Preparation of 2-azetidinones by cyclocondensation of carboxylic acids and imines via diphosphorustetraiodide

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ABSTRACT
One-pot mild synthesis of 2-azetidinones was carried out by the reaction of imines and carboxylic acids in dry dichloromethane at room temperature using diphosphorus tetraiodide. It was also applied for synthesis of 3-spiro-2-azetidinones. The synthesized compounds were characterized by analytical and spectral (infrared, $^1$H NMR, $^{13}$C NMR, and elemental analysis) data.

INTRODUCTION
Diphosphorus tetraiodide (P$_2$I$_4$) is a well-characterized, stable, crystalline solid that is a useful reagent in organic synthesis.$^{[1]}$ Several methods have been reported for synthesis of diphosphorus tetraiodide$^{[2,3]}$ and it is commercially available. It has been introduced for the synthesis of alkyl halides from alcohols,$^{[4]}$ amides from carboxylic acids and amines,$^{[5]}$ aldoximes from nitriles,$^{[2]}$ and nitriles from carboxylic acids$^{[6]}$ and for decarboxylative bromination.$^{[7]}$

The β-lactam (2-azetidinone) skeletal structure is the key component of the β-lactam antibiotics, which are the widespread antimicrobial agents. The β-lactam antibiotics include penicillins, cephalosporins, penems, carbapenems, monobactams, and others.$^{[8]}$ As a consequence of the antibiotic pressure, the emergence and dispersion of resistant bacterial strains increase dramatically through mutation and β-lactamase gene transfer, and then research efforts have to be devoted to the discovery of new antibacterial agents.$^{[9]}$ Recently, new and interesting biologically active substrates, based on the β-lactam (2-azetidinone) structure, have been reported,$^{[10]}$ including a cholesterol absorption inhibitor, ezetimibe, a new activity of 2-azetidinones for clinical use.$^{[11]}$ In addition, 2-azetidinones take place as intermediates in the synthesis of numerous organic compounds,$^{[12,13]}$ for example, in the semisynthesis of taxol derivatives.$^{[14]}$

There are several methods for synthesis of 2-azetidinones because of their immense importance to mankind.$^{[15,16]}$ The most frequently employed methodology for the
synthesis of the 2-azetidinone ring is the [2 + 2] ketene–imine cycloaddition (Staudinger reaction).[17–21] Although a number of methods for preparation of ketenes have been introduced, reaction of acyl halides with tertiary amines remains the most preparative and useful approach because of the availability of starting material.[22,23] Sometimes application of acyl halides shows unfavorable results such as poor stability, poor yield of product, and difficulties in handling and preparation.

For ketene generation without need of acid chlorides, activation of a carboxylic acid with acid activator reagents in the presence of a base has been reported.[24–42] Unfortunately some of these acid activators are unavailable and require harsh conditions or difficult purification of products. The need for low or high temperatures, inconvenient reaction conditions, and painful chromatographic separations for purification of products are disadvantages of some of these acid activators.

We observed that diphosphorus tetraiodide could be used at room temperature for the direct conversion of carboxylic acids and imines to the corresponding 2-azetidinones.

**Results and discussion**

For our initial studies, (4-methoxyphenyl)-1-phenylmethanimine 1a and phenoxyacetic acid were chosen as model substrates. A mixture of imine 1a, phenoxyacetic acid, diphosphorus tetraiodide, and triethylamine in anhydrous dichloromethane was stirred at room temperature overnight. After workup and purification by crystallization from ethyl acetate, 2-azetidinone 3a was isolated in 78\% yield.

The reactions were carried out in the presence of various anhydrous solvents and the results are presented in Table 1; dry dichloromethane showed the best result. When this reaction was performed at 0 °C in dry dichloromethane, the yield of 2-azetidinoe decreased to 51\%. For optimization of quantity of reagent, 1.0 mmol of imine and 1.5 mmol of phenoxyacetic acid have been used in entries 7–9. As shown in the table, the highest yield of 3a was obtained when 1.0 mmol of imine 1a reacted with 1.5 mmol of phenoxyacetic acid using 0.5 mmol of P 2I 4 in dry dichloromethane at room temperature (entry 9).

Encouraged by these results and optimization of reaction condition, we subjected various carboxylic acids and imines to the reaction, and the results are presented in Table 2.

**Table 1.** Optimization of condition in the synthesis of 3a using P 2I 4.

| Entry | Solvent | Temp. | Amount (mmol) of PhOCH 2CO 2H | Amount (mmol) of P 2I 4 | Isolated yield (\%) |
|-------|---------|-------|-------------------------------|------------------------|---------------------|
| 1     | CH 2Cl 2| rt    | 1.0                          | 1.0                    | 78                  |
| 2     | Toluene | rt    | 1.0                          | 1.0                    | 55                  |
| 3     | THF     | rt    | 1.0                          | 1.0                    | 36                  |
| 4     | CH 3CN  | rt    | 1.0                          | 1.0                    | 59                  |
| 5     | DMF     | rt    | 1.0                          | 1.0                    | 63                  |
| 6     | CH 2Cl 2| 0°C   | 1.0                          | 1.0                    | 51                  |
| 7     | CH 2Cl 2| rt    | 1.5                          | 1.0                    | 83                  |
| 8     | CH 2Cl 2| rt    | 1.5                          | 0.75                   | 84                  |
| 9     | CH 2Cl 2| rt    | 1.5                          | 0.5                    | 92                  |
2-Azetidinones 3a–j were obtained in good to excellent yields under mild condition at room temperature (Scheme 1, Table 2), which were purified by crystallization from EtOAc after simple aqueous workup.

