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Regiocontrol in the 1,3-Dipolar Cycloaddition Reactions of Mesoionic Compounds with Acetylenic Dipolarophiles.

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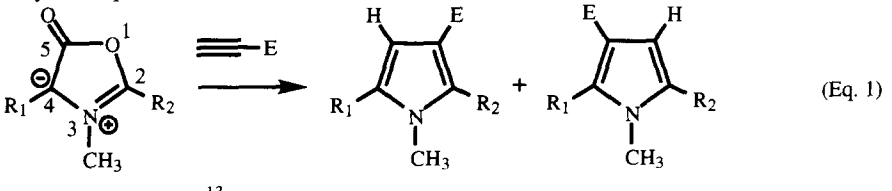
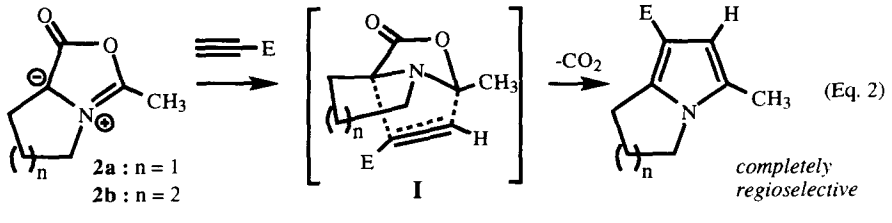
Abstract: The regioselectivity of 1,3-dipolar cycloaddition reactions between mesoionic compounds with singly-tethered substituents is examined. The results with propiolate dipolarophiles are compared with other singly and doubly-tethered examples according to a model using an asynchronous, concerted transition state. The isolation and reaction of a novel, non-aryl substituted mesoionic compound **7** is reported. A regiodirected synthesis starting with *N*-(2-thiazolinyl)proline gives a complementary dihydropyrroline compared with the reaction between *N*-formylproline and alkyl propiolates.

We have been examining factors influencing the regiochemical outcome of 1,3-dipolar cycloaddition reactions of münchnones and related mesoionic compounds with acetylenic dipolarophiles. Previously, we elaborated the conventional Frontier Molecular Orbital (FMO) model to include the synchronicity of the bond formations during the cycloaddition based on differential torsional accessibility of the reacting centers as well as non-covalent interactions between the groups on those centers.[1,2] For example, we interpreted the remarkable difference in regioselectivity between our münchnones **1a-b**[2,3] (Eq. 1) and Pizzorno's **2a-b**[4,5] (Eq. 2) as the ability for the untethered C-2 centers in **2a-b** to become more pyramidalized at the transition state, thereby allowing for a greater degree of bond formation with the ß-carbon of the propiolate dipolarophile. Our view of this transition state structure, which is also supported by previous computational searches, is represented by **I** in Equation 2.



(Eq. 1)

1a : $R_1 = CH_3$, $R_2 = {}^{13}CH_3$	55	:	45	
1b : $R_1 = {}^{13}CH_3$, $R_2 = CH_3$	55	:	45	$E = CO_2CH_3$



(Eq. 2)

completely regioselective

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Our central hypothesis is that the tethering of alkyl substituents on the reacting centers of these mesoionic compounds results in a more mechanical than molecular orbital origin for the regioselectivity. There are three generic cases for tethering substituents. Münchnones **2a-b**, or comparable cases,[6] represent the situation of a C-4 substituent tethered to the mesoionic nucleus. A non-münchnone analogy for this type of tethering might involve replacing the carbonyl oxygen atom with a nitrogen atom, and constructing the compounds where the C-4 substituent is part of a fused ring involving an imidate at C-5 rather than a lactone (Fig. 1). We have previously reported the cycloaddition chemistry of **3a-c** as a second type, where the substituents at both C-2 an C-4 are tethered (Fig. 2). There are a number of other possibilities for a doubly-tethered substrate. We selected the **3a-c** system for convenience of preparation as well as to make the best comparison between the two singly tethered cases. We wish to report here our results with the final member of this generic series, where the C-2 substituent is tethered. We have also completed our first example of a regiodirected synthesis using an intermolecular cycloaddition based on the results from our model compounds.

