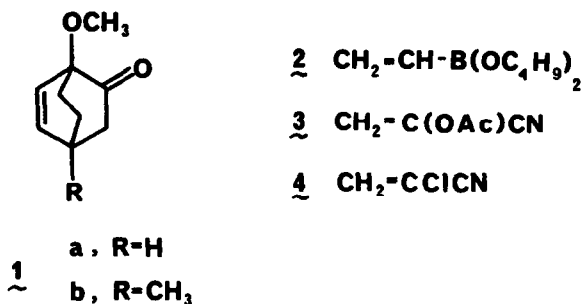


EVALUATION OF KETENE EQUIVALENTS IN THE
SYNTHESIS OF BICYCLO[2.2.2]OCTENE DERIVATIVES

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As part of our general synthetic program¹ which has required the availability of substituted bicyclo[2.2.2]oct-5-en-2-ones (e.g. 1), we have taken the occasion to evaluate the overall effectiveness of the ketene equivalents 2-4 in Diels-Alder reactions with two dihydroanisole derivatives. At the current time little information is available on the regio-specificity of Diels-Alder reactions between unsymmetrically substituted cyclic dienes and dienophiles. Furthermore, relatively few such bicyclo[2.2.2]octenones have actually been reported.²

As dienophiles, both 2-acetoxyacrylonitrile (3)^{3a,4} and 2-chloroacrylonitrile⁵ (4) have found use in synthesis; however, no direct comparison between the two reagents has been made. Conversely, the synthetic potential of the vinylboronate ester 2 as a ketene equivalent in both photochemical and thermal cycloadditions has been ignored.⁶ In fact, the only example of the reaction of 2 with an unsymmetrical diene (isoprene) has been provided by Matteson and Waldbillig.^{6a} Their report that a single isomeric alcohol was obtained upon peroxide oxidation has prompted us to further explore the regioselectivity conferred upon the Diels-Alder reaction by

the boron function.⁷ As illustrated in Table I a direct comparison between these dienophiles in the Diels-Alder reaction with the two dihydroanisole derivatives illustrated below has been made.

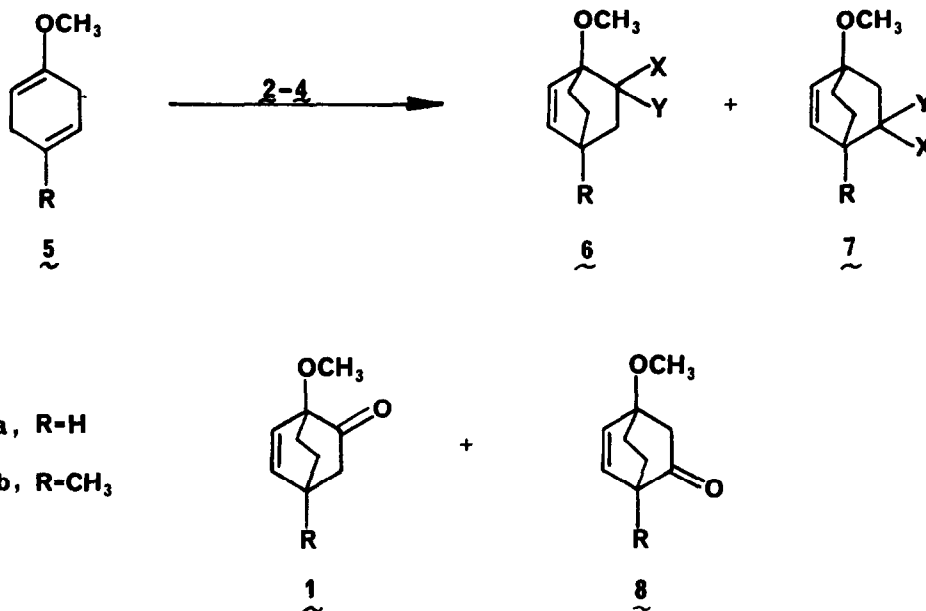
The most striking conclusion from this work is the extremely high degree of regioselectivity that is observed with 2-chloroacrylonitrile. For the two dienes studied, the Diels-Alder reaction appears to be completely selective with this reagent. This is to be contrasted with the lower regioselectivity exhibited by 2-acetoxyacrylonitrile (3) and the vinylboronic ester 2. In addition, as illustrated in column 3 of Table I, 2-chloroacrylonitrile (3) is by far the most reactive of the three dienophiles screened.

