Pergamon

*Tetrahedron* Vol. 50, No. 4, pp. 1063-1072, 1994

0040-4020/94 $6.00+0.00

0040-4020(93)E0076-R

# THERMAL ENE REACTION OF 4-(2-ALKENYLAMINO)-3-FORMYL-2(2*H*)-CHROMENONES

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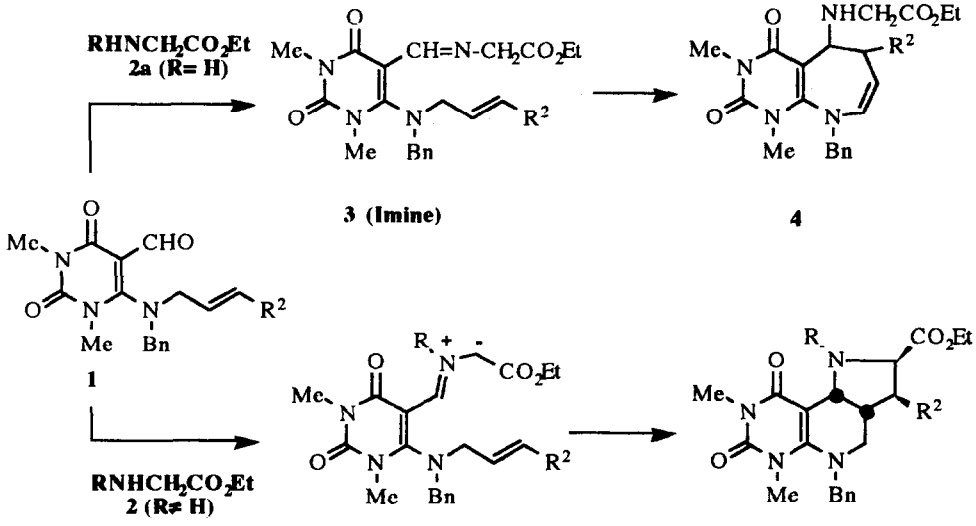
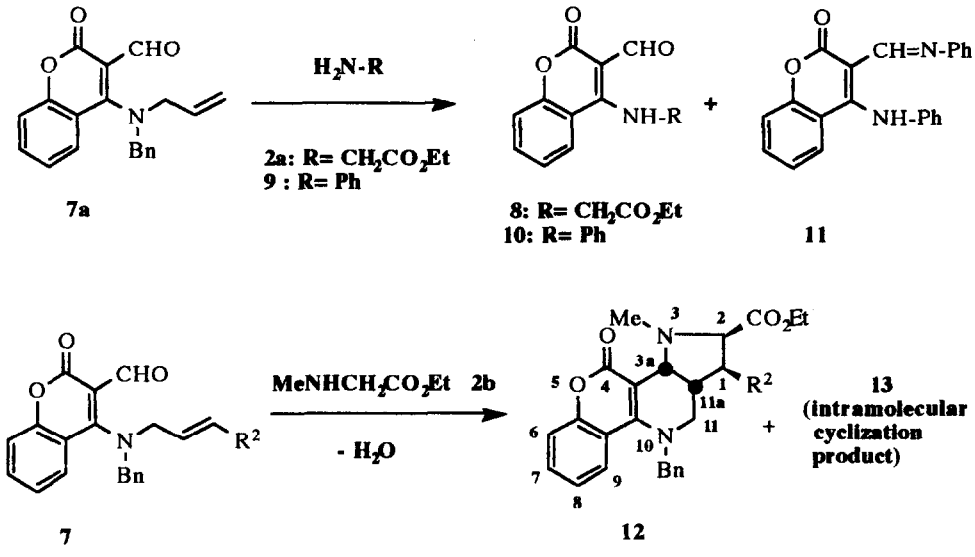
***Abstract*** Intramolecular ene reaction of 4-(2-alkenylamino)-3-formyl-2(2*H*)-chromenones **7** involving carbonyl enophile proceeded stereoselectively to afford 5-hydroxychromen[3,4-*b*]-azepines **14**. The intramolecular nucleophilic attack of hydroxy group to the enemine moiety in **14** gave 1,2-dihydro-2,4-ethanochromen[4,3-*d*][1,3]oxazin-5(4*H*,5*H*)-one derivatives **13** as final products. PM3 MO calculations of the process reveal that this ene reaction proceeds with two steps through an intermediate.

In a previous paper,[1] we reported an interesting cyclization reaction of 6-(2-alkenylamino)-5-formyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinediones (**1**) with *N*-unsubstituted α-amino esters (**2**: R= H) under reflux in toluene affording pyrimid[4,5-*b*]azepines (**4**). On the other hand, a similar reaction of **1** with *N*-substituted α-amino esters (**2**: R≠ H) gave azomethine ylide intermediates (**5**) through a well-known condensation process, which underwent an intramolecular 1,3-dipolar cyclization leading to pyrrolo[2',3':4,5]pyrido[2,3-*d*]pyrimidines (**6**). For the pathway to pyrimidazepines **4**, we proposed[2] the intramolecular imine-ene reaction (so-called Type III[3]) of 6-(2-alkenylamino)-1,3-dimethyl-5-(substituted imino)methyl-2,4(1*H*,3*H*)-pyrimidinediones (**3**) (Scheme 1).

