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A Facile Generation and Stereoselective Cycloaddition Reactions of 5,6-Dihydro-5,6-bis(methylene)-2,4(1*H*,3*H*)-pyrimidinedione Intermediate[1]

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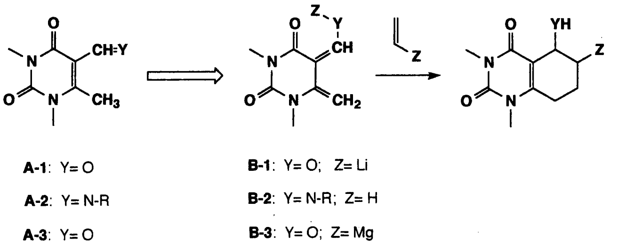
Synopsis. The treatment of 5-formyl-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**1**) with a magnesium salt and DBU in dichloromethane gave the corresponding magnesium dienolate. The dienolate underwent [4+2] cycloaddition reaction with olefinic dienophiles in highly regio- and stereoselective manners.

Much attention has been focused on the chemistry of novel diene systems which are located at the periphery of heterocycles. Recently, we reported the synthetic usefulness of 5,6-dihydro-5,6-bis(methylene)-2,4(1*H*,3*H*)-pyrimidinedione (**B**), which underwent inter- and intramolecular cyclization reactions leading to fused pyrimidine derivatives.[2]



Scheme 1.

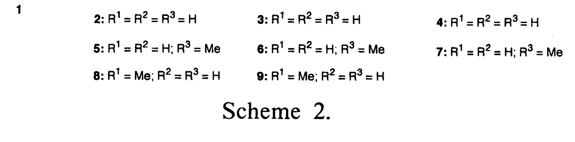
Two typical methods were known for the generation of the intermediate **B**: One involves the use of a strong base (e.g. LDA) to form **B-1** by enolization of the corresponding formyl substrate **A-1**.[3] Another involves the thermal 1,5-hydrogen shift of the imine substrate **A-2** giving 5,6-dihydro-5-aminomethylene-6-methylene-2,4(1*H*,3*H*)-pyrimidinedione (**B-2**).[2b] The [4+2] cycloaddition reactions using these diene intermediates **B** were also reported in the literature.[2,3] These generation methods, however, have some limitations. While the diene intermediate **B-2** has a relatively high reactivity, the 1,5-hydrogen shift of **A-2** requires an elevated reaction temperature. This results in the lowering of the stereoselectivity of the cycloaddition reaction. On the other hand, the use of a strong base would lean the equilibrium toward enolate **B-1** exclusively. However, the reaction of **B-1** with olefins bearing one electron-withdrawing substituent afforded only disappointing results.[3] We, therefore, decided to develop metal dienolates possessing higher reactivity and selectivity.

We wish to report here a facile and improved generation method of a magnesium dienolate **B-3** using magnesium salts and an organic base. The highly controlled [4+2] cycloaddition reactions of **B-3** with olefins bearing one electron-withdrawing substituent will be described.

At first the treatment of **1** with a metal salt and an organic base for the lithium dienolate generation was investigated; the treatment of 5-formyl-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**1**) with lithium chloride and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU)[4] in THF in the presence of methyl acrylate (**2**) gave the desired quinazoline derivatives **3** and **4** (**3**/**4**=8/1) in 50% yield. The structural elucidation based on their spectral data revealed that the formation of **3** ($J_{5,6}$=3.3 Hz; cis) was due to an endo approarch of **2** to the magnesium dienolate **B-3** with *Z*-configuration,[2b] and that **4** ($J_{5,6}$=8.4 Hz, trans) was due to an exo one.

The effect of metal ion species was investigated. Magnesium salts gave the best results among the examined salts of lithium, magnesium, manganese, copper, zinc, and so on. Interestingly, Lewis acid catalysts such as tetrabutyltin chloride, ethylaluminum dichloride, diethylaluminum chloride, and bis(cyclopentadienyl)titanium dichloride afforded only disappointing results. With magnesium salts, the effect of solvent was examined. The use of dichloromethane without purification (containing methanol as a stabilizer) gave the best results. The treatment of **1** with magnesium dibromide etherate and DBU in dichloromethane gave **3** as a single product in a quantitative yield. Surprisingly, the magnesium dienolate is stable in methanol to give **3** and **4** in 75% yield (Run 6). The alternative use of magnesium dichloride or magnesium dibromide etherate in the presence of DBU in dichloromethane afforded optimal results in the reaction with olefinic dienophiles bearing one electron-withdrawing substituent; the reaction of **1** with methyl methacrylate (**5**) gave diastereomeric products **6** and **7** in 80% yield (**6**/**7**=10/1) (Run 16). A single product **9** was obtained by the reaction with methyl crotonate (**8**) in 54% yield (Run 18). The selected results are summarized in Table 1.

