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One-step synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines and their use in the synthesis of highly functionalized 2,3,5,6,7- and 2,3,4,5,7-substituted indoles

Sangmeshwer P. Sawargave, Ananada S. Kudale, Jaydeep V. Deore, Dattatry S. Bhosale, Jaisingh M. Divse, Subhash P. Chavan, Hanumant B. Borate *

Division of Organic Chemistry, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India

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ABSTRACT

A three-component, one-step method for the synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines involving reaction of alkyl aldehyde, malononitrile and aryl aldehyde in presence of morpholine is reported. Highly functionalized 2,3,5,6,7- and 2,3,4,5,7-substituted indoles were prepared from these dicyanoanilines by reaction with ethyl bromoacetate. These substituted dicyanoanilines and indoles have a potential to be converted into various other compounds taking advantage of various functional groups present in these molecules.

2,6-Dicyanoanilines are useful as important substrates for non-linear optical materials[1] and molecular electronic devices.[2] They are strongly fluorescent[3] and have been reported to exhibit biological activities like antileishmanial activity.[4] 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 large number of aromatic compounds. There are a number of methods reported for the synthesis of substituted 2,6-dicyanoanilines[3,5] and conversion of dicyanoanilines into substituted indoles is known in the literature.[6] During our efforts to develop new antifungal agents[7], we desired to prepare variously substituted indoles **1** (Fig. 1) and intended to use the dicyanoanilines **2** as intermediates in order to construct the indole skeleton by a reaction with ethyl bromoacetate.[6] Literature survey revealed that though there are a large number of methods reported for the synthesis of substituted 2,6-dicyanoanilines, most of the methods describe the synthesis of 3,5-disubstituted-2,6-dicyanoanilines **3**. There are a very few reports describing synthesis of 3,4-dialkyl-2,6-dicyanoanilines **4**[8] and there is only one method[8c] reported by Khaidem et al. for the synthesis of 4-alkyl-3-aryl-2,6-dicyanoaniline **2** wherein 4-methyl-3-phenyl-2,6-dicyanoaniline was prepared from propiophenone by a three-step reaction sequence in low yields. We envisioned that a three-component reaction of alkyl aldehyde, malononitrile and aryl aldehyde in presence of base would afford 4-alkyl-3-aryl-2,6-dicyanoaniline **2** and the results are reported herein. The reaction of propionaldehyde, malononitrile and 4-methoxybenzaldehyde was attempted as a model reaction in presence of various bases like potassium carbonate, triethylamine, morpholine, basic alumina etc with or without

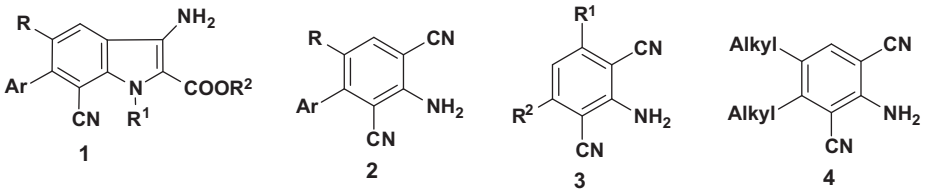

Figure 1. General structures of pentasubstituted indoles and 2,6-dicyanoanilines.

* Corresponding author. Tel.: +91 2025902546; fax: +91 202590269.
E-mail address: hb.borate@ncl.res.in (H.B. Borate).

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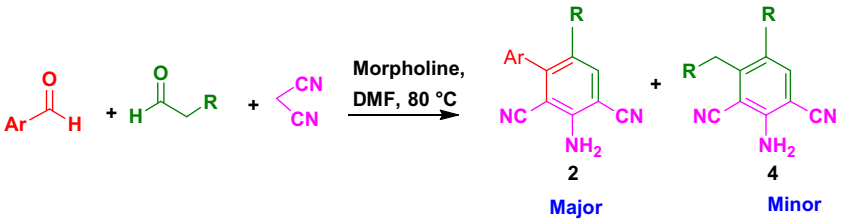


Scheme 1. Preparation of 4-alkyl-3-aryl-2,6-dicyanoanilines.

