Nucleophilic Vinylic Substitution (S_NV) of Activated Alkoxymethylene Derivatives with 6-Aminoquinoxaline

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Dedicated to Prof. D. Belluš on the occasion of his 65th birthday

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Treatment of 6-aminoquinoxaline with β,β-diactivated alkoxymethylene derivatives gave the corresponding *N*-(quinoxalin-6-yl)enamines. A variant of the S_NV reaction mechanism was proposed for substitution of the alkoxymethylene compounds, on the basis of the structures of the precursor enol ether and the vinylic substitution product and on computations.

Introduction

Quinoxalines and many of their condensed derivatives have been prepared in studies designed to produce biologically active materials:[1] imidazoquinoxalines, for example, have been found to be strong carcinogens in food.[2] In continuation of our work on the synthesis of polyheterocyclic fused systems containing the quinoxaline moiety we report here the synthesis and spectral properties of new quinoxaline derivatives, each substituted at C-6 with a substituted vinylamino group, which serve as precursors for fused quinoxalines. The mechanism and stereochemistry of nucleophilic substitution of alkoxy groups in alkoxymethylene derivatives of propanedioic acid, 3-oxobutanoic acid and cyanoacetic esters with amines have not been reported so far, despite the importance of this reaction, which is the first step of the tandem Gould–Jacobs reaction often exploited for preparation of compounds containing the condensed pyridone nucleus of antibacterial compounds of the nalidixic acid type.[3]

Even though these compounds have very often been exploited in the preparation of nalidixic acid analogues,[4] only a few reviews about them[5,6] (i.e., on diethyl ethoxymethylenemalonate,[3,7] ethoxymethylenemalononitrile[8] or aminomethylenemalonates[9]) have been published.

Results and Discussion

Addition of amines to activated carbon–carbon double bonds[10] is a variant of the Michael addition.[11] In the case of primary amines in acidic media, the monoaddition product affords,[11] without catalysis, the bis(adduct).[12] Several reactions have been reviewed[13] and the mechanism of the reaction has been studied over the past few decades[14] and also very recently.[15] Treatment of a nucleophile with an activated α,β-unsaturated system containing a β-leaving group (nucleofuge) results in nucleophilic vinylic substitution (S_NV) of the nucleofuge,[16] and different reaction mechanisms for the S_NV route have been reviewed.[16,17]

α-Alkoxymethylene compounds **1** substituted with two electron-withdrawing groups at C_β are typical push-pull systems. In such enol ethers or trifunctional electrocyclophiles[7] the nucleophilic replacement of the alkoxy group is the predominant reaction,[18] as demonstrated in Scheme 1 for the reaction with 6-aminoquinoxaline (**2**), which gives the enamines **3**.

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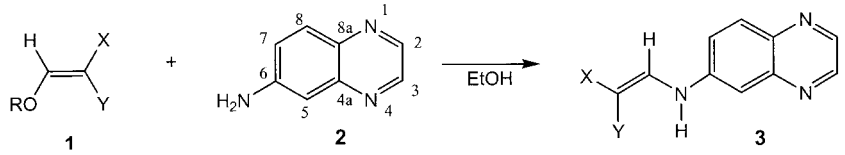


1 **2** **3**

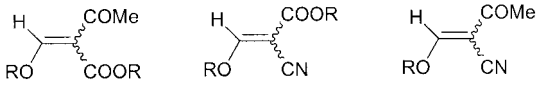
a: R = Me, X = CO_2Me, Y = CO_2Me
b: R = Et, X = CO_2Et, Y = CO_2Et
c: R = Et, X = CN, Y = CN
d: R = Et, X = COMe, Y = COMe
e: R = Me, X = COMe, Y = CO_2Me
f: R = Et, X = COMe, Y = CO_2Et
g: R = Et, X = COMe, Y = CN
h: R = Me, X = CN, Y = CO_2Me
i: R = Et, X = CN, Y = CO_2Et
j: R = Et, CXY = *c*-CCO-O-C(Me)$_2$-O-CO
k: R = Me, X = COMe, Y = CN

Scheme 1. Substituents for **1** and **3** (stereochemistry is discussed below).

The known configurations of the precursor alkoxymethylene derivatives **1** and the products **3** suggest an S_NV reaction mechanism. These conclusions can be extended for reactions of (*E*)/(*Z*) mixtures of compounds **1** in which one isomer predominates.[19]

To provide evidence for S_NV mechanisms for the displacement by amines of the alkoxy group in **1** and those in related alkoxy ethers activated by two electron-withdrawing groups (EWGs) it is first necessary to establish the configuration of the enol ether. If the β-EWGs are identical, as in derivatives of propanedioic or Meldrum's acids and pentane-2,4-dione, only one product is formed; thus, such derivatives give no stereochemical information. With 3-oxobutanoic and cyanoacetic acid derivatives, however, the relationship between the configurations of the enol ether precursors and the enamine products can serve as a mechanistic probe. Enol ethers **1e**–**1i** are available at present as (*E*)/(*Z*) mixtures and have not yet been separated into their (*E*) and (*Z*) isomers. In the previously described syntheses of methoxy- or ethoxymethylene-3-oxobutanenitrile only the (*E*) isomers were obtained.[20]

This is shown by the NMR spectrum of the enol ether **1k**. In the isolated product the low value of the observed vicinal coupling constant of the olefinic proton with the cyano carbon atom in the ^{13}C NMR spectrum of **1k** ($^3J_{H–CN}$ = 10.0 Hz) could be attributable to either isomer, as it is in the borderline region for values of either *cis* or *trans* coupling constants. However, the spectrum of the crude reaction mixture also shows ca. 10% of the other isomer, with a lower *J* value ($^3J_{H–CN}$ = 5.2 Hz), thus establishing an (*E*) configuration for the major isomer (Tables 1 and 2). The same conclusion also applies in the case of enol ether **1g**, whilst a similar situation exists for the cyanoacetic acid derivatives, in which the (*E*)/(*Z*) ratios for **1h** and **1i** are also close to 10:1 (Scheme 2), according to the similar coupling constants. This is consistent with the much smaller bulk of the linear cyano group in relation to the ester or the acetyl groups, which makes the (*E*) isomers (with the alkoxy group and the bulkier alkoxycarbonyl group *trans*) thermodynamically more stable, and thus predominant in both **1g** and **1k**. In contrast, due to the much closer sizes of the acetyl and alkoxycarbonyl groups, the alkoxymethylene derivatives of 3-oxobutanoic esters **1e** and **1f** exist as ca. 1:1



1e and **1f**: 1:1 **1h** and **1i**: 10:1 **1g** and **1k**: 10:1

Scheme 2. (*E*)/(*Z*) ratios for **1e**–**1i** and **1k**.

