2-Aminothiophenes by the Gewald Reaction

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The review presents the most elegant and promising set of synthetic routes for the synthesis of 2-aminothiophenes by the Gewald reaction. Applications of this facile methodology to pharmaceuticals and dyestuffs have been demonstrated.

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1. Introduction.

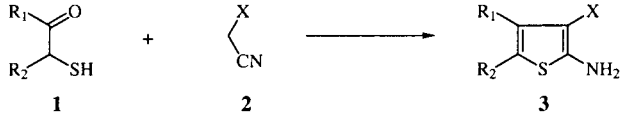
Many methods of synthesis of 2-aminothiophenes have been published in the last 30 years. 2-Aminothiophenes attract special attention because of their applications in pharmaceuticals, agriculture, pesticides and dyes. A series of reviews have been published dealing with the latest accomplishments of 2-aminothiophenes [1-8]. The chemistry of 2-aminothiophenes has received much attention because of the convenient availability through the most versatile, synthetic method developed by Gewald [9]. The various existing preparative methods can be summarized as follows, reduction of the nitro group [10], nucleophilic displacement of hydroxy [11], mercapto [12,13], halo [14-16], methoxy [17,18], *p*-nitrophenoxy [19,20], and benzenesulfonyl groups [21], the Beckmann rearrangement [22], the Hofmann reaction [23], the Schmidt reaction [24], the Curtius rearrangement [25,26], and the cyclization of thioamides and their *S*-alkylates [27-32]. Simultaneous passage of hydrogen sulfide and hydrogen chloride through a methanol solution of γ-ketonitrile yields 2-aminothiophenes [33]. Stacy and Eck [34,35] reported a multistep synthetic route for 2-aminothiophenes. Condensation of ethyl chloroacetoacetate with isothiocynates in the presence of sodium hydride gives 2-aminothiophenes [36,37]. All the above synthetic routes involve difficult preparation of the starting materials and multistep synthesis. These routes do not always produce good yields and high purity. The key intermediates for the synthesis of 2-aminothiophenes by the above routes are generally expensive. We have earlier described various synthetic approaches in the Gewald reaction [8]. However, tremendous work, particularly their applications to pharmaceuticals and dyestuffs have been reported in the last five years. This review provides useful and up-to-date data for medicinal and dye chemists.

2. Synthesis of 2-Aminothiophenes by the Gewald Reaction.

Gewald *et al.* devised the most facile and promising set of synthetic routes leading to 2-aminothiophenes with electron withdrawing substituents such as cyano, carbethoxy, and carboxamido *etc.* in the 3-positions and alkyl, aryl, cycloalkyl, and hetaryl groups in the 4- and 5-positions. This method offers considerable improvements over all the other existing synthetic methods for 2-aminothiophenes. The three major variations of this reaction are described in detail.

Version 1.

Scheme 1



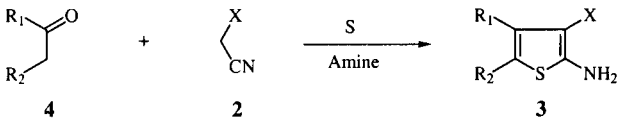
1 **2** **3**

R_1, R_2 = H, alkyl, aryl, cycloalkyl, hetaryl
X = CN, COOMe, COOEt, COPh, CO-hetaryl

In one of the versions of the Gewald reaction [38-52], α-mercaptoaldehyde or α-mercaptoketone **1** is treated with an activated nitrile **2** bearing an electron withdrawing groups such as methyl cyanoacetate, malononitrile, benzoylacetonitrile or *p*-nitrobenzyl cyanide in solvents such as ethanol, dimethylformamide, dioxane, or water in the presence of a basic catalyst such as triethylamine or piperidine at 50° (Scheme 1). An α-mercaptoaldehyde or an α-mercaptoketone is often generated *in situ* by reaction of alkali sulfides with the corresponding α-halocarbonyl compounds. This particular version of the Gewald reaction has few drawbacks such as it utilizes starting compounds which are unstable and difficult to prepare. This methodology appears to be limited to aliphatic α-mercapto derivatives. Non-activated nitriles such as cyanoacetic acid and benzyl cyanide do not undergo the Gewald reaction.

Version 2.

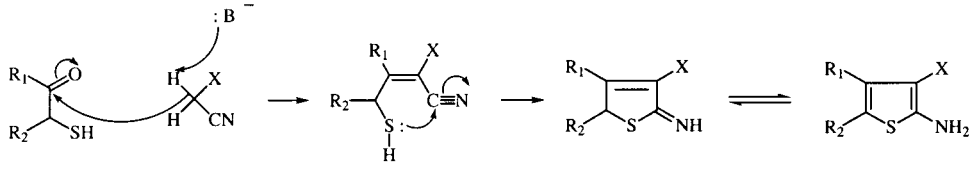
Scheme 2



4 **2** **3**

R_1, R_2 = H, alkyl, aryl, cycloalkyl, hetaryl
X = CN, COOMe, COOEt, COPh, CO-hetaryl, $CONH_2$

The most elegant and simpler version of the Gewald reaction has been introduced. The second version of the Gewald reaction [9,42,46,53-73,116-118,121,123,124, 135,161] consists of a one-pot procedure which can be very extensively used for the synthesis of numerous 2-aminothiophenes. This convenient technic includes the

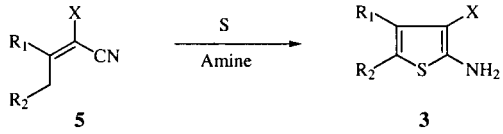


R_1, R_2 = H, alkyl, aryl, cycloalkyl, hetaryl
X = CN, COOMe, COOEt, COPh, CO-hetaryl

condensation of aldehydes, ketones or 1,3-dicarbonyl compounds **4** with activated nitriles **2** such as malononitrile, cyanoacetic esters, cyanoacetamide and its *N*-substituted derivatives, heteroarylacetonitriles, α-cyanoketones and sulfur in the presence of amine at room temperature. Ethanol, dimethylformamide, dioxane, excess ketone such as methyl ethyl ketone, or cyclohexanone are preferred solvents and amines like diethylamine, morpholine, or triethylamine have been employed. This method offers considerable improvements by replacing an α-mercaptoaldehyde or an α-mercaptoketone by simpler staring materials. It is necessary to use 0.5-1.0 molar equivalents of amine, based on the amount of nitrile, whereas a catalytic amount of base was used in the first version. The yields are much higher in the second version (Scheme 2).

