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1,3-Dipolar Cycloadditions of Trimethylsilyldiazomethane Revisited: Steric Demand of the Dipolarophile and the Influence on Product Distribution

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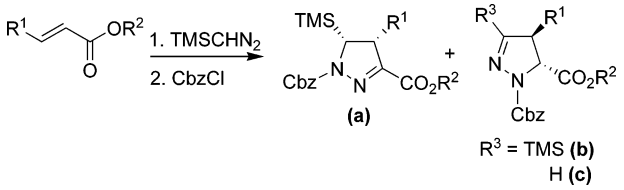
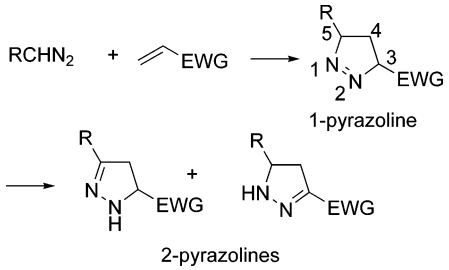


The 1,3-dipolar cycloaddition of trimethylsilyldiazomethane with α,*β*-unsaturated esters was examined. The resulting 1-pyrazolines isomerize to regioisomeric 2-pyrazolines (**a** or **b**) or undergo desilylation (**c**). Acrylates yield only **b** or **c**. *β*-Substituted dipolarophiles may yield all three types of products. This work demonstrates that the distribution of 2-pyrazoline products is highly dependent on the relative configuration of the substituents on the 1-pyrazoline intermediate.

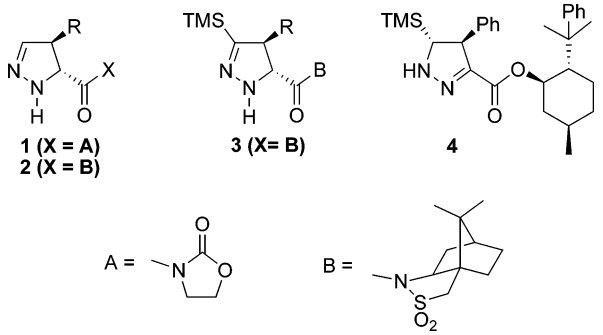
Trimethylsilyldiazomethane has been most frequently used as a source of carbene for cyclopropanation reactions[1] and has enjoyed only limited synthetic utility in 1,3-dipolar cycloadditions. In fact, Seyferth et al. reported that among a series of dipolarophiles examined, only acrylonitrile reacted with TMS diazomethane to produce a cycloadduct in a synthetically useful yield.[2,3] Recently, with its commercial availability, TMS diazomethane has become somewhat more popular as a synthetic reagent, particularly in the preparation of novel amino acid analogues.[4,5]

1,3-Dipolar cycloadditions of diazoalkanes and alkenes yield 1-pyrazolines. In most instances, when the dipolarophile is an α,*β*-unsaturated ester, HOMO−LUMO interactions dictate that the regioselectivity is such that the carbon atom of the diazoalkane attacks the *β*-carbon of the ester (Scheme 1). 1-Pyrazolines tend to be unstable and isomerize to the 2-pyrazolines with the regioselectivity of the isomerization dependent on the substituents. When the dipolarophile is an α,*β*-unsaturated carbonyl compound, isomerization typically yields the conjugated 2-pyrazoline.[6,7]

SCHEME 1. 1,3-Dipolar Cycloaddition of Diazoalkanes Followed by Isomerization Yields 2-Pyrazolines



A survey of the recent literature indicates that the regioselectivity of the double bond isomerization of TMS-substituted 1-pyrazolines does not always follow the typical course and is, at first glance, unpredictable. Carreira, Kanemasa, and coworkers have reported the 1,3-dipolar cycloaddition of TMSCHN$_2$ with camphorsultam and oxazolidinone derivatives, respectively.[4,5,8,9] These 1-pyrazoline products undergo proteodesilylation to yield 2-pyrazolines (**1** and **2**) or loss of the proton α to TMS (**3**). On the other hand, Barluenga et al.[10] recently described the cycloaddition of the menthol ester of *trans*-cinnamic acid to produce the conjugated 2-pyrazoline, with retention of the TMS group (**4**).



