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ORIGINAL ARTICLE

Development of one-pot three component reaction for the synthesis of *N*′-aryl-*N*-cyanoformamidines, essential precursors of formamidine pesticides family

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Abstract Efficient one-pot three component reaction of aniline derivatives with cyanoamide and triethyl orthoformate at reflux in toluene affords *N*′-aryl-*N*-cyanoformamidines in high yields just by the distillation of the azeotrope toluene/ethyl alcohol. Labelled d_9-Amitraz is prepared by the application of this procedure in the synthesis of formamidine pesticides family.

1. Introduction

The usual procedure for the synthesis of organic compounds is the stepwise formation of the individual bonds in the target molecule. However, it would be much more efficient if one could form several bonds in one sequence without isolating the intermediates, changing the reaction conditions, or adding reagents (Tietze and Beifuss, 1993; Waldmann, 1995; Hall, 1994). Thus, multicomponent condensation was an active field in the research of organic reactions because it can readily construct complicated heterocyclic scaffolds (Yu et al., 2011; Dondoni and Massi, 2006). It is obvious that the one-pot multicomponent reactions represent a possible instrument to perform a near ideal synthesis building-up complex molecules with maximum simplicity and brevity (Hudlicky, 1996), minimizing the waste production, and allowing an ecologically and economically favorable process.

Generally the preparation of aromatic cyanoformamidines is realized, either in two steps by the isolation of cyanoformimidates and subsequent substitution with aromatic amines (Cereda et al., 1986) or, in few examples, in a one-pot reaction without solvent in 39–96 % yields (Schaefer and Gewald, 1976). Now, herein we report an extended and improved three

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component reaction involving commercially available aromatic primary amines **1** with triethyl orthoformate **2** and cyanoamide **3** in toluene to provide *N*′-aryl-*N*-cyanoformamidines **4** by a one-pot method (Scheme 1).

Cyanoformamidines are important intermediates for the synthesis of asymmetric formamidines that have been extensively checked as pesticides (Leung et al., 1999; Nakayama et al., 1997; Baxter and Barker, 1999; Moss, 1996; Beeman and Matsumura, 1973) (i.e. Amitraz, Chlordimephorm, Formethanate) and as pharmacological agents (Gall et al., 1988; Donetti et al., 1984; Scott et al., 1983). In fact, unlike the formamidines which easily hydrolyze, the presence of a nitrile group on the structure of the cyanoformamidines makes these compounds more stable and increases the electrophilicity of the formyl carbon to nucleophilic attack for further transformations. For example *N*′-aryl-*N*-cyanoformamidines were converted to a variety of *N*′-aryl-*N*-alkylformamidines with excess of alkyl or dialkylamines (Yu et al., 2011; Dondoni and Massi, 2006) and in 2-substituted 6-aryl-1,3-oxazin-4-ones by reaction with aroylketenes (Nekrasov, 2001).

2. Results and discussion

In our effort to develop a one pot synthesis of *N*′-aryl-*N*-cyanoformamidines **4**, from primary amines **1**, triethyl orthoformate **2** and cyanoamide **3** by the sequential nucleophilic attack of amine and cyanoamide to the triethyl orthoformate we examined several reaction conditions. We chose toluene as the solvent system because it forms an azeotrope with the ethanol that can be removed from the system by distillation, allowing rapid and complete transformation of the reagents (entry 5, Table 1).

To explore the feasibility, scope and limitations of this one-pot approach, a number of amines **1** were utilized and the results are summarized in Table 2. In almost all cases, the cyanoformamidine formation was quick and in good yields but when aliphatic amines were utilized and the nucleophilicity was comparable with the cyanoamide, the reactions were unselective, the main product was a mixture of double addition of cyanamide or aliphatic amine and only traces of cyanoformamidine were obtained (entries 24–25, Table 2).

