Cycloadditions with Heterocycles. Reactions of *tert*-Butylcyanoketene with 2-(Dimethylamino)thiazoles

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tert-Butylcyanoketene (TBCK) combines with 2-(dimethylamino)thiazole (**1a**) and the 5-methyl derivative **1b** in benzene to give in each case 2:1 cycloadducts (from 2 mol of TBCK and 1 mol of 1) which proved by spectroscopic and X-ray analyses to be pairs of diastereomeric δ-lactones condensed with the thiazole ring across its former C_4–C_5 bond, namely, thiazolo[4,5-*d*]-2-tetrahydropyranones **3** and **4**. From the reaction of **1a**, an open-chain substitution product at C_5 was also obtained in low yield. At room temperature the main products were the annulated lactones **3**; in refluxing benzene the ratios reversed in favor of **4**. Thermolysis of **3** in benzene and methanol showed that they rearrange to the diastereomers **4** through open-chain intermediates, one of which was trapped as an adduct with methanol. A reaction scheme with competing pathways involving dipolar intermediates accounts for both the formation of the adducts and their conversion. The distribution of the diastereomers **3** and **4** at room temperature is accounted for in terms of conformational effects controlling the stereochemistry of the cyclization of their open-chain precursors, whereas their relative stabilities appear to be related to the strains of the lactone ring. The failure to obtain a [2 + 2] cycloadduct is briefly examined on the basis of frontier molecular orbital theory.

There is considerable interest for both synthetic and mechanistic reasons in [2 + 2] and [4 + 2] cycloadditions[1,2] where five-membered-ring heterocycles enter as 2π components. Studies on these cycloadditions, however, are quite limited since many heterocycles are reluctant to undergo addition reactions and prefer to give substitution reactions[3] which preserve their aromatic character. For instance, although the aromatic character of thiazoles has been questioned,[4a,b] their reactivities in electrophilic[4b] as well as nucleophilic[4c] substitution reactions is well documented,[4d] whereas their activity as cycloaddition partners is limited to the reaction with dimethyl acetylenedicarboxylate which has been proved to give a 2:1 cycloadduct by addition across the C=N bond of the thiazole ring.[5]

As a part of our program to investigate the mechanism and stereochemistry (regio- and periselectivity) as well as the synthetic utility of cycloadditions to thiazoles and other sulfur heterocycles, we present in this paper the results from the study of the reaction of 2-(dimethylamino)-1,3-thiazoles with *tert*-butylcyanoketene. This report should be of general synthetic interest because, for the first time, it provides an example of formation of carbon–carbon bonds by addition to the C_4–C_5 double bond of the thiazole ring.

Results and Discussions

Of the numerous substrates which in principle could give cycloadditions to the double bonds of the thiazole ring, ketenes appeared to be the best candidates, owing to their well-known propensity to take part in thermally induced [2 + 2] cycloadditions to C=C and C=N double bonds.[1,6] The preference was given to the highly reactive and still readily accessible *tert*-butylcyanoketene (TBCK).[7] Since

Scheme I

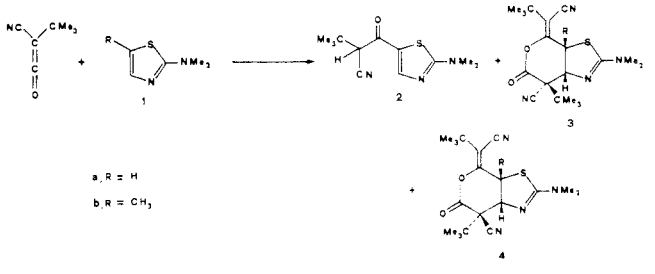

Table I. Reactions[a] of *tert*-Butylcyanoketene (TBCK) with 2-(Dimethylamino)thiazoles (1)

thiazole	[TBCK]:[1][b]	% yield[c]	[2]:[3]:[4][d]	reaction time
1a	1	53	0.48:3:1	3 h
	2	60	0.45:3:1	3 h
	3	95	0.42:3:1	3 h
	1[e]	50	1:0.7:1.1	ca: 12 h
	2[f]	67	1:1.75:0.75	3 h
1b	1	30	3:1[g]	4 days
	3	90	3:1[g]	4 days

[a] In benzene at room temperature unless otherwise stated; reaction initiated by slow addition of 1 to TBCK. [b] Molar ratio of reactants. [c] Overall yield of the various products calculated with respect to the thiazole. [d] Molar ratio of products. [e] Under reflux of the solvent. [f] Reaction initiated by slow addition of TBCK to 1. [g] Ratio of 3b to 4b.

(1) D. N. Reinhoudt, *Adv. Heterocycl. Chem.*, **21**, 253 (1977).
(2) P. Caramella, G. Cellerino, K. N. Houk, F. Marinone Albini, and C. Santiago, *J. Org. Chem.*, **43**, 3006 (1978).
(3) J. H. Ridd, *Phys. Methods Heterocycl. Chem.*, **4**, 55 (1971); G. Marino, *Adv. Heterocycl. Chem.*, **13**, 235 (1971).
(4) (a) L. Forlani, L. Lunazzi, and A. Medici, *Tetrahedron Lett.*, 4525 (1977); (b) L. Forlani and A. Medici, *J. Chem. Soc., Perkin Trans. 1*, 1169 (1978); (c) M. Bosco, L. Forlani, P. E. Todesco, L. Troisi, *J. Chem. Soc., Perkin Trans. 2*, 398 (1976). (d) For a recent review on thiazoles, see B. Iddon and P. A. Lowe, *Spec. Period. Rep.: Org. Compd. Sulphur, Selenium, Tellurium*, **4**, Chapter 12 (1977).
(5) Reference 1, p 272.
(6) L. Ghosez and M. J. O'Donnell, in "Pericyclic Reactions", Vol. II, A. P. Marchand and R. E. Lehr, Eds., Academic Press, New York, 1977.
(7) W. Weyler, Jr., W. Duncan, H. W. Moore, *J. Am. Chem. Soc.*, **97**, 6187 (1975); D. M. Kunert, R. Chambers, F. Mercer, L. Hernandez, Jr., and H. W. Moore, *Tetrahedron Lett.*, 929 (1978); H. W. Moore and D. S. Wilbur, *J. Am. Chem. Soc.*, **100**, 6523 (1978).

