# MICROWAVE-ASSISTED [3 + 2] CYCLOADDITIONS OF AZOMETHINE YLIDES WITH (*E*)-4-ARYLIDENE-*N*-PHENYL-(2*H*)-ISOQUINOLINE-1,3-DIONE

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**ABSTRACT:** New spiro-compounds basis of isoquinoline-1,3-dione were prepared by microwave-assisted 1,3-dipolar cycloaddition reactions with azomethine ylides. The reactions performed under microwaves were compared with the same reactions conducted under the classical conditions of thermal heating.

**Keywords:** Isoquinoline-1,3-dione, 1,3-dipolar cycloaddition, microwave, Azomethine ylides.

**RÉSUMÉ:** Ce travail a porté sur la synthèse de nouveaux composés spiranique à base d'isoquinoléine-1,3-diones via une cycloaddition 1,3-dipolaire avec des ylures d'azométhines par irradiation aux micro-ondes. Les rendements des réactions effectuées sous micro-ondes ont été comparés avec ceux des réactions réalisées par chauffage thermique.

**Mots clés:** Isoquinoléine-1,3-dione, Cycloaddition 1,3-dipolaire, Micro-ondes, Ylures d'azométhines.

## INTRODUCTION

1,3-Dipolar cycloadditions represent one of the most versatile tools for the construction of five-membered heterocycles [1]. The chemistry of azomethine ylides has gained significance in recent years as it serves as an important route for the construction of nitrogen containing five-membered heterocycles, which are often central ring systems of numerous natural products [2].

Imines derived from *N*-substituted aminoesters can be isomerized to azomethine ylides [3] that undergo 1,3-dipolar cycloadditions with dipolarophiles to afford pyrrolidine derivatives [4]. The effective and eco-friendly microwave methodology to generate azomethine ylides from *N*-substituted aminoesters imines avoids harsh reaction conditions and the use of silver or lithium salts [5]. By the classical heating in the absence of a Lewis acid catalyst, these cycloadditions can require long reaction times and high temperatures to afford moderate yields [6].

The microwave technique has several advantages [7-10] over traditional methods of synthesis. Reduced reaction times, less effect on the environment, solvent and waste minimization and better reaction yields are some of the common advantages of using microwaves.

In the present paper, we describe the use of domestic microwave conditions for the condensation of (*E*)-4-arylidene-*N*-phenyl-(2*H*)-isoquinoline-1,3-dione with *N*-substituted aminoesters. The cycloaddition reaction involves a polar 1,3-dipole intermediate. We therefore reasoned that, as such, the reaction should be well suited for this mode of activation [11]. Since our objective was to explore the influence of the microwaves on the reaction as opposed to simple heating, parallel comparative reactions were performed.

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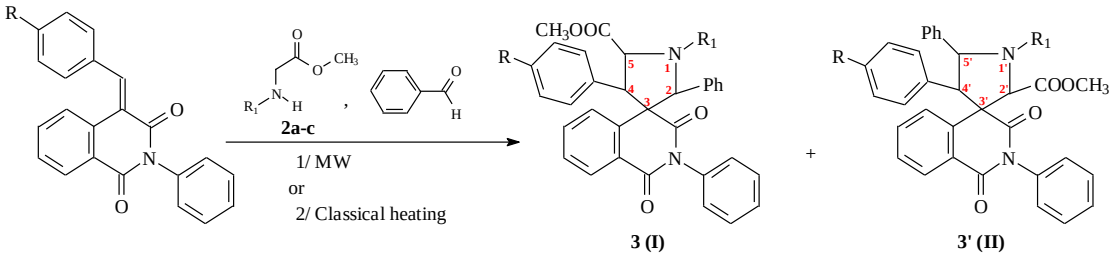
## RESULTS AND DISCUSSION

The *(E)*-4-arylideneisoquinoline-1,3-diones derivatives **1a-d** were obtained by the condensation of different aromatic aldehydes with *N*-phenylhomophthalimide in dry chloroform and in the presence of piperidine as catalyst [12].

The *N*-substituted aminoesters **2a-c** needed for the proposed reactions were synthesized using protocols described in the literature [13].

The condensation of compounds **1a-d** with azomethine ylides generated *in situ* by reacting benzaldehyde with *N*-substituted aminoesters **2a-c** was performed by two different protocols.

In the first instance (conditions 1) the reactions submitted to microwave irradiation [14] at 700 W and the second (conditions 2) was performed by heating the mixture in a preheated oil bath at 130 °C. A minimal amount of nonpolar solvent (xylene) was added to ensure thorough contact between the components (Scheme 1). In all cases, the evolution of the reaction was monitored by thin-layer chromatography (TLC). The cycloaddition afforded a mixture of two regioisomeric spiro-isoquinoline-1,3-dione.




**1a-d : R = H , $CH_3$ , $OCH_3$ , Br** **2a-c : $R_1$ = *i*Bu , B*n* , Furfuryl**

Conditions : 1/ Mw : minimal xylene, microwave irradiation
2/ Classical heating : minimal xylene, heat in a preheated oil bath at 130°C

**Scheme 1.** [3 + 2] Cycloadditions of Azomethine Ylides **2a-c** with (*E*)-4-arylidene-*N*-phenyl-(2*H*) isoquinoline-1,3-dione **1a-d**.

The product ratios were also established by $^1$H NMR of the crude reaction mixture. These ratios were determined by the integration of the pyrrolidine protons $H_2$, $H_4$ and $H_5$ signals in the NMR spectra (Table I). When attempts to isolate them were carried out, we could not achieve their full preparative separation on the column and only the major one was isolated.

