# DBU As A Novel and Highly Efficient Catalyst for The Synthesis of 3,5-Disubstituted-2,6-dicyanoanilines Under Conventional and Microwave Conditions

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**ABSTRACT:** *3,5-disubstituted-2,6-dicyanoaniline derivatives have been synthesized via the reaction of arylmethylene- and 1-arylethylidenemalonodinitriles using 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) as a novel and highly efficient catalyst under conventional as well as microwave conditions. Use of non-hazardous, inexpensive and readily available base catalyst, convenient procedure, short reaction time and improved product yields are some added advantages of the present protocol.*

**KEY WORDS:** *1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU); 3,5-Disubstituted-2,6-dicyanoanilines; Microwave; 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, 3]. They are the basis for artificial photosynthetic systems [4], materials presenting non-linear optical properties [5] and molecular electronic devices [6]. Moreover, 2,6-dicyanoanilines are useful intermediates for building blocks for cyclophanes to create a large molecular cavity and host-guest complex [7]. Also, these compounds exhibit strong fluorescence in UV light [8] and may have utility as fluorescent materials.

2,6-Dicyanoanilines have been reported to be prepared from arylidenemalonodinitriles and arylethylidenemalonodinitriles in the presence of piperidine [9]. *Elgmeie et al.* have synthesized these compounds by the reaction of cycloalkylidene-malonodinitriles with arylmethylenecyanoacetamides catalyzed by $Et_3N$ [10]. Very recently, they have been prepared via one-pot, three-component reaction of aldehydes, ketones and propanedinitrile in the catalytic presence of $Et_3N$ [8], $K_2CO_3$[11] and zinc titanatenanopowder [12]. However, inspite of their potential utility, most of these methods suffer from one or more disadvantages, such as harsh reaction conditions, unsatisfactory yields, prolonged reaction times, tedious procedures and use of hazardous liquid organic base catalysts.

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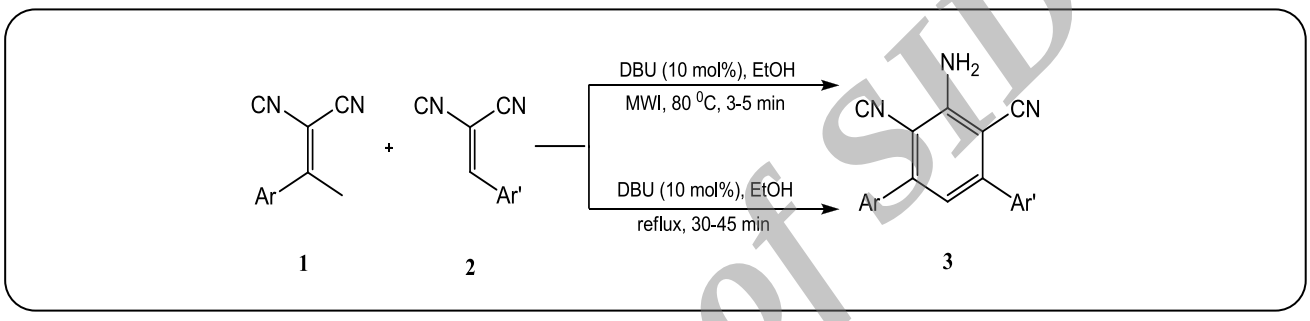
***Table 1: Optimization of reaction conditions for the synthesis of compound 3a using DBU as a catalyst under refluxing conditions.***

| Entry | Amount of catalyst (mol%) | Solvent | Time (h) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | 10 | EtOH | 0.5 | 79 |
| 2 | 10 | $CH_2Cl_2$ | 3 | 36 |
| 3 | 10 | THF | 3 | 45 |
| 4 | 10 | $CH_3CN$ | 2 | 69 |
| 5[b] | 10 | EtOH | 4 | 58 |
| 6 | 5 | EtOH | 1 | 63 |
| 7 | 20 | EtOH | 0.5 | 82 |




***Scheme 1: Synthesis of 3,5-disubstituted-2,6-dicyanoanilines catalyzed by DBU under microwave and conventional conditions.***

In recent years, microwave irradiation has been widely used in the synthesis of heterocyclic compounds with good yields and short reaction times [13, 14]. On the other hand, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) has been found to be superior to other tertiary amines as catalyst for a variety of organic reactions in recent years [15-17]. DBU is one of the strongest organic neutral base (pKa = 12) and measomeric +M effect of the adjacent nitrogen stabilizes the protonated species.