Version 3.

Scheme 3



R_1, R_2 = H, alkyl, aryl, cycloalkyl, hetaryl
X = CN, COOMe, COOEt, COPh, CO-hetaryl, $CONH_2$

In the third version of the Gewald reaction [9,42,46,56, 63,64,72-85,116,117,119,120,156] a two-step procedure is preferred. An α,β-unsaturated nitrile **5** is first prepared by a Knoevenagel-Cope condensation and then treated with sulfur and amine. The third two-step version of the Gewald reaction gives higher yields. Alkyl aryl ketones do not give thiophenes in the one-pot modification, but gives acceptable yields in the two-step technique (Scheme 3).

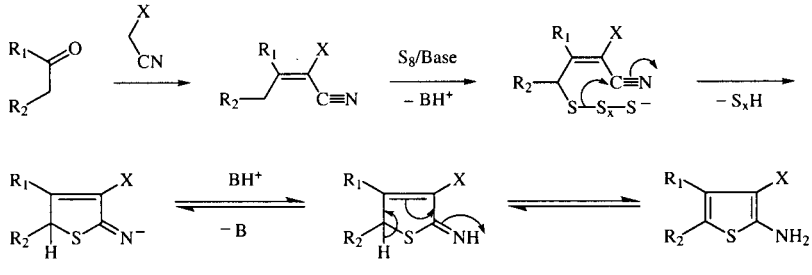
3. Mechanism.

Version 1.

R_1, R_2 = H, alkyl, aryl, cycloalkyl, hetaryl
X = CN, COOMe, COOEt, COPh, CO-hetaryl

It is likely that the first step of the reaction is the condensation of an activated nitrile with an α-mercaptocarbonyl function with the formation of a γ-mercaptonitrile which then cyclizes to a 2-aminothiophene [8,9,130].

Versions 2 and 3.



R_1, R_2 = H, alkyl, aryl, cycloalkyl, hetaryl
X = CN, COOMe, COOEt, COPh, CO-hetaryl, $CONH_2$

Gewald favors that an activated nitrile first condenses with a ketone yielding a Knoevenagel-Cope condensation product (styryl) which is then thiolated at the methylene group with elemental sulfur, followed by ring closure [8,9,130].

4. Scope and Limitations.

Scope.

The scope and synthetic utility of the Gewald reaction has been demonstrated by various examples listed in Table 1-Table 3. The Gewald reaction goes more readily with cyclic ketones, *e. g.* cyclohexanones and cycloalkylidene derivatives of methylene active nitriles and with cyclopentanones. More complex cyclic ketones and steroids such as androstane-3,17-dione [86], azepinones [87], 3-cholestanone [42,88], indanones [54], tropinones [53], quinuclidinones [89], pyranones [68,84], piperidones [42,59,63,64,66,69], α- and β-tetralones [64], thiacyclopentanones [78], dithiacycloalkanones [79,82], bicyclo-[2.1.1]heptanone [90], benz[*f*]isoindolone [91] undergo the Gewald reaction. The yields are high. The reaction time is short. The procedure involves only one step. The method generates very active species such as 2-amino-3-substitued-thiophenes. The method not only has enormous

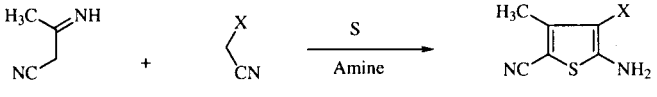
applications in organic reactions but also in several applied fields. It produces 2-aminothiophenes which opens a new door in another very important branch of organic chemistry such as dyes. The method produces electron withdrawing groups such as -COOEt, -CN, -$CONH_2$, -COPh which are key intermediates for the synthesis of fused heterocycles. The data demonstrates that the Gewald reaction is the most convenient and promising route for the synthesis of 2-aminothiophenes. All these facts give every reason to consider the Gewald reaction as a very useful and elegant method in organic synthesis. This method will undoubtedly remain a very stimulating field of research for the organic chemist in the years to come.

Limitations.

The only limitation is for version 1 which uses starting material such as an α-mercaptoaldehyde or an α-mercaptoketone which are difficult to prepare and are unstable. This version appears to be limited to aliphatic α-mercapto derivatives. Non-activated nitriles such as cyanoacetic acid and benzyl cyanide do not undergo the Gewald reaction. Version 2 overcomes these drawbacks which is a one-pot method and uses easily available commercial starting materials.

5. Variations.

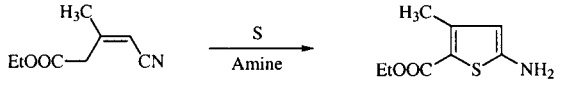
Scheme 4



6 **7** **8**

The acetonitrile dimer (imine) **6** condenses with an activated nitrile **7** producing 2-aminothiophene **8** in 80% yield [92] (Scheme 4).

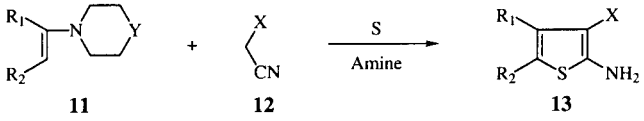
Scheme 5



9 **10**

Ethyl cyanoacetate reacts with cyanoacetic acid to yield α,β-unsaturated nitrile **9**, which undergoes the Gewald reaction generating 2-aminothiophene **10** [93]. These results indicate that 2-aminothiophenes without electron-withdrawing groups in the 3-position can also be synthesized. However, the ethoxycarbonyl group is necessary to activate the methylene group for the thiation (Scheme 5).

Scheme 6



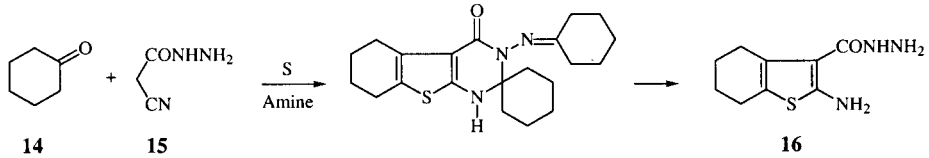
11 **12** **13**

R_1, R_2 = H, CH_3, C_2H_5, C_6H_5, -$(CH_2)_4$-; Y = O, CH_2; X = CN, COOEt

Enamines **11** undergo the Gewald reaction with activated nitriles **12** to give 2-aminothiophenes **13** [94,95] (Scheme 6).

