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Research article

UTILITY OF CYANOACETAMIDE DERIVATIVES IN THE SYNTHESIS OF NOVEL BENZIMIDAZOLPYRIMIDINE, PYRIDOTHIENOPYRIMIDINE, THIENOQUIONLINONE AND DIAMINOTHIOPHENE DERIVATIVES *VIA* MULTICOMPONENT –ONE POT REACTION

Fatima Al-Omran[*a] and Adel Abou El-Khair[a]

[a]Department of Chemistry, Faculty of Science, Kuwait University, P.O. Box 12613,Safat 13060, Kuwait

ABSTRACT: An environmentally friendly methodology utilizing cyanoacetamide derivative **4**for synthesis a variety of heterocyclic compounds have been described. Three component reaction of compound **4**, DMF-DMA and 2-aminobenzimidazole afforded the corresponding benzimidazolpyrimidine **10** in excellent yield *via* a one-pot two –step process. Reaction of cyanoacetamide derivative **4** with active methylene reagents such as benzylidinemalononitrile or malononitrile afforded the corresponding pyridothienopyrimidine derivatives **14** and **19** respectively. An efficient one-pot multicomponent reaction for synthesis thienoquionlinone derivative **23** and diaminothiophene **26** in excellent yield has been described. Reaction of cyanoacetamide derivative **4** with p-methoxybenzaldehydeyielded the *p*-methoxyphenylacrylamide derivative **27**. The reactions of enaminone **32** with aminotetrazole **33** or with hydrazine hydrate afforded respectively **34** and **35** in excellent yield. The structure of the synthesis compounds has been established on the basis of elemental analyses. ^{1}H –NMR,^{13}C NMR and MS spectra.

Keywords: MCRs, one-pot reaction**,** cyanoacetamide, benzotriazole, thiophene

*Corresponding author: Fatima Al-Omran, Department of Chemistry, Faculty of Science, Kuwait University, P.O. Box 12613,Safat 13060, Kuwait, E-mail: fatima.alomran@ku.edu.kw Tel: +965 24987078

INTRODUCTION

As the world's population increases and health problems expand, consequently a large numeral of the researchers' chemistry is needed to concentrate along the design of drug molecules and identify novel therapeutics. Therefore, the design of drug molecules offers some of the greatest hopes for success in the present and future era. In that respect there are huge numbers of pharmacological active heterocyclic compounds, many of which are in regular clinical use and they have been widely distributed in nature and are essential for life (Mishr *et al* 2011). Benzotriazoles as fused aromatic nitrogen heterocyclic of a benzene ring with possessing a larger conjugated system to form π-π stacking interactions , where three nitrogen atoms make it easy to form hydrogen bonds and coordination bonds. Therefore, benzotriazole derivatives are more ready to bind with a variety of enzymes and receptors in biological system *via* diverse non-covalent interactions, resulting in a broad spectrum of biological activities.

In the recent years, several publications pointed that benzotriazole derivatives found to have strong anticancer activity. For instance, the benzotriazole acrylonitrile I exhibited more potent anticancer activities in comparison to the standard drug etoposide and greater potential than 6-mercaptopurine against a serial publication of human cell lines (Carta *et al* 2011). Benzotriazole-substituted benzoate derivative **II** was synthesized and evaluated for its anti-proliferative activity against several cancer cell lines (Wan *et al* 2010). Moreover, a lot of researchers and exploitations have been devoted to benzotriazoles due to their potentiality as novel antifungal agents (Patel *et al* 2010; Rezaei *et al* 2009) such as structures **III** and **IV**. The introduction of benzotriazole into coumarin ring afforded compound **V** with a broad antibacterial spectrum against both Gram-positive and Gram-negative bacteria (Shi *et al* 2011; Ren *et al* 2014).

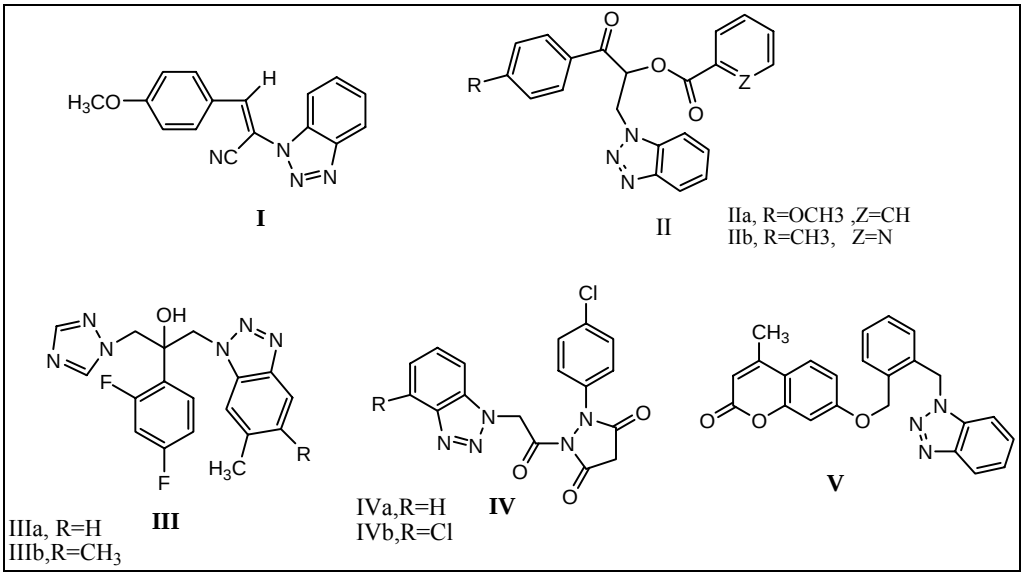


Figure 1: Benzotriazole containing biologically active molecules

On the other hand, thiophene derivatives have exhibited various pharmacological activities such as anti-platelet (Jagadish *et al* (2013), anti-inflammatory (Rajender *et al* 2004), antioxidant (Molvi *et al* 2008), analgesic (Wardakhan *et al* 2008), antibacterial (El-Bahaie *et al* 1988), antifungal activity (Aly *et al* 2011), anti-neoplastic (Anderson *et al* 1984) and so on. Encouraged by all these facts and in connection with our current studies of the development of new, selective, and environmentally friendly methodologies for the synthesis of fused systems, particularly those containing benzotriazole moieties (Al-Omran 2000; Al-Omran *et al* 2000, 2002). It was thought that it would be worthwhile to design and synthesize compounds containing both the core structures of benzotriazole linked to thiophene, that connected with cyanoacetamide function. The 2-cyanoacetamide derivative **4**, will be highly versatile and useful building block for the synthesis of a variety of heterocyclic by one–pot reaction, such as benzimidazolpyrimidine derivative**10**, pyrido-thieno-pyrimidine derivative **14** and thienoquinolinone derivative **23**. These moieties of known importance were incorporated with benzotriazole ring into a single structure, in hope develop benzotriazole-based drug with high bioactivity and low toxicity.

