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A FACILE SYNTHESIS OF NEW PYRROLO [2,3-*d*] ISOXAZOLES BY UNEXPECTED RING OPENING OF AZIRIDINES

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Abstract

Phosphomolybdic acid (PMA, $H_3PMo_{12}O_{40}$) is found to be an efficient catalyst for aziridation of aminostyrylisoxazoles in the presence of inexpensive Chloramine-T as a nitrogen source. The initially formed unisolated aziridine underwent unexpected ring opening by attack of amino nucleophile, leading to the formation of a new N-C bond, ultimately producing pyrrole ring to give title compounds.

Keywords: Phosphomolybdic acid catalyst, Chloramine-T as a nitrogen source, opening of aziridine ring, facile synthesis, pyrrolo[2,3-*d*]isoxazoles

Introduction

Nitrogen-containing heterocycles are ubiquitous motifs[1] of biologically active compounds, such as alkaloids. Consequently, the formation of nitrogen-carbon bond is of utmost importance, and many classical methods exist, such as reductive cyclization[2] and de-oxygenative cyclization[3] for N-C bond formation. Furthermore, powerful metal-catalyzed amidation of aryl halides have been recently added to the armory of the synthetic chemist[4] for N-C bond formation. These methods rely on the presence and elaboration of functional groups, which is a common feature in organic synthesis.

Aziridine, an important three-membered hetrocyclic ring, represent a valuable class of useful and highly versatile synthon for several biologically important compounds such as amino acids, amino sugars and alkaloids[5]. Due to the intrinsic high strain of aziridine ring, this is capable of undergoing nucleophilic ring opening reactions leading to the formation of a wide variety of nitrogen-containing heterocyclic compounds [6,7] Aziridation of olefins can be achieved either by transition-metal catalyzed reaction of olefin with nitrene[8] (generated *in situ*) or with Chloramine-T[9,11] and bromamine-T[12] (nitrogen source). But these procedures suffer one or more disadvantages, which include use of hazardous or expensive reagents, longer reaction time, low yields, and besides this, they require large excess of substrate (olefin).

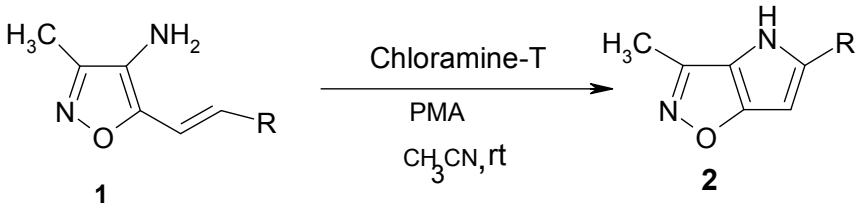
Heteropolyacids(HPA) are solid acids, which can act as bifunctional catalyst and possess high activity and selectivity, when compared to conventional catalysts and they are green catalysts. As a result, a variety of organic functional group transformations has been developed using HPA as catalysts. These include Fries rearrangement[13], Friedel-craft acylation[14], oxidation

of alcohols[15] and epoxidations[16]. HPA is found to be an efficient catalyst for aziridation of olefins in the presence of inexpensive Chloramine-T as a nitrogen source[17]. This prompted us to investigate a practical and simple protocol for aziridation of olefin. As a sequel to our study on biologically active isoxazoles green synthesis[18-22], in this article, we describe an unexpected ring opening of aziridine, leading to the synthesis of pyrrolo[2,3-*d*]isoxazoles by employing a simple approach with PMA catalyst using inexpensive Chloramine-T. Pyrrole derivatives are important in organic synthesis, because they are present in many natural, medicinal, agricultural products and also found in various bioactive drug molecules such as atorvartin, anti-inflammatories, antitumor agents and immunosuppressants[23]. In view of this, the title compounds synthesis is more significant, which are produced unexpectedly during our reaction.

Results and Discussion

To investigate the scope of the PMA catalyzed aziridation reaction, several aminostyrylisoxazoles were examined. Actually, we intended to get aziridne ring by the reaction of olefin with Chloramine-T (nitrogen source). To our surprise, the reaction led to the formation of pyrrole[2,3-*d*]isoxazole, probably by the ring opening of strained aziridine resulting in a pyrrole ring. So, ultimately we could achieve the synthesis of pyrrolo[2,3-*d*]isoxazoles by a green protocol, which is otherwise difficult to prepare, and involves tedious procedures. Gorugantula *et al*.[24] did not achieve the synthesis of pyrrolo[2,3-*d*]isoxazoles by reductive *N*-heterocyclization of nitrostyrylisoxazoles with $Pb(dba)_2$ eventhough they reported cyclization of several heterocyclic nitrostyryl compounds. We earlier reported the synthesis of pyrrolo[2,3-*d*] isoxazoles by de-oxygenative cyclization of nitrostyrylisoxazoles[25] and by Sharpless epoxidation of aminostyrylisoxazoles[26]. But, these methods involve utilization of expensive and toxic reagents and the method is costlier and not environmentally benign. In view of this, our present protocol is a valuable method for the synthesis of new pyrrole[2,3-*d*]isoxazoles, as it involves inexpensive reagent and catalyst, and the reaction is conducted at ambient temperature.

