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Amidine–enediamine tautomerism: addition of isocyanates to 2-substituted 1*H*-perimidines. Some syntheses under microwave irradiation

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Summary — The regioselective *C*-electrophilic addition of isocyanates **4** to ethyl 1*H*-perimidine-2-acetate **3a** and 1*H*-perimidine-2-acetonitrile **3b** has been investigated and leads to new heterocyclic ketene aminals **5'a–j** in yields ranging from 60–94%. ^{1}H and ^{13}C NMR spectra of these compounds are discussed and assigned. The chemical structure of these compounds incorporates an exocyclic double bond which is strongly polarized by a 'push–pull' effect. Ethyl 2-methyl-1*H*-perimidine-2-acetate **3c** gave no reaction with ethyl isocyanate **4a**. The synthesis of some compounds **5'** using solvent-free conditions under microwave irradiation or in an oil bath is also reported.

perimidine / isocyanate / electrophile / ketene aminal / 'push–pull' effect / microwave irradiation

Résumé — Tautomérisme amidine-ènediamine: addition d'isocyanates à des 1*H*-périmidines substituées en 2. Quelques synthèses sous irradiation micro-ondes. *La C-addition électrophile et régiosélective des isocyanates* **4** *au 1H-périmidine-2-acétate d'éthyle* **3a** *et au 1H-périmidine-2-acétonitrile* **3b** *est étudiée et permet d'accéder à de nouvelles ène-diamines hétérocycliques* **5'a-j** *avec des rendements variant de 60 à 94 %. Les spectres RMN ^1H et ^{13}C de ces composés sont discutés. Leur structure comporte une double liaison exocyclique qui est fortement polarisée par un effet «donneur-accepteur». Le 2-méthyl-1H-périmidine-2-acétate d'éthyle* **3c** *ne donne aucune réaction avec l'isocyanate d'éthyle* **4a**. *La synthèse de quelques composés* **5'** *sans solvant sous irradiation micro-ondes ou au bain d'huile est décrite.*

périmidine / isocyanate / électrophile / ène-diamine / effet «donneur-accepteur» / irradiation micro-onde

Introduction

The majority of perimidine syntheses [1, 2] are based on the reaction of 1,8-diaminonaphthalene (DAN) and its derivatives with various compounds containing a carbonyl group. Moreover, a convenient synthesis of 2-substituted 1*H*-perimidines **3** with an electron-withdrawing group (EWG) substituent by the interaction of DAN with iminoesters [3] has been reported. The spectroscopic properties of these 2-substituted 1*H*-perimidines have been studied [4] and show a rapid prototropic tautomerism with annular nitrogen atoms. Due to the electron-donating ability of nitrogen atoms and the electron-withdrawing abilities of the EWG substituent on C_β, the double bond C_α=C_β in **3'** (scheme 1) is highly polarized and the electron density at C_β is increased, leading to greater nucleophilicity at carbon than at nitrogen [5]. Our interest in this field has been focused on the synthetic use of amphoteric perimidines **3a,b** with isocyanates **4** in electrophilic additions.

As part of our program related to the study of organic synthesis using solvent-free conditions [6], eventually under microwave irradiation [7], we have developed an easy synthesis of some new heterocyclic ketene aminals **5** under focused irradiation in a Synthewave 402 microwave oven [8a]. We now report the results of our investigations which describe the reactivity of perimidines **3a–c** with a variety of isocyanates **4**. Preparative procedures and NMR (^{1}H, ^{13}C) structure and tautomerism studies of these new heterocyclic ketene aminals are presented here.

Results and discussion

Synthesis

The starting perimidine **3a** was readily obtained by modification of the procedure of Wamhoff et al [3] from ethyl 2-(ethoxycarbonyl)acetimidate hydrochloride **2a** [9] and 1,8-diaminonaphthalene **1** in refluxing

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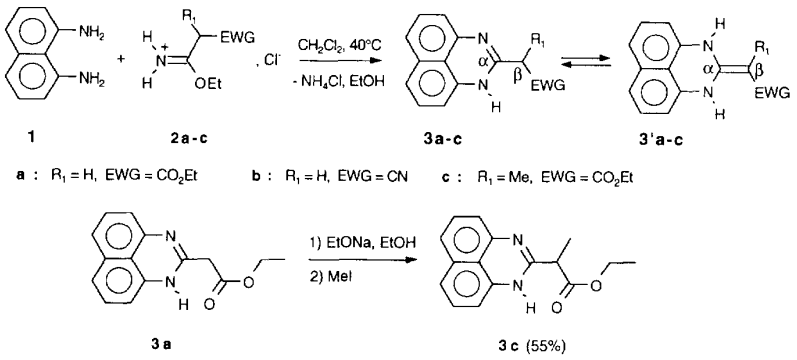
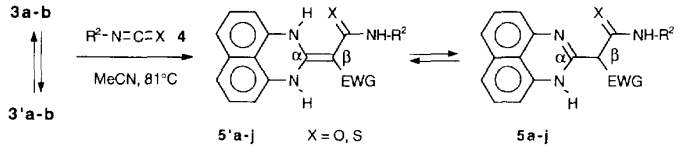


Scheme 1



Scheme 2

Table I. Synthesis of heterocyclic ketene aminals **5'a–j** from **3a,b** and isocyanates **4a–g**.

Entry	*Reagent*	R^2	*X*	*Product*	*EWG*	*Ratio* **3/4**	*Time (h)*[a]	*Yield (%)*[b]
1	**4a**	Et	O	**5'a**	CO_2Et	1:1.1	15	83
2	**4b**	Ph	O	**5'b**	CO_2Et	1:1.2	15	94
3	**4c**	Pr	O	**5'c**	CO_2Et	1:1.2	46	66
4	**4d**	Me	S	**5'd**	CO_2Et	1:1.1	163	72
5	**4e**	*p*-ClC_6H_4	O	**5'e**	CO_2Et	1:1.1	16	98
6	**4f**	EtO_2CCH_2	O	**5'f**	CO_2Et	1:1.2	46	80
7	**4g**	EtO_2C	S	**5'g**	CO_2Et	1:1	6 min[c]	98
8	**4f**	EtO_2CCH_2	O	**5'h**	CN	1:1.2	39	82
9	**4c**	Ph	O	**5'i**	CN	1:1.1	63	72
10	**4e**	*p*-ClC_6H_4	O	**5'j**	CN	1:1.1	63	80

[a] Reaction time. [b] Yield in **5'** after crystallization. [c] At room temperature.

dry methylene chloride (scheme 1). This process was then extended, for the first time, to the synthesis of 1*H*-perimidine-2-acetonitrile **3b** [10] in 63% yield and to ethyl 2-methyl-1*H*-perimidine-2-acetate **3c** (in 73% yield) from imidate hydrochloride **2c**. This imidate **2c** was available from ethyl 2-cyanopropanoate in anhydrous ethanol using the method developed by Pinner [11]. We have also found that treatment of perimidine **3a** with a solution of sodium ethoxide generated in situ, followed by addition of methyl iodide leads mainly to **3c**, isolable as the *C*-monoalkylated product in 55% yield after purification on silica gel (scheme 1).

The 2-substituted 1*H*-perimidines **3a,b** reacted smoothly with a wide range of isocyanates **4a–g** in refluxing anhydrous acetonitrile (except for the activated thioisocyanate **4g** which reacts at room temperature, entry 7, table I). Treatment of the crude reaction mixture with diethyl ether gave the heterocyclic ketene aminals **5'a–j** as colorful products in yields ranging from 66 to 98% (scheme 2).

