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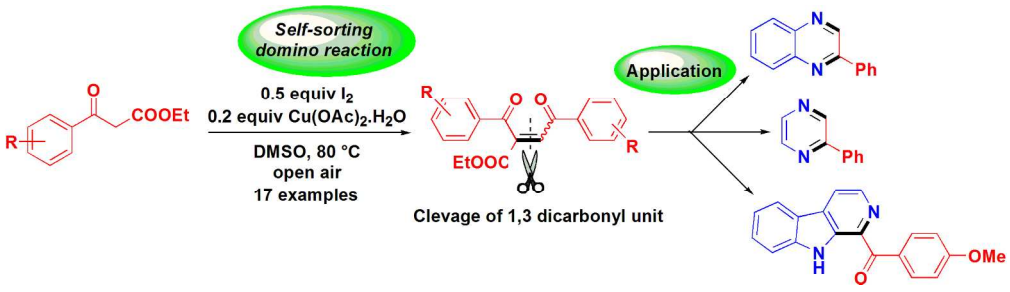

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ARTICLE

I_2/Cu-mediated Self-sorting Domino Reaction of Aryl β-Ketoesters into Symmetrical 2-Carboalkoxy-1,4-Enediones: Application to Synthesis of Pyrazine, β-Carboline and Quinoxalines

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A self-sorting domino reaction of aryl β-ketoesters into symmetrical 1,4-enediones is reported by I_2/Cu system. The reaction proceeds through tandem iodination, self-dimerization and Krapcho dealkoxycarbonylation in one pot under open air condition. Further, 1,4-enediones were successfully employed for the synthesis of bioactive pyrazine, β-carboline and quinoxalines via aza-Michael addition, intramolecular cyclization and C-C bond cleavage of 1,3-dicarbonyl unit under mild reaction condition.

Introduction

Development of simplified strategies for the synthesis of complex molecules is always an exciting and challenging task. In the past few decades a significant development of domino reactions was witnessed, mainly due to its influent advantages such as, high atom economy, reduction of labour, easy resource management and production of complex molecules in one pot.[1] Although, different type of domino approaches namely intramolecular, intermolecular, multicomponent, and focusing were well established, studies on self-sorting domino (SSD) reactions are only limited.[2] This is because, in a SSD reaction one should manage to control the reactivity of *in situ* generated intermediates from a single starting material to get the desired product in high yield. As this helps effective utilization of a single starting material, SSD reaction could be considered as one of the most efficient domino reactions.

1,4-enedione is a privileged structural motif found among scores of bio-active compounds, and marine natural products.[3] It has been extensively used as an admirable starting material for the synthesis of enamine diones, oxygen and nitrogen heterocycles, etc by conjugate addition of carbon, phosphorus and nitrogen nucleophiles (Figure 1).[4] Traditional approaches followed for the synthesis of 1,4-enediones are ring opening of furan or thiophene derivatives,[5] decomposition of diazo carbonyl compounds[6] and oxidation of enone unit.[7] Recently, Kirsch et al. reported the construction of Z-enediones in moderate yield by oxidative rearrangement of 2-alkynyl alcohols.[8] Similarly, Wang et al. described the complete E-selective synthesis of 1,4-enediones from aromatic methyl ketones via a tandem pathway (Scheme 1).[9] Notably, Wu's research group reported the synthesis of E:Z mixture of unsymmetrical 1,4-enediones by reaction of 1,3 dicarbonyl compounds with acetophenones/ styrenes/ secondary alcohols/ α-halo acetophenones via Kornblum oxidation followed by Knoevengal condensation.[10] While these investigations are impressive, the need of multiple substrates and stoichiometric amount of reagents necessitates the development of a simple and sustainable protocol for the construction of 1,4-enediones.

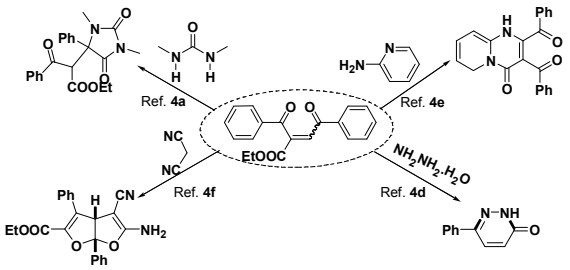

Figure 1. Synthetic utility of 1,4-enediones.

On the other hand, the cleavage of unstrained and unactivated carbon-carbon *σ* bonds under mild reaction conditions is a challenging task and such reactions are only few.[11] Under the methods reported so far, the C-C bond cleavage is achieved by using activating group and driven by relieving steric strain[12] or employing high temperature/pressure.[13] Very recently, study on C-C bond cleavage of 1,3-dicarbonyl unit has gained much importance[14] and such cleavage was reported by Kotora,[14a] Zhai,[14j] Li[14c-d] and Wu[14e] separately by employing various catalytic systems.

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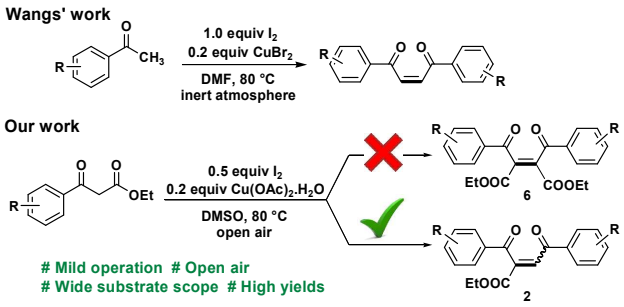


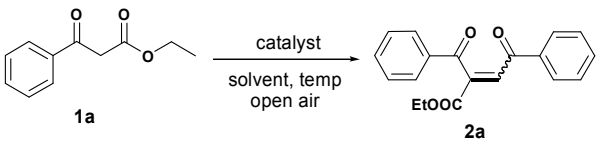
Scheme 1. Synthetic strategies of 1,4-enediones.

Based on our previous experience of C-H activation of 2'-aminoacetophenones using $Cu(OAc)_2.H_2O$[15a] and I_2,[15b] we envisaged that aryl β-ketoester in the presence of I_2/Cu system would undergo self dimerization to give diethyl 2,3-dibenzoylmaleate (**10**). However, to our surprise, the reaction furnished 2-carboalkoxy-1,4-enediones (**2**) via self dimerization followed by Krapcho dealkoxycarbonylation in one pot.[16] To the best of our knowledge, a self-sorting domino reaction of aryl β-ketoester as well as Krapcho dealkoxycarbonylation in the presence of I_2/Cu system was observed for the first time. Considering the rare occurrence of SSD reaction and synthetic importance of 1,4-enedione, herein we report a novel SSD reaction of aryl β-ketoesters into symmetrical 1,4-enediones. Further, 1,4-enediones were underwent C-C bond cleavage of 1,3-dicarbonyl unit to give rise biologically important pyrazine, β-carboline and quinoxalines in high yields.

