Arabian Journal of Chemistry (2016) 9, 32–37

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

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

Antonio De Nino [a,*], **Loredana Maiuolo** [a,*], **Monica Nardi** [a], **Raffaele Pasceri** [b], **Antonio Procopio** [b], **Beatrice Russo** [a]

[a] *Dipartimento di Chimica, Universita‘ della Calabria, Ponte Bucci, 87030 Arcavacata di Rende, CS, Italy*
[b] *Dipartimento di Scienze della Salute, Universita‘ degli Studi "Magna Græcia", Germaneto, CZ, Italy*

Received 30 September 2014; accepted 13 June 2015
Available online 30 June 2015

KEYWORDS

Cyanoformamidines;
Pesticides;
One-pot reaction;
Labelled compounds

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

---

[*] Corresponding authors. Tel.: +39 0984492043.
E-mail addresses: denino@unical.it (A. De Nino), maiuolo@unical.it (L. Maiuolo).

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2015.06.016

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.**

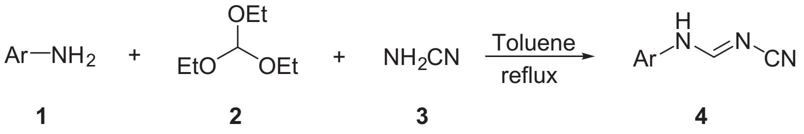
Entry	Amine	Solvent	Time (min)	Temp	Yield[a] (%)
1	Aniline	THF	60	Reflux	52
2	Aniline	Dioxane	60	Reflux	55
3	Aniline	Acetonitrile	60	Reflux	50
4[b]	Aniline	Toluene	60	Reflux	77
5[c]	Aniline	Toluene	30	Reflux	96

[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	$\text{4-MeC}_6\text{H}_4$	**4b**	95
3	$\text{2-}i\text{-PrC}_6\text{H}_4$	**4c**	87
4	$\text{4-}i\text{-PrC}_6\text{H}_4$	**4d**	90
5	$\text{2,4-Me}_2\text{C}_6\text{H}_3$	**4e**	97
6	$\text{3,4-Me}_2\text{C}_6\text{H}_3$	**4f**	97
7	$\text{2-MeOC}_6\text{H}_4$	**4g**	96
8	$\text{3-MeOC}_6\text{H}_4$	**4h**	93
9	$\text{4-MeOC}_6\text{H}_4$	**4i**	87
10	$\text{2,4-(MeO)}_2\text{C}_6\text{H}_3$	**4j**	89
11	$\text{2,5-(MeO)}_2\text{C}_6\text{H}_3$	**4k**	91
12	$\text{2-ClC}_6\text{H}_4$	**4l**	76
13	$\text{3-ClC}_6\text{H}_4$	**4m**	84
14	$\text{4-ClC}_6\text{H}_4$	**4n**	81
15	$\text{2,3-Cl}_2\text{C}_6\text{H}_4$	**4o**	75
16	$\text{2,4-Cl}_2\text{C}_6\text{H}_4$	**4p**	88
17	$\text{2,5-Cl}_2\text{C}_6\text{H}_4$	**4q**	77
18	$\text{2-BrC}_6\text{H}_4$	**4r**	71
19	$\text{3-BrC}_6\text{H}_4$	**4s**	77
20	$\text{4-BrC}_6\text{H}_4$	**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.