**Table I.** Results for the cycloaddition in microwave oven.

| Entry | compound | R | $R_1$ | Reaction time [min] | Product ratio 3 : 3'[a] | Overall yield (%) |
|---|---|---|---|---|---|---|
| **1** | 3aa-3'aa | H | *i*Bu | 30 | 60.2 : 39.8 | 80 |
| **2** | 3ba-3'ba | $CH_3$ | *i*Bu | 40 | 64.8 : 35.2 | 70 |
| **3** | 3ca-3'ca | $OCH_3$ | *i*Bu | 40 | 70.5 : 29.5 | 65 |
| **4** | 3da-3'da | Br | *i*Bu | 30 | 74.0 : 26.0 | 73 |
| **5** | 3ab-3'ab | H | Bn | 35 | 66.6 : 33.4 | 82 |
| **6** | 3bb-3'bb | $CH_3$ | Bn | 30 | 65.2 : 34.8 | 79 |
| **7** | 3cb-3'cb | $OCH_3$ | Bn | 35 | 69.3 : 30.7 | 74 |
| **8** | 3db-3'db | Br | Bn | 30 | 70.1 : 29.9 | 83 |
| **9** | 3ac-3'ac | H | Furfuryl | 30 | 62.5 : 37.5 | 71 |
| **10** | 3bc-3'bc | $CH_3$ | Furfuryl | 40 | 65.5 : 34.5 | 68 |
| **11** | 3cc-3'cc | $OCH_3$ | Furfuryl | 35 | 67.0 : 33.0 | 65 |
| **12** | 3dc-3'dc | Br | Furfuryl | 35 | 68.8 : 31.2 | 80 |

[a] determined by $^1$H NMR

According to the literature,[12a] the cycloaddition with the same dipolarophile gives rise to two regioisomers and not a mixture of diastereoisomers. This behavior can be explained by the fixed geometry of dipolarophile, only the stereoisomer (*E*). On the other hand, the presence of the only two regioisomers reflects the orientation of the substituents in the 1,3-dipole reacting in the cycloaddition step, which displays a *s-trans* orientation of the methoxycarbonyl with respect to the substituent on the nitrogen atom, this was mentioned in the review of I. Coldham et al.,[15] the S-shaped ylide geometry is often favored using secondary amino esters and aldehydes. This confirms the obtaining of the two regioisomers.

The cycloadducts **3** and **3'** present respectively four new chiral centers, i.e the quaternary spiroatom $C_3$, $C_2$, $C_4$ and $C_5$ of pyrrolidine ring. The relative stereochemistry of these carbon results from preservation of the (*E*) configuration of the initial olefin and the *s-trans* orientation of the azomethine ylide.

The structure of **3** and **3'** was elucidated with using the NMR spectroscopic data. Thus, the $^1$H NMR spectrum of regioisomer **3ba** shows a signal at 4.39 ppm (d, $H_5$, J = 10.8Hz), 4.55 ppm (d, $H_4$, J = 10.8Hz) and 4.89 ppm (s, $H_2$). The larger coupling (10.8 Hz) for the protons $H_4$ and $H_5$ indicates that they are *trans*. The $^{13}$C NMR data also confirmed this result. Finally the X-ray crystal structure analysis of the product confirms the assigned structure (figure 1).

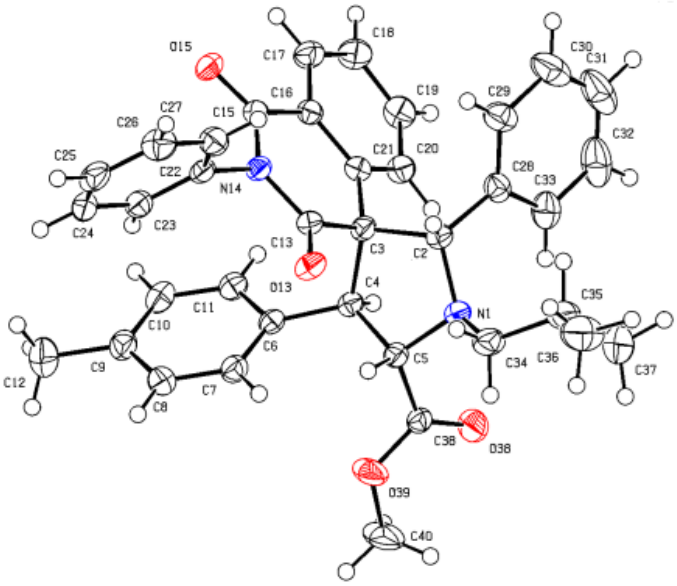



**Figure 1.** X-ray crystallographic structure of **3ba**.

The other regioisomer **3'ba** exhibited peaks at 4.64 ppm (d, $H_{5'}$, J = 7.5Hz), 4.92 ppm (s, $H_{2'}$) and 5.03 ppm (d, $H_{4'}$, J = 7.5Hz), which are in good agreement with the proposed structure. The $^{13}$C spectrum of the product accords with this expectation.

The spirocarbon resonance of all adducts was between 63.9 and 67.4 ppm. This value also supported the literature reports [16,17].

Three reactions were performed under the classical conditions of thermal heating in xylene and were compared with the same reactions under microwaves. The results are presented in table II. The reactions under microwave are significantly faster and the yield is almost quantitative after 30 - 40 minutes. The yields obtained after 2 days were comprised between 45% and 50%. The regioselectivity, is better under the microwave conditions.

