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Strong deshielding in aromatic isoxazolines

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ABSTRACT: Very strong proton deshielding was found in di/tri-aromatic isoxazoline regioisomers prepared from acridin-4-yl dipolarophiles and stable benzonitrile oxides (BNO). Three alkenes, (acridin-4-yl)-CH=CH-R (R = $COOCH_3$, Ph, and $CONH_2$), reacted with three BNO dipoles (2,4,6-trimethoxy, 2,4,6-trimethyl, 2,6-dichloro) to give pairs of target isoxazolines with acridine bound to C-4 or C-5 carbon of the isoxazoline (denoted as 4-Acr or 5-Acr). Regioselectivity was dependent on both the dipolarophile and dipole character. The ester and amide dipolarophile displayed variable regioselectivity in cycloadditions whereas the styrene one afforded prevailing 4-Acr regioisomers. 2,4,6-Trimethoxy-BNO was most prone to form 5-Acr isoxazolines while mesitonitrile oxide gave major 4-Acr isoxazolines. Basic hydrolysis of the amide cycloadduct led to an unexpected isoxazolone product. The structure of the target compounds was studied by NMR, MS, and X-ray crystallography. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: NMR; ^{1}H; ^{13}C; 1,3-dipolar cycloadditions; regioselectivity; acridine; benzonitrile oxides; isoxazolines

Introduction

Though many acridine derivatives have been studied in the past as potent fluorophores and DNA ligands it is surprising that only limited attention was devoted to 1,3-dipolar cycloadditions (DCs) of acridine dipolarophiles so far.[1a–d] DCs with nitrile oxides (NOs), for example, should afford isoxazolines transformable into β-hydroxyketones and γ-aminoalcohols, versatile intermediates for synthesis of natural products analogues.[2a–3] Isoxazolines themselves have also revealed a broad range of activities against influenza viruses[4] and fungi,[5] an inhibition of group II phospholipase A2,[6] glycoprotein IIb/IIIa receptor antagonism,[7] spermicidal and anti-HIV activities,[8a–c] β-adrenergic receptor antagonist properties,[9] and other valuable features.[10a–d] Thus, appropriate derivatization of acridines by the isoxazoline scaffold could bring new perspective pharmacophores.

Even though reactivity and regioselectivity of 1,3-dipolar cycloadditions of unsymmetrical alkenes with nitrile oxides have been often studied,[11–13a–c] their mechanism is still poorly understood. Selectivity prediction by a Frontier Molecular Orbital theory (FMO) is not as fruitful as at classical cycloadditions because electronic and steric effects can significantly alter the cycloaddition course.[14] To rationalize it, explanations using a Houk model,[15a–c] secondary orbital interactions, kinetic effects,[16a,b] etc., have been attempted; nevertheless, further experimental data are still desired to elucidate the matter. Polarity of the dipolarophilic double bond and steric constraints may hinder or facilitate an approach of the bulky dipole from a more or less sterically hindered face of the dipolarophile and thus substantially alter the rate of formation and ratio of formed regioisomeric products.[17]

Numerous papers have dealt with DCs of cinnamaldehydes,[15b,18a,b] cinnamates,[1a,16b] lactones,[19] cinnamamides,[20] cinnamonitriles,[21] and stilbenes[22a–e] with the nitrile oxides up to now, but only few works studied acridine dipolarophiles.[23,24] As 4-substituted acridines, especially carboxamides, are strong tumor suppressors, we were interested in dipolarophiles with the alkene moiety on acridine C-4 carbon. The acridine flanking ring together with the alkenoic substituent on C-4 composes aromate-alkenoate/aromate-alkene systems similar to cinnamates/stilbenes.

DCs of 1,2-disubstituted alkenes with the nitrile oxides can in principle afford two isoxazoline regioisomers resulting from two mutually reversed orientations of the dipolarophilic CH=CH bond and the dipole in the transition state. Consequently, two regioisomeric products differ each from other by mutually exchanged substituents on isoxazoline C-4/C-5 carbons. To examine the effects of dipolarophile substituents in a systematic manner, we synthesized three starting (acridin-4-yl)alkenes with $COOCH_3$ (**4**), phenyl (**5**), or $CONH_2$ (**6**) substituent. As the dipoles, three stable benzonitrile oxides, 2,4,6-trimethoxy-BNO (**7a**), mesitonitrile oxide (MNO, **7b**), and 2,6-dichloro-BNO (**7c**) were used in this work, while unstable *p*- and *m*-substituted BNOs, which dimerized easily, were set aside for a separate study. To compare the effects of the flanking *versus* middle acridine ring on the reactivity and regioselectivity, we shall present DCs of relative 9-substituted acridine dipolarophiles, methyl 3-(acridin-9-yl)propenoate and 9-(2-styryl)acridine with the BNOs **7a–c** in the following paper.

Results and Discussion

Acridine dipolarophiles **4–6** were obtained from acridine-4-carbaldehyde (**3**) that was synthesized by a simple Klanderman's method in high yield.[25] To prepare **3**, starting 4-methylacridine (**1**) was first transformed to 4-bromomethylacridine (**2**) with NBS in tetrachloromethane under 2,2′-azobis(isobutyronitrile) (AIBN) catalysis (Scheme 1).[26] Subsequent reaction of **2** with 2-nitropropane and sodium in dry methanol afforded the aldehyde **3** in 89% yield. The synthesis of **3** as given is an alternative of a Takahashi method.[27]

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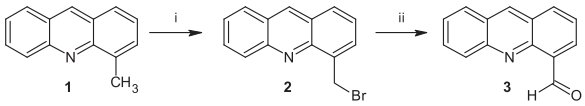
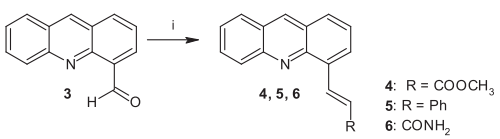


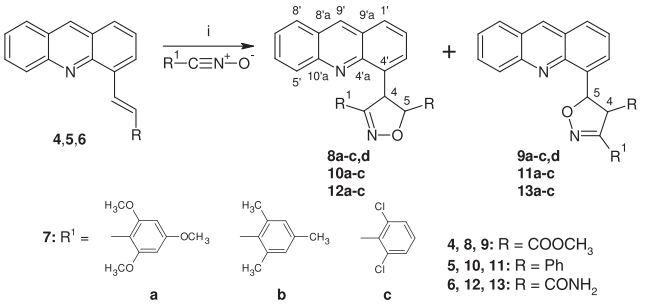
Scheme 1. Synthesis of acridin-4-carbaldehyde (**3**). Reagents and conditions: (i) NBS, AIBN, CCl_4, 4 h, (ii) 2-nitropropane/Na/MeOH, DMSO, rt, 3 h.

The aldehyde **3** was further transformed to the ester **4**, methyl 3-(acridin-4-yl)propenoate, using a Wittig reaction with methyl (triphenylphosphoran ylidene) acetate by a mild Märkl and Merz method in 42% yield (Scheme 2).[28] A styryl moiety was incorporated into 4-(2-styryl)acridine (**5**) by a Vedejs's method.[29,30] Benzyltriphenylphosphonium chloride was deprotonated by sodium hydride at low temperature to give an ylide as an orange suspension. To this mixture, the aldehyde **3** was added to form the dipolarophile **5** in 41% yield after 12 h. We used the same method also for the synthesis of 3-(acridin-4-yl)propenamide (**6**), in which amidomethyltriphenylphosphonium chloride was transformed to a corresponding ylide by treatment with sodium hydride to give the amide **6** after 24 h in 55% yield. ^{1}H and ^{13}C NMR signals of the dipolarophiles **4–6** in $CDCl_3$ were assigned using HMBC transfers from both alkene protons to corresponding acridine carbons and to phenyl C-1‴ and C-2‴,6‴ carbons of styrene (in **5**). Coupling constants 16.0–16.4 Hz between these protons confirmed a *trans* (*E*) configuration—none *cis* (*Z*) isomers were detected in the crude reaction mixture.

