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THE GEWALD SYNTHESIS

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THE GEWALD SYNTHESIS

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Dedicated to Dr. D. W. Rangnekar on the occasion of his 50th birthday

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This review article presents a systematic collection of results from the facile and elegant method called the Gewald synthesis, which leads to the synthesis of 2-aminothiophenes. The present review illustrates the details of the Gewald synthesis with reference to its simplicity, superiority and advantages over other existing methods.

Key words: Gewald synthesis, 2-aminothiophenes.

CONTENTS

1. INTRODUCTION

The bulk of the literature dealing with the chemistry of 2-aminothiophene has forced us to restrict this review to only one superior and efficient preparative method called the Gewald synthesis which leads to the synthesis of 2-aminothiophenes. Although a large number of publications have appeared on the chemistry of 2-aminothiophenes during the last three decades, it is quite surprising that no review emphasizing the Gewald synthesis has appeared so far. The present review illustrates the details of this method with reference to its advantages, superiority and simplicity compared to other existing methods.

In recent years, many reviews[1-6] have appeared dealing with the latest accomplishments in the synthetic chemistry of 2-aminothiophenes. There are various routes for the synthesis of 2-aminothiophenes involving reduction of a nitro group,[7] Curtius rearrangement,[8-9] Hoffmann reaction,[10] Schmidt reaction,[11] Beckmann rearrangement,[12] nucleophilic displacement of substituents such as mercapto,[13-14] halo,[15-17] and hydroxy,[18] and cyclisation of thioamides and their *S*-alkyl derivatives.[19-24] Stacy and Eck[25-26] developed a multistep route for the synthesis of unsubstituted 2-aminothiophenes. Condensation of ethyl γ-chloroacetoacetate with isothiocyanates in the presence of sodium hydride gives 2-aminothiophenes.[27-28] Simultaneous passage of hydrogen sulfide and hydrogen chloride through methanol solutions of γ-keto nitriles yields hydrochlorides of simple 2-aminothiophenes.[29] All the above routes constitute multistep syntheses and involve difficult preparations of starting materials. These routes do not always produce good yields. Gewald and coworkers devised an extremely useful, simple and widely applicable set of synthetic procedures leading to 2-aminothiophenes in excellent yields.

2. THE GEWALD SYNTHESIS

The Gewald synthesis constitutes an extremely elegant and promising set of synthetic routes leading to 2-aminothiophenes with electron-withdrawing substituents in the 3-position and alkyl and/or aryl groups in the 4- and 5-positions. The three major variations of this synthesis are described in detail.

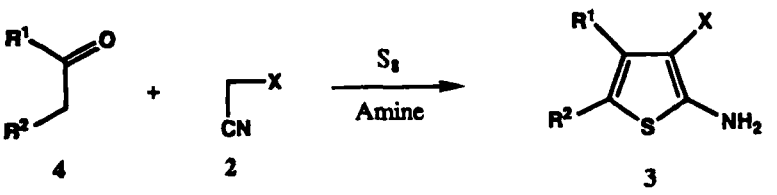
2.1. *Version 1*

1 2 3

SCHEME 1

In one of the versions of the Gewald synthesis[30-44] (Scheme 1), α-mercapto aldehyde or α-mercapto ketone **1** (often generated *in situ* by reaction of alkali sulfides with appropriate α-halo carbonyl compounds) is treated with an activated nitrile **2** bearing an electron withdrawing group such as malononitrile, methyl cyanoacetate, benzoylacetonitrile or p-nitrobenzyl cyanide in solvents such as ethanol or DMF in the presence of triethylamine or piperidine as catalyst at about 50 °C. Recently dioxane has been recommended as solvent.[39,42] With malononitrile, water can also be used as solvent. Nonactivated nitriles, e.g. benzyl cyanide, cyanoacetic acid or phenacyl mercaptan do not react under mild conditions. This particular route has certain disadvantages in that it utilizes starting compounds which are unstable and difficult to prepare.

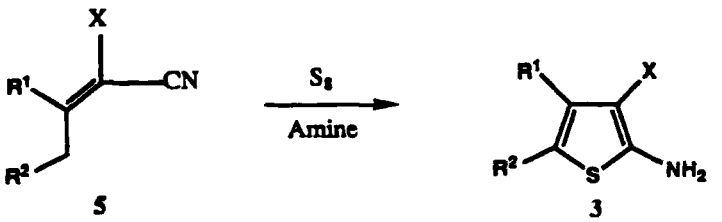
2.2. *Version 2*



SCHEME 2

The second version of the Gewald synthesis[34,38,45-66] (Scheme 2) consists of a one-pot procedure which can be very extensively used for the synthesis of a variety of 2-aminothiophenes **3**. This route may afford considerable improvement by replacing an α-mercapto aldehyde or α-mercapto ketone by other starting materials. This convenient technique includes the condensation of aldehydes, ketones or 1,3-dicarbonyl compounds **4** with activated nitriles **2** like cyanoacetic esters, cyanoacetamide and its *N*-substituted derivatives, malononitrile, heteroarylacetonitriles, α-cyano ketones and sulfur in the presence of an amine. Ethanol, DMF, dioxane, or excess ketone are preferred solvents and amines like diethylamine, morpholine, and triethylamine have been employed. It is necessary to use 0.5 to 1.0 molar equivalents of amine, based on the amount of nitrile. This is in contrast to the first version of the Gewald synthesis in which a catalytic amount of the amine is used.

