Thermal Decomposition of Carbamoyl Meldrum's Acids a Starting Point for the Preparation of 1,3-oxazine Derivatives.

Sławomir Makowiec*, Ewelina Najda, Karolina Janikowska

Department of Organic Chemistry, Faculty of Chemistry, Gdansk University of Technology,

Narutowicza 11/12, 80-952 Gdansk, Poland

(phone: +48 58 3471724 fax: +48 58 3472694; e-mail: mak@pg.gda.pl)

ABSTRACT

Ability to undergo [4+2] versus [2+2] cycloaddition was under investigation for ketenes thermally generated from carbamoyl Meldrum's acid. Usually 1,3-oxazino-5-carbamoylo-4,6-diones are formed when carbamoyl Meldrum's acid reacts with imine. However in some cases a reaction takes an unexpected course, leading to the formation of tetraponerines alkaloids derivatives or cyclic iminoethers.

INTRODUCTION

Derivatives of Meldrum's acid have a broad scope of application in heterocyclic chemistry [1, 2]. Depending on the type of Meldrum's acid derivative used and in addition the conditions of the process, various compounds can be prepared for example β-lactams [3, 4], 1,3-oxazinones [5], pilicides [6, 7], isooxazolols [8], tetramic acid derivatives [9], cyclic nitrones [10, 11] prodigiosin family antibiotics analogues[12] or substituted pyridines [13]. Also valuable non-

cyclic compounds can be easily prepared using Meldrum acid as a β-ketoacylium synthon for example we can cite formation of 1,3-diones [14], ketoesters [15-19], ketoamides [20, 21]. The main stream of aforementioned reactions of Meldrum's acid derivatives is connected with their tendency to form ketenes during thermal decomposition, once formed ketene may react with various types of nucleophiles. When the nucleophile is an alcohol or amine the ketene simply form an S_N acyl product, whereas nucleophile is an imine, vinyl ether [22] or other π-electronic system reaction can take place by a [4+2] or [2+2] cycloaddition pathway. Both types of cycloaddition lead to valuable products however it is difficult to unambiguously predict which kind of product will be formed after the use of a new combination of reagents or a slight change in the reaction conditions. This unpredictability, prevents a reliance on the results of similar experiments in planning new syntheses and sometimes can lead to erroneous conclusions. Almquist and co-workers suggested that acyl Meldrum's acid in combination with imine in the presence of HCl should give a [2+2] cycloaddition product [3], mistakenly recognizing the product of the reaction between Δ^2-thiazoline and acyl Meldrum's acid as a 6-acylpenam [23] which was only later correctly identified as a bicyclic 1,3-oxazinone [24]. The reaction of ordinary ketenes with imines is properly described by a stepwise mechanism leading to an azetidone ring as the only product [25], whereas thermolysis of acyl Meldrum's acids produce 3-oxo-ketenes or even 3-oxo-2-carboxyketenes [5, 22] which allow six membered heterocycles to be formed through [4+2] cycloaddition. Moreover our own research results seem to indicate that the reaction of acyl Meldrum's acid with nucleophile may take place even before a loss of acetone and CO_2 [26].

Recently we have focused on the synthetic application of carbamoyl Meldrum's acid thus developing protocols for forming 3-carbamoyl-β-lactams [4] or pseudopeptides [27]. In our most in-depth research, we focused on possibly forming 3-carbamoyl-β-lactams, however

some combinations of reagents eluded the usual rules, leading to unexpected products. In this paper we wish to present the results of this research.

RESULTS AND DISCUSSION

As previously reported the reaction of carbamoyl Meldrum's acids with aldimines in the presence of HCl (gas) gave 3-carbamoyl-β-lactams with good yields provided that Meldrum's acid derivative contained aryl group on nitrogen [4]. While the reaction of 5-[hydroxy (ethylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1a**) with N-benzylideneisopropylamine (**2a**) in the presence of HCl leads to the formation of a complex mixture of products where only 2-phenyl-3-isopropyl-1,3-oxazino-5-(ethylcarbamoyl)-4,6-dione (**3aa**) was compound in high enough concentration for isolation, but even traces of 3-carbamoyl-β-lactams were not formed, the use of higher boiling solvents such as toluene of ethylbenzene did not affect the reaction yield or the distribution of products. The similar experiments performed without HCl allowed the aforementioned **3aa** to be obtained with a high yield. In addition, 5-[(cyclohexylamino)hydroxy)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **1b** as well as other aldimines react in the same manner. The results of these experiments are presented in the Table 1. In addition, 5-[(phenylamino)hydroxy)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1c**) react in these conditions with **2a** to yield **3**. Since a change of substitution in Meldrum's acid derivative has such a tremendous influence on the reaction course, we decided to check if substitution in the imine component could also have similar significance. As reported [4] β-lactams were formed for the following combination of reagents: N-aryl Meldrum's acid and imine of aromatic or aliphatic aldehyde, therefore we performed a reaction of **1c** and ethyl (tert-butylimino)acetate (**2d**). Surprisingly in the case of this imine in both scenarios, with and without the presence of HCl the same product was

