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# SYNTHESIS OF 3-METHYLTHIO-4-ARYL-3-PYRROLINE-2,5-DIONES AND 3-ARYLPYROLIDINE-2,5-DIONES BY REACTION OF NITROKETENE DITHIOACETAL WITH ARYLACETONITRILES

Yasuhiro Shigemitsu[a] and Yoshinori Tominaga*[b]

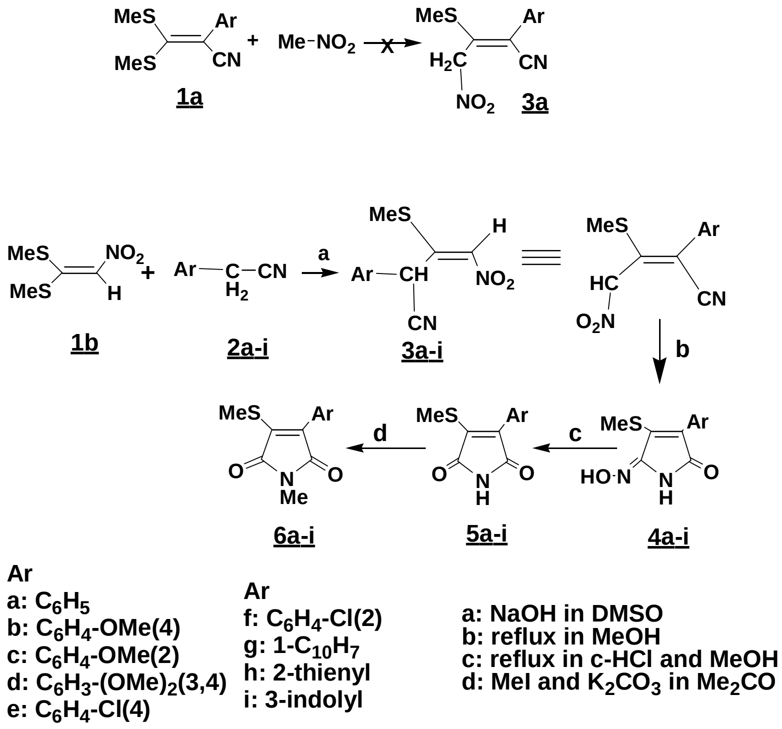
[a]Industrial Technology Center of Nagasaki, 2-1303-8 Ikeda, Omura, Nagasaki 856-0026, Japan; [b]Center of Instrumental Analysis, Nagasaki University, 1-14, Bunkyo-machi, Nagasaki 852-8521, Japan

Abstract — The reaction of nitroketene dithioacetal (**1a**), i.e., 2,2-bis(methylthio)-1-nitroethylene, with arylacetonitriles (**2a-I**) in the presence of the base like sodium hydroxide gave 4-nitrobut-2-enenitriles (**3a-I**) which were converted into 5-hydroxyimino-4-methylthio-3-phenyl-3-pyrrolin-2-ones (**4a-i**) under refluxing in methanol. Title compounds (**5a-i**) were readily obtained by the treatment of **4a-i** with hydrochloric acid and were finally led to *N*-methylated products (**6a-I**) with methyl iodide. The reduction of maleimides (**4 – 6**) with zinc dust in acetic acid afforded the corresponding 3-arylpyrrolidine-2,5-diones (**7a-i**) that can be converted to pharmacologycally active compounds like mesembrines.

It is considered useful and significant to newly exploit an efficient synthetic route to afford 3-arylpyrrolidine-2,5-diones, very important starting materials of some natural products like mesembrine which is isolated from *Mesembryanthemum tortuosum*.[1,2] We previously reported the synthesis of 4-methylthiomaleimides (3-methylthio-3-pyrroline-2,5-diones) bearing a cyano or a methoxycarbonyl group as an electron-withdrawing group *via* the reaction of ketene dithioacetal[3] with nitromethane in the presence of appropriate base.[4] With their high electrophilic nature, 4-methylthiomaleimides serve as key intermediates for the preparation of some heterocycles like pyridazine derivatives with chemiluminescence and are also applicable to the synthesis of other heterocycles. Following the similar strategy for preparing 4-methylthiomaleimides, we now wish to report the convenient synthesis of 3-methylthio-4-aryl-3-pyrroline-2,5-diones by using the reaction of nitroketene dithioacetal[5] with aryl acetonitriles followed by their reduction with zinc dust that gives 3-arylpyrrolidine-2,5-diones, i.e., arylsuccinimides.

