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An Efficient $FeCl_3$ Catalyzed Synthesis of N,N'-Diarylformamidines

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ABSTRACT

An efficient $FeCl_3$ catalyzed synthesis of N,N'-diarylformamidines using triethylorthoformate (1 equivalent) and primary aryl amines (2 equivalents) at ambient temperature has been described. This methodology provides an eco-friendly and simple procedure without using any hazardous and expensive chemicals.

Keywords: Fe(III) Chloride; Diarylformamidines; Aryl Amines; Triethylorthoformate

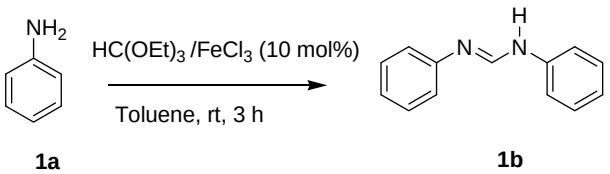
1. Introduction

Formamidines have structural similarity to the imidazole ring, a part of the histamine molecule, are supposed to possess enormous biological activities. The biochemical aims of formamidines include monoamine oxidase inhibitor [1,2], adrenergic, neurochemical receptors [3-8] and prostaglandin E2 synthesis [9]. Formamidines are also noted for their complexation with transition metals [10,11] and usage as auxiliaries in asymmetric synthesis [12,13], electrophiles [14]. The utility of formamidines as support linkers in solid phase synthesis [15] is now well established in the field of organic synthesis. Formamidines are now vastly used for the preparation of imidazolium salts which are the precursor for the synthesis of N-Heterocyclic carbenes [16]. Moreover, formamidines are useful subject of interest to the physical chemists for dynamic NMR study [17]. There have also been reported some cryoscopic molecular weight determination experiments utilizing the molecular association property of diarylformamidines in benzene solution [18].

2. Results and Discussion

There are only a few reports [16,19-26] in the literature for the synthesis of formamidines specially using triethyl orthoformate and amines. However, there is still scope for further improvement in this field since most of the reported methods suffer from long reaction times, elevated temperature or use of toxic and expensive reagents. Very recently, Sadek *et al.* [26] reported the synthesis of diarylformamidines using ceric ammonium nitrate (CAN) in water. But it is well known that CAN is a toxic and strong oxidizing reagent and especially in water it shows strong acidic property to affect many sensitive functional groups. So, a mild and efficient method is still desirable. We report herein an efficient $FeCl_3$ catalyzed synthesis of N,N'-diarylformamidines using triethylorthoformate (1 equivalent) and primary aryl amines (2 equivalents) at ambient temperature. Compared to other methods this method is much more environment friendly due to not using any toxic chemicals. In a preliminary experiment, a solution of aniline (1a) (2 mmol) and triethyl orthoformate (1 mmol) in the presence of a catalytic amount of $FeCl_3$ (10 mol%) in toluene (10 mL) was stirred for 3 h at room temperature. Solvent was removed and the solid mass obtained was purified by column chromatography over silica gel to afford pure formamidine 1b in excellent yield (**Scheme 1**).

Thus, a series of diarylformamidines have been synthesized using the reaction conditions and the results are summarized in **Table 1**. All the products were characterized by spectral and analytical studies and were compared with the reported data (10,13b,13d,13f-h). The probable mechanism of the formation of the product may be suggested with the line of the report by Sadek *et al.* [26] (**Scheme 2**). It is proposed that $FeCl_3$ as a Lewis acid activates ethoxy groups and enhances the C-O bond cleavage to generate a stable carbocation which facilitates the subsequent nucleophilic displacements by aromatic amines.



1a **1b**

Scheme 1. Synthesis of diarylformamidines.