TABLE I^a

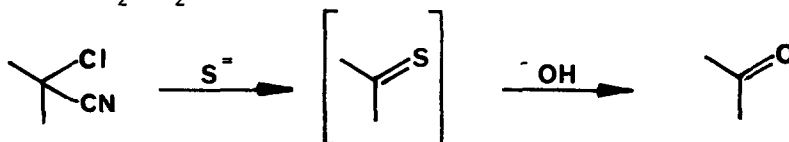
Diene	Dienophile	Conditions ^b	Yield, % <u>6+7</u>	Yield, % <u>1+8</u>	Isomer Ratio, % <u>1</u> <u>8</u>	
	$\text{CH}_2=\text{CHB}(\text{OC}_4\text{H}_9)_2$ ^e ₂	200°/66 hr ^d	57 ^e X,Y=H,OH	67	89	11
	$\text{CH}_2=\text{C}(\text{OAc})\text{CN}$	150°/15 hr	--	40 ^f	94	6
	$\text{CH}_2=\text{CClCN}$ ^g	61°, CHCl ₃ /7 hr ^h	50	80	>99.9	<.1
	$\text{CH}_2=\text{CHB}(\text{OC}_4\text{H}_9)_2$ ^e ₂	200°/72 hr ^d	73 ^g X,Y=H,OH	76	85	15
	$\text{CH}_2=\text{C}(\text{OAc})\text{CN}$	150°/15 hr	--	67 ^f	95	5
	$\text{CH}_2=\text{CClCN}$	80°, C ₆ H ₆ /9 hr ^h	75	92	>99.9	<.1

^a) Consistent spectral data and combustion analyses were obtained on all new compounds reported;

^b) equimolar quantities of diene and dienophile were employed with phenothiazine added as a stabilizer; ^c) see ref. 6 for prep.; ^d) 5% CHCl₃ was added to the reaction mixture to catalyze diene isomerization; ^e) the crude Diels-Alder adduct was oxidized with basic H₂O₂; ^f) overall yield from equimolar quantities of diene and dienophile; ^g) available from Aldrich Chemical Co.; ^h) for the sake of convenience in maintaining a constant temperature this reaction was carried out at reflux in the indicated solvent.



The other major factor which is influential in the evaluation of the overall utility of dienophiles 2-4 as ketene equivalents centers around the problem of transforming the initial diene adducts 6 and 7 into the ketones 1 and 8. Although methods are available for the conversion of the chloro nitrile adducts 6a,b (X-Cl,CN) into the corresponding ketones 1a,b using KOH,⁸ we have found that the overall yield of this sequence can be improved from 63% (KOH) to over 80% by the use of Na₂S·9H₂O in refluxing ethanol.⁹



As illustrated above, this transformation presumably proceeds through the thioketone which is subsequently converted in situ to the desired ketone under the reaction conditions.

In conclusion, this study clearly points to the superiority of 2-chloroacrylonitrile (3) as a useful ketene equivalent in Diels-Alder reactions. These results in conjunction with the recent work of Corey and coworkers⁵ on the use of 3 with cupric fluoroborate as a Lewis Acid catalyst should extend the utility of this reagent in organic synthesis. Whether or not the commercially available¹⁰ 2-chloroacrylonitrile will ultimately prove to be a more regioselective reagent than the recently developed ketene equivalent, 2-chloroacrylyl chloride¹¹ can't be determined at this time.

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