RSC Advances



PAPER

View Article Online



Cite this: RSC Adv., 2022, 12, 578

Cycloaddition of Huisgen 1,4-dipoles: synthesis and rapid epimerization of functionalized spiropyrido[2,1-b][1,3]oxazine-pyrroles and related products*

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1,4-Dipolar cycloaddition has emerged as a powerful tool for the synthesis of various cyclic compounds. In the present work, 1H-pyrrole-2,3-diones are proposed as new dipolarophiles for 1,4-dipolar cycloaddition. Their [4 + 2] cycloaddition with dipoles generated from dimethyl acetylenedicarboxylate and pyridine was found to proceed regioselectively affording spiro[pyrido[2,1-b][1,3]oxazine-2,3'-pyrroles] as diastereomeric mixtures which exist in rapid equilibrium in solution. It was established that this phenomenon of rapid epimerization is a characteristic of other similar spiropyrido[2,1-b][1,3]oxazines and even related spiroquinolizines, which was demonstrated by the investigation of related products of previously reported, and reproduced in this work, 1.4-dipolar cycloaddition reactions.

Received 15th November 2021 Accepted 15th December 2021

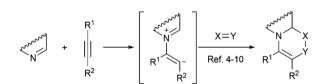
DOI: 10.1039/d1ra08384h

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Introduction

In the last two decades, researchers have shown an increased interest in 1,4-dipolar cycloaddition.1 Zwitterionic 1,4-dipolar species, that can be generated both by metal catalysis and without catalysts, 1d,e,3 have been successfully applied in the preparation of diverse carbo- and heterocycles. However, 1,4dipole chemistry is still far less developed than 1,3-dipole chemistry.

Within the field of 1,4-dipolar cycloaddition, the reactions of 1,4-dipoles, generated from dimethyl acetylenedicarboxylate



Scheme 1 Cycloaddition of 1,4-dipoles, generated from acetylenes and heterocycles.

(DMAD) or other activated acetylenes and azaheterocycles, the so-called Huisgen 1,4-dipoles, with carbonyl compounds (isatins, quinones, b, aldehydes, etc.), alkenes, alkynes and imines46,10 have been extensively studied (Scheme 1). Nevertheless, the search for new dipolar ophiles, especially those containing several reaction sites, is still relevant.

We have a long-standing interest in the chemistry of 1Hpyrrole-2,3-diones,11 which contain at least three dipolarophilic sites providing their diverse reactivity. Recently, we have reported several 1,3-dipolar cycloaddition reactions involving an endo-cyclic double bond12 of 1H-pyrrole-2,3-diones as well as both C^2 =O and C^3 =O carbonyl groups (Scheme 2A), ¹³ that differs from reactivity of related isatins¹⁴ (only the addition to C³=O; Scheme 2B). To the best of our knowledge, the dipolar cycloaddition of 1H-pyrrole-2,3-diones with 1,4-dipoles has not been reported. Considering the above facts, we could expect the formation of at least three distinct types of skeletally diverse cycloadducts A-C in such reactions (Scheme 3). Herein, we report the first study on the 1,4-dipolar cycloaddition of 1Hpyrrole-2,3-diones with dipoles generated from DMAD and pyridine.

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† Electronic supplementary information (ESI) available: General information, characterisation data, copies of NMR spectra, and experimental procedures. CCDC 2119396 (3a), 2119397 (3f), 2119399 (8b), and 2119398 (8c). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra08384h

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Results and discussion

Initially, we carried out the reaction of 1,5-diphenyl-1H-pyrrole-2,3-dione 1a with DMAD 2a and pyridine in CHCl₃ at room temperature (RT) and successfully isolated the spirocyclic [4 + 2] cycloadduct 3a as a diastereomeric mixture in a vield of 52% (Scheme 4). The structure of compound 3a was confirmed by the single crystal X-ray analysis (CCDC 2119396†). Noteworthy, only

Scheme 2 Cycloaddition of 1H-pyrrole-2,3-diones and isatins with 1,3-dipoles.

only C3=O

C³=O cycloaddition product 3a (type B, Scheme 3) was detected in the reaction mixture by HPLC-MS, while regioisomeric products A and C (Scheme 3) were not observed, probably due to the fact that ketone C3=O group is more electrophilic than lactam C²=O group or enone C⁵=C⁴ moiety. ¹H NMR analysis (in CDCl₃) of the reaction mixture, as well as isolated product 3a, showed a diastereomeric ratio (dr) of 5:1. However, an additional set of signals belonging to unidentified minor impurities was observed in the ¹H NMR spectrum of product 3a, which was pure by HPLC, and the intensity of these signals increased with time. We assumed that these impurities were the result of the compound decomposition15 in a CDCl3 solution which is known to be slightly acidic due to its degradation during storage. As expected, when the spectrum was recorded in DMSO- d_6 , the decomposition was not observed, but to our surprise, dr changed to 1.5:1. This dependence of dr from the

Scheme 3 Possible pathways of cycloaddition of 1*H*-pyrrole-2,3-diones with Huisgen 1,4-dipoles.

Scheme 4 Synthesis of cycloadduct 3a.

solvents indicated the existence of a rapid equilibrium between the diastereomers in the solution. This fact was also confirmed by different dr values in the 1 H NMR spectra of $C_{6}D_{6}$ and acetone- d_{6} solutions (Scheme 4).

It should be pointed out that the substituents with different electron-withdrawing properties can be readily introduced in 1*H*-pyrrole-2,3-diones, that may affect the regioselectivity of the dipolar cycloaddition. Therefore, despite the rapid epimerization of diastereomers in the solution, we performed the optimization of the reaction conditions and studied the substrate scope.

The model reaction of 1*H*-pyrrole-2,3-dione **1a** with DMAD and pyridine proceeded smoothly in all tested solvents for 24 h at RT (Table 1). Moderate yields were observed in 1,2-dimethoxyethane and CH₂Cl₂ (Table 1, entries 2, 5). Other solvents showed similar yields, and ultimately, we chose EtOAc as a greener solvent among the tested ones. A 20% excess of DMAD and pyridine slightly improved the yield up to 85% (the optimal conditions, Table 1, entry 9).

To explore the scope of the reaction, we investigated the cycloaddition of a variety of 1*H*-pyrrole-2,3-diones bearing electronically diverse substituents (Table 2). The reactions of 4-unsubstituted 5-aryl-1*H*-pyrrole-2,3-diones proceeded smoothly; the presence of electron-withdrawing or electron-

Table 1 Optimization of the reaction conditions for the preparation of ${\bf 3a}^a$

Entry	Solvent	Yield ^b , %		
1	$CHCl_3$	76		
2	1,2-Dimethoxymethane	56		
3	1,4-Dioxane	83		
4	Toluene	83		
5	CH_2Cl_2	55		
6	Acetone	81		
7	Ethyl acetate	78		
8 ^c	Ethyl acetate	82		
9^d	Ethyl acetate	85		

 $[^]a$ Reagents and conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), pyridine (0.1 mmol), solvent (1 mL), in a capped vial. b Yields were determined by HPLC. c 1.1 equiv. of **2a** and pyridine were used. d 1.2 equiv. of **2a** and pyridine were used.