1,3-Dipolar cycloadditions of methyl 3-(acridin-4-yl)propenoate (**4**) with **7a–c** were performed at room temperature to ensure a kinetic control presumed for DCs of alkenes with NOs,[31] until the dipolarophile had been consumed (TLC and NMR monitoring). To determine the conversion and regioselectivity precisely, parallel reactions of the dipolarophile (0.04 mmol) and dipole (0.12 mmol) in $CDCl_3$ (0.6 mL) were carried out in a sealed NMR tube at room temperature. Despite a triple molar excess of the dipoles was used, it took days to achieve a complete or at least prevailing conversion of the dipolarophile into mixtures of two regioisomeric isoxazolines, methyl 4-(acridin-4-yl)-3-(substituted phenyl)-4,5-dihydro-2-isoxazoline-5-carboxylates **8a–c** denoted as 4-Acrs and methyl 5-(acridin-4-yl)-3-(substituted phenyl)-4,5-dihydro-2-isoxazoline-4-carboxylates **9a–c** denoted as 5-Acrs (Scheme 3, Table 1). The fastest reaction of **4** with **7a** was finished in 13 days and that with **7b** in 29 days, both with 100% conversion, while the slowest one was that of **7c** with 81% conversion in 50 days. The best regioselectivity for **8a**/**9a** = 1:7.08 and moderate for **8b**/**9b** = 1:0.67, **8c**/**9c** = 1:2.47 indicated that selectivity was dependent on both, the character of the dipolarophile and substituent effects within the dipole. Because of the laborious separation of regioisomers with close R_f values, from all reactions only small amounts of pure cycloadducts were obtained. The reaction with **7a** afforded 23% of **9a** with a minimal amount of **8a** (not isolated), together with 11% of a monobrominated side product, methyl 5-(acridin-4-yl)-3-(3-bromo-2,4,6-trimethoxyphenyl)-4,5-dihydro-2-isoxazoline-4-carboxylate (**9d**) coming from 2,4,6-trimethoxy-BNO (**7a**) contaminated by 3-bromo-2,4,6-trimethoxy-BNO (**7d**). Cycloaddition with MNO (**7b**) led to the best summary yield of both regioisomers **8b**, **9b** (76%), while only 33% yield was found for the regioisomers **8c**, **9c**, together with some unreacted ester **4**.



Scheme 2. Synthesis of 4-substituted acridine dipolarophiles **4–6**. Reagents and conditions: i) $Ph_3P=CHCOOCH_3$, CH_2Cl_2, rt, 12 h or $Ph_3P^+CH_2Ph\ Cl^-$, NaH, THF, −20 °C → rt, 12 h or $Ph_3P^+CH_2CONH_2\ Cl^-$, NaH, CH_2Cl_2, −10 °C → rt, 24 h.



Scheme 3. 1,3-Dipolar cycloaddition reactions of the dipolarophiles **4–6** with the nitrile oxides **7a–c**. Reagents and conditions: (i) NOs **7a–c**, $CHCl_3$, rt.

Table 1. 1,3-Dipolar cycloadditions of **4–6** with **7a–d**: Reaction time, conversion, yields, and ratios of regioisomeric isoxazolines **8–13**

Reactants	Regio-isomers 4-Acr + 5-Acr	Time (days)	Conversion (%)	Ratios[a] 4-Acr + 5-Acr (%)	Isolated yields[b] (%)
R = COOCH$_3$ (4)					
4 + 7a	**8a + 9a + 9d**[c]	13	100	12.4:87.6	0 + 23 + 11
4 + 7b	**8b + 9b**	29	100	59.8:40.2	44 + 32
4 + 7c	**8c + 9c**	50	81	28.8:71.2	17 + 16
R = Ph (5)					
5 + 7a	**10a + 11a**	14	—[d]	68.9:31.1	34 + 17
5 + 7b	**10b + 11b**	14	—[d]	90.1:9.9	63 + 8
5 + 7c	**10c + 11c**	14	—[d]	95.2:4.8	56 + 3
R = CONH$_2$ (6)					
6 + 7a	**12a + 13a**	8	100	25.2:74.8	11 + 15
6 + 7b	**12b + 13b**	14	81	71.4:28.6	11 + 8
6 + 7c	**12c + 13c**	6	89	59.7:40.3	18 + 11

[a]Determined from experiment in a sealed NMR tube by integration of H-4 and H-5 methine doublets in ^{1}H NMR spectra of the crude reaction mixtures in $CDCl_3$.

[b]Isolated yields after column chromatography and crystallization based on the dipolarophiles **4**, **5**, **6**.

[c]Isoxazoline **8a** was not isolated after repeated chromatography. The compound **9d** was isolated in 11% yield.

[d]Conversion could not be determined.

Cycloadditions of 4-(2-styryl)acridine (**5**) with **7a–c** in the ratio 1:3 showed better regioselectivity (Scheme 3, Table 1). Improved purification of **7a** after bromination led exclusively to two trimethoxyphenyl isoxazolines **10a**, **11a**. Conversion of the styrene **5** could not be followed by NMR because of an overlap of olefinic and aromatic signals. Nevertheless, the reaction time did not exceed 14 days (TLC). All reactions afforded major 4-(acridin-4-yl)-5-phenyl-3-(substituted phenyl)-4,5-dihydro-2-isoxazolines **10a–c** (4-Acrs) and the ratio **10**/**11** gradually increased from 1:0.45 (**a**), through 1:0.11 (**b**), to 1:0.05 (**c**). A possible reason of this trend may come from a growing steric repulsion in the transition state

of a minor regioisomer formation caused by *ortho*-disubstituted phenyl of the dipole. This idea was supported by our recent findings on cycloadditions of **5** with *para*-substituted BNOs lacking *ortho*-substituents in which only negligible regioselectivity has been noted (results not given here). The acridin-4-yl skeleton of the target isoxazolines in this study is believed to adopt a relaxed position relative to both benzene rings of the dipole and the styryl unit.

Cycloadditions of a new amide dipolarophile, 3-(acridin-4-yl) propenamide (**6**), with NOs **7a–c** in the ratio 1:1 in dry chloroform at room temperature produced again two regioisomers, 4-(acridin-4-yl)-3-(substituted phenyl)-4,5-dihydro-1,2-oxazol-5-carboxamides **12a–c** and 5-(acridin-4-yl)-3-(substituted phenyl)-4,5-dihydro-1,2-oxazol-4-carboxamides **13a–c** with close R_f factors, moderate regioselectivity, and high conversion in reasonably short time (Scheme 3, Table 1). Full conversion of **6** was observed only with **7a** in 8 days, 89% conversion in 6 days was found with **7c**, whereas **7b** showed 81% conversion in 14 days. As the NMR spectra of the mixtures **b**, **c** taken one week later still showed some starting amide **6**, the DCs were reversible with free energy differences of about 4 kJ.mol^{-1}. The product ratios with MNO and 2,6-dichloro-BNO favored moderately 4-Acr regioisomers over 5-Acrs, **12b**/**13b** = 1:0.40 and **12c**/**13c** = 1:0.68, resp., but not with trimethoxy-BNO (**12a**/**13a** = 1:2.97).

The structure of cycloaddducts **8–13** was established by concerted application of NMR methods (^{1}H and ^{13}C NMR, DEPT, H, H-COSY, gHSQC, gHMBC, NOESY, Tables 2 and 3) and X-ray crystallography. Although absolute configuration of C-4 and C-5 stereogenic centres in the products was not determined, relative configuration of isoxazoline protons H-4, H-5 should be *trans* as in the parent dipolarophile owing to a concerted cycloaddition mechanism. ^{13}C NMR signals of C-4 and C-5 carbons in the isoxazolines were of prime importance for distinguishing the regioisomers. Downfield-shifted signals between 82.7–90.3 ppm unequivocally pertain to C-5 carbons next to O-1 oxygen, whereas upfield-shifted signals between 54.2 and 66.7 ppm belong to C-4 carbons. Two regioisomeric structures were then resolved by analysis of the HSQC and HMBC spectra as exemplified on a regioisomeric pair **8b–9b**. The ^{13}C NMR spectrum of the 4-Acr derivative **8b** displayed a C-5 signal at 84.7 ppm and that of C-4 at 54.8 ppm which provided HSQC cross-peaks with a H-5 signal at 5.50 ppm and that of H-4 at 6.95 ppm, resp. ($^3J_{45}$ = 5.2 Hz). Surprisingly, H-4 proton was more deshielded than H-5 close to oxygen because of a magnetic anisotropy effect of two nearby aromatic skeletons. To distinguish the regioisomers 4-Acr vs. 5-Acr, following HMBC correlations were crucial (Table 4): in **8b**, magnetization transfer from isoxazoline H-4 pointed at three-bond distant acridine signals C-3′ (128.5 ppm) and C-4′a (146.0 ppm), which on turn showed no cross-peaks with the isoxazoline H-5 signal. Hence, acridine is attached to isoxazoline C-4 carbon suggesting that **8b** is a 4-(acridin-4-yl)-5-carboxylate (4-Acr) regioisomer.

