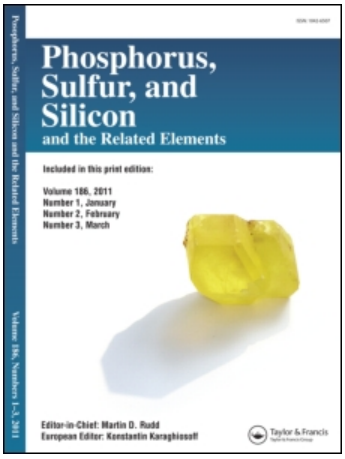

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New Perspectives in Thiazole Chemistry

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NEW PERSPECTIVES IN THIAZOLE CHEMISTRY*

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Abstract Carbon-carbon bond forming reactions at C-2 of the thiazole ring have been carried using two strategies, one involving the addition of organometallic reagents (lithium carbanions of esters, Grignard salts, silyl enol ethers, silyl ketene acetals, silylazoles) to N-acylthiazolium salts; the other involving the addition of carbon electrophiles (ketenes, acyl chlorides, anhydrides, aldehydes) to N-acylthiazolium ylides generated in situ. The reactions have been applied to 1,3-thiazole and 2-trimethylsilyl-1,3-thiazole, the latter being more reactive than the former toward electrophiles. This methodology constitutes a new entry to a variety of functionalized thiazoles and thiazolines which are potential building blocks for the synthesis of natural compounds and analogues of biologically active molecules (penems, arylpropionic acids). Some ring transformations of thiazoles induced by carbon-sulfur bond cleavage are also described. The fundamental role played by the sulfur atom of the thiazole ring in the observed reactions is pointed out and briefly discussed.

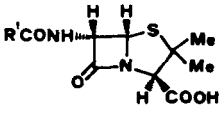
INTRODUCTION

My task in this Symposium on the Organic Chemistry of Sulfur is to deal with our research work in an area where sulfur plays a fundamental role, that is the chemistry of 1,3-thiazoles, a very important class of sulfur heterocycles. Let me start with some introductory remarks which may be helpful to get more logically into the main subject of this lecture, that is our contribution to developping useful methods for the carbon-carbon bond formation at the thiazole ring.

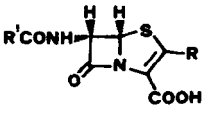
Since the identification of 1,3-thiazoles [1] nearly a

* Dedicated to Professor Giuseppe Leandri on his 70th birthday.

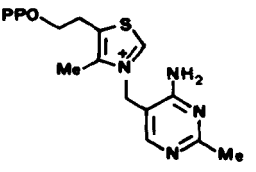
century ago by Arthur Hantzsch and his collaborator J.H. Weber, as the constituents of an homogeneous class of heterocyclic compounds containing nitrogen and sulfur, the chemistry of these heterocycles has attracted the continous interest of many researchers. The presence of the thiazole skeleton in compounds endowed with biological activity, mainly β-lactam antibiotics such as penicillins and penems, as well as natural products



Penicillin

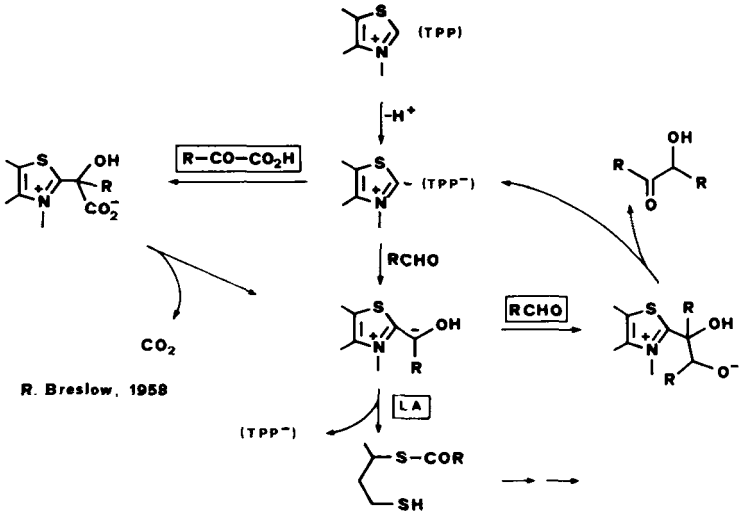


Penem

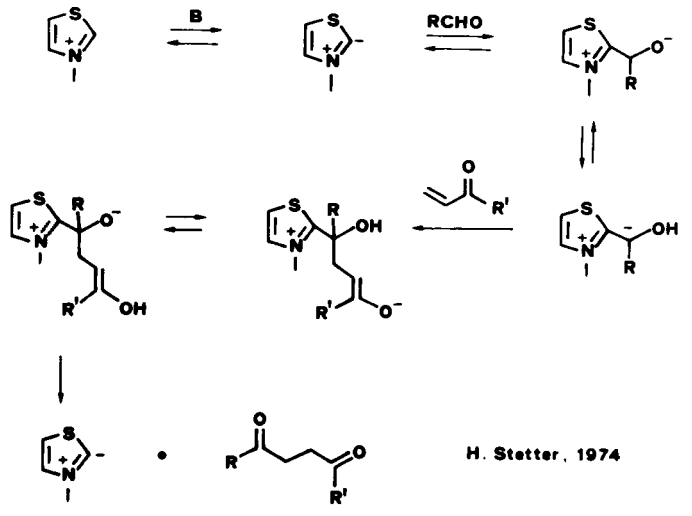


Thiamine pyrophosphate
(Vitamin B_1)

such as thiamine, the coenzyme of vitamin B_1, has contributed over the years to enlarge the interest for thiazoles from pure organic chemists to pharmaceutical chemists and biochemists. Particularly significant in this respect for its biological implications and extensions to synthetic organic chemistry was the elucidation of the mechanism of the thiamine pyrophosphate (TPP) action in the decarboxylation of α-ketoacids, mainly pyruvic acid, an essential step in the energy-releasing oxidation of glucose. In 1958, R. Breslow indicated [2] the thiazole ring as the essential part of the molecule for thiamine activity since the decarboxylation of the ketoacid involves the attack by its carbonyl carbon on the ylide (TPP^-) derived by deprotonation at C-2 of the thiazole.

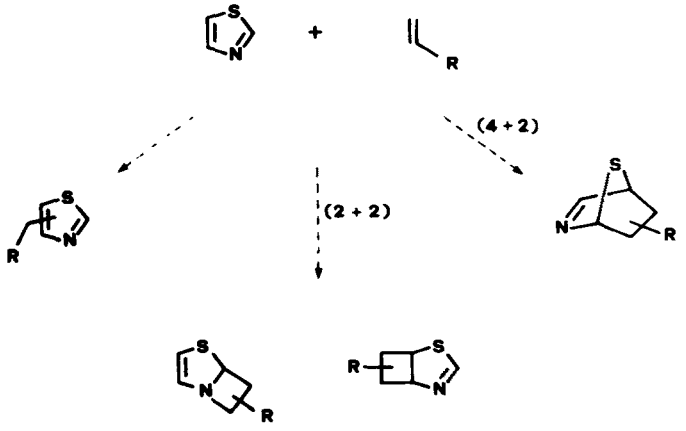


The loss of carbon dioxide from the α-hydroxycarboxylate chain of the resulting zwitterion and the transfer of the acyl anion to lipoic acid (LA) regenerates the catalyst (TPP^-) and gives another reactive intermediate which evolves toward the final products. The numerous investigations which followed in this area [3] confirmed the correctness of the Breslow's interpretation. By an identical mechanism, thiamine, as well as thiazolium salts in the presence of bases, induce also the benzoin condensation and are in general effective catalysts in nucleophilic acylations [2]. An important extension of these findings in synthetic organic chemistry is the Stetter reaction [4], that is the nucleophilic addition of aldehydes to activated olefins using thiazolium salts as 'umpolung' catalysts.

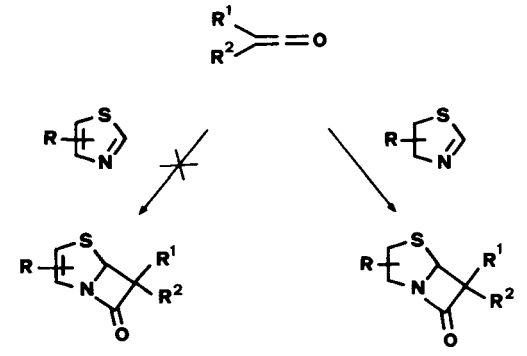


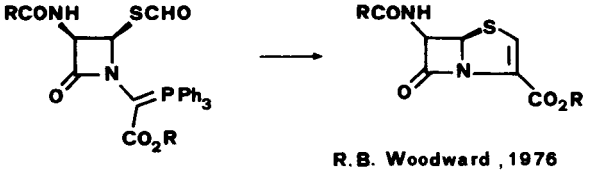
The chemistry as well as the spectroscopic and other physical properties of 1,3-thiazoles have been reviewed several times [5].

