RSC Advances

PAPER

View Article Online
View Journal | View Issue

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†

Andrew R. Galeev, ‡ Anna A. Moroz, ‡ Maksim V. Dmitriev * and Andrey N. Maslivets*

Received 15th November 2021
Accepted 15th December 2021

DOI: 10.1039/d1ra08384h

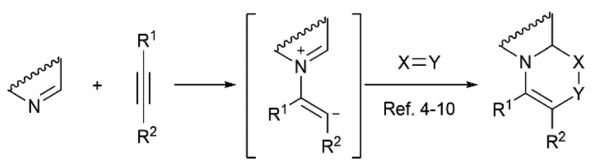
rsc.li/rsc-advances

1,4-Dipolar cycloaddition has emerged as a powerful tool for the synthesis of various cyclic compounds. In the present work, 1*H*-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.

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[1a,b,2] and without catalysts,[1d,e,3] have been successfully applied in the preparation of diverse carbo- and heterocycles. However, 1,4-dipole 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 (DMAD) or other activated acetylenes and azaheterocycles, the so-called Huisgen 1,4-dipoles, with carbonyl compounds (isatins,[4] quinones,[4b,5] aldehydes,[4c,6] *etc.*[7]), alkenes,[8] alkynes[9] and imines[4c,10] have been extensively studied (Scheme 1). Nevertheless, the search for new dipolarophiles, especially those containing several reaction sites, is still relevant.



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

We have a long-standing interest in the chemistry of 1*H*-pyrrole-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 bond[12] of 1*H*-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 isatins[14] (only the addition to C^3=O; Scheme 2B). To the best of our knowledge, the dipolar cycloaddition of 1*H*-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 1*H*-pyrrole-2,3-diones with dipoles generated from DMAD and pyridine.

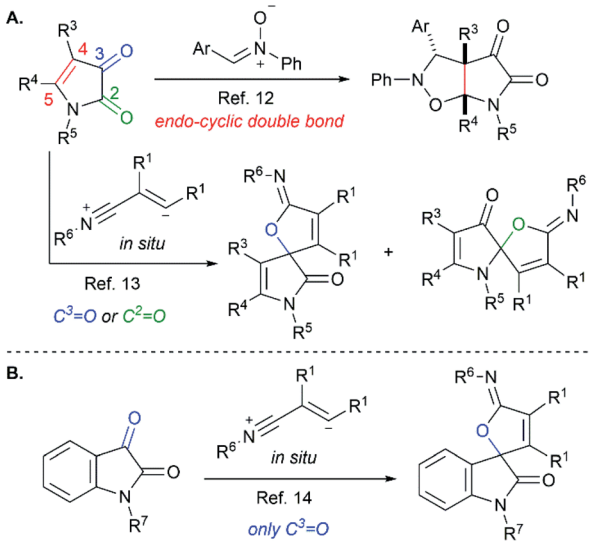
Results and discussion

Initially, we carried out the reaction of 1,5-diphenyl-1*H*-pyrrole-2,3-dione **1a** with DMAD **2a** and pyridine in $CHCl_3$ at room temperature (RT) and successfully isolated the spirocyclic [4 + 2] cycloadduct **3a** as a diastereomeric mixture in a yield of 52% (Scheme 4). The structure of compound **3a** was confirmed by the single crystal X-ray analysis (CCDC 2119396†). Noteworthy, only

Department of Chemistry, Perm State University, ul. Bukireva 15, Perm, 614068, Russia. E-mail: dmax@psu.ru; koh2@psu.ru