In continuation to our endeavor for the development of simple and highly expedient methods for the synthesis of biologically significant compounds [18, 19], in the present study, we have synthesized 3,5-disubstituted-2,6-dicyanoanilines by reaction of arylmethylenemalonodinitriles with 1-arylethylidenemalonodinitriles in the presence of DBU as a basic catalyst avoiding the use of hazardous liquid organic bases like piperidine and triethylamine.

## EXPERIMENTAL SECTION

All the chemicals were purchased from Merck and Sigma-Aldrich and used without further purification. The key intermediates arylmethylene- and 1-arylethyl-idenemalonodinitriles were prepared via Knoevenagel reaction of the corresponding aldehyde or ketone with malononitrile as reported in the literature [20]. The microwave assisted reactions were performed in a RAGA's modified Electromagnetic Microwave System whereby microwaves are generated by magnetron at a frequency of 2450 MHz having adjustable output power levels *i.e.* 10 levels from 140 to 700 Watts and with an individual sensor for temperature control with attachment of reflux condenser with constant stirring (thus avoiding the risk of high pressure development). Melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded on Perkin Elmer-1430 spectrophotometer using potassium bromide pellets. $^1H$ and $^{13}C$ NMR spectra were obtained at 400 and 100 MHz, respectively with a Bruker (AVANCE) WM-400 spectrometer using DMSO-$d_6$ as solvent and TMS as an internal standard. The elemental analyses were performed using Carlo Erba-1108 analyzer. It is notable that HCN

is released during the reaction. Therefore, the reactions were performed under the fumed hood.

*General conventional procedure for the synthesis of 3,5-disubstituted-2,6-dicyanoanilines* **3**

To a mixture of 1-arylethylidenemalonodinitriles **1** (10 mmol) and arylmethylenemalonodinitrile **2** (10 mmol) in anhydrous ethanol (10 mL) was added DBU (10 mol%) and the resulting mixture was stirred under gentle reflux. After the completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature and the precipitate formed was filtered and washed with aqueous ethanol (1:1) to obtain the pure product **3a-3n**.

*General microwave procedure for the synthesis of 3,5-disubstituted-2,6-dicyanoanilines* **3**

1-Arylethylidenemalonodinitriles **1** (10 mmol), arylmethylenemalonodinitrile **2** (10 mmol) and DBU (10 mol%) were thoroughly mixed in anhydrous ethanol (5 mL). The reaction mixture was irradiated at medium power level of 280 W and 80 $^0$C for 3-5 minutes (monitored by TLC) and then allowed to cool at room temperature. The resulting precipitate was filtered and washed with aqueous ethanol (1:1) to yield the pure product **3a-3n**.

***Spectroscopic data***

*2-Amino -4-(1*H*-pyrrol-2-yl) -6-(thiophen-2-yl) isophthalonitrile* (**3m**)

Yellow needles; m.p. 338-339 °C (from EtOH). IR (KBr, cm$^{-1}$): 3433, 3378, 3268 (ArN–H), 2210 (ArC≡N), 1570 (ArC=C), 1333 (ArC–N), 1251, 1095, 748. $^1$H NMR (400 MHz, DMSO-$d_6$, δ/ ppm): 6.38 (s, 2H, $NH_2$), 6.65-6.67 (m, 2H, pyrrol), 7.41-7.42 (m, 2H, pyrrol + thiophene), 7.57 (s, 1H, ArH), 7.76 (m, 2H, thiophene), 10.00 (s, 1H, NH of pyrrol). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ/ ppm): 96.73, 96.77, 106.24, 112.78, 115.00, 115.29, 118.15, 125.95, 126.48, 127.05, 127.38, 128.02, 136.38, 142.21, 146.41, 150.38. Anal. Calcd. for $C_{16}H_{10}N_4S$: C, 66.19; H, 3.47; N, 19.30%. Found: C, 66.32; H, 3.64; N, 19.16%.