All reaction times were monitored by TLC with the appropriate eluent (see the *Experimental section*) and the skeleton of products **5'** was established by ^1H and ^{13}C NMR spectroscopic data, IR, MS and elemental analyses. In all cases, the C_β-electrophilic addition of isocyanates **4** to the respective perimidines **3a,b** leads to a single heterocyclic ketene aminal **5'**, as shown by the presence of only one set of signals in each of ^1H and ^{13}C NMR spectra (temperature of the probe 25 ± 5 °C). To prove this regioselectivity assumption, we submitted compound **3a** to *N,C*-addition reaction with 2 equivalents of **4b** (R = Ph) for 63 h in refluxing acetonitrile; we observed only the C_β-addition product **5'b** together with unreacted **4b**. Moreover, we extended the *N,C*-addition reaction of ethyl isocyanate **4a** to ethyl α-methyl-1*H*-perimidine-2-acetate **3c** under the same reaction conditions [12]; no product corresponding to electrophilic attack of isocyanate **4a** at the C_β or *N*-1 position of **3c** was detected. These experiments agree with the low nucleophilic character of *N*-1 in the ketene aminal structure **5'b** and the poor reactivity of the potential *N,C*-bis nucleophile synthon **3c** (*N*-1 and C_β atoms) with isocyanate as electrophile.

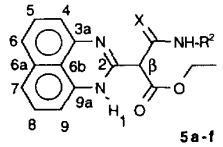
Owing to the long reaction times in solution (table I), we tried to shorten the synthesis of **5'** by using solvent-free conditions in an oil bath or under focused microwave irradiation [13]. We used a Synthewave 402 microwave oven, which is monitored by a

Table II. Synthesis of some heterocyclic ketene aminals **5′** using solvent-free conditions in an oil bath or under focused microwave irradiation.

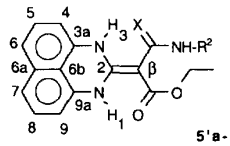
						Yield of **5′**[a]	
Product	*EWG*	R^2	*X*	*Reaction time (min)*	*Temp (°C)*	*MW*[b]	*Oil bath*[c]
5′c	CO_2Et	Pr	O	25	83	(99) 75	(99)
5′d	CO_2Et	Me	S	15	115	(99) 75	(99)
5′f	CO_2Et	CH_2CO_2Et	O	10	180	(99) 80	(99)
5′h	CN	CH_2CO_2Et	O	15	180	(99) 80	(99)

[a] Yield (%) for crude product by ^1H NMR spectroscopy and isolated product after recrystallization. [b] Reactions were run in a microwave oven (Synthewave 402); the reaction temperature was evaluated by infrared detection [8b]. [c] In an oil bath: temperature variation ±1 °C.

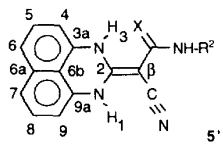
Table III. Selected ^1H and ^{13}C NMR data (δ values) of **5′a–j** and **5a–f** with TMS as internal standard.



5a-f



5′a-g



5′h-j

Product	*NH*	*H-1, H-3*	*H-4, H-9*	*C-2*	C_β	*CO, C=X*	*CN*
5′a[a]	8.0	12.2, 14.4	6.33, 6.45	155.9	75.3	169.1, 169.9	–
5′b[a]	10.0	12.4, 14.0	6.45, 6.55	156.0	76.0	168.7, 168.8	–
5′c[a]	8.1	11.9, 14.4	6.40, 6.49	156.0	75.4	169.0, 170.0	–
5′d[a]	9.5	13.4, 13.4	6.44, 6.48	154.4	84.8	168.3, 190.8	–
5′e[a]	9.9	11.8, 14.1	6.38, 6.51	156.0	76.0	168.7	–
5′f[a]	8.5	12.0, 14.1	6.41, 6.48	156.0	75.5	169.3, 170.0	–
5′g[b]	10.8	10.9, 11.4[c]	6.78	154.3	94.0	162.8, 164.1	–
5′h[b]	7.7	11.4[c]	6.50	154.4	55.2	169.7	119.1
5′i[b]	8.0	11.4[c]	6.70	155.4	56.6	169.2	120.0
5′j[b]	7.6	11.4[c]	6.58	154.2	55.7	167.9	121.2

Product	*NH*	*H-1*	H_β	*H-4, H-9*	*C-2*	C_β	*CO, C=X*
5a[b]	8.36	12.9	5.12	6.81	153.5	52.2	162.8
5b[b]	9.87	11.4	5.25	6.82	153.3	53.2	161.0, 163.1
5c[b]	8.21	11.2	5.03	6.85	153.1	52.7	162.9, 163.1
5d[b]	9.67	13.0	5.25	6.76	154.1	58.4	164.5, 188.7
5e[b]	9.85	11.3	5.20	6.85	153.0	53.2	161.8, 163.0
5f[b]	8.70	11.2	5.20	6.82	153.0	52.4	162.9, 170.4

[a] $CDCl_3$ solvent. [b] $CDCl_3/CF_3CO_2H$ solvent (9:1). [c] H-1 and/or H-3 are masked by CF_3CO_2H.

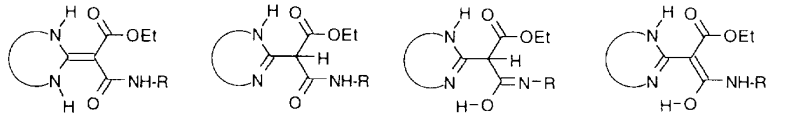
computer that allows adjustment of the temperature of the reaction mixture according to the boiling point of the isocyanates **4**. Some typical examples are reported in table II. The main features of this technique are complete addition in less than 25 min and easier purification of **5′**. When the same reaction mixture was heated in an oil bath previously set at the same boiling point for the same reaction time, the results were analogous. In these cases, we can exclude a specific microwave effect, but microwave heating affords a clean, more straightforward and efficient method for the preparation of **5′**.

^1H and ^{13}C NMR spectrum studies

Advances in the chemistry of perimidines are in many respects due to ^1H NMR data discussed in great details by Pozharskii [14] and more recently by Woodgate [4].

A characteristic feature of the ^1H NMR spectra of compounds **5′a–j** (table III) and **3a–c** (table IV) is the considerable upfield shift of the two separated doublets H-4 and H-9 (**5′a–j**, δ 6.33–6.50, J = 6.3 and 6.7 Hz) compared to others; the H-5, H-8 protons give rise to a downfield complex multiplet, which merges with the signals assigned to the H-6 and H-7 protons.

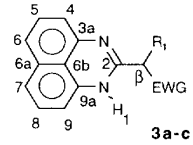
In $CDCl_3$ solution, the ketene aminals **5′a–j** do not tautomerize to A (amidine form), B or C at all (scheme 3), because there is only one set of signals in each of the ^1H and ^{13}C NMR spectra. The existence of three NH signals (NH, H-1 and H-3) and the absence of methine proton signals in the ^1H NMR spectra of **5′a–g** (in $CDCl_3$ solution, table III) exclude *N*-addition reactions [12] of the isocyanates **4a-g**. Furthermore, the downfield shift of H-1, H-3 signals (δ 11.8–14.4) proves the existence of an intramolecular hydrogen bond (internal solvation) [15] and confirms the proposed consti-



5'a-g : ene diamine form A : amidine form B : amidine - enol α form C : amidine - enol β form

Scheme 3

Table IV. Selected ^1H and ^{13}C NMR data (δ values) of **3a–c** with TMS as internal standard.



