An Efficient and Facile Synthesis of 2-Amino-4,6-diarylbenzene-1,3-dicarbonitrile and 1,2-Dihydro-2-oxo-4,6-diarylpyridine-3-carbonitrile under Solvent-free Conditions

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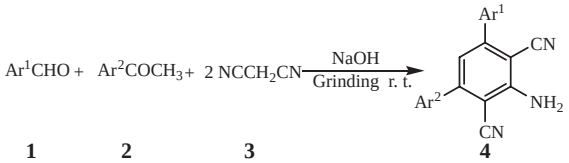
A one-pot three-component condensation of aromatic aldehyde, aromatic ketone, and malononitrile leading to an efficient synthesis of 2-amino-4,6-diarylbenzene-1,3-dicarbonitrile and 1,2-dihydro-2-oxo-4,6-diarylpyridine-3-carbonitrile has been carried out in a mortar just by grinding or heating under solvent-free conditions. Compared with the classical reaction conditions, these new synthetic methods have the advantages of excellent yields, shorter reaction time, and mild reaction conditions.

Over the past several years, chemists have been aware of the environmental implications of their chemistry. Nowadays, they are trying to develop new synthetic methods, reaction conditions, and uses of chemicals that reduce risks to humans and the environment. Organic solvents are high on the list of damaging chemicals because they are employed in huge amounts and are usually volatile liquids that are difficult to store. In recent years the dramatic increases in the investigation of the solvent-free reactions have been seen, such as the Grignard reaction,[1] Knoevenagel condensation,[2] Aldol condensation,[3] Dieckmann condensation,[4] Reformatsky reaction,[5] reduction,[6] and other reactions.[7] The advantages of these processes are higher efficiency, milder conditions, easier workup, and environmental acceptability. Some solvent-free reactions could be carried out just by grinding.[8]

The polysubstituted 2,6-dicyanoanilines are the very important compounds of their optical properties.[9] Synthesis of these compounds have brought the much attention of chemists. Though various methods for the synthesis of them are reported,[10] many of these procedures are not fully satisfactory with regard to operational simplicity, cost of the reagent and isolated yield, moreover, the majority of those synthetic methods were carried out in nocuous organic solvent. For example, Pedro et al.[10a] have reported that polysubstituted 2,6-dicyanoanilines could be synthesized by the reaction between malononitrile and α,β-unsaturated ketones in the sodium methoxide/methanol solution. However, this method suffered from several disadvantages such as longer reaction times, excess of organic solvents, harsh refluxing conditions, especially, the poor yields (5–20%). In continuation to our ongoing endeavour on the application of solvent-free conditions for the synthesis of organic compounds,[11] herein, we wish to report a practical and simple method to prepare polysubstituted 2,6-dicyanoaniline derivatives **4** by grinding the starting materials under dry conditions at room temperatures. The synthetic procedure[12] of polysubstituted 2,6-dicyanoanilines derivatives **4** was operated as follows (Scheme 1): The aromatic aldehyde **1**, aromatic ketone **2**, and malononitrile (**3**) were mixed together in a mortar in the presence of 1.5 equivalents NaOH. The mixture was ground with a pestle and the reaction could be completed within 3–5 min with high yields. The results of reaction are listed in Table 1.

In order to investigate the reactions conditions of synthesis of polysubstituted 2,6-dicyanoanilines derivatives, we put the 4-chlorobenzaldehyde, acetophenone, malononitrile and 1.5 equivalents of NaOH in a reaction flask and let them keep under 70 °C, however, we could not get the anticipated target compound **4e**. Surprisingly, we gained another new compound: 4-(4-chlorophenyl)-1,2-dihydro-2-oxo-6-phenylpyridine-3-carbonitrile. This prompted us to extend our studies toward the incorporation of different aldehydes and ketones (Scheme 2). A series of 1,2-dihydro-2-oxo-4,6-diarylpyridine-3-carbonitrile derivatives[13] **5** could be obtained via the reaction of aromatic aldehyde, aromatic ketone, and malononitrile under heating conditions in good yields. The structure of compound **5** was confirmed by X-ray diffraction analysis.[14] The results are summarized in Table 2.

