Synthesis of Methylthiomaleimides for the Preparation of Pyridazines and Related Compounds.

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New functionalized maleimides (3-methylthio-2,5-dioxo-1*H*-pyrroles) were obtained by the reaction of ketene dithioacetals with nitromethane or the reaction of nitro ketene dithioacetal with active methylene compounds in the presence of the appropriate base in dimethyl sulfoxide followed by treatment with methanol.

These maleimides reacted with various nucleophilic reagents such as electron-rich aromatic and heteroaromatic compounds like dialkylanilines, aminophenols, indoles, indolizines, and cyalazines to give the corresponding 3-aryl- or heteroaryl-1*H*-pyrole-2,5-diones. Styryl and merocyanine dyes, and polycyclic pyridazine-diones as chemiluminophors and succinimides were also obtained from these maleimides with good results.

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Fused or functionalized maleimides are synthetically useful intermediates for the preparation of polycyclic and functionalized pyridazine derivatives [1]. In an extension of our study on ketene dithioacetals for the synthesis of heterocycles, we were able to prepare new functionalized maleimides by the reaction of nitromethane with ketene dithioacetals or the reaction of active methylene compounds with nitro ketene dithioacetal [2]. Appropriately functionalized ketene dithioacetals are versatile reagents and have been extensively utilized in heterocyclic synthesis [3]. This review primarily describes the synthesis of 5-substituted 4-methylthiomaleimides (3-substituted 4-methylthio-1*H*-pyrrole-2,5-dione) and their reaction with various nucelophilic reagents for the preparation of a variety of aromatic and heteroaromatic dyes, merocyanine dyes, and polycyclic pyridazines as chemiluminescence compounds, and their reduction to give succinimide derivatives.

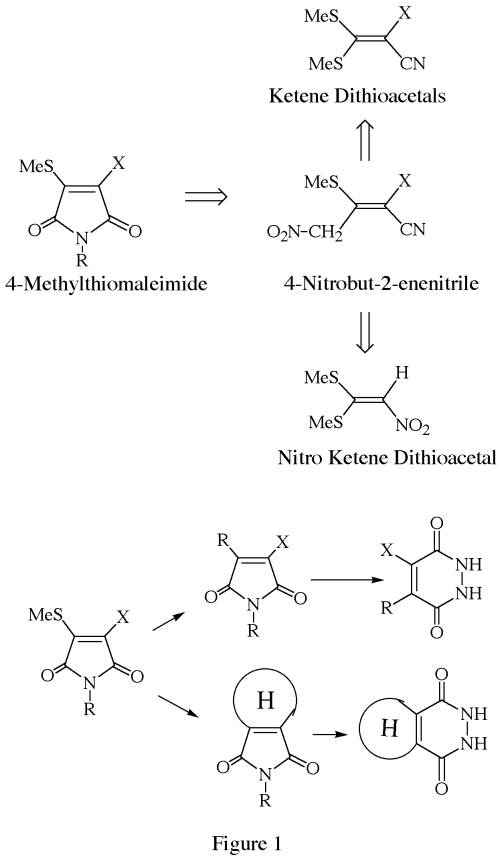


Figure 1

1. Synthesis of 4-Methylthiomaleimides.

Ketene dithioacetals react smoothly with active methylene compounds to give the corresponding replacement products in good yield. Generally, this reaction is carried out using an appropriate base such as potassium carbonate, sodium hydride, or sodium hydroxide.

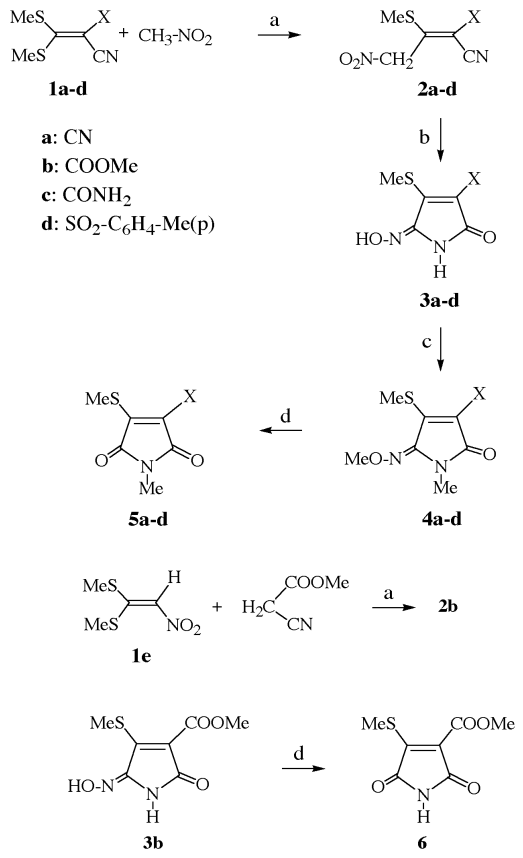
The reaction of **1b** with nitromethane in the presence of potassium carbonate as a base gave an expected product, **2b**, crotonate derivative, which can also be obtained by the reaction of nitro ketene dithioacetal (**1e**) with methyl cyanoacetate under similar reaction conditions [4].

It is commonly known that nitro compounds are quite reactive. Primary or secondary aliphatic nitro compounds can be hydrolyzed, respectively, to aldehydes or ketones by treatment of their salts with sulfuric acid. This is called the Nef reaction [5]. When primary nitro compounds are treated with sulfuric acid without previous conversion to the salt form, they give carboxylic acids. Hydroxamic

acids are intermediates and can be isolated. Therefore this is also a method for their preparation. Both the Nef reaction and the hydroxamic acid process involve the acid form and the difference in products arises from higher aciditics.

The products, **2a-d**, derived from **1a-d** have a nitromethyl group and are useful for the synthesis of heterocyclic compounds. Compounds **2a-d** were refluxed in methanol to give the corresponding maleimide derivatives (**3a-d**) in good yield. The methylation of **3a-d** with dimethyl sulfate in the presence of sodium hydroxide in dimethyl sulfoxide (DMSO) readily gave the corresponding dimethyl products (**4a-d**), which were readily converted to 1-methyl-4-methylthio-1*H*-pyrrole-2,5-diones (**5a-d**) in good yields by hydrolysis with concentrated hydrochloric acid in methanol. Hydrolysis of **3b** with hydrochloric acid solution in refluxing methyl cellosolve gives 4-methylthio-3-methoxycarbonyl-maleimide (**6**) in 40% yield [6].

Scheme 1



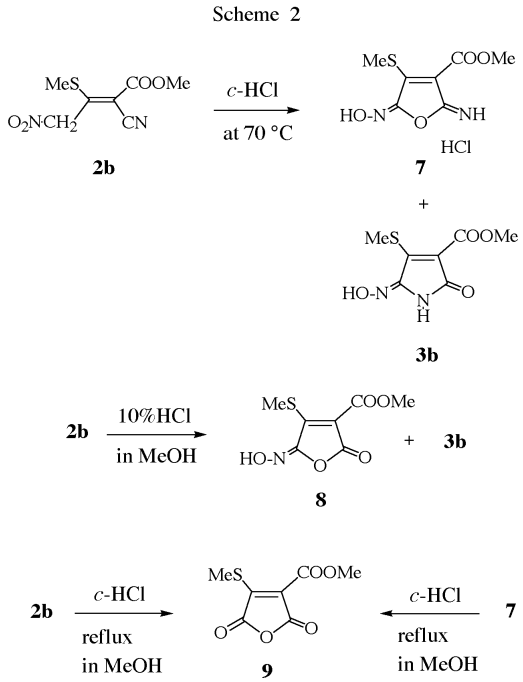
a: K_2CO_3 in DMSO;
b: reflux in MeOH;
c: 10%NaOH, Me_2SO_4 in DMSO;
d: reflux in c-HCl and $MeOCH_2CH_2OH$.

Table 1
4-Methylthioamleimides

X	mp(°C)	Yield (%)	No.
CN	273-275	64	**3a**
COOMe	268-270	53	**3b**
$CONH_2$	255-257	85	**3c**
Tolyl	243-245	63	**3d**
X	mp(°C)	Yield (%)	No.
CN	160-161	92	**4a**
COOMe	71-72	80	**4b**
$CONH_2$	249-252	67	**4c**
Tolyl	120-126	76	**4d**
X	mp(°C)	Yield (%)	No.
CN	110-112	52	**5a**
COOMe	108-109	62	**5b**
$CONH_2$	197-199	32	**5c**
Tolyl	204-208	38	**5d**

Treatment of **2b** with concentrated hydrochloric acid at 70 °C gave **3b** and 2-hydroxyimino-5-imino-4-methoxycarbonyl-3-methylthio-2,5-dihydrofuran hydrochloride (**7**), which was refluxed in methanol to yield **3b**. When **2b** was refluxed in a mixture of methanol and 10% hydrochloric acid solution, two products, **3b** and 2-hydroxyimino-4-methoxycarbonyl-3-methylthio-2,5-dihydro-

Scheme 2



furan-5-one (**8**), were formed. Compound **2b** was readily converted to the maleic anhydride derivative (**9**) by hydrolysis with concentrated hydrochloric acid in dioxane. Compound **9** was also readily obtained by dealing with **7** in hydrochloric acid [6].

We also tried to obtain 5-aryl-4-methylthiomaleimides (3-aryl-4-methylthio-1*H*-pyrrole-2,5-diones) by using the reaction of nitroketene dithioacetal (**1e**) with aryl acetonitriles.

At the start of this study, the reaction of ketene dithioacetal, bis(methylthio)methylenephenylacetonitrile (**1f**) with nitromethane to prepare 3-methylthio-4-nitro-2-phenylbut-2-enenitrile (**11a**) was attempted in the presence of sodium hydroxide in DMSO. Although the key intermediate, **11a**, was not obtained in this reaction, the following reaction was carried out to obtain **11a**.

The reaction of nitroketene dithioacetal (**1e**) with phenylacetonitrile (**10a**) in the presence of powdered sodium hydroxide in DMSO at room temperature occurred smoothly to yield **11a**, which was a key intermediate of the desired maleimides and was used in the next reaction without purification. Compound **11a** was treated with methanol under reflux to yield 5-hydroxyimino-4-methylthio-3-phenyl-1*H*-pyrrol-2-one (**12a**) in 84% yield (from **1e**). Similarly, other 2-hydroxymaleimide derivatives (**12b-f**, **12i-j**) except for the 4- and 2-nitro compounds (**12g, h**) were also readily synthesized from the corresponding aryl- and heteroarylacetonitriles (**10a-f**, **10i-j**) and **1e** in 54-85% yields. While the reaction of **1e** with 4- and 2-nitrophenylacetonitriles (**2g, h**) under similar reaction conditions did not occur, this problem was eliminated by using potassium carbonate instead of sodium hydroxide as a base. When potassium carbonate was used in this reaction, the desired products (**12g, i**) were obtained in 48 and 87% yields, respectively. An outline of the reaction pathway from **11** to **12** is shown in Figure 2.