Results and discussion

Our initial study began with the reaction of ethyl benzoylacetate (**1a**) with I_2 (1.0 equiv) and $Cu(OAc)_2.H_2O$ (1.0 equiv) in DMSO at room temperature (Table 1, entry 1). Since no reaction took place at r.t., the reaction temperature was raised to 80 °C and we were heartened to know that self dimerization followed by dealkoxycarbonylation took place to give 1,4-enedione **2a** in 68% isolated yield (entry 2). There was no appreciable change in the yield when quantity of I_2 and $Cu(OAc)_2.H_2O$ was decreased to 0.5 equiv (entry 3). Interestingly, the yield was improved to 78% by lowering the quantity of $Cu(OAc)_2.H_2O$ to 0.2 equiv (entry 4). Increasing or decreasing the temperature from 80 °C, only led to decrease in yield (entries 5 and 6). In the absence of either I_2 or $Cu(OAc)_2.H_2O$ a mixture of products was obtained which indicates that both are essential for this reaction (entries 7 and 8). Screening various copper salts revealed that $Cu(OAc)_2.H_2O$ is the superior for this reaction (entries 9-14). Among different solvents, DMSO furnished highest yield (entries 15-18). As a result of the screening study, I_2 (0.5 equiv), and $Cu(OAc)_2.H_2O$ (0.2 equiv) in DMSO at 80 °C was found to be the optimum condition for further study.

Table 1. Optimization study for the formation of **2a**[a]



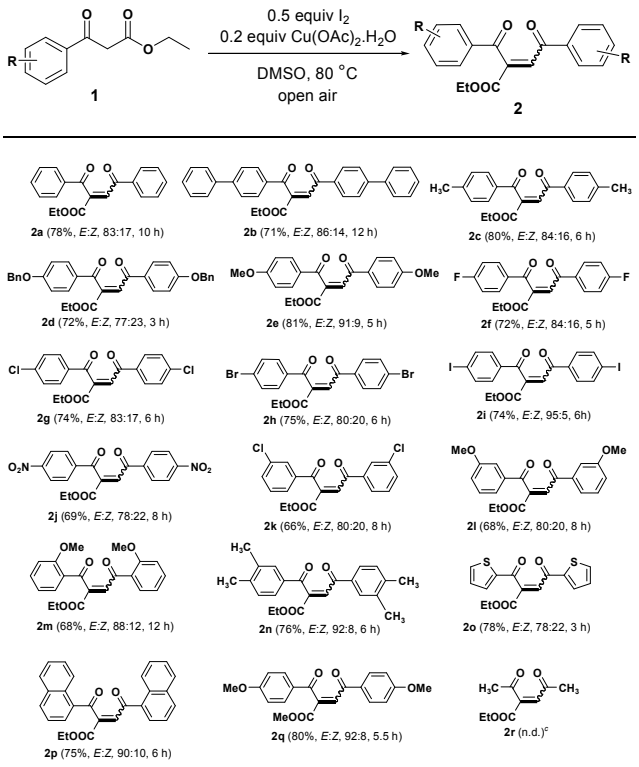
Entry	Iodine (equiv)	Copper salt (equiv)	Solvent	Temp [°C] /Time [h] /Yield [%][b]
1[c]	I_2 (1.0)	$Cu(OAc)_2.H_2O$ (1.0)	DMSO	r.t./20/n.r.
2	I_2 (1.0)	$Cu(OAc)_2.H_2O$ (1.0)	DMSO	80 /8/68
3	I_2 (0.5)	$Cu(OAc)_2.H_2O$ (0.5)	DMSO	80 /10/70
4	**I_2 (0.5)**	**$Cu(OAc)_2.H_2O$ (0.2)**	**DMSO**	**80/ 12 /78**
5	I_2 (0.5)	$Cu(OAc)_2.H_2O$ (0.2)	DMSO	100/ 7/70
6	I_2 (0.5)	$Cu(OAc)_2.H_2O$ (0.2)	DMSO	60/ 16/68
7	I_2 (0.5)	-	DMSO	80/15/43
8[d]	-	$Cu(OAc)_2.H_2O$ (0.2)	DMSO	80/12/n.d.
9	I_2 (0.5)	$CuCl_2$ (0.2)	DMSO	80/15 /42
10	I_2 (0.5)	$CuBr_2$ (0.2)	DMSO	80/12/57
11	I_2 (0.5)	$Cu(NO_3)_2$ (0.2)	DMSO	80/18/38
12	I_2 (0.5)	$Cu(SO_4)_2$ (0.2)	DMSO	80/20/trace
13	I_2 (0.5)	CuI (0.2)	DMSO	80/12/48
14	I_2 (0.5)	CuBr (0.2)	DMSO	80/ 12/36
15	I_2 (1.0)	$Cu(OAc)_2.H_2O$ (0.2)	DMF	80/ 24/61
16	I_2 (1.0)	$Cu(OAc)_2.H_2O$ (0.2)	Toluene	80/ 24/48
17	I_2 (1.0)	$Cu(OAc)_2.H_2O$ (0.2)	CH_3OH	80/ 24/42
18[d]	I_2 (1.0)	$Cu(OAc)_2.H_2O$ (0.2)	CH_3CN	80/24/n.d.

[a]Unless otherwise stated, all the reactions were performed using **1a** (1.0 mmol) in solvent (3.0 ML); [b]Isolated yield; [c]No reaction; [d]Not determined.

