



Synthesis and Evaluation of Coupler 4-Aryl-2-Aminothiophene-3-Carbonitrile and its Derivatives as Potential Coupling Component in Dye Synthesis

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Abstract: Thiophene nucleus has been established as the potential entity in the large growing chemical world of heterocyclic compounds possessing promising coupling characteristics. A series of coupler 4-aryl-2-aminothiophene-3-carbonitrile derivatives were synthesized. The synthetic method involves the reaction of ketones, aldehydes or 1,3-dicarbonyl species with activated nitriles and elemental sulphur in the presence of an amine base. Characterization of these coupling components was carried out by UV-Visible spectroscopy, Fourier-transform infrared spectroscopy (FT-IR), gas chromatography–mass spectrometry (GC-MS) and nuclear magnetic resonance spectroscopy (NMR) analysis. The synthesized compounds were purified, characterized and evaluated for spectroscopic properties. They were found to possess good coupling properties as well as high degree of brightness and a colour deepening effect compared to other heterocyclic couplers.

Keywords: Heterocyclic compounds; synthesis; absorption spectroscopy; NMR; Gewald reaction

1. Introduction

Interest in the design of azo dyes containing heterocyclic moieties stems from their high degree of brightness compared to azo dyes derived from anilines.^[1] The 2-aminothiophene based azo dyes are known as disperse dyes with excellent brightness of shade. This class of dyes was established as an alternative to more expensive anthraquinone dyes.^[2] Thiophene belongs to a class of heterocyclic compounds containing a five membered ring made-up of one sulphur atom with the formula of C₄H₄S. Thiophene and its derivatives exist in petroleum or coal. Thiophene is taken from the word theion, the Greek word for sulfur, and another Greek word phaino which means shining. Thiophene structure can be found in certain natural products and is also incorporated in several pharmacologically active compounds.^[3] The thiophene-containing azo dyes have many advantages including a colour deepening effect as an intrinsic property of the thiophene ring and small molecular structure leading to better dye ability. The heterocyclic nature of the thiophene ring has also allowed for excellent sublimation fastness on the dyed fibres.^[4] Increasing the electron-withdrawing strength of the substituents on the thiophene ring resulted in bathochromic shifts. Additionally, the sulphur atom plays a decisive role by acting as an efficient electron sink as explained by valence band theory.^[5]

Synthetic approaches to the construction of thiophene and substituted thiophene have been efficiently developed. Thiophene ring can be constructed from non-heterocyclic precursors by two reaction pathways; (a) Construction of thiophene ring from appropriately substituted open chain precursors (this method involves the introduction of sulphur into a starting material containing the complete carbon skeleton) and (b) the functionalization at the positions α and β to the sulphur atom of the preconstructed thiophene nucleus.^[6] Gao et al.,^[7] synthesized conjugated ladder-type heteroacenes bearing pyrrole and thiophene ring units. Alike, Romagnoli et al.,^[8] prepared thiophene analogues of chalcones and the prepared compounds were studied for biological evaluation. We presumed that the synthesis of coupler 4-aryl-2-aminothiophene-3-carbonitrile derivatives would be suitable for biological and other textile dye applications. In our previous work, we reported synthesis and characterization of various biologically and textile important coupler compounds.

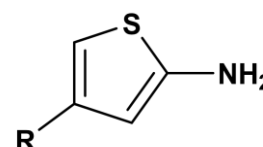


Fig. 1. Molecular structure of 2-amino-4-arylthiophene.