Let me just recall here that the thiazole ring is an heteroaromatic system which, like pyridine, is aza-deactivated of electrophilic substitutions [6] and very reluctant to enter in (2+2) and (4+2) cycloadditions [7]. In fact, the most direct methodology for carbon-carbon bond formation, such as the reaction of 1,3-thiazole with an activated π-system to give either substitution or cycloaddition products is scarcely applied in thiazole chemistry. This has limited a more extensive use of thia-

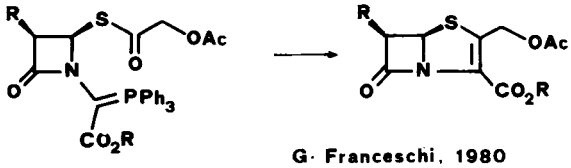


zoles in synthetic organic chemistry, particularly its use as a masked functionality [8] or building block of more complex molecular systems. Because of this difficulty, the alternative strategy followed is the construction of the thiazole ring by intramolecular cyclization between appropriate functional groups already present in the system under elaboration. This is well known to those working in the field of β-lactam antibiotics. For instance, the (2+2)cycloaddition of ketenes across the carbon-nitrogen double bond of thiazoles has not been observed so far, whereas the reaction occurs smoothly with thiazolines [9]. Accordingly, the classical penem syntheses by Woodward [10] and that by Farmitalia-C. Erba researchers [11] involve the building up of the





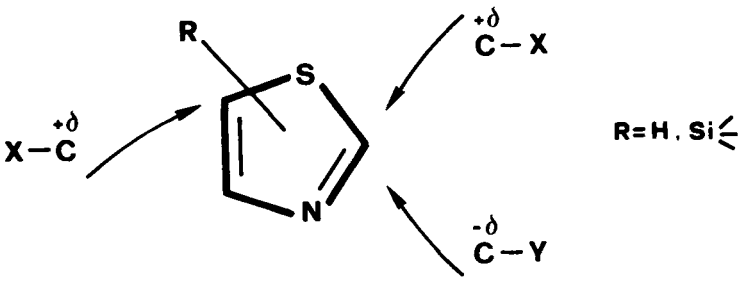
R.B. Woodward, 1976



G. Franceschi, 1980

thiazole ring by an intramolecular Wittig reaction in functionalized β-lactam systems.

Our work is directed toward the elaboration of convenient methods which overcome the aforementioned inertness of the thiazole ring. I shall describe here some new reactions of thiazoles with carbon electrophiles and nucleo-

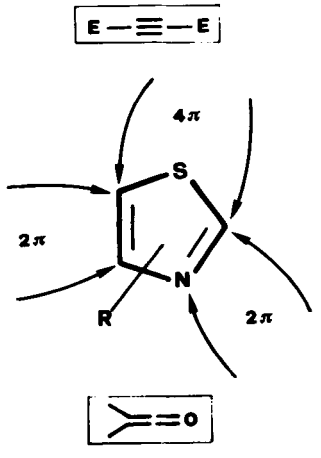


philes which exploit the combined action of the two heteroatoms, nitrogen and sulfur, of the heterocycle as well as the properties of the silyl group as a substituent.

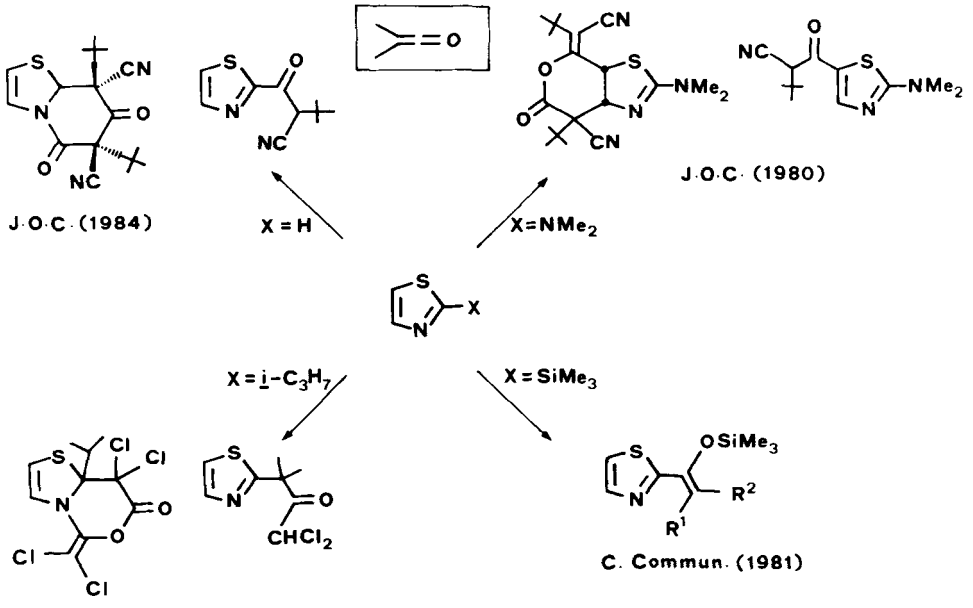
2. Reactions with C-Electrophiles

2a. Ketenes

At the beginning of our work in this area,on 1979, we were mainly interested in cycloaddition reactions to thiazoles. As we were aware of the work of Acheson [12] about the reluctance of thiazole to enter (4+2) cycloadditions with a strong dienophile such as an acetylenic ester, we



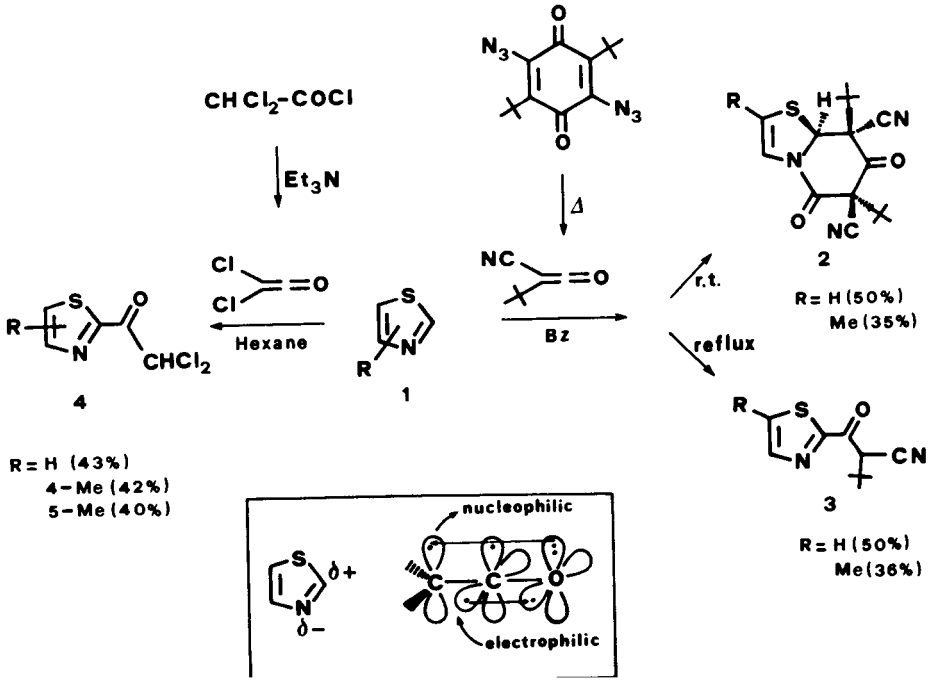
focussed our attention to the (2+2) cycloadditions since these reactions appeared more feasible and could eventually lead to products of considerable synthetic value. To this purpose, ketenes appeared the most appropriate reactants due to their well documented reactivity [13] as 2π-electron partners in thermally induced (2+2)cycloadditions to carbon-carbon and carbon-nitrogen double bonds. Our efforts toward the achievement of this initial goal have been so far unsuccesful since under different conditions, including substituent and solvent changes, no (2+2) cycloadduct could be isolated. On the other hand, 2:1 cycloadducts and/or substitution products at different sites of the thiazole ring were obtained, depending on the substituent X.



A strong electron-donor group X, such as dimethylamino, directs the reactions [14] towards the addition of two molecules of ketene across the C=C bond and the substitution at C-5, whereas much weaker electron-donating sub-

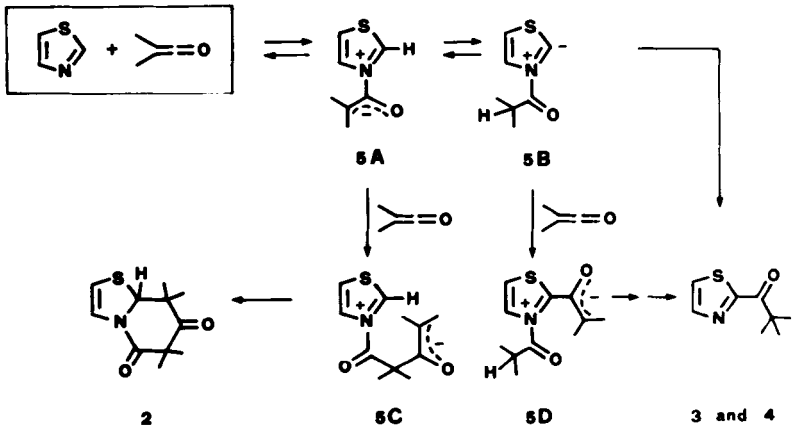
stituents, such as the trimethylsilyl and the i-propyl group, as well as hydrogen induce [15,16] the cycloaddition to occur across the C=N bond and the substitution at C-2 or even at the group X. It is worth mentioning here that all these reactions are synthetically useful since they lead to products such as 2- and 5-acylthiazoles which are accesible only with difficulty by other methods, or because they give compounds such as silyl enol ethers and the α-methylene-δ-lactones which appear suitable for various synthetic elaborations. Some interesting aspects of these reactions, such as the competition between cycloaddition and substitution as well as the regiochemistry at the ketene in the former process, will not be considered here. On the other hand, I shall discuss only the reactions of ketenes with 1,3-thiazole and its 2-trimethylsilyl derivative because just in these systems the sulfur atom of the heterocycle plays a fundamental role.