Table 2 Synthesis of [4 + 2]-cycloadducts $3a-k^a$

$$R^{1}$$
 R^{2}
 R^{3}
 R^{3}
 R^{3}
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Entry	1 <i>H</i> -Pyrrole-2,3-dione $(R^1/R^2/R^3)$	R^4	Product (yield b)	dr
1	1a (H/Ph/Ph)	OMe	3a (70%)	5 : 1 ^c
2	1b (H/C ₆ H ₄ OMe-4/Ph)		3b (82%)	1.5:1 ^d
_	,			
3	$1c \left(H/C_6H_4Br-4/Ph \right)$		3c (79%)	$1.5:1^{d}$
4	1d (Et/Ph/Ph)	ОМе	3d (84%)	$7.3:1^d$
5	1e (COOEt/Ph/Ph)	OMe	3e (80%)	$6.5:1^{c}$
				$2.2:1^{d}$
6	1f (COOEt/Ph/C ₆ H ₄ Me-4)	OMe	3f (76%)	$9:1^{c}$
7	1g (COOEt/Ph/Me)	OMe	3g (74%)	$2.3:1^{d}$
8	1h (COPh/Ph/Bn)	OMe	3h (77%)	$2.3:1^{c}$
9	1i (COOMe/COOMe/Ph)	OMe	3i (48%)	$1.5:1^{d}$
10	1j (COOMe/COOMe/C ₆ H ₄ Me-4)	OMe	3j (20%)	$5:1^{c}$
11	1e (COOEt/Ph/Ph)	Ph	3k (56%)	$5.3:1^{c}$

 ^a Reagents and conditions: 1 (1 mmol), 2 (1.2 mmol), pyridine (1.2 mmol), ethyl acetate (10 mL), in a closed glass flask.
 ^b Isolated yields.
 ^c dr was determined by NMR analysis of isolated products in CDCl₃.
 ^d dr was determined by NMR analysis of isolated products in DMSO-d₆.

donating groups in the 5-aryl substituent did not significantly affect the product yields (Table 2, entries 1–3, **3a-c**). The introduction of an alkyl group into the 4-position of the 1*H*-pyrrole-2,3-diones also did not lead to a decrease in the yield (entry 4, **3d**). The same regioselectivity was observed in the reactions of 5-aryl-1*H*-pyrrole-2,3-diones bearing EWGs in the 4-position which led to the products **3e-h** in good yields (entries 5–8). The reaction was also tolerant to the substituents in N¹ position. When two methoxycarbonyl substituents were introduced in the 4- and 5-positions of 1*H*-pyrrole-2,3-diones, the reaction was complicated by the formation of side-products, and the compounds **3i,j** were isolated in lower yields (entries 9–10). Employing dibenzoylacetylene instead of DMAD, the product **3k** was isolated in moderate yield (entry 11).

Having established the substrate scope of the cycloaddition, we were interested in how well this diastereomeric equilibrium is described in the literature. The analysis of the literature revealed that the rapid equilibrium of [1,3]oxazines is known (Fig. 1). For example, during synthetic studies towards total synthesis of alkaloids of xestospongin/aguspongine family, Hoye *et al.* found that perhydropyrido [2,1-b][1,3] oxazines **D** exist in solution in rapid diastereomeric equilibrium through ringchain tautomerism (Fig. 1).17 Similar epimerization in solution was observed on oxazolo[2,3-a]isoquinoline E in work by Seidel, Houk et al. 18 Substituent effects on ring-chain tautomerism of naphth[1,2-e][1,3]oxazines F and G were studied in a series of works by Fülöp et al.19 Nevertheless, these cases deal with saturated or partially saturated pyrido[1,3]oxazine systems, while as a result of 1,4-dipolar cycloaddition to carbonyl group, unsaturated pyrido[1,3]oxazines are formed, for which the

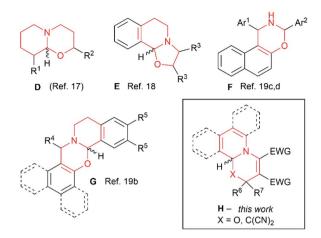


Fig. 1 Examples considering in this work and literature examples of [1,3]oxazines and oxazoles existing in the diastereomeric equilibrium.

equilibrium between diastereomers and its consequences on observed dr have not been studied, and reported dr values could be incorrect. Considering this, we decided to investigate this possible epimerization on early reported cycloadducts obtained from Huisgen 1,4-dipoles (Fig. 1, structure H).

To this end, the model 1,4-dipolar cycloadditions of N-substituted isatins or 11*H*-indeno[1,2-*b*]quinoxalin-11-one with DMAD and azines (pyridine, isoquinoline and quinoline) were studied by HPLC and NMR methods (Tables 3 and 4).

We began our study with 1,4-dipolar cycloaddition of *N*-alkyl isatins 4. For the reaction with pyridine (Table 3, entry 1), HPLC analysis of the reaction mixture and the isolated product 5a showed a broad peak of inseparable diastereomers. The 1 H NMR spectra of isolated product 5a (in CDCl₃) showed a dr of 4.8 : 1 (with close agreement with the literature data, 4e dr 5 : 1). The same dr value was observed in K_2CO_3 -treated CDCl₃, at the same time, a significantly different dr was observed in DMSO- d_6 (1.2 : 1). These observations confirm the existence of a rapid epimerization as in the case of products 3a–k.

The reaction of N-benzylisatin with DMAD and isoquinoline has been reported two times,20 however, only one work20b provided information about dr. This reaction was successfully reproduced, and the HPLC analysis of the reaction mixture showed two well separated peaks of diastereomers in nearly 1:1 ratio (Table 3, entry 2). Isolation of diastereomeric mixture 5b by crystallization did not significantly change dr (HPLC data). The same dr was observed by NMR method in K2CO3treated CDCl₃ and DMSO-d₆, and thus, this reaction showed no diastereoselectivity in contradistinction to the original work (dr 2.4:1).20b Nevertheless, significant change in dr (4.8:1) was observed in non-treated CDCl3, which clearly indicates the existence of acid-catalyzed isomerization of spiro[1,3]oxazino [2,3-a]isoquinoline 5b (entry 2). A related acid-catalyzed isomerization of spiropyrido[2,1-a]isoquinolines under the action of silica-gel or 37% HCl was recently reported by Cao et al.8d

Harsher conditions (110 °C) for three-component reaction of isatins, DMAD and quinoline have been reported, ^{4b} still HPLC analysis of the reaction mixture and isolated diastereomers 5c

