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Domino reactions of diazodicarbonyl compounds with α,β-unsaturated δ-amino esters: convenient way towards 2-oxopiperidines, dihydropyridinones and isoquinolinediones

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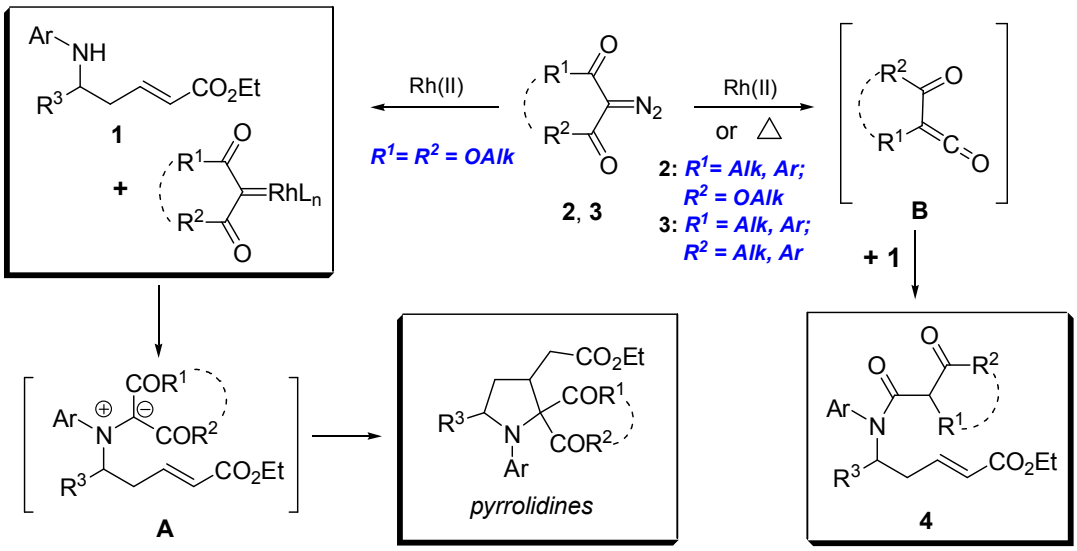
Abstract - Thermal decomposition of a series of diazodicarbonyl compounds in the presence α,β-unsaturated δ-amino esters and sodium hydride gives rise to a variety of nitrogenous heterocycles. The direction of these processes is highly dependent on the structure of the initial reagents giving rise to the formation of multi-functionalized 2-oxopiperidines, 5,6-dihydropyridin-2(1*H*)-ones or tetrahydroiso-quinoline-1,6(2*H*,8a*H*)-diones. The reactions occur in domino processes involving the Wolff rearrangement of diazocarbonyl compounds, NaH-catalyzed *anti*-stereoselective intramolecular Michael addition to the α,β-unsaturated system of amino esters, and in some cases also cycloelimination and intramolecular Claisen condensation of the initially products formed.

Introduction

Domino processes[1] with participation of diazo compounds have acquired last years a great popularity owing to their remarkable synthetic potential.[2a-d] This is first of all related to transition metal-catalyzed reactions of diazocarbonyl compounds,[2e-i] as well as to thermal and MW-assisted processes.[3] Of special interest are domino reactions of diazo compounds with different amino substrates, since they provide a way for the preparation of a variety of useful nitrogenous heterocyclic compounds.[3b-d,4]

It was shown recently, that Rh(II)-catalyzed decomposition of *diazo esters* in the presence of α,β-unsaturated δ-amino esters **1** gives rise to multi-functionalized *N*-arylpyrrolidines with good yields by way of intermediate *N*-ylide formation followed by Michael addition (Scheme 1, left pathway).[5] However, all attempts to extend the same methodology to *diazo ketoesters and diazo diketones* **2** and **3** were unsuccessful.



Scheme 1. Two basic directions of diazodicarbonyl compounds **2** and **3** reactions with amino esters **1** proceeding *via* reactive intermediates **A** and **B**.

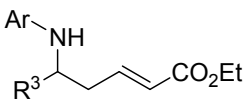
It turned out that under the same reaction conditions Rh(II)-catalyzed decomposition of diazo compounds **2**, **3** gives rise to α-oxoketenes **B** through *intramolecular* Wolff rearrangement followed by formation of amides **4** (Scheme 1, right pathway), instead of *intermolecular* generation of N-ylides **A** and their subsequent reactions.[2a,d]

It would be expected that amides **4**, having a readily enolizable 1,3-dicarbonyl system, are very promising precursors for the synthesis of *N*-containing heterocyclic compounds by use of subsequent intramolecular Michael addition, which is known for the similar systems.[6]

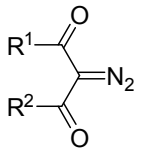
Based on these assumptions and preliminary findings, we have studied in detail reactions of a series of diazo ketoesters **2** and diazo diketones **3** with α,β-unsaturated δ-amino esters **1**, which gave rise to a variety of nitrogenous heterocycles 2-oxopiperidines, 5,6-dihydropyridin-2(1*H*)-ones and tetrahydroiso-quinoline-1,6(2*H*,8a*H*)-diones. In the current report the main results of this research are represented and discussed.

Results and discussion

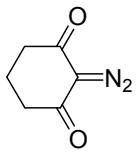
A series of α,β-unsaturated δ-amino esters **1** with different aryl substituents at the N-atom of the amino group (Ar = PMP for **1a-c**, Ar = 3,4-MeO-C_6H_3 for **1d**) and R^3 on the carbon atom C-5 of alkyl chain (**1a-c**; R^3 = Ph, *o*-Me-C_6H_4, (*E*)-Styryl) were used in the study.[7] As for diazo compounds, typical representatives of diazodicarbonyl compounds with dissimilar nature of substituents R^1 and R^2 (Ar, Me, AlkO) but favourable towards the Wolff rearrangement[8] were selected for the study, namely - the acyclic diazo ketoesters (**2a**,**b**) and diazo diketones (**2c-f**) as well as carbocyclic 2-diazo-1,3-cyclohexanedione (**3)** (Figure 1).



1a; Ar = *p*-OMe-C_6H_4 (PMP); R^3 = Ph;
1b; -//- ; (*E*)-Styryl
1c; -// ; *o*-Me-C_6H_4
1d; 3,4-MeO-C_6H_4; Ph



2a; R^1 = Me; R^2 = OMe
2b; Ph; OEt



3e

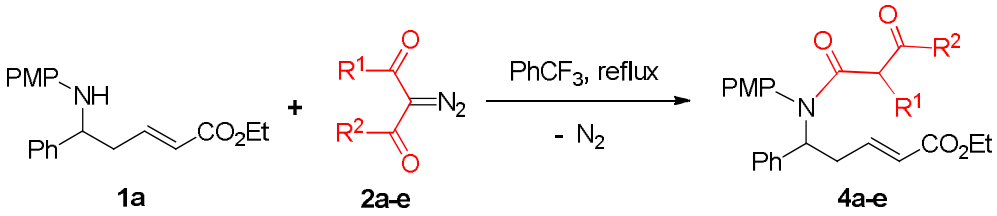
3a; Ph; Ph
3b; *p*-ClC_6H_4; *p*-ClC_6H_4
3c; Me; Me
3d; Me; *p*-Tol

Figure 1. The structures of aminoesters **1** and diazo compounds **2**, **3** used in the study.

During preliminary experiments it was established that thermolysis of diazodicarbonyl compounds **2** and **3** provided much better yields of the Wolff rearrangement products **4**, than Rh(II)-catalyzed reaction of these diazo compounds.[8e] Accordingly, the reactions were carried out under simple thermal conditions without any catalyst.

On heating diazodicarbonyl compounds **2** and **3** in the presence of α,β-unsaturated δ-amino esters **1** the initial prevailing process was the Wolff rearrangement producing α-oxoketenes **B** which easily reacted with NH-group of the amino ester **1** to furnish amides **4a-e** with high yields (Table 1; 81-91%,).

Table 1. Thermolysis of diazodicarbonyl compounds **2a-e** in the presence of amino ester **1**[a].