**Synthesis of 3-methylthio-4-aryl-3-pyrroline-2,5-diones (arylmaleimides).**

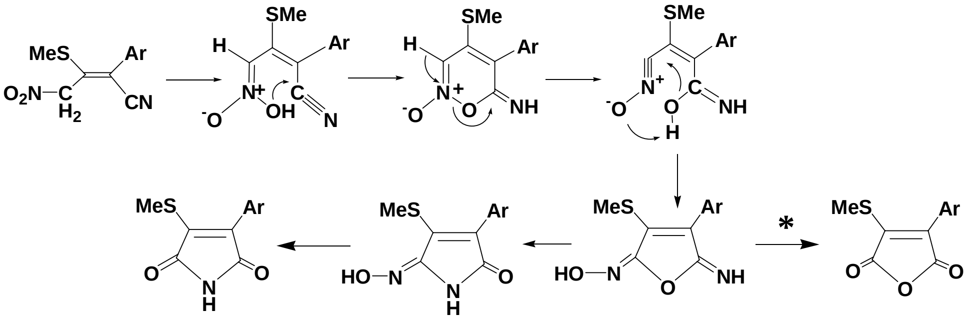
A synthesis of arylmaleimides were initially examined by the reaction of ketene dithioacetal (**1a**) with nitromethane in the presence of sodium hydroxide in dimethyl sulfoxide (DMSO) in an attempt to prepare 3-methylthio-4-nitro-2-phenylbut-2-enenitrile (**3a**).[6] Since we found this reaction did not proceed smoothly, alternative reaction was newly explored to obtain **3a** as described in Scheme 1. The reaction of nitroketene dithioacetal (**1b**) with phenylacetonitriles (**2a-i**) in the presence of powdered sodium hydroxide in DMSO at room temperature smoothly occurred to yield **3a-i** that are key intermediates of the desired maleimides and were used in next reaction without purification. Compounds (**3a-i)** were treated with methanol under refluxing to yield 5-hydroxyimino-4-methylthio-3-phenyl-3-pyrrolin-2-ones (**4a-i**). The outline of reaction pathway from **3** to **4** is shown in Scheme 2. Conversion of **4a-i** into **5a-i** was promptly carried out by the hydrolysis of hydroxyimino group with ***conc.*** hydrochloric acid in moderate to good yields (74-98%). We subsequently tried the methylation of **5a-i** as one of the simplest alkylations with methyl iodide in the presence of potassium carbonate in acetone. This reaction gave the corresponding methylated products (**6a-i**) in good yields as shown in Table1.



**Scheme 1**

**Table 1 Melting points and yields of 5-aryl-4-methylthiomaleimides**

| Entry | R | 4 | mp(°C)<br>Yield(%) | 5 | mp(°C)<br>Yield(%) | 6 | mp(°C)<br>Yield(%) |
|---|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | 4a | 234-235<br>84 | 5a | 93-94<br>91 | 6a | 61-62<br>94 |
| 2 | $C_6H_4OMe(4)$ | 4b | 214-215<br>85 | 5b | 175-178<br>90 | 6b | 74-75<br>94 |
| 3 | $C_6H_4OMe(2)$ | 4c | 195-196<br>77 | 5c | 131-132<br>84 | 6c | 91-92<br>94 |
| 4 | $C_6H_3(OMe)_2(3,4)$ | 4d | 202-203<br>84 | 5d | 182-183<br>91 | 6d | 110-111<br>95 |
| 5 | $C_6H_4Cl(4)$ | 4e | 250-251<br>74 | 5e | 134-135<br>84 | 6e | 70-71<br>96 |
| 6 | $C_6H_4Cl(2)$ | 4f | 200-202<br>67 | 5f | 127-128<br>98 | 6f | 58-59<br>95 |
| 7 | 1-naphtyl | 4g | 250-251<br>75 | 5g | 144-145<br>74 | 6g | 124-125<br>92 |
| 8 | 2-tienyl | 4h | 239-241<br>54 | 5h | 152-153<br>79 | 6h | 69-70<br>92 |
| 9 | 3-indolyl | 4i | 249-251<br>38 | 5i | 185-187<br>88 | 6i | 131-132<br>92 |



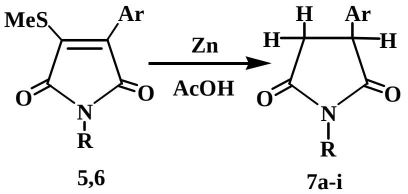
**Scheme 2 Reaction Mechanism**

(* Treatment of 3 with *conc.* hydrochloric acid gave 3-methylthio-4-arylfuran-2,5-diones.)