MATERIAL AND METHOD

All m.p values were reported uncorrected and have been determined on a Gallenkamp apparatus. The Fourier Transform-Infrared (FTIR) spectra have been recorded on a FT-IR (Jasco FT/IR-6300) using a KBr disc. The ^{1}H and ^{13}C-NMR spectra have been recorded on a Bruker DPX 400 MHz spectrometer, with DMSO-d_6 or $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts have been reported as δ unit (ppm). Mass spectra have been measured on GC/ MS DFS, THERMO instrument. Microanalyses have been performed on a CHNS-Vario Micro Cube Analyzer (Germany), a single-crystal X-ray crystallography instrument (Rigaku, Rapid II, Japan), and a Bruker X8 Prospector (Bruker, Germany) in the Chemistry Department of Kuwait University. Compound 3 has been prepared by a method reported in the literature (Al-Omran *et al* 2002).

Experimental

N- [*5-(Benzotriazol-1-yl)-3-cyano-4-methylthiophen-2-yl-*] *-2-cyanoacetamide* ***(4):***A mixture of cyanoacetic acid (0.85gm, 10.0 mmol) in acetic anhydride (20mL) and 1,4- dioxane (20 ml) was heated for 15 minutes. To a stirred reaction mixture a compound **3** (2.55gm, 10 mmol) was added and heated for a further 1 hour at 100^{o}C. The reaction mixture was allowed to cool to room temperature. The solid product, so formed was collected by filtration and crystallized from ethanol as brown crystals. Yield: 2.44g, 76%; m.p : 176-178 ^{o}C. FTIR (KBr): $\nu_{max/cm-1}$: 3269(NH), 2218(2CN), 1697(CO) . ^{1}H-NMR : (400 MHz DMSO-d_6) : δ_H 2.64(s, 3H, CH_3), 4.21 (s, 2H, CH_2), 7.53-7.99(m, 4H, Ar-H) , 12.57 ppm (s, 1H, NH , D_2O exchangeable) .^{13}C NMR : (400 MHz DMSO-d_6): δ_C 162.7 (CO) ,145.8, 144.0 , 133.5 128.4 , 127.5 , 126.3, 124.9, 119.8, 115.6, 113.5, 110.5, 94.9 (Ar-C & 2 CN), 26.2 (CH_2), 13.8 ppm (CH_3); MS (EI): *m/z* (%)= 322 (M+,100). *Elem.anal. Calculated* for $C_{15}H_{10}N_6OS$ (322.34): C, 55.89; H 3.13;N, 26.07 %. Found: C: 55.72, H: 3.22, N: 26.15 %.

***N- [5'-(Benzotriazol -1- yl)-3'- cyano -4'-methylthiophen-2'-yl]-4- aminobenzimidazol-[2,1- b] pyrimidine -3-carboxamide hydrochloride* (10) :** A mixture of compound **4** (3.22gm, 10.0 mmol) and 2-aminobenzimidazole (**5)** (1.33gm, 10.0 mmol) were suspended in a mixture of *DMF DMA*: 1,4-dioxane (20:40 mL). The reaction mixture was heated under refluxed for 2 hours, then cooled and neutralized by pouring into ice/water containing a few drops of HCl. The solid product formed was collected by filtration and crystallized from ethanol as yellow crystals. Yield: 3.60 g, 72%; m.p 153- 155 ^{o}C . FTIR(KBr): $\nu_{max/cm-1}$3269 (NH_2), 3219 (NH) , 2217 (CN) and 1652 cm^{-1} (CO).^{1}H-NMR : (400 MHz DMSO-d_6) : δ_H 2.62(s,3H, CH_3), 7.18-7.86 (m, 8H, Ar-H), 8.05 (s,1H, H-2), 8.14 (s,1H, NH , D_2O exchangeable), 8.18 ppm (s, 2H , NH_2 , D_2O exchangeable), ^{13}C NMR : (400 MHz DMSO-d_6): δ_C163.5 (CO) ,162.7, 162.2 , 149.8, 147.3, 144.7 , 138.0 ,134.0, 133.5, 131.8 ,129.0, 128.4 , 124.9 ,124.0 , 121.9, 119.8, 117.5 , 115.1 , 113.6, 113.6, 110.5, 93.8 (Ar-C & CN) and 14.0 ppm (CH_3) ; MS(EI): *m/z* (%)= 465 (M^+-HCl , 11%) *Elem.anal. Calculated* for $C_{23}H_{16}$ Cl N_9OS (501.95): C, 55.03; H, 3.21; N, 25.11 %. Found: C 55.14; H, 3.11; N, 25.01 %.

***2-(Benzotriazol -1- yl)-9-imino-4-oxo -7-phenyl-3-methyl-5,9-dihydro-4H-pyrido [2,1- a] thieno[3,2-e]pyrimidine -6,8-dicarbonitrile* (14) :**A mixture of compound **4** (3.22gm, 10.0 mmol) and benzylidenemalononitrile (1.54 mL, 10.0 mmol) in ethanol (20 mL) and 2-3 drops of piperidine were stirred at refluxed for 3-4 hours. The reaction mixture was allowed to cool to room temperature. The solid product so formed, was collected by filtration and crystallized from ethanol as brown crystals. Yield: 3.50 g, 74%; m.p 177-179^{o}C. FTIR(KBr): $\nu_{max/cm-1}$3417, 3325 (2NH), , 2223 (2CN) and 1656 cm^{-1} (CO) . ^{1}H-NMR : (400 MHz DMSO-d_6) : δ_H 2.57(s,3H, CH_3), 7.28-8.24 (m, 9H, Ar-H), 9.56 (s,1H, NH , D_2O exchangeable), 12.31 ppm (s, 1H , NH , D_2O exch-angeable).^{13}C NMR : (400 MHz DMSO-d_6): δ_C163.6 (CO) ,159.5, 157.0 , 144.9 , 144.5 , 134.3,134.0, 130.5, 129.6,129.0, 128.7 , 128.3 ,127.9 , 125.2 ,124.8, 120.0, 116.1 , 115.5 , 115.2, 110.4, 86.4 , 84.1 (Ar-C & 2 CN) and 14.2 ppm (CH_3) ; MS(EI): *m/z* (%)= 474 (M^+, 7%) *Elem.anal. Calculated* for $C_{25}H_{14}$ N_8OS (474.5): C, 63.28; H, 2.97; N, 23.62 %. Found: C 63.40; H, 3.25; N, 23.61 %.

***7-Amino- 2-(benzotriazol -1- yl)-9-imino -3-methyl-4-oxo-5,9-dihydro-4H-pyrido[2,1- a] thieno[3,2-e]pyrimidine -6-carbonitrile* (19) :**A mixture of compound **4** (3.22gm, 10.0 mmol) and malononitrile (0.66 gm, 10.0 mmol) in ethanol (20 mL) and 2-3 drops of piperidine were stirred at refluxed for 3-4 hours. The reaction mixture was allowed to cool to room temperature. The solid product so formed was collected by filtration and crystallized from ethanol as brown crystals. Yield: 3.06 g, 79%; m.p 166-168^{o}C. FTIR (KBr): $\nu_{max/cm-1}$3426-3207 (br. NH_2, NH & C=NH), 2219 (CN) and 1621 cm^{-1} (CO). ^{1}H-NMR : (400 MHz DMSO-d_6) : δ_H 2.59(s,3H, CH_3), 4.45 (s, 2H , NH_2 , D_2O exchangeable) , 7.42-8.17 (m, 5H, Ar-H), 12.19 (s,1H, NH , D_2O exchangeable), 12.60 ppm (s, 1H , NH , D_2O exchangeable).^{13}C NMR : (400 MHz DMSO-d_6): δ_C163.6 (CO) ,162.7 , 162.1 , 147.1 , 145.7, 143.6 ,134.3,133.6, 131.9,129.1, 126.1 , 119.9, 117.6 , 115.5 , 110.4, 95.0 , 85.6 (Ar-C & CN) and 14.2 ppm (CH_3) ; MS(EI): *m/z* (%)= 388 (M^+, 5%) *Elem.anal. Calculated* for $C_{18}H_{12}$ N_8OS (388.41): C, 55.66; H, 3.11; N ,28.85 %. Found: C, 55.40; H, 3.28; N, 28.63 %.