Under the optimal reaction condition, the substrate scope of various aryl β-ketoesters was investigated (Table 2). As shown, compound **1b** with phenyl substituent underwent slow reaction to give 1,4-enedione **2b** in 71% yield. Substrates **1c-i** bearing electron donating and halo substituent's provided 1,4-enediones **2c-i** in high yield. The electron withdrawing NO_2 group in **1j** was well tolerated the present reaction condition and offered corresponding enedione **2j** in 69% yield. The β-ketoesters **1k-m** with substituent in sterically and electronically disadvantaged *ortho* and *meta* position afforded expected 1,4-enediones **2k-m** in moderate to good yield. Dimethyl substituted β-ketoester **1n** gave the desired product **2n** in 76% yield. Aryl β-ketoester **1o** containing heterocyclic thiophene motif well tolerated the optimal condition and corresponding 1,4-enedione **2o** was obtained in 78% yield. Similarly, ethyl naphthoylacetate (**1p**) gave desired enedione **2p** in 75% yield. Further, similar to ethyl ester **1e**, the corresponding methyl ester **1q** also provided the expected product **2q** in almost same yield. However, the aliphatic β-ketoester, ethyl acetoacetate (**1r**) failed to deliver the desired product **2r**. All the substrates **1a-q** were provided the corresponding 1,4-enediones **2a-q,** as *E*/*Z* mixture, and the thermodynamically stable *E*-isomers were the major products. This was confirmed from the ^{1}H-NMR spectra.

The present method is applicable to a wide variety of aryl β-ketoesters containing different electron donating groups such as 4-OMe, 4-OBn, 4-CH_3, 3,4-dimethyl, sterically hindered 2-OMe, biphenyl, naphthyl, heterocyclic (thiophene), inductively electron withdrawing halogens and electron withdrawing 4-NO_2 groups.

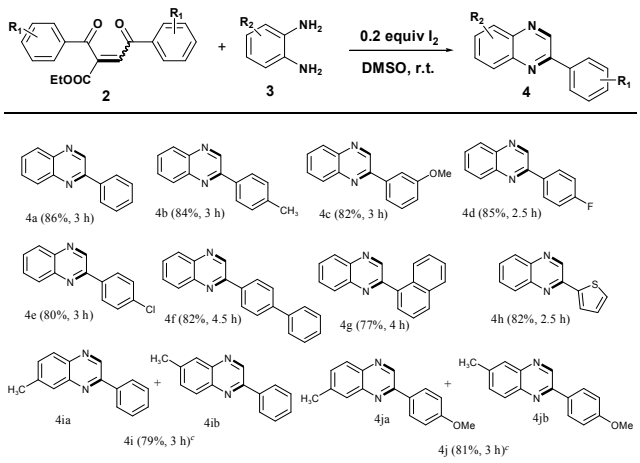
Table 2. Substrate scope of β-ketoesters[a,b]



[a]Reaction Condition: **1** (1.0 mmol), I_2 (0.5 mmol), Cu salt (0.2 mmol) in DMSO (3.0 mL) at 80 °c; [b]Isolated yield; [c]Not determined.

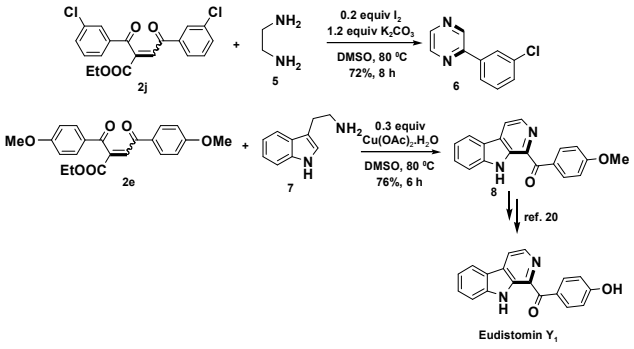
Further, to demonstrate the synthetic utility of obtained 1,4-enediones (**2**), we have examined an iodine-mediated intermolecular nucleophilic addition of 1,4-enedione **2a** with 1,2-diamino benzene (**3a**) (Table 3). To our delight, the reaction furnished quinoxaline **4a** by loss of a 1,3-dicarbonyl unit at room temperature. Since quinoxaline is an important structural motif in many drugs,[17] organic semiconductors,[18] electroluminescent materials,[19] and synthetic dyes,[20] we investigated the reaction to improve the yield by employing other iodine sources, such as NIS and TBAI. However none of them provided the desired product. DMSO was the choice of solvent to get best yield of quinoxaline **4a**. Under suitable condition, 1,4-enedione bearing electron rich and halo groups provided quinoxalines **4b**-**4e** in 80-84% yields. Steric effect of 1,4-enediones did not influence the rate of reaction and corresponding quinoxalines **4f** and **4g** were obtained in 82% and 77% yield respectively. Thiophene motif containing 1,4-enedione **2m** was well tolerated and delivered the corresponding quinoxaline **4h** in 82% yield. The reaction of 3-methyl-1,2-diamino benzene (**3b**) with **2a** and **2e** afforded the corresponding quinoxalines **4i** (**4ia+4ib**) and **4j** (**4ja+4jb**) as regio-isomeric mixtures.

Table 3. Synthetic application of 1,4-enediones for the synthesis of quinoxalines[a,b]



[a]Reaction Conditions: **2** (1.0 mmol), **3** (1.1 mmol), I_2 (0.2 mmol) in DMSO (2.0 mL) at room temp; [b]Isolated yield; [c]Regio-isomeric mixture.

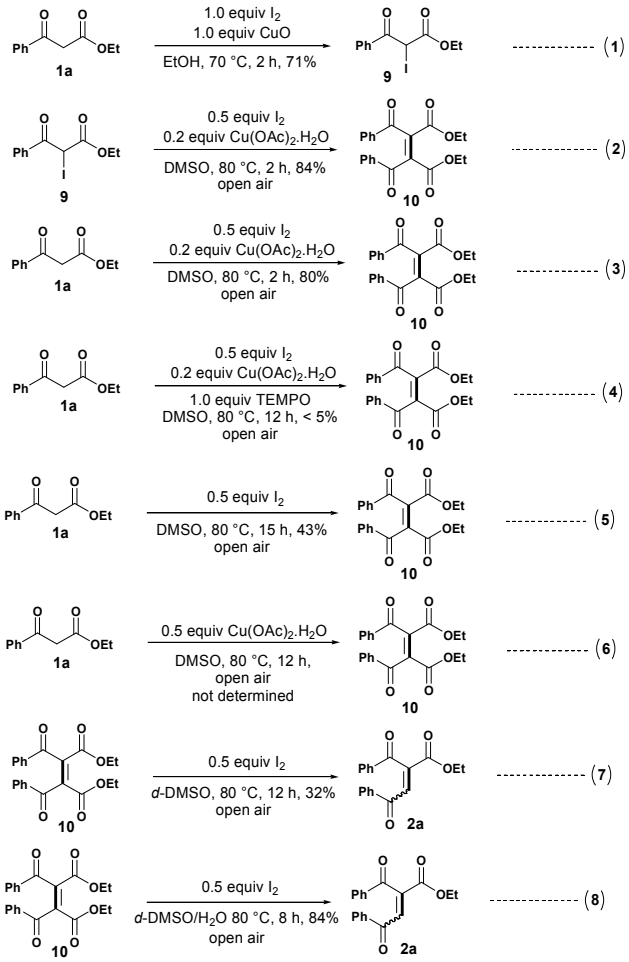
Next, we examined the reaction feasibility of 1,4-enedione **2j** with 1,2-diamino ethane (**5**) (Scheme 2). Delightfully, the expected pyrazine **6** was obtained by loss of a 1,3-dicarbonyl unit followed by oxidation in 72% isolated yield. Importantly, the present method can also be applied in the total synthesis of natural product, eudistomin Y_1. As shown in scheme 2, the reaction of 1,4-enedione **2e** with tryptamine (**6**) provided β-carboline **8** in good yield by losing 1,3-dicarbonyl unit. Further, β-carboline **8** was transformed to eudistomin Y_1 according to the reported procedure.[21]