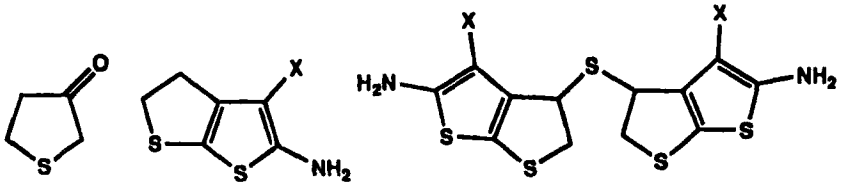
2.3. *Version 3*



SCHEME 3

In the third version of the Gewald synthesis (Scheme 3), a two-step procedure is preferred.[34,38,46,51,58,59,67-78] An α,β-unsaturated nitrile **5** is first prepared by a Knoevanagel-Cope condensation and then treated with sulfur and an amine. In many cases, this third two-step version gives higher yields. Certain ketones such as alkyl aryl ketones do not give thiophenes in the one-pot version, but give good yields with the two-step technique.[37,67]

Acetone and acetaldehyde do not give 2-aminothiophenes with the one-pot technique. However, if acetone is first condensed with ethyl cyanoacetate and then treated with sulfur and triethylamine 2-amino-5-thiophenethiol is produced.[70]



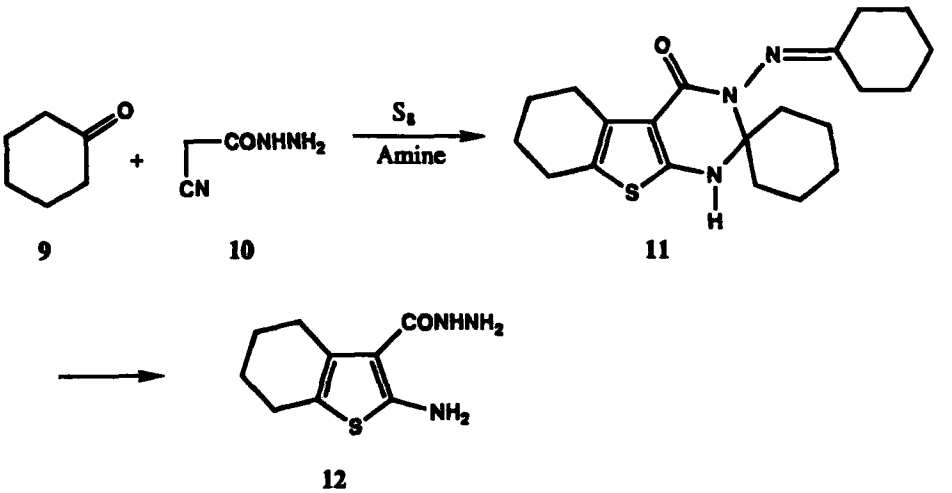
6 7 8

SCHEME 3a

3-Thiacyclopentanone **6** gives two different products, depending upon the temperature. Condensation of **6** with methyl cyanoacetate and sulfur in the presence of diethylamine at 40 °C gives **7** in 30% yield. However, when the reaction was carried out at room temperature or at 60 °C, the sulfide **8** was obtained in 36% yield.[71]

Sterically crowded ketones without methylene groups, e.g. methyl isopropyl, methyl cyclohexyl, and methyl *t*-butyl ketone do not react with nitriles and sulfur. However, their condensation products with nitriles give 2-aminothiophenes with electron-withdrawing substituents in the 3-position.[70]

The Gewald synthesis goes more easily with cyclic ketones e.g. cyclohexanone, its derivatives, fused systems incorporating cyclohexanones, higher cycloalkanones and cycloalkylidene derivatives of methylene-active nitriles,[31,34,46,50–52,54–56,58–60,65,78] and with the cyclopentanones.[46,60] More complex cyclic ketones e.g. 3-cholestanone,[50,87] androstane-3,17-dione[89] and other steroids, bicyclo[2.2.1]heptanone,[88] benz[*f*]isoindolone,[86] pyranones,[63,77] tropinones,[58] indanones,[59] α- and β-tetralones,[59] thiacyclopentanones,[71] dithiacycloalkanones,[72,75] piperidones,[34,54,58,59,61,64] quinuclidinones,[96] and azepinones[97] also undergo the Gewald reaction.

