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Conversion of Amines to Imines Employing Polymer-Supported Sulfoxide (PSS) and Polymer-Supported Perruthenate (PSP): Synthesis of Pyrrolo[2,1-*c*][1,4]benzodiazepines

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Abstract: An efficient method for the oxidation of secondary amines to the corresponding imines has been developed by employing polymer-supported reagents. This protocol has been extended for the generation of a combinatorial library of substituted pyrrolo[2,1-c][1,4]benzodiazepine derivatives and provides a rapid and clean preparation avoiding conventional purification techniques.

Keywords: combinatorial synthesis; 'green' chemistry; oxidation of secondary amines; polymer-supported reagents; pyrrolo[2,1-*c*][1,4]benzodiazepines

Introduction

The use of combinatorial methods for the generation of chemical libraries[1] has recently increased at a tremendous pace. These methods are being adopted by the chemical industry to prepare novel materials particularly in the area of pharmaceutical chemistry and catalysis.[2] Solid-phase organic synthesis is a powerful and rapid method for the generation of chemical libraries employing linear synthetic sequences on polymer-supported substrates. This technique has greatly simplified the preparation of products, however, there are several associated problems and drawbacks that have not been completely addressed. Therefore, a somewhat modified strategy that allows the preparation of a large number of molecules in solution, in a linear or convergent manner,[3] through the sequential use of polymer-supported reagents in a multi-step process is increasingly becoming popular.[4] The need for such a strategy is of practical significance due to its ability to incorporate in-line purification protocols such as scavenging of the reagent and by-products,[5] and catch-and-release[6] procedures. This enables the possibility for the direct high-throughput synthesis of molecules with higher purities that could be screened for biological activity without the need for further purification, i.e., avoiding chromatographic processes.

The oxidation of an amine to the corresponding imine functionality is a very useful transformation, particularly in the field of natural products.[7] Vederas and co-workers developed a polymer-supported sulfoxide (PSS) for the Swern oxidation process.[8] Similarly, polymer-supported perruthenate (PSP) has been prepared by Ley and co-workers[9] for the oxidation of alcohols to aldehydes and ketones. This reagent has been extensively utilized for various applications in organic transformations.[4a] The amine to imine oxidation process that has been reported[10] by the use of activated DMSO, has also been applied by us for the oxidation of cyclic secondary amines to the corresponding imines.[11] Also, TPAP is known for the oxidation of amines to imines[12] and this process, as well, has been extended for the preparation of imine-containing pyrrolo[2,1-*c*][1,4]benzodiazepines.[13]

In recent years, there has been considerable interest in ring systems such as pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) that can recognize and bind to specific sequences of DNA.[14] These compounds have been produced naturally from various *Streptomyces* species, that possess antitumor antibiotic activity, e.g., anthramycin.[14c] These compounds bind selectively in the minor groove of the DNA while a covalent aminal bond is formed between the electrophilic C11-position of the PBD and the nucleophilic attack of the C2-amino group of a guanine base[15] is generally responsible for the biological activity. The DNA binding ability and anticancer activity depends on the type of substitution in the A and C rings as seen from the large number of compounds that have been synthesized based on this ring system (Figure 1). One of the PBD dimers (SJG-136), with an affinity for Pu-GATC-Py, is presently under clinical evaluation.[16] Previous studies on the PBD-based compounds have not only led to structurally modified PBDs[17] but also to the development of new synthetic strategies,[18] including solid-phase synthetic strategies.[19] In continua-

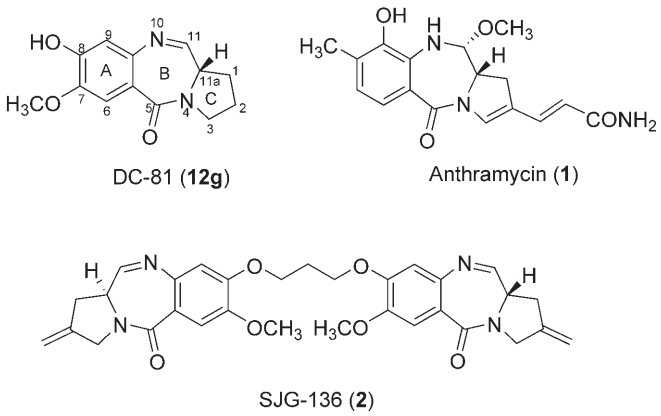


Figure 1. Biologically important pyrrolo[2,1-*c*][1,4]benzodiazepines.

