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An elegant method for the preparation of 3-cyanomethyl derivatives of imidazo[1,2-a]pyridines

Rajendiran Chinnapillai*, Ravikumar Reddy Nallamaddi, Eswaraprasad Rao Daliparthi and Eswaraiah Poguri

R&D Laboratories, Suven Life Sciences Ltd, IDA Jeedimetla, Hyderabad – 500055, India

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ABSTRACT

*A series of 3-cyanomethylimidazo[1,2-a]pyridine derivatives (**4**) have been synthesized by using a novel method of utilizing ethylchloroformate as alkylating agent for making quaternary ammonium salts (**7**) from 3-(dimethylamino)methyl imidazo[1,2-a]pyridines (**6**) followed by cyanation. This method is hitherto unknown in the literature and the process is elegant and simple with excellent yields.*

Key words: Cyanomethylation; Ethylchloroformate; Imidazo[1,2-a]pyridine; quaternary salts

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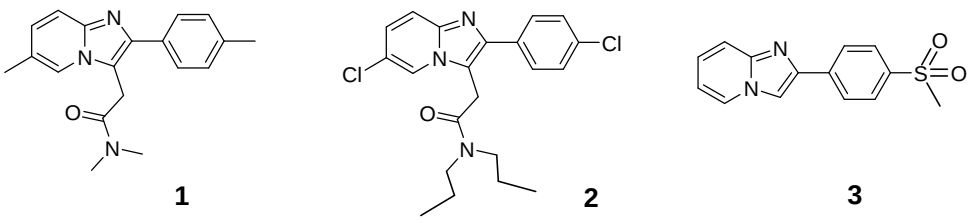
INTRODUCTION

Imidazo[1,2-a]pyridine moieties represent important class of compounds with high biological activities and medicinally useful agents such as anti viral [1], anti bacterial [2], anti inflammatory, analgesic, anti pyretic [3], hypno selective and anxio selective activities [4,5]. Several imidazo[1,2-a]pyridine derivatives have already been in the market including hypnotic drug Zolpidem (**1**), non sedative anxiolytic drug Alpidem (**2**) and an anti ulcer agent Zolmidine (**3**).(Figure 1)

Figure 1



1 **2** **3**

In the literature, several synthetic methods have been described for the preparation of 3-cyanomethyl imidazo[1,2-a]pyridines (**4**) using a quaternary salt formation with methyl iodide followed by cyanation [6] or formylation of imidazo[1,2-a]pyridines, reduction to alcohol, tosylation followed by cyanation [7]. These reported methods were not suitable for commercial scale and involving toxic and expensive reagents. However, to the best of our knowledge the use of ethylchloroformate for the formation of quaternary salts (**7**) followed by cyanation seldom reported. Herein, we report the synthesis of various substituted 3-cyanomethyl imidazo[1,2-a]pyridines (**4**) using ethylchloroformate as a key reagent for making quaternary salt and substitute with cyanide group.

MATERIALS AND METHODS

Melting points were determined in open capillaries and are uncorrected. Progress of the reaction monitored by thin layer chromatography using silica gel – GF 254 (Merck) coated plates. Purity of compounds was determined by HPLC. The IR spectra were recorded in the solid state as KBr dispersion using Perkin-Elmer model-2000 instrument. ^{1}HNMR spectra were recorded on a Brucker 400 MHz instrument with TMS as internal standard (chemical shift in δ, ppm) and Mass spectra have been recorded on API 4000 model.

General procedure for the preparation of cyanomethyl derivatives of imidazo[1,2-a]pyridines (4 a-j):
To the solution of Dimethylaminomethyl derivatives (**6**) of Imidazopyridines (**5**) in dichloromethane added ethylchloroformate under cooling and stirred for 30 minutes. Distilled off the solvents under reduced pressure. Obtained solid dissolved in water and adjusted the pH 8.0 using sodium hydroxide solution. To this aqueous solution, added sodium cyanide and stirred at 50-55 ^{o}C for 3-4 hours. After cooling to room temperature, extracted with chloroform and the organic layer washed with water and brine. Dried with anhydrous sodium sulfate and concentrated under reduced pressure. Obtained crude product purified by slurring with methanol.

