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Soluble Polymer-Supported Synthesis of Imines and β-Lactams

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Abstract: The first synthesis of β-lactams bound to a soluble/insoluble polyethylene glycol monomethylether polymeric matrix has been realized by standard reactions carried out on immobilized imines. β-Lactams removal from the polymer has been accomplished under acidic and basic conditions.

The advent of combinatorial chemistry [1] has led to a revival of the use of polymeric matrixes as supports for the construction of small organic molecules.[2] In this context, polyethylene glycol monomethylether of molecular weight 5000 (MeOPEG) recently emerged among *soluble* polymers as a very convenient support.[3] This inexpensive polymer [4] features the relevant peculiarity of being soluble in many organic solvents and insoluble in a few others, such as hexane, diethylether, and *t*-butylmethylether. Thus, one can carry out a reaction on a MeOPEG immobilized compound in homogeneous conditions (*e.g.* in dichloromethane) and avoid the need for large excess of reagents and iterative procedures typical of solid phase synthesis.[2] After the reaction, the products can be easily purified by simply precipitating the polymer with diethylether and removing the unreacted materials by filtration.

In a seminal series of papers Janda and co-workers [3,5] showed that MeOPEG can be used for the supported synthesis of pentapeptides, [5a] sulfonamides,[5a] and azatides.[5c] They also described MeOPEG bound linkers that allow "traceless" removal of the polymer and of the spacer from the products.[5b,6] In addition, Janda [7] and Bolm [8] anchored chiral ligands for asymmetric dihydroxylation reaction on MeOPEG.[9]

We wish to report here the synthesis of imines immobilized [10] on MeOPEG and their transformation into β-lactams by two different procedures.[11] The removal of the β-lactams from the polymer has also been realized under acidic and basic conditions.

The synthesis of the imines is described in the Scheme. Mono MeOPEG succinate **1** [8,12] was condensed with *N*-(4-hydroxyphenyl)-*O*-benzylcarbamate [13] (1.5 mol equiv) in the presence of dicyclohexylcarbodiimide (DCC, 2.0 mol equiv) and 4-dimethylaminopyridine (DMAP, 0.1 mol equiv) to afford diester **2** in 96% yield.[12] From this, the free amine **3** was obtained by hydrogenation (10% Pd/C, 20 mg of catalyst/g of polymer, H_2 1 atm, MeOH, 23°C, 48h) in 94% yield.[12]

The representative imines **4-6** were prepared by adding the aldehyde (2.0 mol equiv) to the melted amine 3 (90°C) followed by stirring the thick oily mixture for 1h, and removing the unreacted aldehyde and the released water under vacuum. By this procedure imine **4** was obtained in ≥ 90% yield as a pure product, while imines **5** and **6** were obtained in 70% yield, along with 30% of the unreacted amine.[12,14,15]

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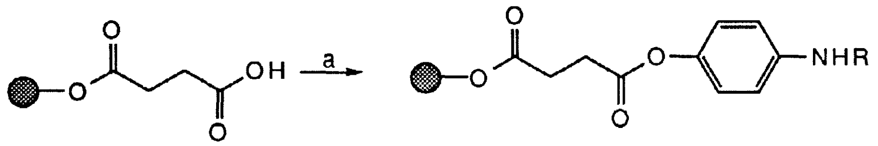
Scheme



= MeOPEG

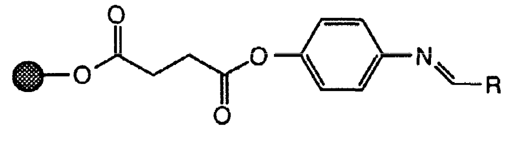
1

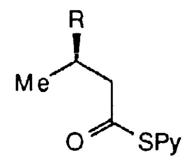
2 R = $COOCH_2Ph$

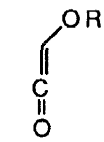
3 R = H

b

3 $\xrightarrow{c}$



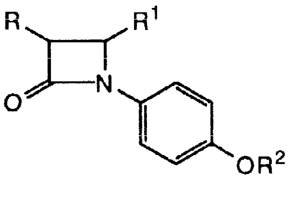




4, R = Ph; **5**, R = 2-thienyl; **6**, R = *E* - CH=CHPh; **7**, R = *c*-C_6H_{11}; **8**, R = $COOCH_2CH{=}CH_2$