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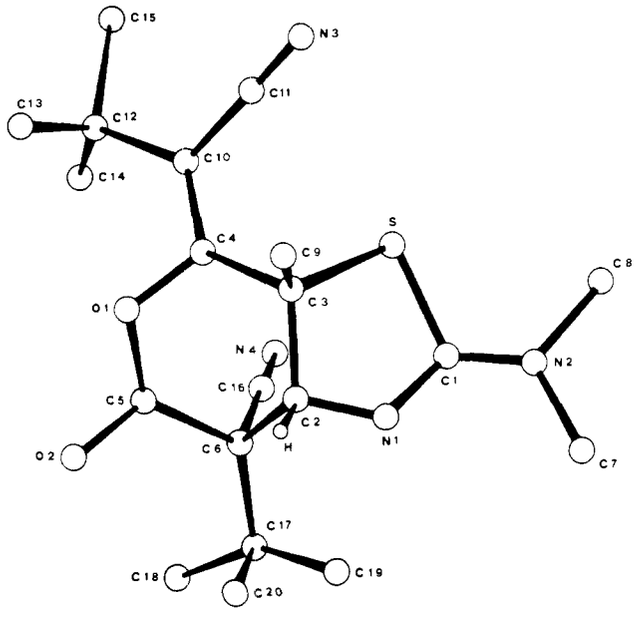


Figure 1. Perspective drawing and numbering scheme of **3b**; hydrogens have been omitted for clarity. Relevant bond distances (Å) are C_2–C_3 = 1.570 (6), C_2–C_6 = 1.594 (6), C_5–C_6 = 1.526 (6), C_5–O_2 = 1.171 (5), C_5–O_1 = 1.370 (5), O_1–C_4 = 1.393 (5), and C_3–C_4 = 1.519 (6).

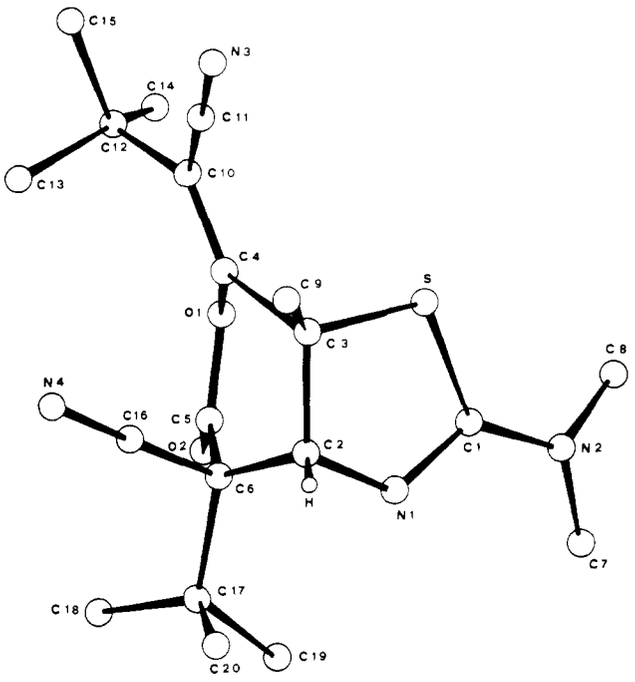


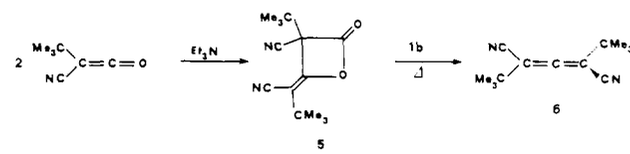
Figure 2. Perspective drawing and numbering scheme of **4b**; hydrogens have been omitted for clarity. Relevant bond distances (Å) are C_2–C_3 = 1.574 (5), C_2–C_6 = 1.569 (5), C_5–C_6 = 1.520 (5), C_5–O_2 = 1.191 (4), C_5–O_1 = 1.373 (4), O_1–C_4 = 1.407 (4), and C_3–C_4 = 1.521 (5).

ketenes are well-known to have a strong electron-acceptor character owing to the low-energy LUMO and hence react more easily with electron-rich ketenophiles characterized by the high-energy HOMO, we chose as a counterpart 2-(dimethylamino)thiazole (**1a**) (IE = 7.84 eV)[8a] and the 5-methyl derivative **1b** (IE = 7.51 eV)[8a] which for their first ionization potentials appeared to be better electron donors than the parent 1,3-thiazole (IE = 9.50 eV) and other 2-substituted derivatives.[8b]

Reactions occurred smoothly between TBCK and 2-(dimethylamino)thiazoles **1**, whereas other ketenes and thiazoles were practically unreactive.[9] The observed reactions are presented in Scheme I, and the results from various experiments are summarized in Table I. 2-(Dimethylamino)thiazole (**1a**) and 1 equiv of TBCK in benzene afforded after 3 h at room temperature a mixture (53% yield) of the 1:1 open-chain adduct **2** and the two cycloadducts **3a** and **4a** derived from 2 mol of TBCK and 1 mol of **1a**. The adducts **2**, **3a**, and **4a** were formed in a 0.48:3:1 ratio. The overall yield became virtually quantitative (95%) when the reaction was carried out with a threefold excess of TBCK with respect to **1a**, whereas the relative amounts of the products remained unchanged. In no instance, however, was a 1:1 cycloadduct, viz., an anulated cyclobutanone, identified in the crude reaction mixture even when the mixing of the reactants was reversed and TBCK was slowly added to the solution of the thiazole **1a**. In this case, however, the amount of the open-chain adduct **2** increased substantially.

