On the Mechanism of the Formation of 2-Substituted 1,1-Diphenylthio Cyclobutane[1]

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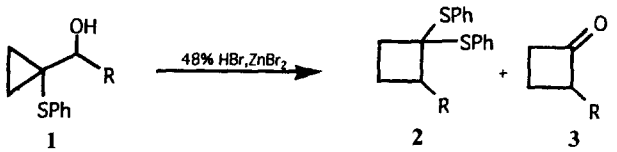
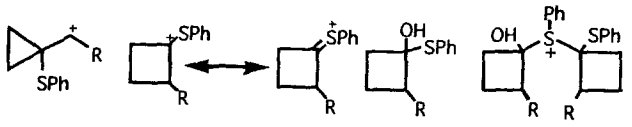
Our continuing interest in homoallylic S_N2' reactions of cyclopropylcarbinyl halides led us to prepare 1-thiophenylcyclopropylcarbinyl halides from the corresponding alcohol. This was accomplished with thionyl bromide and subsequent treatment with lithium dialkyl cuprates provided the homoallylically substituted vinyl sulfide.[2] The ring opening is analogous to our previous S_N2' reactions of cyclopropyl carbinyl halides with cuprates[3] and amines.[4] The conversion of cyclopropylcarbinyl alcohols to the bromide with thionyl bromide was interesting since Trost has reported that reaction of 1-thiophenylcyclopropyl-1-cyclohexyl methanol with thionyl bromide at 100℃ gave 2-cyclohexyl-2-thiophenylcyclobutene.[5] It was also known that reaction of cyclopropylcarbinyl alcohols with zinc bromide and HBr gave mixtures of the cyclopropylcarbinyl bromide, cyclobutyl bromide, and homoallylic bromide.[6] In contrast to those results, our previous work showed that 1-thiophenylcyclopropyl-1-carbinols, **1**, react with 48% HBr and Zinc bromide to give 1,1-diphenylthiocyclobutanes, **2**[7-9] To our surprise, the one thiophenyl group in one molecule gave two thiophenyl substituted product and cyclobutanone derivatives. The product distribution appears interesting since we anticipated that **1** would give the bromide or the β-ketosulfide observed by Miller.[10]



1 **2** **3**

R=(a) Et, (b) iPr,
(c) c-C_6H_{11}, (d) Ph

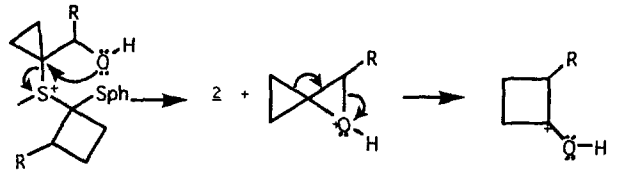
The mechanism of this reaction could be proposed as follows. Clearly two molecules are involved in the reaction to give dithio ketal cyclobutane derivatives. Initial ionization of **1** to the cyclopropylcarbinyl cation, **4**, is assisted by zinc bromide and the acidic medium. It is well known that cyclopropylcarbinyl cations exist in equilibrium with the cyclobutyl cation, **5**.[6] In no instance did we detect the cyclobutyl bromide, the cyclopropylcarbinyl bromide, or the homoallylic bromide. All products are derived from either **5** or **4** but bromide ion was not the primary nucleophilic reactant. One could envision reaction of the cations with water to give **6** which would react with **5** to give **7**. Fragmentation would provide the observed products. If this were correct, all aqeuous acid hydrolysis of thiophenylcyclopropylcarbinyl alcohols should give the products we observed. We thereby discount this pathway and those which involve a cyclopropyl cation (acid catalysis of cyclopropyl alcohols lead to preferential ring opening).[11]



4 **5** **6** **7**

If the previous pathways are wrong, the mechanism may have to involve the three species, **1**, **4**, and **5**. Nucleophilic attack by the sulfide moiety of **1** on **5** generates intermediate **8**. The intermediate, **8**, is precursor of dithioketal and an oxaspiropentane intermediate such as **9**. The unstable intermediate, **9**, is rearranged to cyclobutanol cation, **10**, which leads to the cyclobutanone derivative, **3**. Compound 1 was initially treated with 48% HBr and $ZnBr_2$ to give only 45.3% of **2**.[8] The low yield of dithioketal, **2**, can be rationalized by intermediate, **8**. In the absence of thiophenol, two molecules derived from the cyclopropylcarbinyl precursor could be involved and a reasonable fragmentation loses the dithioketal to liberate the protonated oxaspiropentane **9**. Acid catalyzed rearrangement of oxaspiropentanes to cyclobutanones is well documented[12] and formation of **8** and **9** are consistent with the observed products, although they remain speculative. Reaction of **5** with bromide or water is so slow that the nucleophilic sulfide may dominate the reaction. This is in sharp contrast to other acidic media which have been used in this system.[11]

If R group is an alkyl group, the cyclopropyl cation, **4**, undergoes rearrangement to cyclobutyl cation, **5**, and it should also be possible to 'trap' **5** by addition of an external nucleophile such as a thiol. Simiar reaction with a large excess of methanol or ethanol gave only **2** and **3** with none of the alkoxythiophenyl derivative. This is consistent with the increased nucleophilicity of thiols relative to alcohols and with formation of intermediate **8**.