formed - ethyl 5-(N-phenylcarbamoyl)-3-tert-butyl-4,6-dioxo-1,3-oxazinane-2-carboxylate (**3cd**), pointing to the fact that [2+2] cycloaddition is a particular exception rather than a general rule.

The formation of **3** may occur in two ways (Scheme 1). First: by a direct attack of aldimine on the carbonyl carbon in the Meldrum's acid derivative **1** before the loss of acetone and CO_2 (path A) similarly to the "direct acylation pathway" proposed by Fillion [28] for acylation with quaternized Meldrum's acid, however, this is in contrast with findings of Grabowski [29]. The second possibility for forming **3** is the initial partial decomposition of **1** with a loss of acetone and reaction of 3-oxo-2-carboxyketenes (**4**) with aldimine (path B). A similar mechanism for the reaction of acyl Meldrums acids was previously proposed by Yamamoto [5]. It should be added that reaction between **4** and **2** may lead by [4+2] concerted mechanism, omitting an ionic intermediate (path B'). In the light of our previous studies on the mechanism reaction of carbamoyl Meldrums acids [26], path A seems to be unlikely because of the use of high boiling solvent which cause the complete decomposition of **1** within ca. 3 h as well as a low nucleophilicity of aldimines. Most probably the observed reaction occurs through path B with **4** as an intermediate which under moderately basic conditions is relatively stable allowing a high yield of [4+2] cycloaddition.

It should be stressed that a slight change in the part of molecule which is not directly involved in the reaction occurring, cause a change in the course of the reaction. This fact illustrates how difficult it is to anticipate the course of a reaction when using carbamoyl Meldrum's acid derivatives.

As mentioned above Almqvist and co-workers have experienced problems during intended synthesis of β-lactams, they obtain instead 1,3-oxazinones [23, 24]. A check in relation to the reactivity of 2-phenyl-4,5-dihydro-1,3-thiazol, 4-methoxycarbonyl-4,5-dihydro-1,3-thiazol and 2-phenyl-5,6-dihydro-4H-1,3-thiazine toward a ketene species

generated from alkyl and aryl carbamoyl Meldrum acid was made under various conditions with or without HCl in high or low boiling solvents, neither of them gave suitable β-lactams or 1,3-oxazinones, instead a complex mixture of products was obtained. Taking into account above facts, it seems clear that thiazoline derivatives are prone to produce only 1,3-oxazinones and only in combination with a particular derivative of Meldrum's acid. Hence we decided to check if cyclic imines without sulphur are able to form β-lactams or 1,3-oxazinones. As we reported previously the reaction of alkyl and aryl carbamoyl Meldrum's acids with 1-pyrroline trimer catalysed by boron trifluoride with the intention of obtaining a carbapenam type of compound, instead led to a new boron difuoride complex of carbamoyl Meldrum's acids [30]. Therefore we ran reactions of 3,4-dihydroisoquinoline (**6**) with **1c** in both boiling DCE and toluene in the presence of HCl, surprisingly we obtained **7** with 62% and 22% yields respectively depending on the solvent used. This new compound **7** is most probably formed as a result of [4+2] cycloaddition of carbamoyl ketene (**5**) to 3,4-dihydroisoquinoline (Scheme 2). In the case of aforementioned process it should rather expected that [2+2] cycloaddition will be the predominant process. Acidic condition promote decarboxylation and loss of acetone in effect leading to formation of ketene **5**, additionaly, stericaly unhindered cyclic imine should be especially prone to the formation of trans-β-lactam ring. Surprisingly, the faster nucleophilic attack of amide oxygen lone pair results in [4+2] cycloaddition occuring as a main process.

