# SYNTHESIS OF AMINO-PYRIMIDOPYRIDAZINES AS CHEMILUMINESCENT COMPOUNDS BY REACTION OF FUNCTIONALIZED MALEIMIDE WITH VARIOUS AMINE DERIVATIVES

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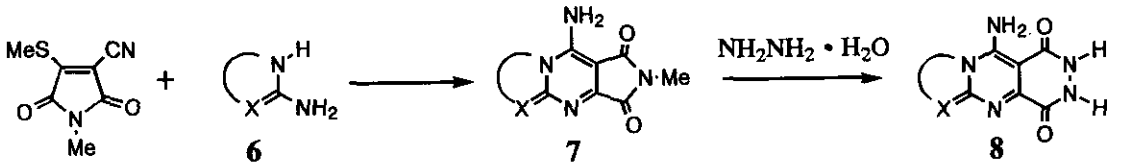
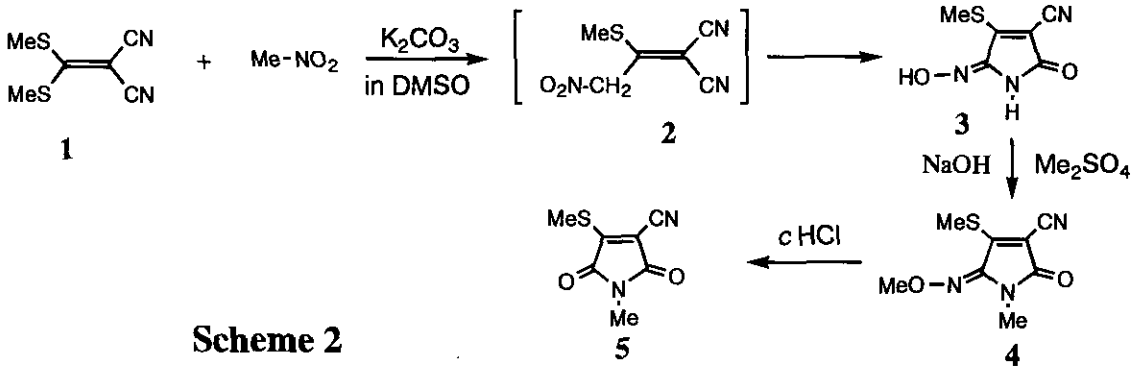
**Abstract**-------The reaction of ketene dithioacetal, bis(methylthio)methylenepropanedinitrile, with nitromethane gave 2-hydroxyimino-4-cyano-3-methylthiomaleimide (**3**) which was readily derived to the corresponding 4-cyano-3-methylthiomaleimide (**5**) by methylation with dimethyl sulfate followed by hydrolysis with hydrochloric acid. Compound **5** smoothly reacted with various amine compounds to give the corresponding amino-polycyclic pyrimidines containing a pyrroline ring, which were readily converted to the desired polycyclic pyridazine derivatives in good yields.

Fused or functionalized maleimides are synthetically useful intermediates for the preparation of polycyclic and functionalized pyridazine derivatives.[1,2] In an extension of our study on ketene dithioacetals for the synthesis of heterocycles,[3] we now wish to report here the preparation of new functionalized maleimides from ketene dithioacetal and their application to the synthesis of amino-polycyclic pyridazinediones which are to be anticipated the chemiluminescent compounds like luminol. In a previous paper, 1,3-disubstituted 4-amino-1*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazine-5,8(*6H,7H*)-diones were evaluated for their chemiluminescence in the presence of hydrogen peroxide, a phosphate buffer, and peroxidase in a dimethyl sulfoxide solution.[4] It has been reported that reaction of 1,3-disubstituted 5-aminopyrazole-4-carbonitriles with dimethyl acetylenedicarboxylate (DMAD) gave dimethyl 1,3-disubstituted 4-aminopyrazolo[3,4-*b*]pyridine-5,6-dicarboxylates which are key intermediates for the preparation of the above chemiluminescent compounds.[5] This addition-cyclization of *o*-aminonitrile compounds with DMAD is an important and general method for the simultaneously direct introduction of both the amino and dicarboxylate groups. In some cases, however, the formation of a pyridazine ring from the diesters does not proceed so smoothly as that from fused maleimide derivatives.[6] In the development of a new 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 as illustrated in Scheme 1.




