

A Simple and Clean Synthesis of Polysubstituted 2,6-Dicyanoanilines Catalyzed by KF/alumina

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ABSTRACT. A simple and clean synthesis of polysubstituted 2,6-dicyanoanilines has been developed via the reaction of arylidenemalonodinitriles with 1-arylethylidenemalonodinitriles in ethanol catalyzed by KF/ alumina. Use of non-hazardous solid base as a catalyst, operational simplicity and improved product yields are the key advantages of the present protocol.

Key words: Polysubstituted 2,6-dicyanoanilines, Heterogeneous catalyst, Synthesis

INTRODUCTION

2,6-Dicyanoanilines are typical acceptor-donor-acceptor (A-D-A) systems comprising one electron-donor and two electron-acceptors.¹ These molecular systems have attracted much attention because of their optical properties.² They are the basis for artificial photosynthetic systems,³ materials presenting semi-conducting or nonlinear optical properties⁴ and molecular electronic devices.⁵ Moreover, 2,6-dicyanoanilines are useful intermediates for building blocks for cyclophanes to create a large molecular cavity and host-guest complex.⁶ In addition, their biaryl unit is represented in several types of compounds of current interest including natural products, polymers, liquid crystals, ligands and medicinal compounds.⁷ Also, these compounds exhibit strong fluorescence in UV light⁸ and may have utility as fluorescent materials. The amino and cyano groups can be converted into various other functional groups, hence these 2,6-dicyanoanilines can be used as starting materials for a number of aromatic compounds.

2,6-Dicyanoanilines have been reported to be prepared from arylidene-malonodinitriles and 1-arylethylidene-malonodinitriles in the presence of piperidine.⁹ Elgmeie et al. have synthesized these compounds by the reaction of cycloalkylidene-malonodinitriles with arylmethylene-cyanoacetamides catalyzed by Et₃N.¹⁰ The reaction of chalcones with malononitrile also gave 2,6-dicyanoanilines.¹¹ Further, they have been prepared under microwave irradiation⁸ and using grinding method.¹² However, most of these methods suffer from serious limitations, such as use of hazardous liquid base catalysts, unsatisfactory yields, tedious work-up and long reaction times. Therefore, the development of facile, efficient and eco-safe methods

for their preparation is still necessary.

Organic reactions catalyzed by a solid heterogeneous catalyst have attracted much attention and offer advantages of operational simplicity, high selectivity and easy separation and recovery of the products, catalyst and solvent. Potassium fluoride coated alumina (KF/ alumina) has been recognized as an effective solid base catalyst to promote a wide range of organic reactions.¹³ In view of the above mentioned observations, we decided to investigate the catalytic activity of KF/ alumina, an inexpensive, safe to handle and commercially available heterogeneous base, for the synthesis of polysubstituted 2,6-dicyanoanilines.

EXPERIMENTAL

All chemicals were purchased from Merck and Sigma-Aldrich as 'synthesis grade' and used without further purification. The key intermediates arylidene- and 1-arylethylidenemalonodinitriles were prepared via Knoevenagel reaction of the corresponding aldehyde or ketone with malononitrile as reported in the literature.¹⁶ Melting points were determined in open glass capillaries and are uncorrected. UV-vis absorption spectra were recorded on a Perkin Elmer Lambda 9 spectrometer. Fluorescence spectra were measured using a SPEX Fluorolog 3 spectrometer. IR spectra were recorded on a Perkin Elmer-1430 spectrophotometer using potassium bromide pellets. ¹H and ¹³C NMR spectra were obtained at 400 MHz with a Bruker (AVANCE) spectrometer using DMSO-d₆ as solvent and TMS as an internal standard. MS spectra were measured at Micromass ZMD ESI (70 eV) system. Elemental analyses were performed using Carlo Erba-1108 analyzer.

General Procedure for the Synthesis of Polysubstituted 2,6-Dicyanoanilines 3

To a magnetically stirred solution of 1-arylethylidene-malonodinitrile **1** (1 mmol) and arylidenemalonodinitrile **2** (1 mmol) in ethanol (10 ml) was added KF/ alumina (10 mol%). The reaction mixture was stirred under reflux for 60-90 minutes to complete the reaction (monitored by TLC) and then allowed to cool at room temperature. The resulting precipitate was filtered and washed with ethanol (25 ml) to obtain the pure product **3**.

