Preparation of 3-(2*H*-Pyran-2-on-6-yl)indolizines and the Diels-Alder Reactions with Some Olefinic and Acetylenic Dienophiles

Tetsuro Shimo*, Masayuki Ohe and Kenichi Somekawa*

Department of Applied Chemistry and Chemical Engineering,
Faculty of Engineering, Kagoshima University, Korimoto,
Kagoshima 890, Japan

Otohiko Tsuge

Department of Industrial Chemistry, Kumamoto
Institute of Technology, Ikeda,
Kumamoto 860, Japan

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3-(2*H*-Pyran-2-on-6-yl)indolizines **6a-d** were prepared by 1,3-dipolar cycloaddition reactions of *N*-(2*H*-pyran-2-on-6-yl)methylpyridinium bromides **5a,b** with dimethyl acetylenedicarboxylate (DMAD). All of the cycloaddition reactions of **6b** with *N*-phenylmaleimide, *p*-benzoquinone, and DMAD took place at the 2-pyrone ring to give 3-substituted indolizines.

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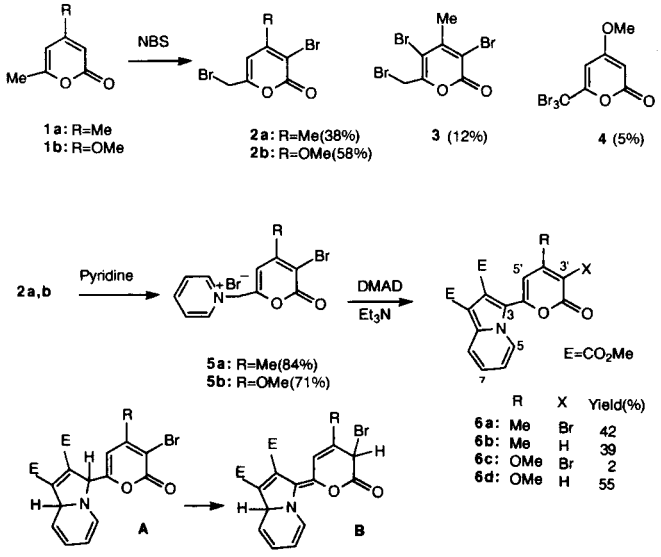
Indolizines have been known to undergo [8+2] cycloaddition reaction with electron deficient olefins to give such a novel type of heterocycles as cyclazines [1], in addition to showing a wide range of biological activity [2]. On the other hand, 2-pyrones have been known to be subjected to [4+2] cycloaddition with olefins to give mono- and/or bis-adducts [3]. Some of the reactions have been used as the key step in the syntheses of colchicine [4] and barrelene [5], by taking advantage of the ease of decarboxylation of the mono-adducts. Hence, the cycloaddition reactions of 3-(2*H*-pyran-2-on-6-yl)indolizines, which are 4π-8π systems of the combination of 2-pyrone-indolizine rings, are interesting concerning the reactivity and the products.

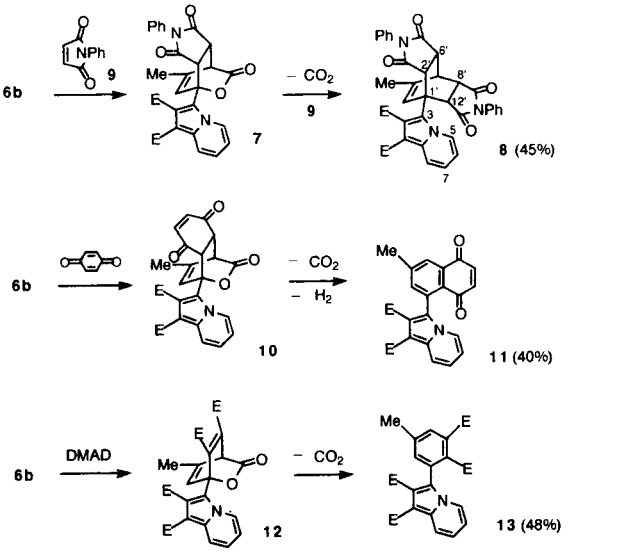
In this paper, the cycloaddition reactions of 3-(2*H*-pyran-2-on-6-yl)indolizines with olefinic and acetylenic dienophiles are investigated with the aim of determining the reactivity.

