# Synthesis of Dimethyl Heterocyclic-*o*-Dicarboxylates Using Dimethyl Acetylenedicarboxylate



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Dimethyl acetylenedicarboxylate (DMAD) is a very important and useful reagent for the preparation of dimethyl heterocyclic-*o*-dicarboxylates, which are key intermediates in the synthesis of fused pyridazine derivatives. The synthesis of thiopyranes by the Diels-Alder reaction of dithiocarboxylate derivatives, synthesis of various cyclazines by [2 + 8] cycloaddition reactions, and synthesis of dimethyl pyrazolo[3,4-*b*]pyridine-5,6-dicarboxylates and polycyclic heterocycles containing the 1,6-naphthyridine ring system by the reaction of *o*-aminonitrile compounds with DMAD are described here.

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Dialkyl heterocyclic or arene *o*-dicarboxylates are one of the most important starting materials for fused pyridazine derivatives, and have been extensively studied for their great importance in biological and medicinal chemistry [1]. Generally, fused pyridazine derivatives have been synthesized by the reaction of *o*-dicarboxylates with hydrazine compounds. In this paper, we show the syntheses of dimethyl heterocyclic *o*-dicarboxylates which have been developed in our group.

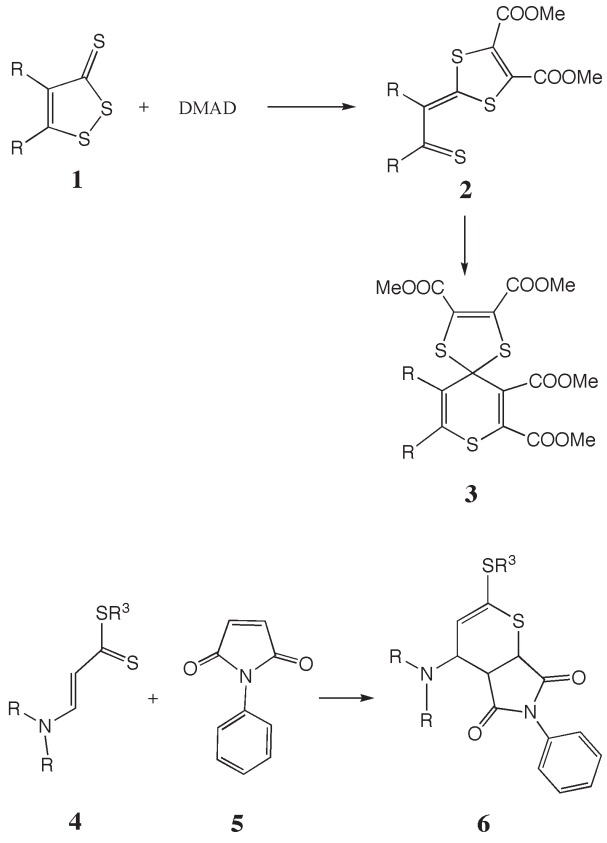
Dimethyl acetylenedicarboxylate (DMAD) has been extensively utilized in organic syntheses as a dienophile in the Diels-Alder cycloaddition reaction, as a dipolarophile in the 1,3-dipolar cycloaddition reaction, as a Michael Acceptor, etc [2].

## 1. Reaction of Dithiocarboxylates with DMAD

In contrast to the thorough studies on the Diels-Alder reactions of oxa- and aza-butadienes, the [4 + 2] cycloaddition reactions of 1-thia-1,3-butadienes have not studied extensively. Although the general participation of thiabutadienes in $LUMO_{diene}$-controlled [4 + 2] cycloaddition reactions has been recognized and experimentally verified, most investigations have detailed their 4π participation in $HOMO_{diene}$-controlled reactions with typical electron-deficient dienophiles like DMAD. The Diels-Alder reactions of 1-thia-1,3-butadienes including thiocarbonyl have become the generalized reactions at present, and are applied to the synthesis of many useful compounds [3]. These similar reactions were not studied when we started investigating the Diels-Alder reactions of 1-thia-1,3-butadienes. First, the Diels-Alder reaction was simply reported as a side reaction in the 1,3-dipolar cycloaddition reaction of 1,3-dithiols with DMAD [4]. Afterwards, Smutny reported the Diels-Alder reaction of an enaminodithiocarboxylate (**4**) with *N*-phenylmaleimide (**5**) to give the corresponding Diels-Alder product (**6**) [5].

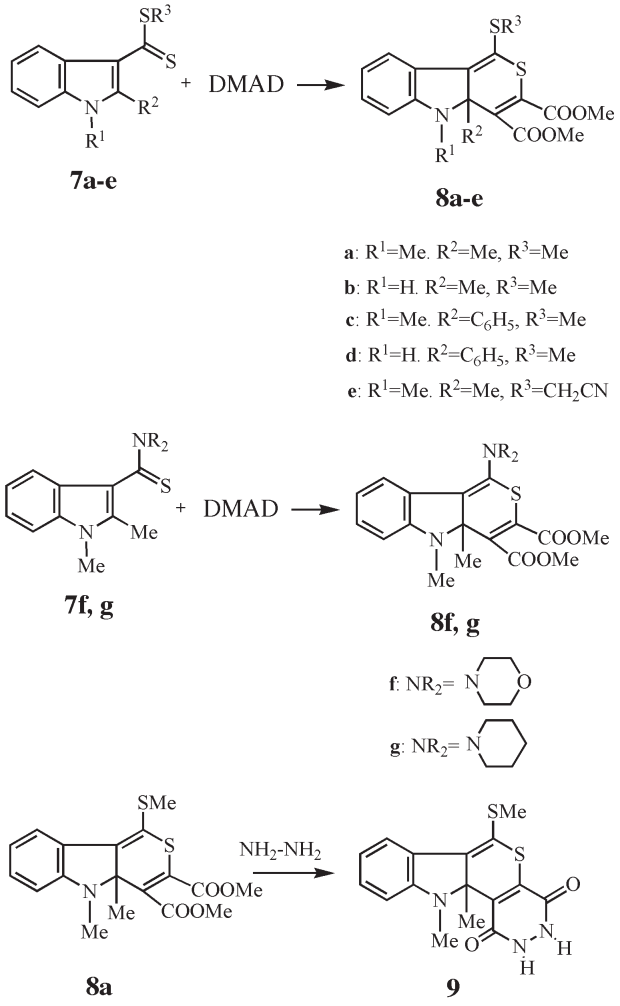
We will describe the Diels-Alder reactions of thia-1,3-butadienes including various dithiocarboxylates with DMAD. Alkyl indole-3-dithiocarboxylates have a diene system in the thiocarbonyl group of their part of dithiocarboxylic acid and a double bond between the 1- and 2-positions of indole [6]. It is possible to regard these alkyl indole-3-dithiocarboxylate derivatives as a kind of enaminodithiocarboxylate derivative. The reaction of alkyl indole-3-dithiocarboxylates (**7a-e**) with DMAD in DMF at 100°C for 5-10 min gave the corresponding Diels-Alder products (**8a-e**) in good yields. While the reaction of methyl 1-methylindole-3-dithiocarboxylate with DMAD did not afford the Diels-Alder product. This reaction needs a substituted group at the 2-position of indole. In a similar manner to the above, the reaction of thioamide derivatives (**7f, g**), which were obtained by the reaction of **7a** with morpholine or piperidine, with DMAD also gave the

Scheme 1



Diels-Alder reaction products (**8f, g**) in good yields. These diester products can be used as key intermediates for the synthesis of fused pyridazine-dione derivatives. The reaction of **8a** with hydrazine hydrate under refluxing methanol gave a fused pyridazinedione (**9**) in 60% yield.

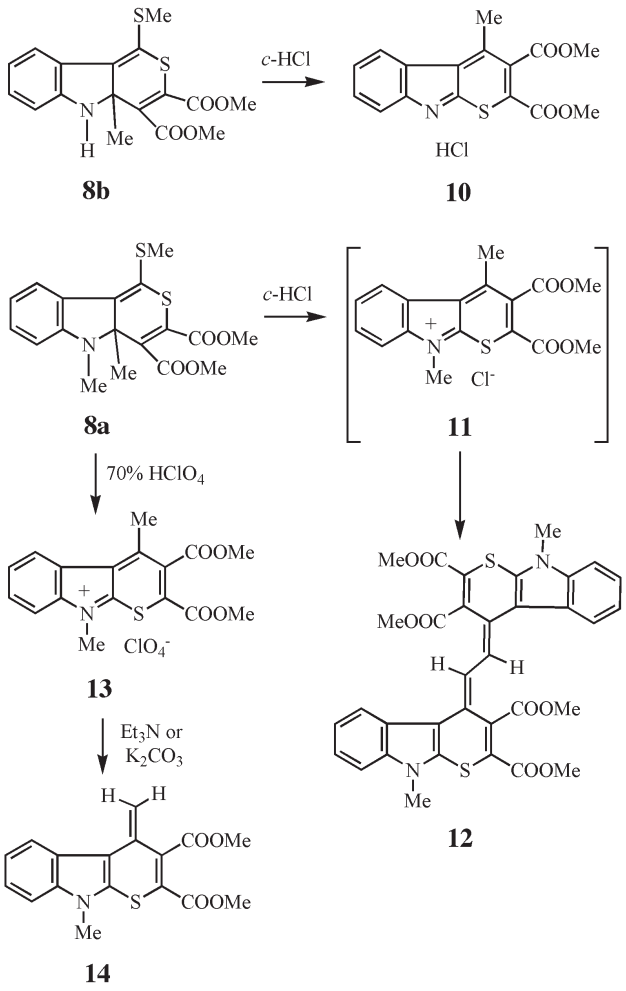
Scheme 2




The Diels-Alder products were easily converted to 1,5-disubstituted 2,3-bis(methoxycarbonyl)indolo[2,3-*b*]thiopyrylium salts (**10**, **13**) in good yields. Compound **8a** was treated with 10% hydrochloric acid in methanol to give the dimer (**12**) of dimethyl 1-methylene-5-(methyl)thiopyrano[2,3-*b*]indole-2,3-dicarboxylate (**11**) in 66% yield. Compound **13** could be transformed to **14** as a free base in 94% yield, by treatment with a base such as potassium carbonate in dimethyl sulfoxide [7].