Characterization Data for the Representative Compounds

3-Amino-5-(furan-2-yl)-4'-nitro-biphenyl-2,4-dicarbonitrile (3g): Yellow solid; Yield 74%; m.p. 277-278 °C; Anal. Calcd. for C₁₈H₁₀N₄O₃: C, 65.45; H, 3.05; N, 16.96%. Found: C, 65.76; H, 3.27; N, 16.72%; UV-vis (CH₂Cl₂, λ_{max}/nm): 363; IR (KBr, cm⁻¹): 3472, 3365, 2925, 2212, 1637, 1540, 1296, 1039, 824; ¹H NMR (400 MHz, DMSO-d₆, δ/ppm): 6.60 (s, 2H, NH₂), 6.66-6.68 (m, 1H, ArH), 7.19 (s, 1H, ArH), 7.44 (d, 1H, ArH, *J* = 3.5 Hz), 7.77 (d, 1H, ArH, *J* = 1.7 Hz), 7.82-7.84 (m, 2H, ArH), 8.36-8.38 (m, 2H, ArH); ¹³C NMR (400 MHz, DMSO-d₆, δ/ppm): 89.96, 93.01, 99.49, 112.50, 112.90, 114.01, 115.32, 115.78, 123.52, 129.52, 136.48, 143.68, 144.80, 147.21, 147.77, 148.41, 154.17; MS: *m/z* = 331 (M⁺).

3-Amino-4'-nitro-5-(thiophen-2-yl)biphenyl-2,4-dicarbonitrile (3h): Yellow solid; Yield 68%; m.p. 272-273 °C; Anal. Calcd. for C₁₈H₁₀N₄O₂S: C, 62.42; H, 2.91; N, 16.18%. Found: C, 62.68; H, 2.96; N, 16.34%; UV-vis (CH₂Cl₂, λ_{max}/nm): 358; IR (KBr, cm⁻¹): 3458, 3260, 3131, 3088, 2293, 1649, 1555, 1342, 1053, 790; ¹H NMR (400 MHz, DMSO-d₆, δ/ppm): 6.74 (s, 2H, NH₂), 6.91 (s, 1H, ArH), 7.22 (t, 1H, ArH, *J* = 4.6 Hz), 7.70-7.73 (m, 2H, ArH), 7.84 (d, 2H, ArH, *J* = 8.6 Hz), 8.36 (d, 2H, ArH, *J* = 8.6 Hz); ¹³C NMR (400 MHz, DMSO-d₆, δ/ppm): 96.73, 96.77, 115.00, 115.29, 117.52, 123.54, 128.06, 128.82, 129.68, 133.24, 138.04, 141.75, 143.45, 147.34, 152.28, 154.31; MS: *m/z* = 347 (M⁺).

2-Amino-4-(furan-2-yl)-6-(thiophen-2-yl)isophthalonitrile (3i): Yellow rods; m.p. 323-325 °C; Anal. Calcd. for C₁₆H₉N₃OS: C, 65.96; H, 3.11; N, 14.42%. Found: C, 65.98; H, 3.24; N, 14.37%; UV-vis (CH₂Cl₂, λ_{max}/nm): 368; IR (KBr, cm⁻¹): 3452, 3281, 2224, 1590, 1570, 1357, 1235, 1148, 741; ¹H NMR (400 MHz, DMSO-d₆, δ/ppm): 6.31 (s, 2H, NH₂), 6.65-6.66 (m, 2H, ArH), 7.41-7.42 (m, 2H, *J* = 3.6 Hz, ArH), 7.58 (s, 1H, ArH), 7.74 (m, 2H,

ArH); ¹³C NMR (400 MHz, DMSO-d₆, δ/ppm): 88.70, 91.60, 112.52, 112.72, 113.37, 116.04, 116.07, 128.05, 128.49, 128.87, 136.26, 138.38, 141.44, 144.94, 148.41, 154.68; MS: *m/z* = 292 (M⁺).

2-Amino-4,6-di(thiophen-2-yl)isophthalonitrile (3j): Yellow rods; m.p. 314-316 °C; Anal. Calcd. for C₁₆H₉N₃S₂: C, 62.52; H, 2.95; N, 13.67%. Found: C, 62.71; H, 2.82; N, 13.56%; UV-vis (CH₂Cl₂, λ_{max}/nm): 372; IR (KBr, cm⁻¹): 3376, 3195, 2223, 1662, 1576, 1336, 1262, 835, 751; ¹H NMR (400 MHz, DMSO-d₆, δ/ppm): 6.30 (s, 2H, NH₂), 6.69-6.71 (m, 2H, ArH), 7.41-7.42 (m, 2H, ArH), 7.53 (s, 1H, ArH), 7.83 (m, 2H, ArH); ¹³C NMR (400 MHz, DMSO-d₆, δ/ppm): 92.14, 115.96, 117.04, 128.06, 128.59, 128.95, 138.12, 141.47, 154.70; MS: *m/z* = 308 (M⁺).