4a: [6-Methyl-2-(4-methylphenyl) imidazo[1,2-a]pyridine-3-yl] acetonitrile
off-white solid; Yield 85%; purity by HPLC 99.6%; IR (cm^{-1}) 2250.2 (CN); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.42 (s, 6H), 4.11 (s, 2H), 7.16 (dd, J = 1.4 Hz, J = 9.1 Hz, 1H), 7.31 (d, J = 7.9 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 9.4 Hz, 1H), 7.80 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ13.8, 18.3, 21.2, 107.0, 115.1, 117.1, 120.4, 123.0, 128.2 (3C), 129.5 (2C), 130.3, 138.2, 144.3, 144.9 ; ESI MS: 262.2 (M+1);

4b: [6-Chloro-2-(4-methylphenyl) imidazo[1,2-a]pyridine-3-yl] acetonitrile
off-white solid; Yield 82%; purity by HPLC 99.2%; IR (cm^{-1}) 2248.4 (CN); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.42 (s, 3H), 4.12 (s, 2H), 7.28 (dd, J = 1.7 Hz, J = 9.6 Hz, 1H), 7.31 (d, J = 7.9 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 9.5 Hz, 1H), 8.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ13.9, 21.3, 108.0, 114.6, 118.2, 120.7, 121.6, 126.6, 128.3 (2C), 129.7 (3C), 138.8, 143.7, 146.2; ESI MS: 282.4(M+1);

4c: [6-Bromo-2-(4-methylphenyl) imidazo[1,2-a]pyridine-3-yl] acetonitrile
Pale yellow solid; Yield 80%; purity by HPLC 99.0%; IR (cm^{-1}) 2248.8 (CN); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.43 (s, 3H), 4.14 (s, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.40 (dd, J = 1.6 Hz, J = 9.5 Hz, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 9.5 Hz, 1H), 8.19 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ13.6, 21.2, 107.1, 110.3, 117.1, 118.3, 125.0, 128.1 (2C), 128.6, 129.7 (2C), 130.5, 138.0, 143.1, 144.2; ESI MS: 326.2 (M+1), 328.2 (M+3);

4d: [7-Methyl-2-(4-methylphenyl) imidazo[1,2-a]pyridine-3-yl] acetonitrile
off-white solid; Yield 83%; purity by HPLC 99.1%; IR (cm^{-1}) 2246.9 (CN); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.41 (s, 3H), 2.44 (s, 3H), 4.11 (s, 2H), 6.80 (dd, J = 1.5 Hz, J = 6.9 Hz, 1H), 7.30 (d, J = 7.9 Hz, 2H), 7.44 (s, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ13.6, 21.1 (2C), 106.6, 115.1, 115.5, 116.0, 121.8, 128.0 (2C), 129.4 (2C), 130.2, 136.0, 138.0, 144.6, 145.5; ESI MS: 262.2 (M+1);

4e: [7-Chloro-2-(4-methylphenyl) imidazo[1,2-a]pyridine-3-yl] acetonitrile
off-white solid; Yield 83%; purity by HPLC 99.1%; IR (cm^{-1}) 2246.9 (CN); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 3.61 (s, 2H), 6.70 (dd, J = 1.7 Hz, J = 9.4 Hz, 1H), 7.29 (d, J = 7.9 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 1.9 Hz, 1H), 8.48 (d, J = 9.4Hz,1H); ^{13}C NMR($CDCl_3$, 400 MHz) δ 15.5, 21.3, 116.4, 120.4, 124.0, 124.8, 125.7 (2C), 129.5 (2C), 130.0, 131.7, 134.8, 141.0, 145.5, 146.2; ESI MS: 282.2(M+1);