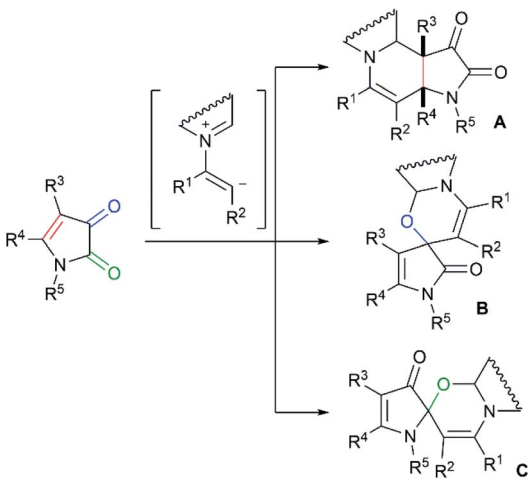
† Electronic supplementary information (ESI) available: General information, characterisation data, copies of NMR spectra, and experimental procedures. CCDC 2119396 (**3a**), 2119397 (**3f**), 2119399 (**8b**), and 2119398 (**8c**). For ESI and crystallographic data in CIF or other electronic format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

‡ These authors contributed equally to this work.

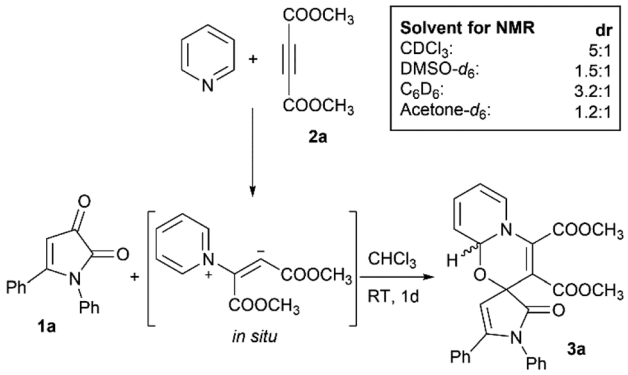


Scheme 2 Cycloaddition of 1*H*-pyrrole-2,3-diones and isatins with 1,3-dipoles.

C^3=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 C^3=O group is more electrophilic than lactam C^2=O group or enone C^5=C^4 moiety. ^{1}H NMR analysis (in $CDCl_3$) 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 ^{1}H 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 decomposition[15] in a $CDCl_3$ 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_6D_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 CH_2Cl_2 (Table 1, entries 2, 5). Other solvents showed similar yields, and ultimately, we chose EtOAc as a greener solvent among the tested ones.[16] A 20% excess of DMAD and pyridine slightly improved the yield up to 85% (the optimal conditions, Table 1, entry 9).

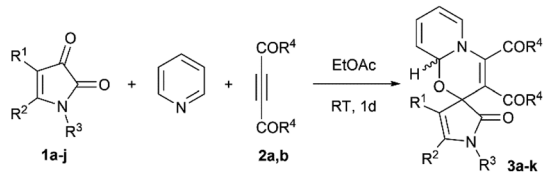
To explore the scope of the reaction, we investigated the cycloaddition of a variety of 1*H*-pyrrole-2,3-diones bearing electronically diverse substituents (Table 2). The reactions of 4-unsubstituted 5-aryl-1*H*-pyrrole-2,3-diones proceeded smoothly; the presence of electron-withdrawing or electron-

Table 1 Optimization of the reaction conditions for the preparation of **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]



Entry	1*H*-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_6H_4OMe-4/Ph)	OMe	**3b** (82%)	1.5 : 1[d]
3	**1c** (H/C_6H_4Br-4/Ph)	OMe	**3c** (79%)	1.5 : 1[d]
4	**1d** (Et/Ph/Ph)	OMe	**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_6H_4Me-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_6H_4Me-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 $CDCl_3$. [d] dr was determined by NMR analysis of isolated products in DMSO-d_6.