Table 3 Repetition of 1,4-dipolar cycloaddition of N-alkyl isatins: diastereoselectivity and diastereomeric equilibrium study

						dr observed in this work				
_								By NMR for isolated product in		
Entry	Compound, isolated yield	Heterocycle	Alk	Conditions, ref.	dr from literature by NMR (solvent)	reaction mixture	By HPLC for isolated product	$CDCl_3$	K_2CO_3 -treated $CDCl_3$	DMSO- d_6
1	5a , 70%	Pyridine	Bn	DME, Ar, RT, 6 h (ref. 4 <i>c</i>)	5:1 (CDCl ₃ -CCl ₄ , 3:1)	a	a	4.8:1	4.8:1	1.2:1
2	5b , 86%	Isoquinoline	Bn	DCM, RT, 24 h (ref. 20 <i>b</i>)	2.4:1 (CDCl ₃)	1:1	1.1:1	4.8:1	1:1	1:1
3	5c , 77%	Quinoline	All	Tol, 110 °C, 12 h (ref. 4 <i>b</i>)	4:1 (CDCl ₃)	1.1:1	$1:1.1^{b}$	1:1	1 1	1:1

^a The diastereomers were inseparable by HPLC. ^b The major diastereomer in the reaction mixture became the minor diastereomer after the isolation, probably due to the different solubility of the diastereomers.

showed *ca.* 1 : 1 ratio, instead of reported 4 : 1 (Table 3, entry 3). The same dr was observed by NMR method in DMSO-d₆ and K₂CO₃-treated CDCl₃, even acidic CDCl₃ did not change dr, and thus the products derived from quinoline are stable to acidcatalyzed isomerization. The discrepancy with reported dr probably arise from the fact that diastereomers 5c are separable,

Table 4 Repetition of 1,4-dipolar cycloaddition of 11H-indeno[1,2-b]quinoxalin-11-one 6: diastereoselectivity and diastereomeric equilibrium study

dr observed in this work By NMR for isolated product in Compound, isolated dr from literature By HPLC for By HPLC for K2CO3-treated yield by NMR (CDCl₃) Entry Heterocycle reaction mixture isolated product $CDCl_3$ $CDCl_3$ DMSO- d_6 Single diastereomer²¹ 8a, 53% Pyridine 16:1 16:1 3.2:1 1 $1:1.2^{b}$ 8b, 82% Single diastereomer²¹ 1.2:1 1.3:1 2 Isoquinoline $2.6:1 \rightarrow 12:1^{c}$ 1.1:1 8c, 86% Quinoline 1.2:1 (ref. 21) 1:1 1:1

^a The diastereomers were inseparable by HPLC. ^b The major diastereomer in the reaction mixture became the minor diastereomer after the isolation. ^c The change in dr was observed within 30 min after dissolution of compound 8b.

Table 5 Repetition of 1,4-dipolar cycloaddition of isatylidene malononitrile 9: diastereoselectivity and diastereomeric equilibrium study

						By NMR for isolated product in		
Entry	Compound, isolated yield	Heterocycle	dr from literature by NMR (CDCl ₃)	By HPLC for reaction mixture	By HPLC for isolated product	CDCl_3	K ₂ CO ₃ -treated CDCl ₃	DMSO-d ₆
1 2	10a , 62% 10b , 76%	Pyridine Isoquinoline	10.1 : 1 (ref. 8 <i>c</i>)	a 1.1 : 1	_a 1.2:1	9:1 1.4:1	9:1 1.4:1	1.5 : 1 1.4 : 1

^a The diastereomers were inseparable by HPLC. ^b Compound 10b is unknown in the literature.

as judged by TLC, but were not separated in the original work, ^{4b} and incomplete collection of fractions during column chromatography could have happened. ^{4b}

Next, we investigated the reaction of readily accessible 11*H*-indeno[1,2-*b*]quinoxalin-11-one **6** with DMAD and azines (Table 4). The choice of this substrate was determined by the interesting fact that its reaction with DMAD and azines was known, however, the formation of spirolactones 7 rather than spirooxazines **8** was reported.²¹ Authors deduced structures of spirolactone products **7a–c** based solely on IR, 1D NMR and mass spectra, without confirmation by single crystal X-ray analysis. By repeating the original work and performing X-ray analysis (CCDC 2119399 – **8b**, CCDC 2119398 – **8c**†), we were able to revise the reported structure **7** to be spirooxazines **8** (for full comparison with published data, see the ESI†).

For these reactions, HPLC analyses showed the results similar to N-alkyl isatins. In the case of pyridine, single broad peak was observed (Table 4, entry 1), and in the case of isoquinoline and quinoline, two separated peaks were observed in a nearly 1 : 1 ratio (Table 4, entries 2, 3). The 1 H NMR spectra of pyridine product 8a showed good dr (about 16 : 1) in CDCl₃ and 5-fold decreased dr in DMSO- d_6 (Table 4, entry 1). Acid-catalyzed isomerization for isoquinoline product 8b was observed in untreated CDCl₃: dr was 2.6 : 1 after dissolution, and it became 12 : 1 within 30 min at 303 K (entry 2). Quinoline product 8c showed stability to acid-catalyzed isomerization (entry 3).

Finally, we focused on 1,4-dipolar cycloaddition to C=C bond with the expectation that the absence of aminal fragment will result in the increased stability of cycloadducts (Table 5). Reaction of isatylidene malononitrile 9 with DMAD and pyridine in refluxing THF was reported to result in the formation of spirocyclic quinolizine 10a with a dr of 10 : 1.8c HPLC analysis of the reaction mixture as well as isolated product showed single peak of inseparable diastereomers (Table 5, entry 1). The ^1H NMR spectra of diastereomeric mixture in untreated CDCl₃ or K_2CO_3 -treated CDCl₃ showed dr similar to the literature. At the

same time, the ¹H NMR spectrum in DMSO-*d*₆ solution resulted in extensively broad peaks, among which two sets of signals could be seen in a ratio close to 1.5:1, that confirms the existence of a rapid equilibrium between diastereomers. Additional confirmation obtained with utilization of NOESY (EXSY) spectrum (see the ESI, S56†), which indicated the presence of the chemical exchange between diastereomers.²² Reaction of compound **9** with DMAD and quinoline was presented in the same work,^{8c} and diastereomers were obtained in a ratio of 1.2:1 (similar to products **5c** and **8c**); therefore this reaction was not repeated in our study.

Reaction of isoquinoline, DMAD, and isatylidene malononitrile **9** was not reported. However, Cao *et al.* recently published a similar reaction of isoquinoline with CF_3 -propiolate and isatylidene malononitriles, which led to spirocyclic pyrido [2,1-a] isoquinolines with dr in ranges of 1:0.9 to $1:1.1.8^{aa}$ Adopting the conditions presented in the work, ^{8c} we were able to synthesize pyrido [2,1-a] isoquinoline **10b** in 76% yield. HPLC analysis of the reaction mixture and isolated product showed dr of nearly 1:1 (Table 5, entry 2); finally, close dr (1.4:1) was observed in NMR spectra (CDCl₃ and DMSO- d_6). In contrast to [1,3] oxazine products **5b** and **8b** derived from isoquinoline, no acid-catalyzed isomerization of **10b** took place in acidic CDCl₃.

Based on 1,4-dipolar cycloaddition of pyrrole-2,3-diones and reproduced previously reported 1,4-dipolar cycloaddition reactions, several trends for this type of 1,4-cycloaddition can be derived:

- (a) Addition of 1,4-dipoles derived from pyridine to C=O or C=C bonds results in an inseparable mixture of rapid interconverted diastereomers. These cycloaddition reactions are probably not diastereoselective, although apparent solvent-dependent dr values can be high.
- (b) Isoquinoline-based 1,4-dipoles lead to almost equimolar diastereomeric mixtures in the case of C=O dipolarophiles. Utilization of acidic CDCl₃ (as a result of its decomposition) for recording NMR spectra can result in incorrect dr values.

