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1,2-Dioxo-3-isopropyloxy-4-methyl-3-cyclobutene as a nucleophilic synthon. Synthesis of Sq-containing cinnamic acid derivatives

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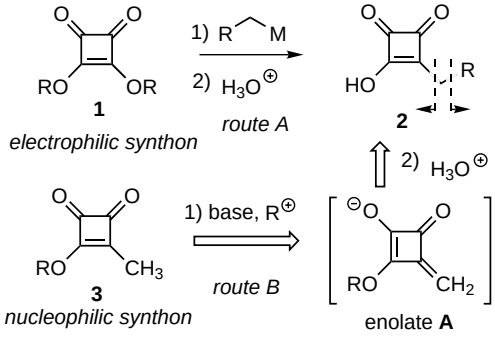
Abstract—An enolate-like intermediate **A** derived from 1,2-dioxo-3-isopropyloxy-4-methyl-3-cyclobutene (**6**) has proven to be a novel nucleophilic synthon for an aldol condensation reaction with an arylaldehyde to give a variety of 4-hydroxy-2,3-dioxocyclobut-1-enyl group (Sq group)-containing cinnamic acid derivatives.

The 4-hydroxy-2,3-dioxocyclobut-1-enyl group (squaryl (Sq) group), has attracted much attention as an isostere of carboxylic acid and phospholic acid in medicinal chemistry,[1] a novel chromophore for developing organic optical materials,[2] and a synthon of quinones,[3] triquinanes,[4] cyclopentenone,[5] and furanones[5a–f] in organic synthesis. In order to extend the utility of squaric acid which possesses intriguing physicochemical properties such as strong acidity, chelating ability to metal ions, and aromaticity, the carbon–carbon bond-forming reaction to squaric acid becomes an important subject in the above mentioned area. A typical method to prepare Sq-containing molecules **2** in which the Sq moiety was connected with a carbon–carbon bond was based on the nucleophilic addition of alkyllithium or Grignard reagent to dialkyl squarate **1** (route A, Scheme 1).[6] Route A is a practical and convenient method for this purpose while the strong nucleophilicity of organometallics was occasionally incompatible with other unstable functional groups. To this problem, we and other groups have demonstrated efficient methods which involve an addition reaction of allylsilane,[4d,5c,5d,5f,7] silylenol ether,[4b,5c,5d,7] ester enolate,[1c,5f] organozinc reagent,[8] or Wittig reagent,[9] and transition metal-catalyzed cross-coupling reactions.[10] Complementary methods to route A for the preparation of a variety of Sq-containing molecule **2** are still sought.

Since the Sq group possesses a potent electron-withdrawing property, we envisioned that an enolate-like intermediate **A** derived from **3** would perform as a nucleophilic synthon which reacts with an electrophile to give **2** under mild reaction conditions (route B). We herein report generation of the enolate **A** in an aprotic media and its aldol condensation with aromatic aldehydes to afford novel Sq-containing cinnamic acid analogs whose carboxyl group is replaced by a strongly acidic Sq group. Although an example to form the enolate has been demonstrated by deuteration of **4** with NaOD in D_2O (Scheme 2) in 1970,[11] its synthetic application to carbon–carbon bond forming reaction has not been reported to date. We initially examined the enolate formation **7** from methylcyclobutenedione **6**[6d] in THF using several bases (Table 1). Treatment of **6** with LDA at −78°C in THF followed by quenching with excess amounts of AcOD gave mono-deuterated compound **8** in 57% yield with 55% *d*-incorporation.



Scheme 1.

Keywords: squaric acid; cinnamic acids; aldol condensation; nucleophilic synthon.

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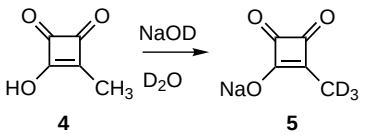


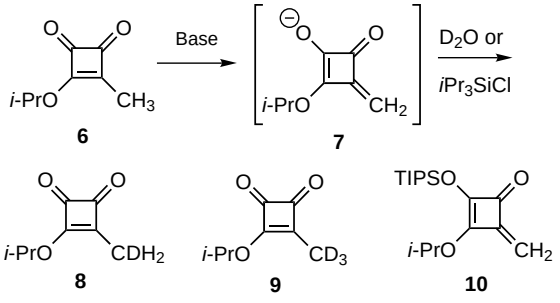
Scheme 2.

