HOW REGIOSELECTIVE ARE 1,3-DIPOLAR CYCLOADDITIONS WITH CARBONYL YLIDES ?

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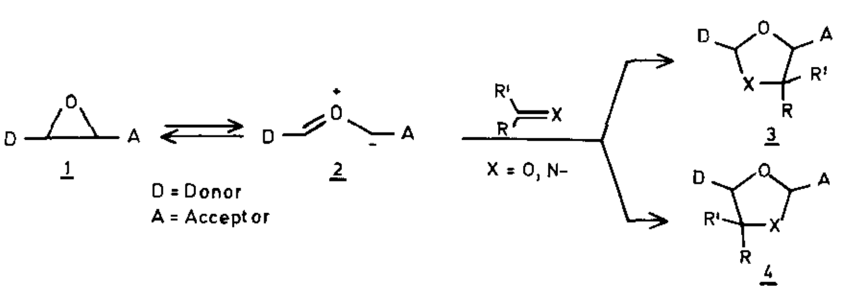
Abstract- Several cycloaddition reactions of asymmetrically substituted carbonyl ylides are described.

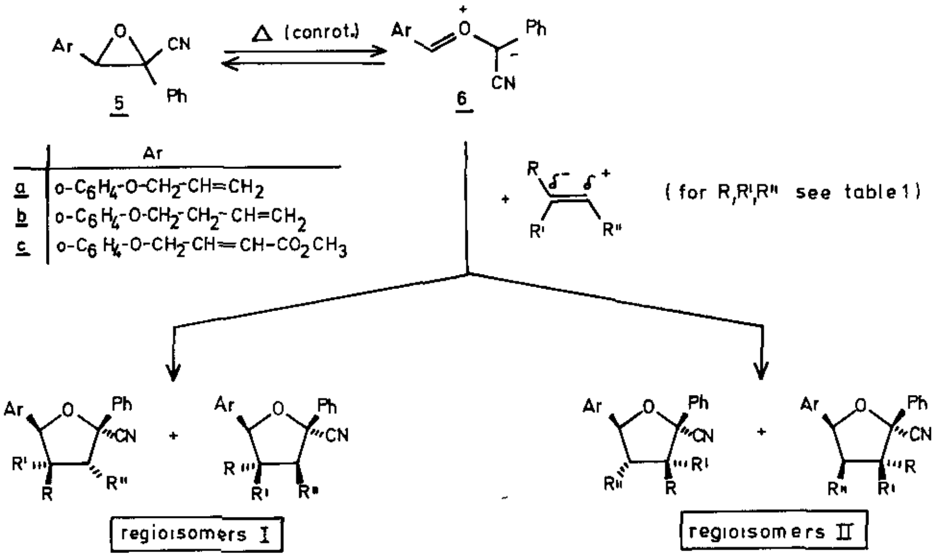
Although 1,3-dipolar cycloaddition reactions have been successfully employed for decades in organic chemistry [1], it is only within the last ten years that a better understanding of the phenomena reactivity/stereoselectivity/regioselectivity has begun to emerge [2]. For instance, the preferential formation of certain regioisomers may be obvious in many cases by considering electronic and steric effects, but a consistent explanation of the orientation has been made possible applying MO perturbation theory which predicts bonding between the atoms with the larger and smaller coefficients, respectively [2-5].

The regiochemical course during the cycloaddition of carbonyl ylides has been studied mainly with heteronuclear double bonds as ene-components. These experiments have shown that the reactions with asymmetrically substituted carbonyl ylides of type 2 give , indeed, rise to the exclusive formation of compounds with structure 3 (X = O [6], X = N– [7]). To the best of our knowledge it is only isobutene which has been used as a C=C-dipolarophile up to now: studying the photochemistry of several aryl-cyano-substituted epoxides, Griffin and coworkers observed the formation of compounds of type 3 as the only cycloadducts, too [8].