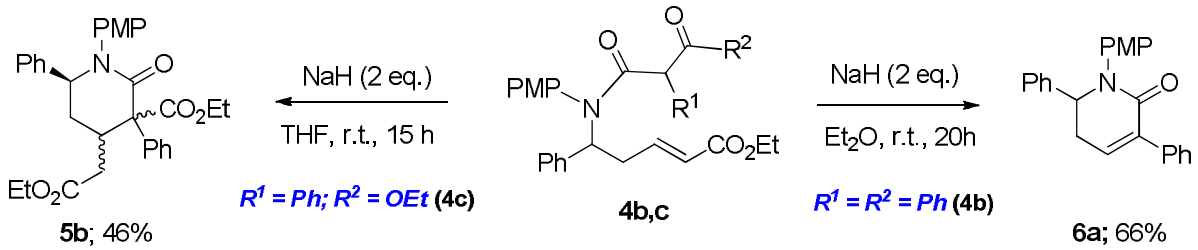
Entry	Diazo; R^1; R^2	Time, h	Yield,[b] (%)
1	**2a**; Me; OMe	35	**4a**; 84
2	**2b**; Ph; OEt	5	**4b**; 91
3	**3a**; Ph; Ph	2	**4c**; 84 (99)[c]
4	**3b**; *p*-ClC_6H_4; *p*-ClC_6H_4	2.5	**4d**; 81 (88)[c]
5	**3c**; Me; Me	2	**4e**; 86

[a] Diazo compound **2**,**3** (1.1-2 eq), $PhCF_3$, reflux. [b] Isolated yields. [c] ^{1}H NMR yields.

The facility by which the diazo compounds **2** and **3** were converted into amides **4** was dictated by their thermal stability, which was amply dependent on their structure.[9] It took 35 hours to complete reaction of diazo ketoester **2a** (Table 1, entry 1), while in the case of diazo compounds **2b-e** thermolysis was completed within 2-5 hours (entries 2-5). During decomposition of the diazo ketoesters **2a,b**, only migration of substituents on the acyl group (R^1 = Me or Ph) was observed. It is worth nothing that α–oxoketenes intermediate **B** (Scheme 1) formed in the course of this process selectively reacted with NH-group of amino ester **1**. The formation of plausible [2+2]- or [4+2]-cycloaddition products[10] by reaction of the *in situ* α–oxoketenes formed and the α,β-double bond of the amino ester **1** was never observed.

As it was already mentioned above, the amides of 1,3-keto acids **4** possess an acidic hydrogen atom between the carbonyl groups. Thus, these compounds can be considered as potential precursors for intramolecular Michael reaction with ring closure.[6] To realize these reactions we employed sodium hydride which is often used with the structures similar to amides **4**.[11]

It was shown that intramolecular Michael reaction with amides **4b,c** initiated by NaH occurred even at room temperature. As this took place, amide **4b** was formed as a mixture of diastereomeric 2-oxopiperidines **5b** with 46% yield (Scheme 2, left way).



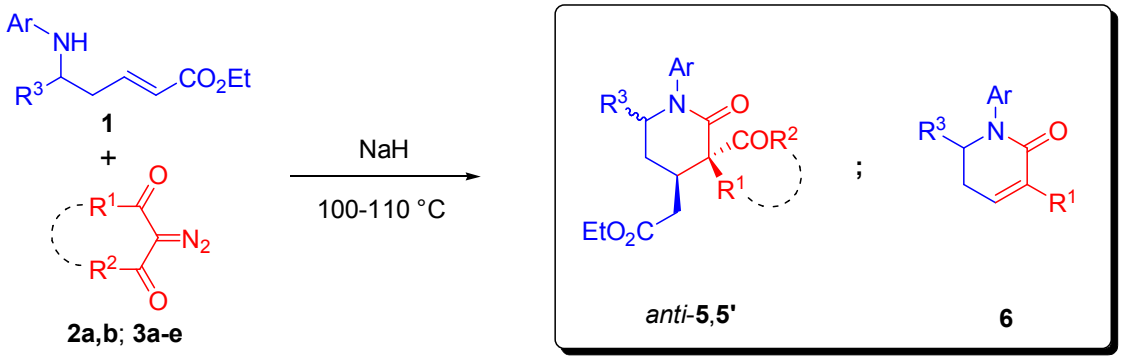
Scheme 2. Intramolecular condensation of amides **4b,c** in the presence of sodium hydride.

But unlike amide **4b** the same reaction with amide **4c** did not produce the expected 2-oxopiperidines **5c**. Instead, the main reaction product in this case proved to be 5,6-dihydropyridine-2(1*H*)-one **6a** in the yield of 66% (Scheme 2, right way).

Considering that thermolysis of diazodicarbonyl compounds **2** and **3** in the presence of α,β-unsaturated δ-amino esters **1** produced almost quantitatively the associated amides **4**, it was suggested that subsequent Michael reaction can be realized without preliminary isolation of amides **4** in a pure state, that is the whole process is carried out as a one-pot reaction. The subsequent experiments had shown that reaction in the presence of NaH actually proceeded as a domino process of Wolff rearrangement followed by Michael cyclization.

To elucidate the best reaction conditions for the preparation of oxopiperidines **5** and dihydropyridineones **6**, the domino process was examined in two different protocols *(**A*** and ***B**)* using a series of diazo compounds **2** and **3** and amino esters **1a**,**d** as the starting material (Table 2):
*(**A**)* a mixture of diazo compound **2** or **3**, amino ester **1** and sodium hydride was refluxed in solution of toluene or trifluoro toluene until the completion of the reaction (3-19 h);
*(**B**)* initially, conversion of diazodicarbonyl compounds **2** or **3** with amino ester **1** into amide **4** was carried out in PhMe or $PhCF_3$ (2-16 h), whereupon sodium hydride was added and the reaction mixture was refluxed until full conversion of amide **4** (5-6 h).

Table 2. Thermal decomposition of diazo compounds **2a**,**b** and **3a-e** with α,β-unsaturated δ-amino esters **1** in presence of NaH.



Entry	Diazo compound; R^1, R^2	Amine; R^3, Ar	Approach; Reaction time, h	Products		
				Yield **5**, %	d.r.[a]	Yield **6**, %
1	**2a**; Me, OMe	**1a**; Ph, PMP	***A***; 19	**5a**; 55	5.9 : 1	-
2	**2a**; -//-	-//-	***B***; 16+5	**5a**; 60	5.2 : 1	-
3	**2b**; Ph, OEt	-//-	***A***; 3	**5b**; 63	2.5 : 1	**6a**; 22 (85)[b]
4	**3c**; Me, Me	**1d**; Ph, 3,4-OMe-C_6H_3	***A***; 2	**5c**; 72	3.9 : 1	**6f**; 14 (86)[b]
5	**3c**; Me, Me	**1a**; Ph, PMP	***A***; 1	-	-	-
6	**3e**; -$(CH_2)_3$-	**1a**; Ph	***A***; 6	**5d**; 78.5	1.3 : 1	-
7	**3e**; -//-	-//-	***B***; 2+6	**5d**; 73	1.2 : 1	-
8	**3a**; Ph, Ph	-//-	***A***; 2	-	-	**6a**; 69
9	**3b**; *p*-ClPh, *p*-ClPh	-//-	***A***; 2.5	-	-	**6b**; 75
10	**3b**; -//-	**1c**; *o*-MeC_6H_4, PMP	***A***; 2.5	-	-	**6d**; 54
11	**3b**; -//-	**1b**; (*E*)-Styryl, PMP	***A***; 2	-	-	**6c**; 34
12	**3d**; *p*-Tol, Me	**1a**; Ph, PMP	***A***; 1	28[c]		**6e**; 19 (47)[b]

[a]Ratio of (4R*,6S*)-**5** / (4S*,6S*)-**5'**; [b]Total yields of the reaction products **6** and **5** are indicated in brackets; [c]Mixture of isomeric 2-oxopiperidines that were not isolated as single racemate.

During further experiments it was established that on interaction of diazo ketoesters **2a**,**b** with amino ester **1a** using both protocols *(**A** and **B**)* 2-oxopiperidines **5a** and **5b** were formed in the yields of 55-63% (Table 2, entries 1-3) as a mixture of two stereoisomers *(4R*,6S*)*-**5** and *(4S*,6S*)*-**5'** (Figure 2), As this takes place, in both cases substituents at the atoms C-3 and C-4 of oxopiperidine ring have *anti*-configuration,*) suggesting a *anti*-selectivity of the Michael reaction stage. The process also occurred with low, but notable diastereoselectivity (Table 2, entries 1-3).

Thermal decomposition of diazoacetoacetate **3c** with amino ester **1d** and sodium hydride (protocol ***A***) also produced a mixture of 2-oxopiperidines **5c** in 72% yield (Table 2, entry 4). The stereochemical assignment of the reaction products **5a-c** and **5'a-c** formed was made based on the NOE experiments (Figure 2).