Scheme 2. Synthetic application of 1,4-enediones for pyrazine and β-carboline synthesis.

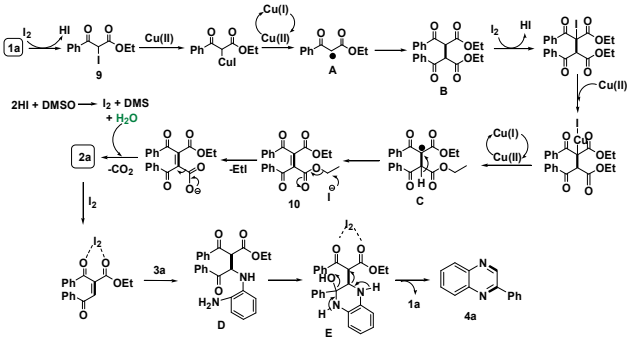
To gain insight into the mechanism for the formation of 1,4-enedione (**2**), some control experiments were carried out (Scheme 3). Initially the α-iodo-β-ketoester **9** was prepared by iodination of ethylbenzoyl acetate (**1a**, Scheme 3, eq 1),

further which on treatment with I_2 (0.5 equiv) and $Cu(OAc)_2.H_2O$ (0.2 equiv) provided diethyl 2,3-dibenzoylmaleate (**10**) in 84% isolated yield (Scheme 3, eq 2). When the reaction of **1a** was stopped prematurely after 2 h, compound **10** was obtained in 80% yield (Scheme 3, eq 3). However, in the presence of TEMPO, the formation of **10** was drastically decreased, indicates that the reaction takes place through a radical pathway (Scheme 3, eq 4). In the absence of either I_2 or $Cu(OAc)_2.H_2O$ a mixture of products were obtained (Scheme 3, eq 5 and eq 6). When compound **10** was treated with 0.5 equiv of I_2 in *d*-DMSO gave the desired product **2a** only in 32% yield (Scheme 3, eq 7). Interestingly, when same reaction was carried out in *d*-DMSO and H_2O mixture, it gave **2a** in 84% yield by dealkoxycarbonylation (Scheme 3, eq 8).[16] These two reactions clearly indicate that, the carbanion is protonized by H_2O and not DMSO.



Scheme 3. Controlled experiments to study reaction mechanism.

On the basis of above information and the literature knowledge,[9] a plausible mechanism is proposed (Scheme 4). Initially, ethylbenzoyl acetate (**1a**) undergoes α-iodination to give **9**, which further may give radical **A**.[22] Subsequently, radical **A** may undergo self dimerization to give 2,3-Dibenzoyl-succinic acid diethyl ester **B**.[23] Again **B** on α-iodination followed by copper insertion is expected to give radical **C**, which further may undergo easy deprotonation to form diethyl 2,3-dibenzoylmaleates **10**.



Scheme 4. Proposed mechanism.

Finally, the iodide ion, which is generated during the course of reaction, is expected to react with **10** to afford the desired product **2a** by losing EtI and CO_2 *via* Krapcho dealkoxycarbonylation.[16] When **2a** was treated with 1,2-diamino benzene (**3a**) in the presence of I_2, it undergoes a sequential aza-Michael addition (**D**) followed by intramolecular cyclization to form the intermediate **E**. Finally, **E** provides quinoxaline **4a** by losing ethylbenzoyl acetate **1a.**

Conclusion

In conclusion, we have developed a practical and efficient self-sorting domino reaction of commercially available aryl β-ketoesters into symmetrical 2-carboalkoxy-1,4-enediones under open air condition, using simple catalytic system. The method is mild and flexible for the synthesis of a variety of symmetrical 1,4-enediones. The reaction proceeds through tandem iodination, self dimerization and Krapcho dealkoxycarbonylation in one pot. A suitable reaction mechanism is proposed by means of control experiments. Further, the synthetic utility of 1,4-enedione as an intermediate is successfully demonstrated by its conversion into a variety of biologically active β-carboline, pyrazine and quinoxalines *via* aza-Michael addition, intramolecular cyclization and C-C bond cleavage in a single reactor. Further mechanistic studies of this reaction are under way.

Experimental

General Information:

All the reagents were purchased commercially and used as received. ^{1}H NMR and ^{13}C NMR were recorded with Bruker 400MHz. ^{1}H NMR (400MHz) and ^{13}C NMR (100MHz) spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard. Multiplicities are reported using the following

abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad resonance. All the NMR spectra were acquired at ambient temperature. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 Å F254 pre-coated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and staining with I_2 on silica gel. The elemental analysis was carried out with vario MICRO V1.3.2 Elemental Analyser system, GmbH instruments.

General method A: Typical experimental procedure for the synthesis of *E/Z* mixture of 2-Benzoyl-4-oxo-4-phenyl-but-2-enoic acid ethyl esters:

To a solution of aryl β-ketoester (**1**, 1.0 equiv) in DMSO (3 mL), I_2 (0.5 equiv) and $Cu(OAc)_2.H_2O$ (0.2 equiv) was added at room temperature and heated at 80 °C under the atmosphere of air. Progress of the reaction was monitored by TLC. Upon on completion, the reaction mixture was allowed to cool to room temperature and quenched with sodium thiosulfate water and ethyl acetate. The organic phase was separated, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel column chromatography using hexane / ethyl acetate as eluent.

