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

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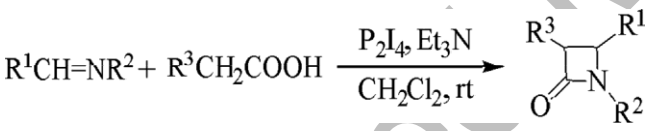
Abstract

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 (IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis) data.



KEYWORDS: β-Lactam, 2-Azetidinone, Staudinger reaction, Diphosphorustetraiodide, Ketene, Imine

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INTRODUCTION

Diphosphorus tetraiodide (P_2I_4) is a well characterized, stable, crystalline solid which it is useful reagent in organic synthesis.[1] Although several methods has been reported for synthesis of diphosphorus tetraiodide[2-3] but 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]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, and 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 interesting biologically active substrates, based on β-lactam (2-azetidinone) structure, have been reported[10] which cholesterol absorption inhibitor in Ezetimibe is 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 semi-synthesis 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] But, sometimes application of acyl halides shows unfavorable results such as low stability, low yield of product, and difficulties in handling and preparation.

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Then for ketene generation without need to acid chlorides, activation of a carboxylic acid with acid activator reagents in the presence of a base have been reported.[24-42]Unfortunately some of these acid activators are unavailable and require harsh conditions and diffucult purification of products. Need 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 acidwas 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 work-up 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 which dry dichloromethane showed the best result. When this reaction performed at 0 ^{o}C in dry dichlromethane, 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 entry 7-9. As it is shown in the table, the highest

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yield of **3a** was obtained when 1.0 mmol of imine **1a** react with 1.5 mmolphenoxyacetic 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. 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 work-up.

The formation of 2-azetidinones were characterized by 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 ^1H NMR spectra, they show appearance of peak due to proton 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 carbonyl of 2-azetidinoe 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 triethylamineby this method and purified by crystallization from EtOAc (Scheme 2).

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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 to 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 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_2Cl_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

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was dried (Na_2SO_4), filtered and the solvent was removed to give the crude product, which was purified by crystallization from EtOAc to give pure β-lactams **3a-j** and **5a-b**.

3-(4-Chlorophenoxy)-1-(4-Methoxyphenyl)-4-Phenylazetidin-2-One (3c)

White solid.m.p: 177-179 °C. IR (KBr) cm^{-1}: 1749 (CO, β-lactam). ^1H 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, β-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.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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REFERENCES

1. Moeller, T.; Hufieey, J. E. *J. Inorg. Nucl. Chem.* **1962**, *24*, 315.
2. Suzuki, H.; Fuchita, T.; Iwasa, A.; Mishina, T. *Synhtesis* **1978**, 905.
3. Groh, M. F.; Mueller, U.; Ahmed, E.; Rothenberger, A.; Ruck, M. Z. *Natureforsch. B* **2013**, *68*, 1108.

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4. Regnier, L. B.; Van Eenoo, M.; Denis, J. N.; Krief, A. *Tetrahedron Lett.* **1979**, *20*, 1801.

5. Suzuki, H.; Tsuji, J.; Hiroi, Y.; Sato, N.; Osuka, A. *Chemistry Lett.* **1983**, *4*, 449.

6. Telvekar, V. N.; Rane, R. A. *Tetrahedron Lett.* **2007**, *48*, 6051.

7. Telvekar, V. N.; Chettiar, S. N. *Tetrahedron Lett.* **2007**, *48*, 4529.

8. Hwu, J. R.; Ethiraj, S. K.; Hakimelahi, G. H. *Mini-Rev. Med. Chem.* **2003**, *3*, 305.

9. Dive, G.; Bouillon, C.; Sliwa, A.; Valet, B.; Verlaine, O.; Sauvage, E.; Marchand-Brynaert, J. *Eur. J. Med. Chem.* **2013**, *64*, 365.

10. Mehta, P. D.; Sengar, N. P. S.; Pathak, A. K. *Eur. J. Med. Chem.* **2010**, *45*, 5541.

11. Clader, J. W. *Curr. Top. Med. Chem.* **2005**, *5*, 243.

12. Palomo, C.; Oiarbide, M. *in Topics in Heterocyclic Chemistry*, Banik, B. K. (Ed.), Springer-Verlag; Berlin, **2010**, Vol. 22, pp 211-259.

13. Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437.

14. Suffness, M. *Taxol Science and Applications*, CRC Press, Boca Raton, Florida, USA, **1995**.

15. Abdellaoui, H.; Xu, J. *Tetrahedron.* **2014**, *70*, 4323.

16. Pitts, C. R.; Lectka, T. *Chem. Rev.* **2014**, *114*, 7930.

17. Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oirabide, M. *Eur. J. Org. Chem.* **1999**, *8*, 3223.

18. Jarrahpour, A.; Zarei, M. *Molecules* **2007**, *12*, 2364.

19. Keri, R. S.; Hosamani, K. M.; Shingalapur, R. V.; Reddy, H. R. S. *Eur. J. Med. Chem.***2009**, *44*, 5123.

20. Jarrahpour, A.; Fadavi, A.; Zarei, M. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 320.

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21. Zarei, M. *J. Chem. Res.* **2012**, *36*, 118.

22. Tidwell, T. T. *Ketenes II*. John Wiley & Sons, New Jersey, **2006**, pp 55-192.

23. Bellus, D.; Danheiser, R. L. In: *Science of Synthesis*, Danheiser, R. L. (Eds), **2006**, Vol. 23, Thieme, Stuttgart, Germany.