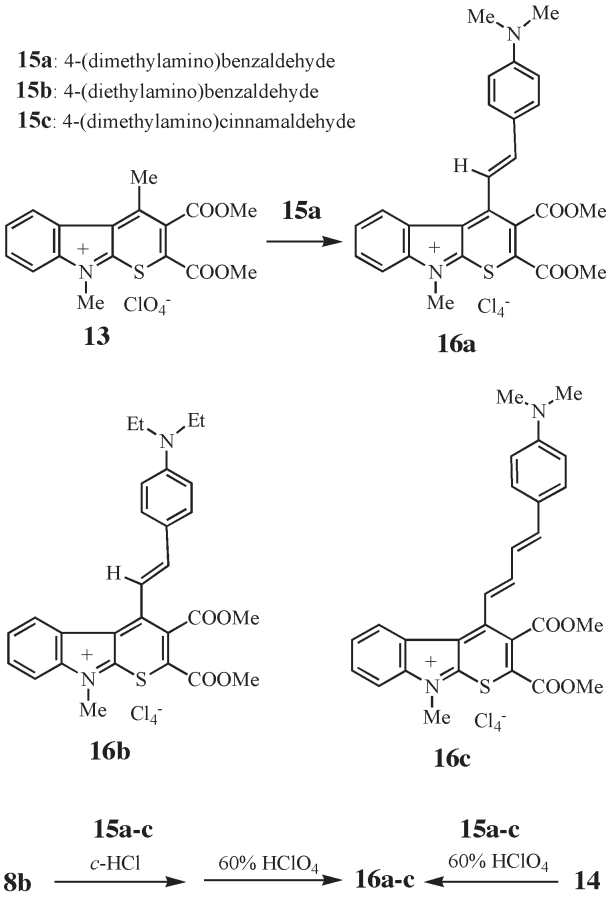
Compounds **13** and **14** are important and versatile starting materials as terminal heterocyclic compounds for the synthesis of new thiopyrylocyanine and merocyanine dyes [7]. The reaction of **14** with aromatic aldehydes [4-(*N*,*N*-dimethylamino)benzaldehyde (**15a**), 4-(*N*,*N*-diethylamino)benzaldehyde (**15b**), and 4-(*N*,*N*-dimethylamino)-cinnamaldehyde (**15c**)] gave the corresponding thiopyrylocyanine dyes (**16a-c**) in good yields. The compounds (**16a-c**) are brilliant green in dimethyl ethanol solution, showing at 710 (log ε: 4.70), 704 (log ε: 4.05), and 798 (log ε: 4.73) nm in the UV-VIS spectra, respectively.

Scheme 3

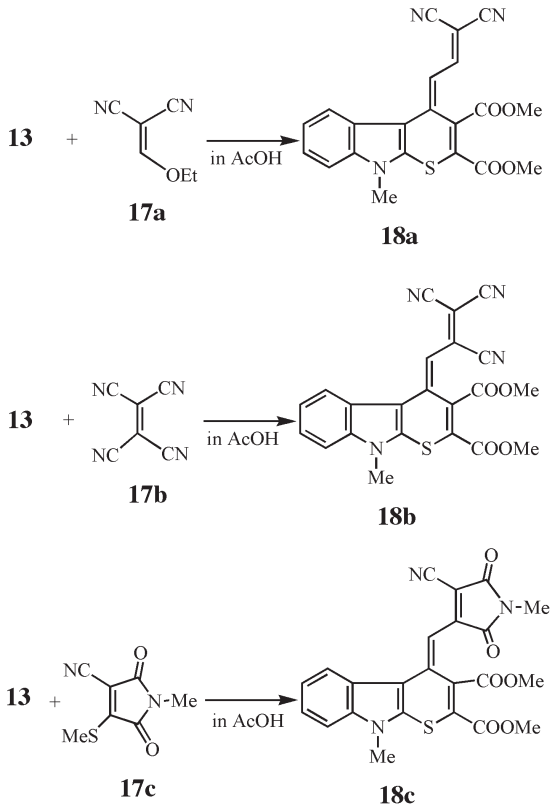



Compound **13** should react at an exocyclic double bond with electrophilic reagents such as ethoxymethylenemalononitrile (**17a**), tetracyanoethylene (**17b**), and 4-cyano-1-methyl-3-methylthio-1*H*-pyrrole-2,5-dione (**17c**) to give the 4-substituted (methylene)thiopyrano[2,3-*b*]indole derivatives (**18a-c**) in 71, 29, and 15% yields, respectively. The maximum absorption in the long wavelength region of the UV-VIS spectra of **18a-c** appeared at 551 (log ε: 4.33), 640 (log ε: 4.45), and 645 (log ε: 4.50) nm, respectively [7].

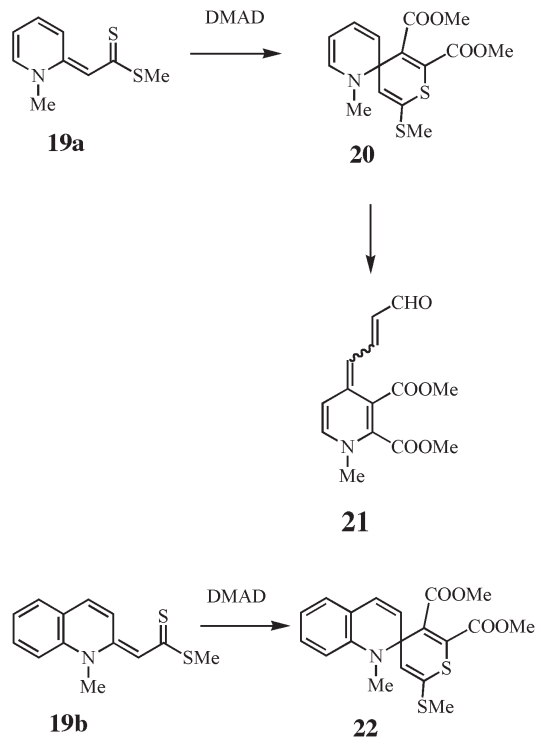
Scheme 4




Scheme 5




Scheme 6



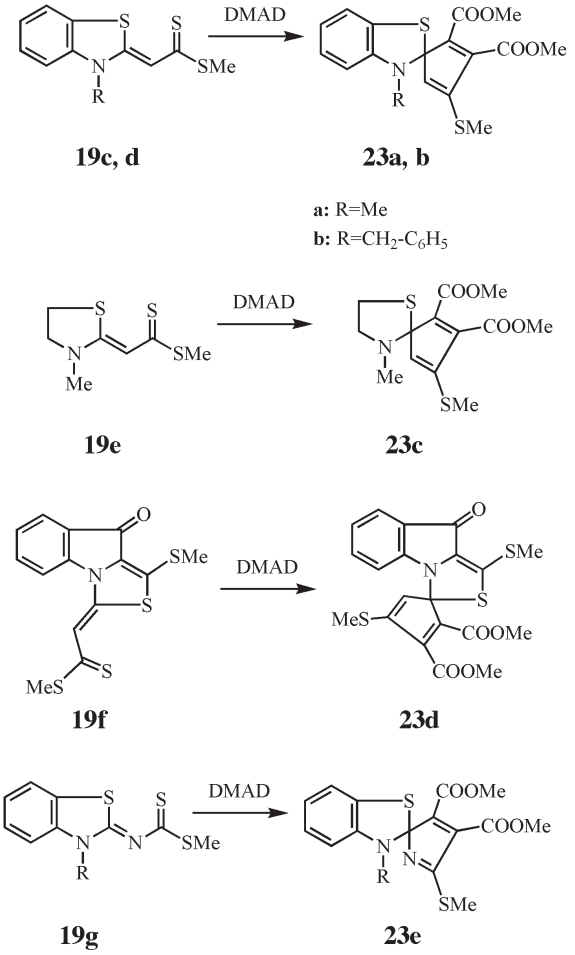

The above Diels-Alder cycloaddition reactions of alkylindole-3-dithiocarboxylates with DMAD are capable of synthesizing various fused thiopyran derivatives.

The reaction of methyl dithiocarboxylate (**19a**) with DMAD at 100°C for 3 hr afforded a product in which the pyridine ring was opened, dimethyl 4-(3-formylbut-2-enylidene-2-methylthio-4*H*-thiopyrone-5,6-dicarboxylate (**21a**), in 15% yield. The formation of **21a** can be explained by assuming the spiro-compound as an intermediate which might be the usual Diels-Alder reaction product of the above reaction [8b].

In a similar manner, the reaction of **19b** with DMAD gave a brown oil in 75% yield. This compound was the general Diels-Alder reaction product, spiro(quinoline-2-thiopyrane) (**22**). Under these conditions, the reaction did not give a ring-opened product of a spiro compound [8b].

The reaction of enaminodithiocarboxylates (**19c-f**) with DMAD in DMF at 100°C for 5 hr gave spiro(benzothiazolinecyclopentadiene) (**23a, b**) and spiro(thiazolinecyclopentadiene) derivatives (**23c, d**) in 95, 90, 85, and 70% yields, respectively. Similarly, the reaction of **19g** with DMAD at 150°C for 5 hr afforded the spiro(benzothiazole-2*H*-pyrrole) derivative (**23e**) in 30% yield. A strong S---S interaction works effectively in these desulfurization reactions [8b]. This desulfurization reaction phenomenon is only observed in thiazole and thiazoline derivatives containing a sulfur atom [9].