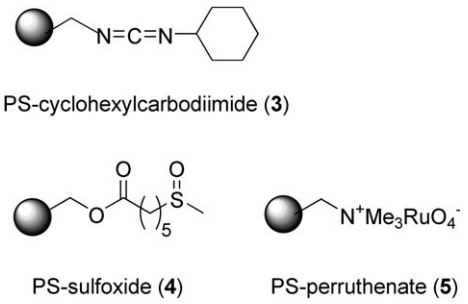
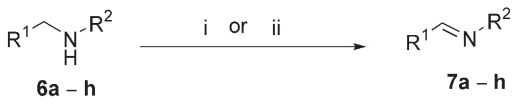


Figure 2. Polymer-supported reagents.

tion of this work it has been considered of interest to investigate the use of polymer-supported sulfoxide (**4**) as well as perruthenate (**5**) (Figure 2) with regard to the conversion of an amine to an imine functionality. This protocol has also been extended to the synthesis of imine-containing pyrrolo[2,1-*c*][1,4]benzodiazepines.

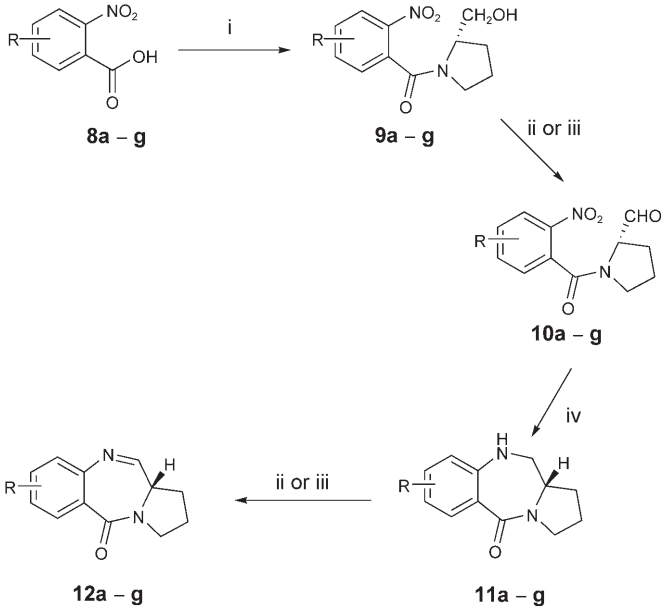
Results and Discussion

The reaction of various amines with polymer-supported sulfoxide **4** and perruthenate **5** provide the corresponding imines in good yields (Scheme 1) and the results are illustrated in Table 1. It is observed that the use of PS-sulfoxide[8] **4** takes place under normal Swern conditions and **4** is an effective substitute for DMSO and does not produce any of the unpleasant by-products like dimethyl sulfide. The PS-sulfide obtained after the oxidation process could be repeatedly recycled and reused without diminishing its effectiveness (after oxidation of the reagent with sodium periodate) and thus has potential for application in combinatorial chemistry. However, oxidation of secondary amines to imines employing PS-perruthenate[9] **5** in conjunction with a co-oxidant such as *N*-methylmorpholine *N*-oxide (NMO) gave higher yields (Table 1). The use of stoichiometric PS-perruthenate reagent provides a cleaner process for the preparation of imines from amines. Moreover, this polymer-supported reagent can be filtered and reused in combination with a co-oxidant. Overall, the use of polymer-supported reagents afford the desired products free from the contamination of by-products or excess reagents and more importantly there is no need for time-consuming work-up as well as purification steps.