Since the mobility of the hydrogen on C_5 of the thiazole **1a** could prevent isolation of a four-membered 1:1 cycloadduct, reactions were carried out on the 5-methyl derivative **1b**. The reactivity of **1b** with 1 molar equiv of TBCK was much lower than **1a** but produced similar results, viz., a mixture (30% yield) of the 2:1 adducts **3b** and **4b** in a 3:1 ratio, and no detectable amounts of the 1:1 cycloadduct. Also in this case, the conversion of the thiazole was considerably improved (90%) by using an excess of TBCK.

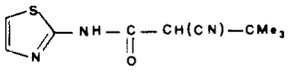
Moreover, since it has been recently shown that the lack of [2 + 2] cycloaddition in the reaction of TBCK with azomethines[10] and azetines[11] (cyclic imino ethers) was due to the ketene reacting as a dimer, the occurence of a similar event was examined in our case. After dimerization of TBCK to the corresponding δ-lactone **5** by catalysis with triethylamine[12] and treatment of the solution with 1 equiv of thiazole **1b**, the only isolable compounds were unaltered **1b** and 1,3-di-*tert*-butyl-1,3-dicyanoallene (**6**; 95%) derived



from the fragmentation[12] of **5**. In addition to these observations, the much lower basicity of aminothiazoles **1** (pK_a of **1a** is 5.27)[13] with respect to Et_3N (pK_a = 10.75)[14]

(8) (a) G. Distefano, private communication; (b) F. Bernardi, L. Forlani, P. E. Todesco, F. P. Colonna, and G. Distefano, *J. Electron Spectrosc. Relat. Phenom.*, **9**, 217 (1976); G. Salmona, R. Faure, E. J. Vincent, C. Guimon, and G. Pfeister-Guillouzo, *J. Mol. Struct.*, **48**, 205 (1978).

(9) No reaction was observed between diphenyl- or phenylmethylketene and **1a** (benzene, room temperature or reflux, several days). Similarly, only decomposition products of TBCK and the unaltered thiazole were obtained from TBCK and 2-methoxy-1,3-thiazole (IE = 8.8 eV)[8b] after 5 days at room temperature. On the other hand, TBCK and 2-amino-1,3-thiazole (IE = 8.45 eV)[8b] gave (benzene, 2 h at room temperature) the amide **10**: mp 181–183 °C (from benzene); IR (KBr) 3180 (NH), 2240 (C≡N), 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 9, CMe_3), 3.42 (s, 1, >CH), 7.1 (d, 1, =CH, $J \simeq 4$), 7.5 (d, 1, =CH, $J \simeq 4$); mass spectrum *m/e* 223 (M^+), 208, 167, 127, 100, 57.



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(10) E. Schaumann and H. Mrotzek, *Chem. Ber.*, **111**, 661 (1978).
(11) D. H. Aue and D. Thomas, *J. Org. Chem.*, **40**, 2552 (1975).
(12) H. W. Moore and W. G. Duncan, *J. Org. Chem.*, **38**, 156 (1973).
(13) L. Forlani, G. Breviglieri, and P. De Maria, *J. Chem. Soc., Perkin Trans. 2*, 163 (1979).
(14) A. Albert, *Phys. Methods Heterocycl. Chem.*, 1, Chapter 1 (1963).

Table II. ^1H and ^{13}C NMR Spectra[a] in $CDCl_3$ of Thiazolo[4,5-*d*]-2-tetrahydropyranones (3) and (4)

	spectrum	chem shift data
3a	^1H	1.24 (s, 9, CMe_3), 1.29 (s, 9, CMe_3), 3.05 (s, 6, NMe_2), 4.72 (d, 1, CH, J = 6.8 Hz), 5.41 (d, 1, CH, J = 6.8 Hz)
	^{13}C	26.6 (q, CMe_3), 29.4 (q, CMe_3), 34.2 (s, CMe_3), 39.6 (s, CMe_3), 40.3 (q, NMe_2), 52.3 (d, >CH), 59.9 (s, >C), 69.5 (d, >CH), 108.6 (s, =C), 115.7 (s, C≡N), 116.7 (s, C≡N), 156.4 (s, OC=), 161.4 (s, C=N), 163.5 (s, C=O)
4a	^1H	1.30 (s, 9, CMe_3), 1.40 (s, 9, CMe_3), 2.95 (s, 6, NMe_2), 5.08 (d, 1, CH, J = 7.2 Hz), 5.36 (d, 1, CH, J = 7.2 Hz)
	^{13}C	27.3 (q, CMe_3), 29.1 (q, CMe_3), 33.9 (s, CMe_3), 38.0 (s, CMe_3), 40.0 (q, NMe_2), 53.3 (d, >CH), 55.7 (s, >C), 72.9 (d, >CH), 109.4 (s, =C), 115.2 (s, C≡N), 116.8 (s, C≡N), 157.9 (s, OC=), 160.4 (s, C=N), 162.9 (s, C=O)
3b	^1H	1.33 (s, 9, CMe_3), 1.36 (s, 9, CMe_3), 1.97 (s, 3, Me), 3.04 (s, 6, NMe_2), 4.32 (s, 1, CH)
	^{13}C	27.0 (q, CMe_3), 29.2 (q, CMe_3), 30.4 (q, CH_3), 35.1 (s, CMe_3), 38.6 (s, CMe_3), 39.8 (q, NMe_2), 55.9 (s, >C), 64.4 (s, >C), 80.0 (d, >CH), 109.7 (s, =C), 114.3 (s, C≡N), 116.9 (s, C≡N), 159.9 (s, OC=), 161.0 (s, C=N), 163.3 (s, C=O)
4b	^1H	1.32 (s, 9, CMe_3), 1.40 (s, 9, CMe_3), 2.42 (s, 3, CH_3), 2.91 (s, 6, NMe_2), 4.58 (s, 1, CH)
	^{13}C	27.4 (q, CMe_3), 28.2 (q, CH_3), 29.1 (q, CMe_3), 35.0 (s, CMe_3), 38.0 (s, CMe_3), 39.8 (q, NMe_2), 54.4 (s, >C), 64.5 (s, >C), 82.2 (d, >CH), 107.1 (s, =C), 115.1 (s, C≡N), 117.0 (s, C≡N), 158.3 (s, OC=), 161.4 (s, C=N), 164.6 (s, C=O)