3a: R_1 = H, EWG = CO_2Et
3b: R_1 = H, EWG = CN
3c: R_1 = Me, EWG = CO_2Et

3a-c

Product	*H-1*	H_β	*H-4, H-9*	*C-2*	C_β	*CO*	*CN*
3a[a,*]	10.9	3.86	6.74	155.1	34.4	167.3	–
3b[a]	10.7	4.23	6.86	152.0	21.1	-	110.7
3c[b]	8.57	3.47	6.48	154.5	45.4	173.3	–

[a] $CDCl_3/CF_3CO_2H$ solvent (9:1). [b] $CDCl_3$ solvent. * In $CDCl_3$ solution, this ester exists as a mixture of tautomers **3a** and **3'a**, see ref [4].

tution of the heterocyclic ketene aminal **5'**; the other NH signal is in agreement with an amide shift (δ 7.6–10.8).

The conjugation of the ester and amide groups with the C-2=C_β double bond and the formation of the intramolecular hydrogen bond both stabilize the product in the ene-diamine form **5'**. In this ene-diamine, the rotation barrier around the formal C-2/C_β is considerably reduced [16]. This can be explained by the *peri*-amidine resonance [17] which decreases the double bond character around *N*-3/*C*-2. The presence of an amide carbonyl carbon signal (C=X) in the ^{13}C NMR spectra excludes also the tautomers B and C (δ_{CO} 168.3 and δ_{CS} 190.8 in **5'd**, δ_{CO} 169.2–169.7 in **5'h–j**).

The upfield shift of C_β (EWG = CO_2Et, δ 75.3–84.8) indicates a high electron density on this β-carbon and the downfield shift of C-2 reflects the π-deficient nature of the heterocyclic ring. Moreover, the location of C-2 between two annular nitrogen atoms (*N*-1, *N*-3) results in the lowest intensity of any tertiary carbon in the molecule which allows increased delocalization of the lone pair of *N*-1, *N*-3. In fact, the C-2=C_β double bond is highly polarized as a consequence of a 'push–pull' effect [18].

Meanwhile, we found that the tautomeric equilibrium between **5** and **5'** is drastically dependent on the solvents [19]; for example in $CDCl_3$/trifluoroacetic acid (TFA) solution (9:1), the molecule is protonated and the equilibrium is shifted towards the amidine tautomer A (scheme 3) for the compounds **5a–f**, but not for the thiocarbamoyl perimidine derivative **5g**. In the ^1H NMR spectrum, the signal due to H_β is a sharp singlet at δ 5.12–5.20 (in agreement with an alkyl methylene group) and the ^1H resonance-coupled ^{13}C NMR spectra showed the presence of the C_β-doublet centered at δ 52.2–53.2 (J = 137 Hz). The predominant ene-diamine form (internal solvation) of compound **5'g** in a protic medium may be explained by the lower electronegativity of the sulfur atom which makes the C-2=C_β double bond more polarized due to the more electron-donating nature of the N-3 atom. Moreover, for compounds **5a–f** with a more electronegative oxygen atom, the polarization of the double bond is prevented by hydrogen bonding between the protic solvent (TFA) and solute **5**; this leads to inhibition of prototropic tautomerism of the β-carbon protons with the annular nitrogen atoms (N-1, N-3).

It seems worthwhile to note the small chemical shifts of the C_β-signal in **5'h–j** (δ 55.2–54.8) in a $CDCl_3$/TFA solution (9:1) and a singlet is observed in the ^1H off-resonance decoupled ^{13}C NMR spectrum which indicates that the ene-diamine form for compounds **5'h–j** is predominant. The presence of the cyano group on C_β is apparently responsible for a high increase in net electron density of the C_β atom by conjugation, so the C-2=C_β double bond in compounds **5'h–j** is strongly polarized.

Of the remaining tertiary carbons in the naphthalene moeity of **5'a–j**, C-4/C-9 are the most upfield signals (δ 105–109). Likewise, C-9b also displays an upfield signal (ie, δ 116.3–117.1). The resonances due to quaternary carbons are also readily assigned: C-3a, C-9a (formally *ipso* carbons) and C-6a gave downfield shifts (δ 131.4–134.8) and are not affected by the nature of EWG and other substituents on the C_β-atom.

The ^1H NMR spectrum of **3b** (R^1 = H, EWG = CN) in $CDCl_3/CF_3CO_2H$ solution (9:1) is indicative of a relatively slow rate of tautomerism (table IV). The signal assigned to H_β appears as a singlet at δ 4.23; this value is in agreement with that expected for an alkyl methylene group rather than a vinyl proton in **3'b**; in this medium the molecule is fully protonated [4]. This is confirmed in the ^1H-resonance-coupled ^{13}C NMR spectrum by the triplet centered at δ 21.1 (J = 138 Hz). However, we observed no proton exchange between N-3 and H_β in the ^1H NMR spectrum of **3c** (R^1 = Me, EWG = CO_2Et) which confirms the low nucleophilic character of C_β and the poor reactivity with isocyanate **4a**.

Conclusion

From the above results it can be concluded that the addition of isocyanates **4a–g** to perimidines **3a,b** in solution is regioselective. The electrophilic attack takes place only at C_β due to its high electron density. This reaction leads to new heterocyclic ketene aminals **5'a–j**. ^1H and ^{13}C NMR spectra of these compounds have been assigned and reflect inhibition of prototropic tautomerism by an intramolecular hydrogen bonding due to the delocalization of the nitrogen lone pair of electrons (N-1, N-3). From the spectral characteristics,

the heterocyclic ketene aminals **5′** exhibit a strongly conjugated system involving the nitrogen atoms, the double bond and the electron-withdrawing substituents.

The synthesis of these compounds has been easily realized using solvent-free conditions under focused microwave irradiation or in an oil bath. The use of perimidines **3a,b** as potential N,C-bis nucleophiles and the extension of this strategy to other electrophiles is underway in our laboratory [20].

Experimental section

General

Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were taken with a Perkin-Elmer 157G spectrometer. ^{1}H NMR spectra were recorded on Bruker WP 80 CW (80 MHz) and Bruker AC 300 P (300 MHz) spectrometers and ^{13}C NMR spectra on a Bruker AC 300 P (75 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. The mass spectra (MS) were taken on a Varian MAT 311 at a ionizing potential of 70 eV in the Centre de mesures physiques de l'Ouest (CRMPO, Rennes). Elemental analyses were performed at the Laboratoire central de microanalyses–CNRS (Lyon). Thin-layer chromatography (TLC) was achieved on 0.2 mm precoated plates of silica gel 60 F-254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm). For preparative column chromatography, silica gel 60 Merck (230-240 mesh ASTM) was used.

Reactions under microwave irradiation were performed in a Synthewave 402 (Prolabo) microwave reactor with a single-mode focused system.

All reagents were purchased from Janssen Chimica and Aldrich Chimie and used without further purification; ethyl cyanopropanoate was purchased from Merck. Acetonitrile, methylene chloride, chloroform were distilled over calcium chloride after standing overnight and stored over molecular sieves (3 Å). Absolute ethanol was distilled over magnesium after standing overnight and stored over molecular sieves (3 Å). Ether was distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Solvents were evaporated with a Buchi rotary evaporator.

Ethyl 2-(ethoxycarbonyl)acetimidate hydrochloride **2a** and ethyl 2-cyanoacetimidate hydrochloride **2b** were prepared by the method of McElvain and Schroeder [9].

Preparation of perimidines **3a–c** *and precursors*

- *Ethyl 1H-perimidine-2-acetate* **3a**

In a 250 mL two-necked flask under nitrogen were placed 1,8-diaminonaphthalene **1** (8.01 g, 51.15 mmol), ethyl 2-(ethoxycarbonyl)acetimidate hydrochloride **2a** (10 g, 51.15 mmol) and dry methylene chloride (200 mL). The resulting mixture was refluxed for 48 h with vigorous stirring. After filtration and removal of the solvent in vacuo, the residue (11.94 g, 92% yield) crystallized on standing. Recrystallization from chloroform/pentane (1:1) gave the desired compound **3a** (10.53 g, 81%) as deep yellow needles. Mp = 152–153 °C, Lit [3] 152–154 °C.