Paper

Addition of isoquinoline-based dipoles to C=C bonds produces pyridoisoguinolines in a non-diastereoselective fashion, and no epimerization in acidic CDCl3 is observed. However, more acidic conditions may facilitate epimerization.8d

(c) In all cases of addition of quinoline dipoles to C=O or C=C bonds, equimolar mixture of diastereomers is observed, and their ratios are not affected by acidic CDCl₃.²³

Conclusions

In conclusion, we have shown that spiro[pyrido[2,1-b][1,3]oxazine-2,3'-pyrroles] can be synthesized as diastereomeric mixtures in 20-84% yields via the three-component reaction of 1H-pyrrole-2,3-diones, DMAD, and pyridine. Different substituents in 1H-pyrrole-2,3-diones did not affect the regioselectivity of 1,4-cycloaddition. Rapid equilibrium between synthesized diastereomers in solution was observed, that encouraged us to examine the existing literature by the repetition of known 1,4cycloaddition reactions. From this analysis, several trends for this type of 1,4-cycloaddition were derived.

The 1,4-dipolar cycloaddition reactions with other azaheterocycles or imines as well as other types of acetylenes and dipolarophiles were beyond the scope of this work, and their diastereoselectivity can be further revised.

As a general conclusion for the development of stereoselective methods, special emphasis should be paid to experimental data including analysis of reaction mixtures and the possible existence of isomeric equilibrium and factors influencing it.

Experimental section

The experimental procedure for the synthesis of compounds 3 and their characterisation data are given below. General information, characterisation data, NMR spectra, crystallographic data (for 3a, 3f, 8b and 8c) and experimental procedures for all other compounds are given in the ESI.†

Deposition numbers CCDC 2119396 (for 3a), 2119397 (for 3f), 2119399 (for 8b), and 2119398 (for 8c) contain the supplementary crystallographic data for this paper.†

The general procedure for the synthesis of compounds 3

A round-bottom flask was charged with 1H-pyrrole-2,3-dione 1 (1 mmol), acetylene 2 (1.2 mmol), and anhydrous ethyl acetate (10 mL). Pyridine (97 μL, 1.2 mmol) was added to the resulted solution, and the reaction mixture was stirred at RT for 1 day in the closed flask. The solvent was evaporated under reduced pressure. The residue was purified by appropriate method as indicated below to afford 3.

Dimethyl 2'-oxo-1',5'-diphenyl-1',2'-dihydro-9*aH*-spiro[pyrido[2,1-b][1,3]oxazine-2,3'-pyrrole]-3,4-dicarboxylate (3a). Thecompound was prepared according to the general procedure employing 1H-pyrrole-2,3-dione 1a (249 mg, 1 mmol) and DMAD (147 µL, 1.2 mmol) and purified by crystallization from EtOH. Yellow solid (330 mg, 70% yield); $R_{\rm f} = 0.62$ (C₆H₆/EtOAc 5:1); mp 181-182 °C (decomp.); IR (cm⁻¹): 1746, 1683, 1663,

1638, 1594, 1561; ¹H NMR (400 MHz, CDCl₃), mixture of inseparable diastereomers, d.r. = \sim 5 : 1 (A : B): δ = 7.32–7.18 (6H, m, A+B), 7.18-7.13 (2H, m, A+B), 7.11-7.07 (2H, m, A+B), 6.59 (0.84 H, dd, J = 3.4, 1.3 Hz, A), 6.41-6.23 (2 H, m, A + B), 5.82(0.16H, dd, J = 3.4, 1.3 Hz, B), 5.72 (0.84H, ddt, J = 10.0, 3.4,1.1 Hz, A), 5.66-5.62 (0.32H, m, $2 \times B$), 5.37-5.31 (0.84H, m, A), 5.30-5.26 (1H, m, A + B), 3.96 (2.52H, s, A), 3.91 (0.48H, s, B), 3.70 (2.52H, s, A), 3.68 (0.48H, s, B). ¹³C NMR (101 MHz, CDCl₃): δ (A, major) = 175.2, 163.9, 163.6, 150.6, 144.9, 135.5, 130.9, 129.3, 128.8 (2C), 128.4 (2C), 127.8 (2C), 127.1, 126.9 (2C), 125.4, 124.8, 116.7, 107.5, 106.8, 101.7, 78.8, 78.6, 53.4, 52.1; ¹H NMR (400 MHz, DMSO- d_6), mixture of inseparable diastereomers, d.r. = 1.5 : 1 (A : B).: δ = 7.39–7.22 (6H, m, A + B), 7.19–7.12 (2H, m, A + B), 7.08–7.02 (2H, m, A + B), 6.57 (0.4H, dt, J = 7.5, 1.1 Hz, B), 6.53 (0.6H, dt, J = 7.6, 1.1 Hz, A), 6.41-6.26 (1.4H, m, A + B), 6.05(0.6H, s, A), 6.00 (0.6H, dd, J = 3.4, 1.3 Hz, A), 5.75 (0.4H, ddt, J =9.9, 3.4, 1.1 Hz, B), 5.68 (0.6H, ddt, J = 9.9, 3.5, 1.2 Hz, A), 5.45-5.40 (0.8H, m, $2 \times B$), 5.39–5.33 (0.6H, m, A), 3.91 (1.2H, s, B), 3.88 (1.8H, s, A), 3.65 (1.2H, s, B), 3.62 (1.8H, s, A). ¹³C NMR (101 MHz, DMSO- d_6): δ (A, major) = 175.1, 163.4, 162.5, 146.4, 143.6, 135.3, 130.1, 129.1, 128.6 (2C), 128.2 (2C), 127.3 (2C), 127.0, 126.8 (2C), 126.0, 125.1, 115.9, 108.4, 108.2, 101.0, 79.8, 79.2, 53.3, 52.0. ¹³C NMR (101 MHz, DMSO- d_6): δ (B, minor) = 174.6, 163.0, 162.6, 149.5, 144.3, 135.0, 130.1, 129.1, 128.6 (2C), 128.2 (2C), 127.2 (2C), 127.0, 126.7 (2C), 125.2, 124.9, 116.1, 107.3, 105.7, 101.6, 77.9, 77.8, 53.4, 51.9; ¹H NMR (400 MHz, acetone d_6), mixture of inseparable diastereomers, dr = \sim 1.3 : 1 (A : B): $\delta = 7.37 - 7.20$ (8H, m, A + B), 7.15 - 7.07 (2H, m, A + B), 6.55 - 6.52 $(1.14H, m, 2 \times A)$, 6.48 (0.43H, dt, J = 7.6, 1.1 Hz, B), 6.39-6.28 (1H, m, A + B), 5.98 (0.43H, dd, J = 3.4, 1.3 Hz, B), 5.94 (0.43H, s, A + B)B), 5.71 (0.57H, ddt, J = 9.9, 3.3, 1.1 Hz, A), 5.67 (0.43H, ddt, J =9.9, 3.4, 1.2 Hz, B), 5.40 (0.57H, ddd, J = 7.5, 6.2, 1.1 Hz, A), 5.33 (0.43H, ddd, J = 7.4, 6.0, 1.1 Hz, B), 5.30 (0.57H, s, A), 3.95(1.7H, s, A), 3.91 (1.3H, s, B), 3.70 (1.7H, s, A), 3.68 (1.3H, s, B); 1 H NMR (400 MHz, benzene- d_{6}), mixture of inseparable diastereomers, d.r. = \sim 3.2 : 1 (A : B): δ = 7.15–6.81 (10.76H, m, A + B), 6.38 (0.76H, dt, J = 7.5, 1.1 Hz, A), 6.24 (0.24H, dt, J = 7.5, 1.1 Hz, B), 5.84 (0.24H, ddt, J = 9.9, 6.1, 1.2 Hz, B), 5.78 (0.76H, ddt, J = 10.0, 6.0, 1.2 Hz, A), 5.54–5.46 (1H, m, A + B), 5.45–5.38 (0.24H, m, B), 5.34 (0.24H, s, B), 5.11 (0.76H, s, A), 4.91-4.86 (0.76H, m, A), 4.86-4.81 (0.24H, m, B), 3.57 (2.28H, s, A), 3.47 (0.72H, s, B), 3.29 (0.72H, s, B), 3.24 (2.28H, s, A); HRMS (ESI): m/z calcd for $C_{27}H_{22}N_2O_6$: 471.1551 [M + H]⁺; found: 471.1544.