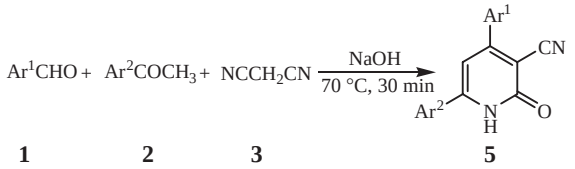
Under the different reaction conditions, two types of products **4** and **5** could be gained. When grinding aromatic aldehyde **1**, aromatic ketone **2**, and malononitrile (**3**) at room temperature (Scheme 1), the compound **4** was only obtained. However, when heating the starting materials (Scheme 2), the compound **5** could be obtained, accompanied with a trace amount of byproduct **4**.



Scheme 1.

Table 1. Synthesis of product **4** by the grinding method

Entry	Ar^1	Ar^2	Time /min	Product	Yields /%
1	4-$CH_3C_6H_4$	C_6H_5	3	**4a**	79
2	3,4-$Cl_2C_6H_3$	C_6H_5	3	**4b**	70
3	2-ClC_6H_4	C_6H_5	3	**4c**	71
4	3-ClC_6H_4	C_6H_5	3	**4d**	73
5	4-ClC_6H_4	C_6H_5	4	**4e**	76
6	4-FC_6H_4	C_6H_5	3	**4f**	73
7	4-ClC_6H_4	4-ClC_6H_4	3	**4g**	70
8	4-ClC_6H_4	4-BrC_6H_4	3	**4h**	69
9	4-ClC_6H_4	4-$CH_3OC_6H_4$	5	**4i**	70
10	C_6H_5	3-ClC_6H_4	3	**4j**	72



1 **2** **3** **5**

Scheme 2.

Table 2. Synthesis of product **5** by the heating method

Entry	Ar^1	Ar^2	Product	Yields/%
1	C_6H_5	4-$CH_3OC_6H_4$	**5a**	80
2	C_6H_5	4-ClC_6H_4	**5b**	78
3	4-ClC_6H_4	C_6H_5	**5c**	81
4	2,4-$Cl_2C_6H_3$	C_6H_5	**5d**	83
5	2-ClC_6H_4	C_6H_5	**5e**	81
6	4-FC_6H_4	C_6H_5	**5f**	83
7	4-BrC_6H_4	C_6H_5	**5g**	79
8	4-$CH_3C_6H_4$	4-BrC_6H_4	**5h**	87
9	3,4-$Cl_2C_6H_3$	2,4-$(CH_3)_2C_6H_3$	**5i**	70
10	3,4-$(CH_3)_2C_6H_3$	4-$CH_3C_6H_4$	**5j**	72

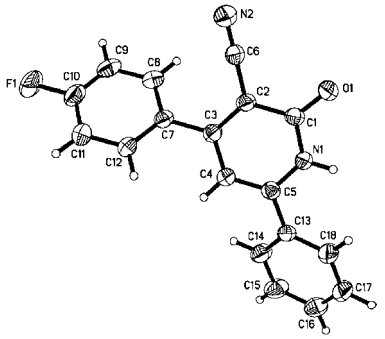
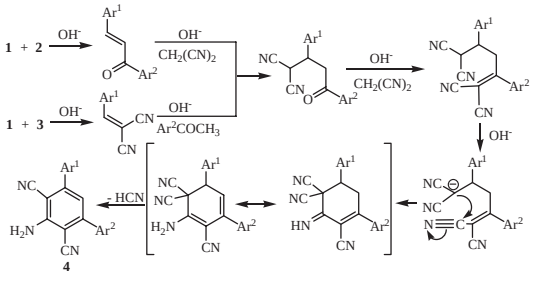


Figure 1. The structure of compound **5f**.



