Passerini multicomponent reaction of protected α-aminoaldehydes as a tool for combinatorial synthesis of enzyme inhibitors

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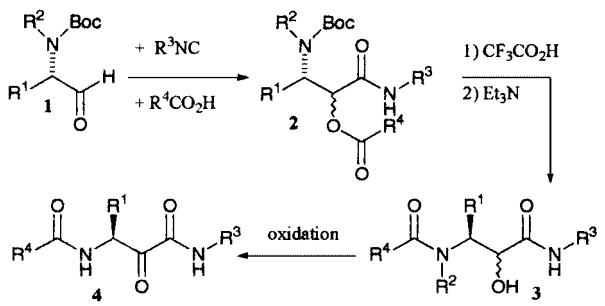
Three-component Passerini condensation of *N*-Boc-α-aminoaldehydes with various isocyanides and carboxylic acids leads, after Boc-deprotection/transacylation, to complex peptide-like structures containing an α-hydroxy-β-aminoacid unit or, after oxidation, an α-oxo-β-aminoacid unit.

Isocyanide employing multicomponent reactions have emerged as very powerful tools for the combinatorial synthesis of various pharmacologically important derivatives.[1] Of the two classical reactions belonging to this family, the Ugi condensation has been more widely studied and used in the generation of chemical libraries. On the other hand, the Passerini reaction, although older, has been employed less in combinatorial chemistry.[2] The reasons for this lower success are associated with the fact that a four-component condensation (Ugi) introduces a higher degree of diversity than a three-component one (Passerini). Moreover, the two amide bonds that link the components in Ugi adducts are more suitable for the synthesis of peptidomimetics, than the combination of one ester and one amide bond produced in the Passerini reaction. Finally, intramolecular variants declass the Passerini process to a two-component reaction, making it less suited for combinatorial chemistry.

In this work we show that, when protected α-aminoaldehydes are employed in Passerini condensation, a simple rearrangement of the reaction products allows an easy combinatorial entry to peptide-like structures, making this old methodology more valuable, particularly in the field of peptidomimetics and enzyme inhibitors.

The general strategy is depicted in Scheme 1 and involves condensation of *N*-Boc protected α-aminoaldehydes **1** with various isocyanides and various carboxylic acids, followed by one-pot Boc deprotection and acyl migration. This two step protocol gives rise to complex peptide-like substances **3** possessing a central α-hydroxy-β-aminoacid unit. This type of monomer has been widely used in the synthesis of enzyme inhibitors.[3] Moreover, a simple oxidation will produce oligopeptides **4** containing an α-oxo-β-aminoacid unit, which is an even more attractive structure, thanks to its similarity with protease transition state.[4]

Only two examples of Passerini reactions involving protected α-aminoaldehydes have been reported previously.[5] In one case, however,[5a] the carboxylic component was not retained during course of the synthesis; in the other case the yields were low and no further manipulation of the condensation adduct was attempted.[5b]



Scheme 1

The L-*N*-Boc protected α-aminoaldehydes employed in this work are all known[4c,6] and have been prepared either through $LiAlH_4$ reduction of Weinreb hydroxamates,[6b] or by Swern oxidation of the corresponding *N*-Boc aminoalcohols,[6d,e] in turn prepared by $BH_3{\cdot}Me_2S$ reduction of the *N*-Boc aminoacids.[6a] The latter are all commercially available compounds except for *O*-methyl-*N*-Boc-serine, which was prepared as previously described.[7]

Table 1 reports the results obtained in this two-step protocol for various combination of six *N*-Boc-α-aminoaldehydes, six isocyanides and ten carboxylic acids (including also protected aminoacids). In particular, isocyanides and carboxylic acids were chosen in order to check the effect of various kinds of side chains with different steric and electronic requirements. All isocyanides and carboxylic acids were commercially available, apart from benzyl 3-isocyanopropionate, which was prepared in two steps (1, BnOH, DCC, DMAP, 70%; 2, diphosgene, *N*-methylmorpholine, CH_2Cl_2, −15 °C, 67%) from known *N*-formyl-β-alanine.[8]

Although we did not perform all the 360 possible combinations, we think that the 20 examples shown represent a good 'statistical sample', which gives an idea of the generality of the presented methodology. In all cases, even when the reaction involved bulky substrates (*e.g.* entry 18), the yields of the Passerini condensation were satisfactory. Surprisingly, notwithstanding the wide variety of substrates employed, the stereoselectivity was at nearly the same level in all cases, being *ca.* 2 : 1. In view of combinatorial applications, the modest diastereoselection is not necessarily a drawback. Moreover, if the final targets are α-oxoamides **4**, diastereoselection at this level is unimportant.

When enantiomerically pure carboxylic acids were employed (entries 10–12, 14 and 15), only two diastereoisomers were detected by NMR spectroscopy, indicating that the starting α-aminoaldehydes do not undergo significant racemization under the reaction conditions. For entries 14 and 15 the diastereoisomeric mixtures were also checked by HPLC, which showed only 2–5% of isomers deriving from aldehyde racemization. This percentage was shown to depend on the method of preparation of the α-aminoaldehyde, the reduction–oxidation protocol turning out better from this point of view.

