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BIS HETEROANNULATION 6. THE FIRST EXAMPLE OF A DIELS-ALDER REACTION INVOLVING A THIAZOLE RING WITH AN ACETYLENIC DIENOPHILE. GEOMETRICAL CONTROL OF REACTION PATHWAY

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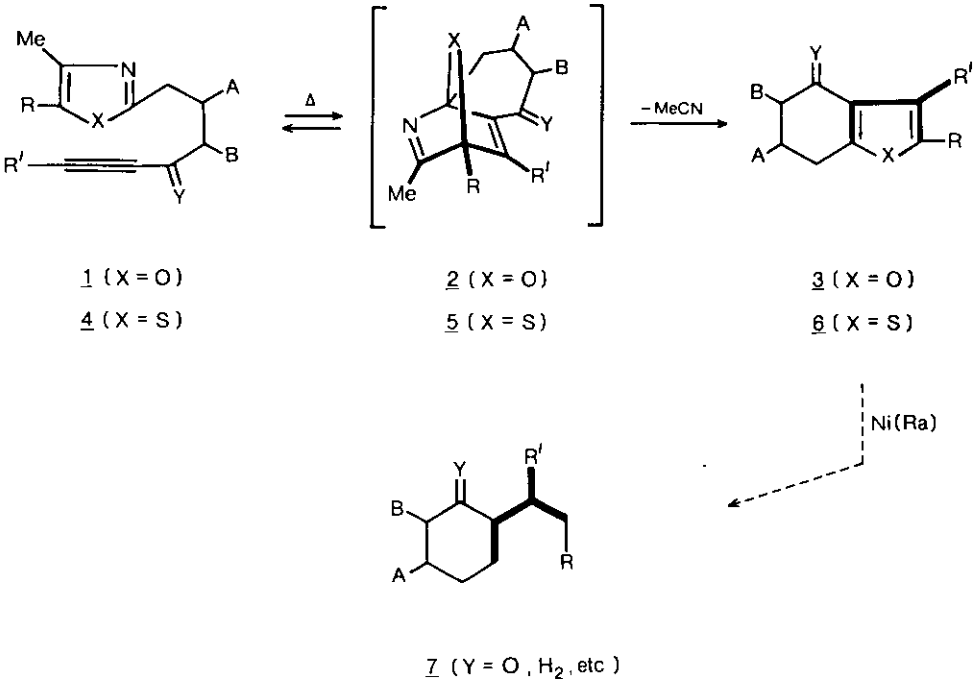
Abstract — Acetylenic thiazoles of proper design have been shown to undergo an intramolecular Diels-Alder reaction leading directly to fused-ring thiophene derivatives.

We have recently reported that acetylenic oxazoles of type 1 undergo a facile intramolecular Diels-Alder reaction, leading, via intermediate 2, to highly substituted furans of type 3 ("Bis Heteroannulation", Scheme 1).[1] This methodology has been successfully applied to the synthesis



1 (X = O)
4 (X = S)

2 (X = O)
5 (X = S)

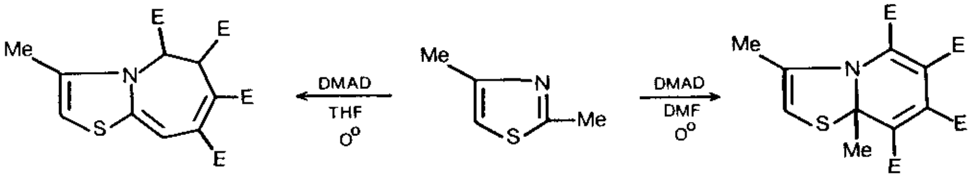
3 (X = O)
6 (X = S)

7 (Y = O, H_2, etc)