IR (Nujol): 3 240, 1 650, 1 630, 1 600, 1 570 cm^{-1}.

^{1}H NMR ($CDCl_3/CF_3CO_2H$ (9:1), 300 MHz): δ 1.32 (t, 3H, J = 7.2 Hz), 3.86 (s, 2H), 4.33 (q, 2H, J = 7.2 Hz), 6.74 (d, 2H, Ar), 7.27 (t, 2H, Ar), 7.38 (d, 2H, Ar), 10.9 (broad s, 1H, NH).

^{13}C NMR ($CDCl_3/CF_3CO_2H$ (9:1), 75 MHz): δ 13.2 (qt, J = 128, 2.7 Hz), 34.4 (C_β), 64.2 (tq, J = 150, 4.5 Hz), 109.0 (d, J = 165 Hz, C-4, C-9), 120.2 (C-9b), 124.4 (d, J = 164 Hz, C-5, C-8), 128.4 (C-6, C-7), 130.3 (C-3a, C-9a): 134.7 (C-6a), 155.1 (C-2), 167.3 (CO).

- *1H-Perimidine-2-acetonitrile* **3b**

A suspension of 1,8-diaminonaphthalene **1** (4.74 g, 30 mmol) and ethyl 2-cyanoacetimidate hydrochloride **2b** (5.35 g, 36 mmol) in dry methylene chloride (100 mL) was heated at 40 °C for 48 h with vigorous stirring. Then the hot mixture was filtered through a Büchner funnel and the filtrate was washed with water (3 × 10 mL). Drying of the organic layer over $MgSO_4$ and removal of the solvent in vacuo, gave a brown viscous residue which crystallized on standing. Recrystallization from chloroform gave **3b** (3.92 g, 63% yield) as fluorescent colorful needles. Mp = 181–182 °C.

IR (Nujol): 2 320, 1 620, 1 590, 1 560 cm^{-1}.

^{1}H NMR ($CDCl_3/CF_3CO_2H$ (9:1), 300 MHz): δ 4.23 (s, 2H), 6.86 (d, 2H, J = 7.4 Hz, Ar), 7.36 (t, 2H, J = 7.6 Hz, Ar), 7.49 (d, 2H, J = 8.5 Hz, Ar), 10.7 (broad s, 1H, NH).

^{13}C NMR ($CDCl_3/CF_3CO_2H$ (9:1), 75 MHz): δ 21.1 (t, J = 138 Hz, C_β), 109.0 (d, J = 165 Hz, C-4, C-9), 110.7 (CN), 120.1 (C-9b), 125.1 (d, J = 165 Hz, C-5, C-8), 128.3 (d, J = 165 Hz, C-6, C-7), 129.9 (C-3a, C-9a), 134.8 (C-6a), 152.0 (C-2).

MS, m/z: 207.0786 found (calc for $C_{13}H_9N_3$: 207.0796), M^+.

- *Ethyl 2-(ethoxycarbonyl)propanimidate hydrochloride* **2c**

A solution of ethyl 2-cyanopropanoate (10.27 g, 81 mmol) and anhydrous ethanol (3.72 g, 81 mmol) in dry ether (150 mL) was cooled in an ice bath with exclusion of moisture ($CaCl_2$ tube). Dry HCl was passed in until about 0.2 mol had been absorbed (a large excess increases the reaction rate with no apparent deleterious effect). After standing in the refrigerator for 3 days, the precipitated product was filtered, washed with anhydrous ether, and vacuum-dried in a dessicator over H_2SO_4 to afford the expected imidate **2c** (15.65 g, 92%) as white needles. Mp < 50 °C.

^{1}H NMR ($CDCl_3$, 80 MHz): δ 1.20 (d, 2H, J = 7.0 Hz), 1.35 (t, 3H, J = 7.0 Hz), 1.47 (t, 3H, J = 7.0 Hz), 3.37 (q, 1H, J = 7.0 Hz), 4.25 (q, 2H, J = 7.0 Hz), 4.72 (q, 2H, J = 7.0 Hz), 10.9 (broad s, 1H, NH), 11.4 (broad s, 1H, NH).

- *Ethyl α-methyl-1H-perimidine-2-acetate* **3c**

Procedure 1: A mixture of 1,8-diaminonaphthalene **1** (5 g, 31.6 mmol) and ethyl 2-(ethoxycarbonyl)propanimidate hydrochloride **2c** (6.62 g, 31.6 mmol) in dry methylene chloride (115 mL) was heated at 40 °C for 48 h under nitrogen with vigorous stirring. After filtration through a Büchner funnel and removal of the solvent in vacuo, the crude residue (7.45 g, 88%) was triturated with ether (80 mL). After filtration, the desired material was dried in a desiccator to give a pale greenish powder (6.18 g, 73%). Mp = 88–90 °C.

Procedure 2: To a solution of sodium ethoxide with exclusion of moisture ($CaCl_2$ tube), prepared from sodium (320 mg, 14.2 mmol) in anhydrous ethanol (25 mL), was added **3a** (3 g, 11.8 mmol). The reaction mixture was stirred for 30 min at 78 °C. Then methyl iodide (2 g, 14.2 mmol) was added dropwise during 30 min. The reaction mixture was refluxed with vigorous stirring for 3.5 h and was allowed to cool. After removal of the solvent by rotary evaporation, methylene chloride (30 mL) was added to the viscous residue, it was washed with water (3 × 10 mL) and the organic layer was dried (anhydrous $MgSO_4$), filtered and the filtrate concentrated in vacuo to a viscous oil (2.62 g, 83%) which was purified by chromatography on silica gel 60 Merck. After elution with methylene chloride/acetonitrile (9:1), the fraction

(R_f: 0.5) gave the desired compound **3c** (1.73 g, 55%) as a viscous oil which crystallized on standing. Mp = 89–90 °C.

IR (Nujol): 1 720, 1 620, 1 590 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ 1.27 (t, 3H, J = 7.1 Hz), 1.57 (d, 3H, J = 7.4 Hz), 3.47 (q, 1H, J = 7.4 Hz), 4.19 (q, 2H, J = 7.1 Hz), 6.48 (m, 2H, Ar), 7.07 (m, 4H, Ar), 8.57 (broad s, 1H, NH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0 (qt, J = 125, 2.6 Hz), 17.3 (qd, J = 131, 5.2 Hz), 45.4 (dq, J = 135, 4.0 Hz, C_β), 61.9 (tq, J = 148, 4.7 Hz), 104.2–104.9 (d, J = 165 Hz, C-4, C-9), 118.9 (d, J = 165 Hz, C-5, C-8), 122.0 (C-9b), 128.2 (d, J = 165 Hz, C-6, C-7), 135.2 (C-3a, C-9a, C-6a), 154.5 (C-2), 173.3 (CO).

MS, m/z: 268.1217 found (calc for $C_{16}H_{16}N_2O_2$: 268.1212), M^+.

• *Representative procedure for C_β-electrophilic addition of isocyanates* **4** *to ethyl 1H-perimidine-2-acetate* **3a** *and 1H-perimidine-2-acetonitrile* **3b**

General procedure: A mixture of perimidine **3** and isocyanate **4** in dry acetonitrile (3.5 mL) was refluxed under nitrogen with vigorous stirring for the appropriate time (monitored by TLC over 0.2 mm precoated plates of silica gel 60F 254, Merck) The reaction mixture was allowed to cool. After removal of the solvent in vacuo, the crude residue was triturated with dry ether (20 mL). The precipitated product was filtered through a Büchner funnel, washed with ether (2 × 5 mL) and dried in a desiccator to give the desired compound **5** or **5′**.