[a] Chemical shifts are in δ from Me_4Si. Assignments of C resonances are based on chemical shifts and off-resonance decoupled spectra and are tentative.

and the failure to detect the allene **6** as a byproduct of adducts **3** and **4** strongly indicate that TBCK does not take part as a dimer in the reaction with thiazoles **1**.

The structure of the 1:1 adduct **2** stemmed from spectral evidence, viz., the carbonyl absorption at 1620 cm^{-1} and the two singlets at δ 3.83 (aliphatic CH) and 7.88 (C_4 hydrogen), whereas the structures of the 2:1 cycloadducts **3b** and **4b** were assigned on the basis of single-crystal X-ray analyses.[15] Compounds **3b** (Figure 1) and **4b** (Figure 2) turned out to be two diastereomeric δ-lactones condensed with the thiazoline ring by cis annelation across C_2 and C_3, their stereochemical difference being determined by the configuration at C_6 of the lactone system. On the other hand, **3b** and **4b** have the same stereochemistry at the ethylenic carbon C_{10}, since in both compounds CN is syn and the bulkier *tert*-butyl group is anti to the thiazoline ring. A similar formation of diastereomeric 2:1 cycloadducts has been reported for the reaction of TBCK with azomethines.[10]

The ^1H and ^{13}C NMR spectra (Table II) as well as the fragmentation patterns in the mass spectra of thiazolo[4,5-*d*]-2-tetrahydropyranones **3b** and **4b** were almost superimposable as expected for two diastereomers. Accordingly, structures analogous to **3b** and **4b** were assigned to adducts **3a** and **4a**, respectively, on the basis of their identical spectroscopic characteristics (Table II). The only notable difference between diastereomers **3** and **4** appeared in the IR carbonyl absorptions (see Experimental Section); these, however, are likely to reflect differences in the C_5–O_2 bond distances as shown for **3b** (1.171 Å) and **4b** (1.191 Å).

The adducts isolated from reactions at room temperature were primary products since they were shown to be stable under the reaction conditions or during the work-up procedures for their separations. In refluxing benzene, however, the ratios of the products changed in favor of adducts **4** (Table I). Under these conditions the product distribution reflected thermodynamic stability since thermolysis of cycloadduct **3a** in benzene gave the diastereomer **4a** together with a very small amount of the open-chain adduct **2**; similarly, cycloadduct **3b** rearranged[16] cleanly to **4b**. Moreover, the conversion **3** → **4** appeared practically irreversible, since **4a** and **4b** were recovered unaltered after 4 days of reflux in benzene. The different stability of the diastereomeric δ-lactones **3** and **4** may be attributed, inter alia, to a more strained conformation of the lactone ring in the former, as indicated by a considerably longer C_2–C_6 bond distance (1.594 Å) in **3b** compared to the almost normal bond lengths and angles observed in **4b**.

A consistent interpretation of these observations is given in Scheme II. The reaction pathway involves the rate-determining formation of the highly stabilized 1,4-dipole **7** which, depending on R, gives the open-chain adduct **2** by migration of the hydrogen[17] of the former C_5 of the thiazole and/or captures a molecule of TBCK to form a second dipolar intermediate **8** which cyclizes regioselectively to the 2:1 adducts **3** and **4**. The reversibility of some steps accounts for the thermodynamically controlled product distribution. The formation of **7** can simply be viewed as an electrophilic attack by the central carbon of the cumulene system of TBCK on C_5 of the thiazole ring, a reaction which fits in the framework of the chemistry of both reactants.[4b-d,6,7] Similar mechanisms, involving 1,4-dipoles like **7** which undergo cyclization with a second molecule of ketene to six-membered-ring 2:1 cycloadducts, have been proposed for the reaction of TBCK with azomethines[10] and dimethylketene with enamines.[18] However, in the absence of a larger set of experimental data, we cannot exclude for our case a more complex mechanism than the one outlined in Scheme II, due to the intervention of transient 1,2-cycloadducts along the reaction pathway.[19]

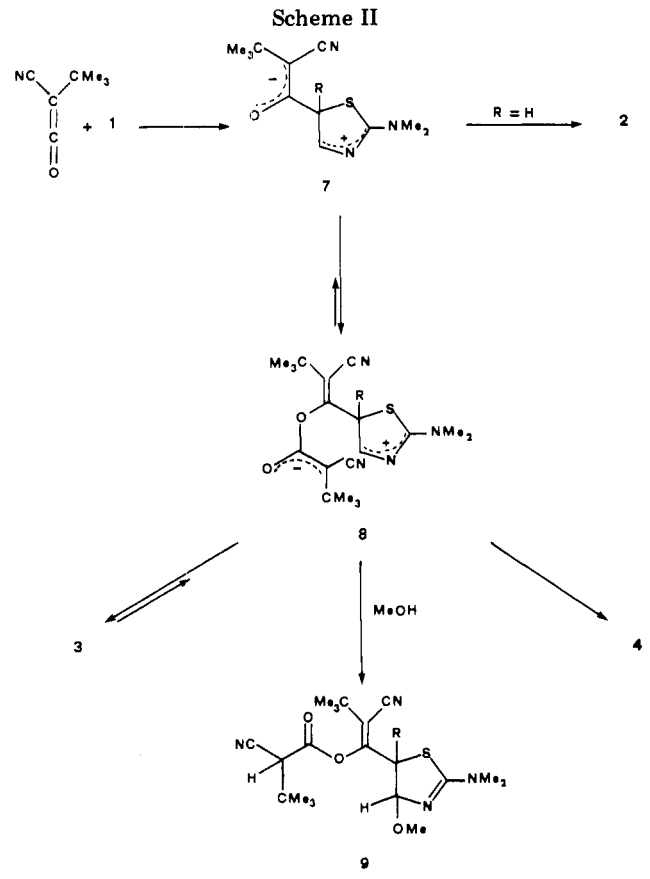
(15) V. Bertolasi, A. Dondoni, G. Gilli, and A. Medici, to be submitted for publication.

