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Potassium ferrocyanide promoted an efficient synthesis of benzoxazoles and benzothiazoles under solvent free condition

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Abstract: In the family of heterocycles that includes benzoxazoles and benzothiazoles, there exist compounds with a wide range of biological activity. Because of this characteristic, we designed a moderate and effective technique for the synthesis of 2-substituted benzoxazole and benzothiazole using condensation of aldehyde and 2-aminophenol or 2-aminothiophenol via oxidation of carbon-nitrogen bond. Potassium ferrocyanide catalyzed one-pot synthesis is efficient and provides for quick reaction times, simple set-up and high yields. As a result, we provide here a technique for the rapid solvent free synthesis of benzoxazoles and benzothiazoles. Some synthesized products were identified by ^{1}H-NMR, ^{13}C-NMR and MASS. The role of potassium ferrocyanide as a catalyst is represented by plausible reaction mechanism.

Keywords: Aldehyde; potassium ferrocyanide; benzoxazoles; benzothiazoles; solvent free.

1. Introduction

Benzoxazoles and benzothiazoles are frequent heterocyclic scaffolds in physiologically active and pharmaceutically relevant chemicals and they belong to a large family of molecules. Benzoxazoles are essential scaffolds in natural compounds[1-2] and drug development[3-5]. Benzoxazole compounds with appropriate substitutions have been shown to exhibit a variety of medicinal properties including antibacterial activity[6], antimicrobial[7-10], antiviral[11], topoisomerase I, II inhibitory[12], antitumor activities[13], anticancer agent[14-15] NSC-693638, L-697,661, antiviral[16] and antibacterial[17] UK-1, AJI9561. According to recent research, substituted 2-benzylbenzoxazoles exhibit antibacterial, antifungal[18], antimicrobial[19-21] and anti-measles virus[22] properties (Figure 1).

The tiny and simple benzothiazole nucleus is found in compounds with intriguing biological properties such as anticonvulsant[23-24], antimalarial[25], antitubercular[26], antimicrobial[27-28],antitumour[29-32], anthelmintic[33], anti-inflammatory, analgesic properties[34]. The benzothiazole ring may be found in a variety of natural substances, both marine and terrestrial, that have significant biological activity. Many natural products, such as epothilone-A, lyngbyabellin A, dolastatin 10 & bleomycin, include thiazole nucleus molecules[35]. The synthesis of these molecules is of significant interest due to their substantial medicinal value. Riluzole is a benzothiazole derivative-containing medication used to treat amyotrophic lateral sclerosis. In certain patients, it may postpone the need for a tracheostomy or a ventilator and it

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can extend life by 3–5 months. Benzothiazoles and benzoxazoles are heterocyclic compounds with a wide range of biological characteristics. (Figure 1)[36-41].

