International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2013): 6.14 | Impact Factor (2013): 4.438

Efficient One-Pot Synthesis of Fused Isoxazolo [5,4-b] Pyridines

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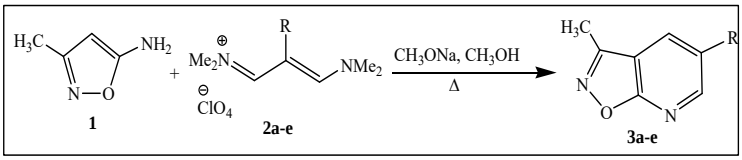
Abstract: ***A series of substituted isoxazolo[5,4-b]pyridines derivatives has been prepared in one step from condensation of symmetrical vinamidinium salts with 5-amino-3-methylisoxazole. This efficient synthesis has the advantages of high yields and easy operation.***

Keywords: isoxazolo[5,4-b]pyridines, vinamidinium salts,5-amino-3-methylisoxazole, cyclocondensation.



Scheme 1: Synthesis of substituted isoxazolo[5,4-b]pyridines derivatives 3a-e

1. Introduction

The derivatives of isoxazolopyridines were already shown to have a very broad spectrum of pharmacological activity, including bacteriostatic, analgesic, anti-inflammatory, antiasthmatic, cardiotonic, hypotensive, myolytic, antilipidemic and anxiolotic [1]-[10].

Two techniques of Friedländer condensation have been reported for the synthesis of isoxazolopyridines. The first method is a Friedländer annulation in the presence of pyridine as the solvant and base catalyst [11]. The second is the condensation of substituted isoxazoles with β-dicarbonyl compounds in a one-step reaction [12]- [14].

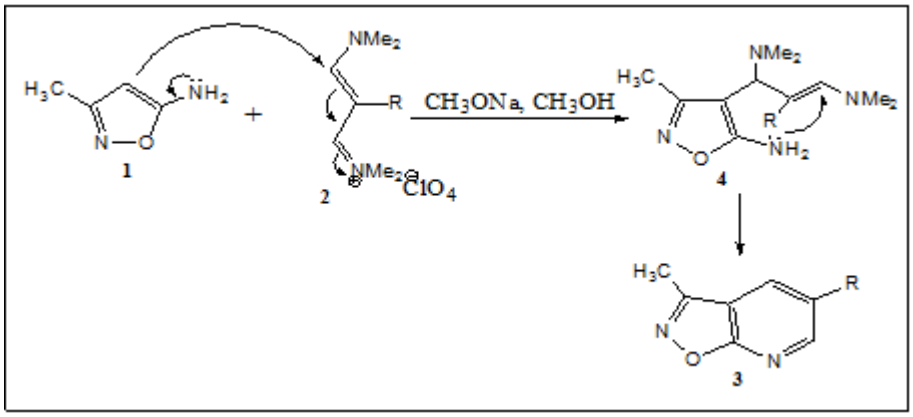
Hence, the development of flexible, efficient and simple methodology is still needed for the synthesis of 5-substituted isoxazolo[5,4-b]pyridines.

On the other hand, it is well known that vinamidinium salts have been used to prepare many different heterocyclic compounds including isoxazoles [15], pyrazoles [15], pyrimidines [15], [16],pyrroles [17] and thiophenes [18]. Moreover, We have reported the preparation of pyridin-2-ones [19], 3-acyl-6-aryl-2-pyridones [20], pyrido[2,3-d]pyrimidines [21], 2-amino-5-arylpyridine-3-carbonitrile [22] and pyrazolo[3,4-b]pyridin-3-ones [23] using vinamidinium salts. In continuation of our efforts towards the synthesis of functionalized aromatic and heterocyclic compounds,we present in this work a new and efficient synthetic approach to 5-substituted isoxazolo[5,4-b]pyridines based on vinamidinium salts chemistry.

2. Results and Discussion

The present work is devoted to a one-pot synthesis of derivatives of 3-methylisoxazol [5,4-b]pyridines (Scheme 1). The readily available 5-amino-3-methylisoxazole **1** was reacted with symmetrical vinamidinium salts perchlorates **2a-e** [24] in methanol at 80°C for 24 h in the presence of sodium methoxide, to furnish the desired 5-substituted isoxazolo[5,4-b]pyridines **3a-d** in excellent yields(Table 1). Alternatively, when the reaction was carried out using the 2-(N-phtaloyl)-1,3-bis(dimethylimonio)propane diperchlorate **2e**, **2-(3-methylisoxazolo[5,4-b]pyridin-5-yl)isoindoline-1,3-dione 3e** was obtained in good yield. The imidemoiety provides a synthetic handle for subsequent functionnalization of bicyclical compound **3e** to a variety of different structures.

We assumed that the formation of **4** was directed via initial Michael addition of β-carbon of the enamino group of 5-amino-3-methylisoxazole **1** to the symmetrical vinamidinium salts **2** and its further cyclisation due the nucleophilic attack by the NH_2-group giving the isoxazolo[5,4-b]pyridines **3** (scheme 2).



Scheme 2: A possible mechanism for the reaction shown in Scheme 1

3. Conclusion

In conclusion, we have developed an efficient and applicable protocol for the synthesis of 5-substituted isoxazolo[5,4-b]pyridines by the use of vinamidinium salts and 5-amino-3-methylisoxazole.