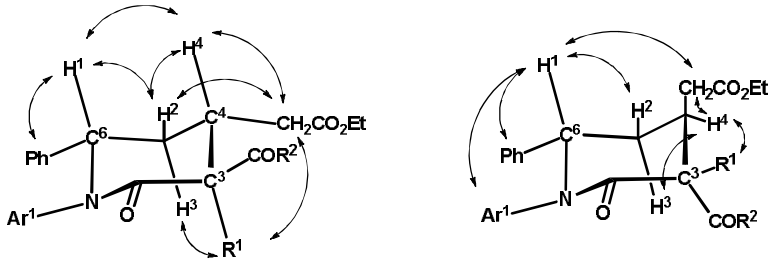


Figure 2. Configuration of *anti*-**5** and *anti*-**5'** isomers as revealed by NOESY experiments.

Reaction of carbocyclic 2-diazo-1,3-cycohexanedione **3e** with amino ester **1a** using both protocols *(**A** and **B**)* occurred in a similar manner. However, in spite of the relatively high yields of the target 2-oxopiperidines **5d** (73-78%), the process was not stereoselective. As a result of intramolecular

*) Hereinafter these stereoisomers are denoted as *anti*-**5** and *anti*-**5'** keeping in mind relative configuration of substituents on C-3 and C-4 atoms, while *cis/trans*-nomenclature is used to denote relative configuration of substituents at atoms C-4 and C-6 of heterocycle formed.

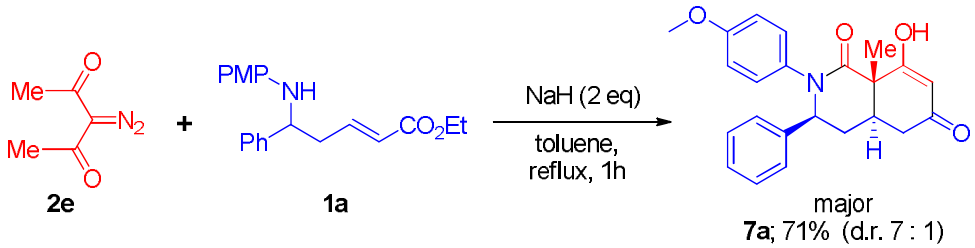
cyclization of intermediate amide **4**, a complex mixture of isomeric 2-oxopiperidines **5d** was formed with the ratio of *cis*-/*trans*-isomers **5d** ~ 1.3 : 1 and complete absence of *anti*-selectivity at the Michael reaction stage (Table 2, entries 6,7).

Hence employment of different protocols ***A*** or ***B*** to perform reactions of diazo compounds **2** with amino esters **1** did not considerably influence the efficiency and selectivity of the whole process.

However, it was recognized that the origin of the final products was completely determined by the structure of the initial diazo compounds: reactions with diazo ketoesters **2a,b** and diazo diketones **3c**,**e** with alkyl substituents R^1, R^2 gave rise to formation of 2-oxopiperidines **5** with 55-78% yield (Table 2, entries 1-7), while in the case of diazo diketones **3a,b,d** having aroyl groups in the structure, the 5,6-dihydropiperidine-2(1*H*)-ones **6** were formed with yields of up to 75% (Table 2, entries 8-12). Employment of diazo compounds with acetyl or alkoxy carbonyl groups (**2b**,**3c-d**) decreases efficiency of the process down to 14-22% (entries 3,4,12).

Varying of substituents R^1 and R^2 and aryl groups Ar on the N-atom of amino esters **1** also markedly affected the outcome of the process. Thus, incorporation of the (*E*)-styryl group in the structure of amino ester **1b** reduced the yield of desirable dihydropyridine-2(1*H*)-one **6c** to 34% (entry 11). On decomposition of diazoacetylacetone **3c** in the presence of amino esters **1a**,**d** and NaH, the target dihydropyridine-2(1*H*)-one **6f** was formed with only amine **1d** (Ar = 3,4-MeO-C_6H_3) and in low yield (14%, entry 4), while reaction of diazo diketone **3c** with amino ester **1a** (Ar = PMP) did not produce corresponding dihydropyridineone **6** or 2-oxopiperidine **5** at all (entry 5).

The real exception to all these reactions in hand was observed upon thermolysis of diazoacetylacetone **3c** in the presence of amino ester **1a** and NaH. In this case the major reaction product was found to be tetrahydroisoquinoline-1,6(2*H*,8a*H*)-dione **7a** isolated as a mixture of two diastereomers with 71% yield (d.r. 7:1) (Scheme 3).



Scheme 3. Thermolysis of diazoacetylacetone **2e** in the presence of amino ester **1a** and NaH.

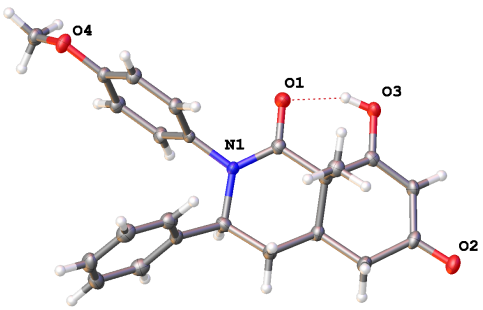
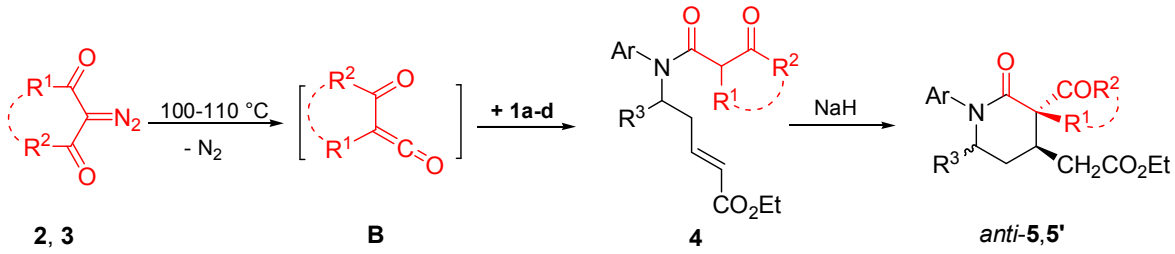


Figure 3. OLEX-2-generated[12] structure of the major isomer (3*S**,4a*R**,8a*S**) **7a**.

The bicyclic structure and configuration of the main stereoisomer of isoquinolinedione **7a** was unambiguously established using X-ray analysis (Figure 3).

By this means it was established that thermal one-pot reactions of acyclic **2a-b**, **3a-d** and carbocyclic **3e** diazodicarbonyl compounds with amino esters **1a-d** in the presence of sodium hydride gave rise to the formation of *N*-heterocycles of three types, namely: 2-oxopiperidinones **5**, dihydropyridine-2(1*H*)-ones **6** and tetrahydroisoquinoline-(2*H*,8a*H*)-diones **7**.

Oxopiperidinones **5** were formed *via* a three-stage process (Scheme 4), involving thermal Wolff rearrangement of diazodicarbonyl compounds[3,8] followed by interaction of the generated α-oxoketenes **B** with nucleophilic N-H-group of amino ester **1** to produce amides **4**,[8a,13] which were the final products of the process in the absence of base (Table 1). At the next key stage of the process the resulting amides **4** were subjected to stereoselective intramolecular Michael addition initiated by NaH to produce 3,4-*anti*-substituted 2-oxopiperidines **5**,**5'** (Table 2, entries 1-7).



