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A New Polymer-Supported Reagent for the Synthesis of β-Lactams in Solution

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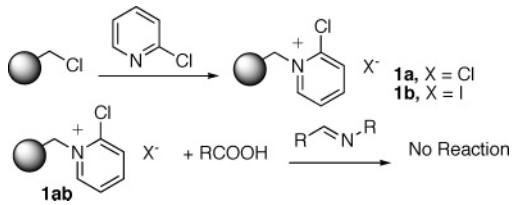
Abstract: A modified Mukaiyama reagent was prepared on a PS-DVB resin. This reagent was used for the preparation of β-lactams, using the Staudinger reaction. The products were obtained by generating the ketene from a carboxylic acid under sonication with the resin followed by reaction with the imine. Excess of the imine was removed by reduction followed by acid scavenging.

Recently polymer-supported reagents have received considerable interest with the growth of high throughput solution phase synthesis.[1] This approach allows for the preparation of arrays of compounds by using reactions that are often clear, that can be monitored with standard analytical techniques, and that should give the products with simple filtration and evaporation of the solvents. Although polymer-supported reagents have been described for many transformations,[2] there is still a need for new reagents that would give access to additional classes of compounds.

The β-lactam ring is the key component of commonly used antibiotics as penicillins, cephalosporins, carbapenems, and monobactams and is present in several peptidomimetics with interesting activities as protease inhibitors.[3] Despite their importance, relatively few examples of β-lactam synthesis on the solid phase have been reported recently[4] and no example of polymer-assisted preparation of β-lactams in solution has been described.[5]

SCHEME 1



Following our interest in β-lactam and polymer-supported syntheses,[6] we were attracted by the possibility of preparing β-lactams using polymer-supported reagents. This would be the starting point for the production of libraries of compounds for biological screening. We now report, to the best of our knowledge, the first example of the synthesis of β-lactams in solution using the Staudinger reaction promoted by a polymer-supported Mukaiyama-type reagent. One of the most popular approaches to the preparation of β-lactams is, in fact, the Staudinger reaction, the cycloaddition between a ketene and an imine.[7] The ketene is generated by a base-mediated elimination of an acyl chloride or another activated carboxylic acid derivative. 2-Chloro-1-methylpyridinium iodide (the Mukaiyama reagent) is one of the most effective reagents for this activation.[8] Consequently, we decided to investigate the possibility of immobilizing a 2-chloropyridinium salt on a polymer by evaluating its reaction with carboxylic acids and imines. A potentially straightforward approach was the alkylation of 2-chloropyridine with a Merrifield resin (Scheme 1). This reaction was carried out in toluene at 110 °C for 36 h and the product **1a** was obtained after filtration of the solvent. Compound **1a** was mixed with phenoxyacetic acid in the presence of Et_3N and after 2 h at 40 °C, *N*-benzyliden(phenyl)methanamine (obtained from benzaldehyde and benzylamine in the presence of trimethylorthoformate)[9] was added, but no reaction was observed.

We tried a variety of reaction conditions, but never observed the formation of the desired β-lactam via either the chloride **1a** or the iodide **1b**.[10]

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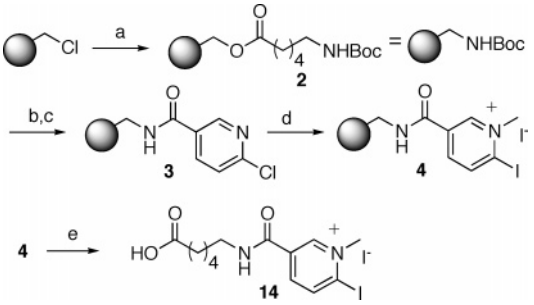
SCHEME 2[a]



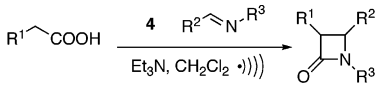
[a] Reagents and conditions: (a) *N*-Boc-6-aminocaproic acid, Cs_2CO_3, DMF, 80 °C, 3 days. (b) TFA, CH_2Cl_2.(c) 6-Chloronicotinoyl chloride in CH_2Cl_2/DIPEA. (d) MeI 75 °C, 2 h. (e) d-TFA neat, 70 °C, 2 h.