Reaction Mechanism

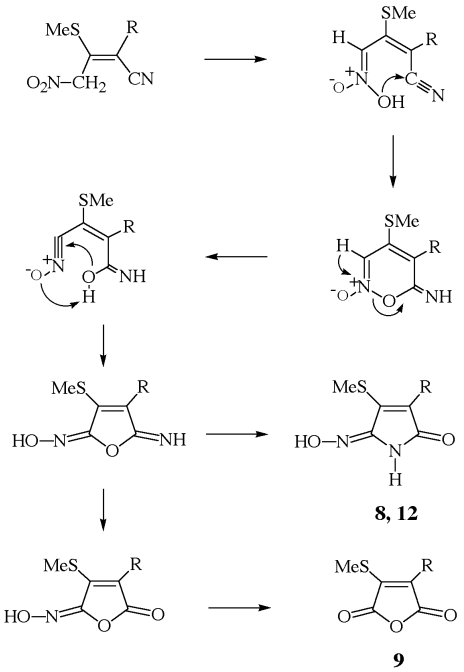
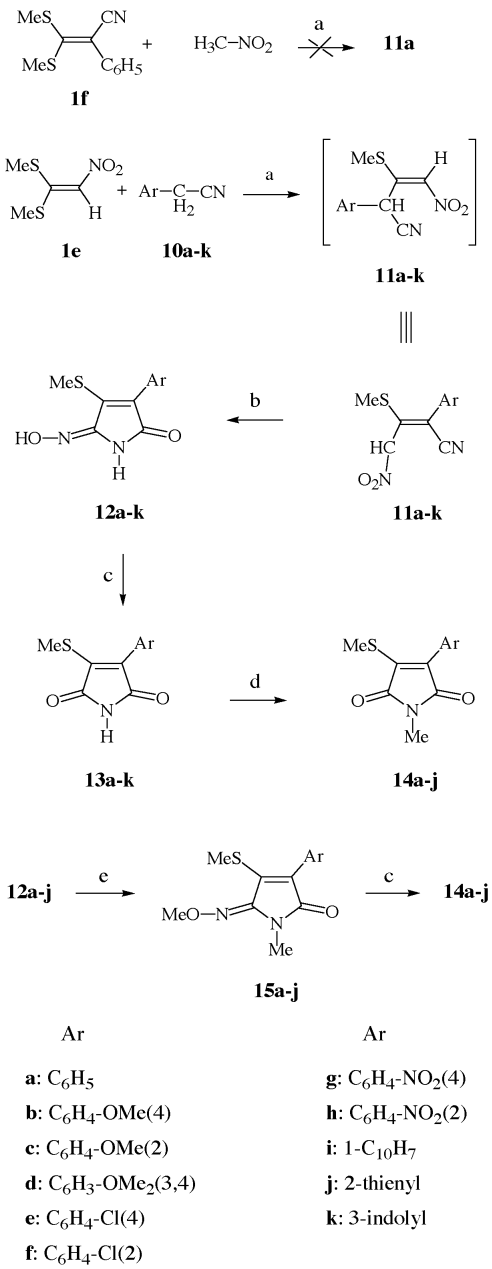


Figure 2

Scheme 3



Ar	Ar
a: C_6H_5	**g**: C_6H_4-NO_2(4)
b: C_6H_4-OMe(4)	**h**: C_6H_4-NO_2(2)
c: C_6H_4-OMe(2)	**i**: 1-$C_{10}H_7$
d: C_6H_3-OMe_2(3,4)	**j**: 2-thienyl
e: C_6H_4-Cl(4)	**k**: 3-indolyl
f: C_6H_4-Cl(2)	

a: NaOH in DMSO; b: reflux in MeOH; c: reflux in *c*-HCl and MeOH; d: MeI, K_2CO_3 in acetone: e: 10% NaOH, Me_2SO_4 in DMSO

Table 2
The Yields and Mp of 12

No.	R	mp(°C)	Yield(%)
12a	C_6H_5	234-235	84
b	C_6H_4-OMe(4)	214-215	85(92) [a]
c	C_6H_4-OMe(2)	195-196	77(92) [a]
d	C_6H_3-OMe_2(3,4)	202-203	84(87) [a]
e	C_6H_4-Cl(4)	250-251	74
f	C_6H_4-Cl(2)	200-202	67(91) [a]
g	C_6H_4-NO_2(4)	233-235	48
h	C_6H_4-NO_2(2)	215-216	87
i	1-$C_{10}H_7$	250-251	75
j	2-thienyl	239-241	54
k	3-indolyl	249-251	36

[a] The yields are from compounds **11.**

Table 3
The Yields and Mp of 13

No.	R	mp(°C)	Yield(%)
13a	C_6H_5	93-94	91
b	C_6H_4-OMe(4)	175-178	90
c	C_6H_4-OMe(2)	131-132	84
d	C_6H_3-OMe_2(3,4)	182-183	91
e	C_6H_4-Cl(4)	134-135	84
f	C_6H_4-Cl(2)	127-128	98
g	C_6H_4-NO_2(4)	141-142	92
h	C_6H_4-NO_2(2)	145-147	82
i	1-$C_{10}H_7$	144-145	74
j	2-thienyl	152-153	79
k	3-indolyl	185-187	88

Table 4
The Yields and Mp of 14

No.	R	mp(°C)	Yield(%)
14a	C_6H_5	61-62	94(72) [a]
b	C_6H_4-OMe(4)	74-73	94(58) [a]
c	C_6H_4-OMe(2)	101-102	94
d	C_6H_3-OMe_2(3,4)	110-111	95
e	C_6H_4-Cl(4)	70-71	96(73) [a]
f	C_6H_4-Cl(2)	58-59	95(97) [a]
g	C_6H_4-NO_2(4)	137-139	86(92) [a]
h	C_6H_4-NO_2(2)	124-125	74
i	1-$C_{10}H_7$	110-111	92(75) [a]
j	2-thienyl	69-70	92(78) [a]
k	3-indolyl	131-132	92

[a] The yields are from compounds **11.**

Table 5
The Yields and Mp of 15

No.	R	mp(°C)	Yield(%)
15a	C_6H_5	99-100	64
b	C_6H_4-OMe(4)	72-73	89
c	C_6H_4-OMe(2)	oil	82
d	C_6H_3-OMe_2(3,4)	99-100	61
e	C_6H_4-Cl(4)	108-110	98
f	C_6H_4-Cl(2)	oil	72
g	C_6H_4-NO_2(4)	140-141	89
h	C_6H_4-NO_2(2)	---	--
i	1-$C_{10}H_7$	156-158	92
j	2-thienyl	54-55	92
k	3-indolyl	----	--

Conversion of hydroxyimino compounds (**12a-k**) into 4-aryl-3-methylthio-1*H*-pyrrole-2,5-diones (**13a-k**) was carried out smoothly by hydrolysis of the hydroxyimino group with concentrated hydrochloric acid in good yields (74-98%). The introduction of a useful functional group into the nitrogen atom in the pyrrole ring is one of the most important chemical protections and derivations in pyrrole chemistry. We here attempted a methylation of **13a-k** as one of the simplest alkylation with methyl iodide in the presence of potassium carbonate in acetone. This reaction gave the corresponding methylated products (**14a-j**) in good yields. Compounds **14a-j** were also obtained by the methylation of **8a-j** with dimethyl sulfate in the presence of sodium hydroxide in DMSO followed by hydrolysis with concentrated hydrochloric acid in good yields. The intermediates were dimethyl products, **15a-j**. The possible reaction mechanism for the formation of maleimides is shown in Figure 2 [7].

4-Substituted 3-methylthio-1*H*-pyrrole-2,5-dione derivatives were readily obtained by the reaction of nitroketene dithioacetal with active methylene compounds baring the cyano group, aryl- or heteroarylacetonitriles.

2. Reaction of 4-Methylthiomaleimides with Electron-Rich Compounds.

Maleimide and its analogs readily react with a wide variety of dienes and a variety of 1,3-dipoles including azomethine ylides, carbonyl ylides, and nitrones [8].

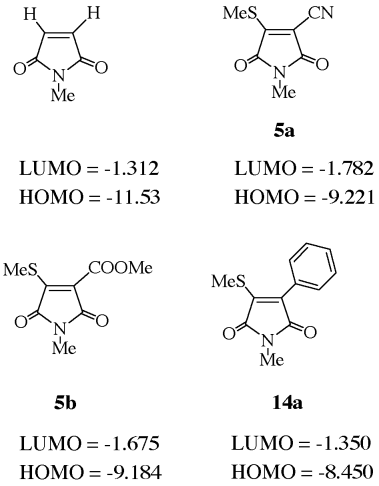


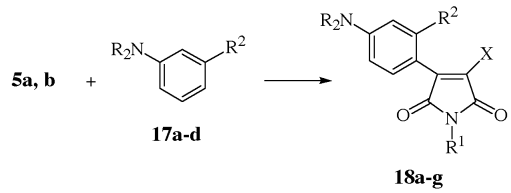
Figure 3

Substituted amines also add in a Michael fashion to *N*-phenyl- and *N*-alkylmaleimides. The reactivity of methylthiomaleimides (**5a, b, 14**) in a nucleophilic reaction with nucleophiles can be understood by consideration of interactions of the corresponding molecular orbitals. It is important to recognized the dominant interaction between the highest occupied molecular orbital (HOMO) of the nucleophilic reagents and the lowest unoccupied molecular orbital (LUMO) of the maleimide [9]. The majority of nucleophilic-substitution-elimination reaction of 4-methylthiomaleimides (**5a, b, 14**) are accommodated by this HOMO-LUMO interaction. In order to predict the reactivity, it becomes necessary to know the relative magnitude of the coefficients in the HOMO and LUMO of the maleimides and nucleophiles. The HOMO and LUMO energies of the corresponding maleimides are shown in Figure 3.

This section presents the synthesis of 3-(4-dialkylamino)phenyl-maleimides and 7-dialkylamino-2*H*,4*H*-[1]benzopyrano[3,4-*c*]pyrrole-1,3,4-triones for polymethine dyes through the use of the above maleimides. The methine or arylidine class of dyes has found widespread use in the coloration of acetate and polyester textiles. Only one brilliant disperse polymethine blue is commercially available, however, and it has certain disadvantages such as limited chemical stability and below-average light fastness [10].

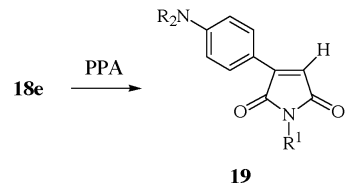
In general, in the case of the reaction of ketene dithioacetals with aryl or heteroaryl compounds, the corresponding Grignard reagents or lithium compounds are used for the synthesis of arylacrylnitriles and aryl acrylate derivatives. In contrast, we have previously reported that cyano(methylthio)methylene compounds are allowed to react with *N*,*N*-dialkylaminophenyl compounds under heating in acetic acid, yielding the (cyano)(dialkylaminophenyl)methylene derivatives with good results [11]. This method is applicable to the synthesis of new dyes bearing maleimides. Compound **5b** reacted with *N*,*N*-dimethylaniline (**17a**) under refluxing in acetic acid for 9 hours to give dark violet needles, **18a**, in 87% yield. The color of a DMSO solution of **18a** is very brilliant violet. The UV/V spectrum of **18a** appeared at 543 nm (log ε 4.85). The reaction of **5a** with other *N*,*N*-dialkylanilines (**17b-d**) under the same reaction conditions gave the corresponding 3-(4-dialkylamino)phenylmaleimides (**18b-g**) in good yields. Similarly, methyl ester (**18e**) was also readily obtained by the reaction of **5b** with **17a** in 64% yield. 3-(4-Dimethylaminophenyl)maleimide (**19**) is a basic compound used to compare the bathochromic shift due to a functional group on the maleimide ring. Compound **19** was prepared by the treatment of **18e** with polyphosphoric acid at 150-160 °C for 6 hours. This compound was obtained in the form of yellow needles, and the absorption at 459 nm (log ε 4.24) appeared in the UV spectrum. Compounds **18e-g** were synthesized by reactions of **5b** and **6** with *N*,*N*-dialkylanilines (**17a, b**) under similar reaction conditions. The cyclic amine, Julolidine (**17e**), also reacted with **5a** to yield **18h** as a violet product with maximum UV/V absorption at 576 nm.

Table 6
5-Substituted 4-Aryl-2-methylmaleimides



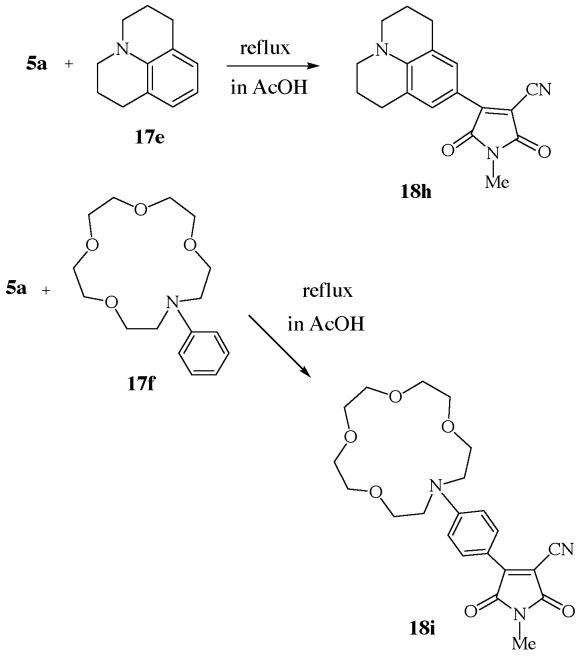
No.	R^1	X	R^2	NR_2	Yield(%)	EtOH UVλmax(log ε)
18 a	Me	CN	H	NMe_2	87	543(4.85) [a]
b	Me	CN	H	NEt_2	53	544(4.51)
c	Me	CN	H	NBu_2	35	547(4.35)
d	Me	CN	Me	NMe_2	38	534(4.24)
e	Me	COOMe	H	NMe_2	64	495(3.65)
f	Me	COOMe	H	NEt_2	36	508(4.24)
g	H	COOMe	H	NMe_2	14	478(4.08)

[a] solvent(DMSO)



Crown ethers are large-ring compounds containing several oxygen atoms and have the property of forming complexes with metallic or ammonium ions [12]. Chromoionophores which are consistent from both ionophoric part of a crown ether for metal recognition and the chromophoric part for optical signal detection are also one of the most important and interesting groups in crown ether chemistry. The reaction of crown ether (**17f**) with **5a** in acetic acid also occurred to yield a desired product, **18i**, in 29% yield, although the reaction time was slightly longer than that for the above described reaction.