***N*-[5'-(1*H*-Benzotriazol-1-yl)-3'-cyano-4'-methylthiophen-2'-yl]-2-oxo-1,2-dihydroquinoline-3-carboxamide (23).**A suspension of cyanoacetic acid (0.85g, 10.0mmol) in Ac_2O (20ml) and 1,4 dioxane (20 ml) was heated for 15 minutes. To a stirred reaction solution a compound **3** (2.55gm, 10 mmol) was added and heated for a further 1 hour at 100^{o}C. A solution of EtOH (20 ml) containing a salicyladehyde **20** (1.22g, 10 mmol) and 2-3 drop of triethyl amine was added to the reaction mixture.

Then the mixture was refluxed for 2 hours, allowed to cool to room temperature. The solid product so formed was collected by filtration and crystallized from ethanol as brown crystals. Yield: 3.53 g , 83%, mp: 165-167^{o}C; IR (KBr): ν/cm^{-1} 3426 & 3328(2 NH) , 2214(CN), 1676 & 1643(2CO); ^{1}H-NMR : (400 MHz DMSO-d_6) : δ_H 2.61(S, 3H, CH_3), 6.99- 8.20 (m, 10H, Ar-H & ,NH, D_2O exchangeable), 11.30 ppm (br, D_2O exchangeable, 1H, NH) ;^{13}C NMR : (400 MHz DMSO-d_6): δ_C 163.6, 162.6 (2CO) ,157.7 ,153.4 ,144.2, 143.6, 136.4, 135.4, 134.6, 134.1, 130.1, 129.6, 128.5, 127.9, 125.6, 124.8, 120.0, 119.8, 118.4, 115.4, 85.5(Ar-C & CN), 14.1 ppm (CH_3) ; MS (EI): *m/z* (%)= 426 (M+,77). *Elem.anal. Calculated* for $C_{22}H_{14}N_6O_2S$ (426.09): C, 61.96; H, 3.31; N,19.71. Found: C, 61.99; H, 3.47; N, 19.89.

***N*-[5'- (1*H*- Benzotriazol-1-yl)-3'- cyano-4'-methyl thiophen -2'- yl] -3,5- diamino -4- cyanothiophene -2-carboxamide (26).** A suspension of cyanoacetic acid (0.85g, 10.0mmol) in Ac_2O (20ml) and 1,4 dioxane (20 ml) was heated for 15 minutes. To a stirred reaction solution a compound **3** (2.55g, 10 mmol) was added and heated for 1 hour at 100^{o}C. A solution of EtOH (20 ml) containing of a malononitrile (0.66g, 10 mmol), elemental sulfur (0.32 g,10 mmo;) and 2-3 drop of piperidine was added to the stirred reaction mixture then, refluxed for 3-5 hours . The reaction mixture allowed to cool to room temperature. The solid product so formed was collected by filtration and crystallized from ethanol as brown crystals. Yield:3. 19 g, 76%, m.p: 155-157 ^{o}C. IR (KBr): ν/cm^{-1} 3336,3212 (2 NH_2). 3202(NH) , 2217(CN), 1641(CO); ^{1}H-NMR: : (400 MHz DMSO-d_6) : δ_H 2.63 (S, 3H, CH_3), 4.20 (br, D_2O exchangeable, 2H, NH_2), 7.41-8.21(m,6H,4 Ar-H & NH_2 ,D_2O exchangeable), 12.52 (br, D_2O exchangeable, 1H, NH); ^{13}C NMR : (400 MHz DMSO-d_6): δ_C δ_C 163.6 (CO), 153.4 ,148.9, 147.1 ,145.8, 144.6, 134.4, 133.1, 128.0, 124.3, 119.4, 118.4, 115.5 ,115.1 ,110.4 ,96.7, 95.0 (Ar-C & 2CN), 14.1 ppm (CH_3) ; MS (EI): *m/z* (%)= 420 (M^+, 10%) .*Elem.anal.Calculated*for $C_{18}H_{12}N_8OS_2$: (420.47): C, 51.42; H, 2.88; N, 26.65. Found: C, 51.28; H, 3.01; N, 26.57.

(E)-N-[5'-(1H-Benzotriazol-1-yl)-3'-cyano-4'-methylthiophen-2'-yl]-2–cyano-3-(4''-methoxyphenyl) acrylamide hydrochloride **(27) :**A mixture of compound **4** (3.22gm, 10.0 mmol) *p*-methoxybenzaldehyde **26** (1.36gm, 10.0 mmol) and ammonium acetate (0.77 gm, 10.0 mmol) in ethanol (20 mL) and *DMF* (10 mL) was refluxed for 4 hours . The reaction mixture was allowed to cool to room temperature, poured into ice- water and neutralized with HCl (10%) . The solid product so formed was collected by filtration and crystallized from ethanol as yellow crystals. Yield: 3.85 g, 81%, m.p 145-147^{o}C. FT-IR(KBr): $\nu_{max/cm-1}$3428 (NH), 2218 (2CN) and 1676 cm^{-1} (CO).^{1}H-NMR : (400 MHz DMSO-d_6) : δ_H 2.64(s,3H, CH_3), 3.84(s,3H, OCH_3), 7.01-8.11 (m, 8H, Ar-H), 8.15 (s,1H, H-3), 12.21 (s,1H, NH , D_2O exchangeable), .^{13}C NMR : (400 MHz DMSO-d_6): δ_C164.2 (CO) ,163.5, 153.2 , 145.1, 144.7 , 143.9 ,133.3 , 129.3, 127.8 , 127.4, 125.0 ,124.2 , 122.3, 119.3, 117.6 , 116.4 , 110.4, 100.2 , 95,9 (Ar-C , Olifinic -C & CN) 55.8 (OCH_3) and12.3 ppm (CH_3) ; MS(EI): *m/z* (%)= 440 (M^+- HCl , 15%).*Elem.anal.Calculated* for $C_{23}H_{17}$ Cl N_6O_2S (476.94) : C, 57.92; H, 3.59; N ,17.62 %. Found: C , 58.07;H, 3.79; N ,17.60 %.