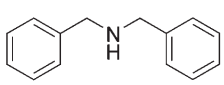
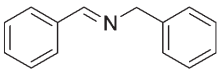
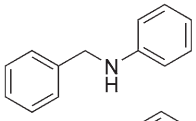
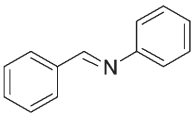
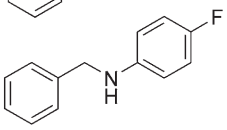
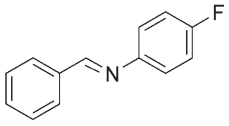
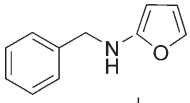
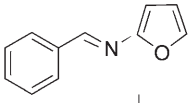
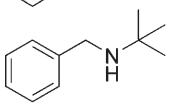
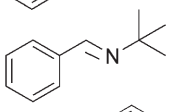
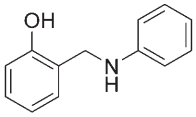
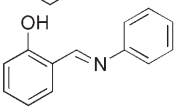
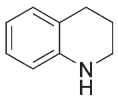
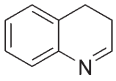
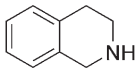
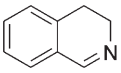
Scheme 1. Conversion of secondary amines to imines by employing PS-reagents. *Reagents and conditions:* i) **4**, $(COCl)_2$/Et_3N, CH_2Cl_2, $-50\,^{\circ}C$ to room temperature for 3–5 h, 62–78% ; ii) **5**, NMO, CH_2Cl_2, room temperature, 8–10 h, 81–96%.

In conjunction with our earlier studies on the use of polymer-supported reagents[20] for the preparation of the pyrrolo[2,1-*c*][1,4]benzodiazepine ring system, the imine formation occurs through aza-Wittig reductive cyclization employing substituted 2-azidobenzoic acid as the starting material, whereas the present methodology employs substituted 2-nitrobenzoic acid as the starting material which proceeds through the oxidation of a secondary amine to an imine. Therefore, we herein describe a new synthetic procedure for the preparation of PBDs by employing the polymer-supported reagents (Figure 2). It has been observed in previous studies[11,13]



Scheme 2. Polymer-assisted solution-phase strategy for the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines. *Reagents and conditions:* i) L-prolinol, **3**, CH_2Cl_2, room temperature, overnight, 94–96%; ii) **4**, $(COCl)_2/Et_3N$, CH_2Cl_2, $-50\,^{\circ}C$ to room temperature, 3–3.5 h; iii) **5**, NMO, CH_2Cl_2, room temperature, 8–9 h; iv) 10% Pd-C, H_2 (1.5 atm), C_2H_5OH, room temperature, 6 h, 80%.

Table 1. Oxidation of secondary amines by employing PS-sulfoxide (**4**) and PS-perruthenate (**5**).

Entry	Secondary amine **6**	PS-sulfoxide **4** Yield [%][a]/Time [h]	PS-perruthenate **5** Yield [%][a]/Time [h]	Imines **7**[b]
a		65/3	90/8	
b		62/3	92/8	
c		74/3.5	92/8.2	
d		83/3	96/8	
e		78/3.5	90/8.5	
f		74/4	88/8.4	
g		68/5	84/9.3	
h		60/5.2	81/10	

[a] Isolated yields.
[b] Products were characterized by ^{1}H NMR and mass spectroscopy.