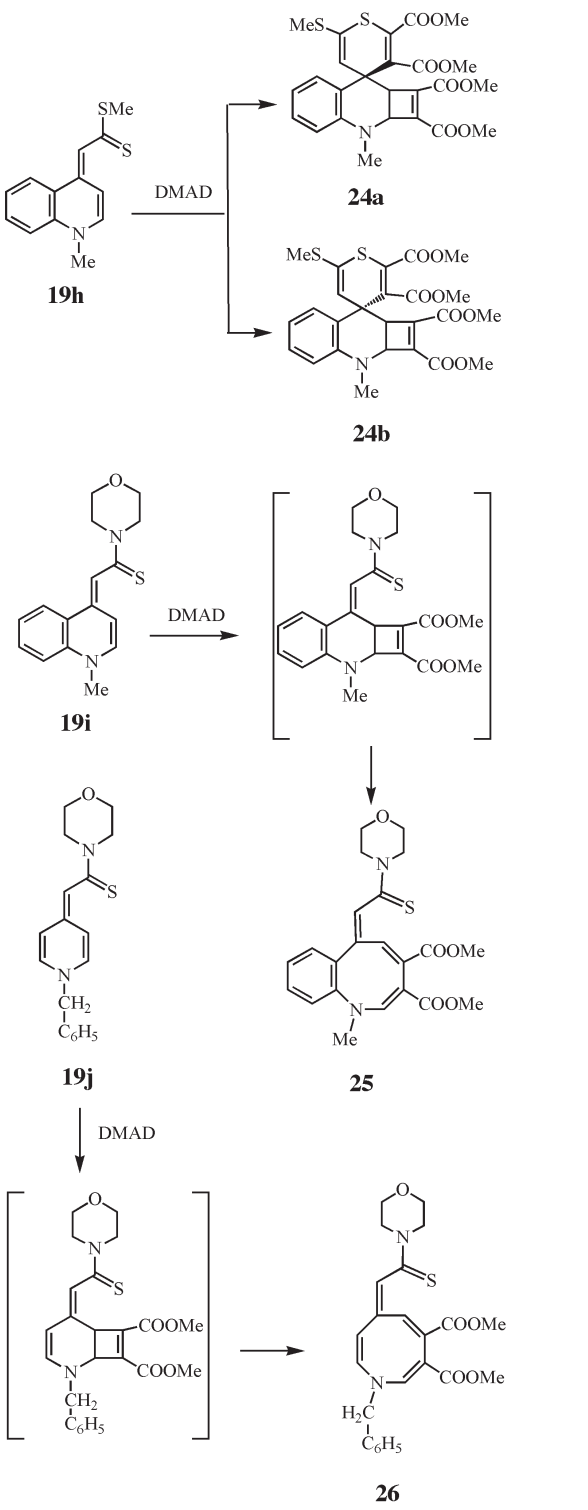
Scheme 7




An enaminodithiocarboxylate (**19h**) reacted with DMAD in dioxane at 100°C for 4 hours to give double cycloaddition reaction products (**24a, b**). These double cycloaddition reactions were carried out by [4+2] cycloaddition reaction of a thiabutadiene system of the thiocarbonyl group and the 4-methylene group of quinoline with DMAD, and [2+2] cycloaddition reaction of an enamine system of the 2 and 3 positions of the quinoline ring [8b].

Compound **19i** also reacted with DMAD in dioxane by refluxing for 10 hr to give the corresponding 1,4-cycloaddition reaction product (**25**) in 55% yield.

Scheme 8

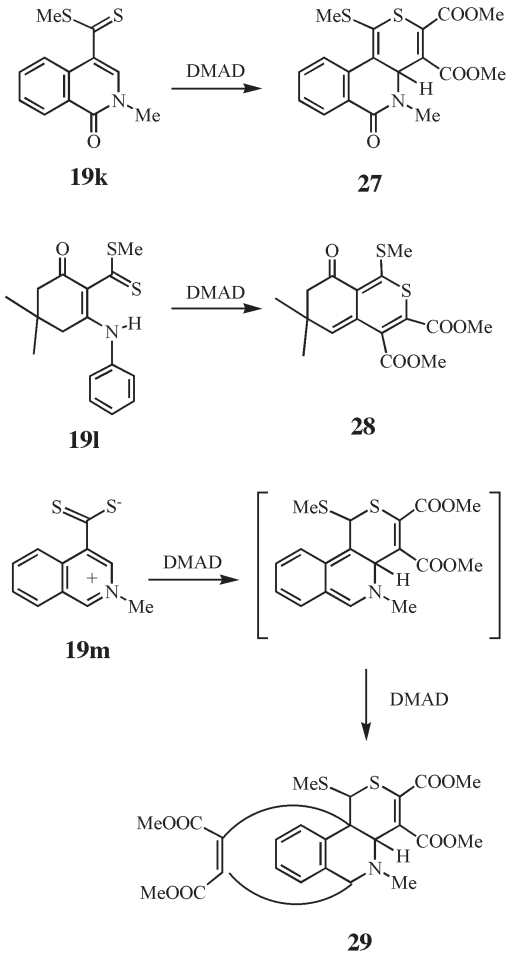


The reaction of the thioamide (**19i**) with DMAD afforded the benzoazocine derivative (**25**) in 53% yield, which was derived from the direct cleavage of the cyclobutene ring as the intermediate. This reaction was also applied to another thiocarbamoyl methylene derivative (**19j**) with DMAD [8b]. It is well known that enamines react with electrophilic alkynes to form cyclobutene adducts which undergo stepwise ring opening under mild thermal conditions to afford ring-expanded dienamines. These synthetic methods for 1,4-dihydrobenzoazocine and 1,6-dihydroazocine derivatives by the [2+2] cycloaddition reactions of quinoline and 1,4-dihydropyridine derivatives with DMAD are useful and interesting, and can be applied to the synthesis of various methylene azocine derivatives.

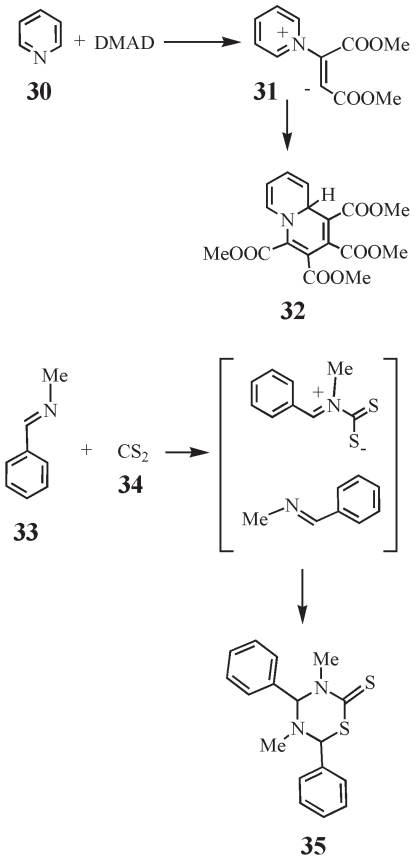
The enaminodithiocarboxylate **19k** also reacted with DMAD in dioxane by refluxing for 10 hours to give the corresponding 1,4-cycloaddition reaction product, dimethyl 5-methyl-1-methylthio-4a,5,6-trihydrothiapyrano[4,3-*c*]isoquinolin-6-one (**27**), as colorless needles in 65% yield [8b]. Reaction of **19l** with DMAD in benzene was readily carried out followed by elimination of the aniline group to give the corresponding Diels-Alder product **28** in 21% yield [10].

The above [4+2] cycloaddition reactions of enaminodithiocarboxylates with DMAD are thought to be 1,4-dipolar addition reported by Huisgen [11]. Typical examples of 1,4-dipolar reactions are shown in Scheme 10. A typical 1,4-dipolar cycloaddition reaction is also shown. Reaction of **19m** with DMAD in DMF gave the 6,10a-ethenothiapyrano[4,3-*c*]isoquinoline derivative (**29**) which might have resulted from both cycloaddition reactions, simultaneous 1,4-dipolar cycloaddition and Diels-Alder reaction [12].