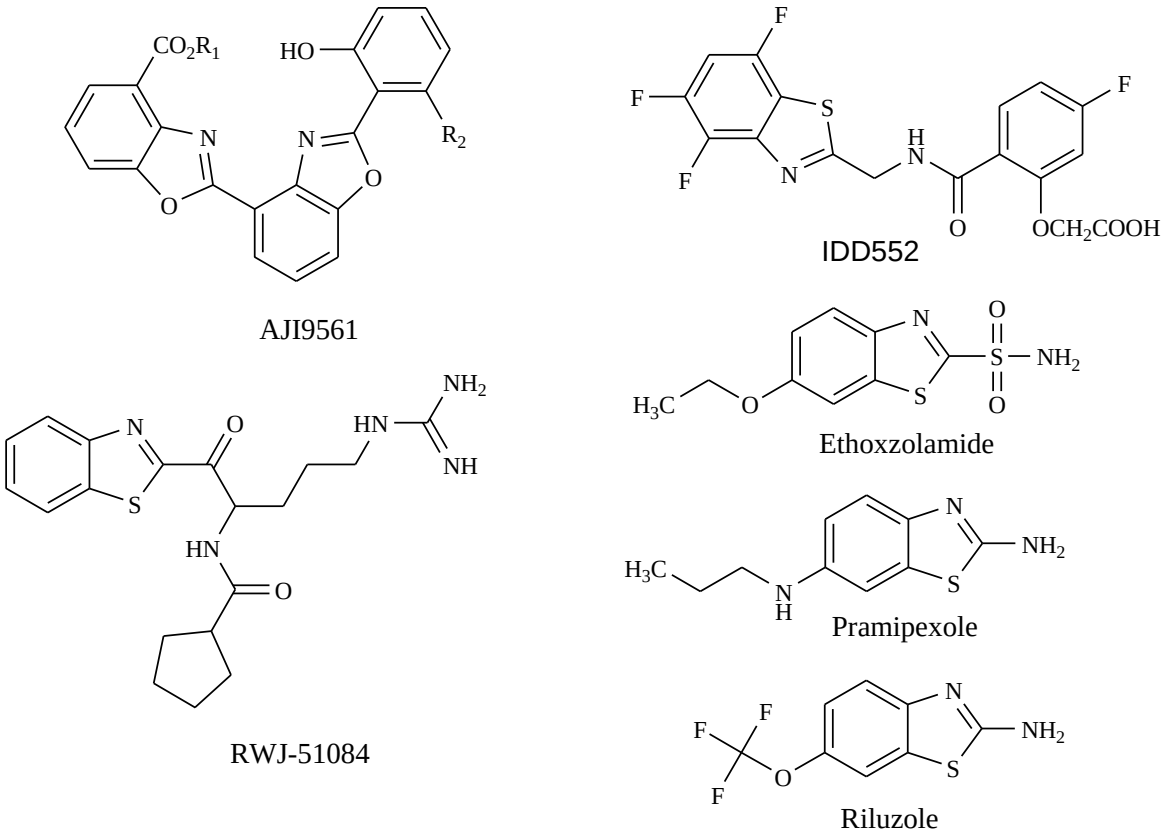


Figure 1. Some biologically active benzoxazole and benzothiazoles

However, a variety of techniques for synthesizing benzoxazoles[42-46] and benzothiazoles[47-52] are now available, there is still a need for novel and easy processes that enable a broad range of structural diversity and substitution patterns in the target library.

The condensation of o-aminobenzenethiol or o-aminophenol with substituted aldehydes[53], nitriles[54], acyl chlorides[55] or carboxylic acids[56-58] is the most frequently used synthesis technique for obtaining benzoxazole and benzothiazole. These techniques often require lengthy response times and harsh circumstances. An example from recent times is the synthesis of benzoxazoles and benzothiazoles from alcohol[59]. However, several of these techniques have one or more disadvantages, such as high acidic conditions, lengthy reaction durations, poor product yields, laborious workup, the requirement for excessive quantities of reagent and the use of hazardous reagents, catalysts or solvents. As a result, there is a significant need for a highly efficient and ecologically friendly technique of synthesizing these heterocycles. Thus, developing an effective and easy chemical process or technique for the synthesis of physiologically active molecules from a simple reagent is always a difficult challenge for chemists working in the area of organic synthesis. Thus, the superiority of this research article is we overcome all the above problems to synthesize benzoxazoles and benzothiazoles by using potassium ferrocyanide as an environment friendly catalyst.

$K_4[Fe(CN)_6]$ has recently played an important role as a catalyst in the production of the anti-Alzheimer medication (-) Galanthamine[60]. Because of its high stability, oxidising power selectivity and harmless byproduct Fe(III), it also facilitated oxidative cyclization of 5-S Cysteinyldopa[61]. Yu and Gu investigated the release of cyanide into the environment, which has terrestrial implications for ecosystems[62]. Other researchers are interested in $K_4[Fe(CN)_6]$ because Gaffar and Abu-El Fadl investigated the kinetics of potassium ferro cyanide[63] since it has several benefits such as good solubility in water, simple handling, low cost, eco-friendliness, availability and strong reactivity.