The thermal ene reactions utilizing imine enophiles[4] are relatively rare comparing with those of carbonyl versions. To the best of our knowledge, severer reaction conditions than those in **3** were requisite for the performance of the ene-reactions utilized non-activated C=N enophiles. We suggested that the facilitation of the imine-ene reaction of **3** ascribed to the characteristic electronic feature of 6-amino-5-formyl-2,4(1*H*,3*H*)-pyrimidinedione system in **3**;[2] a push-pull π-electron system bearing highly polarized C=C and C=N bonds at the periphery of 2,4(1*H*,3*H*)-pyrimidinedione. With the hope of expanding to other system and elucidating the nature of this ene reaction, we investigated the reaction of 4-(2-alkenylamino)-3-formyl-2(2*H*)-chromenones (**7**) with ethyl glycinate (**2a**) and ethyl sarcosinate (**2b**). In the reaction of **7** with **2a**, the desired imine was not formed but replacement of the amino moiety at the 4-position occurred. On the other hand, 1,3-dipolar cyclization reaction of the azomethine ylides and the carbonyl-ene reaction utilizing the formyl group of **7** were competitive in the with **2b**. This paper details a facile carbonyl-ene reaction of **7** under non-catalyzed conditions and the pathway of the ene reaction is also discussed using PM3 MO calculations.




**Scheme 1**

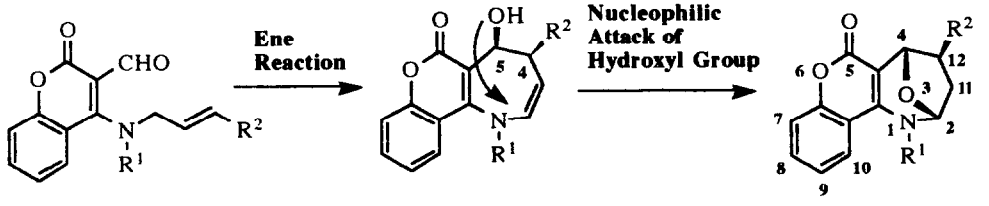



**Scheme 2**

Reaction of 4-(*N*-allylbenzylamino)-3-formyl-2(2*H*)-chromenone (**7a**) with **2a** gave 4-(ethoxycarbonylmethylamino)-3-formyl-2(2*H*)-chromenone (**8**) in more than 80% yield. A similar reaction of **7a** with aniline (**9**) gave 4-anilino-3-formyl-2(2*H*)-chromenone (**10**) and its imine (**11**) in 62% and 30% yield, respectively. The reaction of **7** with **2b** was also examined. The reaction of **7a** with **2b** in benzene under reflux for 3 h gave 10-

benzyl-2-ethoxycarbonyl-3-methyl-2,3,3a,10,11,11a-hexahydrochromeno[4,3-*b*]pyrrolo[2,3-*d*]pyridin-11(11*H*)-one (**12a**) in 76% yield together with a trace (3%) of another product **13a**, an intramolecular cyclization product of **7a**. The reaction of 4-{*N*-benzyl-[(*E*)-2-butenylamino]}-3-formyl-2(2*H*)-chromenone (**7b**) with **2b** in benzene under reflux for 12 h gave also chromenopyrrolopyridines **12b** (44%) and the corresponding **13b** (5%) together with small amounts of unidentified products. The structure of **12** (including stereochemistries in the pyrrole ring) was confirmed on the basis of the spectral data comparing with those of the related compounds.[1,5]

Therefore, heating **7a** in toluene under reflux for 26 h afforded **13a** in 63% yield together with polymeric materials. The structure of **13a** was deduced to be 1-benzyl-1,2-dihydro-2,4-ethanochromeno[4,3-*d*]-[1,3]oxazin-5(4*H*,5*H*)-one from the following spectral data comparing with those of the similar type of imine-ene reaction products in 2,4(1*H*,3*H*)-pyrimidinedione system;[1,2] in its $^{13}C$ NMR spectrum five signals at δ 31.8, 37.6(11- and 12-C), 57.2($CH_2$-Ph), 73.4(4-C), and 90.0(2-C) were assigned to $sp^3$-carbon ones, respectively. The $^1H$ NMR spectrum of **13a** showed an array of the methine (2-H; δ 5.28, d, *J*= 4.9 Hz), methylene, methylene (11- and 12-H; δ 2.1; overlapping each other), and methine proton (4-H; δ 5.11, d, *J*= 6.8 Hz) for the 2,4-ethano[1,3]oxazine ring by NOESY technique. In order to explain the formation of **13a** we assume that the intramolecular ene reaction of **7a** leading to chromen[3,4-*b*]azepine **14a**, in which an intramolecular nucleophilic attack of the hydroxy group to the α-position of the enamine moiety gives 2,4-ethanochromeno[4,3-*d*]-[1,3]oxazine **13a** as a final product (Scheme 3). Similar reactions of **7b**, 4-[*N*-benzyl-(*trans*-cinnamyl)amino]- (**7c**), 4-{*N*-benzyl-[(*E*)-3-(ethoxycarbonyl)-2-propenyl]}amino- (**7d**), and 4-(*N*,*N*-diallylamino)-3-formyl-2(2*H*)-chromenone (**7e**) gave the corresponding **13b-e** in good yields (Table 1).




**7** **14** **13**

**Scheme 3**

Table 1. Thermal Reaction of 4-(2-Alkenylamino)-3-formyl-2(2*H*)-chromenones **7** in Refluxing Toluene.