In an effort to develop a mechanistic rationale for the cycloaddition/isomerization process, which could account for the products obtained, we undertook a systematic survey of 1,3-dipolar cycloadditions between TMS diazomethane and α,*β*-unsaturated esters. The dipolarophiles vary in terms of the size of the ester group and the substituents at the *β*-carbon. The results of these studies are summarized in Table 1. Because 1- and 2-pyrazolines oxidize readily to pyrazoles, the cycloaddition products were immediately converted to the Cbz (benzyloxy-

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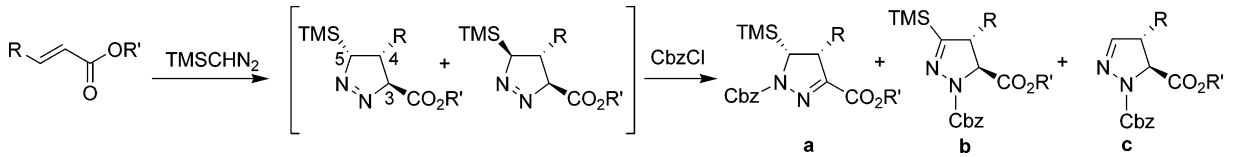
TABLE 1. 1,3-Dipolar Cycloadditions of TMS Diazomethane and Various Dipolarophiles



entry	compd	R	R'	cycloaddition conditions	% yield[a]	product ratio **a**:**b**:**c**	relative configuration of 1-pyrazoline (3,5-*trans*/3,5-*cis*)
1	**5**	H	Me	2 equiv of $TMSCHN_2$, $PhCH_3$/hexane (1:1), rt, 8.5 h	20[b]	0:60:40	not determined
2	**6**	H	Et	1.5 equiv of $TMSCHN_2$, C_6H_6/hexane (1:1), rt, 24 h	90	0:35:65	50:50
3	**7**	H	*t*-Bu	1.2 equiv of $TMSCHN_2$, C_6H_6/hexane (1:1), rt, 24 h	71	0:44:56	50:50
4	**8**	H	Mt[c]	1.5 equiv of $TMSCHN_2$, C_6H_6/hexane (1:1), rt, 24 h	50	0:45:55	50:50
5	**9**	Me	Et	3 equiv of $TMSCHN_2$, C_6H_6/hexane (1:1), reflux, 8.5 h	40	0:37:63	6:94
6	**9**	Me	Et	3 equiv of $TMSCHN_2$, toluene, reflux, 8.5 h	49	16:16:68	50:50
7	**10**	Me	*t*-Bu	2 equiv of $TMSCHN_2$, C_6H_6/hexane (1:1), reflux, 8 h	47	0:76:24	not determined
8	**11**	Me	Mt	2 equiv of $TMSCHN_2$, C_6H_6/hexane (1:1), reflux, 8 h	62	0:5050	not determined
9	**12**	Ph	Et	2 equiv of $TMSCHN_2$, C_6H_6/hexane (1:1), rt, 8 h	7.5	5:20:75	7:93
10	**12**	Ph	Et	2 equiv of $TMSCHN_2$, C_6H_6/hexane reflux, 8 h		complex mixture	not determined
11	**13**	Ph	*t*-Bu	2 equiv of $TMSCHN_2$, C_6H_6/hexane (1:1), reflux, 8 h	35	11:33:56	10:90
12	**13**	Ph	*t*-Bu	2 equiv of $TMSCHN_2$, toluene, reflux, 8.5 h	45	43:43:14	50:50
13	**14**	Ph	Mt	2 equiv of $TMSCHN_2$, C_6H_6/hexane (1:1), reflux, 8 h	71	24:0:76	100:0 (2-pyrazoline)

[a] Isolated yield. [b] Yield based on acryloyl chloride. [c] Mt = menthyl.

carbonyl) derivatives of the 2-pyrazolines for characterization. However, we were able to observe the 1- or 2-pyrazolines by ^1H NMR. This allowed us to make assignments of relative configurations of the cycloadducts.

