A SIMPLE AND CONVENIENT PREPARATION OF 2-CHLORO-5-METHYLPYRIDINE-3-CARBALDEHYDE IMINES†

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Abstract: A series of new 2-chloro-5-methylpyridine-3-carbaldehyde imines **3a-o** were prepared conveniently by the reaction of 2-chloro-5-methylpyridine carbaldehyde **1** and amines **2a-o** in excellent yields.

Introduction

The imines[1] are an important synthetic organic compounds in that they have been reported as potential herbicides[2], fungicides[3], neoplasm inhibitors[4], antiviral[5], anti convulsants[6], anti microbial[7], anti cancer & tubercular[8], as plant growth regulators[9], and also have role in biology (vision and ATP synthesis).[10-11] Pyridine Schiff bases are very good synthons for the preparation of α -nornicotin derivatives[12] and as pesticides[13]. The most of the Schiff base reactions are acid catalyzed and are generally carried out by refluxing the carbonyl compounds and amines[1b] in a suitable solvent. Imine formation between aliphatic aldehydes & amines requires mild conditions like low temperatures[14]. Some Schiff base preparations were carried out using titanium chloride catalyst[15], Lewis acids[16], alumina[17] catalysts and the liberated water removal was achieved by azeotropic means, using KOH/NaOH base and also molecular sieves[18].

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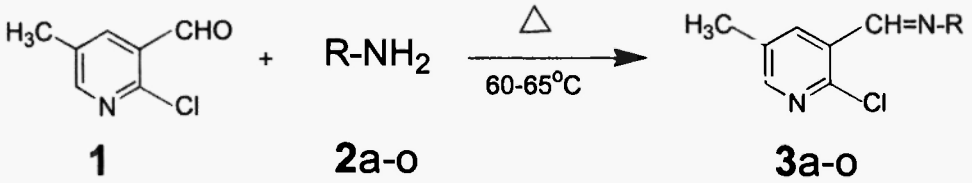
Results and Discussion

In continuation of our work on biologically active molecules[19], and on pesticidal compounds[20], makes us here to report a simple and convenient preparation of a series of new 2-Chloro-5-methylpyridine-3-carbaldehyde derived imines. 2-Chloro-5-methyl pyridine-3-carbaldehyde was prepared by acetylating the propionaldehyde/benzylamine Schiff base and the resulting enamide was cyclized under Villsmeyer formylation conditions to give the corresponding aldehyde[21]. Thus prepared 2-Chloro-5-methyl pyridine-3-carbaldehyde[22] was used to synthesize a series of new imines (Schiff bases) in excellent yields. The results of these studies are arranged in Table. The general synthetic reaction is depicted in Scheme. The synthesized imines were characterized by spectral means and the spectral data is provided in experimental section.

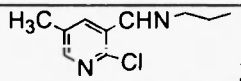
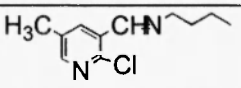
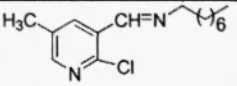
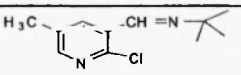
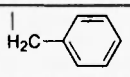
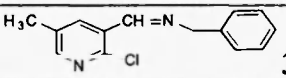
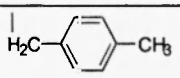
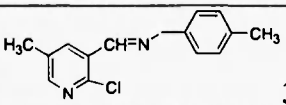
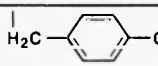
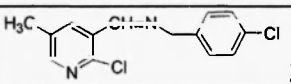
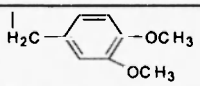
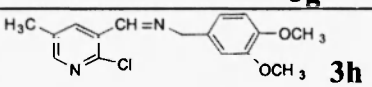
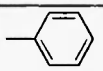
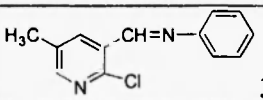
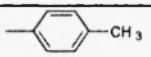
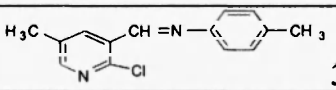
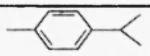
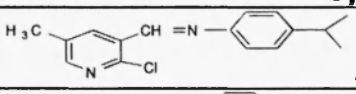
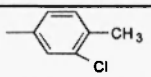
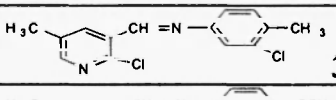
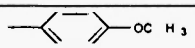
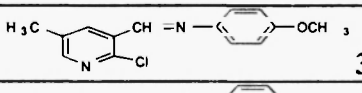
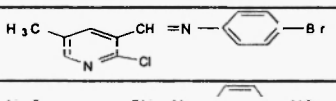
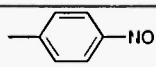
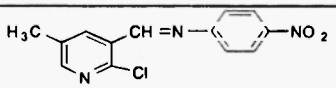
Scheme



