

PHOTOCHEMICAL CYCLOBUTANONE EXPANSIONS¹Michael C. Pirrung*² and Carl V. DeAmicis

Department of Chemistry, Stanford University

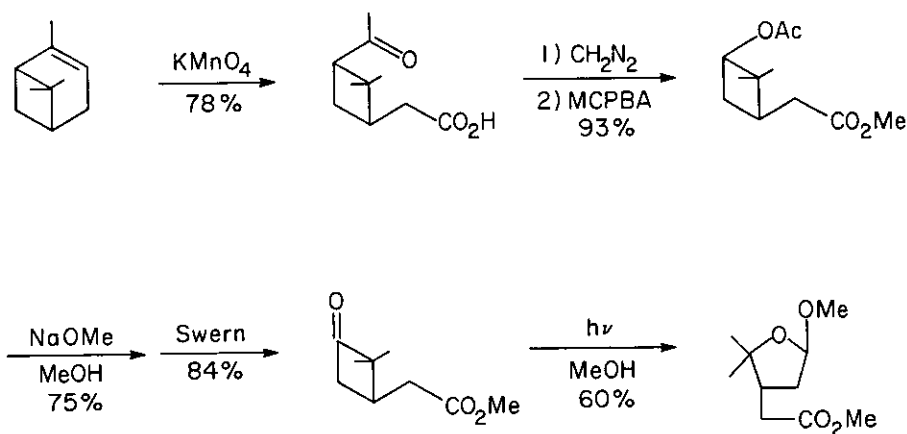
Stanford, California 94305, USA

Abstract - As a model for a new approach to bond formation at anomeric carbons, the addition of various heteroatom derivatives to oxacarbenes generated by the photochemical ring expansion of cyclobutanones has been examined. Practical procedures have been developed for the insertion of such carbenes into heteroatom-H bonds from alcohols, thiols, and amines using minimal excess trapping reagent.

The photochemical ring expansion of cyclobutanones to give 2-tetrahydrofuranylidenes and their insertion into alcohols is a fairly well-understood reaction³⁻⁵. This sequence could offer a convergent route to various furanosides (since cyclobutanones are themselves readily accessible via ketene-olefin cycloaddition) provided a practical method were available to insert into a broad range of heteroatom-H bonds. With the exception of two reports concerning intramolecular trapping of tetrahydrofuranylidenes by alcohols^{6,7}, all previous examples of the photochemical ring expansion were conducted in methanol as solvent and trap. This report concerns the development of optimal conditions for trapping the carbene in inert solvent with various heteroatom derivatives.

RESULTS

For the purpose of screening conditions and heteroatoms in the insertion reaction, a cyclobutanone which undergoes efficient ring expansion was required in fairly large quantities. Pinene proved to be a convenient starting material. Along lines previously described⁸, *cis*-pinonic acid was esterified and subjected to Baeyer-Villiger oxidation. Methanolysis and Swern oxidation deliver the cyclobutanone. If purification is conducted only at the conclusion of this sequence, the overall yield is 80%.



On irradiation in methanol, ring expansion occurs to provide a 1:1 mixture of anomers in 60% yield. It was unsurprising that poor stereoselectivity is observed in this particular insertion reaction, but since the primary goal of this study was to find optimum conditions and traps for ring expansion, this substrate proved suitable. In all of the expansions reported herein, 1:1 anomeric mixtures were obtained.

The first point to be established was the viability of trapping in inert solvent. Methylene chloride was chosen due to its beneficial effect in previous studies of the intramolecular reaction⁶. Table I shows the yield of ring expansion product with methanol as trapping agent. With 10 equiv. of MeOH, the reaction is faster and higher yielding than with MeOH as solvent.

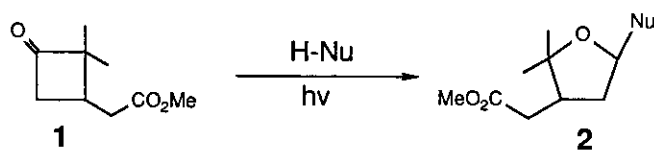
TABLE I



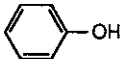
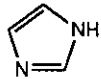
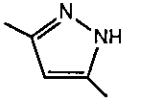
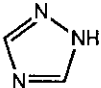
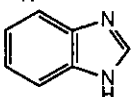
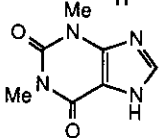
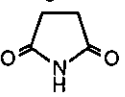

Entry	MeOH Equiv.	Solvent	Reaction Time, hr	Yield, %	S.M., %
1	-	MeOH	15.5	60	3
2	10	CH ₂ Cl ₂	10	65	<1
3	5	CH ₂ Cl ₂	10	65	<1
4	3	CH ₂ Cl ₂	15.5	63	1
5	2	CH ₂ Cl ₂	15.5	53	3
6	1	CH ₂ Cl ₂	15.5	43	6

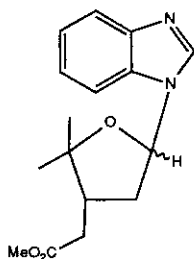
Reduction of the amount of methanol below three equivalents results in lower yields, and attempts to overcome this limitation by increasing the concentration lead to slower reaction and dimer formation. Consequently, a standard protocol for the intermolecular insertion was adopted consisting of 50 mM cyclobutanone in dry degassed CH₂Cl₂ containing 5 equiv. of the heteroatom derivative. Irradiation was conducted in Pyrex test tubes under illumination by a 450-W Hanovia lamp. Reactions were followed by capillary gas chromatography. After consumption of cyclobutanone, the reaction mixture was concentrated and the product isolated by flash chromatography. The results are summarized in Table II on the following page, where yield and reaction time are given for each insertion product.

Several points concerning these reactions are noteworthy. Primary and secondary alcohols and phenols are effective substrates, but tertiary alcohols and carboxylic acids do not lead to synthetically useful yields of products. Mercaptans, pi-excessive nitrogen heterocycles and imides give expansion-insertion products as well. With simple primary and secondary amines, while some of the expected products are produced (as detected by gas chromatography and NMR), attempted isolation leads to hemiacetal products. Increasing the bulkiness of the trapping agent results in a slower reaction. Thus after 10 h irradiation there is <1% starting material with methanol, 10% with cyclohexanol and 26% with t-butanol as trap. Finally, the structural similarities of several of the insertion products, particularly from benzimidazole, to naturally-occurring nucleosides is to be noted.

Table 2. Ring expansion of cyclobutanone 1



Entry	H-Nu	Time, hr	Yield 2, %
1	MeOH	10	65
2		13	66
3		15	59
4	t-BuOH	10	13
5		13	45
6		19	63
7		15	65
8		15	71
9		30	55
10		30	36
11		50	25
12		30	59



CONCLUSION

The irradiation of cyclobutanones in the presence of trapping agents constitutes an effective preparation of 2-substituted tetrahydrofurans. With appropriate oxygenation and stereocontrol, such reactions should provide concise syntheses of furanosides. Studies along these lines are underway.

ACKNOWLEDGMENTS

Financial support by an NSF Presidential Young Investigator Award (NSF CHE-8451324) with matching contributions from Syntex, Pfizer, Chevron, Eli Lilly & Co., and Johnson & Johnson is gratefully acknowledged. NMR spectra were obtained on instruments provided by NSF equipment grants CHE 8109 064 and 8414329.

REFERENCES AND NOTES

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Received, 2nd June, 1986