Table 1. ^{13}C NMR spectroscopic data (δ in ppm) for **1k** and **1g**.

Compound		CH_3	CH_2	CH_3CO–	>C=	–CH=	CN	CO	$^3J_{H–CN}$ [Hz]
1k	(*E*)-	64.32	–	27.80	94.90	173.26	114.05	191.32	10.0
	(*Z*)-	62.87	–	25.32	91.96	169.45	115.63	185.21	5.2
1g	(*E*)-	74.19	15.27	28.28	94.61	172.06	114.53	191.78	10.8
	(*Z*)-	66.40	18.42	24.76	92.65	167.69	115.50	184.99	5.6

Table 2. ^1H NMR spectroscopic data (δ in ppm) for the isomers of **1k** and **1g**.

Compound	**1k**		**1g**		% (*E*) isomer[a]	% (*E*) isomer[a]
	(*E*)-	(*Z*)-	(*E*)-	(*Z*)-	**1k**	**1g**
CH_3	4.18	3.85	1.46	1.24	93	95
CH_2	–	–	4.38	3.71	–	98
CH_3CO–	2.37	2.41	2.38	2.43	83	86
–CH=	7.99	8.68	8.03	8.73	89	89

[a] Estimated from corresponding signal.

(*E*)/(*Z*) mixtures (based on the $^3J_{H,C}$ coupling constants and integration of the relevant signals).

Michael addition reactions are routinely used in many syntheses involving alkoxymethylenepropanedioic acid derivatives,[7,8] and the mechanism of substitution of an alkoxy group attached to a double bond has been investigated in detail by Bernasconi et al.[21] and by Rappoport et al. for amino nucleophiles.[22] Only in recent years have works studying nucleophilic vinylic substitution with inversion of configuration appeared.[23]

We prepared the products of reactions between 6-aminoquinoxaline (**2**) and ten different enol ethers **1**. The reactions were carried out by mixing the components in ethanol at room temperature and monitoring the disappearance of **2** by TLC [R_f(amine) ≈ 0 in $CHCl_3$/MeOH, 10:1]. The reaction times were between 2 and 30 h. The reaction mixtures were then concentrated to dryness at a temperature <40 °C, and the crude reaction mixtures were analysed by NMR in $CDCl_3$ for **3e**, **3f** and **3i**, or in DMSO (due to their low solubilities) for **3c** and **3f**–**3i**. The (*E*)/(*Z*) ratios are given in Table 3 (in the row "before heating"). All products were then recrystallized from appropriate solvents and dried, and the (*E*)/(*Z*) ratios of **3e**–**3i** after crystallization were again determined and are given in Table 3 (row "after heating"). Assignment of the structures of the isomers was based on the $^3J_{H,C}$ coupling constants, and the isomer ratios were determined from the integrated intensities of corresponding signals of both isomers, mainly in the aliphatic region. The NMR spectroscopic data are given in the Exp. Sect.

Table 3. (*E*)/(*Z*) ratios of the products **3e**–**3i** formed by the reactions between **1e**–**1i** and 6-aminoquinoxaline (**2**).

	3e	**3f**	**3g**	**3h**	**3i**
Before heating	53:47	49:51	7:93	12:88	9:91
After heating	85:15	87:13	45:55	67:33	81:19

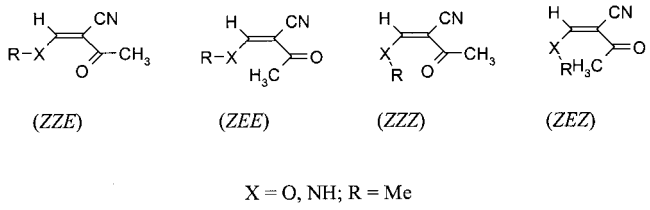
By comparison of the pairs of results it could be concluded that the reaction proceeds under kinetic conditions with inversion of configuration, in contrast to almost all known observed and deduced[22] nucleophilic vinylic substitutions,[17] but in agreement with the results obtained for the reaction between methoxymethylene-substituted Meldrum's acid (in relation to thermodynamic vs. kinetic product) and *o*-aminothiophenol[24] and the computational results below.

After heating of the reaction mixtures at reflux and/or recrystallization (heating at reflux in an appropriate crystallization solvent while dissolving), thermal isomerization takes place and the isomer ratios indicate higher percentages of the (*E*) isomers (cf. Table 3), due to relatively low isomerization barriers between the isomers (83.3–100.9 kJ mol^{-1})[25] and the formation of the sterically favoured isomers with the bulkier substituents and the alkylamino groups in **3h**/**3i** in *trans* relationships. If the effective bulks of the two groups are comparable (e.g., for **3e** and **3f**), the formation of an intramolecular hydrogen bond has a major effect on the formation of the thermodynamically more stable product (e.g., the intramolecular hydrogen bond with the carbonyl group of the acetyl group is stronger than that to the ester group).[25] Both effects are important in the case of **3g**, as is corroborated by the fact that the (*Z*) isomer content prevails in the cyanoacetic esters **3h**/**3i**, whereas the (*E*)/(*Z*) ratio in **3g** is close to equimolar. The change of the solvent from $CDCl_3$ to DMSO does not have any significant influence on the isomer ratios.[25c]

Computations

Stabilities of the Isomers/Conformers of 1k and Its Product with Methylamine

For computational modelling of the reaction pathway between the studied β,β-diactivated alkoxymethylene compounds and 6-aminoquinoxaline we chose the reaction between **1k** and methylamine, as the simplest alkylamine representing 6-aminoquinoxaline. The reactant **1k** [Me–O–CH=C(CN)$COCH_3$] and the Me–NH–CH=C(CN)$COCH_3$ product (**4**) can exist in several geometric and conformational forms [the structures for the (*Z*) isomers are given in Scheme 3].



Scheme 3. Conformers of the (*Z*) isomers of **1k** and **4**.