1 **2a-o** **3a-o**

Experimental section

^{1}H NMR spectra were recorded on a Gemini (200MHz) Spectrometer in $CDCl_3$ using TMS as internal standard. IR spectra were recorded on a Nicolet 740 FTIR Spectrometer and Mass spectra on a VG Micro Mass 7070H. The melting points were determined in open glass capillaries on Toshniwal melting point apparatus and are uncorrected.

No.	Amine R =	Temp. ^{0}C	Time hr	Product	Mp ^{0}C	% Yield
1	—$(CH_2)_2$-CH_3	65	1	 **3a**	liquid	98
2	—$(CH_2)_3$-CH_3	65	1	 **3b**	liquid	99
3	—$(CH_2)_7$-CH_3	65	1	 **3c**	42	98
4	—C-$(CH_3)_3$	65	1	 **3d**	liquid	98
5		65	1	 **3e**	liquid	98
6		65	1	 **3f**	liquid	98
7		72	2	 **3g**	80	92
8		80	3	 **3h**	liquid	65
9		65	1	 **3i**	liquid	98
10		65	1	 **3j**	58	96
11		65	1	 **3k**	liquid	94
12		65	3	 **3l**	123	85
13		65	1	 **3m**	84	90
14		90	3	 **3n**	106	75
15		110	4	 **3o**	144	60

Preparation of 3a-o; General procedure:

2-Chloro-5-methylpyridine-3-carbaldehyde **1** (0.2 g, 0.00129 moles) and n-prop amine **2a** (0.076 g, 0.00129 moles) was heated to 60-65^{0}C in an oil bath for one hour. The reaction mixture was cooled and extracted with dichloromethane. The organic layer was

separated, dried over sodium sulfate. The solvent was removed under reduced pressure to give the liquid 3a in 98% (0.247 g) Yield.

Spectral Data:

3a. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.98 (t, 3H, CH_3), 1.70 (m, 2H, CH_2), 2.37 (s, 3H, CH_3), 3.62 (t, 2H, N-CH_2), 8.12 (s, 1H, hetero aromatic), 8.22 (s, 1H, hetero aromatic), 8.58 (s, 1H, -N=CH); IR (Neat $CHCl_3$): 2960, 1640, 1480, 1080 cm^{-1}; MS: M^+, m/z 195.
3b. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 3H, CH_3), 1.24 (m, 2H, CH_2), 1.68 (p, 2H, CH_2), 2.38 (s, 3H, CH_3), 3.64 (t, 2H, -N-CH_2), 8.14 (s, 1H, hetero aromatic), 8.20 (s, 1H, hetero aromatic), 8.58 (s, 1H, -N=CH); IR (Neat $CHCl_3$): 2960, 1640, 1480, 1080 cm^{-1}; MS: M^+, m/z 210.
3c. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.92 (t, 3H, CH_3), 1.35 (m, 10H, $5CH_2$), 1.68 (m, 2H, CH_2), 2.38 (s, 3H, CH_3), 3.62 (t, 2H, -N-CH_2), 8.14 (s, 1H, hetero aromatic), 8.20 (s, 1H, hetero aromatic), 8.58 (s, 1H, -N=CH); IR (Neat $CHCl_3$): 2980, 1650, 1480, 1080 cm^{-1}; MS: M^+, m/z 266.
3d. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 9H, $3CH_3$), 2.38 (s, 1H, CH_3), 8.14 (s, 1H, hetero aromatic), 8.20 (s, 1H, hetero aromatic), 8.56 (s, 1H, -N=CH); IR (Neat $CHCl_3$): 2960, 1650, 1470, 1070 cm^{-1}; MS: M^+, m/z 210.
3e. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.38 (s, 3H, CH_3), 4.88 (s, 2H, N-CH_2), 7.38 (m, 5H, aromatic), 8.24 (s, 1H, hetero aromatic), 8.30 (s, 1H, hetero aromatic), 8.78 (s, 1H, -N=CH); IR (Neat $CHCl_3$): 3030, 2940, 1650, 1440, 1360, 1080 cm^{-1}; MS: M^+, m/z 244.
3f. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2,38 (s, 6H, $2CH_3$), 4.82 (s, 2H, -N-CH_2), 7.10-7.25 (m, 4H, aromatic), 8.24 (s, 1H, hetero aromatic), 8.28 (s, 1H, hetero aromatic), 8.72 (s, 1H, -N=CH); IR (Neat $CHCl_3$): 3040, 2950, 1640, 1460, 1070 cm^{-1}; MS: M^+, m/z 258.
3g. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.38 (s, 3H, CH_3), 4.80 (s, 2H, N-CH_2), 7.18 - 7.38 (m, 4H, aromatic), 8.20 (s, 1H, hetero aromatic), 8.26 (s, 1H, hetero aromatic), 8.72 (s, 1H, -N=CH); IR (Neat $CHCl_3$): 3400, 1640, 1240, 1040 cm^{-1}; MS: M^+, m/z 279.
3h. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.37 (s, 3H, CH_3), 3.82 (s, 3H, -OCH_3), 3.84 (s, 3H, -OCH_3), 4.78 (s, 2H, -N-CH_2), 6.80 (m, 3H, aromatic), 8.20 (s, 1H, hetero aromatic), 8.24 (s, 1H, hetero aromatic), 8.70 (s, 1H, -N=CH); IR (Neat $CHCl_3$): 2940, 2840, 1655, 1490, 1250 cm^{-1}; MS: M^+, m/z 304.
3i. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 7.18-7.32 (m, 3H, aromatic), 7.38-7.42 (m, 2H, aromatic), 8.30 (s, 1H, hetero aromatic), 8.38 (s, 1H, hetero aromatic), 8.80

