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# Syntheses of Novel Planar Metacyclophanes by Claisen-Schmidt Condensation and Thermal Stabilities of Their Photoisomers

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**Abstract:** The novel metacyclophanes with chalcone moieties were synthesized by Claisen-Schmidt condensation. These $\alpha,\beta$-unsaturated ketones were photoisomerized from the all-*trans* configuration to the partial *trans* configuration by 365 nm light irradiation, and then, these *cis* photoisomers were thermally reversed.

**Keywords:** $\alpha,\beta$-unsaturated ketone, Aldol reaction, chalcone, Claisen-Schmidt condensation, metacyclophane, photoisomerization.

Photoreversible *trans-cis* isomerization of C=C bonds or N=N bonds has been developed into one of the molecular functionalizations of micromaterials [1]. Thermodynamically, the *trans* isomer is more stable than the *cis* isomer although they are interconvertible by light irradiation. The isomerization mechanism is accounted for in terms of a path way involving rotation and inversion process [2]. However, the simple rotation and inversion model is insufficient to elucidate isomerization mechanism, especially in previtamin D system [3]. For the rationalization, the hula-twist mechanism has been suggested by Liu *et al.*, which gives compatible interpretation of the isomerization in the limited space and for the molecule involving the steric hindrance against the free rotation around the double bond [4]. This mechanism is also applicable to the isomerization of macrocycle comprised of pseudoconjugated double bonds with aromatic rings [5]. The hula-twist mechanism suggests that even highly strained macrocycle potentiates reversible photoisomerization.

For these challenges, macrocyclic $\alpha,\beta$-unsaturated ketones were targeted in the study about the photoisomerization. One of the characteristics of the $\alpha,\beta$-unsaturated ketones is rigid and planar configuration. So far no macrocyclic compound constituting of trimeric chalcone has been synthesized as the compound in conformity. However, the preparation of the tetrameric macrocycles bridged by $\alpha,\beta$-unsaturated ketones has been already reported [6]. Therefore, the similar reaction, Claisen-Schmidt condensation, is available for the synthesis of the new compound. Here, we report the synthesis of the cyclic chalcone derivatives and their photoisomerization in limited space.

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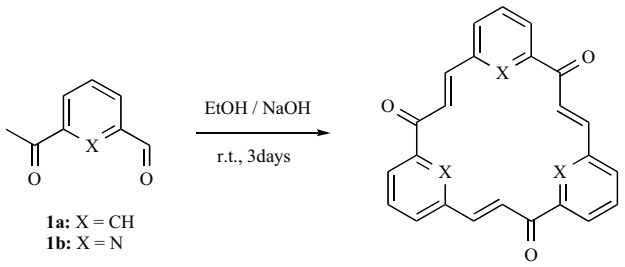


**Scheme 1.** Preparation of macrocycle **2** by Claisen-Schmidt condensation.

## RESULTS AND DISCUSSIONS

For the first time, the target compound **2a** was designed as a product of the simple synthesis route depicted in Scheme **1**. The Claisen-Schmidt condensation of 3-acetylbenzaldehyde (**1a**) in EtOH with NaOH gave mainly a yellow polymer.

The reaction mixture was column-chromatographed on active alumina with $CH_2Cl_2$-THF as an eluent to furnish macrocycle **2a** as monohydrate exhibiting colorless crystals (Fig. (**1**)). On the other hand, neither of macrocycle **2a** nor any further macrocycle was obtained by use of the alternative solvent and reagent, THF and potassium *tert*-butoxide. Consecutively, the similar reaction with 6-acetylpryidine-2-carbaldehyde (**1b**) afforded **2b** in 19% isolated yield. In view of alternation of CH-atoms with N-atom, the steric hindrance was diminished to result in increase of the yield. In addition, the template effect of $Na^+$ ion for pyridine ring is possibly operated.