Since all four substituents at the double bond differ, both compounds can exist as two isomers, with the methoxy or methylamino group *trans* or *cis* to the acetyl group. This relationship is represented in the designator by the first letter (*E* or *Z*). Each isomer has conformers obtained by rotation of the acetyl group, in which the carbonyl oxygen atom may be oriented away from or towards the C=C double bond (*anti* or *syn* position represented by the second letter *E* or *Z*). Rotation of the methoxy or methylamino group can similarly orient their methyl group with reference to the C=C double bond (the *anti* or *syn* position is represented by the third letter *E* or *Z*). Quantum chemical calculations of the energies of all four possible conformers of both isomers of **1k**, as well as for both isomers of the product based on the AM1, PM3 and ab initio method using 6-31G and 6-31G** basis sets, are given in Table 4.

From Table 4 it is clear that the (*EZE*) conformer is the most stable conformer for MeO–CH=C(CN)COMe according to ab initio (AI) and PM3 calculations, but according to AM1 calculations it is the (*EZZ*) form. It is known that the AM1 method overestimates hydrogen–electronegative atom interactions when the hydrogen atom is bonded to a carbon atom, and this is perhaps the reason why the

Table 4. Calculated relative energies [kJ mol^{-1}] for the conformers of Me–O–CH=C(CN)(COMe) and Me–NH–CH=C(CN)(COMe).

Conformer	Me–O–CH=C(CN)(COMe)				Me–NH–CH=C(CN)(COMe)			
	MP2+HF+ZPE 6-31G**	HF 6-31G	AM1	PM3	MP2+HF+ZPE 6-31G**	HF 6-31G	AM1	PM3
(*EZE*)	0.0	0.0	5.3	0.0	15.5	11.2	5.9	1.2
(*EZZ*)	1.8	2.9	0.0	1.7	22.8	22.0	14.6	16.4
(*EEE*)	14.9	24.8	22.7	13.0	30.1	36.9	24.0	9.2
(*EEZ*)	14.7	21.9	15.0	12.1	40.3	50.2	33.9	23.2
(*ZZE*)	16.7	30.5	18.5	7.9	0.0	0.0	0.0	0.0
(*ZZZ*)	23.0	24.4	14.3	12.5	44.1	49.7	28.5	23.3
(*ZEE*)	15.2	22.6	20.9	-	53.0	61.7	34.6	16.9
(*ZEZ*)	–	–	–	–	–	–	–	–

values differ from those obtained by the ab initio method. However, the tendency to prefer the (*E*) isomer with the (*Z*) conformation of the acetyl group over other isomers and conformations is evident, supporting the conclusions drawn from the NMR measurements. For the unsymmetric enol ethers, the presence of the conformers was evident (in the ^{13}C NMR spectrum of **1e**, for example, four signals with one dominating were detected for the methyl part of the acetyl group, together with four signals for the methyl and the carbonyl carbon atoms of the methoxycarbonyl group).

For the product Me–NH–CH=C(CN)COMe, the (*ZZE*) conformer is the most stable conformer according to all three methods. This reflects the effect of the intramolecular hydrogen bond between the amino hydrogen atom and the carbonyl oxygen atom. These results are confirmed by ab initio calculations at the MP2 level with full optimization of geometry and inclusion of zero point energy (ZPE) for all reactant and product conformers in the larger 6-31G** basis set.

The Reaction Pathway

We performed calculations on the reaction pathways from the (*EZE*) conformer of **1k** by the ab initio and PM3 methods and from the (*EZZ*) conformer of **1k** by the AM1 method. The calculated energies, relative energies and several isomeric parameters for reactants, intermediates (INT), transitions states (TS) and products are given in Tables 5 and 6. The computed ab initio reaction path profile is shown in Figure 1, together with the calculated structures of the reactants, intermediates, transition states and products. Similar plots based on the semiempirical AM1 and PM3 methods are given in Figure 2. The atom numbering for all structures is given in Figure 3.

The reaction proceeds through two reaction intermediates and two transition states. Initially, in a slightly exothermic process, the reactants **1k** and $MeNH_2$ create a reaction complex INT1 with a distance of approximately 3.4–4.0 Å between the H_2N nitrogen atom and C_1, in which the amino hydrogen atoms H_{17} are H_{23} are oriented toward the carbonyl oxygen atom O_4. The nitrogen atom of methylamine is thus approaching with its lone electron pair oriented toward the olefinic hydrogen atom H_9 and therefore not from the π-direction or from the in-plane backside of the σ-orbital of the C–OR bond. This orientation is supported by the negative charge on the carbonyl oxygen atom O_4 and the positive charge on the olefinic carbon atom C_1 and the olefinic hydrogen atom H_9. The reactants then pass through the first transition state TS1, 70 kJ mol^{-1} above INT1, to the second intermediate complex INT2. During this step the distance between the amino nitrogen atom and C_1 is shortened to 1.9–2.0 Å in TS1 and 1.5–1.6 Å in INT2. Simultaneously, the bond between the methoxy oxygen atom O_{18} and C_1 is elongated to 1.4 Å. Because of the changes in the bonding character of the C_1 carbon atom the C=C bond length increases. Simultaneously, one of the amino hydrogen atoms (H_{17}) is oriented towards the carbonyl oxygen atom O_4, forming an intramolecular hydrogen bond, whereas the second hydrogen atom H_{23} is orientated

Table 5. Calculated energies and relative energies (right-hand column) for the reactants, intermediates, transition states and products of the reaction Me–O–CH=C(CN)(COMe) + $MeNH_2$ → Me–NH–CH=C(CN)(COMe) + MeOH.