Scheme 9



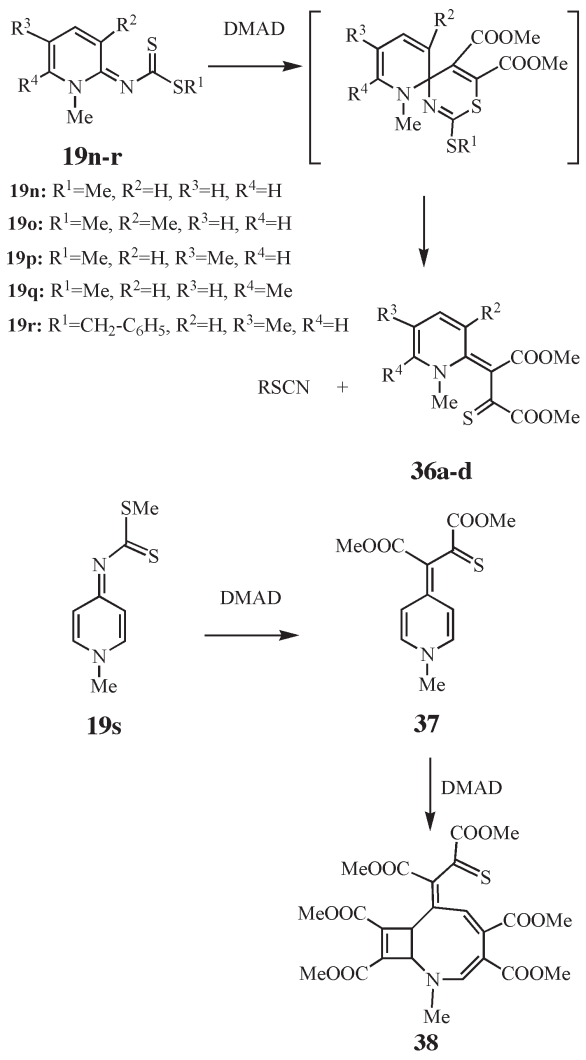

Scheme 10




As shown in the above [4+2] cycloaddition reactions, conjugated dienes and their thiaheteroanalogs have been thoroughly investigated in various cycloaddition reactions. However, few studies regarding the cycloaddition reactions of diheterodienes bearing a thiocarbonyl group and a carbon-nitrogen double bond have been reported. We show here the [4+2] cycloaddition reactions of

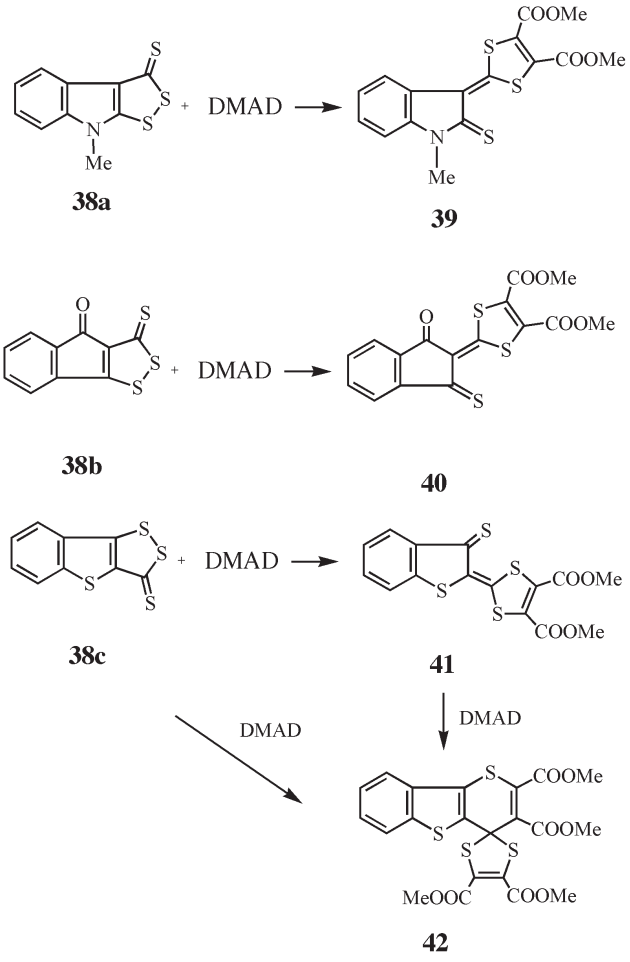
methyl dithiocarbamate derivatives which have a conjugated diheterodiene system. Reaction of **19n** with DMAD gave 1-methyl-2-[1,2-bis(methoxycarbonyl)-2-thioxoethylidene]-1,2-dihydropyridine (**36a**) which was accompanied by the elimination of methylthiocyanate in good yield. To investigate the reaction mechanism, the reaction of **19p** with DMAD was examined under similar conditions, and two products, **36c** and benzylthiocyanate, were obtained. 4-(Methylthio)thiocarbonylimino-1-methyl-1,4-dihydropyridine (**19s**) reacted with DMAD at room temperature for 72 hr to give cyclobuta[*b*]azocine (**38**) in 40% yield [9].

Scheme 11



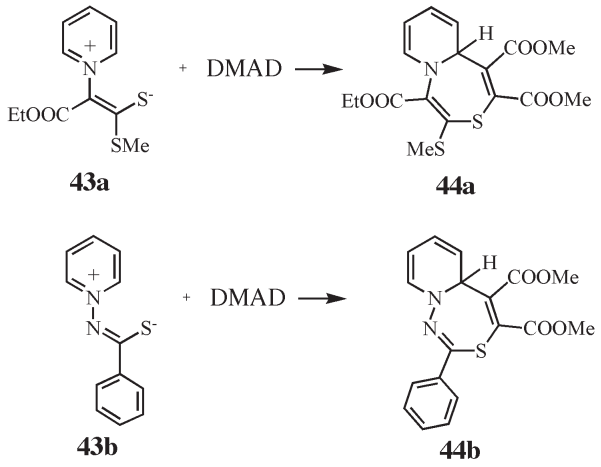

It is well known that 1,3-dipolar cycloaddition reactions of trithione with various activated dipolarphiles, such as maleic anhydride, and DMAD occur in appropriate solvents to give the corresponding 1,2-dithiole derivatives. We also tried some 1,3-dipolar cycloaddition reactions using DMAD [13]. First, the reaction of **38a** with DMAD gave the indole-2-ylidene-1,2-dithiole derivative (**39**) [14]. Compound **38b** also reacted with DMAD to yield 1,2-dithiole-4,5-dicarboxylate (**40**) in 21% yield *via* a 1,3-dipolar cycloaddition reaction [14]. When **38c** was allowed to react with DMAD, a separable mixture of **41** and **42** was obtained [15].

Scheme 12




Kakehi et al., reported the smooth formation of the 10a*H*-pyrido[1,2-*d*][1,4]thiazepine derivative (**44a**) and its intramolecular Diels-Alder adducts in the reactions of various 1-pyridinio[(alkylthio)thiocarbonyl]methylides (**43a**) with DMAD [16]. Similarly, the reaction of amidate (**43b**) with DMAD at 50-60°C gave dimethyl 2-phenyl-6-methyl-5a*H*-pyrido[1,2-*d*][1,3,4]thiadiazepine-4,5-dicarboxylate (**44b**) in 22% yield [17].

Scheme 13




2. Syntheses of Dimethyl [2.2.3]Cyclazine-2,3-dicarboxylate Derivatives and Their Related Compounds.

[2.2.3]Cyclazine is a peripheral conjugate aromatic compound involving delocalized 10π electrons [18]. For general synthesis of [2.2.3]cyclazine and related compounds, the [8+2] cycloaddition reaction of indolizine derivatives with an acetylenic compound has been widely utilized [18b, 19]. In order to obtain functionalized [2.2.3]cyclazine derivatives, we also reported the synthesis of cyclazine derivatives. The key intermediates for the synthesis of cyclazines are indolizine derivatives. A convenient and effective synthetic method for synthesizing indolizine derivatives as starting materials for the synthesis of cyclazines was established [20].

The reaction of indolizine (**45a**) with DMAD in the presence of Pd-C in refluxing toluene gave the desired dimethyl[2.2.3]cyclazine-1,2-dicarboxylate (**46a**) along with a dihydro[2.2.3]cyclazine derivative [21]. Dimethyl 3-phenyl and 3,4-diphenyl[2.2.3]cyclazine-1,2-dicarboxylates (**45b**) were also prepared in a manner similar to that described for the preparation of **46b**. The reaction of 6,8-dimethylindolizine (**45d**) with DMAD in the presence of 5% palladium on charcoal in boiling toluene gave the desired cyclized product, dimethyl 5,7-dimethylcycl[2.2.3]azine-1,2-dicarboxylate (**46d**), in 25% yield. 5-Methylcycl[2.2.3]azine-1,2-dicarboxylate (**46c**) was also prepared from **45c** in a manner similar to that described for **46c** in 34% yield. The [8 + 2] cycloaddition reaction of 2-methylthioindolizine (**45e**) with DMAD was also prepared to give the corresponding dimethyl 3-methylthiocycl[2.2.3]-azine-1,2-dicarboxylate (**46e**) in 38% yield. Dimethyl 5,7-dimethyl-3-methylthiocycl[2.2.3]azine-1,2-dicarboxylate (**45f**) and dimethyl 5-methyl-3-methylthiocycl[2.2.3]azine-1,2-dicarboxylate (**46f**) were prepared in a manner similar to that described for **46a, b** in 40% and 49% yields, respectively [22b]. Indolizines are key intermediates for the synthesis of cycl[2.2.3]azines. We also succeeded in the convenient synthesis of indolizine derivatives such as **45c-f** by the reaction of 1-ethoxycarbonylmethylthiopyridinium bromides with nitro ketene dithioacetal, 1,1-bis(methylthio)-2-nitroethylene, in the presence of triethylamine in ethanol [23].

Many polycyclic hydrazides have been synthesized in the effort to increase the efficiency of light production [23]. Pyridazino[4,5-*a*][2.2.3]cyclazine-1,4(2*H*,3*H*)-diones (**47a**, **b**) were readily prepared by the reaction of **46a**, **b** with hydrazine hydrate in 82% and 77% yields, respectively. In these polycyclic pyridazine derivatives, a dimethylamino group is a very important functional group for increasing the chemiluminescent properties of the polycyclic pyridazinedione derivatives [24].