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 N^1 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/agusponge family, Hoye *et al.* found that perhydropyrido[2,1-*b*][1,3]oxazines **D** exist in solution in rapid diastereomeric equilibrium through ring-chain 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

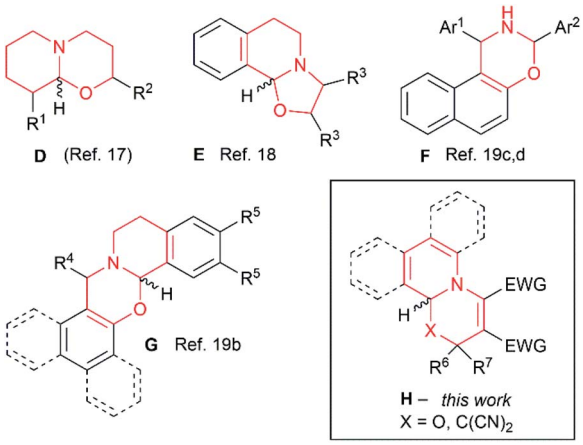


Fig. 1 Examples considering in this work and literature examples of [1,3]oxazines and oxazoles existing in the diastereomeric equilibrium.

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**).

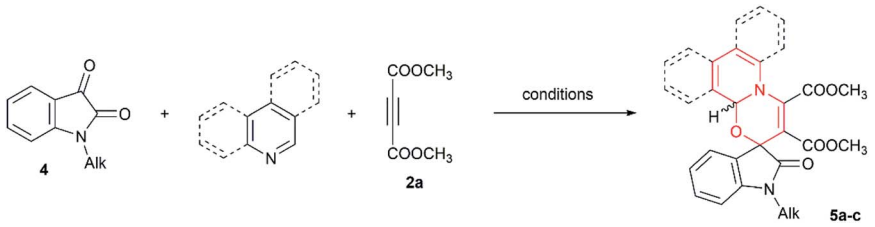
To this end, the model 1,4-dipolar cycloadditions of N-substituted isatins or 11*H*-indeno[1,2-*b*]quinoxalin-11-one with DMAD and azines (pyridine, isoquinoline and quinoline) were studied by HPLC and NMR methods (Tables 3 and 4).

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 $CDCl_3$) showed a dr of 4.8 : 1 (with close agreement with the literature data,[4c] dr 5 : 1). The same dr value was observed in K_2CO_3-treated $CDCl_3$, 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 work[20b] 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 K_2CO_3-treated $CDCl_3$ and DMSO-d_6, 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 $CDCl_3$, 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

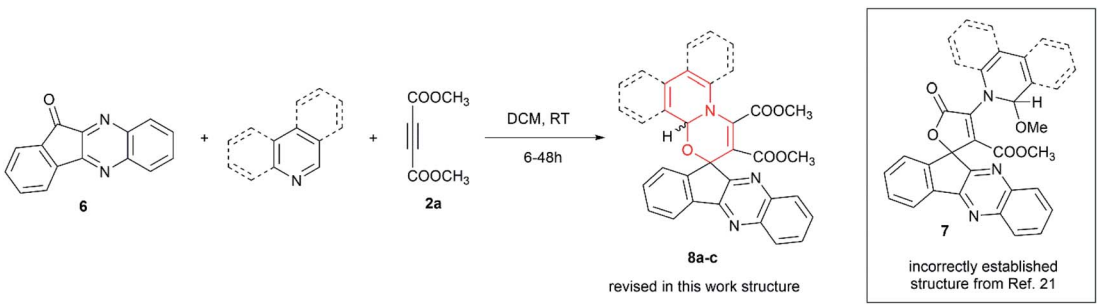


Entry	Compound, isolated yield	Heterocycle	Alk	Conditions, ref.	dr from literature by NMR (solvent)	dr observed in this work: By HPLC for reaction mixture	By HPLC for isolated product	By NMR for isolated product in: $CDCl_3$	K_2CO_3-treated $CDCl_3$	DMSO-d_6
1	**5a**, 70%	Pyridine	Bn	DME, Ar, RT, 6 h (ref. 4*c*)	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*b*)	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*b*)	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-d_6 and K_2CO_3-treated $CDCl_3$, even acidic $CDCl_3$ did not change dr, and thus the products derived from quinoline are stable to acid-catalyzed isomerization. The discrepancy with reported dr probably arise from the fact that diastereomers **5c** are separable,