Table 1
Synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines **2**

Entry	Ar	R	Product **2**	Yield[a] (%)
1	4-Methoxyphenyl	Me	**2a**	77
2	4-Methoxyphenyl	*n*-Pr	**2b**	64
3	4-Methoxyphenyl	*n*-Hex	**2c**	69
4	1-Naphthyl	*n*-Pr	**2d**	77
5	1-Naphthyl	Me	**2e**	52
6	3,4-(Methylenedioxy)phenyl	Me	**2f**	75
7	2-Thienyl	*n*-Hex	**2g**	56
8	2-Thienyl	Me	**2h**	70
9	2-Furanyl	*n*-Hex	**2i**	10
10	2-Furanyl	Me	**2j**	17
11	4-Hydroxyphenyl	Me	**2k**	53
12	4-Nitrophenyl	Me	**2l**	62

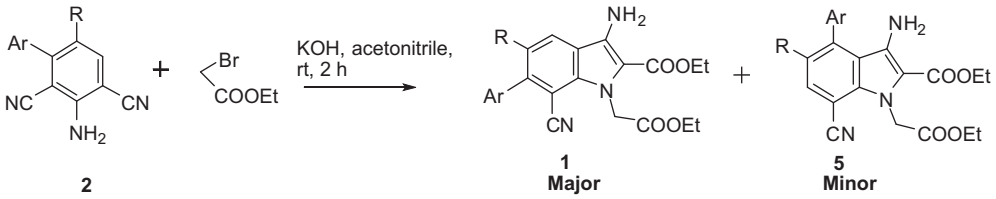
[a] The yields given are for the isolated desired products. In addition, the corresponding products **4** were isolated in 8–18% yields.

solvent (dimethylformamide, ethyl acetate, acetonitrile) at various temperatures ranging from room temperature to 100 °C and it was observed that the reaction[9,10] in presence of morpholine in DMF at 80 °C afforded the desired 3-amino-4′-methoxy-6-methyl-[1,1′-biphenyl]-2,4-dicarbonitrile (**2a**) as major product in 77% isolated yield and 2,6-dicyano-5-ethyl-4-methyl-aniline (**4**, R = Me)[8d] as a minor product in 8% yield (Scheme 1). These two products were easily separated by column chromatography. Product **2a** is formed by a three- component reaction involving anisaldehyde, propionaldehyde and malononitrile while the side product **4** is formed by reaction of propionaldehyde and malononitrile. Therefore, propionaldehyde is required in slightly more amount than anisaldehyde.

The reaction was done with various combinations of aryl and aliphatic aldehydes to see the generality and the various compounds prepared[9] are shown in Table 1.

It was observed that dicyanoanilines with a wide variety of substituents could be prepared by this method. This protocol provides easy access to a regiospecific synthesis of unsymmetrical, polyfunctional biaryls, which would be difficult to make by conventional methods. It is also noteworthy that the present method makes use of easily available starting materials, does not use expensive catalysts/reagents and the conditions are mild.

Narsaiah et al. have reported[6] that reaction of 2,6-dicyanoanilines with ethyl bromoacetate in presence of potassium carbonate and potassium iodide affords substituted indoles. Accordingly, reaction of the 3-amino-4′-methoxy-6-methyl-[1,1′-biphenyl]-2,4-dicarbonitrile (**2a**) with ethyl bromoacetate was carried out in presence of bases like potassium carbonate, potassium hydroxide pellets, sodium hydroxide pellets etc in different solvents like ethyl acetate, acetonitrile, dimethyl formamide etc at various temperatures and it was observed that the reaction[11] in presence of potassium hydroxide pellets in acetonitrile at room temperature afforded ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-6-(4-methoxyphenyl)-5-methyl-1*H*-indole-2-carboxylate (**1a**) as major product in 69% yield and ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-4-(4-methoxyphenyl)-5-methyl-1*H*-indole-2-carboxylate (**5a**) as minor product in 12% yield (Scheme 2). The structures



Scheme 2. Synthesis of 2,3,5,6,7- and 2,3,4,5,7-substituted indoles **1** and **5**.