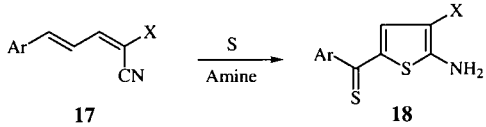
When cyclohexanone **14** is condensed with cyanoacetic acid hydrazide (**15**) and sulfur in the presence of morpholine, thienopyrimidine is formed which undergoes acid hydrolysis yielding the corresponding hydrazide in 75% yield [96]. Cyclopentanone undergoes an analogous Gewald reaction [96] (Scheme 7). 3-Thiacyclopentanone reacts differently yielding two products depending on the temperature. 3-Thiacyclopentanone reacts with methyl cyanoactate and sulfur at 40° yielding corresponding thiophene in 30% yield whereas the sulfide is generated in 36% yield when reaction is carried out at room temperature or at 60° [78].

Scheme 7



14 **15** **16**

Scheme 8



17 **18**

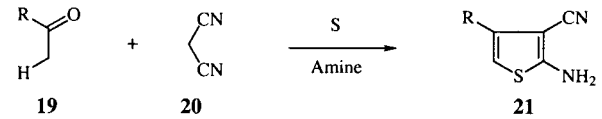
Ar = C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4; X = COPh, COOEt, COC_6H_4-4-Me, COC_6H_4-4-MeO

Cinnamaldehyde undergoes the Gewald reaction with ethyl cyanoacetate and sulfur producing a thioketone. The Knoevenagel condensation **17** product undergoes a two-step mechanism yielding thioketone alternatively [97] (Scheme 8).

Ethyl cyanoactate reacts with sulfur in the presence of triethylamine giving diethyl 2,5-diamino-3,4-thiophenedicarboxylate [98], whereas malononitrile undergoes a similar reaction giving a mixture of two products [99]. The Gewald method has been used to introduce radioactive sulfur into the thiophene nucleus [67]. The Gewald reaction is widely used in synthesizing 4,5-hetero-substituted 2-aminothiophenes which have tremendous applications in the applied fields. The numerous heterocyclic ketomethylene derivatives used are 2-pyridinecarbonyl [45,89,100], 2-furancarbonyl [42,43,85], 2-thiophenecarbonyl [42,43] and 2-thiazolecarbonyl [101]. There can be many more biologically active 2-aminothiophenes synthe-

sized using heterocyclic ketomethylene compounds [63,66,68,69,78,82,84,102-108].

Scheme 9



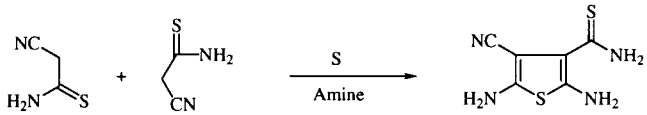
19 **20** **21**

R = Me, Ph

2-Aminothiophene-3-carbonitrile **21** with an open position 5 can be synthesized [109] (Scheme 9).

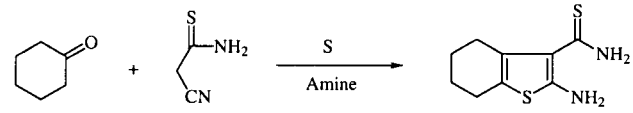
Cyanothioacetamide **22** acts as both, ketomethylene and activated nitrile and condense with sulfur to give 2,5-diaminothiophene derivative **24** [110] (Scheme 10). Cyanothioacetamide **26** reacts with ketomethylene compound **25** to yield the corresponding 2-aminothiophene derivatives **27** [110] (Scheme 11).

Scheme 10



22 **23** **24**

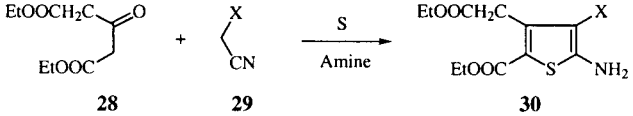
Scheme 11



25 **26** **27**

6. Recent Developments.

Scheme 12

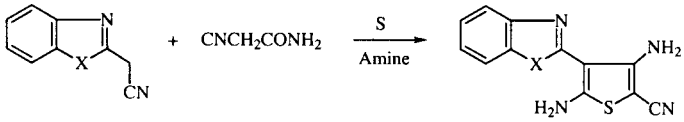


28 **29** **30**

X = CN, COOEt

Sabnis and Rangnekar [116,117] developed the most versatile key compounds in more than 90% yields by condensing diethyl acetonedicarboxylate **28** with sulfur and an activated nitrile **29** (Scheme 12). These compounds have demonstrated tremedous applications in synthesizing novel dyes and biologically active compounds.

Scheme 13

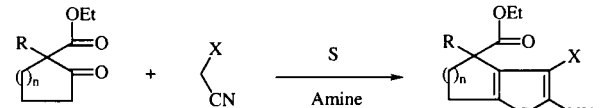


31 **32** **33**

X = S, NH

The scope of the Gewald reaction can further be broadened by introducing heterocyclic moieties into the thiophene nucleus. It has been found that heating of equimolar amounts of 2-cyanomethylbenzothiazole or 2-cyanomethyl-1*H*-benzimidazole **31** with sulfur and cyanoacetamide **32** gives 3,5-diamino-4-substituted-thiophene-2-carbonitrile **33** in excellent yield [118] (Scheme 13).

Scheme 14

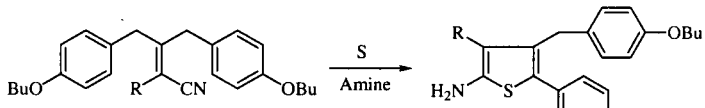


34 **35** **36**

n = 1, 2, 3; X = CN, COOEt

Alicyclic β-ketoesters **34** as keto compounds react with sulfur and activated nitrile **35** to yield new trifunctional thiophene derivatives **36** [119] (Scheme 14). The alicyclic β-ketoesters used contained 5- to 7-membered rings with or without an alkyl substituents at position 1.

Scheme 15

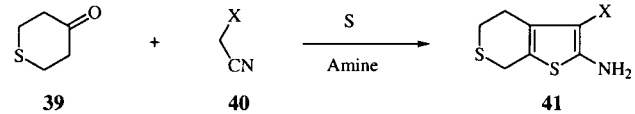


37 **38**

R = CN, COOMe

The versatility of the Gewald reaction can not only be strengthened by different substituents in the 4- and 5-positions of the thiophene ring, but also by using different electrophilic substituents in the 3-position. This approach helps in the design of new drugs [120] (Scheme 15).