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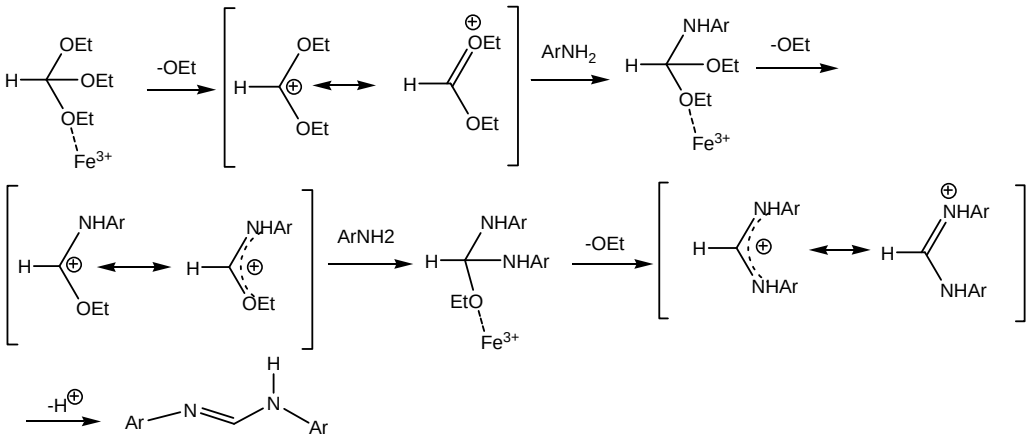
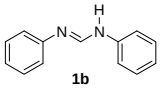
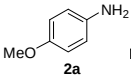
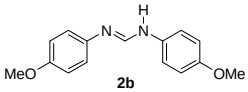
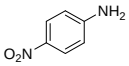
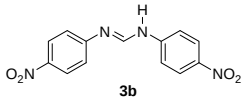
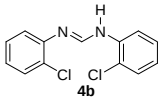
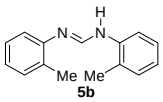
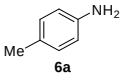
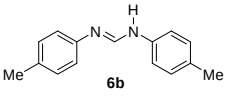
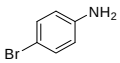
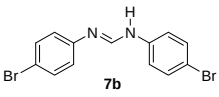
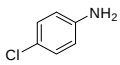
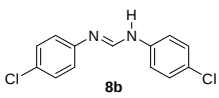
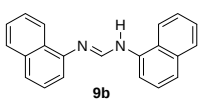


Scheme 2. Plausible mechanism for the formation of diarylformamidines.

Table 1. Synthesis of N,N'-diarylformamidines.

Entry	Amine	Product	Time	Yield (%)[a]	Ref.
1	 **1a**	 **1b**	3 h	87	10
2	 **2a**	 **2b**	3 h	82	13f
3	 **3a**	 **3b**	3 hr[b]	55	13b
4	 **4a**	 **4b**	3 h	76	13d
5	 **5a**	 **5b**	3 h	79	10
6	 **6a**	 **6b**	3 h	88	13g
7	 **7a**	 **7b**	3 h	89	13h
8	 **8a**	 **8b**	3 h	88	13f
9	 **9a**	 **9b**	3 h	91	10

[a]Yields refer to pure isolated products. [b]Refluxed in toluene.

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3. Conclusion

In conclusion, we have developed a mild and efficient method for the direct conversion of primary aryl amine to N,N'-diarylformamidines using a catalytic amount of $FeCl_3$. This provides an eco-friendly and simple method without using any toxic and expensive reagents.

4. Experimental Section

4.1. General Procedures

All melting points were taken on a Gallenkamp melting point apparatus and are uncorrected. The ^1H and ^{13}C NMR were recorded in $CDCl_3$ using TMS as an internal standard on 300 and 75 MHz spectrometer (Bruker) respectively and IR were recorded using a Shimadzu FT IR-8300 instrument. High-resolution mass spectra were obtained using a Qt of Micro YA263 instrument. Toluene was dried over sodium. Chloroform was freshly distilled from phosphorus pentoxide. Petroleum ether of boiling range 60˚C - 80˚C and silica gel of 60 - 120 mesh were used for column chromatography.

4.2. Experimental Section

4.2.1. Representative Procedure for the Synthesis of Diarylformamidines

To a well stirred a solution of aniline (1a) (186 mg, 2 mmol) and triethyl orthoformate (148 mg, 1 mmol) in the presence of a catalytic amount of $FeCl_3$ (10 mol%) in toluene (10 mL) was stirred for 3 h at room temperature. Solvent was removed under reduced pressure and the solid mass was dissolved in chloroform (30 mL) and then filtered through a Whatmann filter paper. The solvent was removed under reduced pressure and the crude residue obtained was purified by column chromatography over silica gel (100 - 200 mesh) (40% ethyl acetate in petroleum ether) to afford N,N'-diphenylformamidine (1b) as a pale yellow solid; m.p.139˚C -140˚C. IR (KBr): 3356, 3037, 2875, 1685, 1600, 1498, 1442, 1313, 1174, 1028, 752, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.04-7.18 (m, 6H), 7.29 - 7.34 (m, 4H), 8.19 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 118.9, 120.2, 124.8, 125.3, 129.1, 129.8, 136.8, 137.0, 159.5 ; HRMS: calcd. for $C_{13}H_{13}N_2$ $[M+H]^+$: 197.1073; found: 197.1072.