The reaction between 1,3-thiazole (1a) with an excess of t-butylcyanoketene (TBCK) generated in situ by thermolysis of the appropriate azidoquinone is temperature dependent [16]: as at room temperature, it leads to a 2:1 cyc-



loadduct, viz. the condensed bicyclic system 2, whereas in refluxing benzene it gives the Michael-type 1:1 adduct, the 2-acylthiazole 3. The same types of products are formed from TBCK and 5-methyl-1,3-thiazole (1c) whereas the 4-methyl derivative 1b is unreactive. The addition of the three thiazoles 1a-c to dichloroketene (DCK) formed *in situ* by dehydrochlorination of dichloroacetyl chloride by Et_3N affords, irrespectively of the reaction temperature, the corresponding Michael-type adducts 4a-c. Ketenes are well known heterocumulenes featuring a 1,2-dipolar character at the C=C bond, with the terminal carbon as the nucleophilic and the central as the electrophilic center [13,17]. This central carbon is the site of TBCK and DCK which forms a bond with the C-2 of thiazole in the products 3 and 4. To my knowledge, there are no precedents of direct electrophilic substitution at C-2 in thiazoles nor known properties of these heterocycles which can anticipate such a reactivity. In fact, nearly all the numerous theoretical methods which have been employed to study the electronic structure of thiazoles [18] indicate that at C-2 of the parent term 'the total net charge is positive or vanishing, its π net charge being also positive'; on the other hand, the total net charge on nitrogen is definitively negative. Interestingly enough, these generalizations on ketene and thiazole features are met in the regiochemistry of the 2:1 cycloadduct 2 where in fact one molecule of TBCK is bonded by its electrophilic carbon to nitrogen of thiazole and a second molecule is bonded by its nucleophilic terminal carbon at C-2. This suggests that an initial nitrogen(thiazole)-carbon(ketene) bond formation may be also involved in the reaction sequence leading to the substitution products 3 and 4. Therefore,

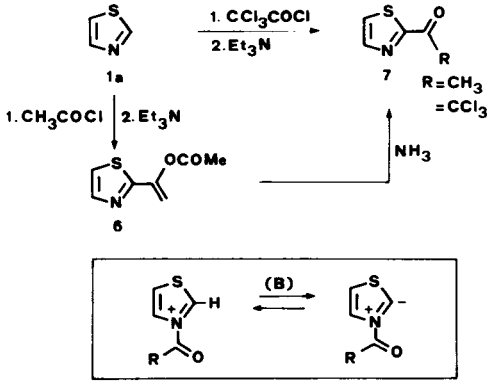
a mechanism is advanced where the highly stabilized zwitterion 5A is formed in a primary process; the exchange of the hydrogen between the C-2 of the ring and



the N-enolate portion in the intermediate 5A gives the N-acylthiazolium ylide 5B. The species 5A and 5B are the activated forms of 1 which lead to the observed products. The attack of a molecule of ketene at C-2 of 5B gives the substitution products 3 and 4, whereas the attack at carbon of the enolate portion of 5A gives the cycloadduct 2. Trapping experiments showing the existence of 5D allow to exclude the possibility that the ylide 5B converts into 3 or 4 by an intramolecular 1,2-migration of the N-acyl group [19]. The results fit quite well in this Scheme.From the reaction of TBCK, the cycloadduct 2 is formed at low temperature, whereas the substitution product 3 is obtained at reflux temperature of the solvent; this temperature dependence of the product distribution is likely to be a kinetic effect at the stage of conversion of 5A into 5B. From the reaction of DCK, the substitution product 4 is formed exclusively; this is likely to be due to the increased concentra-

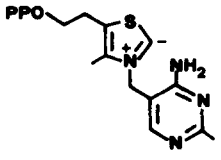
tion of the ylide 5B owing to the catalysis of Et_3N employed for the ketene generation.

An interesting feature of the ketene/thiazole system is that although involving an ylide as intermediate, the base catalysis is not necessary for the reaction to occur. This self-activating process can be profitably employed for the acylation of the thiazole ring when the exclusion of a base is required. This becomes even more significant when the reaction of 1,3-thiazole (1a) with acyl chlorides is considered. In fact, 1a reacts

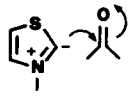


with acetyl- and trichloroacetyl chloride only in the presence of Et_3N to give the thiazolyl enol ester 6 and the 2-acylthiazole 7 respectively. This indicates that the base is necessary to deprotonate at C-2 the N-acylthiazolium salt to form the thiazolium ylide which then adds a molecule of acyl chloride (formation of 7) or ketene (formation of 6). Interestingly enough, the former reaction can be viewed as a base-catalyzed electrophilic substitution at C-2 of the thiazole ring, a reaction which does not have any precedents in other systems.

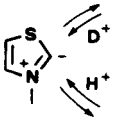
The acylation of the thiazole ring at C-2 either by ketenes or acyl chlorides is likely to involve the N-acylthiazolium ylide as an intermediate. The occurence of a C-2 thiazolium ylide has been often postulated in order to explain some peculiar properties of thiazoles which do not find equivalence in other nitrogen heterocycles. Classical examples are provided by the thiamine activi-



R. Breslow, 1958 (Ref.2)



H. Stetter, 1974 (Ref.4)

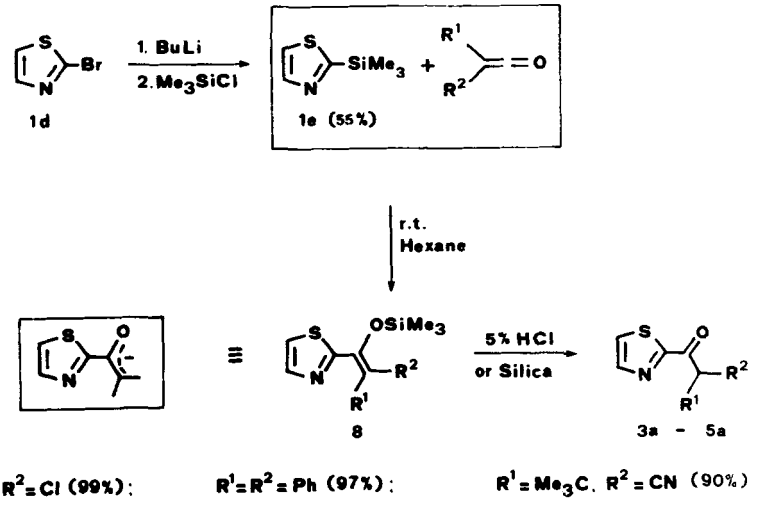


P. Haake, 1969 (Ref.20)
R. A. Olofson, 1966 (Ref.20)

ty [2,3], the catalytic effect of thiazolium salts in nucleophilic acylations [4], and the kinetics of H/D exchange in thiazolium salts [20]. By comparison with other azoles, mainly oxazoles and imidazoles [20a, 21, 22] it is well ascertained that the high thermodynamic stability of the 2-thiazolium ylide derives from the ability of sulfur to stabilize an adjacent negative charge. Nevertheless, the nature of the electronic interactions responsible for such an effect is still controversial since sulfur 3d orbitals participation [23] by dp-π [24] or d-σ [20] con-

jugation has been considered important in the past whereas more recent approaches favour sulfur polarizability. It is worth mentioning that this is just a particular case of the problem concerning the stereochemistry, reactivity, and stability of α-thiocarbanions [25,26].

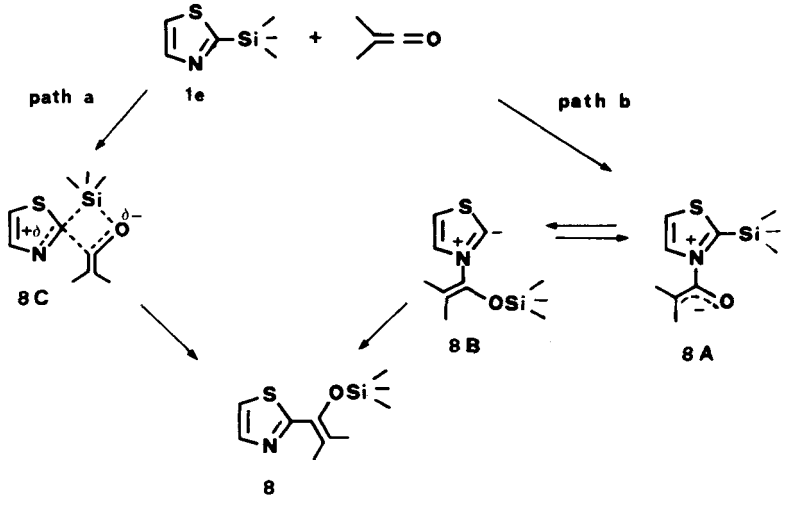
Let us now go back to the main subject of this lecture, that is the development of a synthetically useful methodology for the carbon-carbon bond formation at the thiazole ring. The substitution of the C-2 hydrogen of the thiazole with a silyl group enlarges the scope of the reaction with ketenes and extends the methodology to other electrophiles. Treatment of 2-trimethylsilylthiazole (1e) with various ketenes [15], including the scarely reactive diphenyl ketene, gives exclusively the corresponding thiazolyl silyl enol ether 8 in practically quantitative yields. In this case too, bonding occurs between the cen-



tral carbon of the ketene and C-2 of thiazole while the silyl group has been transferred to oxygen. The thiazo-

lyl silyl enol ether 8 is a product of a relevant synthetic value since its reactivity as a stabilized enolate [27] can be exploited for a wide functionalization of the thiazole ring. As an immediate application of this criterion, the silyl enol ethers 8a-c are transformed into the corresponding 2-acylthiazoles 3a-5a under very mild conditions. This constitutes a new entry to 2-acylthiazoles which overcomes the preclusion of thiazoles to acylation under Friedel-Crafts conditions [6].

