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NUCLEOPHILIC RING CLEAVAGE OF MONO-ACTIVATED CYCLOPROPANES VIA SODIUM AND LITHIUM PHENYL SELENOLATE

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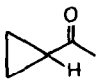
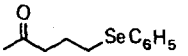
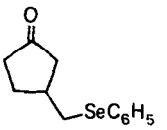
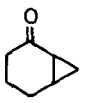
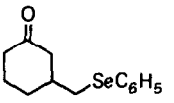
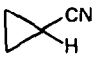
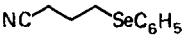
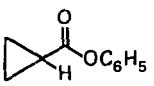
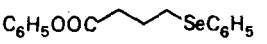
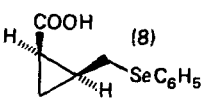
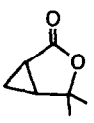
Although the nucleophilic ring-cleavage reaction of diactivated cyclopropanes has enjoyed recent elegant application[1,2,3] in the total synthesis of complex natural products, similar reactions of mono-activated cyclopropanes are rare. Indeed, with one exception,[4] they have been observed only in highly strained bicyclic systems.[5-7] In this letter we report that the cyclopropyl ring, mono-activated with either a ketone or nitrile functionality, suffer in good to excellent yield, nucleophilic cleavage when subjected to the powerful nucleophilic anion, phenyl selenolate. The results of this study are illustrated in Table 1.

Initially, we examined sodium phenyl selenolate generated from diphenyl diselenide and $NaBH_4$ in DMF since recent work from these laboratories[8] demonstrated that this reagent possessed sufficient nucleophilicity to effect cleavage of the alkyl-oxygen bond of simple lactones. Under these conditions mono-activated cyclopropanes 1-5 led via cyclopropyl ring cleavage to the corresponding selenide.[9,10] Interestingly, lactone 6 possessing two potential sites of nucleophilic attack, (i.e. the cyclopropyl ring and the γ-carbon) led exclusively via alkyl-oxygen bond cleavage to a high yield of cyclopropane 8. On the other hand, substrate 7 specifically chosen to eliminate lactone ring cleavage[11] and thereby provide an excellent test for the activating power of the lactone functionality, was recovered quantitatively.

The yields of the selenides under these conditions were however poor except in the case of nitrile 4. Presumably, the low yields, especially those observed

Table 1. Nucleophilic Ring Cleavage of Mono-activated Cyclopropanes

	Substrate	Reaction time (hours)	Yield (percent)[9]		Phenylselenide[10]
			$NaBH_4/DMF/120°$	$C_6H_5SeLi/C_6H_6/\Delta$	
1		15	13	90	
2		15	10	47	
3		15	12	64	
4		12	47		
		24		0	
5		24	< 6	6	
6		6	81		 (8)
		24		0	
7		24	0	0	

with the cyclopropyl ketones (1-3) result from carbonyl reduction prior to nucleophilic attack by the excess $NaBH_4$ required to generate sodium phenyl selenolate. To circumvent this side reaction, we investigated the preparation and nucleophilicity of lithium phenyl selenolate. To this end, diphenyl diselenide was quantitatively reduced with aqueous hypophosphorous acid to phenyl selenol,[12,13] which was extracted into benzene and then dried over magnesium sulfate.[8a] Conversion to the desired lithium phenyl selenolate was then effected by addition of one equivalent of n-butyl lithium. With this reagent in hand, we reexamined the cyclopropyl substrates. Best results with lithium phenyl selenolate were obtained when the substrate and reagent were heated at reflux in the presence of a catalytic amount of the lithium crown ether, 12-crown-4. Under these conditions a marked improvement in the yield of derived selenide was noted for the cyclopropyl ketones while little or no improvement occurred with cyclopropanes activated by the ester and lactone functionalities. In addition under these conditions no reaction occurred with nitrile 4. Collectively, the above results are in general agreement with the expected ability of the activating functionality (i.e. ketone, nitrile and ester-lactone) at stabilizing an adjacent negative charge.

In summary, we have demonstrated in this letter that the phenyl selenolate anion is an effective reagent for ring cleavage of mono-activated cyclopropane. Both cyclopropyl ketones and nitriles undergo this transformation efficiently, the former with lithium phenyl selenolate, the latter with sodium phenyl selenolate. Combination of this transformation with the now numerous reactions of phenyl selenides (e.g. oxidative elimination,[14,15]) forshadows the synthetic utility of the above transformation.

Preparation and Reaction of Lithium Phenyl Selenolate: A solution containing 470 mg (1.5 mmol) of diphenyl diselenide, 5 ml of tetrahydrofuran and 1.5 ml of 50% aq. hypophosphorous acid was heated at reflux for 20 min. Upon cooling the resultant phenyl selenol was extracted into 40 ml benzene. The benzene solution was next filtered (suction) through a pad of magnesium sulfate and transferred to a dry reaction vessel fitted with condenser and nitrogen inlet. Lithium phenyl selenolate was generated via addition of 1.05 eq of n-butyl lithium. After ten minutes at room temperature the reaction vessel was charged with 3.0 mmol of the approp-

riate mono-activated cyclopropane and a catalytic amount (0.055 mmol) of the crown ether, 12-crown-4. The resultant mixture was then heated at reflux for the times indicated in Table 1. At the end of this period the reaction was quenched with 10% aqueous HCl and the resultant selenide isolated in the usual manner along with varying amounts of diphenyl diselenide.

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References and Footnotes

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9. All yields recorded here were based on isolated material which was > 95% pure.

10. The structure assigned to each selenide was in accord with its infrared and 220 or 360 MHz spectra. Analytical samples of each new selenide, obtained by preparative vapor phase chromatography (vpc) gave C and H combustion analysis within 0.4% of theory.

11. Previous work from this laboratory demonstrated that γ,γ-dimethyl-γ-butyrolactone was recovered quantitatively under these conditions. See reference 8.

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