N- [5-(Benzotriazol-1-yl)-3-cyano-4-methylthiophen-2-yl]-2-cyano -3-(dimethylamino)acrylamide (32) :A suspension of cyanoacetic acid (0.85gm, 10.0 mmol) in Ac_2O (20mL) and 1,4- dioxane (20 ml) was heated for 15 minutes . To a stirred reaction solution a compound **3** (2.55gm, 10 mmol) was added and heated for a further 1 hour at 100^{o}C. A solution of *N, N*- dimethyl formamide dimethyl acetal (*DMFDMA*) (1.33mL, 10.0 mmol) in dioxane (20 mL) was added to the reaction mixture and refluxed for 2 hours. The mixture was allowed to cool to room temperature. The solid product so formed was collected by filtration and crystallized from ethanol as yellow crystals. Yield: 2.94 g, 78%; m.p: 160-162 ^{o}C. FTIR (KBr): $\nu_{max/cm-1}$: 3436 (NH), 2215 & 2193 (2CN), 1652(CO) . ^{1}H-NMR : (400 MHz DMSO-d_6) : δ_H 2.62 (s, 3H, CH_3), 3.28 (s, 3H, NCH_3), 3.33 (s, 3H, NCH_3), 7.47-8.21 (m, 4H, Ar-H) , 11.12 ppm (s, 1H, NH , D_2O exchangeable) .^{13}C NMR : (400 MHz DMSO-d_6): δ_C 164.6 (CO) 158.8 ,145.2, 144.4 , 134.5 , 132.0, 129.7 , 128.2 ,127.5, 125.4, 119.8,115.6, 110.9, 97.6, 95.5 (Ar-C , olefinic –C & 2 CN), 47.9 (*N*CH_3), 38.9 (*N*CH_3), 14.2 ppm (CH_3); MS (EI): *m/z* (%)= 377 (M+,20%). *Elem.anal.Calculated*for $C_{18}H_{15}N_7OS$ (377.42): C, 57.28; H, 4.01; N, 25.98 %. Found: C: 57.37; H: 4.12; N: 25.82 %.

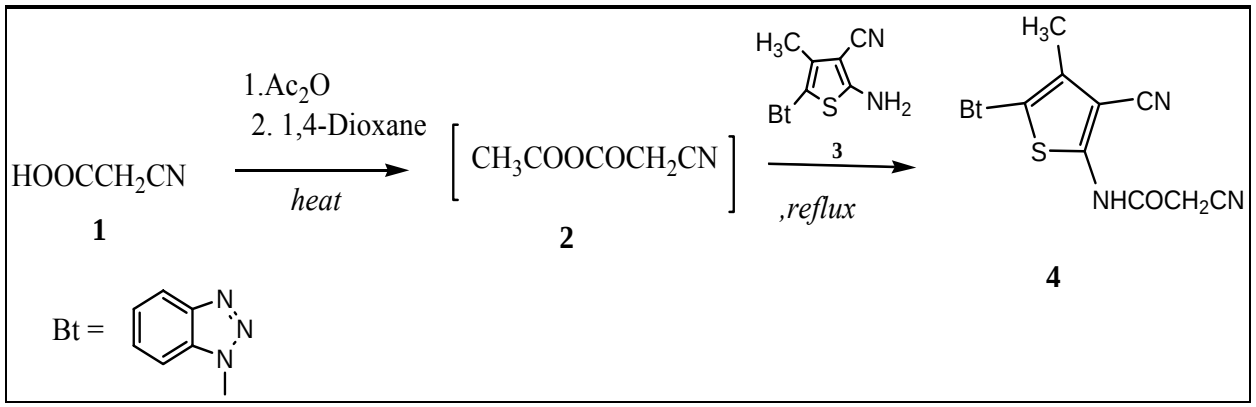
***N- [5'-(1H- Benzotriazol -1- yl) -3'- cyano -4'- methyl thiophen -2'- yl] -7- aminotetrazolo[1,5- a] pyrimidine -6-carboxamide* (34):**A mixture of compound **32** (3.77gm, 10.0 mmol) and aminotetrazole **33** (0.85gm, 10.0 mmol) in *ethanol* (20 mL) was refluxed for 4 hours. The reaction mixture was allowed to cool to room temperature. The solid product so formed was collected by filtration and crystallized from ethanol as brown crystals.

Yield: 3.37 g, 81 %; m.p 133-135°C. FTIR (KBr): $\nu_{max/cm-1}$3414 (NH_2), 3317 (NH), 2211 (CN) and 1641 cm^{-1} (CO) . ^{1}H-NMR: (400 MHz DMSO-d_6) : δ_H 2.16 (s,3H, CH_3), 7.53-8.75 (m, 6H, Ar-H & NH_2, D_2O exchangeable), 8.77 (s,1H, H-5), 13.78 ppm (s, 1H , NH,D_2O exchangeable).^{13}C NMR: (400 MHz DMSO-d_6): δ_C163.3 (CO) ,160.7, 149.6, 146.9 , 145.6 , 134.8,131.5, 129.9, 127.6 , 125.6 ,122.4 , 120.2 , 116.4 , 115.3 , 110.7, 94.3 (Ar-C & 2 CN) and 13.7 ppm (CH_3); MS(EI): *m/z* (%)= 417 (M^+, 4%) . *Elem.anal. Calculated* for $C_{17}H_{11}N_{11}OS$ (417.41): C, 48.92; H, 2.66; N, 36.91 %. Found: C, 48.88; H, 2.45; N, 36.38 %.

***N-[5'-(1H-Benzotriazol-1-yl)-3'-cyano-4'-methylthiophen-2'-yl]-5-amino-1H-pyrazole-4-carboxamide hydrochloride* (35):** A mixture of compound **32** (3.77gm, 10.0 mmol) and hydrazine hydrate (0.50gm, 10.0 mmol) in ethanol (20 mL) was refluxed for 3 hours. The reaction mixture was allowed to cool to room temperature, poured into ice- water and neutralized with HCl (10%). The solid product so formed was collected by filtration an crystallized from ethanol as pale brown crystals. Yield: 2.95 g, 81 %; m.p 202-204°C. FTIR (KBr): $\nu_{max/cm-1}$3444 (NH_2), 3276 (NH), 2220 (CN) and 1660 cm^{-1} (CO) . ^{1}H-NMR : (400 MHz DMSO-d_6) : δ_H 2.65 (s,3H, CH_3), 6.62 (s, 2H , NH_2 , D_2O exchangeable). 7.51-8.21 (m, 6H, ArH & NH, D_2O exchangeable), 11.98 ppm (s, 1H , NH , D_2O exchangeable).^{13}C NMR : (400 MHz DMSO-d_6): δ_C163.2 (CO) , 144.7, 143.3 , 134.1 , 131.5, 129.2, 127.3 , 126.1 ,124.9 , 119.8 , 117.7 , 115.1 , 114.4 , 110.5, 92.7 (Ar-C & CN) and 12.3 ppm (CH_3) ; MS(EI): *m/z* (%)= 365 (M^+ - HCl, 3%) . *Elem.anal. Calculated* for $C_{16}H_{13}ClN_8OS$ (400.85): C, 47.94; H, 3.27, N; 27.95 %. Found: C, 48.09; H, 3.19; N, 28.01 %.