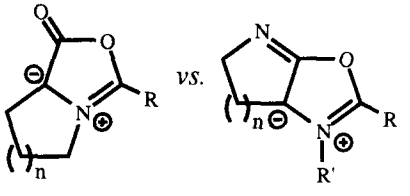
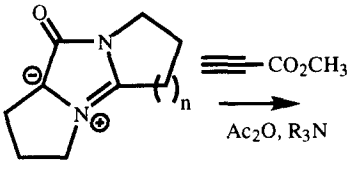


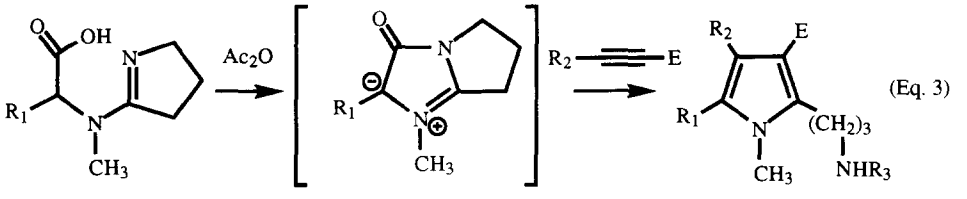
Figure 1. C-4 tethers



3a-c : n = 1-3

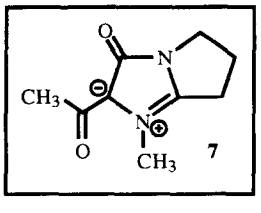
Figure 2. C-2 and C-4 tethers

We prepared *N*-(2-pyrrolinyl)-*N*-methylalanine **4a** and *N*-(2-pyrrolinyl)sarcosine **4b** by the same method we reported for the corresponding proline derivatives used to produce **3a-c**.[1] Under standard cycloaddition conditions [0.5-0.6 M **4a** or **4b** in Ac_2O or Ac_2O/toluene; 65-75°C, 2-4 hr; stoichiometric to a 3-fold excess of dimethyl acetylenedicarboxylate (DMAD) or methyl propiolate; 0.01 mL triethylamine or Hünig's base], **4a** and **4b** give **5a-b** and **6a-b**, respectively, in good yields and with complete regioselectivity (where applicable) by spectroscopic criteria (Eq. 3).



4a : $R_1 = CH_3$
4b : $R_1 = H$

$E = CO_2CH_3$

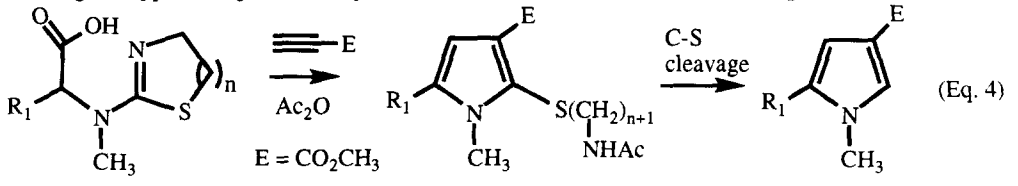


7

5a : $R_1 = CH_3$, $R_2 = E$, $R_3 = Ac$ (74%)
5b : $R_1 = CH_3$, $R_2 = H$, $R_3 = Ac$ (71%)
6a : $R_1 =$ Ac, $R_2 = E$, $R_3 = Ac$ (50%)
6b : $R_1 =$ Ac, $R_2 = H$, $R_3 = Ac$ (25%)
8 : $R_1 =$ Ac, $R_2 = H$, $R_3 = E$ (75%)

Acetylation of the mesoionic intermediate derived from **4b** to give **6a-b** is precedented.[7] In the case of **4b**, no products derived from the expected C-4(H) intermediate were observed with either DMAD or methyl propiolate. Surprisingly, we were able to isolate the C-4(acetyl) mesoionic compound **7** as a stable, crystalline solid (**4b** heated at 65°C in Ac_2O for 30 min.; 81% yield of an orange solid from ether; m.p.-dec. 169°C). It is unusual to isolate a mesoionic compound that does not have at least one appended aryl ring. Heating **7** with methyl propiolate in refluxing toluene for 4 days,[8,9] followed by treatment with methanol to derivatize the isocyanate released in the cycloreversion step that makes the pyrrole, gives the methyl carbamate **8** analogous to the amide **6b** that is formed in the *in situ* reaction. *In both reactions with methyl propiolate, the regioselectivity follows our prediction that the center with the untethered substituent will preferentially combine with the β-carbon of the unsaturated ester.*

Our first conception of a tether-based regiocontrol strategy for synthesizing 2,4-disubstituted pyrroles is shown in Equation 4. By starting with *N*-(2-thiazolinyl) secondary amino acid derivatives, we imagined that the cycloadditions would give the same high regioselectivities as the *N*-(2-pyrrolinyl) compounds. Subsequent cleavage of the carbon-sulfur bond would result in the formation of the pyrrole regioisomer shown, representing the opposite regioselectivity from that which is observed from the analogous münchnones.[1,2]