The geometries of the double bonds of macrocycles **2a** were confirmed by $^1$H NMR as all-*trans* ("all-*E*") configuration, which was evidenced by the observation of *J* coupling

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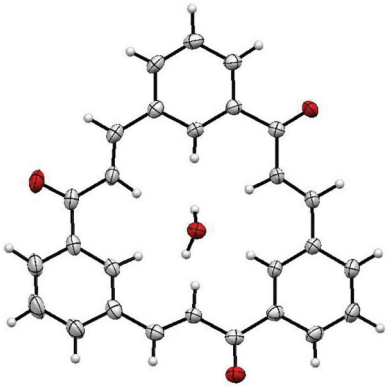
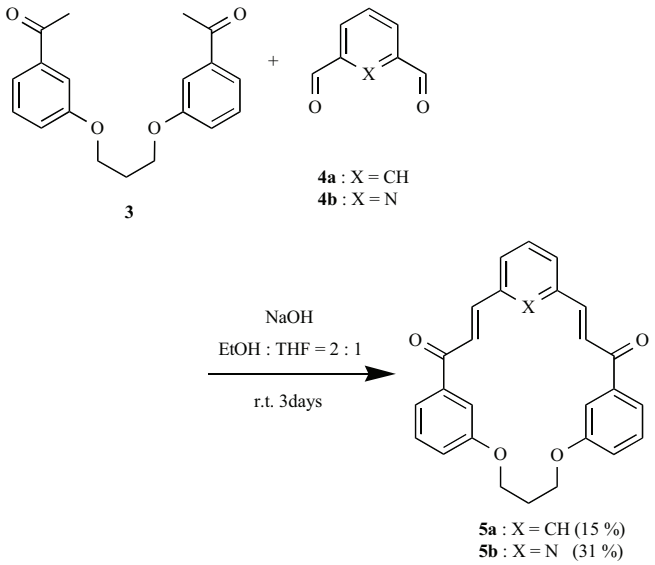


**Fig. (1).** Molecular structure of macrocycle **2a**. CCDC deposition number 884911, $C_{27}H_{20}O_4$, $M_r$ = 408.43, monoclinic, space group $P2_1/c$, $a$ = 9.601(7), $b$ = 13.756(9), $c$ = 15.457(11) Å, $\beta$ = 101.360(8)°, $V$ = 2001(2) Å$^3$, $Z$ = 4, $D_{calc}$ = 1.356 g cm$^{-3}$, μ(MoKα) = 0.091 mm$^{-1}$, $N_{ref}$ ( $I > 2\ \sigma(I)$, $\theta < 27.380°$)= 4529, $R_1$ = 0.0791 (3861), w$R_2$ = 0.2049 (4529).

value (15.6 Hz). Moreover, the *in situ* photoreaction of the macrocycle **2a** in $CDCl_3$ solution by irradiation with a 6W Hg arc lamp for 1 hour under 365 nm light, gave two unseparated photoisomers, (*trans, trans, cis*)- and (*trans, cis, cis*) -**2a**. They were identified by change of signal intensities and the coupling constants ($J$ 12.8Hz). As a result, it is observed that the all-*trans* **2a** in solution decreased to 14% upon irradiation. Prolonged irradiation decreased all isomers and increased an insoluble matter. These photoisomers of **2a** were comparatively stable under the NMR-measuring conditions.

To make an improvement of poor solubility of **2a**, we designed the modified macrocycles in Scheme **2**. Conclusively, macrocycles **5a** and **5b** were prepared from the ether-linked diacetyl compound **3** in 15%, and 31% isolated yields, respectively (Fig. (**2**)). In the formation of **5a** and **5b**, the steric hindrance among the hydrogen atoms in the cavity effected on the yields as described above.

The macrocycle **5a** was also photoisomerized under the same conditions as in the case of **2a**, and the single product of (*trans,cis*)-**5a** was obtained, whose structure was characterized by the observed $J$ value (12.8Hz). The ratio of (*trans,cis*)-**5a** to the total amount reached 60% within 1 hour. Although this photoisomer was hardly able to be isolated, no