General method B: Typical experimental procedure for the synthesis of quinoxalines:

To a solution of 2-Benzoyl-4-oxo-4-phenyl-but-2-enoic acid ethyl ester (2, 1.0 equiv) in DMSO, Benzene-1,2-diamine (3, 1.1 equiv) and I2 (0.2 equiv) was added at room temperature and stirred. Progress of the reaction was monitored by TLC. Upon on completion, the reaction mixture was allowed to cool to room temperature and quenched with sodium thiosulfate water and ethyl acetate. The organic phase was separated, dried over Na2SO4, filtered and concentrated. The crude product was purified by silica gel column chromatography using hexane / ethyl acetate as eluent.

(*E/Z*)-2-Benzoyl-4-oxo-4-phenyl-but-2-enoic acid ethyl ester (2a):[10a]

The reaction was carried out according to general method A using 3-Oxo-3-phenyl-propionic acid ethyl ester (1a, 100 mg, 0.520 mmol), I_2 (66.0 mg, 0.260 mmol), $Cu(OAc)_2.H_2O$ (20.8 mg, 0.104 mmol) and DMSO (3 mL). Conditions: 80 °C, 10 h. The title compound 2a (125.1 mg, 78% yield) was obtained as yellow oil after passing through a silica gel column chromatography.

(*E*:*Z* = 83:17); (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.64-7.57 (m, 2H), 7.52-7.46 (m, 4H), 4.30 (q, *J* = 14.2 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 188.5, 163.7, 144.9, 136.3, 136.0, 134.2, 133.5, 130.2, 128.9, 128.9, 128.7, 128.6, 62.4, 13.9.

(*E/Z*)-2-(Biphenyl-4-carbonyl)-4-biphenyl-4-yl-4-oxo-but-2-enoic acid ethyl ester (2b):

The reaction was carried out according to general method A using 3-Biphenyl-4-yl-3-oxo-propionic acid ethyl ester (1b, 100 mg, 0.372 mmol), I_2 (47.3 mg, 0.186 mmol), $Cu(OAc)_2.H_2O$ (14.9 mg, 0.074 mmol) and DMSO (3 mL). Conditions: 80 °C, 12 h. The title compound 2b (121.8 mg, 71% yield) was obtained as light yellow semi solid after passing through a silica gel column chromatography.

(*E*:*Z* = 86:14); (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 1H), 8.05 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.71-7.60 (m, 8H), 7.48-7.45 (m, 6H), 4.31 (q, *J* = 14.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.1, 187.9, 163.8, 147.0, 146.3, 144.9, 140.0, 139.5, 135.0, 134.7, 133.5, 130.8, 130.1, 129.6, 129.2, 129.1, 129.0, 129.0, 128.6, 128.3, 127.6, 127.5, 127.4, 127.2, 62.6, 14.0. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{31}H_{24}NaO_4$: 483.1567; found: 483.1728.

(*E/Z*)-2-(4-Methyl-benzoyl)-4-oxo-4-*p*-tolyl-but-2-enoic acid ethyl ester (2c):

The reaction was carried out according to general method A using 3-Oxo-3-*p*-tolyl-propionic acid ethyl ester (1c, 100 mg, 0.484 mmol), I_2 (61.5 mg, 0.242 mmol), $Cu(OAc)_2.H_2O$ (19.4 mg, 0.096 mmol) and DMSO (3 mL). Conditions: 80 °C, 6 h. The title compound 2c (130.4 mg, 80% yield) was obtained as semi solid after passing through a silica gel column chromatography.

(*E*:*Z* = 84:16); (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.20-7.16 (m, 4H), 4.19 (q, *J* = 14.2 Hz, 2H), 2.34 (s, 3H), 2.32 (s, 3H), 1.14 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2, 187.9, 163.9, 145.4, 144.6, 144.5, 133.9, 133.6, 133.4, 129.6, 129.5, 129.1, 128.7, 62.4, 21.8, 21.8, 13.9. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{19}H_{16}NaO_4$: 359.1254; found: 359.1254.

(*E/Z*)-4-Oxo-2-(4-phenoxy-benzoyl)-4-(4-phenoxy-phenyl)-but-2-enoic acid ethyl ester (2d):

The reaction was carried out according to general method A using 3-(4-Benzyloxy-phenyl)-3-oxo-propionic acid ethyl ester (1d, 100 mg, 0.335 mmol), I_2 (44.6 mg, 0.175 mmol), $Cu(OAc)_2.H_2O$ (14.0 mg, 0.070 mmol) and DMSO (3 mL). Conditions: 80 °C, 3 h. The title compound 2d (125.6 mg, 72% yield) was obtained as yellow oil after passing through a silica gel column chromatography.

(*E*:*Z* = 77:23); (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.34-7.30 (m, 10H), 6.93-6.90 (m, 4H), 5.05 (s, 2H), 5.02 (s, 2H), 4.18 (q, *J* = 14.4 Hz, 4H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 186.9, 164.0, 163.6, 163.1, 144.0, 136.2, 135.9, 133.6, 132.3, 131.4, 130.9, 129.8, 129.6, 128.7, 128.7, 128.3, 128.2, 127.5, 127.5, 115.0, 114.8, 114.6, 70.3, 70.2, 62.3, 13.9. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{33}H_{28}NaO_6$: 543.1778; found: 543.1972.

(*E/Z*)-2-(4-Methoxy-benzoyl)-4-(4-methoxy-phenyl)-4-oxo-but-2-enoic acid ethyl ester (2e):

The reaction was carried out according to general method A using 3-(4-Methoxy-phenyl)-3-oxo-propionic acid ethyl ester (1e, 100 mg, 0.449 mmol), I_2 (57.1 mg, 0.224 mmol), $Cu(OAc)_2.H_2O$ (18.0 mg, 0.089 mmol) and DMSO (3 mL). Conditions: 80 °C, 5 h. The title compound 2e (134.2 mg, 81% yield) was obtained as semi solid after passing through a silica gel column chromatography.

(*E*:*Z* = 91:9); (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 3.2 Hz, 2H), 7.00 (d, *J* = 3.6 Hz, 2H), 4.35 (q, *J* = 14.2 Hz, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100

MHz, $CDCl_3$): δ 192.1, 186.8, 164.4, 164.0, 163.9, 144.0, 133.5, 131.4, 130.9, 129.5, 129.3, 114.2, 114.0, 62.3, 55.6, 55.5, 14.0. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{21}H_{20}NaO_6$: 391.1152; found: 391.1152.