(16) In refluxing benzene the diastereomeric oxazinones from the reaction of TBCK with azomethines fragment and rearrange to the same product, viz., the 1:1 four-membered cycloadduct (β-lactame).[10]

(17) The hydrogen migration can occur by a [1,3] H shift; this however, is forbidden by orbital symmetry considerations (R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie, Weinheim, 1970) or by intermolecular processes.

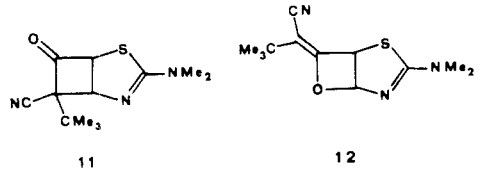
(18) R. Huisgen and P. Otto, *J. Am. Chem. Soc.*, 91, 5922 (1969).

Scheme II



Although the formation of the substitution product **2** and 2:1 cycloadducts **3** and **4** is itself a proof for the existence of the zwitterions **7** and **8**, further evidence was sought to detect these intermediates. Unfortunately, the instability of TBCK in protic solvents prevented proper trapping experiments. However, heating thiazolo[4,5-*d*]-2-tetrahydropyranone **3b** in methanol suppressed the formation of diastereomer **4b** and gave instead the Δ^2-thiazoline **9b** (24%) and thiazole **1b** (56%). Evidence for the structure of **9b** rests on the ^{1}H NMR spectrum which, besides other resonances, showed singlets at δ 3.82 (OCH_3), 4.0 (CHCNBu-*t*) and 4.85 (C_4 hydrogen of the thiazole ring);[20] the mass spectrum showed a weak peak at *m/e* 421 due to the molecular ion and an intense signal at *m/e* 364 corresponding to the fragment $(M - CMe_3)^+$. The product gave a satisfactory elemental analysis. The formation of **9b** is consistent with the addition of a molecule of methanol to the zwitterion **8b**, which thus appears to be a very likely intermediate both in the conversion of **3b** to **4b** and in the formation of these adducts from TBCK and **1b**. However, when **3a** was heated in methanol, the only isolable products were the open-chain 1:1 adduct **2** (90%) and traces of **4a**. Several reasons can be envisaged for the failure to intercept the intermediate **8a**. These include the instability of **9a** in case it is formed, because of the facile 1,2 elimination of methanol from the thiazoline ring,[4b] and, less likely, a different couse of fragmentation of **3a** in the polar solvent methanol.

(19) Possible 1,2-cycloadducts are the condensed cyclobutanone **11** and the oxetane **12** which may derive from the reversible ring closure of the zwitterion **7**; **11** could also be formed by a $[_\pi 2_s + _\pi 2_s]$ concerted process between TBCK and **1**. If formed, **11** was expected to be detected. In fact, cyclobutanones have been obtained alongside 2:1 cycloadducts in ketene–enamine additions where concurrent dipolar and concerted mechanisms are operative.[18] Moreover, there are stable bicyclic compounds formally related to **11**, namely, thiazolines condensed across C_4–C_5 with a β-lactame ring [R. D. G. Cooper and F. L. José, *J. Am. Chem. Soc.*, **92**, 2575 (1970)].



11 **12**

(20) Although the product appeared pure on TLC and elemental analysis, its NMR spectrum showed some additional peaks; these however, disappeared after repeated crystallizations. It is likely that the original product is a mixture of diastereomers having opposite configurations at C_4 of the thiazoline ring.

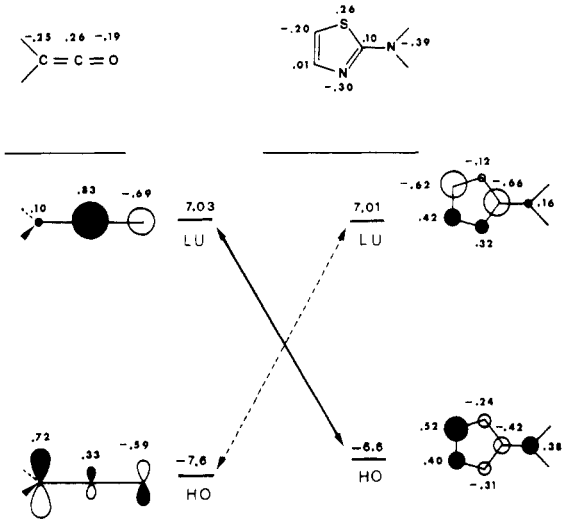
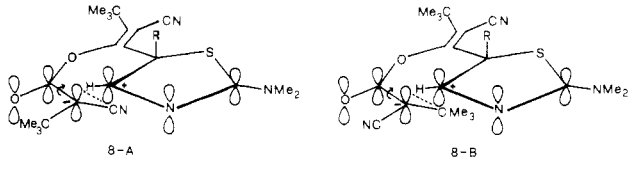


Figure 3. Frontier molecular orbital energies (eV) and coefficients of ketene and 2-aminothiazole. Numbers on the top formulas are net atomic charges.