3-(2*H*-Pyran-2-on-6-yl)indolizines **6a-d** were prepared from 4,6-dimethyl-2-pyrone (**1a**) and 4-methoxy-6-methyl-2-pyrone (**1b**) by bromination with NBS followed by pyridinium methylidation from pyridinium salts, and 1,3-dipolar cycloaddition with DMAD (Scheme 1). Tribromo-2-pyrones, **3** and **4**, were also formed in addition with dibromo-2-pyrones **2a,b** in the bromination reaction. In the 1,3-dipolar cycloaddition initiated by triethylamine, dehydrobrominated products **6b,d** were obtained *via* a 1,5-sigmatropic reaction of the intermediate **A**, together with the dehydrogenated products **6a,c**. The next step is a Diels-Alder reaction of 3-(2*H*-pyran-2-on-6-yl)indolizine **6b**. Compound **6b** reacted with *N*-phenylmaleimide in benzene at 140° (in a sealed tube) to give the bis-adduct **8**

Scheme 1



Scheme 2



in 45% yield (Scheme 2). The stereochemistry of **8** was inferred to be an endo-endo configuration of the imide groups from the ^{1}H nmr spectral data whose chemical shifts at the position of 2'-H and 12'-H, and 6'-H and 8'-H occurred at δ 3.91 (J = 8.0 Hz) and 3.34 (J = 3.0, 8.0 Hz), respectively. It is inferred that **8** was formed through decarboxylation of the mono-adduct **7**, followed by addition of another molecule of *N*-phenylmaleimide.

Similarly, the reaction of **6b** with *p*-benzoquinone afforded **11** in 40% yield. The reaction of **6b** with DMAD in toluene under reflux gave **13** in 22% yield. The yield of **13** increased to 48% by using a catalytic amount of trifluoroacetic acid. It is assumed that the products **11** and **13** were formed by way of decarboxylation of the mono-adducts **10** and **12** respectively.

On the other hand, since the similar reactions of **6a** and **6d** with *N*-phenylmaleimide showed too many spots containing starting materials for the tlc, it was difficult to isolate the products. In the photochemical reactions of **6d** with maleimide, *p*-benzoquinone, DMAD, and ethyl vinyl ether by using 400W high-pressure mercury lamp, **6d** was recovered quantitatively from each of the reactions.

As mentioned above, 3-(2*H*-pyran-2-on-6-yl)indolizine **6b** having a 4π-8π system reacted with dienophiles to give products *via* Diels-Alder reactions of the 2-pyrone ring. The results show that the reactivity was lower than that of just 2-pyrones [3a]. It is considered that the stabilization of **6b** by a conjugated structure between the 2-pyrone and the indolizine rings makes the cycloaddition reactions difficult to occur.

EXPERIMENTAL

All melting points were measured on a Yanagimoto Mel-temp apparatus and are uncorrected. The ir, ^{1}H nmr, and mass spectra were recorded on JASCO A-3, JEOL JNM-MH-100 (100 MHz), and JEOL JMSOISG spectrometers, respectively. The ^{1}H nmr spectra were measured with TMS or DSS as an internal standard.

3-Bromo-6-bromoethyl-4-methyl-2-pyrone (**2a**), 3-Bromo-6-bromomethyl-4-methoxy-2-pyrone (**2b**), 3,5-Dibromo-6-bromomethyl-4-methyl-2-pyrone (**3**), and 6-Tribromomethyl-4-methoxy-2-pyrone (**4**).

1) 4,6-Dimethyl-2-pyrone (**1a**) [6] (5.0 g, 40.3 mmoles) and NBS (15.8 g, 88.7 mmoles) were refluxed in anhydrous carbon tetrachloride (70 ml) for 20 hours in the presence of a catalytic amount of benzoyl peroxide. The mixture was filtered and the solvent was evaporated. The residue was chromatographed on a silica gel column (Wakogel C-200) using benzene as the eluent to give **2a** (4.2 g, 38%) and **3** (1.7 g, 12%).

2) A mixture of 4-methoxy-6-methyl-2-pyrone (**1b**) [7] (1.0 g, 7.1 moles), NBS (2.6 g, 14.6 mmoles) and benzoyl peroxide (catalytic amount) in carbon tetrachloride (20 ml) was refluxed for 20 hours. The same work up mentioned above gave **2b** (1.23 g, 58%, mp 163-166°) (lit [8], mp 162-164°) and **4** (0.13 g, 5%).

Compound **1a** had mp 114-115°; ir (potassium bromide): 1720, 1640, 1525 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.28 (s, 3H, Me), 4.11 (s, 2H, CH_2), 6.25 (s, 1H, 5-H); ms: m/z (relative intensity) 284 (M+4, 14), 282 (M+2, 30), 280 (M$^+$, 16), 201 (100).