*2-Amino -4-(5-methylthiophen-2-yl) -6-(thiophen-2-yl) isophthalonitrile* (**3n**)

Yellow needles; m.p. 249-251 °C (from EtOH). IR (KBr, cm$^{-1}$): 3472, 3346 (ArN–H), 2953 (ArC–H), 2216 (ArC≡N), 1552 (ArC=C), 1257 (ArC–N), 1112, 786. $^1$H NMR (400 MHz, DMSO-$d_6$, δ/ ppm): 2.56 (s, 3H, $CH_3$), 6.36 (s, 2H, $NH_2$), 6.82-6.93 (m, 2H, thiophene), 7.19-7.21 (dd, 1H, $J_1$ = 3.7 Hz, $J_2$ = 1.4 Hz, thiophene), 7.53-7.68 (m, 3H, ArH + thiophene). $^{13}$C NMR (100 MHz, DMSO-$d_6$, δ/ ppm): 13.52, 96.73, 96.77, 104.57, 115.00, 115.29, 125.95, 126.48, 127.05, 127.38, 128.02, 136.38, 142.21, 146.41, 150.38, 152.05, 152.21. Anal. Calcd. for $C_{17}H_{11}N_3S_2$: C, 63.53; H, 3.45; N, 13.07%. Found: C, 63.76; H, 3.52; N, 13.04%.

## RESULTS AND DISCUSSION

The title compounds were synthesized in good to high yields by two ways *i.e.* by reaction of 1-arylethylidenemalonodinitriles **1** and arylmethylenemalonodinitriles **2** in the presence of DBU as a catalyst under conventional refluxing conditions as well as microwave irradiation (Scheme 1).

First, we attempted the conventional method for the synthesis of title compounds. 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 different solvents using various amounts of DBU as a catalyst. The results are summarized in Table 1. As shown in Table 1, the best results were obtained with 10 mol% of DBU in ethanol under reflux. The reaction also underwent when carried out at room temperature in ethanol in the presence of 10 mol% of DBU. However, the product yield was inferior (58%) despite of longer reaction time (Table 1, entry 5). Reaction with 5 mol% of the catalyst required longer reaction time and only 63% yield of the desired product was obtained (Table 1, entry 6). Excessive amount of catalyst (20 mol%) did not increase the yield remarkably (Table 1, entry 7).

Further, in order to make the reaction times shorter and to improve product yields, we attempted microwave irradiation method for the synthesis of these compounds. The comparative study based on the optimization of both methods is depicted in Table 2 which shows that the reactions were efficiently promoted by microwave irradiation. The reaction time was strikingly shortened from 30-45 min (under conventional heating conditions) to 3-5 min (under microwave irradiation) and quantitative yields were obtained.

***Table 2: DBU-catalyzed synthesis of 3,5-disubstituted-2,6-dicyanoanilines under conventional and microwave conditions.***