As shown in Table 2, this protocol can be excellently applied on aromatic amines with either electron-withdrawing groups (such as halogens) or electron-donating groups (such as alkyl or alkoxyl groups). In general, the reaction is complete when the azeotrope is totally distilled off (30 min) at the temperature of reflux (76.5 °C), the *N*′-aryl-*N*-cyanoformamidines **4** crystallizes out and is isolated in a pure form simply by filtration.

In the past years, our group has developed original and accurate analytical method for assay of microcomponents (De Nino et al., 2005; Di Donna et al., 2009), compounds for the food sophistication (Di Donna et al., 2004; Sindona et al., 2009; De Nino et al., 2007) and pesticides (Maiuolo et al., 2009). In this context and to further extend the utility of the procedure, we report a convenient access to d_9-1,5-di-(2,4-dimethylphenyl)-3-methyl-1,3,5-triazapenta-1,4-diene (d_9-Amitraz) (Scheme 2). Other acaricide-insecticides, of the formamidines family can be prepared using the same procedure with different cyanoformamidines. Amitraz (Leung et al., 1999; Baxter and Barker, 1999; Nakayama et al., 1997; Shin and Hsu, 1994; Queirozneto et al., 1994) is a triazapentadiene compound, a member of the formamidine class chemical family. It is used to control red spider mites, leaf miners, scale insects, and aphids (Cozzani and Di Pietrogiacomo, 1989). On animals, it is used to control ticks, mites, lice and other pests (Harrison et al., 1972; Tolim, 1994; Tudek et al., 1988).

Table 1 Optimization of conditions for the synthesis of **4.**

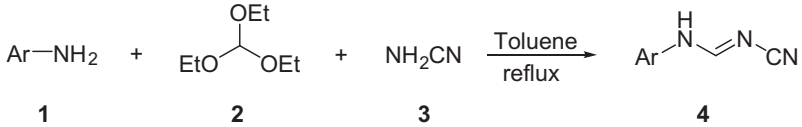
Entry	Amine	Solvent	Time (min)	Temp	Yield[a] (%)
1	Aniline	THF	60	Reflux	52
2	Aniline	Dioxane	60	Reflux	55
3	Aniline	Acetonitrile	60	Reflux	50
4[b]	Aniline	Toluene	60	Reflux	77
5[c]	Aniline	Toluene	30	Reflux	96

[a] Isolated yields.
[b] Without distilling the toluene/ethanol azeotrope.
[c] Distilling the toluene/ethanol azeotrope.

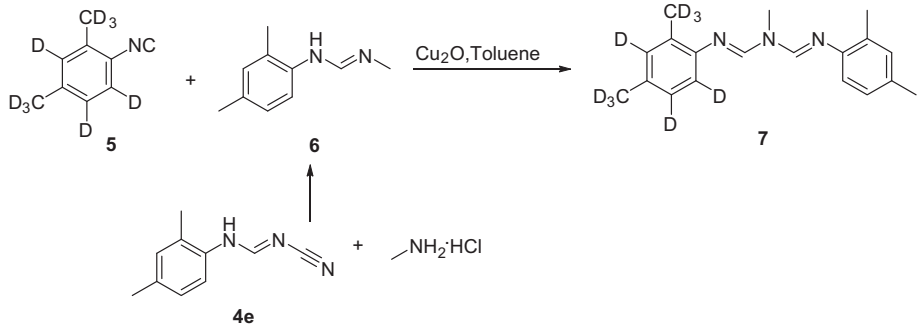
Table 2 One-pot synthesis of *N*′-aryl-*N*-cyanoformamidines.

