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Synthesis and Antimicrobial Evaluation of some Novel Dithiolane, Thiophene, Coumarin and 2-Pyridone Derivatives

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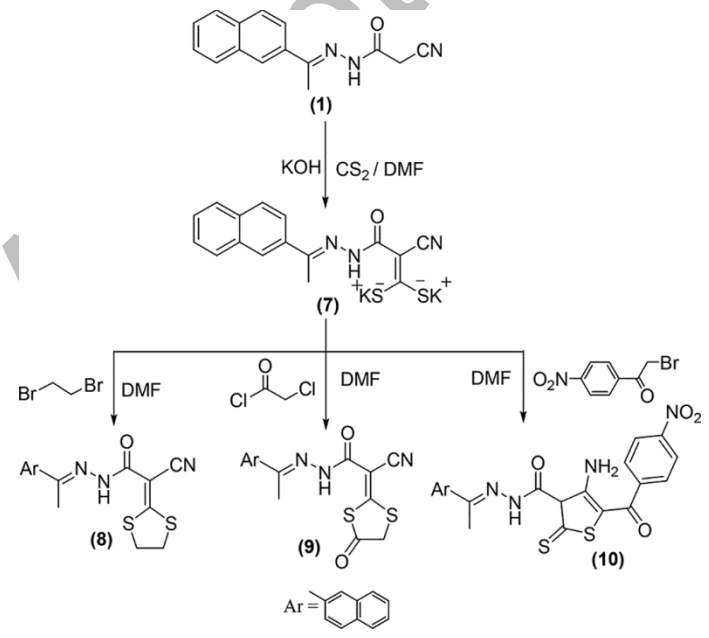
Abstract

Novel 2-cyano-*N*-[1-(naphtha-2-yl)ethylidene] acetohydrazide **1** was utilized as key intermediate for the synthesis of some new dithiolane, thiophene, coumarin, 2-pyridone, and other related products containing a hydrazide moiety. Newly synthesized compounds were characterized by elemental analyses and spectral data (IR, ^{1}H NMR, ^{13}C NMR and mass spectra). The antimicrobial activity of the synthesized compounds was evaluated.

Graphical Abstract



KEYWORDS: Hydrazide-hydrazone, Cyanoacetohydrazide, dithiolane derivatives, thiophene derivatives

INTRODUCTION

The bicyclic naphthalene skeleton constitutes a large number of clinical drugs, such as propranolol[1], naphazoline (a cardiovascular agent)[2], naproxen[3], nabumetone (an anti-inflammatory agent)[4] and methallenestril (a non-steroid oestrogen)[5]. It is well known that naphthalene derivatives (e.g., 2-(3-(3,4-dimethylphenyl)-5-(naphthalen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-one, etc.) display anti-tumor, anti-arrhythmia, and antioxidant activities[6]. A number of hydrazide–hydrazone derivatives have been claimed to have exciting bioactivity such as antimicrobial, antitubercular,[7,8] anticonvulsant,[9] analgesic,[10] anti-inflammatory,[11] antiplatelet aggregation,[12] anticancer,[13,14] antifungal,[15] antiviral,[16] antibacterial,[17] and antimalarial[18] activities. Furthermore, coumarin derivatives have attracted considerable attention because of a large number of natural and synthetic products containing coumarin nucleus. Also, they have been reported to exert notable antimicrobial,[19] antifungal,[20,21] and cytotoxic[22] activities. In addition, some 2-pyridones are also reported to possess antitumor,[23] antibacterial[24] and other biological activities[25,26]. In view of the previously mentioned facts and in continuation of our interest to identify new candidates that may be valuable in designing new, potent, selective, and less toxic antimicrobial agents[27–31], we report herein the synthesis of a series of hydrazide–hydrazone derivatives together with their use in a series of heterocyclic transformations and evaluation as antimicrobial agents.

RESULTS AND DISCUSSION

In the present work, Condensation of 2-cyanoethanoic hydrazide with 2-acetyl naphthalene in refluxing dioxane afforded the corresponding condensation product 2-cyano-*N*-[1-(naphtha-2-yl) ethylidene] acetohydrazide **1**. (Scheme 1) The assignment of structure **1** was supported by elemental analysis and spectral data. The observation of δ 4.3 ppm integrated for 2H attributable for the cyano methylene protons and singlet integrated for one proton disappeared with D_2O at δ 11.09 ppm (NH) in the ^{1}H-NMR spectrum which completely in accord with the assigned structure **1**. Moreover, the IR spectrum displayed υ_{NH} at 3256 cm^{-1}, $\upsilon_{C\equiv N}$ at 2266 cm^{-1} representing the saturated nitrile group.