**Scheme 2.** Preparation of macrocycles **5** starting from bis-aldehydes **4** and bis-ketone **3**.

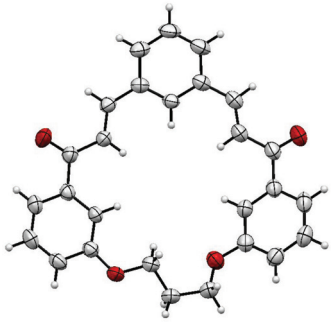


**Fig. (2).** Molecular structure of macrocycle **5a**. CCDC deposition number 855449, $C_{27}H_{22}O_4$, $M_r$ = 410.45, monoclinic, space group $P2_1/c$, a = 10.5992(19), b = 10.0469(17), c = 19.918(4) Å, β = 97.082(3)°, $V$ = 2104.9(6) Å$^3$, $Z$ = 4, $D_{calc}$ = 1.295 g cm$^{-3}$, μ(MoKα) = 0.086 mm$^{-1}$, $N_{ref}$ ( $I > 2\ \sigma(I)$, $\theta < 27.470°$)= 4783, $R_1$ = 0.0443 (3846), w$R_2$ = 0.1274 (4729).

peak except for (*trans,trans*)-**5a** and (*trans,cis*)-**5a** was detected with the $^1$H NMR spectroscopy [7]. The thermal stability of (*trans,cis*)-**5a** was calculated using the Eyring plot by measuring the first-order rate constant; the half-life time at 40 °C in $CDCl_3$ of 86 hours, that in $C_6D_6$ was 212 hours.

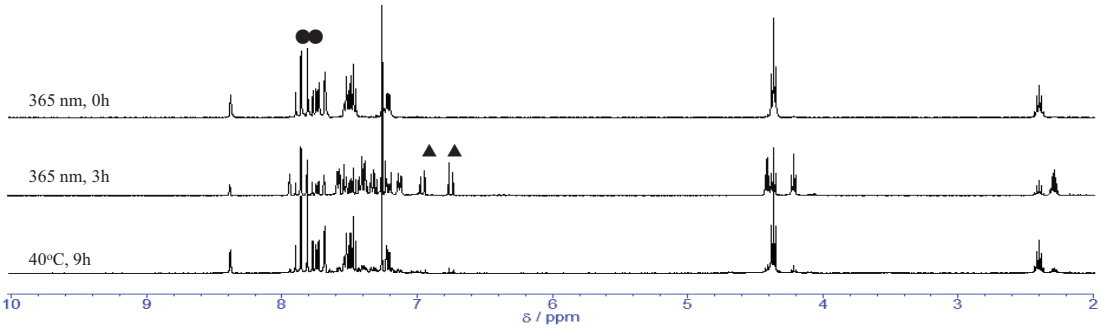
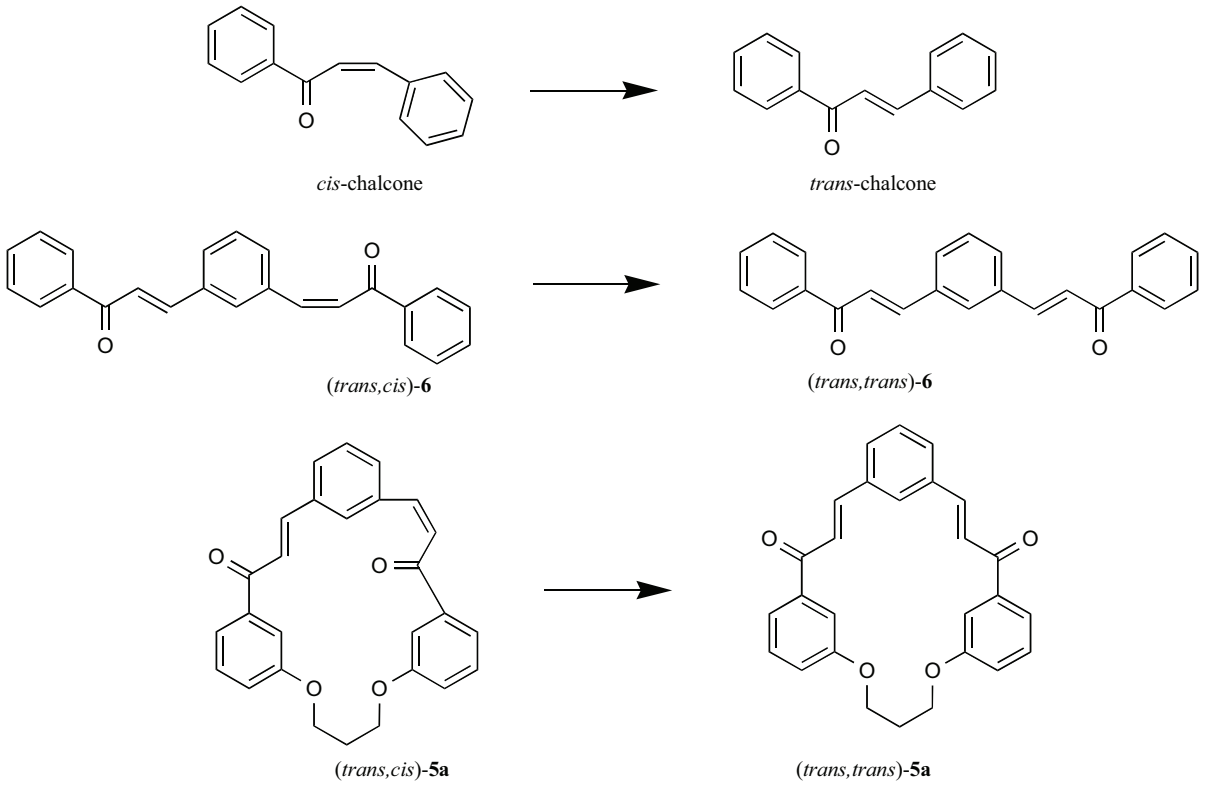