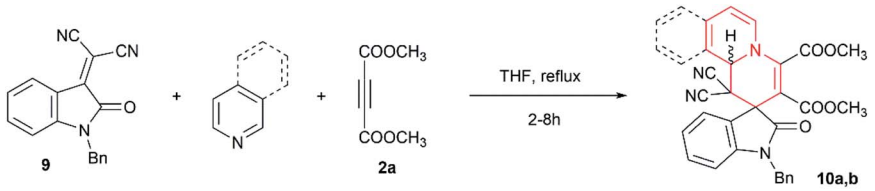
Table 4 Repetition of 1,4-dipolar cycloaddition of 11*H*-indeno[1,2-*b*]quinoxalin-11-one **6**: diastereoselectivity and diastereomeric equilibrium study



Entry	Compound, isolated yield	Heterocycle	dr from literature by NMR ($CDCl_3$)	dr observed in this work: By HPLC for reaction mixture	By HPLC for isolated product	By NMR for isolated product in: $CDCl_3$	K_2CO_3-treated $CDCl_3$	DMSO-d_6
1	**8a**, 53%	Pyridine	Single diastereomer[21]	—[a]	—[a]	16 : 1	16 : 1	3.2 : 1
2	**8b**, 82%	Isoquinoline	Single diastereomer[21]	1.2 : 1	1 : 1.2[b]	2.6 : 1→12 : 1[c]	1.1 : 1	1.3 : 1
3	**8c**, 86%	Quinoline	1.2 : 1 (ref. 21)	1 : 1	1 : 1	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. [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



				dr observed in this work				
						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_2CO_3-treated $CDCl_3$	DMSO-d_6
1	**10a**, 62%	Pyridine	10.1 : 1 (ref. 8*c*)	—[a]	—[a]	9 : 1	9 : 1	1.5 : 1
2	**10b**, 76%	Isoquinoline	—[b]	1.1 : 1	1.2 : 1	1.4 : 1	1.4 : 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 $CDCl_3$ and 5-fold decreased dr in DMSO-d_6 (Table 4, entry 1). Acid-catalyzed isomerization for isoquinoline product **8b** was observed in untreated $CDCl_3$: 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 ^{1}H NMR spectra of diastereomeric mixture in untreated $CDCl_3$ or K_2CO_3-treated $CDCl_3$ showed dr similar to the literature. At the same time, the ^{1}H 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.[8a] 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 ($CDCl_3$ 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 $CDCl_3$.

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 $CDCl_3$ (as a result of its decomposition) for recording NMR spectra can result in incorrect dr values.

Addition of isoquinoline-based dipoles to C=C bonds produces pyridoisoquinolines in a non-diastereoselective fashion, and no epimerization in acidic $CDCl_3$ 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 $CDCl_3$.[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 1*H*-pyrrole-2,3-diones, DMAD, and pyridine. Different substituents in 1*H*-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 1,4-cycloaddition 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 1*H*-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). The compound was prepared according to the general procedure employing 1*H*-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_f = 0.62 (C_6H_6/EtOAc 5 : 1); mp 181–182 °C (decomp.); IR (cm^{-1}): 1746, 1683, 1663, 1638, 1594, 1561; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of inseparable diastereomers, d.r. = ~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 (0.84H, dd, J = 3.4, 1.3 Hz, A), 6.41–6.23 (2H, 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× 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). ^{13}C NMR (101 MHz, $CDCl_3$): 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; ^{1}H 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× 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). ^{13}C 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. ^{13}C 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; ^{1}H NMR (400 MHz, acetone-d_6), mixture of inseparable diastereomers, dr = ~1.3 : 1 (A : B): δ = 7.37–7.20 (8H, m, A + B), 7.15–7.07 (2H, m, A + B), 6.55–6.52 (1.14H, m, 2× 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, 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. = ~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.