Scheme 4



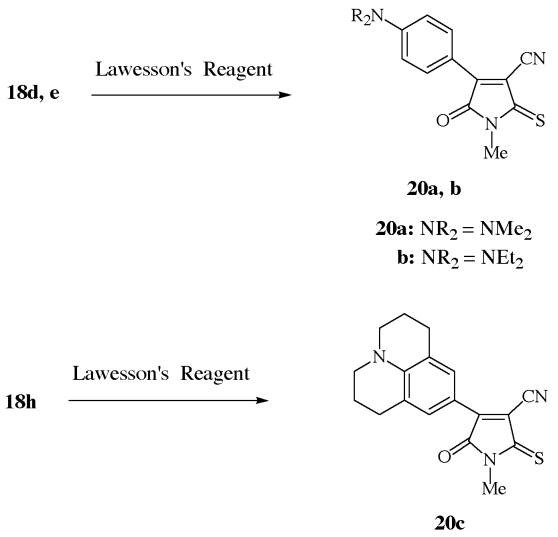
Thioimidization reactions of maleimides **18a**, **b**, and **h** with Lawesson's reagent [13] under refluxing in toluene gave thioamides **20a-c** as the only products, possibly due to steric effect, in moderate yields, respectively. Interesting, the bathochromic shift of 63 nm at the long-wavelength band in the UV/V spectrum was observed for the thioimidation of the general maleimides (**18d, e**) to thioimides **20a, b**. In particular, the absorption maximum of the UV/V spectrum of **20c** appeared at 665 nm in the field of near infrared region, which was the most bathochromic shift (See Table 7).

Table 7

4-Substituted 1-methyl-5-oxo-1*H*-pyrrole-2-thiones(**20a-c**)

No.	NR_2	Yield(%)	mp(°C)	EtOH UVλmax(log ε)
20a	NMe_2	72	>300	624(4.31)
b	NEt_2	49	189-190	614(4.50)
c	--	59	261-264	665(4.66)

Scheme 5



7-Dimethylaminocoumarin is an important laser dye [14]. Pyrrolocoumarin dyes were obtained by using the synthetic method of 3-(4-dialkylamino)phenylmaleimide derivatives. The reaction of 3-dialkylaminophenol (**17g-i**) with **5b** under refluxing in acetic acid gave the desired product, 7-dialkylamino-2-methyl-2*H*,4*H*-[1]benzopyrano[3,4-*c*]pyrrole-1,3,4-trione (**21a-c**) in good yields. When **5a** was allowed to react with **17i** under refluxing in acetic acid, the reaction also occurred smoothly to produce **21c** in 28.4% yield. The intermediate imino compound (**22**) was not obtained in this reaction.

The reaction of **5b** with 8-hydroxyjulolidine (**17j**) occurred under similar reaction conditions to give 1,2,5,6,7-pentahydro-10-methyl-3*H*,10*H*,12*H*-pyrrolo-[3',4':3,4][1]benzopyrano[6,7,8-*ij*]quinolizine-9,11,12-trione (**23**) in 96% yield, for which a slight bathochromic shift was observed. When resorcinol (**17k**) was allowed to react with **5b** under refluxing in acetic acid, the product (**24**) was obtain in quite low yield. We tried the reaction of resorcinol (**17k**) with **5b** under basic conditions. The reaction of **5b** with **17k** under refluxing in the presence of sodium hydride in tetrahydrofuran (THF) gave the desired product (**24**) as orange needles in 60% yield.

1-Methyl-3-methylthiomaleimides (**5a-c**) were found in this study to be useful electrophilic reagents for obtaining new methine dyes, 3-(4-dialkylamino)-phenylmaleimides, and 7-dialkylamino[1]benzopyrano[3,4-*c*]-pyrrole derivatives. This dye synthesis provides an efficient and convergent synthetic route to a variety of aromatic dyes bearing the pyrrole ring, since the reaction proceeds under mild conditions with readily available starting materials.

Scheme 6

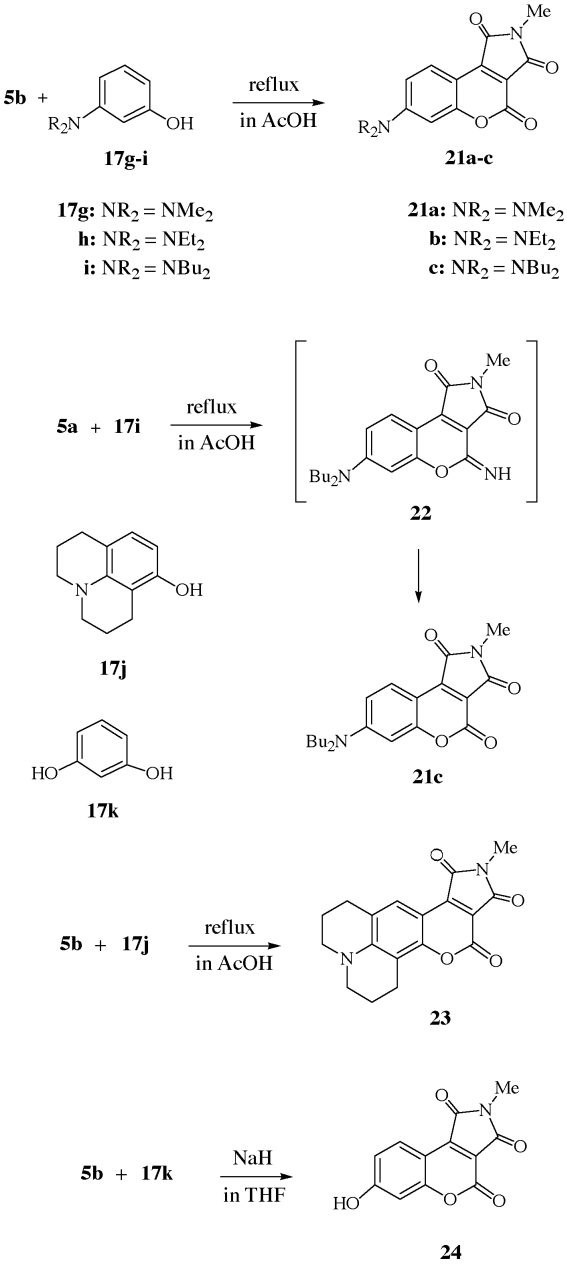
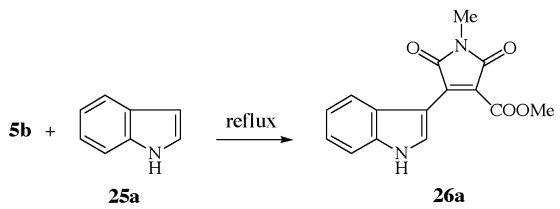


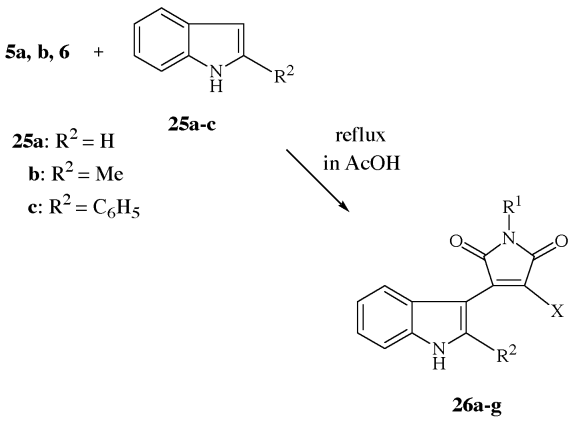
Table 8

Reaction of 5b with indole(26a)



Entry	Solvent	Reaction condition	Time (h)	Yield (%)
1	AcOH	reflux	2	91
2	Toluene	reflux	8	11
3	MeOH	reflux	9	17
4	DMF	reflux	7	35
5	Methyl Cellosolve	reflux	3	34
6	Toluene	BF_3·OEt	9	19

Scheme 7



26a: R^1 = Me, R^2 = H, X = COOMe
b: R^1 = Me, R^2 = Me, X = COOMe
c: R^1 = Me, R^2 = C_6H_5, X = COOMe
d: R^1 = H, R^2 = H, X = COOMe
e: R^1 = Me, R^2 = H, X = CN
f: R^1 = Me, R^2 = Me, X = CN
g: R^1 = Me, R^2 = C_6H_5, X = CN

3. Reaction of 4-Methylthiomaleimides with Electron-rich Aromatic Heterocycles.

Indoles and indolizines are known as electron-rich aromatic heterocycles [15]. The electrophilic substitution reaction of these heterocycles under acidic reaction conditions occurs easily to give the desired product with good results.

In order to obtain the best results, various reaction conditions were tried in the reaction of **5b** with indoles. The reaction of **5b** with indole (**25a**) was selected as the model procedure to provide **26a**. For the best results, the reaction condition included heating in acetic acid (See Table 8). The reaction of indole derivatives [indole (**25a**), 2-methylindole (**25b**), 2-phenylindole (**25c**)] with maleimides (**5a**, **b**, **6**) under refluxing in acetic acid gave the corresponding 3-substituted products (**26a-g**) in the yields shown in Table 9. Compound **26d** was obtained in low yield.

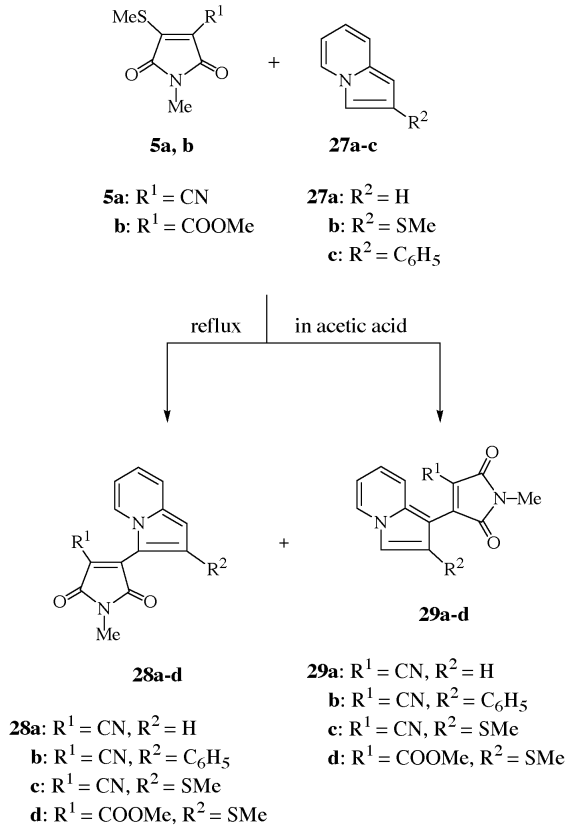
Table 9
4-(Indol-3-yl)-2,5-dioxo-1*H*-pyrroles(26a-g)

No	Yield(%)	mp(°C)	λmax/nm(log ε) (in EtOH)
26a	91	250-252	456(4.13)
b	64	201-204	485(3.92)
c	39	228-230	493(3.79)
d	26	281-283	444(4.07)
e	86	308-311	470(4.28)
f	78	264-266	497(4.08)
g	40	326	504 [a]

[a] Insufficient solubility.

Indolizines, which are peripheral conjugate aromatic compounds with delocalized 10π-electrons, are interesting hetero aromatic compounds from both theoretical and practical standpoints [16]. However, their potential to act as key compounds for the synthesis of dyes and pigments is less recognized, and they have not been widely used. Maleimides (**5a** and **b**) have previously been found to be very highly active electrophilic reagents. We show here the reaction of various indolizines with **5a** and **b** under the influence of acetic acid to give a new class of methine dyes bearing indolizin-1-yl or –3-yl groups as electron-donating groups with good results.

