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SYNTHESES OF OXAZOLIDINONE, IMIDAZOLIDINONE AND THIAZOLIDINONE DERIVATIVES USING A POLYMER-SUPPORTED DIPHENYLPHOSPHORYL AZIDE

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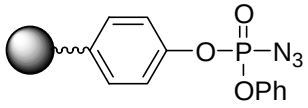
Abstract – By using a polymer-supported diphenylphosphoryl azide (PS-DPPA), oxazolidinone, imidazolidinone and thiazolidinone derivatives were successfully prepared from carboxylic acids bearing different reactive functional groups in the β position , such as alcohols, thiols, primary or secondary amines. The desired compounds were obtained in good yields *via* Curtius rearrangement and subsequent intramolecular cyclization.

INTRODUCTION

Syntheses of *N*-heterocyclic rings have been studied for some time. These sorts of compounds, including oxazolidinones, have received increased attention since they are known to be the core structural unit of compounds with antibacterial,[1] antiallergy[2] and immunosuppressant[3] activities. In recent years, solid-phase supported synthesis has proven to be an efficient technique for the preparation of a large number of heterocyclic compounds, in response to increasing interest from the pharmaceutical industry in the generation of diverse libraries of heterocyclic compounds.[4]

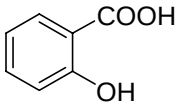
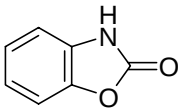
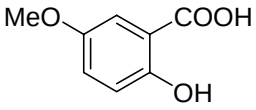
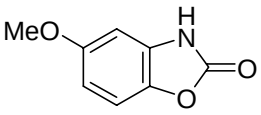
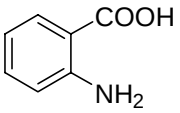
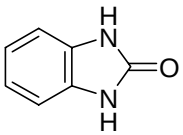
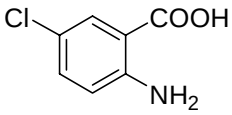
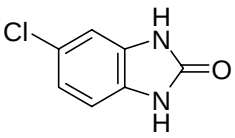
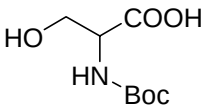
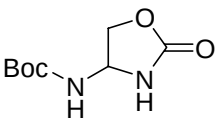
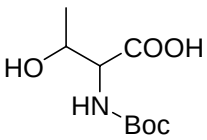
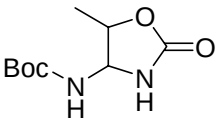
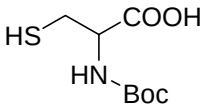
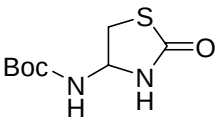
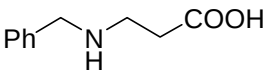
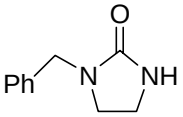
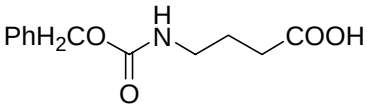
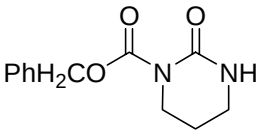
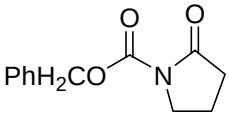
We have developed a polymer-supported diphenylphosphoryl azide (PS-DPPA, **1**) and have reported a series of Curtius rearrangement reactions, converting a variety of carboxylic acids to urethanes and ureas using this solid-phase reagent and various alcohols and amines.[5] The advantages of polymer-supported DPPA, such as moisture tolerance, lower toxicity and easier workup compared to the traditional methods are attractive. Herein, we report the syntheses of a variety of heterocyclic compounds using PS-DPPA (Table 1).