Anal. Calcd. for $C_7H_6O_2Br_2$: C, 29.81; H, 2.13. Found: C, 29.87; H, 2.18.

Compound **3** had mp 133-135°; ir (potassium bromide): 1730, 1610, 1515 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.50 (s, 3H, Me), 4.37 (s, 2H, CH_2); ms: m/z (relative intensity) 364 (M+6, 5), 362 (M+4, 15), 360 (M+2, 16), 358 (M$^+$, 6), 281 (100).

Anal. Calcd. for $C_7H_5O_2Br_3$: C, 23.30; H, 1.40. Found: C, 23.35; H, 1.38.

Compound **4** had mp 191-193°; ir (potassium bromide): 1725, 1700, 1640, 1530 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.08 (s, 3H, Me), 6.30, 6.68 (each s, 1H, 3-, 5-H); ms: m/z (relative intensity) 380 (M+6, 5), 378 (M+4, 15), 376 (M+2, 15), 374 (M$^+$, 5), 297 (100).

Anal. Calcd. for $C_7H_5O_3Br_3$: C, 22.48; H, 1.33. Found: C, 22.29; H, 1.33.

N-(3-Bromo-5-methyl-2*H*-pyran-2-on-6-yl)methylpyridinium Bromide (**5a**) and *N*-(3-Bromo-5-methoxy-2*H*-pyran-2-on-6-yl)methylpyridinium Bromide (**5b**).

A solution of **2a** (1.5 g, 5.3 mmoles) and pyridine (0.5 g, 6.3 mmoles) in ethanol (10 ml) was refluxed for 1 hour. The resulting solid was filtered and recrystallized from ethanol to give **5a** (1.6 g, 84%). Similar reaction of **2b** (5.0 g, 16.8 mmoles) with pyridine (1.4 g, 17.7 mmoles) afforded **5b** (4.5 g, 71%).

Compound **5a** had mp 245-248° dec; ir (potassium bromide): 1725, 1655, 1640, 1500 cm^{-1}; ^{1}H nmr (deuterium oxide): δ 2.38 (s, 3H, Me), 5.72 (s, 2H, CH_2), 6.82 (s, 1H, 5-H), 8.16, 8.66, 9.00 (pyridine); ms: m/z (relative intensity) 284 (M-C_5H_5N+4, 10), 282 (M-C_5H_5N+2, 21), 280 (M-C_5H_5N, 10), 79 (100).

Anal. Calcd. for $C_{12}H_{11}NO_2Br_2$: C, 39.91; H, 3.05; N, 3.88. Found: C, 39.85; H, 3.03; N, 4.24.

Compound **5b** had mp 201-202° dec; ir (potassium bromide): 1740 (sh), 1705, 1660, 1540 cm^{-1}; ^{1}H nmr (deuterium oxide): δ 4.15 (s, 1H, Me), 5.84 (s, 2H, CH_2), 7.23 (s, 1H, 5-H), 8.26, 8.74, 9.08 (pyridine); ms: m/z (relative intensity) 298 (M-C_5H_5N+2, 0.2), 219 (M-C_5H_5N-Br+2, 0.3), 217 (M-C_5H_5N-Br, 0.3), 94 (100).

Anal. Calcd. for $C_{12}H_{11}NO_3Br_2$: C, 38.23; H, 2.95; N, 3.72. Found: C, 38.29; H, 3.00; N, 3.71.

1,2-Dimethyl 3-(3-Bromo-4-methyl-2-pyran-2-on-6-yl)indolizidinedicarboxylate (**6a**), 1,2-Dimethyl 3-(4-Methyl-2*H*-pyran-2-on-6-yl)-indolizinedicarboxylate (**6b**), 1,2-Dimethyl 3-(3-Bromo-4-methoxy-2*H*-pyran-2-on-6-yl)indolizinedicarboxylate (**6c**), and 1,2-Dimethyl 3-(4-Methoxy-2*H*-pyran-2-on-6-yl)indolizinedicarboxylate (**6d**).

1) A mixture of **5a** (1.0 g, 3.2 mmoles), DMAD (0.4 ml, 3.2 mmoles), and triethylamine (0.94 ml, 6.4 mmoles) in THF (40 ml) was refluxed for 10 hours. The reaction mixture was filtered and evaporated. The residue was chromatographed on a silica gel column using benzene-acetone 50:1 v/v mixture as the eluent to give **6a** (0.58 g, 42%) and **6b** (0.42 g, 39%).