9, R = H; **10**, R = $OSiMe_2Bu$-*t*

13, R = Ph; **14**, R = $PhCH_2$



11, R = Et, R^1 = Ph, R^2 = $CO(CH_2)_2COOPEGOMe$;
12, R = (*R*)-MeCH($OSiMe_2Bu$-*t*), R^1 = Ph, R^2 = $CO(CH_2)_2COOPEGOMe$;
15, R = PhO, R^1 = Ph, R^2 = $CO(CH_2)_2COOPEGOMe$;
16, R = $PhCH_2O$, R^1 = Ph, R^2 = $CO(CH_2)_2COOPEGOMe$;
17, R = PhO, R^1 = 2-thienyl, R^2 = $CO(CH_2)_2COOPEGOMe$;
18, R = Et, R^1 = Ph, R^2 = H; **19**, R = (*R*)-MeCH(OH), R^1 = Ph, R^2 = H;
20, R = PhO, R^1 = Ph, R^2 = H; **21**, R = $PhCH_2O$, R^1 = Ph, R^2 = H;
22, R = PhO, R^1 = 2-thienyl, R^2 = H;
23, R = (*R*)-MeCH($OSiMe_2Bu$-*t*), R^1 = Ph, R^2 = Me

Reagents. a: 4-$PhCH_2OCONH$-C_6H_4-OH, DCC, DMAP; b: H_2, 10% Pd/C; c: RCHO.

Among the variety of applications of imines in synthesis, β-lactam formation was selected to test the reactivity of the immobilized reagent.[11] Since imines can be involved in two main types of β-lactam synthesis (the condensation with an enolate [16a] and the cycloaddition with a ketene [16b]), both processes were attempted (Scheme). Imine **4** was reacted (CH_2Cl_2, 15h, 23°C) with the titanium enolate of 2-pyridylthioesters **9** and **10** (2.0 mol equiv) [17] to afford β-lactams **11** and **12**. Alternatively, the cycloadditions (CH_2Cl_2, 15h, 23°C) of imine **4** with ketenes **13** and **14** (generated *in situ* from the corresponding acid chlorides and triethylamine, 20 mol equiv each), gave β-lactams **15** and **16**. In the same conditions, compound **17** was obtained from ketene **13** and imine **5**.

While ^1H NMR analysis allowed a satisfactory determination of the stereoisomeric composition of the products bound to the polymer,[18] the yield of the β-lactam formation was better determined by azetidinone removal from the MeOPEG matrix, a reaction that served to establish a possible synthetic application of this supported β-lactam synthesis. The removal was obtained by two equally efficient procedures occurring in different conditions. Thus, by acid catalyzed methanolysis (MeOH, cat. conc. H_2SO_4, 60°C, 4h)[19] of the polymer-bound compounds **11,12,15,16,** and **17**, β-lactams **18** (54% overall yield from the amine; *trans:cis* ratio = 85:15), **19** (30%; ≥ 98:2),[20] **20** (52%; 85:15), **21** (30%; 75:25), and **22** (35%; 92:8) were obtained. Compound **18** was also obtained from **11** (56%; 85:15) under basic conditions by reaction with MeOH in

CH_2Cl_2 in the presence of catalytic diazabicycloundecene (23°C, 15h).[19,21]

In conclusion, the first synthesis of imines and β-lactams on a soluble polymeric matrix has been realized, and convenient procedures for the removal of the β-lactams from the polymer have been established.

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4. By comparing the prices of different polymers functionalized with primary OH groups, and considering the number of functional groups per gram of polymer ("loading", expressed in meq/g) MeOPEG 5000 ("loading" = 0.2) costs 10 to 500 times less than other commercially available polymeric matrixes.
5. a) Han, H.; Wolfe, M.M.; Brenner, S.; Janda, K.D. *Proc. Nat'l Acad. USA* **1995**, *92*, 6419; b) Jung, K.W.; Zhao, X.; Janda, K.D. *Tetrahedron Lett.* **1996**, *37*, 6491 and **1997**, *38*, 977. c) Han, H.; Janda, K.D. *J. Am. Chem. Soc.* **1996**, *118*, 2539.
6. MeoPEG has been previously used as support for the iterative synthesis of polypeptides, oligonucleotides, and oligosaccharides. For a list of leading references, see Ref. 3.
7. a) Han, H.; Janda, K.D. *J. Am. Chem. Soc.* **1996**, *118*, 7632, and *Tetrahedron Lett.* **1997**, *38*, 1527.
8. Bolm, C.; Gerlach, A. *Angew. Chem. Int. Ed. Engl.* **1997**,*36*, 741.
9. For the immobilization of different catalysts on soluble polymers, see: Bergbreiter, D.E.; Zhang, L.; Mariagnanam, V.M. *J. Am. Chem. Soc.* **1993**, *115*, 9295, and references therein.
10. The synthesis of imines on *insoluble* polymers has been described in Ref. 2c.
11. Only one synthesis of polymer immobilized β-lactams has been described: Ruhland, B.; Bhandari, A.; Gordon, E.M.; Gallop, M.A. *J. Am. Chem. Soc.* **1996**, *118*, 253. The polymer was insoluble (Sasrin), and the azetidinones were formed by a ketene/imine cycloaddition using a 1000 fold excess of ketene precursor. The attachment of two commercially available β-lactams to MeOPEG and their modification to afford a β-lactam library has been claimed: Janda, K.D.; Hyunsoo, H. *Pat. Appl. WO 96/03418*. Very recently, the solid-phase synthesis of β-sultams has been reported: Gordeev, M. F.; Gordon, E.M.; Patel, D. V. *J. Org. Chem.* **1997**, *62*, 8177.
12. Compound **1** was prepared in 95% yield by reaction of MeOPEG with succinic anhydride and catalytic DMAP in refluxing CH_2Cl_2. The yields of compounds **1-9** were determined assuming a molecular weight of 5000 daltons for the MeOPEG fragment. The purity of the supported products was determined by 300 MHz ^1H NMR analysis in $CDCl_3$ (with pre-saturation of the CH_2 signals of the polymer), exploiting the MeOPEGOCO-CH_2-$\underline{CH_2}$-COOR signal at 4.20 ppm as internal standard. The estimated integration error is ± 7%.