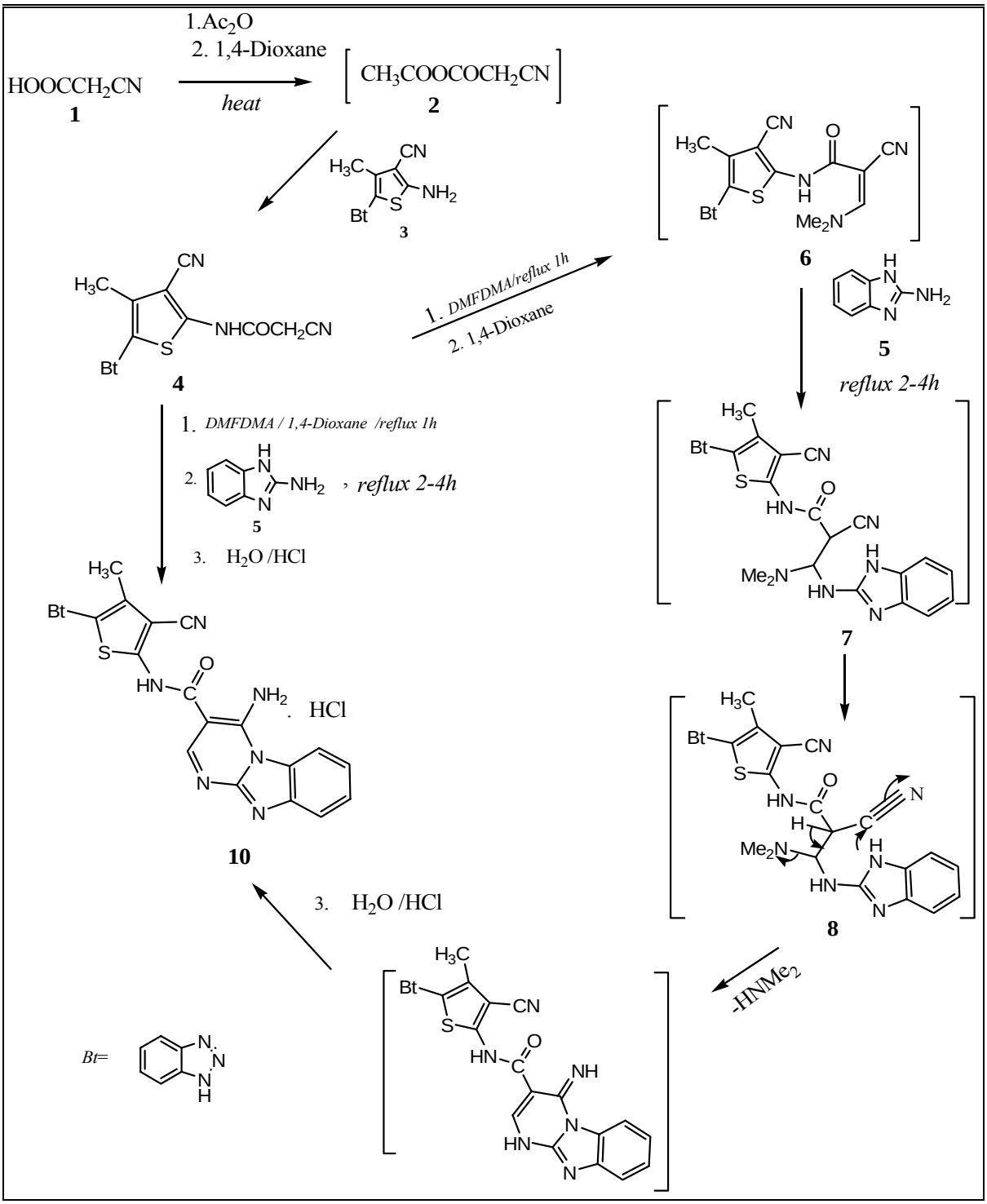
RESULTS AND DISCUSSION

"One-pot reaction" is one of the most powerful tools in organic chemistry, in particular, to emphasize that a sequence of chemical transformations is run in a single flask. At that point the synthetic chemist seeks to save time and resources by avoiding purifications between individual steps within a multistep synthesis, thus minimizing the transfer of material between vials" (Vaxelaine *et al* 2011). Therefore, the *N*-[5-(benzotriazol-1-yl) -3-cyno-4-methylthiophen-2-yl] -2-cyanoacetamide (4) has been synthesized in excellent yield (Scheme 1), by one-pot reaction of *2-amino*-5-(benzotriazol-1-yl) -3-cyno-4-methylthiophene (3) and cyano anhydride 2. The latter compound has been generated by condensation of cyanoacetic acid with acetic anhydride in the presence of 1,4-dioxane in situ. The structural elucidation of the new compound 4 has been established by analysis of the corresponding NMR, infrared and mass spectrometry data. The ^{1}H-NMR spectrum of compound 4 shows two aliphatic singlet signals corresponding to methyl and methylene protons. Likewise, the ^{1}H NMR spectrum showed the presence of one D_2O- exchangeable proton attributed to a NH function at δc 12.57 ppm.



Scheme 1: Synthesis of 2-cyanoacetamide derivative 4

Moreover, ^{13}C NMR spectrum revealed highest frequency signal at δc about 163 ppm assignable to the amide carbonyl carbons and two signals at δc 115.6 and 113.5 ppm corresponding to two CN groups.



Scheme 2: Theone –pot reaction for synthesis of benzimidazopyrimidine derivative10

Therefore, as a part of our continuing work on the synthesis of novel functionally substituted heteroaromatic compounds (Al-Omran &El-Khair 2014; Al-Omran *et al* 2013) we have developed a novel one –pot reaction for synthesis of benzimidazopyrimidine derivative **10** *via* a three-component reaction of acyanoacetamide derivative **4**, dimethylformamide dimethyl acetal (DMF-DMA) and 2-aminobenzimidazole at reflux temperature. The structure of latter product was confirmed on the basis of their correct elemental analysis and spectral data of the isolated reaction product (*cf*. Experimental Section). The IR spectrum exhibited absorption bands at 3269, 3219, 2217 and 1652 cm^{-1} characteristic of NH_2,NH,CN and amido carbonyl carbon groups respectively.

Its ^{1}H NMR spectrum revealed an aromatic multiplet in the region δ 7.18-7.86 ppm, a singlet at (8.05 p.m. due to fused pyrimidine (H-2) proton and two broad singlets at δ 8.14 and 8.18 ppm attributed to NH and NH_2 groups ,which readily underwent H/Dexchange upon addition of deuterium oxide. Also, the structure of **10** was judged by mass spectrum, it showed the molecular ion peak at m/z 465 (M^+ -HCl, 11%) which is in agreement with with its molecular formula $C_{23}H_{16}ClN_9OS$.

The formation of compound **10** assumed to take place *via* an initial Micheal addition of the exocyclic amino group in compound **5** to the activated bond in non-isolable enaminonitrile **6** to give the acyclic non - isoluble intermediate **7.**The latter intermediate **7** underwent *via* the nucleophilic addition of the ring nitrogen atom to nitrile function followed by hydrolysis and elimination of the dimethylamine molecule to give the target product **10** (scheme 2).