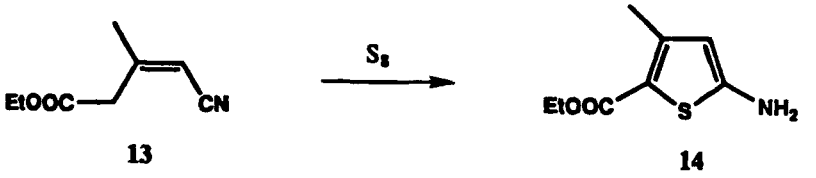


9 10 11 12

SCHEME 4

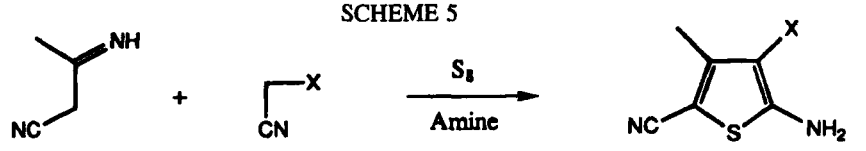
Condensation of cyclohexanone **9** with cyanoacetic acid hydrazide **10** and sulfur in the presence of an amine yields the thienopyrimidone **11** which upon acid hydrolysis gives

the 2-aminothiophene-3-carboxylic acid hydrazide **12** (Scheme 4).[84] Cyclohexanone and methyl ethyl ketone undergo a similar reaction with *N*-(cyanoacetyl)phenylhydrazine or *N*-(cyanoacetyl)urethane giving the corresponding thienopyrimidones.[58,68] On the other hand, cyclopentanone gives a 2-aminothiophene-3-carboxhydrazide.[84]



13 **14**

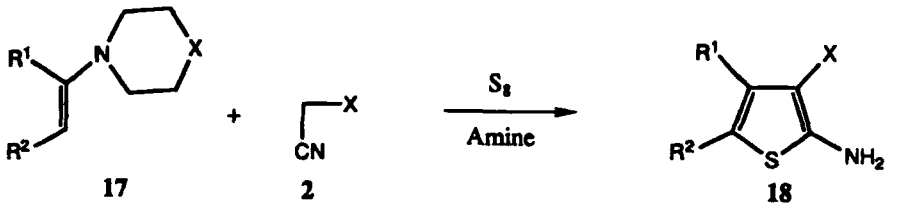
SCHEME 5



15 **2** **16**

SCHEME 6

Reaction of α,β-unsaturated nitrile **13** (synthesized by condensation of ethyl acetoacetate and cyanoacetic acid) with sulfur and diethylamine in ethanol yields 68% of the 2-aminothiophene **14** (Scheme 5).[90] These results indicate that 2-aminothiophenes without electron-withdrawing groups in the 3-position can be synthesized. The ethoxycarbonyl group is necessary to activate the methylene group for the thiation.



17 **2** **18**

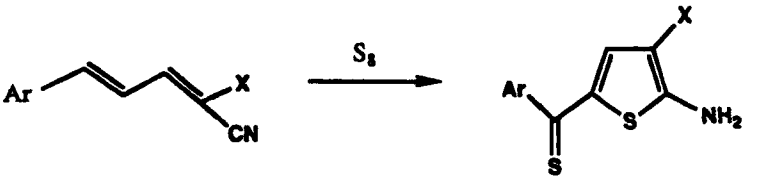
R^1	R^2	X
CH_3	C_6H_5	O
C_6H_5	C_6H_5	O
	$-(CH_2)_4-$	O
H	C_2H_5	CH_2

SCHEME 7

The imine (acetonitrile dimer) **15** condenses with an activated nitrile producing the 2-aminothiophene **16** in good yield (80%; Scheme 6).[91] Enamines **17** also undergo Gewald reactions with activated nitriles **2** to give the 2-aminothiophenes **18** (Scheme 7).[92,93]

This method has been used to introduce radioactive sulfur (^{35}S) into the thiophene nucleus. ^{35}S-Labelled sulfur has been used for the synthesis of ^{35}S-labelled thiophenes.[62]

It was recently reported that condensation of ethyl cyanoacetate with sulfur in the presence of triethylamine gives diethyl 2,5-diamino-3,4-thiophenedicarboxylate.[94] The Knoevenagel condensation product **19** of cinnamaldehyde and activated nitriles react with sulfur in the presence of triethylamine to give the thioketones **20** (Scheme 8).[95]



19 **20**

Ar	X
C_6H_5	COC_6H_5
C_6H_5	COOEt
C_6H_5	COC_6H_4Me-4
C_6H_5	COC_6H_4OMe-4
4-MeC_6H_4	COC_6H_5
4-MeC_6H_4	COOEt
4-$MeOC_6H_4$	COC_6H_5
4-$MeOC_6H_4$	COOEt