**Scheme 1**

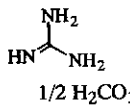
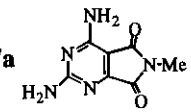
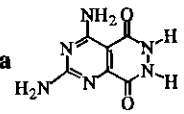
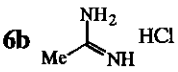
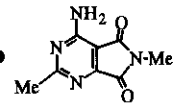
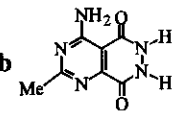
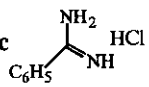
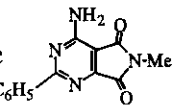
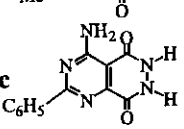
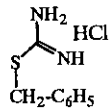
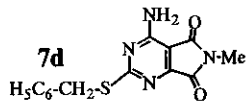
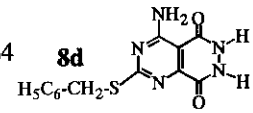
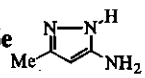
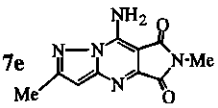
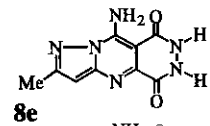
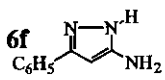
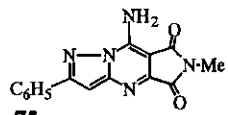
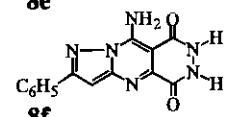
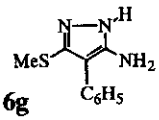
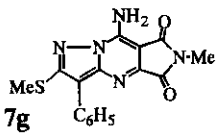
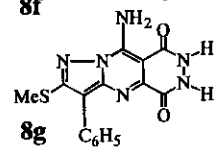
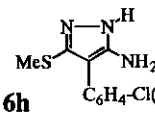
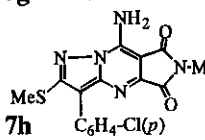
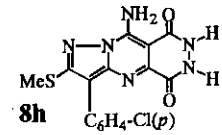
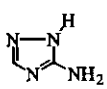
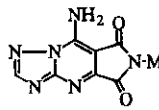
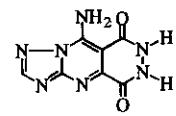
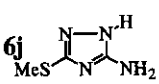
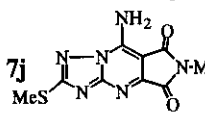
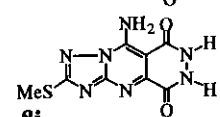
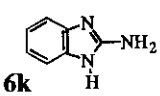
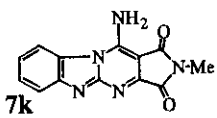
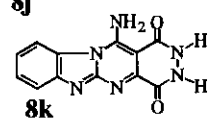
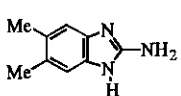
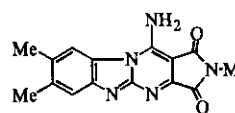
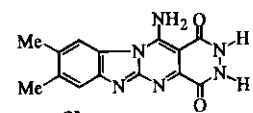
In the course of our studies on nitro ketene dithioacetal, we found an efficient method for the synthesis of 2-hydroxyimino-4-methoxycarbonyl-3-methylthiomaleimide derivatives by the reaction of nitro ketene dithioacetal with methyl cyanoacetate.[7] This method is useful for the synthesis of cyano-methylthio-maleimide derivatives. The reaction of bis(methylthio)methylenepropanedinitrile with nitromethane in the presence of potassium carbonate in dimethyl sulfoxide followed by treatment with hydrochloric acid gave 2-hydroxyimino-4-cyano-3-methylthiomaleimide (**3**) in 42% yield. The desired maleimide product (**5**)[8] was obtained by the methylation of **3** followed by hydrolysis with conc. hydrochloric acid in 48% yield (from **3**).




