Synthesis of Functionalized Cyclobutene Derivatives via Selective S_N2' Reaction of Dichlorocyclobutenes

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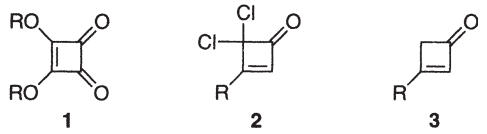
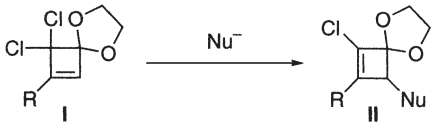
Dichlorocyclobutenone acetals, available via the cycloaddition of dichloroketene and alkynes followed by acetalization, undergo selective S_N2' attack by various nucleophiles to give a variety of functionalized cyclobutene derivatives in high yields.

Cyclobutene derivatives display various useful reactivities in organic synthesis.[1] In this regard, squarate esters **1** have been extensively used, due to the ability to assemble one or two nucleophilic components followed by reorganization.[1] However, less known is the fact that squarates often cause severe contact dermatitis,[2] as experienced in our laboratories.



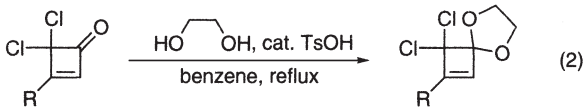
1 **2** **3**

We became interested in dichlorocyclobutenone **2** as an alternative starting point, which is readily available by [2 + 2] cycloaddition of alkynes and dichloroketene.[3] Although the oxidation level of **2** is lower than **1**, our hope was that two chlorides in **2** could be used for assemblage of molecules via nucleophilic displacement, while they are usually just reductively removed *en route* to cyclobutene **3**.[4] Experiments along these lines revealed a clean and reliable S_N2' reactivity inherent to protected dichlorocyclobutenones **I**, reacting with various nucleophiles uniformly in a site-selective manner,[5,6] to give functonalized cyclobutene derivatives **II** (eq 1).



I **II** (1)

Three known dichlorocyclobutenones **2a–c**[7] were converted to the corresponding ethylene acetals **4a–c** (ethylene glycol, cat. TsOH, benzene, Dean–Stark apparatus).

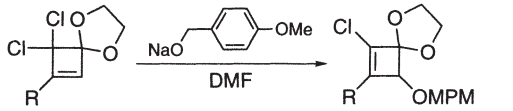


2a; R = Ph
2b; R = *n*-Bu
2c; R = TMS

4a; R = Ph: 86%
4b; R = *n*-Bu: 89%
4c; R = TMS: 63%

(2)

Acetals **4a–c** undergo clean reaction with a variety of nucleophiles. The reaction of **4a** with sodium *p*-methoxyphenylmethoxide is representative: To a solution of *p*-$CH_3OC_6H_4CH_2O^-Na^+$ (1.5 equiv NaH, 2.0 equiv *p*-CH_3O-$C_6H_4CH_2OH$) in DMF was added cyclobutene **4a** in DMF at 0 °C, and stirred for 1 h. After quenching with water, purification by silica-gel flash column chromatography gave the S_N2' product **5a**[8] in quantitative yield (eq 3). None of the S_N2 product, if any, was detected. The corresponding reaction of **4b** also gave the S_N2' product **5b** in high yield.

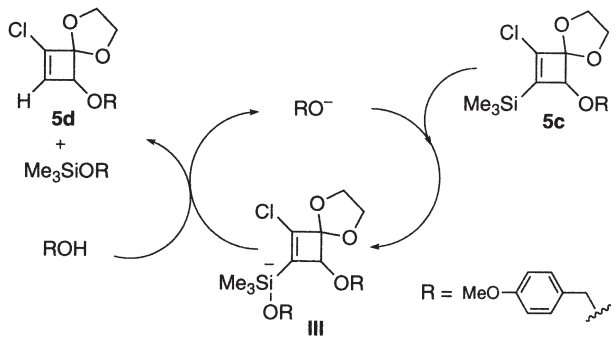


4a; R = Ph
4b; R = *n*-Bu
4c; R = TMS

5a; R = Ph: quant.
5b; R = *n*-Bu: 83%
5d; R = H: 67%,
(**5c**; R = TMS: 0%)

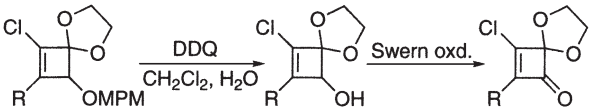
(3)

Interestingly, although the substitution cleanly occurred also for the silyl congener **4c**, the product **5d** was without the silyl group (eq 3). Since tlc assay showed that **5d** was already present in the reaction mixture prior to workup, the formation of **5d** could be rationalized by the protonation by *p*-$CH_3OC_6H_4CH_2OH$ of the initially formed S_N2' product **5c**, via the corresponding silicate **III** (Scheme 1).[9]



Scheme 1.