**Table II.** Comparison of the reaction yields of cycloaddition under different reaction conditions. (Entry **1**,**7** and **8**).

| Entry | Compound | R | $R_1$ | Yields and ratio[a] with microwave (≈ 30 min) | Yields and ratio[a] with thermal heating (≈ 2 days) |
|---|---|---|---|---|---|
| **1** | 3aa-3'aa | H | *i*Bu | 80% (60.2 : 39.8) | 45% (60.0 : 40.0) |
| **7** | 3cb-3'cb | $OCH_3$ | Bn | 74% (69.3 : 30.7) | 48% (61.3 : 38.7) |
| **8** | 3db-3'db | Br | Bn | 83% (70.1 : 29.9) | 50% (62.7 : 37.3) |

[a] determined by $^1$H NMR

## CONCLUSION

In this part we have synthesized a series of new spiro-isoquinoline-1,3-dione taking advantage of the complementarity of the eco-friendly microwave technology. Compared to the classical method (thermal heating) the microwave-assisted reaction is faster and gives higher yields. The process reported herein can be considered as a "green chemistry" method.

## EXPERIMENTAL

### General

All reactions were monitored by TLC Merck 60F-254 silica gel plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (70-230 mesh) using ethyl acetate and cyclohexane mixture as eluents. Melting points were determined on an Electrothermal 9002 apparatus and are uncorrected. NMR spectra were recorded on a BRÜKER AC-300 spectrometer [300 MHz ($^1$H) and 75 MHz ($^{13}$C)]. All chemical shifts were reported as δ values (ppm) relative to internal tetramethylsilane. IR spectra (KBr) were recorded on a FTIR-8400 SHIMADZU spectrophotometer. High resolution mass spectra (HR-MS) were obtained on a Waters Micromass Q-Tof Micro instrument. Microwave irradiation was carried out in a microwave oven Whirlpool Easytronic MD115 (900 W, 2.450 MHz). The crystal data for $C_{37}H_{36}N_2O_4$ were recorded on a Bruker APEX-II CCD area-detector diffractometer, M= 572.68, Triclinic, P-1, a = 9.5823(3) Å, b = 12.6045(3) Å, c = 14.7249(4) Å, α = 106.3590(10), β = 101.0640(10), γ =109.9110(10), V = 1520.62(7) Å$^3$, Z = 2, $D_c$ = 1.251 mg/m$^3$, X-ray source Mo Kα (radiation), k = 0.71073 Å, F(000) = 608.0, T = 150 K, colorless plates 0.22 × 0.20 × 0.06 mm. The structure was worked out by direct methods and refined anisotropically using a full-matrix with least squares based on $F^2$ to give R1 = 0.0420, wR2 = 0.1124 for 5292 independent observed reflections and 392 parameters. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as a supplementary publication number CCDC 863992.

The (*E*)-4-arylidene-*N*-phenyl-(2*H*)-isoquinoline-1,3-dione **1** [12] and the *N*-substituted aminoesters **2** [13] were prepared according to the literature procedures.

***General Method for the Preparation of spiro-isoquinoline-1,3-dione : Microwave – Assisted Cycloaddition.***

The reaction under microwave is carried out in Pyrex glass tubes of 2 cm in diameter which are placed in hot areas. These latter have been determined to be using a mapping according to the technique described by Villemin [18].

The (*E*)-4-arylidene-*N*-phenyl-(2*H*)-isoquinoline-1,3-dione **1a-d** (1.0 mmol) was mixed with *N*-substituted aminoesters **2a-c** (2.0 mmol) and benzaldehyde (1.0 mmol). The mixture was homogenized with a minimal of xylene (1mL) in a Schlenk tube, placed in the microwave oven at 700 W. The reaction temperature (153°C) was controlled by a thermocouple immersed into the reaction mixture. The progress of the reaction was monitored by TLC; after irradiating the reaction mixture for 30 - 40 min (5 min at a time with 10 s interval). The crude residue was purified by column chromatography [$SiO_2$ / Cyclohexane : Ethyl acetate (90:10)].

**Methyl-1'-isobutyl-1,3-dioxo-2,2',4'-triphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-5'-carboxylate (3aa)**

Obtained as yellow solid; mp = 81-83 °C; Rf = 0.36 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 0.85 (d, $CH_3$-*i*Bu), 1.07 (d, $CH_3$-*i*Bu), 1.67 (m, CH-*i*Bu), 2.53 (dd, $CH_2$-*i*Bu), 3.78 (s, $OCH_3$), 4.55 (d, $H_5$, J= 10.8Hz), 4.89 (d, $H_4$, J= 10.8Hz), 4.94 (s, $H_2$), 6.23-8.12 (m, 19$H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 21.1(2$CH_3$-*i*Bu), 26.9 (CH-*i*Bu), 52.1 ($OCH_3$), 59.5 ($CH_2$-*i*Bu), 64.0 ($C_4$), 65.4 ($C_3$), 70.4 ($C_5$), 80.8 ($C_2$), 125.1-140.0 ($C_{arom}$), 163.2 (CO), 164.5 (CO), 170.7 (CO); HRMS Calcd for $C_{36}H_{34}N_2O_4$ $[M+H]^+$: 558.2518, Found: 558.2525.

**Methyl-1'-isobutyl-1,3-dioxo-2,4',5'-triphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-2'-carboxylate (3'aa)**

Obtained as yellow solid; mp = 84-86 °C; Rf = 0.34 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 0.79 (d, $CH_3$-*i*Bu), 1.12 (d, $CH_3$-*i*Bu), 1.85 (m, CH-*i*Bu), 2.66 (m, $CH_2$-*i*Bu), 3.84 (s, $OCH_3$), 4.70 (d, $H_{5'}$, J= 7.5 Hz), 5.24 (s, $H_{2'}$), 5.51 (d, $H_{4'}$, J= 7.5 Hz), 6.22-8.13 (m, 19$H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 20.8(2$CH_3$-*i*Bu), 26.6 (CH-*i*Bu), 52.0 ($OCH_3$), 59.5 ($CH_2$-*i*Bu), 63.6 ($C_{4'}$), 64.8 ($C_{3'}$), 70.4 ($C_{5'}$), 82.5 ($C_{2'}$), 123.8-144.4 ($C_{arom}$), 162.2 (CO), 164.5 (CO), 170.8 (CO); HRMS Calcd for $C_{36}H_{34}N_2O_4$ $[M+H]^+$: 558.2518, Found: 558.2523.