24. Zarei, M. *J. Chem. Res.* **2013**, *37*, 25.

25. Khademi Shiraz, A.; Zarei, M. *Monatsh. Chem.* **2015**, *146*, 941.

26. Zarei, M. *Lett. Org. Chem.* **2015**, *12*, 44.

27. Zarei, M.; Jarrahpour, A. *Heterocycl. Commun.* **2014**, *20*, 355.

28. Jarrahpour, A.; Heiran, R. *J. Iran. Chem. Soc*. **2014**, *11*, 75.

29. Zarei, M. *Monatsh. Chem.* **2013**, *144*, 1021.

30. Nahmany, M.; Melman, A. *J. Org. Chem.* **2006**, *71*, 5804.

31. Jarrahpour, A.; Zarei, M. *Tetrahedron Lett.* **2007**, *48*, 8712.

32. Zarei, M.; Jarrahpour, A. *Synlett.* **2011**, 2572.

33. Zarei, M. *Tetrahedron Lett.* **2014**, *55*, 5354.

34. Jarrahpour, A.; Zarei, M. *Tetrahedron Lett.* **2009**, *50*, 1568.

35. Jarrahpour, A.; Zarei, M. *Tetrahedron.* **2009**, *65*, 2927.

36. Zarei, M. *Monatsh. Chem.* **2014**, *145*, 1495.

37. Darvishi, A.; Zarei, M.; Akhgar, M. R. *Lett. Org. Chem.* **2013**, *10*, 645.

38. Zarei, M.; Mohamadzadeh, M. *Tetrahedron.* **2011**, *67*, 5832.

39. Matsui, S.; Hashimoto, Y.; Saigo, K. *Synthesis* **1998**, 1161.

40. Zarei, M. *Tetrahedron.* **2013**, *69*, 6620.

41. Jarrahpour, A.; Zarei, M. *Tetrahedron.* **2010**, *66*, 5017.

42. Zarei, M. *Bull. Chem. Soc. Jpn.* **2012**, *85*, 360.

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43. Georg, G. I. *The Organic Chemistry of β-Lactams*, Verlag Chemie, New York, 1993.

44. Zarei, M.; Karimi-Jaberi, Z.; Movahedi, A. *Synth. Commun*. **2013**, *43*, 728.

45. Jarrahpour, A.; Motamedifar, M.; Zarei, M.; Mimouni, M. *Phosphorus Sulfur and Silicon* **2010**, *185*, 287.

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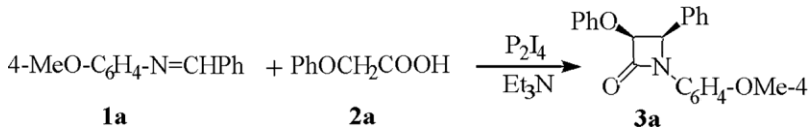
Table 1. Optimization of condition in the synthesis of **3a** using P_2I_4



1a **2a** **3a**

Entry	Solvent	Temp	mmol $PhOCH_2CO_2H$	mmol 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 ^oC	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

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

Entry	R^1	R^2	R^3	*cis/trans*	Product	Isolated yield (%)
1	4-$MeOC_6H_4$	C_6H_5	PhO	*cis*	**3a**	92
2	4-$MeOC_6H_4$	C_6H_5	2,4-$Cl_2C_6H_3O$	*cis*	**3b**	78
3	4-$MeOC_6H_4$	C_6H_5	4-ClC_6H_4O	*cis*	**3c**	91
4	4-$MeOC_6H_4$	C_6H_5	MeO	*cis*	**3d**	80
5	4-$MeOC_6H_4$	C_6H_5	PhthN	*trans*	**3e**	85
6	4-ClC_6H_4	4-$(NMe_2)C_6H_4$	PhO	*cis*	**3f**	88
7	4-ClC_6H_4	4-$(NMe_2)C_6H_4$	2,4-$Cl_2C_6H_3O$	*cis*	**3g**	85
8	4-ClC_6H_4	4-$(NMe_2)C_6H_4$	4-ClC_6H_4O	*cis*	**3h**	90
9	4-ClC_6H_4	4-$(NMe_2)C_6H_4$	MeO	*cis*	**3i**	81
10	4-ClC_6H_4	4-$(NMe_2)C_6H_4$	PhthN	*trans*	**3j**	88

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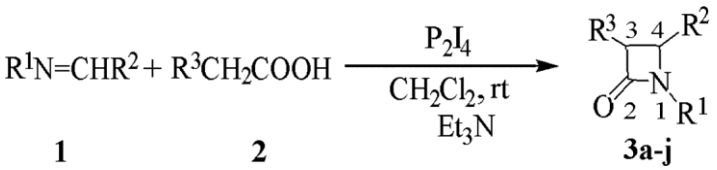
Scheme 1. Synthesis of 2-azetidinones **3a-j**



1 **2** **3a-j**

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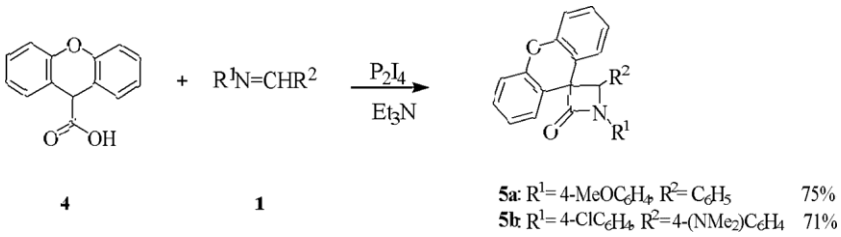
Scheme 2.



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5a: R^1= 4-$MeOC_6H_4$, R^2= C_6H_5 75%
5b: R^1= 4-ClC_6H_4, R^2=4-$(NMe_2)C_6H_4$ 71%

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