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Tandem UPS: Sequential Mono- and Dialkylation of Resin-Bound Glycine *via* Automated Synthesis

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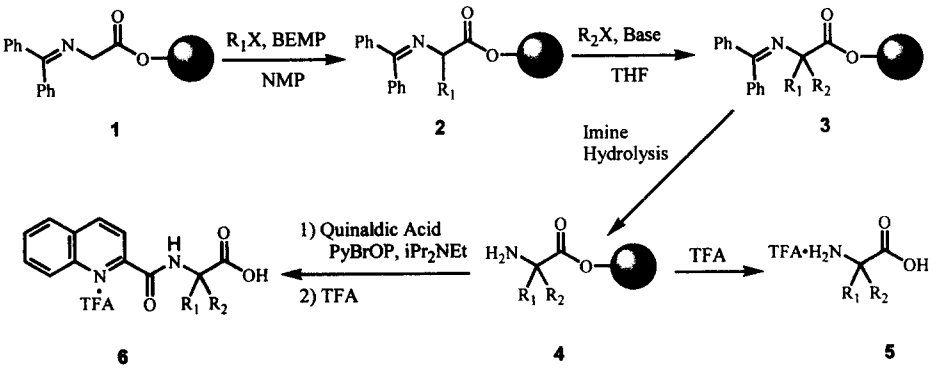
Abstract: A method has been developed for the synthesis of racemic α,α-disubstituted amino acids by a tandem alkylation process ("Tandem UPS") on solid-support. Consecutive alkylations of Wang resin-bound benzophenone imines of glycine afforded unnatural, disubstituted amino acid derivatives. Automated chemical synthesis was used to efficiently optimize conditions for both formation and hydrolysis of resin-bound disubstituted benzophenone imines and to generate a matrix of disubstituted amino acid derivatives.. © 1997 Elsevier Science Ltd.

Efficient strategies for carbon-carbon bond formation on solid support continue to be of considerable interest in organic synthesis.[1] Recently, methods have been reported for the synthesis of a wide range of unnatural amino acids and peptides on solid support and in solution.[2-4] Alkylation of benzophenone imines of resin-bound glycine esters and amides has been utilized to efficiently prepare unnatural amino acids and peptides (Unnatural Peptide Synthesis (UPS)).[2] In this case, selective monoalkylation is achieved using the organic-soluble, non-ionic iminophosphorane base, BEMP.[5] Alkylation of resin-bound aldimine esters of α-amino acids has also been developed to prepare α,α-disubstituted amino acid derivatives ("di-UPS").[3] The use of less active alkyl halides in the UPS methodology has also been reported.[6]

The objective of the present work was to develop a tandem alkylation procedure for the synthesis of α,α-disubstituted amino acid derivatives from the resin-bound benzophenone imine of glycine ("Tandem UPS", Scheme 1). BEMP may be utilized for selective monoalkylation; however, a general method was required to achieve the second alkylation without changing the benzophenone imine to an aldimine activating group. For the development of the "tandem UPS" protocol, and to handle the strong bases and anhydrous conditions, we utilized the Nautilus 2400™ for chemistry development studies.

Scheme 1. Tandem UPS.



After identifying preliminary model alkylation conditions to give good conversions to the resin bound benzophenone imine of α-benzyl phenylalanine (Scheme 1: **3**, $R_1 = R_2 = PhCH_2$), we focused our automation studies on finding optimal conditions for the pre-cleavage hydrolysis of the imine intermediate. This hydrolysis is particularly difficult with the sterically demanding disubstituted amino acid, α-benzyl phenylalanine (Scheme 1: **3** to **4**, $R_1 = R_2 = PhCH_2$). Although $NH_2OH{\cdot}HCl$ is the reagent of choice for the room temperature hydrolysis of resin-bound benzophenone imines of monosubstituted amino acid derivatives[2] or aldimines of the α,α-disubstituted compounds,[3] this mild, neutral method was not effective in the present case. Benzophenone imine hydrolyses using both neutral (aqueous $NH_2OH{\cdot}HCl$, THF)[2] and acidic (5% TFA, wet THF or 1N HCl, THF) hydrolysis conditions were evaluated for several reaction times and temperatures (Table 1). The hydrolysis of the benzophenone imine was independently evaluated using an internal standard method to track the release of benzophenone. In the subsequent cleavage (Scheme 1: **4** to **5**, $R_1 = R_2 = PhCH_2$), the yield of the α-benzyl phenylalanine·TFA salt was monitored to ensure that imine hydrolysis was not accompanied by cleavage of the linker. Both of the acidic conditions afforded nearly complete hydrolysis and did not lead to premature cleavage of the ester linkage. In succeeding optimization studies, we used 1 N HCl/THF (1:2) for 4 hours at room temperature (Entry 5) as an optimal hydrolysis condition.