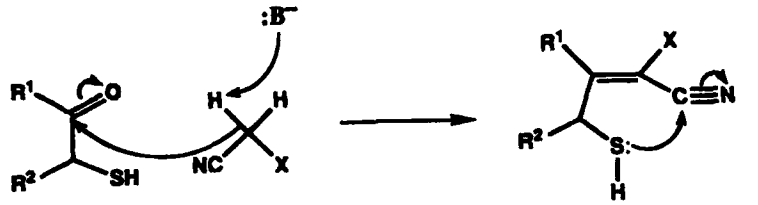
SCHEME 8

The scope and synthetic utility of the Gewald synthesis can be further broadened by using a variety of heteroaromatic analogs in which the arenecarbonyl group X is 2-thiophenecarbonyl,[34,35] 2-furancarbonyl,[34,35,78] 2-pyridinecarbonyl,[37,96,98] or 2-thiazolecarbonyl.[99] In order to generate novel pharmacologically active compounds, the Gewald synthesis can be further extended to heterocyclic ketones.[58,61,63,64,71,75,77,101–107]

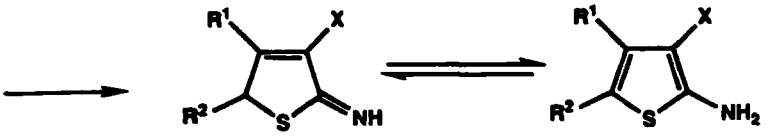
5-Unsubstituted 2-aminothiophenes can also be synthesized.[108] Cyanothioacetamide undergoes the Gewald reaction in the presence of sulfur to give 2-aminothiophene.[109]

3. MECHANISM

3.1. *Version 1*



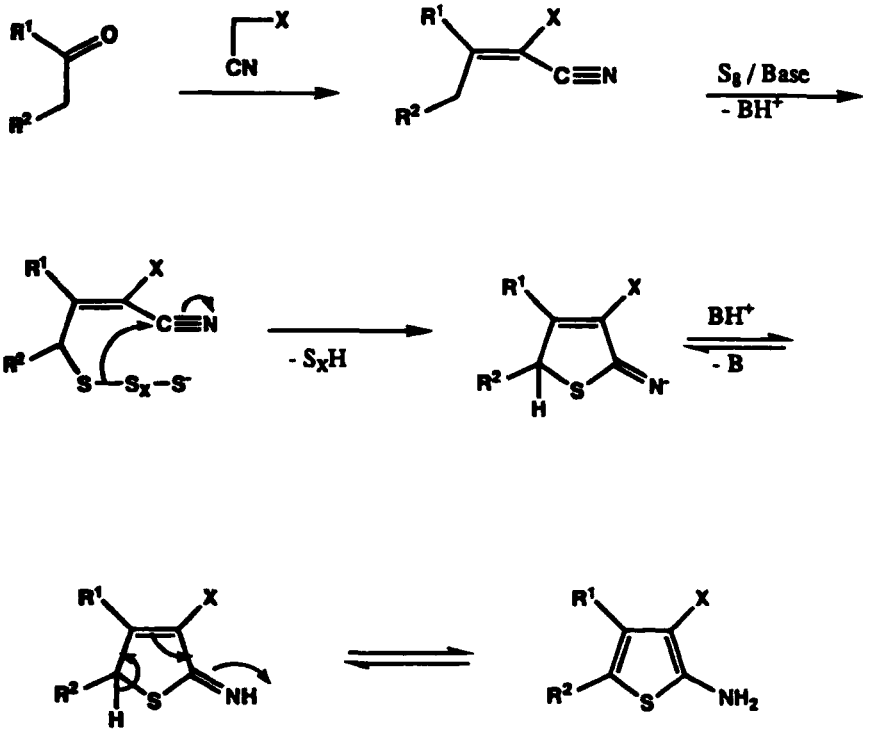
SCHEME 8a



SCHEME 8b

It is likely that the first step of the reaction is the condensation of an activated nitrile with an α-mercapto carbonyl function with the formation of a γ-mercapto nitrile which then cyclizes to a 2-aminothiophene.