The reaction with 2-cyclohexen-1-one (**10**) gave a benzoquinazoline derivative **12** as a final product

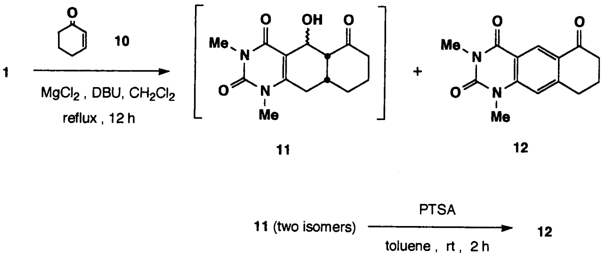


Scheme 2.

Table 1. Reaction of 5-Formyl-1,3,6-trimethyl-2,4(1*H*,3*H*)pyrimidinedione (**1**) with Metal Salt and DBU in the Presence of Dienophiles **2**, **5**, and **8**

Run	Metal salt	Dienophile	Solvent	Time/h	Temp	Products Ratio of products[a)] (Total yield[b)]/%)
1	None	**2**	THF	24	r.t.	No reaction
2	$MgCl_2$	**2**	THF	3	r.t.	**3**/**4**=8/1 (68)
3	$MgCl_2$	**2**	THF	3	Reflux	**3**/**4**=6/1 (81)
4	$MgCl_2$	**2**	CH_2Cl_2	12	r.t.	**3**/**4**=9/1 (85)
5	$MgCl_2$	**2**	CH_2Cl_2[c)]	12	Reflux	**3**/**4**=5/1 (91)
6	$MgCl_2$	**2**	CH_3OH	0.5	Reflux	**3**/**4**=5/1 (75)
7	$(C_2H_5)_2OMgBr_2$	**2**	CH_2Cl_2[c)]	12	r.t.	**3** (quant.)
8	LiCl	**2**	CH_2Cl_2	12	r.t.	**3**/**4**=9/1 (69)
9	LiCl	**2**	THF	12	r.t.	**3**/**4**=9/1 (52)
10	$MnCl_2$	**2**	CH_2Cl_2[c)]	4	Reflux	**3**/**4**=1/1 (39)
11	Bu_4SnCl	**2**	CH_2Cl_2[c)]	24	Reflux	**3**+**4**[d)] (25)
12	$(C_2H_5)AlCl_2$	**2**	CH_2Cl_2[c)]	24	Reflux	**3**+**4**[d)] (25)
13	$(C_5H_5)_2TiCl_2$	**2**	CH_2Cl_2[c)]	24	Reflux	(Trace)
14	$CuCl_2$	**2**	CH_2Cl_2[c)]	24	Reflux	(Trace)
15	$ZnCl_2$	**2**	CH_2Cl_2[c)]	24	Reflux	No reaction
16	$MgCl_2$	**5**	CH_2Cl_2[c)]	24	Reflux	**6**/**7**=10/1 (80)
17	$(C_2H_5)_2OMgBr_2$	**5**	CH_2Cl_2[c)]	24	Reflux	**6**/**7**=7/1 (66)
18	$(C_2H_5)_2OMgBr_2$	**8**	CH_2Cl_2[c)]	24	Reflux	**9** (54)
19	$MgCl_2$	**8**	CH_2Cl_2[c)]	24	Reflux	**9** (48)

a) Determined by ^{1}H NMR spectrum of the crude products. b) Based on isolated products. c) Contains methanol (below 0.7%) as a stabilizer. d) The ratio was not determined.



Scheme 3.

(Scheme 3).

This paper described the improved method for dienolate generation from 5-formyl-1,3,6-trimethyl-2,4-(1*H*,3*H*)-pyrimidinedione (**1**) using magnesium salts and organic bases. We believe that this method will give a powerful tool for the dienolate generation in similar heterocyclic systems.