**Methyl-1'-isobutyl-4'-(4-methylphenyl)-1,3-dioxo-2,2'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-5'-carboxylate (3ba)**

Obtained as yellow solid; mp = 82-84 °C; Rf = 0.37 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 0.84 (d, $CH_3$-*i*Bu), 1.07 (d, $CH_3$-*i*Bu), 1.66 (m, CH-*i*Bu), 2.31 (s, $CH_3$), 2.68 (m, $CH_2$-*i*Bu), 3.70 (s, $OCH_3$), 4.39 (d, $H_5$, J= 10.8Hz), 4.55 (d, $H_4$, J= 10.8Hz), 4.89 (s, $H_2$), 6.54-8.06 (m, 18$H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 21.0(2$CH_3$-*i*Bu), 21.3 ($CH_3$), 27.3 (CH-*i*Bu), 51.9 ($OCH_3$), 59.5 ($CH_2$-*i*Bu), 63.6 ($C_4$), 65.2 ($C_3$), 70.5 ($C_5$), 80.6 ($C_2$), 123.8-140.3 ($C_{arom}$), 163.2 (CO), 164.5 (CO), 170.3 (CO); HRMS Calcd for $C_{37}H_{36}N_2O_4$ $[M+H]^+$: 572.2753, Found: 572.2762.

**Methyl-1'-isobutyl-4'-(4-methylphenyl)-1,3-dioxo-2,5'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-2'-carboxylate (3'ba)**

Obtained as yellow solid; mp = 87-89 °C; Rf = 0.35 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 0.76 (d, $CH_3$-*i*Bu), 1.09 (d, $CH_3$-*i*Bu), 1.83 (m, CH-*i*Bu), 2.26 (s, $CH_3$), 2.53 (m, $CH_2$-*i*Bu), 3.77 (s, $OCH_3$), 4.64 (d, $H_{5'}$, J= 7.5 Hz), 4.92 (s', $H_2$), 5.03 (d, $H_{4'}$, J= 7.5 Hz), 6.28-8.15 (m, 18$H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 20.8(2$CH_3$-*i*Bu), 21.3 ($CH_3$), 26.9 (CH-*i*Bu), 51.5 ($OCH_3$), 59.5 ($CH_2$-*i*Bu), 63.5 ($C_{4'}$), 65.6 ($C_{3'}$), 70.8 ($C_{5'}$), 82.4 ($C_{2'}$), 123.8-144.4 ($C_{arom}$), 162.2 (CO), 164.5 (CO), 170.8 (CO); HRMS Calcd for $C_{37}H_{36}N_2O_4$ $[M+H]^+$: 572.2753, Found: 572.2764.

**Methyl-1'-isobutyl-4'-(4-methoxyphenyl)-1,3-dioxo-2,2'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-5'-carboxylate (3ca)**

Obtained as yellow solid (50%); mp = 82-84 °C; Rf = 0.35 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 0.91 (d, $CH_3$-*i*Bu), 1.09 (d, $CH_3$-*i*Bu), 1.90 (m, CH-*i*Bu), 2.69 (m, $CH_2$-*i*Bu), 3.51 (s, $OCH_3$), 3.75 (s, $OCH_3$), 4.46 (d, $H_5$, J= 10.8Hz), 4.59 (d, $H_4$, J= 10.8Hz), 4.91 (s, $H_2$), 6.31-8.20 (m, 18$H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 21.1(2$CH_3$-*i*Bu), 27.0 (CH-*i*Bu), 52.0 ($OCH_3$), 55.1 ($OCH_3$), 58.7 ($CH_2$-*i*Bu), 63.0 ($C_4$), 65.8 ($C_3$), 70.4 ($C_5$), 80.1 ($C_2$), 113.3-157.3 ($C_{arom}$), 163.2 (CO), 164.5 (CO), 170.3 (CO); HRMS Calcd for $C_{37}H_{36}N_2O_5$ $[M+H]^+$: 588.2624, Found: 588.2628.

**Methyl-1'-isobutyl-4'-(4-methoxyphenyl)-1,3-dioxo-2,5'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-2'-carboxylate (3'ca)**

Obtained as yellow solid; mp = 80-82 °C; Rf = 0.34 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 0.86 (d, $CH_3$-*i*Bu), 1.13 (d, $CH_3$-*i*Bu), 1.66 (m, CH-*i*Bu), 2.56 (m, $CH_2$-*i*Bu), 3.51 (s, $OCH_3$), 3.82 (s, $OCH_3$), 4.74 (d, $H_{5'}$, J= 7.5 Hz), 4.97 (s, $H_{2'}$), 5.10 (d, $H_{4'}$, J= 7.5 Hz), 6.22-8.13 (m, 18$H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 21.3(2$CH_3$-*i*Bu), 27.0 (CH-*i*Bu), 51.9 ($OCH_3$), 55.1 ($OCH_3$), 58.7 ($CH_2$-*i*Bu), 63.2 ($C_{4'}$),

66.0 ($C_{3'}$), 70.5 ($C_{5'}$), 81.9 ($C_{2'}$), 113.3-157.3 ($C_{arom}$), 163.2 (CO), 164.5 (CO), 170.3 (CO); HRMS Calcd for $C_{37}H_{36}N_2O_5$ $[M+H]^+$: 588.2624, Found: 588.2621.