4.2.2. N,N'-Bis(4-methoxyphenyl) formamidine (2b)

Colourless solid; m.p. 85˚C - 86˚C. IR (KBr): 2835, 1672, 1504, 1319, 1242, 1109, 1033, 825, 719, 580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 6H), 6.89 - 6.92 (d, J = 8.8 Hz, 4H), 7.09 - 7.12 (d, J = 8.8 Hz, 4H), 8.06 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5, 55.6, 114.3, 115.0, 121.7, 121.9, 129.7, 130.1, 156.8, 157.7, 163.3; HRMS: calcd. for $C_{15}H_{17}N_2O_2$ $[M+H]^+$: 257.1285; found: 257.1283.

4.2.3. N,N'-Bis(4-nitrophenyl) formamidine (3b)

Pale yellow solid; m.p. 239˚C - 240˚C (decomposed). IR (KBr): 3086, 2885, 1687, 1562, 1500, 1411, 1330, 1271, 1111, 854, 752, 688, 540 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.82 - 7.97 (m, 5H), 8.22 - 8.25 (m, 3H), 8.42 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 112.9, 119.5, 125.6, 126.9, 136.2, 143.1, 144.7, 156.2, 161.1; HRMS: calcd. for $C_{13}H_{10}N_4O_4$ $[M+H]^+$: 286.0775; found: 286.0776.

4.2.4. N,N'-Bis(2-chlorophenyl) formamidine (4b)

Pale yellow solid; m.p. 141˚C -142˚C. IR (KBr): 3010, 2981, 1685, 1503, 1363, 1091, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.96 - 7.35 (m, 8H), 8.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 115.9, 119.0, 119.3, 124.2, 127.6, 127.8, 129.4, 129.9, 143.0; HRMS: calcd. for $C_{13}H_{11}N_2Cl_2$ $[M+H]^+$: 265.0294; found: 265.0292.

4.2.5. N,N'-Di-O-tolylformamidine (5b)

Light brown solid; m.p. 152˚C -153˚C IR (KBr): 3010, 2806, 1662, 1580, 1480, 1465, 1310, 1210, 1187, 996, 780, 744, 723, 613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 6H), 6.92 - 6.97 (m, 4H), 7.08 - 7.18 (m, 4H), 7.98 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.0, 117.6, 123.8, 127.1,128.8, 130.5, 130.9, 147.8; HRMS: calcd. for $C_{15}H_{17}N_2$ $[M+H]^+$: 225.1386; found: 225.1386.

4.2.6. N,N'-Di-P-tolylformamidine (6b)

Brownish solid; m.p. 140˚C - 141˚C. IR (KBr): 3342, 2922, 1693, 1518, 1356, 1215, 1037, 817, 669, 509 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.24 (brs, 6H), 7.18 - 7.28 (m, 8H), 8.76 (brs, 1H); HRMS: calcd. for $C_{15}H_{17}N_2$ $[M+H]^+$: 225.1386; found: 225.1385.

4.2.7. N,N'-Bis(4-bromophenyl) formamidine (7b)

White solid; m.p. 19˚C - 192˚C. IR (KBr): 3003, 2976, 1697, 1491, 1352, 1076, 819, 634, 495 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.51 - 7.59 (m, 4H), 7.65 - 7.68 (m, 4H), 8.98 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 117.6, 118.4, 120.4, 121.6, 132.2, 132.9, 135.9, 136.0, 159.0; HRMS: calcd. for $C_{13}H_{11}N_2Br_2$ $[M+H]^+$: 352.9283; found: 352.9283.

4.2.8. N,N'-Bis(4-chlorophenyl) formamidine (8b)

Light brown solid; 179˚C - 180˚C. IR (KBr): 3013, 2974, 1691, 1501, 1367, 1100, 823, 656, 476 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.02 - 7.10 (m, 2H), 7.26 - 7.33 (m, 3H), 7.43 - 7.58 (m, 3H), 8.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.2, 121.4, 129.2, 129.9, 130.9, 135.4, 135.5, 159.3; HRMS: calcd. for $C_{13}H_{11}Cl_2N_2$ [M+H]: 265.0294 ; found: 265.0295.

4.2.9. N,N'-Dinaphthalen-1-Yl-formamidine (9b)

Light purple solid; m.p. 200˚C - 201˚C. IR (KBr): 3047,

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1660, 1573, 1394, 1300, 1263, 993, 788, 765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.48 - 7.68 (m, 10H), 7.90 (s, 2H), 8.30 (s, 2H), 8.50 (brs, 1H); HRMS: calcd. for $C_{22}H_{16}N_2$ $[M+H]^+$: 297.1386; found: 297.1386.

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