Scheme 8



5a, b **27a-c**

5a: R^1 = CN
b: R^1 = COOMe

27a: R^2 = H
b: R^2 = SMe
c: R^2 = C_6H_5

28a-d **29a-d**

28a: R^1 = CN, R^2 = H
b: R^1 = CN, R^2 = C_6H_5
c: R^1 = CN, R^2 = SMe
d: R^1 = COOMe, R^2 = SMe

29a: R^1 = CN, R^2 = H
b: R^1 = CN, R^2 = C_6H_5
c: R^1 = CN, R^2 = SMe
d: R^1 = COOMe, R^2 = SMe

Compound **5a** reacted with unsubstituted indolizine (**27a**) under refluxing in the presence of acetic acid in toluene for 4 hours to give a separable mixture of 4-indolizin-3-yl-1-methyl-2,5-dioxo-1*H*-pyrrole-3-carbonitrile (**28a**) and 4-indolizin-1-yl-1-methyl-2,5-dioxo-1*H*-pyrrole-3-carbonitrile (**29a**) in 93 and 2% yields, respectively. The color of a DMSO solution of **28a** was very brilliant violet. The UV/V spectrum of **28a** appeared at 551 nm (log ε 4.39) and showed a more bathochromic shift than that of **18a** (543 nm: log ε 4.85). The color of a DMSO solution of **29a** was very brilliant violet. The UV/V spectrum of **29a** appeared at 533 nm (log ε 4.00). The reaction of **5a** with other 2-substituted indolizines (**27b, c**) under the same reaction conditions also gave each separable mixture of the corresponding 3-(2-substituted indolizin-3-yl)-1-methyl-2,5-dioxo-1*H*-pyrrole-3-carbonitriles (**28b, c**) and 3-(2-substituted indolizin-1-yl)-1-methyl-2,5-dioxo-1*H*-pyrrole-3-carbonitriles (**29b, c**) in good yields. The UV/V spectrum of **28c** showed at 554 nm with small bathochromic shift due to the donating effect of the methylthio group at the 2-position on the indolizine ring. Similarly, methyl ester (**5b**) also reacted smoothly with 2-methylthioindolizine under similar reaction conditions to give a mixture of **28d** and **29d**, which were not separated by any methods.

Benzannulated indolizine, 2-methylthiopyrrolo[2,1-*a*]-isoquinoline (**27d**) also reacted with **5a** and **5b** under similar reaction conditions to give the corresponding electrophilic substituted products (**30a** and **b**) at the 1-position of the indolizine ring with good results. These UV/V spectra showed at 548 and 547 nm, respectively, indicating that there was no benzannulated effect on indolizine ring.

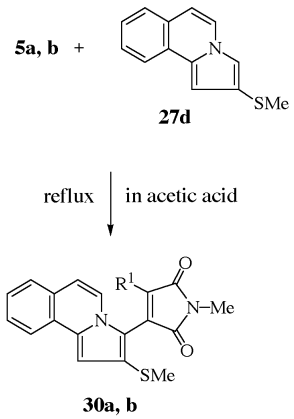
It is well known that the dialkyl amino group on aromatic or heteroaromatic compounds show a large bathochromic effect, as previously mentioned [17]. When 7-dimethylaminoindolizine (**27d**) was allowed to react with **5a** under refluxing in the presence of acetic acid in toluene solution, an expected product, 3-(7-dimethylaminoindolizine-3-yl)-1-methyl-2,5-dioxo-1*H*-pyrrole-3-carbonitrile (**28e**), was obtained in 78% yield, along with a trace of **31a** which could not be separated from the reaction mixture because of the very low yield. In the case of the reaction of 7-dimethylamino-2-methylthioindolizine (**27e**) with **5a** under the same reaction conditions a mixture of **28f** and **31b** was obtained in a 1: 2 ratio. Although these reactions were carried out in only acetic acid, the products were respectively each only disubstituted compounds (**31a**, **b**) that were obtained by the simultaneous substitution reaction at the 1 - and 3-positions on the indolizine ring. In

this reaction, monosubstituted products like compound **28** were not present in any of the reaction mixtures. When **27b** and **c**, bearing a methylthio group at 2-position on the indolizine ring, were used, the formation of **29b** and **c** increased in comparison with the previous reaction of **5a** with **27a**. Compound **28e** exhibited a brilliant blue color in dimethyl sulfoxide solution and showed at 601 nm (log ε: 4.53) in the UV/V spectrum. Even 7-dimethylaminoindolizine (**27g**) bearing a cyano group as an electron-withdrawing group at the1-position on the indolizine ring was allowed to react with **5a** and **b** to give the corresponding maleimide derivatives (**28g**, **h**) in 64 and 65% yields, respectively. These compounds are brilliant blue dyes showing at 634 (log ε: 4.36) and 627 (log ε: 4.23) nm in the UV/V spectra. In a similar manner, the reaction of ethyl 7-dimethylaminoindolizine-3-carboxylate (**27h**) with **5a**, **b** under refluxing in acetic acid solution gave the corresponding indolizin-1-ylmaleimide derivatives (**29e-g**) in good yields. The reaction of 7-dimethylamino-2-methylthioindolizine-3-carbonitrile (**27i**) with **5a** occurred smoothly to give a desired blue dye (**29h**) in 93% yield.

The reaction of indolizines with **5a**, **b** in the presence of acetic acid gave the expected brilliant violet or blue dyes based on indolizine chemistry. A dimethylamino group at the 7-position and the withdrawing groups like cyano or ester groups at the1- or 3-position on the indolizine ring showed effectively bathochromic shifts. The results of this investigation suggest considerable potential for the preparation of dyes bearing an indolizine ring.

Cycl[2.2.3]azine, a derivative of indolizine with one more fused pyrrole ring, is a particularly interesting aromatic compound possessing 10 π-electrons and conforming to Hückels' rule [18]. It is also known that the protonation, nitration, and acetylation of [2.2.3]cyclazine under Fridel-Crafts conditions occurs smoothly at the 1-position in accordance with the results of localization-

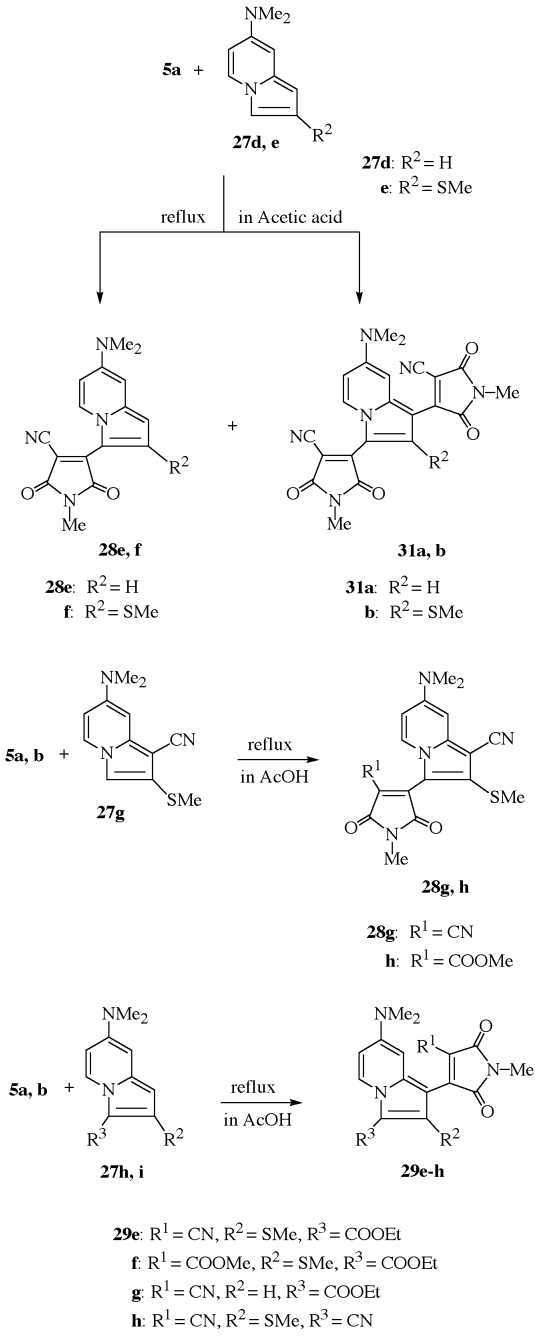
Scheme 9



30a, b

a: R^1 = CN
a: R^1 = COOMe

Scheme 10



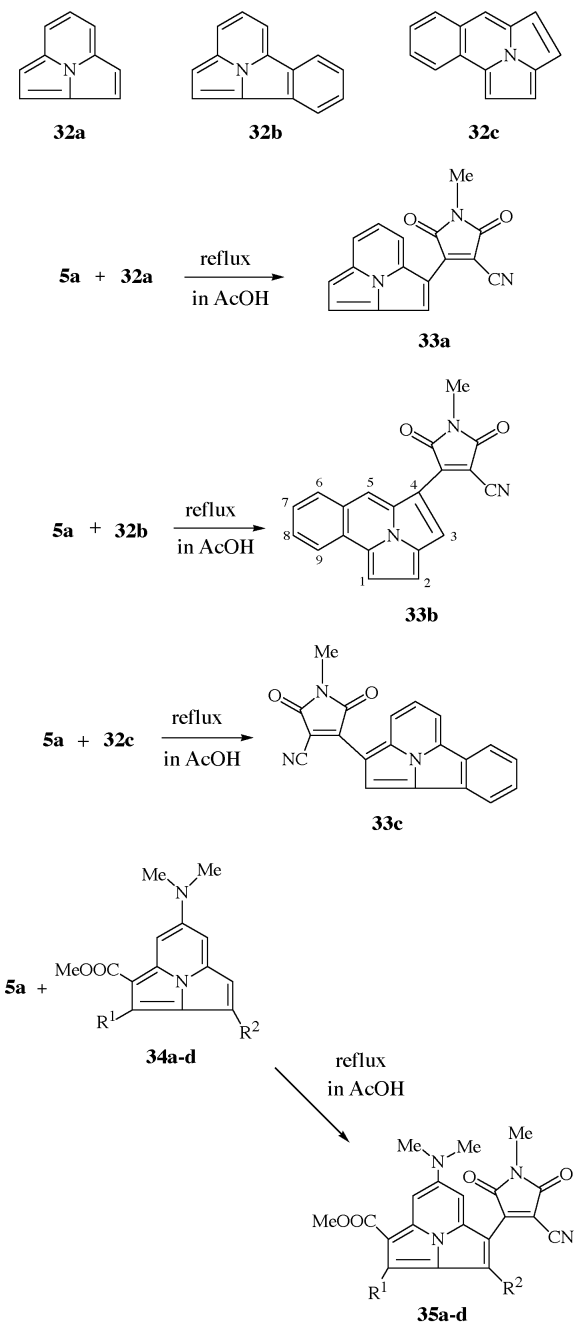
energy calculations. Whatever literature we may examine, we find that the reaction of cyclazines with unsaturated compounds bearing strongly electron-withdrawing groups such as teteracyanoethylene, has not yet been touched upon. This section presents the electrophilic substitution reaction of cyclazines with **5a** to give 4–cyclazinyl-2,5-dioxo-1*H*-pyrrole-3-carbonitriles that are dyes and to know whether cyclazine is an electron rich aromatic compound or not.

Compound **5a** reacted with [2.2.3]cyclazine (**32a**) under refluxing in acetic acid for 11 hours to give 4-([2.2.3]-cyclazin-1-yl)-2,5-dioxo-1*H*-pyrrole-3-carbonitrile (**33a**) as dark red needles, in 78% yield. The color of a DMSO solution of **33a** is very brilliant red. The long wavelength in the UV/V spectrum of **33a** appeared at 513 nm (log ε 4.52) and showed a larger red shift than that of **18a** (543 nm: log ε 4.85).

Benzoannulated [2.2.3]cyclazines (**32b**, **c**) present decreased diatropicity as compared to the corresponding nonbenzannulated parent system (**32a**) based on the results of NMR studies [19]. The reaction of benzo[*a*][2.2.3]-cyclazine (**32b**) with **5a** under refluxing in acetic acid for 9 hours gave 4-(benzo[*a*][2.2.3]cyclazin-2-yl)-1-methyl-2,5-dioxo-1*H*-pyrrole-3-carbonitrile (**33b**) as dark brown needles, mp 310-315 °C, in 82% yield. In a similar manner, the reaction of benzo[*g*][2.2.3]cyclazine (**32c**) with **5a** smoothly occurred to give 4-(benzo-[*g*][2.2.3]cyclazin-4-yl)-1-methyl-2,5-dioxo-1*H*-pyrrole-3-carbonitrile (**33c**) as dark violet needles, in 78% yield.