(*E*/*Z*)-2-(4-Fluoro-benzoyl)-4-(4-fluoro-phenyl)-4-oxo-but-2-enoic acid ethyl ester (2f):

The reaction was carried out according to general method A using 3-(4-Fluoro-phenyl)-3-oxo-propionic acid ethyl ester (1f, 100 mg, 0.475 mmol), I_2 (60.4 mg, 0.237 mmol), $Cu(OAc)_2.H_2O$ (19.0 mg, 0.095 mmol) and DMSO (3 mL). Conditions: 80 °C, 5 h. The title compound 2f (118.0 mg, 72% yield) was obtained as yellow oil after passing through a silica gel column chromatography.

(*E*:*Z* = 84:16); (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 8.03-7.97 (m, 2H), 7.93-7.85 (m, 2H), 7.22-7.08 (m, 4H), 4.28 (q, *J* = 14.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, t); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.8, 186.9, 167.8, 167.3, 165.2, 164.8, 163.5, 144.8, 133.2, 131.8, 131.7, 131.2, 131.1, 116.4, 116.2, 116.1, 115.9, 62.6, 13.9. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{19}H_{14}F_2NaO_4$: 367.0752; found: 367.0856.

(*E*/*Z*)-2-(4-Chloro-benzoyl)-4-(4-chloro-phenyl)-4-oxo-but-2-enoic acid ethyl ester (2g):

The reaction was carried out according to general method A using 3-(4-Chloro-phenyl)-3-oxo-propionic acid ethyl ester (1g, 100 mg, 0.441 mmol), I_2 (56.0 mg, 0.220 mmol), $Cu(OAc)_2.H_2O$ (17.6 mg, 0.088 mmol) and DMSO (3 mL). Conditions: 80 °C, 6 h. The title compound 2g (123.1 mg, 74% yield) was obtained as light semi solid after passing through a silica gel column chromatography.

(*E*:*Z* = 83:17); (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.48-7.43 (m, 4H), 4.31-4.25 (m, 2H), 1.22 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 187.2, 163.4, 145.0, 141.1, 140.2, 134.4, 134.2, 133.1, 130.8, 130.3, 129.9, 129.4, 129.2, 62.7, 13.9. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{19}H_{14}Cl_2NaO_4$: 399.0161; found: 399.0161.

(*E*/*Z*)-2-(4-Bromo-benzoyl)-4-(4-cbromo-phenyl)-4-oxo-but-2-enoic acid ethyl ester (2h):

The reaction was carried out according to general method A using 3-(4-Bromo-phenyl)-3-oxo-propionic acid ethyl ester (1h, 100 mg, 0.368 mmol), I_2 (46.8 mg, 0.184 mmol), $Cu(OAc)_2.H_2O$ (14.7 mg, 0.073 mmol) and DMSO (3 mL). Conditions: 80 °C, 6 h. The title compound 2h (128.9 mg, 75% yield) was obtained as yellow oil after passing through a silica gel column chromatography.

(*E*:*Z* = 80:20); (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.64-7.60 (m, 4H), 4.30-4.24 (m, 2H), 1.22 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.3, 187.4, 163.3, 145.0, 134.8, 134.7, 133.1, 132.4, 132.1, 130.3, 129.5, 62.7, 13.9. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{19}H_{14}Br_2NaO_4$: 486.9151; found: 486.9151.

(*E*/*Z*)-2-(4-Iodo-benzoyl)-4-(4-iodo-phenyl)-4-oxo-but-2-enoic acid ethyl ester (2i):

The reaction was carried out according to general method A using 3-(4-Iodo-phenyl)-3-oxo-propionic acid ethyl ester (1i, 100 mg, 0.314 mmol), I_2 (39.9 mg, 0.157 mmol), $Cu(OAc)_2.H_2O$ (12.5 mg, 0.062 mmol) and DMSO (3 mL). Conditions: 80 °C, 6 h. The title compound 2i (130.3 mg, 74% yield) was obtained as yellow oil after passing through a silica gel column chromatography.

(*E*:*Z* = 95:5); (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.86-7.81 (m, 4H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 4.27 (q, *J* = 14.0 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.6, 187.7, 163.3, 145.0, 138.4, 138.1, 135.3, 135.1, 133.0, 130.1, 129.8, 103.0, 101.9, 62.7, 13.9. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{19}H_{14}I_2NaO_4$: 582.8874; found: 582.8874.

(*E*/*Z*)-2-(4-Nitro-benzoyl)-4-(4-nitro-phenyl)-4-oxo-but-2-enoic acid ethyl ester (2j).

The reaction was carried out according to general method A using 3-(4-Nitro-phenyl)-3-oxo-propionic acid ethyl ester (1j, 100 mg, 0.421 mmol), I_2 (53.5 mg, 0.21 mmol), $Cu(OAc)_2.H_2O$ (16.8 mg, 0.084 mmol) and DMSO (3 mL). Conditions: 80 °C, 8 h. The title compound 2j (115.9 mg, 69% yield) was obtained as semi solid after passing through a short silica gel column chromatography.

(*E*:*Z* = 78:22); (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30-8.26 (m, 4H), 8.09 (s, 1H), 8.06 (d, *J* = 9.2 Hz, 2H), 7.99 (d, *J* = 9.2 Hz, 2H), 4.25 (q, *J* = 14.4 Hz, 2H), 1.17 (t, *J* = 7.2Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.5, 187.1, 162.7, 151.0, 150.7, 145.8, 140.0, 140.0, 132.8, 130.0, 129.4, 124.3, 124.1, 63.2, 13.9. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{19}H_{14}N_2NaO_8$: 421.0648; found: 421.0648.

(*E*/*Z*)-2-(3-Chloro-benzoyl)-4-(3-chloro-phenyl)-4-oxo-but-2-enoic acid ethyl ester (2k):

The reaction was carried out according to general method A using 3-(3-Chloro-phenyl)-3-oxo-propionic acid ethyl ester (1k, 100 mg, 0.441 mmol), I_2 (56.0 mg, 0.220 mmol), $Cu(OAc)_2.H_2O$ (17.6 mg, 0.088 mmol) and DMSO (3 mL). Conditions: 80 °C, 8 h. The title compound 2k (109.8 mg, 66% yield) was obtained as yellow oil after passing through a silica gel column chromatography.