In a typical experiment, 4-amino-3-methyl-5-heterostyrylisoxazole **1**[27] is reacted with Chloramine-T in presence of PMA, in CH_3CN and neutral buffer (pH 6.86, phosphate buffer) in 1:1 ratio was employed as the solvent for the reaction, because of the poor solubility of Chloramine-T in acetonitrile at room temperature, under N_2 atmosphere to afford 3-methyl-5-heteryl-4*H*-pyrrolo[2,3-*d*]isoxazole **2** in excellent yields **(Scheme-I)**.



1 **2**

2a, R = 2-napthyl

2b, R = 2-furyl

2c, R = 2-pyrrolyl

2d, R = 2-thienyl

2e, R = 2-pyridyl

2f, R = 3-indolyl

2g, R = 4-pyrazolyl

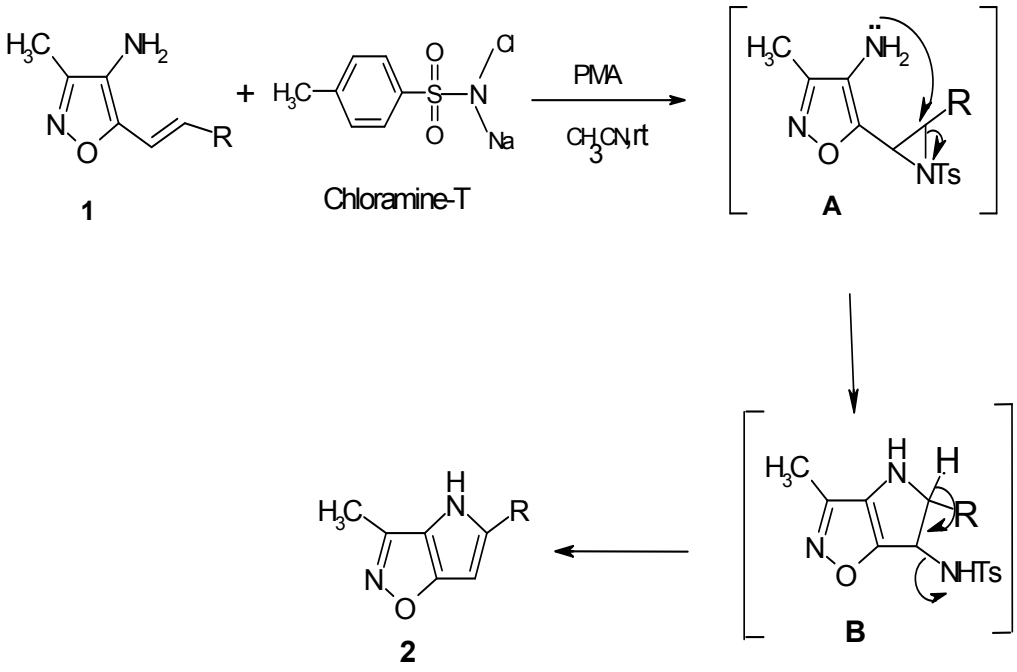
2h, R = 1-isoquinolyl

2i, R = 5-thiadiazolyl

Scheme I

Encouraged by this result, we further examined the scope of this methodology by conducting the reaction with a variety of aminoheterostyrylisoxazoles. A diverse set of pyrrolo [2,3-*d*]isoxazoles **2** possessing different heterocyclic systems such as furan, pyrrole, thiophene, indole, pyrazole rings etc., were synthesized under optimized conditions (Table 1, entries **2a-i**). Having these results in hand, we further studied the reaction by using different catalysts such as PMA, $H_3PW_{12}O_{40}$ and MoO_3, and the best result was obtained with PMA (Table 2, entries 1-4). In the absence of Chloramine-T, the reaction did not yield the product. Different solvents such as diethyl ether, THF, 1,4-dioxane, and CH_3CN were also employed in order to study the effect of the solvent on this reaction. CH_3CN is proved to better as in the presence of neutral buffer it produced higher yields compared to other solvents (Table 3, entries 1-4).