• *Ethyl α-ethylcarbamoyl-1H-perimidine-2-acetate* **5a**, *ethyl 2-ethylcarbamoyl-2-(1H-perimidin-2-ylidene)acetate* **5′a**

From ethyl 1*H*-perimidine-2-acetate **3a** (2.2 g, 8.66 mmol) and ethyl isocyanate **4a** (0.74 g, 10.4 mmol), reaction time: 15 h. TLC: R_f = 0.8 with CH_2Cl_2/MeCN (9:1) as eluent. 83% yield (2.34 g) of **5a** as a brown powder. Mp = 179–180 °C.

IR (Nujol): 3 420, 1 620, 1 580 cm^{-1}.

For **5a**: ^1H NMR ($CDCl_3/CF_3CO_2H$ (9:1), 300 MHz): δ 1.24 (t, 3H, J = 7.3 Hz); 1.31 (t, 3H, J = 7.1 Hz), 3.41 (q, 2H, J = 7.3 Hz), 4.34 (q, 2H, J = 7.1 Hz), 5.12 (s, 1H), 6.81 (d, 2H, J = 6.3 Hz, Ar), 7.26 (m, 4H, Ar), 8.36 (broad s, 1H, NH), 12.9 (broad s, 1H, NH).

^{13}C NMR ($CDCl_3/CF_3CO_2H$ (9:1), 75 MHz): δ 13.2 (qt, J = 128, 2.5 Hz), 13.4 (qt, J = 128 Hz), 36.3 (tq, J = 138, 3.2 Hz), 52.2 (d, J = 136 Hz, C_β), 64.6 (tq, J = 155, 4.3 Hz), 109.5 (d, J = 169 Hz, C-4, C-9), 120.7 (C-9b), 124.1 (d, J = 170 Hz, C-5, C-8), 128.5 (d, J = 163 Hz, C-6, C-7), 130.8 (C-3a, C-9a), 134.6 (C-6a), 153.5 (C-2), 162.8 (CO).

For **5′a**: ^1H NMR ($CDCl_3$, 300 MHz): δ 1.18 (t, 3H, J = 7.3 Hz), 1.36 (t, 3H, J = 7.1 Hz), 3.30 (q, 2H, J = 7.3 Hz), 4.23 (q, 2H, J = 7.1 Hz), 6.33 (d, 1H, J = 6.3 Hz, Ar), 6.45 (d, 1H, J = 6.6 Hz, Ar), 7.09 (m, 4H, Ar), 8.0 (broad s, 1H, NH), 12.2 (broad s, 1H, H-1), 14.4 (broad s, 1H, H-3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.4 (qt, J = 127, 2.5 Hz), 14.7 (qt, J = 126, 2.5 Hz), 34.2 (tq, J = 139, 3.2 Hz), 60.3 (tq, J = 144, 4.3 Hz), 75.3 (C-10), 105.0–106.0 (d, J = 162 Hz, C-4, C-9), 116.9 (C-9b), 119.2–119.4 (d, J = 160 Hz, C-5, C-8), 127.8–128.1 (d, J = 162 Hz, C-6, C-7), 133.7–133.8 (C-3a, C-9a), 134.4 (C-6a), 155.9 (C-2), 169.1 (CO), 169.9 (CO).

MS, m/z: 325.1461 found (calc for $C_{18}H_{19}N_3O_3$: 325.1426), M^+.

Anal calc for $C_{18}H_{19}N_3O_3$: C, 66.46; H, 5.85; N, 12.92; O, 14.77. Found: C, 66.19; H, 5.94; N, 12.95; O, 14.92.

• *Ethyl α-phenylcarbamoyl-1H-perimidine-2-acetate* **5b**, *ethyl 2-phenylcarbamoyl-2-(1H-perimidin-2-ylidene)acetate* **5′b**

From perimidine **3a** (2.2 g, 8.66 mmol) and phenyl isocyanate **4b** (1.24 g, 10.4 mmol), reaction time: 15 h. TLC: R_f = 0.68 with CH_2Cl_2 as eluent. 94% yield (2.85 g) of **5b**. Mp = 182–183 °C.

IR (Nujol): 3 360, 1 610, 1 580 cm^{-1}.

For **5b**: ^1H NMR ($CDCl_3/CF_3CO_2H$ (9:1), 300 MHz): δ 1.31 (t, 3H, J = 7.1 Hz), 4.39 (q, 2H, J = 7.1 Hz), 5.25 (s, 1H), 6.82 (d, 2H, J = 7.2 Hz, Ar), 7.31 (m, 7H, Ar), 7.53 (d, 2H, Ar), 9.87 (broad s, 1H, NH), 11.4 (broad s, 1H, NH).

^{13}C NMR ($CDCl_3/CF_3CO_2H$ (9:1), 75 MHz): δ 13.3 (qt, J = 128, 2.4 Hz), 53.2 (t, J = 137 Hz, C_β), 65.2 (tq, J = 151, 4.3 Hz), 109.6 (dd, J = 162 Hz, C-4, C-9), 120.8 (C-9b), 121.4 (d, J = 165 Hz, C-5, C-8), 124.3 (d, J = 161 Hz, C-4′, Ar), 127.1 (dt, J = 162, 7.4 Hz, 2 × C-3′, Ar), 128.5 (d, J = 163 Hz, C-6, C-7), 129.4 (dd, J = 162, 8.0 Hz, 2 × C-2′, Ar), 130.7 (C-3a, C-9a), 134.7 (C-6a), 135.4 (sm, C_{ipso}, Ar), 153.3 (C-2), 161.0 (CO), 163.1 (CO).

For **5′b**: ^1H NMR ($CDCl_3$, 300 MHz): δ 1.44 (t, 3H, J = 7.1 Hz), 4.30 (q, 2H, J = 7.1 Hz), 6.45 (d, 1H, J = 6.3 Hz, Ar), 6.55 (d, 1H, J = 6.6 Hz, Ar), 7.10 (m, 5H, J = 7.1 Hz, Ar), 7.30 (t, 2H, J = 7.0 Hz, Ar), 7.47 (d, 2H, J = 7.0 Hz, Ar), 10.0 (broad s, 1H, NH), 12.4 (broad s, 1H, H-1), 14.0 (broad s, 1H, H-3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.4 (qt, J = 127, 2.4 Hz), 60.8 (tq, J = 149, 4.5 Hz), 76.0 (C_β), 105.5–106.3 (d, J = 162 Hz, C-4, C-9), 117.1 (C-9b), 119.6–119.7 (d, J = 160 Hz, C-5, C-8), 120.9 (C-4′, Ar), 123.6 (dt, 2× C-3′, Ar), 127.9–128.2 (d, J = 160 Hz, C-6, C-7), 128.9 (dd, 2 × C-2′, Ar), 133.6 (C-3a, C-9a), 134.4 (C-6a), 138.6 (sm, C_{ipso}, Ar), 156.0 (C-2), 168.7 (CO), 168.8 (CO).

MS, m/z: 373.1437 found (calc for $C_{22}H_{19}N_3O_3$: 373.1426), M^+.

Anal calc for $C_{22}H_{19}N_3O_3$: C, 70.78; H, 5.09; N, 11.26; O, 12.87. Found: C, 70.79; H, 5.21; N, 11.43; O, 12.57.