Scheme 4. The assumed pathway to *anti*-oxopiperidines **5**,**5'**

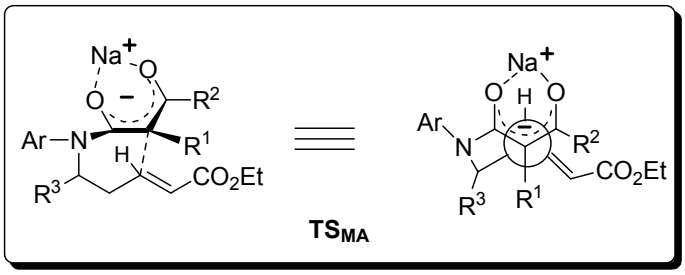
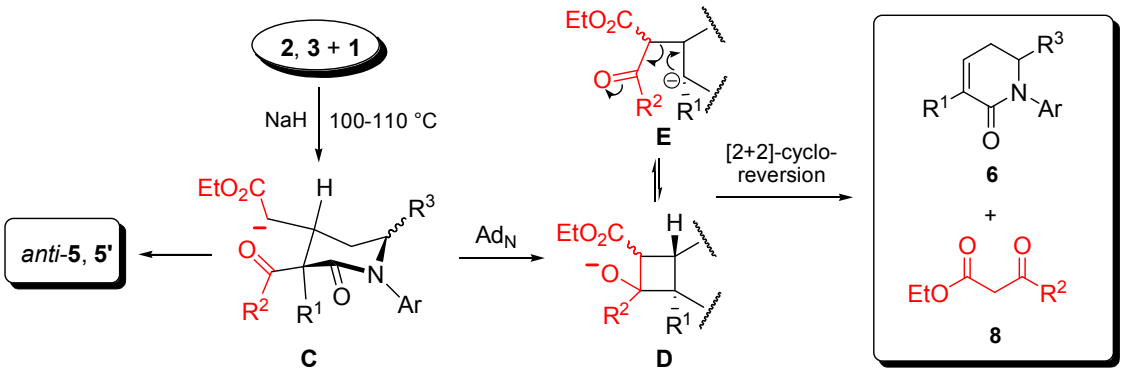


Figure 4. The proposed **TS** for the Michael addition step.

The stereochemistry of this *anti*-addition was apparently controlled by the assumed transition state of the process $\mathbf{TS_{MA}}$ (Figure 4).

The *cis-trans*-selectivity of the Michael reaction was markedly affected by the nature and steric bulk of R^1 and R^2 substituents. Optimal yields (Table 2, entries 1,2,4; 55-72%) and relatively high diastereoselectivity of this process were achieved by using diazo compounds with a modest bulk of R^1, R^2 groups (**2a**,**3c**; R^1=Me, R^2=Me; OMe: d.r. *cis/trans* from ~ 4:1 to ~ 6:1), while with 2-diazo-1,3-cyclohexanedione **3e** the reaction proceeded essentially in a nonselective manner.

At the intramolecular Michael addition stage, occurring apparently through intermediate transition state $\mathbf{TS_{MA}}$, formation of the anion **C** initially takes place, which is further stabilized *via* addition of a proton from the medium to furnish 2-oxopiperidineones *anti*-**5** and **5'** (Scheme 4, left pathway).



Scheme 5. The assumed pathways to the structures of *anti*-2-oxopiperidines **5**, **5'** and 5,6-dihedropyridin-2(1*H*)-ones **6**.

However, neutralization of the anion **C** by this way is not the single channel for its stabilization. The resulting anion **C** is located in the transition state $\mathbf{TS_{MA}}$ in the immediate proximity to 3-acylic carbonyl group. This, apparently, initiates the intramolecular attack of the anion **C** onto carbon atom of C=O-group followed by nucleophilic addition (Ad_N) to produce a cyclobutane ring fused with dihydropyridinic structure **D** (Scheme 5, right pathway). The process is apparently facilitated by a conformation with equatorial orientiation of both reacting groups (EtO_2CH_2 and R^2CO; Scheme 5). The cyclobutane intermediate **D** formed by nucleophilic addition, then undergoes a formal [2+2]-cycloelimination to produce 5,6-dihydropyridine-2(1*H*)-ones **6** and β-oxoesters **8** as the final products of the entire process. It is most likely that these [2+2]-cycloreversions occur as a stepwise process *via* anion **E**, appeared from cyclobutane intermediate **D** by a reversible nucleophilic addition of the anion **E** to carbonyl group (Scheme 5).[14b]

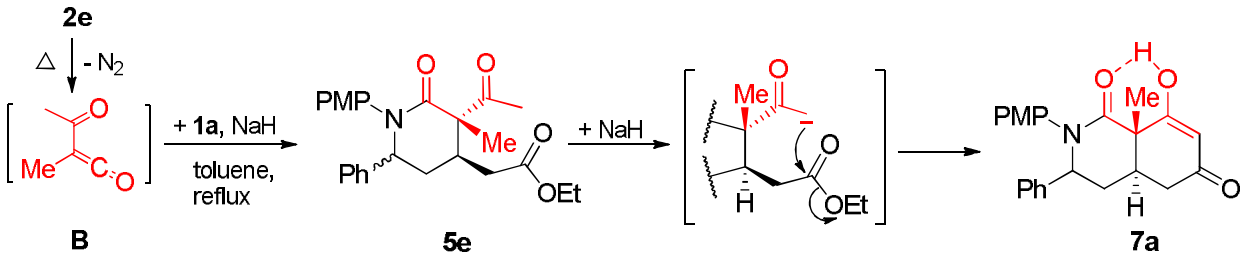
The observation of esters **8** in the reaction mixture was established experimentally and can be considered as one of the arguments in favor of the proposed mechanism of the process (Scheme 5). Similar reactions are rather characteristic for the systems with alkoxy anion generated in cyclobutane ring, which is probably the driving force of this reaction.[14] Thus, similar fragmentation process was observed by Snider and co-workers during treatment of 5-arylbicyclo[3.2.0]heptan-6-oles with potassium hydride.[14a]

The nature of substituents R^1 and R^2 in the structure of diazo compounds **2** and **3** was, most likely, the determining factor directing the process into the left or right pathways. In the case when R^1 = Me and even with R^2 = Alk, the main reaction products were 2-oxopiperidines **5** (Table 2, entry 4), while in the case of R^1 = Ar the occurrence of 5,6-dihydropyridine-2(1*H*)-ones **6** was the predominant process (Table 2, entries 8-10). It is evident that with the acyl group the Ad_N reaction had to proceed much easier than with R^2 = OAlk, when the main reaction products were 2-oxopiperidines **5** (Table 2, entries 1-3). In a few cases, however, a competition between these two processes was observed. Thus, in reaction of diazo ketoester **2b** (R^2 = OEt; R^1 = Ph), in addition to 2-oxopiperidine **5b** (63%), a small amount of dihydropyridineone **6a** (22%) was isolated from reaction mixture, and in reaction of diazoacetylacetone **3c** with amino ester **1d**, oxopiperidine **5c** and dihydropyridineone **6f** were formed in the yields of 72% and 14%, respectively.

Summing up the foregoing experimental results, one can conclude that with diazo compounds bearing two aryl substituents (as, for example, in **3a,b**) mainly 5,6-dihydropyridine-2(1*H*)-ones **6** are formed, while occurrence in diazo molecule of alkyl and ester groups (**2a,b,3c**) directed reaction

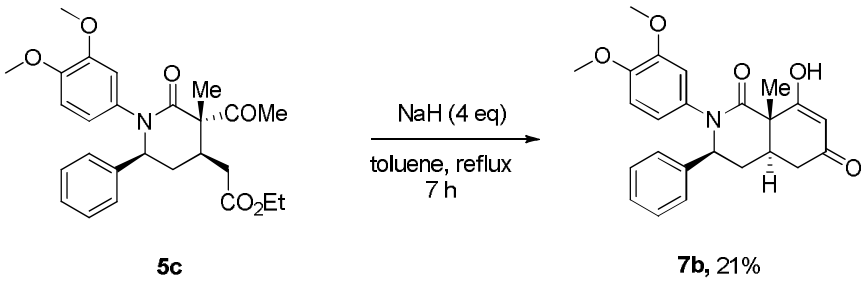
into formation of 2-oxopiperidines **5**. In the case of diazo ester **2b** and diazo diketones **3c,d** a competition between two processes was formally observed and dihydropyridineones **6** in this case were formed with low yields (14-22%) though the total yield of the reaction products **5** and **6** was reasonably high (Table 2; up to 86%).

As for the isoquinoline **7a**, it is evident that it was formed through a domino process similarly to the scheme 4. Initially, appeared at the first stage α-oxoketene **B** reacted with aminoester **1a** to give the appropriate amide **4**, which underwent stereoselective intramolecular Michael cyclization to produce *anti*-oxopipyridine **5e** (Scheme 6). The latter was converted into the final reaction product, tetrahydroisoquinolinedione **7a**, by means of intramolecular Claisen condensation.[15]



Scheme 6. The proposed reaction mechanism for the formation of the isoquinolinedione **7**.