| Product | Ar | Ar' | Conventional | | Microwave | | Mp |
|---|---|---|---|---|---|---|---|
| | | | Time (min) | Yield (%) | Time (min) | Yield (%) | Found [reported] ($^0$C) |
| 3a | 4-$O_2NC_6H_4$ | $C_6H_5$ | 30 | 79 | 3 | 86 | 243-244 (244-246) [18] |
| 3b | 3-$O_2NC_6H_4$ | $C_6H_5$ | 30 | 76 | 3 | 82 | 235-236 (234-236) [9] |
| 3c | 4-$O_2NC_6H_4$ | 4-$O_2NC_6H_4$ | 45 | 62 | 5 | 74 | 350-351 (352-353) [9] |
| 3d | 2-$CH_3OC_6H_4$ | $C_6H_5$ | 45 | 59 | 5 | 68 | 172-173 (168-169) [21] |
| 3e | 2-Furanyl | 4-$O_2NC_6H_4$ | 30 | 75 | 3 | 84 | 275-276 (277-278) [18] |
| 3f | 2-Thienyl | 4-$O_2NC_6H_4$ | 30 | 73 | 3 | 79 | 272-274 (272-273) [18] |
| 3g | 4-$CH_3C_6H_4$ | 2-Thienyl | 30 | 64 | 3 | 75 | 227-228 (227-229) [12] |
| 3h | 4-$ClC_6H_4$ | 2-Thienyl | 30 | 68 | 3 | 76 | 277-279 (279-281) [12] |
| 3i | 4-Pyridyl | $C_6H_5$ | 30 | 65 | 3 | 72 | 278-280 (279-281) [12] |
| 3j | 2-Furanyl | 2-Furanyl | 30 | 83 | 3 | 87 | 318-319 (318) [18] |
| 3k | 2-Thienyl | 2-Furanyl | 30 | 80 | 3 | 84 | 325-326 (323-325) [18] |
| 3l | 2-Thienyl | 2-Thienyl | 30 | 78 | 3 | 81 | 315-316 (314-316) [18] |
| 3m | 2-Pyrrolyl | 2-Thienyl | 30 | 64 | 3 | 69 | 338-339 |
| 3n | 5-Me-2-Thienyl | 2-Thienyl | 45 | 69 | 3.5 | 76 | 249-251 |

***Table 3: Comparison of DBU with reported catalysts for synthesis of 3a***

| Entry | Conditions | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | Piperidine, $CH_3CN$, reflux | 3 | 77 [9] |
| 2 | GIL, 60 $^0$C | 5 | 32 [21] |
| 3 | DBU, EtOH, reflux | 0.5 | 79 |

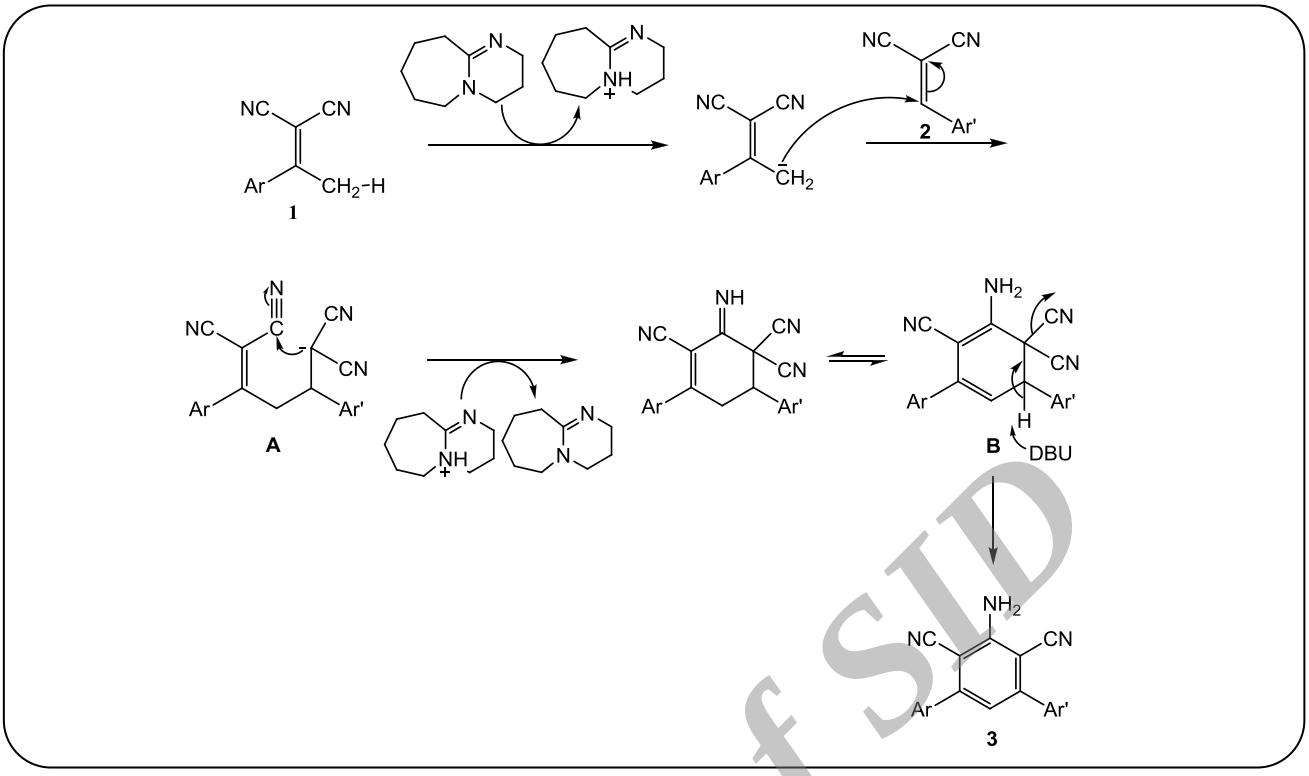
To demonstrate the efficiency of the present work in comparison with previously reported procedures, synthesis of **3a** was considered as a representative example. As shown in Table 3, DBU was found to be an effective catalyst with respect to reaction time and yield. Except for compounds **3m** and **3n**, all products are known compounds which were characterized by comparing their melting points with those reported in the literature. The structures of products **3m** and **3n** were confirmed by elemental analyses and spectral data (IR, $^1$H NMR and $^{13}$C NMR).

