Figure 2. Transmission electron micrographs of silver metal particles prepared under various conditions of (a) *x*=2 at 175 °C and (b) *x*=2 at 150 °C.

higher probability of particle collisions and adhesion, and those have led to lowering the surface area of particles.[6]

The silver particles of 50 nm prepared in this work is thought to be polymeric silver metal clusters consisted of 3.8×10^6 number of silver atoms, which was calculated by using the silver atomic radius of 2.9 Å, and the packing fraction of *ccp* array, 0.74. In the face-centered cubic structure, a silver atom is coordinated by twelve neighboring silver atoms, which could be assumed as the first metal cluster. Such small clusters can be aggregated together to form

large particles through many steps, which accounts for the difference of particle sizes in between XRD and TEM.

References

1. (a) Choy, J. H.; Han, Y. S.; Song, S. W. *Mater. Lett.* **1994**, *19*, 257. (b) Choy, J. H.; Han, Y. S.; Song, S. W.; Chang, S. H. *J. Mater. Chem.* **1994**, *4*, 1271. (c) Choy, J. H.; Han, Y. S. *J. Am. Ceram. Soc.* **1995**, *78*, 11691.
2. Granqvst, C. G.; Buhrman, R. A. *Solid State Commun.* **1976**, *18*, 123.
3. (a) Charvolin, J.; Froidevaux, C.; Taupin, C. *Solid State Commun.* **1966**, *4*, 357. (b) Marignier, J. L.; Belloni, J.; Decourt, M. O.; Chevalier, J. P. *Nature* **1985**, *31276*, 344.
4. Tsai, K. L.; Dye, J. L. *Chem. Mater.* **1993**, *5*, 540.
5. (a) Bonnenman, H.; Brijoux, W.; Joussen, T. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 273. (b) Glavee, G. N.; Klabunde, K. J.; Sorensen, C. M.; Hadjipanayis, G. C. *Inorg. Chem.* **1993**, *32*, 474.
6. (a) Fievet, F.; Lagier, J. P.; Figlarz, M. *MRS Bull.* **1989**, 29. (b) Ducamp-Sanguesa, C.; Herrera-urbina, R.; Figlarz, M. *J. Solid State Chem.* **1992**, *100*, 272. (c) Ducamp-Sanguesa, C.; Herrera-urbina, R.; Figlarz, M. *Solid State Ionics*, **1993**, *63-65*, 25. (d) Hirai, H. *J. Macromol. Sci. Chem.* A **1979**, *13*, 633. (e) Silvert, P-Y.; Herrera-Urbina, R.; Duvauchelle, N.; Vijayakrishnan, V.; Elhsissen, K. T. *J. Mater. Chem.* **1996**, *6*, 573.
7. Choy, J. H.; Song, S. W. Korean patent application No. 95-7922, 1995.
8. Cullity, B. D. In *Elements of X-ray Diffraction*, Cohen, M., Ed.; Addison Wesley: Reading, U. S. A., 1978; p 102.
9. Lamer, V. K.; Dinegar, R. *J. Am. Chem. Soc.* **1950**, *72*, 4847.
10. (a) Napper, D. H. *J. Colloid Interface Sci.* **1977**, *58*, 390. (b) Buscall, R.; Ottewill, R. H. In *Polymer Colloids*, Buscall, R.; Corner, T.; Stageman, J. F. ed., Elsevier, essex, 1985.

3-Nitrobenzophenone Oxime Resin-A New Reliable Polymer Support for Solid Phase Peptide Fragment Synthesis

Dong-Hyun Park[†], Kyung-Won Roh, and Yoon-Sik Lee*

[†]*Science and Technology Policy Institute, Korea Institute of Science and Technology, P.O. Box 255 Cheongryang, Seoul 136-791, Korea*
Department of Chemical Technology, Seoul National University, Seoul 151-742, Korea
Received August 12, 1996