Dimethyl 5'-(4-methoxyphenyl)-2′-oxo-1′-phenyl-1′,2′-dihydro-9*aH*-spiro[pyrido[2,1-*b*][1,3]oxazine-2,3′-pyrrole]-3,4-dicarboxylate (3b). The compound was prepared according to the general procedure employing 1*H*-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_f = 0.30 ($PhCH_3$/EtOAc 5 : 1); mp 177–178 °C (decomp.); IR (cm^{-1}): 1740, 1729, 1713, 1654, 1635, 1600, 1569; ^{1}H NMR (400 MHz, DMSO-d_6), mixture of inseparable diastereomers, d.r. = ~1.5 : 1 (A : B): δ = 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). ^{13}C 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. ^{13}C 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-9*aH*-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 1*H*-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 ($PhCH_3$/EtOAc 5 : 1); mp 173–174 °C (decomp.); IR (cm^{-1}): 1739, 1709, 1684, 1652, 1633, 1595, 1567; ^{1}H NMR (400 MHz, DMSO-d_6), mixture of inseparable diastereomers, d.r. = ~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). ^{13}C 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. ^{13}C 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.

Dimethyl 4′-ethyl-2′-oxo-1′,5′-diphenyl-1′,2′-dihydro-9*aH*-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 ($PhCH_3$/EtOAc 5 : 1); mp 138–140 °C (decomp.); IR (cm^{-1}): 1743, 1729, 1706, 1656, 1600, 1567; ^{1}H NMR (400 MHz, DMSO-d_6), mixture of inseparable diastereomers, d.r. = ~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). ^{13}C 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-9*aH*-spiro[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 (C_6H_6/EtOAc 5 : 1); mp 179–182 °C (decomp.); IR (cm^{-1}): 1746, 1733, 1703, 1602, 1594, 1563; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of inseparable diastereomers, d.r. = ~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). ^{13}C 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; ^{1}H NMR (400 MHz, DMSO-d_6), mixture of inseparable diastereomers, d.r. = ~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). ^{13}C 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-9*aH*-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 1*H*-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_f = 0.50 (C_6H_6/EtOAc 5 : 1); mp 173–175 °C (decomp.); IR (cm^{-1}): 1742, 1695, 1653, 1627, 1595, 1564; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of inseparable diastereomers, d.r. = ~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, B). ^{13}C NMR (101 MHz, $CDCl_3$): 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.

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 1*H*-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_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; ^{1}H NMR (400 MHz, DMSO-d_6), mixture of inseparable diastereomers, d.r. = ~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). ^{13}C 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. ^{13}C 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 $C_{25}H_{24}N_2O_8$: 481.1605 $[M + H]^+$; found: 481.1612.

Dimethyl 4′-benzoyl-1′-benzyl-2′-oxo-5′-phenyl-1′,2′-dihydro-9*aH*-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 1*H*-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_f = 0.13 (toluene/EtOAc 5 : 1); mp 162–164 °C (decomp.); IR (cm^{-1}): 1743, 1727, 1713, 1650, 1637, 1596, 1577, 1563; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of inseparable diastereomers, d.r. = ~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), 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, $CDCl_3$): 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. ^{13}C NMR (101 MHz, $CDCl_3$): 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-9*aH*-spiro[pyrido[2,1-*b*][1,3]oxazine-2,3′-pyrrole]-3,4,4′,5′-tetracarboxylate (3i). The compound was prepared according to the general procedure employing 1*H*-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_f = 0.15 (toluene/EtOAc 8 : 1); mp 180–181 °C (decomp.); IR (cm^{-1}): 1754, 1738, 1712, 1694, 1684, 1656, 1629, 1601, 1567; ^{1}H NMR (400 MHz, DMSO-d_6), mixture of inseparable diastereomers, d.r. = ~1.5 : 1 (A : B): δ = 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, J = 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). ^{13}C 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. ^{13}C 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-9*aH*-spiro[pyrido[2,1-*b*][1,3]oxazine-2,3′-pyrrole]-3,4,4′,5′-tetracarboxylate (3j). The compound was prepared according to the general procedure employing 1*H*-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 ($PhCH_3$/EtOAc 5 : 1); mp 168–170 °C (decomp.); IR (cm^{-1}): 1755, 1715, 1657, 1628, 1602, 1566; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of inseparable diastereomers, d.r. = ~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). ^{13}C NMR (101 MHz, $CDCl_3$): 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 1*H*-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_f = 0.54 ($PhCH_3$/EtOAc 5 : 1); mp 159–160 °C (decomp.); IR (cm^{-1}): 1745, 1683, 1663, 1638, 1594, 1561; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of inseparable diastereomers, d.r. = ~5.3 : 1 (A : B): δ = 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). ^{13}C NMR (101 MHz, $CDCl_3$): 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.