2. Experimental

2.1 General Procedure for the Synthesis of Benzoxazoles and Benzothiazoles on Grinding

At room temperature, a mortar with a pestle was used to grind a combination of 2-aminophenol or 2-aminothiophenol (1 mmol), aldehyde (1 mmol) and potassium ferro-cyanide (10 mol%). TLC was used to track the progress of the reaction. The crude product was washed with water, dried and recrystallized with ethanol once the reaction was completed (< 2 min).

2.2 General Experimental Methods

On a Stuart-SMP10 melting point apparatus, the melting points of the prepared compounds were measured in open-glass capillaries. IR absorption spectra were recorded on a Perkin Elmer 1650 FTIR using KBr pellets in the range of 4000-450cm^{-1}. A Bruker spectrometer running at 300 MHz was used to record ^{1}H-NMRs. The chemical shifts in ^{1}H-NMR are given as parts per million (ppm) downfield from the internal standard TMS (Me_4Si). The chemical shifts (scale) are given in parts per million in the ^{13}C NMR spectra obtained at 75 MHz (ppm). On an LCQ ion trap mass spectrometer, mass spectra were captured. Purity of the compounds were checked by thin layer chromatography (TLC) on Merck silica gel 60 F254 pre-coated sheets in benzene/methanol mixture and spots were developed using iodine vapor as visualizing agents.

2-phenyl-1,3-benzoxazole[65]***(a)***: White solid, mp: 102 ºC. IR: (KBr, cm^{-1}) ν 3019.50, 1634.07, 1526.79, 1453.36, 1225.91, 1054.34; ^{1}H NMR: ($CDCl_3$, 300 MHz), δ: 8.18 (d, 2H), 7.76-7.72 (m, 2H), 7.67-7.60 (m, 3H), 7.40-7.36 (d, 2H) ppm; ^{13}C NMR: ($CDCl_3$, 75 MHz,) δ: 161.4, 151.4, 138.5, 132.7, 128.6, 128, 127.8, 127.6, 124.3, 119.9, 110.6; MS (ES): Calculated for $C_{13}H_9NO$ *m/z*: 195.21, found 195.10.

2-(4-bromophenyl)-1,3-benzoxazole[65]***(b)***: White solid, mp:158 ºC.

2-(4-methylphenyl)-1,3-benzoxazole[66]***(c)***: Light brown solid, mp: 113 ºC. ^{1}H NMR: ($CDCl_3$, 300 MHz), δ: 8.10-8.08 (d, 2H), 7.78 (t, 2H), 7.41-7.39 (m, 4H), 2.41 (s, 3H) ppm; ^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 161.4, 151.4, 141.6, 138.5, 129, 127.6, 126.5, 124.3, 119.4, 110.6, 21.5; MS (ES): Calculated for $C_{14}H_{11}NO$ *m/z*: 209.24, found 209.16.

2-(4-chlorophenyl)-1,3-benzoxazole[65]***(d)***: White solid**,** mp:148 ºC. ^{1}H NMR: ($CDCl_3$, 300 MHz), δ: 8.21-8.26 (d, 2H), 7.53-7.57 (d, 2H), 7.80-7.81 (m, 1H), 7.61, 7.63 (m, 1H), 7.40-7.43 (m, 2H) ppm; ^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 161.4, 151.4, 138.5, 137.3, 129.3, 128.3, 127.6, 124.3, 119.9, 110.6; MS (ES): Calculated for $C_{13}H_8ClNO$ *m/z*: 229.66, found 229.46.