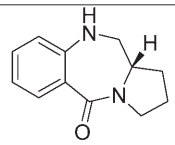
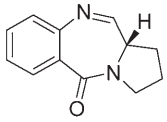
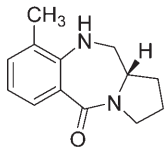
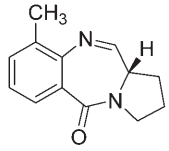
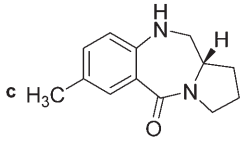
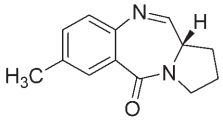
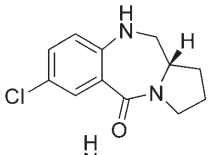
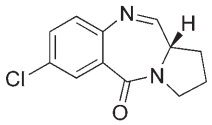
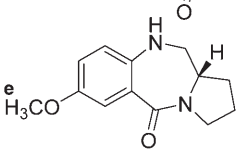
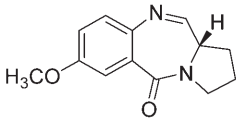
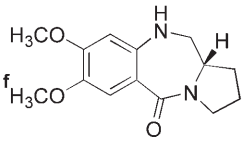
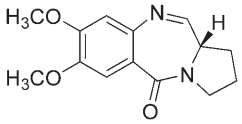
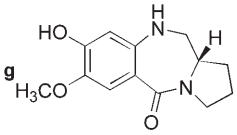
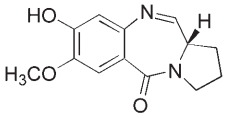
in the solution phase that this oxidative methodology does not endanger the stereochemical integrity at the C11a position, which is extremely important with respect to biological activity. Therefore, the development of a clean and efficient synthesis for pyrrolo[2,1-*c*][1,4]benzodiazepines employing polymer-supported reagents based on the oxidation of cyclic secondary amines is of immense significance.

The synthetic route comprises of the coupling of L-prolinol with the corresponding 2-nitrobenzoic acids (**8a**–**g**). Interestingly, in the coupling reaction of prolinol to the nitrobenzoic acid by using PS-cyclohexylcarbodiimide (**3**)[21] (as shown in Figure 2) there is an excess of acid and urea by-products that can be simply filtered from the *N*-(2-nitrobenzyl)pyrrolidine-2-carbinols (**9a**–**g**). The *N*-(2-nitrobenzyl)pyrrolidine-2-carboxaldehydes (**10a**–**g**) have been obtained by the oxidation of **9a**–**g** using PS-sulfoxide (**4**) or PS-perruthenate (**5**). The reductive cyclization of the nitroaldehyde (**10a**–**g**) employing Pd/C affords the secondary amines (**11a**–**g**). These amines (**11a**–**g**) have been treated with PS-sulfoxide (**4**) or alternatively by PS-perruthenate (**5**) to afford the desired imines **12a**–**g** (Scheme 2) in yields ranging from 50–75% as shown in Table 2. Apart from the advantage of reuse of the PS-reagents there is an absence of side-products and no unpleasant smell of DMSO, particularly when PS-sulfoxide is employed. Moreover, the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine antitumour antibiotics employing PS-reagents is a rapid and efficient procedure.

Conclusion

In conclusion, a clean process has been developed for the conversion of the amine to the imine functionality.

Table 2. Oxidation of cyclic secondary amines (PBD) by employing PS-sulfoxide (**4**) and PS-perruthenate (**5**).

Entry	Cyclic secondary amine **11**	PS-sulfoxide **4** Yield [%][a]/Time [h]	PS-perruthenate **5** Yield [%][a]/Time [h]	Imine**12** [b]
a		50/3	62/8	
b		60/3.5	67/8.2	
c		63/3.5	65/8.1	
d		64/3	73/8	
e		65/3	75/8.2	
f		63/3.2	72/8.5	
g		62/3.5	70/9	

[a] Isolated yields.
[b] Products were characterized by ^{1}H NMR and mass spectroscopy.

This process has also been extended to the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine antibiotics and further the use of orchestrated multi-step PS-reagents has also been demonstrated in their total synthesis. This facile preparation of imines from amines has potential for use in combinatorial chemistry. A noteworthy aspect is that these polymer-supported reagents can be recovered and reused with negligible loss of activity and are enormously beneficial from the environmental and economic points of view.