Table 2
Synthesis of 2,3,5,6,7- and 2,3,4,5,7-substituted indoles **1** and **5**

Entry	Ar	R	Substituted aniline **2**	Product **1**		Product **5**	
				Compd no.	Yield[a] (%)	Compd no.	Yield[a] (%)
1	4-Methoxyphenyl	Me	**2a**	**1a**	69	**5a**	12
2	4-Methoxyphenyl	*n*-Pr	**2b**	**1b**	65	**5b**	15
3	4-Methoxyphenyl	*n*-Hex	**2c**	**1c**	85	**5c**	9
4	1-Naphthyl	Me	**2d**	**1d**	62	**5d**	18
5	1-Naphthyl	*n*-Pr	**2e**	**1e**	61	**5e**	13
6	3,4-(Methylenedioxy)phenyl	Me	**2f**	**1f**	69	**5f**	23
7	2-Thienyl	Me	**2g**	**1g**	64	**5g**	12
8	2-Thienyl	*n*-Hex	**2h**	**1h**	77	**5h**	11
9	2-Furanyl	*n*-Hex	**2j**	**1i**	69	**5i**	15

[a] The yields given are for the isolated products.

of the isomers were assigned based on spectral data[11] and literature precedent.[6] The various novel 2,6-dicyanoanilines **2** synthesized above were subjected to the above reaction conditions and the results are shown in Table 2.

It is interesting to note that all the substituents on indoles **1** prepared in the present work are different and they can act as intermediates in the preparation of a large number of substituted indoles, and compounds derived from indoles, taking advantage of different reactivities of various groups present in these molecules. The same is true with the compounds **5**. In conclusion, the present manuscript describes a three-component, one-step method for the synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines **2** using easily available starting materials. The dicyanoanilines prepared above were utilized for the preparation of highly functionalized 2,3,5,6,7- and 2,3,4,5,7-substituted indoles **1** and **5** in one step under mild conditions. The present method has a potential to generate a large number of new compounds for structure-property studies in order to explore their utility as new substrates for non-linear optical materials or molecular electronic devices. Also, these molecules exhibit strong fluorescence in UV light (except **2l**) and may have utility as fluorescent materials. We are using these molecules as intermediates for the synthesis of new molecules being studied for their antifungal activity and the results will be published elsewhere.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.064.