*2-[3-fluoro-4-(trifluoromethyl)phenyl]-1,3-benzoxazole(****e****)*: White Sticky Semi-solid. IR: (KBr, cm^{-1}) ν 3253.19, 2923.60, 1641.42, 1501.51, 1258.21, 1134.63, 1019.10; ^{1}H NMR: ($CDCl_3$, 300 MHz), δ: 7.76-7.69 (m, 3H), 7.61 (d, 1H), 7.40-7.36 (m, 2H) ppm; ^{13}CNMR: (75 MHz, $CDCl_3$) δ: 162.7, 162.7, 162.7, 161.5, 160.7, 160.6, 151.3, 138.5, 132, 132.9, 128.1, 127.6, 125.1, 124.3, 121.7, 119.6; MS (ES): Calculated for $C_{14}H_7F_4NO$ *m/z*: 281.20, found 281.10.

2-(4-methoxyphenyl)-1,3-benzoxazole[65]***(f)***: White solid, mp: 99 ºC.

5-chloro-2-(4-nitrophenyl)-1,3-benzoxazole[69]***(g)***: White Sticky Semi-solid. IR: (KBr, cm^{-1}) ν 3025.54, 2871.9, 1641.32, 1503.51, 1134.63, 1020.10, 748.10; ^{1}H NMR: ($CDCl_3$, 300 MHz), δ: 8.35 (d, 2H), 8.22 (d, 2H), 7.81 (s, 1H), 7.75 (d, 1H), 7.40 (d, 1H) ppm; ^{13}C NMR: (75 MHz, $CDCl_3$) δ: 161.5, 150, 148.9, 137.8, 134.6, 129.1, 128.9, 126.3, 124.2, 117.4, 111.7; MS (ES): Calculated for $C_{13}H_7ClN_2O_3$ *m/z*: 274.65, found 274.40.

Synthesis of benzoxazoles and benzothiazoles

*5-chloro-2-[3-fluoro-4-(trifluoromethyl)phenyl]-1,3-benzoxazole(**h**)*: White Sticky Semi-solid. ^{1}H NMR: (CDCl3, 300 MHz) δ: 7.15-7.49 (m, 6H) ppm; ^{13}CNMR: (75MHz, $CDCl_3$), δ: 160.4, 151.6, 148.1, 141.5, 130.7, 127.4, 122.9, 120.9, 118, 114.3, 112.2, 108.5 MS (ES): Calculated for $C_{14}H_6ClF_4NO$ *m/z*: 315.65 found 315.38.

*5-chloro-2-phenyl-1,3-benzoxazole[67](**i**)*: Yellow solid, mp: 111°C. ^{1}H NMR: ($CDCl_3$, 300 MHz), δ: 8.31-8.33 (d, 2H), 7.63 (s, 1H), 7.56-7.58 (m, 3H), 7.50-7.51 (d, 1H), 7.21-7.22 (d, 1H) ppm; ^{13}C NMR: ($CDCl_3$, 75 MHz) δ:161.5, 150, 137.8, 132.7, 129.1, 128, 127.8, 126.3, 117.4, 111.7; MS (ES): Calculated for $C_{13}H_8ClNO$ *m/z*: 229.66, found 229.40.

*2-(4-methylphenyl)-5-nitro-1,3-benzoxazole(**j**)*: Yellow solid, mp: 192 °C. ^{1}H NMR: (DMSO-d_6, 300 MHz), δ:8.58 (d, 1H), 7.85 (m, 1H), 7.78 (d, 2H), 7.32 (m, 1H), 7.23 (m, 2H), 2.40 (d, 3H) ppm; ^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 161.5, 151.3, 141.6, 141.2, 139.4, 129, 126.3, 120.8, 119.2, 110.9, 21.1; MS (ES): Calculated for $C_{14}H_{10}N_2O_3$ *m/z*: 254.24, found 254.18.

*2-(4-nitrophenyl)-5-nitro-1,3-benzoxazole[73](**k**)*: White solid, mp: 262 °C.