Table 1. Optimization of Imine Hydrolysis of Dialkylated Product (Scheme 1: **3** to **4**, $R_1 = R_2 = PhCH_2$).

Entry	Hydrolysis Conditions	Temperature (°C)	Time (h)	% Imine Removed[a]
1	1 N $NH_2OH{\cdot}HCl$/THF (1:2)	40	4	0
2	"	"	8	13
3	"	60	4	45
4	"	"	8	60
5	1 N HCl/THF (1:2)	25	4	100
6	"	"	8	95
7	"	40	4	100
8	"	"	8	98
9	TFA/THF/H_2O (5:90:5)	25	2	93
10	"	"	4	91

[a]Based on HPLC analysis (acetonitrile/water with 0.1 % TFA, 2-40% (12 min.), 40-90% (3 min.), 90% (2 min.)) of benzophenone and α-benzyl phenylalanine·TFA salt using dimethylbenzamide (Aldrich) as an internal standard.

With satisfactory imine hydrolysis conditions in hand, we were able to undertake an enolate alkylation optimization study using the benzophenone imine of phenylalanine Wang resin as a representative substrate.[7] Alkylations[8] were performed on the Nautilus 2400 at -40 °C, comparing three bases (LDA, KHMDS and P_4-tBu[9]), two additives (HMPA and DMPU[10]) and two alkylating agents (benzyl bromide and methyl iodide). (Table 2).[5,11] In general, alkylations gave clean and complete conversion with either KHMDS or P_4-tBu as base, with or without additive (Entries 1-4). Reactions using LDA led to low recoveries and incomplete conversion (Entries 5-7). Control experiments with enolate formation and alkylation at room temperature using KHMDS indicated that the deprotonation/alkylation sequence could be performed at room temperature, albeit with lower product yield (Entry 8).

Table 2. Optimization of Second Alkylation (Scheme 1: **2** to **3** to **5**, $R_1 = PhCH_2$).

Entry	Base	R_2X[a]	Additive	Temperature (°C)	% Starting Material[b] (**5**, R_2=H)	% Product[b] (**5**, R_2=$PhCH_2$)
1	P_4-tBu	$PhCH_2Br$	None	-40	5	81
2	KHMDS	$PhCH_2Br$	None	-40	0	93
3	"	"	HMPA	"	0	90
4	"	"	DMPU	"	0	93
5	LDA	$PhCH_2Br$	None	-40	15	7
6	"	"	HMPA	"	31	13
7	"	"	DMPU	"	20	7
8	KHMDS	$PhCH_2Br$	None	25	0	77

[a] Alkylation with MeI gave similar results.

[b] HPLC analysis (acetonitrile/water with 0.1% TFA, 2-90% (13 min.)) of α-methyl phenylalanine and α-benzyl phenylalanine TFA salts using dimethylbenzamide (Aldrich) as an internal standard.

Finally, the complete "Tandem UPS" protocol, starting from resin-bound glycine, was tested on the Nautilus using various representative activated and deactivated alkylating agents (Scheme 1: **1** to **3** to **6**) (Table 3). BEMP alkylations were performed according to previously described methods.[2] For subsequent anhydrous alkylations, KHMDS (5 eq.) was utilized as base at -40 °C without an additive. After alkylation, resin-bound benzophenone imines were hydrolyzed and the amines were acylated with quinaldic acid.[12] After cleavage with TFA/DCM/H_2O (45:50:5, 2 h), dialkylated products were concentrated and analyzed by HPLC. Mass balance yields for products were generally in the 60-95% range. Initial alkylation using BEMP as base is best followed by anhydrous alkylation with a relatively activated alkylating agent (Table 3: Entries 9 vs 19 and 16 vs 20). In addition, alkylations employing alkyl halides that are prone to β-elimination (Entries 11-12) gave poor conversions.