When methyl 6-dimethylamino[2.2.3]cyclazine-1-carboxylate (**34a**) was allowed to react with **5a** under refluxing in acetic acid for one hour, the expected product 3-(6-dimethylamino-1-methoxycarbonyl[2.2.3]cyclazin-4-yl)-1-methyl-2,5-dioxo-1*H*-pyrrole-4-carbo-nitrile (**35a**), was obtained in 42% yield. In a similar manner, the reaction of methyl 3-methylthio-6-dimethylamino[2.2.3]cyclazine-1-carboxylate (**34b**) with **5a** gave the desired product (**35b**) as black needles, in 86% yield. Even the reaction of diester compounds (**35c, d**) with **5a** readily occurred under refluxing in acetic acid for 7 or 16 hours to give the corresponding desired products (**35c**, **d**) in 54 and 29% yields, respectively. Compounds **35a-d** showed a brilliant blue color in DMSO solution and showed at 590-624 nm (log ε: 4.18-4.37) in the UV/V spectra. [2.2.3]Cyclazine,

Scheme 11



35a: R^1 = H, R^2 = H, mp 315-318°, Yield 42%
b: R^1 = H, R^2 = SMe, mp 243-2458°, Yield 86%
c: R^1 = COOMe, R^2 = H, mp 320-324°, Yield 54%
d: R^1 = COOMe, R^2 = SMe, mp 234-235°, Yield 29%

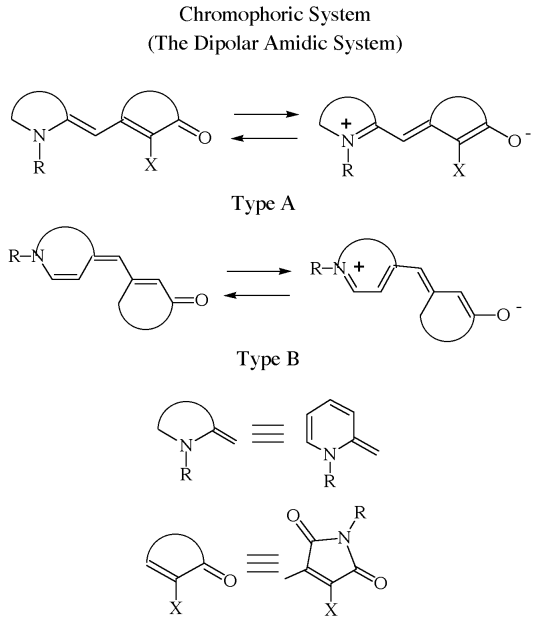


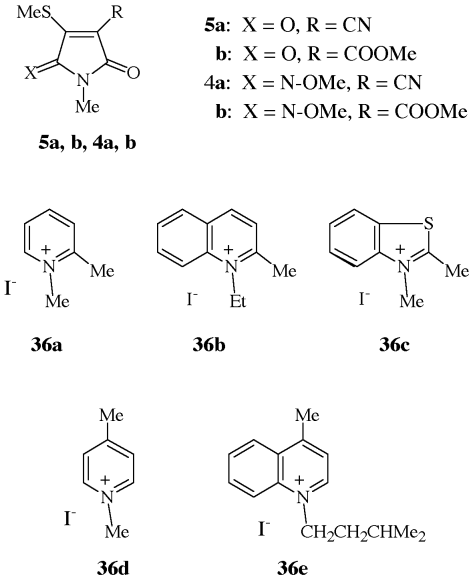
Figure 4

benzo[*a*][2.2.3]cyclazine, and benzo[g][2.2.3]cyclazine behave primarily as a very reactive electron-rich aromatic compound towards electrophilic reagent **5a**. A dimethylamino group on the [2.2.3]cyclazine ring greatly contributes to the bathochromic shift. The results of this investigation suggest considerable potential for the preparation of dyes bearing a cyclazine ring.

4. Synthesis of a Merocyanine Class of Dyes Bearing a Maleimide Ring Incorporated into the Methine Chains.

The present section describes the synthesis of new polymethine dyes with a pyrrole ring as a heterocycle incorporated into the methine chain, as shown in Figure 4 [20]

Methylene bases prepared from the corresponding quaternary salts were recognized early as nucleophilic reagents with reactivities paralleling the Brooker derivatives of the basic heterocycles. The reaction of 2-picolinium methiodide (**36a**) with **5a** in the presence of potassium carbonate as a base in dimethyl sulfoxide at room temperature gave a red violet product, **37a** in 47% yield. Compound **36a** also smoothly reacted with **5b** bearing a methyl ester group to give the corresponding polymethine dye (**37b**) in 39% yield. The reaction of quinaldine ethiodide (**36b**) with **5a** under the same reaction conditions gave the corresponding methine dye **37c** in 89% yield. The other polymethine dyes (**37c-n**) were also readily obtained by the reaction of the corresponding quaternary salts (**36c-e**), giving the corresponding polymethine dyes **37c-n** in good yields as shown in Table 10. Abosorption maxima of **Type B** are expected to show bathochromic shift against **Type A** because of the elongation of π-conjugation compared to **37a-h**. For instance, **37i** exhibited a 21 nm bathochromic



5a: X = O, R = CN
b: X = O, R = COOMe
4**a**: X = N-OMe, R = CN
b: X = N-OMe, R = COOMe

5a, b, 4a, b

36a **36b** **36c**

36d **36e**

Figure 5

Scheme 12

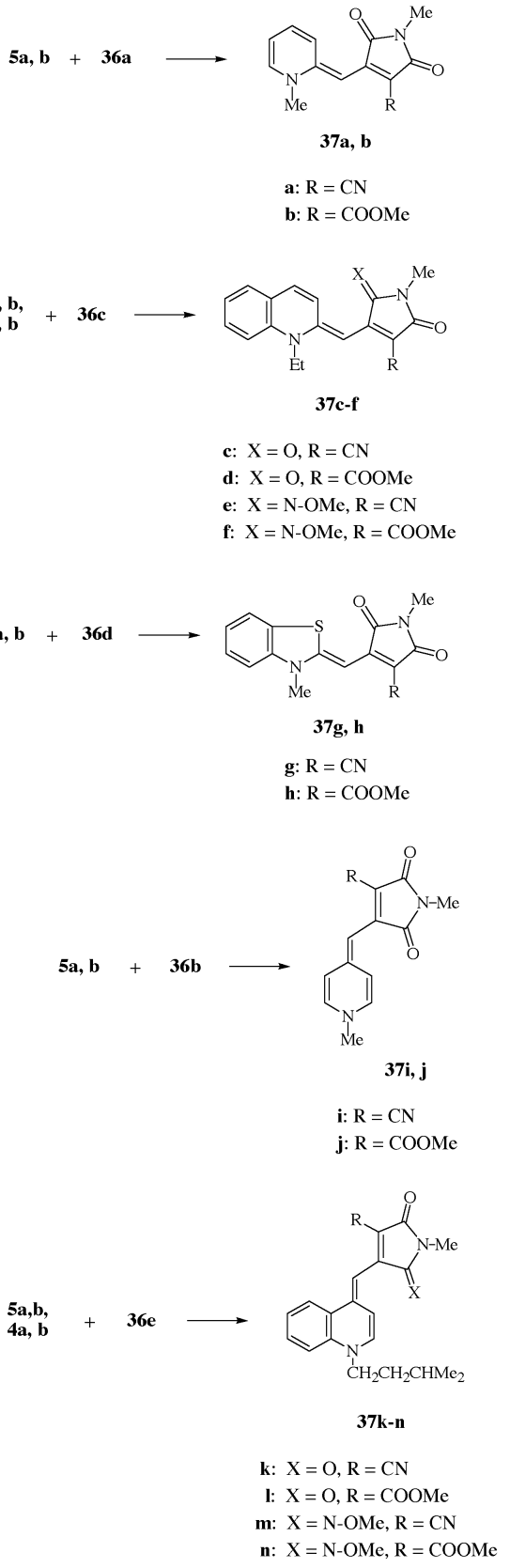


Table 10

Yields, Mp, Appearance, and Color of solution, UV/V spectra, and Theoretical excitation energiesof Poly Methine Dyes

Compound	Yield(%)	mp(°C)	Appearance	Color of DMSO solution	UV/V λ max (EtOH) nm(log ε)	Ecalc(nm) (f)
37a	47	276-279	dark red needles	wine red	524 (4.32)	534 (0.643)
b	39	256-258	greenish black needles	wine red	535 (4.46)	519 (0.728)
c	81	294-296	green needles	blue	574 (4.69)	552 (0.725)
d	66	120-122	greenish black needles	blue	563 (4.55)	532 (0.693)
e	94	210-212	green prisms	purple	578 (4.75)	502 (0.475)
f	98	137-139	black needles	wine red	566 (4.86)	532 (0.306)
g	92	329-330	black violet needles	wine red	542 (4.59) [a]	467 (0.406)
h	88	315-318	black needles	purple	546 (4.73)	485 (0.446)
i	92	313-315	black needles	blue	545 (4.51)	523 (0.657)
j	80	263-265	black violet needles	wine red	534 (4.47)	537 (0.586)
k	97	235-237	dark greenish leaflets	blue	604 (4.77)	565 (0.104)
l	87	204-206	dark violet needles	blue	595 (4.62)	544 (0.683)
m	86	203-205	dark violet leaflets	blue	614 (4.92)	501(0.406)
n	86	158-160	golden yellow needles	blue violet	587 (4.61)	511 (0.292)

[a] Solvent was DMSO; f: oscillator strength.

shift compared to the corresponding compound **37a**. Among the compounds **37a-n**, compound **37m** showed the largest bathochromic shift, suggesting that it could be promising for medical use such as a chromogenic reagent in clinical diagnosis.

We carried out molecular orbital calculations for the molecules in question to elucidate the UV/V is absorption properties [21]. It is well known that at simple PPP MO calculation including only π-electrons predict an λ max for merocyanines that is considerably shorter than is obtained experimentally [21]. In our INDO/S calculation, which consider up to σ-electrons, reasonable agreement between theoretical and experimental λ max were obtained, excluding some exceptions like for compounds bearing the methoxyimino group (**36e, f, m, n**) and benzothiazole derivatives (**36g, h**), for which significantly short λ max values were predicted. The lowest excited state described best by HOMO-LUMO π-π* single electron excitation, indicating that the CI coefficients of HOMO-LUMO configuration in the ground states of **37a** and **37**e are 0.969 and 0.954 respectively. In common with compounds **37a-n**, their HOMOs were found to reside on the quinoline, benzothiazole, or pyridine moiety, while their LUMOs were found to be primarily localized on the maleimide ring, which means that the lowest excitation state of the molecule is primarily expressed by a charge transfer configuration between two bridged moieties, which is a commonly seen characteristic among merocyanine dyes [21]. The optimized bond lengths for the chains linking two moieties show that single-double bond alternations exist in the molecules whose merocyanine portions have quinoide rather than resonance structues in the ground states.

5. Syntheasis of Polycyclic Pyridazine-diones

Since its discovery by Albrecht in 1928, the analytical usefulness of the chemiluminescence (CL) of luminol has been the subject of extensive study [22]. CL of luminol has been developed not only for metal analysis of Co(II), Cu(II), Ni(II), Fe(II) and others, but has also been found