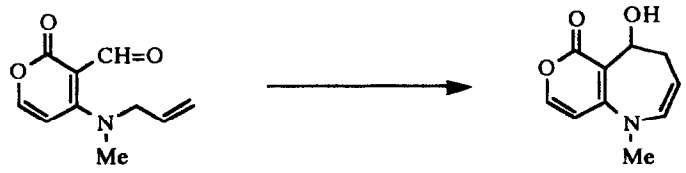
| Entry | $R^1$ | $R^2$ | Reaction Time (h) | Products (Yield[a]: %) |
|---|---|---|---|---|
| 1 | Bn | H | 26 | **13a** (63) |
| 2 | Bn | Me | 40 | **13b**[b] (71) |
| 3 | Bn | Ph | 12 | **13c**[b] (64) |
| 4 | Bn | $CO_2Et$ | 24 | **13d**[b] (82) |
| 5 | $CH_2CH=CH_2$ | H | 8 | **13e** (72) |
| 6 | Ph | H | 4 | **14f** (70) |
| 7 | Ph | H | 36 | **13f** (53) + **14f** (14) |

a. Isolated yield. b. Single isomer.

On the other hand, the reaction of 4-(*N*-allylanilino)-3-formyl-2(2*H*)-chromenone (**7f**) in toluene under reflux for 4 h gave 1-benzyl-4-hydroxy-2,3,4,5-tetrahydrochromeno[3,4-*b*]azepin-6(1*H*,6*H*)-one (**14f**) in 70% yield. Prolonged heating the toluene solution of **7f** gave a mixture of **13f** and **14f** (Table 1).

Products **13b-d** exist as single diastereomers and the configuration of the substituents ($R^2$) at the 12-position is deduced to be *exo* from the coupling constants between 4- and 12-H (*ca.* 0 Hz). This suggests that the ene reaction of **7** gives **14** with 4,5-*cis* configuration (Scheme 3). While the imine-ene reaction of 2,4(1*H*,3*H*)-pyrimidinediones **3** gave a mixture of 4,5-*cis* and -*trans* azepine derivatives, this carbonyl-ene reaction of **7**, interestingly, proceeds in a highly stereoselective manner. The geometry of the transition state of the ene reaction was also investigated using molecular models. Only a boat-formed transition state seems to be possible. With the aim to test this hypothesis, heating of 4-[*N*-benzyl-(2-cyclohexenyl)amino]-3-formyl-2(2*H*)-chromenone (**7g**) in boiling toluene or xylene resulted in the recovery of the starting **7g** in more than 95% yield. Therein, it is impossible for **7g** to attain the boat-formed transition state due to its high bond strain.

In order to obtain further understandings for the reaction profiles, we examine the semi-emperical molecular orbital (MO) calculations utilizing PM3 method (See Experimental section). The calculations were carried out with a 2(2*H*)-pyrone system bearing *N*-methylallylamino group (**15**) instead of the 2(2*H*)-chromenone one to avoid conformational and computational complexities. The conversion of **15** to **16** simultated is shown in Scheme 4.




**15** **16**

**Scheme 4**

The PM3 calculations reveal that this reaction proceeds with two steps through an intermediate. The schematic energy diagram for the reaction and the calculated structures for the transition states and intermediate are shown in Fig. 1 and 2, respectively.

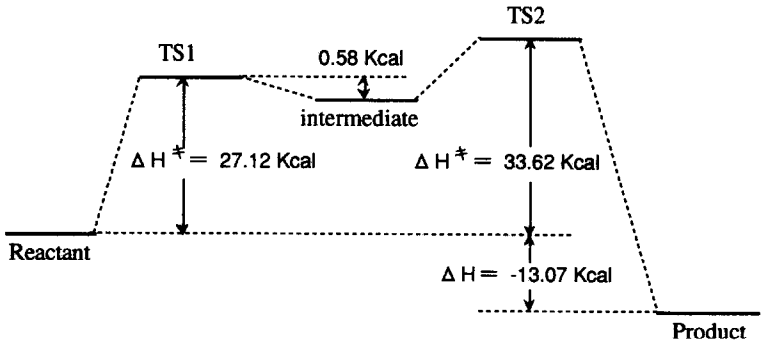
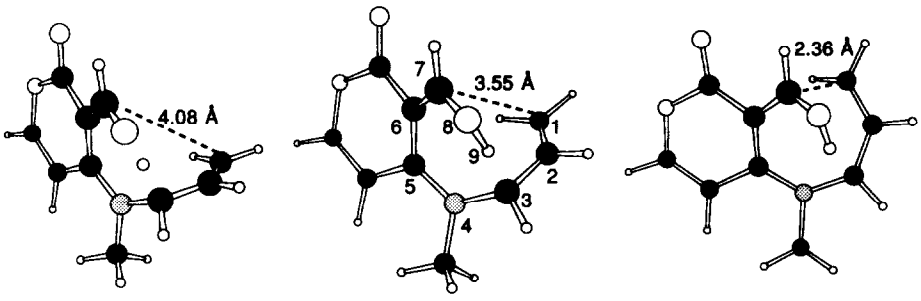



Fig. 1. Energy Diagram for the Conversion of **15** to **16**.