*2-phenyl-1,3-benzothiazole[65](**l**)*: Yellow solid, mp: 112 °C. IR: (KBr, cm^{-1}) ν; 3246.73, 2923.64, 1507.77; ^{1}H NMR: ($CDCl_3$, 300 MHz), δ: 8.19 (d, 1H), 8.04-8.00 (m, 3H), 7.54-7.48 (m, 5H) ppm; ^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 166.6, 151.8, 136, 134.9, 132.1, 129.3, 127.3, 126.3, 126, 123.5, 123.2; MS (ES): Calculated for $C_{13}H_9NS$ *m/z*: 211.28, found 212.20.

*2-(4-methylphenyl)-1,3-benzothiazole[67](**m**)*: Yellow solid, mp: 88 °C. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ: 8.29–7.18 (m, 8H), 2.64 (s, 3H) ppm; ^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 166.6, 151.8, 139, 136, 132.7, 129.3, 127.9, 126, 123.5, 123.2, 21.2; MS (ES): Calculated for $C_{14}H_{11}NS$ m/z: 225.30, found 225.20.

*2-(4-methoxyphenyl)-1,3-benzothiazole[68](**n**)*: Yellow solid, mp: 123 °C.

*4-(1,3-benzothiazol-2-yl)phenol[70](**o**)*: Yellow solid, mp: 225 °C. IR: (KBr, cm^{-1}) ν 3404.14, 2928.27, 2845.32, 1626.86, 1491.60, 1021.10; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ: 8.17 (d, 1H), 8.02 (d, 1H), 7.73 (d, 2H), 7.54-7.48 (m, 2H), 6.86 (d, 2H), 5.13 (s, 1H) ppm; ^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 166.6, 161.4, 151.8, 136, 130, 126.3, 126, 123.6, 123.5, 123.2, 116.7; MS (ES): Calculated for $C_{13}H_9NOS$ *m/z*: 227.28, found 227.17

*2-(4-bromophenyl)-1,3-benzothiazole[72](**p**)*: Yellow solid, mp: 133 °C.

*2-(4-chlorophenyl)-1,3-benzothiazole[71](**q**)*: White solid, mp: 117 °C.

*2-(2-chlorophenyl)-1,3-benzothiazole[68](**r**)*: White solid, mp: 70 °C. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ: 8.17 (d, 1H), 8.03 (d, 1H), 7.73 (d, 1H), 7.54-7.48 (m, 3H), 7.39-7.33 (m, 2H) ppm; ^{13}C NMR: (75 MHz, $CDCl_3$) δ: 166.1, 151.8, 136, 133.9, 132.3, 131.3, 130, 128.2, 128.1, 126.3, 126, 123.5, 123.2; MS (ES): Calculated for $C_{13}H_8ClNS$ *m/z*: 245.72, found 247.2.

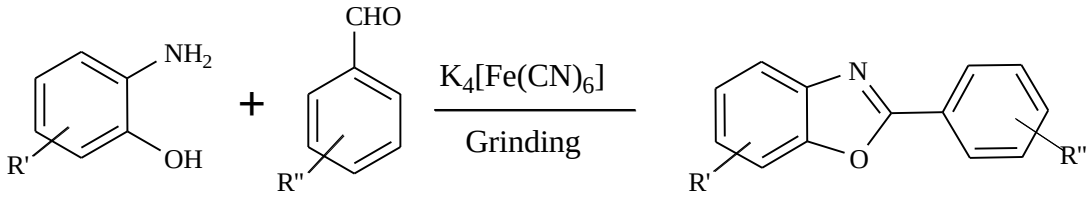
*2-[3-fluoro-4-(trifluoromethyl)phenyl]-1,3-benzothiazole(**s**)*: White solid, mp: 185 °C. ^{1}H NMR: ($CDCl_3$, 300 MHz), δ: 8.13 (s 1H, Ar–H), 8.11 (d, 1H, *J*= 8.5 Hz, Ar–H), 7.95 (d, 1H, *J*=8Hz, Ar–H), 7.27–7.53 (m, 4H, Ar–H) ppm; ^{13}C NMR: (75 MHz, $CDCl_3$), δ: 165.7, 163.4, 161.4, 161.3, 151.8, 141.5, 141.4, 136, 128.5, 126, 125, 124.7, 123.9, 121.8, 121.2, 121.1, 119.6, 119.6; MS (ES): Calculated for $C_{13}H_8ClNS$ *m/z*: 297.27, found 297.20.