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9. Spectral data for all compounds prepared in the present work are available as Supplementary data for this Letter.
Representative procedure for preparing 3-aryl-4-alkyl-2,6-dicyanoanilines 2
Preparation of 3-amino-4′-methoxy-6-methyl-[1,1′-biphenyl]-2,4-dicarbonitrile (**2a**): To a mixture of propionaldehyde (2.00 g, 34.48 mmol), 4-methoxybenzaldehyde (3.75 g, 27.58 mmol) and malononitrile (4.55 g, 68.96 mmol) in dry DMF (20 mL) taken in a round bottom flask equipped with reflux condenser and guard tube, was added morpholine (6.60 g, 75.85 mmol) at 0 °C. The mixture was allowed to come to rt and then stirred at 80 °C for 12 h. It was then cooled to room temperature, diluted with ice-cold water (100 mL), extracted with ethyl acetate (3 × 75 mL), dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel using pet ether–ethyl acetate (3–20% ethyl acetate in pet ether) as eluent to give 3-ethyl-4-methyl-2,6-dicyanoaniline (**4**, R = Me)[8d] as a white solid in initial fractions (0.255 g, 8%). Further elution afforded pure 3-amino-4′-methoxy-6-methyl-[1,1′-biphenyl]-2,4-dicarbonitrile **2a** as white solid (5.58 g, 77%), mp: 199 °C. IR (chloroform):1270, 1477, 1514, 1606, 1644, 2218, 2915, 3247, 3349, 3434 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.05 (s, 3H), 3.87 (s, 3H), 5.07 (br s, 2H), 7.01 (d, *J* = 8 Hz, 2H), 7.21 (d, *J* = 10 Hz, 2H), 7.47 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 18.8, 55.3, 96.1, 98.0, 114.1 (2C), 116.1, 116.7, 124.7, 129.4, 130.1 (2C), 138.9, 150.5, 151.1, 159.6. MS (ESI) *m*/*z*: 262.14 (M-1).
10. Part of this work was presented as a poster during the CRSI zonal meeting held at NCL, Pune during May 13–14, 2011.
11. *Representative procedure for preparing 2,3,5,6,7- and 2,3,4,5,7-substituted indoles* **1** *and* **5** *Preparation of ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-6-(4-methoxyphenyl)-5-methyl-1H-indole-2-carboxylate* (**1a**) *and ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-4-(4-methoxyphenyl)-5-methyl-1H-indole-2-carboxylate* (**5a**): The 3-amino-4′-methoxy-6-methyl-[1,1′-biphenyl]-2,4-dicarbonitrile (**2a**) (263 mg, 1 mmol) and ethyl bromoacetate (0.34 mL, 3 mmol) were dissolved in acetonitrile (5 mL) in a 2-necked RB flask equipped with guard tube at rt and the pellets of potassium hydroxide (336 mg, 6 mmol) were added. The reaction mixture was stirred at room temperature for 2 h. It was then diluted with excess of cold water and extracted with ethyl acetate (3 × 10 mL), dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel using pet ether-ethyl acetate (5–7% ethyl acetate in pet ether) as eluent. Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-4-(4-methoxyphenyl)-5-methyl-1*H*-indole-2-carboxylate (**5a**) was obtained as yellow solid (53 mg, 12.15%); mp: 167 °C. IR (chloroform): 1274, 1330 1515, 1609, 1672, 1751, 2219, 2912, 2982, 3374, 3476 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 6 Hz, 6H), 2.09 (s, 3H), 3.90 (s, 3H), 4.23–4.37 (m, 4H), 4.49 (bs, 2H), 5.57 (s, 2H), 7.05 (d, *J* = 8 Hz, 2H), 7.23 (d, *J* = 8 Hz, 2H), 7.56 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 14.2, 46.9, 55.2, 60.1, 61.4, 92.7, 109.5, 114.1 (2C), 118.1, 118.5, 127.0, 129.1, 129.6 (2C), 135.4, 135.9, 137.9, 141.2, 159.5, 162.4, 169.3. MS (ESI) *m*/*z*: 458.20 (M+1). Further elution provided ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-6-(4-methoxyphenyl)-5-methyl-1*H*-indole-2-carboxylate (**1a**) as yellow solid (301 mg, 69.2%); mp: 188 °C. IR (chloroform): 1270, 1621 1682, 1733, 2215, 3370, 3476 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 6Hz, 3H), 1.41 (t, *J* = 6 Hz, 3H), 2.18 (s, 3H), 3.87 (s, 3H), 4.28 (q, *J* = 8 Hz, 2H), 4.39 (q, *J* = 6 Hz, 2H), 4.97 (bs, 2H), 5.60 (s, 2H), 7.00 (d, *J* = 10 Hz, 2H), 7.22 (d, *J* = 10 Hz, 2H), 7.62 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 14.3, 20.6, 46.7, 55.1, 60.3, 61.4, 95.0, 110.2, 113.8 (2C), 117.3, 119.5, 124.9, 127.5, 130.2 (2C), 130.4, 136.2 (2C), 147.4, 159.4, 162.4, 169.6. MS (ESI) *m*/*z*: 458.14 (M+1). ^1H–^{13}C HMBCNMR spectroscopy supported the assigned structures.