In the compound **9b** (Table 4), isoxazoline signals at 65.4 ppm (C-4) and 83.6 ppm (C-5) correlated (HSQC) with doublets at 4.48 ppm (H-4) and 7.17 ppm (H-5), resp. ($^3J_{45}$ = 7.4 Hz). HMBC transfers to acridine C-3′,4′a signals were observed from a very

Table 2. ^{1}H NMR chemical shifts (ppm) and J_{HH}[a] (Hz) in $CDCl_3$

Comp.	Isoxazoline			Acridine								Dipole				Ph (styryl)			Me
	H_α H-4	H_β H-5	$J_{\alpha\beta}$ J_{45}	1′	2′	3′	5′	6′	7′	8′	9′	*meta* 3″	*para* 4″	o-Me	p-Me	*ortho* 2‴	*meta* 3‴	*para* 4‴	
4	7.07	9.05	16.2	8.02	7.55	8.02	8.33	7.81	7.55	8.02	8.76	—	—	—	—	—	—	—	3.90
5	7.49	8.70	16.0	7.91	7.53	8.08	8.33	7.77	7.56	8.00	8.72	—	—	—	—	7.73	7.43	7.31	—
6	7.20	8.76	16.0	8.22	7.68	8.18	8.31	7.93	7.68	8.22	9.17	—	—	—	—	—	—	—	—
8a	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
8b	6.95	5.50	5.2	7.91	7.49	7.82	8.06	7.72	7.49	7.91	8.64	6.55	—	2.22	1.98	—	—	—	3.90
8c	7.08	5.65	5.2	7.92	7.52	7.95	8.03	7.69	7.49	7.91	8.66	7.02	6.88	—	—	—	—	—	3.91
9a	4.51	7.17	7.6	7.96	7.57	8.09	8.06	7.73	7.52	7.98	8.76	6.08	—	3.68	3.80	—	—	—	3.80
9b	4.48	7.17	7.4	7.99	7.58	8.09	8.03	7.74	7.54	8.01	8.79	6.83	—	2.14	2.25	—	—	—	3.80
9c	4.63	7.36	6.8	7.98	7.57	8.06	8.03	7.74	7.53	7.99	8.77	7.28	7.28	—	—	—	—	—	3.86
10a	6.67	5.64	5.2	7.87	7.44	7.90	8.15	7.74	7.52	7.97	8.70	5.95	—	3.67	3.65	7.81	7.44	7.34	—
10b	6.78	6.06	5.6	7.90	7.54	8.00	8.00	7.69	7.47	7.90	8.63	6.52	—	2.17	1.96	7.59	7.40	7.33	—
10c	6.93	6.19	6.4	7.93	7.54	8.09	8.02	7.67	7.47	7.91	8.65	7.00	6.86	—	—	7.63	7.41	7.34	—
11a	4.84	6.81	4.2	7.96	7.58	8.06	7.96	7.71	7.52	8.00	8.78	5.95	—	3.49	3.71	7.52	7.37	7.29	—
11b	4.66	7.02	3.6	7.98	7.59	8.11	7.75	7.65	7.51	7.98	8.78	6.66	—	1.79	2.15	7.37	7.41	7.36	—
11c	5.03	7.06	4.8	7.99	7.59	8.07	7.77	7.67	7.51	7.99	8.78	7.12	7.12	—	—	7.49	7.38	7.38	—
12a	6.67	5.12	5.6	7.93	7.47	7.78	8.16	7.78	7.56	8.02	8.79	5.93	—	3.67	3.66	—	—	—	—
12b	6.84	5.44	5.6	7.82	7.42	7.78	7.94	7.61	7.40	7.84	8.55	6.45	—	2.05	1.89	—	—	—	—
12c[b]	6.80	5.79	4.4	8.11	7.64	7.97	7.83	7.77	7.55	8.07	9.01	7.15	7.02	—	—	—	—	—	—
13a	4.66	7.06	5.2	8.17	7.57	7. 98	8.14	7.78	7.57	8.19	8.83	6.10	—	3.65	3.79	—	—	—	—
13b	4.43	7.08	4.8	8.08	7.61	8.08	8.02	7. 82	7.61	8.08	8.88	6.81	—	2.13	2.23	—	—	—	—
13c[b]	4.42	7.11	6.4	8.20	7.68	7.94	8.07	7.89	7.68	8.20	9.18	7.50	7.50	—	—	—	—	—	—
15c *cis*	—	9.29	—	8.27	7.74	9.73	7.96	7.79	7.56	8.01	8.80	7.60	7.60	—	—	—	—	—	—
15c *trans*	—	9.53	—	7.94	6.93	7.26	8.31	7.85	7.56	8.01	8.73	7.23	7.23	—	—	—	—	—	—

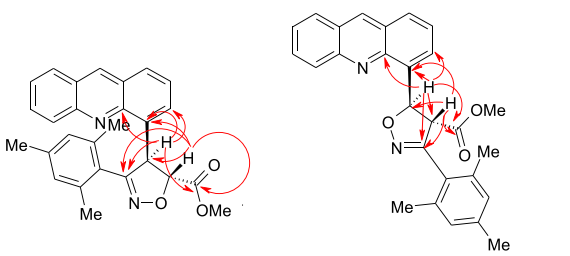
[a] $J_{1'2'}$ = 8.0–8.8 Hz, $J_{2'3'}$ = 6.6–7.4 Hz, $J_{1'3'}$ = 0.8–1.2 Hz, $J_{5'6'}$ = 8.2–8.8 Hz, $J_{6'7'}$ = 6.0–6.8 Hz, $J_{7'8'}$ = 8.0–8.8 (9.2 Hz-**15c** *cis*) Hz, $J_{5'7'}$ = 0.8–1.2 Hz, $J_{6'8'}$ = 1.2–1.6 Hz; $J_{3''4''}$ = 8.4 (**8c**), 8.0 (**10c**), 7.2 (**12c**) Hz; $J_{2'''3'''}$ = 7.2–8.0 Hz, $J_{3'''4'''}$ = 7.2–7.6 Hz, $J_{2'''4'''}$ = 1.2–1.6 Hz.
[b] Measured in DMSO-D_6.

Table 3. ^{13}C NMR chemical shifts (ppm) in $CDCl_3$ and DMSO-D_6

Compound	S[a]	Isoxaz.	C_α	C_β	Acridine												
		C=N	C-4	C-5	1′	2′	3′	4′	5′	6′	7′	8′	9′	8′a	9′a	4′a	10′a
4 - $COOCH_3$	C	-	120.3	141.8	129.4	126.2	130.6	132.9	130.1	130.5	126.6	127.9	136.2	126.6	125.2	146.9	148.8
5 - Ph	C	-	130.5	125.2	127.6	125.6	125.8	135.9	130.0	130.1	125.6	127.9	136.0	126.8	126.5	147.0	148.4
6 - $CONH_2$	C	-	124.3	135.7	130.0	125.5	128.3	132.5	128.5	130.9	126.0	129.2	136.8	126.1	126.2	146.1	147.9
4A[b]-8a $COOCH_3$		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4A-8b $COOCH_3$	C	159.5	54.8	84.7	127.8	125.2	128.5	135.5	129.9	130.0	126.0	128.2	135.8	126.5	126.2	146.0	148.3
4A-8c $COOCH_3$	C	156.2	54.2	84.5	127.8	125.4	128.7	134.4	129.8	130.0	126.0	128.3	135.7	126.4	126.2	146.1	148.1
5A[b]-9a $COOCH_3$	C	150.1	64.7	83.0	127.8	125.8	126.2	138.0	129.8	130.0	125.5	128.0	135.8	126.4	126.5	146.1	148.1
5A-9b $COOCH_3$	C	154.4	65.4	83.6	128.1	125.5	125.9	137.7	129.6	130.2	126.0	128.1	136.0	126.6	126.5	145.9	148.1
5A-9c $COOCH_3$	C	150.9	63.8	83.8	128.0	125.4	126.1	137.1	129.7	130.2	125.9	128.1	136.0	126.5	126.4	145.7	148.0
4A-10a Ph	C	155.5	59.0	90.3	127.7	125.9	129.0	137.8	130.1	130.1	125.9	128.2	136.0	126.6	126.8	147.2	148.5
4A-10b Ph	C	159.7	58.3	89.4	128.1	125.3	128.4	136.9	129.9	129.9	125.8	127.8	135.8	126.4	126.4	146.3	148.3
4A-10c Ph	C	156.2	57.4	90.0	128.2	125.5	128.8	135.7	129.8	129.8	125.9	127.8	135.7	126.3	126.3	146.4	148.1
5A-11a Ph	C	155.2	65.6	87.1	127.4	125.7	126.2	139.1	129.9	129.8	125.7	128.0	135.7	126.3	126.6	146.5	148.1
5A-11b Ph	C	160.3	66.7	87.0	128.0	125.4	126.0	138.6	129.9	130.0	125.8	127.8	135.9	126.4	126.7	146.4	148.0
5A-11c Ph	C	156.4	65.0	88.4	127.9	125.5	126.2	138.0	129.8	130.0	125.8	128.0	135.9	126.4	126.6	146.2	148.0
4A-12a $CONH_2$	C	154.7	54.6	84.9	127.4	125.3	128.2	135.6	128.8	129.6	124.8	127.4	135.6	125.7	125.8	147.4	145.8
4A-12b $CONH_2$	C	160.2	54.3	83.8	126.7	124.1	127.5	134.8	129.0	128.7	124.9	126.8	136.0	125.4	125.2	144.9	147.2
4A-12c $CONH_2$	D	155.8	54.8	83.6	128.6	125.9	128.1	133.9	128.5	130.3	125.5	128.1	136.2	125.6	125.7	145.4	147.0
5A-13a $CONH_2$	C	151.0	64.6	82.7	126.8	126.0	127.9	137.7	128.9	130.6	125.7	128.3	136.6	126.8	126.5	146.0	148.0
5A-13b $CONH_2$	C	155.5	65.1	83.1	128.3	125.6	128.5	138.8	128.5	131.0	126.1	128.3	137.1	126.9	126.6	145.8	148.0
5A-13c $CONH_2$	D	152.2	64.3	83.2	128.2	125.3	125.7	137.5	129.0	130.6	126.0	128.2	136.5	126.1	126.0	145.2	147.3
15c *cis*	C	162.1	117.6	148.5	135.5	125.6	136.9	129.8	129.8	131.1	126.5	128.1	136.9	126.1	126.1	146.8	148.7
15c *trans*	C	157.7	119.1	150.9	132.4	123.5	133.0	129.6	130.1	131.1	126.7	128.1	136.4	125.9	125.9	146.9	149.2