Products **5a** and **5b** (eq 3) are particularly attractive, in that they are convertible to **8a** and **8b**, which could be viewed as mono-protected cyclobutenedione derivatives with high synthetic versatility (eq 4). Deprotection of the MPM ether (DDQ, wet CH_2Cl_2) in **5a** and **5b** followed by Swern oxidation gave mono-acetals **8a** and **8b** in high yields, respectively.



5a; R = Ph
5b; R = *n*-Bu

7a; R = Ph: 92%
7b; R = *n*-Bu: 89%

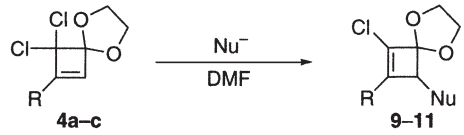
8a; R = Ph: 86%
8b; R = *n*-Bu: 91%

(4)

Other substrate/nucleophile combinations were tested under similar conditions. Three hetero-nucleophiles ($CH_3OC_6H_4O^-$,

N_3^-, $C_6H_5S^-$) were reacted with dichlorocyclobutenes **4a–c**, and the results are summarized in Table 1. In general, the reactions proceeded cleanly to give the corresponding S_N2' products in excellent yields. Two exceptions were observed for substrate **4b** (R = *n*-Bu), which failed to react with phenoxide or NaN_3 at all. Repeated attempts under various conditions resulted only in the recovery of **4b**, although the reasons remain unclear.

Table 1. Reaction of **4a–c** with hetero-nucleophiles



4a–c **9–11**

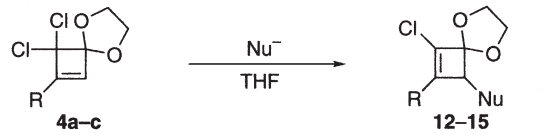
Nucleophile	Yield/%		
R =	Ph	*n*-Bu	TMS
NaO–⟨⟩–OMe	**9a**: 97[b,e]	**9b**: 0[d,f]	**9c**: 86[b,e]
NaN_3	**10a**: 88[c]	**10b**: 0[d,f]	**10c**: 88[d]
NaSPh	**11a**: 99[a,e]	**11b**: 95[b,e]	**11c**: 96[a,e]

[a]0 °C. [b]0 °C → room temperature. [c]Room temperature. [d]Room temperature → 40 °C. [e]Performed in THF. [f]No reaction.

The S_N2' reactivity of **4a–c** was also observed with carbon nucleophiles (Table 2). When **4a** was treated with *n*-BuLi (1.2 equiv.) in THF at −78 °C, the S_N2' reaction occurred to give **12a** in quantitative yield. In a similar manner, treatment of **4c** with *n*-BuLi also gave **12c** in 96% yield. However, in the case of the substrate **4b** (R = Bu), yield of the desired S_N2' product **12b** was low, giving an intractable mixture of products, presumably due to the acidity of the allylic proton, where *n*-BuLi acted as a base to induce side reactions.

Other carbon nucleophiles, i.e., vinyl-, and aryllithiums reacted cleanly with acetals **4a–c** (Table 2). In these cases, **4b** also behaved as a good substrate for the S_N2' reaction to give the corresponding substitution products **13b** and **15b** in high yields, respectively. Again with no obvious reason, peculiar lack of reactivity was seen for the reaction of alkynyllithium. Although

Table 2. Reaction of **4a–c** with carbon nucleophiles



4a–c **12–15**

Nucleophile	Yield/%		
R =	Ph	*n*-Bu	TMS
n-BuLi	**12a**: quant[a]	**12b**: 15[a]	**12c**: 96[a]
Me, Li	**13a**: 91[a,d]	**13b**: 88[b,d]	**13c**: 85[a,d]
Li–≡–Me	**14a**: 91[c]	**14b**: 0[c,e]	**14c**: 0[c,e]
Li–⟨⟩–OMe	**15a**: 93[a]	**15b**: 83[a]	**15c**: 94[a]

[a]–78 °C. [b]–78 → 0 °C. [c]–78 °C → room temperature. [d]Performed in Et_2O. [e]No reaction.

propynyllithium reacted cleanly with **4a**, in the case of the substrates **4b** (R = Bu) and **4c** (R = TMS), the expected products were not obtained at all. Examination under various conditions were unfruitful.

In summary, we have described a new route to highly functionalized cyclobutenes by the selective S_N2' reaction of the dichlorocyclobutene acetals. Further studies are currently underway in our laboratories.