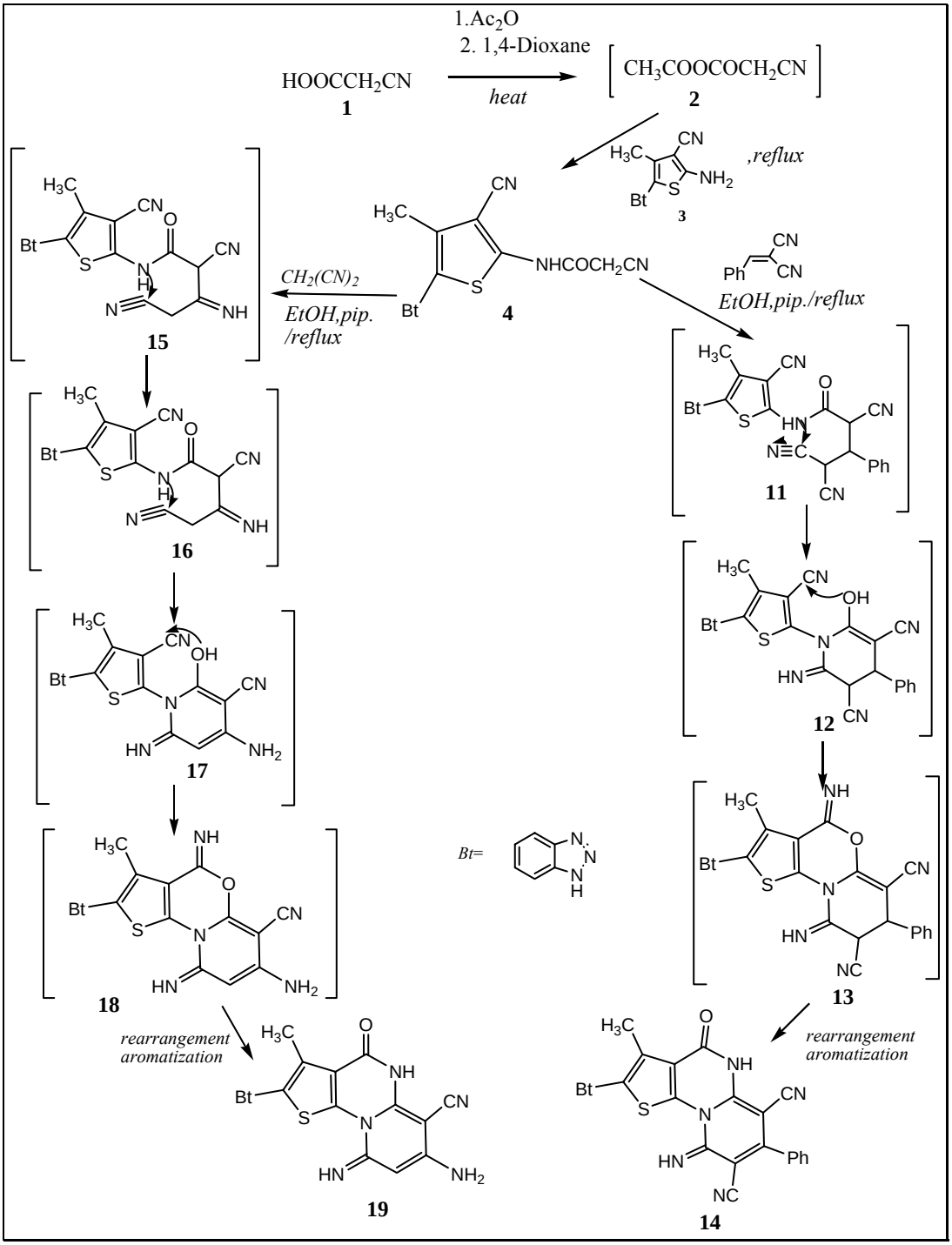
Similarly, acyanoacetamide derivative **4** reacted with benzylidenemalononitrilein ethanol containing a catalytic amount of piperidine to afford the substituted pyridothienopyrimidine derivative **14** (Scheme **3**). The structure of the latter product was confirmed on the basis of their

correct elemental and spectral data (*cf*. experimental).The formation of **14** assumed to take place, *via* an initial Micheal addition of the methylene group in compound **4**to the double bond of benzylidenemalononitrile to give the acyclic non-isolable intermediate **11** that undergoes cyclization, Dimroth rearrangement and aromatization *via* the intermediary of **12-13.**In a similarmanner, another class of pyridothienopyrimidine derivative **19** could be prepared by reaction of acyanoacetamide **4** with malononitrile, in refluxing ethanol a containing catalytic amount of piperidine *via* the intermediacy **15-18** (*cf*. Scheme 3). The chemical structure of **19** has been elucidated on the basis of its elemental analysis and spectral data. Its ^{1}H NMR spectrum displayed three broad signals at δ 4.45,12. 19 and 12.6 ppm, exchangeable with D_2O, assignable to one NH_2 and two NH protons respectively.

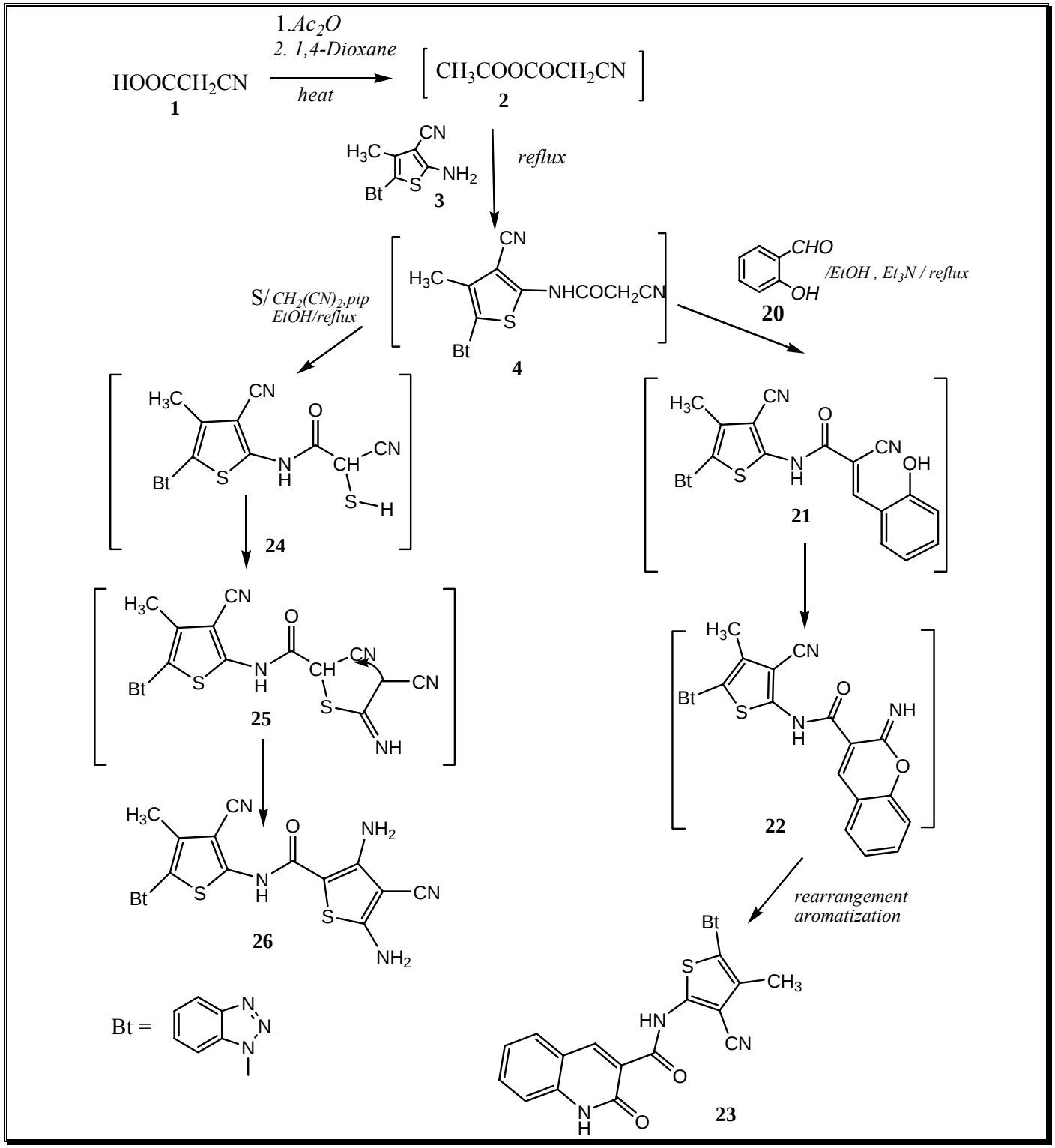
On the other hand, the multicomponent reactions (MCRs) of cyanoacetic acid in the presence of a mixture of acetic anhydride /1,4-dioxane and compound **3**with salicylaldehyde **20** was investigated as a modelto demonstrate the feasibility of the strategy. The reaction was performed in a one –pot-two-step process**.** Subsequently, the first –step from condensation of compound **3** with cyanoacetic acid in the presence of a mixture of acetic anhydride /1,4-dioxane, salicylaldehyde **20** was added in thepresence a catalytic amount of trimethylamine under reflux (Scheme **4**) afforded thienoquionlinone derivative **23.**