[a]C = $CDCl_3$, D = DMSO-D_6; [b] 4A = 4-Acr, 5A = 5-Acr.

Table 4. Selected gHMBC correlations (→) in **8b** and **9b**



8b, 4-Acr				**9b, 5-Acr**			
From H-4 6.95 ppm		**From H-5 5.50 ppm**		**From H-4 4.48 ppm**		**From H-5 7.17 ppm**	
C3′	**128.5**					**C3′**	**125.9**
C4′a	**146.0**					**C4′a**	**145.9**
C4′	135.5	C4′	135.5	C4′	137.7	C4′	137.7
		C4	54.8			C4	65.4
C5	84.7			C5	83.6		
C=N	159.5	C=N	159.5	C=N	154.4	C=N	154.4
C=O	171.2	C=O	171.2	C=O	169.5	C=O	169.5

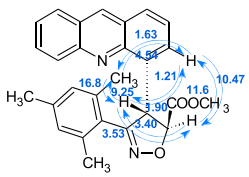


Figure 1. Structure of the isoxazoline **8b** and selected NOE enhancements (→) confirming the structural elucidation.

deshielded isoxazoline methine H-5 signal at 7.17 ppm which had on turn a HSQC cross-peak with the C-5 signal at 83.6 ppm. H-5 showed also other expected HMBC correlations with C-4′, C-4, C=N, and C=O signals. Transfers from H-4 pointed at C-4′, C-5, C=N, and C=O signals, and from acridine H-3′ back to C-5. This evidenced that acridine was attached to isoxazoline C-5 carbon. Strong deshielding of H-5 at 7.17 ppm is caused by magnetic anisotropy of two nearby aromatic skeletons together with deshielding by O-1 and **9b** is thus a reversed 5-(acridin-4-yl)-4-carboxylate (5-Acr) regioisomer.

Assignments of other acridine signals in **8–13** started from acridine H-9′ singlet at ca. 8.7 ppm, which had NOESY correlation with nearby H-1′/H-8′ protons. The NOEDIFF spectra of **8b** (Fig. 1) that showed mutual enhancements 3.90/1.21% between the isoxazoline H-4 and acridine H-3′ signals and 11.60/10.47% between the H-5 and H-3′ signals indicated that H-5 and acridine H-3′ are disposed on the same face of the isoxazoline ring. NOE enhancements between H-4 and H-5 (3.53/3.40%) and especially large between H-4 and *o*-CH_3 (9.25/16.80%) demonstrate a compressed mutual arrangement of isoxazoline and phenyl ring. Thus, 1,3-dipolar cycloadditions follow a stereoconservative concerted mechanism with unknown degree of potential unsynchronicity.

The structure of **9b** was established unequivocally also by a single crystal X-ray analysis (Fig. 2) that revealed one intramolecular hydrogen bond O-1…H-3′–C-3′ (Table 5). Mesityl and isoxazoline planes in **9b** are mutually orthogonal. The acridin-4-yl skeleton is

Table 3. (Continued)

Compound	Dipole phenyl						COOMe		Ph (styryl)			
	i-1″	o-2″	m-3″	p-4″	o-Me	p-Me	$CONH_2$	OCH_3	i-1‴	o-2‴	m-3‴	p-4‴
4 - $COOCH_3$	-	-	-	-	-	-	167.9	51.7	-	-	-	-
5 - Ph	-	-	-	-	-	-	-	-	138.0	127.0	128.6	127.6
6 - $CONH_2$	-	-	-	-	-	-	167.0	-	-	-	-	-
4A[b]-8a $COOCH_3$	-	-	-	-	-	-	-	-	-	-	-	-
4A-8b $COOCH_3$	124.3	137.3	128.3	138.2	20.2	20.8	171.2	52.7	-	-	-	-
4A-8c $COOCH_3$	127.4	135.5	127.8	130.4	-	-	170.8	52.9	-	-	-	-
5A[b]-9a $COOCH_3$	99.1	159.8	90.7	162.6	55.9	55.3	169.8	52.3	-	-	-	-
5A-9b $COOCH_3$	124.4	137.1	128.6	138.9	19.7	21.1	169.5	52.6	-	-	-	-
5A-9c $COOCH_3$	127.5	135.5	128.0	131.1	-	-	168.2	52.9	-	-	-	-
4A-10a Ph	100.9	160.0	91.1	162.3	56.1	55.4	-	-	142.1	126.8	128.3	127.7
4A-10b Ph	125.1	137.2	128.3	137.9	20.3	20.8	-	-	141.6	125.6	128.6	127.8
4A-10c Ph	128.2	135.6	127.8	130.1	-	-	-	-	140.9	126.1	128.5	128.1
5A-11a Ph	100.3	159.7	90.9	162.1	55.8	55.2	-	-	139.5	128.7	128.0	126.9
5A-11b Ph	125.0	137.1	128.6	138.3	19.8	21.0	-	-	138.8	128.5	128.2	127.5
5A-11c Ph	127.7	135.5	128.3	130.6	-	-	-	-	137.9	128.8	128.4	127.6
4A-12a $CONH_2$	98.6	158.9	90.1	161.6	55.3	55.2	172.7	-	-	-	-	-
4A-12b $CONH_2$	123.1	138.8	127.1	137.3	18.9	19.7	173.1	-	-	-	-	-
4A-12c $CONH_2$	127.3	134.2	127.6	131.2	-	-	172.2	-	-	-	-	-
5A-13a $CONH_2$	100.2	159.8	91.2	162.4	56.1	55.3	171.6	-	-	-	-	-
5A-13b $CONH_2$	125.0	137.4	128.8	137.3	20.0	21.1	170.7	-	-	-	-	-
5A-13c $CONH_2$	127.1	134.7	128.3	131.9	-	-	168.1	-	-	-	-	-
15c *cis*	126.7	131.1	128.5	132.3	-	-	168.2	-	-	-	-	-
15c *trans*	126.9	131.1	128.0	131.6	-	-	169.5	-	-	-	-	-

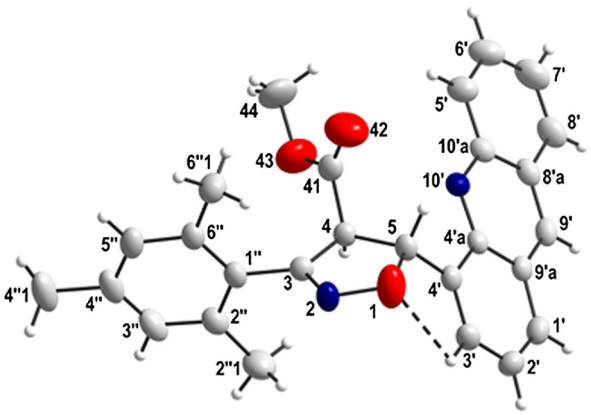


Figure 2. View of the compound **9b** with displacement ellipsoids at the 25% probability level.

turned out of the orthogonality with the isoxazoline plane owing to a less confined arrangement.

In the HMBC spectra of the products **10b** and **11b** from 4-(2-styryl)acridine (**5**), new transfers from particular isoxazoline protons to *ortho* carbons C-2‴,6‴ enabled again unequivocal resolution of the both regioisomers (Table 6). In the first amidic regioisomer **12b**, signals of C-5 (83.8 ppm) and C-4 (54.3 ppm) correlated with those of H-5 (5.44 ppm) and H-4 (6.84 ppm), resp.. Typical HMBC transfers from H-4 to acridine C-3′ and C-4′a enabled unambiguous assignment of a 4-Acr regioisomer, 4-(acridin-4-yl)-3-(2,4,6-trimetylphenyl)-4,5-dihydro-1,2-oxazol-5-carboxamide (**12b**). The molecule of reversed 5-Acr regioisomer, 5-(acridin-4-yl)-3-(2,4,6-trimethylphenyl)-4,5-dihydro-1,2-oxazol-4-carboxamide (**13b**) showed analogous structure-confirming magnetization transfer from H-5 to C-3′ (Table 7).