Entry	Ar	Product	Yield[a] (%)
1	C_6H_5	**4a**	96
2	4-MeC_6H_4	**4b**	95
3	2-*i*-PrC_6H_4	**4c**	87
4	4-*i*-PrC_6H_4	**4d**	90
5	2,4-$Me_2C_6H_3$	**4e**	97
6	3,4-$Me_2C_6H_3$	**4f**	97
7	2-$MeOC_6H_4$	**4g**	96
8	3-$MeOC_6H_4$	**4h**	93
9	4-$MeOC_6H_4$	**4i**	87
10	2,4-$(MeO)_2C_6H_3$	**4j**	89
11	2,5-$(MeO)_2C_6H_3$	**4k**	91
12	2-ClC_6H_4	**4l**	76
13	3-ClC_6H_4	**4m**	84
14	4-ClC_6H_4	**4n**	81
15	2,3-$Cl_2C_6H_4$	**4o**	75
16	2,4-$Cl_2C_6H_4$	**4p**	88
17	2,5-$Cl_2C_6H_4$	**4q**	77
18	2-BrC_6H_4	**4r**	71
19	3-BrC_6H_4	**4s**	77
20	4-BrC_6H_4	**4t**	79
24	Cyclohexyl	**4u**	8[b]
25	Butyl	**4v**	10[b]

[a] Isolated yields.
[b] Gas-chromatographic yields.



Scheme 1 General synthesis of aromatic cyanoformamidines.



Scheme 2 Synthetic route to d_9-Amitraz **7**.

In the synthetic procedure the *N′*-(2,4-dimethylphenyl)-*N*-cyanoformamidine **4e** undergo nucleophilic attach by methylamine on formyl carbon and, by the elimination of cyanoamide hydrochloride, furnish an asymmetrical formamidine **6**, that in toluene and in the presence of copper(I) oxide attach the labelled isocyanide **5** to give d_9-Amitraz **7**. This product could be employed for absolute quantitative determinations in biological matrices, using the synthetic labelled analogue as an internal standard.

Labelled isocyanide **5** was prepared according to the following Scheme 3.

3. Experimental

All solvents and reagents were obtained commercially and used without further purification. ^{1}H NMR spectra were recorded on a 300 MHz Bruker instrument in the DMSO-d_6 solvents except for the compounds **6** and **7** ($CDCl_3$). Chemical shifts are given in ppm, and coupling constants are in Hertz. In solution the cyanoformamidines exist in two tautomeric forms2 (Scheme 4) giving NMR spectra complicated by the presence of more signals in comparison with those expected. Melting points are uncorrected and were determined with a Kofler hot stage. Elemental analyses (C, H, and N) were obtained using a Flash 2000, Thermo Fisher Scientific elemental analyzer.

3.1. General procedure for one-pot synthesis of cyanoformamidines ***4***

A mixture of the primary amine (5 mmol), triethyl orthoformate (5 mmol) and cyanoamide (7.5 mmol) in toluene (7.5 mL) was stirred at 75–80 °C in a round-bottom flask fitted with a distillation apparatus until the azeotrope (76.5 °C) toluene/ethanol had been completely removed (30 min). After completion the reaction mixture was cooled, the product filtered and crystallized from ethanol.

3.1.1. N′-phenyl-N-cyanoformamidine ***4a***

White solid; yield 96%; mp 142–143 °C (lit.[3] 144–145 °C); ^{1}H NMR (DMSO-d_6) 11.19 (bs, 1H, NH) 9.12–8.53, (bs, s, 1H, CH), 7.75–6.98 (m, 5H, Ar); ^{13}C NMR (DMSO-d_6) 163.5,161.2, 137.8, 136.9, 129.4, 128.8, 125.3, 124.9, 121.1, 117.9. Anal. calcd for $C_8H_7N_3$: C, 66.19 H, 4.86 N, 28.95. Found: C, 66.25 H, 4.82 N, 28.93.

3.1.2. N′-4-tolyl-N-cyanoformamidine ***4b***

White solid, yield 95%; mp 182–183 °C (lit.[3] 183–185 °C); ^{1}H NMR (DMSO-d_6) 11.25–10.85 (2bd, J_1 = 11.6 Hz, J_2 = 4.9 Hz, 1H, NH) 8.47, 9.04 (2d, J_1 = 11.6 Hz, J_2 = 4.9 Hz, 1H, CH), 6.94–7.63 (m, 4H, Ar), 2.26, 2.28 (2s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) 162.64, 160.13, 134.60, 133.97, 133.80, 133.54, 129.08, 128.54, 120.40, 117.29, 19.69, 19.52. Anal. calcd for $C_9H_9N_3$: C, 67.90 H, 5.70 N, 26.40. Found: C, 67.86 H, 5.72 N, 26.42.

