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Solid-phase synthesis of phosphine–oxazoline peptides

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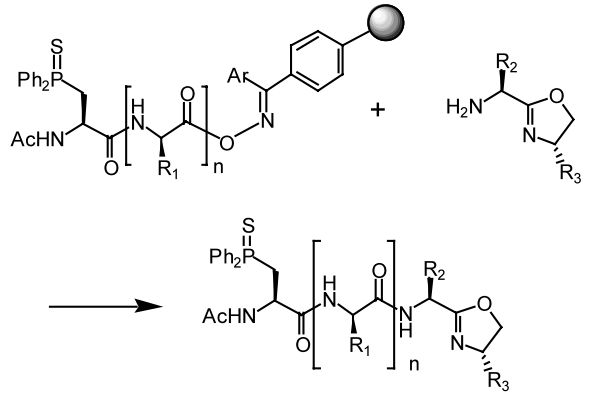
Abstract—An approach is presented that allows for the synthesis of phosphine–oxazoline ligands by solid-phase synthesis. The method involves the synthesis of amino oxazolines and their use in the cleavage of phosphine sulfide peptides from Kaiser oxime resin. It was discovered that the addition of a catalytic amount of sodium cyanide allows the nucleophilic cleavage from the resin to take place at room temperature and without the addition of acid.

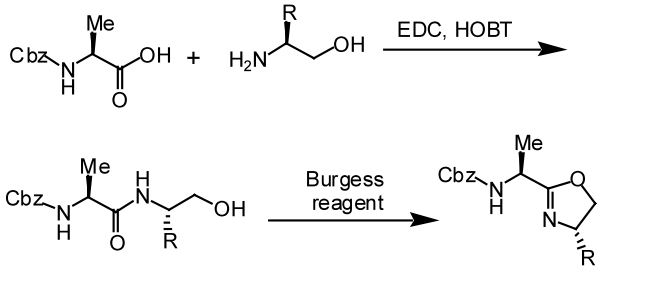
We have been involved in the development of phosphine–oxazoline ligands as well as the use of peptide chemistry in the synthesis of libraries of bis-phosphine ligands.[1–4] Consequently we have been interested in routes to peptide based phosphine–oxazoline ligands.[5] Ideally these ligands would be synthesized by standard solid-phase methods. In addition to their considerable use in asymmetric catalysis, oxazolines have been shown to be selective inhibitors of α_2-adrenoreceptors,[6] as active derivatives of patellamide A[7] and as a structural element in vibriobactin.[8] Any general system that allows for their facile incorporation into peptide structure would be of use in catalyst development as well as the synthesis of biologically active molecules. This paper reports the development of such a system (Scheme 1).



Scheme 1.

After attempting a number of approaches for the incorporation of oxazolines and phosphines into peptides, a method that involves the use oxime resin was developed.[9,10] The Kaiser oxime linker allows for the cleavage of peptides synthesized on solid support by reaction with a nucleophile. The approach reported here utilizes a nucleophilic oxazoline building block as the agent that both removes the peptide from the support and adds to the peptide. For this approach to be viable, a number of issues needed to be addressed. First, an approach to a nucleophilic oxazoline building block had to be developed. Second, conditions had to be worked out that allowed for the efficient cleavage of the phosphine–oxazoline peptides from the oxime resin.

Synthesis of oxazoline building blocks. Oxazolines with a variety of alkyl groups as well as a carboxyl group were synthesized (Scheme 2). The oxazoline with a carboxyl



10	R = *i*-propyl	77%	
11	R = *t*-butyl	80%	
12	R = CH_2Ph	95%	
13	R = CO_2CH_3	90%	
14	R = *i*-propyl	72%[a]	
15	R = *t*-butyl	88%[a]	
16	R = CH_2Ph	90%[a]	
17	R = CO_2CH_3	93%[b]	

Scheme 2. *Reagent and conditions*: (a) Burgess reagent in THF at room temperature over night; (b) Burgess reagent in THF, reflux at 70°C for 3 h. Also obtained 12% elimination product.