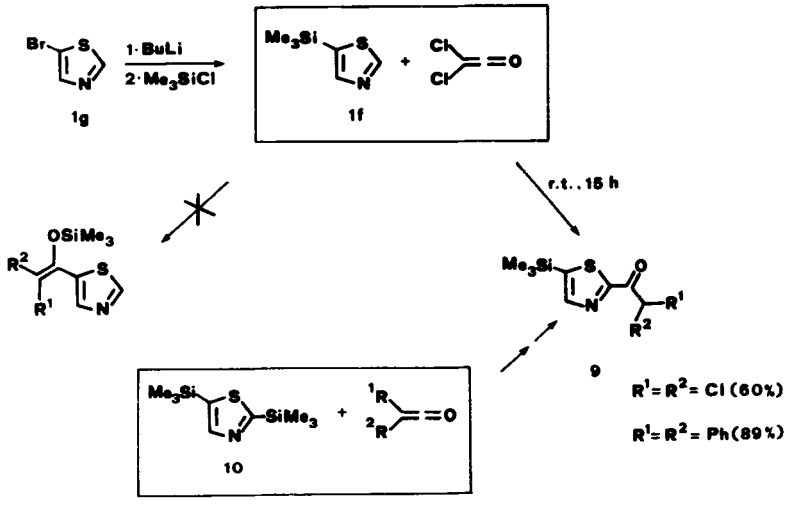
There are at least two mechanisms which may account for the reaction of 1e with ketenes. One involves the direct



attack of the ketene at the silylthiazole 1e (path a); the other proceeds via activated forms of 1e, viz. the thiazolium enolate 8A and the thiazolium ylide 8B (path b). In the former case the transition state (or intermediate) 8C can enjoy some effects of silicon [28], such as the assistance in the cleavage of the carbon-silicon bond by the concomitant formation of the stronger oxygen-silicon bond, and the stabilization of the positive

charge in a β-position by silicon. In the latter case, in addition to the above effects due to silicon, there is also a contribution by sulfur: the stabilization of the ylide 8B. Should this mechanism be operating, the reaction takes place readily due to the sequential and favorable action of the three heteroatoms, viz. nitrogen for the activation, silicon for the ylide formation, and sulfur for its stabilization.

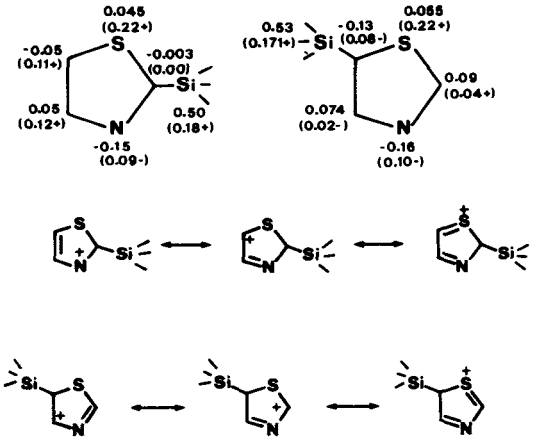
The study of the reactivity of other silylthiazoles toward ketenes was synthetically useful and mechanistically clarifying. Treatment of 5-trimethylsilylthiazole (1f) with DCK [15] does not result in the ipso- substitution of the silyl group to give the corresponding thia-



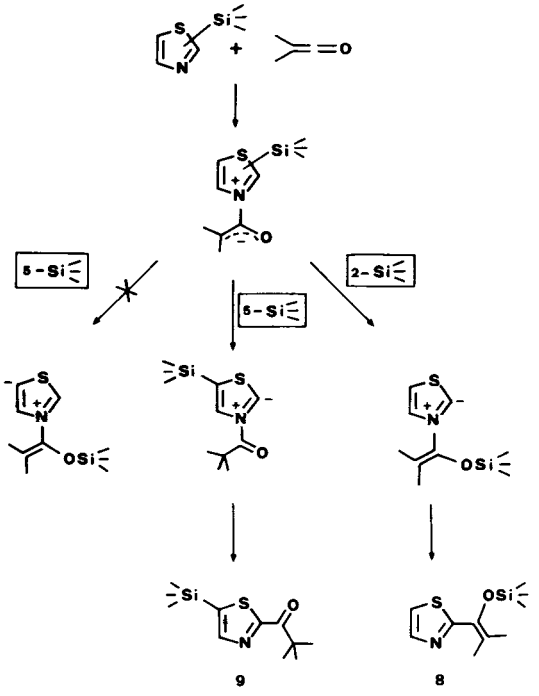
zolyl silyl enol ether, but leads to the 5-silyl-2-acylthiazole 9a. The same product is obtained from 2,5-bistrimethylsilylthiazole (10). This illustrates the remarkable different reactivity of the silyl group at C-2 and C-5 of the thiazole ring and proves that whilst it is a super-proton when bonded at C-2, it becomes weaker

than a proton at C-5. On the assumption of mechanism a, we cannot see any differentiating properties between 1e and 1f or between the corresponding transition states, which can explain such a dramatic change of reactivity. In fact, molecular orbital calculations [29] (CNDO/2) indicate that C-5 in 1f is slightly more negative than C-2 in 1e, and the charge delocalization in the corresponding intermediate arising from an electrophilic attack suggest at least a comparable stability. It appears therefore

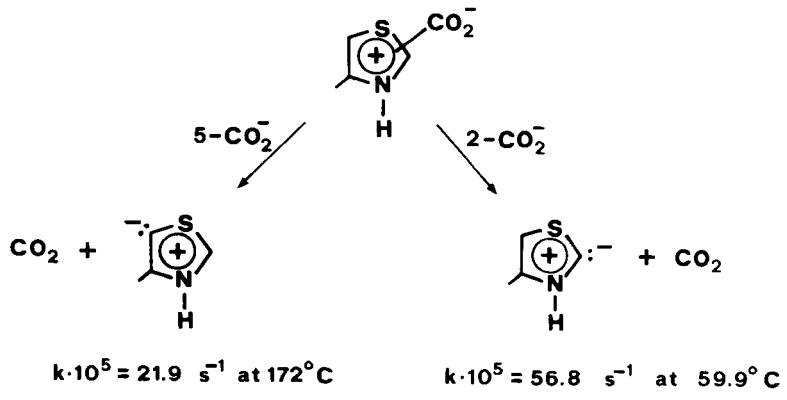
Total charge density and (in parentheses) excess π-charge distribution



that mechanism b via the thiazolium ylide as an intermediate is followed for the acylation at C-2 of both 1e and 1f. The lack of desilylation of 1f should therefore reflect the much greater energy of activation for the



5-thiazolium ylide formation with respect to the 2-isomer. This is in agreement with Hakee's measurements of the rate of decarboxylation of thiazole-2- and thiazole-5-carboxylic acids [21], a reaction which has been assumed to proceed via the corresponding thiazolium carboxylates to give the 2- and 5-thiazolium ylide. Since the structure of the ylide should be close to that of the corresponding transition state, reasonings on the ylide stability were used to explain the considerable

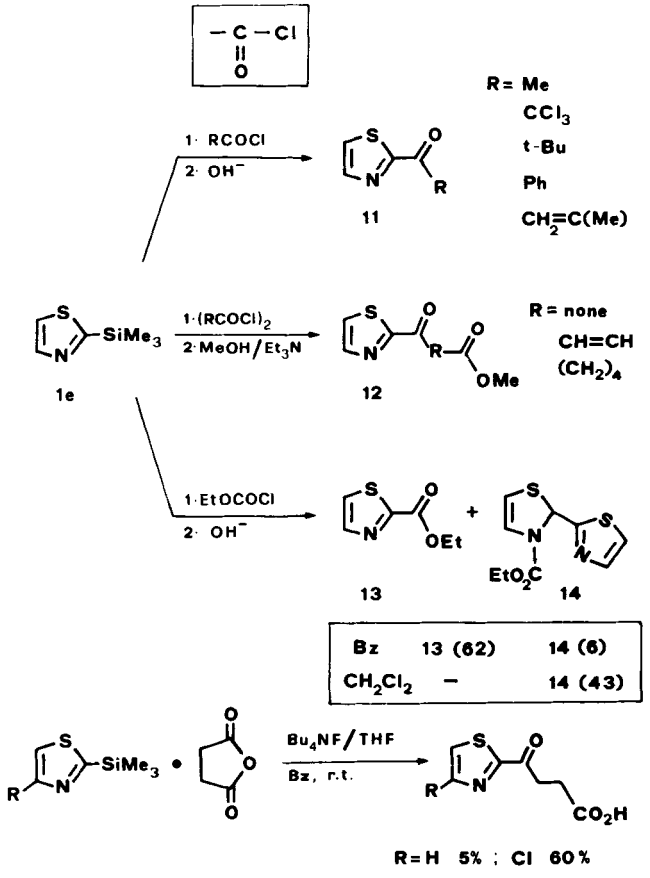


P. Haake, 1971

higher rate of the 2-carboxylic acid with respect to the 5-isomer. While there must be a stabilizing interaction between sulfur and the ylide carbon as well at C-5 as at C-2, the greater stability of the 2-ylide has been ascribed to:a shorter C(2)-S bond distance (1.68 A) with respect to C(5)-S (1.75 A), the proximity of the positively charged nitrogen; an extense conjugation across the heteroallylic system S-C(2)-N leading to a carbenoid structure, which by contrast cannot occur in the 5-ylide.