2-(4-nitrophenyl)-1,3-benzothiazole[68] ***(t)***: Yellow solid, mp: 229 °C. IR: (KBr, cm^{-1}) ν 3120.46, 1622.97, 1595.78, 1470.85, 1188.49; ^{1}H NMR: ($CDCl_3$, 300 MHz), δ: 8.27 (d, 2H), 8.18 (s, 1H), 8.12 (d, 2H), 8.02 (d, 1H), 7.55-7.49 (m, 2H) ppm; ^{13}C NMR: (75 MHz, $CDCl_3$) δ: 166.6, 151.8, 148.9, 142.3, 136, 127.8, 126.3, 126, 124.9, 123.5, 123.2; MS (ES): Calculated for $C_{13}H_8ClNS$ *m/z*: 256.28, found 256.16.

2-(4-florophenyl)-1,3-benzothiazole [72] ***(u)***: White solid, mp: 99 °C.

3. Results and Discussion

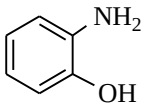
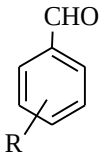
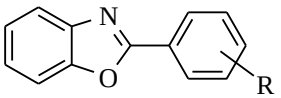
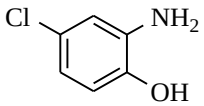
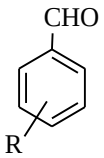
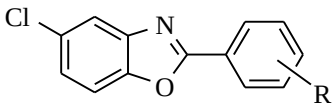
We present an effective and ecologically friendly approach for synthesizing benzoxazole and benzothiazole under solvent-free conditions using catalytic quantities of $K_4[Fe(CN_6)]$.



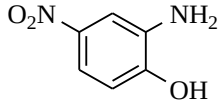
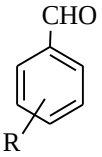
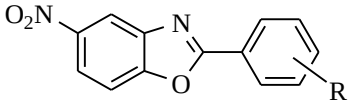
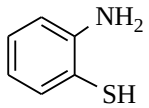
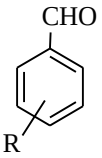
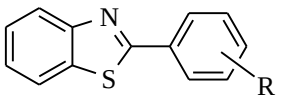
Scheme 1. $K_4[Fe(CN_6)]$ catalyzed synthesis of benzoxazoles on grinding

To determine the best reaction conditions, o-aminophenol was treated with benzaldehyde in the presence of $K_4[Fe(CN_6)]$ (Scheme 1, Table 1). The best molar ratio of o-aminophenol:aldehyde at room temperature under solvent-free conditions is 1:1 and 2-phenylbenzoxazole was produced in 94 percent yield after 2 minutes under these circumstances (Entry 1, a, Table 1). To establish the involvement of $K_4[Fe(CN_6)]$, the same reaction was carried out at ambient temperature in the absence of a catalyst and no product production was seen after 20 minutes. These findings imply that $K_4[Fe(CN_6)]$ has a high catalytic activity in this reaction. The procedure's generality was next tested using reactions of different aldehydes with o-aminophenols. The result demonstrated that the reaction completed within 2-3 minutes with excellent yield of the products (Entry 1-3, Table 1).