1, polymer-supported DPPA

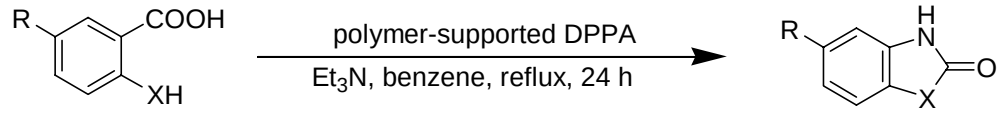
RESULTS AND DISCUSSION

Table 1. Heterocyclic derivatives synthesized by polymer-supported DPPA

Entry	Reactant	Product	Yield [a,b](%)
1			69[6]
2			53[7]
3			75[6]
4			64[8]
5			60[9]
6			59
7			67
8			53[10]
9			< 10[c]
			> 90[c]

[a] Isolated yields after column chromatography, based on fully azide loaded resin. [b] The spectral data of all the known compounds were identical to those reported in literature. [c] Ratio was obtained based on ^{1}H-NMR spectrometry.

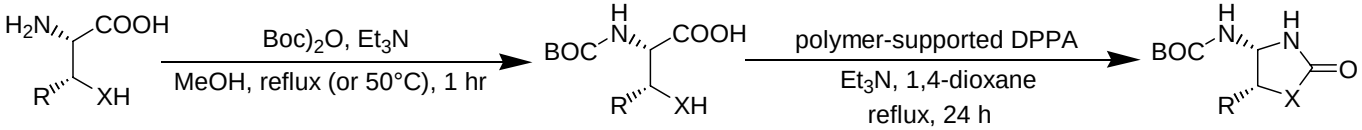
Salicylic acid, anthranilic acid and their derivatives were our first candidates for evaluation of cyclization with polymer-supported DPPA and triethylamine in benzene (Scheme 1, Entries 1-4). The two functional groups, carboxylic acid and hydroxyl (or amino) group, in the *ortho*-position are poised to form a five-membered ring following Curtius rearrangment. Since the azide loading on polymer beads is not normally assayed for each run, a slight excess of the acid is used. The reactions were heated to reflux for 24 hours. After workup, the crude products were obtained with acceptable quality (95% pure). Column chromatography was performed to obtain pure bicyclic oxazolidinone and imidazolidinone derivatives. The yields ranged from 53% to 75% after chromatography, based on the resin as the limiting reagent.



X = O, NH; R = H, OMe, Cl

Scheme 1

Encouraged by these results, further applications of polymer-supported DPPA were explored on various amino acids (Scheme 2, Entries 5-7). *L*-Serine, *L*-threonine and *L*-cysteine were selected because of their structural characteristics for forming five-membered rings. The free amino acids were first protected as BOC-derivatives following methods in the literature.[11] BOC-protected amino acids were used because they offer better solubility than free amino acids in organic solvents. Additionally, the bulky BOC group also reduced the possibility of intermolecular reactions, and increased the possibility of intramolecular reactions to form five-membered rings. The BOC-protected amino acids were heated with polymer-supported DPPA and triethylamine to reflux in 1,4-dioxane for 24 hours. Following the general workup procedure, the crude products were obtained in 98% purity. Purification by column chromatography afforded the pure oxazolidinone and thiazolidinone derivatives with yields form 59% to 67%. Considering the mechanism of Curtius rearrangement, the chiral centers in these amino acids should be retained. While the cyclization products are optically active, their optical purity was not assessed. In the case of threonine (R=CH_3, X=O), the diastereomer with the indicated *cis* orientation of substituents is the only product observed by NMR spectroscopy (based on coupling constant of 7.3 Hz).[12]

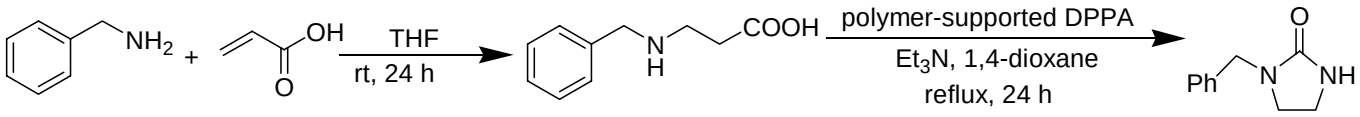


X = O, S; R = H, Me

Scheme 2

While the trapping of isocyanate formed in the Curtius rearrangement usually makes use of alcohols and primary amines, we investigated a secondary amine in our reaction (Scheme 3, Entry 8).