		HF/6-31G a.u.	kJ mol^{-1}	AM1 kJ mol^{-1}	kJ mol^{-1}	PM3 kJ mol^{-1}	kJ mol^{-1}
Reactants:	(*EZE*)	–435.226701				–133.518	
	(*EZZ*)			–153.425			
	$MeNH_2$	–95.170903		–30.903		–21.710	
	both	–530.397604	0.0	–184.328	0.0	–155.231	0.0
INT1		–530.409947	–32.4	–198.442	–14.1	–168.279	–13.0
TS1		–530.380657	44.5	–125.053	59.2	–105.171	50.0
INT2		–530.395612	5.2	–137.155	47.1	–121.588	33.6
TS2		–530.340055	151.1	18.930	203.1	25.992	181.1
Products:	(*ZZE*)	–415.439177		–13.222		7.573	
	CH_3OH	–114.988166		–238.764		–217.200	
	both	–530.427343	–78.1	–251.986	–67.6	–209.627	–54.4

Table 6. Calculated structural parameters for the reactants, intermediates, transitions states and products of the reaction Me–O–CH=C(CN)(COMe) + $MeNH_2$ → Me–NH–CH=C(CN)(COMe) + MeOH.

		r_{C-N}	r_{C-O}	$r_{C=C}$	r_{N-H17}	r_{N-H23}	r_{O-H17}	r_{O-H23}	$r_{=O-H17}$	$r_{=O-H23}$
	AI		1.331	1.341	0.994	0.994				
Reactants	AM1		1.349	1.361	1.000	1.000				
	PM3		1.358	1.359	0.999	0.999				
	AI	3.386	1.327	1.347	1.000	0.998	4.221	4.639	2.259	3.766
INT1	AM1	3.771	1.348	1.363	1.002	1.002	4.542	4.589	2.448	2.474
	PM3	3.955	1.357	1.359	1.000	0.998	4.333	5.596	3.161	4.713
	AI	1.904	1.351	1.432	1.008	1.001	3.283	2.896	2.060	3.388
TS1	AM1	1.871	1.372	1.413	1.012	1.005	3.334	2.824	2.296	3.619
	PM3	1.996	1.354	1.396	1.018	0.999	3.370	2.972	1.908	3.305
	AI	1.518	1.403	1.498	1.039	1.006	3.143	2.458	1.698	3.117
INT2	AM1	1.588	1.400	1.459	1.033	1.018	3.253	2.710	2.054	3.359
	PM3	1.568	1.416	1.475	1.042	1.004	3.192	2.483	1.749	3.132
	AI	1.451	1.899	1.391	1.014	1.187	2.841	1.293	1.827	3.139
TS2	AM1	1.477	1.527	1.449	1.015	1.393	2.771	1.280	2.086	3.147
	PM3	1.499	1.530	1.448	1.027	1.414	2.763	1.275	1.766	3.224
	AI	1.322		1.378	1.000			0.950	1.941	
Products	AM1	1.349		1.384	1.002			0.964	2.122	
	PM3	1.378		1.375	1.014			0.949	1.854	

		$\delta_{O=C-C=C}$	$\delta_{O-C=C-C}$	$\delta_{N-C=C-C}$	$\delta_{H-C=C-C}$	$\delta_{C-O-C=C}$	$\delta_{C-N-C=C}$
	AI	0.0	180.0		0.0	180.0	
Reactants	AM1	0.0	180.0		0.0	0.0	
	PM3	0.0	180.0		0.0	180.0	
	AI	–0.3	179.6		–0.1	177.1	–105.6
INT1	AM1	–0.2	180.0		0.0	0.0	
	PM3	10.8	–178.9		0.7	–179.1	
	AI	10.3	174.4	–66.1	32.1	35.6	175.8
TS1	AM1	14.6	169.0	–74.4	26.7	26.8	174.2
	PM3	32.6	176.2		29.9	26.8	
	AI	7.4	–171.2	–54.8	59.7	–83.2	171.4
INT2	AM1	15.3	169.8	–66.5	45.5	40.4	176.9
	PM3	17.6	–167.6	–54.4	62.4	–87.7	168.5
	AI	–4.1	–83.7	12.0	166.6	–20.5	130.6
TS2	AM1	2.6	–75.6	28.2	165.8	5.4	125.3
	PM3	–1.6	–86.8	14.0	152.8	–9.5	126.3
	AI	0.0		0.0	180.0		180.0
Products	AM1	0.1		–0.4	179.8		179.0
	PM3	2.5		–7.8	175.7		162.6

towards the methoxy oxygen atom. Because of bonding of the methylamino group at carbon atom C_1 there is a tendency towards deviation of the olefinic hydrogen atom H_9 from the (*Z*) (*syn*) position and also towards rotation of the methoxy group towards the (*Z*) (*syn*) position. In the last part of the reaction pathway, methanol is split off via the four-centred transition state (C_1–O_{18}–H_{23}–N_{12}) TS2, in which H_{23} is shifted from the amino nitrogen atom to the methoxy oxygen atom O_{18}, and which is ca. 145–150 kJ mol^{-1} above INT2. The geometric parameters of TS2 calculated by the three methods are quite similar, except that the ab initio method gave longer and shorter C_1–O and N–H_{23} bond lengths, respectively, than the semiempirical methods. In TS2 the olefinic hydrogen atom H_9 and the amino nitrogen atom N_{12} at C_1 are already turned close toward the (*E*) (*anti*) and (*Z*) (*syn*) positions, respectively. This causes inversion of configuration at the olefinic carbon atom C_1. Figure 4 presents the ab initio energy profiles along the intrinsic reaction coordinates (IRCs) for the last part of the reaction pathway from intermediate INT2 to the products via transition state TS2. The IRCs were traced from TS2 ($s = 0$), which has an imaginary vibrational mode of 1521*i* cm^{-1}, towards both intermediate INT2 ($s < 0$) and products ($s > 0$) directions. The energy and geometric parameters are approaching those for the intermediate INT2 and products for $s < 0$ and $s > 0$, respectively, as can be seen from Figure 5 for the C_1–O_{18} and C_1–N_{12} bond lengths.

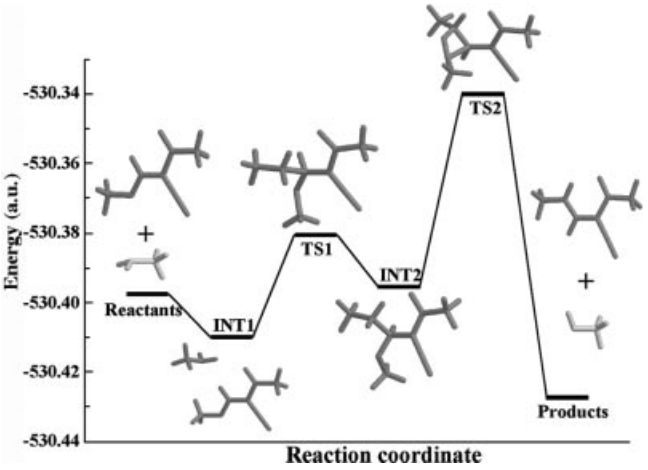


Figure 1. Potential energy profile (a.u.) for the MeOCH=C(CN)COMe + $MeNH_2$ reaction obtained by use of ab initio 6-31G energies at the HF level.