(s, 1H, -N=CH); IR (Neat $CHCl_3$): 2940, 1640, 1450, 1380, 1080 cm^{-1} ; MS: M^+, m/z 230.

3j. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.12 - 7.20 (m, 4H, aromatic), 8.30 (s, 1H, hetero aromatic), 8.40 (s, 1H, hetero aromatic), 8.82 (s, 1H, -N=CH); IR (Neat $CHCl_3$): 2950, 1650, 1480, 1360, 1080 cm^{-1}; MS: M^+, m/z 244.

3k. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.30 (d, 6H, $2CH_3$), 2.40 (s, 3H, CH_3), 2.98 (m, 1H, -CH), 7.18 (m, 2H, aromatic), 7.26 (m, 2H, aromatic), 8.30 (s, 1H, hetero aromatic), 8.38 (s, 1H, hetero aromatic), 8.80 (s, 1H, -N=CH); IR (Neat $CHCl_3$): 2960, 1640, 1480, 1090 cm^{-1}, MS: M^+, m/z 272.

3l. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.42 (s, 6H, $2CH_3$), 7.20 - 7.26 (m, 3H, aromatic), 8.30 (s, 1H, hetero aromatic), 8.36 (s, 1H, hetero aromatic), 8.80 (s, 1H, -N=CH); IR (Neat $CHCl_3$): 2950, 1640, 1480,1410, 1360 cm^{-1}; MS: M^+, m/z 278.

3m. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.42 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 6.82 - 6.88 (m, 2H, aromatic), 7.20 - 7.32 (m, 2H, aromatic), 8.24 (s, 1H, hetero aromatic), 8.36 (s, 1H, hetero aromatic), 8.80 (s, 1H, -N=CH); IR (Neat $CHCl_3$): 2940, 1640, 1470, 1240, 1080 cm^{-1}; MS: M^+, m/z 260.

3n. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.42 (s, 3H, CH_3), 7.02 - 7.18 (m, 2H, aromatic), 7.24 - 7.40 (m, 2H, aromatic), 8.38 (s, 1H, hetero aromatic), 8.42 (s, 1H, hetero aromatic); 8.76 (s, 1H, -N=CH); IR (Neat $CHCl_3$): 2960, 1640, 1480, 1340, 1080 cm^{-1}; MS: M^+, m/z 309.

3o. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.42 (s, 3H, CH_3), 7.28 (m, 2H, aromatic), 7.32 (m, 2H, aromatic), 8.30 (s, 1H, hetero aromatic), 8.34 (s, 1H, hetero aromatic), 8.80 (s, 1H, -N=CH); IR (Neat $CHCl_3$): 3480, 3340, 2960, 1640, 1480, 1100 cm^{-1}; MS: M^+, m/z 275.