Experimental Section

General Remarks

All reagents obtained were from commercial sources and used without further purification. ^{1}H NMR spectra were recorded at 200 MHz and chemical shifts are given in δ units relative to the tetramethylsilane (TMS) signal as an internal reference in $CDCl_3$. Coupling constants (*J*) are reported in Hertz (Hz). Electron-impact (EI) mass spectral data were recorded in the form of *m*/*z* (intensity relative to base 100) on a VG 7070H Micromass mass spectrometer at 200 °C, 70 eV, with a trap current

200 μA and 4 kV acceleration. Analytical TLC for all reactions was performed on Merck prepared plates (silica gel 60 F254 on glass).

Typical Procedures for Imines

Employing PS-sulfoxide: PS-sulfoxide[8] **4** was swollen in CH_2Cl_2 at room temperature for 30 min and then cooled to $-50\,^{\circ}C$. To this cooled solution oxalyl chloride (1 equiv.) in CH_2Cl_2 was added dropwise. After 1 h at that temperature, the secondary amine (1 equiv.) in CH_2Cl_2 was added, and the mixture was stirred for 2 h before the addition of Et_3N (1.5 equivs.). The mixture was allowed to warm to room temperature and stirred for 3–5 h. The resin was removed by filtration and washed with CH_2Cl_2. The filtrate was washed three times with water. The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated to afford the corresponding imine.

Employing PS-perruthenate: To a solution of the secondary amine in CH_2Cl_2 was added 4 Å powdered molecular sieves, NMO (1.5 equivs.), PS-perruthenate[9] **5** (250 mg, 0.05 mmol) and the mixture was stirred at room temperature for 8–10 h. On completion of the reaction, the resin was removed by filtration and washed with CH_2Cl_2. The filtrate was evaporated under vacuum and the product directly analyzed by ^1H NMR spectroscopy without further purification to afford the corresponding imine.

Preparation of Compound 12 g

PS-sulfoxide **4** (2.20 mmol/g, 0.52 mmol) was swollen in CH_2Cl_2 (5 mL) at room temperature for 30 min and then cooled to $-50\,^{\circ}C$. To this cooled solution oxalyl chloride (66 mg, 0.52 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After 1 h at that temperature, secondary amine **11 g** (100 mg, 0.40 mmol) in CH_2Cl_2 (1 mL) was added, and the mixture was stirred for 2–3 h before the addition of Et_3N (79 mg, 0.78 mmol). The mixture was allowed to warm to room temperature and stirred for 3.5 h. The resin was removed by filtration and washed with CH_2Cl_2. The filtrate was washed three times with water. The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated to afford product **12 g**; yield: 62%.

Alternatively, to the solution of the secondary amine **11 g** (100 mg, 0.40 mmol) in CH_2Cl_2 (5 mL) were added 4 Å powdered molecular sieves (250 mg), NMO (132 mg, 1.0 mmol), PS-perruthenate **5** (250 mg, 0.05 mmol) and the mixture stirred at room temperature for 9 h. On completion of the reaction, the resin was removed by filtration and washed with CH_2Cl_2. The filtrate was evaporated under vacuum and the product directly analyzed by ^1H NMR spectroscopy without further purification to afford **12 g**; yield: 70%. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.04-2.12$ (2H, m), 2.28–2.33 (2H, m), 3.57–3.60 (1H, m), 3.68–3.71 (1H, m), 3.74–3.77 (1H, m), 3.96 (3H, s), 6.40 (OH, brs), 6.92 (1H, s), 7.49 (1H, s), 7.65 (1H, d, $J = 4.4$ Hz); MS (EI): $m/z = 246$ [M^+]; $[\alpha]_D^{26}$: +272 (*c* 0.02, $CHCl_3$); lit.[22] $[\alpha]_D^{22}$: +135 (*c* 0.2, $CHCl_3$).

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