We hypothesized that, probably, the reactive center was too close to the resin surface to efficiently react with the carboxylic acid, so we decided to introduce a spacer, changing the architecture of the reagent (Scheme 2). Thus, *N*-Boc-6-aminocaproic acid was linked to a Merrifield resin under standard conditions (Cs_2CO_3, DMF, 80 °C, 3 days, 96% yield). Compound **2** was deprotected at the nitrogen with TFA and the loading determined with a quantitative ninhydrin test.[11]

The resin-bound amine was coupled with 6-chloronicotinoyl chloride[12] in CH_2Cl_2/DIPEA. The reaction was very rapid (negative Kaiser test)[11] and compound **3** was obtained in high yield. On this resin, we tried different procedures for alkylation. When mild conditions were used, compound **4** was obtained in low yield. Heating for long times produced a dark resin where no traces of the expected product were found. Finally, a correct protocol arose from heating the resin at 80 °C in MeI in a sealed tube for no more than 2 h. After washing with dry dichloromethane,[13] and drying the resin, the structure of product **4** was determined by cleavage from hot TFA.[14] ^{1}H NMR analysis confirmed the molecular structure and the mass spectrum, showing a single peak at *m/z* 377, suggested the formation of the 2-iodopyridinium salt.[15] The presence of the second atom of iodine (as the anion) was confirmed by microanalysis.[16] Starting from a Merrifield resin loading of 1.6 mmol/g, we obtained a resin with about 1.2−1.0 mmol/g of product determined through the N contents obtained by microanalysis (87−75% yield).

Again, we tried the reaction between phenoxyacetic acid and the aldimine to test our supported reagent.

SCHEME 3



β-Lactam	R^1	R^2	R^3	Yield (%)
5	-OC_6H_5	-C_6H_5	-$CH_2C_6H_5$	65[a]
6	-C_6H_5	-C_6H_5	-$CH_2C_6H_5$	60[a]
7	-OC_6H_5	-C_6H_5	-*p*C_6H_4OMe	70[a]
8	-C_6H_5	-C_6H_5	-*p*C_6H_4OMe	65[a]
9	-C_2H_5	-C_6H_5	-$CH_2C_6H_5$	62[b]
10	PhtN-	*p*C_6H_4OMe	-*p*C_6H_4Me	71[c]
11	-N_3	*p*C_6H_4OMe	-*p*C_6H_4Me	72[a]
12	CbzNH-	*p*C_6H_4OMe	-*p*C_6H_4Me	70[a]
13	-OC_6H_5	*p*C_6H_4OMe	-*p*C_6H_4Me	88[a]

[a] Cis isomer. [b]Trans isomer. [c]Cis/trans mixture 3:1.

Following standard conditions (generation of the ketene from the acid, the pyridinium salt, and a tertiary amine in boiling CH_2Cl_2 followed by addition of the imine) the expected β-lactam was recovered in very low yields. Better results were obtained by mixing all the reagents together in dry CH_2Cl_2 in a sealed vial placed into an ultrasound bath for 2 h. Filtration on a short path of silica gel, followed by evaporation of the solvent, gave the β-lactam **5** together with unreacted imine. We tried to use a stoichiometric amount of the imine to prevent the contamination of the crude product with the excess of the imine but the yield was very low.

Obliged to use 2 equiv of imine, we looked for a scavenger. We did not find any example of scavenging of imine in the literature. Consequently, we decided to reduce the excess of the imine with $NaBH_4$ or macroporous triethylammomium methylpolystyrene borohydride[17] to give the corresponding dibenzylamine. After filtration and evaporation of the solvent, the amine was removed through filtration over silica gel or SCX columns. After this protocol, β-lactam **5** was isolated in 60% yield with a good level of purity (80−85% at ^{1}H NMR, see the Supporting Information).

Nevertheless, we observed in the ^{1}H NMR spectrum a singlet at δ 4.45 that was finally attributed to *N*-benzylphenoxyacetamide, a byproduct previously observed in Staudinger reactions.[4f] The formation of this product was avoided changing again the order of addition. Phenoxyacetic acid was mixed with resin **4** in dry CH_2Cl_2 in the presence of Et_3N and the vial placed in an ultrasound bath for 2 h.[18] To this mixture was added the imine and the reaction mixture was heated at 70 °C overnight. The solvent evaporated and $NaBH_4$ in EtOH added at room temperature. After 10 min of stirring, the

(10) During the writing of this paper, the preparation of compound **1b** was described together with its use for the synthesis of carbodiimides: Convers, E.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2004**, *45*, 3401.