Having convincing evidence on the existence of the intermediate **8**, we may put forth some comments about the



8-A **8-B**

factors controlling the stereochemistry of the cycloaddition of **8** to the diastereomeric δ-lactones **3** and **4**. In the dipole **8** several rotations around single bonds must occur before it reaches the appropriate arrangement for cyclization to **3** and **4**. In the less crowded conformation **8-A**, the enolate portion of the side chain, which is blocked in a planar arrangement owing to conjugation, lies below the plane of the heterocyclic ring and keeps the bulky *tert*-butyl group far away from it. Bonding can occur by a slight rotation around the former C–C bond of the ketene as indicated by the arrow, thus allowing interaction of the upper lobe of the carbanion with the lower lobe of the empty orbital of the positive carbon of the thiazole ring. This provides the correct stereochemistry for the kinetically favored thiazolo[4,5-*d*]-2-tetrahydropyranones (**3**), viz., cis annelation between the two condensed rings and the *tert*-butyl group of the C_6 on the same side of the hydrogen of the former C_4 of the thiazole. On the other hand, the formation of the diastereomer **4** appears less favored since it requires either the opposite rotation around the C–C bond in **8-A**, which is expected to be inhibited for steric reasons, or the intervention of the more crowded conformation **8-B**. Hence, the diastereoselectivity of the ring closure in **8** may be accounted for in terms of conformational factors, whereas the regioselectivity, viz., the exclusive cyclization on carbon of the enolate system, is consistent with an orbital rather than a charge-density control.[21]

In conclusion, the reactions between TBCK and 2-(dimethylamino)thiazoles 1 to give the open-chain adduct 2 and the 2:1 cycloadducts 3 and 4 can be interpreted in terms of a multistep process involving the dipolar intermediates 7 and 8 (Scheme II). A rather simplified explanation of the observed reaction course may be obtained by using approximate frontier orbital theory.[22] We compared the frontier molecular orbitals of ketene and 2-aminothiazole obtained by an ab initio SCF–MO treatment at the STO/3G level.[23] The relative orbital energies and symmetries (Figure 3) indicate that the major interaction in the early stages of the reaction is between the LUMO of ketene and the HOMO of thiazole[24] since these frontier orbitals are closest in energy, and the sizes of the coefficients show that the most favorable interaction is between C_1 of the cumulene and C_5 of the thiazole ring. Hence, formation of intermediate 7 is consistent both with frontier orbital control and with the charge distribution on the reactants since the central carbon of the cumulene bears a large positive charge and the C_5 of the thiazole ring is negatively charged. On the other hand, bonding between the terminal carbon of the ketene and C_4 of the thiazole in a concerted process appears inhibited both by the large energy separation[24] between the HOMO of ketene and the LUMO of thiazole[25] and by the considerable steric hindrance of the *tert*-butyl group of TBCK. The 1,4-dipole 7, also due to the particularly favorable delocalization of the charges, has enough stability to undergo addition and isomerization reactions before ring closure to the four-membered cycloadduct takes place.

Experimental Section

General Procedures. All melting points are uncorrected. ^1H NMR spectra were obtained on a 80-MHz Varian Associates CFT-20 spectrometer, and ^{13}C NMR spectra (in $CDCl_3$) were recorded on a 100-MHz Varian Associates XL-100 instrument. Chemical shifts are given in parts per million from Me_4Si. Mass spectra were recorded at 70 eV on a Varian MAT 111 low-resolution mass spectrometer. IR spectra were obtained (KBr pellets) on a Perkin-Elmer Model 257 grating spectrometer.

tert-Butylcyanoketene (TBCK) was generated in situ just before each experiment by thermal decomposition of the proper azido quinone.[26] 2-(Dimethylamino)-1,3-thiazole[4b] (**1a**) [bp 83–85 °C (15 mmHg)] and 2-(dimethylamino)-5-methyl-1,3-thiazole[27] (**1b**) [bp 86–88 °C (15 mmHg)] were prepared as described. All experiments were carried out under N_2 and with freshly distilled and dried solvents (benzene over Na wire and methanol over Mg wire).

Reaction of 2-(Dimethylamino)-1,3-thiazole (1a) with TBCK. A solution of 256 mg (2 mmol) of thiazole **1a** in 20 mL of benzene was added with stirring to an equivalent solution of TBCK in the same amount of solvent. After 3 h at room temperature the solvent was removed under vacuum, and the crude mixture was chromatographed (silica, 2:2:1 benzene–ethyl ether–cyclohexane) to give, in order, 70 mg (9.3%) of **4a**, 120 mg (47%) of **1a**, 215 mg (28.7%) of **3a**, and 22 mg (4.5%) of **2**.

The condensed δ-lactone **4a** exhibited the following data: mp 148–149 °C (from *n*-hexane); IR (KBr) 2220 (C≡N), 1800 (C=O) cm^{-1}; mass spectrum *m/e* (relative intensity) 374 (M^+, 10), 359 (7), 236 (15), 234 (12), 129 (29), 128 (100), 108 (35), 99 (27), 57 (48), 53 (33).

Anal. Calcd for $C_{19}H_{26}N_4O_2S$: C, 60.93; H, 6.99; N, 14.96. Found: C, 60.75; H, 7.01; N, 14.89.

The condensed δ-lactone **3a** gave the following: mp 174–176 °C (from ethyl ether); IR (KBr) 2210 (C≡N), 1770 (C=O) cm^{-1}; mass spectrum *m/e* (relative intensity) 374 (M^+, 7), 359 (5), 236 (7), 234 (17), 178 (14), 129 (21), 128 (100), 113 (6), 108 (9), 99 (19), 57 (19).