Coumarin derivatives are widely used for production of highly effective fluorescent dyes for synthetic fibers and day-light fluorescent pigments.[32] It was reported that the reaction of cyanoacetamido compounds with salicylaldehyde yielded the coumarin derivatives. Herein cyclocondensation of **1** with salicylaldehyde in dioxane containing triethylamine or ammonium acetate furnished smoothly the 2-imino coumarin derivative **2**. (Scheme 2) The presence of sharp stretching absorption bonds at 3311, 1674 and 1643 cm^{-1} characteristic for NH, CO and C=N group frequencies and the absence of carbonyl band for δ-lactone confirm the imino coumarin structure. Moreover, ^{1}H-NMR spectrum of the product revealed the presence of signals for five types of protons and the highest recorded peak in the mass spectrum at m/z = 355 (9.8%) representing the molecular ion peak for molecular formula $C_{22}H_{17}N_3O_2$.

The reaction of cyanoacetohydrazide derivative **1** with 4-methoxybenzylidene malononitrile in boiling dioxane in the presence of a catalytic amount of piperidine afforded on hot a crystalline product with molecular formula $C_{14}H_{11}N_5O_2$. (Scheme 2) The ^{1}H-NMR spectrum of this product revealed the absence of naphthalene, methyl protons and the presence of two NH_2 protons which ruled out the expected structure **3** and confirm the structure **4**. Moreover, the IR spectrum of this product displayed the coupling bands for υ_{NH2} at 3455, 3395, 3320, 3269 cm^{-1}, $\upsilon_{C\equiv N}$ (sharp band) at 2216 cm^{-1} and $\upsilon_{C=O}$ at 1641 cm^{-1} (the low frequency of the carbonyl band may be due to the H-bonding with the adjacent amino group). Also the highest recorded peak in the mass spectrum at m/z = 281 attributable for the correct molecular ion peak and the base peak for molecular formula $C_{14}H_{11}N_5O_2$. Furthermore, the strong clue for the structure **4** is forthcoming by authentic sample prepared from the reaction of cyanoethanoic acid hydrazide with 4-methoxy benzylidene malononitrile in boiling dioxane in the presence of catalytic amount of piperidine (TLC, m.p and IR comparison). (Scheme 2) Probably the reaction mechanism is assumed to proceed via initial attack of the carbanion derived from the active methylene of the acetamido group to the β-carbon of the activated nitrile to give the Michael adduct followed by intramolecular cyclization then hydrolysis of the imino group with elimination of 2-acetyl naphthalene. (Scheme 3)

Hydrazinolysis of cyanoacetohydrazide derivative **1** using hydrazine hydrate (80%) in refluxing dioxane yielded a crystalline product with molecular formula $C_{24}H_{20}N_2$ [M.Wt= 336] which by spectral data identified as the azine of 2-acetyl

naphthalene **5** as a clear cut product in good yield without affording the expected pyrazole structure of type **6**. (Scheme 2) The IR spectrum of this product lacked the absorption bands for CN and NH_2 groups and only one absorption band observed at 1596 cm^{-1} which may be attributable for C=N group. ^{1}H-NMR spectrum of the product consistent with the azine structure **5** and revealed signals characteristic for aromatic protons as multiplet at 8.22-6.88 ppm integrated for 14H. The methyl protons observed up field at δ2.36 ppm. A further support for the structure of the azine **5** is forthcoming from the identity with an authentic sample prepared from the condensation of 2-acetyl naphthalene with excess hydrazine hydrate in refluxing ethanol.

The active methylene group in the cyanoacetohydrazide derivative **1** readily adds to one carbon donor such as carbon disulphide in DMF containing potassium hydroxide at room temperature to give the dipotassium dithiocarbazate salt **7** which separated in pure crystalline form then underwent heterocyclization upon treatment with dihalide and α-halocarbonyl compounds such as 1,2-dibromoethane, chloroacetyl chloride and *ω*-bromo-4-nitroacetophenone to afford the corresponding 1,3-dithiolane, 1,3- dithiolone and thiophene derivatives **8-10**, respectively. (Scheme 4) The assignment of the structures **8-10** were based on elemental analysis and spectral data. The element test in general showed the presence of sulfur element. All data for compound **8** were consistent with the proposed structure. Thus, the absence of the δ-^{1}H CH_2 cited for the acetamido methylene protons observed with **1** at δ 4.3 ppm and the appearance of a multiplet integrated for 4H at δ 3.3-3.25 ppm attributable for -CH_2-CH_2- protons of 1,3-dithiolane ring. Furthermore, the mass spectrum of **8** show the correct molecular ion peak at m/z =