The most striking conclusion of NMR analysis is that the acridinyl substituent dramatically increases chemical shifts of vicinal isoxazoline CH protons:

5-CH signals in 5-Acr regioisomers **9**,**11**,**13** are shifted downfield by 0.87–1.94 ppm more than in 4-Acr regioisomers **8**,**10**,**12**,

4-CH signals in 4-Acr regioisomers **8**,**10**,**12** are shifted downfield even by 1.83–2.47 ppm more than in 5-Acr regioisomers **9**,**11**,**13**.

To assess whether cycloadditions were controlled thermodynamically or kinetically we measured temperature effects on the reactivity and ratio of products in three reactions of the amide **6** with the dipoles **7a–c** in the NMR tube at room and elevated temperatures 40 °C and 60 °C in $CDCl_3$ until all dipolarophile had been consumed (Table 8).

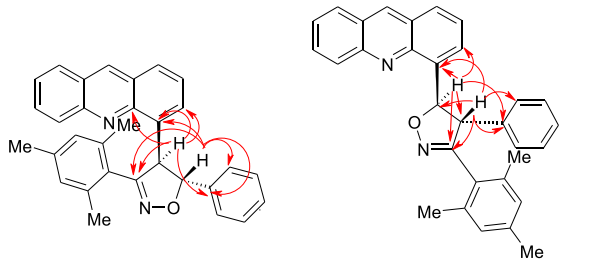
At 60 °C, the cycloaddends reacted two to four-times faster than at room temperature, thus reaction rate increased only moderately. The temperature, growth had practically no effect on the ratio of regioisomers. Were the cycloadditions kinetically controlled, competitive reactions leading to two regioisomers would probably be influenced to a different extent by temperature change, shifting thus the ratio of regioisomers in the mixture. As this was not the case it may be assumed that either (a) an activation energy of both cycloaddition routes is too high relatively to a small temperature change used or (b) the thermodynamic control of cycloadditions, which is enabled by very long reaction times, determines resulting product ratios, despite only laboratory temperature was used in almost all the synthetic and NMR experiments.

To obtain a free carboxylic acid **14c** as a precursor of new intended isoxazoline derivatives, we studied basic hydrolysis of

Table 5. Selected geometric parameters with estimated standard deviations for **9b**

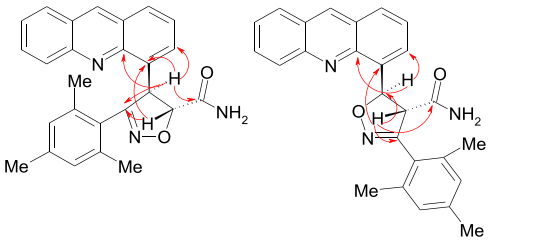
		Distance [Å]	Angle [°]
Cell setting	Triclinic	O1–C5, 1.457 (3)	N2–C3–C1″, 121.20 (2)
Space group	$P\bar{1}$	O1–N2, 1.414 (2)	N2–C3–C4, 113.70 (2)
a [Å]	8.483 (4)	C3–C4, 1.506 (3)	C1″–C3–C4, 124.90 (19)
b [Å]	9.417 (2)	C3–C1″, 1.479 (3)	C41–C4–C3, 113.00 (18)
c [Å]	14.715 (6)	C3–N2, 1.276 (3)	C41–C4–C5, 113.10 (2)
α [°]	100.09 (3)	C4–C5, 1.531 (3)	C3–C4–C5, 101.54 (17)
β [°]	92.18 (3)	C4–C41, 1.504 (3)	C4–C5–C4′, 113.53 (17)
γ [°]	101.27 (3)	C5–C4′, 1.503 (3)	O1–C5–C4, 104.80 (16)
V [Å^3]	1131.8 (7)		O1–N2–C3, 110.11 (17)
Z	2		N2–O1–C5, 109.82 (15)
Dihedral angles [°]			
C4–C3–N2–O1	0.6 (3)	C6″–C1″–C3–C4	−95.3 (3)
C3–N2–O1–C5	−0.1 (2)	C3–C4–C41–O42	83.5 (3)
C3–C4–C5–O1	0.7 (2)	C4–C5–C4′–C4′a	72.2 (2)

Table 6. Selected gHMBC correlations (⟶) in **10b** and **11b**



10b, 4-Acr				**11b, 5-Acr**			
From H-4 6.78 ppm		**From H-5 6.06 ppm**		**From H-4 4.66 ppm**		**From H-5 7.02 ppm**	
C3′	**128.4**					**C3′**	**126.0**
C4′a	**146.3**						
		C2‴,6‴	**125.6**	**C2‴,6‴**	**128.5**		
C4′	136.9	C4′	136.9	C4′	138.6	C4′	138.6
C1‴	141.6	C1‴	141.6	C1‴	138.8	C1‴	138.8
						C4	66.7
				C5	87.0		
C=N	159.7	C=N	159.7	C=N	160.3	C=N	160.3

Table 7. Selected gHMBC correlations (⟶) in **12b** and **13b**



12b, 4-Acr				**13b, 5-Acr**			
From H-4 6.84 ppm		**From H-5 5.44 ppm**		**From H-4 4.43 ppm**		**From H-5 7.08 ppm**	
C3′	**127.5**					**C3′**	**128.5**
C4a′	**144.9**					**C4′a**	**145.8**
C4′	134.8	C4′	134.8	C4′	138.8		
				C5	83.1		
C=N	160.2	C=N	160.2	C=N	155.5		
C=O	173.1			C=O	170.7		

Table 8. Reaction times and ratios of the regioisomers from cycloadditions of the amide **6** with the nitrile oxides **7a–c** after complete conversion

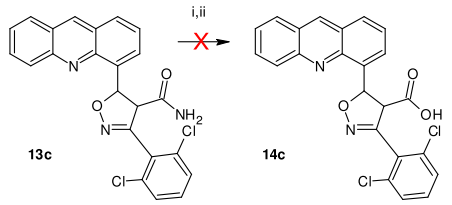
Regioisomers	25 °C Time (h)	40 °C Time (h)	60 °C Time (h)	Ratio[a]
12a + 13a	192	96	48	1.0:2.0
12b + 13b	336	240	192	1.9:1.0
12c + 13c	144	120	96	1.2:1.0

[a]The ratio was constant within the whole temperature range used.

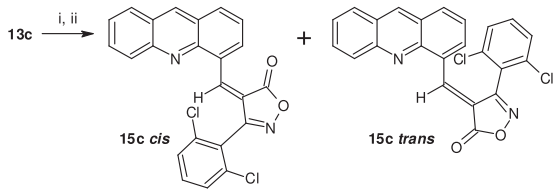
the minor carboxamide regioisomer **13c** with 10 equiv. of KOH in ethanol over 4 h at elevated temperature to achieve its complete conversion to only one product spot on the TLC plate. In the ^{1}H NMR spectrum, however, no isoxazoline signals of the acid **14c** were observed (Scheme 4). Instead, two diverse products with equal number of protons, similar chemical shifts and signal shapes were obtained in the ratio 3.3:1. Our attempts to separate them by chromatography using different mobile phases were unsuccessful.

NMR analysis suggested a mixture of isoxazolones **15c *cis*** (77%) and **15c *trans*** (23%) (Scheme 5). Attempts to resolve the spectra of two components in the mixture by selective three-bond ^{1}H,^{13}C-HMBC transfers optimized for J_{CH} = 12 or 5 Hz from exocyclic =CH protons to key isoxazolone C=O and C=N carbons were not successful and did not allow to safely assign the signals (Fig. 3).

Fortunately, repeated crystallization of the mixture of stereoisomers afforded orange needles of the major stereoisomer whose crystallographic analysis proved a *cis* configuration, **15c *cis*** (Fig. 4, Table 9). The dihedral angle between acridine and isoxazolone planes, C3′–C4′–C41–C4, was small, −28.81°, and indicated a high degree of coplanarity, while that between the isoxazolone and



Scheme 4. Hydrolysis of the amide **13c**. Reagents and conditions: (i) 10 equiv. KOH, EtOH, 40 → 60 °C; (ii) HCl (1:3).



Scheme 5. Reagents and conditions: (i) KOH, EtOH, 40 → 60 °C, 4 h; (ii) HCl (1:3), **15c *cis***: 77%, **15c *trans***: 23%.