4f: [7-Bromo-2-(4-methylphenyl) imidazo[1,2-a]pyridine-3-yl] acetonitrile
Pale yellow solid; Yield 80%; purity by HPLC 99.0%; IR (cm^{-1}) 2248.8 (CN); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 3.61 (s, 2H), 7.00 (dd, J = 1.7 Hz, J = 9.4 Hz, 1H), 7.29 (d, J = 7.9 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 1.9 Hz, 1H), 8.57 (d, J = 9.4Hz,1H);^{13}C NMR ($CDCl_3$, 100 MHz) 15.5, 21.3, 116.4, 125.7 (2C), 126.4, 127.0, 127.6, 129.5 (2C), 130.0, 131.7, 133.2, 134.8, 144.8, 145.5; ESI MS: 326.2 (M+1), 328.2 (M+3);

4g: [6-Bromo-7-methyl-2-(4-methylphenyl) imidazo[1,2-a]pyridine-3-yl] acetonitrile
Pale yellow solid; Yield 85%; purity by HPLC 99.2%; IR (cm^{-1}) 2243.8 (CN); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.42 (s, 3H), 2.50 (s, 3H), 4.12 (s, 2H), 7.31 (d, J = 7.7 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.57 (s, 1H), 8.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 21.2, 22.6, 106.8, 112.0, 114.8, 116.8, 122.8, 128.2 (2C), 129.6 (2C), 129.8, 136.0, 138.6, 144.6, 145.6; ESI MS: 340.2 (M+1), 342.2 (M+3);

4h: [6-Chloro-7-methyl-2-(4-methylphenyl) imidazo[1,2-a]pyridine-3-yl] acetonitrile
Pale yellow solid; Yield 85%; purity by HPLC 99.2%; IR (cm^{-1}) 2247.3 (CN); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 2.36 (s, 3H), 3.61 (s, 2H), 7.29 (d, J = 7.7 Hz, 2H), 7.60 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 8.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.5, 19.9, 21.3, 116.4, 123.5, 125.1, 125.7 (2C), 129.5 (2C), 130.0, 131.7, 132.6, 134.8, 144.8, 145.5, 146.3; ESI MS: 296.3(M+1);

4i: [5-Methyl-2-(4-methylphenyl) imidazo[1,2-a]pyridine-3-yl] acetonitrile
Pale yellow solid; Yield 80%; purity by HPLC 99.1%; IR (cm^{-1}) 2242.2 (CN); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.41 (s, 3H), 2.45 (s, 3H), 4.12 (s, 2H), 6.81 (m, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.44 (m, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ13.2, 21.7 (2C), 106.4, 115.5, 115.7, 116.2, 121.6, 128.2 (2C), 129.3 (2C), 130.4, 136.2, 138.2, 144.5, 145.8; ESI MS: 262.2 (M+1);

4j: 2-(4-methylphenyl) imidazo[1,2-a]pyridine-3-acetonitrile
Off-white solid; Yield 86%; purity by HPLC 99.3%; IR (cm^{-1}) 2247.2 (CN); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.43 (s, 3H), 4.16 (s, 2H), 7.00 (t, J = 6.4 Hz, 1H), 7.30 (d, J = 5.4 Hz, 1H), 7.33 (d, J = 7.6 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 9.0 Hz, 1H), 8.05 (d, J = 6.8Hz, 1H);^{13}C NMR ($CDCl_3$, 100 MHz) 13.8, 21.2, 107.3, 113.1, 115.0, 117.8, 122.7, 125.1, 128.2 (2C), 129.5 (2C), 130.1, 138.3, 145.1, 145.2; ESI MS: 248.2 (M+1);