(11) For the qualitative and quantitative colorimetric tests used through this paper see: Gaggini, F.; Porcheddu, A.; Reginato, G.; Rodriquez, M.; Taddei, M. *J. Comb. Chem*. **2004**, *6*, 805.

(12) Commercially available from Aldrich.

(13) Warning: washing the resin with dry DMF gave lower yields of **4**.

(14) An analogous MW assisted cleavage from Merrifield resin has been previously reported: Stadler A.; Kappe, C. O. *Eur. J. Org. Chem*. **2001**, 919.

(15) This exchange reaction of α-halogenated pyridines has been previously described: Bradlow, H. L.; Vanderwerf, C. A. *J. Org. Chem.* **1951**, *16*, 1143.

(16) The percentage of C, H, and N found was correct exclusively inserting a second iodine atom in the structure. See the Supporting Information.

(17) We obtained successful results exclusively using supported borohydride purchased from Argonaut.

(18) The use of ultrasounds allowed the formation of **5** in yield higher than with conventional heating, probably for a more efficient motion of the beads.

solvent was evaporated and the residue passed through an SCX column to remove the amine.[19] Evaporation of the solvent gave β-lactam **5** (as a single cis isomer) without traditional column chromatography, as generally required to separate the byproducts of Mukaiyama reagent from the desired β-lactam.

To explore the general applicability of the Mukaiyama solid supported reagent, we examined the preparation of diverse β-lactams, as reported in Scheme 3. Results were always satisfactory in terms of yield and purity (higher than 90% at ^{1}H NMR analysis). Compounds **6**−**13** were obtained as a single isomer or as a mixture of cis/trans isomers depending on the substituents, as observed in the homogeneous phase.[20]

In conclusion we have prepared an efficient polymer-supported Mukaiyama-type reagent[21] that was suitable for the generation of ketenes for Staudinger cycloaddition with imines. In addition, we also developed a protocol for the scavenging of imines and for the isolation of pure β-lactams that can be easily applied to a parallel synthesis.

Experimental Section

6-(*tert*-Butoxycarbonylamino)caproic Acid. Di-*tert*-butoxycarbonate (24 g, 0.11 mol) was dissolved in 200 mL of THF. The mixture was added dropwise into a solution of 6-aminocaproic acid (13.2 g, 0.1 mol) in NaOH (0.5 M, 220 mL) at 0 °C and the resulting mixture was stirred for 6 h at room temperature. The reaction mixture was quenched with water (100 mL), and the whole mixture was extracted with ether (3 × 200 mL). The aqueous layer was acidified at pH 5 with a buffered solution of sodium citrate/HCl (pH 2−3) at 0 °C, then extracted with ether (4 × 400 mL), dried over $MgSO_4$, and filtered, then the solvent was evaporated to give a crude oil, which was cooled at −20 °C. Petroleum spirit was added at −20 °C to give the product as colorless fine needles (19.3 g, 88%). Mp 31−32 °C (lit.[22] mp 32.5−33.5 °C).

Linkage of 6-(*tert*-Butoxycarbonylamino)caproic Acid on Merrifield Resin 2. 6-(*tert*-Butoxycarbonylamino)caproic acid (2.1 g, 9.6 mmol) was added to a solution of Cs_2CO_3 (3.2 g, 9.6 mmol) in dry DMF (120 mL), followed by addition of the Merrifield resin (chloride form, 2 g, 3.2 mmol). The mixture was heated at 80 °C for 72 h in a rotatory apparatus. The beads were collected on a glass filter and washed with DMF (5 mL), a 20% solution of TFA in CH_2Cl_2 (2 × 5 mL), DMF (3 × 5 mL), and CH_2Cl_2 (4 × 5 mL). Then, the beads were treated with 1/1 TFA/CH_2Cl_2 solution (3 × 20 min) at room temperature. The reaction completion was monitored by the Kaiser test. The beads were washed with DMF (3 × 5 mL) and CH_2Cl_2 (5 × 5 mL) and dried at 60 °C under vacuum under P_2O_5 to give resin **2** (3.1 g). Microanalysis: C, 74.80; H, 6.87; N, 1.39 corresponding to a loading of 1.22 mmol/g of resin (96% yield).