**Methyl-4'-(4-bromophenyl)-1'-isobutyl-1,3-dioxo-2,2'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-5'-carboxylate (3da)**

Obtained as yellow oil; Rf = 0.34 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 0.90 (d, $CH_3$-*i*Bu), 1.08 (d, $CH_3$-*i*Bu), 1.72 (m, CH-*i*Bu), 2.21 (m, $CH_2$-*i*Bu), 3.85 (s, $OCH_3$), 4.46 (d, $H_5$, J= 10.8Hz), 4.86 (d, $H_4$, J= 10.8Hz), 5.11 (s, $H_2$), 6.41-8.20 (m, $18H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 20.0 ($2CH_3$-*i*Bu), 26.9 (CH-*i*Bu), 52.1 ($OCH_3$), 58.9 ($CH_2$-*i*Bu), 63.8 ($C_4$), 65.6 ($C_3$), 69.1 ($C_5$), 80.4 ($C_2$), 119.5-140.3 ($C_{arom}$), 163.2 (CO), 164.5 (CO), 170.3 (CO); HRMS Calcd for $C_{36}H_{33}BrN_2O_4$ $[M+H]^+$: 636.1623, Found: 636.1629.

**Methyl-4'-(4-bromophenyl)-1'-isobutyl-1,3-dioxo-2,5'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-2'-carboxylate (3'da)**

Obtained as yellow oil; Rf = 0.32 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 0.85 (d, $CH_3$-*i*Bu), 1.12 (d, $CH_3$-*i*Bu), 1.64 (m, CH-*i*Bu), 2.62 (m, $CH_2$-*i*Bu), 3.88 (s, $OCH_3$), 4.65 (d, $H_{5'}$, J= 7.5 Hz), 4.94 (s, $H_{2'}$), 5.03 (d, $H_{4'}$, J= 7.5 Hz), 6.35-8.01 (m, $18H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 20.8($2CH_3$-*i*Bu), 26.9 (CH-*i*Bu), 51.8 ($OCH_3$), 58.9 ($CH_2$-*i*Bu), 64.0 ($C_{4'}$), 65.8 ($C_{3'}$), 70.0 ($C_{5'}$), 82.6 ($C_{2'}$), 119.5-144.4 ($C_{arom}$), 162.2 (CO), 164.5 (CO), 170.8 (CO); HRMS Calcd for $C_{36}H_{33}BrN_2O_4$ $[M+H]^+$: 636.1623, Found: 636.1619.

**Methyl-1'-benzyl-1,3-dioxo-2,2',4'-triphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-5'-carboxylate (3ab)**

Obtained as yellow solid; mp = 78-80 °C; Rf = 0.33 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 3.39 (s, $OCH_3$), 4.03 (d, $CH_2$-Ph, J=14.7Hz), 4.19 (d, $CH_2$-Ph, J=14.7Hz), 4.36 (d, $H_5$, J= 10.8Hz), 4.46 (d, $H_4$, J= 10.8Hz), 5.08 (s, $H_2$), 6.22-8.20 (m, $24H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 52.0 ($OCH_3$), 58.9 ($CH_2$-Ph), 60.7 ($C_4$), 63.9 ($C_3$), 73.0 ($C_5$), 81.0 ($C_2$), 123.8-140.8 ($C_{arom}$), 163.2 (CO), 164.5 (CO), 169.2 (CO); HRMS Calcd for $C_{39}H_{32}N_2O_4$ $[M+H]^+$: 592.2362, Found: 592.2359.

**Methyl-1'-benzyl-1,3-dioxo-2,4',5'-triphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-2'-carboxylate (3'ab)**

Obtained as yellow solid; mp = 81-83 °C; Rf = 0.32 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 3.62 (s, $OCH_3$), 3.88 (d, $CH_2$-Ph, J=14.7Hz), 4.13 (d, $CH_2$-Ph, J=14.7Hz), 4.66 (d, $H_{5'}$, J= 7.8Hz), 4.98 (d, $H_{4'}$, J= 7.8Hz), 5.15 (s, $H_{2'}$), 6.61-7.98 (m, $24H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 52.3 ($OCH_3$), 58.9 ($CH_2$-Ph), 61.3 ($C_{4'}$), 65.0 ($C_{3'}$), 72.5 ($C_{5'}$), 82.4 ($C_{2'}$), 123.8-144.6 ($C_{arom}$), 162.2 (CO), 164.5 (CO), 169.7 (CO); HRMS Calcd for $C_{39}H_{32}N_2O_4$ $[M+H]^+$: 592.2362, Found: 592.2360.

**Methyl-1'-benzyl-4'-(4-methylphenyl)-1,3-dioxo-2,2'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-5'-carboxylate (3bb)**

Obtained as yellow solid; mp = 95-97 °C; Rf = 0.35 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 2.29 (s, $CH_3$), 3.14 (s, $OCH_3$), 3.63 (d, $CH_2$-Ph, J=14.7Hz), 4.07 (d, $CH_2$-Ph, J=14.7Hz), 4.36 (d, $H_5$, J= 10.8Hz), 4.48 (d, $H_4$, J= 10.8Hz), 5.12 (s, $H_2$), 6.22-8.08 (m, $23H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 21.4 ($CH_3$), 52.1 ($OCH_3$), 58.8 ($CH_2$-Ph), 62.0 ($C_4$), 64.1 ($C_3$), 71.9 ($C_5$), 80.5 ($C_2$), 123.8-140.8 ($C_{arom}$), 163.2 (CO), 164.5 (CO), 169.2 (CO); HRMS Calcd for $C_{40}H_{34}N_2O_4$ $[M+H]^+$: 606.2518, Found: 606.2511.