Scheme 1

of a variety of furanosesquiterpenes,[1] and we have been intrigued with the possibility that thiazoles of type 4 might exhibit similar reactivity. Such a transformation could be of considerable practical importance since it is obvious, for example, that a β-substituted thiophene can be considered as a latent "isopreneoid" unit.[2] Furthermore, substitution patterns of the type generalized in 7 are both exceedingly common in nature and sometimes difficult to obtain using presently available techniques.[3]

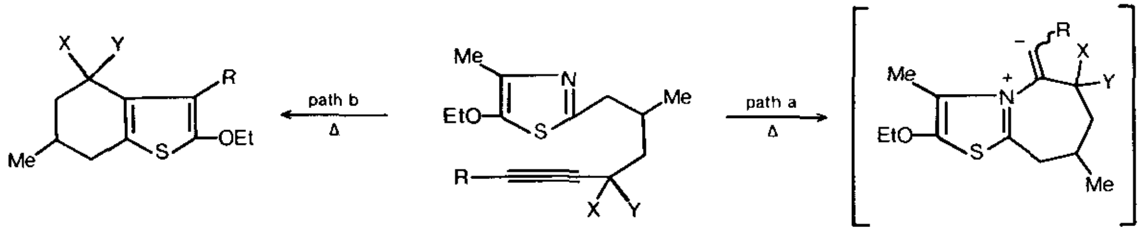
A major difficulty with this approach is the lack of reactivity of thiazoles in Diels-Alder reactions.[4] To the best of our knowledge there has been only one report of a reaction of this class,[5] and even in this case the primary adduct was not isolated. This lack of reactivity is presumably due to the greater aromaticity of thiazoles relative to oxazoles,[4] as well as to the high nucleophilicity of the thiazole ring.[6,7] 2,4-Dimethylthiazole (8), for example, reacts with dimethyl acetylenedicarboxylate to give adducts 9 and 10 as the only isolated products (Scheme 2).[7] We have now found, however, that intramolecular variants of this reaction are possible if proper geometrical restraints are imposed.



9 8 10

Scheme 2

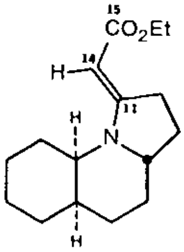
Thiazoles 11a - d were prepared following standard literature procedures,[1,8] and they were subjected to a range of cyclization conditions (Scheme 3). Not surprisingly, both 11a and 11b



13a	11a (R = CO_2Me, X = OH, Y = H)	12a
13b	11b (R = CO_2Me; X,Y = O)	12b
13c	11c (R = Me, X,Y = O)	12c
13d	11d (R = CH_2OMe: X,Y = O)	12d

Scheme 3

reacted exclusively to give products derived from intermediates 12a and 12b (path a).[7] In each case models clearly indicate that the 7-exo-dig transition state required for path a is highly favored,[9] and no trace of thiophenes 13a or 13b could be detected in the crude reaction mixtures. Thus, for example, after brief heating (refluxing ethylbenzene, 3 h) all 11a was consumed and a single major product was evident by TLC (Rf = 0.60, 20% acetone/hexane, silica gel). This product was isolated as a highly unstable crystalline solid, mp 90 - 92° C (yield 55 - 60% yield), and assigned structure 14 on the basis of mechanistic considerations[7] as well as the following



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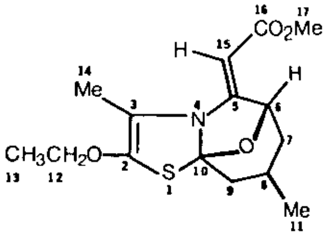
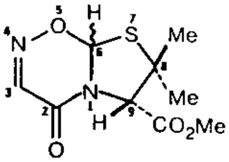