5'-(4-methoxyphenyl)-2'-oxo-1'-phenyl-1',2'-dihydro-9aH-spiro[pyrido[2,1-b][1,3]oxazine-2,3'-pyrrole]-3,4dicarboxylate (3b). The compound was prepared according to the general procedure employing 1H-pyrrole-2,3-dione 1b (279 mg, 1 mmol) and DMAD (147 µL, 1.2 mmol) and purified by crystallization from EtOH. Yellow solid (409 mg, 82% yield); $R_{\rm f}$ = 0.30 (PhCH₃/EtOAc 5:1); mp 177-178 $^{\circ}$ C (decomp.); IR (cm⁻¹): 1740, 1729, 1713, 1654, 1635, 1600, 1569; ¹H NMR (400 MHz, DMSO- d_6), mixture of inseparable diastereomers, d.r. = $\sim 1.5 : 1 (A : B): \delta = 7.39 - 7.34 (2H, m, A + B), 7.30 - 7.25 (1H, m, A)$ + B), 7.10-7.03 (4H, m, A + B), 6.87-6.80 (2H, m, A + B), 6.57 (0.4H, dt, J = 7.5, 1.1 Hz, B), 6.53 (0.6H, dt, J = 7.5, 1.1 Hz, A),6.39 (0.4H, dd, J = 3.4, 1.3 Hz, B), 6.38-6.29 (1H, m, A + B), 5.98(0.6H, dd, J = 3.4, 1.3 Hz, A), 5.95 (0.6H, s, A), 5.74 (0.4H, ddt, J =

9.9, 3.3, 1.1 Hz, B), 5.67 (0.6H, ddt, J=9.9, 3.4, 1.1 Hz, A), 5.42 (0.4H, ddd, J=7.3, 6.1, 1.1 Hz, B), 5.36 (0.6H, ddd, J=7.3, 6.0, 1.1 Hz, A), 5.32 (0.4H, s, B), 3.91 (1.2H, s, B), 3.87 (1.8H, s, A), 3.72 (3H, s, A + B), 3.64 (1.2H, s, B), 3.62 (1.8H, s, A). ¹³C NMR (101 MHz, DMSO- d_6): δ (A, major) = 175.2, 163.4, 162.5, 159.8, 146.1, 143.4, 135.5, 128.8 (2C), 128.6 (2C), 126.9, 126.9 (2C), 126.0, 125.1, 122.2, 115.9, 113.7 (2C), 108.6, 106.8, 100.9, 79.8, 79.3, 55.1, 53.2, 51.9. ¹³C NMR (101 MHz, DMSO- d_6): δ (B, minor) = 174.7, 163.0 162.6, 159.7, 149.2, 144.2, 135.1, 128.7 (2C), 128.6 (2C), 126.9, 126.8 (2C), 125.2, 124.9, 122.4, 116.1, 113.7 (2C), 105.9, 105.6, 101.5, 77.9, 77.8, 55.1, 53.3, 51.9; HRMS (ESI): m/z calcd for $C_{28}H_{24}N_2O_7$: 501.1656 [M + H]⁺; found: 501.1657.

Dimethyl 5'-(4-bromophenyl)-2'-oxo-1'-phenyl-1',2'-dihydro-9aH-spiro[pyrido[2,1-b][1,3]oxazine-2,3'-pyrrole]-3,4-

dicarboxylate (3c). The compound was prepared according to the general procedure employing 1H-pyrrole-2,3-dione 1c (328 mg, 1 mmol) and DMAD (147 µL, 1.2 mmol) and purified by crystallization from EtOH. Yellow solid (435 mg, 79% yield); R_f = 0.41 (PhCH₃/EtOAc 5:1); mp 173-174 $^{\circ}$ C (decomp.); IR (cm⁻¹): 1739, 1709, 1684, 1652, 1633, 1595, 1567; ¹H NMR (400 MHz, DMSO- d_6), mixture of inseparable diastereomers, d.r. = \sim 1.5 : 1 (A : B): δ = 7.52–7.43 (2H, m, A + B), 7.42–7.33 (2H, m, A + B), 7.33-7.24 (1H, m, A + B), 7.12-7.03 (4H, m, A + B), 6.58 (0.4H, d, J = 7.5 Hz, B), 6.54 (0.6H, d, J = 7.5 Hz, A), 6.39-6.29(1.4H, m, A + B), 6.11 (0.6H, s, A), 5.99 (0.6H, d, J = 2.7 Hz, A),5.75 (0.4H, B dd, J = 10.0, 3.2 Hz), 5.67 (0.6H, dd, J = 9.9, 3.3 Hz)A), 5.52 (0.4H, s, B), 5.46-5.40 (0.4H, m, B), 5.40-5.34 (0.6H, m, A), 3.91 (1.2H, s, B), 3.88 (1.8H, s, A), 3.64 (1.2H, s, B), 3.62 (1.8H, s, A). ¹³C NMR (101 MHz, DMSO- d_6): δ (A, major) = 175.0, 163.3, 162.4, 145.3, 143.7, 135.1, 131.3 (2C), 129.3 (2C), 129.3, 128.7 (2C), 126.7 (2C), 126.6, 125.9, 125.2, 122.6, 115.9, 108.7, 108.2, 101.0, 79.9, 79.2, 53.3, 52.0. ¹³C NMR (101 MHz, DMSO d_6): δ (B, minor) = 174.5, 163.0, 162.5, 148.4, 144.4, 134.8, 131.3 (2C), 129.2 (2C), 128.7 (2C), 127.1 (2C), 125.2, 124.8, 122.5, 116.0, 108.1, 105.5, 101.7, 78.0, 77.7, 53.4, 51.9, two carbons were not separated/found; HRMS (ESI): m/z calcd for $C_{27}H_{21}BrN_2O_6$: 551.0635 [M + H]⁺; found: 551.0633.