TS1 Intermediate TS2

| | TS1 | Intermediate | TS2 | Reactant | Product |
|---|---|---|---|---|---|
| Heat of formation ( Kcal / mol ) | -38.48 | -39.05 | -31.98 | -65.60 | -78.67 |
| Distances ( Å ) | | | | | |
| C1-C2 | 1.33 | 1.33 | 1.36 | 1.33 | 1.48 |
| C1-C7 | 4.08 | 3.55 | 2.36 | ---- | 1.54 |
| C2-C3 | 1.46 | 1.45 | 1.41 | 1.49 | 1.34 |
| C3-N4 | 1.45 | 1.41 | 1.38 | 1.49 | 1.44 |
| C3-H9 | 1.45 | 1.67 | 2.32 | 1.11 | ---- |
| N4-C5 | 1.36 | 1.35 | 1.37 | 1.42 | 1.43 |
| C5-C6 | 1.43 | 1.45 | 1.43 | 1.38 | 1.37 |
| C6-C7 | 1.41 | 1.38 | 1.39 | 1.48 | 1.51 |
| C7-O8 | 1.27 | 1.31 | 1.34 | 1.21 | 1.41 |
| O8-H9 | 1.10 | 1.00 | 0.95 | ---- | 0.96 |
| Angles ( degree ) | | | | | |
| ∠C1C2C3 | 127.1 | 127.2 | 127.6 | 122.2 | 129.2 |
| ∠C2C3N4 | 117.3 | 122.0 | 128.9 | 114.0 | 128.0 |
| ∠C3N4C5 | 123.9 | 124.2 | 128.3 | 117.2 | 119.2 |
| ∠N4C5C6 | 126.0 | 124.6 | 125.5 | 126.7 | 120.7 |
| ∠C5C6C7 | 129.0 | 127.9 | 128.5 | 127.9 | 122.4 |
| ∠C6C7O8 | 127.4 | 127.5 | 126.8 | 123.3 | 115.1 |
| ∠C7O8H9 | 112.5 | 111.0 | 111.0 | ---- | 108.7 |
| ∠O8H9C3 | 159.6 | 155.1 | 129.8 | ---- | ---- |
| ∠H9C3C2 | 106.3 | 97.7 | 78.3 | 109.2 | ---- |
| Torsional angles ( degree ) | | | | | |
| τ C1C2C3N4 | -12.1 | -8.7 | 7.3 | -124.3 | 3.3 |
| τ C2C3N4C5 | 86.0 | 62.8 | 24.3 | 75.5 | -38.3 |
| τ C3N4C5C6 | 8.4 | 11.0 | 5.8 | -140.8 | 56.7 |
| τ N4C5C6C7 | 17.7 | 26.7 | 24.7 | 16.6 | -1.1 |
| τ C5C6C7O8 | 2.1 | 1.3 | 32.0 | 49.2 | 165.5 |
| τ C6C7O8H9 | -24.6 | -32.1 | -32.5 | ---- | 33.7 |
| τ C7O8H9C3 | 1.6 | 3.8 | -38.7 | ---- | ---- |

**Fig.2 Calculated PM3 Structures for TS1, Intermediate, TS2, Reactant and Product**

Table 2. Atomic Charge Distribution of Reactant and Intermediate.

| Atom | Reactant | Intermediate |
|---|---|---|
| C1 | -0.13 | -0.27 |
| C2 | -0.18 | -0.02 |
| C3 | -0.05 | -0.65 |
| N4 | 0.04 | 0.58 |
| C5 | 0.15 | -0.09 |
| C6 | -0.41 | -0.35 |
| C7 | 0.37 | 0.26 |
| O8 | -0.33 | -0.29 |
| H9 | 0.03 | 0.29 |

At the first step, the transition state (TS1) corresponds to the migration of hydrogen atom (H9) from C3 to O8 leading to an intermediate. The structure of TS1 has distances of 1.45 Å for C3-H9 and of 1.10 Å for O8-H9, respectively. The distance between C1 and C7 is 4.08Å, which is so long that no covalent interaction may exist. The intermediate is more stable only by 0.58 Kcal/mol than TS1 and its structure exhibits that C3-H9 and O8-H9 distances are 1.67 Å and 1.00 Å. This indicates that H9 atom bounds almost completely with O8 atom and further interacts with C3. C1-C7 Distance (3.55Å) in the intermediate is shorter than that of TS1, but still too long to interact covalently. Apparent differences in bond lengths between the intermediate and the reactant are also observed; C3-N4, N4-C5, and C6-C7 bond in the intermediate are shortened by 0.07-0.10 Å, on the other hand, C5-C6 and C7-O8 bond stretch by 0.07-0.10 Å comparing with those of the reactant. This indicates that the formers have a double bond character and the latter reduce a double bond character. The atomic charge calculation for the intermediate shows large negative charge at C3 atom and large positive charge at N4 one (Table 2). These results suggest that the intermediate is considered to have delocalized azomethine ylide with 8π electrons.

The second transition state (TS2), which is located between the intermediate and product and has a higher energy than TS1, corresponds to the step of ring closure. TS2 has a helicoidal shape and C1-C7 distance of 2.36 Å, O8-H9 distance of 0.95 Å, and C3-H9 distance of 2.32 Å. TS2 seems to be compatible with the transition state of 8π electrocyclization reaction. The bond formation between C1 and C7 in TS2 results in the azepine ring and the introduction of *trans* substituent at C1 leads to 4,5-*cis* azepine derivatives.

The PM3 calculation results mentioned above are consistent with the profiles and stereoselectivity of the thermal ene reaction of 6-(2-alkenylamino)-3-formyl-2(2*H*)-chromenones **7**. The characteristic electronic features of 2,4(1*H*,3*H*)-pyrimidinedione and 2(2*H*)-chromenone systems would be attributed to the lowering the energy of the intermediates in imine- and carbonyl-ene reaction process, respectively.