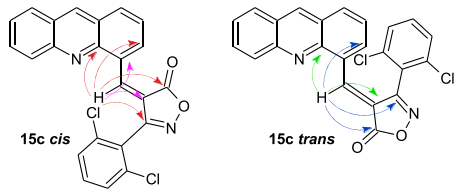


Figure 3. Selected gHMBC (→) correlations in **15c**. The experiment was optimized for couplings of 12 Hz →, 5 Hz →, 12 Hz →, 5 Hz →. Left—the major isomer **15c *cis***, right—the minor isomer **15c *trans***.

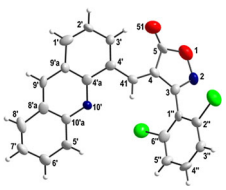


Figure 4. Crystallographic structure of the isoxazolone **15c *cis***.

2,6-dichlorophenyl moiety, N2–C3–C1″–C2″, was larger, 69.42°, suggesting a closer-to-perpendicular arrangement of the particular rings. The configuration *cis* seems to be energetically preferred with these compounds, similarly to isoxazolones we have prepared from unstable nitrile oxides.

The NMR spectra confirmed that near-to-coplanar mutual position of acridin-4-yl and isoxazolone skeletons in the solid state persisted also in the solution of *cis* and *trans* isomers. Whereas acridine H-3′ signal in **15c *trans*** was found at 7.26 ppm as expected, H-3′ signal in **15c *cis*** was considerably, by 2.47 ppm, deshielded (9.73 ppm, Table 10). So a large difference follows from a magnetic anisotropy effect of the spatially close isoxazolone C=O group in **15c *cis*** (Figs. 3 and 4). Smaller differences of corresponding chemical shifts were registered also for proton signals more distant from the C=O group, H-2′ (0.81 ppm) and H-1′ (0.33 ppm). In addition, a synergic action of two electron-acceptor groups, C=O and C=N, elicited a strong deshielding of exocyclic =CH proton to 9.29 ppm in **15c *cis*** and 9.53 ppm in **15c *trans*** as well as strong polarization of the exocyclic double bond (=C-4 ≈ 117–119 ppm, =C—H ≈ 148–151 ppm, Table 11).

Table 9. Selected geometric parameters with estimated standard deviations for **15c *cis***

			Distance [Å]
Cell setting	Orthorombic	C4′–C41	1.420 (14)
Space group	$P2_12_12_1$	C41–H41	0.929
a [Å]	6.9961 (19)	C41–C4	1.368 (14)
b [Å]	12.783 (4)	C4–C5	1.468 (14)
c [Å]	21.158 (6)	C5–O51	1.209 (12)
α [°]	90	C5–O1	1.382 (12)
β [°]	90	O1–N2	1.439 (12)
γ [°]	90	N2–C3	1.326 (13)
V [Å^3]	1892.1 (9)	C3–C4	1.421 (14)
Z	4	C3–C1″	1.478 (14)
Dihedral angles [°]			
C3′–C4′–C41–C4	−28.81 (2)	O51–C5–O1–N2	178.72 (9)
C4′a–C4′–C41–H41	−23.44 (1)	O1–N2–C3–C1″	−176.10 (9)
H41–C41–C4–C3	−0.91 (2)	N2–C3–C1″–C2″	69.42 (1)
H41–C41–C4–C5	174.88 (1)	C3–C1″–C6″–C(H_3)	2.09 (2)
C41–C4–C5–O51	5.13 (2)		

Table 10. Selected proton chemical shifts (ppm) of **15c *cis*** and **15c *trans*** and their difference Δ

Isomer	=CH	H-1′	H-2′	H-3′	H-5′
15c *cis*	9.29	8.27	7.74	9.73	7.96
15c *trans*	9.53	7.94	6.93	7.26	8.31
Δ, ppm	0.24	0.33	0.81	2.47	0.35

Table 11. Selected carbon chemical shifts (ppm) of **15c *cis*** and **15c *trans***

Isomer	C=O	C=N	=CH	=C-4	C-1′	C-2′	C-3′
15c *cis*	168.2	162.1	148.5	117.6	135.5	125.6	136.9
15c *trans*	169.5	157.7	150.9	119.1	132.4	123.5	133.0
Δ, ppm	1.3	4.4	2.4	1.5	3.1	2.1	3.9

After all, we were interested in a mechanism of isoxazolone formation, as only one similar transformation of isoxazolinyl esters of our type to the isoxazolone structure has been described so far.[32] On this route, ring-opening of the isoxazoline skeleton under irradiation or acid/base addition has been described repeatedly in recent years.[33a–c] On this basis it was assumed that basic hydrolysis can afford corresponding oximes which further undergo the Beckmann rearrangement after acidification. In our case, however, a concurrence of an ester hydrolysis and ring opening may be expected. Taking into account the resulting structure, the isoxazoline ring opening in basic conditions to potassium oxime salt seems to run faster than hydrolysis of the amide to the carboxylic acid. A subsequent nucleophilic addition of an oxime oxygen anion onto the amide carbonyl (maybe already partially hydrolyzed) giving a tetrahedral intermediate and following elimination of ammonium chloride after acidification afforded finally the both stereoisomers.

Conclusions

Dipolar cycloadditions of methyl 3-(acridin-4-yl)propenoate (**4**) and 3-(acridin-4-yl)propenamide (**6**) with activated *o,p*-substituted benzonitrile oxides **7a–c** (2,4,6-trimethoxy, 2,4,6-trimethyl, 2,6-dichloro) contrasted with those of 4-(2-styryl)acridine (**5**). A detailed NMR analysis of two series of isoxazoline regioisomers, 4-Acr and 5-Acr, allowed a closer insight on the regioselectivity of these DCs. Correlation found between the regioselectivity and ^{13}C NMR chemical shifts of the dipolarophile may contribute to explanation of the DC reaction mechanism. Whereas the ester **4** and amide **6** showed a stronger tendency to afford major 5-(acridin-4-yl)-isoxazoline regioisomers, the phenyl group in the styrylacridine **5** significantly increased the regioselectivity in favor of 4-(acridin-4-yl)-isoxazoline ones. Regarding the dipoles, 2,4,6-trimethoxybenzonitrile oxide was most prone to give the 5-Acr isoxazolines while mesitonitrile oxide strongly preferred the 4-Acr ones. Unusually high chemical shifts have been observed for isoxazoline H-4, H-5 protons surrounded by aromatic substituents. The isoxazoline **13c** upon hydrolysis underwent an unexpected transformation to isoxazolones **15c *cis*** and **15c *trans***. In the former, a very strong deshielding of acridine protons close to the C=O group has been found.

The data obtained from this series and following one studying acridin-9-yl dipolarophiles gave the basis for analysis of main factors influencing the regioselectivity, i.e. polarity of the dipolarophilic CH=CH double bond, electron-donor effects of substituents in the BNO dipoles, and interactions between the aromatic rings in the target isoxazolines.

Experimental

General information and materials

Reagents were commercial and used without further purification. Solvents were distilled and dried using standard methods. Melting points were measured on a Boetius apparatus and are uncorrected. Thin-layer chromatography (TLC) was carried out on the aluminum TLC plates coated with silica gel ALUGRAM* SIL G/UV_{254} (Macherey–Nagel, Germany) and visualized under UV light ($\lambda = 254$ nm). Column chromatography (CC) was performed on 230–400-mesh silica gel (Merck). Preparative thin-layer chromatography (PTLC) was made on the glass plates (25x10 cm) coated with 2 mm silica gel layer.

^{1}H, ^{13}C, and 2D NMR (DEPT, H,H-COSY, gHSQC, gHMBC, NOESY) spectra were recorded on a Varian Mercury Plus NMR spectrometer (400.13 MHz for ^{1}H) in deuteriochloroform or dimethyl sulfoxide-D_6 (**12c**, **13c** only) with tetramethylsilane as an internal standard (0.00 ppm) at room temperature. To determine the conversion and regioselectivity of dipolar cycloadditions, parallel reactions of the dipolarophile (0.04 mmol) and the dipole (0.12 mmol) in $CDCl_3$ (0.6 mL) were carried out in a sealed NMR tube at room temperature. The percentage of conversion and the molar ratio of the regioisomers formed was determined by comparing the integrals of alkene protons signals and a sum of integrals of isoxazoline H-4 and H-5 signals. It was found, generally, that quantitative ratios of both regioisomers were constant over the whole reaction course with a less than 5% NMR integration error.

Mass spectra (MS) were taken on a MALDI-TOF IV instrument (Shimadzu, Kratos Analytical, England) with a positive matrix-assisted laser desorption/ionization coupled with in-source decay (ISD) and combined with a time-of-flight analyzer. 2,5-Dihydroxybenzoic acid (DHB) was used as a matrix. The sample (1 mg) was dissolved in 1 mL of acetonitrile/water 1:1. For the spot preparation, a mixture of 1 μL of the matrix DHB with an analyte solution (10 pmol/μL) was used. The sample spots were air-dried at room temperature. Ion acceleration voltage was set to 5 kV. Samples were irradiated by a nitrogen laser at 337 nm. Typically, 100 shots were summed into a single mass spectrum.