8 **9** **10**

When the phenyl derivative (2; R=Ph) was subjected to identical reaction conditions without added thiophenol, the difference in reactivity results from increased resonance stabilization of **4** by conjugation with the phenyl ring. Such stabilization was previously demonstrated by Trost with the cation of 1-phenylthio-1-dimethoxycyclopropane, which did not undergo ring enlargement.[13] Trapping thiophenol on cyclopropylcarbinyl cation, 4 (R=Ph) is analogous to Gadwood's report in which an allylic cyclopropyl disulfide was obtained as the major product when 1-(1-thiophenylcyclopropyl)-3-cyclohexene-1-ol was treated with HBF_4.[14] Although other ionization pathways can not be completely discounted, **8** is consis-

tent with known reactions of cyclopropylcarbinyl cations and explains the results in this system.

Formation of 2-ethyl-1,1-dithiophenylcyclobutane, 2a: To 5.4 g (24.3 mmol) of anhydrous $ZnBr_2$ in 4.6 mL of 48% HBr was added 1.4 g (6.8 mmol) of **1a** in 2.9 mL (5 eq.) of thiophenol. After stirring for 2 hour, the mixture was poured into 0.25 L of ice cold water overlaid with 0.5 L of pentane. Further extraction with pentane was followed by drying with $MgSO_4$. Removal of solvents under reduced pressure was followed by chromatography (SiO_2/pentane) to give 1.9 g (6.5 mmol, 95.2%) of **2a** as a clear oil (R_f=0.3, pentane/silica gel). ^{1}H-NMR ($CDCl_3$) 7.77-7.17 (10H, m), 2.55 (1H, m), 2.20-1.45 (6H, m), 0.82 (3H, t); ^{13}C-NMR ($CDCl_3$): 136.24 (s), 134.06 (s), 128.76 (d), 128.63 (d), 127.70 (d), 66.31 (s), 50.24 (d), 32.70 (t), 24.19 (t), 23.17 (t), 11.58 (q); Infrared (neat); 3200 (s), 2950 (s), 1570 (m), 1470 (m), 1450 (m), 1060 (s), 900, 745, 670 cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 300 (7), 271 (2), 244 (16.8), 223 (11), 191 (100), 135 (73), 109 (35.3), 91 (44.8), 81 (69.1). 65 (34).

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8.

Alcohol	R	Dithioketal	% 2	
1a	Et	**2a**	95[a]	45[c,e]
1b	iPr	**2b**	92[a]	59[c,f]
1c	c-C_6H_{11}	**2c**	92[a]	
1d	Ph	**2d**	27[d]	
			36[a]	
			67[b]	

[a]RT, 5 eq. PhSH. [b]65℃, 25 eq. PhSH. [c]RT, no PhSH. [d]RT, 1 eq. PhSH. [e]48% 3a. [f]10% 3b.

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A Convenient Method for β-Lactam Formation from β-Amino Acids Using (3-Nitropyridyl) Dialkyl Phosphate

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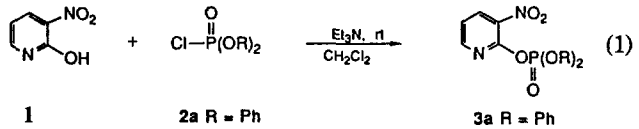
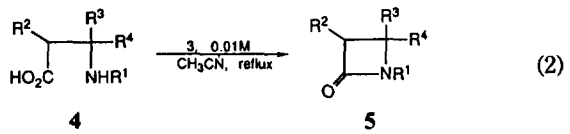
Intramolecular condensation is one of the important reactions which are frequently used in the formation of β-lactam rings from β-amino acids in the presence of suitable condensing reagents[1]. Recently, new organophosphate type condensing reagents have been introduced[2] for the construction of β-lactams, esters, and peptides.

In the course of our work in developing new effective condensing reagents[3], we have examined the β-lactams (**5**) formation from β-amino acids (**4**) using organophosphate compounds. Compounds studied in this work involve (3-nitropyridyl)diphenyl phosphate (**3a**, **3-NDP**) and (3-nitropyridyl) diethyl phosphate (**3b**, **3-NDE**). These reagents can be easily prepared by the reaction of 2-hydroxy-3-nitropyridine (**1**) with dialkyl chlorophosphate (**2a**, or **2b**), and triethylamine in dichloromethane at room temperature for 1 h (Eq. (1)). **3-NDP** reagent was obtained as an orange crystal in essentially quantitative yield (92-94%) and can be stored in a refrigerator for several weeks without any decomposition. However, **3-NDE** reagent was obtained as a reddish oil and was easily decomposed into the starting material (**1**) within two weeks.



(1)



(2)

We have briefly studied solvent and concentration effects using 3-benzylaminobutanoic acid, 1.2 equivalent of **3-NDP** reagent and triethylamine at room temperature or at refluxing condition. The best result was obtained in case of the substrate concentration of 0.01 M in acetonitrile with refluxing for 24 h.

Some experimental results are summarized in Table 1 to illustrate the efficiency of the present method. N-Substituted β-amino acids were cleanly cyclized into the corresponding β-lactams in moderate to high yields whereas N-unsubstitued β-amino acids gave poor results due to the poor solubility.

In conclusion, **3a** is a crystalline solid having excellent