## EXPERIMENTAL

Melting points are uncorrected. IR spectra were measured on a JASCO IR-Report-100 spectrophotometer as KBr discs. $^{1}H$ and $^{13}C$ NMR spectra in deuteriochloroform solutions were recorded on JEOL GSX-400 and/or 270 spectrometers. TMS was used as an internal standard and J-values are given in Hz. Mass spectra were determined on a JEOL JMS-D spectrometer. Elemental analyses were performed on a Hitachi 026 CHN analyzer. All nonaqueous reactions were run under a positive pressure of argon. All solvents were dried by

standard methods before use. The progress of reactions was monitored by TLC (Silica Gel 60F-254, Merck). Chromatographic purification was performed with Wakogel C-200 (Wako Pure Chemical Industries) and/or Silica Gel 60 (230-400 mesh, Merck). Amino esters **2a** and **2b** were obtained by the treatment of the corresponding hydrochlorides with diisopropylethylamine *in situ*.

Starting materials **7** were prepared by the reaction of 4-chloro-3-formyl-2(2*H*)-chromenone[6] with the corresponding amines similarly to the method reported.[7]

**4-(*N*-Allylbenzylamino)-3-formyl-2(2*H*)-chromenone (7a)**. M.p. 131-134 °C; $^1$H NMR δ 4.15(2H, d, NC*H*$_2$CH=, *J*= 8), 4.63(2H, s, C*H*$_2$Ph), 5.2-5.4(2H, m, =C*H*$_2$), 5.82(1H, m, =C*H*-), 7.2-7.7(aromatic-H), 10.12(1H, s, C*H*O). Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 74.90; H, 5.41; N, 4.37.

**4-[*N*-Benzyl-(*E*)-2-butenylamino]-3-formyl-2(2*H*)-chromenone (7b)**. M.p. 133-135 °C; $^1$H NMR δ 1.76(3H, d, Me, *J*= 5), 5.15(2H, d, NC*H*$_2$CH=, *J*= 4), 4.70(2H, s, C*H*$_2$Ph), 5.60(2H, m, -C*H*=C*H*-), 7.3(9H, aromatic-H), 10.14(1H, s, C*H*O). Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74; N, 4.20. Found: C, 76.03; H, 5.73; N, 4.12.

**4-[*N*-Benzyl-(*trans*-cinnamyl)amino]-3-formyl-2(2*H*)-chromenone (7c)**. M.p. 124-126 °C; $^1$H NMR δ 4.28(2H, d, NC*H*$_2$CH=, *J*= 7), 4.65(2H, s, C*H*$_2$Ph), 6.0-6.6(2H, m, -C*H*=C*H*-), 7.1-7.8(14H, aromatic-H), 10.20(1H, s, C*H*O). Anal. Calcd for $C_{26}H_{21}NO_3$: C, 78.96; H, 5.35; N, 3.54. Found: C, 78.88; H, 5.31; N, 3.39.

**4-{*N*-Benzyl-[(*E*)-3-(ethoxycarbonyl)-2-propenyl]}-3-formyl-2(2*H*)-chromenone (7d)**. M.p. 113-114 °C; $^1$H NMR δ 1.31(3H, t, OCH$_2$C*H*$_3$, *J*= 6.9), 4.2(4H, m, NC*H*$_2$CH= and OC*H*$_2$CH$_3$), 4.61(2H, s, C*H*$_2$Ph), 5.94(1H, dt, -C*H*=, *J*= 1.7 and 16.8), 6.85(1H, dt, -C*H*=, *J*= 6.3 and 16.8), 7.2-7.7(9H, aromatic-H), 10.16(1H, s, C*H*O). Anal. Calcd for $C_{23}H_{21}NO_5$: C, 70.57; H, 5.41; N, 3.58. Found: C, 70.72; H, 5.53; N, 3.64.

**4-(*N*,*N*-Diallylamino)-3-formyl-2(2*H*)-chromenone (7e)**. M.p. 58-59 °C; $^1$H NMR δ 4.22(2H, d, NC*H*$_2$CH=, *J*= 5.9), 4.58(2H, d, NC*H*$_2$CH=, *J*= 6.3), 5.2-5.5(4H, m, =C*H*$_2$), 5.8-6.0(2H, m, -C*H*=), 7.2-8.1(4H, aromatic-H), 8.45(1H, s, C*H*O). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.60; H, 5.55; N, 5.38.

**4-(*N*-Allylanilino)-3-formyl-2(2*H*)-chromenone (7f)**. M.p. 109-110 °C; $^1$H NMR δ 4.54(2H, dt, NC*H*$_2$CH=, *J*= 1.7 and 7.6), 5.2-5.3(2H, m, =C*H*$_2$), 5.86(1H, m, -C*H*=), 6.9-7.5(9H, aromatic-H), 10.20(1H, s, C*H*O). Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.61; H, 5.03; N, 4.70.

**4-[*N*-Benzyl-(2-cyclohexenyl)amino]-3-formyl-2(2*H*)-chromenone (7g)**. M.p. 116-117 °C; $^1$H NMR δ 1.8-2.2(6H, m, -C*H*$_2$-), 4.58, 4.78(each 1H, 2x d, C*H*$_2$Ph, *J*= 16.0), 4.89(1H, m, NC*H*), 6.0-6.1(2H, m, -C*H*=C*H*-), 7.1-7.8(9H, aromatic-H), 10.00(1H, s, C*H*O). Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.77; H, 5.99; N, 4.00.

**Reaction of 7a with ethyl glycinate (2a)**. General procedure for the reaction of **7a** with primary amines: To a suspension of **7a** (0.16 g, 0.5 mmol) and glycine ethyl ester hydrochloride (0.12 g, 0.85 mmol) in benzene (5 ml) diisopropylethylamine (0.13 g, 1.0 mmol) was added. The reaction mixture was heated under reflux for 2 h and evaporated to dryness. Extraction with dichloromethane (3x 10 ml) and crystallization gave **8** (0.24 g, 84%).