Scheme 16



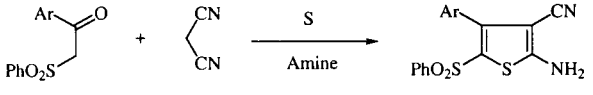
39 **40** **41**

X = CN, COOEt

Tetrahydrothiopyran-4-one **39** reacts with activated nitrile **40** and sulfur giving the corresponding 2-aminothiophene derivatives **41** (Scheme 16). These compounds are vital intermediates for synthesizing pharmacologically active moieties such as thiazolo-, thiazino-, pyrido-, azepino-fused thiopyrano[4'3':4,5]thieno[2,3-*d*]pyrimidines in a one-pot reaction [121]. A modification of the Gewald reaction [122] which renders 4-*n*-alkyl substituted-2-aminothiophene derivatives which bear no substituent at position 5. The three-step procedure involves monotosylation of diols, oxidation of a secondary hydroxy group and a one-pot reaction yielding the title compounds. The Gewald reaction of 4-methyl-2-pentanone with alkyl cyanoacetate was investigated [123]. Alkyl-2-amino-4-isobutylthiophene-3-carboxylate was formed as the main product along with two by-products. The absence of any 4-methyl substituted aminothiophenes in the product mixtures was unexpected.

2-Aminothiophenes with a 5-sulfonyl group can also be synthesized by the Gewald reaction. Phenylsulfonylacetophenones **42** react with elemental sulfur and activated nitrile **43** giving 2-amino-5-phenylsulfonylthiophene **44** (Scheme 17). These compounds are important intermediates for synthesizing thieno[2',3':3,4]pyrazolo-[1,5-*a*]pyrimidines [124].

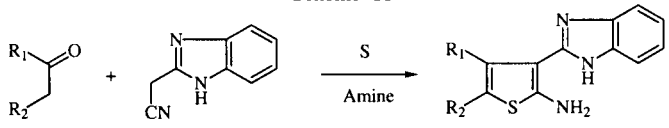
Scheme 17



42 **43** **44**

Ar = C_6H_5, 4-Br-C_6H_4

Scheme 18

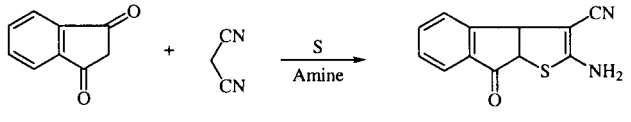


45 **46** **47**

R_1, R_2 = H, CH_3, -$(CH_2)_4$-

3-(Benzimidazol-2-yl)-2-aminothiophenes **47** can be directly synthesized from ketomethylene **45**, 2-cyanomethylbenzimidazole **46** and sulfur using the Gewald reaction [161] (Scheme 18).

Scheme 19



48 **49** **50**

1,3-Indanedione **48** is condensed with malononitrile **49** to yield the key precursor **50** for dyes [156] (Scheme 19).

7. Experimental Conditions

Solvents.

Preferred solvents in the Gewald reaction are ethanol, methanol, cyclohexanone, methyl ethyl ketone, *N,N*-dimethylformamide, excess of ketone and water.

Bases.

The most often employed organic bases include diethylamine, morpholine, piperidine and triethylamine.

Temperature.

The most preferred temperature is 40-50°. The temperature should not generally exceed 60°, however, some reactions are carried out at the ethanol reflux temperature (78°).

Reaction Time.

The ideal time for reaction completion is 3 hours, in some cases, it may also exceed 5-7 hours.

8. Typical Experimental Procedure.

A mixture of ketomethylene (0.1 *M*), activated nitrile (0.1 *M*), sulfur (0.11 *M*), ethanol (10-30 ml) and diethylamine or morpholine (10 ml) was stirred on a waterbath for 3 hours at 40-50°. The reaction temperature should not generally exceed 60°. The solid which seperated was filtered, washed with ethanol, dried and recrystallized from a suitable solvent (preferably ethanol).

9. Tabular Survey.

A systemic tabular survey of all versions of the Gewald reaction is presented.

Table 1: Version 1 of the Gewald reaction is listed which include substrates, yields and references.

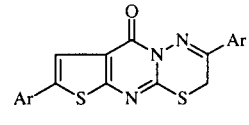
Table 2: Version 2 of the Gewald reaction is listed which include substrates, yields and references.

Table 3: Version 3 of the Gewald reaction is listed which include substrates, yields and references.

10. Applications in Pharmaceuticals.

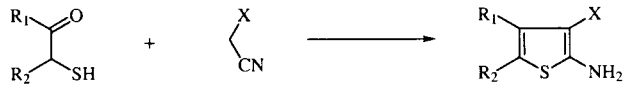
The Gewald method has an enormous scope as it produces 2-amino-3-cyano, 2-amino-3-carbethoxy and 2-amino-3-carbonyl substituted thiophenes which are of considerable importance for the generation of thienopyridines, thienopyrimidines and thienodiazepines. These molecules show great promise in biomedicine [129]. The versatility of a Gewald precursor as a synthetic entry to thieno[2,3-*d*]pyrimidines in a structure-based drug design program has been investigated [120]. Thieno[2,3-*d*]-pyrimidines were screened as antimalarial [103,128], antibacterial [103], antiinflammatory [126], anticonvulsant properties [63], central nervous system (CNS) depressant activity [125,163], hypnotic agents [158], and antiaggregating agents [136]. Thieno[2,3-*d*]pyrimidines show the most promising pharmacological evolution. These compounds exhibit significant antimalarial activity in *Plasmodium berghei, Plasmodium gallinaceum* and *Plasmodium falciparum in vitro*. These molecules were also tested for prominent antibacterial activity *in vitro* against *Streptococcus faecalis, Staphylococcus aureus, Pseudonomas aeruginosa, Escherichia coli* and *Shigella sonnei*. Antimetabolite effects were observed in *Streptococcus faecium* and *Lactobacillus casei* by incorporating thieno[2,3-*d*]pyrimidines [64]. Several new thieno[2,3-*d*]pyrimidines with alkyl, aryl, carbocyclic, heterocyclic, solfoxide or sulfone at the substituted 5,6 positions were screened as effective antimalarial agents [66,74,134]. A series of thieno[2,3-*d*]pyrimidine analogs of the potent dihydrofolate reductase (DHFR) inhibitors trimetrexate (TMQ) and piritrexim (PTX) were synthesized as potential drugs against *Pneumocystis carinii* and *Toxoplasma gondii*, which are major causes of severe opportunistic infections in AIDS patients [157].