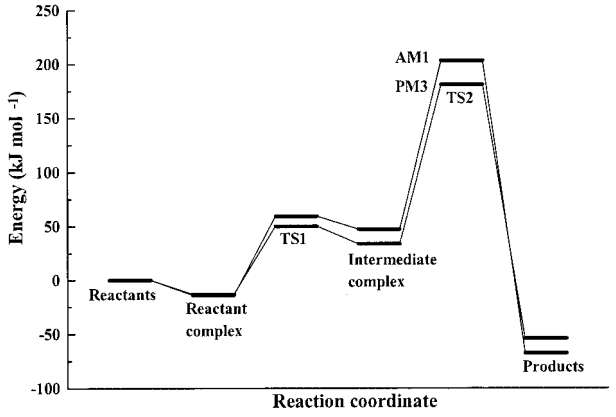


Figure 2. Potential energy profile [kJ mol^{-1}] for the MeOCH=C(CN)COMe + $MeNH_2$ reaction obtained by use of semiempirical AM1 and PM3 energies.

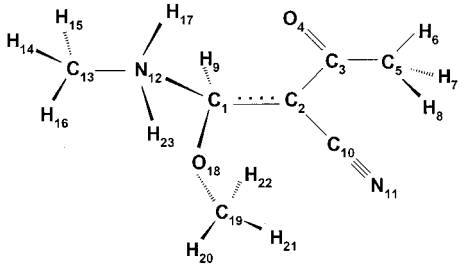


Figure 3. Schematic drawing and numbering of the atoms.

From Figure 5 we see that, from the almost identical values of the C_1–O_{18} and C_1–N_{12} bond lengths in ITN2, the C_1–N_{12} bond length decreases towards the value in the product whereas the C_1–O_{18} bond length increases due to the expulsion of methanol.

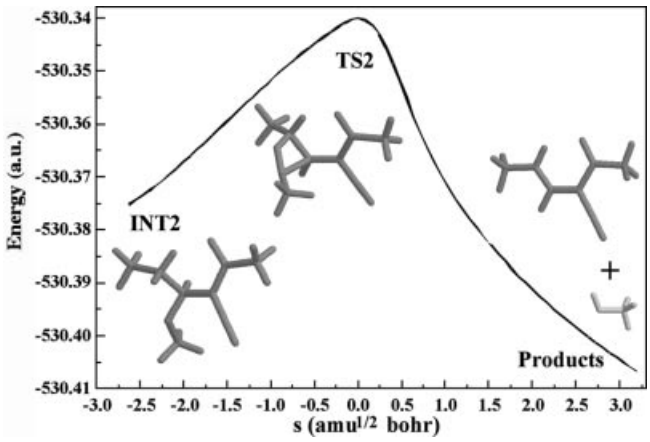


Figure 4. Plot of the potential energy (a.u.) along the minimum-energy pathway between the intermediate complex and the products.

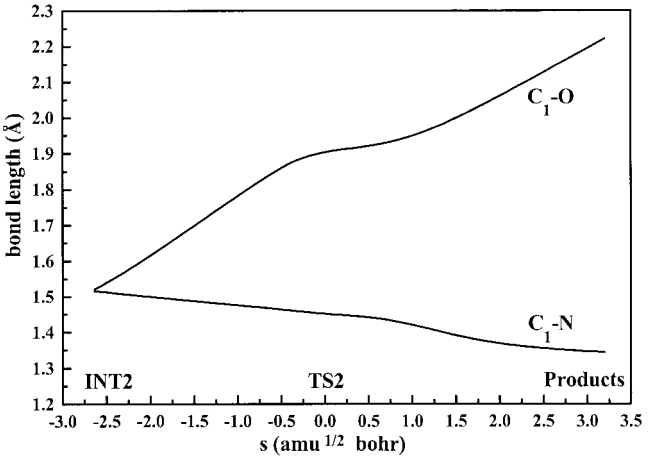


Figure 5. Distances [Å] between the amino nitrogen atom and the methoxy oxygen atom and the doubly bonded carbon atom C_1 along the minimum-energy pathway between the intermediate complex and the products.

Conclusions

Two effects – the bulk of the EWG and hydrogen bonding – influence the configurations of the S_NV products.

(i) The stereochemistry in the proposed nucleophilic vinylic substitution mechanism based on the quantum chemical calculations is in good agreement with the observed results under kinetic control: inversion of configuration on the olefinic carbon atom takes place during nucleophilic vinylic substitution in this type of compounds.

(ii) A cyano group is much smaller than an acetyl or alkoxycarbonyl group and the isomers with the cis-substituted amino and cyano groups are sterically preferred.

(iii) When the bulks of two groups are nearly equal (e.g., acetyl and alkoxycarbonyl) the preferred configuration is that involving the stronger intramolecular hydrogen bond.[25]

Experimental Section

General Methods: ^{1}H, ^{13}C and ^{15}N NMR spectra of 6-aminoquinoxalines were recorded with a Bruker DPX 400 spectrometer at 400, 100.61 and 40.56 MHz, respectively. Other spectra were recorded with a Varian VXR-300 at 300 and 75.45 MHz, respectively. Chemical shifts (ppm) are relative to TMS or nitromethane (^{15}N) in [D_6]DMSO; coupling constants are in Hz. Data measured in $CDCl_3$ (due to the better solubility) are given. The EI MS were measured with an MS 902S (AEI Kratos) instrument at 70 eV and 100 μA current trap. IR (0.5 mg of substance per 300 mg of KBr) and UV spectra (in MeOH) were recorded with FTIR PU 9802 (Philips) and Specord (Zeiss, Jena) spectrophotometers. Elemental analyses were performed with an EA-1108 (Carlo Erba) apparatus. Melting points (uncorrected) were measured with a Kofler micro hot-stage.