**4-(Ethoxycarbonyl)methylamino-3-formyl-2(2*H*)-chromenone (8)**. Colorless prisms; m.p. 187-188 °C; IR 3450(NH), 1725, and 1705 cm$^{-1}$(CO); $^1$H NMR δ 1.35(3H, t, OCH$_2$C*H*$_3$, *J*= 7.3), 4.42(2H, q, OC*H*$_2$CH$_3$, *J*= 7.3), 4.63(2H, d, NHC*H*$_2$, *J*= 5.3), 7.2-8.0(aromatic-H), 10.20(1H, s, C*H*O), 12.5(1H, br s, N*H*). Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 60.88; H, 4.70; N, 5.17.

**4-Anilino-3-formyl-2(2*H*)-chromenone (10)**. Pale yellow crystals; m.p. 176-177 °C; IR 3400(br) (NH), 1705, and 1635 $cm^{-1}$ (CO); $^1H$ NMR δ 6.8-7.5(9H, aromatic-H), 10.26(1H, s, C*H*O), 13.20(1H, br, N*H*). Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.32; H, 4.18; N, 5.54.

**4-Anilino-3-(phenylimino)methyl-2(2*H*)-chromenone (11)**. Yellow prisms (EtOH); m.p. 155-156 °C; IR 3450(br)(NH) and 1700 $cm^{-1}$(CO); $^1H$ NMR δ 6.8-7.5(14H, aromatic-H), 9.16(1H, s, C*H*=N), 14.43(1H, br, N*H*). Anal. Calcd for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.55; H, 4.80; N, 8.13.

**Reaction of 7a with ethyl sarcosinate (2b)**. General procedure for the reaction of **7** with **2b**: To a suspension of **7a** (0.296 g, 0.92 mmol) and sarcosine ethyl ester hydrochloride (0.25 g, 1.4 mmol) in benzene (5 ml) diisopropylethylamine (0.25g, 1.9 mmol) was added. The mixture was heated under reflux for 3 h and evaporated to dryness. The residue was extracted with dichloromethane (3x 10 ml) and the solvent was distilled out. Column chromatography of the residue on silica gel with hexane-ethyl acetate (7:1 to 5:1) gave **13a** (0.008 g, 3%) and **12a** ( 0.272 g, 76%).

**10-Benzyl-2-ethoxycarbonyl-3-methyl-2,3,3a,10,11,11a-hexahydrochromeno[4,3-*b*]pyrrolo[2,3-*d*]pyridin-4(1*H*,4*H*)-one (12a)**. Yellow prisms (ethyl acetate); m.p. 178-180 °C; IR 1735 and 1680 $cm^{-1}$ (CO); $^1H$ NMR δ 1.32(3H, t, $OCH_2CH_3$, *J*= 7.0), 1.71(1H, ddd, 1-H, *J*= 1.1, 8.8, and 13.6), 2.02(1H, m, 11a-H), 2.28(1H, ddd, 1-H, *J*= 3.7, 8.4, and 13.6), 2.52(3H, s, 3-Me), 3.01(1H, dd, 11-H, *J*= 4.4 and 12.8), 3.21(1H, dd, 11-H, *J*= 12.4 and 12.8), 3.72(1H, dd, 2-H, *J*= 3.7 and 8.8), 4.2(2H, m, $OCH_2CH_3$), 4.30(1H, d, 3a-H, *J*= 4.8), 4.61, 4.87(each 1H, 2x d, $CH_2Ph$, *J*= 17.0), 7.0-7.6(9H, phenyl-H); $^{13}C$ NMR δ 14.0($CH_2CH_3$), 29.5, 30.8(3- and 3a-C), 35.1(1-Me), 50.9($CH_2Ph$), 55.2(4-C), 57.9(11b-C), 59.9($OCH_2CH_3$), 62.7(2-C), 102.7(11a-C), 115.5(9b-C), 117.2, 122.7, 124.3, 126.2, 127.3, 128.7, 130.7, 136.5, 152.9, 155.5(5a- and 9a-C), 162.0(11-C), 173.7($CO_2$); MS 418($M^+$). Anal. Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69. Found: C, 71.81; H, 6.30; N, 6.45.

**10-Benzyl-2-ethoxycarbonyl-1,3-dimethyl-2,3,3a,10,11,11b-hexahydrochromeno[4,3-*b*]-pyrrolo[2,3-*a*]-pyridin-4(1*H*,4*H*)-one (12b)**. Pale yellow prisms (ethyl acetate); m.p. 119-120 °C; IR 1730 and 1680 $cm^{-1}$ (CO); $^1H$ NMR δ 1.03(3H, d, 1-Me, *J*= 7.3), 1.32(3H, t, $OCH_2CH_3$, *J*= 7.3), 1.87(1H, m, 1-H), 2.28(1H, m, 11a-H), 2.58(3H, s, 3-Me), 3.13(2H, m, 11-H), 3.82(1H, d, 3a-H, *J*= 8.1), 4.22(2H, q, $OCH_2CH_3$, *J*= 7.3), 4.50, 4.93(each 1H, 2x d, $CH_2Ph$, *J*= 16.9), 7.0-7.5(9H, aromatic-H); MS 432($M^+$). Anal. Calcd for $C_{27}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.41; H, 6.39; N, 6.47.

**Thermal ene reaction of 7**. General procedure: A solution of **7a** (0.208 g, 0.65 mmol) in toluene (10 ml) was heated under reflux for 26 h. Evaporation of the solvent and chromatography of the residue on silica gel with hexane-ethyl acetate (4:1) gave **13a** (0.131 g, 63%).

