

AUXILIARY-CONTROLLED SITE SELECTIVITY
[4+2] CYCLOADDITION REACTIONS OF α,β -UNSATURATED
CARBONYL COMPOUNDS TO 4,4-BIS-(TRIFLUOROMETHYL)-
SUBSTITUTED HETERO-1,3-DIENES

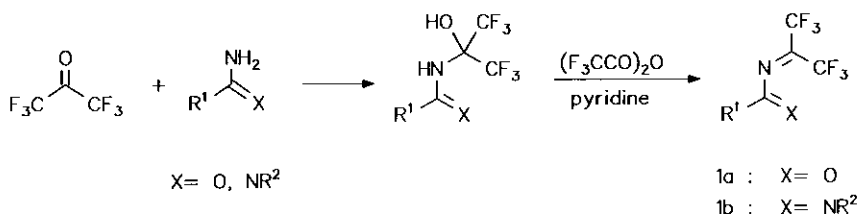
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Dedicated to Professor Alan R. Katritzky on the
 occasion of his 65th birthday

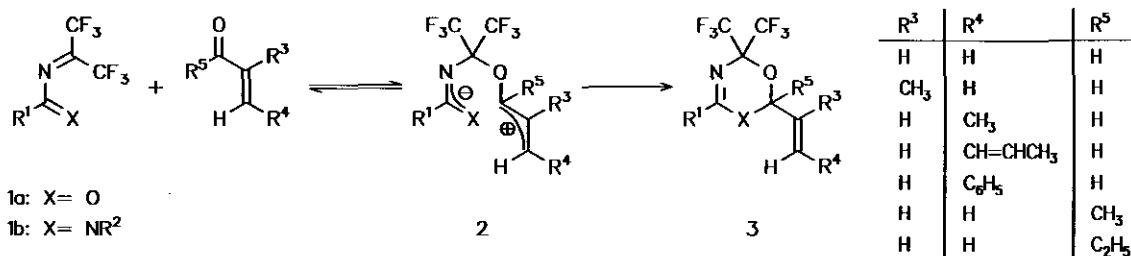
Abstract - [4+2] Cycloaddition reactions of α,β -unsaturated carbonyl compounds to 4,4-bis(trifluoromethyl)-1-hetero-3-azabuta-1,3-dienes occur exclusively across the carbon-oxygen double bond. A complete change of site selectivity is observed in the presence of equimolar amounts of 4-dimethylaminopyridine (DMAP).

4,4-Bis(trifluoromethyl)-1-oxa-3-azabuta-1,3-dienes (**1a**) ($X = O$) and 4,4-bis(trifluoromethyl)-1,3-diazabuta-1,3-dienes (**1b**) ($X = NR^2$) are readily available on reaction of carboxamides or amidines with hexafluoroacetone and subsequent elimination of water on treatment with trifluoroacetic acid anhydride/pyridine in ether.^{1,2}



4,4-Bis(trifluoromethyl)substituted hetero-1,3-dienes (1) are highly electron deficient species. Their polarity pattern causes reaction behaviour similar to 1,4-dipoles. Cycloaddition reactions readily occur with electron-rich as well as with electron-poor dienophiles.³⁻⁸

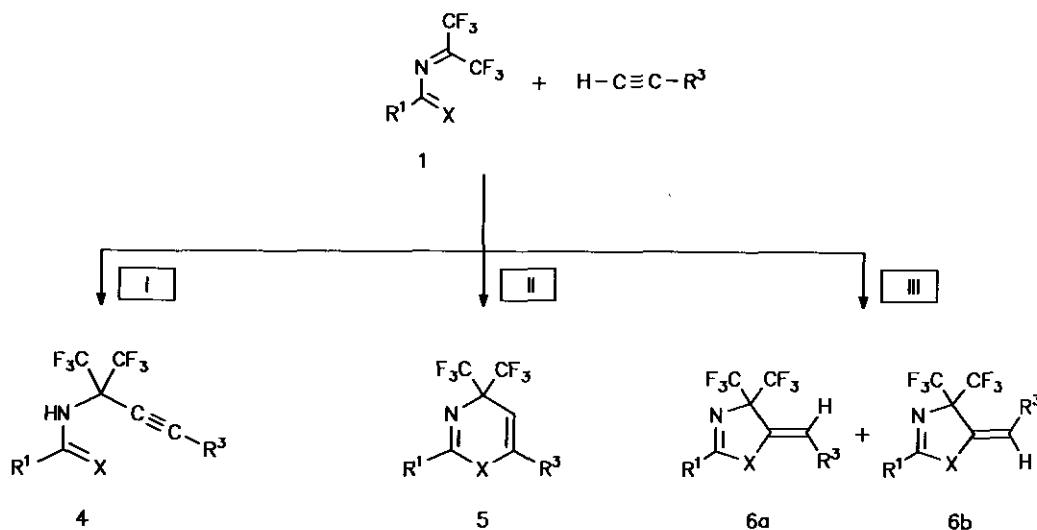
Hetero-1,3-dienes (1) react with α,β -unsaturated carbonyl compounds (e.g. acrolein, methacrolein, crotonaldehyde) in some cases already at room temperature to yield [4+2] cycloadducts (3).⁹⁻¹¹