In accordance with the mechanism suggested in literature [9], the first step of the present reaction may involve the vinylogous Michael addition of 1-arylethylidenemalonodinitriles to **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** in the presence of DBU gave the 3,5-disubstituted-2,6-dicyanoanilines (Scheme 2).

## CONCLUSIONS

The present work describes a rapid, convenient and highly efficient method for the synthesis of 3,5-disubstituted-2,6-dicyanoanilines by a DBU-catalyzed reaction of arylmethylenemalonodinitriles with




***Scheme 2: The proposed mechanism for the synthesis of 3,5-Disubstituted-2,6-dicyanoanilines catalyzed by DBU.***

1-arylethylidenemalonodinitriles in ethanol under microwave as well as conventional refluxing conditions. The operational simplicity, short reaction times, excellent yields and use of safe and readily available base catalyst make it a preferred procedure for the preparation of these compounds.

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**REFERENCES**

[1] Borate H.B., Kudale A.S., Agalave S.G., Synthesis of Substituted 2,6-Dicyanoanilines and Related Compounds. A Review, *Organic Preparations and Procedures International*, **44**: 467-521 (2012).

[2] Sepiol J., Milart P., A New and Efficient Synthesis of 3,5_Diarylaminobenzenes from Arylidenemalonodinitriles and 1-Arylethylidenemalonodinitriles, *Tetrahedron.*, **41**: 5261-5265 (1985).

[3] Griffiths J., Lockwood M., Roozpeikar B., Orientation Effects in The Benzene Chromophore Bearing One Donor and Two Acceptor Groups. Electronic Absorption Spectra of The Dicyanoanilines, *J. Chem. Soc. Perkin Trans. 2*, 1608-1610 (1977).

[4] Prasad P.N., Williams D.J., "Introduction to Nonlinear Optical Effects in Molecules and Polymers", John Wiley, New York, (1991).

[5] Kurreck H., Huber M., Model Reactions for Photosynthesis-Photoinduced Charge and Energy Transfer Between Covalently Linked Porphyrin and Quinone Units, *Angew. Chem. Int. Ed.*, **34**: 849-866 (1995).

[6] Petty M.C., Bryce M.R., Bloor D., "Introduction to Molecular Electronics", Oxford University Press: New York, (1995).

[7] Raghukumar V., Murugan P., Ramakrishnan V.T., A Facile One Pot Synthesis of m-Terphenyl and Biaryl Derivatives, *Synth. Commun*., **31**: 3497-3505 (2001).