Crystal data were obtained on a Bruker SMART 1000, Oxford Diffraction Gemini R CCD diffractometer, and Oxford Diffraction Xcalibur2 CCD. Data collection: CrysAlis CCD (Oxford Diffraction, 2006). Cell refinement: CrysAlis CCD. Data reduction: CrysAlis RED (Oxford Diffraction, 2006). The program used to solve the structure: SHELXS97 (Sheldrick, 1997). The program used to refine the structure: SHELXL97 (Sheldrick, 1997). Molecular graphics: DIAMOND (Brandenburg, 1998).[34,35]

Elemental analysis was performed on a Perkin-Elmer CHN 2400 elemental analyzer.

Synthesis of acridine-4-carbaldehyde (3)

To a stirred suspension of 4-bromomethylacridine (**2**, 1.00 g, 3.67 mmol) in dried dimethyl sulfoxide (2 mL), a solution that was prepared by addition of 2-nitropropane (0.393 g, 0.040 mL, 4.41 mmol) to sodium (0.093 g, 4.04 mmol) in dry methanol (2 mL) was added dropwise over 1 h. The reaction mixture changed from yellow to dark red and became homogenous. After 1 h stirring at room temperature, the reaction mixture was poured into water (100 mL) and a yellow precipitate that formed was filtered off, washed with cold water, and dried to give the aldehyde **3** (0.68 g, 89%, 118.0–119.0 °C (*n*-hexane)[27]).

Synthesis of methyl 3-(acridin-4-yl)propenoate (4)

A mixture of a methyl (triphenylphosphoranylidene) acetate ylide[36] (1.66 g, 4.95 mmol) and acridin-4-carbaldehyde (**3**, 1.0 g, 4.83 mmol) in dry chloroform (5 mL) was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (eluent cyclohexane/acetone, 9:1 *v/v*) and crystallized from ethyl acetate to give the ester **4** as a pure *E* isomer.

Yield 530 mg, 42%. Bright yellow solid. Mp 120.0–122.0 °C. [Found: C 77.40, H 4.86, N 5.19; $C_{17}H_{13}NO_2$ (263.30); requires C 77.55, H 4.98, N 5.34].

Synthesis of 4-(2-styryl)acridine (5)

Sodium hydride (60%, 145 mg, 6.03 mmol) was added to a solution of benzyltriphenylphosphonium chloride (1 g, 2.65 mmol) in anhydrous tetrahydrofuran (5 mL). The solution was cooled below −10 °C, stirred for 30 min, an equimolar amount of the aldehyde **3** (500 mg, 2.40 mmol) was added, stirring continued at −10 °C for 1 h, and at room temperature for next 12 h. The solvent was evaporated under reduced pressure and the rest was purified by column chromatography with an eluent cyclohexane/ethyl acetate (5:1 *v/v*) to obtain the dipolarophile **5**. Styrylacridine **5** was obtained as a pure *E* isomer.

Yield 275 mg, 41%. Bright yellow solid. Mp 130.0–131.0 °C. [Found: C 89.42, H 5.48, N 4.91; $C_{21}H_{15}N$ (281.36) requires C 89.65, H 5.37, N 4.98].

Synthesis of 3-(acridin-4-yl)propenamide (6)

Sodium hydride (60% purity, 0.115 g, 4.82 mmol) was added to a solution of amidomethyl triphenylphosphonium chloride (0.858 g, 2.41 mmol) in dry dichloromethane (5 mL). The solution was cooled below 0 °C and stirred for 30 min, then the aldehyde **3** (0.500 g, 2.41 mmol) was added, stirring continued at −10 °C for 1 h and at room temperature for next 24 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (cyclohexane/ethyl acetate, 1:4 *v/v*) to give the amide **6** as a pure *E* isomer.

Yield 654 mg, 55%. Yellow solid. Mp 250.0–252.0 °C (ethanol). [Found: C 77.25, H 4.60, N 11.38; $C_{16}H_{12}N_2O$ (248.28) requires C 77.40, H 4.87, N 11.28].

General procedure for the synthesis of esters 8a–c, 9a–c, and phenyl derivatives 10a–c, 11a–c

To a solution of the alkene **4**, **5** (100 mg, 1 equiv.) in dry chloroform (4 mL), the nitrile oxide **7a–c** (3 equiv.) was added. The reaction mixture was stirred at room temperature (^{1}H NMR monitoring). The solvent was evaporated under reduced pressure and a solid was purified by column chromatography and/or preparative thin-layer chromatography (see the eluent bottom) to give the corresponding regioisomers.

Methyl 5-(acridin-4-yl)-3-(2,4,6-trimethoxyphenyl)-4,5-dihydro-2-isoxazoline-4-carboxylate (**9a**)

CC: dichloromethane. Yield 41 mg, 23%. Yellow solid. Mp 163.0–165.0 °C (acetone/*n*-heptane). [Found: C 68.40, H 5.28, N 5.75; $C_{27}H_{24}N_2O_6$ (472.50) requires C 68.63, H 5.12, N 5.93].

Methyl 5-(acridin-4-yl)-3-(3-bromo-2,4,6-trimethoxyphenyl)-4,5-dihydro-2-isoxazoline-4-carboxylate (**9d**)

Yield 20 mg, 11%. White solid. Mp 209.0–210.0 °C (acetone/*n*-heptane). [Found: C 58.58, H 4.39, N 4.84; $C_{27}H_{23}BrN_2O_6$ (551.40) requires C 58.81, H 4.20, N 5.08]; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.77 (1H, s, H-9′), 8.05 (1H, d, *J* 8.4 Hz, H-5′), 8.05 (1H, d, *J* 8.4 Hz, H-3′), 8.00–7.96 (2H, m, H-1′,8′), 7.74 (1H, ddd, *J* 8.4, 6.4, 1.2 Hz, H-6′), 7.58–7.51 (2H, m, H-2′,7′), 7.21 (1H, d, *J* 6.8 Hz, H-5), 6.27 (1H, s, H-5′′), 4.53 (1H, d, *J* 6.8 Hz, H-4), 3.90 (3H, s, OCH_3-6″), 3.81 (3H, s, OCH_3), 3.73 (3H, s, OCH_3-4″), 3.72 (3H, s, OCH_3-2″).

Methyl 4-(acridin-4-yl)-3-(2,4,6-trimethylphenyl)-4,5-dihydro-2-isoxazoline-5-carboxylate (**8b**)

CC: *n*-heptane/acetone, 4:1. Yield 71 mg, 44%. Yellow crystals. Mp 59.0–60.0 °C (ethanol). [Found: C 76.31, H 5.48, N 6.45; $C_{27}H_{24}N_2O_3$ (424.50) requires C 76.40, H 5.70, N 6.60]; EI-MS (70 eV): *m/z* (%) = 463 (8) $[M+K]^+$., 447 (36) $[M+Na]^{+\cdot}$, 425 (100) $[M]^{+\cdot}$, 409 (88), 367 (10), 340 (43), 305 (8), 282 (20), 265 (8), 200 (16), 179 (60), 156 (12), 139 (24).

Methyl 5-(acridin-4-yl)-3-(2,4,6-trimethylphenyl)-4,5-dihydro-2-isoxazoline-4-carboxylate (**9b**)

CC: *n*-heptane/acetone, 4:1. Yield 51 mg, 32%. Yellow crystals. Mp 168.0–170.0 °C (ethanol). [Found: C 76.58, H 5.68, N 6.68; $C_{27}H_{24}N_2O_3$ (424.50) requires C 76.40, H 5.70, N 6.60]; EI-MS (70 eV): *m/z* (%) = 425 (100) $[M]^{+\cdot}$, 407 (14), 348 (14), 295 (14), 210 (12).

Methyl 4-(acridin-4-yl)-3-(2,6-dichlorophenyl)-4,5-dihydro-2-isoxazoline-5-carboxylate (**8c**)

CC: dichloromethane. Yield 29 mg, 17%. Yellow solids. Mp 190.0–191.0 °C (acetone). [Found: C 63.64, H 3.30, N 6.04; $C_{24}H_{16}Cl_2N_2O_3$ (451.31) requires C 63.87, H 3.57, N 6.21]; EI-MS (70 eV): *m/z* (%) = 451 (86) $[M]^{+\cdot}$, 439 (66), 394 (74), 392 (86), 363 (33), 313 (47), 285 (43), 280 (100), 257 (6), 222 (56), 194 (6).

