 Vista liquid chromatograph. The linear gradient 60 → 100%B, 20 min. was applied (A = 0.1% TFA/water, B = MeCN)

In summary, we have elaborated a new, simple and efficient method of N-alkylamino acid synthesis. The procedure comprises synthesis of Pmc-amino acid esters, **2**, alkylation of the sulphonamide derivatives under Mitsunobu conditions leading to fully protected N-alkylamino acids, **3**, and one-step deprotection using HBr/AcOH. The method described allows fast and efficient synthesis of N-alkylamino acids, **4**, from amino acid esters and does not require time-consuming chromatographic work-up after N-alkylation. Selective alkylation of α-nitrogen of diamino acids can also be performed.

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