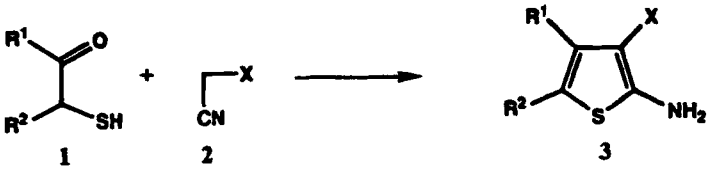
3.2 and 3.3. *Versions 2 and 3*



SCHEME 8c

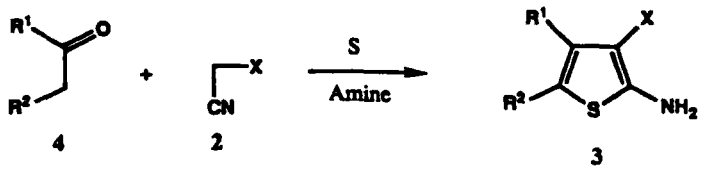
Gewald favors that an activated nitrile first condenses with a ketone yielding a Knoevenagel-Cope condensation product (styryl) which is then thiolated at the methylene group, followed by ring closure.

TABLE 1 Gewald synthesis via α-mercapto ketones (Version 1)



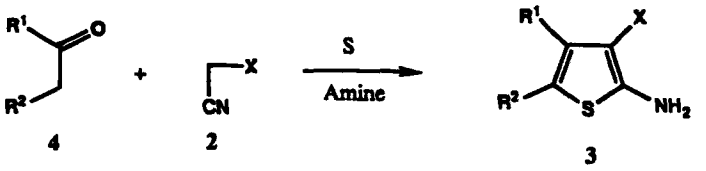
R^1	R^2	X	Yield (%)	Reference
CH_3	CH_3	$COOCH_3$	45	31
CH_3	H	$COOCH_3$	75	31
H	H	$COOCH_3$	46,58	31,32
CH_2COOEt	H	$COOCH_3$	—	41
CH_3	H	$COOC_2H_5$	88	36
C_6H_5	CH_3	$COOC_2H_5$	97	36
C_6H_5	H	$COOC_2H_5$	75	36
$-(CH_2)_4-$		$COOC_2H_5$	80	31
CH_3	CH_3	CN	70	31
CH_3	H	CN	73	31
C_2H_5	CH_3	CN	51	31
H	H	CN	55	31
$-(CH_2)_4-$		CN	70	31
CH_3	H	$CONH_2$	53	31
H	H	$CONH_2$	60	35
CH_3	H	COC_6H_5	40	31
H	H	COC_6H_5	70	35
CH_3	H	$C_6H_4NO_2$-4	34	31
H	H	2-$CH_3C_6H_4CO$	42	42
H	H	2-$CH_3C_6H_4CO$	60	35
H	H	2-$CH_3C_6H_4CO$	73	42
H	H	2-FC_6H_4CO	58	42
H	H	2-$CH_3SO_2C_6H_4CO$	79	42
H	H	2-$NO_2C_6H_4CO$	48	43
H	H	3-$NO_2C_6H_4CO$	—	39
H	H	2-$CF_3C_6H_4CO$	78	42
		3-NO_2-5-$CH_3C_6H_3CO$	78	42
H	H	2,6-$F_2C_6H_3CO$	56	42
H	H	3,5-$Cl_2C_6H_3CO$	74	42
H	H	2,6-$Cl_2C_6H_4$	82	40
H	H	$NCCH_2NHCO$	44	38
H	H	$CSNH_2$	88	33
CH_3	H	2-ThCO	48	34
H	H	2-ThCO	70	35
H	H	2-Furyl-CO	60	35
H	H	2-Pyridyl-CO	—	37
H	H	3-CH_3-2-pyridyl-CO	—	37

TABLE 2 Gewald synthesis via keto methylenes (Version 2)