Table 1. Synthesis of benzoxazoles and benzothiazoles on grinding

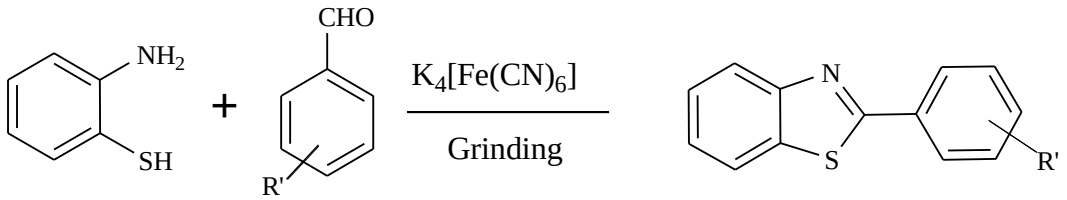
Entry	Substituted 2-aminophenol/ aminothiophenol	Aldehydes	Product	Yield[a] %
1			 R = a. H; b. 4-Br; c. 4-CH_3; d. 4-Cl; e. 3-F, 4-CF_3; f. 4-OCH_3	a. 94 b. 92 c. 90 d. 92 e. 93 f. 87
2			 R = g. 4-NO_2; h. 3-F, 4-CF_3; i. H	g. 96 h. 88 i. 90

Synthesis of benzoxazoles and benzothiazoles

3			 R = j. 4-CH_3; k. 4-NO_2	j. 94 k. 92
4			 R = l. H; m. 4-CH_3; n. 4-OCH_3; o. 4-OH; p. 4-Br; q. 4-Cl; r. 2-Cl; s. 3-F, 4-CF_3; t. 4-NO_2; u. 4-F	l. 92 m. 90 n. 89 o. 90 p. 92 q. 94 r.91 s. 94 t. 95 u. 90

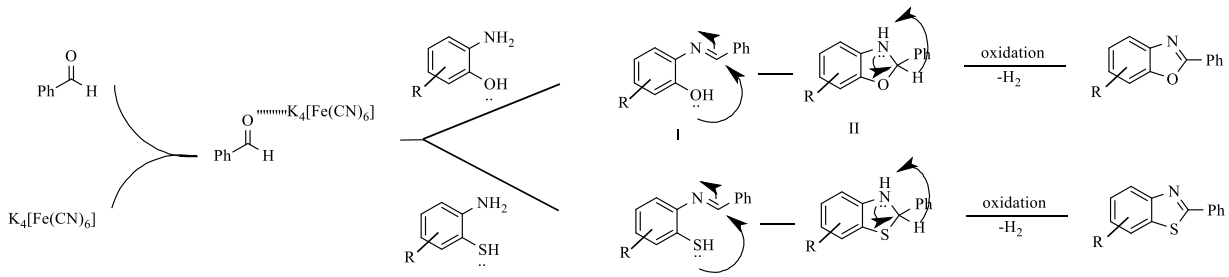
[a] Isolated yield of the products

This protocol also extended by the reaction of various aldehydes with o-aminothiophenol (Scheme 2). 2-aminothiophenol was grind with a variety of aldehydes at room temperature in $K_4[Fe(CN_6)]$ catalysis under solvent free condition (Entry 4, Table 1). All the reactions proceed to completion in just 2-3 min. at room temperature without any organic solvent. In all instances, the corresponding benzothiazoles could be recovered with high yields (Entry 4, Table 1).



Scheme 2 $K_4[Fe(CN_6)]$ catalyzed synthesis of benzothiazoles on grinding

Scheme 3 depicts one proposed mechanism for this process. The $K_4[Fe(CN)_6]$ increases the electrophilic character of the carbonyl carbon, allowing for the nucleophilic addition of 2-aminothiophenol or 2-aminophenol to provide an intermediate I, which upon cyclisation followed by oxidation produces the desired product.



Scheme 3. Proposed mechanism for the synthesis of benzoxazoles and benzothiazoles

4. Conclusion

Potassium ferro-cyanide was discovered to be a gentle and effective catalyst for the production of benzoxazoles and benzothiazoles. This technique is feasible, environmentally benign and economically appealing due to the utilization of this affordable, readily accessible and reusable catalyst under solvent-free conditions. The proposed approach also has the benefits of a simple work-up process, moderate reaction conditions, extremely short reaction periods, excellent product yields and non-toxicity of the catalyst.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

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