3.1.3. N′-2-isopropylphenyl-N-cyanoformamidine ***4c***

White solid; yield 87%; mp 125–126 °C; ^{1}H NMR (DMSO-d_6) 10.56 (bs, 1H, NH), 8.65, 8.58, (2s, 1H, CH), 7.48–7.10 (m, 4H, Ar), 3.21–3.05, (2ept, J_1 = 6.9 Hz, J_2 = 6.8 Hz, 1H, CH), 1.15 (d, J_1 = 6.9 Hz, 6H, CH_3); ^{13}C NMR (DMSO-d_6) 164.59, 161.12, 143.60, 141.15, 140.28, 130.88, 126.98, 126.46, 126.06, 125.66, 125.02, 124.77, 124.44, 124.12, 123.96, 121.54, 25.30, 24.77, 21.51, 21.13. Anal. calcd for $C_{11}H_{13}N_3$: C, 70.56 H, 7.00 N, 22.44. Found: C, 70.65 H, 6.97 N, 22.38.

3.1.4. N′-4-isopropylphenyl-N-cyanoformamidine ***4d***

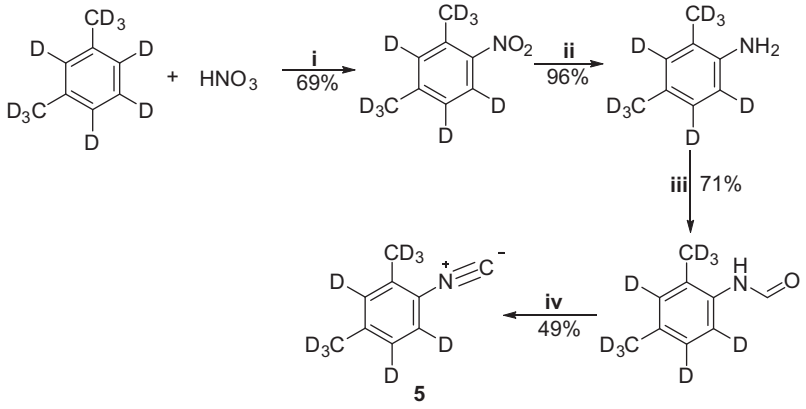
White solid; yield 90%; mp 90–91 °C; ^{1}H NMR (DMSO-d_6) 11.10 (bs, 1H, NH), 8.47, 9.03 (2s, 1H, CH), 7.23–7.58 (m, 4H, Ar), 2.78, 2.95 (m, 1H, CH), 1.181.16, (2d, J_1 = 6.9 Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6) 161.80, 158.94, 146.35, 133.59, 132.84, 127.46, 21.75, 21.80, 30.84, 31.00, 115.83, 119.11, 121.06, 124.70, 125.26, 125.50. Anal. calcd for $C_{11}H_{13}N_3$: C, 70.56 H, 7.00 N, 22.44. Found: C, 70.61 H, 6.97 N, 22.42.

3.1.5. N′-2,4-dimethylphenyl-N-cyanoformamidine ***4e***

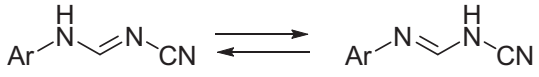
White solid; yield 97%; mp 138–139 °C; ^{1}H NMR (DMSO-d_6) 11.05 (bs, 1H, NH), 8.50, 8.95 (2s, 1H, CH), 6.87–7.35 (m, 3H, Ar), , 2.23, 2.21, 2.15 (3s, 6H, CH_3); ^{13}C NMR (DMSO-d_6) 161.58, 158.68, 135.43, 133.50, 132.84, 131.41, 130.94, 128.25, 127.71, 119.90, 116.78, 116.50, 116.25, 113.21, 17.56, 17.53, 17.35, 16.90, 16.65. Anal. calcd for $C_{10}H_{11}N_3$: C, 69.34 H, 6.40 N, 24.26. Found: C, 69.41 H, 6.37 N, 24.22.