(*E*:*Z* = 80:20); (*E*/*Z*)-mixture: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.99-7.97 (m, 1H), 7.92-7.91 (m, 1H), 7.87-7.83 (m, 1H), 7.75-7.71 (m, 1H), 7.60-7.53 (m, 1H), 7.44-7.38 (m, 2H), 4.32-4.25 (m, 2H), 1.24-1.21 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 189.6, 189.2, 187.2, 163.2, 162.8, 162.1, 145.1, 142.2, 142.0, 137.5, 137.3, 137.2, 136.8, 135.4, 135.3, 135.2, 135.1, 134.7, 134.3, 134.2, 133.9, 133.8, 133.6, 133.1, 131.0, 130.3, 130.2, 130.1, 129.8, 128.9, 128.9, 128.4, 128.3, 127.5, 127.1, 127.0, 126.6, 62.9, 62.8, 13.9, 13.7. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{19}H_{14}Cl_2NaO_4$: 399.0161; found: 399.0161.

***(E/Z)*-2-(3-Methoxy-benzoyl)-4-(3-methoxy-phenyl)-4-oxo-but-2-enoic acid ethyl ester (2l):**

The reaction was carried out according to general method A using using 3-(3-Methoxy-phenyl)-3-oxo-propionic acid ethyl ester (1l, 100 mg, 0.449 mmol), I_2 (57.1 mg, 0.224 mmol), $Cu(OAc)_2.H_2O$ (18.0 mg, 0.089 mmol) and DMSO (3 mL). Conditions: 80 °C, 8 h. The title compound 2l (112.7 mg, 68% yield) was obtained as yellow semi solid after passing through a silica gel column chromatography.

(*E*:*Z* = 80:20); (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.52-7.50 (m, 1H), 7.45-7.44 (m, 1H), 7.36-7.30 (m, 3H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.09-7.03 (m, 2H), 4.20 (q, *J* = 14.2 Hz,

2H), 3.78 (s, 3H), 3.73 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2, 188.1, 163.7, 160.1, 159.9, 144.9, 137.6, 137.1, 133.3, 129.9, 129.8, 121.7, 121.6, 121.3, 120.5, 112.5, 112.0, 62.5, 55.5, 55.4, 13.9. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{21}H_{20}NaO_6$: 391.1152; found: 391.1311.

(*E*/*Z*)-2-(2-Methoxy-benzoyl)-4-(2-methoxy-phenyl)-4-oxo-but-2-enoic acid ethyl ester (2m):

The reaction was carried out according to general method A using using 3-(3-Methoxy-phenyl)-3-oxo-propionic acid ethyl ester (1m, 100 mg, 0.449 mmol), I_2 (57.1 mg, 0.224 mmol), $Cu(OAc)_2.H_2O$ (18.0 mg, 0.089 mmol) and DMSO (3 mL). Conditions: 80 °C, 12 h. The title compound 2m (112.7 mg, 68% yield) was obtained as yellow oil after passing through a silica gel column chromatography.

(*E*:*Z* = 88:12); (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.78 (s, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.58-7.42 (m, 2H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.92 (t, *J* = 6.8 Hz, 3H), 4.25 (q, *J* = 14.2 Hz, 2H), 3.89 (s, 3H), 3.76 (s, 3H), 1.19 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 190.4, 164.4, 159.5, 159.3, 145.2, 134.8, 134.7, 134.4, 131.0, 130.1, 127.1, 126.1, 121.1, 120.8, 112.1, 111.8, 61.5, 55.8, 55.5, 14.0. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{21}H_{20}NaO_6$: 391.1152; found: 391.1231.

(*E*/*Z*)-2-(3,4-Dimethyl-benzoyl)-4-(3,4-dimethyl-phenyl)-4-oxo-but-2-enoic acid ethyl ester (2n).

The reaction was carried out according to general method A using 3-(4-Nitro-phenyl)-3-oxo-propionic acid ethyl ester (1n, 100 mg, 0.454 mmol), I_2 (57.6 mg, 0.227 mmol), $Cu(OAc)_2.H_2O$ (18.1 mg, 0.09 mmol) and DMSO (3 mL). Conditions: 80 °C, 5.5 h. The title compound 2n (125.7 mg, 76% yield) was obtained as semi solid after passing through a short silica gel column chromatography.

(*E*:*Z* = 92:8); (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.65-7.62 (m, 3H), 7.51 (dd, *J* = 1.6 Hz, 1.6 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 4.20 (q, *J* = 14.4 Hz, 4H), 2.23 (s, 3H), 2.21 (s, 9H), 1.15 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 188.0, 164.1, 144.6, 144.1, 143.3, 137.4, 137.1, 134.2, 133.9, 133.5, 130.1, 130.0, 130.0, 129.4, 126.7, 126.5, 62.4, 20.2, 20.2, 19.8, 19.7, 14.0. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{23}H_{24}NaO_4$: 387.1572; found: 387.1572.

(*E*/*Z*)-4-Oxo-2-(thiophene-2-carbonyl)-4-thiophen-2-yl-but-2-enoic acid ethyl ester (2o):

The reaction was carried out according to general method A using 3-Oxo-3-thiophen-2-yl-propionic acid ethyl ester (1o, 100 mg, 0.504 mmol), I_2 (64.0 mg, 0.252 mmol), $Cu(OAc)_2.H_2O$ (20.1 mg, 0.1 mmol) and DMSO (3 mL). Conditions: 80 °C, 3 h. The title compound 2o (126.0 mg, 78% yield) was obtained as yellow oil after passing through a short silica gel column chromatography.

(*E*:*Z* = 78:22); (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.88 (dd, *J* = 0.8Hz, 1.0 Hz, 1H), 7.75 (dd, *J* = 1.2 Hz, 0.8 Hz, 1H), 7.69 (dd, *J* = 1.2 Hz, 0.8 Hz, 1H), 7.19 (t, *J* = 4.4 Hz, 3H), 7.09 (t, *J* = 4.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.9, 180.0, 163.4, 144.1, 143.4, 143.0, 136.4, 134.5, 133.9, 133.3, 133.1, 128.7, 128.2, 62.6, 13.9. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{12}NaO_4S_2$: 343.0069; found: 343.0152.

(*E*/*Z*)-2-(Naphthalene-1-carbonyl)-4-naphthalen-1-yl-4-oxo-but-2-enoic acid ethyl ester (2p):

The reaction was carried out according to general method A using 3-Naphthalen-1-yl-3-oxo-propionic acid ethyl ester (1p, 100 mg, 0.412 mmol), I_2 (52.4 mg, 0.206 mmol), $Cu(OAc)_2.H_2O$ (16.5 mg, 0.082 mmol) and DMSO (3 mL). Conditions: 80 °C, 6 h. The title compound 2p (126.4 mg, 75% yield) was obtained as yellow oil after passing through a silica gel column chromatography.