14



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observations.[10] First, elemental analysis and mass spectral data showed that 14 was isomeric with 11a, thereby ruling out the possibility of an intramolecular Diels-Alder reaction with loss of acetonitrile.[1] Second, the infrared spectrum ($CHCl_3$) of 14 was devoid of absorptions in the regions expected for hydroxyl or acetylenic bond stretching, and all attempts at preparing an acetate derivative failed. The major IR peaks (1690, 1605 cm^{-1}), however, agreed precisely with those expected for a β-aminoacrylate system (cf. compound 15, IR 1690, 1595 cm^{-1})[11]. Third, the ^{13}C NMR data was in full accord with structure 14 and in particular indicated the absence of an aromatic thiazole ring.[10] Absorptions for C-2 and C-3, however, were readily apparent at 137.5 and 114.7 ppm, and of particular importance the assigned values for C-5, C-15, and C-16 (159.2, 84.6 and 167.9 ppm, respectively) are in excellent agreement with those found in the model system 15 (164.1, 77.3 and 169.7 ppm, respectively, for C-11, C-14 and C-15).[11] These absorptions would appear to be highly characteristic of the β - aminoacrylate system. In addition, the position of absorption for C-10 (110.3 ppm) is in total agreement with the closely related system 16[12] (95.1 ppm for C-6) after correcting for standard incremental substituent effects.[12] Fourth, the ^1H NMR spectrum of 14, including exhaustive decoupling experiments, is in full accord with the assignments made above.[10] In particular, the E-configuration at C_5 - C_{15} is based on the logical expectation of a facile equilibration to the thermodynamically most stable isomer, as well as the strongly deshielding influence of the ester functionality on H-6 (5.91 ppm). Finally, it is interesting to note that although 14 is undoubtedly an unusual structure, Dreiding models of this compound are virtually free of strain.

In contrast to the results presented above neither **11c** nor **11d** are electronically disposed to undergo the 7-*exo*-*dig* process, and the alternative 8-*endo*-*dig* cyclization is geometrically impossible. Therefore, we believed, these materials should be more amenable to undergoing an intramolecular Diels-Alder reaction. Our initial efforts in this area, however, were unrewarding. Thus, thiazole **11c** suffered mainly slow decomposition to polar products over a period of several days in refluxing ethylbenzene (~ 138° C), and all attempts at catalyzing this process were either ineffective ($BF_3 \cdot Et_2O$, $Hg(OAc)_2$, TsOH, $ZnCl_2$), or led to addition reactions at the acetylenic triple bond ($AlCl_3$).[13] Also, higher temperatures led to rapid decomposition which could not be controlled by the addition of various radical scavengers, including, for example, 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide and 4,4'-butylidene-*bis*-6-*tert*-butyl-*m*-cresol.[14] With thiazole **11d**, however, the additional activating influence of a methoxyl group apparently facilitates the Diels-Alder process. Thus, in the presence of a catalytic amount of methylene blue,[15] **11d** gave a 60% yield of thiophene **13d** after 3 days at reflux in degassed mesitylene (165°). That **13d** was actually in hand was unequivocally established by all of the usual criteria,[16] as well as the fact that its ^1H NMR spectrum was virtually superimposable with that of the previously described furan analog [3-methoxymethyl-4-keto-6-methyl-4,5,6,7-tetrahydrobenzofuran].[17] This example, then, provides the first conclusive evidence that thiazoles can undergo the Diels-Alder reaction with acetylenic dienophiles in exactly analogous fashion as their oxazole counterparts.

In closing, we might only add that the intramolecular nature of these reactions should be even more favorable in multicyclic systems such as **4** (A, B = cycloalkyl) since the reacting centers are held more rigidly in proximity to each other. Therefore, we believe, reactions of this type might find considerable applicability in the synthesis of naturally occurring terpenes.