On the basis of the above facts it is easy to predict results for the reaction of 3,4-dihydroisoquinoline with acyl Meldrum's acid. The experiment between **6** and 5-(1-hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**8**) in boiling DCE in the presence of HCl has confirmed our supposition, from the reaction mixture we isolated 2-methyl-7,11b-dihydro-4H,6H-[1,3]oxazino[2,3-a]isoquinolin-4-one (**9**) with a 40% yield [31] (Scheme 3). In contrast, although for slightly different cyclic imines with α-protons, Almquist has reported

that the formation of 11b-methyl-2-phenyl-7,11b-dihydro-4H,6H-[1,3]oxazino[2,3-a]isoquinolin-4-one occurs only in basic conditions [32].

In these circumstances, a very surprising result proved to be the reaction of **6** with **1c** in the boiling toluene without HCl. It is expected that 1,3-oxazino-5-carbamoylo-4,6-dione will form as a direct analogy to reaction **1c** with acyclic aldimines. However, from the reaction mixture we isolated as a main product 6-Oxo-5,6,8,12b,13,14-hexahydro-4bH,7H-6a,12c-diaza-benzo[c]chrysene-5-carboxylic acid phenylamide (**11**) (Scheme 4). In order to explain the observed phenomena, it can be assumed that, as in the case of the reaction with acyclic imines, in the first step 3-oxo-2-carboxyketene (**4c**) is formed and reacts readily with **6** to form an intermediate **10** (Scheme 4). Surprisingly the intramolecular ring closure unlike in the case of acylic imines is slower than interamolecular nucleophilic addition of the second molecule of **6** , subsequent decarboxylation allows for the final six membered ring closure. At this point it should be noted that in the case of the reaction described above of **1c** with **6** carried out with HCl also a small amount (5%) of **11** was observed. This fact supports the hypothesis that lower acidic conditions slowing decarboxylation, enables the attack of the second 3,4-dihydroisoquinoline molecule. Compound **11** is an analogue of tetraponerines alkaloids which were last in the spotlight due to their cytotoxic activity [33].

The experimental material indicates that cyclic imines as well as thiazolines or thiazines are not prone to reaction through a [2+2] cycloaddition pathway with ketenes generated form acyl and carbamoyl Meldrum's acids. Therefore in continuation we decided to check if acyclic imino thioethers are able to form β-lactam rings. On the other hand such a process in the case of ketenes generated from acyl chlorides is known and led to the formation of useful precursors of 4-unsubstituted β-lactams [34]. However attempts to trap a ketene generated from **1a or 1c** with dimethyldithio-N-butylcarbonimidate or dimethyldithio-N-benzylcarbonimidate with HCl being present or not have failed. When ketenes was generated

from **1c** or **1d** in the boiling DCE without HCl and trapped with ethyl benzylimidothioformate (**12**), the only products from the reaction mixture we isolated were S-ethyl-N-phenyl malonamic acid ester (**13c**) and S-ethyl-N-phenyl malonamic acid ester (**13d**) respectively, formed in the reaction of cabamoyl-ketenes and ethyl thiol raising as a result of the decomposition of **12** under harsh condition (Scheme 5). However ketene generated from 5-[hydroxy(phenyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**14**) in the reaction with **12** gave new 3-benzyl-2-(ethylthio)-6-phenyl-2,3-dihydro-4H-1,3-oxazin-4-one (**15**) by a [4+2] cycloaddition pathway. The same product was formed regardless to the presence or absence of HCl, however it should be added that compound **15** is acid labile and even traces of HCl present in CDCl$_3$ during NMR spectra collection cause its fast decomposition.

In conclusion, we have explored reactivity of carbamoyl Meldrum's acids toward various types of imines under thermolytic conditions. The obtained results strongly suggest that [4+2] cycloadditions are the preferred way of reaction with imines for ketenes generated from carbamoyl Meldrum's acids, and [2+2] cycloaddition leading to β-lactam system is rather an exception. We have developed an easy method for the preparation of 1,3-oxazino-5-carbamoylo-4,6-diones and in addition unexpected formations of 6-Oxo-5,6,8,12b,13,14-hexahydro-4bH,7H-6a,12c-diaza-benzo[c]chrysene-5-carboxylic acid phenylamide an analogue of tetraponerines alkaloids, have been observed by us.