Table 1. Trapping of enolate **8** with D_2O or *i*-Pr_3SiCl

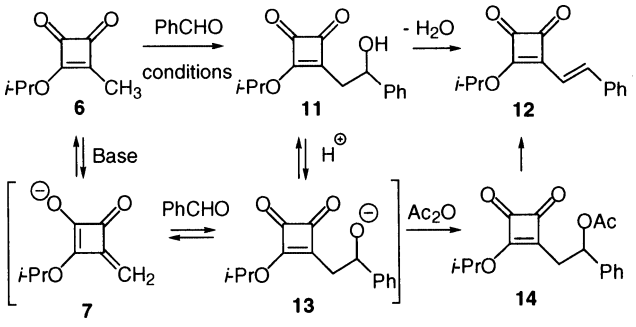
Entry	Conditions (equiv.)	Products (yield, *d*-incorporation)
1	LDA (1), THF, −78 to 20°C 1 h, then AcOD (13), D_2O (43), −78 to 0°C, 1 h	**8** (57%, 55%)
2	Et_3N (1), D_2O (15), THF, 0°C, 1.5 h	**9** (87%, 89%)
3	LDA (1.05), THF, −78 to 20°C, 1 h, then TIPSCl (1), −78 to 20°C, 3 h	**10** (>90%)

The incorporation took place when **6** was subjected to triethylamine and D_2O to give tri-deuterated **9** (>90% *d*-incorporation). Moreover, lithium enolate **7** was trapped with TIPSCl to afford novel silyl enolate **10** in 90% yield. These results confirmed the presence of the conjugated enolate **7** in organic solvent (Scheme 3).

Having the enolate **7** in hand, we next examined its reaction with benzaldehyde (Scheme 4, Table 2). Initial treatment of **6** with LDA in THF and subsequent addition of benzaldehyde at −20°C did not give any aldol product and the starting material **6** was recovered (entry 1). Switching the base to triethylamine provided the same result as entry 1 (entry 2). These results



Scheme 3.



Scheme 4.

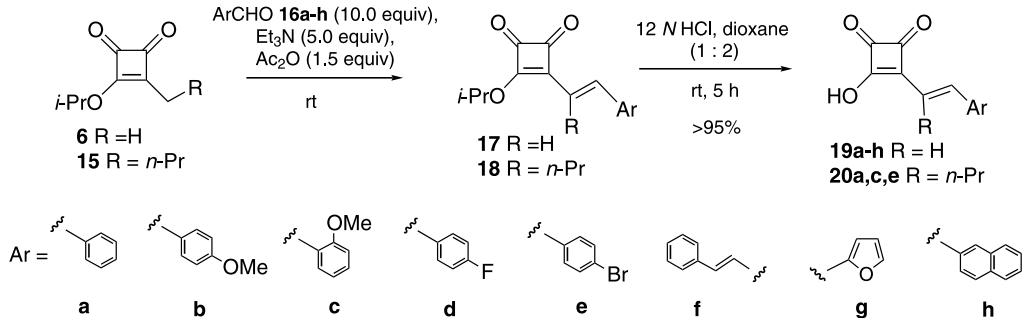
suggest that a retro-aldol process from **11** to **6** via alkoxide **13** would predominate under these conditions. In order to prevent the reversible equilibrium, we attempted to trap the putative intermediate **13** with an electrophile. Addition of a small amount of H_2O in the reaction gave a trace amount of the desired adduct **11** (2%) (entry 3), suggesting that certain equilibrium exists between **7** and **13** while the yield was only 2%. We considered that dehydration of **11** or trapping the alkoxide **13** with an electrophile would improve the yield. Thus, addition of Ac_2O into the reaction condition was found to provide α,β-unsaturated olefin **12**[12] in 17% yield. Presumably, the reaction proceeded through acetylation of **13** and subsequent β-elimination of acetic acid from the resulting **14** (not isolated) gave **12** (entry 4). After several attempts to increase the yield, the unsaturated olefin **12** was obtained in 36% upon treatment with Ac_2O and Et_3N without any solvent (entry 5).[13]

A variety of aldehydes **16a–h** were condensed with **6** or **15** to give *E*-squaryl styrene derivatives **12**, **17b–h**, **18a**, **18c**, and **18e** in a range of 16–76% yields (Scheme 5, Table 3).[15,16] Similarly, the reaction of butylcyclobutenone **15**[7c] with **16a** or **16e** afforded *E*-trisubstituted olefin **18a** or **18e** in good yield, respectively (entries 9 and 11). The presence of a methoxy group on the aromatic ring led to lower yields of **17b** and **18c** (entries 2 and 10). The isopropyl group of these adducts was removed smoothly by treatment with 12*N* HCl in dioxane to give the corresponding Sq-containing cinnamic acid derivatives in quantitative yields. The pK_a value of the squaryl group is estimated to be less than 0 which is much stronger acidity than that of cinnamic acid.[17]

In conclusion, the generation of enolate **7** derived from **3** in aprotic media is reported for the first time and its synthetic utility has been demonstrated as an aldol condensation reaction with various aromatic aldehydes. The present method provides a facile entry to prepare a novel class of cinnamate derivatives whose pK_a value is ~0 and conjugate system is extended (UV λ_{max} = 350 nm).[18] Preliminary bioassays indicated that **17b** and **17h** exhibited antibacterial activities against *Rhizoctonia solan* at micro mole level.[19] Further studies regarding

Table 2. Optimization of the condensation reaction

Entry	Conditions (equiv.)	Results (yield, %)
1	LDA (1), THF, −78 to 20°C, 1 h, then PhCHO (1), −78 to −20°C, 2.5 h	**6** (34)
2	Et_3N (1.05), PhCHO (1), THF, rt, 24 h	**6** (64)
3	Et_3N (1.05), PhCHO (1), few drops of H_2O, THF, rt, 5 h	**11** (2), **6** (77)
4	Et_3N (1.05), PhCHO (1), Ac_2O (1.05), THF, 0°C to reflux, 16 h	**12** (17), **6** (26)
5	Et_3N (5), Ac_2O (1.5), PhCHO (10), neat, rt, 5 days	**12** (36)



Scheme 5.