2) A mixture of **5b** (2.0 g, 5.4 mmoles), DMAD (0.68 ml, 5.4 mmoles), and triethylamine (1.7 ml, 10.8 mmoles) in THF (50 ml) was refluxed for 15 hours. The work up afforded **6c** (0.05 g, 2%) and **6d** (1.06 g, 55%).

Compound **6a** had mp 199-203°; ir (potassium bromide): 1730, 1698, 1625, 1510 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.34, 3.88, 3.94 (each s, 3H, Me), 6.46 (s, 1H, 5'-H), 6.92 (bt, 1H, 6-H, $J_{6,5}$ =

$J_{6,7}$ = 8.0 Hz), 7.24 (t, 1H, 7-H, $J_{7,6}$ = $J_{7,8}$ = 8.0 Hz), 8.24 (bd, 1H, 8-H, $J_{8,7}$ = 8.0 Hz), 8.62 (d, 1H, 5-H, $J_{5,6}$ = 7.5 Hz); ms: m/z (relative intensity) 421 (M+2, 100), 419 (M^+, 96).

Anal. Calcd. for $C_{18}H_{14}NO_6Br$: C, 51.45; H, 3.36; N, 3.33. Found: C, 51.71; H, 3.51; N, 3.28.

Compound **6b** had mp 189-191°; ir (potassium bromide): 1740, 1728, 1715, 1700, 1632, 1550, 1510 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.17, 3.86, 3.92 (each s, 3H, Me), 6.03 (bs, 1H, 3'-H), 6.37 (s, 1H, 5'-H), 6.88 (bt, 1H, 6-H, $J_{6,5}$ = $J_{6,7}$ = 8.0 Hz), 7.22 (dd, 1H, 7-H, $J_{7,6}$ = 8.0, $J_{7,8}$ = 9.0 Hz), 8.22 (bd, 1H, 8-H, $J_{8,7}$ = 9.0 Hz), 8.64 (d, 1H, 5-H, $J_{5,6}$ = 8.0 Hz); ms: m/z (relative intensity) 342 (M+1, 21), 341 (M^+, 100), 254 (77).

Anal. Calcd. for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.44; N, 4.10. Found: C, 63.35; H, 4.58; N, 4.16.

Compound **6c** had mp 224-225°; ir (potassium bromide): 1740, 1710, 1625, 1520 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.88, 3.93, 4.00 (each s, 3H, Me), 6.72 (s, 1H, 5'-H), 6.96 (bt, 1H, 6-H, $J_{6,5}$ = $J_{6,7}$ = 8.0 Hz), 7.24 (t, 1H, 7-H, $J_{7,6}$ = $J_{7,8}$ = 8.0 Hz), 8.26 (bd, 1H, 8-H, $J_{8,7}$ = 8.0 Hz), 8.76 (d, 1H, 5-H, $J_{5,6}$ = 7.0 Hz); ms: m/z (relative intensity) 437 (M+2, 100), 435 (M^+, 98).

Anal. Calcd. for $C_{18}H_{14}NO_7Br$: C, 49.56; H, 3.24; N, 3.21. Found: C, 49.87; H, 3.58; N, 3.02.

Compound **6d** had mp 183-185°; ir (potassium bromide): 1725, 1700, 1635, 1510 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.83, 3.88, 3.94 (each s, 3H, Me), 5.52 (d, 1H, 3'-H, $J_{3',5'}$ = 2.0 Hz), 6.30 (d, 1H, 5'-H, $J_{5',3'}$ = 2.0 Hz), 6.90 (bt, 1H, 6-H, $J_{6,5}$ = $J_{6,7}$ = 7.0 Hz), 7.24 (dd, 1H, 7-H, $J_{7,6}$ = 7.0, $J_{7,8}$ = 8.0 Hz), 8.22 (bd, 1H, 8-H, $J_{8,7}$ = 8.0 Hz), 8.66 (d, 1H, 5-H, $J_{5,6}$ = 7.0 Hz); ms: m/z (relative intensity) 357 (M^+, 100), 270 (98).

Anal. Calcd. for $C_{18}H_{15}NO_7$: C, 60.50; H, 4.24; N, 3.92. Found: C, 60.52; H, 4.25; N, 3.91.

1,2-Dimethyl 3-(14-Methyl-4,10-diphenyl-3,5,9,11-tetraoxo-4,10-diazatetracyclo[5.5.2.$0^{2,6}$.$0^{8,12}$]tetradec-13-en-1-yl)indolizinedicarboxylate (**8**).