3-Benzylaminopropionic acid was prepared through the reported method,[13] and used directly. Heating with polymer-supported DPPA and triethylamine in 1,4-dioxane for 24 hours followed by workup and column chromatography purification afforded pure 1-benzylimidazolidin-2-one in 53% yield.



Scheme 3

In addition, *N*-CBZ-*γ*-amino-*n*-butyric acid was used in an attempt to form the six-membered ring system. However, lactam formation through intramolecular cyclization was the major product (> 90% from ^{1}H NMR spectrum, Entry 9). It would appear that trapping of the intermediate phosphoryl anhydride before rearrangement predominates when five membered ring formation can occur. In the previous entries, such a process would afford a β lactam, a clearly disfavored process.

In conclusion, by using the polymer-supported DPPA, *N*-heterocyclic compounds, such as oxazolidinone, imidazolidinone and thiazolidinone derivatives, could be synthesized successfully through Curtius rearrangement and subsequent cyclization with good yields. The immobilized DPPA may have considerable use in synthetic organic chemistry.

EXPERIMENTAL

All manipulations were performed in oven-dried glassware under a nitrogen atmosphere unless otherwise mentioned. All solvents and reagents were dried or purified using standard procedures and were distilled freshly before use. The standard workup included washing the reaction mixture with water followed by brine. The separated organic phase was dried over magnesium sulfate, and concentrated in *vacuo*. Column chromatography was performed on silica gel (Natland International Corp. 200 – 400 mesh) using the indicated solvents. TLC analyses were carried out using C4 silica gel plates (Silicycle Inc.). ^{1}H and ^{13}C NMR spectra were recorded on a 200 or 300 MHz FT-NMR spectrometer (Bruker Avance 200) in $CDCl_3$ or DMSO-d_6 (Aldrich). IR spectra were determined as neat film (using NaCl plate) or KBr pellet on a Perkin-Elmer 1600 FT-IR spectrophotometer. High-resolution MS spectra were performed on the Micromass LCT Electrospray mass spectrometer by the Mass Spectrometry and Protemics Facility, Ohio State University, Columbus, OH.

General procedure for the syntheses of five-membered cyclic urethane and urea derivatives. Polymer-supported DPPA[5] (1.0 eq., based on fully azide loaded resin), carboxylic acid derivative (1.2

eq.) and triethylamine (1.3 eq.) were mixed in a round-bottom flask with benzene or 1,4-dioxane (10 mL). The mixture was heated to reflux under a nitrogen atmosphere for 24 h. After cooling to rt, the resin was removed by filtration and washed with ethyl acetate (100 mL). The combined filtrates were washed with aqueous sodium hydroxide (1 M, 30 mL × 3), distilled water (30 mL × 3) and brine (30 mL). After drying over magnesium sulfate, solvent was removed under vacuum to afford the crude product.

Synthesis of 3*H*-benzooxazol-2-one (Entry 1). The general procedure was followed using polymer-supported DPPA (1.00 g, ~1.5 mmol), salicylic acid (0.25 g, 1.8 mmol) and triethylamine (0.20 g, 2.0 mmol) in benzene. Purification was performed on silica gel column chromatography (1:1 petroleum ether/ether) to give pure 3*H*-benzooxazol-2-one as a yellow solid (0.14 g, 69%, mp 107-109 ºC): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.07-7.21 (m, 4H), 9.95 (br, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 110.11, 110.24, 122.71, 124.20, 129.40, 143.86, 156.34. The spectral data were identical to the reported data.[6]