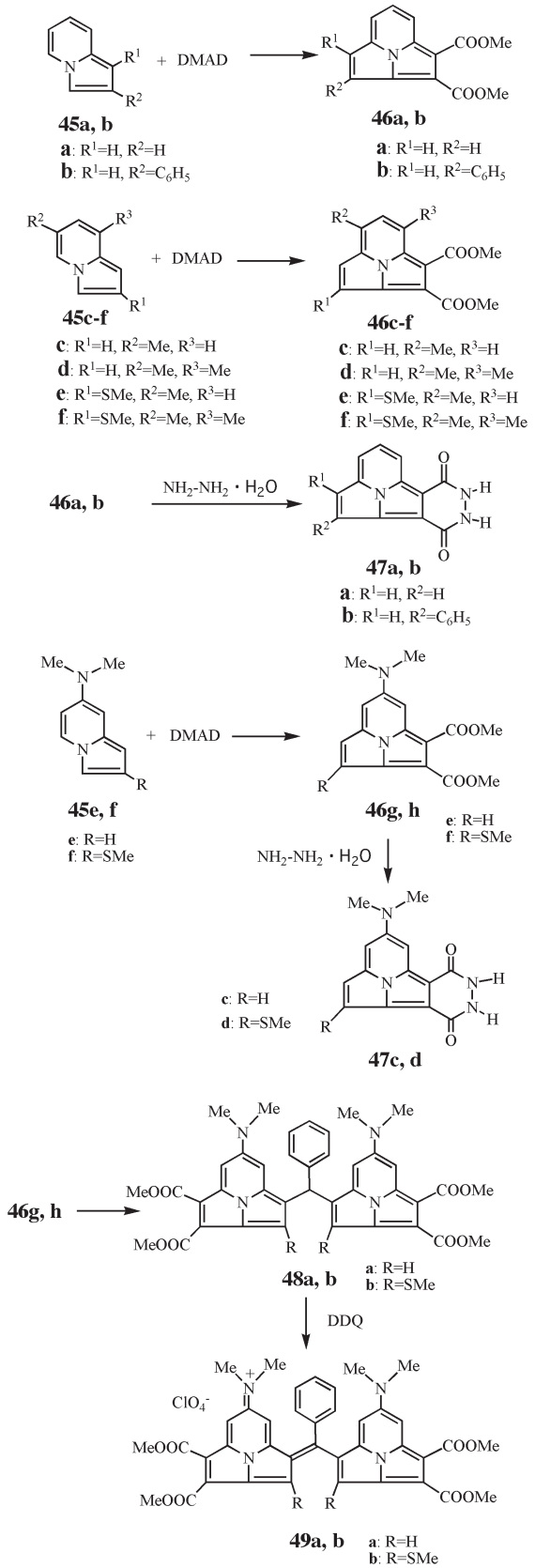
The desired 6-dimethylaminopyridazino[4,5-*a*]-[2.2.3]cyclazine-1,4(2*H*,3*H*)-diones (**47c**, **d**) were obtained by the reaction of **46g** and **h** with a large excess of 80% hydrazine hydrate in 90% and 77% yields, respectively [24].

Compounds **47a, b** were found to chemiluminesce efficiently, similarly to luminol, in the presence of hydrazine peroxide and horseradish peroxidase in a phosphate buffer solution at pH 8.0 [24].

Triarylmethyl cations, which are easily prepared by oxidation of the corresponding triphenylmethanes with an oxidizing agent such as DDQ, are not only one of the oldest classes of synthetic dyes, but also organic catalysts in organic synthesis. These oxidations have been successfully applied to analytical methods in diagnostic medicine and in the biological sciences in general [25]. [2.2.3]Cyclazine derivatives (**46g, h**) are expected to be chromogenic reagents. The reaction of **46g, h** with benzaldehyde in the presence of trifluoroacetic acid in refluxing dichloromethane for 7 hours gave triarymethane derivatives (**48a, b**) in good yields. The leuco bases (**48a, b**) were converted into dye cations (**49a, b**) by oxidation with DDQ in dichloromethane. The free dye cations were then precipitated as perchlorate salts by the addition of 60% perchloric acid into the reaction mixture [25].

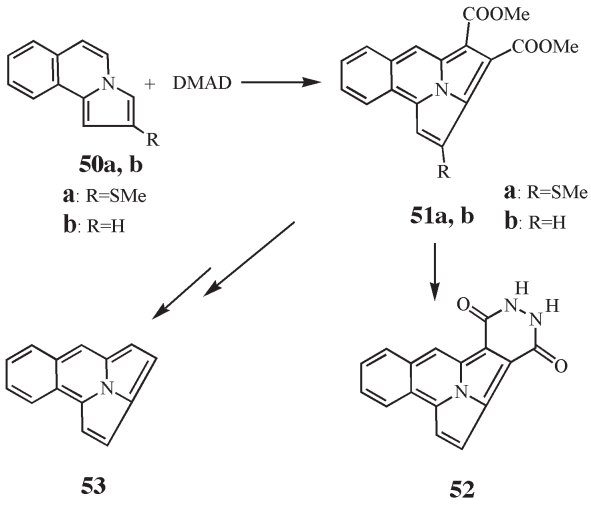
There has been considerable effort to try and rationalize the effects of benzo-fusion on aromatic annulenes. It is generally recognized that benzannelation reduces the

Scheme 14




diatropicity or paratropicity of the macrocyclic system, and the reasons for this are indicated in terms of increased bond localization in the macrocyclic ring. We applied the above reaction to the synthesis of pyrrolo-[2,1-*a*]isoquinoline, which is otherwise inaccessible. The cycloaddition reaction of **50a** with DMAD in the presence of 5% palladium on charcoal at reflux for 30 hours in toluene gave a separable mixture of three compounds. One of these was the expected cycloaddition product, dimethyl 2-methylthiobenzo[g]cycl[2.2.3]-azine-3,4-dicarboxylate (**51a**) in 27% yield. The desulfurization of **51a** with Raney-nickel occurred easily to give dimethyl benzo[*g*]cycl[2.2.3]azine-3,4-dicarboxylate (**51b**) in 44% yield. Of course, these dimethyl [2.2.3]cyclazine-1,2-dicarboxylates (**51a, b**) are very important key intermediates for the synthesis of pyridazinocyclazine (**52**) and the parent benzo[*g*][2.2.3]-cyclazine (**53**). The diester compound (**51b**) was allowed to react with hydrazine hydrate to give the desired pyridazine-dione compound (**52**) [22b].

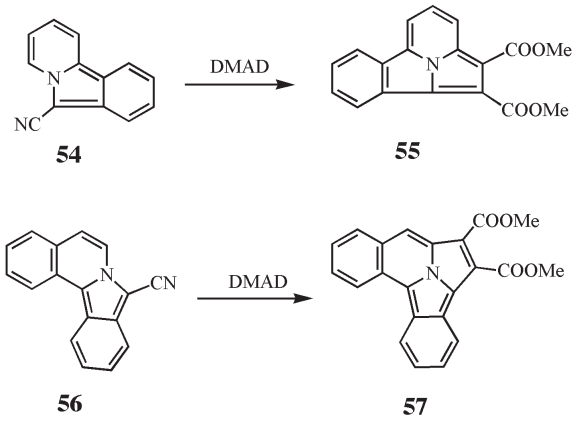
Scheme 15




Generally, in the case of [8 + 2] cycloaddition of indolizines with DMAD, the yields of the desired [2.2.3]cyclazines belong to the functional group on the indolizine ring. In particular, the presence of a leaving group at the 3 position on indolizines offers very effective results for the synthesis of [2.2.3]cyclazine derivatives [26]. For example, the [12 + 2] cycloaddition reaction of **54** with DMAD under refluxing for 20 hours in toluene gave the expected product, dimethyl benzo[*g*][2.2.3]-cyclazine-1,2-dicarboxylate (**55**), in 54% yield [27]. In a similar manner, compound **56** was allowed to react with

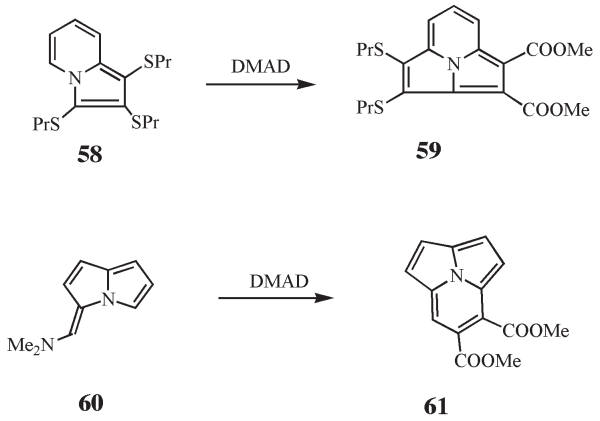
DMAD in the presence of a small amount of acetic acid under refluxing for 20 hours in toluene to give dimethyl dibenzo[*a*,*h*][2.2.3]cyclazine-1,2-dicarboxylate (**57**) in 26% yield [28].