**1-Benzyl-1,2-dihydro-2,4-ethanochromen[4,3-*c*][1,3]oxazin-5(4*H*,5*H*)-one (13a)**. Colorless prisms (EtOH); m.p. 158-159 °C; IR 1690 $cm^{-1}$(CO); $^1H$ NMR δ 2.06-2.34(4H, m, 11- and 12-H), 4.55, 4.86(each 1H, 2x d, $CH_2Ph$, *J*= 17.1), 5.11(1H, d, 4-H, *J*= 6.8), 5.28(1H, d, 2-H, *J*= 4.9), 7.1-7.5(9H, phenyl-H); $^{13}C$ NMR δ 31.8, 37.6(11- and12-C), 57.2($CH_2Ph$), 73.4(4-C), 90.0(2-C), 112.1(4a-C), 116.5(10a-C), 118.1(7-C), 123.5, 124.1(9- and 10-C), 123.1, 128.1, 129.4, 131.5(phenyl-C), 152.3, 153.8(6a- and 10b-C), 160.1(5-C); MS 319($M^+$). Anal. Calcd. for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.32; N, 4.39. Found: C, 75.01; H, 5.43; N, 4.36.

**1-Benzyl-12-methyl-1,2-dihydro-2,4-ethanochromen[4,3-*d*][1,3]oxazin-5(4*H*,5*H*)-one (13b)**. Colorless prisms (EtOH); m.p. 164-165 °C: IR 1685 $cm^{-1}$ (CO); $^1H$ NMR δ 1.11(3H, d, 3-Me, *J*= 6.8), 1.77(1H, ddd, 11-H, *J*= 1.0, 5.9, and 13.7), 2.20(1H, dd, 11-H, *J*= 7.3 and 13.7), 2.71(1H, m, 12-H), 4.54, 4.85(each 1H, 2x d, $CH_2Ph$, *J*= 17.1), 4.86(1H, s, 4-H), 5.12(1H, d, 2-H, *J*= 5.9), 7.1-7.6(9H, phenyl-H); $^{13}C$ NMR δ 20.3(Me), 40.3, 45.2(11- and 12-C), 56.8($CH_2Ph$), 78.3(4-C), 89.9(2-C), 111.9(4a-C), 116.3(10a-C), 117.9(7-C), 123.3, 123.8(9- and 10-C), 126.9, 127.9, 129.2, 131.2, 137.1(8-C and phenyl-C), 151.6, 153.6(6a- and 10b-C), 160.0(5-C); MS 333($M^+$). Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74; N, 4.20. Found: C, 75.87; H, 5.76; N, 4.33.

**1-Benzyl-12-phenyl-1,2-dihydro-2,4-ethanochromen[4,3-*c*][1,3]oxazin-5(4*H*,5*H*)-one (13c)**. Colorless prisms (EtOH); m.p. 214-215 °C; IR 1700 $cm^{-1}$(CO); $^1H$ NMR δ 2.42(1H, ddd, 11-H, *J*= 2.0, 5.9, and 14.2), 2.63(1H, dd, 11-H, *J*= 8.8, 14.2), 3.79(1H, dd, 12-H, *J*= 2.0 and 8.8), 4.57, 4.92(each 1H, 2x d, $CH_2Ph$, *J*=

17.1), 5.18(1H, s, 4-H), 5.32(1H, d, 2-H, *J*= 5.9), 7.1-7.5(14H, phenyl-H); $^{13}$C NMR δ 40.4(11-C), 55.9, 57.0(12-C and $CH_2$Ph), 78.9(4-C), 90.0(2-C), 111.8(4a-C), 116.2(10a-C), 118.0(7-C), 123.3, 123.9, 126.8, 126.9, 127.1, 128.0, 128.6, 129.2, 131.4, 137.0, 143.7(8-, 9-, and 10-C and phenyl-C), 151.7, 153.7(6a- and 10b-C), 159.8(5-C); MS 395 ($M^+$). Anal. Calcd for $C_{26}H_{21}NO_3$: C, 78.96; H, 5.35; N, 3.54. Found: C, 78.71; H, 5.24; N, 3.49.

**1-Benzyl-12-ethoxycarbonyl-1,2-dihydro-2,4-ethanochromen[4,3-*d*][1,3]oxazin-5(4*H*,5*H*)-one (13d).** Colorless needles (EtOH); m.p. 148-149 °C; IR 1735 and 1700 cm$^{-1}$ (CO); $^1$H NMR δ 1.30(3H, t, $OCH_2CH_3$, *J*= 7.3), 2.27(1H, dd, 11-H, *J*= 8.8 and 13.7), 2.78(1H, m, 11-H), 3.41(1H, d, 12-H, *J*= 6.8), 4.20(1H, q, $OCH_2CH_3$, *J*= 7.3), 4.53, 4.89(each 1H, 2x d, $CH_2$Ph, *J*= 16.8), 5.20(1H, d, 2-H, *J*= 6.4), 5.58(1H, s, 4-H), 7.1-7.6(9H, phenyl-H); $^{13}$C NMR δ 14.2($OCH_2CH_3$), 34.2(11-C), 54.4(12-C), 57.0, 61.4($OCH_2CH_3$ and $CH_2$Ph), 75.3(4-C), 89.4(2-C), 110.0(4a-C), 115.9(10a-C), 117.9(7-C), 123.2, 123.9(9- and 10-C), 126.8, 127.9, 129.1, 131.5, 136.6(8-C and phenyl-C), 152.2, 153.6(10- and 6a-C), 159.4(5-C), 171.6($CO_2$); MS 391($M^+$). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 70.57; H, 5.41; N, 3.58. Found: C, 70.87; H, 5.49; N, 3.57.