353 (36.4%) together with the base peak at m/z = 170 which confirm the structure **8**. The structures **9** and **10** were deduced from the study of spectral data. The observed carbonyl stretching absorption band at 1717 cm^{-1} attributable for five-membered ringed ketone in the IR spectrum and the correct molecular ion peak at m/z = 367 (22.9%) in the mass spectrum of compound **9** in consistent with the assigned structure. Moreover, the presence of coupling bands at 3423, 3340 cm^{-1} characteristic for NH_2 group and the absence of nitrile group in the IR spectrum of **10** together with the recorded peak at m/z = 490 (81%) representing the molecular ion peak and finally, the ^{1}H-NMR spectrum revealed all the signals which completely in accord with the proposed structure **10**.

Treatment of the dipotassium dithiocarbazate salt **7** with ethyl chloroacetate in refluxing dioxane gave the uncyclized *S*-alkylation product **11** and no evidence was recorded for the cyclized products **9** or **12**. (Scheme 5) The appearance of strong absorption band for the nitrile group 2178 cm^{-1} and the carbonyl ester group at 1729 cm^{-1} with the absence of vibrational coupling bands for NH_2 group in the IR spectrum of the product, completely in agreement with the structure **11** and ruled out the cyclized products **9** or **12**. Moreover, ^{1}H-NMR spectrum of the product revealed the existence of triplet at δ 1.23 ppm and quartet at δ 4.14 ppm with equal coupling constants characteristic for ethyl protons and no recorded signals for the NH_2 protons.

The ketene *S,S*-dithioacetal **13** was prepared by alkylation of the dipotassium dithiocarbazate salt **7** with methyl iodide. (Scheme 5) The structure of **13** was elucidated on the basis of the elemental analysis and spectral data. The IR spectrum showed the

appearance of absorption bands at 3178, 2198, 1652 cm^{-1} for NH, C≡N and C=O groups, respectively. It's ^{1}H-NMR spectrum ($CDCl_3$) showed singlet signal at δ 2.73 ppm for 6 protons of two similar *S*-methyl protons, signal for the CH_3 protons at δ 2.41 ppm and signal for NH proton at δ 9.22 ppm disappeared with D_2O.

PHARMACOLOGY

Antimicrobial evaluation. All the newly synthesized compounds were evaluated for in vitro antibacterial activity against Gram-positive bacteria (*Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*) and fungi (Candida albicans) using a conventional broth dilution method.[33] Ampicillin and amphotericin B were used as reference drugs. The results were recorded for each tested compound as the average diameter of inhibition zones of bacterial or fungal growth around the disks in mm. The minimal inhibitory concentrations (MICs) for compounds that showed significant growth inhibition zones (>10mm) were determined using a twofold serial dilution method.[34] The inhibition zone diameters and MIC (μmol/ml) values are recorded in Tables 1 and 2.

The results revealed that the synthesized compounds showed varying degrees of inhibition against the tested microbes. In general, the best activity was displayed by compounds **8**, **9**, **11**, and **13** (Tables 1 and 2), because they showed potential antibacterial activity against almost all bacterial pathogens tested. Compounds **11** and **13** exhibited the highest affectivity against all tested microorganisms with inhibition zones range from 11 to 17 mm (% activity index from 57.8 to 100) with minimum inhibitory concentrations (MIC) range from 50.4 to 205 μg/ml. On the other hand, compounds **11** and **13** were

equipotent to ampicillin in inhibiting the growth of *E. Coli*. All compounds exhibited activity ranges from very weak activity to strong activity against C. albicans as compared with standard amphotericin B.