3.1.6. N′-3,4-dimethylphenyl-N-cyanoformamidine ***4f***

White solid; yield 97%; mp 170–172 °C; ^{1}H NMR (DMSO-d_6) 11.02 (bs, 1H, NH), 9.01–8.44, (2s, 1H, CH), 7.42–6.96 (m, 3H, Ar), 2.21, 2.19, 2.17 (3s, 6H, CH_3); ^{13}C NMR (DMSO-d_6) 161.61, 158.72, 135.45, 133.53, 132.89, 131.43, 130.92, 128.26, 127.75, 119.96, 116.82, 116.52, 116.25, 113.18, 17.58, 17.51,



Scheme 3 Synthesis of labelled isocyanide **5**.



Scheme 4 Equilibrium of tautomeric forms.

17.41, 16.92, 16.73. Anal. calcd for $C_{10}H_{11}N_3$: C, 69.34 H, 6.40 N, 24.26. Found: C, 69.40 H, 6.37 N, 24.23.

3.1.7. N′-2-methoxyphenyl-N-cyanoformamidine ***4g***

White solid; yield 96%; mp 125–126 °C, ^{1}H NMR (DMSO-d_6) 10.50 (bs, 1H, NH), 8.73, 8.39, (2s, 1H, CH), 8.00–6.86 (m, 4H, Ar), 3.86, 3.83, (2s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6) 163.69, 161.09, 159.68, 128.89, 127.58, 127.06, 126.54, 124.50, 123.37, 120.76, 119.06, 118.95, 118.85, 118.30, 110.28, 109.52, 53.98, 53.88. Anal. calcd for $C_9H_9N_3O$: C, 61.70 H, 5.18 N, 23.99. Found: C, 61.79 H, 5.15 N, 23.95.

3.1.8. N′-3-methoxyphenyl-N-cyanoformamidine ***4h***

White solid; yield 93%; mp 167–168 °C; ^{1}H NMR (DMSO-d_6) 11.16 (bs, 1H, NH), 8.50, 9.14 (2s, 1H, CH), 7.35–6.68 (m, 4H, Ar), 3.78, 3.75 (2s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6) 163.58, 161.37, 160.25, 159.55, 139.07, 138.11, 130.28, 129.77, 117.75, 113.40, 110.84, 110.73, 110.22, 107.20, 103.60, 55.29, 55.20. Anal. calcd for $C_9H_9N_3O$: C, 61.70 H, 5.18 N, 23.99. Found: C, 61.77 H, 5.16 N, 23.96.

3.1.9. N′-4-methoxyphenyl-N-cyanoformamidine ***4i***

White solid; yield 87%; mp 143–144 °C (lit.[3] 143–145 °C); ^{1}H NMR (DMSO-d_6) δ_H 10.86, 11.21(2bs, 1H, NH), 8.94, 8.43, (2s, 1H, CH), 7.60–6.90 (m, 4H, Ar), 3.79, 3.74, (2s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6) 163.59, 162.73, 160.45, 156.74, 156.61, 130.74, 129.92, 122.62, 119.42, 118.36, 114.64, 114.02, 55.25,55.20. Anal. calcd for $C_9H_9N_3O$: C, 61.70 H, 5.18 N, 23.99. Found: C, 61.75 H, 5.17 N, 23.96.