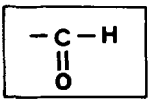
2b. Acyl Chlorides and Aldehydes

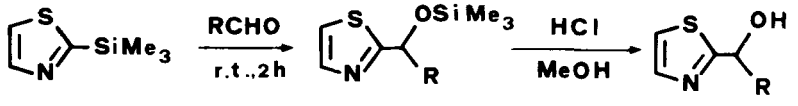
The ready desilylation of 2-trimethylsilylthiazole (1e) by ketenes indicated than an analogous reaction could occur with other activated carbonyl compounds. In fact, acyl chlorides, including various alkyl derivatives as well as an aryl and an alkenyl derivative, react with 1e to give the corresponding acyl thiazoles 11 in satis-



factory yield [30]. Moreover, the reactions of acyl chlorides of dicarboxylic acids and quenching with methanol and Et_3N lead to the correponding thiazolyl ketoester 12. The reaction appears to be a simple and versatile method, which can be used as an alternative to that employing ketenes for the acylation of the thiazole ring at C-2 in the absence of base catalysis; moreover, this reaction allows the introduction of a composite carbonyl functionality, such as the ketoester group. It is noteworthy

that another entry to a thiazolyl ketoacid is provided by the reaction of a 2-silylthiazole with succinic anhydride in the presence of tetrabutylammonium fluoride[31]. The scope of this reaction is still under investigation. A special comment is necessary in the case of the reaction of 1e with ethyl chloroformate. This gives both the substitution product 13 and the addition product 14 in variable ratios depending on the solvent. The formation of 14 proves that the silylthiazole 1e must be present, at least in part, in the form of its quaternary salt which can add a nucleophilic thiazole species, very likely the silylthiazole itself or the thiazolium ylide. The substitution of the silyl group in 1e occurs quite readily even with weak electrophiles as aldehydes [30] to give the corresponding 2-(α-siloxy)- alkylthiazoles 15





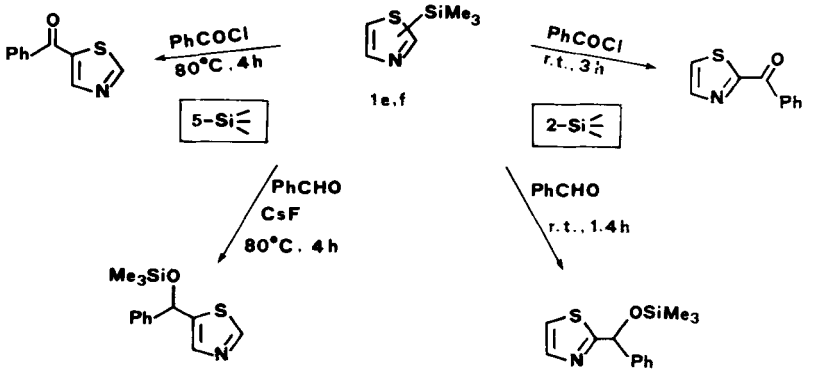
1e 15 16

R = Ph (98%), Me_2CH (98%)

in a few hours at room temperature. The reaction corresponds to a formal 1,2-addition of the carbon-silicon bond of 1e to the carbonyl group of the aldehyde. The compound 15 can be isolated or desilylated in situ with diluted hydrochloric acid to the carbinol 16. The stereochemistry of this new synthesis of secondary alcohols

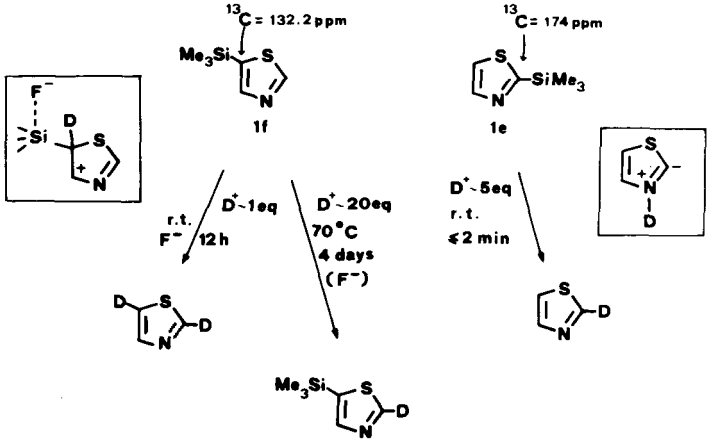
containing the thiazolyl group is under investigation using chiral aldehydes.

The mechanisms of the reactions of acyl chlorides and aldehydes with the silylthiazole 1e, too, are worth a short discussion particularly in this Symposium because they point out once more the exceptional role exerted by sulfur in thiazole chemistry. As for the reaction with ketenes, we have to consider two main alternatives for the substitution of the silyl group, viz. the reaction of the carbonyl compound directly with the silylthiazole or with an activated species derived therefrom. The comparison of the reactivity of 2- and 5-trimethylsilylthiazole 1e and 1f appeared very instructive in that respect. The silyl group of 1e is displaced rapidly by both ben-



zoyl chloride and benzaldehyde under very mild conditions, whereas the silyl group of 1f requires in one case more drastic conditions, in the other the presence of fluoride ion [32], a well known catalyst for the carbon-silicon bond cleavage in the presence of an electrophile [33]. The

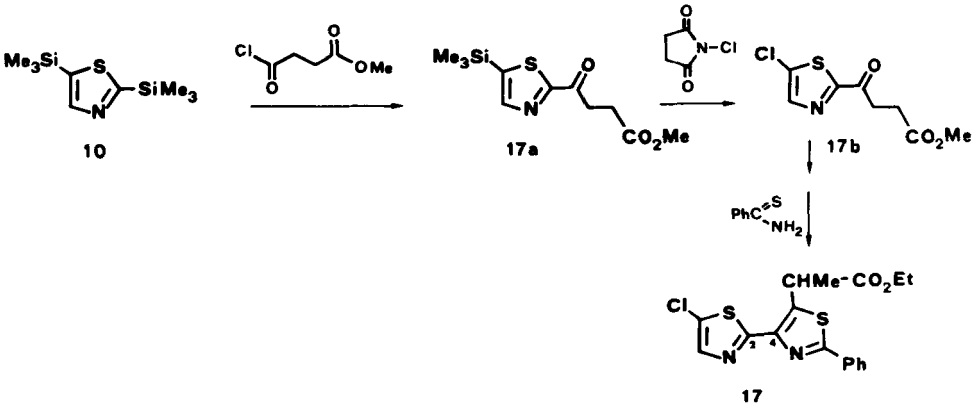
deuteriodesilylation of 1e and 1f under acid conditions [34] confirmed the enormous difference of reactivity between the 2- and 5-silyl group. Silicon-deuterium exchange at C-2 is very fast at high concentration of D^+,



whereas the exchange does not occur at C-5 even in the presence of fluoride ion; desilylation takes place at C-5 at lower D^+ concentration and in the presence of fluoride ion. This suggests that different mechanisms are followed in the two cases. The C-2 desilylation should occur via the thiazolium ylide, whereas the C-5 desilylation should involve the thiazole itself and the assistance of the halide ion. As already mentioned, this change of mechanism reflects the higher energy request for the 5-ylide formation with respect to that of the 2-isomer. The same conclusions can be applied to the reactions of 1e and 1f with acyl chlorides and aldehydes.

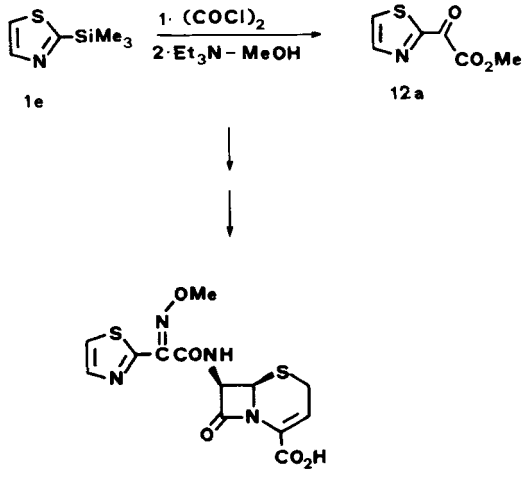
The effect of sulfur in silylthiazole chemistry is thus as large as to control the kinetic and the mechanism of the reactions with electrophiles! This can be profitably exploited in synthetic sequences as it appears in a scheme we have developped for the synthesis of the bis-thia-

zolyl propionic ester 17 [35], a potential non-steroidal antiinflammatory agent [36]. The key step of the process is the selective acyldesilylation of the 2,5-bis-trimethylsilyl thiazole (10) to give the 5-silylthiazolyl ketoester 17a. The silyl group which has been preserved at C-5 is then replaced by chlorine to give the 5-chlorothiazolyl ketoester 17b. The carbonyl function of 17b



is employed to build up the second thiazole ring by conventional methods (bromination, cyclization) to give the final product 17.