Experimental[5)]

The Reaction of 1 with a Metal Salt and DBU in the Presence of Methyl Acrylate (2). General Procedure: To a suspension of **1** (0.182 g, 1.0 mmol), methyl acrylate (**2**, 1.1 mmol), and magnesium dichloride (0.5 mmol) in dichloromethane (4 mL), DBU (1.0 mmol) in dichloromethane (1 mL) was added. The reaction mixture was heated under reflux for 12 h. The solvent was evaporated to dryness. The residue was subjected to chromatography through a short silica gel column (hexane/ethyl acetate=1/4) to give a mixture of **3** and **4** (0.224 g; 91%; **3**/**4**=5/1). Flash chromatography of the mixture on silica gel (hexane/ethyl acetate=1/3) gave **3** and **4**, respectively.

***r*-5-Hydroxy-*c*-6-methoxycarbonyl-1,3-dimethyl-5,6,7,8-tetrahydro-2,4(1*H*,3*H*)-quinazolinedione (3):** Colorless prisms (ethyl acetate); mp 151—152 °C; IR 3430, 1710, 1700, 1650 cm^{-1}; ^{1}H NMR δ=2.15 (2H, ov, 7-H), 2.4—2.6 (2H, ov, 6- and 8-H), 2.78 (1H, m, 8-H), 3.29 (1H, br, OH), 3.36, 3.41 (each 3H, 2s, N-CH$_3$), 3.78 (3H, s, OCH$_3$), 5.26 (1H, t, J=3.3 Hz, 5-H); ^{13}C NMR δ=18.2 (7-C), 26.6 (8-C), 28.1, 31.0 (N-CH$_3$), 43.9 (6-C), 52.1 (OCH$_3$), 61.9 (5-C), 110.4 (4a-C), 150.4 (8a-C), 151.8 (2-C), 162.7 (4-C), 172.2 (COO); MS *m/z* 268 (M$^+$). Anal. Calcd for $C_{12}H_{16}N_2O_5$: M, 268.3.

***r*-5-Hydroxy-*t*-6-methoxycarbonyl-1,3-dimethyl-5,6,7,8-tetrahydro-2,4(1*H*,3*H*)-quinazolinedione (4):** Colorless prisms (ethyl acetate); mp 147—149 °C; IR 3430, 1740, 1700, 1650 cm^{-1}; ^{1}H NMR δ=2.0, 2.2 (each 1H, 2m, 7-H), 2.5—2.7 (2H, ov, 8-H), 2.80 (1H, m, 6-H), 3.36, 3.40 (each 3H, 2s, N-CH$_3$), 3.74 (3H, s, OCH$_3$), 4.18 (1H, br, OH), 5.15 (1H, d, J=8.4 Hz, 5-H); ^{13}C NMR δ=21.2 (7-C), 25.4 (8-C), 28.0, 31.1 (N-CH$_3$), 45.0 (6-C), 52.2 (OCH$_3$), 64.9 (5-C), 109.5 (4a-C), 149.6 (8a-C), 151.6 (2-C), 163.4 (4-C), 173.3 (COO); MS *m/z* 268 (M$^+$). Anal. Calcd for $C_{12}H_{16}N_2O_5$: M, 268.3.

***r*-5-Hydroxy-*c*-6-methoxycarbonyl-1,2,6-trimethyl-5,6,7,8-tetrahydro-2,4(1*H*,3*H*)-quinazolinedione (6):** Colorless prisms (ethyl acetate); mp 176—178 °C; IR 3430, 1730, 1700, 1630 cm^{-1}; ^{1}H NMR δ=1.12 (3H, s, 6-CH$_3$), 2.0 (1H, m, 7-H), 2.2—2.4 (3H, ov, 7- and 8-H), 2.72 (1H, ddd, J=16.8, 5.9, 2.2 Hz, 8-H), 3.34 (1H, br, OH), 3.36, 3.41 (each 3H, 2s, N-CH$_3$), 3.37 (3H, s, OCH$_3$), 4.89 (1H, dd, J=4.0, 1.5 Hz, 5-H); ^{13}C NMR δ=19.0 (6-CH$_3$), 23.4, 23.8 (7- and 8-C), 28.1, 30.9 (NCH$_3$), 44.9 (6-C), 52.1 (OCH$_3$), 67.0 (5-C), 108.8 (4a-C), 149.5 (8a-C), 151.8 (2-C), 163.0 (4-C), 175.8 (COO); MS *m/z* 282 (M$^+$). Anal. Calcd for $C_{13}H_{18}N_2O_5$: M, 282.3.