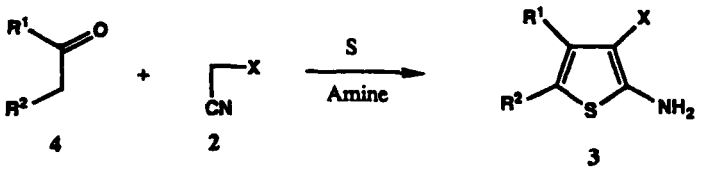
R^1	R^2	X	Yield (%)	Reference
CH_3	$COCH_3$	$COOCH_3$	31	46
C_2H_5	CH_3	$COOCH_3$	40	46
CH_3	CH_3	$COOC_2H_5$	39	46
CH_3	CH_2COOH	$COOC_2H_5$	30	58
CH_3	$COOC_2H_5$	$COOC_2H_5$	32	46
CH_3	$CONHC_6H_5$	$COOC_2H_5$	30	58
H	CH_3	$COOC_2H_5$	42,47	46
H	C_2H_5	$COOC_2H_5$	75,65	46
H	$CH(CH_3)_2$	$COOC_2H_5$	40	57
$CH_2COOC_2H_5$	$COOC_2H_5$	$COOC_2H_5$	87	48
-$(CH_2)_3$-		$COOC_2H_5$	45	46
-$(CH_2)_4$-		$COOC_2H_5$	82	46,54,65
-$(CH_2)_5$-		$COOC_2H_5$	59	65
-$[CH_2CH(CH_3)(CH_2)_2]$-		$COOC_2H_5$	34	65
-$[(CH_2)_2$-$CH(CH_3)CH_2]$-		$COOC_2H_5$	70	65
-$[CH(C_6H_5)(CH_2)_3]$-		$COOC_2H_5$	50	58
-$[CH_2N(CH(CH_3)_2)CH_2]$-		$COOC_2H_5$	61	64
-$[CH_2CH(C_6H_5)NHCH(C_6H_5)]$-		$COOC_2H_5$	35	58
-$[CH_2CH(C_6H_5)NCH_3CH(C_6H_5)]$-		$COOC_2H_5$	40	58
-$[CH(CH_3)CH(C_6H_5)NCH_3CHC_6H_5]$-		$COOC_2H_5$	53	58
-$[H_8C_4ONCH_2CH(CH_2)_3]$-		$COOC_2H_5$	50	58
CH_3	CH_3	CN	42	46,54
CH_3	$C_6H_5CH_2$	CN	17	67
CH_3	$C_6H_5CH_2CH_2$	CN	29	67
CH_3	$CONHC_6H_5$	CN	70	100
CH_3	$CONHC_6H_4Cl$-4	CN	60	100
CH_3	$CONHC_6H_4CH_3$-4	CN	63	100
CH_3	$CONHC_6H_3Cl_2$-2,5	CN	68	100
CH_3	3,4-$Cl_2C_6H_3CH_2$	CN	18	67
CH_3	3,4-$Cl_2C_6H_3CH_2CH_2$	CN	24	67
$CH_2COOC_2H_5$	$COOC_2H_5$	CN	84	47
-$(CH_2)_4$-		CN	86	46,50,54,56,59
-$(CH_2)_5$-		CN	44	50,56
-$(CH_2)_6$-		CN	64	56
-$(CH_2)_{10}$-		CN	42	56
2-Tetralone		CN	40	59
2-Indanone		CN	41	59
Tropinone		CN	50	58
Cholestan-3-one		CN	30	50
-$[(CH_2)_2SCH_2]$-		CN	61	59
-$[CH_2CHC_6H_5SCHC_6H_5]$-		CN	83	61

TABLE 2 Gewald synthesis via keto methylenes (Version 2)—continued



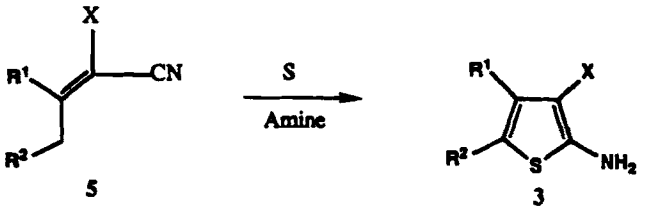
R^1	R^2	X	Yield (%)	Reference
-[$CH_2CH(3,4\text{-}Cl_2C_6H_3)SCH(3,4\text{-}Cl_2C_6H_4)$]-		CN	85	61
-[$CH_2CH(4\text{-}CF_3C_6H_4)SCH(4\text{-}CF_3C_6H_4)$]-		CN	98	61
-[$CH(CH_3)(CH_2)_3$]-		CN	45	58
-[$(CH_2)_2CH(CH_3)CH_2$]-		CN	86	56
-[$CH_2CH(CH_3)(CH_2)_2$]-		CN	90	56
-[$CH_2CH(CH_3)CH(CH_3)CH_2$]-		CN	80	56
-[$(CH_2)_2CH(C(CH_3)_3)CH_2$]-		CN	79	56
-[$(CH_2)_2CH(C_6H_5)CH_2$]-		CN	63	59
-[$(CH_2)_2N(CH_3)CH_2$]-		CN	62	56
-[$(CH_2)_2N(CH(CH_3)_2)CH_2$]-		CN	74	64
-[$(CH_2)_2N(C_4H_9)CH_2$]-		CN	43	56
-[$(CH_2)_2N(CH_2C_6H_5)CH_2$]-		CN	71	56
-[$CH_2CH(C_6H_5)N(CH_3)CHC_6H_5$]-		CN	51	61
-[$CH_2CH(3,4\text{-}Cl_2\text{-}C_6H_3)N(CH_3)CH(3,4Cl_2C_6H_4)$]-		CN	58	61
-[$HO(CH_2CH_2)_2CH_2CH(CH_2)_3$]-		CN	50	58
H	C_6H_5	$CONH_2$	45	46
-$(CH_2)_4$-		$CONH_2$	61,25	46,51,55
-[$(CH_2)_2CH(OCOC_6H_5)CH_2$]-		$CONH_2$	42	55
-$(CH_2)_4$-		$CONHCH_3$	29	55
-$(CH_2)_4$-		$CONHC_2H_5$	35	58
-$(CH_2)_4$-		$CONHC_6H_5$	41	58
-$(CH_2)_4$-		$CONHC_6H_4CH_3$-4	62	52
CH_3	CH_3	COC_6H_5	72	60
CH_3	H	COC_6H_5	—	53
CH_3	n-C_3H_7	COC_6H_5	—	60
H	CH_3	COC_6H_5	—	34,53
H	C_2H_5	COC_6H_5	70	60
H	n-C_4H_9	COC_6H_5	—	60
i-C_3H_7	H	COC_6H_5	—	60
-$(CH_2)_3$-		COC_6H_5	51	60
-$(CH_2)_4$-		COC_6H_5	40	46
-[$(CH_2)C(CH_3)_2OCH_2$]-		COC_6H_5	41	63
H	C_6H_5	COC_6H_5	86	34
CH_3	CH_3	2-ClC_6H_4CO	59	60
CH_3	CH_3	4-ClC_6H_4CO	52	60
CH_3	CH_3	3-$F_3CC_6H_4CO$	—	60
H	CH_3	2-ClC_6H_4CO	75	60
H	C_2H_5	2-ClC_6H_4CO	61	60