Table 1. Physical characteristic of 4-aryl-2-aminothiophene-3-carbonitrile derivatives, **AI₁-AI₆**

Coupler code	Colour of crystals	Melting point (°C)	% yield
AI ₁	Pale orange	162-164	86
AI ₂	Crystalline brown	106-108	68
AI ₃	Black crystal	184	89
AI ₄	Pale white	188-190	72
AI ₅	Pale yellow	191	70
AI ₆	Pale white	203-205	78

Fig. 1 shows the molecular structure of 2-amino-4-arylthiophene. Herein, we synthesized a series of coupler 4-aryl-2-aminothiophene-3-carbonitrile derivatives. The synthetic method involves the reaction of ketones, aldehydes or 1,3-dicarbonyl species with activated nitriles and elemental sulphur in the presence of an amine base. The obtained coupling components were characterized by means of UV-Visible spectroscopy, Fourier-transform infrared spectroscopy (FT-IR), gas chromatography–mass spectrometry (GC-MS) and nuclear magnetic resonance spectroscopy (NMR) analysis. The synthesized compounds were purified, characterized and evaluated for spectroscopic properties. They were found to possess good coupling properties as well as high degree of brightness and a colour deepening effect compared to other heterocyclic couplers.

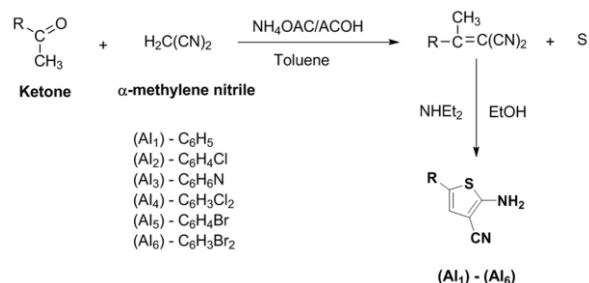
2. Experimental Section

2.1. Materials and methods

All the chemicals used in the synthesis of the coupling components were of analytical grade. They were obtained from Sigma Aldrich and Molport and were used without further purification. The melting point of the synthesized compounds was determined in open capillary tubes using melting point apparatus expressed in °C and is uncorrected. The purity of the compound was checked by TLC on silica gel plates using diethyl ether: ethanol (75%: 25%) solvent mixture. The Visible absorption spectra were measured using CARY 630 UV-Visible Spectrophotometer Model: Agilent technology. The functional groups that made up the structure of the compound were confirmed by infra-red spectrum on FT-IR Nexus 670 spectrometer in KBr disc (Thermo Nicolet) and absorption bands are expressed in cm^{-1} .

2.2. Synthesis of coupler 4-aryl-2-aminothiophene-3-carbonitrile and its derivatives (**AI₁-AI₆**)

The starting materials for the synthesis was obtained using the method of Gewald et al,^[4] which involves the condensation of corresponding ketone (0.03 mol, acetophenone) and malonitrile (0.06 mol, 3.96 g) in benzene using a heterocatalytic system. The reaction mixture was refluxed in the presence of catalytic amount of acetic acid and ammonium acetate to produce arylidenemalonitrile as an intermediate, followed by the cyclisation with sulphur, using diethylamine and ethanol as catalysts at 65°C for 2-3 h to give the desired products.^[3] The thick sticky dark product obtained was cooled overnight, filtered, washed with ethanol, ethanol and water 1:1 and dried.^[11] It was purified and recrystallized from hot ethanol. The purity was checked by spotting on a TLC Plate coated with silica gel.

**Scheme 1.** Synthesis of 4-aryl-2-aminothiophene-3-carbonitrile derivatives.

Similarly, **AI₂**, **AI₃**, **AI₄**, **AI₅** and **AI₆** were synthesized by using the starting material of para-chloro acetophenone, para-amino acetophenone, 2,4-dichloroacetophenone, para-bromo acetophenone/phenylacetyl bromide and 2,4-dibromoacetophenone, respectively. Scheme 1 shows the synthesis of 4-aryl-2-aminothiophene-3-carbonitrile derivatives.

2.3. Recrystallization

All amino thiophene derivatives were purified by 3-4 recrystallizations from hot ethanol. A known weight of the intermediate was dissolved in small quantity of ethanol and heated up. It was then filtered off using a Buchner funnel with a suction pump. The crystals were collected, washed severally with water and dried. After the recrystallization, the purity of each compound was checked by spotting on a thin layer chromatography plate and further subjected to spectroscopic test of UV-Visible, FT-IR, GC-Mass spectroscopy and NMR spectroscopy.