Table 3. α,α-Disubstituted Amino Acid Derivatives Prepared by Tandem UPS (Scheme 1: **1** to **3** to **6**).

Entry	R_1	R_2	% Mono[a] (**6**, R_2=H)	% Di[a] (**6**, R_2≠H)
1	MeI	MeI	0	100
2	"	$PhCH_2Br$	0	100
3	"	Allyl Br	0	100
4	"	Octyl I	0	97
5	"	2-NaphthCH_2Br	0	98
6	BnBr	MeI	0	98
7	"	$PhCH_2Br$	0	100
8	"	Allyl Br	0	96
9	"	Octyl I	17	75
10	"	2-NaphthCH_2Br	0	99
11	MeI	$PhCH_2CH_2Br$	90	5
12	BnBr	"	91	2
13	Allyl Br	MeI	0	99
14	"	$PhCH_2Br$	0	100
15	"	Allyl Br	0	97
16	"	Octyl I	6	69
17	"	2-NaphthCH_2Br	0	98
18	Octyl I	MeI	0	97
19	"	$PhCH_2Br$	0	100
20	"	Allyl Br	0	98
21	"	Octyl I	12	68
22	"	2-NaphthCH_2Br	0	97
23	2-NaphthCH_2Br	MeI	0	98
24	"	2-NaphthCH_2Br	0	98

[a]Yields of **6** determined by HPLC analysis (acetonitrile/water with 0.1 % TFA, 2-90% (13 min.), 254 nm.

In conclusion, a "Tandem UPS" protocol for the consecutive dialkylation of benzophenone imine esters of glycine on solid support has been developed. The protocol is complementary to previously described methods using BEMP for alkylation of aldimines derived from preformed amino acid esters on solid support. Chemistry development in this series has been facilitated by automated chemical synthesis approaches. Further studies on the use of dialkylated amino acid derivatives in the synthesis of heterocyclic compounds will be reported from these laboratories in due course.

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5. Abbreviations: BEMP: 2-[(1,1-dimethylethyl)imino]-N,N-diethyl-2,2,3,4,5,6-hexahydro-1,3-dimethyl-1,3,2-diazaphosphorin-2(1H)-amine; NMP: 1-methyl-2-pyrrolidinone; TFA: trifluoroacetic acid; PyBrOP: bromo-tris-pyrrolidino-phosphonium hexafluorophosphate; LDA: lithium diisopropylamide; KHMDS: potassium hexamethyldisilazane; HMPA: hexamethylphosphoramide; DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
6. O'Donnell, M. J.; Lugar, C. W.; Pottorf, R. S.; Zhou, C.; Scott, W. L.; Cwi, C. L. *Tetrahedron Lett.*, 1997, 38, 7163.
7. Polystyrene Wang resin (Novabiochem, 100-200 mesh) was acylated with FMOC phenylalanine according to: Blankemeyer-Menge *et. al. Tetrahedron Lett.* **1990**, *31*, 1701. FMOC-Phe Wang resin was added to a polypropylene cartridge and washed 3x NMP. 20% piperidine/NMP was added and the mixture was agitated for 30 min. The resin was washed with NMP (10 m, 3x) and then NMP (3x). The deprotected resin was suspended in dry NMP (10 mL/g), and benzophenone imine (12 equiv.) and AcOH (9 equiv), were added and the contents agitated overnight. Finally the resin was washed with NMP (6x), THF/H_2O (2:1) (6 x), THF (6x), CH_2Cl_2 (6x), and the resin dried in a vacuum desiccator overnight.
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11. *Representative automation procedure for enolate alkylations:* The benzophenone imine resin was washed with dry THF (3x), and additive (10 eq, 1.0 M in dry THF) was added, followed by dry THF (10mL/g resin). The reaction was cooled to -40 °C. Anhydrous base (5 eq) and 10 mL/g THF was then added. After 45 minutes, alkylating agent (10 eq, 1.0 M in THF) was added followed by dry THF (10 mL/g) and the reaction temperature set to -40 °C (1h), -20 °C (1h), 0 °C (1h), 25 °C (1 h). Finally, the resin was drained and washed with THF (3x), THF/H_2O (2:1) (3x), THF/H_2O (2:1) (10m, 3x), and THF (3x).
12. Quinaldic acid (10 eq.), PyBrOP (10 eq.), and iPr_2NEt (10 eq.) in NMP for 24 h.

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