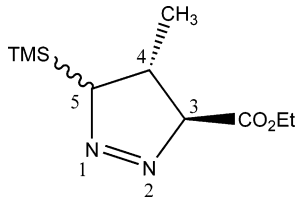
As shown in Table 1, three products may be obtained from the isomerization of the intermediate 1-pyrazoline: the conjugated 2-pyrazoline (**a**), isomerization with loss of the proton α to the TMS group (**b**), or the desilylation product (**c**). In contrast to earlier reports, we found that the acrylates react with $TMSCHN_2$ at ambient temperature to provide cycloadducts in good to excellent yield (entries 1−4). Products **b** and **c** were formed exclusively and with little selectivity. The *β*-substituted dipolarophiles (entries 5−13) require elevated temperatures or extended reaction times to provide cycloadducts in moderate yields. Previous reports have indicated that the 1,3-dipolar cycloaddition with TMS diazomethane is suprafacial with respect to the dipolarophile,[4,5,8,9] and our data are consistent with this as well. The crotonate esters, like the acrylates, yield products **b** and **c** when the cycloaddition reaction is performed in refluxing benzene/hexane (entries 5, 7, and 8). However, the product distribution appears to be highly sensitive to the temperature of the cycloaddition, as performing the reaction with ethyl crotonate in refluxing toluene yields a mixture of **9a**, **9b**, and **9c** upon protection (entry 6). Under reflux in benzene/hexane, ethyl cinnamate produces a complex mixture of at least eight products (entry 10). However, a mixture of **12a**, **12b**, and **12c** could be isolated in poor yield after performing the reaction at room temperature (entry 9). Ethyl and *t*-butyl cinnamates (entries 9−12) behave like the crotonates, in that products **12b/13b** and **12c/13c** are formed predominantly with the proportion of **12a** and **13a** increasing with increasing temperature (entries 11 and 12). Surprisingly, in refluxing benzene/hexane, menthyl cinnamate yields a mixture of **14a** and **14c** with no **14b** observed (entry 13).

While we were unable to isolate 1-pyrazolines, in most cases they could be observed by ^1H NMR immediately after the cycloaddition step. The only exception to this was menthyl cinnamate, in which we observed a 2-pyrazoline (vide infra). Therefore, we can conclude that (with this single exception) the isomerization does not take place until the protection step. Furthermore, as the isomerization/protection step was performed under identical conditions in all examples, we must conclude that the regioselectivity of the isomerization is dependent on the distribution of the stereoisomeric 1-pyrazolines formed in the cycloaddition step. These observations prompted us to examine the distribution of 1-pyrazolines more carefully.

Analysis of the crude reaction mixtures of acrylates (entries 2−4) with $TMSCHN_2$ by ^1H NMR revealed the presence of 3,5-*cis* and 3,5-*trans* 1-pyrazoline cycloadducts, in an approximate 1:1 ratio. Apparently, the size of the ester group has little influence on the relative configuration of the newly generated stereocenters, at least not for the acrylates. We assume that both the *cis* and *trans* isomers lead to products **b** and **c**, although we cannot be certain about this as we were unable either to separate the *cis* and *trans* 1-pyrazolines or to prepare one isomer selectively.

In contrast to the acrylates, the ^1H NMR of the 1-pyrazoline derived from the cycloaddition of ethyl crotonate and $TMSCHN_2$

TABLE 2. Difference NOE of 1-Pyrazoline, Ethyl 4-Methyl-5-(trimethylsilyl)-4,5-dihydro-3*H*-pyrazole-3-carboxylate (the Major Isomer from the Cycloaddition in Refluxing Benzene/Hexane)



	irradiate	
observe	H-4 (%)	4-CH_3 (%)
H-3 (δ 4.73)	2	4
H-4 (δ 2.16)		4
H-5 (δ 3.95)	2	3
4-CH_3 (δ 1.03)	15	
TMS (δ 0.14)	5	0