**Scheme 2**

It is known that the reaction of ketene dithioacetal (**1**) with bifunctionalized nucleophiles such as hydrazine or amidine derivatives gives the corresponding pyrazoles or pyrimidines in satisfactory yields.[3,9] The reaction of **5** with guanidine carbonate (**6a**) in the presence of triethylamine under refluxing in ethanol gave 2,4-diamino-6-methyl-6*H*-pyrrolo[3,4-*d*]pyrimidine-5,7-dione (**7a**) in 74% yield. Similarly, reaction of **5** with acetamidine hydrochlroride (**6b**), benzamidine hydrochloride (**6c**), and *S*-benzylisothiourea hydrochloride (**6d**) gave the corresponding fused pyrimidine derivatives (**7b-d**) in 56, 84, and 75% yields respectively. This method for preparation of pyrimidines was being applied to synthesis of polycyclic pyrrolopyrimidine derivatives. At first, the reaction of **5** with 3-amino-5-methylpyrazole (**6e**) under refluxing in ethanol gave 9-amino-2-methyl-1*H*-pyrrolo[3,4-*d*]pyrazolo[1,5-*a*]pyrimidine-1,3(2*H*)-dione (**7e**) in 91% yield. In a similar manner, 6-phenyl derivative (**7f**) was also obtained by the reaction of **5** with 2-amino-5-phenylpyrazole (**6f**) in 91% yield. In a previous paper on the study of chemiluminescence of polycyclic pyridazinediones, both methylthio and aryl groups were found to be very important substituted groups for increasing chemi-luminesence effects. 5-Aryl-6-methylthiopyrrolopyrazolopyrimidines (**7g, h**) are key intermediates for the final desired 5-aryl-6-methylthiopyrazolopyridopyridazinediones (**8g, h**). 5-Amino-3-methylthio-4-phenyl-pyrazole (**6g**), which was obtained by the reaction of 2-phenyl-3,3-bis(methylthio)-acrylonitrile, reacted with **5** under refluxing in ethanol to give **7g** in 92% yield. Compound (**7h**)[10] was also synthesized in 86% yield from **6h** and **5** in a manner similar to that described for the preparation of **7e**. 3-Aminotriazoles (**6i**, and **j**) were also smoothly reacted with **5** under the same reaction conditions to yield pyrrolotriazopyrimidines (**7i, j**) in 86 and 94% yields, respectively. Four ring system, pyrrolopyrimidobenzimidazole (**7k**)[11] was also synthesized by the reaction of **5** with 2-aminobenzimidazole (**6k**) in 93% yield. Similarly, 7,8-dimethyl derivative (**7l**) was synthesized from **5** and **6l** in 93% yield. The reaction of **7a-l** with hydrazine hydrate in ethanol afforded the corresponding polycyclic aminopyridazinediones (**8a-l**) in good yields as shown in Table

**Table 1. Synthesis of Amino-polycyclic Pyrrolopyrimidines and Polycyclic Pyridazinediones**

| Entry | Amines | 7 | mp °C Yield | 8 | mp °C Yield |
|---|---|---|---|---|---|
| 1 | **6a**  1/2 $H_2CO_3$ | **7a**  | >360 74% | **8a**  | >360 62% |
| 2 | **6b**  | **7b**  | 304-305 56% | **8b**  | >360 94% |
| 3 | **6c**  | **7c**  | 236-237 84% | **8c**  | >360 99% |
| 4 | **6d**  | **7d**  | 183-184 75% | **8d**  | 320-325 79% |
| 5 | **6e**  | **7e**  | >360 91% |  **8e** | >360 98% |
| 6 | **6f**  |  **7f** | >360 91% |  **8f** | >360 87% |
| 7 |  **6g** |  **7g** | 296-298 92% |  **8g** | >360 92% |
| 8 |  **6h** |  **7h** | 351-352 86% |  **8h** | >360 98% |
| 9 | **6i**  | **7i**  | 356-357 86% |  **8i** | >360 84% |
| 10 | **6j**  | **7j**  | 357-359 94% |  **8j** | >360 94% |
| 11 |  **6k** |  **7k** | 346-347 93% |  **8k** | >360 87% |
| 12 |  **6l** |  **7l** | >360 93% |  **8l** | >360 92% |

1.[11]

It is evident from the present data that the new maleimide (**5**) is a very useful and convenient reagent for the synthesis of amino-polycyclic heterocycles.