The preference of the carbon-oxygen multiple bond in comparison to the carbon-carbon double bond as dienophile is also observed in the case of [4+2] cycloaddition reactions of other extremely electron deficient hetero-1,3-dienes, like acylketenes,¹² thioacylisocyanates^{13,14} and α,β -unsaturated keteneiminium salts.^{15,16} On the other hand the electron-rich Danishefsky's diene (1-methoxy-3-trimethylsilyloxy-1,3-butadiene) exhibits the same selectivity phenomena.¹⁷

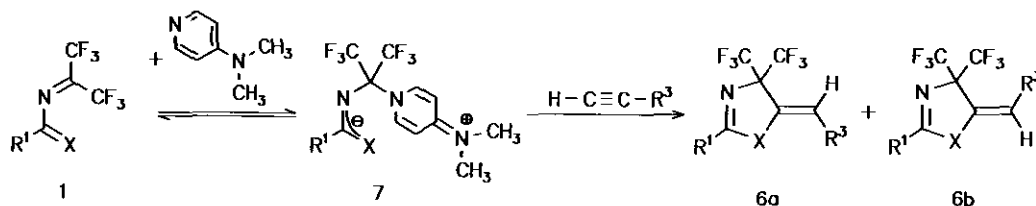
A charge-controlled reaction mechanism plausibly explains this kind of site selectivity. The first step of the reaction is a nucleophilic attack of the centre of highest electron density (oxygen-atom) of the α,β -unsaturated carbonyl compound at C-4, which is the centre of the highest electron deficiency of the bis(trifluoromethyl)substituted heterodienes (1). This leads to well stabilized 1,x-dipolar intermediates (2), which subsequently undergo ring closure to give [4+2] cycloadducts (3).^{9,11}

On reaction of hetero-1,3-dienes (1) with terminal alkynes three products are obtained. The product distribution very much depends on the substituent pattern.^{18,19}



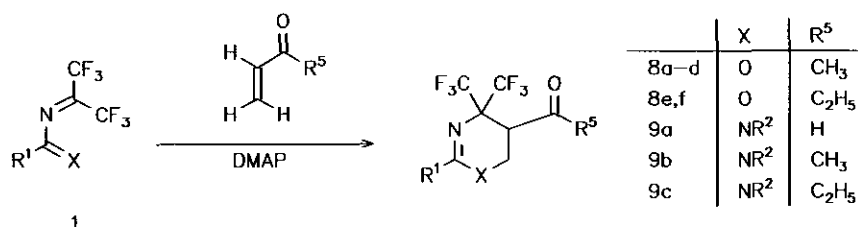
Noteworthy, this reaction can be controlled by addition of equimolar amounts of 4-dimethylaminopyridine (DMAP)²⁰ to give predominantly five membered ring systems (**6**).^{18,19}

DMAP causes a reversible blocking of the electrophilic centre at C-4 in compounds (**1**). On the other hand in the labile intermediate adducts (**7**) the nucleophilic capacity of the heteroatoms X is increased by charge separation.^{18,19} This results in a suppression of reaction pathways I and II, which are supposed to start with a nucleophilic attack at position 4 of the hetero-1,3-dienes (**1**). Consequently, pathway III is the only favoured process.