4'-ethyl-2'-oxo-1',5'-diphenyl-1',2'-dihydro-9aH-Dimethyl spiro[pyrido[2,1-b][1,3]oxazine-2,3'-pyrrole]-3,4-dicarboxylate (3d). The compound was prepared according to the general procedure employing 1*H*-pyrrole-2,3-dione **1d** (277 mg, 1 mmol) and DMAD (147 µL, 1.2 mmol) and purified by crystallization from EtOH. Yellow solid (418 mg, 84% yield); $R_f = 0.46$ (PhCH₃/ EtOAc 5 : 1); mp 138-140 °C (decomp.); IR (cm⁻¹): 1743, 1729, 1706, 1656, 1600, 1567; ¹H NMR (400 MHz, DMSO-*d*₆), mixture of inseparable diastereomers, d.r. = \sim 7.3 : 1 (A : B): δ = 7.34-7.22 (5H, m, A + B), 7.21–7.13 (3H, m, A + B), 7.03–6.93 (2H, m, A + B), 6.68 (0.12H, d, J = 7.5 Hz, B), 6.62 (0.88H, d, J = 7.5 Hz, A), 6.43-6.35 (1H, m, A + B), 6.33 (0.88H, dd, J = 3.5, 1.2 Hz, A), 5.85-5.71 (1.12H, m, A + B), 5.49-5.38 (1H, m, A + B), 3.92 (2.64H, s, A), 3.87 (0.36H, s, B), 3.69 (3H, s, A + B), 2.28-2.19 (0.24H, m, B), 1.93 (1.76H, q, J = 7.5 Hz, A), 0.99 (0.36H, t, J =7.5 Hz, B), 0.88 (2.64H, t, J = 7.5 Hz, A). ¹³C NMR (101 MHz, DMSO- d_6): δ (A, major) = 173.7, 163.1, 162.7, 145.0, 143.0, 135.0, 129.7, 128.6 (3C), 128.4 (2C), 128.2 (2C), 126.7 (2C), 126.6, 125.2, 124.8, 119.1, 116.1, 106.0, 101.7, 79.3, 77.8, 53.4, 51.9, 17.0, 13.8;

HRMS (ESI): m/z calcd for $C_{29}H_{26}N_2O_6$: 499.1864 [M + H]⁺; found: 499.1858.

4'-Ethyl 3,4-dimethyl 2'-oxo-1',5'-diphenyl-1',2'-dihydro-9aHspiro[pyrido[2,1-b][1,3]oxazine-2,3'-pyrrole]-3,4,4'-tricarboxylate (3e). The compound was prepared according to the general procedure employing 1*H*-pyrrole-2,3-dione **1e** (321 mg, 1 mmol) and DMAD (147 µL, 1.2 mmol) and purified by crystallization from EtOH. Yellow solid (432 mg, 80% yield); $R_f = 0.46$ (C₆H₆/ EtOAc 5:1); mp 179-182 °C (decomp.); IR (cm⁻¹): 1746, 1733, 1703, 1602, 1594, 1563; ¹H NMR (400 MHz, CDCl₃), mixture of inseparable diastereomers, d.r. = \sim 6.5 : 1 (A : B): δ = 7.33–7.16 (8H, m, A + B), 7.08-6.89 (2H, m, A + B), 6.57-6.22 (3H, m, A + B), 5.75 (1H, dd [A], J = 10.0, 3.4 Hz, A + B), 5.50-5.21 (1H, m, A + B), 4.07-3.89 (5H, m, A + B), 3.77 (3H, s, A + B), 1.06 (2.6H, t, J =7.1 Hz, A), 0.94 (0.4H, t, J = 7.1 Hz, B). ¹³C NMR (101 MHz, $CDCl_3$): δ (A, major) = 174.3, 163.8, 163.6, 161.9, 159.8, 146.1, 134.1, 129.9, 129.7, 129.3 (2C), 128.9 (2C), 128.0 (2C), 127.97, 127.8 (2C), 125.7, 125.1, 116.3, 108.8, 107.2, 101.7, 79.0, 77.9, 60.0, 53.3, 52.2, 14.0; ¹H NMR (400 MHz, DMSO-d₆), mixture of inseparable diastereomers, d.r. = \sim 2.2 : 1 (A : B): δ = 7.35–7.17 (8H, m, A + B), 7.11-7.04 (2H, m, A + B), 6.65 (0.31H, d, J =7.6 Hz, B), 6.62 (0.69H, d, J = 7.5 Hz, A), 6.42–6.34 (1H, m, A + B), 6.32-6.25 (1H, m, A + B), 5.81-5.71 (1H, m, A + B), 5.49-5.37 (1H, m, A + B), 3.92 (2.07H, s, A), 3.89 (0.93H, s, B), 3.91-3.80 (2H, m, A + B), 3.73 (2.07H, s, A), 3.72 (0.93H, s, B), 0.94 (2.07H, t, J =7.1 Hz, A), 0.79 (0.93H, t, J = 7.1 Hz, B). ¹³C NMR (101 MHz, DMSO- d_6): δ (A, major) = 173.6, 163.1, 162.6, 160.8, 158.9, 145.7, 133.5, 129.4, 129.2, 128.8 (2C), 128.7 (2C), 128.1, 127.9 (2C), 127.6 (2C), 125.5, 125.3, 115.7, 108.1, 106.0, 101.4, 78.1, 77.0, 59.1, 53.3, 52.0, 13.5. 13 C NMR (101 MHz, DMSO- d_6): δ (B, minor) = 173.9, 163.8, 162.9, 162.3, 157.3, 143.0, 133.8, 129.3, 128.7 (2C), 128.6 (2C), 127.9 (2C), 127.5 (2C), 126.5, 125.3, 115.4, 111.1, 110.0, 101.0, 79.4, 77.9, 59.4, 53.3, 52.2, 13.2, two carbons were not separated/found; HRMS (ESI): m/z calcd for $C_{30}H_{26}N_2O_8$: 543.1762 [M + H]⁺; found: 543.1759.