[8] Cui S.L., Lin X.F., Gang W.Y., Parallel Synthesis of Strongly Fluorescent Polysubstituted 2,6-Dicyanoanilines via Microwave-Promoted Multicomponent Reaction, *J. Org. Chem.*, **70**: 2866-2869 (2005).

[9] Milart P., Wilamowski J., Sepiol J.J., Synthesis of Di- and Triamino-l,l':3',l''-terphenyls from Arylethylidene- and Arylidenemalonodinitriles, *Tetrahedron.*, **54**: 15643-15656 (1998).

[10] Elgemei G.E.H., Elzanate A.M., Mansour A.K., Novel Synthesis of Indans, Tetralones, Condensed Benzocarbocyclic Nitriles and Condensed Pyridine-2(1*H*)-thiones from the Reactions of Cycloalkylidenemalononitriles with Arylmethylene(cyano)-acetamide and –thioacetamide, *J. Chem. Soc. Perkin Trans.1*, **1**: 1073-1074 (1992).

[11] Shaterian H.R., Honarmand M., Oveisi A.R., Multicomponent Synthesis of 3,5-Diaryl-2,6-Dicyanoanilines Under Thermal Solvent-Free Conditions, *Monatsh. Chem*., **141**: 557-560 (2010).

[12] Das P., Butcher R.J., Mukhopadhyay C., Zinc Titanate Nanopowder: An Advanced Nanotechnology Based Recyclable Heterogeneous Catalyst for The One-Pot Selective Synthesis of Self-Aggregated Low-Molecular Mass Acceptor–Donor–Acceptor–Acceptor Systems and Acceptor–Donor–Acceptor Triads, *Green Chem.*, **14**: 1376-1387 (2012).

[13] Ashry E.S.H.El., Kassem A.A., Account of Microwave Irradiation for Accelerating Organic Reactions, *ARKIVOC*., **ix**: 1-16 (2006).

[14] Elander N., Jones J.R., Lu S.Y., Elander S.S., Microwave-Enhanced Radiochemistry, *Chem. Soc. Rev*., **29**: 239-249 (2000).

[15] Aggarwal V.K., Mereu A., Superior Amine Catalysts for The Baylis-Hillman Reaction : The Use of DBU and Its Implication, *Chem. Commun.*, 2311-2312 (1999).

[16] Yeom C.E., Kim M.J., Kim M.B., 1,8-Diazabicyclo[5.4.0]Undec-7-Ene (DBU) Promoted Efficient and Versatile Aza-Michael Addition, *Tetrahedron*, **63**: 904-909 (2007).

[17] Yoshida M., Komatsuzaki Y., Ihara M. Synthesis of 5-Vinylideneoxazolidin-2-Ones by DBU-Mediated $CO_2$ Fixation Reaction of 4-(Benzylamino)-2-Butynyl Carbonates Benzoates, *Org. Lett.*, **10**: 2083-2086 (2008).

[18] Jain S., Keshwal B.S., Rajguru D., A Clean and Efficient L-Proline-Catalyzed Synthesis of Polysubstituted Benzenes in The Ionic Liquid 1-Butyl-3-Methylimidazolium Hexafluorophosphate, *J. Serb. Chem. Soc.*, **77**: 1345-1352 (2012).

[19] Rajguru D., Keshwal B.S., Jain S., Solvent-Free, Green and Efficient Synthesis of Pyrano[4,3-*b*]Pyrans by Grinding and Their Biological Evaluation as Antitumor and Antioxidant Agents, *Med. Chem. Res.*, **22**: 5934-5939 (2013).

[20] Mukhopadhyay C., Datta A., A Simple, Efficient and Green Procedure for the Knoevenagel Condensation of Aldehydes with *N*-Methylpiperazine at Room Temperature under Solvent-Free Conditions, *Synth. Commun.*, **38**: 2103-2112 (2008).

[21] Xin X., Wang Y., Xu W., Lin Y., Duan H., Dong D., A Facile and Efficient One-Pot Synthesis of Polysubstituted Benzenes in Guanidinium Ionic Liquids, *Green Chem.* **12**: 893-898 (2010).