These findings prompted us to test the effect of DMAP on [4+2] cycloaddition reactions of α,β -unsaturated carbonyl compounds to 4,4-bis-(trifluoromethyl)substituted hetero-1,3-dienes (**1**). When **1** and α,β -unsaturated ketones are reacted in the presence of DMAP, [4+2] cycloadducts across the carbon-carbon double bond can be identified (¹⁹F-Nmr analysis).

Reversible blocking of position 4 with simultaneous increase of the nucleophilic capacity of the heteroatom X should favour a Michael type addition of **1** to the α,β -unsaturated ketone. Ring closure of the 1,x-dipolar species occurs with nucleophilic displacement of DMAP and formation of 5-substituted 4,4-bis(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazines (**8**) and 1,4,5,6-tetrahydropyrimidines (**9**).



Under these reaction conditions, the [4+2] cycloaddition exclusively occurs across the carbon-carbon double bond of the α,β -unsaturated ketone. Cycloaddition of acrolein to **1b** in the presence of DMAP gives analogous results. However, the reaction of acrolein with **1a** results in polymerization of acrolein. No [4+2] cycloadducts can be detected ¹⁹F nmr spectroscopically.

The efficiency of DMAP to control site selectivity very much depends on the structure of the substrates. No change of site selectivity is observed in the case of substituted α,β -unsaturated aldehydes. As a result of the reversible blocking of position 4 of the hetero-1,3-dienes (**1**), yields of compounds (**3**) are decreased. The results are summarized in Table 1.

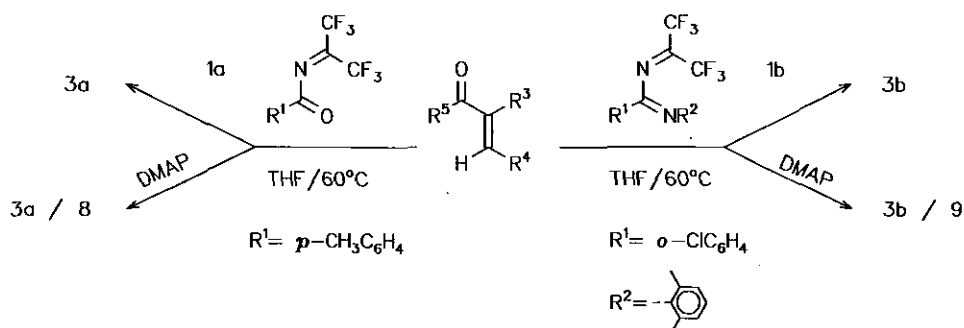


Table 1 : Product distribution in the absence and the presence of DMAP :

reaction of 1a				α,β -unsaturated carbonyl compound	R ³	R ⁴	R ⁵	reaction of 1b			
without DMAP		with DMAP						without DMAP		with DMAP	
3a	8	3a	8					3b	9	3b	9
83	-	a)	-	acrolein	H	H	H	65	-	-	19
85	-	42	-	methacrolein	CH ₃	H	H	68	-	48	-
79	-	72	-	crotonaldehyde	H	CH ₃	H	75	-	68	-
88	-	74	-	cinnamic aldehyde	H	C ₆ H ₅	H	70	-	64	-
45	-	-	32	methyl vinyl ketone	H	H	CH ₃	54	-	-	40
39	-	-	45	ethyl vinyl ketone	H	H	C ₂ H ₅	56	-	-	56

a) Polymerization is observed. No [4+2]-cycloadducts can be detected

The structural assignment of the products (8) and (9) is based on the spectroscopical data (Tables 3, 4 and 5). The ¹³C Nmr resonance absorption in the region of $\delta = 200$ ppm indicates the presence of a C=O group, which also can be identified by an ir-absorption at $\nu = 1710$ cm⁻¹. Compounds (8) show a ¹³C resonance absorption at ca. $\delta = 62$ ppm (OCH₂) and 9 at ca. $\delta = 45$ ppm (NCH₂), respectively. The large shift differences for the methylene groups is in agreement with the postulated regiochemistry of the [4+2] cycloaddition process. Two quartets in the ¹³C nmr as well as in the ¹⁹F nmr spectra show magnetically nonequivalent trifluoromethyl groups. The ¹H and ¹³C nmr spectra demonstrate the absence of a vinyl substructure.

The mass spectrometric degradation pattern [M⁺], [M⁺-CF₃], [M⁺-COR⁵], [R¹CX⁺], especially the fragment [R⁵CO⁺] is in agreement with the proposed structures.