Pharmacological evaluation of pyrimido[2,1-*b*]-thieno[2',3':4,5][1,3,4]thiadiazin-9-ones **51** suggests excellent analgesic and antiinflammatory activities [160]. Pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidines presents a novel class of potent, orally active antiallergy agents [71]. Triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidines show promising antiinflammatory activites [132,133].

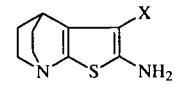


51

Table 1



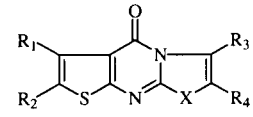
R_1	R_2	X	Yield (%)	Reference
CH_3	CH_3	CN	70	39
CH_3	H	CN	73	39
C_2H_5	CH_3	CN	51	39
H	H	CN	55	39
	$-(CH_2)_4-$	CN	70	39
CH_3	H	$CONH_2$	53	39
H	H	$CONH_2$	60	43
CH_3	H	COOEt	88	44
C_6H_5	CH_3	COOEt	97	44
C_6H_5	H	COOEt	75	44
	$-(CH_2)_4-$	COOEt	80	39
CH_3	CH_3	COOMe	45	39
CH_3	H	COOMe	75	39
H	H	COOMe	46,58	39,40
CH_2COOEt	H	COOMe	----	49
CH_3	H	COC_6H_5	40	39
H	H	COC_6H_5	70	43
CH_3	H	4-NO_2-C_6H_4	34	39
H	H	2-$CH_3OC_6H_4CO$	42	50
H	H	COC_6H_4-2-CH_3	60	43
H	H	2-$CH_3C_6H_4CO$	73	50
H	H	2-F-C_6H_4CO	58	50
H	H	2-$CH_3SO_2C_6H_4CO$	79	50
H	H	2-$NO_2C_6H_4CO$	48	51
H	H	3-$NO_2C_6H_4CO$	---	47
H	H	2-$CF_3C_6H_4CO$	78	50
H	H	2,6-F_2-C_6H_3CO	56	50
H	H	3,5-Cl_2-C_6H_3CO	74	50
H	H	2,6-Cl_2-C_6H_4	82	48
H	H	$NCCH_2NHCO$	44	46
H	H	$CSNH_2$	88	41
CH_3	H	2-Th-CO	48	42
H	H	2-Th-CO	70	43
H	H	2-Furyl-CO	60	43
H	H	2-Pyridyl-CO	---	45
H	H	3-CH_3-2-pyridyl-CO	---	45



52

X = CN, COOEt, $CONH_2$, $CSNH_2$

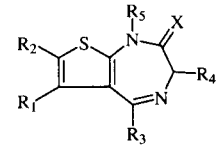
Thieno[2,3-*b*]pyridines **52** were evaluated as antiviral agents [107]. Pyrrolidinonaphtho[2,3-*b*]thiophenes were synthesized by the Gewald reaction as active analgesic and antiviral agents [91].



53

R_1, R_2, R_3, R_4 = H, alkyl, aryl, $-(CH_2)_4$, COOEt; X = S, O

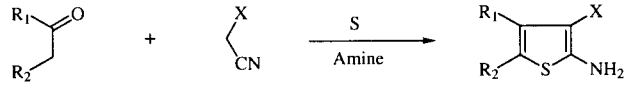
2-Amino-3-carbethoxythiophenes, generated by the Gewald procedure were reacted with 2-chlorobenzothiazole or 2-chlorobenzoxazole yielding thieno[2',3':4,5]-pyrimido[2,1-*b*]benzothiazoles or thieno[2',3':4,5]pyrimido[2,1-*b*]benzoxazoles **53**. These compounds were tested in a variety of pharmacological assays for their putative analgesic/antiinflammatory activities, ulcerogenicity and potential action on the central nervous system (CNS). The compounds showed the best pharmacological profile with considerable analgesic, antiinflammatory activities and high gastric tolerance. They do not show any effect on the CNS at therapeutic doses [159]. Synthetic application of thiophenes as precursors for potential enzyme inhibitors has been investigated [123].



54

R_1, R_2, R_3, R_4, R_5 = H, alkyl, cycloalkyl, aryl; X = O, S

Table 2



R_1	R_2	X	Yield (%)	Reference
CH_3	CH_3	CN	42	9,59
CH_3	$C_6H_5CH_2$	CN	17	74
CH_3	$C_6H_5CH_2CH_2$	CN	29	74
CH_3	$CONHC_6H_5$	CN	70	115
CH_3	$CONHC_6H_4$-4Cl	CN	60	115
CH_3	$CONHC_6H_4$-4Me	CN	63	115
CH_3	$CONHC_6H_3$-2,5Cl_2	CN	68	115
CH_3	3,4-$Cl_2C_6H_3$-CH_2	CN	18	74
CH_3	3,4-$Cl_2C_6H_3CH_2CH_2$	CN	24	74
CH_3	5-Thienyl	CN	40	135
C_6H_5	SO_2Ph	CN	68	124
4-Br-C_6H_4	SO_2Ph	CN	62	124
CH_2COOEt	COOEt	CN	84	116
	$-(CH_2)_4-$	CN	86	9,55,59

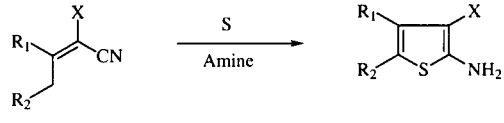
Table 2 (continued)