Structure–activity relationship. The structure–antimicrobial activity relationship of the synthesized compounds against the pathological strains of bacteria and fungi revealed that compounds **8**, **9**, **10**, **11**, and **13** have higher antimicrobial activities than other compounds. The increased antimicrobial activity of these compounds is thought to be due to the larger size of the sulfur atom.[35] Sulfur atoms might block enzymatic activity in microorganisms and in doing so prevent bacterial division and growth.[36]

EXPERIMENTAL

All melting points were taken on a Griffin and Geory melting-point apparatus and are uncorrected. IR spectra were recorded on Pye Unicam SP1200 spectrophotometer using the KBr wafer technique. ^{1}H NMR and ^{13}C NMR spectra were determined on a Varian Gemini 300MHz using tetramethylsilane (TMS) as internal standard (chemical shifts in scale). EI-MS were measured on a Schimadzu-GC-MS operating at 70 eV. Elemental analyses were carried out at the Microanalytical Unit, Faculty of Science, Ain Shams University, using a Perkin-Elmer 2400 CHN elemental analyzer, and satisfactory analytical data (±0.4) were obtained for all compounds. The homogeneity of the synthesized compounds was controlled by thin layer chromatography (TLC) using aluminum sheet silica gel F_{254} (Merck).

Synthesis Of (Z)-2-Cyano-N$^{/}$-(1-(Naphthalene-2-Yl) Ethylidene)Acetohydrazide 1

A mixture of 2-acetyl naphthalene (2g, 11mmol) and 2-cyanoacetohydrazide (1.15 g, 11 mmol) in dioxane (30 mL) was refluxed for 2hrs. The deposited solid on hot was filtered off, dried and recrystallized from dioxane to give **1** as white crystals; mp: 220-222^{o}C, yield: 51%. Anal. Calc. for $C_{15}H_{13}N_3O$ (251.28): C, 71.70; H, 5.21; N, 16.72. Found: C, 71.59; H, 5.11; N, 16.58. IR (υ/cm^{-1}): 3256 (NH), 2266 (C≡N), 1710 (C=O), 1685 (C=N). MS m/z (%): 251 ($M^{+\cdot}$; 65.2), 250 (100), 211 (14.6), 183 (40.8), 153 (41.7), 127 (46.7). ^{1}H-NMR (DMSO-d_6) δ (ppm): 11.09 (s, 1H, NH, exchangeable with D_2O), 8.27-7.52 (m, $7H_{arom}$), 4.3 (s, 2H, CH_2), 2.38 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6) (ppm) δ: 13.63, 24.95, 123.50, 126.28, 126.42, 126.55, 126.82, 127.44, 127.68, 128.47, 132.68, 133.24, 133.33, 135.06, 148.91, 165.83.

SUPPORTING INFORMATION

Full experimental details and spectroscopic data (IR spectra, 1H-NMR and MS) for compounds **2, 4, 5, 7-11, 13** can be found via the Supplementary Content section of this article's Web page.

ANTIMICROBIAL EVALUATION

The disks of a Whatman filter paper were prepared with standard size (5.0-mm diameter) and kept into 1.0-oz screw-capped wide-mouthed containers for sterilization. These bottles are kept into a hot air oven at a temperature of 150°C. Then, the standard sterilized filter paper disks impregnated with a solution of the test compound in DMSO (1 mg/mL) were placed on nutrient agar plate seeded with appropriate test organism in

triplicates. Standard conditions of 106 colony forming U/mL (CFU/mL) and 104 CFU/mL were used for antibacterial and antifungal assay, respectively. Pyrex glass Petri dishes (9 cm in diameter) were used, and two disks of the filter paper were inoculated in each plate. The utilized test organisms were S. aureus as examples of Gram-positive bacteria and E. coli as examples of Gram-negative bacteria. They were also evaluated for their in vitro antifungal potential against C. albicans fungal strain. Ampicillin and amphotericin B were used as standard antibacterial and antifungal agents, respectively. DMSO alone was used as control at the same previously mentioned concentration, and because of this, there was no visible change in bacterial growth. The plates were incubated at 36°C for 24 h for bacteria and for 48 h for fungi. Compounds that showed significant growth inhibition zones (>10mm) using the twofold serial dilution technique were further evaluated for their MICs.

MIC measurement. The microdilution susceptibility test in Müller-Hinton Broth (Oxoid) and Sabouraud Liquid Medium (Oxoid) was used for the determination of antibacterial and antifungal activity, respectively. Stock solutions of the tested compounds, ampicillin and amphotericin B were prepared in DMSO at a concentration of 1000 μg/mL. Each stock solution was diluted with standard method broth (Difco) to prepare serial twofold dilution at concentrations of 500, 250 to 3.125 μg/mL); 10mL of the broth containing about 106 CFU/mL of test bacteria was added to each well of a 96-well microliter plate. The sealed microplates were incubated at 36°C for 24 h for antibacterial activity and at 36°C for 48 h for antifungal activity in a humid chamber. At the end of the incubation period, the MIC values were recorded as the lowest

concentrations of the substance that had no visible turbidity. Control experiments with DMSO and uninoculated media were run parallel to the test compounds under the same conditions.