The assumed intermediate acyloxopypiridine **5e** was not detected in the course of this reaction. But similar in the structure *anti*-3-acetyl-2-oxopypiridine **5c** was isolated as the main reaction product upon thermolysis at the same conditions of diazoacetylacetone **3c** in the presence of amino ester **1d**, and this can be considered as an argument in support of the proposed scheme for the isoquilinone **7a** formation. On heating oxopiperidinone *anti*-**5c** in toluene with 4 equivalents of NaH for 7 h gave rise to formation of the expected product **7b** as a single stereoisomer but in low yield (21%, Scheme 7), with the major portion of the initial oxopiperidinone **5c** being unchanged.



Scheme 7. Cyclization of 2-oxopiperidine **5c** into isoquinolinedione **7b**.

Hence it is evident that replacement of the PMP with 3,4-OMe-C_6H_3-group on the N-atom of aminoester has also considerable effect on the reactivity of 2-oxopiperidinones **5e** and **5c** giving rise to different reaction products in this process. It seems also obvious, that preparation of isoquilinones **7** by this approach can be only realized with 3-acetyl-group in the structure of 2-oxopiperidineone **5**, that is in reactions of diazoacetylacetone **3c** or its analogues having CH_3C=O-group in diazo molecule, which is necessary for the subsequent intramolecular Claisen condensation.

Conclusions

Thermal one-pot reactions of diazodicarbonyl compounds with α,β-unsaturated *N*-(aryl)substituted δ-amino esters in the presence of sodium hydride provides a way for the preparation of nitrogenous heterocyclic compounds of three types: multi-functionalized 2-oxopiperidines (55-78%), 5,6-dihydropyridine-2(1*H*)-ones (up to 75%) and tetrahydroisoquinoline-1,6(2*H*,8a*H*)-diones (up to 71%). The reactions proceed as a domino processes involving as the key steps the Wolff rearrangement and *anti*-stereoselective intramolecular Michael reaction. In some cases additional processes of cycloelimination and intramolecular Claisen condensation were observed and were most likely dictated by the origin of substituents of the initial diazodicarbonyl compounds and α,β-unsaturated δ-amino esters.

Supporting information

Components of the Experimental section, ^{1}H and ^{13}C NMR spectra for all new compounds, examples of the NOESY spectra for 2-oxopiperidines **5**, and crystallographic data for compound **7a** (CCDC 1406083).

Acknowledgements

The authors gratefully acknowledge generous financial support from the DFG (SCHN 441/10-1) and the DAAD. This project was carried out in part using the resources of the "Center for Chemical Analysis and Materials Research", "Center for Magnetic Resonance", "Center for Optical and Laser Methods Research" and "X-ray Diffraction Centre" of St-Petersburg State University.

Experimental section

General methods

All reactions were carried out in the solvents dried and purified before use by common methods. Monitoring of the reaction course was accomplished by thin-layer chromatography (TLC) on precoated silica gel SIL G/UV254 plates (Marchery, Nagel & Co.) Flash chromatography was performed using Merck silica gel 60 230–400 mesh. ^{1}H and ^{13}C NMR spectra were recorded in CDCl3 solutions using Varian Gemini 200 and 2000 (200 MHz), Varian Gemini 300BB (300 MHz) and Brucker Avance DRX 400 (400 MHz) spectrometers. Chemical shifts are reported in ppm, and coupling constants are given in Hz. All signals in NMR spectra were normalized relative to signals of CDCl3 (δ = 7.26 ppm in 1H NMR and δ = 77.0 in 13C NMR spectra).

A single crystal of the (3*S**,4a*R**,8a*S**)-**7a** was selected from the analytical sample; the supplementary crystallographic data for **7a** (CCDC 1406083) are provided in the ESI.† IR spectra were obtained with a FT-IR spectrometer Genesis ATIMattson/Unicam and FT-IR spectrometer Nicolet 8700. Melting points are uncorrected. All the ESI/HR mass spectra were recorded on a Brucker APEX II FT-ICR and ultra high-resolution TOF mass spectrometer "Maxis" BrukerDaltonik GmbH (Germany). Amino esters **1a-d** and diazo compounds **2**,**3** were prepared using previously described protocols. [7,16]

General procedure for preparation of amides 4a-e:

A solution of amino ester **1a** (0.35 - 1 mmol, 1 equiv) and diazo compound **2a,b,3a-c** (0.46 - 1.2 mmol; 1.1 - 2 equiv) in $C_6H_5CF_3$ (4 - 30 ml) was refluxed for 2 - 35 h until full conversion of amino

ester **1a** (monitoring the process by TLC, reaction time depends on the stability of diazo compound **2a,b,3a-c**). The solvent was removed *in vacuo*, and the obtained residue was separated using silica gel flash chromatography (eluent: Hexane-Acetone 5 : 1) to give amides **4a-e** as a mixture of two diastereomers (The detailed description of these experiments is given in ESI,† p2).

(***E***)**-Ethyl 5-(3-methoxy-*N*-(methoxyphenyl)-2-methyl-3-oxopropanamido)-5-phenylpent-2-enoate 4a** (*mixture of diastereomers in the ratio 1 : 1*). Bright brown oil. *Diastereomer A:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01-7.27 (m, 6H), 6.92-7.00 (m, 1H), 6.87-6.92 (m, 1H), 6.57-6.66 (m, 1H), 6.28 (t, J = 6.8 Hz, 1H), 6.12-6.14 (m, 1H), 5.93-5.97 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.77 (s, 3H), 3.57 (s, 3H), 3.18 (q, J = 7.0 Hz, 1H), 2.68-2.84 (m, 2H), 1.31 (d, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 170.7, 166.3, 159.7, 144.8, 138.9, 131.6, 131.4, 130.3, 128.7, 128.4, 128.1, 124.0, 114.4, 60.5, 56.1, 55.5, 52.4, 44.4, 33.6, 14.4, 14.1; *Diastereomer B*: IR (CCl_4) ν_{max} 2981, 2852, 1740, 1657, 1595, 1494, 1226 cm^{-1}; Bright brown oil; 1H NMR (300 MHz, $CDCl_3$) δ 7.09-7.27 (m, 6H), 6.95-7.04 (m, 1H), 6.88-6.92 (m, 1H), 6.59 (dd, J = 8.7, 2.9 Hz, 1H), 6.28 (t, J = 6.8 Hz, 1H), 6.01-6.04 (m, 1H), 5.95-6.00 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.78 (s, 3H), 3.68 (s, 3H), 3.16 (q, J = 7.0 Hz, 1H), 2.65-2.88 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.23 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 170.7, 166.4, 159.7, 144.8, 138.9, 131.6, 131.4, 130.2, 128.7, 128.5, 128.1, 123.8, 114.4, 60.4, 56.0, 55.5, 52.4, 44.3, 33.6, 14.4, 14.1; HRMS (ESI) calcd for $C_{25}H_{29}NO_6$ $[M+Na]^+$ 462.1887, found 462.1888.

(***E***)**-Ethyl 5-(3-ethoxy-*N*-(methoxyphenyl)-3-oxo-2-phenylpropanamido)-5-phenylpent-2-enoate 4b** (*mixture of diastereomers in the ratio 1 : 1*). Bright brown oil. *Diastereomer A*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02-7.27 (m, 12H), 6.96 (dt, J = 15.8, 6.6 Hz, 1H), 6.44-6.47 (m, 1H), 6.20 (t, J = 7.8 Hz, 1H), 5.96 (dt, J =15.7, 1.5 Hz, 1H), 5.64 (dd, J = 8.8, 2.6 Hz, 1H), 4.39 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.17 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 2.70-2.89 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 169.0, 168.4, 166.4, 159.7, 144.7, 138.6, 133.5, 132.5, 131.9, 129.7, 129.6, 128.6, 128.4, 128.3, 128.0, 127.8, 123.9, 114.2, 114.0, 61.6, 60.4, 56.6, 56.0, 55.5, 33.6, 14.4, 14.2; *Diastereomer B*: IR (film) ν_{max} 2980, 2872, 1751, 1719, 1654, 1605, 1583, 1509, 1296, 1273, 1250 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.27 (m, 10H), 6.87 (dt, J = 15.8, 6.6 Hz, 1H), 6.74 (dd, J = 8.7, 3.0 Hz, 1H), 6.57-6.64 (m, 2H), 6.32 (t, J = 7.8 Hz, 1H), 6.21 (dd, J = 6.9, 3.4 Hz, 1H), 5.86 (dt, J = 15.7, 1.5 Hz, 1H), 4.34 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.78 (s, 3H), 2.65-2.68 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 168.6, 166.2, 159.7, 144.5, 138.7, 133.7, 132.0, 131.9, 129.8, 129.6, 128.7, 128.4, 128.3, 128.1, 127.9, 123.9, 114.3, 113.9, 61.5, 60.4, 56.8, 56.1, 55.5, 33.6, 14.4, 14.1; HRMS (ESI) calcd for $C_{31}H_{33}NO_6$ $[M+Na]^+$ 538.2206, found 538.2223.