3.1.10. N′-2,4-dimethoxyphenyl-N-cyanoformamidine ***4j***

White solid; yield 89%; mp 156–157 °C; ^{1}H NMR (DMSO-d_6) 10.60, 10.23, (2bd, J_1 = 11.4 Hz, J_2 = 4.7 Hz, 1H, NH), 8.56, 8.28 (2d, J_1 = 11.4 Hz, J_2 = 4.7 Hz, 1H, CH), 7.80–6.45 (m, 3H, Ar), 3.79, 3.76, 3.71 (3s, 6H, OCH_3); ^{13}C NMR (DMSO-d_6) 161.50, 159.27, 154.11, 153.52, 142.96, 142.85, 126.28, 125.91, 117.66, 117.38, 112.47, 111.04, 110.74, 110.48, 107.93, 103.09, 56.39, 56.31, 55.85, 55.82. Anal. calcd for $C_{10}H_{11}N_3O_2$: C, 58.53 H, 5.40 N, 20.48. Found: C, 58.47 H, 5.38 N, 20.52.

3.1.11. N′-2,5-dimethoxyphenyl-N-cyanoformamidine ***4k***

White solid; yield 91%; mp 124–125 °C; ^{1}H NMR (DMSO-d_6) 10.54, 10.18 (2bd, J_1 = 11.7 Hz, J_2 = 4.7 Hz, 1H, NH), 8.50, 8.26 (2d, J_1 = 11.7 Hz, J_2 = 4.7 Hz, 1H, CH), 7.77–6.43 (m, 3H, Ar), 3.75, 3.70, 3.64 (3s, 6H, OCH_3); ^{13}C NMR (DMSO-d_6) 161.50, 159.13, 154.15, 153.63, 142.90, 142.83, 126.31, 125.85, 117.62, 117.31, 112.42, 110.97, 110.71, 110.52, 107.96, 103.13, 56.34, 56.28, 55.80, 55.76. Anal. calcd for $C_{10}H_{11}N_3O_2$: C, 58.53 H, 5.40 N, 20.48. Found: C, 58.46 H, 5.37 N, 20.52.

3.1.12. N′-2-chlorophenyl-N-cyanoformamidine ***4l***

White solid; yield 76%; mp 156–157 °C; ^{1}H NMR (DMSO-d_6) 10.79 (bs, 1H, NH), 8.81, 8.59 (2s, 1H, CH), 7.82–7.18 (m, 4H, Ar); ^{13}C NMR (DMSO-d_6) 164.78, 161.15, 158.39, 132.95, 132.27, 130.99, 127.81, 127.47, 126.99, 126.14, 125.77, 125.66, 125.61, 123.51, 115.34, 113.84. Anal. calcd for $C_8H_6ClN_3$: C, 53.50 H, 3.37 N, 23.40. Found: C, 53.57 H, 3.40 N, 23.34.

3.1.13. N′-3-chlorophenyl-N-cyanoformamidine ***4m***

White solid; yield 84%; mp 183–184 °C. ^{1}H NMR (DMSO-d_6) 11.28 (bs, 1H, NH), 9.16, 8.57 (2s, 1H, CH), 8.60–7.18 (m, 4H, Ar); ^{13}C NMR (DMSO-d_6) 162.61, 161.17, 159.88, 157.93, 137.46, 136.47, 131.90, 131.14, 129.08, 128.72, 123.06, 122.45, 118.56, 117.55, 115.36, 114.35. Anal. calcd for $C_8H_6ClN_3$: C, 53.50 H, 3.37 N, 23.40. Found: C, 53.55 H, 3.40 N, 23.37.

3.1.14. N′-4-chlorophenyl-N-cyanoformamidine ***4n***

White solid; yield 81%; mp 191–192 °C (lit.[3] 191–193 °C); ^{1}H NMR (DMSO-d_6) 11.19 (bs, 1H, NH), 9.05, 8.49 (2s, 1H, CH), 7.65–7.23 (m, 4H, Ar); ^{13}C NMR (DMSO-d_6) 162.15, 159.54,

134.92, 133.97, 127.33, 127.23, 127.00, 126.89, 120.83, 117.61, 115.57. Anal. calcd for $C_8H_6ClN_3$: C, 53.50 H, 3.37 N, 23.40. Found: C, 53.56 H, 3.41 N, 23.34.