2-Amino-4-(furan-2-yl)-6-(5-methyl-thiophen-2-yl)isophthalonitrile (3k): Yellow needles; m.p. 334-335 °C; Anal. Calcd. for C₁₇H₁₁N₃OS: C, 66.87; H, 3.63; N, 13.76%. Found: C, 66.94; H, 3.48; N, 13.58%; UV-vis (CH₂Cl₂, λ_{max}/nm): 365; IR (KBr, cm⁻¹): 3458, 3260, 3088, 2293, 1649, 1555, 1342, 1253, 1091, 790; ¹H NMR (400 MHz, DMSO-d₆, δ/ppm): 2.12 (s, 3H, CH₃), 6.30 (s, 2H, NH₂), 6.98 (s, 1H, ArH), 7.20-7.22 (m, 1H, ArH), 7.65 (d, 1H, *J* = 0.9 Hz, ArH), 7.67 (d, 1H, *J* = 0.9 Hz, ArH), 7.69 (d, 1H, *J* = 1.0 Hz, ArH), 7.70 (d, 1H, *J* = 1 Hz, ArH); ¹³C NMR (400 MHz, DMSO-d₆, δ/ppm): 14.15, 92.04, 108.94, 110.28, 111.41, 117.88, 118.65, 122.55, 123.73, 127.43, 135.74, 136.96, 145.82, 146.39, 150.48, 154.60, 163.30; MS: *m/z* = 306 (M⁺).

RESULTS AND DISCUSSION

As part of our current studies on developing clean synthesis methodologies, we describe herein a convenient and efficient procedure for the synthesis of polysubstituted 2,6-dicyanoanilines by the reaction of 1-arylethylidenemalonodinitriles with arylidenemalonodinitriles using KF/ alumina as a strongly basic heterogeneous catalyst and thus, avoiding use of hazardous liquid organic bases like piperidine and triethylamine.

In order to optimize the reaction conditions, the reaction of 2-(1-phenylethylidene)malononitrile **1a** and 2-(4-nitrobenzylidene)malononitrile **2a** as a model reaction was carried out in ethanol under reflux in presence of different catalysts, for example, ZnO, basic alumina, KF, K₂CO₃ and KF/ alumina to afford **3a**. The results obtained with different catalysts are summarized in *Table 1*.

The best results in terms of reaction, time and yield were obtained with a catalytic amount of KF/ alumina under

Table 1. Synthesis of **3a** in ethanol in presence of different catalysts under reflux

Entry	Catalyst (mol%)	Time (h)	Yield ^a (%)
1	ZnO (10)	6	24
2	Basic alumina (10)	6	19
3	KF (10)	4	35
4	K ₂ CO ₃ (10)	6	Nil
5	KF/ alumina (10)	1	72
6 ^b	KF/ alumina (10)	8	38

^aIsolated yield.^bThe reaction was carried out at room temperature.

reflux. The product formation was also observed when the reaction was carried out at room temperature in ethanol in the presence of KF/ alumina (10 mol%). The reaction, however, required longer reaction time and the product yield was inferior (38%, *Table 1*, entry 6).

Under the optimized reaction conditions, various kinds of 1-arylethylidenemalonodinitriles **1** and arylidenemalonodinitriles **2** were made to react to give the corresponding polysubstituted 2,6-dicyanoaniline derivatives **3** (*Table 2*). As can be seen from *Table 2*, all of **1** and **2**, either bearing electron-withdrawing or electron-donating groups, afforded the desired products **3** in high to excellent yields under same reaction conditions. It is noteworthy that the methodology worked well for hetroaromatic substrates (*Table 2*, entries 7–11).

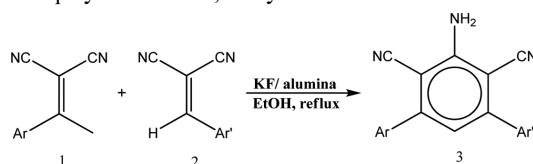
Products **3d** and **3e**, however, were obtained in slightly poor yields (*Table 2*, entries 4 and 5). These results were found to be consistent with previous reports.⁹