(***E***)**-Ethyl 5-(*N*-(4-methoxyphenyl)-3-oxo-2,3-diphenylpropanamido)-5-phenylpent-2-enoate 4c** (*mixture of diastereomers in the ratio 1.3 : 1*). Bright brown oil. IR (CCl_4) ν_{max} 1717, 1684, 1648, 1510, 1322, 1252 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.67 (m, 4H), 7.40-7.51 (m, 2H), 7.02-7.34 (m, 25H), 6.87-7.00 (m, 2H), 6.57-6.79 (m, 3H), 6.49 (t, J = 2.8 Hz, 1H), 6.46 (t, J = 2.8 Hz, 1H), 6.35 (t, J = 7.8, 1H), 6.22 (t, J = 7.9 Hz, 1H), 6.10 (dd, J = 8.8, 2.6 Hz, 1H), 5.96 (d, J = 15.8 Hz, 1H), 5.89 (d, J = 15.8 Hz, 1H), 5.79 (dd, J = 8.8, 2.6 Hz, 1H), 5.27 (s, 1H), 5.19 (s, 1H), 4.09-4.23 (m, 4H), 3.69 (s, 3H), 3.67 (s, 3H), 2.48-3.10 (m, 4H), 1.28 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 193.7, 168.7, 168.5, 166.2, 166.0, 159.5,

159.4, 144.5, 144.4, 138.8, 138.2, 136.2, 136.0, 133.8, 133.6, 132.8, 132.6, 132.2,131.4, 131.3, 129.8, 129.8, 129.6, 129.2, 128.6, 128.5, 128.3, 128.3, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.6, 127.6, 123.9, 123.8, 114.5, 114.2, 113.8, 113.6, 60.2, 59.9, 59.8, 56.7, 55.6, 55.3, 53.4, 33.7, 33.0, 14.2, 14.1; HRMS (ESI) calcd for $C_{35}H_{33}NO_5$ $[M+Na]^+$ 570.2256, found 570.2269.

(*E*)-Ethyl 5-(2,3-bis(4-chlorophenyl)-*N*-(4-methoxyphenyl)-3-oxopropanamido)-5-phenylpent-2-enoate 4d (*mixture of diastereomers in the ratio 2 : 1*). Bright brown oil. IR (film) ν_{max} 1708, 1359, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.68 (m, 4H), 6.85-7.39 (m, 25H), 6.77 (td, J = 8.9, 2.9 Hz, 2H), 6.63 (dd, J = 8.7, 2.6 Hz, 1H), 6.45-6.57 (m, 2H), 6.34 (t, J = 7.8 Hz, 1H), 6.15-6.25 (m, 1H), 6.10 (dd, J =; 8.8, 2.6 Hz, 1H), 6.00 (d, J = 15.8, 1H), 5.90 (d, J = 15.8 Hz, 1H), 5.75 (dd, J = 8.8, 2.6, 1H), 5.18 (s, 1H), 5.09 (s, 1H), 4.15-4.27 (m, 4H), 3.75 (s, 3H), 3.74 (s, 3H), 2.53-3.02 (m, 4H), 1.32 (t, J = 7.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4, 192.3, 168.3, 168.1, 166.0, 159.8, 159.7, 144.4, 144.3, 139.5, 138.7, 138.2, 134.4, 133.9, 132.6, 132.2, 132.0, 131.8, 131.2, 131.1, 129.5, 129.0, 128.8, 128.8, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 124.0, 123.9, 114.6, 114.3, 114.1, 113.9, 60.4, 59.3, 59.1, 56.9, 55.8, 55.4, 33.6, 33.0, 14.2; HRMS (ESI) calcd for $C_{35}H_{31}Cl_2NO_5$ $[M+Na]^+$ 638.1477, found 638.1485.

(*E*)-Ethyl 5-(*N*-(4-methoxyphenyl)-2-methyl-3-oxobutanamido)-5-phenylpent-2-enoate 4e (*mixture of diastereomers in the ratio 1.5 : 1*). Bright brown oil. IR (CCl_4) ν_{max} 2983, 2959, 2937, 1725, 1656, 1510, 1455, 1389, 1341, 1295, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.83-7.33 (m, 16H), 6.59-6.62 (m, 2H), 6.28-6.39 (m, 2H), 5.85-6.09 (m, 4H), 4.17 (q, J = 7.1 Hz, 4H), 3.79 (s, 6H), 3.19 (q, J = 7.0 Hz, 2H), 3.15 (q, J = 7.0 Hz, 2H), 2.60-2.94 (m, 4H), 2.05 (s, 3H), 1.90 (s, 3H), 0.88-1.49 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.3, 204.3, 171.3, 171.2, 166.1, 166.1, 159.5, 144.7, 144.5, 138.6, 138.6, 131.8, 131.7, 130.9, 129.8, 128.4, 128.3, 128.0, 128.0, 123.9, 123.8, 114.4, 114.4, 114.2, 114.2, 60.3, 55.8, 55.7, 55.3, 52.2, 52.1, 33.4, 33.2, 28.0, 27.9, 14.1, 13.8, 13.6; HRMS (ESI) calcd for $C_{25}H_{29}NO_5$ $[M+H]^+$ 424.2124, found 424.2122.

One pot procedure for preparation of 2-oxopiperidines 5a-c.

*Approach **A**:* A mixture of δ-amino ester **1a** (0.3-0.7 mmol, 1 equiv), diazo compound **2a,b** or **3d-e** (0.34-1.2 mmol, 1.1-1.8 equiv) and NaH (2 equiv) in 4-12 ml of toluene (or trifluorotoluene) was refluxed for 2-19 h (monitoring by TLC, reaction time depends on the stability of diazo compounds **2**,**3**). Reaction mixture was separated by silica gel flash chromatography (eluent: hexan-acetone 20:1→2:1) to give 2-oxopiperidines **5a-d** as a mixture of diastereomers. Pure isomers were isolated using preparative TLC. (The detailed description of these experiments is given in ESI,† p3-4).

*Approach **B**:* A solution of δ-amino ester **1a** (0.2-0.7 mmol, 1 equiv), diazo compound **2a, 3e** (0.9-0.2 mmol, 1.2 equiv) in trifluorotoluene (3-8 ml) was refluxed for 2-16 h until full conversion of aminoester **1a** (monitoring the process by TLC, reaction time depends on the stability of diazo compound **2, 3**), whereupon 2 equiv were added to reaction mixture and it was refluxing for 5 h more. Reaction mixture was separated by silica gel flash chromatography (eluent: hexane-acetone 20:1→2:1) to give 2-oxopiperidines **5a,c** as a mixture of diastereomers. Pure isomers were isolated using preparative TLC. (The detailed description of these experiments is given in ESI,† p3-4).

(*3R*,4R*,6S)-Methyl 4-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-3-methyl-2-oxo-6-phenylpiperidine-3-carboxylate 5a (*anti*-5a)**. Colorless oil. IR (CCl_4) ν_{max} 2997, 2953, 1746, 1659, 1511, 1466, 1443, 1397, 1320, 1294, 1249 cm^{-1}; NMR (400 MHz, $CDCl_3$) δ 7.06-7.22 (m, 5H), 6.90 (d, J = 9.0 Hz, 2H), 6.67 (d, J = 9.0 Hz, 2H), 4.97 (dd, J = 11.4, 5.2 Hz, 1H), 4.05-4.18 (m, 2H), 3.75 (s, 3H), 3.66 (s, 3H), 3.18-3.32 (m, 1H), 2.14-2.34 (m, 3H), 1.95 (td, J = 13.4, 11.7 Hz, 1H), 1.65 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 171.6, 171.6, 157.9, 140.8, 133.1, 128.9, 128.5, 127.8, 127.3, 113.9, 64.9, 60.8, 55.2, 52.8, 35.5, 35.3, 34.5, 16.6, 14.1; HRMS (ESI) calcd for $C_{25}H_{29}NO_6$ $[M+H]^+$ 440.2073, found 440.2067.