EXPERIMENTAL

Reagents were purchased from Sigma-Aldrich. Toluene was distilled from potassium under argon. 1,2-dichloroethane was distilled from K$_2$CO$_3$ Analytical TLC was performed on aluminium sheets of silica gel UV-254 Merck. Flash chromatography was performed using 40-63 microns of Zeochem silica gel. The ^{1}H, ^{13}C were recorded on Varian Gemini 200 and

Varian Unity Plus 500, chemical shifts (δ) in ppm rel. to internal Me₄Si; coupling constants J in Hz. High-resolution (HRMS) was recorded on MicroMas Quattro LCT mass spectrometer. Melting points were determined with Warsztat Elektromechaniczny W-wa apparatus and have not been corrected. Commercially unavailable reagents were prepared using literature procedures as follows: 5-[Hydroxy(ethylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1a**) [4], 5-[Hydroxy(cyclohexylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1b**) [4], 5-[Hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione -4,6-dione (**1c**) [35], aldimines **2a-c** [36], ethyl (tert-butylimino)acetate (**2d**) [37], 2-phenyl-4,5-dihydro-1,3-thiazol [38], 4-metoxycarbonyl-4,5-dihydro-1,3-thiazol [39], 2-phenyl-5,6-dihydro-4H-1,3-thiazine [36], 3,4-dihydroisoquinoline (**6**) [38], 5-(1-hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**8**) [5], dimethyldithio-N-butylcarbonimidate [34], dimethyldithio-N-benzylcarbonimidate [34], ethyl benzylimidothioformate (**12**) [41], 5-[hydroxy(phenyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**14**) [5].

Syntheses of 1,3-oxazino-5-(carbamoyl)-4,6-diones (3). General procedure.

To a solution of **1** (1 mmol) in anhd. toluene 5 ml, aldimine **2** (1 mmol) was added. (If specified in the Table 1, the reaction mixture was saturated with gaseous HCl with cooling). The resulting mixture was stirred and heated to reflux for the time specified in Table 1. After the disappearance of the starting material, solvents were removed under reduced pressure, and the residue was purified as follows:

2-phenyl-3-isopropyl-1,3-oxazino-5-(ethylcarbamoyl)-4,6-dione (**3aa**)

Purification by flash column chromatography on silica gel (EtOAc-hexanes, 2:9); Colorless oil, 0.25 g (82%); ¹H NMR (500 MHz, CDCl₃): δ 1.14 (d, 3 H, J = 7.3 Hz), 1.20 (t, 3 H, J = 7.3 Hz), 1.37 (d, 3 H, J = 6.8 Hz), 3.31-3.44 (m, 2 H), 4.65-4.71 (m, 1 H), 6.25 (s, 1

H), 7.38-7.40 (m, 3 H), 7.41-7.49 (m, 2 H), 8.80 (br s, 1 H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 15.1, 20.7, 21.6, 35.1, 46.4, 76.9, 82.4, 127.1, 129.2, 129.8, 138.2, 165.5, 170.6, 171.3; HRMS (ESI):[Found: *m/z* 327.1246 (M + Na)$^+$, Calcd for C$_{16}$H$_{20}$N$_2$O$_4$Na: M, 327.1288].

2-phenyl-3-ethyl-1,3-oxazino-5-(cyclohexylcarbamoyl)-4,6-dione (**3bb)**

Purification by flash column chromatography on silica gel (EtOAc-hexanes, 2:11); 0.22 g (64%); M. p. 74 – 75 °C; ^{1}H NMR (200 MHz, CDCl$_3$): δ 0.78-0.86 (m, 1 H), 1.11 (t, 3 H, J = 7.2 Hz), 1.56-1.61 (m, 1 H), 1.62-1.79 (m, 2 H), 1.80-1.99 (m, 2 H), 2.87-3.01 (m, 1 H), 3.71-3.85 (m, 2 H), 6.11 (s, 1 H), 7.35-7.39 (m, 5 H), 8.86 (br s, 1 H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 13.9, 24.9, 25.8, 33.1, 33.2, 39.4, 49.4, 75.4, 86.2, 127.5, 129.2, 130.3, 136.3, 165.5, 170.6, 170.8; HRMS (ESI):[Found: *m/z* 367.1635 (M + Na)$^+$, Calcd for C$_{19}$H$_{24}$N$_2$O$_4$Na: M, 367.1634].

2-phenyl-3-ethyl-1,3-oxazino-5-(ethylcarbamoyl)-4,6-dione (**3ab)**

Purification by flash column chromatography on silica gel (EtOAc-hexanes, 2:9); 0.16 g (55%); M. p. 84 – 86 °C; ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.16 (t, 3 H, J = 6.8 Hz), 1.23 (t, 3 H, J = 7.3 Hz), 2.97-3.04 (m, 1 H), 3.35-3.45 (m, 2 H), 3.80-3.89 (m, 1 H), 6.14 (s, 1 H), 7.41-7.49 (m, 5 H), 8.88 (br s, 1 H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 13.9, 15.1, 35.2, 39.4, 75.5, 86.2, 127.5, 129.4, 130.3, 136.3, 165.5, 170.9, 171.5; HRMS (ESI):[Found: *m/z* 313.1151 (M + Na)$^+$, Calcd for C$_{15}$H$_{18}$N$_2$O$_4$Na: M, 313.1175].