Computational Methods and Details: Quantum mechanical calculations were carried out with the Gaussian 94[26] and MOPAC6[27] program packages. Traditional Hartree–Fock (HF) ab initio methods with the simple 6-31G basis set and semiempirical AM1 and PM3 methods for calculation of the reaction pathway were used. The geometries of all reactants, intermediates, transitions states and products were optimized at the levels of theory mentioned above without imposition of any symmetry constraints. Vibrational analysis was systematically carried out in order to ensure that all optimized geometries corresponded to a local minimum with no imaginary frequency mode or a transition state with only one imaginary frequency mode. For all transition states the intrinsic reaction coordinate (IRC) analysis in mass-weighted Cartesian coordinates with gradient step size of 0.08 bohr amu½ were carried out in order to confirm that the transition structure connected the desired reactants and products. The reaction coordinate s is defined as the distance from the transition state, with $s > 0$ referring to the product side. In order to confirm the conformational stability of the reactant and product, ab initio calculations of the energy at the MP2 level with full geometry optimization and including zero point energy (ZPE) by use of the 6-31G** basis set were also conducted.

Solvents and Materials: The alkoxymethylene derivatives **1a**, **1b** and **1c** are commercially available. 3-Ethoxymethylene-2,4-pentanedione (**1d**), methyl (**1e**) and ethyl (**1f**) 2-alkoxymethylene-3-oxobutanoic acids, and 3-alkoxy-2-cyanopropenoic acids **1h** and **1i** were synthesized by condensation of methyl or ethyl orthoformate with the corresponding methylene compound (pentane-2,4-dione, methyl or ethyl 3-oxobutanoate and methyl or ethyl cyanoacetate).[28] Improved methods for the preparation of **1g** and **1j** were used.[29]

6-Aminoquinoxaline (2): 6-Nitroquinoxaline[30] (440 mg, 2.5 mmol) was dissolved in ethanol (50 mL), treated with Pd/C catalyst (3%, 50 mg) and hydrogenated with magnetic stirring and an overpressure of H_2 (20 kPa) until hydrogen consumption stopped (about 110 mL). The catalyst was filtered off, the filtrate was concentrated to dryness, and the product was recrystallized from toluene. Yield 277 mg (76%). M.p. 164–165 °C (ref.[28] m.p. 159–160 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (d, ^3J = 1.7 Hz, 1 H), 8.45 (d, ^3J = 1.7 Hz, 1 H), 7.74 (d, ^3J = 9 Hz, 1 H), 7.25 (dd, ^3J = 9, ^4J = 2.4 Hz, 1 H), 6.93 (d, ^4J = 2.4 Hz, 1 H), 6.06 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.61 (d, ^2J = 9.9 Hz), 145.07 (dd, ^1J = 180.8, ^2J = 11.3 Hz), 144.96 (dd, ^2J = 10.9, ^3J = 5.3 Hz), 139.78 (dd, ^1J = 182.7, ^2J = 11.0 Hz), 136.60 (td, ^2J = 10.0, ^3J = 5.3 Hz), 129.73 (d, ^1J = 162.1 Hz), 122.48 (dd, ^1J = 159.65, ^2J = 6.6 Hz), 105.08 (dd, ^1J = 159.5, ^3J = 4.8 Hz) ppm. ^{15}N NMR (40 MHz, $CDCl_3$): δ = –49.9 (N-1), –58.1 (N-4), –309.1 (NH_2) ppm.

Aminomethylene-quinoxaline Derivatives 3: The 6-aminoquinoxaline filtrate, prepared as described above, was treated with solutions of **1a**–**1j** (10 mmol) in ethanol (20 mL). The reaction mixtures were stirred at room temperature until the amine had disappeared (TLC monitoring, eluent $CHCl_3$/MeOH, 10:1). The resulting mixture was then analysed by NMR ($CDCl_3$) for the ratio of isomers (for **3e**–**3i**). After concentration of the reaction mixtures to dryness, the residue was recrystallized from the appropriate solvent.

Dimethyl 2-(Quinoxalin-6-ylaminomethylene)propanedioate (3a): M.p. 177–178 °C (EtOH). Yield 0.90 g (52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83, 3.90 (2×s, 2×3 H), 7.58 (dd, J = 9.1, $J_{7,5}$ = 2.5 Hz, 1 H), 7.81 (d, J = 2.5 Hz, 1 H), 8.12 (d, J = 9.1 Hz, 1 H), 8.68 (d, J = 13.3 Hz, 1 H), 8.78, 8.83 (2×d, J = 1.8 Hz, 2×1 H), 11.27 (d, J = 13.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.7, 51.9, 95.3, 113.4, 121.7, 131.5, 140.2, 140.6, 143.8, 144.1, 146.0, 151.1, 165.4, 169.1 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1692, 1607, 1229 cm^{-1}. UV/Vis (MeOH): λ_{max} (log ε) = 225 (3.46), 259 (3.40), 305 (3.26), 333 (2.98), 374 (2.99) nm. EI MS: m/z (%) = 287 $[M]^{+\cdot}$ (100), 255 (75), 227 (38), 196 (100), 169 (25), 129 (38). $C_{14}H_{13}N_3O_4$ (287.28): calcd. C 58.53, H 4.56, N 14.63; found C 58.59, H 4.42, N 14.51.

Diethyl 2-(Quinoxalin-6-ylaminomethylene)propanedioate (3b): M.p. 112–115 °C (EtOH). Yield 1.04 g (55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37, 1.41 (2×t, 2×3 H), 4.30, 4.36 (2×q, 2×2 H), 7.58 (dd, J = 9.0, $J_{7,5}$ = 2.4 Hz, 1 H), 7.80 (d, $J_{7,5}$ = 2.4 Hz, 1 H), 8.12 (d, J = 9.0 Hz, 1 H), 8.68 (d, J = 13.3 Hz, 1 H), 8.78, 8.83 (2×d, J = 1.8 Hz, 2×1 H), 11.27 (d, J = 13.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 14.5, 60.4, 60.8, 96.1, 113.1, 121.8, 131.5, 140.4, 140.6, 143.9, 143.9, 146.0, 150.7, 165.1, 168.8 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1694, 1645, 1615, 1260, 1240 cm^{-1}. UV/Vis (MeOH): λ_{max} (log ε) = 226 (3.16), 248 (2.90), 298 (3.32), 316 (3.30), 362 (3.21) nm. EI MS: m/z (%) = 315 $[M]^{+\cdot}$ (100), 269 (85), 242 (20), 213 (65), 196 (80), 169 (50), 145 (25), 129 (38), 102 (25). $C_{16}H_{17}N_3O_4$ (315.33): calcd. C 60.94, H 5,43, N 13.33; found C 60.99, H 5.45, N 13.22.