Synthesis of 5-methoxy-3*H*-benzooxazol-2-one (Entry 2). The general procedure was followed using polymer-supported DPPA (1.00 g, ~1.5 mmol), 5-methoxysalicylic acid (0.30 g, 1.8 mmol) and triethylamine (0.20 g, 2.0 mmol) in benzene. Purification was performed on silica gel column chromatography (1:1 petroleum ether/ ether) to give pure 5-methoxy-3*H*-benzooxazol-2-one as a white solid (0.13 g, 53%, mp 150-152 ºC): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.78 (s, 3H), 6.62 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.67 (d, *J* = 2.6 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 9.33 (br, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.94, 96.75, 107.85, 110.45, 129.97, 138.00, 156.35, 156.85. The spectral data were identical to the literature data.[7]

Synthesis of 1,3-dihydrobenzoimidazol-2-one (Entry 3). The general procedure was followed using polymer-supported DPPA (1.00 g, ~1.5 mmol), anthranilic acid (0.25 g, 1.8 mmol) and triethylamine (0.20 g, 2.0 mmol) in benzene. Purification was performed on silica gel column chromatography (1:2 petroleum ether/ether) to give pure 1,3-dihydrobenzoimidazol-2-one as a white solid (0.15 g, 75%, mp 166-169 ºC): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.90 (s, 4H), 10.56 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 108.44, 120.37, 129.66, 155.24. The spectral data were identical to the literature data.[6]

Synthesis of 1,3-dihydrobenzoimidazol-2-one (Entry 4). The general procedure was followed using polymer-supported DPPA (1.00 g, ~1.5 mmol), 5-chloroanthranilic acid (0.31 g, 1.8 mmol) and triethylamine (0.20 g, 2.0 mmol) in benzene. Purification was performed on silica gel column chromatography (1:2 petroleum ether/diethyl ether) to give pure 1,3-dihydrobenzoimidazol-2-one as a white solid (0.16 g, 64%, decomposes >300 ºC): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.88-6.99 (m, 3H),

10.76 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 108.38, 109.52, 120.11, 124.50, 128.63, 130.85, 155.22. The spectral data were identical to those reported in the literature.[8]

Synthesis of 2-oxooxazolidin-4-ylcarbamic acid *tert*-butyl ester (Entry 5). *L*-Serine (0.21 g, 2.0 mmol) reacted with di-*tert*-butyl dicarbonate (0.52 g, 2.4 mmol) in 10% solution (20 mL, 20mmol) of triethylamine in methanol to obtain BOC-protected serine.[11] The general procedure was followed using polymer-supported DPPA (1.00 g, ~1.5 mmol), BOC-protected serine (0.37 g, 1.8 mmol) and triethylamine (0.20 g, 2.0 mmol) in 1,4-dioxane. Purification was performed on silica gel column chromatography (1:1 petroleum ether/ ether) to give pure 2-oxooxazolidin-4-ylcarbamic acid *tert*-butyl ester as a white solid (0.18 g, 60%, mp 187 ºC): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.38 (s, 9H), 3.97 (dd, *J* = 9.2, 3.7 Hz, 1H), 4.43 (t, *J* = 8.8 Hz, 1H), 5.29 (m, 1H), 7.81 (d, *J* = 8.7 Hz, 1H), 8.22 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 28.16, 59.62, 68.98, 78.60, 154.65, 157.87. The spectral data were identical to those reported in the literature.[9]