R_1	R_2	X	Yield (%)	Reference
				61,64
-$(CH_2)_5$-		CN	44	55,61
-$(CH_2)_6$-		CN	64	61
-$(CH_2)_{10}$-		CN	42	61
2-Tetralone		CN	40	64
2-Indanone		CN	41	64
Tropinone		CN	50	63
Cholestan-3-one		CN	30	55
-[$(CH_2)_2SCH_2$]-		CN	61	64,121
-[$CH_2CHC_6H_5SCHC_6H_5$]-		CN	83	66
-[$CH_2CH(3,4\text{-}ClC_6H_3)SCH(3,4\text{-}Cl_2C_6H_4)$]-		CN	85	66
-[$CH_2CH(4\text{-}CF_3C_6H_4)SCH(4\text{-}CF_3C_6H_4)$]-		CN	98	66
-[$CH(CH_3)(CH_2)_3$]-		CN	45	63
-[$(CH_2)_2CH(CH_3)CH_2$]-		CN	86	61
-[$CH_2CH(CH_3)(CH_2)_2$]-		CN	90	61
-[$CH_2CH(CH_3)CH(CH_3)CH_2$]-		CN	80	61
-[$(CH_2)_2CH(C(CH_3)_3)CH_2$]-		CN	79	61
-[$(CH_2)_2CH(C_6H_5)CH_2$]-		CN	63	64
-[$(CH_2)_2N(CH_3)CH_2$]-		CN	62	61
-[$(CH_2)_2NCH(CH_3)_2CH_2$]-		CN	74	69
-[$(CH_2)_2N(C_4H_9)CH_2$]-		CN	43	61
-[$(CH_2)_2N(CH_2C_6H_5)CH_2$]-		CN	71	61
-[$CH_2CH(C_6H_5)N(CH_3)CHC_6H_5$]-		CN	51	66
-[$CH_2CH(3,4\text{-}Cl_2\text{-}C_6H_3)NCH_3CH$-(3,4-$Cl_2C_6H_4$)]-		CN	58	66
-[$HO(CH_2CH_2)_2CH_2CH(CH_2)_3$]-		CN	50	63
H	C_6H_5	$CONH_2$	45	9
-$(CH_2)_4$-		CONH2	61,25	9,56,60
-[$(CH_2)_2CH(OCOC_6H_5)CH_2$]-		$CONH_2$	42	60
-$(CH_2)_4$-		$CONHCH_3$	29	60
-$(CH_2)_4$-		$CONHC_2H_5$	35	63
-$(CH_2)_4$-		$CONHC_6H_5$	41	63
-$(CH_2)_4$-		$CONHC_6H_4$-4-Me	62	57
CH_3	CH_3	COOEt	39	9
CH_3	CH_2COOH	COOEt	30	63
CH_3	COOEt	COOEt	32	9
CH_3	$CONHC_6H_5$	COOEt	30	63
H	CH_3	COOEt	42,47	9
H	C_2H_5	COOEt	75,65	9
H	$CH(CH_3)_2$	COOEt	40	62
Isobutyl	H	COOEt	27	123
CH_2COOEt	COOEt	COOEt	87	117
-$(CH_2)_3$-		COOEt	45	9
-$(CH_2)_4$-		COOEt	82	9,59,70
-$(CH_2)_5$-		COOEt	59	70
-[$(CH_2)_2SCH_2$]-		COOEt	---	121
-[$CH_2CH(CH_3)(CH_2)_2$]-		COOEt	34	70
-[$(CH_2)_2CH(CH_3)CH_2$]-		COOEt	70	70
-[$CH(C_6H_5)(CH_2)_3$]-		COOEt	50	63
-[$CH_2N(CH(CH_3)_2)CH_2$]-		COOEt	61	69
-[$CH_2CH(C_6H_5)NHCH(C_6H_5)$]-		COOEt	35	63
-[$CH_2CH(C_6H_5)NCH_3CH(C_6H_5)$]-		COOEt	40	63
-[$CH(CH_3)CH(C_6H_5)NCH_3CH(C_6H_5)$]-		COOEt	53	63
-[$H_8C_4ONCH_2CH(CH_2)_3$]-		COOEt	50	63
CH_3	$COCH_3$	COOMe	31	9
Isobutyl	H	COOMe	23	123
C_2H_5	CH_3	COOMe	40	9
CH_3	CH_3	COC_6H_5	72	65
CH_3	H	COC6H5	---	58
CH_3	$n\text{-}C_3H_7$	COC_6H_5	---	65
H	CH_3	COC_6H_5	---	42,58
H	C_2H_5	COC_6H_5	70	65
H	$n\text{-}C_4H_9$	COC_6H_5	---	65
$i\text{-}C_3H_7$	H	COC_6H_5	---	65

Table 2 (continued)

R_1		R_2	X	Yield (%)	Reference
	$-(CH_2)_3-$		COC_6H_5	51	65
	$-(CH_2)_4-$		COC_6H_5	40	9
	$-[(CH_2)C(CH_3)_2OCH_2]-$		COC_6H_5	41	68
H		C_6H_5	COC_6H_5	86	42
CH_3		CH_3	2-Cl-C_6H_4CO	59	65
CH_3		CH_3	4-Cl-C_6H_4CO	52	65
CH_3		CH_3	3-CF_3-C_6H_4CO	---	65
H		CH_3	2-Cl-C_6H_4CO	75	65
H		C_2H_5	2-Cl-C_6H_4CO	61	65
H		i-C_3H_7	2-Cl-C_6H_4CO	---	65
H		C_2H_5	2-Br-C_6H_4CO	60	65
H		C_2H_5	2-F-C_6H_4CO	68	65
H		C_2H_5	2-MeO-C_6H_4CO	73	65
H		C_2H_5	2-Me-C_6H_4CO	58	65
	$-(CH_2)_4-$		2-MeO-C_6H_4CO	71	65
	$-(CH_2)_4-$		3-CF_3-C_6H_4CO	60	65
	$-(CH_2)_4-$		4-Cl-C_6H_4CO	68	65
	$-[CH_2C(CH_3)_2OCH_2]-$		2-Cl-C_6H_4CO	66	68
	$-[CH_2C(CH_3)_2OCH_2]-$		2-Br-C_6H_4CO	50	68
	$-[CH_2C(CH_3)_2OCH_2]-$		3-NO_2-C_6H_4CO	46	68
	$-[CH_2C(CH_3)_2OCH_2]-$		4-Br-C_6H_4CO	51	68
	$-[CH_2C(CH_3)_2SCH_2]-$		2-Cl-C_6H_4CO	46	68
	$-(CH_2)_5-$		C_6H_5CO	58	65
	$-[(CH_2)_2CH(CH_3)CH_2]-$		C_6H_5CO	67	65
CH_3		H	benzimidazol-2-yl	63	161
	$-(CH_2)_4-$		benzimidazol-2-yl	75	161
NH_2		CN	$NCCH_2$benzimidazole	61	118
NH_2		CN	$NCCH_2$benzothiazole	64	118
H		H	COO-t-Bu	58	164
i-Pr		H	COO-t-Bu	53	164
Me		Me	COO-t-Bu	35	164
	$-(CH_2)_4-$		COO-t-Bu	89	164