TABLE 2 *Gewald synthesis via keto methylenes (Version 2)—continued*



R^1	R^2	X	Yield (%)	Reference
H	*i*-C_3H_7	2-ClC_6H_4CO	—	60
H	C_2H_5	2-BrC_6H_4CO	60	60
H	C_2H_5	2-FC_6H_4CO	68	60
H	C_2H_5	2-$CH_3OC_6H_4CO$	73	60
H	C_2H_5	2-$CH_3C_6H_4CO$	58	60
-$(CH_2)_4$-		2-$CH_3OC_6H_4CO$	71	60
-$(CH_2)_4$-		3-$CF_3C_6H_4CO$	60	60
-$(CH_2)_4$-		4-ClC_6H_4CO	68	60
-[$CH_2C(CH_3)_2OCH_2$]-		2-ClC_6H_4CO	66	63
-[$CH_2C(CH_3)_2OCH_2$]-		2-BrC_6H_4CO	50	63
-[$CH_2C(CH_3)_2OCH_2$]-		3-$NO_2C_6H_4CO$	46	63
-[$CH_2C(CH_3)_2OCH_2$]-		4-BrC_6H_4CO	51	63
-[$CH_2C(CH_3)_2SCH_2$]-		2-ClC_6H_4CO	46	63
-$(CH_2)_5$-		C_6H_5CO	58	60
-[$(CH_2)_2CH(CH_3)CH_2$]-		C_6H_5CO	67	60

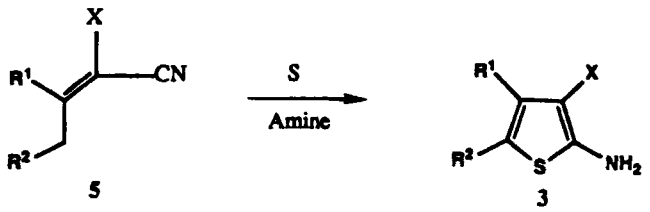
TABLE 3 Gewald synthesis via α,β-unsaturated nitriles (Version 3)



5 3

R^1	R^2	X	Yield (%)	Reference
C_2H_5	CH_3	$COOCH_3$	50	46
C_6H_{11}	H	$COOCH_3$	—	70
-[CH_2CH_2S]-		$COOCH_3$	41	71
CH_3	CH_3	$COOC_2H_5$	49	46, 74, 76
CH_3	H	$COOC_2H_5$	—	70
CH_3	$CH_2CH_2OCOCH_3$	$COOC_2H_5$	77	73
CH_3	C_6H_5	$COOC_2H_5$	38	46
C_6H_5	CH_3	$COOC_2H_5$	50	46, 68, 76
C_6H_5	H	$COOC_2H_5$	62	46, 74, 76
4-F+C_6H_4	H	$COOC_2H_5$	68	68
4-NO_2+C_6H_4	H	$COOC_2H_5$	60	76
4-CH_3+C_6H_4	H	$COOC_2H_5$	78	73
4-CH_3O+C_6H_4	H	$COOC_2H_5$	69	73
2, 4-$(CH_3)_2C_6H_3$	H	$COOC_2H_5$	72	73
2, 5-$(CH_3)_2C_6H_3$	H	$COOC_2H_5$	22	73
2, 4-$(CH_3O)_2C_6H_3$	H	$COOC_2H_5$	60	73
3, 4-$(CH_3O)_2C_6H_3$	H	$COOC_2H_5$	93	73
3, 4, 5-$(CH_3O)_3C_6H_2$	H	$COOC_2H_5$	60	68, 76
-[$CH(C_6H_5)(CH_2)_3$]-		$COOC_2H_5$	50	58
2-Th	H	$COOC_2H_5$	33	74
-$(CH_2)_3$-		$COOC_2H_5$	52	46
-$(CH_2)_4$-		$COOC_2H_5$	91	46
-$(CH_2)_5$-		$COOC_2H_5$	85	51
-$(CH_2)_6$-		$COOC_2H_5$	96	51
CH_3	CH_3	CN	41	46
C_6H_5	C_6H_5	CN	95	67
$C_6H_5CH_2$	C_6H_5	CN	98	67
$C_6H_5CH_2$	CH_3	CN	34	67
4-ClC_6H_4	CH_3	CN	95	67
4-ClC_6H_4	C_2H_5	CN	86	67
$(CH_3)_2CH$	H	CN	—	70
$(CH_3)_3C$	H	CN	48	70
-$(CH_2)_4$-		CN	90	46
-$(CH_2)_5$-		CN	65	51
-$(CH_2)_6$-		CN	65	51
-$(CH_2)_{10}$-		CN	60	51
-$(CH_2)_{13}$-		CN	50	51
-[$CH(CH_3)(CH_2)_3$]-		CN	45	58
-[$CH_2C(CH_3)_2OCH_2$]-		CN	83	77
-[$CH_2SCH_2CH_2S$]-		CN	68	75