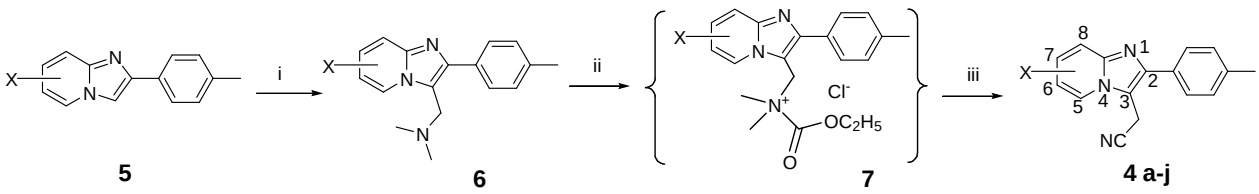
RESULTS AND DISCUSSION

The substituted imidazo[1,2-a]pyridines (**5**) were prepared by the condensation of appropriately substituted 2-aminopyridines with 2-chloro-1-(4-methylphenyl)ethanone[8]. Mannich reaction of various imidazo[1,2-a]pyridines using paraformaldehyde, aqueous dimethylamine in the presence of acetic acid produce the corresponding 3-(dimethylamino)methyl derivatives of imidazo[1,2-a]pyridines (**6**) in good yield [6].

The existing methods for the synthesis of 3-cyanomethyl imidazo[1,2-a]pyridine derivatives (**4**) are not suitable for large scale reactions due to its low boiling and expensive methyl iodide; it was imperative to search for an alternate methods utilizing cheap raw material with scalable process for the preparation of key intermediates 3-cyanomethyl imidazo[1,2-a]pyridines (**4**). Our initial hypothesis was; could ethylchloroformate be used instead of methyl iodide to make quaternary salt followed by cyanation to get the cyanomethyl derivatives. As expected and to our surprise not only the formation of quaternary salt (**7**) was instantaneous but also cyanation of it was much faster in environment friendly water as solvent with very good yields (75-85%) and quality (99%).

Treatment of various substituted mannich derivatives of imidazo[1,2-a]pyridines (**7**) with ethylchloroformate [9], followed by cyanation with sodium cyanide to produce the corresponding 3-cyanomethyl derivatives of imidazo[1,2-a]pyridines **4a-j** (Scheme 1) and depicted in Table 1.

Scheme 1



Scheme 1: *i) Dimethylamine, Paraformaldehyde, Aceticacid, 50-55 °C, 3-4h, 85-90% ii)1.Ethylchloroformate, MDC, 0-5 °C, 0.5 h.iii) NaCN, H_2O, 50-55 °C, 3-4 h, 74-85%*

Table 1: Cyanomethyl derivtives of imidazo[1,2-a]pyridines

Entry	Product	X	Time	Yield
1	4a	6-CH_3	3h	85%
2	4b	6-Cl	3h	82%
3	4c	6-Br	3.5h	84%
4	4d	7-CH_3	3h	83%
5	4e	7-Cl	3.5h	78%
6	4f	7-Br	4h	80%
7	4g	6-Br-7-CH_3	4h	76%
8	4h	6-Cl-7-CH_3	4h	80%
9	4i	5-CH_3	4h	74%
10	4j	H	4h	76%

We have also evaluated the process for the preparation of [6-methyl-2-(4-methylphenyl) imidazo[1,2-a]pyridine]-3-acetonitrile (**4a)** with variety of alkylchloroformates. Ethylchloroformate is replaced with other alkylchloroformates and the results shown in Table 2. It is noteworthy and significance that synthesis of 3-cyanomethyl imidazo[1,2-a]pyridine derivatives using ethylchloroformate producing around 80% yields where as using other alkylchloroformates the yields were around 30-70%.

Table 2: Preparation of 4a with alkylchloroformates

Entry	Alkylchloroformate	Time	Yield
1	Methylchloroformate	4h	48.0%
2	Ethylchloroformate	3h	85.0%
3	Isopropylchloroformate	4h	37.5%
4	Isobutylchloroformate	4h	42.5%
5	Phenylchloroformate	4h	32.0%
6	Benzylchloroformate	4h	74.5%

CONCLUSION

In summary, we have developed a novel, commercially viable and simple method for the synthesis of a series of 3-cyanomethyl imidazo[1,2-a]pyridine derivatives using ethylchloroformate as alkylating agent for making quaternary ammonium salt, as facilitator for cyanation reaction thereby providing an alternate method for the preparation of cyano derivatives from mannich derivatives imidazo[1,2-a]pyridines. This process is simple, cost effective and scalable with good yields.

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