**Fig. (3).** The $^1$H NMR (400MHz, TMS as reference) for macrocycle **5a** in $CDCl_3$. The doublet peaks at δ 7.88 (J = 15.6 Hz) and δ 7.79 (J = 15.6 Hz), assigned to *trans* enone moiety(●)of (*trans, trans*)-**5a**, gradually decreased by 365 nm light irradiation, and the new doublet peaks at δ 6.96 (J = 12.8 Hz) and δ 6.75 (J = 12.8 Hz), assigned to *cis* enone moiety(▲) of (*cis,trans*)-**5a**, were generated. The photoisomer (*cis,trans*)-**5a** was thermally reverted to the original (*trans, trans)*-**5a**, following first-order kinetics. The rate of the thermal isomerization from (*cis,trans*)-**5a** to (*trans, trans)*-**5a** is $k$ = 505 s$^{-1}$, the half-life is $t_{1/2}$ = 5 h (at 40 °C, in $CDCl_3$).

**Table 1. Thermal Stability of the Partial *cis* Photoisomers in $C_6D_6$.**




| Entry | Compound | Half-life time at 40 °C (h) | Enthalpy $\Delta H^{\ddagger}$ (kJ/mol) | Entropy $\Delta S^{\ddagger}$ (J/mol K) |
|---|---|---|---|---|
| 1 | *cis*-chalcone | 51 | 13 | -170 |
| 2 | (*trans,cis*)-**6** | 131 | 37 | -104 |
| 3 | (*trans,cis*)-**5a** | 212 | 47 | -76 |

The enthalpy and entropy were estimated as $\Delta H^{\ddagger}$ = 65 kJ/mol, $\Delta S^{\ddagger}$ = -8 J/mol K (in $CDCl_3$); $\Delta H^{\ddagger}$ = 47 kJ/mol, and $\Delta S^{\ddagger}$ = -76 J/mol K (in $C_6D_6$). Moreover, the thermal stabilities of photoisomers of the linear model compound were estimated as shown in Table **1**. The isomer, (*trans,cis*)-***5a***, exhibits the highest enthalpy among the isomers since the ether-linkage to aromatic rings stabilizes the structure of macrocycles thermodynamically. The stabilization is consistent with the hula-twist path [4, 5].

In conclusion, novel macrocycles were synthesized by Claisen-Schmidt condensation. These planar macrocycles are photoisomerized by 365 nm light. The fact was found that the *cis* configuration of the macrocycle is thermally more stable than those of linear structures. These macrocycles bridged by $\alpha,\beta$-unsaturated ketones have potentials for photo-/thermal-switchable molecular devices [1, 8].