The reaction initially involves the formation of unisolated aziridine **A**, which is subsequently ring-opened by an attack of the amino group to give unisolated dihydropyrrole **B**. **B** could undergo deamination to give the product **2 (Scheme II).**



Scheme II

All the compounds **2a-i**, are reported for the first time. All of the structures were characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data.

Due to the biological significance of fused pyrroles, our synthetic strategy resulting in a variety of pyrrolo[2,3-*d*]isoxazoles substituted with different heterocycles is an attractive feature and the newly synthesized compounds may be future drug candidates. Finally, the results indicate that our method is compatible with various heterocyclic rings and the approach proved to be of general applicability. To the best of our knowledge, this report is the first of its kind to construct a pyrrole ring by opening of aziridine ring in a single step.

In conclusion, we have demonstrated a simple procedure for the synthesis of different heterocyclic substituted pyrrolo[2,3-*d*] isoxazoles by using PMA/ Chloramine-T as inexpensive efficient catalyst and reagent. Short reaction times, easy work-up, and conducting the reaction in one-step at ambient temperature are some advantages of this protocol.

Experimental Section

All the melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Analytical TLC was performed on Merck precoated 60 F_{254} silica gel plates. Visualization was done by exposure to iodine vapour. IR spectra (KBr pellet) were recorded on a Perkin-Elmer BX series FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. ^{13}C NMR spectra were recorded on a Bruker 75 MHz spectrometer. Chemical shift values are given in ppm (δ) with tetramethyl silane as an internal standard. Mass spectral measurements were carried out by EI method on a Jeol JMC-300 spectrometer at 70eV. Elemental analyses were performed on a Carlo Erba 106 and Perkin-Elmer model 240 analyzers.

General procedure for the synthesis of pyrrolo[2,3-*d*]isoxazoles 2a-i

To a mixture of aminostyryl isoxazole (1 mmol) in CH_3CN and neutral buffer (5mL/ 5 mL) PMA (0.1 equiv.), Chloramine-T (1.1 equiv.), is added under nitrogen atmosphere and stirred at room temperature for 1.0 to 1.5h. After the completion of the reaction as indicated by TLC, the reaction mixture is filtered through Celite and concentrated under reduced pressure and purified by column chromatography over silica gel by eluting with ethylacetate: hexane (30:70) to give the pure product.

Compound 2a : IR (KBr): 3300, 1610, 980; ^{1}H NMR ($CDCl_3$, 300MHz) : δ 2.52 (s, 3H), 7.40-7.75 (m, 7H), 7.80 (s, 1H), 7.95 (s, 1H, D_2O exchangeable), ^{13}C NMR ($CDCL_3$, 75MHz) : δ 12.0, 100.2, 110.5, 126.2, 126.8, 127.2, 128.0, 128.8, 130.5, 131.2, 132.8, 133.5, 136.0, 138.0, 143.5, 152.5. MS (EI): *m/z* 249 $[M+H]^+$.

Compound 2b : IR (KBr): 3315, 1620, 980; ^{1}H NMR ($CDCl_3$, 300MHz) : δ 2.50 (s, 3H), 6.1-7.0 (m, 3H), 7.35 (s, 1H), 8.05 (s, 1H, D_2O exchangeable), ^{13}C NMR ($CDCl_3$, 75MHz) : δ 11.0, 105.6, 110.8, 119.2, 120.5, 139.8, 142.3, 150.6, 152.5, 156.7. MS (EI) : *m/z* 189 $[M+H]^+$.

Compound 2c : IR (KBr): 3275, 1600, 980; ^{1}H NMR ($CDCl_3$, 300MHz) : δ 2.40 (s, 3H), 6.60-7.15 (m, 3H), 7.60 (s, 1H), 7.80 (s, 1H, D_2O exchangeable), ^{13}C NMR (CDCl3, 75MHz) : δ 11.5, 100.5, 110.8, 118.5, 119.5, 128.0, 135.0, 139.9, 150.2, 156.2. MS (EI) : *m/z* 188 $[M+H]^+$.

Compound 2d : IR (KBr) : 3320, 1575, 980; ^{1}H NMR ($CDCl_3$, 300MHz) : δ 2.40 (s, 3H), 7.00-7.25 (m, 3H), 7.50 (s, 1H), 7.90 (s, 1H, D_2O exchangeable), M S (EI) : *m/z* 205 $[M+H]^+$.