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Table 1. Diameter of inhibition zone (mm) of the newly synthesized compounds

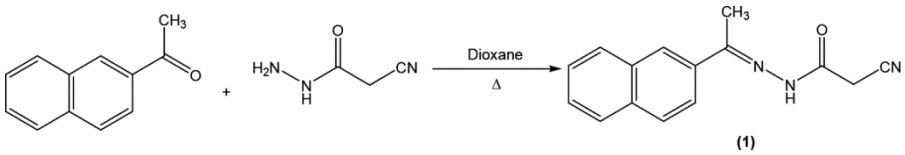
Compound no.	Diameter of inhibition zone (mm) of bacteria				Fungi	
	Gram negative bacteria		Gram positive bacteria			
	E. coli	% activity index	*S. aureus*	% activity index	*C. albicans*	% activity index
1	NA	_	NA	_	NA	_
2	NA	_	NA	_	13	68.4
8	10	83.3	16	88.8	NA	_
9	11	91.6	14	77.7	NA	_
10	NA	_	12	66.6	NA	_
11	12	100	15	83.3	11	57.8
13	12	100	13	72.2	17	89.4
Ampicillin	12	100	18	100	NA	_
Amphotericin B	NA	_	NA	_	19	100

NA, no activity.

Table 2. Minimal inhibitory concentration (MIC, μmol/ml) of the newly synthesized compounds

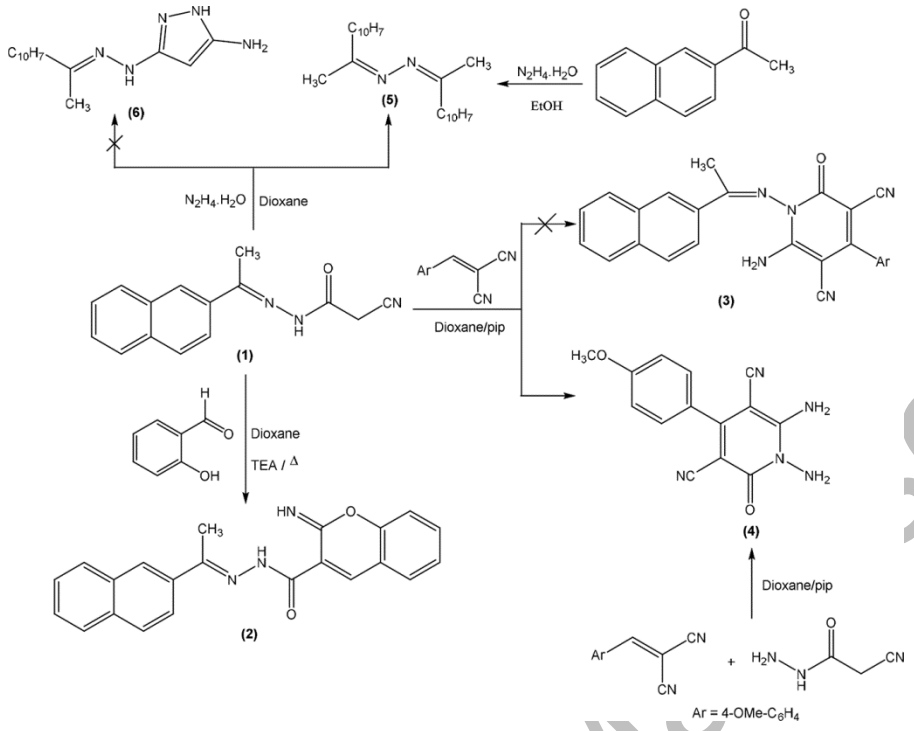
Compound no.	MIC, in μmol/ml		Fungi
	Gram negative bacteria	Gram positive bacteria	
	E. coli	*S. aureus*	*C. albicans*
2	–	–	92.5
8	204	192	–
9	175	198	–
10	–	225	–
11	125	193	165
13	125	205	50.4
Ampicillin	125	187.5	–
Amphotericin B	–	–	9.8

Scheme 1.