(*3S*,4S*,6S)-Methyl 4-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-3-methyl-2-oxo-6-phenylpiperidine-3-carboxylate 5a (*anti*-5'a)**. Colorless oil. NMR (400 MHz, $CDCl_3$) δ 7.18-7.45 (m, 5H), 7.05 (d, J = 9.0 Hz, 2H), 6.75 (d, J = 9.0 Hz, 2H), 4.99 (dd, J = 5.7, 3.9 Hz, 1H), 3.90-4.08 (m, 2H), 3.86 (s, 3H), 3.71 (s, 3H), 3.10 (ddd, J = 11.1, 7.6, 4.3 Hz, 1H), 2.15-2.45 (m, 3H), 1.91-2.06 (m, 1H), 1.54 (s, 3H), 1.05 (t, J = 7.1 Hz, 3H); HRMS (ESI) calcd for $C_{24}H_{21}NO_2$ $[M+H]^+$ 440.2073, found 440.2067.

(*3S*,4R*,6S)-Ethyl 4-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-2-oxo-3,6-diphenylpiperidine-3-carboxylate (*anti*-5b)**. Colorless oil; IR (film) ν_{max} 1727, 1720, 1652, 1509, 1361, 1292, 1242, 1217, 1167 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.4 Hz, 2H), 7.48 (t, J =7.7 Hz, 2H), 7.39 (t, J = 7.3 Hz, 1H), 7.08-7.23 (m, 5H), 7.00 (d, J = 8.9 Hz, 2H), 6.73 (d, J = 8.9 Hz, 2H), 5.01 (dd, J = 11.8, 5.1 Hz, 1H), 4.21-4.35 (m, 2H), 4.01-4.21 (m, 2H), 3.70 (s, 3H), 3.64-3.72 (m, 1H), 2.62 (dd, J = 15.7, 2.7 Hz, 1H), 2.15 (dd, J = 15.8, 11.4 Hz, 1H), 2.05 (ddd, J = 13.9, 5.1, 2.1 Hz, 1H), 1.77 (dd, J = 25.8, 12.9 Hz, 1H), 1.19-1.36 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 170.4, 169.1, 158.1, 140.3, 135.6, 133.5, 130.6, 128.9, 128.5, 127.8, 114.1, 66.1, 66.0, 62.1, 60.8, 55.3, 36.9, 36.8, 33.1, 14.2, 14.0; HRMS (ESI) calcd for $C_{31}H_{33}NO_6$ $[M+H]^+$ 516.2381, found 516.2383.

(*3R*,4S*,6S)-Ethyl 4-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-2-oxo-3,6-diphenylpiperidine-3-carboxylate (*anti*-5'b)**. Colorless oil. IR (CCl_4) ν_{max} 1727, 1714, 1646, 1510, 1296, 1242 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.52 (m, 2H), 7.31-7.46 (m, 8H), 7.21 (d, J = 9.0 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 5.14 (dd, J = 6.0, 3.6 Hz, 1H), 4.36-4.50 (m, 2H), 3.81-3.99 (m, 2H), 3.75 (s, 3H), 3.57-3.66 (m, 1H), 3.43 (dd, J = 15.2, 3.8 Hz, 1H), 2.17-2.35 (m, 1H), 1.84-2.01 (m, 2H), 1.45 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 170.6, 168.7, 158.1, 141.1, 135.5, 134.5, 130.1, 128.5, 128.4, 128.3, 127.7, 127.6, 127.5, 127.0, 114.2, 63.7, 62.1, 60.5, 55.3, 36.7, 33.5, 32.4, 14.1, 13.9; HRMS (ESI) calcd for $C_{31}H_{33}NO_6$ $[M+H]^+$ 516.2381, found 516.2379.

Ethyl 2-(7-(4-methoxyphenyl)-1,6-dioxo-8-phenyl-7-azaspiro[4.5]decan-10-yl)acetate 5d *(mixture of cis- [8S*,10R*] and trans- [8S*,10S*] isomers in ratio 1.1 : 1.0)*. Bright yellow oil. IR (film) ν_{max} 1726, 1631, 1604, 1510, 1294, 1238, 1162 cm^{-1}; NMR (400 MHz, $CDCl_3$) δ 7.24-7.38 (m, 4H), 7.04-7.23 (m, 6H), 6.97 (d, J = 8.9 Hz, 2H), 6.84 (d, J = 8.9 Hz, 2H), 6.71 (d, J = 9.0 Hz, 2H), 6.65 (d, J = 8.9 Hz, 2H), 4.97 (t, J = 5.3 Hz, 1H), 4.88 (dd, J = 11.4, 5.5 Hz, 1H), 4.04-4.21 (m, 2H), 3.86 (m, 2H), 3.67 (s, 3H), 3.64 (s, 3H), 3.09-3.22 (m, 1H), 2.94-3.06 (m, 1H), 1.78-2.74 (m, 20H), 1.24 (t, J = 7.1 Hz, 3H), 1.01 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.7, 216.2, 172.4, 171.2, 171.1, 171.1, 158.0, 157.9, 140.9, 140.6, 134.0, 132.8, 128.9, 128.4, 128.4, 128.3, 127.7, 127.5, 127.3, 127.2, 114.0, 113.9, 65.0, 63.3, 60.7, 60.6, 59.7, 59.4, 55.2, 55.1, 39.6,

39.1, 35.7, 35.7, 35.3, 33.5, 33.2, 31.5, 30.9, 30.8, 19.7, 19.6, 14.1, 13.8; HRMS (ESI) calcd for $C_{26}H_{29}NO_5$ $[M+Na]^+$ 458.1938, found 458.1941.

Ethyl 2-((3S*,4R*,6S*)-3-acetyl-1-(3,4-dimethoxyphenyl)-3-methyl-2-oxo-6-phenylpiperidin-4-yl)acetate (*anti*-5c). Brown oil. IR (film) ν_{max} 2979, 2932, 2837, 1712, 1637, 1595, 1511, 1230, 1160 cm^{-1}; NMR (400 MHz, $CDCl_3$) δ 6.93-7.43 (m, 5H), 6.68 (d, J = 8.5 Hz, 1H), 6.59 (dd, J = 8.5, 2.2 Hz, 1H), 6.37 (d, J = 2.2 Hz, 1H), 4.96 (dd, J = 11.4, 5.3 Hz, 1H), 4.07-4.16 (m, 2H), 3.76 (s, 3H), 3.65 (s, 3H), 2.89-3.20 (m, 1H), 2.28 (s, 3H), 1.90-2.38 (m, 4H), 1.58 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.0, 172.3, 171.8, 148.7, 147.7, 140.4, 133.2, 128.5, 128.0, 127.4, 119.6, 112.0, 110.8, 65.3, 60.9, 59.6, 55.8, 34.9, 34.4, 33.7, 26.7, 15.9, 14.1; HRMS (ESI) calcd for $C_{26}H_{31}NO_6$ $[M+Na]^+$ 476.2044, found 476.2041.

Ethyl 2-((3R*,4S*,6S*)-3-acetyl-1-(3,4-dimethoxyphenyl)-3-methyl-2-oxo-6-phenylpiperidin-4-yl)acetate (*anti*-5'c). Brown oil. NMR (400 MHz, $CDCl_3$) δ 7.17-7.40 (m, 5H), 6.71 (d, J = 8.6 Hz, 1H), 6.65 (dd, J = 8.5, 2.2 Hz, 1H), 6.54 (d, J = 2.2 Hz, 1H), 4.96 (t, J = 5.4 Hz, 1H), 3.86-4.17 (m, 2H), 3.78 (s, 3H), 3.70 (s, 3H), 2.92-3.19 (m, 1H), 2.45 (s, 3H), 2.11-2.38 (m, 3H), 1.92-2.10 (m, 1H), 1.52 (s, 3H), 1.10 (t, J = 7.1 Hz, 1H); HRMS (ESI) calcd for $C_{26}H_{31}NO_6$ $[M+Na]^+$ 476.2044, found 476.2041.

One pot procedure for preparation of 5,6-dihedropyridin-2(1*H*)-ones 6a-f:

A mixture of amino ester **1a-d** (0.2-0.7 mmol, 1equiv), diazo compound **2b,3a-d** (0.2-0.8 mmol, 1.1 equiv) and NaH (2 equiv) in 5-12 ml of toluene was refluxed for 2.5 h. Reaction mixture was separated by silica gel flash chromatography (eluent: hexane-acetone 10:1→2:1) to afford 5,6-dihedropyridin-2(1*H*)-ones **6a-f**. (The detailed description of these experiments is given in ESI,† p 4-5).