Compound 2e : IR (KBr) : 3285, 1610, 975; ^{1}H NMR ($CDCl_3$, 300MHz) : δ 2.50 (s, 3H), 7.61 (s, 1H), 7.72-8.65 (m, 4H), 8.00 (s, 1H, D_2O exchangeable), MS (EI) : *m/z* 200 $[M+H]^+$.

Compound 2f : IR (KBr) : 3310, 3215, 1615, 980; ^{1}H NMR ($CDCl_3$, 300MHz) : δ 2.42 (s, 3H), 7.10-7.76 (m, 5H), 7.71 (s, 1H), 8.10 (s, 1H, D_2O exchangeable), 8.55 (s, 1H, D_2O exchangeable), MS (EI) : *m/z* 238 $[M+H]^+$.

Compound 2g : IR (KBr) : 3375, 3220, 1600, 980; ^{1}H NMR ($CDCl_3$, 300MHz) : δ 2.52 (s, 3H), 7.20-7.32 (m, 2H), 7.52 (s, 1H), 7.90 (s, 1H, D_2O exchangeable), 8.25 (s, 1H, D_2O exchangeable), MS (EI) : *m/z* 189 $[M+H]^+$.

Compound 2h : IR (KBr) : 3310, 1585, 980; ^{1}H NMR ($CDCl_3$, 300MHz) : δ 2.48 (s, 3H), 7.52-8.70 (m, 6H), 7.41 (s, 1H), 8.90 (s, 1H, D_2O exchangeable), MS (EI) : *m/z* 250 $[M+H]^+$.

Compound 2i : IR (KBr): 3300, 1615, 980; ^{1}H NMR ($CDCl_3$, 300MHz) : δ 2.52 (s, 3H), 7.55 (s, 1H), 8.05 (s, 1H) 8.20 (s, 1H, D_2O exchangeable), MS (EI) : *m/z* 207 $[M+H]^+$.

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Table — I Characterization data of pyrrolo[2,3-*d*] isoxazoles using different 4-amino-3-methyl-5-heterostyrylisoxazoles **2a-i**

Compd	R	M.P (^{o}C)	Yield (%)	Time(h)	Mol.Formula	Found(%) (calcd)		
						C	H	N
2a	2-napthyl	140-142	75	1.0	$C_{16}H_{12}N_2O$	77.36 (77.41	4.90 4.83	11.33 11.29)
2b	2-furyl	130-133	75	1.15	$C_{10}H_8N_2O_2$	63.76 (63.82	4.30 4.25	14.94 14.89)
2c	2-pyrrolyl	170-175	60	1.50	$C_{10}H_9N_3O$	64.22 (64.17	4.88 4.81	22.40 22.45)
2d	2-thienyl	140-143	73	1.25	$C_{10}H_8N_2OS$	58.85 (58.82	3.89 3.92	13.76 13.72)
2e	2-pyridyl	150-155	65	1.50	$C_{11}H_9N_3O$	66.29 (66.33	4.49 4.52	21.14 21.10)
2f	3-indolyl	175-179	62	1.30	$C_{14}H_{11}N_3O$	70.84 (70.88	4.69 4.64	17.74 17.72)
2g	4-pyrazolyl	196-199	64	1.20	$C_9H_8N_4O$	57.40 (57.44	4.28 4.25	29.65 29.62)
2h	1-isoquinolyl	153-157	70	1.45	$C_{15}H_{11}N_3O$	72.24 (72.28	4.45 4.41	16.82 16.86)
2i	5-thiadiazolyl	145-149	61	1.30	$C_8H_6N_4OS$	(46.58 (46.60	2.88 2.91	27.21) 27.18)

Table —II Optimization of reaction conditions for entry **2a-i** of Table **I**

Entry	Catalyst (0.1)equiv)	Nitrogen source (1.1 equiv.)	Solvent	Yield (%)[a]
1	PMA	_	CH_3CN/neutral buffer[b]	_
2	PMA	Chloramine-T	CH_3CN/neutral buffer	90
3	$H_3PW_{12}O_{40}$	Chloramine-T	CH_3CN/neutral buffer	48
4	MoO_3	Chloramine-T	CH_3CN/neutral buffer	30

[a]Isolated yields, [b]pH 6.86, Phosphate pH standard solution.

Table — III Study of solvent effect on entry **4** of Table **II**

Entry	Solvent	Yield(%)[a]
1	Diethyl ether/neutral buffer[b]	30
2	Tetrahydrofuran/neutral buffer	42
3	1,4 Dioxane/neutral buffer	50
4	Acetonitrile/neutral buffer	90

[a]Isolated yields, [b]pH 6.86, Phosphate pH standard solution.