4. Experimental Section

4.1 General experimental procedure for the preparation of 3a-e:

To a flame dried one-necked round-bottomed flask equipped with magnetic stirring, reflux condenser and nitrogen atmosphere was added vinamidinium salt **2** (0.48 mmol), 5-amino-3-methylisoxazole **1** (0.48mmol), sodium methoxide (0.96mmol) and anhydrous methanol (6mL). The mixture was allowed to reflux overnight under a nitrogen atmosphere in an oil bath. The flask was cooled to room temperature and the obtained precipitate was filtered off to give product **3**.

Table 1: Synthesis of 5-substituted isoxazolo[5,4-b] pyridines 3a-e

Entry	vinamidinium salt	R	Product[a]	Yield (%)
1	2a	Ph	3a	96
2	2b	*p*-MeOC_6H_4	3b	98
3	2c	OC_6H_5	3c	93
4	2d	*p*-ClC_6H_4	3d	95
5	2e	N-phthaloyl	3e	90

[a]All products were characterized from their ^{1}H NMR, ^{13}C NMR and mass spectroscopic data

4.1 Spectral data of products 3a-e:

3-methyl-5-phenylisoxazolo[5,4-b]pyridine(3a): Yield: 96 %; orange solid; mp = 257°C ; ^{1}H-NMR (300MHz, $CDCl_3$) δ (ppm): 2.67 (s, 3H), 7.41-7.61 (m, 5H,), 8.17 (d, *J*=2.1 Hz, 1H), 8.83 (d, *J*=2.1 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ : 169.2, 155.7, 150.0, 137.2, 133.6, 129.3, 129.2, 128.3, 127.5, 113.8, 10.9; Anal. Calcd for $C_{13}H_{10}N_2O$(210.24) : C, 74.27; H, 4.79; N, 13.32 %. Found: C, 74.24; H, 4.77; N, 13.35 %. Mass *m/z* (EI, 30 eV): $\mathbf{M}^+$ 210.

5-(4-methoxyphenyl)-3-methylisoxazolo[5,4-b] pyridine(3b): Yield: 98 %; yellow solid; mp = 251°C ; ^{1}H-NMR (300MHz, $CDCl_3$) δ (ppm): 2.65 (s, 3H), 3.90 (s, 3H), 7.05 (d, *J*= 8.7 Hz, 2H), 7.52 (d, *J*=8.7 Hz, 2H), 8.10 (d, *J*=2.6 Hz, 1H), 8.78 (d, *J*= 2.6 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ : 168.9, 159.8, 155.7, 149.7, 133.3, 129.6, 128.7, 128.0, 114.7, 113.7, 55.4, 10.90 ; Anal. Calcd for $C_{14}H_{12}N_2O_2$ (240.26) : C, 69.99; H, 5.03; N, 11.66 %. Found: C, 70.04; H, 5.01; N, 11.68%. Mass *m/z* (EI, 30 eV): $\mathbf{M}^+$ 240.

3-methyl-5-(phenoxy)isoxazolo[5,4-b] pyridine(3c): Yield: 93 %; white solid; mp = 163°C; ^{1}H-NMR (300MHz, $CDCl_3$) δ (ppm): 1.99 (s, 3H), 6.51-6.78 (m, 3H), 7.23 (d, *J* = 8.2 Hz, 2H), 8.33 (s, 1H), 8.51 (s, 1H) ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ : 170.2, 160.4, 160.2, 159.1, 159.0, 129.0, 128.9, 119.5, 114.5, 114.4, 11.3; Anal. Calcd for $C_{13}H_{10}N_2O_2$ (226.23) : C, 69.02; H, 4.46; N, 12.38 %. Found: C, 68.99; H, 4.51; N, 12.35%. Mass *m/z* (EI, 30 eV): $\mathbf{M}^+$ 226.

5-(4-chlorophenyl)-3-methylisoxazolo[5,4-b] pyridine (3d): Yield: 95 %; white solid; mp= 212°C; ^{1}H-NMR (300MHz, $CDCl_3$) δ (ppm): 2.66 (s, 3H), 7.28 (m, *J*= 8.7 Hz, 2H), 8.05 (d, *J* = 8.7 Hz, 2H), 8.28 (d, *J*=1.8 Hz, 1H), 8.74 (d, *J*=1.8 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ : 169.1, 155.7, 149.6, 134.2, 133.3, 129.5, 129.2, 127.0, 125.9, 113.7, 10.8 ; Anal. Calcd for $C_{13}H_9ClN_2O$(244.68) : C, 63.82; H, 3.71; N, 11.45; Cl, 14.49%. Found: C, 63.78; H, 3.76; N, 11.47%. Mass *m/z* (EI, 30 eV): $\mathbf{M}^+$ 244(100%), 246(32.5%).

2-(3-methylisoxazolo[5,4-b]pyridin-5-yl)isoindoline-1,3-dione(3e): Yield: 90 %; Brown solid; mp= 192°C;^{1}H-NMR(300MHz, $CDCl_3$)δ (ppm): 2.16 (s, 3H), 7.09 (s, 1H), 7.78 (d, J= 8.4 Hz, 2H), 7.92 (d, J= 8.4 Hz, 2H), 8.25 (s, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$)δ ((ppm): 172.15, 168.96, 168.86, 161.25, 156.75, 153.26, 134.29, 134.21, 132.26, 132.24, 123.91, 123.85, 104.83, 101.27, 12.06 ; Anal. Calcd for $C_{15}H_9N_3O_3$(279.25) : C, 64.52; H, 3.25; N, 15.05 %. Found: C, 64.49; H, 3.27; N, 15.01 %. Mass *m/z* (EI, 30 eV): $\mathbf{M}^+$ 279.

5. Acknowledgment

The authors thank the DGRS (Direction Générale de la Recherche Scientifique) from the Tunisian Ministry of Higher Education and Research for the financial support of this research.

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