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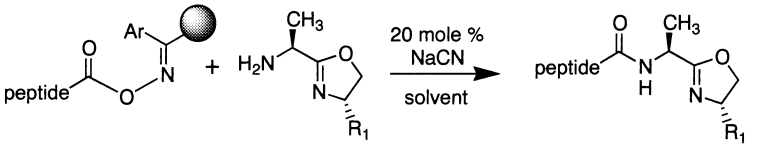
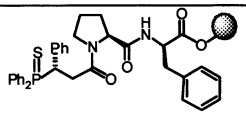
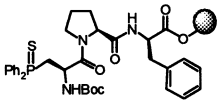
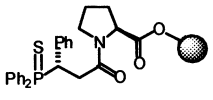
group was used to allow for the addition of other groups at that location of the molecule. As expected, coupling of alanine with the selected amino alcohols using EDC and HOBT proceeded in good yield. Oxazoline formation with Burgess reagent also proceeded in good yield. For reasons that are not clear the carbonyl containing oxazoline required elevated temperature and, as a consequence, also produced a small amount of the product from the elimination of the hydroxyl. Removal of the Cbz group by reaction with H_2 catalyzed by palladium on carbon provided the free amines in the series.

Reaction with oxime resin. Next, conditions were worked out for the removal of the phosphine moiety from the oxime resin. While the reaction with glycine proceeded in good yield, the addition of more substituted nucleophiles produced the expected phosphine-sulfide–oxazoline products but in low yield (Table 2, Scheme 3). This may be due to the more hindered nature of the α-branched oxazoline amine. It is quite common that hindered nucleophiles can be problematic in the nucleophilic cleavage from oxime resins.

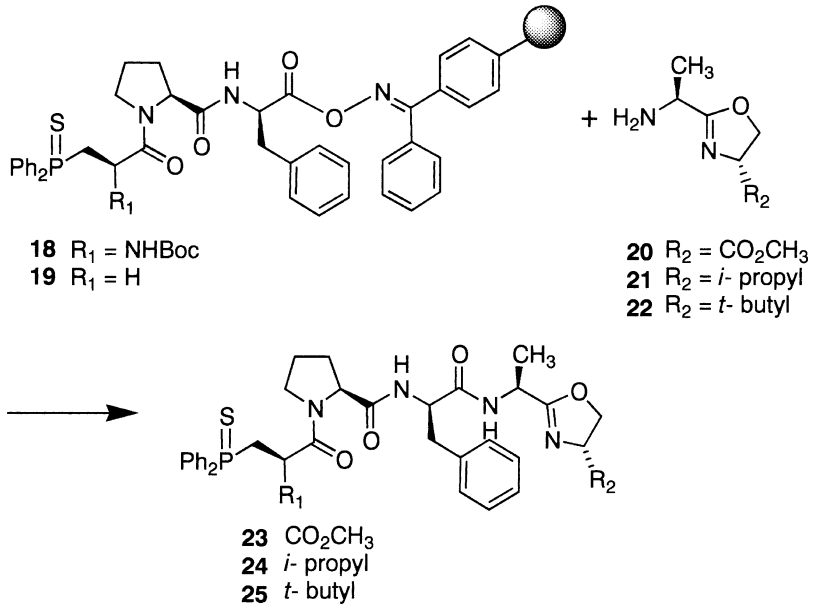
Sodium cyanide has been used successfully in the aminolysis of esters.[11] Given this observation, it was reasoned that the addition of sodium cyanide may act as a catalyst for the desired cleavage. The belief was that the small nucleophile, CN, would be able to remove the peptide from the polymer support and once in solution the acyl cyanide intermediate would then react with the more hindered amine nucleophile. When the cleavage of resin **26** is attempted with oxazoline **22** in methanol (Scheme 4), the peptide is removed from

Table 1. NaCN-catalyzed cleavage of oxime resin bound peptide[c]



Entry	Resin bound peptide	R_1	Reaction time (d)	Solvent	Product	Yield, %[a]	Purity, %[b]
1		CH_2Ph	7	CH_2Cl_2	**29**	54	93
2		*t*-Butyl	6	CH_2Cl_2	**30**	42	80
3		*t*-Butyl	1	THF	**30**	60	88
4		*t*-Butyl	4	THF	**30**	69	90
5		*i*-Propyl	5	THF	**31**	61	87
6		CO_2CH_3	5	THF	**32**	67	86
7		CO_2CH_3	5	THF	**33**	60	89
8		*i*-Propyl	5	THF	**34**	66	84
9		CH_2Ph	5	THF	**35**	83	100
10		*t*-Butyl	5	THF	**36**	60	93
11		*t*-Butyl	1	THF	**37**	61	93

[a] Based on the isolated weight of peptide as compared to the loading. [b] Determined by NMR of crude product. [c] The NMR data for the compounds in this table can be found in Ref. 13.