TABLE 3 Gewald synthesis via α,β-unsaturated nitriles (Version 3)—continued



5 3

R^1	R^2	X	Yield (%)	Reference
-[$CH_2C(CH_3)_2SCH_2$]-		CN	92	77
-[$CH(C_6H_5)(CH_2)_3$]-		CN	30	59
-[$CH(C_6H_5)(CH_2)_4$]-		CN	4	51
1-Tetralone		CN	48	59
1-Indanone		CN	25	59
CH_3	C_6H_5	$CONH_2$	58	46
-$(CH_2)_4$-		$CONH_2$	71, 75	46, 51
-$(CH_2)_5$-		$CONH_2$	66	51
-$(CH_2)_6$-		$CONH_2$	80	51
-$(CH_2)_{10}$-		$CONH_2$	48	51
-[$CH(C_6H_5)(CH_2)_4$]-		$CONH_2$	11	51
-[$CH_2SCH_2CH_2S$]-		$CONH_2$	96	75
-[$CH_2S(CH_2)_3S$]		$CONH_2$	—	72
C_2H_5	CH_3	C_6H_5CO	65	38
C_2H_5	C_2H_5	C_6H_5CO	79	34
C_6H_5	H	C_6H_5CO	39	34, 70
-$(CH_2)_4$-		C_6H_5CO	80	46
-$(CH_2)_6$-		C_6H_5CO	-	34
-[$(CH_2)_2SCH_2$]-		C_6H_5CO	56	34
-[$(CH_2)_2N(COOC_2H_5)CH_2$]-		C_6H_5CO	53	34
-$(CH_2)_4$-		$C_6H_{11}CO$	95	34
-$(CH_2)_4$-		$CONHC_6H_5$	41	58
-$(CH_2)_4$-		2-FC_6H_4CO	48	34
-$(CH_2)_4$-		2-ClC_6H_4CO	37	34
-$(CH_2)_4$-		2-$CH_3C_6H_4CO$	81	34
-$(CH_2)_4$-		3-ClC_6H_4CO	46	34
-$(CH_2)_4$-		3-$CH_3OC_6H_4CO$	64	34
-$(CH_2)_4$-		4-$CH_3OC_6H_4CO$	91	34
-$(CH_2)_4$-		2-Naphthyl-CO	—	34
-$(CH_2)_4$-		2-ThCO-	76	34
-$(CH_2)_4$-		2-Furyl-CO-	77	34, 78

SOLVENTS

Preferred solvents in the Gewald synthesis are methanol, ethanol, DMF, dioxane, water, and excess ketone (e.g., methyl ethyl ketone, cyclohexanone, etc.).

BASES

The most often employed organic bases are diethylamine, morpholine, triethylamine, piperidine, etc.

ADVANTAGES

The yields are generally high. The reaction time is short. The procedure involves only one step. The work-up is convenient. This method generates an amino compound (2-aminothiophene) which leads to the opening of an entire new door to dye chemistry. The presence of a diazotizable amino group adjacent to electron-withdrawing groups such as cyano, carbethoxy, and carboxamido results in the deepening of the dye hues on synthetic fibers. This particular method has 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 fused heterocycles such as thienodiazepins, thienopyridines, and thienopyrimidines. These compounds have promising applications in biomedicine.

CONCLUSION

The data presented in this review demonstrate that the Gewald synthesis is the most convenient and promising route for the synthesis of 2-aminothiophenes. This particular method has extensive applications in the fields of textile dyes and biomedicine. All these facts give every reason to consider the Gewald synthesis 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.

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