Scheme 13

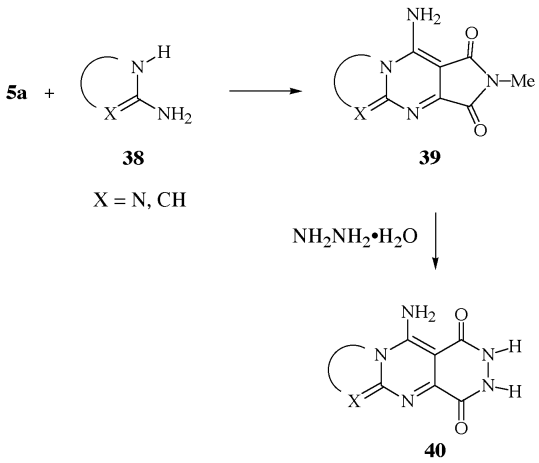
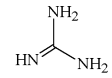
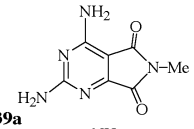
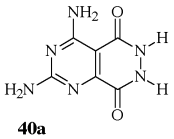
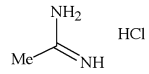
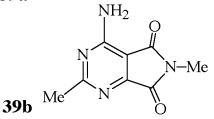
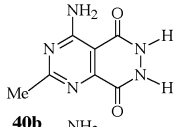
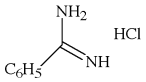
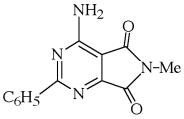
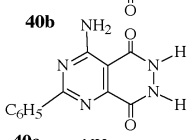
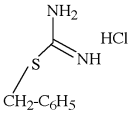
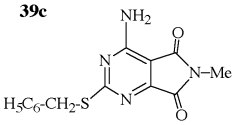
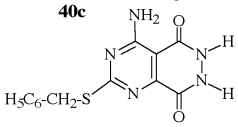
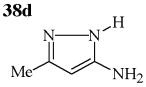
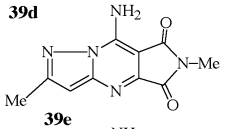
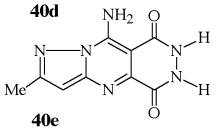
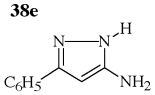
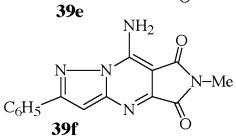
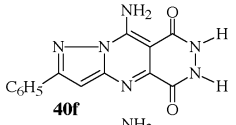
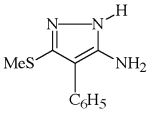
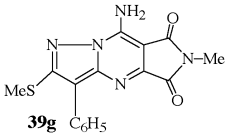
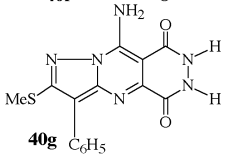
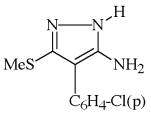
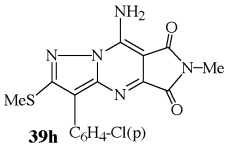
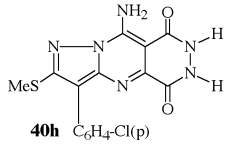
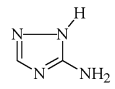
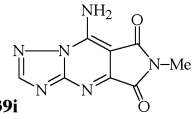
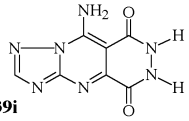
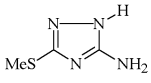
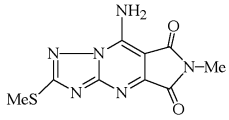
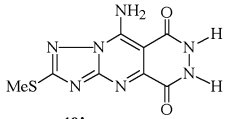
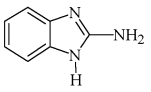
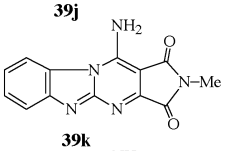
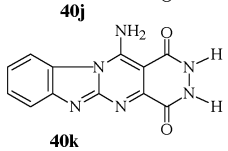
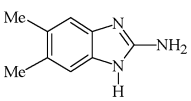
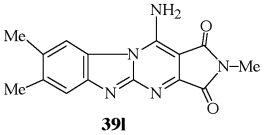
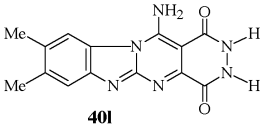


Table 11
Synthesis of Amino-polycyclic Pyrrolopyrimidines and Polycyclic Pyridazinedione Derivatives

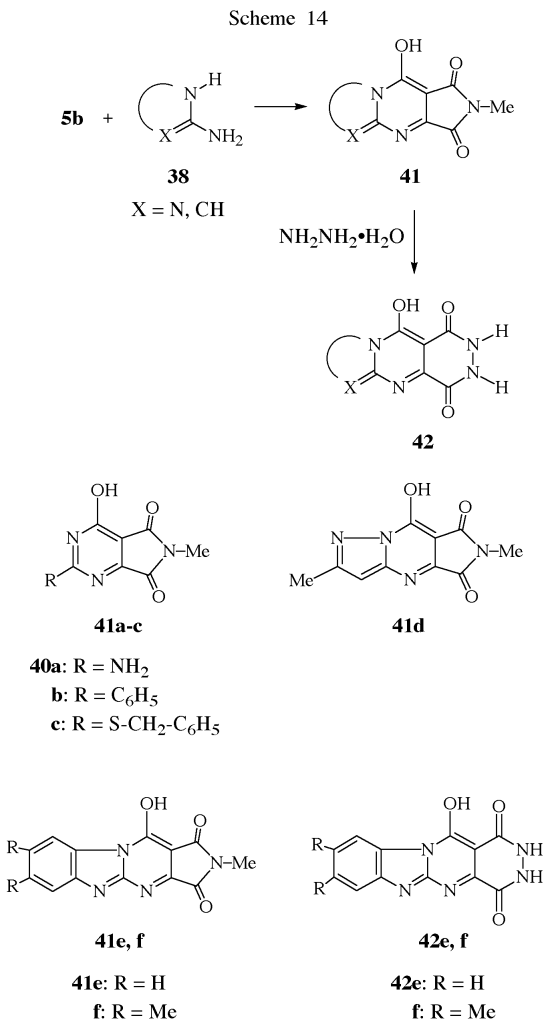
Entry	Amines	39	mp °C Yield	40	mp °C Yield
1	 **38a**	 **39a**	>360 74%	 **40a**	>360 62%
2	 **38b**	 **39b**	304-305 56%	 **40b**	>360 94%
3	 **38c**	 **39c**	236-237 84%	 **40c**	>360 99%
4	 **38d**	 **39d**	183-184 75%	 **40d**	320-325 79%
5	 **38e**	 **39e**	>360 91%	 **40e**	>360 98%
6	 **38f**	 **39f**	>360 91%	 **40f**	>360 87%
7	 **38g**	 **39g**	296-298 92%	 **40g**	>360 92%
8	 **38h**	 **39h**	351-352 86%	 **40h**	>360 98%
9	 **38i**	 **39i**	356-357 86%	 **39i**	>360 84%
10	 **38j**	 **39j**	357-359 94%	 **40j**	>360 94%
11	 **38k**	 **39k**	346-347 93%	 **40k**	>360 87%
12	 **38l**	 **39l**	>360 93%	 **40l**	>360 92%

ideal for application to clinical chemistry such as quantitative determination of blood glucose using enzyme-induced CL of luminol. The synthetic development of luminol derivatives and their analogs has been pursued actively to meet the requests of clinical analysts for something more useful than luminol

In the development of a new and efficient method for the synthesis of polycyclic pyridazinediones bearing an amino group, a convenient approach to the synthesis of an amino-polycyclic pyridazinedione nucleus is considered to be the the pathway illustrated in Scheme 13.

It is known that the reaction of ketene dithioacetal, **1a-d**, with bifunctionalized nucleophiles such as hydrazine or amidine derivatives gives the corresponding pyrazoles or pyrimidines in efficient yields [2d]. The reaction of **5a** with guanidine carbonate (**38**a), acetamidine hydrochlroride (**38b**), benzamidine hydrochloride (**38c**), and S-benzylisothiourea (**38d**), respectively in the presence of triethylamine under ethanol refluxing conditions gave 1,3-diamino-6-methyl-5,7-dihydropyrrolo[3,4-*d*]pyrimidine-5,7-diones (**39a-d**) in 56-84% yields. This method of preparation of pyrimidine derivatives is being applied to the synthesis of polycyclic pyrrolopyrimidine derivatives. The reaction of **5a** with amino-heterocycles (**39e-j**) under refluxing in ethanol gave aminopyrrolopyrimidinediones (**39e-j**) in good yields. In a four-ring system, pyrrolo-pyrimidobenzimidazole derivatives (**39k, l**) were also synthesized by the reaction of **5a** with 2-aminobenzimidazoles (**38k, l**) in good yields. The reaction of **39a-l** with hydrazine hydrate in ethanol afforded the corresponding polycyclic aminopyridazinediones (**40a-l**) in good yields as shown in Table 11 [23].

Scheme 14



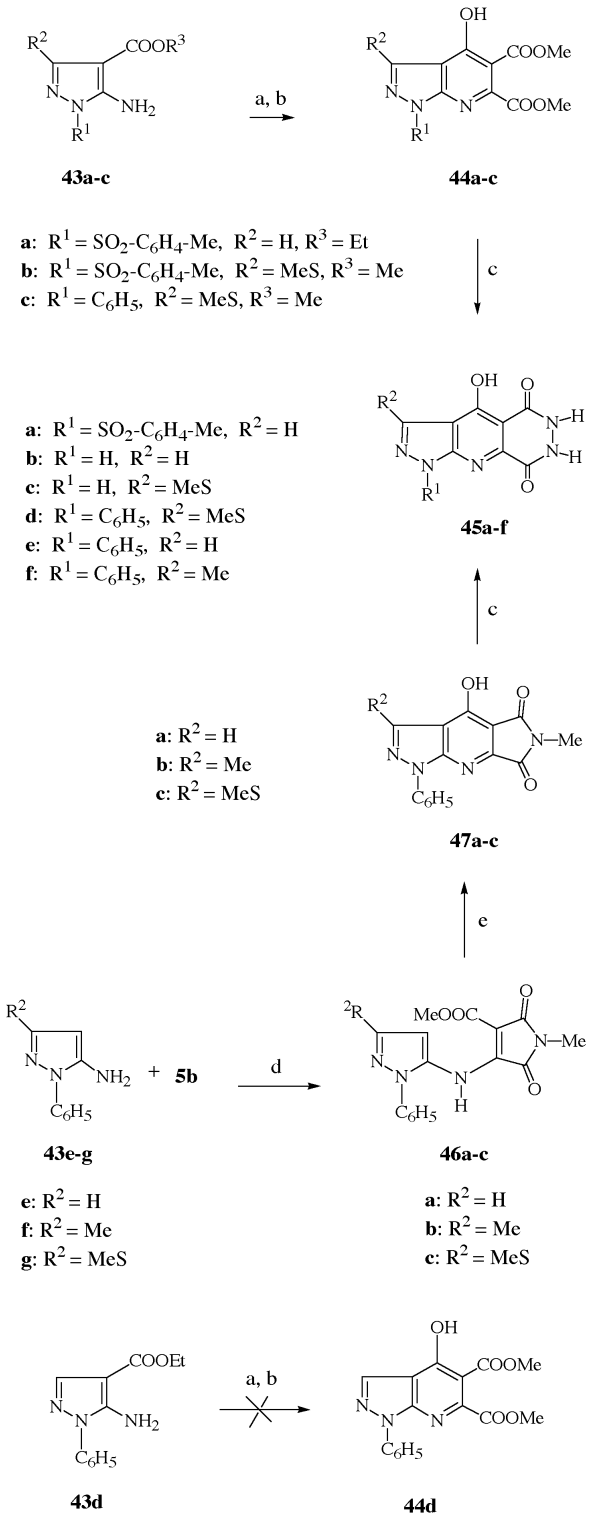
The reaction of ester compound **5b** with various amidine derivatives and 2-aminoheterocycles was occurred smoothly to give the corresponding hydroxy polycyclic heterocycles (**41**) which are also key intermediates for the preparation of chemiluminophores (**42**).

4-Amino-1*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazine-5,8(6*H*,7*H*)-diones have previously been shown to be more efficient than luminol in light production. The authors have directed attention to the chemiluminescence of the compounds bearing a hydroxy group instead of an amino group. In some cases, the hydroxy group was shown capable of affecting fluorescence and light production. No study on the CL of polycyclic pyridazinediones or related compounds bearing a hydroxy group have been conducted to date. Details regarding the CL of 1,3-disubstituted 4-hydroxypyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazine-5,8(6*H*,7*H*)-diones are presented.

The chemiluminescent compounds, 4-amino-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazine-5,8(6*H*,7*H*)-diones, were prepared from dimethyl 4-aminopyrazolo[3,4-b]pyridine-5,6-dicarboxylates obtained by reactions of 5-aminopyrazole-4-carbonitriles with dimethyl acetylenedicarboxylate (DMAD) in the presence of potassium carbonate as a base in DMSO [24]. This type of process was considered to be applicable to a synthesis of key compounds, dimethyl 4-hydroxypyrazolo[3,4-*b*]-pyridine-5,6-dicarboxylates. The reactions of ethyl 5-amino-4-carboxylates (**43a, b**) with DMAD in the presence of potassium carbonate as a base in DMSO gave the corresponding dimethyl 4-hydroxypyrazolo[3,4-*b*]pyridine-5,6-dicarboxylates (**44a, b**) in 61 and 48% yield, respectively. While the reaction of **43c** with DMAD gave the desired product (**44c**) in only 3% yield, the desired product (**44d**) could not be obtained at all from the reaction of ethyl 5-amino-1-phenylpyrazole-4-carboxylate (**43d**) with DMAD under the same conditions. 3-Unsubstituted 1-aryl compounds were not obtained by the this method.