**1-Allyl-1,2-dihydro-2,4-ethanochromen[4,3-*d*][1,3]oxazin-5(4*H*,5*H*)-one (13e).** Colorless prisms (EtOH); m.p. 214 °C; IR 1690 cm$^{-1}$ (CO); $^1$H NMR δ 1.98-2.30(4H, m, 11- and 12-H), 3.96(1H, tdd, $NCH_2CH$=, *J*= 1.5, 5.4, and 18.1), 4.18(1H, tdd, $NCH_2CH$=, *J*= 1.5, 3.4, 18.1), 5.18(1H, dd, 2-H, *J*= 2.0 and 4.4), 5.23(1H, d, 4-H, *J*= 5.4), 5.42(1H, tdd, -CH=C$H_2$, *J*= 1.5, 3.4, and 10.3), 5.58(1H, tdd -CH=C$H_2$, *J*= 1.5, 3.4, and 17.1), 6.05(1H, m, $CH_2CH$=$CH_2$), 7.2-7.6(9H, phenyl-H); $^{13}$C NMR δ 31.6(12-C), 37.3(11-C), 55.8($NCH_2CH$=), 73.0(4-C), 89.6(2-C), 111.2(4a-C), 116.1(10a-C), 117.4, 117.7(7-C and $CH_2CH$=$CH_2$), 123.4, 123.6(9- and 10-C), 131.1(8-C), 133.6($CH_2CH$=$CH_2$), 152.1, 153.4(6a- and 10b-C), 159.8(5-C); MS 269($M^+$). Anal. Calcd for $C_{26}H_{21}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.22; H, 5.62; N, 4.96.

**Thermal reaction of 7f.** A solution of **7f** (0.260 g, 1.01 mmol) in toluene (10 ml) was heated under reflux for 36 h. Usual working-up and column chromatograpy on silica gel gave **14f** (0.036 g, 14%) and **13f** (0.138 g, 53%) as eluent of hexane-ethyl acetate (6:1) and (5:1), respectively.

**1-Phenyl-1,2-dihydro-2,4-ethanochromen[4,3-*d*][1,3]oxazin-5(4*H*,5*H*)-one (13f).** Colorless needles (EtOH); m.p. 155-156 °C; IR 1690 cm$^{-1}$ (CO); $^1$H NMR δ 2.2-2.4(4H, m, 11- and 12-H), 5.37(1H, d, 4-H, *J*= 5.0), 5.53(1H, d, 2-H, *J*= 5.4), 6.8-7.4(9H, aromatic-H); $^{13}$C NMR δ 32.6, 37.3(11- and 12-C), 73.5(4-C), 94.4(2-C), 111.0(4a-C), 115.4, 117.2(7- and 10a-C), 122.9, 125.7, 126.0, 126.6, 129.9, 130.7, 146.7(7-, 8-, and 9-C and phenyl-C), 148.0(11b-C), 153.5(7a-C), 160.0(5-C); MS 305 ($M^+$). Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; H, 4.59. Found: C, 74.55; H, 5.03; N, 4.51.

**4-Hydroxy-1-phenyl-4,5-dihydrochromen[4,3-*b*]azepine-6(1*H*,6*H*)-one (14f).** Yellow crystals; m.p. 102-105 °C; IR 3480 (OH) and 1680 cm$^{-1}$ (CO); $^1$H NMR δ 2.64(2H, m, 4-H), 4.33(1H, d, 5-H, *J*= 8.8), 5.14(1H, m, 3-H), 5.43(1H, m, 2-H), 6.9-7.4(10H, aromatic-H and OH); $^{13}$C NMR δ 34.3(4-C), 66.9(5-C), 111.1(5a-C), 117.1, 117.4, 118.5, 123.1, 123.7, 123.8, 126.0, 129.7, 129.8, 131.0(8-, 9-, 10, and 11-H and phenyl-H), 145.0(7a-C), 151.3, 152.9(2- and 11b-C), 162.5(6-C); MS 305 ($M^+$). Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.43; H, 4.96; N, 4.52.

**Computational Procedure.** The calculations were carried out with a 2(2*H*)-pyrone ring system. Such simplifications were not unreasonable, because the benzo group of 2(2*H*)-chromenone ring and *N*-substituents were not considered to be essential in the present reaction. Heats of formation in the ground state and product were calculated as follows. The five lowest conformers were generated with MM2 force field using the MacroModel program (Version 3.5a).[8] They were surved as initial geometries and fully optimized individually with PM3 method[9] using MOPAC program (Version 6.00).[10] The lowest heat of formation thus obtained each for reactant and product was selected as that of ground state. Locations of transition structures were searched by constructing roughly potential energy surfaces as two reaction coordinates (C1-C7 and O8-H9 distance). Transition structures were optimized using the keyword TS and PRECISE implemented in the MOPAC program.

The FORCE calculation for the optimized transition structures showed one negative eigenvalue in the Hessian matrix with the correct displacement coordinates, which was further confirmed by the IRC calculations. The calculated structures and data for the transition states and intermediate are summarized in Fig. 1 and 2 and Table 2. All calculations were performed on the VAX 4000 in Ube Laboratory, Corporate Research & Development, Ube Industries. LTD.

Financial support of this work by the Ministry of Education, Science, and Culture of Japan (Grant No. 03650705) is gratefully acknowledged. We also thank Professors M. Tashiro and S. Kanemasa of Kyushu University for measurements of elemental analyses and NMR spectra.

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(*Received in Japan* 20 *September* 1993; *accepted* 25 *October* 1993)