## EXPERIMENTAL

General procedures for the preparation of macrocycle **1a** and **1b**: NaOH (3mmol) in EtOH(50ml) was added to a flask containing **1a** (10mmol) (or **1b** [9]) in EtOH (700ml). The mixture was stirred for 74 hours at room temperature. The reaction mixture was neutralized with HCl*aq* and $NaHCO_3$*aq*, and concentrated *in vacuo*. The residue was dissolved in $CH_2Cl_2$, and the organic layer was washed with water, brine, and dried over $Na_2SO_4$, and then, concentrated. The residue obtained was purified by column chromatography on alumina ($CH_2Cl_2$-THF for **1a**, or $CH_2Cl_2$-THF with 0.5%$Et_3N$ for **1b**) followed by recrystallization to give the desired macrocycle.

**(*E, E, E*)-1,5,9(1,3)-tribenzenadodecaphan-3,7,11-trien-2,6,10-trione (2a)**: Colorless crystalline as a monohydrate (1.4%); m.p. 327.3 $^{o}$C(decomposition); EI-MS *m/z* (rel. int.) 390 ($M^{+}$, 100), 361 (73), 333 (41), 289 (14), 231 (25), 202 (29), 129 (31), 116 (38), 101 (64), 84 (74), 76 (47), 51 (44); $^{1}$H NMR ($CDCl_3$, 400 MHz, TMS as reference) δ 8.82 (s, 3H), 8.24 (d, J = 7.8 Hz, 3H), 8.17 (d, J = 15.6 Hz, 3H), 7.99 (d, J = 15.6 Hz, 3H), 7.75 (d, J = 7.4 Hz, 3H), 7.64 (t, J = 7.8, 7.3 Hz, 3H); $^{13}$C NMR (DMSO-$d_6$, 400 MHz, DMSO residual peak at δ 39.52 ppm as a reference); δ187.9, 140.9, 137.6, 135.8, 135.7,129.6, 128.8, 128.7, 125.1; IR (KBr, $cm^{-1}$) 2923, 2849, 1666(-C=O stretch), 1614 (-C=C- stretch (aromatic)), 1570 (-C=C- stretch (enone)), 1484, 1344, 1321, 1272, 1236, 1183, 1039, 991 (=C-H out-of-plane bending (enone)), 790, 680; Anal. Calcd. for $C_{27}H_{18}O_3 \cdot H_2O$: C 79.4, H 4.9%; found C 79.6, H 4.9%; Crystallographic data for the structure have been deposited at the Cambridge Crystallographic Data Centre (CCDC deposition number 884911).

**(*E, E, E*)-1,5,9(2,6)-tripyridinadodecaphan-3,7,11-trien-2,6,10-trione (2b)**: Yellow crystalline or powder (18.9%); m.p. 268.5 °C(decomposition); FD-MS *m/z* 393 ($M^+$); $^1$H NMR ($CDCl_3$, 500 MHz, TMS as reference) δ 9.51 (d, J = 15.5Hz,3H), 8.28 (d, J = 8.0 Hz, 3H), 8.00 (d, J = 15.5 Hz, 3H), 7.98 (t, J = 8.0, 7.5 Hz, 3H), 7.68 (d, J = 7.5 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 500 MHz, $CHCl_3$ residual peak at δ 77.16 ppm as a reference); δ189.4, 153.8, 152.7, 141.5, 138.3,129.8, 125.0, 123.6; IR (KBr, $cm^{-1}$) 3086, 3059, 2849, 1670(-C=O stretch), 1616 (-C=C- stretch (aromatic)), 1574 (-C=C- stretch (enone)), 1454, 1423, 1331, 1265, 1230, 1173, 1161, 1084, 1045, 984 (=C-H out-of-plane bending (enone)), 798; Anal. Calcd. for $C_{24}H_{15}N_3O_3$: C 73.3, H 3.8, N 10.7%; found C 73.0, H 3.9, N 10.7%; Crystallographic data for the structure have been deposited at the Cambridge Crystallographic Data Centre (CCDC deposition number 888368).