3. Results and Discussions

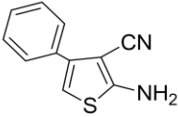
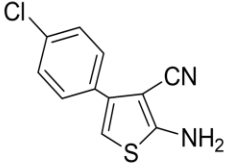
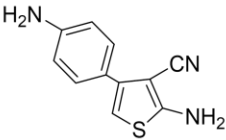
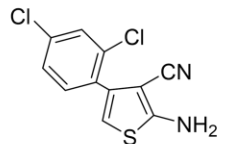
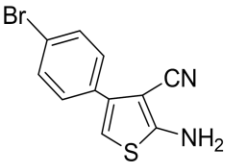
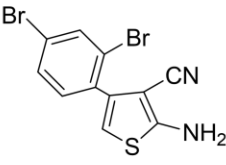
3.1. Confirmation of 4-aryl-2-aminothiophene-3-carbonitrile derivatives, **AI₁-AI₆**

Following the stepwise reaction, the dark thick sticky solution obtained was allowed to cool overnight, filtered and washed with ethanol to remove oily substance. A pale orange crystal was obtained; it was purified by recrystallization in hot ethanol. Fig. 1, Fig. S1-S4 shows the FT-IR spectra of 4-aryl-2-aminothiophene-3-carbonitrile derivatives, **AI₁-AI₆**.

Compound **AI₁**: Melting point 162-164°C, 86% yield which correspond to literature values 161-163, 85% yield (Yen Wang, 2004 dyes and pigment). FTIR (KBr)/ cm^{-1}): 1617 (C=C), 846, 726 (CH-Ar bend, double), 2847 (Al_i C-H), 3309 (NH), 1599 (NH Band). 1561 (Ar C=C str), 1349 (C-C), 2202 (C=N), 1054 (C-N), 689 (C-S).

The compound **AI₂** had a yield of product 68%; brown crystals were obtained and recrystallized from hot ethanol. Melting point of 106-108°C, which corresponds to literature values (Jing Wang 2003)

Table 2. Molecular structure and name of the 4-aryl-2- aminothiophene-3-carbonitrile derivatives, Al₁-Al₆

Intermediate code	Name and structure
Al ₁	 2-amino-4-phenylthiophene-3-carbonitrile
Al ₂	 2-amino-4-(4-chlorophenyl)thiophene-3-carbonitrile
Al ₃	 2-amino-4-(4-aminophenyl)thiophene-3-carbonitrile
Al ₄	 2-amino-4-(2,4-dichlorophenyl)thiophene-3-carbonitrile
Al ₅	 2-amino-4-(4-bromophenyl)thiophene-3-carbonitrile
Al ₆	 2-amino-4-(2,4-dibromophenyl)thiophene-3-carbonitrile

