SYNTHESIS OF THE NOVEL TRICYCLIC HETEROCYCLE, 1*H*-1,4,7-TRIAZAPHENALENE, PYRIDINE-CONTAINING RING SYSTEM: HEXAMETHYL 1*H*-1,4,7-TRIAZA-PHENALENE-2,3,5,6,8,9-HEXACARBOXYLATE

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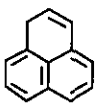
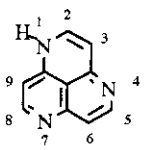
Abstract------The reaction of 3-amino-3-methylthio-2-cyanoacrylonitrile (**1**) with excess dimethyl acetylenedicarboxylate(DMAD) in the presence of potassium carbonate in dimethyl sulfoxide gave a novel tricyclic heterocycle, hexamethyl 1*H*-1,4,7-triazaphenalene-2,3,5,6,8,9-hexacarboxylate (**5**). When one equivalent of DMAD was used in this reaction, dimethyl 4-amino-3-cyano-2-methylthio-pyridine-5,6-dicarboxylate (**3**), a key intermediate of **5**, was obtained.

Ketene N,S-acetals[1-7], readily prepared by reactions of ketene dithioacetals[8-15] with various amine compounds in good yields, are very important and useful as building blocks for the synthesis of a wide variety of compounds. 3-Amino-3-methylthio-2-cyanoacrylonitrile (**1**)[16], readily prepared by reaction of bis-(methylthio)methylenepropanedinitrile[16] with ammonium hydroxide in good yield, is one of the simplest compound in a large number of ketene N,S-acetals and enaminonitriles[17-20]. This compound should prove useful for the synthesis of nitrogen-containing heterocyclic compounds. During the course of our studies on potential uses of ketene N,S-acetals, the reaction of **1** with DMAD was formed to produce a tricyclic hetero-



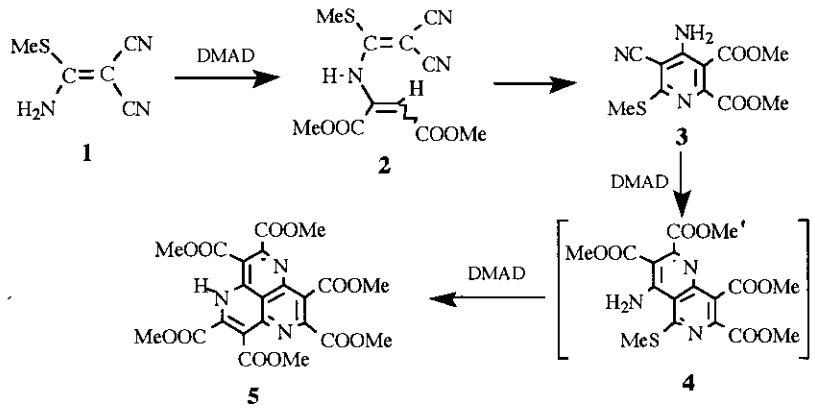
Phenalene



1*H*-1,4,7-Triazaphenalene

cycle, hexamethyl 1*H*-1,4,7-triazaphenalene-2,3,5,6,8,9-hexacarboxylate (**5**) which is a novel heterocyclic ring system.

Scheme 1



Reactions of enaminonitriles with DMAD give a variety of compounds.[19-22] The reaction of 1-substituted 5-aminopyrazole-4-carbonitriles with DMAD in the presence of potassium carbonate as a base gave 4-aminopyrazolo[3,4-*d*]pyridine-5,6-dicarboxylate in moderate yield.[19] This is surely a convenient method for generating poly functionalized pyridine derivatives from **1**. We examined the reaction of **1** with DMAD in the presence of a base to give dimethyl 2-methylthiopyridine-5,6-dicarboxylate, possibly of use for intermediates of biologically active compounds. At the start of the present study, the reaction of **1** with DMAD was studied

Table 1. Reactions of Ketene N, S-Acetal with DMAD in the Presence of a Base [a)]

1 + DMAD $\xrightarrow[\text{in DMSO}]{\text{Base}}$ **2** + **3**

No	Base(mmol)	Reac. Time.	Yield (%)[b)] **2**	Yield (%)[b)] **3**
1	K_2CO_3 (12)	8 h	37.3	24.8
2	K_2CO_3 (30)	24 h , 4 h (at 60°)	48.6	18.1
3	K_2CO_3 (30)	48 h	29.3	30.0
4	K_2CO_3 (40)	72 h	37.5	16.5
5	K_2HPO_4(12)	48 h	20.9	14.6
6	K_3PO_4 H_2O(15)	48 h	39.6	25.6
7	KOH(20)	48 h	22.0	-----
8	*t*-BuOK(12)	48 h	11.8	6.5
9	AcONa(20)	48 h	27.7	13.4
10	K_2HPO_4(10), K_2CO_3(10)	48 h	33.0	29.0

a) Reactions were carried out in a system of **1**(10 mmol) and DMAD(10 mmol) at room temperature in DMSO.
b) Isolated yield.