To obtain the 3-unsubstituted 4-hydroxpyrazolopyrido-pyridazine-5,8-diones and to increase the yield of **44d**, an alternative method of synthesis for the pyrazolopyrido-pyridazine derivatives had to be established. The reaction of 5-amino-1-phenylpyrazole (**43e**) with 1-methyl-3-methylthio-4-methoxycarbonylmaleimide (**5b**) under refluxing in methanol gave the corresponding displacement product of the methylthio group (**46a**) in **5b**

Scheme 15



43a-c

44a-c

a: $R^1 = SO_2\text{-}C_6H_4\text{-}Me$, $R^2 = H$, $R^3 = Et$
b: $R^1 = SO_2\text{-}C_6H_4\text{-}Me$, $R^2 = MeS$, $R^3 = Me$
c: $R^1 = C_6H_5$, $R^2 = MeS$, $R^3 = Me$

a: $R^1 = SO_2\text{-}C_6H_4\text{-}Me$, $R^2 = H$
b: $R^1 = H$, $R^2 = H$
c: $R^1 = H$, $R^2 = MeS$
d: $R^1 = C_6H_5$, $R^2 = MeS$
e: $R^1 = C_6H_5$, $R^2 = H$
f: $R^1 = C_6H_5$, $R^2 = Me$

45a-f

a: $R^2 = H$
b: $R^2 = Me$
c: $R^2 = MeS$

47a-c

43e-g

46a-c

e: $R^2 = H$
f: $R^2 = Me$
g: $R^2 = MeS$

a: $R^2 = H$
b: $R^2 = Me$
c: $R^2 = MeS$

43d

44d

in 82% yield. The cyclization of **46a** by heating in diphenyl ether afforded 4-hydroxy-3-methyl-1-phenylpyrrolo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5,7-dione (**47a**) in 93% yield. In a similar manner, other compounds (**47b, c**) were readily obtained from the corresponding 5-aminopyrazole derivatives (**43f, g**) in 65% and 73% (from **43f, g**) yields, respectively.

Dimethyl 4-hydroxy-3-methylthio-1-phenylpyrazolo-[3,4-*b*]pyridine-5,6-dicarboxylate (**44a**) was refluxed with excess hydrazine hydrate in ethanol, followed by a removal of ethanol by distillation to give **45a** in 87% yield. When hydrazine hydrate was used in large excess, desulfonylation simultaneously occurred to give **45b** in 67% yield. In a similar manner, 4-hydroxy-3-methylthiopyrazolo[4',3':5,6]-pyrido[2,3-*d*]pyridazine-5,8-(6*H*,7*H*)-dione (**45c**) was obtained from **44b** in 62% yield. 1,3-Disubstituted compound (**45d**) was obtained from **44c** in 91% yield. Compounds **45d**, **e**, and **f** were synthesized by reactions of **47a-c** with hydrazine hydrate under refluxing in methanol in 78, 82, and 76% yields, respectively.

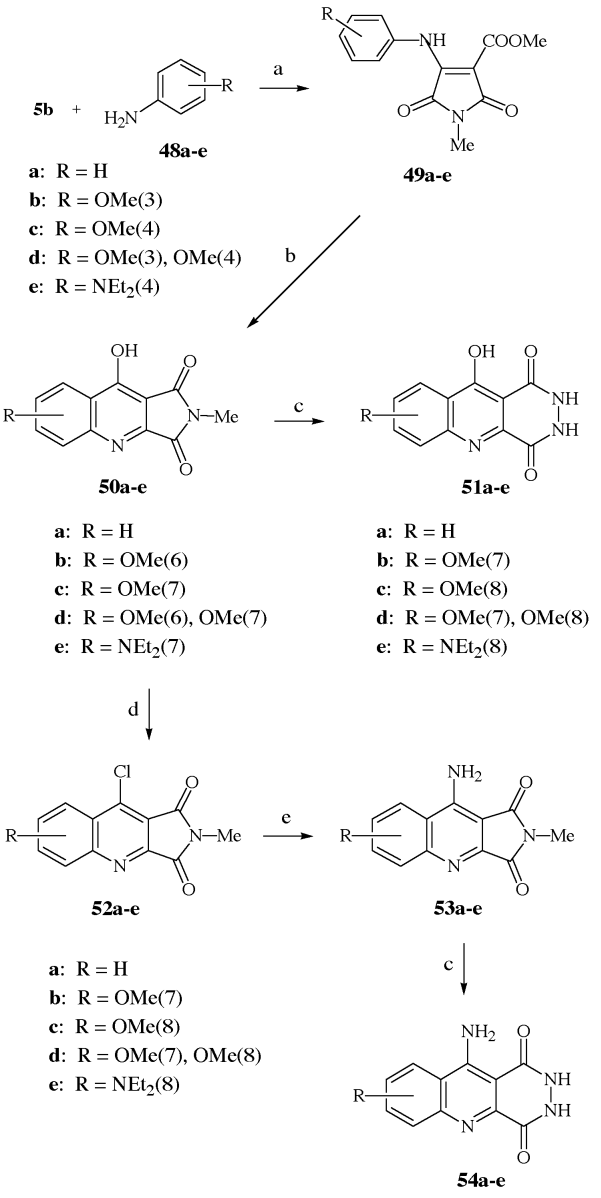
4-Hydroxy-1*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]-pyridazine-5,8(6*H*,7*H*)-diones (**45d-f**) showed nearly the same or somewhat stronger light intensity than luminol at pH 8.0. The unsubstituted compounds **3b, c** did not show CL at pH 8.0. Compounds **45a-f** also showed CL similar to luminol at pH 10.0. The aryl group at the 1-position is very important for CL production. These compounds showed increased light intensity with rises in pH, as also noted for luminol. The use of HRP (horseradish peroxidase) as POD (peroxidase) gave satisfactory results for CL production [25].

This section presents a synthesis of 10-hydroxy-pyridazino[4,5-*b*]quinoline-1,4(2*H*,3*H*)-diones and 10-aminopyridazino[4,5-*b*]quinoline-1,4(2*H*,3*H*)-diones as chemiluminescent compounds through the use of methyl 1-methyl-4-methylthio-2,5-dioxo-3-pyrroline-3-carboxylate (**5b**) [26].

The reaction of **5b** with various aniline derivatives (**48a-e**) in refluxing methanol readily gave the corresponding 3-phenylaminomaleimide derivatives (**49a-e**) in 85-98% yields, and those were smoothly converted in 73-97% yields to pyrrolo[3,4-*b*]quinolines (**50a-e**) under refluxing in diphenyl ether for one hour. The reaction of **50a-e** with a large excess of hydrazine hydrate afforded the corresponding polycyclic hydroxypyridazine-diones, 10-hydroxypyridazino[4,5-*b*]quinoline-1,4-(2*H*,3*H*)-diones (**51a-e**) in 72-97% yields.

The chlorination of **50a-e** with phosphorus oxychloride in the presence of diethylaniline was carried out to give the corresponding 9-chloro-2-methylpyrrolo[2,3-*d*]quinolines (**52a-e**), in 76-98% yields, which were converted to the expected 9-amino-2-methylpyrrolo[2,3-*d*]quinolines (**53a-e**) in 54-82% yields by ammonolysis with 28% ammonium hydroxide at 180 °C in a mini autoclave. The desired 10-aminopyridazino[4,5-*b*]quinoline-1,4(2*H*,3*H*)-dion derivatives (**54a-e**) were readily obtained in 70-93%

Scheme 16



a: reflux in methanol for 30 min -1h; b: reflux in dipheny ether for 1 h; c: reflux in a large excess of NH_2-NH_2•H_2O; d: $POCl_3$ + *N*,*N*-diethylaniline; e: 28% NH_4OH, 180°C in mini autoclave.

yields, respectively, by the general reaction of compounds **53a-e** with a large excess of hydrazine hydrate under refluxing.

Both 10-hydroxy- and 10-aminopyridazino[4,5-*b*]-quinoline-1,4(2*H*,3*H*)-dione derivatives (**51a-d**, **54a-d**) showed nearly the same or somewhat stronger light intensity than luminol at pH 8.0. These compounds also showed increasing light intensity with rises in pH, as noted

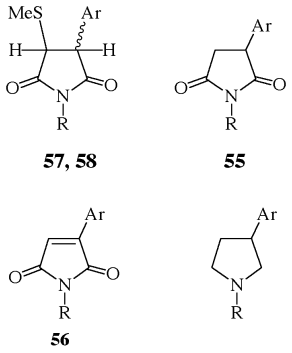
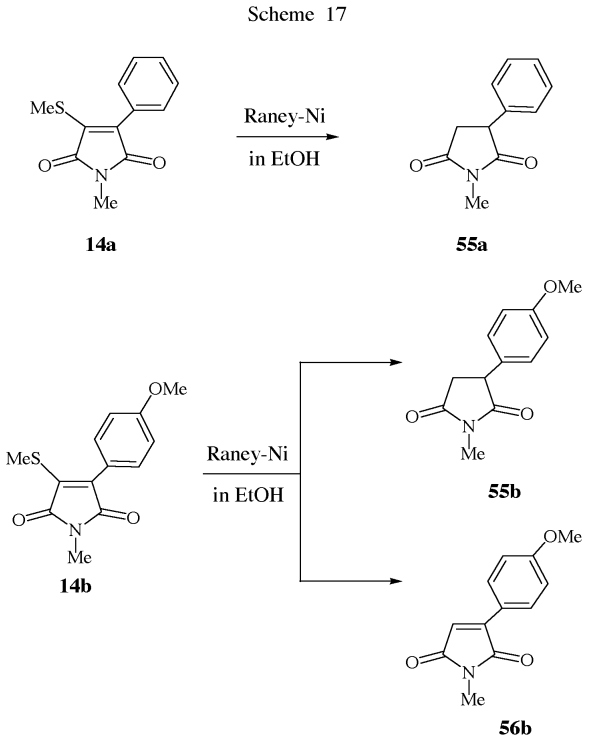


Figure 6

also for luminol. The methoxy and diethylamino groups on the quinoline ring are very important groups for CL production [26].

Scheme 17

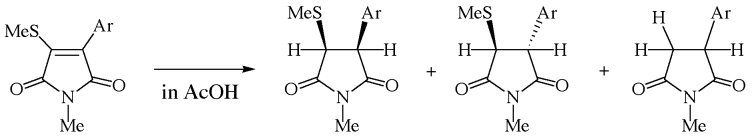


6. Synthesis of Succimides by the Reduction of Maleimides.

Succimides obtained by the reduction of maleimides derivatives are very important as starting materials of natural products like mesembrine and pharmacologically active compounds like methsuximide [27].

Desulfurization of organic compounds with Raney nickel is an old reaction with widespread application [28]. The reduction of **14a** with Raney-nickel (W-2) in reflux ethanol gave only 3-phenylsuccinimide

Table 12
Reduction of 5-Aryl-4-methylthiomaleimides with Metals



14a **57a** **58a** **55a**

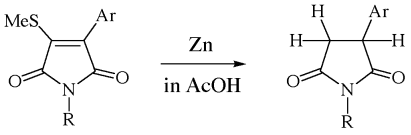
Entry	Metal(equiv.)	Solvent	R.T	**57a**	**58a**	**55a**	Yield(%)
1	Zn(1.5)	AcOH	2 hr	39	20	20	--
2	Zn(3.0)	AcOH(r.t)	1 hr	53	22	25	--
3	Zn(5.0)	AcOH(r.t)	1 hr	53	24	23	-
4	Zn(10.0)	AcOH(r.t)	10 min	15	9	76	--
5	Zn(5.0)	AcOH + EtOH(0°)	10 min	53	23	20	--
6	Zn(3.0)	AcOH+ EtOH(0°)+ H_2O	10 min	81	14	5	--
7	Zn(3.0)	AcOH + EtOH+H_2O(-20°)	10 min	84	16	0	83
8	Zn(3.0)	MeOH +AcOH+ H_2O(0°C)	10 min	91	9	0	82
9	Zn(10.0)	AcOH(reflux)	45 min	0	0	100	92
10	Ni(20.0)	EtOH (reflux)	5 hr	0	0	100	28
11	Ni-Al(10.0)	AcOH (reflux)	1 hr	0	0	100	62
12	Zn(3.0)	EtOH(reflux)	1 hr	0	0	0	0

(1-methyl-3-phenyl-3,4-dihydropyrrole-2,5-dione) (**55a**) in 28% yield. In the case of the reduction of *p*-methoxyphenyl derivatives (**14b**) with Raney-nickel, a mixture of **55b** and desulfurized product **56b** was obtained in quite low yields (See Scheme 17).

Zinc in acetic acid is applicable to a wide range of reduction reactions [29]. This reagent has also been chosen to demonstrate selective reduction in sensitive, poly-functional molecules and has successfully reduced heteroatom substitutes. At the out set of the work, the reduction of malimides with zinc and other metals has been explored in detail under various reaction conditions as shown in Table 12. By using a general method shown in Table 12 (Entry 9), the reduction of **14a** employing zinc dust in acetic acid at reflux afforded the corresponding 3-phenylsuccinimide (**55a**) in 92% yield. In a similar manner, other succinimide products (**55b-I**) were obtained from the corresponding maleimides (**13**, **14**) in good yields, as shown in Table 13. These succinimides (**55a-d**) were also obtained from the corresponding hydroxy imino compounds (**12**) in good yields as shown in Table 14. The intermediates in this reaction are imino compounds that are readily converted to carbonyl compounds formed by hydrolysis.