References and Notes

1 For selected recent examples, see: a) F. Geng, J. Liu, and L. A. Paquette, *Org. Lett.*, **4**, 71 (2002). b) A. R. Hergueta and H. W. Moore, *J. Org. Chem.*, **67**, 1388 (2002). c) S. T. Perri and H. W. Moore, *J. Am. Chem. Soc.*, **112**, 1897 (1990). d) F. Liu and L. S. Liebeskind, *J. Org. Chem.*, **63**, 2835 (1998). e) R. L. Danheiser, S. K. Gee, and J. J. Perez, *J. Am. Chem. Soc.*, **108**, 806 (1986).

2 a) R. Prohens, M. C. Rotger, M. N. Piña, P. M. Deyà, J. Morey, P. Ballester, and A. Costa, *Tetrahedron Lett.*, **42**, 4933 (2001). b) A. Frattasio, M. Germino, S. Cargnello, and P. Patrone, *Contact Dermatitis*, **36**, 118 (1997).

3 For a review, see: W. T. Brady, *Tetrahedron*, **37**, 2949 (1981).

4 R. L. Danheiser and S. Savariar, *Tetrahedron Lett.*, **28**, 3299 (1987).

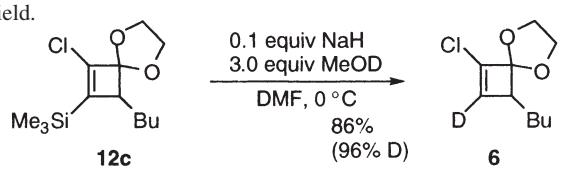
5 For related reactions, see: a) M. C. Caserio, H. E. Simmons, Jr., A. E. Johnson, and J. D. Roberts, *J. Am. Chem. Soc.*, **82**, 3102 (1960). b) Y. Kitahara, M. C. Caserio, F. Scardiglia, and J. D. Roberts, *J. Am. Chem. Soc.*, **82**, 3106 (1960). c) E. F. Jenny and J. Druey, *J. Am. Chem. Soc.*, **82**, 3111 (1960).

6 The S_N2' reactivity of dichlorocyclobutenone **2a** in its "non-protected" form was reported [J. L. Dillon and Q. Gao, *J. Org. Chem.*, **59**, 6868 (1994)]. Our preliminary attempts on the same reaction with harder nucleophiles such as *n*-BuLi led to the competing S_N2' and the carbonyl addition. As described in this paper, use of the acetal allows the reaction with various nucleophiles including carbon nucleophiles, thereby significantly expanding the scope of this class of compounds. We thank one of the referees for bringing this point to our attention.

7 a) R. L. Danheiser and H. Sard, *Tetrahedron Lett.*, **24**, 23 (1983). b) R. L. Danheiser, S. Savariar, and D. D. Cha, "Organic Synthesis," Wiley, New York (1993), Collect. Vol. VIII, pp 82–86. c) A. Hassner and J. L. Dillon, Jr., *J. Org. Chem.*, **48**, 3382 (1983).

8 A typical procedure: To a suspension of NaH (60% dispersion in mineral oil, 23.6 mg, 0.59 mmol) in DMF (0.6 mL) was added *p*-$CH_3OC_6H_4CH_2OH$ (109 mg, 0.789 mmol) in DMF (1.5 mL) at 0 °C, to which was added cyclobutene **4a** (101 mg, 0.393 mmol) in DMF (1.5 mL), and stirred for 1 h. After quenching with water, products were extracted with Et_2O (X3), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica-gel flash column chromatography (hexane/EtOAc = 92/8) to give the S_N2' product **5a** (151 mg, quant.). Recrystallization from hexane/Et_2O gave colorless prisms: mp 93.6–94.2 °C. ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 3.95–4.12 (m, 2H), 4.16–4.24 (m, 2H), 4.62 (s, 2H), 4.91 (s, 1H), 6.89 (d, 2H, J = 8.5 Hz), 7.32 (d, 2H, J = 8.5 Hz), 7.35–7.41 (m, 3H), 7.67–7.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 55.3, 65.6, 65.9, 70.9, 83.9, 111.3, 113.8, 125.2, 127.7, 128.5, 129.7, 130.0, 130.2, 144.6, 159.3; IR (neat) 2884, 1611, 1514, 1322, 1043, 948, 700 cm^{-1}; Anal. Calcd for $C_{20}H_{19}ClO_4$: C, 66.95; H, 5.34. Found: C, 66.69; H, 5.41.

9 The proposed mechanism is supported by the following reaction: treatment of **12c** with NaOMe and MeOD (0.1 equiv NaH, 3.0 equiv MeOD) in DMF gave the deuterated product **6** (96% D) in 86% yield.



12c **6**