2-(tert-butyl)-3-(tert-butyl)-1,3-oxazino-5-(ethylcarbamoyl)-4,6-dione (**3ac)**

Purification by flash column chromatography on silica gel (EtOAc-hexanes, 1:7); 0.08 g (25%); M. p. 99 – 101 °C; ^{1}H NMR (200 MHz, CDCl$_3$): δ 1.00 (s, 9 H), 1.22 (t, 3 H, J = 7.3 Hz), 1.50 (s, 9 H), 3.34-3.42 (m, 2 H), 5.15 (s, 1 H), , 8.90 (br s, 1 H); ^{13}C NMR (50 MHz,

CDCl$_3$): δ 15.2, 27.3, 30.2, 34.9, 40.6, 60.2, 80.4, 90.6, 166.5, 171.4, 174.6; HRMS (ESI):[Found: *m/z* 321.1811 (M + Na)$^+$, Calcd for C$_{15}$H$_{26}$N$_2$O$_4$Na: M, 321.1790].

2-phenyl-3-isopropyl-1,3-oxazino-5-(phenylcarbamoyl)-4,6-dione (**3ca**)

Purification by flash column chromatography on silica gel (EtOAc-hexanes, 1:2); 0.16 g (46%); M. p. 94 – 96 °C; ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.15 (d, 3 H, J = 6.8 Hz), 1.38 (d, 3 H, J = 6.8 Hz), 4.63-4.69 (m, 1 H), 6.30 (s, 1 H), 7.13-7.46 (m, 11 H), 10.70 (br s, 1 H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 20.6, 21.6, 47.1, 77.7, 82.7, 121.9, 125.5, 127.1, 129.4, 129.5, 130.1, 136.7, 137.6, 165.5, 170.3, 170.9; HRMS (ESI):[Found: *m/z* 375.1311 (M + Na)$^+$, Calcd for C$_{20}$H$_{20}$N$_2$O$_4$Na: M, 375.1321].

2-etoxycarbonyl-3-(tert-butyl)-1,3-oxazino-5-(phenylcarbamoyl)-4,6-dione (**3cd**)

Purification by flash column chromatography on silica gel (EtOAc-hexanes, 1:5 with 1% of AcOH); Yellow oil; 0.23 g (64%); ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.30 (t, 3 H, J = 6.8 Hz), 1.57 (s, 9 H), 4.25-4.30 (m, 2 H), 5.80 (s, 1 H), 7.14-7.17 (m, 1 H), 7.30-7.36 (m, 2 H), 7.45-7.48 (m, 2 H), 10.79 (br s, 1 H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 14.5, 29.2, 59.7, 63.4, 77.4, 79.6, 122.0, 125.7, 129.5, 136.6, 165.6, 167.8, 170.7, 172.3; HRMS (ESI):[Found: *m/z* 385.1364 (M + Na)$^+$, Calcd for C$_{18}$H$_{22}$N$_2$O$_6$Na: M, 385.1376].

2-(phenylimino)-2,3,7,11b-tetrahydro-4H,6H-[1,3]oxazino[2,3-a]isoquinolin-4-one (**7**)

To a solution of 0.263 g (1 mmol) 5-[(phenylamino)hydroxy)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1c**) in 5 ml of DCE, 0.131 g (1 mmol) of 3,4-dihydroisoquinoline (**6**) was added. The reaction mixture was cooled to 0°C and saturated

with gaseous HCl. The resulting mixture was stirred and heated to reflux. After 19 h, the mixture was cooled, and solvent were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc-hexanes, 8:1); 0.18 g (62%); M. p. 71 – 72 °C; ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.81-2.89 (m, 1 H), 3.11-3.17 (m, 1 H), 3.26-3.32 (m, 1 H), 3.36 (d, 1 H, J = 18.5), 3.60 (d, 1 H, J = 18.5), 4.65-4.69 (m, 1 H), 6.29 (s, 1 H), 7.06-7.33 (m, 9 H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 27.9, 41.2, 43.4, 71.9, 126.7, 127.1, 127.4, 127.8, 129.2, 129.4, 129.5, 132.1, 136.3, 139.0, 167.0, 167.9; HRMS (ESI):[Found: m/z 315.1118 (M + Na)$^+$, Calcd for C$_{18}$H$_{16}$N$_2$O$_2$Na: M, 315.1109].