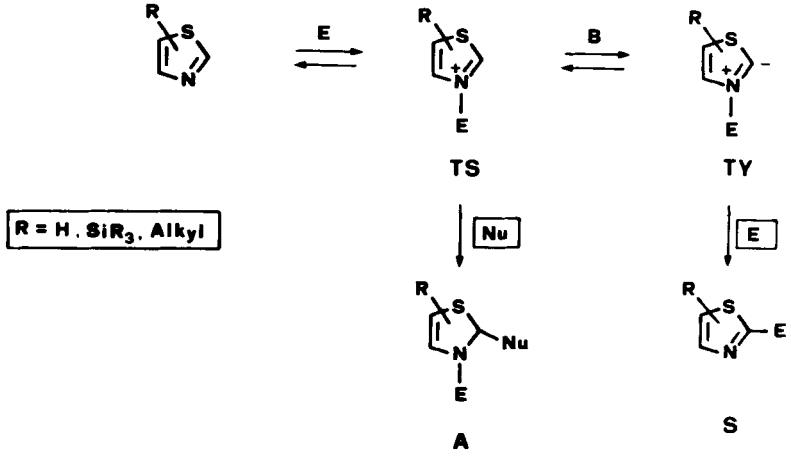
Another example deals with the synthesis of a thiazolyl-



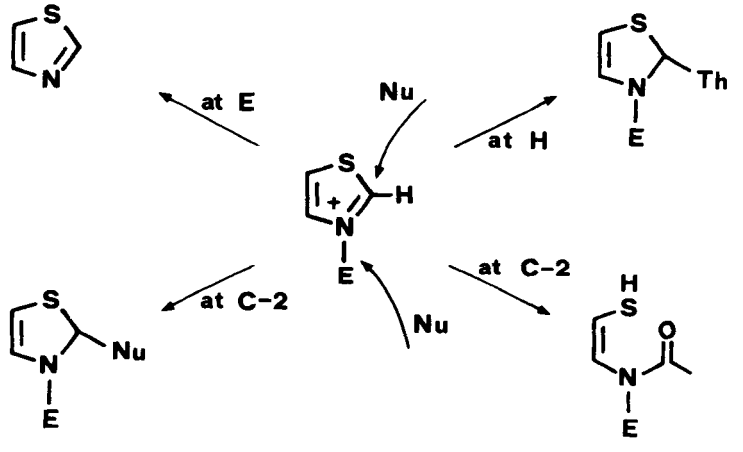
2-methoxyiminoacetamido-3-cephem, which has been carried out in collaboration with chemists of CIBA-GEIGY in Basel [37]. The ready desilylation of the 2-silylthiazole 1e by oxalyl chloride and quenching with triethylamine-methanol leads to the thiazolyl ketoester 12a. This is one of the two building blocks employed for the synthesis of the cephem shown.

3. Reactions with C-Nucleophiles

I have described so far some substitution reactions at C-2 of thiazoles with C-electrophiles producing a substitution product S very likely via a thiazolium ylide TY as an intermediate. In some instances, the main product S was accompanied by a compound A arising from the addition of a nucleophile Nu to the thiazolium salt TS, the precursor of the ylide TY. This suggests that a proper control of the system to maintain the ylide concentration very low may favor the latter route. This is quite attractive because the products, N- and C-2 substituted Δ^4-thiazolines, appear susceptible to various synthetic elaborations such as the conversion into thiazoles or condensed bicyclic systems, or rearrangements into other heterocycles or, finally, the transformation into a simple functionality [8]. This approach is only deceptively simple because there are other reactions which can compete with the addition of Nu to the C-2 of the thiazolium salt. These are: i) ylide formation and its coupling with the thiazolium salt; ii) ring opening by, for instance, hydroxide ion induced carbon-sulfur bond cleavage; iii) attack of the nucleophile at E with displacement of the thiazole group. These difficulties became soon apparent on examination of the reaction of 1,3-thiazole (1a) with lithium diethylmalonate [38]. A satisfactory

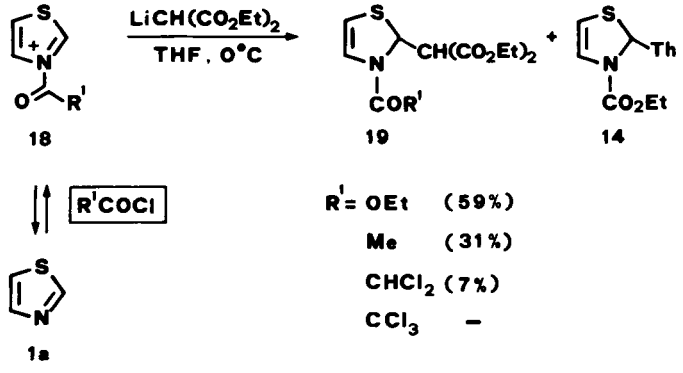


yield of the adduct 19 is obtained using ethyl chloroformate as the activating electrophile. The by-product, N-



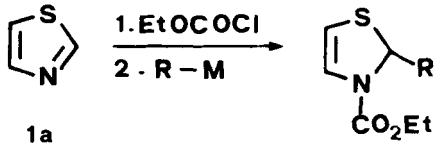
Th = 2-Thiazolyl

carbethoxythiazolyl thiazole 14, very likely arises from the competing attack of the N-carbethoxythiazolium ylide on the thiazolium salt 18a. The yield of 19 decreases



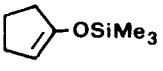
down to zero when an electron-withdrawing group R' is present in the acyl chloride. In this case the malonate ion reacts with the thiazolium salt 18 at the carbonyl carbon atom rather than at C-2.

The extension of the reaction to other C-nucleophiles using ethyl chloroformate as activator [38] indicated that the scope of this carbon-carbon bond forming method at C-2 of the thiazole ring is quite large. The reaction occurs readily with four different organometallic reagents, namely lithium carbanions of esters, Grignard salts, silyl enol ethers, and silyl ketene acetals. The two silylated reactants, which are in fact the equivalents of enolates and α-carbanions of esters respectively, appear to give the best overall yields and eventually a satisfactory stereocontrol as shown by the overwhelming amount of one diastereomer over the other (9:1) in the reaction of O-trimethylsilyl-O-methyl-phenylketene acetal. Hence the diastereo- and enantioselec-



1a

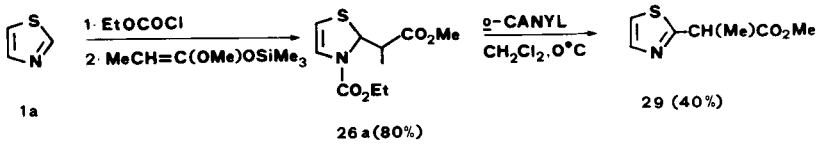
19a - 27a

R - M		Product R =	Isolated yield %
$(EtO_2C)_2CHLi$	19a	$-CH(CO_2Et)_2$	59
$EtO_2C(MeCO)CHLi$	20a	$-CH(COMe)CO_2Et$	46
$CH_3(CH_2)_5MgBr$	21a	$-CH_2(CH_2)_4CH_3$	41
$CH_2=CHMgBr$	22a	$-CH=CH_2$	15
$CH_3(CH_2)_4C\equiv CMgBr$	23a	$-C\equiv C(CH_2)_4CH_3$	40
$CH_2=C(Ph)OSiMe_3$	24a	$-CH_2-COPh$	82
	25a		75 (1:1)
$MeCH=C(OMe)OSiMe_3$	26a	$-CH(Me)CO_2Me$	80 (2:1)
$PhCH=C(OMe)OSiMe_3$	27a	$-CH(Ph)CO_2Me$	84 (9:1)

tivity are attractive aspects of these reactions which are under investigation in our laboratory.

The simplest transformation of the N-acylthiazolines 19a-27a which we envisaged is their oxidative deacylation to thiazoles. Accordingly, the compound 26a is trans-

formed by o-chloroanil into the thiazolylpropionic ester 29. Thus, considering the overall sequence starting from



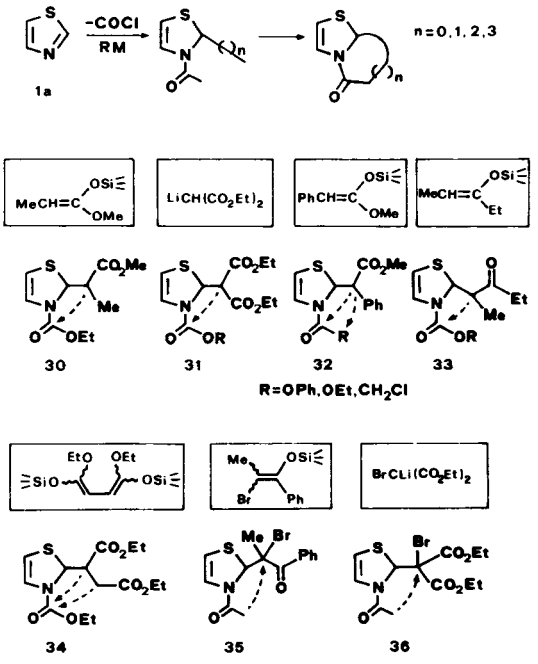
1a

26a (80%)