General procedures for the preparation of macrocycle **5a** and **5b**: Compound **4a** (3mmol) (or **4b**) in THF was dropwise added to a flask containing compound **3** (3mmol) [10] and NaOH (1mmol) in EtOH (500ml) and THF (200ml). After completion, the mixture was stirred for 72 hours at room temperature. The reaction mixture was neutralized with HCl*aq* and $NaHCO_3$*aq*, and concentrated *in vacuo*. The residue was dissolved in $CH_2Cl_2$, and the organic layer was washed with water, brine, and dried over $Na_2SO_4$, and then, concentrated. The residue obtained was purified by column chromatography on silica gel ($CH_2Cl_2$-Methanol) followed by recrystallization to give the desired macrocycle.

**(*E, E*)-10,14-dioxa-1,5,9(1,3)-tribenzenatetradecaphan-3,6-dien-2,8-dione (5a)**: Colorless crystalline (15%); m.p. 246.9 °C; ESI-MS *m/z* 411 ($M+H^+$), 433 ($M+Na^+$), 843 ($2M+Na^+$); $^1$H NMR ($CDCl_3$, 400 MHz, TMS as reference) δ 8.37 (s, 1H), 7.87 (d, J = 15.6 Hz, 2H) 7.78 (d, J = 15.6 Hz, 2H), 7.73 (d, J = 7.8 Hz, 2H), 7.68 (s, 2H), 7.74-7.44 (m, 5H), 7.21 (d, J = 8.3, 2H), 4.36 (t, J = 6.4 Hz, 4H), 2.39 (m, 2H); $^{13}$C NMR ($CDCl_3$, 400 MHz, $CHCl_3$ residual peak at δ 77.16 ppm as a reference); δ189.0, 159.0, 142.9, 139.7, 135.6, 132.9, 130.5, 130.2, 123.1, 122.0, 121.6, 120.6, 115.8, 66.9, 29.2; IR (KBr, $cm^{-1}$) 2935, 2879, 1666(-C=O stretch), 1612 (-C=C- stretch (aromatic)), 1577 (-C=C- stretch (enone)), 1489, 1475, 1433, 1383, 1319, 1290, 1263, 1120, 1155, 1065, 1038, 991 (=C-H out-of-plane bending (enone)), 860, 839, 785, 688; Anal. Calcd. for $C_{27}H_{22}O_4$: C 79.0, H 5.4%; found C 79.1, H 5.3%; Crystallographic data for the structure have been deposited at the Cambridge Crystallographic Data Centre (CCDC deposition number 855449).

**(*E, E*)-10,14-dioxa-5(2,6)-pyridina-1,9(1,3)-dibenzenatetradecaphan-3,6-dien-2,8-dione (5b)**: Yellow crystalline (31%); m.p. 216.3 °C; ESI-MS *m/z* 412 ($M+H^+$); $^1$H NMR ($CDCl_3$, 500 MHz, TMS as reference) δ 8.47 (d, J = 14.9 Hz, 2H), 7.86-7.78 (m, 5H) 7.78 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.68 (s, 2H), 7.46 (t, J = 8.0, 2H) 7.43 (d, J = 7.5 Hz, 2H) 7.20 (d, J = 8.0 Hz, 2H) 4.35 (t, J = 5.7 Hz, 4H) 2.30 (m, 2H); $^{13}$C NMR ($CDCl_3$, 500 MHz, $CHCl_3$ residual peak at δ 77.16 ppm as a reference); δ 189.6, 158.9, 153.0, 141.7, 139.7 138.2, 130.3, 127.0, 125.9, 121.4, 119.5, 117.0 66.6, 28.8; IR (KBr, $cm^{-1}$) 2925, 1672(-C=O stretch), 1581 (-C=C- stretch), 1485, 1448, 1437, 1333, 1288, 1261, 1192, 1055, 991 (=C-H out-of-plane bending (enone)), 972, 872, 791, 754, 687, 560; Anal. Calcd. for $C_{26}H_{21}NO_4$: C 75.9, H 5.1, N 3.4%; found C 75.9, H 5.1, N 3.4%; Crystallographic data for the structure have been deposited at the Cambridge Crystallographic Data Centre (CCDC deposition number 855448).

## CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

## ACKNOWLEDGEMENTS

Declared none.

## SUPPLEMENTAL MATERIALS

Spectral data of photoisomers are available in Supplemental Materials.

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