under various basic conditions. The results are summarized in Table 1. This reaction gave a cyclized product, 4-amino-3-cyano-2-methylthiopyridine-5,6-dicarboxylate(**3**)[23] from basic solution. Acidification of the mother liquor 3-(N-1',2'-bis(methoxycarbonyl)ethenylamino-2-cyano-3-methylthioacrylonitrile (**2**) was obtained. Potassium carbonate as a base gave the most effective results in the reaction of **1** with DMAD at room temperature in dimethyl sulfoxide. Other bases such as dipotassium hydrogen phosphate, tripotassium phosphate *n*-hydrate and potassium *ter*-butoxide also served efficiently as catalysts to give the corresponding **2** and **3**, but potassium hydroxide and sodium hydroxide were not effective for conversion to **3** or **5**. This reaction did not occurr without a base and starting material **1** was recovered. When excess DMAD (1.2 equ.) was used, a third product(**5**)[24] was obtained in 0.6% yield along with **2** in 20.7% and **3** in 19.2% yield. The yield of **5** *via* triple cyclization was improved with increase in the amount of DMAD in the presence of potassium carbonate in DMSO at room temperature, as shown in Table 2.

Table 2. Reaction of Ketene N,S-Acetal with DMAD in The Presence of Base [a)]

1 + DMAD $\xrightarrow[\text{in DMSO}]{\text{Base}}$ **2** + **3** + **5**

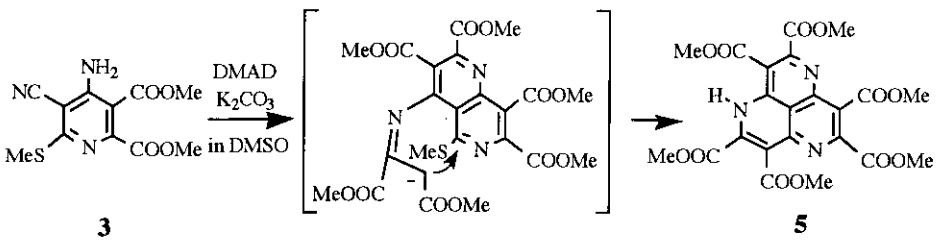
No	DMAD(mmol)	Base(mmol)	Reac. Time.	Yield (%) [b)] **2**	**3**	**5**
1	12	K_2CO_3 (30)	24 h	20.7	19.2	0.6
2	22	K_2CO_3 (30)	48 h	18.0	-----	17.1
3	32	K_2CO_3 (60)	48 h	17.7	-----	21.5
4	30	K_3PO_4 H_2O(40)	48 h	16.5	------	21.1

a) The reactions were carried out at room temperature in DMSO.

b) Isolated yield.

The reaction of **3** with DMAD in the presence of potassium carbonate or tripotassium phosphate hydrate in DMSO gave the expected tricyclic heterocycle, **5**, in 68 and 70% yields, respectively. However, the pyrido[4,3-*c*]pyridine derivative (**4**) of intermediate **5** could not be detect in any reaction mixture. Most crucial to the formation of **5** by reaction of **1** with DMAD was that of **3**.

Scheme 2



3 **5**

In conclusion, ketene N,S-acetal, **1**, is a very useful starting material for preparing of poly functionalized pyridine and a novel tricyclic heterocycle, 1*H*-1,4,7-triazaphenalene derivative which should prove useful for the synthesis of poly fused heterocyclic compounds as starting materials for obtaining biologically active compounds. Further development and application of ketene N,S-acetal reagents in the synthesis of heterocycles is underway at our laboratory and the rsults will be reported.

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23. **3**, mp 173-175°, colorless prisms (MeOH), ir(KBr) cm^{-1}: 3390, 3290(NH_2), 2220(CN), 1745, 1705 (CO). ^{1}H-Nmr($CDCl_3$) δ: 2.61(3H, s, SMe), 3.87(3H, s, OMe), 3.94(3H, s, OMe), 6.87(1H, bs, NH_2).
24. **5**, mp 231-241°, yellow prisms(MeOH + toluene), ir(KBr)cm^{-1}: 3195(NH), 1750, 1740, 1670(CO). ^{1}H-Nmr($CDCl_3$) δ: 3.97(6H, s, OMex2), 3.98(3H, s, OMe), 4.00(3H, s, OMe), 4.05(3H, s, OMe), 4.09(3H, s, OMe), 12.45(1H, bs, NH). FAB ms(M^++1, 518).

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