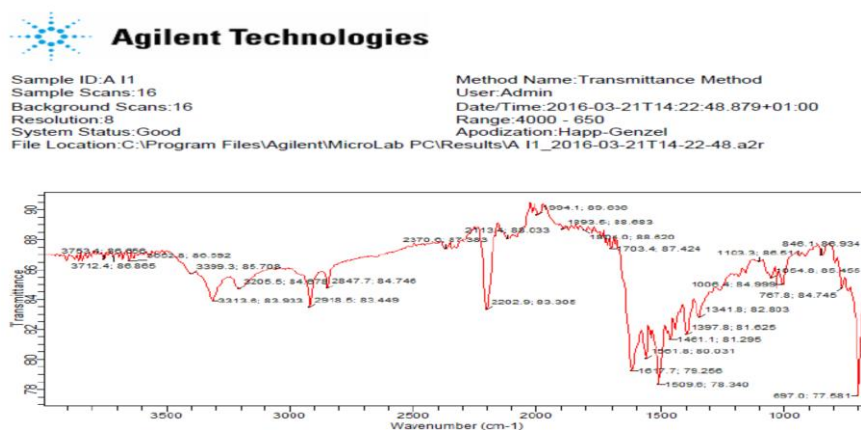


Fig. 2. Infrared spectrum for compound Al₁

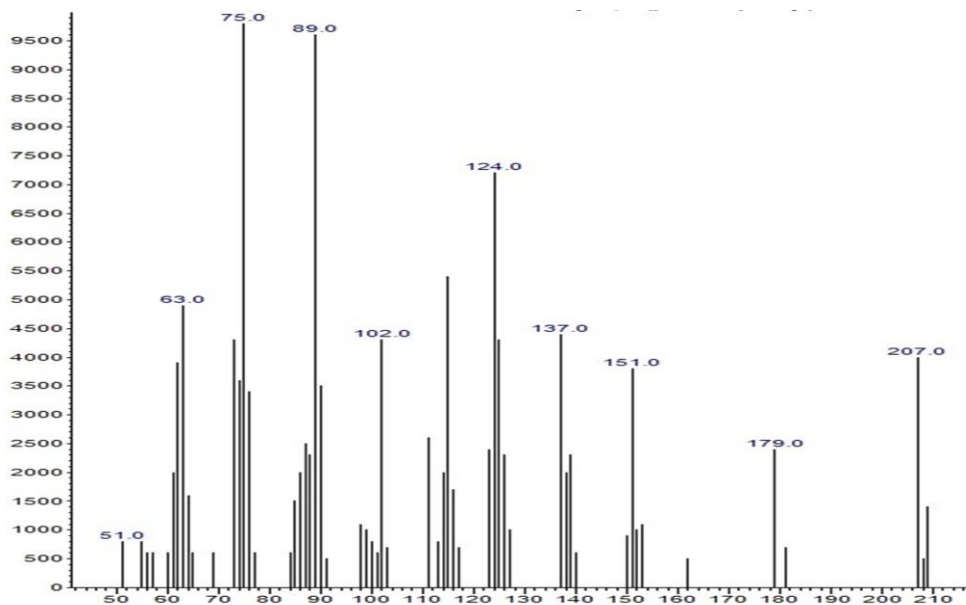


Fig. 3. Mass spectrum of Al₂

Table 3. Chemical shifts for H⁺ NMR CDCl₃, TMS (CH₃)₄Si of 4-aryl-2-aminothiophene-3-carbonitrile derivatives, Al₁-Al₃

Dye code/type of carbon in ppm (δ)	CH ₂ /CH	-C ₆ H ₅	-NH	C=C-H	-OCH ₂	Ar-H
Al ₁		7.216		5.913		7.219
Al ₂	0.622-0.685	2.751-2.787	2.040		2.957	7.542-7.81
Al ₃	1.024	7.544		2.25-2.507	4.9	7.150

FTIR (KBr/cm⁻¹): 1617 (C=C), 820, 787 (CH bend, double), 3399, 3313 (NH), 1587 (Ar C=C str), 1289 (C-C), 2214, 2206 (C=N), 1088 (C-N), 694 (C-S), 1203 (CH Ar).

Compound Al₃ has a yield of product 89%. Black crystals were obtained which was purified by recrystallization in hot ethanol. Melting point is 184°C. FTIR (KBr/cm⁻¹): 1606 (C=C), 2922 (Ar C-H str), 831, 730 (CH bend, double), 3451 (NH Str), 1640 (NH bend), 1505 (Ar C=C str), 1334, 1292 (C-C), 2214 (C=N), 1058 (C-N), 689 (C-S), 957 (CH Ar).

Compound Al₄ has a yield of product 72%; pale white crystals were obtained and purified by recrystallization from toluene: acetic acid 60:40. Melting point 188-189°C. FTIR (KBr/cm⁻¹): 1628 (C=C), 2922 (CH) 823, 670 (CH band, double), 3306 (NH str), 1509 (Ar C=C str), 1386 (C-C), 2214 (C=N), 1028 (C-N), 726 (C-S), 1248 (CH Ar).