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References

1. (a) M..M. Spring, *Chem. Rev.* **26,** 297 (1940); (b) R.W. Layer, *Chem. Rev.* **63**, 489 (1963); (c) E.C. Wagner, *J. Org. Chem.* **19**, 1862 (1954).
2. (a) S. Samadhiya & A. Halve, *Orient .J..Chem.* **17**(1), 119 (2001); (b) S. Kato & S. Igami, *JPn Kokai Tokkyo koho JP* 61137859 (1986); (c) A.I.P. Sinha & M. Bala, *Indian. J. Agric.Chem.* **24**, 37 (1991).
3. W.M. Singh & B.C. Dash, *Pesticides* **22** (11), 33 (1988).

4. (a) B. Sur, S.P. Chatterjee, P. Sur, T. Maity & S. Ray Choudhury, *Oncology,* **47**(5), 433 (1990); (b) A. Halve & V.S. Jolly, *Orient. J. Chem.* **10** (3), 297 (1994).
5. P.H. Wang. J.G. Keck, E.J. Lien & M.C. Lai Michael, *J. Med. Chem.* **33** (2), 608 (1990).
6. A.L. Cates & S. M. Rasheed, *Pharm. Res.* **6**, 271 (1984).
7. (a) M.N. Rottistrov, G.V. Kulik, E.M. Skrynim, T.V. Gorbonos, A.N. Brediskhiva & L.A.Taranova, *Fiziol. Aktiv. Veshchestva.* **5,** 123 (1973); (b) J. John Merianos & P. Adams, *U.S. Patent* 3,960,538 (1976).
8. (a) J. Sengupta, *Indian. J. App. Chem.***2**, 29 (1964); (b) K.P. Sharma. V.S. Jolly & P. Phatak, *Ultra Sci. Phys. Sci.* **10**(2), 263 (1998); (c) Frank D. Popp, *J. Org. Chem.* **26**, 1566 (1961).
9. (a) D. Regine, H. Pierre, H.Y. Jean & V. Claude *C.R. Acad. Sci.* Paris, **265** (25), 1952 (1969); (b) W.G.Y. Wang, Da-xue Yin, J. M. Huang & A.H. Lu, *Gaodeng Xuexiao Huaxue Xuebao,* **17** (1), 91 (1996).
10. V. Jayathirtha Rao, J.P. Zingoni, R. K. Crouch, M. Denny and R. S. H. Liu, *Photochem.Photobiol.*, **41**,171 (1985).
11. V. Jayathirtha Rao, F. Derguini, K. Nakanishi, T. Taguchi, A.Hosada, Y. Hanzawa, Y. Kobayashi, C.M.Pande and R.R.Calleder, *J.Am.Chem.Soc.*,**108**, 6077 (1986).
12. V.H. Peter & D.Reinehr, *Helv.Chim.Acta.* **61,**1115 (1978).
13. (a) H. Szczepanski, H. Kristinsson, P. Maienfisch & J. Ehrenfreund, *WO* 95/18123 (1995); (b) I. Minameida, K. Iwanga & T. Okauchi, *E.P* 0302389 (1989).
14. K.N. Campbell, A.H. Sommers & B.K. Campbell, *J.Am.Chem.Soc.* **66,** 82 (1944).
15. W.A. White & H. Weingarten, *J. Org. Chem.* **32,** 213 (1967).
16. J.H Billmann & K.MTai, *J.Org.Chem*, **23,** 535 (1958).
17. F.T. Boullet, *Syn.Commun.* **8**, 679 (1985).
18. (a) R. Bonnet & T.R. Emerson, *J. Chem..Soc.* 4508 (1965); (b) K.Taguchi, F.H. Westheimer, *J.Org. Chem.* **36**, 1570 (1971).
19. (a) B. China Raju & V. Jayathirtha Rao, U.S. patent applied (2001); (b) B. China Raju & V. Jayathirtha Rao, Indian patent applied (2001); (b) B. China Raju & V. Jayathirtha Rao, Indian patent applied (2001).
20. (a) B. China Raju, V. Raj gopal, V. Jayathirtha Rao & J. Madhusudana Rao, Indian patent No.1418/Del/1999; (b) B. China Raju & V. Jayathirtha Rao, *Indian. .J. Chem. Sec.* B in press (2001).
21. (a) B. China Raju, V. Jayathirtha Rao & K.V. Raghavan Indian patent applied (2001); (b) B. Gangadasu, B. China Raju & V. Jayathirtha Rao Indian patent applied (2001).
22. O. Meth-Cohn & K.T. Westwood, *J. Chem Soc. Perkin. Trans* **1**, 1172(1984).