## Synthesis of Succinimides by the Reduction of Maleimides

Succinimides obtained by the reduction of maleimides derivatives are important as starting materials of natural products like mesembrine and pharmacologically active compounds like methosuximide.[1,2] Desulfurization of **6a** with Raney nickel (W-2) in refluxed ethanol gave only 4-phenylsuccinimide (1-methyl-3-phenylpyrrolidine-2,5-dione) (**7e**) in 28% yield. Incidentally, zinc in acetic acid is applicable to a wide range of reduction reactions.[5] This reagent has also been chosen to demonstrate selective reduction in sensitive, polyfunctional molecules. By using a general method, the reduction of **5a** employing zinc dust in acetic acid under refluxing afforded the corresponding 4-phenylsuccinimide (**7a**) in 98% yield. Other succinimide products (**7b-i**) were obtained in a similar way from the corresponding maleimides (**5**,**6**) in good yields as shown in Table 2. These succinimides (**7a-d**) were also obtained from the corresponding hydroxyimino compounds (**4**) in good yields as shown in Table 3. The intermediates in this reaction are thought to be imino compounds and were readily converted to carbonyl compounds through hydrolysis. In

**Table 2. Synthesis of 4-Arylsuccinimides from 4-Arylmaleimides by Zinc Reduction [a]**



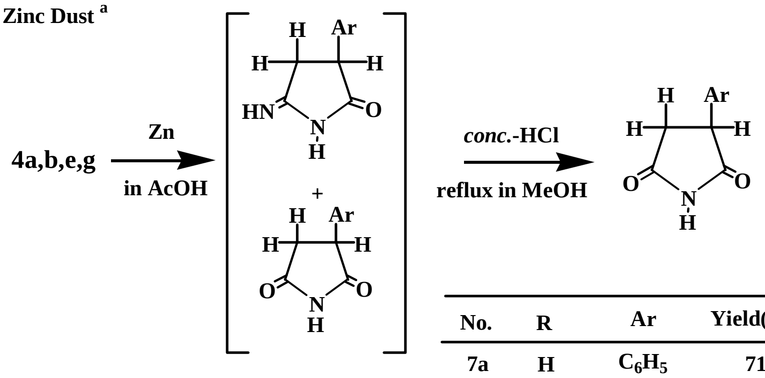
**5,6** **7a-i**

| No. | R | Ar | mp(°C) | Yield(%) |
|---|---|---|---|---|
| 7a | H | $C_6H_5$ | 68-69 | 98(28)[b] |
| b | H | $C_6H_4$-OMe(4) | 128-129 | 92 |
| c | H | $C_6H_4$-Cl(4) | 130-131 | 92 |
| d | H | 1-Naphthyl | 134-135 | 97 |
| e | Me | $C_6H_5$ | 54-55 | 93 |
| f | Me | $C_6H_4$-OMe(4) | 114-115 | 85 |
| g | Me | $C_6H_4$-Cl(4) | 97-98 | 82 |
| h | Me | 1-Naphthyl | 97-98 | 82 |
| i | Me | 2-Thienyl | 75-76 | 83 |

[a] All reactions were carried out in asystem of **5**,**6** (1.0 mmol) and zinc dust (5.0 mmol) in acetic acid (20 mL) under reflux for 1 h.

[b] This yield was obtained by using Raney nickel.

**Table 3. Reduction of 5-Hydroxyimino-4-methylthio-3-phenyl-3-pyrrolin-2-ones with Zinc Dust [a]**



| No. | R | Ar | Yield(%) |
|---|---|---|---|
| 7a | H | $C_6H_5$ | 71 |
| b | H | $C_6H_4$-OMe(4) | 74 |
| c | H | $C_6H_4$-Cl(4) | 72 |
| d | H | 1-Naphthyl | 91 |

[a] All reactions were carried out in a system of **4** (1.0 mmol) and zinc dust (5.0 mmol) in acetic acid (29 mmol) under reflux for 1 h.

conclusion, 4-aryl- and heteroaryl-3-methylthio-3-pyrroline-2,5-dione derivatives were readily obtained through the reaction of nitroketene dithioacetal with aryl- or heteroarylacetonitriles. This is a new synthetic example of nitroktene dithioacetal with active methylene compounds of benzyl types.

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