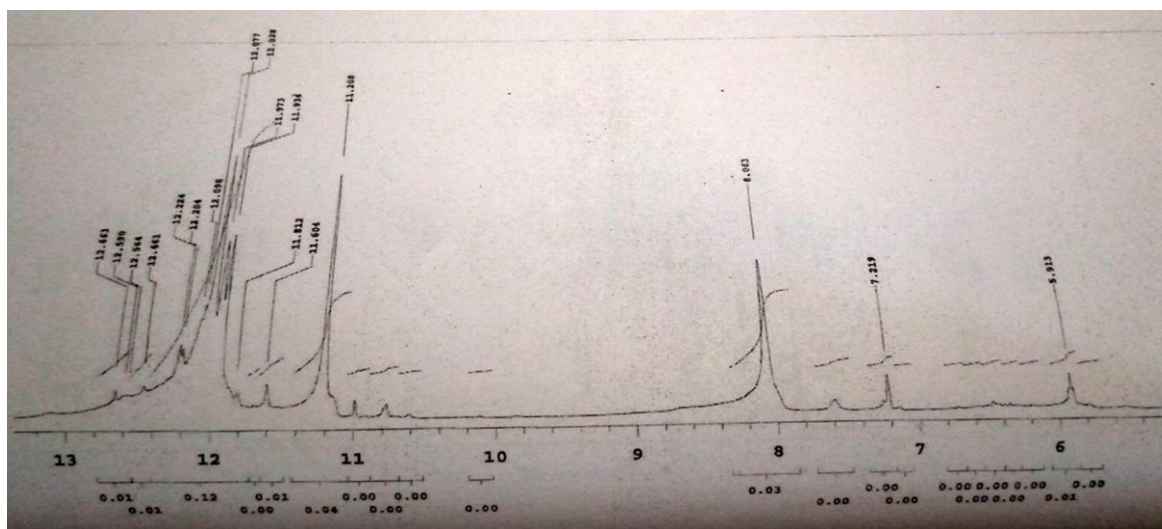
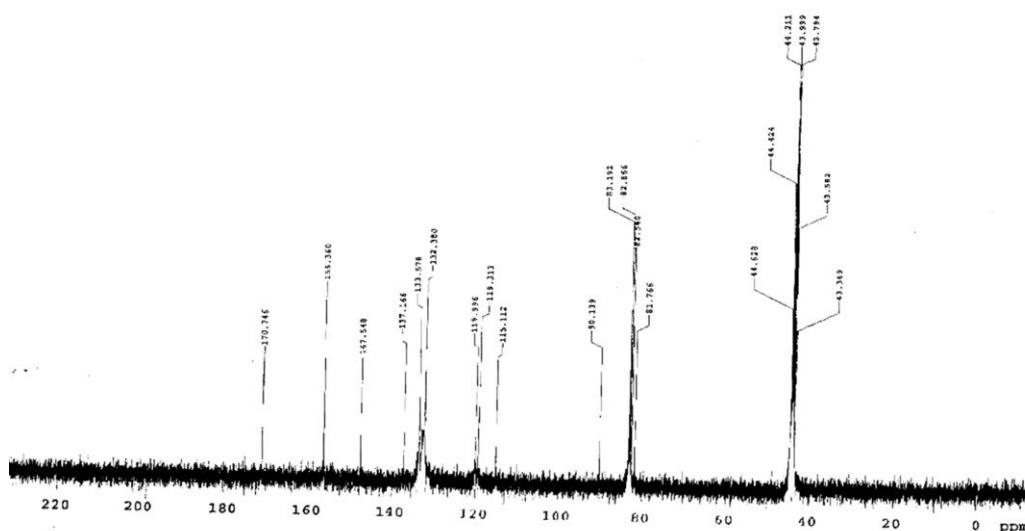
The compound Al₅ has a yield of product 70%. Pale yellow crystals were obtained and recrystallized from acetic acid and toluene 60:40. Melting point 190°C. FTIR (KBr/cm⁻¹): 1684 (C=C), 2918 (CH), 827, 752 (CH bend, double), 3183 (NH str), 1625 (NH bend), 1490 (Ar C=C str), 1359 (C-C), 2214 (C=N), 1010 (C-N), 723 (C-S), 1185 (CH Ar).