References:

1. A. H. Lipkus, Q. Yuan, K. A. Lucas, S. A. Funk, W. F. Bartelt III, R. J. Schenck, A. J. Trippe, *J. Org. Chem*, **73**, 4443 (2008).
2. A. Stefanachi, F. Leonetti, A. Cappa, A. Carothi, *Tetrahedron Lett*, **44**, 2121 (2003),.
3. R. Sudberg, *J. Org. Chem*, **30**, 3604 (1965). (b) C. P. Rao, V. K. Rao,V. Sundaramurthy, *Synthesis*, **3**, 234 (1981). (c) R. S. Mali, V. J. Yadav. *Synthesis,* **10**, 862 (1984).
4. A. Klapars, X. Huang, S. L. Buchwald,. *J.Am. Chem. Soc*, **124**, 7421 (2002).(b) T .Ikawa, T E.Barder, M R.Biscoe, S L. Buchwald, *J.Am.Chem.Soc*. **129**, 13001 (2007).
5. D. Tanner, *Angew Chem Int Ed*. **33**, 599 (1994).
6. X E. Hu, *Tetrahedron*, **60**, 2701 (2004).
7. V. H. Dahanukar, I. A. Zavialov, *Current Opinion in Drug Discovery and Development*.

5, 918 (2002).
8. D. A. Evans, M. M. Faul, M. T. Bioldeau, *J. Am. Chem. Soc*. **116**, 2742 (1994).
9. T. Ando, S. Minaketa, I. Ryu, M. Komatsu, *Tetrahedron Lett***. 39**, 309 (1998).
10. P. Brandt, M. J. Sudergren, P. G. Anderson, P. O. Norrby, *J. Am. Chem. Soc*. **122**, 8013 (2000).
11. S. Minakata, D. Kano, Y. Oderatoshi, M. Komatsu, *Angew Chem Int Ed*. **43**, 79 (2003).
12. B. M. Chanda, R. Vyas, A. V. Bedekar, *J. Org. Chem*. **66**, 30 (2001).
13. F. Kozhevinkova, E. G. Derouane, I. V. Kozhevinkov, C*hem. Commun*. 1178 (2002).
14. J. Kaur, K. Griffin, B. Harrison, I. V. Kozhevinkov, *Catal*. **208**, 448 (2002).
15. H. Firouzabadi, N. Iranpoor, K. Amani, *Synthesis*. 408 (2003).
16. Y. Ishii, K. Yamawaki, T. Ura, H. Yamada, T.Yoshid, M. Ogawa, *J. Org. Chem*, **53**, 3587 (1988).
17. G. D. K. Kumar, S. Baskaran, *Chem. Commun*. 1026 (2004).
18. E. Rajanarendar, Md. Afzal, K. Ramu, *Indian. J. Chem*. **44B**, 376 (2005).
19. E. Rajanarendar, P. Ramesh, M. Srinivas, K. Ramu, G. Mohan, *Synth. Commun*. **36**, 665 (2006).
20. E. Rajanarendar, G. Mohan, Ramesh, P. Srinivas, M. *J. Hetrocyclic. Chem.* **44**, 215 (2007).
21. E. Rajanarendar, P. Ramesh, E. Kalyan Rao, G. Mohan, M. Srinivas, *Arkivoc,* **xiv**, 266 (2007).
22. E. Rajanarendar, M. Nagi Reddy, K. Ramamurthy, *Chinese Chem. Lett*. **21**, 927(2010).
23. (a) C.Y. De Leon, B. Ganem, *Tetrahedron*. **53**, 7731 (1997). (b) P. Cozzi, N. Monpelli, *Curr. Pharm. Dis*. **4**, 181 (1998). (c) A. Furstner, H. Szillat, B. Gabor, R. Mynott, *J.Am. Chem. Soc*, **120**, 8305 (1998). (c) J. M. Muchowski, *Adv. Med. Chem*. **1**, 109 (1992).
24. S.P. Gorugantula, G. M. Carrero-Martinez, S.W. Dantale, B. C. G. Soderberg, *Tetrahedron*. **66**, 1800 (2010).
25. E. Rajanarendar, S. Raju, A. Siva Rami Reddy, K. Govardhan Reddy, M. Nagi Reddy, *Chem. Pharm. Bull*. **58(6)**, 833 (2010).
26. E. Rajanarendar, G. Mohan, P. Ramesh, D. Karunakar, *Tetrahedron Lett*. **47**, 957 (2006).
27. A. K. Murthy, K. S. R. K. M. Rao, N. V. S. Rao, *J. Indian Chem. Soc*. **53**, 1047 (1976).

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