2-(Quinoxalin-6-ylaminomethylene)propanedinitrile (3c): M.p. 270–272 °C (xylene). Yield 0.53 g (40%). ^{1}H NMR (300 MHz, [D_6]-DMSO): δ = 7.97 (dd, J = 9.2, $J_{7,5}$ = 2.4 Hz, 1 H), 8.07 (d, J = 9.2 Hz, 1 H), 8.09 (d, $J_{5,7}$ = 2.4 Hz, 1 H), 8.78 (s, 1 H), 8.85, 8.90 (2×d, J = 1.9 Hz, 2×1 H), 11.46 (s, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 54.2, 113.9, 116.2, 115.0, 122.2, 130.5, 140.0, 140.4, 142.9, 144.9, 146.6, 156.1 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3209, 2226, 1649, 1514, 1329 cm^{-1}. UV/Vis (MeOH, saturated solution): λ_{max} = 226, 247, 297, 315, 355 nm. EI MS: m/z (%) = 221 $[M]^{+\cdot}$ (100), 194 (56), 156 (27), 129 (38), 102 (27). $C_{12}H_7N_5$ (221.22): calcd. C 65.15, H 3.19, N 31.66; found C 65.24, H 3.07, N 31.52.

3-(Quinoxalin-6-ylaminomethylene)pentane-2,4-dione (3d): M.p. 159–161 °C (EtOH). Yield 0.89 g (58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46, 2.60 (2×s, 2×3 H), 7.61 (dd, J = 9.0, $J_{7,5}$ = 2.6 Hz, 1 H), 7.86 (d, $J_{5,7}$ = 2.6 Hz, 1 H), 8.16 (d, J = 9.0 Hz, 1 H), 8.41 (d, J = 12.3 Hz, 1 H), 8.82, 8.86 (2×d, J = 1.8 Hz, 2×1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4, 32.2, 113.9, 114.7, 122.3, 131.7, 140.3, 141.0, 143.7, 144.4, 146.1, 150.6, 195.0, 201.8 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1632, 1611, 1582, 1312 cm^{-1}. UV/Vis (MeOH): λ_{max} (log ε) = 253 (3.28), 300 (3.12), 329 (3.21), 367 (3.39) nm. EI MS: m/z (%) = 255 $[M]^{+\cdot}$ (91), 240 (41), 222 (32), 198 (100), 170 (41), 144 (35), 129 (24), 112 (53). $C_{14}H_{13}N_3O_2$ (255.28): calcd. C 65.87, H 5.13, N 16.46; found C 65.78, H 5.04, N 16.32.

Methyl (*E*)-3-Oxo-2-(quinoxalin-6-ylaminomethylene)butanoate (3e): M.p. 150–151 °C (EtOH). Yield 1.01 g (62%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.60 (s, 3 H), 3.85 (s, 3 H), 7.62 (dd, J = 9.3, $J_{7,5}$ = 2.4 Hz, 1 H), 7.87 (d, $J_{5,7}$ = 2.4 Hz, 1 H), 8.13 (d, J =

9.3 Hz, 1 H), 8.67 (d, *J* = 12.3 Hz, 1 H), 8.82 (2×s, 2×1 H), 12.96 (d, *J* = 12.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.2, 51.4, 104.0, 114.2, 121.9, 131.5, 140.2, 140.9, 143.7, 144.1, 146.0, 151.0, 166.8, 200.7 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2942, 1698, 1638, 1312 cm^{-1}. UV/Vis (MeOH): λ_{max} (log ε) = 244 (3.27), 301 (3.14), 330 (3.26), 367 (3.42) nm. EI MS: *m*/*z* (%) = 271 $[M]^{+\cdot}$ (100), 256 (17), 239 (24), 224 (26), 211 (87), 196 (57), 169 (26), 129 (22). $C_{14}H_{13}N_3O_3$ (271.28): calcd. C 61.99, H 4.83, N 15.49; found C 62.21, H 4.61, N 15.47.

Ethyl (*E*)-3-Oxo-2-(quinoxalin-6-ylaminomethylene)butanoate (3f): M.p. 116–117 °C (EtOH). Yield 1.11 g (65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (t, 3 H), 2.50 (s, 3 H), 4.25 (q, 2 H), 7.9–8.0 (m, 1 H, 1 H), 8.12 (d, *J* = 9.1 Hz, 1 H), 8.65 (d, *J* = 13.1 Hz, 1 H), 8.87 (2×s, 2×1 H), 12.76 (d, *J* = 13.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + [D$_6$]DMSO): δ = 14.5, 31.3, 60.3, 104.4, 114.1, 122.1, 131.5, 140.3, 140.9, 143.7, 144.1, 146.0, 150.9, 166.5, 200.9 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2982, 1713, 1640, 1620, 1250 cm^{-1}. UV/Vis (MeOH): λ_{max} (log ε) = 244 (3.12), 300 (2.98), 326 (3.09), 367 (3.27) nm. EI MS: *m*/*z* (%) = 285 $[M]^{+\cdot}$ (75), 270 (17), 239 (33), 224 (21), 211 (100), 196 (83), 169 (29), 142 (29), 115 (25). $C_{15}H_{15}N_3O_3$ (285.31): calcd. C 63.15, H 5.30, N 14.73; found C 63.02, H 5.16, N 14.55.

3-Oxo-2-(quinoxalin-6-ylaminomethylene)butanenitrile (3g): M.p. 226–228 °C (xylene). Yield 1.06 g (74%). ^{1}H NMR (300 MHz, [D$_6$]-DMSO): (*E*) isomer: δ = 2.37 (s, 3 H), 8.05 (m, 1 H), 8.08 (d, *J* = 9.0 Hz, 1 H), 8.13 (d, $J_{5,7}$ = 2.4 Hz, 1 H), 8.59 (s, 1 H), 8.85, 8.90 (2×d, *J* = 2.0 Hz, 2×1 H), 11.02 (s, 1 H) ppm; (*Z*) isomer: δ = 2.34 (s, 3 H), 8.05 (m, 1 H), 8.08 (d, *J* = 9.0 Hz, 1 H), 8.20 (d, $J_{5,7}$ = 2.4 Hz, 1 H), 8.67 (d, *J* = 13.2 Hz, 1 H), 8.87, 8.90 (2×d, *J* = 1.9 Hz, 2×1 H), 12.20 (d, *J* = 13.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): (*E*) isomer: δ = 26.5, 88.7, 115.0, 116.5, 122.7, 130.5, 139.9, 141.0, 143.0, 144.7, 146.5, 152.5, 192.2 ppm; (*Z*) isomer: δ = 28.5, 85.4, 115.4, 120.0, 122.6, 130.6, 139.8, 140.3, 142.9, 145.0, 146.7, 153.0, 196.1 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2207, 1657, 1617, 1312 cm^{-1}. UV/Vis (MeOH, saturated solution): λ_{max} = 251, 299, 333, 367 nm. EI MS: *m*/*z* (%) = 238 $[M]^{+\cdot}$ (93), 195 (100), 168 (29), 141 (29), 102 (20). $C_{13}H_{10}N_4O$ (238.25): calcd. C 65.54, H 4.23, N 23.52; found C 65.32, H 4.14, N 23.44.