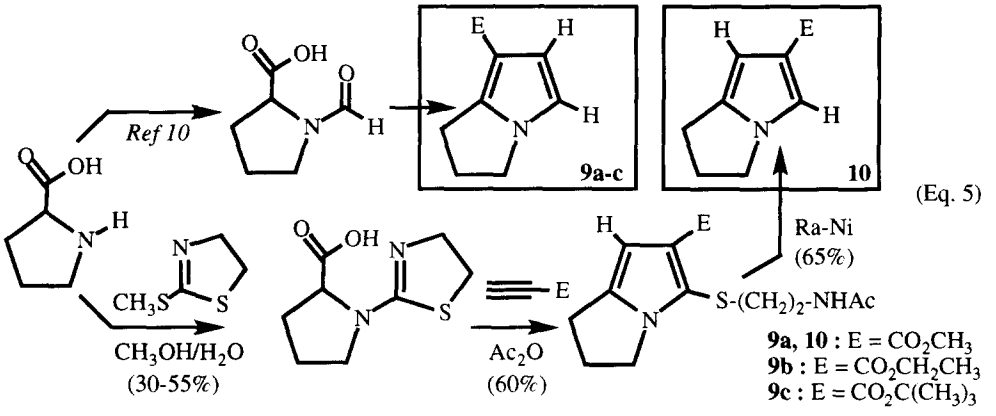


(Eq. 4)

We selected *N*-(2-thiazolinyl)proline as our initial example because it would result in the dihydropyrroline **10** that is regiocomplementary to the Pizzorno product **9b** (from *N*-formylproline,[10] analogous to *N*-acetylproline **2a**). Hence, proline was combined with commercially available 2-(methylthio)thiazoline to give N-(2-thiazolinyl)proline. Cycloaddition with DMAD and methyl propiolate proceeded smoothly under standard conditions. Raney-nickel hydrogenolysis of the propiolate cycloadduct gave 65% of **10** as a single regioisomer as detectable by spectroscopic criteria (Eq. 5).

Because the cycloaddition reaction of the münchnone derived from *N*-formylproline was reported with ethyl propiolate, we repeated the literature procedure with methyl propiolate in order to definitively compare the actual regiocomplementary compounds. Surprisingly, the reaction mixture from the first cycloaddition we conducted with methyl propiolate was less regioselective than all of the literature reports of this and similar compounds. In our hands, 85% of the product in our initial cycloaddition experiment with methyl propiolate corresponded to **9a** (analogous to the reported **9b**),[10] while the other 15% corresponded to the regioisomer **10** that we had already prepared by the *N*-(2-thiazolinyl)proline route. Dubious that the change from the ethyl ester (used by Pizzorno and others) to the methyl ester could produce such an effect, we performed multiple runs of the cycloaddition reactions using *N*-formylproline with methyl (giving 82-88% **9a**), ethyl (86-89% **9b**) and t-butyl (90-92% **9c**) propiolates. While we cannot reconcile the previous reports of complete regioselectivity in the case of ethyl propiolate, we do find additional support for our unsymmetrical transition state model[1,2] in the observation of a slightly higher selectivity from t-butyl propiolate compared with the other two dipolarophiles.

Finally, we attempted to prepare the *N*-thiazolinyl derivatives of six *N*-methylamino acids in order to provide additional examples. With sarcosine, only a small amount (ca. 5%) of the corresponding *N*-thiazolinyl derivative is observed spectroscopically, and even less can be isolated from the unreacted starting materials. Preliminary experiments using this compound did not give substantial evidence for the formation of pyrroles beyond preliminary TLC characteristics, and we were wary of slow cycloadditions and acetylation-based side reactions because of our previous experience with a sarcosine derivative. With *N*-methylalanine, only a trace of the thiazolinyl derivative was observed spectroscopically, but none could be isolated. With *N*-methylvaline, *N*-methylleucine, *N*-methylisoleucine and *N*-methylphenylalanine, no evidence for the thiazolinyl derivative was observed. In each case, the unreacted starting materials were completely recovered. None of the many reaction conditions and structural modifications we have attempted has yielded satisfactory results to date. The difference in reactivity between proline and other secondary amino acids is certainly precedented,[11,12] and so far this differentiation with 2-(methylthio)thiazoline has been nearly absolute. We have begun to examine alternative strategies for the synthesis of non-proline *N*-thiazolinyl secondary amino acid derivatives, and these results will be reported in due course.



(Eq. 5)

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