Scheme 3.

Table 2.

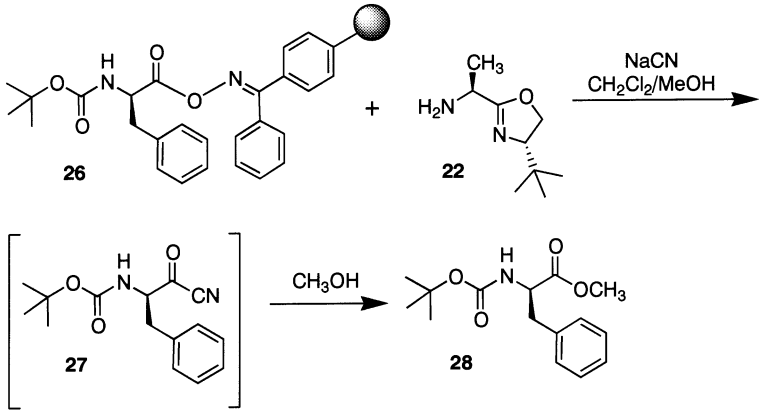
Nucleophile	Yield (%)
Gly-OCH_3	89
20	30
21	20
22	20

the support as the methyl ester rather than the desired amide. Presumably methanol is sufficiently nucleophilic to add to the acylcyanide intermediate before the branched amine. When the reaction is run in dichloromethane or THF, both non-nucleophilic solvents that also swell the polymer support, the desired amide bond is formed in good yield (Table 1).

While the nucleophilic cleavage of peptides from oxime resin is an extremely useful transformation the reaction rates observed with substituted nucleophiles under neutral to slightly basic conditions tend to require elevated temperature.[12] We observed this to be the case as well with our oxazoline-containing nucleophiles. When sodium cyanide is added to the reaction mixture the reactions proceed at room temperature and give good yields of the expected products. Within the confines of our limited solvent study THF appears to be the best solvent for the reaction giving the products in both higher yields and purity.

Acknowledgements

This work was supported by NIH R01 GM56490. We also gratefully acknowledge the Washington University High-Resolution NMR Facility, partially supported by NIH 1S10R02004, and the Washington University Mass Spectrometry Resource Center, partially supported by NIHRR00954, for their assistance.



Scheme 4.

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13. Representative NMR spectra:

(**29**) ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15–8.05 (m, 2H), 7.49–7.00 (m, 23H), 6.75–6.63 (m, 2H), 4.65–4.60 (m, 1H), 4.53–4.48 (m, 1H), 4.40–4.35 (m, 1H), 4.32–4.28 (m, 1H), 4.16–4.13 (1H), 3.96–3.93 (1H), 3.91–3.89 (m, 1H), 3.36–3.29 (m, 2H), 3.00–2.97 (m, 3H), 2.90 (dd, J=9.8, 16.6 Hz, 1H), 2.69 (dd, J=9.4, 16.6 Hz), 2.58 (dd, J=8.4, 14.4 Hz, 1H), 1.90–1.55 (m, 4H), 1.18 (d, J=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 169.1 (d, J_{CP}= 10.8 Hz), 168.8, 167.2, 125.6–136.6, 71.6, 65.9, 59.4, 53.2, 46.6, 42.6, 41.7 (d, J_{CP}=51 Hz), 40.6, 36.3, 34.5, 27.1, 23.6, 17.5; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 52.4.

(**30**) ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11–8.08 (m, 2H), 7.61–7.03 (m, 18H), 6.78 (m, 2H), 4.65–4.61 (m, 1H), 4.51–4.47 (m, 1H), 4.40–4.36 (m, 1H), 4.14–4.02 (m, 2H), 3.88 (m, 1H,), 3.76–3.73 (m, 1H), 3.38–3.29 (m, 2H), 3.06–2.92 (m, 2H), 2.91–2.87 (m, 1H), 2.77–2.74 (m, 1*H*), 1.84–1.72 (m, 2H), 1.71–1.45 (m, 2H), 1.25 (d, J=8.6 Hz, 3H), 0.84 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 170.1 (d, J_{CP}=10.8 Hz), 169.8, 167.5, 126–137, 75.1, 69.4, 60.4, 54.2, 47.6, 43.6, 42.6 (d, J_{CP}=51 Hz), 37.4, 35.6, 33.6, 25.6, 28.2, 24.5, 18.6; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 52.3.