Scheme 3.

As the reactions were carried out in an air atmosphere, and the formation of compound **5** could be due to dehydrogenation by the atmospheric oxygen. Although the detailed mechanism of the above reaction has not been clarified yet, the formation of compound **4** could be explained by a possible mechanism presented in Scheme 3.

In conclusion, we have successfully developed an easy and efficient method to prepare a variety of 2-amino-4,6-diarylbenzene-1,3-dicarbonitrile derivatives and 1,2-dihydro-2-oxo-4,6-diarylpyridine-3-carbonitrile derivatives via the reaction of different aromatic aldehydes, aromatic ketones, and malononitrile under solvent-free conditions. As it is avoided to use toxic organic solvent, this new protocol has the advantages of higher yield, lower cost, reduced environmental impact, and convenient procedure.

References and Notes

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12 The general procedure is represented as follows: aromatic aldehyde **1** (2 mmol), aromatic ketone **2** (2 mmol), malononitrile (**3**) (5 mmol), and NaOH (3 mmol) were added to a mortar. The mixture was ground with a pestle at room temperature. The reaction was completed in 3–5 min and the reaction mixture was poured into water. The product was filtered, dried, and recrystallized from 95% ethanol.
13 The aromatic aldehyde **1** (2 mmol), aromatic ketone **2** (2 mmol), malononitrile (**3**) (3 mmol), and NaOH (3 mmol) were put in a reaction flask and let them keep under 70 °C about 30 min. Then, the reaction mixture was poured into water. The product was filtered, dried, and recrystallized from 95% ethanol.
14 X-ray crystallography for **5f** (Figure 1): Empirical formula $C_{18}H_{11}FN_2O$, fw 290.29, $T = 173(2)$ K, monoclinic, space group $P2_1/c$, $a = 8.705$ (2) Å, $b = 7.9408(18)$ Å, $c = 20462(5)$ Å, $\alpha = 90°$, $\beta = 97.309(5)°$, $\gamma = 90°$, $V = 14029(6)$ Å^3, $Z = 4$, $D_{calcd} = 1.374$ Mg/m^3, λ (Mo Kα) $= 0.71070$ Å, $\mu = 0.096$ mm^{-1}, $F(000) = 600$. $3.26° < \theta < 25.34°$, $R = 0.0624$, $wR = 0.1373$. $s = 1.173$. largest diff. peak and hole: 0.207 and -0.218 e. Å^{-3}. Typical data for representative compounds: compound **4a**: mp 201–202 °C. IR (KBr): 3472, 3364, 3235, 3052, 2215, 1638, 1579, 1568, 1543, 1515, 1448, 1426, 1364, 1314, 1283, 1241, 1176, 866, 810, 774, 765, 723, 700 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.63–7.65 (2H, m, ArH), 7.53–7.56 (5H, m, ArH), 7.34 (2H, d, $J = 8.0$ Hz, ArH), 6.82 (2H, s, NH_2), 6.78 (1H, s, ArH), 2.39 (3H, s, CH_3). Anal. Calcd for $C_{21}H_{15}N_3$: C, 81.53; H, 4.89; N, 13.58%. Found: C, 81.33; H, 4.69; N, 13.81%. **5a**: mp 255–257 °C. IR (KBr): 3417, 3180, 2934, 2220, 1624, 1570, 1516, 1473, 1300, 1268, 1228, 1194, 1180, 1029, 824, 765, 701, 580 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.71 (1H, s, NH), 7.91 (2H, d, $J = 8.4$ Hz, ArH), 7.72–7.74 (2H, dd, $J = 3.2$ Hz, ArH), 7.57 (3H, t, $J = 3.2$ Hz, ArH), 7.08 (2H, d, $J = 8.4$ Hz, ArH), 6.78 (1H, s, C^5–H), 3.84 (3H, s, OCH_3). Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27%. Found: C, 75.65; H, 4.41; N, 9.16%.

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