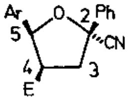
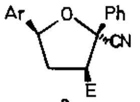
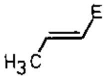
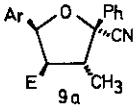
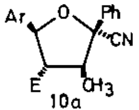
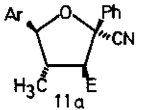
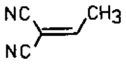
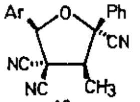
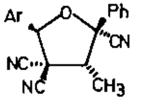
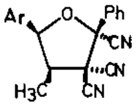
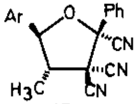
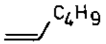
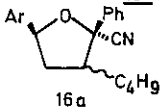
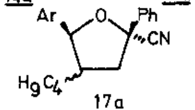
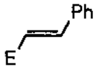
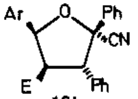
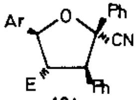
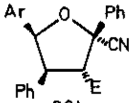
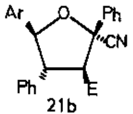
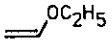
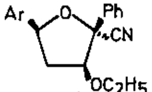
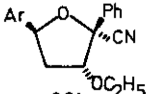
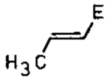
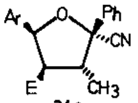
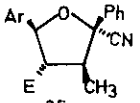
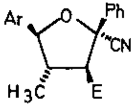
With regard to our continuing interest in intramolecular cycloaddition reactions of carbonyl ylides [9], which lead to annelated and/or bridged products [10], we required further informations concerning the addition mode of some other dipolarophiles containing a polarized C=C-bond.

Therefore we have studied several model reactions using the trisubstituted oxiranes 5a-c as precursors of the dipoles 6a-c, which undergo competitive intramolecular addition only in the case of compound c to a larger extend, and electron deficient as well as electron rich dipolarophiles. The reaction conditions and the product distribution are summarized in table 1, the regioisomers I and II representing the "expected" and "unexpected" cycloadducts, respectively (accounted for on the basis of theoretical considerations [2-5]).



For identification the desired products were separated by thin layer chromatography from excess of starting materials, polymer fractions and possibly formed intramolecular cycloadducts (see footnotes [d-g] in table 1), and the resulting isomer mixtures were subsequently analyzed by means of ^{1}H-nmr spectroscopy. Structure elucidation for the 1:1-adducts could be easily performed with the exception of 16a and 17a, for which the stereochemistry of the butyl groups is still ambiguous. The structural and sterical assignments have been met on the following basis (see table 2): (i) The cis-arrangement of the aryl substituents at C-2/C-5 follows from the configuration of the 1,3-dipoles 6 in which the

Table 1. Intermolecular Cycloadducts of the Oxiranes 5a-c [a]

Run	Oxirane	Dipolarophile (Equiv.)	Reaction-Temp./Time (Convers.)	Yield	Cycloadducts			
					Regioisomers I [b]	Regioisomers II [b]	Ratio of Adducts	I:II
1	5a	 (11.1)	120°C/8h (64%) [c]	90%	 7a	 8a	50: 50	50:50
2	5a	 (5.0)	120°C/8h (95%)	92%	 9a  10a	 11a	66: 4:30	70:30
3	5a	 (3.5)	120°C/8h (50%) [c]	93%	 12a  13a	 14a  15a	39:45: 6:10	84:16
4	5a	 (16)	170°C/9h (75%)	33% [d]	 16a	 17a	81 : 19	81:19
5	5b	 (1.7)	170°C/7h (100%)	78% [e]	 18b  19b	 20b  21b	56:11:17:16	67:33
6	5b	 (21)	220°C/6h (100%)	74% [f]	 22b  23b		50:50	100: 0
7	5c	 (9.4)	170°C/5h (100%)	38% [g]	 24c  25c	 26c	61:13:26	74:26

$E = CO_2CH_3$

[a] Reactions without solvents in sealed tubes. [b] See text. [c] Partial polymerisation of the dipolarophile.
[d] 15% intramol. adduct 9a . [e] 4% intramol. adduct 9a . [f] 7% intramol. adduct 9b. [g] 60% intramol. adduct 10.

favorable *exo*,*exo*-position of the bulky substituents is a consequence of conrotatory ring opening [11-13]. (ii) Amongst the ring protons, 5-H appears at lowest field in the ^{1}H-nmr spectrum due to the combined deshielding effects of the aryl and ether functions (δ = 6.21 - 5.41). (iii) The regiochemistry of the addition products 7a,8a, 12a-15a, 16a,17a and 22b,23b can be easily deduced from the multiplicity of the 5-H signals. In the case of 9a-11a and 24c-26c the differentiation is based upon the reasonable assumption that the proton which is located in geminal position to an ester group gives rise to a signal at lower field. The respective arrangement of the adducts 18b-21b has been determined by ^{13}C-nmr spectroscopy. (iv) Due to the high flexibility of the tetrahydrofuran ring [12,14] coupling constants are not very helpful in stereochemical assignments. However, an important argument in favor of the proposed structures comes from the well known anisotropy effects of aryl groups in five-membered rings which cause significant shielding on *cis*-vicinal nuclei (*i.e.* on protons directly attached to the ring carbon atom as well as on hydrogens of adjacent methyl and ester groups, respectively) [12,14,15].