The formation of 2-azetidinones were characterized by infrared (IR) spectra, which show characteristic C=O stretching vibration at 1739–1784 cm$^{-1}$ with the disappearance of vibration at about 1620 cm$^{-1}$ (C=N of imine). In the $^1$H NMR spectra, they show appearance of peak due to protons on carbon 3 and 4 of the 2-azetidinone ring (H-3 and H-4) observed from 5.05–5.35 and 5.26–5.66 ppm, respectively. The stereochemistry of them were assigned by the comparison of the coupling constant H-3 and H-4 ($J_{3,4} > 4.0$ Hz) for the cis stereoisomer and ($J_{3,4} \leq 3.0$ Hz) for the trans stereoisomer. [43–45]

In $^{13}$C NMR, the peaks appeared at about 164 ppm due to the carbonyl of 2-azetidinone ring.

Diphosphorus tetraiodide was successfully employed for the synthesis of spiro-2-azetidinones 5a,b. 2-Azetidinones 5a,b were easily obtained from xanthene-9-carboxylic acid 4 and imines in the presence of trimethylamine by this method and purified by crystallization from EtOAc (Scheme 2).

### Table 2. 2-Azetidinones from imines and carboxylic acids using diphosphorus tetraiodide.

| Entry | $R^1$   | $R^2$   | $R^3$   | cis/trans | Product  | Isolated yield (%) |
|-------|---------|---------|---------|-----------|----------|--------------------|
| 1     | 4-MeOC$_6$H$_4$ | C$_6$H$_5$ | PhO     | cis       | 3a       | 92                 |
| 2     | 4-MeOC$_6$H$_4$ | C$_6$H$_5$ | 2,4-Cl$_2$C$_6$H$_3$O | cis       | 3b       | 78                 |
| 3     | 4-MeOC$_6$H$_4$ | C$_6$H$_5$ | 4-ClC$_6$H$_4$O | cis       | 3c       | 91                 |
| 4     | 4-MeOC$_6$H$_4$ | C$_6$H$_5$ | MeO     | cis       | 3d       | 80                 |
| 5     | 4-MeOC$_6$H$_4$ | C$_6$H$_5$ | PhthN   | trans     | 3e       | 85                 |
| 6     | 4-ClC$_6$H$_4$ | 4-(NMe)$_2$C$_6$H$_4$ | PhO     | cis       | 3f       | 88                 |
| 7     | 4-ClC$_6$H$_4$ | 4-(NMe)$_2$C$_6$H$_4$ | 2,4-Cl$_2$C$_6$H$_3$O | cis       | 3g       | 85                 |
| 8     | 4-ClC$_6$H$_4$ | 4-(NMe)$_2$C$_6$H$_4$ | 4-ClC$_6$H$_4$O | cis       | 3h       | 90                 |
| 9     | 4-ClC$_6$H$_4$ | 4-(NMe)$_2$C$_6$H$_4$ | MeO     | cis       | 3i       | 81                 |
| 10    | 4-ClC$_6$H$_4$ | 4-(NMe)$_2$C$_6$H$_4$ | PhthN   | trans     | 3j       | 88                 |

Scheme 1. Synthesis of 2-azetidinones 3a–j.

Scheme 2. Synthesis of spiro-2-azetidinones 5a,b.
Conclusions

In conclusion, a novel method has been developed for direct conversion of carboxylic acids and imines to the corresponding 2-azetidinones using diphosphorus tetraiodide in the presence of triethylamine in anhydrous dichloromethane at room temperature. The method is mild and gave good to excellent yields of 2-azetidinones without need for column chromatography.

Experimental

All required chemicals were purchased from Merck, Fluka, and Acros chemical companies. The melting points were determined on a Buchi 535 apparatus. IR spectra were measured on a Shimadzu FT-IR 8300 spectrophotometer. NMR spectra were recorded on a Bruker spectrometer (\(^{1}\)H NMR 250 MHz, \(^{13}\)C NMR 62.9 MHz) using tetramethylsilane as an internal standard and coupling constants are given in cycles per second (Hz). Elemental analyses were run on a Vario EL III elemental analyzer. Thin-layer chromatography (TLC) was carried out on silica-gel 254 analytical sheets obtained from Fluka. Data for new products have been reported in this paper.

General procedure for the synthesis of 2-azetidinones (3a–J and 5a,b)

Diphosphorus tetraiodide (0.5 mmol) was added to a solution of substituted acetic acids (1.5 mmol), imines (1.0 mmol), and triethylamine (5.0 mmol) in dry CH\(_2\)Cl\(_2\) (20 ml) at room temperature and the mixture was stirred overnight. The reaction mixture was washed successively with saturated NaHCO\(_3\) (15 ml) and brine (15 ml). The organic layer was dried (Na\(_2\)SO\(_4\)) and filtered, and the solvent was removed to give the crude product, which was purified by crystallization from EtOAc to give pure \(\beta\)-lactams 3a–j and 5a,b.

3-(4-Chlorophenoxy)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (3c)

White solid, mp 177–179 °C. IR (KBr) cm\(^{-1}\): 1749 (CO, \(\beta\)-lactam). \(^{1}\)H NMR δ 3.79 (MeO, s, 3H), 5.35 (H-4, d, 1H, J = 4.4), 5.61 (H-3, d, 1H, J = 4.4), 6.86–7.28 (ArH, m, 13H); \(^{13}\)C NMR δ 56.0 (MeO), 63.0 (C-4), 80.6 (C-3), 114.4–156.3 (aromatic carbons), 163.0 (CO, \(\beta\)-lactam). Anal. calcd. for C\(_{22}\)H\(_{18}\)ClNO\(_3\): C, 69.57; H, 4.78; N, 3.69. Found: C, 69.70; H, 4.86; N, 3.74.

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