in refluxing benzene/hexane indicated the presence of a mixture of cycloadducts in a ratio of 6:94 (entry 5). It is often difficult to assign relative configurations of five-membered rings on the basis of coupling constants alone. In fact, Macromodel[11] predicts nearly the same ^{1}H coupling constants for the 4,5-*cis* and 4,5-*trans* 1-pyrazolines. The assignment of relative configurations for the major 1-pyrazoline was based on difference NOE (Table 2). Irradiation of H-4 produces an NOE of 5% at the TMS group and the same NOE (2%) at H-3 and H-5. Since H-3 and H-4 must be *trans*, this suggests that H-4 and H-5 are also *trans*. Additionally, irradiation of the methyl group produces essentially the same NOE (3.8 and 3.3%) at both H-3 and H-5 and results in no NOE for TMS. These observations indicate that the relative configuration of the major 1-pyrazoline is 3,4-*trans*-4,5-*trans* and the minor 1-pyrazoline is 3,4-*trans*-4,5-*cis*. When the cycloaddition is performed with ethyl crotonate in refluxing toluene (entry 6), the stereoisomeric 1-pyrazoline cycloadducts are observed, in a ratio of 1:1. On the basis of the isolation of **9a** from this mixture of 1-pyrazolines, we conclude that only the 3,4-*trans*-4,5-*cis* isomer gives rise to product **9a**. As with ethyl crotonate, ^{1}H NMR revealed that a major 1-pyrazoline cycloadduct is produced with ethyl cinnamate at room temperature (entry 9). By analogy with ethyl crotonate, and because this also yields predominantly protected 2-pyrazolines **12b** and **12c**, the major cycloadduct was assigned the 3,4-*trans*-4,5-*trans* relative configuration. Both ethyl and *t*-butyl cinnamate produce predominantly one stereoisomeric 1-pyrazoline (entries 9 and 11), and for *t*-butyl cinnamate, the percentage of the minor cycloadduct increases at elevated temperature (entry 12) as does the proportion of **13a**.

Menthyl cinnamate behaved differently from all other dipolarophiles. We were unable to observe the 1-pyrazoline cycloadduct. Instead, the ^{1}H NMR taken immediately after the cycloaddition step indicated that isomerization to the 2-pyrazolines had occurred. Due to the additional stereocenter in the menthyl group, two stereoisomeric 2-pyrazolines were formed in a ratio of 1.7:1. While we were unable to assign relative configurations for any of the 1-pyrazolines or protected 2-pyrazolines on the basis of coupling constants, we were able to make

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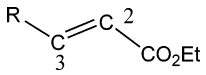
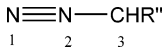
TABLE 3. Energies (eV) of HOMO and LUMO and Largest Atomic Contribution to LUMO for Selected Dipolarophiles



R	E_{HOMO}	E_{LUMO}	a(C-2)	a(C-3)
H	−7.8	−1.6	0.79	0.36
Me	−7.5	−1.3	0.78	0.35
Ph	−6.7	−2.1	0.47	0.37

TABLE 4. Energies of HOMO and LUMO and Largest Atomic Contributions to HOMO for Selected Diazo Compounds



compd	E_{HOMO}	E_{LUMO}	a(N-1)	a(N-2)	a(C-3)
CH_2N_2	−6.3	−1.3	0.68	0.04	1.09
$TMSCHN_2$	−6.1	−1.6	0.75	0.04	1.14

the assignment from the unprotected 2-pyrazoline which corresponds to **14a**. A 12 Hz coupling constant between H-4 and H-5 in both isomers indicated that these cycloadducts had the 3,4-*trans*-4,5-*cis* relative configuration. Additionally, hydrogenolysis of purified **14a** was identical to the 2-pyrazoline observed after the cycloaddition.

From our observations, we conclude that the cycloaddition of acrylates is not stereoselective. However, the introduction of a β-substituent on the dipolarophile increases steric demand in the transition state and dictates that TMS be *trans* to the β-substituent in the preferred cycloadduct. The selectivity for the 4,5-*trans* cycloadduct is diminished with elevated temperature and increased size of the ester group. The influence of the increasing size of the ester group is seen earlier for the cinnamates when compared to the crotonates, as the planar phenyl group is less sterically demanding. For menthyl cinnamate, the influence of the phenyl group is entirely overcome by the large menthyl ester resulting in the exclusive formation of the 4,5-*cis* relative configuration.