Notes and references

1 (*a*) N. De and E. J. Yoo, *ACS Catal.*, 2018, **8**, 48; (*b*) T.-R. Li, Y.-N. Wang, W.-J. Xiao and L.-Q. Lu, *Tetrahedron Lett.*, 2018, **59**, 1521; (*c*) A. Mirzaei, G. Turczel, M. Nagyházi, V. Farkas, Á. Balla, H. Dang Vu and R. Tuba, *Eur. J. Org. Chem.*, 2021, **2021**, 326; (*d*) V. Nair, A. Deepthi, D. Ashok, A. E. Raveendran and R. R. Paul, *Tetrahedron*, 2014, **70**, 3085; (*e*) B. A. Trofimov and K. V. Belyaeva, *Tetrahedron Lett.*, 2020, **61**, 151991.

2 (*a*) J. Du, Y.-D. Hua, Y.-J. Jiang, S. Huang, D. Chen, C.-H. Ding and X.-L. Hou, *Org. Lett.*, 2020, **22**, 5375; (*b*) D. Garayalde and C. Nevado, *ACS Catal.*, 2012, **2**, 1462; (*c*) B. M. Trost and Z. Jiao, *J. Am. Chem. Soc.*, 2020, **142**, 21645.

3 (*a*) A. Bhunia, D. Porwal, R. G. Gonnade and A. T. Biju, *Org. Lett.*, 2013, **15**, 4620; (*b*) A. Bhunia, T. Roy, P. Pachfule, P. R. Rajamohanan and A. T. Biju, *Angew. Chem., Int. Ed.*, 2013, **52**, 10040; (*c*) D. Liu, J. Sun, J. Xie, H. Shi and C.-G. Yan, *J. Org. Chem.*, 2021, **86**, 1827; (*d*) M. S. Sammor, A. Q. Hussein, F. F. Awwadi and M. M. El-Abadelah, *Tetrahedron*, 2018, **74**, 42; (*e*) J. Zhang, H. Gao, J. Sun and C.-G. Yan, *Eur. J. Org. Chem.*, 2014, **2014**, 5598; (*f*) V. E. Zhulanov, V. A. Vigovskaya, M. V. Dmitriev, P. S. Silaichev, A. N. Maslivets and M. Rubin, *Org. Biomol. Chem.*, 2020, **18**, 3382.

4 (*a*) G. Liu, Y. Wu, J. Han, W. He, J. Chen, H. Deng, M. Shao, H. Zhang and W. Cao, *Synthesis*, 2018, **50**, 4668; (*b*) V. Nair, S. Devipriya and E. Suresh, *Tetrahedron*, 2008, **64**, 3567; (*c*) V. Nair, A. R. Sreekanth, N. Abhilash, A. T. Biju, B. Rema Devi, R. S. Menon, N. P. Rath and R. Srinivas, *Synthesis*, 2003, **2003**, 1895; (*d*) I. R. Siddiqui, A. Srivastava, P. Rai, A. Srivastava and A. Srivastava, *J. Heterocycl. Chem.*, 2015, **52**, 1415.