2-methyl-7,11b-dihydro-4H,6H-[1,3]oxazino[2,3-a]isoquinolin-4-one (9)

To a solution of 0.186 g (1 mmol) 5-(1-hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (8) in 10 ml of DCE, 0.131 g (1 mmol) of 3,4-dihydroisoquinoline (6) was added. The reaction mixture was cooled to 0°C and saturated with gaseous HCl. The resulting mixture was stirred and heated to reflux. After 4.5 h, the mixture was cooled, and solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc-hexanes, 1:1); 0.09 g (40%); ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.03 (s, 3 H), 2.79 (dt, 1 H, J = 15.6, J = 3.9 Hz), 2.97-3.03 (m, 1 H), 3.22-3.28 (m, 1 H), 4.10-4.31 (m, 1 H), 5.38 (s, 1 H), 6.08 (s, 1 H), 7.21-7.26 (m, 1 H), 7.32-7.37 (m, 2 H), 7.46-7.49 (m, 1 H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 19.6, 28.7, 37.6, 84.5, 100.8, 127.3, 128.2, 128.8, 129.6, 130.4, 136.5, 164.9, 167.7; [31].

6-Oxo-5,6,8,12b,13,14-hexahydro-4bH,7H-6a,12c-diaza-benzo[c]chrysene-5-carboxylic acid phenylamide (11)

To a solution of 0.263 g (1 mmol) 5-[(phenylamino)hydroxy)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (1c) in 5 ml of DCE, 0.131 g (1 mmol) of 3,4-

dihydroisoquinoline (**6**) was added. The resulting mixture was stirred and heated to reflux. After 2.5 h, the mixture was cooled, and solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc-hexanes, 1:2); 0.13 g (76 %); M. p. 190 – 192 °C; ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.46-2.52 (m, 1 H), 2.57-2.64 (m, 2 H), 2.77-2.89 (m, 1 H), 2.91-3.01 (m, 1 H), 3.31-3.36 (m, 1 H), 3.69 (d, 1 H, J = 8.8 Hz), 4.45 (dt, 1 H, J = 13.2, J = 4.4 Hz), 5.51 (d, 1 H, J = 8.8 Hz), 5.93 (s, 1 H), 7.09-7.20 (m, 5 H), 7.26-7.34 (m, 5 H), 7.59-7.61 (m, 3 H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 28.8, 29.1, 37.3, 39.3, 54.9, 57.9, 74.0, 120.2, 124.5, 126.7, 127.0, 127.3, 127.5, 128.1, 128.2, 128.4, 129.1, 121.2, 132.4, 133.1, 136.8, 137.8, 138.2, 166.3, 166.7; HRMS (ESI):[Found: *m/z* 446.1835 (M + Na)$^+$, Calcd for C$_{27}$H$_{25}$N$_3$O$_2$Na: M, 446.1844].

3-benzyl-2-(ethylthio)-6-phenyl-2,3-dihydro-4H-1,3-oxazin-4-one (**15**)

To a solution of 0.248 g (1 mmol) 5-[hydroxy(phenyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**14**) in 10 ml of DCE, 0.215 g (1.2 mmol) of ethyl benzylimidothioformate (**12**) was added. The resulting mixture was stirred and heated to reflux. After 1 h, the mixture was cooled, and solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc-toluene, 1:16); 0.182 g (56%); M. p. 94 – 96 °C; ^{1}H NMR (200 MHz, acetone-d$_6$): δ 1.28 (t, 3 H, J = 7.3 Hz), 2.70-2.92 (m, 2 H), 4.01 (d, 1 H, J = 15.4 Hz), 5.22 (d, 1 H, J = 15.4 Hz), 6.16 (s, 1 H), 6.82 (s, 1 H) 7.28-7.44 (m, 5 H), 7.46-7.52 (m, 3 H), 7.79-7.86 (m, 2 H); ^{13}C NMR (50 MHz, acetone-d$_6$): δ 16.24, 26.0, 46.6, 95.8, 99.2, 127.2, 128.7, 129.1, 129.8, 130.0, 132.4, 133.2, 138.3, 160.7, 162.2; HRMS (ESI):[Found: *m/z* 348.1044 (M + Na)$^+$, Calcd for C$_{19}$H$_{19}$NO$_2$SNa: M, 348.1034].

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