***r*-5-Hydroxy-*t*-6-methoxycarbonyl-1,3,6-trimethyl-5,6,7,8-tetrahydro-2,4(1*H*,3*H*)-quinazolinedione (7):** Colorless prisms (ethyl acetate); mp 210—222 °C; IR 3430, 1730, 1700, 1630 cm^{-1}; ^{1}H NMR δ=1.36 (3H, s, 6-CH$_3$), 1.97 (1H, m, 8-H), 2.3—2.5 (2H, ov, 7- and 8-H), 2.65 (1H, m, 7-H), 3.28, 3.30 (each 3H, 2s, N-CH$_3$), 3.52 (1H, br, OH), 3.66 (3H, s, OCH$_3$), 5.08 (1H, br, 5-H). Anal. Calcd for $C_{13}H_{18}N_2O_5$: M, 282.3.

***r*-5-Hydroxy-*c*-6-methoxycarbonyl-1,3,*t*-7-trimethyl-5,6,7,8-tetrahydro-2,4(1*H*,3*H*)-quinazolinedione (9):** Colorless prisms (ethyl acetate); mp 220—222 °C; IR 3420, 1740, 1700, 1650 cm^{-1}; ^{1}H NMR δ=1.18 (3H, d, J=6.6 Hz, 7-CH$_3$), 2.11 (1H, dd, J=18.0, 10.3 Hz, 8-H), 2.35 (1H, dd, J=11.7, 3.7 Hz, 7-H), 2.57 (1H, m, 7-H), 2.83 (1H, dd, J=18.0, 5.5 Hz, 8-

H), 3.36, 3.41 (each 3H, 2s, N–CH_3), 3.37 (1H, ov, OH), 5.11 (1H, br t, J=3 Hz, 5-H); ^{13}C NMR δ=19.6 (7-CH_3), 24.8 (8-C), 28.1, 30.9 (N–CH_3), 34.8 (7-C), 50.3 (6-C), 51.9 (OCH_3), 63.1 (5-C), 109.2 (4a-C), 149.6 (8a-C), 151.8 (2-C), 162.5 (4-C), 172.7 (COO); MS m/z 282 (M^+). Anal. Calcd for $C_{13}H_{18}N_2O_5$: M, 282.3.

Reaction of 1 with Magnesium Chloride and DBU in the Presence of 2-Cyclohexen-1-one (10). Similar procedures gave a mixture of the [4+2] cycloadducts **11** (two diastereomers) and **12**. The primarily formed cycloadducts **11** were liable and converted to **12** during working-up. The treatment of the reaction mixture with *p*-toluenesulfonic acid followed by usual column separation gave **12** in 38% yield.

1,3-Dimethyl-8,9-dihydrobenzo[*g*]quinazoline-2,4,6-(1*H*,3*H*,7*H*)-trione (12): Colorless needles (ethyl acetate); mp 283—285 °C; IR 1730, 1700, 1630 cm^{-1}; ^{1}H NMR δ=2.18 (1H, m, 8-H), 2.69 (2H, t, J=6.4 Hz, 9-H), 3.08 (2H, t J=6.1 Hz, 7-H), 3.47, 3.62 (each 3H, 2s, N–CH_3), 7.03 (1H, s, 10-H), 8.84 (1H, s, 5-H); ^{13}C NMR δ=22.7 (8-H), 28.6, 31.1 (N–CH_3), 30.6 (9-C), 38.8 (7-C), 112.9 (10-C), 114.3 (5a-C), 128.0 (5b-C), 129.5 (5-C), 143.1 (10a-C), 151.1, 151.3 (2- and 10b-C), 161.2 (4-C), 195.9 (6-C); MS m/z 258 (M^+). Anal. Calcd for $C_{14}H_{14}N_2O_3$: M, 258.3.

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4) The use of triethylamine also afforded satisfactory results. However, the reaction proceeded more slowly than that using DBU.

5) The general experimental procedures were the same as in Part VIII.[2b)]