The compound Al₆ has a yield of 78%. The Black crystals obtained were purified by recrystallization in acetic acid and ethanol 20:80. Melting point 203-205°C. FTIR (KBr/cm⁻¹): 1625 (C=C), 827, 752 (CH bend, double), 3183 (NH str), 1490 (Ar C=C str), 1359 (C-C), 1010 (C-N), 723 (C-S), 1233 (CH Ar).

The synthesized compounds were found to be crystalline in nature and easily soluble in ethyl acetate, benzene, toluene, DMSO and DMF but insoluble in hexane. The characteristics data or infra-red spectra of aminothiophene derivatives were recorded in KBr; the

compounds Al₁- Al₆ showed two sharp absorption bands of amino group between 3306-3459 cm⁻¹ and nitrile group around 2206-2214 cm⁻¹ and other absorption bands for other derivatives were observed in other region as shown in the result. The functional groups present in the thiophene derivatives showed their various peaks in the corresponding absorption region. They are of bright colour and they give even brighter shade when coupled with a diazo component. Polysubstituted 2-aminothiophenes have also shown to be versatile synthetic building blocks in the dye and other industries. Due to their importance and versatility, the chemistry of 2-aminothiophenes have received much attention and several synthetic methods have been published. Many of the methods reported involve difficult preparation of starting materials and multi-step synthesis. The most convenient method for preparing 2-aminothiophenes with a high degree of substitution is the Gewald reaction (Scheme 1). This method is an improvement over other existing routes for the synthesis of 2-aminothiophenes. The Gewald reaction possesses very good synthetic utility. Table 2 shows molecular structure and name of the 4-aryl-2-aminothiophene-3-carbonitrile derivatives, Al₁-Al₆.

Mass spectrum of a compound is usually presented as a bar graph with m/e values (unit masses) on the x-axis, and intensity (number of ions of a given m/e striking the detector) on the y-axis. GC-MS is a hyphenated technique which combines the separating power of gas chromatography (GC), with the detection power of the mass spectrometry. The mass spectra data for the intermediate are presented in Table 3 and showed relevant protonated peaks i.e. the (M+H)⁺ and the (M+Na)⁺. Fig. 3 and Fig. S5 and S6 show the mass spectra of 4-aryl-2-aminothiophene-3-carbonitrile derivatives, Al₁-Al₆.

Fig. 4. ^1H NMR spectrum of Al_1 Fig. 5. ^{13}C NMR spectrum of Al_1

Mass spectra of Al_2 gave m/z of 51, 63, 75, 89, 124, 137, 151, 179 and 207 corresponding to fragments of $\text{C}_3\text{H}_4\text{N}$, C_5H_4 , C_6H_4 , C_7H_4 , $\text{C}_7\text{H}_4\text{Cl}$, $\text{C}_8\text{H}_5\text{Cl}$, $\text{C}_9\text{H}_6\text{Cl}$, $\text{C}_9\text{H}_6\text{Cl}$ and $(\text{M}+\text{H})^+$ 207. Also, the mass spectra of Al_3 gave mass to charge ratio of 42, 53, 81, 97, 126, 137, 152 and 177 corresponding to fragments of $\text{C}_2\text{H}_3\text{N}$, $\text{C}_3\text{H}_4\text{N}$, $\text{C}_3\text{H}_4\text{NS}$, $\text{C}_6\text{H}_5\text{NS}$, $\text{C}_7\text{H}_6\text{NS}$, $\text{C}_8\text{H}_7\text{NS}$ and parent $(\text{M}+\text{H})^+$ $\text{C}_9\text{H}_{10}\text{N}_2\text{S}$. Mass spectra of Al_6 gave mass to charge ratio (m/z) of 61, 103, 129, 150, 159, 199, 227, 299 and 332 representing the corresponding positive fragments of CHN_2S , C_2HBr , $\text{C}_4\text{H}_2\text{Br}$, $\text{C}_6\text{H}_4\text{Br}$, $\text{C}_6\text{H}_5\text{Br}$, $\text{C}_5\text{H}_4\text{Br}_2$, $\text{C}_{10}\text{H}_8\text{NBr}_2$ and $\text{C}_{10}\text{H}_8\text{NSBr}_2$ ($\text{M}+\text{H})^+$.