It is also interesting to note that, when the cycloaddition of ethyl cinnamate is attempted in refluxing benzene/hexane, a complex mixture of at least eight products is obtained. Yet, both *t*-butyl and menthyl cinnamate gave the typical two or three products. While we did not attempt to purify the products from the mixture obtained from ethyl cinnamate, we suggest that the additional products arise from alternative regioisomers. These different behaviors may be attributed to a competition between stereoelectronic and steric influences. FMO calculations demonstrate that having a phenyl group as β-substituent on the dipolarophile can diminish the regioselectivity of cycloaddition. Attack by the carbon atom of the diazoalkane at the α-carbon of the ester becomes competitive with attack at the β-carbon. Tables 3 and 4 give energies and atomic contributions for the HOMO and LUMO of dipolarophiles ethyl acrylate, ethyl crotonate, ethyl cinnamate, diazomethane, and $TMSCHN_2$ calculated at the B3LYP/TZVP level. In all cases, the dominant interaction is between the HOMO of the diazo compound and the LUMO of the dipolarophile. The LUMO energies are relatively insensitive to dipolarophile's substituents. However, the atomic contributions to the LUMO are sensitive to the dipolarophile's β-substituent. For **6** and **9**, the contribution of C-2 to the LUMO is about twice that of C-3. Since the dominant

contribution to the HOMO of $TMSCHN_2$ is from C-3, the principle of maximum overlap leads to the observed regioselectivity. However, in the case of **12**, the contributions of C-2 and C-3 to the LUMO are nearly equal, although C-2 still makes the larger contribution (0.47 versus 0.37). Thus, at low temperature (Table 1, entry 9), C-2 still dominates and the regioselectivity is the same as for **6** and **9**; but at higher temperature (entry 10), C-3 is able to compete with C-2 and both regioisomers are observed, leading to a large number of products. We note that when all orientations for cycloaddition are considered, eight distinct 2-pyrazolines can be formed upon isomeration and possible loss of TMS.

This behavior is not observed for larger ester groups (O-*t*-Bu or OMt rather than OEt) in combination with a phenyl group as R. Apparently, the steric interaction between TMS and the larger esters sufficiently disfavors alternative regioisomers that the stereoelectronic leveling influence of the phenyl substituent is not observed.

In summary, we have demonstrated that the steric demand of the dipolarophile influences the relative stereochemistry of 1,3-dipolar cycloaddition reactions with $TMSCHN_2$. In turn, the distribution of stereoisomeric 3,4,5-trisubstituted 1-pyrazolines has a profound influence on the outcome of the isomerization step. These steric effects are absent in the cycloaddition of acrylates, and only products **b** and **c** are formed. One can rationalize that the isomerization to products of type **a** would be disfavored as this would increase torsional strain between the substituents. However, for β-substituted dipolarophiles, the β-substituent will generally prefer to be *trans* to TMS unless the ester group is large. The 3,4-*trans*-4,5-*trans* 1-pyrazolines isomerize to a mixture of the **b** and **c** type products, whereas the 3,4-*trans*-4,5-*cis* 1-pyrazolines isomerize to a mixture of **a** and **c**. The reasons for this preference are as yet unclear and are currently under investigation. However, it is now apparent that the product distribution may be controlled through the appropriate choice of ester.

Experimental Section

General Procedure for Cycloaddition/Protection Reactions. Cycloaddition reactions were performed under the conditions described in Table 1. Upon completion, the solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2. Carbobenzyloxy chloride (1.1 equiv) and a solution of $NaHCO_3$ (1.5 equiv) in H_2O were sequentially added to the solution of the 1-pyrazoline at room temperature. The resulting mixture was stirred at room temperature overnight. The organic layer was extracted with CH_2Cl_2 (3×15 mL), dried over Na_2SO_4, and filtered. Solvents were evaporated under reduced pressure, and the residue was purified by automated flash, gravity, or radial chromatography over silica gel with hexane/ethyl acetate 4:1 as eluants.

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Supporting Information Available: Spectroscopic data (^1H NMR, ^{13}C NMR, and HRMS) and copies of ^1H NMR and ^{13}C NMR spectra for all protected 2-pyrazolines and for representative 1-pyrazolines. This material is available free of charge via the Internet at http://pubs.acs.org.

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