1-(4-Methoxyphenyl)-3,6-diphenyl-5,6-dihydropyridin-2(1*H*)-one 6a. Colorless solid, m.p. 179-180 °C. IR (CCl_4) ν_{max} 1668, 1631, 1511, 1425, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 7.1 Hz, 2H), 7.23-7.43 (m, 8H), 7.19 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 6.49 (dd, J = 6.3, 1.8 Hz, 1H), 5.11 (d, J = 5.7 Hz, 1H), 3.75 (s, 3H), 3.38 (ddd, J = 17.6, 7.1, 2.6 Hz, 1H), 2.74 (ddd, J = 17.6, 6.4, 2.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 141.0, 136.7, 135.3, 133.4, 128.7, 128.6, 127.9, 127.7, 127.5, 127.3, 126.6, 114.0, 62.9, 55.4, 33.0; HRMS (ESI) calcd for $C_{24}H_{21}NO_2$ $[M+H]^+$ 356.1651, found 356.1648.

3-(4-Chlorophenyl)-1-(4-methoxyphenyl)-6-phenyl-5,6-dihydropyridin-2(1*H*)-one 6b. Colorless solid, m.p. 177-179 °C. IR (film) ν_{max} 1659, 1509, 1492, 1247 cm^{-1}; NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.5 Hz, 2H), 7.24-7.39 (m, 7H), 7.16 (d, J = 9.0 Hz, 2H), 6.81 (d, J = 9.0 Hz, 2H), 6.46-6.53 (m, 1H), 5.10 (d, J = 5.4 Hz, 1H), 3.75 (s, 3H), 3.37 (ddd, J = 17.7, 7.1, 2.7 Hz, 1H), 2.74 (ddd, J = 17.7, 6.5, 2.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 157.9, 140.8, 136.1, 135.1, 135.1, 133.8, 133.7, 130.0, 128.7, 128.0, 127.7, 127.3, 126.5, 114.1, 62.9, 55.4, 33.1; HRMS (ESI) calcd for $C_{24}H_{20}ClNO_2$ $[M+Na]^+$ 412.1075, found 412.1072.

(*E*)-3-(4-chlorophenyl)-6-styryl-5,6-dihydropyridin-2(1*H*)-one 6c. Bright yellow oil. IR (film) ν_{max} 1658, 1509, 1491, 1248 cm^{-1}; NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.5 Hz, 2H), 7.09-7.37 (m, 9H), 6.88 (d, J = 9.0 Hz, 2H), 6.66 (dd, J = 6.5, 2.4 Hz, 1H), 6.49 (d, J = 15.9 Hz, 1H), 6.37

(dd, J = 15.8, 6.9 Hz, 1H), 4.35-4.67 (m, 1H), 3.79 (s, 3H), 3.05-3.29 (m, 1H), 2.64 (ddd, J = 17.8, 6.2, 2.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 158.1, 136.1, 135.8, 135.1, 134.9, 134.5, 133.7, 132.3, 130.1, 128.7, 128.1, 128.0, 128.0, 127.7, 126.5, 114.2, 61.7, 55.4, 31.0; HRMS (ESI) calcd for $C_{26}H_{22}ClNO_2$ $[M+Na]^+$ 438.1231, found 438.1230.

3-(4-Chlorophenyl)-1-(4-methoxyphenyl)-6-(*o*-tolyl)-5,6-dihydropyridin-2(1*H*)-one 6d. Bright yellow oil. IR (film) ν_{max} 1658, 1510, 1491, 1241 cm^{-1}; NMR (400 MHz, $CDCl_3$) δ 7.41-7.53 (m, 3H), 7.32 (d, J = 8.5 Hz, 2H), 7.09-7.23 (m, 5H), 6.80 (d, J = 9.0 Hz, 2H), 6.29-6.50 (m, 1H), 5.30 (d, J = 6.9 Hz, 1H), 3.74 (s, 3H), 3.34 (ddd, J = 17.7, 7.6, 2.7 Hz, 1H), 2.64 (ddd, J = 17.7, 6.5, 2.1 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 157.9, 138.3, 135.7, 135.3, 135.0, 134.1, 133.7, 131.2, 130.0, 129.0, 128.0, 127.6, 127.2, 126.5, 126.1, 114.1, 59.7, 55.3, 30.9, 19.1; HRMS (ESI) calcd for $C_{25}H_{22}ClNO_2$ $[M+H]^+$ 404.1417, found 404.1414.

1-(4-Methoxyphenyl)-6-phenyl-3-(*p*-tolyl)-5,6-dihydropyridin-2(1*H*)-one 6e. Bright yellow oil. IR (film) ν_{max} 1658, 1511, 1410, 1305, 1243, 1227, 1167 cm^{-1}; NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.0 Hz, 2H), 7.23-7.37 (m, 5H), 7.07-7.23 (m, 4H), 6.81 (d, J = 8.9 Hz, 2H), 6.46 (dd, J = 6.2, 2.0 Hz, 1H), 5.09 (d, J = 5.6 Hz, 1H), 3.75 (s, 3H), 3.37 (ddd, J = 17.5, 7.0, 2.6 Hz, 1H), 2.72 (ddd, J = 17.6, 6.4, 2.2 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 157.7, 141.1, 137.4, 136.9, 135.4, 133.8, 132.6, 128.6, 128.5, 127.5, 127.3, 126.6, 114.0, 62.9, 55.4, 33.0, 21.1; HRMS (ESI) calcd for $C_{25}H_{23}NO_2$ $[M+Na]^+$ 392.1621, found 392.1620.

1-(3,4-Dimethoxyphenyl)-3-methyl-6-phenyl-5,6-dihydropyridin-2(1*H*)-one 6f. Bright brown oil. IR (film) ν_{max} 2919, 2834, 1669, 1630, 1594, 1511, 1448, 1424, 1410, 1233, 1210, 1171 cm^{-1}; NMR (400 MHz, $CDCl_3$) δ 7.10-7.40 (m, 5H), 6.50-6.87 (m, 3H), 6.17 (d, J = 5.8 Hz, 1H), 4.97 (dd, J = 7.1, 2.3 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.00-3.24 (m, 1H), 2.40-2.66 (m, 1H), 1.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 148.7, 147.3, 141.4, 135.6, 132.4, 131.2, 128.5, 127.5, 126.7, 118.0, 110.9, 110.6, 63.2, 55.9, 55.8, 32.7, 17.2; HRMS (ESI) calcd for $C_{20}H_{21}NO_3$ $[M+Na]^+$ 346.1419, found 346.1422.

Reaction of amino ester 1 with diazoacetylacetone 3c:

A mixture of δ-amino ester **1a** (0.47 mmol, 1 equiv), diazo compound **3c** (0.56 mmol, 1.2 equiv) and 40 mg of NaH (60% dispersion in mineral oil; 2 eq) was refluxed in 10 ml of toluene during 2.5 h. Reaction mixture was separated by silica gel flash chromatography (eluent: hexane-acetone 10:1→1:1) to afford isoquinolinedione **7a** in the yield of 126 mg (71%, mixture of 2 isomers in the ratio 7 : 1).

(3*S,4a*R**,8a*S**)-8-hydroxy-2-(4-methoxyphenyl)-8a-methyl-3-phenyl-3,4,4a,5-tetrahydroisoquinoline-1,6(2*H*,8a*H*)-dione 7a**. Colorless solid, m.p. - 191-193 °C. IR (film) ν_{max} 3463, 2944, 2836, 1708, 1630, 1608, 1557, 1508, 1456, 1425; 1411, 1243, 1216 cm^{-1}; NMR (400 MHz, $CDCl_3$) δ 12.22 (s, 1H), 6.98-7.35 (m, 5H), 6.85 (d, J = 8.9 Hz, 2H), 6.73 (d, J = 8.9 Hz, 2H), 5.48 (s, 1H), 4.90 (dd, J = 10.9, 6.7 Hz, 1H), 3.70 (s, 3H). 2.93 (tdd, J = 12.2, 6.0, 3.7 Hz, 1H), 2.05-2.55 (m, 4H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.1, 180.3, 176.6, 158.6, 139.4, 131.7, 128.9, 128.5, 128.4, 127.3, 114.3, 105.3, 65.9, 55.3, 41.8, 38.7, 35.8, 33.7, 21.4; HRMS (ESI) calcd for $C_{23}H_{23}NO_4$ $[M+H]^+$ 378.1700, found 378.1696.

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