REFERENCES AND NOTES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2. *a*) W. A. Noyes and P. K. Porter, *Org. Synth.* Coll. Vol. 1, 1956, 457; *b*) M. Sato and S. Ebine, *Synthesis*, 1981, 472; *c*) R. B. Brundrett, D. F. Roswell, and E. H. White, *J. Am. Chem. Soc.*, 1972, **94**, 7536.
3. a) Y. Tominaga, *Trends in Heterocyclic Chemistry*, 1991, **2**, 43; *b*) Y. Tominaga, S. Kohra, H. Honkawa, and A. Hosomi, *Heterocycles*, 1989, **29**, 1409; *c*) R. K. Dieter, *Tetrahedron*, 1986, **42**, 3029; *d*) H. Junjappa, H. Ila, and C. V. Asoka, *Tetrahedron*, 1990, **46**, 5423; *e*) M. Kolb, *Synthesis*, 1990, 171.
4. Y. Tominaga, N. Yoshioka, S. Kataoka, T. Hata, N. Aoyama, T. Masunari, and A. Miike, *Tetrahedron Lett.*, 1995, **36**, 8641.
5. *a*) Y. Tominaga, J. -K. Luo, L. W. Castle, and R. N. Castle, *J. Heterocycl. Chem.*, 1993, **30**, 267; *b*) Y. Tominaga, R. N. Castle, and N. K. Dalley, *J. Heterocycl. Chem.*, 1993, **30**, 295.
6. *a*) G. Adembri, F. De Sio, R. Nesi, and M. Scotton, *J. Heterocycl. Chem.*, 1975, **12**, 95; *b*) M. N. Khan, *J. Org. Chem.*, 1995, **60**, 4536.
7. *a*) M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, 1973, **93**, 1008; *b*) *Idem*, *Chem. Pharm. Bull.*, 1973, **21**, 1667.
8. **5**, mp 110°C, yellow needles. Ir(KBr) ν $cm^{-1}$: 2220(CN), 1765, 1710 (CO). Nmr($CDCl_3$) δ: 2.94(3H, s, SMe), 3.08(3H, s, NMe). Ms *m/z*: 162($M^+$, 100), 138(28), 125(18), 110(37), 97(81), 82(26).
9. *a*) W. J. Middleton and V. A. Engelhardt, *J. Am. Chem. Soc.*, 1958, **80**, 2829; *b*) Y. Tominaga, S. Kohra, H. Honkawa, and H. Hosomi, *Heterocycles*, 1989, **29**, 1409.
10. Compounds(**8k** and **l**)were found to be efficiently chemiluminescent in a similar to luminol in the presence of $H_2O_2$, horseradish peroxidase in a solution of a phosphate buffer pH 8.0. The result of studies on the chemiluminescence of these compounds (**8a-l**) will be published in a forthcoming paper.
11. Satisfactory spectral (ir, uv, $^1$H-nmr, ms) data were obtained for all new compounds in this work. **7k**: 11-Amino-2-methyl-1*H*-pyrrolo[3',4':4,5]pyrimido[1,2-*a*]benzimidazole-1,3(2*H*)-dione. Ir(KBr)ν $cm^{-1}$: 3400(NH), 3100-2800(broad), 1762, 1705(CO), 1650, 1600, 1515. Uv(EtOH, insufficient solubility)λ max nm: 208, 237, 261, 420. Ms *m/z* 267(73), 182(21), 138(22), 133(32), 58(23), 45(100). **8k**: 12-Aminopyridazino[4',5':4,5]pyrimido[1,2-*a*]benzimidazole-1,4(*2H,3H*)-dione. Ir(KBr) ν $cm^{-1}$: 3400(NH), 3100-2800(broad), 1762, 1705(CO), 1650, 1600, 1515. Uv(EtOH, insufficient solubility)λ max nm: 242, 270, 311, 384. Nmr((DMSO-$d_6$) δ : 7.26(1H, m, aromatic-H), 7.41(1H, m, aromatic-H), 7.61(1H, m, aromatic-H), 8.29(1H, s, NH), 8.65(1H, d, *J*=5.5 Hz, aromatic-H). Ms *m/z* 268($M^+$, 63), 100(12), 98(20), 57(24), 44(100).


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