Kaiser oxime resin (4-nitrobenzophenone oxime resin) has been one of the useful polymer supports in solid-phase peptide fragment synthesis.[1] However, from our previous experiences, a few but critical handicaps have been found. First, the peptide-resin linkage was not sufficiently stable that no little portion of the anchored peptide moiety was

lost during the peptide elongation procedure. Second, the oxime functionality was not sufficiently inert to the peptide synthesis conditions that the resin could hardly be reused many times. Even though several benzophenone oxime resins were synthesized and tested by Kaiser's group before,[1a] no systematic studies were reported to find out proper substituents and positions in the phenyl ring of the benzophenone oxime group for the best performance in solid phase peptide fragment synthesis. Therefore, we have tried to synthesize 2-nitro-, 3-nitro-, 3,5-dinitro- benzophenone oxime resins which can reveal improved physical properties and attempted to demonstrate the reliability of the resins in peptide fragment synthesis.

3-Nitrobenzophenone oxime resin, **4**, and 3,4-dinitrobenzophenone oxime resin, **6**, were prepared according to the known procedure for 4-nitrobenzophenone oxime resin,[b],2 **5**, (Scheme 1) and the results are shown in Table 1. The conversion yields for the oximation steps were 96% (for **4**), 91% (for **5**), 79% (for **6**) which were calculated from N analysis data. After the coupling of Boc-Phe to the oxime resins by DCC, dipeptide fragment, Boc-Phe-Gly-OMTP[1e] was prepared via the aminolysis reaction with glycine 4-(methylthio)phenyl ester(Gly-OMTP)[3] in the presence of acetic acid catalyst (Scheme 2). The reaction times were measured in order to compare the reactivities of the oxime resin esters in aminolysis reactions.[4] All the reactions were finished within 2-5 hrs with 90-95% yields. The data revealed that the reactivity of the resin was in the following order; **5**<**4**<**6** (Table 1).
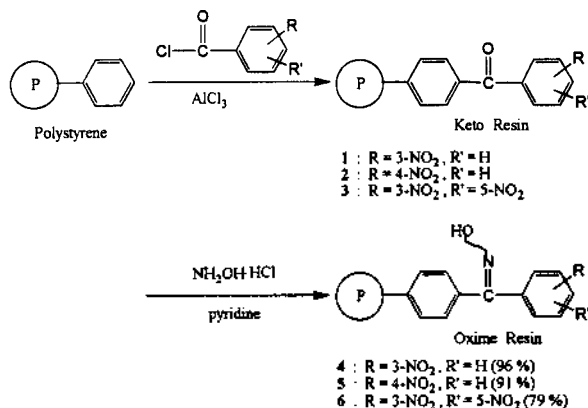
The stability of the oxime functionality was also investigated after repeated use in peptide coupling reactions. After each coupling reactions for Boc-Phe-Gly-OMTP, the resins of the same synthetic history were treated with 10 molar excess of benzylamine in methylene chloride (10 mL/g resin) at 25 °C for 6 hr, and were washed thoroughly with various solvents to regenerate the oxime functionalities. After drying the resins *in vacuum*, nitrogen analyses were performed. The results of the regeneration procedure of the respective oxime resins are summarized in Table 1.

The results confirmed that only 70-72% of the initial oxime groups were regenerated in **5** and **6**. However, most of the oxime groups have survived in **4** during the regeneration procedure although the resin has been previously used twice in the anchoring and coupling steps. The stability of the oxime group in **4** doesn't seem totally unrelated to the high conversion yield (96%) from the keto resin. The stability will enhance the reliability of this polymer support in practical use in solid phase peptide fragment synthesis.

To test this, several dipeptide fragments with different C-terminal protecting groups as well as tri- and pentapeptide MTP esters were synthesized from the oxime resins. The results are summarized in Table 2. Except for Boc-Phe-Gly-OPh and Boc-Phe-ε-ACA-OMTP, all the oxime resins gave similar results (88-94% yield) for the synthesis of dipeptide fragments. For dipeptide phenyl ester, Boc-Phe-Gly-OPh, and tri-, and pentapeptide MTP esters, including Boc-Phe-ε-ACA-OMTP, **4** gave much better results than **5** or **6**. Thus, in the preparation of Boc-Gly-Phe-Leu-OMTP[1e] and Boc-Gly-Phe-Leu-Tyr(OBzl)-Gly-OMTP,[1e] **4** gave 81%, 86% yields while **5** and **6** gave 71%, 74% and 73%, 77% yields respectively. There was no significant indication of racemization during coupling steps.[5]