Table 3



R_1		R_2	X	Yield (%)	Reference
CH_3		CH_3	CN	41	9
C_6H_5		C_6H_5	CN	95	74
$C_6H_5CH_2$		C_6H_5	CN	98	74
$C_6H_5CH_2$		CH_3	CN	34	74
4-Cl-C_6H_4		CH_3	CN	95	74
4-Cl-C_6H_4		C_2H_5	CN	86	74
$(CH_3)_2CH$		H	CN	----	77
$(CH_3)_3C$		H	CN	48	77
	$-(CH_2)_4-$		CN	90	9
	$-(CH_2)_5-$		CN	65	56
	$-(CH_2)_6-$		CN	65	56
	$-(CH_2)_{10}-$		CN	60	56
	$-(CH_2)_{13}-$		CN	50	56
	$-[CH(CH_3)(CH_2)_3]-$		CN	45	63
	$-[CH_2C(CH_3)_2OCH_2]-$		CN	83	84
	$-[CH_2SCH_2CH_2S]-$		CN	68	82
	$-[CH_2C(CH_3)_2SCH_2]$		CN	92	84
	$-[CH(C_6H_5)(CH_2)_3]-$		CN	30	64
	$-[CH(C_6H_5)(CH_2)_4]-$		CN	4	56
	1-Tetralone		CN	48	64
	1-Indanone		CN	25	64

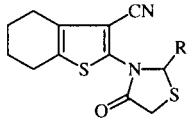
Table 3 (continued)

R_1	R_2	X	Yield (%)	Reference
Ethyl 2-oxo-1-cyclopentanecarboxylate		CN	76	119
Et 2-oxo-1-methyl-1-cyclopentanecarboxylate		CN	46	119
Ethyl 2-oxo-1-ethyl-1-cyclopentanecarboxylate		CN	47	119
Ethyl 2-oxo-1-cyclohexanecarboxylate		CN	---	119
Et 2-oxo-1-methyl-1-cyclopentanecarboxylate		CN	50	119
Ethyl 2-oxo-1-ethyl-1-cyclopentanecarboxylate		CN	48	119
Ethyl 2-oxo-1-cycloheptanecarboxylate		CN	19	119
4-BuO-Ph-methylene	4-BuO-Phenyl	CN	---	120
1,3-Indanedione		CN	60	156
CH_3	C_6H_5	$CONH_2$	58	9
-$(CH_2)_4$-		$CONH_2$	71,75	9,56
-$(CH_2)_5$-		$CONH_2$	66	56
-$(CH_2)_6$-		$CONH_2$	80	56
-$(CH_2)_{10}$-		$CONH_2$	48	56
-[$CH(C_6H_5)(CH_2)_4$]-		$CONH_2$	11	56
-[$CH_2SCH_2CH_2S$]-		$CONH_2$	96	82
-[$CH_2S(CH_2)_3S$]-		$CONH_2$	----	79
CH_3	CH_3	COOEt	49	9,81,83
CH_3	H	COOEt	---	77
CH_3	$(CH_2)_2OCOMe$	COOEt	77	80
CH_3	C_6H_5	COOEt	38	49
C_6H_5	CH_3	COOEt	50	9,75,83
C_6H_5	H	COOEt	62	9,81,83
4-F-C_6H_4	H	COOEt	68	75
4-NO_2-C_6H_4	H	COOEt	60	83
4-Me-C_6H_4	H	COOEt	78	80
4-MeO-C_6H_4	H	COOEt	69	80
2,4-$(Me)_2C_6H_3$	H	COOEt	72	80
2,5-$(Me)_2C_6H_3$	H	COOEt	22	80
2,4-$(MeO)_2C_6H_3$	H	COOEt	60	80
3,4-$(MeO)_2C_6H_3$	H	COOEt	93	80
3,4,5-$(MeO)_3C_6H_2$	H	COOEt	60	75,83
-[$CH(C_6H_5)(CH_2)_3$]-		COOEt	50	63
2-Th	H	COOEt	33	81
-$(CH_2)_3$-		COOEt	52	9
-$(CH_2)_4$-		COOEt	91	9
-$(CH_2)_5$-		COOEt	85	56
-$(CH_2)_6$-		COOEt	96	56
Ethyl 2-oxo-1-cyclopentanecarboxylate		COOEt	13	119
Et 2-oxo-1-methyl-1-cyclopentanecarboxylate		COOEt	25	119
Ethyl 2-oxo-1-ethyl-1-cyclopentanecarboxylate		COOEt	25	119
Ethyl 2-oxo-1-cyclohexanecarboxylate		COOEt	59	119
Et 2-oxo-1-methyl-1-cyclopentanecarboxylate		COOEt	35	119
Ethyl 2-oxo-1-ethyl-1-cyclopentanecarboxylate		COOEt	25	119
Ethyl 2-oxo-1-cycloheptanecarboxylate		COOEt	31	119
C_2H_5	CH_3	COOMe	50	9
C_6H_{11}	H	COOMe	---	77
-[CH_2CH_2S]-		COOMe	41	78
4-BuO-Ph-methylene	4-BuO-Phenyl	COOMe	---	120
C_2H_5	CH_3	C_6H_5CO	65	46
C_2H_5	C_2H_5	C_6H_5CO	79	42
C_6H_5	H	C_6H_5CO	39	42,77
-$(CH_2)_4$-		C_6H_5CO	80	9
-$(CH_2)_6$-		C_6H_5CO	---	42
-[$(CH_2)_2SCH_2$]-		C_6H_5CO	56	42
-$(CH_2)_2N(COOEt)CH_2$]-		C_6H_5CO	53	42
-$(CH_2)_4$-		$C_6H_{11}CO$	95	42
-$(CH_2)_4$-		$CONHC_6H_5$	41	63
-$(CH_2)_4$-		2-F-C_6H_4CO	48	42
-$(CH_2)_4$-		2-Cl-C_6H_4CO	37	42
-$(CH_2)_4$-		2-Me-C_6H_4CO	81	42
-$(CH_2)_4$-		3-Cl-C_6H_4CO	46	42
-$(CH_2)_4$-		3-MeO-C_6H_4CO	64	42
-$(CH_2)_4$-		4-MeO-C_6H_4CO	91	42

Table 3 (continued)

R_1	R_2	X	Yield (%)	Reference
	$-(CH_2)_4-$	2-Naphthyl-CO	----	42
	$-(CH_2)_4-$	2-Th-CO	76	42
	$-(CH_2)_4-$	2-Furyl-CO	77	42,85

Thieno[2,3-*e*][1,4]diazepines **54** were evaluated as antianxiety [42,85], anticonvulsant drugs [42,85] or psychotropic drugs [65]. 2-Thiazolodinylthiophenes **55** were screened as potential antibacterial and antifungal agents [127]. Thiadiazasteroids of great pharmacological applications were synthesized from Gewald precursor [60,131].