5 V. Nair, A. R. Sreekanth, A. T. Biju and N. P. Rath, *Tetrahedron Lett.*, 2003, **44**, 729.

6 (*a*) H. Mehrabi and M. Hatami-Pour, *Chin. Chem. Lett.*, 2014, **25**, 1495; (*b*) T. Sun, Q. Cai, M. Li, Z. Wang, J. Chen, H. Deng, M. Shao, H. Zhang and W. Cao, *Tetrahedron*, 2015, **71**, 622; (*c*) Z. Xu, T. Sun, Q. Cai, F. Ni, J. Han, J. Chen, H. Deng, M. Shao, H. Zhang and W. Cao, *J. Fluorine Chem.*, 2016, **181**, 45.

7 (*a*) K. V. Belyaeva, V. S. Gen, L. P. Nikitina, A. V. Afonin, D. V. Pavlov and B. A. Trofimov, *Tetrahedron Lett.*, 2021, 153431; (*b*) K. V. Belyaeva, L. P. Nikitina, V. S. Gen', A. V. Afonin and B. A. Trofimov, *Synthesis*, 2021, DOI: 10.1055/a-1644-2930; (*c*) A. A. Esmaeili, H. Vesalipoor, R. Hosseinabadi, A. F. Zavareh, M. A. Naseri and E. Ghiamati, *Tetrahedron Lett.*, 2011, **52**, 4865; (*d*) M. Lei, W. Tian, R. Hu, W. Li and H. Zhang, *Synthesis*, 2012, **44**, 2519; (*e*) V. M. Muzalevskiy, Z. A. Sizova, K. V. Belyaeva, B. A. Trofimov and V. G. Nenajdenko, *Molecules*, 2019, **24**, 3594.

8 (*a*) Y. Hu, L. Ye, J. Chen, H. Zhang, H. Deng, J.-H. Lin and W. Cao, *Eur. J. Org. Chem.*, 2021, **2021**, 4405; (*b*) V. Nair, B. Rema Devi and L. R. Varma, *Tetrahedron Lett.*, 2005, **46**, 5333; (*c*) H.-B. Yang, X.-Y. Guan, Y. Wei and M. Shi, *Eur. J. Org. Chem.*, 2012, **2012**, 2792; (*d*) M. Yu, Y. Wu, X. Peng, J. Han, J. Chen, Y. Kan, H. Deng, M. Shao, H. Zhang and W. Cao, *J. Fluorine Chem.*, 2018, **216**, 33; (*e*) Y.-Y. Zhang, Y. Han, J. Sun and C.-G. Yan, *ChemistrySelect*, 2017, **2**, 7382.

9 P. J. Abbott, R. M. Acheson, U. Eisner, D. J. Watkin and J. R. Carruthers, *J. Chem. Soc., Chem. Commun.*, 1975, 155.

10 (*a*) V. Nair, A. R. Sreekanth, N. Abhilash, M. M. Bhadbhade and R. C. Gonnade, *Org. Lett.*, 2002, **4**, 3575; (*b*) H.-W. Zhao, X.-Q. Chen, H.-L. Pang, T. Tian, B. Li, X.-Q. Song, W. Meng, Z. Yang, Y.-D. Zhao and Y.-Y. Liu, *RSC Adv.*, 2016, **6**, 61732.

11 (*a*) E. A. Lystsova, E. E. Khramtsova and A. N. Maslivets, *Symmetry*, 2021, **13**, 1509; (*b*) V. V. Konovalova and A. N. Maslivets, *Mini-Rev. Org. Chem.*, 2019, **16**, 173.