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10. Physical and chemical data for compound 14: Rf 0.60 (20% acetone/hexane, silica gel); Mass spectrum, M^+ m/e 311; IR($CHCl_3$) 1690, 1605 cm^{-1}, no hydroxyl or acetylenic absorptions; ^1H NMR($CDCl_3$) δ 0.95 (d, 3H, J = 6 Hz, collapsing to a singlet upon irradiation at 1.96), 1.28 (t, 3H, J = 7 Hz, collapsing to a singlet upon irradiation at 3.86), 1.46 - 1.80 (br m, 2H), 1.96 (m, 1H, H-8), 2.12 (s, 3H), 2.24 (m, 2H, H-9's), 3.66 (s, 3H, -OMe), 3.86 (q, 2H, J = 7 Hz, collapsing to a singlet upon irradiation at 1.28), 5.29 (d, 1H, J = 0.5 Hz, collapsing to a sharp singlet upon irradiation at 5.91, H-15), 5.91 (br s, 1H, collapsing to a doublet, J = 3 Hz, upon irradiation at 1.74 and sharpening upon irradiation at 1.60, H-6); ^{13}C NMR($CDCl_3$) 11.8 (q, C-14), 14.9 (q, C-13), 20.8 (q, C-11), 25.1 (d, C-8), 33.5 (t, C-7), 46.6 (t, C-9), 50.7 (q, C-17), 69.5 (t, C-12), 81.4 (d, C-6), 84.6 (d, C-15), 110.3 (s, C-10), 114.7 (s, C-3), 137.5 (s, C-2), 159.2 (s, C-5), 167.9 (s, C-16). The analytical sample crystallized from ether/pet ether in the form of colorless needles, mp 90 - 92° C, which,however rapidly decomposed at ambient temperatures and were unsuitable for X-ray analysis: Anal. calcd. for $C_{15}H_{21}NO_4S$: C, 57.84, H, 6.79, N, 4.52; Found: C, 57.59, H, 6.87, N, 4.23.
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16. Physical and chemical data for compounds 11d and 13d: (a) 11d: pale yellow oil, Rf 0.45 (30% acetone/hexane, silica gel); Mass spectrum, M^+ m/e 295; IR($CHCl_3$) 2205, 1715, 1565 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.01 (d, 3H, J = 6 Hz), 1.35 (t, 3H, J = 7 Hz), 2.20 (s, 3H), 2.57 (m, 3H), 2.76 (m, 2H), 3.39 (s, 3H), 4.02 (q, 2H, J = 7 Hz), 4.25 (s, 2H); Anal. calcd for $C_{15}H_{21}NO_3S$: C, 60.99, H, 7.17, N, 4.74, S, 10.85; Found: C, 60.70, H, 7.40, N, 4.44, S, 10.60. (b) 13d: colorless oil, Rf 0.50 (30% acetone/hexane, silica gel); Mass spectrum, M^+ m/e 254; IR($CHCl_3$) 1660, 1555, 1500 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.14 (d, 3H, J = 6 Hz, collapsing to a singlet upon irradiation at 2.42, $\underline{Me}$-6), 1.42 (t, 3H, J = 7 Hz, collapsing to a singlet upon irradiation at 4.13, $-OCH_2C\underline{H}_3$), 2.30 (dd, 1H, J = 14, 12Hz, collapsing to a doublet, J = 12 Hz, upon irradiation at 2.58, H-7), 2.42 (m, 1H, sharpens upon irradiation at 1.14, H-6), 2.58 (m, 2H, simplifies upon irradiation at either 2.30 or 2.95, H-5' and H-7'), 2.95 (dd, 1H, J = 15, 3 Hz, collapsing to a doublet, J = 3 Hz, upon irradiation at 2.58, H-5), 3.41 (s, 3H, $-CH_2OC\underline{H}_3$), 4.13 (q, 2H, J = 7 Hz, collapsing to a singlet upon irradiation at 1.42, $-OC\underline{H}_2CH_3$), 4.60 (s, 2H, $-C\underline{H}_2OCH_3$). Anal. Calcd. for $C_{13}H_{18}O_3S$: C, 61.39, H, 7.13; Found: C, 61.60, H, 7.25.

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