These spectroscopic data unambiguously prove the structures of compounds (8) and (9).

Table 2 : Data of compounds (8) and (9) :

	R ¹ R ²	yield [%]	mp [°C]	formula	elemental analysis		
					C	H	N
8a	4-ClC ₆ H ₄	46	42	C ₁₄ H ₁₀ NO ₂ ClF ₆	Calcd: 45.00	2.70	3.75
	-				Found: 45.08	2.70	4.00
8b	4-FC ₆ H ₄	51	oil	C ₁₄ H ₁₀ NO ₂ F ₇	Calcd: 47.07	2.82	3.92
	-				Found: 47.08	2.99	4.09
8c	4-CH ₃ C ₆ H ₄	32	oil	C ₁₅ H ₁₃ NO ₂ F ₆	Calcd: 51.00	3.71	3.96
	-				Found: 50.96	3.75	3.99
8d	2-C ₁₀ H ₇ ^{b)}	30	oil	C ₁₈ H ₁₃ NO ₂ F ₆	Calcd: 55.53	3.37	3.60
	-				Found: 55.34	3.37	3.62
8e	4-CH ₃ C ₆ H ₄	45	oil	C ₁₆ H ₁₅ NO ₂ F ₆	Calcd: 52.32	4.12	3.81
	-				Found: 52.22	4.22	3.86
8f	2-C ₁₀ H ₇ ^{b)}	38	83	C ₁₉ H ₁₅ NO ₂ F ₆	Calcd: 56.58	3.75	3.47
	-				Found: 56.57	3.71	3.47
9a	2-ClC ₆ H ₄ C ₈ H ₉ ^{c)}	19	118	C ₂₁ H ₁₇ N ₂ OC1F ₆	Calcd: 54.50	3.70	6.05
					Found: 54.69	3.72	6.35
9b	2-ClC ₆ H ₄ C ₈ H ₉ ^{c)}	40	147	C ₂₂ H ₁₉ N ₂ OC1F ₆	Calcd: 55.41	4.02	5.87
					Found: 55.49	4.24	5.84
9c	2-ClC ₆ H ₄ C ₈ H ₉ ^{c)}	56	109	C ₂₃ H ₂₁ N ₂ OC1F ₆	Calcd: 56.28	4.31	5.70
					Found: 55.64	4.43	5.61

^{b)} 2-C₁₀H₇ = 2-naphthyl^{c)} C₈H₉ = 2,6-dimethylphenyl

Table 3 : ^1H Nmr data of compounds (8) and (9) :

	^1H nmr (CDCl_3) : δ [ppm] J [Hz]							
	$\delta(\text{CH}-5)$	$\delta(\text{CH}_2-6)$	$\delta(\text{CH}_2-6)$	$^2J_{\text{gem}}$	$^3J_{\text{tr}}$	$^3J_{\text{cis}}$	$^4J_{\text{HF}}$	$^5J_{\text{HF}}$
8a	3.45, ddq	4.39, dd	4.54, dd	12.0	10.8	5.2	1.0	-
8b	3.45, ddq	4.39, dd	4.54, dd	12.0	10.9	5.3	1.0	-
8c	3.44, ddq	4.37, dd	4.52, dd	12.0	11.0	5.2	1.2	-
8d	3.50, ddq	4.45, dd	4.61, dd	12.1	11.0	5.2	1.1	-
8e	3.45, ddq	4.35, dd	4.53, dd	12.0	10.7	5.4	1.3	-
8f	3.50, dd	4.44, dd	4.61, dd	12.1	10.3	5.1	-	-
9a	3.45, dd	3.50, dd	4.01, dd	13.4	11.7	5.7	-	-
9b	3.58, ddq	3.22, ddq	4.15, dd	13.7	12.6	5.7	1.7	1.7
9c	3.58, ddq	3.22, dd	4.12, dd	13.5	12.3	5.6	1.5	-

Table 4 : ^{19}F Nmr and ir data of compounds (8) and (9) :