The formation of **23** was assumed to take place *via the* addition of the active methylene group of cycnoacetamide to the carbonyl group of salicylaldehyde to give the non-isolable intermediate **21** which underwent in situ cyclization *via* the nucleophilic addition of the ethanolic hydroxyl group to nitrile function followed by Dimroth rearrangement and aromatization of letter intermediate to **23**. The structure of compound **23** has been based on analytical and spectral data (see Experimental Section).The mass spectrum of thienoquionlinone derivative **23** exhibited a molecular ion peak [M+] (m/z 426) ,which is also the base peak corresponding to the molecular formulae $C_{22}H_{14}N_6O_2S$.

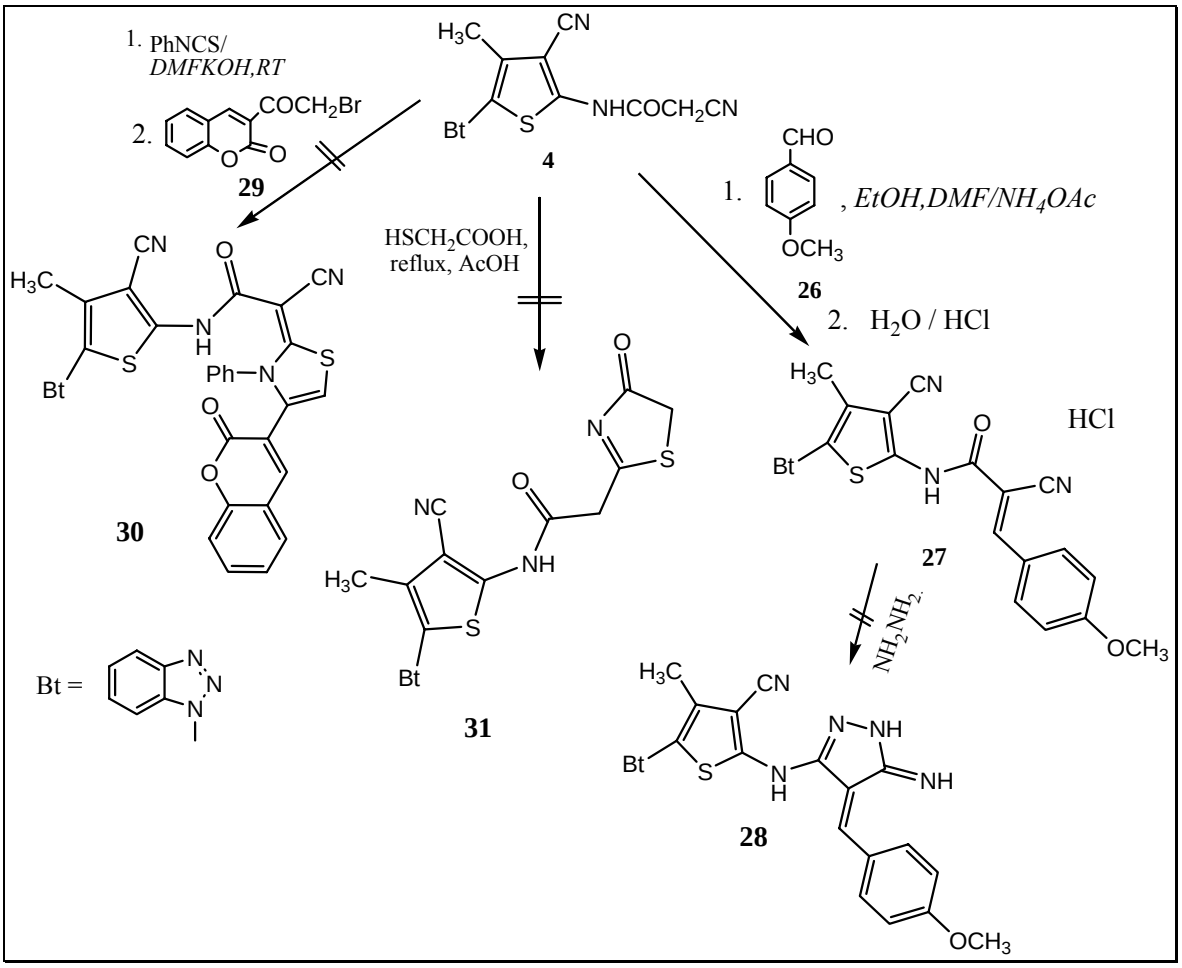
On the other hand , a novel diaminothiophene **26** has been prepared by one–pot synthesis of cyanoacetic acid with acetic anhydride in the presence of 1,4-dioxane followed by reacting the mixture in situ with compound **3**.The intermediate **4**, which has been formed condensation with malononitrile and elemental sulfur in the presence trimethylamine. The data obtained from IR, ^{1}HNMR and Ms spectra are in agreement with the proposed structure **26** (*cf*. Scheme **4**).