Methyl 2-Cyano-3-(quinoxalin-6-ylamino)propenoate (3h): M.p. 238–240 °C (xylene). Yield 0.84 g (55%). ^{1}H NMR (300 MHz, [D$_6$]-DMSO): (*E*) isomer: δ = 3.76 (s, 3 H), 7.98 (m, 1 H), 8.06 (d, $J_{5,7}$ = 2.4 Hz, 1 H), 8.08 (d, *J* = 9.0 Hz, 1 H), 8.73 (d, *J* = 13.8 Hz, 1 H), 8.85, 8.91 (2×d, *J* = 2.1 Hz, 2×1 H), 10.94 (d, *J* = 13.8 Hz, 1 H) ppm; (*Z*) isomer: δ = 3.80 (s, 3 H), 8.05 (m, 1 H), 8.10 (d, *J* = 9.0 Hz, 1 H), 8.19 (d, $J_{5,7}$ = 2.4 Hz, 1 H), 8.55 (d, *J* = 11.4 Hz, 1 H), 8.85, 8.91 (2×d, *J* = 2.1 Hz, 2×1 H), 11.14 (d, *J* = 11.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): (*E*) isomer: δ = 52.0, 76.4, 114.7, 115.5, 122.2, 130.5, 139.8, 140.8, 142.9, 144.6, 146.4, 152.5, 164.7 ppm; $J_{H,C=C-CN}$ = 10.3 Hz; (*Z*) isomer: δ = 51.9, 75.4, 114.8, 117.8, 122.5, 130.4, 140.0, 140.0, 142.9, 144.7, 146.4, 153.5, 166.2 ppm; $J_{H,C=C-CN}$ = 5.7 Hz. IR (KBr): $\tilde{\nu}_{max}$ = 3216, 2211, 1684, 1634, 1250 cm^{-1}. UV/Vis (MeOH, saturated solution): λ_{max} = 226, 247, 298, 317, 358 nm. EI MS: *m*/*z* (%) = 254 $[M]^{+\cdot}$ (100), 222 (72), 195 (91), 156 (83), 129 (57), 102 (35). $C_{13}H_{10}N_4O_2$ (254.25): calcd. C 61.41, H 3.96, N 22.04; found C 61.51, H 4.10, N 21.99.

Ethyl 2-Cyano-3-(quinoxalin-6-ylamino)propenoate (3i): M.p. 207–208 °C (xylene). Yield 0.80 g (50%). ^{1}H NMR (300 MHz, $CDCl_3$ + [D$_6$]DMSO): (*E*) isomer: δ = 1.25 (t, 3 H), 4.19 (q, 2 H), 7.92–8.15 (m, 3 H) 8.51 (s, 1 H), 8.85 (dd, *J* = 1.9 Hz, 2×1 H), 11.10 (s, 1 H) ppm; (*Z*) isomer: δ = 1.35 (t, 3 H), 4.31 (q, 2 H), 7.98 (d, 1 H), 8.07 (d, 1 H), 8.13 (s, 1 H), 8.72 (d, *J* = 13.6 Hz, 1 H), 8.85 (2×s, 2×1 H), 11.03 (d, *J* = 13.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + [D$_6$]DMSO): (*E*) isomer: δ = 14.3, 60.7, 76.8, 114.7, 115.6, 122.2, 130.5, 140.0, 140.9, 142.9, 144.6, 146.4, 152.3, 164.3 ppm; $J_{H,C=C-CN}$ = 9.9 Hz; (*Z*) isomer: δ = 14.1, 60.7, 76.1, 114.5, 117.5, 122.0, 130.6, 139.8, 140.2, 143.2, 144.3, 146.0, 153.1, 166.2 ppm; $J_{H,C=C-CN}$ = 5.2 Hz. IR (KBr): $\tilde{\nu}_{max}$ = 3217, 2215, 1674, 1636, 1248 cm^{-1}. UV/Vis (MeOH, saturated solution): λ_{max} = 245, 298, 316, 359 nm. EI MS: *m*/*z* (%) = 268 $[M]^{+\cdot}$ (80), 222 (60), 195 (100), 156 (40), 129 (35), 91 (35). $C_{14}H_{12}N_4O_2$ (268.28): calcd. C 62.68, H 4.51, N 20.88; found C 62.92, H 4.34, N 20.65.

2,2-Dimethyl-5-(quinoxalin-6-ylaminomethylene)[1,3]dioxane-4,6-dione (3j): M.p. 204–205 °C (xylene). Yield 1.44 g (80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79 (s, 6 H), 7.74 (dd, *J* = 9.1, $J_{7,5}$ = 2.4 Hz, 1 H), 7.98 (d, $J_{5,7}$ = 2.4 Hz, 1 H), 8.21 (d, *J* = 9.1 Hz, 1 H), 8.86 (d, *J* = 14.0 Hz, 1 H), 8.88 (2×s, 2×1 H), 11.51 (d, *J* = 14.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.2, 89.0, 105.5, 116.0, 121.3, 131.9, 138.8, 141.3, 143.6, 144.9, 146.4, 152.4, 163.1, 165.4 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1731, 1680, 1618, 1273, 1223 cm^{-1}. UV/Vis(MeOH, saturated solution): λ_{max} = 224, 244, 299, 323, 347 nm. EI MS: *m*/*z* (%) = 299 $[M]^{+\cdot}$ (18), 241 (38), 196 (100), 169 (50), 142 (15), 115 (35). $C_{15}H_{13}N_3O_4$ (299.29): calcd.C 60.20, H 4.38; N 14.04; found C 60.03, H 4.52, N 14.28.

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