Anal. Calcd for $C_{19}H_{26}N_4O_2S$: C, 60.93; H, 6.99; N, 14.96. Found: C, 60.81; H, 6.92; N, 14.87.

The NMR data of thiazolo[4,5-*d*]-2-tetrahydropyranones **3a** and **4a** are collected in Table II.

The ketone **2** showed the following: mp 172–174 °C (from dichloromethane–*n*-hexane); IR (KBr) 2240 (C≡N), 1620 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (s, 9, CMe_3), 3.21 (s, 6, NMe_2), 3.83 (s, 1, CH), 7.88 (s, 1, =CH); ^{13}C NMR ($CDCl_3$) δ 28.2 (q, $\mathbf{C}Me_3$), 35.6 (s, $\mathbf{C}Me_3$), 40.4 (q, $N\mathbf{Me}_2$), 50.3 (d, >CH), 117.1 (s, C≡N), 128.4 (s, =C), 149.9 (d, =CH), 176.4 (s, C=N), 180.9 (s, C=O); mass spectrum *m/e* (relative intensity) 251 (M^+, 17), 195 (39), 166 (17), 155 (10), 127 (17).

Anal. Calcd for $C_{12}H_{17}N_3OS$: C, 57.34; H, 6.82; N, 16.72. Found: C, 57.18; H, 6.89; N, 16.83.

The reaction was also conducted by the following variations of the above conditions:

(a) The benzene solution of TBCK was added dropwise to the solution of **1a** (molar ratio of TBCK:**1a** = 2) and the mixture was stirred for 3 h at room temperature. The product distribution as monitored by NMR is given in Table I.

(b) A benzene solution of **1a** (192 mg, 1.5 mmol) and a three-fold molar excess of TBCK were stirred for 3 h at room temperature. Chromatography of the reaction mixture as detailed above gave 120 mg (21.4%) of **4a**, 360 mg (64.2%) of **3a**, and 35 mg (9%) of **2**.

(c) A solution of equimolar amounts of TBCK and **1a** (2 mmol) in 40 mL of benzene was refluxed overnight. The analysis of the reaction mixture by NMR revealed the presence of **4a**, **3a**, and **2** in a 1.1:0.7:1.0 ratio.

Reaction of 2-(Dimethylamino)-5-methyl-1,3-thiazole (1b) with TBCK. A solution of 284 mg (2 mmol) of thiazole **1b** in 20 mL of benzene was added portionwise to a stirred solution of TBCK (2 mmol) in 20 mL of benzene at room temperature. After 4 days the solvent was removed under vacuum, and the residue was chromatographed (silica, 2:2:1 benzene–ethyl ether–cyclohexane) to give 50 mg (6.4%) of **4b**, 150 mg (19.3%) of **3b**, and 200 mg (70%) of unaltered **1b**.

The condensed δ-lactone **4b** exhibited the following: mp 136–138 °C (from *n*-hexane); IR (KBr) 2210 (C≡N), 1790 (C=O) cm^{-1}; mass spectrum *m/e* (relative intensity) 389 (M^+, 10), 373 (13), 276 (10), 250 (10), 143 (44), 142 (100), 127 (15), 123 (29), 113 (32), 108 (59), 80 (19), 57 (73), 53 (55).

Anal. Calcd for $C_{20}H_{28}N_4O_2S$: C, 61.83; H, 7.26; N, 14.42. Found: C, 61.97; H, 7.31; N, 14.33.

The condensed δ-lactone **3b** gave the following: mp 124–126 °C (from *n*-hexane); IR (KBr) 2210 (C≡N), 1780 (C=O) cm^{-1}; mass spectrum *m/e* (relative intensity) 389 (M^+, 4), 373 (6), 276 (8), 143 (28), 142 (100), 127 (16), 123 (36), 113 (41), 108 (63), 90 (20), 57 (69), 53 (51).

Anal. Calcd for $C_{20}H_{28}N_4O_2S$: C, 61.83; H, 7.26; N, 14.42. Found: C, 61.78; H, 7.30; N, 14.35.

The NMR data of **3b** and **4b** are collected in Table II. Chromatography gave, from thiazole **1b** (217 mg, 1.53 mmol) and a threefold molar excess of TBCK in 40 mL of benzene at room

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(23) F. Bernardi, private communication. For frontier molecular orbitals of ketene computed at various SCF levels see also: (a) ref 6; (b) K. N. Houk, R. W. Strozier, and J. A. Hall, *Tetrahedron Lett.*, 897 (1974); (c) R. Sustmann, A. Ansmann, and F. Vahrenholt, *J. Am. Chem. Soc.*, **94**, 8099 (1972).

(24) The dominant interaction of the LUMO of ketene with the HOMO of thiazole in the early stages of the reaction as deduced from the model compounds of Figure 3 should be even more significant for the pairs TBCK–(dimethylamino)thiazoles **1**. In fact, the electron-withdrawing group CN in TBCK is expected to lower[22] the energies of both the LUMO and the HOMO with respect to the parent ketene, thus reducing the energy gap with the HOMO of thiazole and increasing the gap with the LUMO of thiazole, respectively.

(25) Reference 6, p 89, and ref 22b, p 239.

(26) W. Weyler, Jr., W. G. Duncan, M. B. Liewen, and H. W. Moore, *Org. Synth.*, **55**, 32 (1976).

(27) M. Selim, M. Selim, O. Tetu, G. Drillen, and P. Rumpf, *Bull. Soc. Chim. Fr.*, 3527 (1965).

temperature for 4 days, 130 mg (21.8%) of **4b** and 390 mg (65.5%) of **3b**.