Synthesis of Supported Reagent 4. Resin **2** (1 g, 1.2 mmol) was suspended in dry CH_2Cl_2 (5 mL), followed by addition of 6-chloronicotinoyl chloride (790 mg, 4.8 mmol) and Et_3N (2 mL). The mixture was shaken for 10 min at room temperature, and then washed with CH_2Cl_2 (2 × 5 mL), DMF (3 × 5 mL), and CH_2Cl_2 (4 × 5 mL). The reaction completion was monitored with a negative Kaiser test. The beads were collected in a vial, MeI (3 mL) was added, and the sealed vial was heated at 80 °C for 2 h (oil bath). After cooling, the beads were collected on a glass filter and successively washed with CH_2Cl_2 (5 × 5 mL) and dried at 60 °C under vacuum and in the presence of P_2O_5 to give the supported reagent **4**. The identity of the product loaded on the resin was monitored by d-TFA assisted cleavage. Thus, 10 mg of dry beads was placed into a NMR tube with neat d-TFA (0.8 mL) and the tube was heated at 70 °C (oil bath) for 2 h. After cooling, the spectrum of the cleaved compound was directly recorded. ^{1}H NMR and mass (ESI) spectra derived from resin **4** are reported in the Supporting Information. Microanalysis of resin **4**: C, 63.15; H, 5.58; N, 2.28, corresponding to a loading of 0.91 mmol/g of resin (98% yield). These data fit exclusively with the presence of two iodine atoms on the resin.

General Procedure for the Syntesis of β-Lactams with Use of Supported Reagent 4: 1-Benzyl-3-phenoxy-4-phenyl-2-azetidinone, 5. Supported reagent **4** (200 mg, 0.2 mmol), phenoxyacetic acid (15 mg, 0.1 mmol), and triethylamine (55 μL, 0.4 mmol) in CH_2Cl_2 (2 mL) were mixed in a sealed vial and heated at 60 °C inside an ultrasound bath. Then, benzylidene(phenyl)methanamine (0.2 mmol) was added and the mixture was heated at 70 °C (oil bath) for an additional 14 h. After evaporation of the solvent under reduced pressure, ethanol was added (3 mL), followed by addition of $NaBH_4$ (16 mg, 0.4 mmol). The mixture was shaken for 10 min, the solvent evaporated, and the residue passed through an SCX-3 cartridge (International Sorbent Technology, IST) with CH_2Cl_2 and petroleum ether as the solvents. Removal of the solvent under reduced pressure gives the crude β-lactam **5** (21 mg, 65% yield). ^{1}H NMR and mass (ESI) spectra are reported in the Supporting Information.

β-Lactams **5**−**13** were prepared following this general procedure. The products were characterized through their melting points (after crystallization or short column chromatography) or comparison with reported spectroscopic data (see the Supporting Information).

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Supporting Information Available: Characterization of **4** and **5**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Filtration through the SCX column also removed the alkylammonium and boron salts byproducts. To elute the required β-lactam, petroleum ether was used. Alternatively, the amine can be scavenged with chlorosulfonate polystyrene and (*N*,*N*-diisopropylaminomethyl)-polystyrene and the solution passed through a short path of silica to remove salts.

(20) The mechanism of β-lactam formation has been investigated extensively. However, the rationale for the observed diastereoselectivity and enantioselectivity remains unknown. It has been shown that the stereoselectivity depends on a number of factors: the structure of the imine, activated acid, sequence of reagent addition, solvent, temperature, and bases. See, for example: (a) Arrieta, A.; Lecea, B.; Cossio, F. P. *J. Org. Chem*. **1998**, *63*, 5869. (b) Cossio, F. P.; Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 2085. (c) Cossio, F. P.; Ugalde, J. M.; Lopez, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc.* **1993**, *115*, 995. (d) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784. (e) Lopez, R.; Sordo, T. L.; Sordo, J. A.; Gonzalez, J. *J. Org. Chem*. **1993**, *58*, 7036. (f) Lynch, J. E.; Riseman, S. M.; Laswell, W. L.; Tschaen, D. M.; Volante, R. P.; Smith, G.; Shinkai, I. *J. Org. Chem*. **1989**, *54*, 3792. (g) Bose, A. K.; Chiang, Y. H.; Manhas, M. S. *Tetrahedron Lett*. **1972**, *13*, 4091.

(21) Reagent **4** eventually could be used for synthetic applications typical of 2-chloro-1-methylpyridinium iodide. See: Mukaiyama, T. *Angew. Chem., Int. Ed. Engl*. **1979**, *18*, 707.

(22) Alam, Md. R.; Maeda, M.; Sasaki, S. *Bioorg Med Chem*. **2000**, *8* 465.