The 4-aryl-2-aminothiophene-3-carbonitrile derivatives, Al_1 - Al_6 , were further confirmed by ^1H and ^{13}C NMR spectra (see Fig. 4, 5 and Fig. S7-S9). The NMR analysis was carried out using chloroform (CDCl_3) as solvent and tetramethylsilane (TMS) as internal standard in order to standardize the NMR spectra. The chemical shifts are positioned in relation to a reference proton set at 0.00 ppm, tetramethylsilane (CH_3Si), is the standard for HNMR. The chemical shift values ppm confirmed the structure of the 4-aryl-2-aminothiophene-3-carbonitrile derivatives, Al_1 - Al_6 .

3.2. Scope of 4-aryl-2-aminothiophene-3-carbonitrile derivatives, Al_1 - Al_6

Thiophene derivatives are very important heterocycles exhibiting remarkable applications in various disciplines.^[12,13] These compounds synthesized can be used effectively as intermediates or coupling component in dye synthesis. They can also be used as diazo component in the synthesis of dyes or other organic compounds. The thiophene-containing azo dyes have many advantages including a colour deepening effect as an intrinsic property of the thiophene ring and small molecular structure leading to better dye ability. The heterocyclic nature of the thiophene ring has also allowed for excellent sublimation fastness on the dyed fibres.^[11] In medicine, thiophene derivatives shows antimicrobial,^[14] analgesic, anti-inflammatory,^[15] antihypertensive, antitumor activity while they are also used as inhibitors of corrosion of metals or in the fabrication of light-emitting diodes in material science.^[16] For instance, Elavarasan et al.,^[17] synthesized five-membered aromatic heterocyclic compounds (tetrazole containing hybrid levofloxacin derivatives). The prepared heterocyclic compounds were studied for antimicrobial

evaluation and molecular docking investigation. They found that the derivatives can be used for the most significant transformations in synthetic organic chemistry because of its much importance in pharmaceutical industry. Alike, Uthayamalar and co-workers^[18] synthesized new pyrazolone Schiff base and the synthesized compounds were characterised and used for the molecular docking and antioxidant studies. Similarly, the heterocyclic compounds are proven to be most important candidates for various applications such as corrosion inhibitors, antibacterial, antitubercular and antimicrobial agents, and useful intermediates in dye synthesis.^[19-21]

Overall, due to the simple synthesis and attractive molecular structure, the 4-aryl-2-aminothiophene-3-carbonitrile derivatives would play very important role in dye synthesis and biological applications.

4. Conclusions

A one-pot efficient and simple method was developed for conducting the organic synthesis with aryl-alkyl-ketones. The method demonstrated that the reaction can be conducted under neat conditions using a heterocatalytic amount of base. It was found that the present method is safe and allows easy preparation of a diverse set of aryl-2-aminothiophenes derivatives of coupling components. As shown here, solvent-free methods can have a large impact in organic synthesis, especially with respect to multicomponent reactions. Gewald reaction is successfully utilized to synthesize the various substituted 2-amino-3-cyano-4-aminothiophene derivatives as important couplers in the organic or dye synthesis. The analytical and other informational data, available in the results obtained, have rendered thiophenes significantly important class of heterocyclic compounds and their applications in ever challenging dye and organic synthesis. They were found to possess good coupling properties as well as high degree of brightness and a colour deepening effect compared to other heterocyclic couplers.

Conflicts of Interest

The authors declare no conflict of interest.

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