12 (*a*) A. A. Moroz, V. E. Zhulanov, M. V. Dmitriev, D. N. Babentsev and A. N. Maslivets, *Russ. J. Org. Chem.*, 2018, **54**, 780; (*b*) E. E. Stepanova, M. V. Dmitriev and A. N. Maslivets, *Tetrahedron Lett.*, 2020, **61**, 151595; (*c*) E. E. Stepanova, M. V. Dmitriev and A. N. Maslivets, *Russ. J. Org. Chem.*, 2021, **57**, 32.

13 A. A. Moroz, V. E. Zhulanov, M. V. Dmitriev and A. N. Maslivets, *Tetrahedron*, 2020, **76**, 130880.

14 (*a*) V. Nair, A. U. Vinod, N. Abhilash, R. S. Menon, V. Santhi, R. L. Varma, S. Viji, S. Mathew and R. Srinivas, *Tetrahedron*, 2003, **59**, 10279; (*b*) L. Tao, Z. Fan, X. Peng, J. Han, W. He, J. Chen, H. Deng, M. Shao, H. Zhang and W. Cao, *Synthesis*, 2018, **50**, 4104.

15 The signals of impurities in the ^{1}H NMR spectrum of **3a** (a set of signals in the range of 8–9.5 ppm) are typical for enals formed by hydrolysis of the adduct of pyridine to acetylenes: B. A. Trofimov, L. V. Andriyankova, K. V. Belyaeva, L. P. Nikitina, A. V. Afonin and A. G. Mal'kina, *Eur. J. Org. Chem.*, 2015, **2015**, 7876.

16 F. P. Byrne, S. Jin, G. Paggiola, T. H. M. Petchey, J. H. Clark, T. J. Farmer, A. J. Hunt, C. Robert McElroy and J. Sherwood, *Sustainable Chem. Processes*, 2016, **4**, 7.

17 (*a*) T. R. Hoye and J. T. North, *Tetrahedron Lett.*, 1990, **31**, 4281; (*b*) T. R. Hoye, J. T. North and L. J. Yao, *J. Org. Chem.*, 1994, **59**, 6904.

18 M. T. Richers, M. Breugst, A. Y. Platonova, A. Ullrich, A. Dieckmann, K. N. Houk and D. Seidel, *J. Am. Chem. Soc.*, 2014, **136**, 6123.

19 (*a*) L. Lázár and F. Fülöp, *Eur. J. Org. Chem.*, 2003, **2003**, 3025; (*b*) I. Szatmári, M. Heydenreich, A. Koch, F. Fülöp and E. Kleinpeter, *Tetrahedron*, 2013, **69**, 7455; (*c*) I. Szatmári, T. A. Martinek, L. Lázár and F. Fülöp, *Eur. J. Org. Chem.*, 2004, **2004**, 2231; (*d*) I. Szatmári, T. A. Martinek, L. Lázár,

A. Koch, E. Kleinpeter, K. Neuvonen and F. Fülöp, *J. Org. Chem.*, 2004, **69**, 3645.

20 (*a*) V. Nair, A. R. Sreekanth, N. P. Abhilash, A. T. N. Biju, L. Varma, S. Viji and S. Mathew, *ARKIVOC*, 2005, **2005**, 178; (*b*) I. Yavari, Z. Hossaini, M. Sabbaghan and M. Ghazanfarpour-Darjani, *Monatsh. Chem.*, 2007, **138**, 677.

21 M. T. Maghsoodlou, S. M. Habibi-Khorassani, A. Moradi, N. Hazeri, A. Davodi and S. S. Sajadikhah, *Tetrahedron*, 2011, **67**, 8492.

22 For utilization of NOESY to exchange studies, see: (*a*) D. X. Hu, P. Grice and S. V. Ley, *J. Org. Chem.*, 2012, **77**, 5198; (*b*) S. R. Hussaini, A. Kuta, A. Pal, Z. Wang, M. A. Eastman and R. Duran, *ACS Omega*, 2020, **5**, 24848.

23 See the ESI (S33 and S48†) for effects of HCl_{conc} and *p*-TSA on dr of products **5c** and **8c**.