• *Ethyl α-propylcarbamoyl-1H-perimidine-2-acetate* **5c**, *ethyl 2-propylcarbamoyl-2-(1H-perimidin-2-ylidene)acetate* **5′c**

From perimidine **3a** (2.2 g, 8.66 mmol) and propyl isocyanate **4c** (0.88 g, 10.4 mmol), reaction time: 46 h. TLC: R_f = 0.65 with CH_2Cl_2 as eluent. 66% yield (1.93 g) of **5c**. Mp = 151–152 °C.

IR (Nujol): 3 460, 1 660 cm^{-1}.

For **5c**: ^1H NMR ($CDCl_3/CF_3CO_2H$ (9:1), 300 MHz): δ 0.96 (t, 3H, J = 7.3 Hz), 1.38 (t, 3H, J = 7.1 Hz), 1.64 (m, 2H, J = 7.3 Hz), 3.30–3.40 (m, 2H), 4.36 (q, 2H, J = 7.3 Hz), 5.03 (s, 1H), 6.85 (d, 2H, J = 7.3 Hz), 7.28 (t, 2H, J = 7.4 Hz), 7.37 (d, 2H, J = 8.3 Hz), 8.21 (broad s, 1H, NH), 11.21 (s, 1H, NH).

^{13}C NMR ($CDCl_3/CF_3CO_2H$ (9:1), 75 MHz): δ 10.6 (qt, J = 126, 4.2 Hz), 13.1 (qt, J = 128, 2.8 Hz), 21.6 (tm, J = 128 Hz), 43.2 (tm, J = 130 Hz), 52.7 (d, J = 13 Hz, C_β), 65.2 (tq, J = 150, 4.5 Hz), 109.5 (d, J = 165 Hz, C-4, C-9), 120.8 (C-9b), 124.5 (dm, J = 162 Hz, C-5, C-8), 128.5 (d, J = 164 Hz, C-6, C-7), 130.5 (C-3a, C-9a), 134.7 (C-6a), 153.1 (C-2), 162.9 (CO), 163.1 (CO).

For **5′c**: ^1H NMR ($CDCl_3$, 300 MHz): δ 0.85 (t, 3H, J = 7.3 Hz), 1.39 (t, 3H, J = 7.1 Hz), 1.58 (q, 2H, J = 7.3 Hz), 3.26 (qt, 2H, J = 7.0 Hz), 4.28 (q, 2H, J = 7.1 Hz), 6.40 (d, 1H, J = 6.3 Hz, Ar), 6.49 (d, 1H,

J = 6.6 Hz, Ar), 7.13 (m, 4H, Ar), 8.1 (broad s, 1H, NH), 11.9 (broad s, 1H, H-1), 14.4 (broad s, 1H, H-3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.7 (qt, J = 127 Hz), 14.4 (qt, J = 127 Hz), 22.7 (td, J = 162 Hz), 41.2 (tt, J = 120 Hz), 60.3 (tq, J = 148 Hz), 75.4 (C_β), 105.3–106.1 (C-4, C-9), 117.0 (C-9b), 119.3–119.5 (d, J = 162 Hz, C-5, C-8), 127.9–128.2 (d, J = 160 Hz, C-6, C-7), 133.8 (C-3a, C-9a), 134.4 (C-6a), 156.0 (C-2), 169.0 (CO), 170.0 (CO).

MS, m/z: 339.1603 found (calc for $C_{19}H_{21}N_3O_3$: 339.1582), M^+.

Anal calc for $C_{19}H_{21}N_3O_3$: C, 67.26; H, 6.19; N, 12.39; O, 14.16. Found: C, 66.97; H, 6.23; N, 12.48; O, 14.32.

• *Ethyl α-[methyl(thiocarbamoyl)]-1H-perimidine-2-acetate* **5d**, *ethyl 2-[methyl(thiocarbamoyl)]-2-(1H-perimidin-2-ylidene)acetate* **5′d**

From perimidine **3a** (2.2 g, 8.66 mmol) and methyl thioisocyanate **4d** (0.84 g, 9.57 mmol), reaction time: 163 h. TLC: R_f = 0.64 with CH_2Cl_2 as eluent. 72% yield (2.04 g) of **5d**. Mp = 151–152 °C.

IR (Nujol): 3 360, 1 610 cm^{-1}.

For **5d**: ^{1}H NMR ($CDCl_3/CF_3CO_2H$ (9:1), 300 MHz): δ 1.32 (t, 3H, J = 7.1 Hz), 3.25 (d, 3H, J = 4.4 Hz), 4.37 (q, 2H, J = 7.1 Hz), 5.25 (s, 1H), 6.76 (d, 2H, J = 7 Hz, Ar), 7.38 (m, 4H, Ar), 9.62 (broad s, 1H, NH), 13.0 (broad s, 1H, NH).

^{13}C NMR ($CDCl_3/CF_3CO_2H$ (9:1), 75 MHz): δ 13.5 (qt, J = 125, 2.5 Hz), 34.0 (q, J = 142 Hz), 58.4 (d, J = 135 Hz, C_β), 65.5 (tq, J = 146, 4.4 Hz), 109.9 (d, J = 163 Hz, C-4, C-9), 121.2 (C-9b), 124.8 (d, J = 160 Hz, C-5, C-8), 128.9 (d, J = 163 Hz, C-6, C-7), 131.6 (C-3a, C-9a), 135.2 (C-6a), 154.1 (C-2), 164.5 (CO), 188.7 (CS).

For **5′d**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (t, 3H, J = 7.1 Hz), 3.18 (d, 3H, J = 4.7 Hz), 4.25 (q, 2H, J = 7.1 Hz), 6.44 (2 × d, 2H, J = 6.7 Hz, Ar), 7.09 (m, 4H, Ar), 9.5 (broad s, 1H, NH), 13.4 (broad s, 2H, H-1, H-3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.4 (qt, J = 127, 2.5 Hz), 32.4 (q, J = 139 Hz), 60.8 (tq, J = 144, 4.3 Hz), 84.8 (C_β), 105.7 (d, J = 160 Hz, C-4, C-9), 117.1 (C-9b), 119.6 (d, J = 160 Hz, C-5, C-8), 128.0 (d, J = 160 Hz, C-6, C-7), 133.5 (C-3a, C-9a), 134.4 (C-6a), 154.4 (C-2), 168.3 (CO), 190.8 (CS).

MS, m/z = 327.1033 found (calc for $C_{17}H_{17}N_3O_2S$: 327.1041), M^+.

• *Ethyl α-[4-(chlorophenyl)carbamoyl]-1H-perimidine-2-acetate* **5e**, *ethyl 2-[(4-chlorophenyl)carbamoyl]-2-(1H-perimidin-2-ylidene)acetate* **5′e**

From perimidine **3a** (2.2 g, 8.66 mmol) and 4-chlorophenyl isocyanate **4e** (1.47 g, 9.57 mmol), reaction time: 16 h. TLC: R_f = 0.85 with CH_2Cl_2 as eluent 98% yield (3.45 g) of **5e**. Mp = 186–187 °C.

IR (Nujol): 3 360, 1 600 cm^{-1}.

For **5e**: ^{1}H NMR ($CDCl_3/CF_3CO_2H$ (9:1), 300 MHz): δ 1.35 (t, 3H, J = 6.4 Hz), 4.25 (q, 2H, J = 6.5 Hz), 5.20 (s, 1H), 6.85 (m, 2H, Ar), 7.37 (m, 8H, Ar), 9.85 (broad s, 1H, NH), 11.30 (broad s, 1H, NH).