**Methyl-1'-benzyl-4'-(4-methylphenyl)-1,3-dioxo-2,5'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-2'-carboxylate (3'bb)**

Obtained as yellow solid; mp = 98-100 °C; Rf = 0.34 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 2.25 (s, $CH_3$), 3.43 (s, $OCH_3$), 3.79 (d, $CH_2$-Ph, J=14.7Hz), 4.24 (d, $CH_2$-Ph, J=14.7Hz), 4.65 (d, $H_{5'}$, J= 8.1Hz), 5.00 (d, $H_{4'}$, J= 8.1Hz), 5.19 (s, $H_{2'}$), 6.22-8.10 (m, $23H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 21.4 ($CH_3$), 52.5 ($OCH_3$), 58.8 ($CH_2$-Ph), 62.0 ($C_{4'}$), 64.1 ($C_{3'}$), 71.9 ($C_{5'}$), 80.5 ($C_{2'}$), 123.8-144.6 ($C_{arom}$), 162.2 (CO), 164.5 (CO), 169.7 (CO); HRMS Calcd for $C_{40}H_{34}N_2O_4$ $[M+H]^+$: 606.2518, Found: 606.2509.

**Methyl-1'-benzyl-4'-(4-methoxyphenyl)-1,3-dioxo-2,2'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-5'-carboxylate (3cb)**

Obtained as yellow solid; mp = 80-82 °C; Rf = 0.35 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 3.51 (s, $OCH_3$), 3.75 (s, $OCH_3$), 3.93 (d, $CH_2$-Ph, J=14.7Hz), 4.01 (d, $CH_2$-Ph, J=14.7Hz), 4.62 (d, $H_5$, J= 10.8Hz), 4.97 (d, $H_4$, J= 10.8Hz), 5.05 (s, $H_2$), 6.23-8.20 (m, $23H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 51.8 ($OCH_3$), 55.1 ($OCH_3$), 59.3 ($CH_2$-Ph), 63.5 ($C_4$), 64.9 ($C_3$), 67.0 ($C_5$), 80.1 ($C_2$), 123.8-140.8 ($C_{arom}$), 163.2 (CO), 164.5 (CO), 169.2 (CO); HRMS Calcd for $C_{40}H_{34}N_2O_5$ $[M+H]^+$: 622.2467, Found: 622.2465.

**Methyl-1'-benzyl-4'-(4-methoxyphenyl)-1,3-dioxo-2,5'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-2'-carboxylate (3'cb)**

Obtained as yellow solid; mp = 83-85 °C; Rf = 0.33 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 3.63 (s, $OCH_3$), 3.74 (s, $OCH_3$), 3.93 (d, $CH_2$-Ph, J=14.7Hz), 4.01 (d, $CH_2$-Ph, J=14.7Hz), 4.74 (d, $H_{5'}$, J= 8.1Hz), 5.20 (s, $H_{2'}$), 5.29 (d, $H_{4'}$, J= 8.1Hz), 6.23-8.20 (m, $23H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 52.3 ($OCH_3$), 55.1 ($OCH_3$), 59.3 ($CH_2$-Ph), 64.2 ($C_{4'}$), 65.3 ($C_{3'}$), 65.7 ($C_{5'}$), 81.7 ($C_{2'}$), 123.8-140.8 ($C_{arom}$), 163.2 (CO), 164.5 (CO), 169.2 (CO); HRMS Calcd for $C_{40}H_{34}N_2O_5$ $[M+H]^+$: 622.2467, Found: 622.2471.

**Methyl-1'-benzyl-4'-(4-bromophenyl)-1,3-dioxo-2,2'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-5'-carboxylate (3db)**

Obtained as yellow solid; mp = 102-104°C; Rf = 0.32 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 3.51 (s, $OCH_3$), 3.86 (d, $CH_2$-Ph, J=14.7Hz), 3.98 (d, $CH_2$-Ph, J=14.7Hz), 4.33 (d, $H_5$, J= 10.8Hz), 5.24 (d, $H_4$, J= 10.8Hz), 5.47 (s, $H_2$), 6.22-8.10 (m, $23H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 51.0 ($OCH_3$), 58.5 ($CH_2$-Ph), 60.5 ($C_4$), 64.4 ($C_3$), 72.5 ($C_5$), 81.0 ($C_2$), 123.8-140.8 ($C_{arom}$), 163.2 (CO), 164.5 (CO), 169.2 (CO); HRMS Calcd for $C_{39}H_{31}BrN_2O_4$ $[M+H]^+$: 670.1467, Found: 670.1461.

**Methyl-1'-benzyl-4'-(4-bromophenyl)-1,3-dioxo-2,5'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-2'-carboxylate (3'db)**

Obtained as yellow solid; mp = 94-96 °C; Rf = 0.31 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 3.63 (s, $OCH_3$), 3.93 (d, $CH_2$-Ph, J=14.7Hz), 4.05 (d, $CH_2$-Ph, J=14.7Hz), 4.23 (d, $H_{5'}$, J= 8.1Hz), 4.31 (s, $H_{2'}$), 5.06 (d, $H_{4'}$, J= 8.1Hz), 6.24-8.08 (m, $23H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 51.7 ($OCH_3$), 58.5 ($CH_2$-Ph), 61.9 ($C_{4'}$), 67.4 ($C_{3'}$), 71.8 ($C_{5'}$), 82.1 ($C_{2'}$), 123.8-144.6 ($C_{arom}$), 162.2 (CO), 164.5 (CO), 169.7 (CO); HRMS Calcd for $C_{39}H_{31}BrN_2O_4$ $[M+H]^+$: 670.1467, Found: 670.1477.