Scheme 1. Preparation of nitrobenzophenone resins and nitrobenzophenone oxime resins.
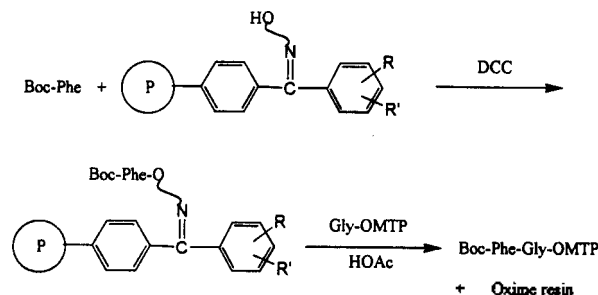
Scheme 2. Preparation of Boc-Phe-Gly-OMTP from oxime resins.

Table 1. The Results of the Regeneration Procedure of the Oxime Resins after Coupling Reactions

Resins[a]	Initial Resins			Boc-Phe-Gly-OMTP preparation[b]		Regenerated Resins			
	N[c] (%)	DF[d] (%)	Deg. Sub.[e]	Yield (%)	Reaction Times(min)	N[c] (%)	DF[d] (%)	Deg. Sub.[e]	regenerated ratio(%)
4	3.02	13.7	1.14	95	250	2.93	13.3	1.10	97
5	3.44	16.1	1.23	90	300	2.41	11.3	0.86	70
6	3.71	11.2	1.08	93	180	2.67	8.1	0.78	72

[a] Each resin was previously used twice in the preparation of Boc-Phe-Gly-OMTP in DMF. [b] Sub. levels of Boc-Phe in each Boc-Phe-oxime resins before the coupling reactions were 0.49 (**4**), 0.51 (**5**), 0.39 (**6**) mmol/g resin. [c] Nitrogen content by elemental analysis of the resins. [d] DF: degrees of functionalization of the introduced functional groups in polystyrene. [e] Degrees of the oxime functionality in mmol/g resin.

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Table 2. The Results of Peptide Fragment Synthesis from Oxime Resins in CH_2Cl_2

Peptide Derivatives	Yield (%)[a]			mp (°C)[b]	$[\alpha]^{20b}$
	4	5	6		
Boc-Phe-Gly-OMe	94	90	94	oil	-
Boc-Phe-Gly-OPh	77	65	57	121-123	-4.0(A)
Boc-Phe-Gly-O'Bu	91	91	97	84-85	19.0(B)
Boc-Phe-Gly-OBzl	93	88	92	133-134	-4.0(B)
Boc-Phe-β-Ala-OMTP	85	89	89	138-140	15.0(B)
Boc-Phe-Leu-OMTP	94	89	85	121-123	-20.0(A)
Boc-Phe-ε-ACA-OMTP	95	74	76	114	0.8(B)
Boc-Gly-Phe-Leu-OMTP	81	71	73	127-129	-
Boc-Gly-Phe-Leu-Tyr(OBzl)-Gly-OMTP	86	74	77	179-180	-

[a] Isolated yields calculated from the amount of first amino acid attached to the resin. [b] Values of the products from 5, c=1, AcOH(A) or $CHCl_3$(B). Those from 4 and 6 gave identical values.

The stability of the oxime resin ester linkage to strong acid such as TFA was also investigated. After treating Boc-Phe-oxime resins with 25% TFA/CH_2Cl_2 in given time intervals, the amount of free amino groups left on the oxime resins were measured by a picric acid titration method.[6] The results showed that 6.5% and 5.7% of Phe were lost from Boc-Phe-4 and Boc-Phe-5 after 2 hrs of exposure, and 17.6% and 13.3%[1a] after 4 hrs exposure in 25% TFA/CH_2Cl_2 respectively. The highly activated ester linkage of Boc-Phe-6 was found to be the least stable such that 8.5% (after 2 hrs exposure) and 26.8% (after 4 hrs exposure) of Phe was lost from the corresponding resin ester. Therefore, the oxime resin ester linkage in 4 proved to be similarly stable under TFA as 5, but much less stable in 6.