^{13}C NMR ($CDCl_3/CF_3CO_2H$ (9:1), 75 MHz): δ 13.2 (qt, J = 128, 2.5 Hz), 53.2 (d, J = 137 Hz, C_β), 65.5 (tq, J = 151, 4.7 Hz), 109.7 (d, J = 164 Hz, C-4, C-9), 120.8 (C-9b), 122.7 (d, J = 162 Hz, C-5, C-8), 124.6 (dd, J = 164 Hz, 2 × C-2′, Ar), 128.5 (d, J = 164 Hz, C-6, C-7), 129.5 (dd, J = 168, 5.3 Hz, 2×C-3′, Ar), 130.5 (C-3a, C-6a), 132.7–133.7 (C_{ipso}, C-4′, Ar), 134.8 (C-6a), 153.0 (C-2), 161.8 (CO), 163.0 (CO).

For **5′e**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.45 (t, 3H, J = 7.1 Hz), 4.31 (q, 2H, J = 7.1 Hz), 6.38 (d, 1H, Ar), 6.51 (d, 1H, Ar), 7.11 (s, 4H, Ar), 7.25 (m, 2H, Ar), 7.43 (d, 2H, J = 7.8 Hz), 9.9 (broad s, 1H, NH), 11.8 (broad s, 1H, NH), 14.1 (broad s, 1H, NH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.4 (qt, J = 127, 2.5 Hz), 60.9 (tq, J = 150, 4.3 Hz), 76.0 (C_β), 105.6–106.4 (d, J = 160, C-4, C-9), 117.0 (C-9b), 119.8 (d, J = 160 Hz, C-5, C-8), 121.8 (d, J = 163 Hz, 2×C-3′, Ar), 127.9–128.3 (d, J = 161 Hz, C-6, C-7), 128.4–128.9 (d, J = 163 Hz, 2 × C-2′, Ar), 133.5 (C-3a, C-9a), 134.5 (C-6a), 137.3 (C_{ipso}, Ar), 156.0 (C-2), 168.7 (CO).

MS, m/z: 407.1005 found (calc for $C_{22}H_{18}ClN_3O_3$: 407.1016), M^+.

Anal calc for $C_{22}H_{18}ClN_3O_3$: C, 64.78; H, 4.42; N, 10.31; Cl, 8.71; O, 11.78. Found: C, 64.71; H, 4.37; N, 10.15; Cl, 8.71; O, 12.06.

• *Ethyl α-{[(ethoxycarbonyl)methyl]carbamoyl}-1H-perimidine-2-acetate* **5f**, *ethyl 2-{[(ethoxycarbonyl)methyl]carbamoyl}-2-(1H-perimidin-2-ylidene)acetate* **5′f**

From perimidine **3a** (2.2 g, 8.66 mmol) and ethyl 2-isocyanatoacetate **4f** (1.34 g, 10.4 mmol), reaction time: 46 h. TLC: R_f = 0.40 with CH_2Cl_2 as eluent 80% yield (2.65 g) of **5f**. Mp = 161–162 °C.

IR (Nujol): 3 390, 1 730, 1 610 cm^{-1}.

For **5f**: ^{1}H NMR ($CDCl_3/CF_3CO_2H$ (9:1), 300 MHz): δ 1.30 (t, 3H, J = 7.1 Hz), 1.32 (t, 3H, J = 7.1 Hz), 4.17 (s, 2H), 4.29 (q, 2H, J = 7.1 Hz), 4.36 (q, 2H, J = 7.1 Hz), 5.20 (broad s, 1H), 6.82 (d, 2H, J = 7.1 Hz, Ar), 7.31 (m, 2H, J = 7.1 Hz), 7.37 (d, 2H, J = 7.1 Hz), 8.7 (broad s, 1H, NH), 11.20 (broad s, 1H, NH).

^{13}C NMR ($CDCl_3/CF_3CO_2H$ (9:1), 75 MHz): δ 13.2 (qt, J = 128 Hz), 13.4 (qt, J = 128 Hz), 42.4 (t, J = 143 Hz), 52.4 (d, J = 138 Hz, C_β), 63.5 (tq, J = 145 Hz), 109.6 (d, J = 165 Hz, C-4, C-9), 120.8 (C-9b), 124.7 (d, J = 163 Hz, C-5, C-8), 128.5 (d, J = 164 Hz, C-6, C-7), 130.6 (C-3a, C-9a), 134.7 (C-6a), 153 (C-2), 162.9 (CO), 163.9 (CO), 170.4 (CO).

For **5′f**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (t, 3H, J = 7.1 Hz), 1.43 (t, 3H, J = 7.1 Hz), 4.06 (d, 2H, J = 6.1 Hz), 4.24 (2 × q, 2 × 2H, J = 7.1 Hz), 6.41 (d, 1H, J = 6.3 Hz, Ar), 6.48 (d, 1H, J = 6.6 Hz, Ar), 7.10 (m, 4H, Ar), 8.5 (broad s, 1H, NH), 12.0 (broad s, 1H, H-1), 14.1 (broad s, 1H, H-3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.2 (qt, J = 127 Hz), 14.3 (qt, J = 127 Hz), 41.9 (t, J = 142 Hz), 60.4 (tq, J = 148 Hz), 61.3 (tq, J = 148 Hz), 75.5 (C_β), 105.0–106.0 (d, J = 160 Hz, C-4, C-9), 117.1 (C-9b), 119.4–119.6 (d, J = 160 Hz, C-5, C-8), 127.9–128.2 (d, J = 160 Hz, C-6, C-7), 133.6 (C-3a, C-9a), 134.4 (C-6a), 156.0 (C-2), 169.3 (CONH), 170.0 (CO), 170.4 (CO).

MS, m/z = 383.1483 found (calc for $C_{20}H_{21}N_3O_5$: 383.1481), M^+.

Anal calc for $C_{20}H_{21}N_3O_5$: C, 62.66; H, 5.48; N, 10.97; O, 20.89. Found: C, 62.37; H, 5.46; N, 11.20; O, 20.97.

• *Ethyl 2-[(ethoxycarbonyl)thiocarbamoyl]-2(1H-perimidin-2-ylidene)acetate* **5′g**

From perimidine **3a** (2.2 g, 8.66 mmol) and ethoxycarbonyl isothiocyanate **4g** (1.25 g, 9.52 mmol), reaction time: 6 min at room temperature. TLC: R_f = 0.75 with CH_2Cl_2 as eluent. 98% yield (3.26 g) of **5′g**. Mp = 186–187 °C.

IR (Nujol): 3 400, 1 720, 1 620 cm^{-1}.

^1H NMR ($CDCl_3/CF_3CO_2H$ (9:1), 300 MHz): δ 1.33 (2 × t, 6H, J = 7.1 Hz), 4.27 (2 × q, 4H, J = 7.1 Hz), 6.78 (m, 2H, Ar), 7.28 (m, 2H, Ar), 7.38 (m, 2H, Ar), 10.8 (broad s, 1H, NH), 10.9 (broad s, 1H, NH), 11.5 (s, 1H, NH) (masked by TFA).

^{13}C NMR ($CDCl_3/CF_3CO_2H$ (9:1), 75 MHz): δ 13.5 (2 × qt, J = 128 Hz), 62.9 (tq, J = 147 Hz), 64.1 (tq, J = 147 Hz), 94.0 (C_β), 109.3 (d, J = 160 Hz, C-4, C-9), 120.4 (C-9b), 124.3 (d, J = 160 Hz, C-5, C-8), 128.5 (d, J = 160 Hz, C-6, C-7), 131.5 (C-3a, C-9a), 134.8 (C-6a), 154.3 (C-2), 153.5 (CO), 162.8 (CO), 164.1 (CS).

MS, m/z: 385.1083 found (calc for $C_{19}H_{19}N_3O_4S$: 385.1096), $M^{+\cdot}$.