Scheme 16



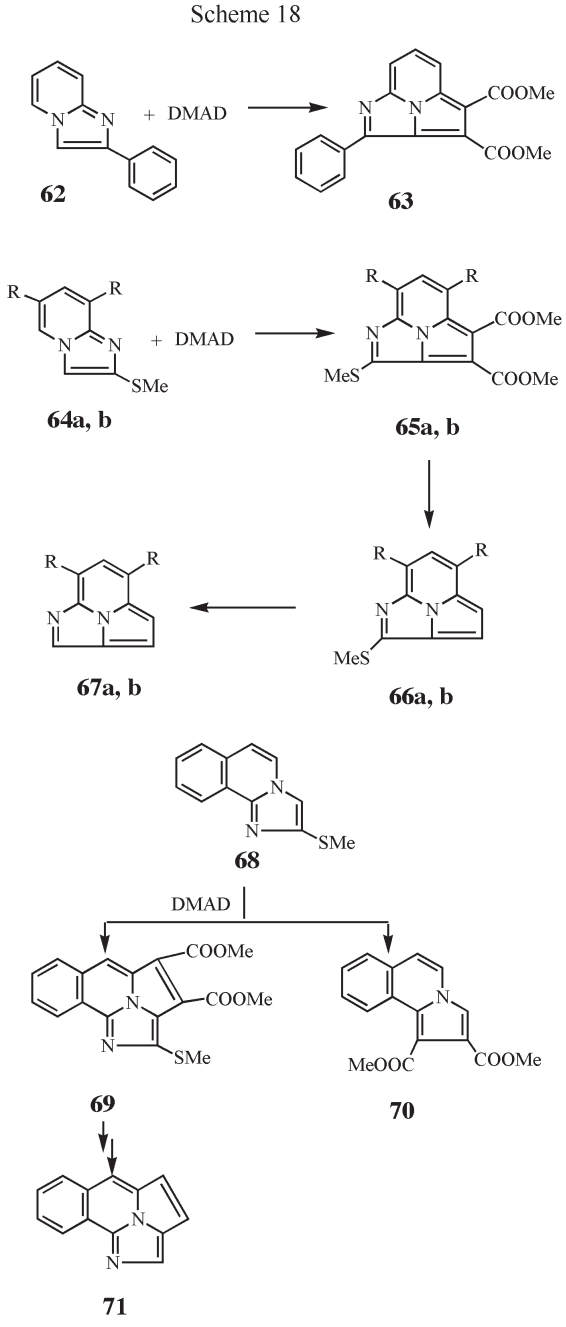

The reaction of **58** with DMAD gave the desired [2.2.3]cyclazine-1,2-dicarboxylate (**59**) in 96% yield [29]. A dimethyl amino group is also effectively used as a leaving group for the synthesis of [2.2.3]cyclazine [30]. Jessep and Leaver reported a convenient and unique [8 + 2] cycloaddition reaction of 3-(dimethylamino)methylene-3*H*-pyrrolizine (**60**) bearing an exo-methylene group with DMAD to give dimethyl [2.2.3]cyclazine-5,6-dicarboxylate (**61**) [30].

Scheme 17




Aza[2.2.3]cyclazine is also an interesting aromatic compound involving delocalized 10π-electrons from a theoretical point of view, similar to [2.2.3]cyclazine. Boekelheide and Kertelj first reported the synthesis of a 5-aza[2.2.3]-cyclazine derivative (**63**) by the [8 + 2] cycloaddition reaction of 7-methyl-2-methylpyrrolo[1,2-c]pyrimidine (**62**) with DMAD in the presence of palladium on charcoal [31]. The reaction of **64a, b** with DMAD in boiling toluene in the presence of palladium on charcoal gave cyclized products, dimethyl 2-methylthio-1-aza[2.2.3]cyclazine-3,4-dicarboxylates (**65a**, **b**), in 36 and 40% yields, respectively. Compounds **65a**, **b** are key intermediates for the synthesis of **66a, b** and **67a, b** [32].

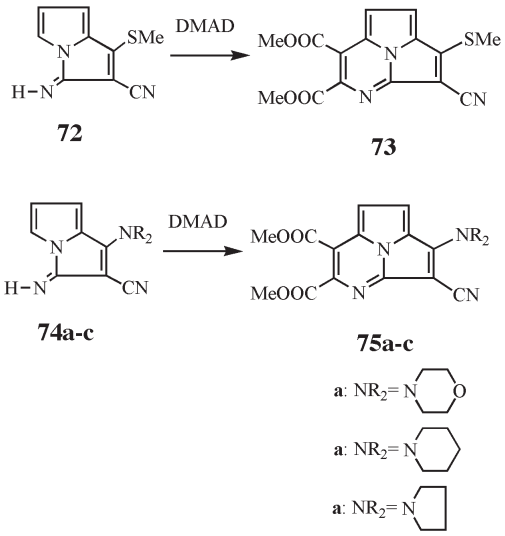
Scheme 18



Imidazo[2,1-*a*]isoquinolines are key intermediates for the synthesis of 1-azabenzo[*h*][2.2.3]cyclazines. A solution of **68** and DMAD in toluene was refluxed for 30 hours using 5% palladium on charcoal to give the expected dimethyl 2-methylthio-1-azabenzo[*h*][2.2.3]cyclazine-3,4-dicarboxylate (**69**) in 6% yield. Parent 1-azabenzo[*h*]-[2.2.3]cyclazine, a typical aromatic compound, was prepared from **69** in good yield [32].

Cycloaddition of **72** with DMAD gave 5-azacyclazine, dimethyl 4-cyano-3-methylthioaza[2.2.3]cyclazine-5,6-dicarboxylate (**73**), in good yield. 3-Amino-5-aza[2.2.3]-cyclazine derivatives (**75a-c**) were also prepared from the corresponding 1-amino-3-imino-3*H*-pyrrolizines (**74a-c**) and DMAD [33].

Scheme 19

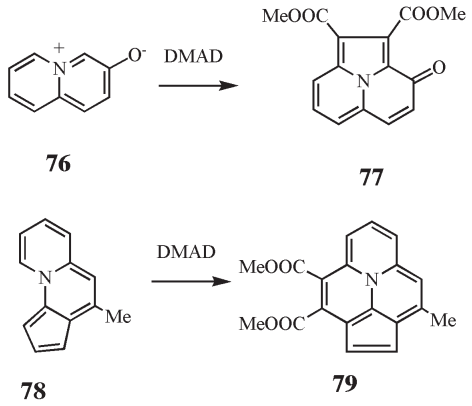



The reaction of **76** with DMAD gave the 1,2-di(methoxycarbonyl)[2.3.3]cyclazinone (**77**) in 44% yield. Compound **77** is a key intermediate of parent 3*H*-[2.3.3]-cyclazin-3-one and [2.3.3]cyclazinylium salt [34].

4-Methylcyclopenta[c]quinolizine (**78**) reacted with DMAD in benzene at room temperature to give cyclopenta[*ij*]pyrido[2,1,6-*de*]quinolizine (cyclopenta-[*cd*][3,3,3]-cyclazine) (**79**) in 84% yield. The NMR spectrum of this product showed evidence of aromatic character [35].

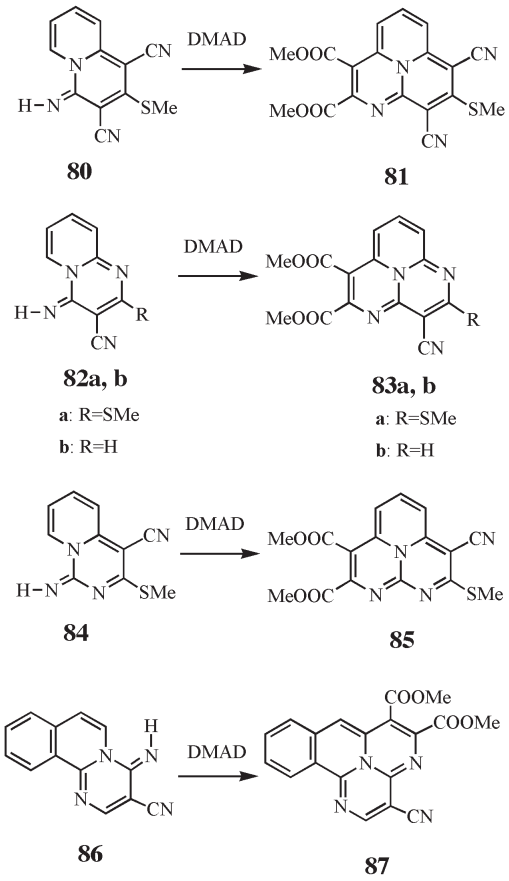
The [3.3.3]cyclazines, which are a well-known 4nπ-electron system of a series of nonbenzenoide aromatic compounds, are particularly interesting for both their chemical and physical properties. The reaction of **80** with DMAD gave dimethyl 7,9-dicyano-8-methylthio-1-aza-

Scheme 20



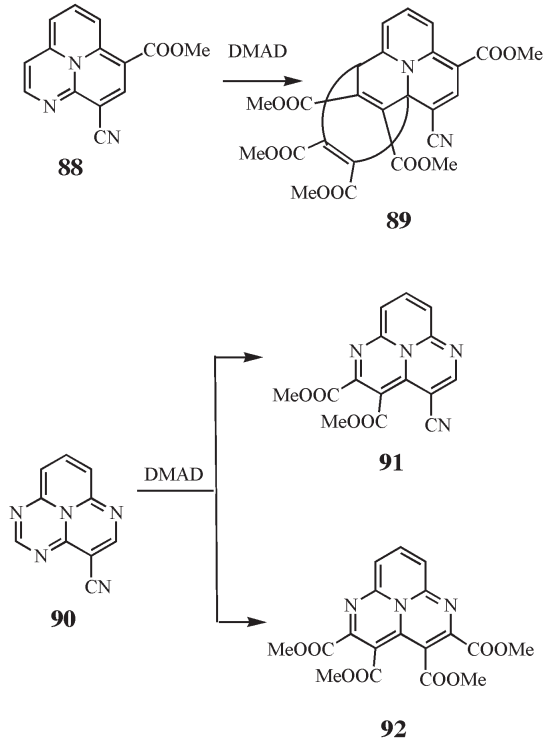

[3.3.3]cyclazine-2,3-dicarboxylate (**81**) [36, 37]. Similarly, other aza[3.3.3]cyclazine derivatives (**83, 85, 87**) were obtained by the cycloaddition reaction of the corresponding 4-iminoaza-4*H*-quinolizines (**82 84, 86**) [37, 38].