Summing up the results of our cycloaddition experiments (see table 1), three observations deserve special consideration:

1) The addition rate of electron deficient olefins (run 1-3, 5, 7) is markedly greater than in the case of electron rich dipolarophiles (run 4, 6); by far the slowest process is the reaction of 5b with ethyl vinyl ether . Apparently, these cycloadditions correspond to "type I" of Sustmann's notation [4] (*i.e.* the reactions are HOMO (dipole)/ LUMO (ene) controlled).

2) The reactions with dipolarophiles containing π -substituents take place with high stereoselectivity (see run 1, 2, 5, 7). The *syn*-preference in these cases is in complete agreement with analogous cycloadditions and probably due to secondary orbital interactions [5].

3) A surprising outcome of our investigations is the fact that the regioselectivity of the 1,3-dipolar cycloadditions with electron poor olefins is relatively small. The ratio amounts to 50:50 (that means no preference) for the reaction of acrylic ester (run 1), and reaches a maximum value with 84:16 in the case of the strongly polarized dicyanopropene (run 3). On the other hand, reaction of 5a with 1-hexene, a weakly polarized electron rich olefin, affords the isomer I with a 81:19 predominance over II, while the "expected" regioisomer I is formed

exclusively using ethyl vinyl ether (run 6).

In conclusion, our experiments have shown that the regioselectivity of cycloadditions with carbonyl ylides of type 6 is high in the case of electron rich olefins, but relatively small with electron deficient ene components.

Table 2. ^{1}H-nmr Data of the Cycloadducts 7-26 [a]

Adduct	δ - Values [b]							$J_{H,H}$ (Hz)	
	3a-H	3b-H	4a-H	4b-H	5-H	CH_3	CO_2CH_3	3,4	4,5
7a	2.87	3.01		3.84	5.93		3.12	6.0[c],9.0[d]	7.9
8a		3.92	2.38	2.88	5.71		3.10	8.0[e],8.5[f]	9.8[g],6.2[h]
9a	3.03			3.39	5.86	1.26	3.14	9.0	9.0
10a		i)	i)		5.78	0.63	3.69	i)	8.0
11a		3.52	2.77		5.41	1.15	3.15	9.0	10.0
12a		3.78			6.03	1.01			
13a	2.92				6.13	1.58			
14a				i)	i)	1.12			i)
15a			3.22		5.58	1.67			7.5
16a[j]	2.8	—	—	3.0	5.60				9.0[g],5.5[h]
	2.8	—	—	3.0	5.66				8.5[g],4.5[h]
17a	2.8	—	—	3.0	5.85				7.0
18b	4.15			4.15	6.21		3.10	$\lvert J_{3,5}+J_{4,5}\rvert$ = 8.5	
19b		4.70	3.53		5.99		3.61	9.5	9.5
20b	3.65			4.61	6.04		3.76	7.5	7.5
21b		4.15	4.15		5.93		3.10	k)	k)
22b		4.43	1.96	3.06	5.59			4.0[e],7.0[f]	8.0[g],8.0[h]
23b	4.0		2.22	2.65	5.72			7.5[e],7.5[f]	7.5[g],7.5[h]
24c	3.07			3.48	6.02	1.32	3.21	9.0	9.0
25c		i)	3.42		5.90	0.73	3.86	7.2	7.2
26c		3.64	2.88		5.49	1.21	3.21	9.0	9.0

[a] Taken from the spectra (250 MHz, $CDCl_3$) of the respective isomer mixtures. [b] The protons a (b) are located cis (trans) with respect to the aryl and phenyl substituents at C-2/C-5. [c] $J_{3a,4}$. [d] $J_{3b,4}$. [e] $J_{3,4a}$. [f] $J_{3,4b}$. [g] $J_{4a,5}$. [h] $J_{4b,5}$. [i] Signals covered. [j] 2 isomers. [k] Complex splitting pattern.

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