**Methyl-1'-(3-furylmethyl)-1,3-dioxo-2,2',4'-triphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-5'-carboxylate (3ac)**

Obtained as yellow solid; mp = 85-87 °C; Rf = 0.31 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 3.51 (s, $OCH_3$), 3.88 (d, $CH_2$-Fur), 4.13 (d, $CH_2$-Fur), 4.32 (d, $H_5$, J= 10.8Hz), 4.57 (d, $H_4$, J= 10.8Hz), 5.12 (s, $H_2$), 6.20-6.42 (m, $H_{Fur}$), 6.66-8.10 (m, $19H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 45.2 ( $CH_2$-Fur), 51.0 ($OCH_3$), 60.3 ($C_4$), 64.3 ($C_3$), 70.8 ($C_5$), 73.2 ($C_2$), 111.5-152.4 ($C_{Fur}$ et $C_{arom}$), 163.2 (CO), 164.5 (CO), 169.0 (CO); HRMS Calcd for $C_{37}H_{30}N_2O_5$ $[M+H]^+$: 582.2154, Found: 582.2159.

**Methyl-1'-(3-furylmethyl)-1,3-dioxo-2,4',5'-triphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-2'-carboxylate (3'ac)**

Obtained as yellow solid; mp = 87-89°C; Rf = 0.30 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 3.65 (s, $OCH_3$), 3.88 (d, $CH_2$-Fur), 4.13 (d, $CH_2$-Fur), 5.05 (d, $H_{5'}$, J= 8.1Hz), 5.10 (s, $H_{2'}$), 5.32 (d, $H_{4'}$, J= 8.1Hz), 6.20-6.42 (m, $H_{Fur}$), 6.70-8.09 (m, $19H_{arom}$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): 45.2 ( $CH_2$-Fur), 51.7 ($OCH_3$), 61.7 ($C_{4'}$), 67.4 ($C_{3'}$), 70.0 ($C_{5'}$), 74.4 ($C_{2'}$), 111.5-152.4 ($C_{Fur}$ et $C_{arom}$), 162.2 (CO), 164.5 (CO), 169.5 (CO); HRMS Calcd for $C_{37}H_{30}N_2O_5$ $[M+H]^+$: 582.2154, Found: 582.2152.

**Methyl-1'-(3-furylmethyl)-4'-(4-methylphenyl)-1,3-dioxo-2,2'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-5'-carboxylate (3bc)**

Obtained as yellow solid; mp = 97-99 °C; Rf = 0.32 (cyclohexane/ethyl acetate 80:20); $^1$H NMR (300 MHz, $CDCl_3$): 2.32 (s, $CH_3$), 3.53 (s, $OCH_3$), 3.89 (d, $CH_2$-Fur), 4.11 (d, $CH_2$-Fur), 4.35 (d, $H_5$, J= 10.8Hz), 4.60

(d, $H_4$, J= 10.8Hz), 5.17 (s, $H_2$), 6.21-6.45 (m, $H_{Fur}$), 6.68-8.11 (m, $18H_{arom}$); $^{13}C$ NMR (75.5 MHz, $CDCl_3$): 21.2 ($CH_3$), 45.2 ( $CH_2$-Fur), 51.1 ($OCH_3$), 61.3 ($C_4$), 64.5 ($C_3$), 70.9 ($C_5$), 73.4 ($C_2$), 111.5-152.4 ($C_{Fur}$ et $C_{arom}$), 163.2 (CO), 164.5 (CO), 169.0 (CO); HRMS Calcd for $C_{38}H_{32}N_2O_5$ $[M+H]^+$: 596.2311, Found: 596.2315.

**Methyl-1'-(3-furylmethyl)-4'-(4-methylphenyl)-1,3-dioxo-2,5'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-2'-carboxylate (3'bc)**

Obtained as yellow solid; mp = 103-105°C; Rf = 0.31 (cyclohexane/ethyl acetate 80:20); $^1H$ NMR (300 MHz, $CDCl_3$): 2.27 (s, $CH_3$), 3.65 (s, $OCH_3$), 3.89 (d, $CH_2$-Fur), 4.11 (d, $CH_2$-Fur), 5.07 (d, $H_{5'}$, J= 8.1Hz), 5.10 (s, $H_{2'}$), 5.35 (d, $H_{4'}$, J= 8.1Hz), 6.21-6.45 (m, $H_{Fur}$), 6.70-8.09 (m, $18H_{arom}$); $^{13}C$ NMR (75.5 MHz, $CDCl_3$): 21.2 ($CH_3$), 45.2 ( $CH_2$-Fur), 51.8 ($OCH_3$), 61.8 ($C_{4'}$), 67.4 ($C_{3'}$), 69.9 ($C_{5'}$), 75.5 ($C_{2'}$), 111.5-152.4 ($C_{Fur}$ et $C_{arom}$), 162.2 (CO), 164.5 (CO), 169.5 (CO); HRMS Calcd for $C_{38}H_{32}N_2O_5$ $[M+H]^+$: 596.2311, Found: 596.2317.