When a reduction of **14a** with zinc dust in acetic acid was carried out at room temperature, a mixture of three compounds, **55**, **57**, and **58**, were obtained. Analysis by ^{1}H nmr

Table 13
Synthesis of 4-Arylsuccinimides
from 4-Arymaleimides by Zinc Reduction [a]



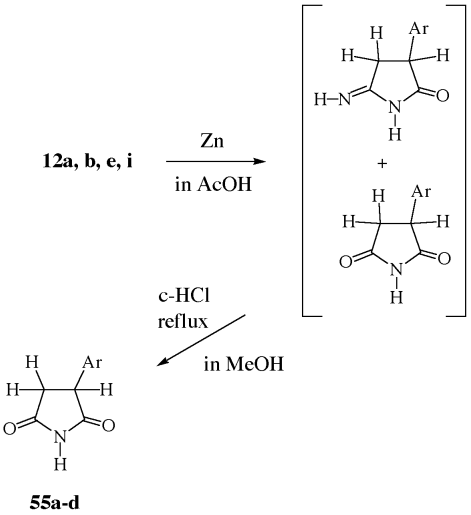
13, 14 **55a-i**

No.	R	Ar	mp(°C)	Yield(%)
55a	H	C_6H_5	68-69	98
b	H	C_6H_4-OMe(4)	128-129	92
c	H	C_6H_4-Cl(4)	130-131	92
d	H	Naphthyl	134-135	97
e	Me	C_6H_5	54-55	93
f	Me	C_6H_4-OMe(4)	114-115	85(32) [b]
g	Me	C_6H_4-Cl(4)	97-98	82
h	Me	Naphthyl	97-98	82
i	Me	2-Thienyl	75-76	83

[a] All reactions were carried out in a system of **13**, **14** (1.0 mmol), and Zinc dust (5.0 mmol) in acetic acid (20 ml) under reflux for 1 hour; [b] This yield was obtained by using Raney-Ni.

Table 14

Reduction of 5-Aryl-3-hydroxyimino-4-methylthiomaleimides with Metals

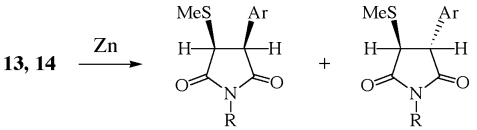


55a-d

No.	R	Ar	mp(°C)	Yield(%)
55a	H	C_6H_5	68-69	71
b	H	C_6H_4-OMe(4)	128-129	74
c	H	C_6H_4-Cl(4)	130-131	72
d	H	Naphthyl	134-135	91

Table 15

Reduction of 5-Aryl-4-methylthio-maleimides with Zinc Dust [a]



57a-h **58a-h**

No.	R	Aryl	**57**	**58**	Yield(%)
a	H	C_6H_5	86(54)	14(46)	75(72) [b]
b	H	C_6H_4-OMe(4)	93	7	92
c	H	C_6H_3-OMe_2(3,4)	89	11	81
d	H	C_6H_4-Cl(4)	80	20	85
e	Me	C_6H_5	91	9	82
f	Me	C_6H_4-OMe(4)	90	10	87
g	Me	C_6H_3-OMe_2(3,4)	90	10	86
h	Me	C_6H_4-Cl(4)	78	22	79

[a] Reaction solvent was a mixture of acetic acid and methanol; [b] All reactions were carried out in a system of **13**, **14** (1.0 mmol), and Zinc dust (3.0 mmol) in a mixture of acetic acid (10 ml), methanol (10 ml), and water (1-3 ml) at room temperature.

Scheme 18

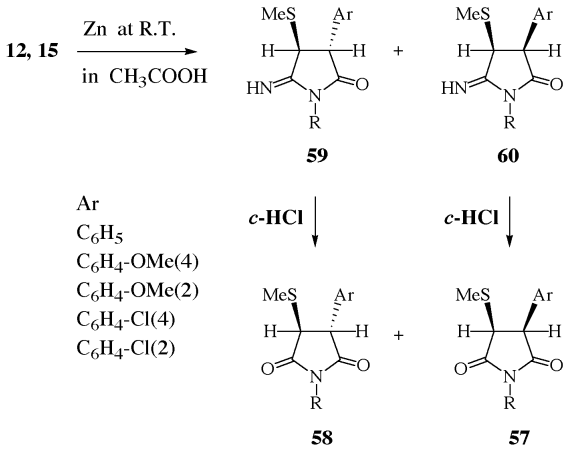
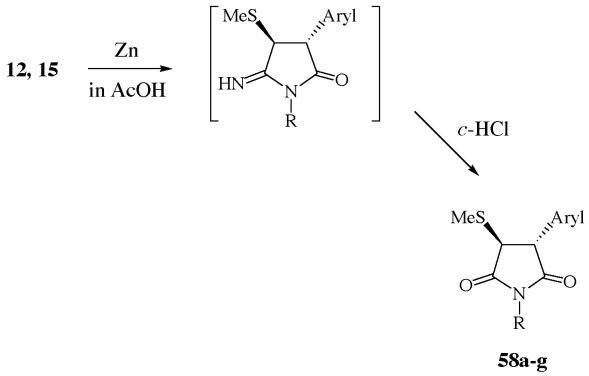


Table 16

Reduction of 5-Aryl-4-methylthio-maleimides with Zinc Dust



58a-g

No.	R	Ar	mp(°C)	Yield(%)
58a	H	C_6H_5	132-133	79
b	H	C_6H_4-OMe(4)	83-84	57
c	H	C_6H_4-OMe(2)	120-121	75
d	H	C_6H_4-Cl(4)	131-132	77
e	H	C_6H_4-Cl(2)	98-99	79
f	Me	C_6H_5	59-60	67
g	Me	C_6H_4-OMe(4)	oil	45

[a] Reaction solvent was a mixture of acetic acid and methanol; [b] All reactions were carried out in a system of **12**, **15** (1.0 mmol) and Zinc dust (3.0 mmol) in a mixture of acetic acid (10 ml), methanol (10 ml), and water (1-3 ml) at room temperature.

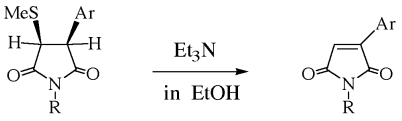
indicated that these were formed as a mixture of *cis* and *trans* isomers and succinimide. The typical coupling constant of 8.9-9.2 Hz observed between H3 and H4 ($J_{3,4}$) indicated that

the 4-phenyl group and the 3-methylthio substituent are in the *cis* configuration for each of the major isomers formed, with the $J_{3,4}$ for the minor isomers formed(4.8-6.0 Hz) being in accord with a *trans* disposition for these substituents (Shown at entry 1-4 in Table 12). The problem of stereoselectivities for the obtained *cis* isomer was eliminated by using a mixture of acetic acid and ethanol or methanol as a solvent at room temperature. In particular, as shown in entry 8, this reduction of **14a** with zinc dust gave *cis* isomer **55a** as a major product (ratio; *cis*: *trans* = 91:9) in 82% yield. The reduction of **13**, **14** with zinc dust in a mixture of water, methanol, and acetic acid at room tempaerature gave the corresponding *cis* isomers as a primary product with excellent stereoselectivities in good yields (See Table 15).

In contrast, the reduction of hydroxyimino and methoxyimino compounds (**12**, **15**) with zinc dust in acetic acid at room temperature gave *trans* isomers of imino compounds (**59**, **60**) with excellent stereoselectivity (trans: *cis* = 93:7). These imino compounds were easily converted into the corresponding carbonyl compounds (**58** and **57**). Actually, the reaction involves *cis* addition and isomerization through the amino group to the more stable *trans* products. Table 16 shows the results for the isolated yields of the *trans* isomers.

The reductive products (**57**) were treated with triethylamine as a base in ethanol at reflux, affording the desulfurization products (**56a-h**) in good yields as shown in Table 17.

Table 17
Elimination of Methylmercaptan from
5-Aryl-4-methylthiosuccinimides [a]

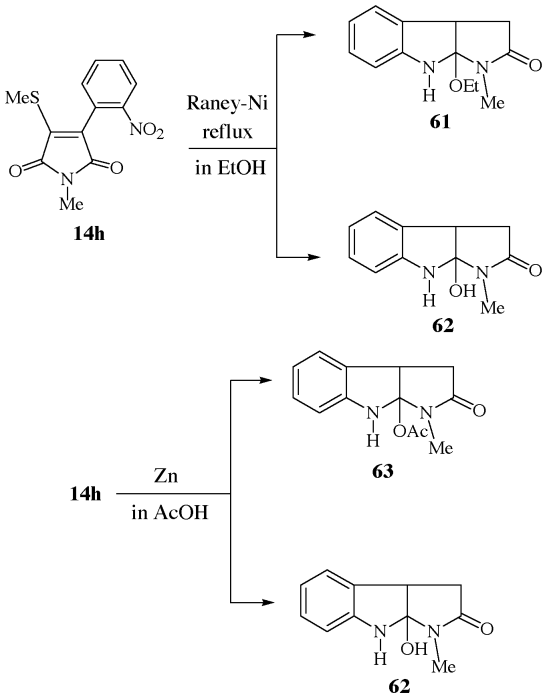


57 **56a-h**

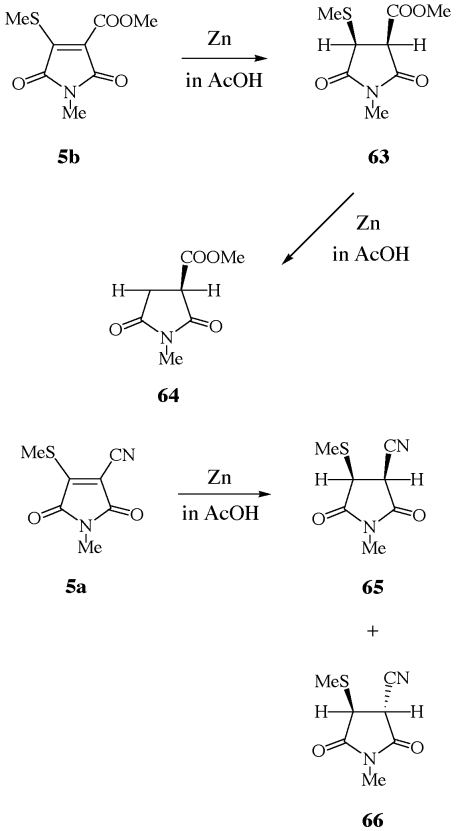
No.	R	Aryl	mp (°C)	Yield(%)
a	H	C_6H_5	150-151	98
b	H	C_6H_4-OMe(4)	194-195	92
c	H	C_6H_3-OMe_2(3,4)	225-226	76
d	H	C_6H_4-Cl(4)	179-180	91
e	Me	C_6H_5	135-136	93
f	Me	C_6H_4-OMe(4)	158-159	85
g	Me	C_6H_3-OMe_2(3,4)	205-206	82
h	Me	C_6H_4-Cl(4)	139-140	94

[a] All reactions were carried out a system of **57** (1.0 mmol) and Et3N (10.0 mmol) in ethanol (10 ml) under reflux.

Scheme 19



Scheme 20



This type of reduction is considered well applicable to the synthesis of pyrrolo[2,3-*b*]indole derivatives [30]. Orthonitro compound (**14h**) was treated with Raney-nickel (W-2) in ethanol at reflux to give a separable mixture of **61** and **62** in moderate yields. In a similar manner, the reduction of **14h** with zinc dust in acetic acid at reflux also gave a separable mixture of **62** and **63**. More detailed experiment are now in progressing.

Interestingly, the reduction of **5b** with zinc dust in acetic acid gave only the corresponding *trans* isomer **63** in good yield. This reduction significantly affected the distribution of isomers, with the thermodynamically favoured *trans* configuration contributing significantly to the isomeric distribution due to the chelate effect of zinc metal between both the ester carbonyl and amide carbonyl groups. The reduction of **5a** in a similar manner, however, gave a mixture of *cis* and *trans* isomers (**65** and **66**) in good yields.

4-Substituted 3-methylthio-1*H*-pyrrole-2,5-dione derivatives were readily obtained by the reaction of nitroketene dithioacetal with active methlene compounds bearing a cyano group, aryl- or heteroarylacetonitriles. These maleimides are key in the synthesis of various heterocycles, especially biologically active compounds.

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