Treatment of β-Lactone 5 Dimer of TBCK with 2-(Dimethylamino)-5-methyl-1,3-thiazole (1b). A solution of TBCK (4 mmol) in 20 mL of benzene was treated at room temperature with a few drops of Et_3N. After 21 h the IR spectrum of the solution did not show the presence of the ketene absorption at 2130 cm^{-1}. Addition of 284 mg (2 mmol) of **1b** in 20 mL of benzene resulted (TLC) in immediate formation of a mixture of products. The solvent was removed under reduced pressure, and the residue was chromatographed (silica, 9:1 benzene–ethyl ether) to give 362 mg (90%) of 1,3-di-*tert*-butyl-1,3-dicyanoallene (**6**), mp 50–51 °C (lit. mp 50.5–51.5 °C),[15] and 250 mg of unchanged **1b**.

Thermolysis of Thiazolo[4,5-*d*]-2-tetrahydropyranone (3a). Method A. A benzene solution (20 mL) containing 187 mg (0.5 mmol) of **3a** was refluxed for 48 h. The solvent was removed under reduced pressure, and the crude mixture was chromatographed (silica, 2:2:1 benzene–ethyl ether–cyclohexane) to give 145 mg (77.5%) of **4a**, 35 mg (18%) of **3a**, and 8 mg (5%) of **2**.

Method B. A methanol solution (20 mL) containing 200 mg (0.53 mmol) of **3a** was refluxed for 12 h. The usual workup as detailed above gave 15 mg (7%) of **4a** and 120 mg (90%) of **2**.

Thermolysis of Thiazolo[4,5-*d*]-2-tetrahydropyranone (3b). Method A. A benzene solution (20 mL) containing 321 mg (0.82 mmol) of **3b** was refluxed for 29 h. The solvent was removed under reduced pressure, and the residue was chromatographed (silica, 2:2:1 benzene–ethyl ether–cyclohexane) to give 200 mg (62.3%) of **4b**, 75 mg (23%) of unaltered **3b**, and 9.7 mg (8.5%) of **1b**.

Method B. A methanol solution (20 mL) containing 148 mg (0.38 mmol) of **3b** was refluxed for 12 h and then worked up by the usual procedure. Chromatography (silica, 9:1 benzene–ethyl ether) gave 53 mg (33%) of Δ^2-thiazoline **9** and 34 mg (62%) of **1b**. Compound **9** gave the following: mp 105–107 °C (from *n*-hexane); IR (KBr) 2240 (C≡N), 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (s, 9, CMe_3), 1.26 (s, 9, CMe_3), 1.98 (s, 3, CH_3), 3.02 (s, 6, NMe_2), 3.82 (s, 3, OCH_3), 4.0 (s, 1, >CH), 4.85 (s, 1, >CH); mass spectrum *m/e* (relative intensity) 364 ($M^+ - CMe_3$, 13), 349 (15), 266 (50), 181 (11), 180 (13), 142 (100), 88 (15), 57 (24).

Anal. Calcd for $C_{21}H_{23}N_4O_3S$: C, 59.98; H, 7.67; N, 13.32; S, 7.61. Found: C, 60.14; H, 7.54; N, 13.48; S, 7.84.

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Registry No. **1a**, 6142-08-1; **1b**, 52963-36-7; **2**, 72228-68-3; **3a**, 72228-69-4; **3b**, 72228-70-7; **4a**, 72258-09-4; **4b**, 72258-10-7; **5**, 72244-63-4; **6**, 36982-41-9; **9**, 72228-71-8; **10**, 72228-72-9; TBCK, 29342-22-1.

Nicotinic Acid Crown Ethers.[1] Synthesis of Macrocyclic Lactones from 2-Chloronicotinic Acid and Polyethylene Glycols. Template Effect on the Cyclization

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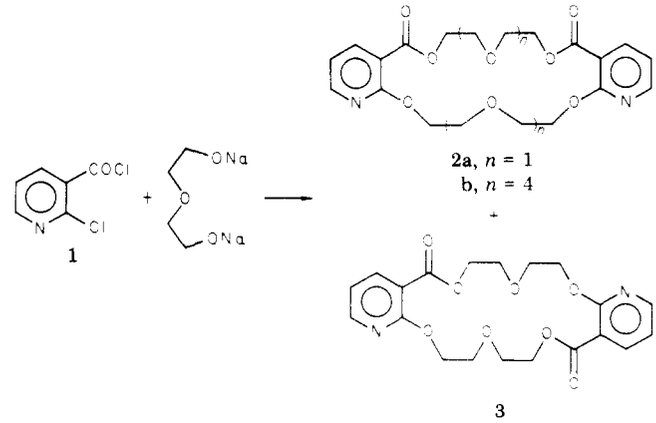
Crown ethers possessing a 2-oxanicotinate moiety were prepared by simple reaction of 2-chloronicotinoyl chloride with disodium di- and pentaethylene glycolates. Transesterification and the template effect on this cyclization were observed; they resulted in the 1:1 lactonic macrocycles as the major product.

During the course of our studies of pyridine-linked nucleotide [NAD(H)] models, the synthesis and chemistry of numerous 2,6-disubstituted nicotinic acid derivatives were conducted.[3] Evaluation of 2- vs. 6-nucleophilic displacement of halide ions on nicotinic acid derivatives has suggested that the 2-chloro substituent is displaced faster than the related 6-halide.[4] In view of the few examples of pyridine macrocyclic lactones[5] and the limited reported chemistry of these substituted nicotinate derivatives, 2-chloronicotinic acid was transformed into a subheterocyclic unit within a crown ether backbone.

Results and Discussion

2-Chloronicotinic acid was smoothly converted by refluxing in excess thionyl chloride[6] into 2-chloronicotinoyl chloride (**1**). Treatment of **1** with 1 equiv of disodium diethylene glycolate in refluxing xylene (138 °C) for 24 h gave an isomeric mixture of **2a** and **3** in 7.4 and 6.9% isolated yield, respectively. As noted previously in related



macrocycles,[7] the anti isomer (**3**) has generally the higher melting point. Definitive structure proof of both **2a** and **3** is based on lactone fragmentation upon treatment with

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