Scheme 21



The reaction of **88** with DMAD in dimethylformamide at 100°C for 10 hours gave 1,3a-dihydro-1,3a-etheno[3.3.3]cyclazine derivatives (**89**) in 80% yields. A mixture of **90** and DMAD in dimethylformamide was heated at 100°C for 10 hours. The reaction mixture was chromatographed on silica gel to give dimethyl 4-cyano-1,6-diaza[3.3.3]cyclazine-2,3-dicarboxylate (**91**) in 20% yield. On the other hand, a solution of **90** and DMAD in acetonitrile was refluxed for 20 hours to give tetramethyl 1,6-diaza[3.3.3]cyclazine-2,3,4,5-tetracarboxylate (**92**) in 15% yield [39].

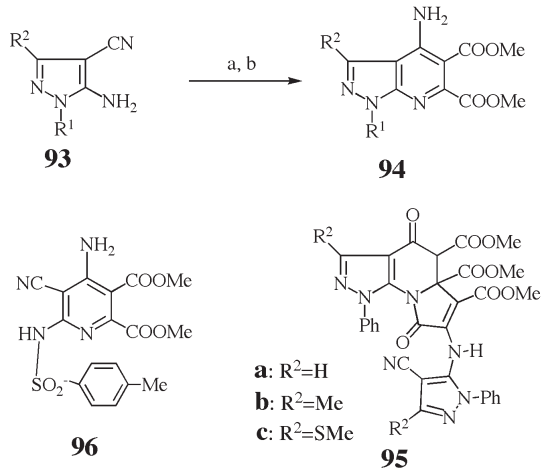
Scheme 22




## 3. Reaction of Amino-nitrile Compounds with DMAD

During the course of our study on the synthesis of a tricyclic pyridazine containing the ring system from dimethyl pyrazolo[3,4-*b*]pyridine-5,6-dicarboxylates, attention was directed to the chemiluminescence properties of 4-aminopyrazolo[4',3':5,6]pyrido[3,4-*b*]pyridazine-5,8(6*H*,7*H*)-diones containing the fundamental pyridopyridazine ring in an effort to assess the chemiluminescence activity. Reaction of 1,3-disubstituted 5-aminopyrazole-4-carbonitrile derivatives (**93a-n**) with DMAD in the presence of potassium carbonate in dimethyl sulfoxide gave the corresponding dimethyl 1,3-disubstituted pyrazolo[3,4-*b*]pyridine-5,6-dicarboxylates (**94a-n**), which were allowed to react with excess hydrazine hydrate under ethanol refluxing conditions followed by heating at 250-300°C, to give 1,3-disubstituted 4-amino-1*H*-pyrazolo aminopyrazolo[4',3':5,6]pyrido[3,4-*b*]pyridazine-5,8(6*H*,7*H*)-diones (**97a-n**) in good yields [40]. These reactions gave **95a-c** and **96** as by-products from the basic solution [41, 42].

Scheme 23




a: DMAD, $K_2CO_3$ in DMSO, room temperature, 20 h; b:10% HCl.

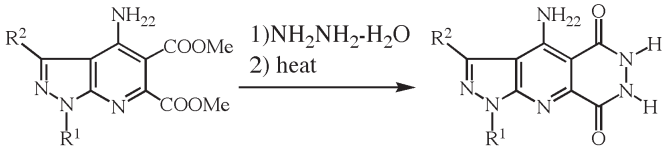
Table 1

Synthesis of Dimethyl 1,2-Disubstituted 4-Aminopyrazolo[3,4-*b*]-pyridine-5,6-dicarboxylates


| No. | $R_1$ | $R_2$ | Yield(%) | mp(°C) |
|---|---|---|---|---|
| **a** | $C_6H_5$ | H | 31 | 178-180 |
| **b** | $SO_2C_6H_4$-Me(p) | H | 38 | 220-222 |
| **c** | $C_6H_5$ | Me | 14 | 190-191 |
| **d** | $C_6H_5$ | $C_6H_5$ | 29 | 177-179 |
| **e** | $C_6H_5$ | $C_6H_4$-$NMe_2$(p) | 21 | 207-208 |
| **f** | $C_6H_5$ | 2-thienyl | 17 | 171-172 |
| **g** | $C_6H_5$ | 2-benzothienyl | 20 | 218-220 |
| **h** | $C_6H_5$ | SMe | 26 | 120-122 |
| **i** | $C_6H_4$-$NO_2$(p) | SMe | 46 | 235-237 |
| **j** | 2-benzothiazolyl | SMe | 53 | 213-215 |
| **k** | $C_6H_5$ | $SC_6H_5$ | 42 | 160-161 |
| **l** | $C_6H_5$ | $SC_6H_4$-Me(m) | 28 | 138-139 |
| **m** | $C_6H_5$ | $SC_6H_4$-Cl(p) | 42 | 189-190 |
| **n** | 2-benzothiazolyl | $SC_6H_4$-Me(m) | 32 | 224-227 |

Table 2

Synthesis of 1,2-Disubstituted 4-Amino-1*H*-pyrazolo[4',3':5,6]-pyrido[2,3-*d*]pyridazine-5,8(6*H*,7*H*)-diones



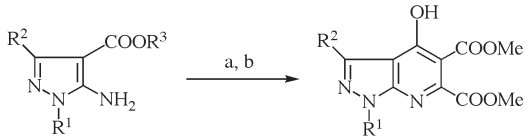

**94a-n** **97a-r**

| No. | $R_1$ | $R_2$ | Yield(%) | mp(°C) |
|---|---|---|---|---|
| **a** | $C_6H_5$ | H | 94 | 353-356 |
| **b** | H | H | 76 | >360 |
| **c** | $C_6H_5$ | Me | 85 | 340-342 |
| **d** | $C_6H_5$ | $C_6H_5$ | 85 | 358-368(dec.) |
| **e** | $C_6H_5$ | $C_6H_4$-$NMe_2$(p) | 92 | 355-368(dec.) |
| **f** | $C_6H_5$ | 2-thienyl | 91 | 355-366(dec.) |
| **g** | $C_6H_5$ | 2-benzothienyl | 95 | 350-361(dec.) |
| **h** | $C_6H_5$ | SMe | 92 | 353-358 |
| **i** | $C_6H_4$-$NO_2$(p) | SMe | 72 | >360 |
| **j** | 2-benzothiazolyl | SMe | 88 | 320-325 |
| **k** | $C_6H_5$ | $SC_6H_5$ | 86 | 320-324 |
| **l** | $C_6H_5$ | $SC_6H_4$-Me(m) | 86 | 288-295 |
| **m** | $C_6H_5$ | $SC_6H_4$-Cl(p) | 97 | >360 |
| **n** | 2-benzothiazolyl | $SC_6H_4$-Me(m) | 94 | >360 |

The reactions of ethyl 5-amino-1-*p*-toluenesulfonylpyrazole-4-carboxylate (**98a**) with DMAD in the presence of potassium carbonate as a base in DMSO gave **99a** in 61% yield. Similarly, the 3-methylthio derivative (**99b**) was prepared by the reaction of **98b** with DMAD in 48% yield. The reaction of **98c** with DMAD gave the desired product **99c** in only 3% yield. Dimethyl 4-hydroxy-1-*p*-toluenesulfonylpyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**99a**) was refluxed with excess hydrazine hydrate in ethanol, followed by removal of the ethanol by distillation, to give 4-hydroxy-1-*p*-toluenesulfonylpyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazine-5,8(6*H*,7*H*)-dione (**100a**) in 87% yield. When the hydrazine hydrate was used in large excess, desufonylation occurred simultaneously to give **100b** in 67% yield. In a similar manner, **100c** was obtained from **99b** in 62% yield. The 1,3-disubstituted compound **100d** was obtained from **99c** in 91% yield [43].

Synthesis of 4-aminopyrazolo[3,4-*d*]pyridine-5,6-dicarboxylate (**94**) by the reaction of 5-aminopyrazole-4-carbonitrile (**93**) in the presence of a base such as potassium carbonate can be conveniently applied to the formation of dimethyl 4-aminopyridine-2,3-dicarboxylate derivatives.

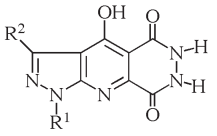
Scheme 24




**98a-c** **99a-c**

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

c




**a**: $R^1$=$SO_2$-$C_6H_4$-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

**100a-d**

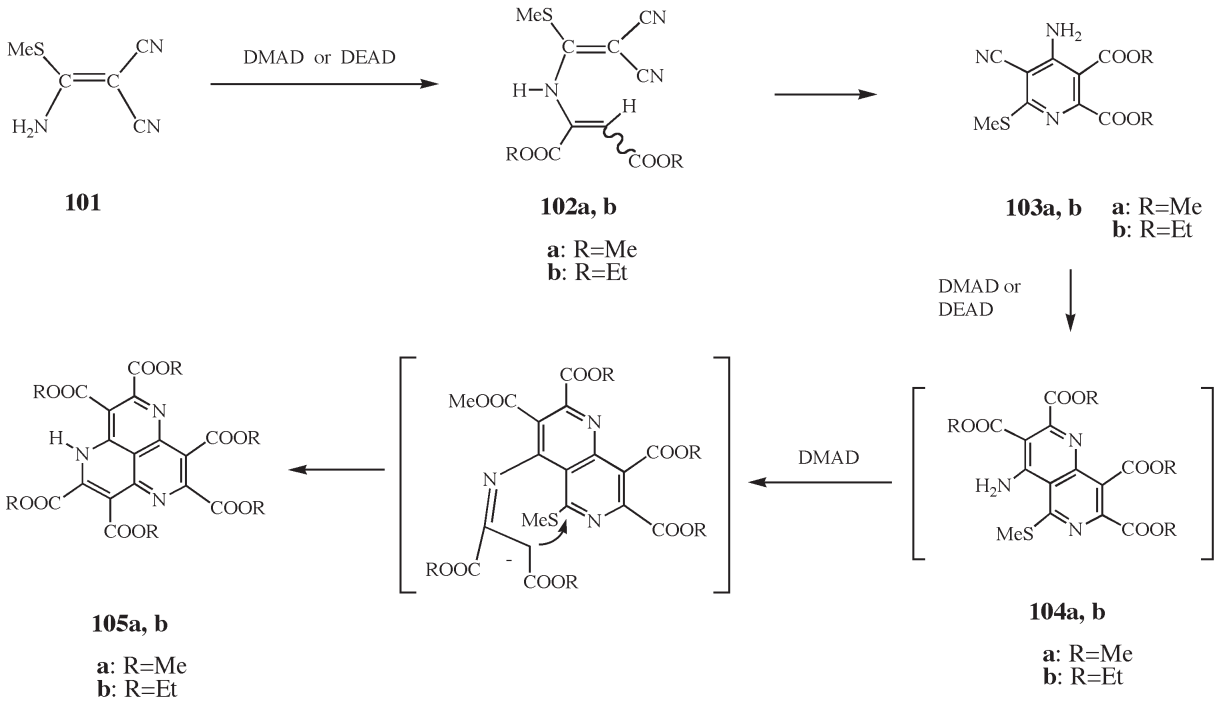
a: DMAD, $K_2CO_3$ in DMSO, room temperature, 20 h; b:10% HCl; c: $H_2NNH_2$-$H_20$, reflux in MeOH; d: reflux in MeOH, 30 min-1 h; e: reflux in diphenyl ether, 30 min;