Anal calc for $C_{19}H_{19}N_3O_4S$: C, 59.22; H, 4.94; N, 10.91; O, 16.62; S, 8.31. Found: C, 58.86; H, 4.97; N, 10.96; O, 16.90; S, 8.31.

• *2-{[(Ethoxycarbonyl)methyl]carbamoyl}-2-(1H-perimidin-2-ylidene)acetonitrile* **5′h**

From 1*H*-perimidine-2-acetonitrile **3b** (2.0 g, 9.66 mmol) and ethyl 2-isocyanatoacetate **4f** (1.5 g, 11.6 mmol), reaction time: 39 h. TLC: R_f = 0.72 with CH_2Cl_2/MeCN (4:1) as eluent. 82% yield (2.66 g) of **5′h**. Mp = 253–254 °C.

IR (Nujol): 2 290, 1 670, 1 500 cm^{-1}.

^1H NMR ($CDCl_3/CF_3CO_2H$ (9:1), 300 MHz): δ 1.35 (t, 3H, J = 7.1 Hz), 4.08 (s, 2H), 4.23 (q, 2H, J = 7.1 Hz), 6.50 (m, 2H, Ar), 7.10 (m, 4H, Ar), 7.70 (broad s, 1H, NH), 11.40 (2H, H-1, H-3) (H-1 and H-3 are masked by TFA).

^{13}C NMR ($CDCl_3/CF_3CO_2H$ (9:1), 75 MHz): δ 13.0 (qt, J = 128 Hz), 41.7 (t, J = 142 Hz), 55.2 (C_β), 63.8 (tq, J = 150 Hz), 107.0 (d, J = 160 Hz, C-4, C-9), 116.6 (C-9b), 119.1 (CN), 121.6 (d, J = 160 Hz, C-5, C-8), 127.9 (d, J = 160 Hz, C-6, C-7), 133.3 (C-3a, C-9a), 134.3 (C-6a), 154.4 (C-2), 169.7 (CONH), 173.1 (CO).

MS, m/z = 336.1226 found (calc for $C_{18}H_{14}N_4O_3$: 336.1223), $M^{+\cdot}$.

Anal calc for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.76; N, 16.67; O, 14.29. Found: C, 64.40; H, 4.65; N, 16.87; O, 14.08.

• *2-Phenylcarbamoyl-2-(1H-perimidin-2-ylidene) acetonitrile* **5′i**

From 1*H*-perimidine-2-acetonitrile **3b** (2.0 g, 9.66 mmol) and propyl isocyanate **4c** (0.99 g, 11.6 mmol), reaction time: 94 h. TLC: R_f = 0.22 with CH_2Cl_2 as eluent. 60% yield (1.69 g) of **5′i**. Mp = 240–241 °C.

IR (Nujol): 2 190, 1 630, 1 580 cm^{-1}.

^1H NMR ($CDCl_3/CF_3CO_2H$ (9:1), 300 MHz): δ 6.70 (m, 2H, Ar), 7.30 (m, 6H, Ar), 7.45 (m, 3H, Ar), 8.00 (broad s, 1H, NH), 11.40 (broad s, 2H, H-1, H-3) (H-1 and H-3 are masked by TFA).

^{13}C NMR ($CDCl_3/CF_3CO_2H$ (9:1), 75 MHz): δ 56.6 (C_β), 108.0 (d, J = 165 Hz, C-4, C-9), 117.4 (C-9b), 120.0 (CN), 122.5 (d, J = 164 Hz, C-5, C-8), 125.1 (dd, J = 160 Hz, Ar), 127.9 (d, J = 163 Hz, C-6, C-7), 128.9–130.2 (dd, J = 160 Hz, Ar), 132.3 (C-3a, C-9a), 135.7 (C_{ipso}), 155.4 (C-2), 169.2 (CO).

MS, m/z = 326.1109 found (calc for $C_{20}H_{14}N_4O$: 326.1168), $M^{+\cdot}$.

Anal calc for $C_{20}H_{14}N_4O$: C, 73.62; H, 4.29; N, 17.18; O, 4.91. Found: C, 73.45; H, 4.38; N, 17.46; O, 4.71.

• *2-[(4-Chlorophenyl)carbamoyl]-2-(1H-perimidin-2-ylidene)acetonitrile* **5′j**

From 1*H*-perimidine-2-acetonitrile **3b** (2.0 g, 9.66 mmol) and 4-chlorophenyl isocyanate **4e** (1.62 g, 10.6 mmol), reaction time: 63 h. TLC: R_f = 0.43 with CH_2Cl_2 as eluent. 86% yield (2.99 g) of **5′j**. Mp > 260 °C.

IR (Nujol): 3 410, 2 180, 1 650, 1 630, 1 580 cm^{-1}.

^1H NMR ($CDCl_3/CF_3CO_2H$ (9:1), 300 MHz): δ 6.58 (m, 2H, Ar), 7.14 (m, 5H, Ar), 7.30 (m, 3H, Ar), 7.58 (broad s, 1H, NH), 11.4 (2H, H-1, H-3) (H-1 and H-3 are masked by TFA).

^{13}C NMR ($CDCl_3/CF_3CO_2H$ (9:1), 75 MHz): δ 55.7 (C_β), 108.6 (dm, J = 163 Hz, C-4, C-9), 116.4 (C-9b), 121.2 (CN), 121.5 (d, J = 162 Hz, C-5, C-8), 124.8 (C-3′, Ar), 125.4 (C-3′, Ar), 127.9 (d, J = 162 Hz, C-6, C-7), 129.3 (dd, 2 × C-2′, Ar), 131.2 (C-3a, C-9a), 132.3 (C-4′, Ar), 133.6 (C_{ipso}, Ar), 134.2 (C-6a), 154.2 (C-2), 167.9 (CONH).

MS, m/z: 360.1323 found (calc for $C_{20}H_{13}ClN_4O$: 360.0778), $M^{+\cdot}$.

Anal calc for $C_{20}H_{13}ClN_4O$: C, 66.57; H, 3.61; N, 15.53; O, 4.44; Cl, 9.85. Found: C, 65.89; H, 3.66; N, 15.54; O, 4.44; Cl, 10.47.

Typical procedure for microwave reaction

A mixture of ethyl 1*H*-perimidine-2-acetate **3a** (0.3 g, 1.18 mmol) or 1*H*-perimidine-2-acetonitrile **3b** (0.24 g, 1.18 mmol) and isocyanate **4** (1.3 mmol) was placed in a cylindrical Pyrex tube. The tube was then introduced into the Synthewave 402 Prolabo microwave reactor (2.45 GHz, adjustable power within the range 0–300 W and a wave guide (singlemode T_{01})) fitted with a rotational system and an IR temperature detector. Microwave irradiation was carried out with a suitable temperature (the microwave oven is monitored by a computer which allows adjustment of the temperature of the reaction mixture according to the boiling point of the isocyanates **4**) for an appropriate time (see table II). The mixture was cooled to room temperature and the crude residue was characterized by ^1H NMR and comparison with samples synthesized according to the standard procedure described for the compounds **5** and **5′**.

Attempted addition reaction of ethyl isocyanate **4a** *to ethyl 2-methyl-1H-perimidine-2-acetate* **3c**

A solution of ethyl α-methyl-1*H*-perimidine-2-acetate **3c** (1.3 g, 1.12 mmol) and ethyl isocyanate **4a** (0.1 g, 1.34 mmol) in dry acetonitrile (5 mL) was refluxed for 12 h. Then, the reaction mixture was allowed to cool. After removal of the solvent in vacuo, the crude residue was analyzed by ^1H NMR in $CDCl_3$; it showed only unreacted **3c**.

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