Scheme 3 : Reaction of cyanoacetamide derivative 4 with benzylidinemalononitrile or malononitril in ethanolic piperidine



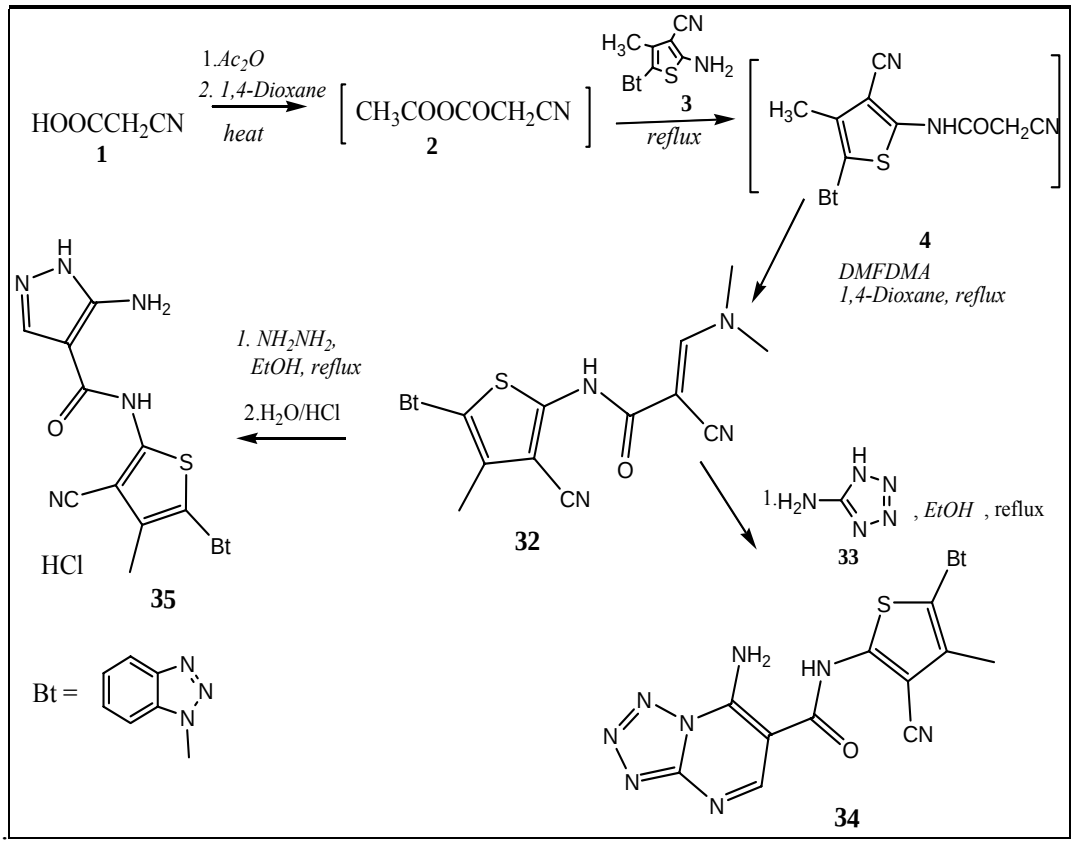
Scheme 4: One-pot multicomponent reaction for synthesis derivatives of the thienoquinolinone 23 and diaminothiophene26



Scheme 5: Reaction of cyanoacetamide derivative 4 with p-methoxybenzaldehyde

Therefore, the ^{1}H NMR of compound **26** revealed the existence of three singlet D_2O exchangeable. The two singlets integrated for two NH_2 groups at δ 4.20 and at range 7.41- 8.21ppm. Also, one singlet at 12.51 ppm due to NH. Moreover, the mass spectrum of **26** showed a molecular ion peak at m/z 420 [M^+]. A formation of **26** took place through the intermediate formation of **24** and **25**.

The Knoevenagel condensation of acyanoacetamide derivative **4** with*p*-methoxybenzaldehyde in refluxing ethanol and DMF contain ammonium acetate afforded the *p*-methoxyphenyl- acrylamide derivative **27**. The structure of the latter has been supported on the basis of elemental analysis and spectral data. The IR spectrum exhibited absorption bands at 3428, 2218 and 1676 cm-1 characteristic of NH, CN and amide carbonyl groups, respectively. Its ^{1}H NMR spectrum revealed a three single proton at 2.64,3.84 and, 8.15 ppm., owing to methyl, methoxy, and vinylic protons respectively. Likewise, a broad singlet at 12.21 ppm exchangeable with D_2O, assignable to NH proton. The the *p*-methoxyphenylacrylamide derivative **27** fail to react with hydrazine hydrate to form pyrazole derivative **28** (Scheme **5**)**.** The reaction of acyanoacetamide derivative **4** with pheny isothiocyanate in DMF containing potassium hydroxide and α-bromocarbonyl compound **29** in an attempt to transform the acyanoacetamide derivative **4** to thiazole derivative **30** was unsuccessful. Likewise, the acyanoacetamide derivative **4** failed to react with the thioglycolic acid (TGA) in boiling glacial acetic acid in an attempt to formed thiazolinone derivative **31** (Scheme 5).



Scheme 6: The reactions of enaminone 32 with aminotetrazole 33 and hydrazine hydrate

Moreover, in continuation of our interest in the synthesis of functionally substituted heteroaromatic compounds utilizing enaminones as starting materials (Al-Omran 2000 ;Al-Omran *et al*2000;Al-Omran &El-Khair 2005 , 2007, 2008, 2009)we report inhere the synthesis of enaminones **32** by a one-pot multicomponent reactions (MCRs),of cyanoacetic acid with acetic anhydride in the presence of 1,4-dioxane .The latter solution reacted in situ with and *2-amino*-5-(benzotriazol-1-yl) -3-cyno-4-methylthiophene (**3)** andwas continuing to react with dimethylformamide dimethyl acetal (DMF-DMA) yield enaminones **32.** The structure of compound **31** has been elucidated on the basis of its elemental analysis and spectral data (Scheme **6**).

The reactivity of enaminones **32** towards nitrogen nucleophile was investigated. Therefore, enaminones **32** reacted with amino-tetrazole **33** in refluxing ethanol gave 7-amino-tetrazolo-pyridine derivative **34** in excellent yields. The structure of **34** product was confirmed on the basis of their correct elemental and spectral data (*cf.* Experimental Section). The formation of compound **34** assumed to take place *via* an initial Michael addition of the exocyclic amino group in compound **33** to the activatedouble bond in **32.** The latter intermediate undergo cyclization (addition of the NH group to the cyano function) and aromatization *via* loss of both dimethylamine and water molecules producing **34**. Similarly, enaminones **32** reacted with hydrazine hydrate to yield 5-aminopyrazole derivative **35** in excellent yield (Scheme 6). The structure of compound **35** has been assigned by means of its spectral properties.

CONCLUSION

An environmentally friendly methodology in one pot reaction utilizing the cyanoacetamide 4 bearing both core structures of thiophene and benzotriazole in one frame structure to synthesize a variety of heterocyclic aromatic compounds (*e.g.*Benzimidazolepyrimidine, pyidothienopyrimidine, thienoquinoline and diaminothiophene derivatives) in excellent to good yield have been interrupted. The structures of the synthesized compounds confirmed by elemental analyses, ^{1}H –NMR, ^{13}C NMR and MS spectra. In hope develops drug with high bioactivity and low toxicity.

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