(**31**) ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18–8.15 (m, 2H), 7.53–7.09 (m, 18H), 6.81 (d, J=7.8 Hz, 2H), 4.72–4.68 (m), 4.59–4.57 (m, 1H), 3.98–3.96 (m, 1H), 3.91–3.88 (m, 1H), 3.46–3.37 (m, 2H), 3.08–3.03 (m, 2H), 2.94 (dd, J=6.0, 14.4 Hz, 1H), 2.80 (dd, J=7.2, 14.4 Hz, 1H), 1.95–1.66 (m, 5H), 1.26 (d, J=7.2 Hz, 3H), 0.91 (d, J=6.6, 3H), 0.85 (d, J=6.6, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 170.0 (d, J_{CP}=10.8 Hz), 169.7, 167.5, 126–137, 71.5, 70.6, 60.4, 54.1, 47.6, 43.6, 42.6 (d, J_{CP}= 51.0 Hz), 37.3, 35.6, 32.3, 28.1, 24.5, 18.6, 17.7; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 52.4.

(**32**) ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18–8.15 (m, 2H), 7.53–7.04 (m, 18H), 6.82 (d, J=7.2 Hz, 1H), 6.70 (d, J=7.8 Hz, 1H), 4.55–4.47 (m, 2H), 4.42–4.39 (m, 1H), 4.00–3.99 (m, 1H), 3.77 (s), 3.62–3.60 (m, 1H), 3.38–3.33 (m, 1H), 3.15–2.98 (m, 3H), 2.56 (dd, J=9, 14.4 Hz, 1H), 2.20–1.55 (m, 4H), 1.29 (d, J=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.2, 171.1, 170.7, 170.3 (d, J_{CP}= 10.8 Hz), 169.9, 126–137, 70.3, 67.6, 60.1, 54.3, 52.6, 47.4, 43.6, 42.5 (d, J_{CP}=51 Hz), 37.0, 35.4, 27.5, 24.5, 18.6; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 52.0.

(**33**) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81–7.13 (m, 16H), 7.08 (d, J=7.8 Hz, 1H), 5.05–5.00 (m, 1H), 4.75 (d, J=8.4 Hz, 1H), 4.71–4.68 (m, 1H), 4.65–4.62 (m, 1H), 4.57–4.55 (m, 1H), 4.39–4.36 (m, 1H), 4.28–4.23 (m, 1H), 4.16–4.10 (m, 1H), 3.67 (s, 3H), 3.66–3.61 (m, 2H), 3.12 (dd, J=6.0, 14.4 Hz, 1H), 3.05 (dd, J=8.4, 14.4 Hz, 1H), 2.81–2.79 (m, 1H), 2.60–2.52 (m, 1H), 1.99–1.76 (m, 4H), 1.34–1.18 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 171.2, 171.1, 170.7. 170.2, 154.3, 126–137, 79.6, 70.3, 67.9, 67.4, 60.5, 53.9, 47.6, 47.4, 43.4, 37.0, 35.0 (d, J_{CP}=56.4 Hz), 28.1, 27.8, 25.6, 18.3; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 39.7, 38.0 (7:1).

(**34**) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82–7.12 (m, 15H), 6.91 (d, J=7.2 Hz, 1H), 4.98–4.92 (m, 1H), 4.81 (d, J=8.4 Hz, 1H), 4.64–4.59 (m, 1H), 4.55–4.52 (m, 1H), 4.28–4.26 (m, 1H), 4.17–4.14 (m, 1H), 3.91–3.89 (m, 1H), 3.79–3.75 (m, 1H), 3.62–3.56 (m, 2H), 3.11–3.00 (m, 2H), 2.84–2.65 (m, 2H), 1.94–1.80 (m, 4H), 1.68–1.61 (m, 1H), 1.27–1.18 (m, 12H), 0.83 (d, J=6.6 Hz, 3H), 0.76 (d, J=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.2 (d, J_{CP}=15 Hz), 171.1, 169.7, 167.5, 154.2, 126–137, 79.6, 71.5, 70.6, 60.6, 54.1, 47.7, 47.4, 43.6, 37.5, 35.2 (d, J_{CP}=56.5 Hz), 32.3, 28.1, 27.8, 24.8, 18.5; ^{31}P (121.5 MHz, $CDCl_3$) δ 39.7, 37.5 (4:1).