A solution of **6b** (100 mg, 0.29 mmole) and *N*-phenylmaleimide (62 mg, 0.36 mmole) in benzene (2 ml) was heated at 140° for 4 days in sealed glass tube. The reaction solution was chromatographed on a silica gel column using benzene-ethyl acetate 3:1 v/v mixture as the eluent to afford **8** (47 mg, 45%). Compound **8** had mp 196-199°; ir (potassium bromide): 1780, 1725, 1715, 1605, 1505 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.00, 3.82, 3.95 (each s, 3H, Me), 3.34 (dd, 2H, 6'-, 8'-H, $J_{6',7'}$ = $J_{8',7'}$ = 3.0, $J_{6',2'}$ = $J_{8',12'}$ = 8.0 Hz), 3.84 (bs, 1H, 7'-H), 3.91 (d, 2H, 2'-, 12'-H, $J_{2',6'}$ = $J_{12',8'}$ = 8.0 Hz), 6.48 (t, 1H, 6-H, $J_{6,5}$ = 7.0 Hz), 6.56 (bs, 1H, 13'-H), 6.94 (dd, 1H, 7-H, $J_{7,8}$ = 10.0, $J_{7,6}$ = 7.0 Hz), 7.10, 7.34 (phenyl), 7.94 (d, 1H, 5-H, $J_{5,6}$ = 7.0 Hz), 8.14 (d, 1H, 8-H, $J_{8,7}$ = 10.0 Hz); ms: m/z (relative intensity) 643 (M^+, 83), 410 (100).

Anal. Calcd. for $C_{37}H_{29}N_3O_8$: C, 69.05; H, 4.51; N, 6.53. Found: C, 69.42; H, 4.28; N, 6.94.

1,2-Dimethyl 3-(7-methyl-1,4-naphthoquinon-5-yl)indolizinedicarboxylate (**11**).

A solution of **6b** (100 mg, 0.29 mmole) and *p*-benzoquinone (40 mg, 0.37 mmole) in benzene (2 ml) was heated at 140° for 4 days. The same work up afforded **11** (24 mg, 40%). Compound **11** had mp 270-271°; ir (potassium bromide): 1730, 1675, 1600, 1510 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.50, 3.65, 3.86 (each s, 3H, Me), 6.60 (t, 1H, 6-H, $J_{6,5}$ = $J_{6,7}$ = 7.0 Hz), 6.72, 6.87 (each d, 1H, naphthoquinone, J = 10.0 Hz), 7.06 (dd, 1H, 7-H, $J_{7,6}$ = 7.0, $J_{7,8}$ = 9.0 Hz), 7.28 (d, 1H, 5-H, $J_{5,6}$ = 7.0 Hz), 7.52, 8.04 (each bs, 1H, naphthoquinone), 8.20 (d, 1H, 8-H, $J_{8,7}$ = 9.0 Hz); ms: m/z (relative intensity) 403 (M^+, 100), 344 (71).

Anal. Calcd. for $C_{23}H_{17}NO_6$: C, 68.49; H, 4.22; N, 3.47. Found: C, 68.16; H, 4.28; N, 3.44.

1,2-Dimethyl 3-(2,3-Dimethoxycarbonyl-5-methylphenyl)indolizinedicarboxylate (**13**).

A solution of **6b** (100 mg, 0.29 mmole) and DMAD (84 mg, 0.59 mmole) in toluene (4 ml) was refluxed for 50 hours. The same work up afforded **13** (18 mg, 22%). Compound **13** was obtained as a pale yellow oil; ir (neat): 1725, 1605, 1510 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.46, 3.52, 3.72 (each s, 3H, Me), 3.90 (s, 6H, Me), 6.68 (t, 1H, 6-H, $J_{6,5}$ = $J_{6,7}$ = 8.0 Hz), 7.13 (dd, 1H, 7-H, $J_{7,6}$ = 8.0, $J_{7,8}$ = 10.0 Hz), 7.40, 7.92 (each s, 1H, phenyl), 7.52 (d, 1H, 5-H, $J_{5,6}$ = 8.0 Hz), 8.18 (d, 1H, 8-H, $J_{8,7}$ = 10.0 Hz); ms: m/z (relative intensity) 439 (M^+, 100).

Anal. Calcd. for $C_{23}H_{21}NO_8$: C, 62.87; H, 4.78; N, 3.19. Found: C, 62.62; H, 4.77; N, 2.90.

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