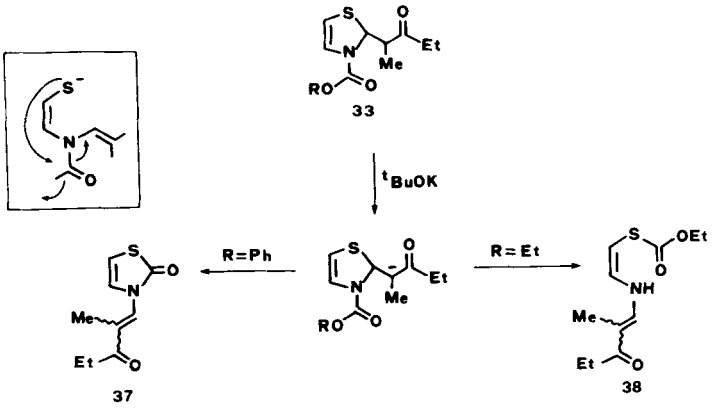
29 (40%)

1a, the method appears quite convenient for the direct introduction of the α-propionic ester group at C-2 of the thiazole ring. The importance of this functionalization rests in the fact that the α-propionic acid group is an essential function in many non-steroidal antiinflammatory agents.[39]

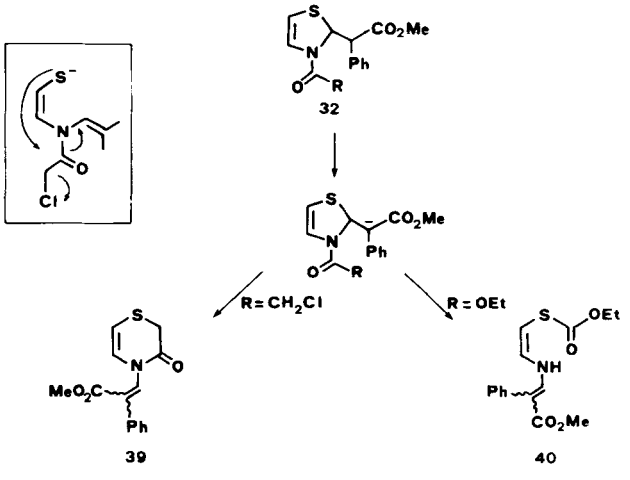
Another feasible synthetic application of N-acylthiazolines is the intramolecular cyclization between the two side chains to form a lactam ring. This is an attractive approach to the synthesis of lactams condensed across the carbon-nitrogen bond of a Δ^4-thiazoline [40], a class of compounds which includes biologically active species such as penems. As a method of cyclization we have so far explored the intramolecular nucleophilic substitution of an appropriate leaving group by a carbanion generated either at the C-2 chain or at the N-acyl group. A number of N-acylthiazolines which appeared suitable for that purpose were already in our hands; other were prepared



from the appropriate organometals and N-acylthiazolium halides [4o]. Unfortunately, the experiments showed that only a small probability exists to build up the β-lactam ring from compounds 3o-33 since the anion generated at the α-carbon atom of the C-2 chain induces the ring opening by carbon-sulfur bond fission [4o]. This is illustrated by the reactivity of thiazolines 33a and 33b. Subsequent to the ring opening, the attack of the thiolate function at the carbonyl carbon results either in the displacement of the OR group (R = Ph) to give the N-vinyl-

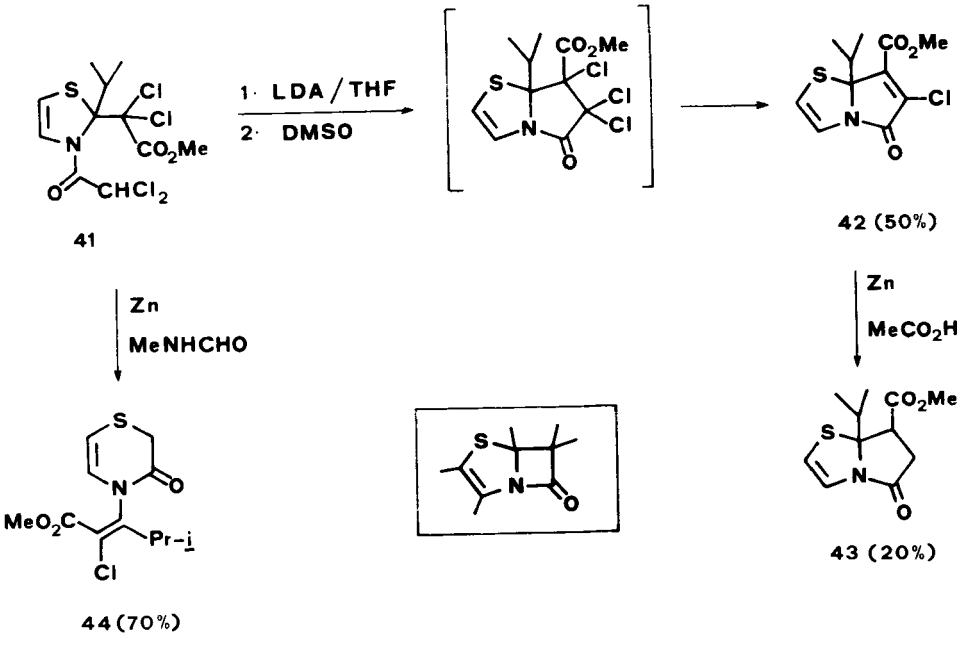


thiazolinone 37 or in the cleavage of the carbon-nitrogen bond to give the open-chain compound 38. In a similar way, the anion generation in the thiazoline 32 is followed neither by the attack at the carbonyl carbon to give a β-lactam (R = OEt) nor at the chloromethyl



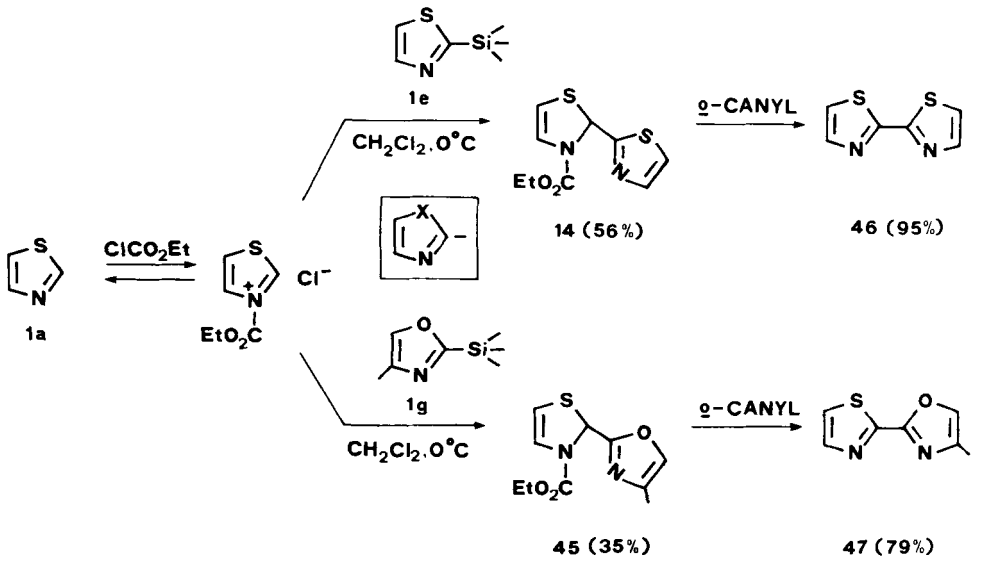
group (R = CH_2Cl) to give a γ-lactam [40]. Instead, subsequent to the carbon-sulfur bond fission, the displacement of the chloride ion by the thiolate function gives the N-vinyl-3,4-dihydro-1,4-thiazinone 39 whereas the displacement of the ethoxide group leads to the open-chain compound 40.

Better possibilities appear to exist for γ-lactam cyclization by generation of the carbanion at the β-carbon atom of the N-acyl group. This approach has been applied already [41]. Treatment of the N-acylthiazoline 41 with lithium diisopropylamide in THF at -78°C, then adding DMSO and warming up to room temperature yields the bicyclic system 42 which in fact contains the amide functionality. The reductive dehalogenation of 42 affords the



γ-lactam 43. This shows some structural features similar to those of a penem: the skeleton of both systems is formed by a Δ^4-thiazoline unit condensed across the carbon-nitrogen bond with a lactam ring. Therefore, the above sequence of reactions indicates a new route toward γ-lactam analogues of penems. J. Baldwin has recently renewed the interest for lactam antibiotics devoid of the β-lactam moiety [42]. The formation of 42 from 41 should involve as a primary process the intramolecular cyclization between the carbanion at the N-acyl group and the α-carbon of the dichloroethanoate chain at C-2, followed by 1,2-dechlorination in the resulting γ-lactam system. Attempts to build up a lactam system from 41 by the Zn-activated coupling between the halogenated carbons give instead the 1,2-thiazinone 44, very likely via the familiar carbon-sulfur bond cleavage and recyclization at the dichloromethyl carbon.

A further application of the reactivity of 1,3-thiazole (1a), via its N-carbethoxythiazolium chloride, toward organometallic reagents, is shown by the reaction with two silylated heterocycles [43], namely 2-trimethylsilylthiazole (1e) and 4-methyl-2-trimethylsilyloxazole (1g). Satisfactory yields of the corresponding adducts 14 and 45 are obtained in a relatively polar solvent such as dichloromethane. In these reactions, the silylazoles 1e and 1g appear to behave as the equivalents of the C-2 thiazolyl [30] and oxazolyl [44] carbanions, respectively. This equivalence is particularly important in the oxazole series since the chemistry of 1,3-oxazoles via their C-2 carbanion is practically precluded due to the ring opening by oxygen-carbon bond cleavage. The adducts 14 and 45 undergo the oxidative deacylation by o-chloroanil to the bis-thiazole 46 and the oxazolyl thiazole



47. The sequence corresponds to an highly selective method for the introduction of a thiazolyl or oxazolyl group at C-2 of the thiazole ring. We are using this methodology in a more extensive way for the preparation of heteroarene oligomers [45] whose importance is related to their presence in various biologically active compounds [46], such as myxothiazol, bleomycin, patellamides, and many others.