3-Amino-3-methylthio-2-cyanoacrylonitrile (**101**), readily prepared by reaction of bis(methylthio)methylenepropanedinitrile with ammonium hydroxide in good yield, is one of the simplest compounds of a large number of ketene *N,S*-acetals and enaminonitriles. This compound should prove useful for the synthesis of nitrogen-containing heterocyclic compounds. Reaction of **101** with DMAD in the presence of potassium carbonate as a base in dimethyl sulfoxide (DMSO) gave the expected tricyclic heterocycle, hexamethyl 1*H*-1,4,7-triazaphenalene-2,3,5,6,8,9-hexacarboxylate (**105a**), in 68% yield. Tripotassium phosphate hydrate could also be employed as the base in this reaction, giving a yield of 70%. Diethyl acetylenedicarboxylate (DEAD) also reacted with **101** under the same reaction conditions to give **105b** in 63% yield [44a].

1*H*-quinolino[2,3,4-*de*][1,6]naphthyridine-2,3,5,6-tetracarboxylate (**108a**) in 33% yield.

In a similar manner, the reaction of 5-amino-6-cyanopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**106b**), which was prepared by the condensation of 6-aminouracils with ketene dithioacetal, bis(methylthio)-methylenepropanedinitrile, with DMAD in the presence of potassium carbonate or tripotassium phosphate gave a tetracyclic heterocycle, **108b**, in 53 and 35% yields, respectively. As shown in Entry 3, the reaction of **106b** with DEAD was also carried out under the same reaction conditions to give the corresponding tetracyclic compound, **108c**, in 59% yield. The corresponding pyrazolopyridine derivatives, **106c** and **d**, were allowed to react with DMAD giving the corresponding tetracyclic

Scheme 25




**101**

**102a, b**
**a**: R=Me
**b**: R=Et

**103a, b** **a**: R=Me **b**: R=Et

**104a, b**
**a**: R=Me
**b**: R=Et

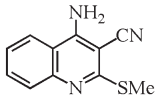
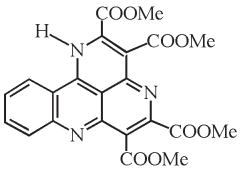
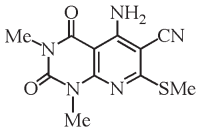
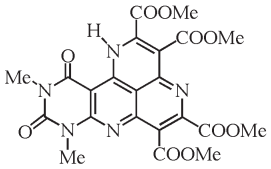
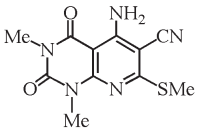
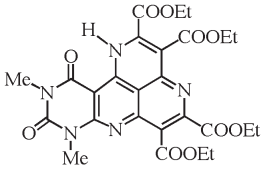
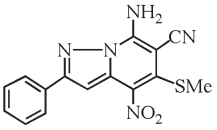
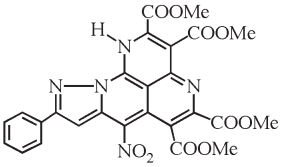
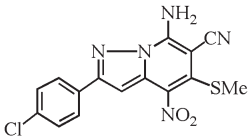
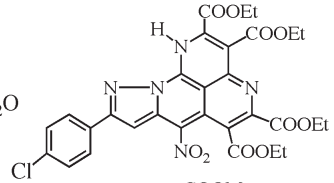
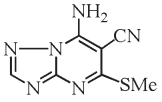
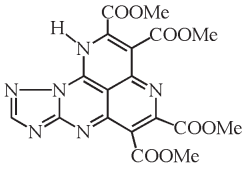
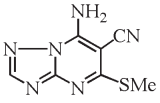
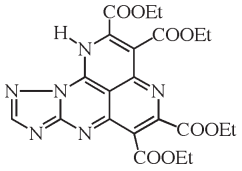
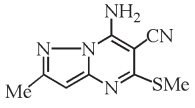
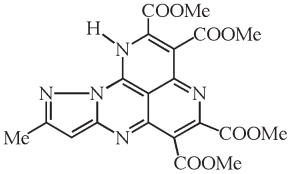
**105a, b**
**a**: R=Me
**b**: R=Et

A system of amino-cyano-methylthio-heterocycles containing pyridine or pyrimidine rings is a very important and versatile synthetic starting material for the construction of fused pyridine or pyrimidine derivatives. These heterocycles are generally obtained by the reaction of ketene dithioacetals with various nucleophiles. This synthesis of tricyclic heterocycles is applicable to the preparation of tetracyclic heterocycles. At first, the reaction of 4-amino-3-cyano-2-methylthioquinoline (**106a**) with DMAD in the presence of potassium carbonate in DMSO gave the corresponding tetramethyl

compounds, **108d** and **e**, in 75 and 56% yields, respectively. The above reaction could be readily applied to the synthesis of fused pyrimido[4,5,6-*d*,*e*][1,6]naphthyridine derivatives (**108f, g**), which were prepared by reaction of the corresponding triazolo[1,5-*a*]pyrimidine derivative (**106e**) with DMAD or DEAD in the presence of potassium carbonate, in 43 and 23% yields, respectively. Similarly, the reaction of pyrazolo[1,5-*a*]pyrimidine derivative (**106f**) with DMAD was carried out to give the corresponding tetracyclic compound, **108h**, in 47% yield [44b].

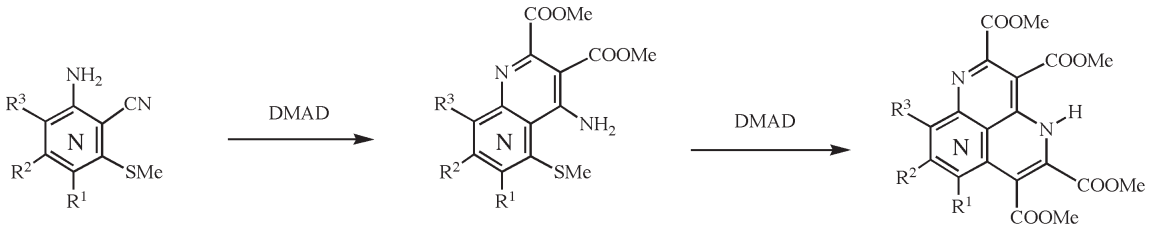
Table 3

Reaction of Amino-cyano-methylthio-heterocycles with Dialkyl Acetylenedicarboxylates in the Presence of Base [a]

| Entry | Aminonitrile | Acetylenic comp. | Base | Product | | Yield(%) |
|---|---|---|---|---|---|---|
| 1 |  **106a** | DMAD | $K_2CO_3$<br>$K_3PO_4$ $H_2O$ |  | **108a** | 33 |
| 2 |  **106b** | DMAD | $K_2CO_3$<br>$K_3PO_4$ $H_2O$ |  | **108b** | 53<br>35 |
| 3 |  **106b** | DEAD | $K_2CO_3$ |  | **108c** | 59 |
| 4 |  **106c** | DMAD | $K_2CO_3$ |  | **108d** | 75 |
| 5 |  **106d** | DEAD | $K_3PO_4$ $H_2O$ |  | **108e** | 56 |
| 6 |  **106e** | DMAD | $K_2CO_3$ |  | **108f** | 43 |
| 7 |  **106e** | DEAD | $K_2CO_3$ |  | **108g** | 23 |
| 8 |  **106f** | DMAD | $K_2CO_3$ |  | **108h** | 47 |

[a] The reactions were carried out in a system of **1** (20 mmol), DMAD or DEAD (30 mmol), and $K_2CO_3$ or $K_3PO_3$ $H_2O$ (50 mmol) at room temperature in DMSO.

Scheme 26




**106** **107** **108**

Ketene *N*,*S*-acetal, **101**, is a very useful starting material for preparing poly-functionalized pyridine and a novel tricyclic heterocycle, 1*H*-1,4,7-triazaphenalene, derivatives which should prove useful for the synthesis of poly-fused heterocyclic compounds as starting materials for obtaining biologically active compounds. The tandem addition-cyclization reaction of amino-cyano-methylthio-pyridine or -pyrimidine derivatives with dialkyl acetylenedicarboxylates in the presence of an appropriate base was found to be a versatile method of forming polycyclic heterocycles containing the 1,6-naphthyridine ring system.

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