	^{19}F nmr (CDCl_3) : δ [ppm] J [Hz]			ir (KBr^{d} , film ^e) ν [cm^{-1}]
	$\delta(\text{CF}_3)$	$\delta(\text{CF}_3)$	4J	
8a	+4.60, q	+9.56, q	11.0	1720, 1660, 1600, 1580 ^d)
8b	+4.66, q	+9.58, q	11.0	1700, 1650, 1600 ^e)
8c	+4.53, q	+9.49, q	11.0	1715, 1645, 1610, 1570 ^e)
8d	+4.68, q	+9.64, q	11.0	1710, 1645, 1600, 1575 ^e)
8e	+4.41, q	+9.60, q	11.1	1715, 1645, 1600 ^e)
8f	+4.55, q	+9.69, q	11.1	1725, 1650, 1585 ^d)
9a	+4.79, mc	+9.87, mc	-	1720, 1615, 1590, 1570 ^d)
9b	+5.37, mc	+11.48, mc	-	1725, 1620, 1590, 1570 ^d)
9c	+5.05, mc	+11.73, mc	-	1725, 1610, 1590 ^d)

Table 5 : ^{13}C Nmr data of compounds (8) and (9) :

^{13}C nmr (CDCl_3): δ [ppm] J [Hz]						
	$\delta(\text{C}-2)$	$\delta(\text{C}-4)$ ^2J	$\delta(\text{CF}_3)$ $\delta(\text{CF}_3)$	^1J ^1J	$\delta(\text{CH}-5)$ $\delta(\text{CH}_2-6)$ ^4J	$\delta(\text{C}=\text{O})$
8a	159.20	65.02, sept 27.9	122.34, q, 287.1 122.93, q, 285.3		43.65 62.30	202.53
8b	159.17	65.08, sept 27.9	122.41, q, 286.9 123.01, q, 285.7		43.78 62.30	202.55
8c	160.14	65.11, sept 27.7	122.51, q, 287.1 123.07, q, 285.6		43.93 62.08, q, 1.9	202.71
8d	160.12	65.26, sept 27.5	122.49, q, 287.9 123.10, q, 286.2		43.98 62.31	202.66
8e	160.01	64.95, sept 27.6	122.46, q, 287.0 123.11, q, 284.9		43.15 62.38	205.46
8f	160.03	65.06, sept 27.7	122.50, q, 287.1 123.12, q, 285.9		43.03 62.58	205.36
9a	157.56	65.47, sept 27.2	123.27, q, 287.6 123.73, q, 285.5		44.40 43.06	195.49
9b	156.66	66.27, sept 26.8	122.86, q, 287.7 123.54, q, 285.8		43.84 45.42, q, 2.1	203.17
9c	156.61	66.07, sept 26.9	122.88, q, 287.8 123.62, q, 286.1		43.13 45.85, q, 2.4	205.91

EXPERIMENTAL

Materials and methods :

Melting points are determined in a Büchi capillary mp apparatus and are uncorrected. The ^1H , ^{13}C and ^{19}F nmr spectra are taken on a Bruker AC-250 instrument (^1H : 250.1 MHz; ^{13}C : 62.9 MHz; ^{19}F : 235.3 MHz). Chemical shifts are calculated from tetramethylsilane (internal standard) for ^1H and ^{13}C , and from trifluoroacetic acid (external standard) for ^{19}F . Ir spectra are measured on a Perkin-Elmer 237 apparatus. Mass spectra are obtained on a AEI MS 9 spectrometer at 70 eV. Column chromatography is performed on silica gel 60 F₂₅₄ (0.063-0.200, Merck).

General reaction procedures :

4,4-Bis(trifluoromethyl)-4H-1,3,5-dioxazines (3) (reaction of 1 with α,β -unsaturated carbonyl compounds in absence of DMAP) :

A solution of 5.0 mmol of 1 and 7.0 mmol of α,β -unsaturated carbonyl compound in 5.0 ml of THF was stirred for 7 d at 60°C. The solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent: CHCl_3 /hexane 1:3).

4,4-Bis(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazines (8) and 4,4-bis-(trifluoromethyl)-1,4,5,6-tetrahydropyrimidines (9) (reaction of 1 with acrolein and α,β -unsaturated ketones in the presence of DMAP) :

7.0 mmol of the α,β -unsaturated carbonyl compound was added to a stirred solution of 5.0 mmol of 1 and 5.2 mmol (0.62 g) of DMAP in 5.0 ml of THF at 60°C. After 5 d, the solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent: CHCl_3 /hexane 1:1).

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