4'-Ethyl 3,4-dimethyl 2'-oxo-5'-phenyl-1'-(p-tolyl)-1',2'-dihydro-9aH-spiro[pyrido[2,1-b][1,3]oxazine-2,3'-pyrrole]-3,4,4'-tricarboxylate (3f). The compound was prepared according to the general procedure employing 1H-pyrrole-2,3-dione 1f (335 mg, 1 mmol) and DMAD (147 µL, 1.2 mmol) and purified by crystallization from EtOH. Yellow solid (424 mg, 76% yield); $R_{\rm f} = 0.50$ $(C_6H_6/EtOAc\ 5:1)$; mp 173–175 °C (decomp.); IR (cm⁻¹): 1742, 1695, 1653, 1627, 1595, 1564; ¹H NMR (400 MHz, CDCl₃), mixture of inseparable diastereomers, d.r. = \sim 9 : 1 (A : B): δ = 7.31-7.17 (5H, m, A + B), 7.04-6.95 (2H, m, A + B), 6.93-6.88 (2H, m, A + B), 6.49 (0.9H, dd, J = 3.5, 1.2 Hz, A), 6.42 (1H, dt [A], J =7.5, 1.2 Hz, A + B), 6.34 (1.1H, ddt [A], J = 9.9, 6.0, 1.2 Hz, A + B), 5.74 (1H, ddt [A], J = 9.9, 3.6, 1.2 Hz, A + B), 5.36 (1H, ddd [A], J =7.3, 6.0, 1.1 Hz, A + B), 4.05-3.94 (2H, m, A + B), 3.96 (2.7H, s, A), 3.91 (0.3H, s, B), 3.76 (2.7H, s, A), 3.75 (0.3H, s, B), 2.26 (2.7H, s, A), 2.23 (0.3H, s, B), 1.06 (2.7H, t, J = 7.1 Hz, A), 0.93 (0.3H, t, J = 7.1 Hz, A) 7.1 Hz, B). ¹³C NMR (101 MHz, CDCl₃): δ (A, major) = 174.4, 163.8, 163.6, 162.0, 160.1, 146.0, 137.9, 131.5, 130.0, 129.6 (3C), 129.3 (2C), 127.8 (2C), 127.7 (2C), 125.7, 125.1, 116.4, 108.6, 107.3, 101.6, 78.9, 77.9, 59.9, 53.3, 52.1, 21.2, 14.0; HRMS (ESI): m/z calcd for $C_{31}H_{28}N_2O_8$: 557.1918 [M + H]⁺; found: 557.1913.

Paper

4'-Ethyl 3,4-dimethyl 1'-methyl-2'-oxo-5'-phenyl-1',2'-dihydro-9*aH*-spiro[pyrido[2,1-*b*][1,3]oxazine-2,3'-pyrrole]-3,4,4'-tricarboxylate (3g). The compound was prepared according to the general procedure employing 1H-pyrrole-2,3-dione 1g (259 mg, 1 mmol) and DMAD (147 µL, 1.2 mmol) and purified by crystallization from EtOH. Yellow solid (355 mg, 74% yield); $R_{\rm f} =$ 0.29 ($C_6H_{14}/EtOAc\ 1:1$); mp 141–143 °C (decomp.); IR (cm⁻¹): 1750, 1743, 1722, 1702, 1650, 1638, 1596, 1564; ¹H NMR (400 MHz, DMSO- d_6), mixture of inseparable diastereomers, d.r. = \sim 2.3 : 1 (A : B): δ = 7.58–7.48 (3H, m, A + B), 7.41–7.31 (2H, m, A + B), 6.61 (0.3H, dt, J = 7.5, 1.1 Hz, B), 6.58 (0.7H, dt, J = 7.5, 1.1 Hz, A), 6.39-6.30 (1H, m, A + B), 6.27 (0.7H, dd, J = 3.4, 1.2 Hz, A), 6.25 (0.3H, dd, J = 3.5, 1.1 Hz, B), 5.74–5.63 (1H, m, A) + B), 5.44-5.36 (1H, m, A + B), 3.90 (2.1H, s, A), 3.88 (0.9H, s, B), 3.84-3.73 (2H, m, A + B), 3.65 (2.1H, s, A), 3.63 (0.9H, s, B), 2.76 (2.1H, s, A), 2.75 (0.9H, s, B), 0.91 (2.1H, t, J = 7.1 Hz, A), 0.76(0.9H, t, J = 7.1 Hz, B). ¹³C NMR (101 MHz, DMSO- d_6): δ (A, major) = 174.31, 162.95, 162.66, 160.64, 159.72, 145.47, 129.75, 129.28, 128.20 (2C), 128.16 (2C), 125.40, 125.29, 115.61, 107.32, 106.17, 101.13, 77.89, 76.78, 58.82, 53.20, 51.83, 27.31, 13.44. ¹³C NMR (101 MHz, DMSO- d_6): δ (B, minor) = 174.63, 163.52, 162.72, 162.35, 158.24, 142.96, 129.67, 129.48, 127.99 (2C), 126.43, 125.18, 115.37, 110.71, 109.26, 100.86, 79.24, 77.71, 59.14, 53.25, 51.99, 27.88, 13.17, two carbons were not separated/found; HRMS (ESI): m/z calcd for C₂₅H₂₄N₂O₈: 481.1605 [M + H]⁺; found: 481.1612.

Dimethyl 4'-benzoyl-1'-benzyl-2'-oxo-5'-phenyl-1',2'-dihydro-9aH-spiro[pyrido[2,1-b][1,3]oxazine-2,3'-pyrrole]-3,4-

dicarboxylate (3h). The compound was prepared according to the general procedure employing 1H-pyrrole-2,3-dione 1h (367 mg, 1 mmol) and DMAD (147 µL, 1.2 mmol) and purified by crystallization from EtOH. Pale yellow solid (451 mg, 77% yield); $R_{\rm f} = 0.13$ (toluene/EtOAc 5 : 1); mp 162–164 °C (decomp.); IR (cm⁻¹): 1743, 1727, 1713, 1650, 1637, 1596, 1577, 1563; ¹H NMR (400 MHz, CDCl₃), mixture of inseparable diastereomers, d.r. = \sim 2.3 : 1 (A : B): δ = 7.36–7.28 (2H, m, A + B), 7.23–7.17 (3H, m, A + B), 7.15-6.90 (10H, m, A + B), 6.52 (0.7H, dd, J = 3.5, 1.2 Hz, A), 6.44 (0.3H, d, J = 7.5 Hz, B), 6.37-6.26 (1.7H, m, A + B), 6.22 (0.3H, d, J = 3.5 Hz, B), 5.78-5.58 (1H, m, A + B), 5.40-5.23 (1H, m, A + B)m, A + B), 4.73-4.57 (2H, m, A + B), 3.93 (0.9H, s, B), 3.90 (2.1H, s, A), 3.60 (3H, s, A + B). 13 C NMR (101 MHz, CDCl₃): δ (A, major) = 190.6, 175.5, 164.0, 163.6, 158.2, 145.9, 139.6, 136.7, 130.8, 130.1, 129.6 (2C), 129.4, 128.8 (2C), 128.6 (2C), 128.1 (3C), 127.6 (2C), 127.4 (2C), 125.8, 125.5, 118.0, 116.1, 107.0, 101.6, 78.9, 78.9, 53.3, 52.0, 44.9. ¹³C NMR (101 MHz, CDCl₃): δ (B, minor) = 163.2, 136.8, 131.3, 130.1, 129.8, 128.9 (2C), 128.6 (2C), 127.8 (2C), 127.7 (2C), 127.5 (2C), 126.3, 125.6, 116.0, 106.3, 101.5, 80.7, 53.3, 52.1, 45.6, eleven carbons were not separated/found; HRMS (ESI): m/z calcd for $C_{35}H_{28}N_2O_7$: 589.1969 [M + H]⁺; found: 589.1965.