**Methyl-1'-(3-furylmethyl)-4'-(4-methoxyphenyl)-1,3-dioxo-2,2'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-5'-carboxylate (3cc)**

Obtained as yellow oil; Rf = 0.32 (cyclohexane/ethyl acetate 80:20); $^1H$ NMR (300 MHz, $CDCl_3$): 3.53 (s, $OCH_3$), 3.75 (s, $OCH_3$), 3.92 (d, $CH_2$-Fur), 4.15 (d, $CH_2$-Fur), 4.32 (d, $H_5$, J= 10.8Hz), 4.60 (d, $H_4$, J= 10.8Hz), 5.20 (s, $H_2$), 6.21-6.45 (m, $H_{Fur}$), 6.68-8.11 (m, $18H_{arom}$); $^{13}C$ NMR (75.5 MHz, $CDCl_3$): 45.2 ( $CH_2$-Fur), 51.5 ($OCH_3$), 55.9 ($OCH_3$), 61.0 ($C_4$), 64.3 ($C_3$), 70.7 ($C_5$), 73.0 ($C_2$), 111.5-152.4 ($C_{Fur}$ et $C_{arom}$), 163.2 (CO), 164.5 (CO), 169.0 (CO); HRMS Calcd for $C_{38}H_{32}N_2O_6$ $[M+H]^+$: 660.1259, Found: 660.1265.

**Methyl-1'-(3-furylmethyl)-4'-(4-methoxyphenyl)-1,3-dioxo-2,5'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-2'-carboxylate (3'cc)**

Obtained as yellow oil; Rf = 0.31 (cyclohexane/ethyl acetate 80:20); $^1H$ NMR (300 MHz, $CDCl_3$): 3.65 (s, $OCH_3$), 3.77 (s, $OCH_3$), 3.92 (d, $CH_2$-Fur), 4.15 (d, $CH_2$-Fur), 5.09 (d, $H_{5'}$, J= 8.1Hz), 5.13 (s, $H_{2'}$), 5.37 (d, $H_{4'}$, J= 8.1Hz), 6.21-6.45 (m, $H_{Fur}$), 6.70-8.09 (m, $18H_{arom}$); $^{13}C$ NMR (75.5 MHz, $CDCl_3$): 45.2 ( $CH_2$-Fur), 51.9 ($OCH_3$), 56.0 ($OCH_3$), 61.6 ($C_{4'}$), 67.4 ($C_{3'}$), 69.8 ($C_{5'}$), 75.6 ($C_{2'}$), 111.5-152.4 ($C_{Fur}$ et $C_{arom}$), 162.2 (CO), 164.5 (CO), 169.5 (CO); HRMS Calcd for $C_{38}H_{32}N_2O_6$ $[M+H]^+$: 660.1259, Found: 660.1268.

**Methyl-4'-(4-bromophenyl)-1'-(3-furylmethyl)-1,3-dioxo-2,2'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-5'-carboxylate (3dc)**

Obtained as yellow solid; mp = 100-102 °C; Rf = 0.31 (cyclohexane/ethyl acetate 80:20); $^1H$ NMR (300 MHz, $CDCl_3$): 3.53 (s, $OCH_3$), 3.90 (d, $CH_2$-Fur), 4.13 (d, $CH_2$-Fur), 4.33 (d, $H_5$, J= 10.8Hz), 4.58 (d, $H_4$, J= 10.8Hz), 5.15 (s, $H_2$), 6.21-6.45 (m, $H_{Fur}$), 6.68-8.11 (m, $18H_{arom}$); $^{13}C$ NMR (75.5 MHz, $CDCl_3$): 45.2 ( $CH_2$-Fur), 51.3 ($OCH_3$), 61.1 ($C_4$), 64.2 ($C_3$), 70.3 ($C_5$), 73.2 ($C_2$), 111.5-152.4 ($C_{Fur}$ et $C_{arom}$), 163.2 (CO), 164.5 (CO), 169.0 (CO); HRMS Calcd for $C_{37}H_{29}BrN_2O_5$ $[M+H]^+$: 612.2260, Found: 612.2268.

**Methyl-4'-(4-bromophenyl)-1'-(3-furylmethyl)-1,3-dioxo-2,5'-diphenyl-2,3-dihydro-1*H*-spiro[isoquinoline-4,3'-pyrrolidine]-2'-carboxylate (3'dc)**

Obtained as yellow solid; mp = 104-106 °C; Rf = 0.30 (cyclohexane/ethyl acetate 80:20); $^1H$ NMR (300 MHz, $CDCl_3$): 3.65 (s, $OCH_3$), 3.90 (d, $CH_2$-Fur), 4.13 (d, $CH_2$-Fur), 5.03 (d, $H_{5'}$, J= 8.1Hz), 5.11 (s, $H_{2'}$), 5.34 (d, $H_{4'}$, J= 8.1Hz), 6.21-6.45 (m, $H_{Fur}$), 6.70-8.09 (m, $18H_{arom}$); $^{13}C$ NMR (75.5 MHz, $CDCl_3$): 45.2 ( $CH_2$-Fur), 52.0 ($OCH_3$), 61.6 ($C_{4'}$), 67.7 ($C_{3'}$), 69.6 ($C_{5'}$), 75.9 ($C_{2'}$), 111.5-152.4 ($C_{Fur}$ et $C_{arom}$), 162.2 (CO), 164.5 (CO), 169.5 (CO); HRMS Calcd for $C_{37}H_{29}BrN_2O_5$ $[M+H]^+$: 612.2260, Found: 612.2262.

*1,3-Dipolar Cycloaddition Under Classical Conditions of spiro-isoquinoline-1,3-dione (Entry **1**, **7** and **8**)*

The (*E*)-4-arylidene-*N*-phenyl-(2*H*)-isoquinoline-1,3-dione **1a-d** (1.0 mmol) was added to the *N*-substituted aminoesters **2a-c** (2.0 mmol) and benzaldehyde (1.0 mmol). The mixture was homogenized with xylene (1mL) in a in a Schlenk tube, and refluxed for 2 days, until all starting materials had disappeared (as tested by TLC). The solvent was then evaporated and the residue obtained was purified by column chromatography [$SiO_2$ / Cyclohexane : Ethyl acetate (90:10)].

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