The known compounds were characterized by ¹H NMR

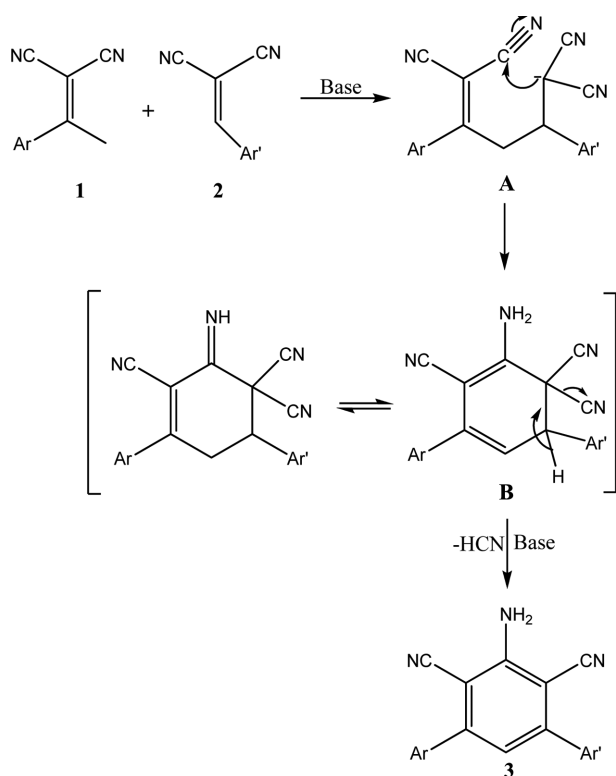
spectra and comparing their melting points with those reported in the literature. The structures of other products were elucidated by UV, IR, ¹H NMR, ¹³C NMR, Mass spectral studies and elemental analysis. The IR spectrum of **3i**, for instance, exhibited the absorption bands at 3452 and 3281 cm⁻¹ due to the presence of N–H (amine). The bands at 2224 cm⁻¹ and 1570 cm⁻¹ depicted the presence of CN (nitrile) and C=C (aromatic) respectively. The ¹H NMR spectrum of **3i** in DMSO-d₆ demonstrated a characteristic singlet at δ 6.31 for the aromatic NH₂ and different signals from δ 6.65 to δ 7.74 for the aromatic protons. The mass spectrum of **3i** showed the molecular ion peak at *m/z* 292 corresponding to its molecular weight.

The compound **3i** strongly absorbs in the violet as evidenced by its yellow colour. The UV-visible spectrum of **3i** recorded in dichloromethane showed a strong absorption band at 368 nm while upon UV excitation, **3i** showed an intense blue fluorescence with maximum emission at 407 nm and a fluorescence quantum yield of Φ_f = 0.10 (using 9,10-diphenylanthracene as standard).¹⁴ The observed photophysical properties and high fluorescence quantum yield are identical to those previously found for 2,6-dicyanoanilines.¹⁵

In accordance with the mechanism suggested in literature,⁹ the first step of the present reaction may involve the vinylogous Michael addition of **1** to arylidenemalonodinitriles **2** to give adduct **A**. The addition is followed by Thorpe cyclization of Michael product **A** to the cyclohexadiene system **B**. Finally, the elimination of hydrogen cyanide from **B** gave the polysubstituted 2,6-dicyanoanilines (*Scheme 1*).

Table 2. KF/ alumina catalyzed synthesis of polysubstituted 2,6-dicyanoanilines

Entry	Ar	Ar'	Product	Time (min)	Yield (%)	m.p. (°C) Found [reported]
1	C ₆ H ₅	4-O ₂ NC ₆ H ₄	3a	60	72	242-245 [244-246] ^{11d}
2	C ₆ H ₅	3-O ₂ NC ₆ H ₄	3b	60	73	236-237 [234-236] ⁹
3	4-O ₂ NC ₆ H ₄	4-O ₂ NC ₆ H ₄	3c	90	62	349-351 [352-353] ⁹
4	C ₆ H ₅	2-CH ₃ OC ₆ H ₄	3d	80	45	167-170 [168-169] ^{11d}
5	C ₆ H ₅	4-H ₂ NC ₆ H ₄	3e	90	42	320-323 [321-322] ⁹
6	4-O ₂ NC ₆ H ₄	4-H ₂ NC ₆ H ₄	3f	70	64	287-290 [286-287] ⁹
7	4-O ₂ NC ₆ H ₄	2-Furanyl	3g	60	74	277-278
8	4-O ₂ NC ₆ H ₄	2-Thienyl	3h	60	68	272-273
9	2-Thienyl	2-Furanyl	3i	60	72	323-325
10	2-Thienyl	2-Thienyl	3j	60	69	314-316
11	2-Furanyl	5-Me-2-Thienyl	3k	70	60	334-335



Scheme 1. Plausible mechanism for the formation of polysubstituted 2,6-dicyanoanilines **3**.

CONCLUSION

In summary, a clean and efficient method for the synthesis of polysubstituted 2,6-dicyanoanilines has been developed via the reaction of 1-arylethylidene malonodinitriles with arylidene malonodinitriles in ethanol under reflux using KF/ alumina as a heterogeneous green catalyst.

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