(**35**) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86–7.14 (m, 21H), 7.00 (d, J=7.2 Hz, 1H), 5.03–5.01 (m, 1H), 4.85 (d, J=8.4 Hz, 1H), 4.68–4.58 (m, 2H), 4.32–4.28 (m, 2H), 4.19–4.16 (m, 1H), 3.97–3.94 (m, 1H), 3.68–3.61 (m, 2H), 3.21–3.18 (m, 1H), 3.06–3.03 (m, 1H), 3.00–2.96 (m, 1H), 2.89–2.68 (m, 2H), 2.63–2.58 (m, 1H), 1.94–1.81 (m, 4H), 1.32–1.23 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 170.1, 168.1, 154.2, 125.6–137.6, 79.7, 72.6, 66.8, 60.6, 54.0, 47.7, 47.6, 43.4, 41.6, 37.5, 35.2 (d, J_{CP}=56.6 Hz), 28.2, 28.1, 24.9; ^{31}P (121.5 MHz, $CDCl_3$) δ 39.7, 37.6 (3:1).

(**36**) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82–7.11 (m, 16H), 6.87 (d, J=6.6 Hz, 1H), 4.96–4.91 (m, 1H α), 4.79 (d, J=7.8 Hz, 1H), 4.61–4.58 (m, 1H), 4.55–4.53 (m, 1H), 4.27–4.26 (m, 1H), 4.11–3.94 (m, 2H), 3.72–3.67 (m, 1H), 3.60–3.54 (m, 2H), 3.14–3.10 (m, 1H), 2.85–2.61 (m, 2H), 1.92–1.79 (m, 4H), 1.25–1.17 (m, 12H), 0.78 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3 (d, J_{CP}=14.5 Hz), 171.1, 170.0, 167.4, 154, 126–137, 79.7, 75.1, 69.4, 60.6, 54.2, 47.7, 47.6, 43.6, 37.6, 33.5, 28.2, 25.7, 25.2, 24.9, 18.6; ^{31}P (121.5 MHz, $CDCl_3$) δ 39.7, 37.4 (3.6:1).

(**37**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19–8.12 (m, 2H), 7.56–7.46 (m, 3H), 7.45–7.32 (m, 2H), 7.31–7.21 (m, 3H), 7.20–7.12 (m, 3H), 7.11–7.05 (m, 3H), 4.70 (dt, J=2.3,

10.8 Hz, 1H), 4.55 (t, $J=6.9$ Hz, 1H), 4.42–4.22 (m, 1H), 4.14 (dd, $J=8.7$, 10.2 Hz, 1H), 4.03 (dd, $J=7.5$, 8.7 Hz, 1H), 3.69 (dd, $J=7.5$, 10.2 Hz, 1H), 3.54–3.47 (m, 1H), 3.38–3.25 (m, 2H), 2.75 (ddd, $J=2.7$, 10.8, 16.2 Hz, 1H), 2.19–1.61 (m, 4H), 1.34 (d, $J=6.9$ Hz, 3H), 0.79 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7 (minor) and 170.2 (major), 170.0 (d, $J_{CP}=17.0$ Hz, major) and 169.9 (d, $J_{CP}=16.9$ Hz, minor), 167.1 (major) and 167.0 (minor), 135.0, 134.9, 132.4, 132.3, 132.2, 131.9, 131.8, 131.7, 131.5, 131.4, 131.3, 131.1, 130.9, 130.7, 129.8, 129.7, 129.6, 128.9, 128.8, 127.9, 127.8, 127.6, 127.4, 75.1 (major) and 75.1 (minor), 69.7 (minor) and 69.4 (major), 59.8, 47.5 (minor) and 47.4 (major), 43.7 (minor) and 43.6 (major), 42.3 (d, $J_{CP}=52.6$ Hz, major) and 42.2 (d, $J_{CP}=53.5$ Hz, minor), 35.6, 33.6 (minor) and 33.5 (major), 27.8 (minor) and 27.7 (major), 19.2 (minor) and 19.0 (major); ^{31}P NMR (120 MHz, $CDCl_3$) δ 51.3 (major), 52.1 (minor).