Methyl 5-(acridin-4-yl)-3-(2,6-dichlorophenyl)-4,5-dihydro-2-isoxazoline-4-carboxylate (**9c**)

CC: dichloromethane. Yield 28 mg, 16%. Yellow solid. Mp 209.0–211.0 °C (acetone). [Found: C 63.69, H 3.70, N 6.06; $C_{24}H_{16}Cl_2N_2O_3$ (451.31) requires C 63.87, H 3.57, N 6.21]; EI-MS (70 eV): *m/z* (%) = 451 (32) $[M]^{+\cdot}$, 438 (100), 313 (44), 285 (50).

4-(Acridin-4-yl)-5-phenyl-3-(2,4,6-trimethoxyphenyl)-4,5-dihydro-2-isoxazoline (**10a**)

CC: petrolether/acetone, 10:1. Yield 60 mg, 34%. Yellow solid. Mp 50.0–53.0 °C (acetone/*n*-hexane). [Found: C 75.70, H 5.22, N 5.78; $C_{31}H_{26}N_2O_4$ (490.56) requires C 75.90, H 5.34, N 5.71]; EI-MS (70 eV): *m/z* (%) = 491 (90) $[M]^{+\cdot}$, 476 (36), 387 (100), 179 (12).

5-(Acridin-4-yl)-4-phenyl-3-(2,4,6-trimethoxyphenyl)-4,5-dihydro-2-isoxazoline (**11a**)

CC: petrolether/acetone, 10:1. Yield 30 mg, 17%. Yellow solid. Mp 60.0–63.0 °C (acetone/*n*-hexane). [Found: C 75.99, H 5.46, N 5.57; $C_{31}H_{26}N_2O_4$ (490.56) requires C 75.90, H 5.34, N 5.71].

4-(Acridin-4-yl)-5-phenyl-3-(2,4,6-trimethylphenyl)-4,5-dihydro-2-isoxazoline (**10b**)

CC: acetone/*n*-hexane, 4:1. Yield 100 mg, 63%. Yellow solid. Mp 74.0–76.0 °C (acetone/*n*-hexane). [Found: C 83.95, H 5.80, N 6.14; $C_{31}H_{26}N_2O$ (442.56) requires C 84.13, H 5.92, N 6.33].

5-(Acridin-4-yl)-4-phenyl-3-(2,4,6-trimethylphenyl)-4,5-dihydro-2-isoxazoline (**11b**)

CC: acetone/*n*-hexane, 4:1. Yield 12 mg, 8%. Yellow solid. Mp 84.0–86.0 °C (acetone/*n*-hexane). [Found: C 84.27, H 6.05, N 6.40; $C_{31}H_{26}N_2O$ (442.56) requires C 84.13, H 5.92, N 6.33].

4-(Acridin-4-yl)-5-phenyl-3-(2,6-dichlorophenyl)-4,5-dihydro-2-isoxazoline (**10c**)

CC: *n*-heptane/acetone, 4:1. Yield 93 mg, 56%. Yellow solid. Mp 220.0–222.0 °C (acetone). [Found: C 71.43, H 3.72, N 5.85; $C_{28}H_{18}Cl_2N_2O$ (469.37) requires C 71.65, H 3.87, N 5.97]; EI-MS (70 eV): *m/z* (%) = 469 (100) $[M]^{+\cdot}$, 438 (84), 433 (11), 363 (15), 313 (53), 298 (83), 285 (51), 110 (8).

5-(Acridin-4-yl)-4-phenyl-3-(2,6-dichlorophenyl)-4,5-dihydro-2-isoxazoline (**11c**)

CC: *n*-heptane/acetone, 4:1. Yield 5 mg, 3%. Yellow solid. Mp 75.0–77.0 °C (acetone).

General procedure for the synthesis of carboxamides 12a–c, 13a–c

To a solution of 3-(acridin-4-yl)propenamide (**6**) (100 mg, 1 equiv.) in dry chloroform (4 mL), the nitrile oxide **7a–c** (3 equiv.) was added. The reaction mixture was stirred at room temperature (^{1}H NMR monitoring). The solvent was evaporated under reduced pressure and the purification was carried out by column chromatography and/or preparative thin-layer chromatography (see the eluent bottom) to give the corresponding solid regioisomers.

4-(Acridin-4-yl)-3-(2,4,6-trimethoxyphenyl)-4,5-dihydro-1,2-oxazol-5-carboxamide (**12a**)

CC: toluene/acetone, 1:1. Yield 20 mg, 11%. Yellow solid. Mp 268.0–269.0 °C (ethanol). [Found: C 68.40, H 5.22, N 9.30; $C_{26}H_{23}N_3O_5$ (457.49) requires C 68.26, H 5.07, N 9.18]; ESI-MS: *m/z* 458 $[M]^{+\cdot}$.

5-(Acridin-4-yl)-3-(2,4,6-trimethoxyphenyl)-4,5-dihydro-1,2-oxazol-4-carboxamide (**13a**)

CC: toluene/acetone, 1:1. Yield 27 mg, 15%. Yellow solid. Mp 199.0–200.0 °C (ethanol). [Found: C 68.43, H 4.90, N 8.99; $C_{26}H_{23}N_3O_5$ (457.49) requires C 68.26, H 5.07, N 9.18]; ESI-MS: *m/z* 458 $[M]^{+\cdot}$.

4-(Acridin-4-yl)-3-(2,4,6-trimethylphenyl)-4,5-dihydro-1,2-oxazol-5-carboxamide (**12b**)

CC: ethyl acetate/dichloromethane/hexsol, 10:5:4. Yield 18 mg, 11%. Yellow solid. Mp 200.0–201.0 °C (ethanol). [Found: C 76.08, H 5.48, N 10.31; $C_{26}H_{23}N_3O_2$ (409.49) requires C 76.26, H 5.66, N 10.26]; ESI-MS: *m/z* 410 $[M]^{+\cdot}$.

5-(Acridin-4-yl)-3-(2,4,6-trimethylphenyl)-4,5-dihydro-1,2-oxazol-4-carboxamide (**13b**)

CC: ethyl acetate/dichloromethane/hexsol, 10:5:4. Yield 13 mg, 8%. Yellow solid. Mp 285.0–286.0 °C (ethanol). [Found: C 76.01, H 5.94, N 10.03; $C_{26}H_{23}N_3O_2$ (409.49) requires C 76.26, H 5.66, N 10.26].

4-(Acridin-4-yl)-3-(2,6-dichlorophenyl)-4,5-dihydro-1,2-oxazol-5-carboxamide (**12c**)

CC: ethyl acetate/chloroform,1:8. Yield 32 mg, 18%. Yellow solid. Mp 245.0–246.0 °C (ethanol). [Found: C 63.49, H 3.20, N 9.33; $C_{23}H_{15}Cl_2N_3O_2$ (436.30) requires C 63.32, H 3.47, N 9.63]; ESI-MS: *m/z* 437 $[M]^{+\cdot}$.

5-(Acridin-4-yl)-3-(2,6-dichlorophenyl)-4,5-dihydro-1,2-oxazol-4-carboxamide (**13c**)

CC: ethyl acetate/chloroform, 1:8. Yield 20 mg, 11%. Yellow solid. Mp 271.0–272.0 °C (ethanol). [Found: C 63.22, H 3.57, N 9.47; $C_{23}H_{15}Cl_2N_3O_2$ (436.30) requires C 63.32, H 3.47, N 9.63]; ESI-MS: *m/z* 437 $[M]^{+\cdot}$.

General procedure for the synthesis of (4*Z*)-4-(acridin-4-ylmethylidene)-3-(2,6-dichlorophenyl)-4,5-dihydro-1,2-oxazole-5-one (15c *cis*) and (4*E*)-4-(acridin-4-ylmethylidene)-3-(2,6-dichlorophenyl)-4,5-dihydro-1,2-oxazole-5-one (15c *trans*)

To an ethanolic solution (5 mL) of the isoxazoline **13c** (100 mg, 0.23 mmol), KOH (129 mg, 2.30 mmol) was added at 40 °C, then temperature was increased to 60 °C and the reaction mixture was stirred for 4 h (TLC, cyclohexane/ethyl acetate, 1:1). The reaction mixture was cooled, the solvent was evaporated and water (10 mL) was added to the residue. The solution was acidified (HCl 3:1), a precipitate that formed was extracted with diethyl ether (2 × 10 mL). Combined organic layers were dried over $MgSO_4$, filtered, and the solvent was evaporated *in vacuo*. Crystallization from methanol gave a mixture of orange crystals of the oxazolones **15c *cis*** and **15c *trans*** (85 mg, 88%). Mp 201.0–204.0 °C. [Found C 65.67, H 2.72, N 6.53; $C_{23}H_{12}Cl_2N_2O_2$ (419.27) requires C 65.89, H 2.88, N 6.68].

Crystallographic data

Crystallographic data of **9b** (CCDC 864812), and **15c *cis*** (CCDC 864705) have been deposited at the Cambridge Crystallographic Database Centre. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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