4. Conclusions

I have described an harvest of reactions, most of which from our own work, showing two new routes for the carbon-carbon bond formation at C-2 of the thiazole ring. Although some special properties of sulfur, mainly its ability to stabilize a negative charge at the α-carbon atom, induce a superior reactivity at C-2, where in fact

reactions with carbon electrophiles and nucleophiles are equally possible, an appropriate substituent such as the silyl group allows reactions with carbon electrophiles to occur also at C-5. Most of the reactions described correspond to the introduction of a carbonyl group directly or indirectly bonded to the thiazole ring. This appears a quite useful functionalization in view of the possible synthetic elaborations which can be carried out by nucleophilic addition to the carbonyl carbon and electrophilic substitution at its α-carbon atom.

The chemistry of 1,3-thiazole is quite peculiar with respect to that of other 1,3-azoles, namely oxazole and imidazole which have been often used for comparison. For instance, there is no oxygen counterpart of thiamine which exerts the same biological activity, nor are oxazolium salts known to catalyze the acyloin condensation [47]. This reinforces the opinion that the chemistry of thiazole is determined to a great deal by its sulfur atom.

Acknowledgement

I am pleased to acknowledge the contribution of my recent co-workers in this area of chemistry: Alessandro Medici, Tiziano Dall'Occo, Giancarlo Fantin, Marco Fogagnolo, Guido Galliani, Annarosa Mastellari, and Paola Pedrini. The results I have presented here would have not been possible without their skilful and dedicated work. The financial supports from the Ministery of Education of the Italian Governement and the National Research Council of Italy are also gratefully acknowledged.

REFERENCES

1. A. Hantzch and H.J. Weber, Berichte, 2o, 3118 (1887).
2. R. Breslow, J.Am.Chem.Soc., 8o, 3719 (1958).
3. Reviews: R. Breslow, Ann. N.Y. Acad. Sci., 98, 445 (1962); A. Schellenberger, ibid., 378, 51(1982); P. Haake and R.M. Nelson, ibid., p. 1o7.
4. H. Stetter and H. Kuhlmann, Angew. Chem. Int. Ed. Engl., 13, 539 (1974); H. Stetter, ibid., 15, 639 (1976).
5. a) "The Chemistry of Heterocyclic Compounds. Thiazole and its derivatives", J.V. Metzger, ed., Wiley, New York, 1979, vol. 34, part I and II.
b) B. Iddon and P.A. Lowe, Spec. Period. Rep.: Org. Compd. Sulphur, Selenium, Tellurium, 5, 358 (1979).
6. Ref. 5a, vol. 44, p. 99.
7. D.N. Reinhoudt, Adv. Heterocyclic Chem., 21, 253 (1977).
8. A.I. Meyers "Heterocycles in Organic Synthesis", Wiley, New York, 1974. E.J. Corey and D.L. Boger, Tetrahedron Lett., May 5 (1978).
9. Ref. 7, p. 276
1o. R.B. Woodward in "Recent Advances in the Chemistry of β-Lactam Antibiotics", ed. J. Elks, Chem. Soc. Spec. Publication n. 28, 1977, p. 167; L. Ernest, J. Gosteli, C.W. Greengran, W. Holick, D.E. Jackman, H.R. Pfaendler, and R.B. Woodward, J. Am. Chem. Soc., 1oo, 8214 (1978).
11. M. Foglio, G. Franceschi, C. Scarafile, F. Arcamone, J. Chem. Soc. Chem. Commun., 7o (198o); Heterocycles, 16, 1919 (1981).
12. P.J. Abbott, R.M. Acheson, D.J. Watkin, J.R. Carruthers, J. Chem. Soc. Perkin Trans. 1, 1269 (1976).
13. L. Ghosez and M.J. O'Donnell in "Pericyclic Reactions", A.P. Marchand and R.E. Lehr, eds., Academic Press, New York, 1977, vol. II, P. 79; K.N. Houk; ibid., p. 181.
14. A. Dondoni, A. Medici, C. Venturoli, L. Forlani, and V. Bertolasi, J. Org. Chem., 45, 621 (198o); A. Medici, P. Pedrini, C. Venturoli, A. Dondoni ibid., 46, 279o (1981).
15. A. Medici, P. Pedrini, and A. Dondoni, J. Chem. Soc. Chem. Commun., 655 (1981).
16. A. Medici, G. Fantin, M. Fogagnolo, P. Pedrini, A. Dondoni, and G.D. Andreetti, J. Org. Chem., 49, 59o (1984).
17. H. Saimoto, C. Houge, A.-M. Hesbain-Frisque, A. Mokel, and L. Ghosez, Tetrahedron Lett., 24, 2251 (1983).
18. Ref. 5a, vol. 34, p. 31.

19. R. Pellicciari, M. Curini, and P. Ceccherelli, J. Chem. Soc. Perkin Trans. 1, 1155 (1977).
20. a) P. Haake, L.P. Bansher, W.B. Miller, J. Am. Chem. Soc., 91, 1113 (1969); b) P. Haake, Tetrahedron Lett., 22, 2939 (1981); c) R.A. Ohlofson and J.M. Landesberg, J. Am. Chem. Soc., 88, 4263 (1966).
21. P. Haake, L.P. Bansher, and J.P. McNeal, J. Am. Chem. Soc., 93, 7045 (1971).
22. H.S. Haldrich, W.L. Alworth, and N.R. Clement, J. Am. Chem. Soc., 100, 2362 (1978); M.M.E. Scheffer-Sap and H.M. Buck, ibid., 101, 4807 (1979).
23. H. Kwart and K.G. King "d-Orbitals in the Chemistry of Silicon, Phosphorus and Sulfur", Springer-Verlag, Berlin, 1977.
24. S. Oae, W. Tegaki, A. Ohno, Tetrahedron, 20,417, 427 (1964).
25. S. Wolfe and D. Schirling, Tetrahedron Lett., 21, 827 (1980); S. Wolfe, L.A. LaJohn, F. Bernardi, A. Mangini, and G. Tonachini, Tetrahedron Lett., 24, 3789 (1983); S. Wolfe, A. Stolow, and L.A. LaJohn, ibid., p. 4071.
26. A. Mangini, Atti Accad. Lincei, 14(2), 33 (1977).
27. J.K. Rasmussen, Synthesis, 91(1977); E.W. Colvin, Chem. Soc. Rev., 7, 15(1978).
28. E.W. Colvin, Quart. Rev., 15(1978); I. Fleming, Chem. Soc. Rev., 10, 83(1981).
29. A. Dondoni and M. Guerra, unpublished results.
30. A. Medici, G. Fantin, M. Fogagnolo, and A. Dondoni, Tetrahedron Lett., 24, 2901 (1983).
31. A. Dondoni and T. Dall'Occo, unpublished results.
32. A. Dondoni, T. Dall'Occo, and A. Medici, unpublished results.
33. A. Ricci, M. Fiorenza, M.A. Grifagni, G. Bortolini, and G. Seconi, Tetrahedron Lett., 23, 5079(1982), and references cited therein.
34. A. Dondoni, T. Dall'Occo, G. Fantin, M. Fogagnolo, unpublished results.
35. A. Dondoni and T. Dall'Occo, unpublished results.
36. K. Brown, D.P. Kater, J.F. Cavalla, D. Green, R.A. Neuberry, and A.B. Wilson, J. Medicinal Chem., 17, 1177 (1974).
37. D. Bellus, A. Dondoni, A. Medici, and H. Wehrly, unpublished results.
38. A. Dondoni, T. Dall'Occo, G. Fantin, M. Fogagnolo, and A. Medici, Tetrahedron Lett., 25, 3633 (1984).
39. P.J. Piper and J.R. Vane, Nature (London), 223, 29 (1969); W.Coyne in "Medicinal Chemistry", A. Burger ed., Wiley, New York, 1970, p. 953.

4o. A. Dondoni, M. Fogagnolo, and A. Medici, unpublished results.
41. A. Dondoni, G. Fantin, M. Fogagnolo, and A. Medici, Heterocycles, 22, 2341 (1984).
42. J.E. Baldwin, Fai Chan Ming, G. Gallacher, P. Monk, and K. Prout, J. Chem. Soc. Chem. Commun., 25o (1983).
43. A. Dondoni, T. Dall'Occo, G. Galliani, A. Mastellari, and A. Medici, Tetrahedron Lett., 25, 3637 (1984).
44. A. Dondoni, T. Dall'Occo, G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, J. Chem. Soc. Chem. Commun., 258 (1984).
45. A. Dondoni and T. Dall'Occo, unpublished results.
46. Myxothiazol: W. Trowitzsch, G. Hofle, and W.S. Sheldrick, Tetrahedron Lett., 22, 3829 (1981); Bleomycin: Y. Aoyagi, K. Katano, H. Suguna, J. Primeau, L. Chanh, and S.M. Hecht, J. Am. Chem. Soc., 1o4, 5537 (1982); Patellamides: C.M. Ireland, A.R. Durso, R.A. Newman, and M.P. Hacker, J. Org. Chem., 47, 18o7 (1982).
47. I.J. Turchi, Ind. Eng. Chem. Prod. Res. Dev., 2o, 32 (1981).