3.1.15. N′-2,3-dichlorophenyl-N-cyanoformamidine **4o**

White solid; yield 75%; mp 156–158 °C; ^{1}H NMR (DMSO-d_6) 10.97 (bs, 1H, NH), 8.78, 8.60 (2s, 1H, CH), 8.10–6.80 (m, 3H, Ar); ^{13}C NMR (DMSO-d_6) 161.09, 158.58, 142.56, 137.48, 134.22, 139.92, 129.69, 126.70, 126.26, 123.79, 120.16, 119.67, 116.64, 114.38, 113.13, 118.20. Anal. calcd for $C_8H_5Cl_2N_3$: C, 44.89 H, 2.35 N, 19.63. Found: C, 44.95 H, 2.32 N, 19.58.

3.1.16. N′-2,4-dichlorophenyl-N-cyanoformamidine **4p**

White solid; yield 88%; mp 194–195 °C; ^{1}H NMR (DMSO-d_6) 10.83 (bs, 1H, NH), 8.79, 8.59 (2s, 1H, CH), 7.86–7.45 (m, 3H, Ar); ^{13}C NMR (DMSO-d_6) 166.15, 163.06, 134.37, 132.27, 131.29, 129.47, 129.24, 128.26, 128.09, 127.84, 127.55, 125.20, 117.20. Anal. calcd for $C_8H_5Cl_2N_3$: C, 44.89 H, 2.35 N, 19.63. Found: C, 44.93 H, 2.31 N, 19.59.

3.1.17. N′-2,5-dichlorophenyl-N-cyanoformamidine **4q**

White solid; yield 77%; mp 161–162 °C; ^{1}H NMR (DMSO-d_6) 10.86 (bs, 1H, NH), 8.88, 8.61 (2s, 1H, CH), 8.07–7.30 (m, 3H, Ar); ^{13}C NMR (DMSO-d_6) 162.61, 160.43, 131.26, 131.21, 130.91, 130.68, 130.33, 129.74, 127.16, 125.14, 124.41, 121.42, 121.18, 120.60, 115.62, 113.82. Anal. calcd for $C_8H_5Cl_2N_3$: C, 44.89 H, 2.35 N, 19.63. Found: C, 44.96 H, 2.31 N, 19.58.

3.1.18. N′-2-bromophenyl-N-cyanoformamidine **4r**

White solid; yield 71%; mp 136–137 °C; ^{1}H NMR (DMSO-d_6) 10.98, 10.65 (2bd, J_1 = 11.7 Hz, J_2 = 4.4 Hz, 1H, NH), 8.70, 8.56 (2d, J_1 = 11.7 Hz, J_2 = 4.4 Hz, 1H, CH), 7.70–7.10 (m, 4H, Ar); δ_C 164.88, 161.17, 136.36, 134.32, 132.41, 131.26, 130.99, 126.93, 126.87, 126.69, 126.33, 125.37, 124.53, 122.84, 116.12, 115.82. Anal. calcd for $C_8H_6BrN_3$: C, 42.88 H, 2.70 N, 18.75. Found: C, 42.82 H, 2.68 N, 18.79.

3.1.19. N′-3-bromophenyl-N-cyanoformamidine **4s**

White solid; yield 77%; mp 174–175 °C; ^{1}H NMR (DMSO-d_6) 11.34 (bs, 1H, NH), 9.16, 8.57 (2s, 1H, CH), 8.15–7.10 (m, 4H, Ar); ^{13}C NMR (DMSO-d_6) 161.14, 159.41, 140.67, 133.45, 129.57, 129.41, 128.87, 127.61, 124.20, 123.55, 123.10, 120.22, 119.89, 119.65, 118.06, 114.60. Anal. calcd for $C_8H_6BrN_3$: C, 42.88 H, 2.70 N, 18.75. Found: C, 42.81 H, 2.66 N, 18.81.