Synthesis of 5-methyl-2-oxooxazolidin-4-ylcarbamic acid *tert*-butyl ester (Entry 6). *L*-Threonine (0.24 g, 2.0 mmol) was treated with di-*tert*-butyl dicarbonate (0.52 g, 2.4 mmol) in 10% solution (20 mL, 20 mmol) of triethylamine in methanol to obtain BOC-protected threonine.[11] The general procedure was followed using polymer-supported DPPA (1.00 g, ~1.5 mmol), BOC-protected threonine (0.39 g, 1.8 mmol) and triethylamine (0.20 g, 2.0 mmol) in 1,4-dioxane. Purification was performed on silica gel column chromatography (1:1 petroleum ether/ether) to give pure 5-methyl-2-oxooxazolidin-4-ylcarbamic acid *tert*-butyl ester as a white solid (0.19 g, 59%, mp 170-173 ºC): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.16 (d, *J* = 6.4 Hz, 3H), 1.38 (s, 9H), 4.68 (quint, *J* = 6.6 Hz, 1H), 5.22 (dd, *J* = 9.3, 7.3 Hz, 1H), 7.70 (d, *J* = 9.6 Hz, 1H), 8.02 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.00, 24.14, 62.32, 75.00, 78.40, 154.77, 157.63; FT-IR (cm^{-1}) ν_{max} 3346, 2938, 1752, 1715, 1681, 1514, 1385, 1231, 1161, 1101, 1074, 974, 877; HRMS (electrospray) *m*/*z* [M+Na^+] calcd for $C_9H_{16}N_2O_4Na^+$: 239.1008, found 239.0996.

Synthesis of 2-oxo-thiazolidin-4-ylcarbamic acid *tert*-butyl ester (Entry 7). *L*-Cysteine (0.24 g, 2.0 mmol) was treated with di-*tert*-butyl dicarbonate (0.52 g, 2.4 mmol) in 10% solution (20 mL, 20mmol) of triethylamine in methanol to obtain BOC-protected cysteine.[11] The general procedure was followed using polymer-supported DPPA (1.00 g, ~1.5 mmol), BOC-protected cysteine (0.40 g, 1.8 mmol) and triethylamine (0.20 g, 2.0 mmol) in 1,4-dioxane. Purification was performed on silica-gel column chromatography (2:1 to 1:1 petroleum ether/ether) to give pure 2-oxothiazolidin-4-ylcarbamic acid tert-butyl ester as a pale yellow solid (0.22 g, 67%, mp 201-203 ºC): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.39 (s, 9H), 3.11 (dd, *J* = 11.5, 3.9 Hz, 1H), 3.67 (dd, *J* = 11.5, 7.3 Hz, 1H), 5.34 (m, 1H), 7.88 (d, *J* =

7.7 Hz, 1H), 8.55 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 28.16, 34.72, 61.94, 78.56, 154.47, 171.69; FT-IR (cm^{-1}) ν_{max} 3364, 3228, 2923, 1679, 1659, 1499, 1356, 1214, 1155, 1027, 958, 846; HRMS (electrospray) *m*/*z* [M+Na^+] calcd for $C_8H_{14}N_2O_3NaS^+$: 241.0623, found 241.0607.

Synthesis of 1-benzylimidazolidin-2-one (Entry 8). Benzylamine (0.47 g. 4.4 mmol, 2.2 eq) and acrylic acid (0.14 g, 2.0 mmol, 1.0 eq.) were added into THF (10 mL) and stirred at rt for 24 h (white solid formed during stirring). After filtration, the white solid was partitioned between ether (30 mL) and NaOH solution (1 M, 30 mL). After separation, the aqueous phase was acidified with HCl (1 M) to pH = 2. The water was removed by rotary evaporation and dried under vacuum (0.1 mmHg) overnight. A mixture of 3-benzylaminopropionic acid and NaCl was obtained as white solid. This crude product was used directly in the subsequent reactions. The general procedure was followed using polymer-supported DPPA (1.00 g, ~1.5 mmol), 3-benzylaminopropionic acid (obtained above) and triethylamine (0.20 g, 2.0 mmol) in 1,4-dioxane. Purification was performed on silica gel column chromatography (ether) to give pure 1-benzylimidazolidin-2-one as a white solid (0.14 g, 53% yield, mp 178-180 ºC): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.24-3.30 (m, 2H), 3.35-3.40 (m, 2H), 4.34 (s, 2H), 5.03 (br, 1H), 7.22-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.03, 44.48, 47.62, 127.38, 128.01, 128.54, 137.08, 162.72. The spectral data were identical to those reported in the literature.[10]

ACKNOWLEDGEMENTS

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