In conclusion, the 3-nitrobenzophenone oxime resin is a better choice than Kaiser oxime resin for peptide fragment synthesis because of the improved stability and higher reactivities. More results of cyclic peptide and long chain peptide fragment syntheses by 3-nitrobenzophenone oxime resin will be reported elsewhere in detail.

References

1. (a) DeGrado, W. F.; Kaiser, E. T. *J. Org. Chem.* **1980**, *45*, 1295. (b) DeGrado, W. F.; Kaiser, E. T. *J. Org. Chem.* **1982**, *47*, 3258. (c) Nakagawa, S. H.; Kaiser, E. T. *J. Org. Chem.* **1983**, *48*, 678. (d) Lee, Y.-S.; You, W.-S. *Bull. Korean Chem. Soc.* **1985**, *6*, 380. (e) Nakagawa, T.; Susaki, T.; Kaiser, E. T. *J. Am. Chem. Soc.* **1987**, *109*, 3808. (f) Lobl, T. J.; Maggiora, L. L. *J. Org. Chem.* **1988**, *53*, 1979. (g) Park, D.-H.; Jung, J.-K.; Lee, Y.-S. *Bull. Korean Chem. Soc.* **1988**, *9*, 394. (h) Findeis, M. A.; Kaiser, E. T. *J. Org. Chem.* **1989**, *54*, 3478. (i) Voyer, N. *J. Am. Chem. Soc.* **1991**, *113*, 1818. (j) Sasaki, T.; Findeis, M. A.; Kaiser, E. T. *J. Org. Chem.* **1991**, *56*, 3159. (k) Hendrix, J. C.; Jarrett, J. T.; Anisfeld, S. T.; Lansbury, P. T., Jr. *J. Org. Chem.* **1992**, *57*, 3414. (l) Osapay, G.; Taylor, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 6966. (m) Verhaeghe, J.; Lacassie, E.; Bertrand, M.; Trudelle, Y. *Tetrahedron Lett.* **1993**, *34*, 461. (n) Park, D.-H.; Lee, Y.-S. *Bull. Korean Chem. Soc.* **1993**, *14*, 419.

2. (a) Synthesis of 2-nitrobenzophenone oxime resin was also tried. Although 2-nitrobenzophenone resin was successfully made, conversion to the corresponding oxime resin was not successful. Through X-ray fluorescence spectroscopy, 14 wt% of aluminum was found to be trapped in the keto resin, while less than 0.8 wt% of aluminum was found in the other keto resins (1, 2, 3). The ortho geometry in 2-nitrobenzophenone might be responsible for the tight binding with aluminum, and preventing from further conversion. (b) Neckers, D. C.; Kooistra, D. A.; Green, G. W. *J. Am. Chem. Soc.* **1972**, *94*, 9284.

3. Johnson, B. J.; Jacobs, P. M. *J. Org. Chem.* **1968**, *33*, 4525.

4. For monitoring of the progress of the reaction, aliquots of the resin mixture were taken out from the reaction vessel periodically. After careful washing and drying steps, IR spectra were taken to follow up the decrease of the absorption intensity of the oxime ester linkage at 1780 cm^{-1}. The reaction times were defined at the moment of >95% decrease of the initial absorption band.

5. After deprotection of Boc-L-Ile-4 followed by benzoylation, Bz-L-Ile-4 was obtained. Aminolysis with Gly-OMTP or Leu-OMTP under the same reaction condition as in ref 1a) Bz-L-Ile-4 gave Bz-Ile-Gly-OMTP or Bz-Ile-Leu-OMTP, and the resulting allo- or D-Ile containing isomers were checked by HPLC. Less than 0.5% of racemized products were detected for both cases which is similar to the reported value.[1a] In case of solution phase reactions of Bz-L-Ile-OBt with Gly-OBzl or Gly-OMTP, 63% and 15% of racemized product was detected respectively.

6. Gisin, B. F. *Anal. Chim. Acta* **1972**, *58*, 248.