13. Caldwell, J.B.; Ledger, R.; Milligan, B. *Aust. J. Chem.* **1966**, *19*, 1297.
14. The variation of the chemical shift of the aromatic protons of the linker together with the disappearance of the NH_2 signal and the appearance of the CH=N one were diagnostic of imine formation. The signals (H *ortho*, H *meta*, NH_2 or CH=N, ppm) of compound **3-8** were at: **3**: 6.60, 6.80, 2.60; **4**: 6.70, 6.87, 8.43; **5**: 7.17, 7.06, 8.50; **6**: 7.20, 7.10, 8.27; **7**: 7.00, 7.00, 8.07; **8**: 7.13, 7.33, 7.93. Imines **4-6** were single isomers, likely of *E* configuration. In the case of compounds **7** and **8** two isomers were detected in a ca. 66:34 ratio. The minor isomers of **7** and **8** showed the CH=N signal at 7.80 and 7.60 ppm, respectively.
15. Thermally unstable imines such as **7** and **8** could also be prepared by stirring a solution of amine **3** (1 g of **3** in 1 mL of CH_2Cl_2) and of the aldehyde (2.0 mol equiv) in the presence of anhydrous $MgSO_4$ (0.1 mol equiv) under a N_2 atmosphere (23°C, 15h). After filtration and evaporation of the solvent, imines **7** and **8** were obtained in 40 and 30% yield, respectively, along with unreacted amine **3** and, surprisingly, monoester **1** (see Ref. 12 and 14). Imines **4-6** can also be obtained by this procedure, but in slightly lower yields with respect to those reported in the text.
16. a) Hart, D.J.; Ha, D.C. *Chem. Rev.* **1989**, *89*, 1447; b) Georg, G.I.; Ravikumar, V.T. in *The Organic Chemistry of β-Lactams*, Georg, G.I., Ed.; VCH Publisher Inc., New York, **1993**, pp 295-368.
17. Annunziata, R.; Benaglia, M.; Chiovato, A.; Cinquini, M.; Cozzi, F. *Tetrahedron* **1995**, *51*, 10025, and references therein.
18. NMR analysis showed the following *trans:cis* ratios for compounds **11**, **12**, **15**, **16**, and **17**. **11**: 80:20; **12**: ≥98:2; **15**: 90:10; **16**: 78:22; **17**: 92:8. The configurational assignment was based on the coupling constant values: J_{trans} 1.5-2.5 Hz; J_{cis} 5.0-6.0 Hz. In the case of compound **12** a single β-lactam was detected (see Ref. 20 for configurational assignment). It seems unlikely that isolation of the products by precipitation in diethylether can alter the original diastereoisomeric ratio.
19. Separate experiments showed that the unbound β-lactams were stable in the conditions employed for removal. The difference in the *trans:cis* ratios observed for the β-lactams attached to and removed from the polymer can be due to partial removal. All new compounds gave analytical and spectral data in agreement with the proposed structures.
20. The configuration of compound **19** (and hence that of **12**) was established as (*3'R,3S,4S*) by chemical correlation, involving methylation of the phenolic oxygen (MeI, K_2CO_3, acetone, 50°C, 4h) and silylation (*t*-$BuMe_2SiCl$, imidazole, DMF, 23°C, 15h) of the secondary alcohol of **19** to give the known azetidinone **23**: Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P.G. *J. Org. Chem.* **1992**, *57*, 4155.
21. When β-lactam **11** was exposed to $Ce(NH_4)_2(NO_3)_6$ (CAN) in acetonitrile/water to attempt the one-step removal of the polymer and of the linker, the reaction proceeded only to the ester hydrolysis stage, affording β-lactams **18** in 45% yield. *N*-deprotection required further reaction with CAN (67% yield), as described by: Georg, G.I.; Kant, J.; Gill, H.S. *J. Am. Chem. Soc.* **1987**, *109*, 1129.