3.1.20. N′-4-bromophenyl-N-cyanoformamidine **4t**

White solid; yield 79%; mp 196–198 °C (lit.[3] 202–204 °C); ^{1}H NMR (DMSO-d_6) 11.43, 11.38, (2bd, J_1 = 5.0 Hz, J_2 = 12.2 Hz, 1H, NH), 9.07, 8.46, (2d, J_1 = 5.0 Hz, J_2 = 12.2 Hz, 1H, CH), 7.62–7.20 (m, 4H, Ar); ^{13}C NMR (DMSO-d_6) 162.28, 159.40, 114.83, 135.34, 134.51, 130.40, 130.21, 129.80, 120.94, 117.71, 115.71, 115.21. Anal. calcd for $C_8H_6BrN_3$: C, 42.88 H, 2.70 N, 18.75. Found: C, 42.83 H, 2.67 N, 18.78.

3.2. Synthesis of N′-(2,4-dimethylphenyl)-N-methylformamidine **6**

Methylamine hydrochloride (1.16 g, 17.4 mmol) was solubilized with 6 mL of water and added to a solution of 0.53 g (3.0 mmol) of N′-(2,4-dimethylphenyl)-N-cyanoformamidine in 3 mL of tetrahydrofuran. The pH was adjusted to about 10 by the addition of a sodium hydroxide solution and the mixture left to react for two hours, and then extracted with diethyl ether. The organic layer was dried over sodium sulfate and concentrated to dryness to provide a crude product usable for the next step without the further purification (0.46 g, yield 98%).

^{1}H NMR ($CDCl_3$) 7.47 (s, H, NH), 6.96 (s, H, NCHN), 6.89–6.65 (m, 3H, Ar), 2.96 (s, 3H, CH_3N), 2.27 (s, 3H, CH_3), 2.22 (s, 3H, CH_3).

3.3. Synthesis of D_9-1,5-di-(2,4-dimethylphenyl)-3-methyl-1,3,5-triazapenta-1,4-diene (d_9-Amitraz) 7

A mixture of d_9-1-isocyano-2,4-dimethylbenzene (0.56 g, 4.00 mmol), N′-(2,4-dimethylphenyl)-N-methylformamidine **(6)** (0.91 g, 5.6 mmol) and copper (I) oxide (0.005 g, 0.08 mmol) was stirred in toluene at reflux temperature for two hours. After completion the reaction mixture was cooled, hydrolyzed with 5 mL of a saturated solution of ammonium chloride and extracted with diethyl ether. The organic layer was dried over sodium sulfate and concentrated to dryness to provide a crude product that, purified by crystallization from cyclohexane, furnished 1.0 g of pure product (white solid; yield 84%; Mp 85–86 °C).

^{1}H NMR ($CDCl_3$) 6.94–6.70 (m, 3H, Ar), 3.49 (s, 3H, CH_3N), 2.30 (s, 3H, CH_3), 2.26 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) 161.35, 160.51, 145.22, 144,15, 129.04, 128.77 (t CD), 127.50, (t, CD), 125.01 (t, CD), 116.21, 120.33, 115.45, 113.92, 26.38, 21.51–19.30 (m, CD_3), 18.92, 18.52–16.89 (m, CD_3), 17.15.

4. Conclusion

We have developed a suitable and general one-pot synthesis of N′-aryl-N-cyanoformamidines **(4)** from primary aromatic amines, triethylorthoformate and cyanoamide *via* double nucleophilic substitution at the formyl carbon. This synthesis allows, in a one-step procedure, the introduction of a N-cyanoimino group that makes the formamidine carbon more electrophilic by electron-withdrawing effect, allowing a double and nucleophilic substitution on the orthoformate as for example in the preparation of unsymmetrical formamidine. This method with respect to those reported in the literature (Cereda et al., 1986; Schaefer and Gewald, 1976), allows its application to a considerable amount of substrates providing products in great yields and high purity without complicated purification processes but only by recrystallization. In fact it is important to note that no column chromatographic separation is needed. In addition, applying this procedure, we have synthesized labelled Amitraz like example of formamidine pesticides.

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