In most cases, treatment of the Passerini adducts **2** with CF_3CO_2H led to both Boc cleavage and *in situ* transacylation to give directly the oligopeptides **3**. However under these conditions, the acyl migration was not always complete and in some cases (entries 16–18) it did not take place at all. Thus the procedure of choice involves brief treatment with Et_3N in CH_2Cl_2 after CF_3CO_2H removal. For adducts deriving from Boc-protected aminoacids as the acid component (entries 12, 14 and 15) this procedure cleaved both Boc groups producing the expected transacylated compounds, whose identity was further confirmed by acylation with various reagents of the free amino group.

The overall yields of the sequence leading to **3** from **1** were in all cases > 50% and often > 70%.

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Table 1 Synthesis of oligopeptides **3** *via* Passerini condensation of *N*-Boc-α-aminoaldehydes followed by deprotection/transacylation[a]

Entry	R^1	R^2	R^3	R^4CO_2H	Yield of **2**[a] (%)	Dr of **2**[b]	Yield **2** → **3**[c] (%)	Overall yield of **3** (%)
1	$PhCH_2$	H	Bn	$PhCH_2CO_2H$	81	67:33	81	77
2	$PhCH_2$	H	Bn	$PhCO_2H$	67	62:38	96	64
3	$PhCH_2$	H	Bu^t	Pr^nCO_2H	82	71:29	86	71
4	$PhCH_2$	H	MeO_2CCH_2	$PhCH_2CO_2H$	91	64:36	99	90
5	$PhCH_2$	H	MeO_2CCH_2	Bu^sCO_2H	73	63:37[d]	68	50
6	Me	H	Bn	Pr^nCO_2H	85	65:35	94	80
7	Me	H	*c*-C_6H_{11}	*p*-Toluic acid	80	67:33	77	62
8	Me	H	MeO_2CCH_2	$PhCH_2CO_2H$	71	63:37	84	60
9	Et	H	Bu^t	$PhCH_2CO_2H$	83	69:31	89	74
10	Et	H	Bu^n	L-(Z)-Leu	65	61:39	91	59
11	Et	H	$BnO_2CCH_2CH_2$	L-(Z)-Leu	69	66:34	92	64
12	Et	H	MeO_2CCH_2	L-(Boc)-Leu	59	66:34	83	49
13	Pr^i	H	MeO_2CCH_2	(Z)-Gly	77	60:40	75	58
14	Pr^i	H	MeO_2CCH_2	L-(Boc)-Phe	95	52:48	75	71
15	Pr^i	H	MeO_2CCH_2	D-(Boc)-Phe	89	63:37	77	72
16	$-(CH_2)_3-$		*c*-C_6H_{11}	$PhCH_2CO_2H$	85	69:31	99	85
17	$-(CH_2)_3-$		Bn	Pr^n	93	62:38	80	65
18	$-(CH_2)_3-$		Bu^t	$PhCH_2CO_2H$	94	65:35	97	91
19	$MeOCH_2$	H	Bn	Pr^n	95	57:43	98	93
20	$MeOCH_2$	H	*c*-C_6H_{11}	$PhCH_2CO_2H$	95	61:59	82	78

[a] Transformation of **1** into **2** was carried out in CH_2Cl_2 at r.t. for 20–40 h, using 1.1 equiv. each of isocyanide and carboxylic acid. Isolated yields (after chromatography) reported. [b] Diastereoisomeric ratio, determined by ^1H NMR spectroscopy and/or HPLC. Relative configuration not determined. [c] Transformation of **2** into **3** was performed by: 1, $CF_3CO_2H–CH_2Cl_2$ (1:3 v/v), r.t., 1 h; 2, (after evaporation of CF_3CO_2H): $Et_3N–CH_2Cl_2$ (1:3 v/v), 1 h. Isolated yields are reported. [d] The ratio of the diastereoisomeric couples differentiated by the relative configuration between CH–N and CH–O is given.

It is worth noting that purification of Passerini adducts **2** could be performed quite simply by fast chromatography of the crude reaction solution on silica gel or alumina. The isocyanides (in excess) in all cases elute much faster than **2**, while the carboxylic acids, especially when alumina is used, remain adsorbed on the column. On the other hand the adducts **3** are usually pure enough to be used as such for further reactions (the only significant by-product being $Et_3NH^+CF_3CO_2^-$ which can be removed by extraction with H_2O). Thus several parallel preparations of compounds **3** can be run and processed in two days by a single operator even without the aid of automatic synthesizers.

Compounds **3** obtained as described in entries 10 and 11 of Table 1 were converted in high yields (NaOClO, KBr, cat. TEMPO$^{\cdot}$, 91 and 80%)[4c] into the corresponding α-ketoamides **4** (R^1 = Et, R^2 = H, R^4CO = (Z)-L-leucyl, R^3 = Bu^n or $CH_2CH_2CO_2Bn$), which are very similar to recently discovered potent calpain inhibitors (where R^3 = Et or Pr^n).[4a,c] This straightforward three-step synthesis of complex peptidomimetics is a clear example of the potentiality of this reported methodology. Accepting a wide variety of substrates, it appears ideally suited for the combinatorial synthesis of oligopeptides containing an α-hydroxy-β-aminoacid or α-oxo-β-aminoacid unit, which are of paramount interest as enzyme inhibitors.

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