Tetramethyl 2'-oxo-1'-phenyl-1',2'-dihydro-9aH-spiro[pyrido [2,1-*b*][1,3]oxazine-2,3'-pyrrole]-3,4,4',5'-tetracarboxylate The compound was prepared according to the general procedure employing 1H-pyrrole-2,3-dione 1i (289 mg, 1 mmol) and DMAD (147 µL, 1.2 mmol) and purified by column chromatography (toluene/EtOAc 8:1) and followed by crystallization from EtOH. Yellow solid (244 mg, 48% yield); $R_{\rm f}=0.15$ (toluene/ EtOAc 8:1); mp 180-181 °C (decomp.); IR (cm⁻¹): 1754, 1738, 1712, 1694, 1684, 1656, 1629, 1601, 1567; ¹H NMR (400 MHz, DMSO- d_6), mixture of inseparable diastereomers, d.r. = \sim 1.5 : 1 (A : B): $\delta = 7.57 - 7.50$ (2H, m, A + B), 7.49 - 7.43 (1H, m, A + B), 7.32–7.23 (2H, m, A + B), 6.67 (0.6H, d, J = 7.5 Hz, A), 6.64 (0.4H, d, J = 7.5 Hz, B), 6.45-6.34 (1H, m, A + B), 6.25 (0.4H, d, J =3.3 Hz, B), 6.08 (0.6H, dd, I = 3.4, 1.2 Hz, A), 5.84–5.72 (1H, m, A) + B), 5.53-5.48 (0.6H, m, A), 5.47-5.40 (0.4H, m, B), 3.93 (1.8H, s, A), 3.89 (1.2H, s, B), 3.703 (1.2H, s, A), 3.696 (1.8H, s, A), 3.69 (1.2H, s, B), 3.67 (3H, s, A + B), 3.60 (1.8H, s, A). ¹³C NMR (101 MHz, DMSO- d_6): δ (A, major) = 172.3, 162.9, 162.3, 160.3, 160.1, 149.7, 146.4, 132.8, 129.5 (2C), 128.9, 126.0 (2C), 125.6, 125.1, 115.8, 108.9, 104.6, 102.2, 78.3, 76.2, 53.5, 53.2, 52.1, 51.5. ¹³C NMR (101 MHz, DMSO- d_6): δ (B, minor) = 173.1, 163.3, 162.0, 161.8, 160.5, 148.4, 144.1, 132.8, 129.5 (2C), 129.1, 126.4 (2C), 126.0, 125.4, 115.5, 109.0, 108.1, 101.6, 79.7, 77.0, 53.5, 53.2, 52.3, 52.1; HRMS (ESI): m/z calcd for $C_{25}H_{22}N_2O_{10}$: 511.1347 [M + H]⁺; found: 511.1349.

Tetramethyl 2'-oxo-1'-(p-tolyl)-1',2'-dihydro-9aH-spiro[pyrido [2,1-*b*][1,3]oxazine-2,3'-pyrrole]-3,4,4',5'-tetracarboxylate The compound was prepared according to the general procedure employing 1H-pyrrole-2,3-dione 1j (303 mg, 1 mmol) and DMAD (147 µL, 1.2 mmol) and purified by crystallization from EtOH. Yellow solid (106 mg, 20% yield); $R_f = 0.26$ (PhCH₃/EtOAc 5:1); mp 168-170 °C (decomp.); IR (cm⁻¹): 1755, 1715, 1657, 1628, 1602, 1566; ¹H NMR (400 MHz, CDCl₃), mixture of inseparable diastereomers, d.r. = \sim 5 : 1 (A : B): δ = 7.25-7.14 (4H, m, A + B), 6.46-6.21 (3H, m, A + B), 5.73 (0.83H, dd, J = 9.9,3.5 Hz, A), 5.69-5.63 (0.17H, m, B), 5.43-5.36 (0.83H, m, A), 5.35-5.30 (0.17H, m, B), 3.95 (2.5H, s, A), 3.91 (0.5H, s, B), 3.76-3.70 (6.5H, m, A + B), 3.67 (2.5H, s, A), 2.37 (3H, s, A + B). ¹³C NMR (101 MHz, CDCl₃): δ (A, major) = 173.3, 163.5, 163.4, 161.2, 161.2, 150.9, 146.7, 139.1, 130.9, 130.2 (2C), 126.4 (2C), 125.8, 124.8, 116.3, 109.4, 105.9, 102.3, 79.1, 77.1, 53.5, 53.2, 52.2, 51.7, 21.3; HRMS (ESI): m/z calcd for $C_{26}H_{24}N_2O_{10}$: $525.1504 [M + H]^{+}$; found: 525.1514.

Ethyl 3,4-dibenzoyl-2'-oxo-1',5'-diphenyl-1',2'-dihydro-9*aH*spiro[pyrido[2,1-b][1,3]oxazine-2,3'-pyrrole]-4'-carboxylate (3k). The compound was prepared according to the general procedure employing 1H-pyrrole-2,3-dione 1e (321 mg, 1 mmol) and dibenzoylacetylene 2b (281 mg, 1.2 mmol) and purified by crystallization from EtOH. Orange solid (356 mg, 56% yield); $R_{\rm f}$ = 0.54 (PhCH₃/EtOAc 5:1); mp 159-160 °C (decomp.); IR (cm⁻¹): 1745, 1683, 1663, 1638, 1594, 1561; ¹H NMR (400 MHz, CDCl₃), mixture of inseparable diastereomers, d.r. = \sim 5.3:1 (A : B): $\delta = 7.74 - 7.56$ (1.84H, m, A + B), 7.51 - 7.44 (1H, m, A + B), 7.41-7.35 (1H, m, A + B), 7.34-7.01 (16.16H, m, A + B), 6.75(0.16H, d, J = 3.4 Hz, B), 6.65 (0.84H, d, J = 3.8 Hz, A + B), 6.46(0.16H, d, J = 7.6 Hz, A + B), 6.41 (1H, ddt [A], J = 9.8, 6.1, 1.0 Hz,A + B, 6.34 (0.84H, d, J = 7.7 Hz, A), 5.94–5.77 (1H, m, A + B), 5.33 (1H, ddd [A], J = 7.4, 6.0, 1.2 Hz, A + B), 4.18–3.95 (0.32H, m, B), 3.94-3.80 (1.68H, m, B), 1.02 (0.48H, t, J = 7.1 Hz, B), 0.82(2.52H, t, J = 7.1 Hz, A). ¹³C NMR (101 MHz, CDCl₃): δ (A, major) = 193.2, 190.4, 175.1, 164.0, 158.7, 147.9, 139.5, 138.0, 134.8,134.4, 132.6, 130.3, 130.1 (4C), 129.29, 129.26 (2C), 128.9 (4C), 128.5 (2C), 128.1 (2C), 128.0, 127.6 (2C), 127.2, 126.1, 123.6,

115.8, 110.1, 101.7, 80.8, 79.8, 60.0, 13.8; HRMS (ESI): m/z calcd for $C_{40}H_{30}N_2O_6$: 635.2177 [M + H]⁺; found: 635.2178.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Russian Science Foundation, project # 19-13-00290.

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