Cyclohexynes.
Generation from Iodonium Salts and Regioselective Reaction with Nucleophile

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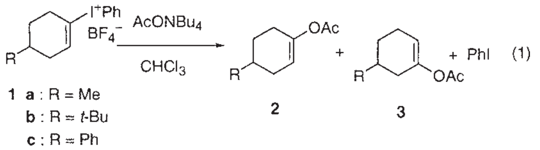
Cyclohexynes are effectively generated by treatment of cyclohex-1-enyliodonium salts with a mild base such as acetate and fluoride ion in chloroform. Regioselectivity of the nucleophilic addition of acetate ion to cyclohexynes depends on the 4-substituent.

1,2-Eliminations of the benzene and cycloalkene derivatives containing leaving groups have been straightforward methods to generate benzynes,[1,2] cycloalkynes,[1,3] and cycloalka-1,2-dienes.[1b,4] These species are highly reactive towards nucleophiles yielding adducts, and have been employed for organic synthesis.[5,6] Among these reactive species, however, synthetic application of cycloalkynes lags far behind that of benzynes[5] and cycloalka-1,2-dienes.[6]

Theoretical calculations[7] and electron transmission spectroscopic data[8] suggest that the ring strain of cycloalkynes lowers the LUMO energy level, which increases the electrophilic reactivity of the alkyne. Nucleophilic addition reactions to cycloalkynes were observed in several examples[9] but the regioselectivities of the addition are not yet fully comprehended.[1,10]

Cycloalkyne production from 1-halocycloalkenes is carried out under strongly basic conditions, but cycloalka-1,2-dienes are often major products.[4] Cycloalkynes isomerize to cycloalka-1,2-dienes under basic conditions. Thus, a mild and general method of selective generation of cycloalkynes is required to study their reactivities. Desilylation of β-silyl vinyl iodonium salts was employed to generate norbornyne derivatives by Kitamura[11] and Gilbert.[12] This method combines the advantage of a facile fluoride-induced desilylation with that of the high nucleofugality of the iodonio group.[13] This strategy is also applied successfully to generate benzynes.[14] We have found that β-elimination of simple cyclohex-1-enyl iodonium salts, instead of β-silylated derivatives, selectively provides cyclohexynes under quite mild conditions. The present communication describes this easy method of generation of cyclohexynes as well as the interesting regioselectivities of the addition of nucleophilic acetate to 4-substituted cyclohexynes.

The reaction of 4-substituted cyclohex-1-enyl(phenyl)-iodonium tetrafluoroborate (**1**)[15] with tetrabutylammonium acetate was carried out in chloroform at 60 °C and gave two regioisomers of cyclohex-1-enyl acetate, **2** and **3**, accompanied by iodobenzene (eq 1). Yields of the products were determined by GC and are summarized in Table 1. In all cases the regio-migrated 5-substituted product **3** was obtained. This is in contrast to the selective formation of the direct substitution product **2** in the acetolysis of **1** in unbuffered acetic acid. The ratio of the regioisomeric products (**2**/**3**) and their structures were confirmed by the analysis of the cyclohexanones obtained upon acid-catalyzed hydrolysis of the product mixture. The ratios of **2**/**3** range from nearly unity to 1/3 depending on the 4-substituent.



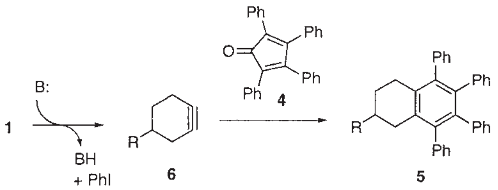
(1)

Table 1. Reaction of **1** in chloroform containing tetrabutylammonium acetate at 60 °C for 2 h

Substrate	Conc. of acetate /mol dm^{-3}	Yield/% **2**	**3**	PhI	**2/3**
1a	0.1	37	44	69	46/54
1a	0.01	38	44	70	46/54
1a[a]		85	0	57	100/0
1b	0.1	20	52	89	28/72
1b	0.01	15	44	73	25/75
1b[a]		89	0	78	100/0
1b′[b]	0.1	15	55	78	21/79
1b′[b]	0.01	9	37	76	20/80
1b′[a,b]		0	65	88	0/100
1c	0.1	36	27	67	57/43
1c	0.01	33	27	64	55/45
1c[a]		60	0	67	100/0

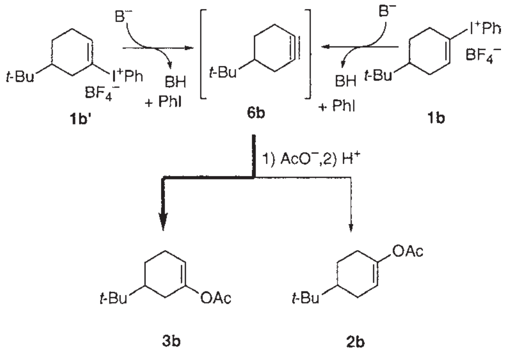
[a]Solvolysis of **1** in acetic acid at 60 °C for 4 h. [b]**1b′** is 5-*tert*-butyl substrate.