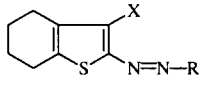


55

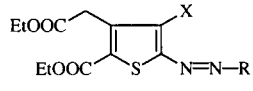
R = aryl, hetaryl

Antitumor activity for thieno[2,3-*b*]azepin-4-one in mice was described [83]. Human leukocyte elastase (HLE) is a serine protease contained in the azurophilic granules of human neutrophils. Thieno[2,3-*d*][1,3]oxazin-4-ones were tested *in vitro* for inhibitory activity toward HLE. The strategy to replace the benzene ring in benzoxazinones by thiophene is based on the consideration that the enhanced electron density at the thiophene carbon atoms might result in an improved intrinsic stability of the thieno[2,3-*d*][1,3]oxazin-4-one system [164].

11. Applications in Dyestuffs.



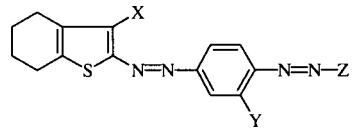
56



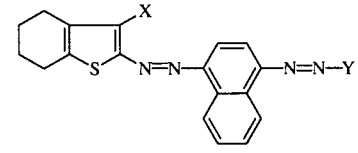
57

X = CN, COOEt, $CONH_2$; R = alkyl, aryl, hetaryl

Rangnekar *et al.* have accomplished pioneering research on new dyestuffs from 2-aminothiophenes using the Gewald reaction [116,117]. Azo dyes derived from the thiophene moiety have many advantages, such as a color deepening effect as an intrinsic property of the thiophene ring, small molecular structure leading to better dyeability and heterocyclic nature of the thiophene ring resulting in excellent sublimation fastness on the dyed fibers. Tetrahydrobenzo[*b*]thiophene dyes are much superior to the corresponding benzo[*b*]thiophene dyes. The hydrophobic nature of tetrahydrobenzo structure is useful for better dispersability and dyeability. 2-Azo-4,5,6,7-tetrahydrobenzo[*b*]thiophene dyes **56** were synthesized from the Gewald precursor. These dyes were brilliant yellow, red, pink and violet and showed good dyeing properties [137,138]. 2-Azothiophenes **57** are highly colored dyes with brilliant orange, brilliant red, pink, magenta, violet and blue shades. These dyes show excellent dyeing properties on synthetic fibers [116,117]. In order to increase the shade range from violet to blue and green, bis-azo dyes **58-59** were synthesized [139,140]. These bis-azo dyes were applied on polyester fibers as disperse dyes and gave red and blue shades.

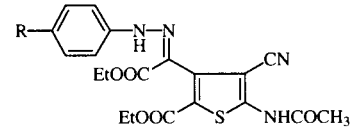


58



59

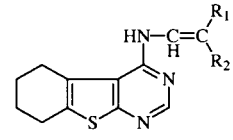
X = CN, COOEt; Y, Z = alkyl, aryl, hetaryl



60

R = H, alkyl, NO_2, Cl

Arylamines were diazotized and coupled with 2-acetamidothiophene-4-acetic acid. The coupling occurs at the active methylene group resulting in brilliant red dyes **60** having good dyeing properties [141].

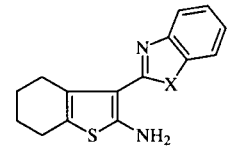


61

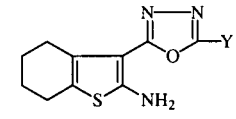
R_1 = CN, COOEt; R_2 = CN, COOEt, $CONH_2$, hetaryl

4-Amino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]-pyrimidine, a versatile key intermediate for dye synthesis was prepared from the Gewald precursor and formamide. The amino compound was condensed with conjugated enol ethers or with triethyl orthoformate and active cyanomethylene compounds giving lemon yellow and brilliant yellow fluorescent dyes **61** [142].

2-Amino-3-hetarylthiophenes can be synthesized in one-pot by condensing 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thio-



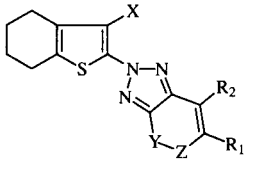
62



63

X = S, O, NH; Y = alkyl, aryl, hetaryl

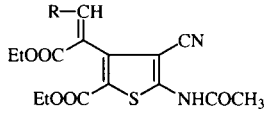
phene with selected *o*-substituted aromatic amines or with aliphatic, aryl or hetaryl acid hydrazide in the presence of polyphosphotic acid. These highly fluorescent compounds **62-63** were evaluated as fluorescent whitening agents on synthetic fibers [143].



64

X = CN, COOEt; Y-Z = -CH=CH-, hetaryl; R_1, R_2 = H, Me, OMe, Benzo, CN

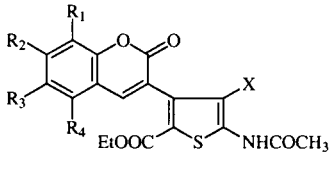
2-Hetarylthiophenes **64** were prepared by diazotizing 2-aminothiophene and coupling with selected aryl- and hetarylamines followed by air oxidation. These compounds show intense bluish violet fluorescence in daylight in most of the organic solvents and were investigated as fluorescent brighters [144].



65

R = aryl, hetaryl

Novel, highly fluorescent styryl disperse dyes **65** can be synthesized by condensing an aryl- or hetarylaldehyde with 2-acetamidothiophene-4-acetic acid [145]. The styryl dyes showed yellow to orange color and intense greenish blue fluorescence.



66

R_1, R_2, R_3, R_4 = H, alkyl, alkoxy, OH, NO_2, NEt_2, Cl; X = CN, COOEt

The Gewald intermediate also plays a vital role in synthesizing coumarin dyes. These compounds are evaluated as coumarin disperse dyes **66** on synthetic fibers. They are yellow to red solids with intense green fluorescence [146,147]. The concept of applying the Gewald reaction to dye chemistry has been much exploited by Sabnis and Rangnekar [116,117,127,137-147,156]. A wide variety of thienyl-2-azo disperse dyes have been synthesized by using the Gewald method [148-156].

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