Table 3. Condensation of **6** or **15** and **16a–h**

Entry	Substrate	Aldehyde	Time (days)	Product	Yield (%)
1	**6**	**16a**	6	**12**	36
2	**6**	**16b**	5	**17b**	32
3	**6**	**16c**	5	**17c**	42
4	**6**	**16d**	5	**17d**	45
5	**6**	**16e**	5	**17e**	43
6	**6**	**16f**	1	**17f**	46
7	**6**	**16g**	12	**17g**	40
8	**6**	**16h**	7	**17h**	37
9	**15**	**16a**	6	**18a**	76
10	**15**	**16c**	6	**18c**	15
11	**15**	**16e**	6	**18e**	58

biological significance of the synthetic compounds are currently investigated in our laboratories.

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12. Configuration of **12** was confirmed by NOE experiments.
13. The starting material **6** was not recovered at all from the reaction mixture due probably to a decomposition of **6** under the alkaline condition to give a substituted product.[14] Moreover, lithium diiospropylamide (LDA) adds to the carbonyl group of **6** under prolonged reaction time to give 1,2-addition product of diisopropylamine (unpublished result). These results suggest that triethylamine adds to **6** followed by uncertain decomposition of the resulting adducts competes with the desired aldol process.
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15. Typical experimental procedure: To a mixture of **6** (156 mg, 1 mmol), benzaldehyde (1.01 mL, 10 mmol), and triethylamine (0.7 mL, 5 mmol) was added dropwise acetic anhydride (0.14 mL 1.5 mmol). The mixture was stirred for 5 days at room temperature, diluted with H_2O, and extracted with AcOEt (×2). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography to give *E*-**12** (87 mg, 36%) as a pale yellow oil. IR (neat) 3413, 2988, 1784, 1760, 1744, 1610, 1580, 1568, 1400, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, $J=16.0$ Hz, 1H), 7.61–7.56 (m, 2H), 7.45–7.35 (m, 3H), 6.98 (d, $J=16.0$ Hz, 1H), 5.52 (sept, $J=6.2$ Hz, 1H), 1.53 (d, $J=6.2$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 193.1, 192.0, 173.8, 142.1, 135.3, 130.5, 129.0, 128.1, 112.9, 79.1, 22.9; HRMS (EI) *m*/*z* calcd for $C_{15}H_{14}O_3$ (M^+ 242.0943, found 242.0936; UV $\lambda_{max}=350$ nm ($CHCl_3$), $\varepsilon_{max}=32\,500$ ($CHCl_3$). A solution of **12** (100 mg, 0.41 mmol), in dioxane (2 mL) and concd HCl (0.5 mL) was stirred for 4 h. The mixture was evaporated in vacuo to give **19a** as pale yellow crystals. mp>250°C (dec.) (from H_2O/THF); IR (neat) 1793, 1707, 1612, 1497, 1473, 1330, 1155, 1038, 970 cm^{-1}; ^1H NMR (300 MHz, D_2O+NaOD) δ 7.40–7.35 (m, 2H), 7.30–7.17 (m, 3H), 2.23 (d, $J=16.3$ Hz, 1H), 6.73 (d, $J=16.3$ Hz, 1H); ^{13}C NMR (75 MHz, D_2O+NaOD) δ 208.5, 199.0, 178.7, 136.9. 136.1, 130.0, 129.0, 127.5, 114.2; HRMS (FAB) *m*/*z* calcd for $C_{12}H_8O_3$ (*M*–H) 199.0412, found 199.0429; UV $\lambda_{max}=354$ nm ($CHCl_3$), $\varepsilon_{max}=19\,000$ (CH_3OH).
16. Other aldehydes such as *n*-octanal and pivalaldehyde did not condense with **6** under the same reaction conditions. It would be necessary to employ more reactive enolate species such as silyl enolate from **6** to perform the coupling with these aldehyde. Such attempts are currently being investigated.
17. pK_a Values of **4**, 3-hydroxy-4-phenyl-1,2-dioxo-3-cyclobutene, and cinnamic acid are −0.22, 0.24, and 4.2, respectively; see Ref. 6e.
18. The *Z*-isomer of **12** has been reported as an intermediate of quinone synthesis. All the *E*-analogs described in this paper are new compounds. See: Turnbull, P.; Meileman, M. J.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 2584–2585.
19. Squaric acid and diisopropyl squarates did not show any antibacterial activity.