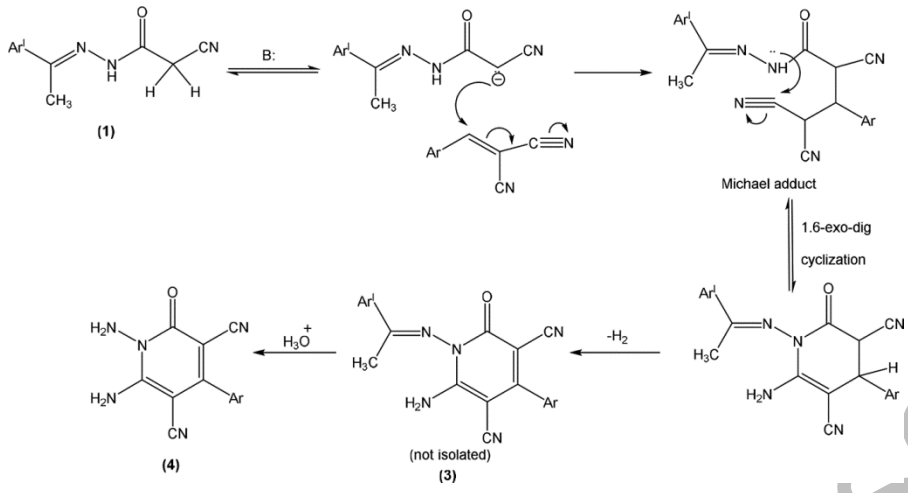


(1)

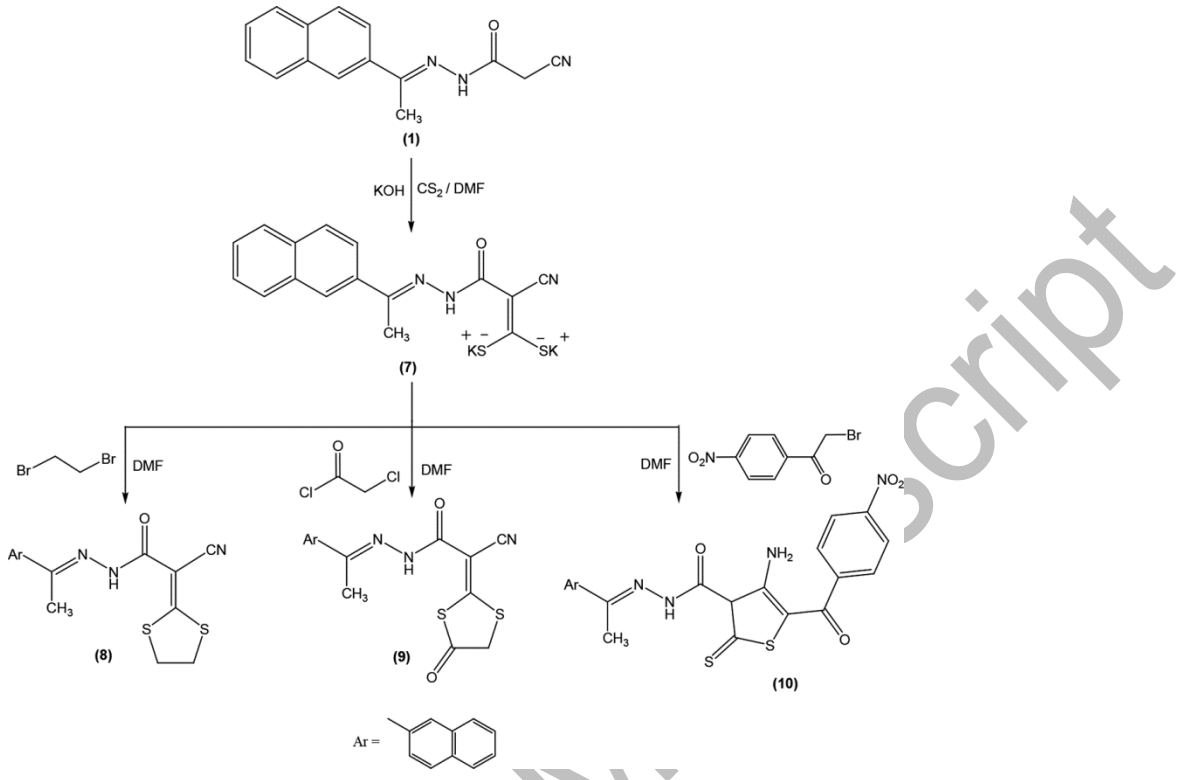
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.