The formation of the regio-migrated product **3** seems to be best interpreted by the intermediate formation of cyclohexyne **6** as reactive intermediate. There are a few examples of formation of alkynes from vinyliodonium salts.[16,17] The formation of cyclohexyne **6** could in fact be confirmed by trapping experiments. The acetate reaction of **1** carried out in the presence of tetraphenylcyclopentadienone (**4**) gave tetrahydronaphthalene **5** (eq 2). The adducts **5a**, **5b**, and **5c** were isolated in 84, 91, and 98% yields, respectively, from the reaction of **1a**–**c**. No reaction occurred between **1** and **4** in the absence of acetate ion. Cyclohexyne **6** was also generated in the reaction of **1** with tetrabutylammonium fluoride in chloroform: in this reaction **6** was also effectively trapped by **4** to give **5** in quantitative yield. These results show that the cyclohexenyliodonium salts readily give cyclohexynes with the action of a mild base. No indication for the formation of cyclohexa-1,2-diene was found in the present reaction.



(2)

The regioselectivity of formation of the acetate products, **2** and **3**, depends on the nature of the 4-substituent of the cyclohexenyl precursor **1**. Both methyl and phenyl derivatives (**1a** and **1c**) give nearly equal amounts of the regioisomers as expected for cyclohexyne intermediate, but the *tert*-butyl substrate **1b** gives three times more regio-migrated product **3b** than the non-migrated substitution product **2b**. This unbalanced formation of the regioisomers is rather unexpected for 4-substituted cyclohexyne. Cyclohexyne **6b** can be generated also from the regioisomeric iodonium salt **1b′**, and so **1b′** was subjected to the acetate reaction (Scheme 1). The reaction of **1b′** gave **2b** and **3b** in the ratio of 20/80, which is almost identical with the ratio of 25/75–28/72 obtained from **1b**. This is compatible with the common cyclohexyne intermediate **6b** in the reactions of **1b** and **1b′**. The regio-convergent product ratio observed indicates that it essentially reflects the intrinsic regioselectivity of the reaction of the cyclohexyne intermediate with acetate ion; a 3–4 fold preference of **3b** over **2b**. Some ambiguities arise because of the possibility of any direct substitution reactions of **1b** and **1b′**, which give selectively **2b** and **3b**, respectively,[13,18] but the effects thereof on the observed ratio **2b : 3b** are small. The cyclohexyne intermediate giving the acetate products is also confirmed by deuterium incorporation at the vinylic position of the acetate products, **2** and **3**, in case the reaction is performed in the presence of methanol-*d*.



The addition of methanol (1% v/v) as a proton source did not affect the isomeric ratio of **3b** and **2b**. That is, the nucleophilic addition step of acetate to **6** is product determining step, which leads to the observed ratio of the acetate products. How is the regioselectivity of the nucleophilic addition to cyclohexynes controlled by the remote 4-substituent? The regioselectivity of nucleophilic addition to substituted benzynes has been extensively studied, and the inductive effect of the substituent is considered to be responsible for the selectivity.[1,2] However, the small difference in electronic effects of alkyl groups may not induce much selectivity. Theoretical calculations indicate that the LUMO of **6** is mainly located at the acetylenic carbons and develops in the plane of cyclohexyne ring, where acetate ion attacks. The population of the LUMO at the carbon 1 of **6b** calculated by B3LYP/6-31G* is smaller than that at the 2 position. The difference in the populations between the 1 and 2 positions of **6a** or **6c** is much smaller than that of **6b**. Thus, the population of the LUMO calculated conforms to the regioselectivity of the acetate reaction of cyclohexyne, in accord with the nucleophilic addition mechanism.

In summary, cyclohexenyliodonium salts can be used as effective cyclohexyne precursors under mild conditions. The easy access to the precursors and simple manipulations needed to generate cyclohexynes open routes to revealing chemistry of this unstable class of compounds.

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