(*E*:*Z* = 90:10); (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 (d, *J* = 8.8 Hz, 2H), 8.35 (d, *J* = 8.4 Hz, 2H), 8.05 (s, 1H), 8.02-7.99 (m, 3H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 3H), 7.55 (t, *J* = 6.6, 3H), 7.42-7.51 (m, 3H), 4.31 (q, *J* = 14.2 Hz, 2H), 1.21 (t, *J* = 7.0 Hz, 3H), ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3, 192.3, 164.3, 144.3, 137.3, 134.3, 133.9, 131.5, 130.4, 128.5, 128.4, 128.4, 128.2, 126.7, 126.6, 126.1, 125.5, 124.2, 124.1, 62.3, 13.9. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{27}H_{20}NaO_4$: 431.1254; found: 431.1386.

(*E*/*Z*)-2-(4-Methoxy-benzoyl)-4-(4-methoxy-phenyl)-4-oxo-but-2-enoic acid methyl ester (2q):

The reaction was carried out according to general method A using 3-Oxo-3-phenyl-propionic acid methyl ester (1q, 100 mg, 0.480 mmol), I_2 (60.9 mg, 0.240 mmol), $Cu(OAc)_2.H_2O$ (19.1 mg, 0.096 mmol) and DMSO (3 mL). Conditions: 80 °C, 5.5 h. The title compound 2q (136.1 mg, 80% yield) was obtained as semi solid after passing through a short silica gel column chromatography.

(*E*:*Z* = 92:8); (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.88 (d, *J* = 8.8 Hz, 2H), 6.96-6.93 (m, 4H), 3.88 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 186.6, 164.6, 164.5, 164.0, 143.5, 133.7, 131.4, 131.0, 129.5, 129.2, 114.2, 114.1, 55.6, 55.5, 53.2. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{20}H_{18}O_6$: 377.0995; found: 377.1115.

2-Phenyl-quinoxaline (4a):[24]

The reaction was carried out according to general method B using 2-Benzoyl-4-oxo-4-phenyl-but-2-enoic acid ethyl ester (2a, 100 mg, 0.324 mmol), Benzene-1,2-diamine (3a 38.6 mg, 0.356 mmol), I_2 (16.5 mg, 0.064 mmol) and DMSO (2 mL). Conditions: r.t., 3 h. The title compound 4a (57.5 mg, 86% yield) was obtained as white crystal after passing through a short silica gel column chromatography.

mp: 71-73 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (s, 1H), 8.21-8.11 (m, 4H), 7.81-7.72 (m, 2H), 7.59-7.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 143.3, 142.4, 141.6, 136.8, 130.3, 130.2, 129.7, 129.6, 129.2, 129.1, 127.6.

2-*p*-Tolyl-quinoxaline (4b):[24]

The reaction was carried out according to general method B using 2-(4-Methyl-benzoyl)-4-oxo-4-*m*-tolyl-but-2-enoic acid ethyl ester (2c, 100 mg, 0.297 mmol), Benzene-1,2-diamine (3a, 35.4, 0.327 mmol), I_2 (15.1 mg, 0.059 mmol) and DMSO (2 mL). Conditions: r.t., 3 h. The title compound 4b (55.0 mg, 84% yield) was obtained as yellow solid after passing through a short silica gel column chromatography.

mp: 90-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.09-8.03 (m, 4H), 7.73-7.64 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 143.1, 142.3, 141.2, 140.6, 133.9, 130.3, 129.9, 129.5, 129.4, 129.0, 127.5, 21.4.

2-(3-Methoxy-phenyl)-quinoxaline (4c):[25]

The reaction was carried out according to general method B using 2-(4-Methoxy-benzoyl)-4-(3-methoxy-phenyl)-4-oxo-but-2-enoic acid ethyl ester (2e, 100 mg, 0.271 mmol), Benzene-1,2-diamine (3a, 32.6 mg, 0.298 mmol), I_2 (13.8 mg, 0.054 mmol) and DMSO (2 mL). Conditions: r.t., 3 h. The title compound 4c (52.6 mg, 82% yield) was obtained as light yellow solid after passing through a short silica gel column chromatography.

mp: 108-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (s, 1H), 8.07-8.01(m, 2H), 7.70-7.62 (m, 4H), 7.37 (t, J = 8.0 Hz, 1H), 6.96 (dd, J = 8.4, 2.4 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 151.6, 143.4, 142.2, 141.7, 138.2, 130.3, 130.2, 129.6, 129.6, 129.1, 119.9, 116.2, 112.7, 55.5.

2-(4-Fluoro-phenyl)-quinoxaline (4d):[25]

The reaction was carried out according to general method B using 2-(4-Fluoro-benzoyl)-4-(3-fluoro-phenyl)-4-oxo-but-2-enoic acid ethyl ester (2f, 100 mg, 0.29 mmol), Benzene-1,2-diamine (3a, 34.5 mg, 0.319 mmol), I_2 (14.7 mg, 0.058 mmol) and DMSO (2 mL). Conditions: r.t., 2.5 h. The title compound 4d (55.3 mg, 85% yield) was obtained as white crystal after passing through a short silica gel column chromatography.

mp: 97-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.30 (s, 1H), 8.21 (d, J = 6.4 Hz, 2H), 8.13 (d, J = 7.8 Hz, 2H), 7.81-7.74 (m, 2H), 7.26 (d, J = 8.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 163.1, 150.8, 142.9, 142.2, 141.5, 133.0, 130.4, 129.6, 129.6, 129.6, 129.5, 129.1, 116.4, 116.1.

2-(4-Chloro-phenyl)-quinoxaline (4e):[24]

The reaction was carried out according to general method B using 2-(4-Chloro-benzoyl)-4-(3-chloro-phenyl)-4-oxo-but-2-enoic acid ethyl ester (2g, 100 mg, 0.265 mmol), Benzene-1,2-diamine (3a, 31.5 mg, 0.291 mmol), I_2 (13.5 mg, 0.053 mmol) and DMSO (2 mL). Conditions: r.t., 3.0 h. The title compound 4e (51.0 mg, 80% yield) was obtained as light yellow crystal after passing through a short silica gel column chromatography.

mp: 130-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (s, 1H), 8.16-8.11 (m, 4H), 7.81-7.73(m, 2H), 7.53 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 142.8, 142.2, 141.7, 136.6, 135.2, 130.5, 129.8, 129.6, 129.2, 128.8.

2-Biphenyl-4-yl--quinoxaline (4f):[24]

The reaction was carried out according to general method B using 2-(Biphenyl-4-carbonyl)-4-biphenyl-4-yl-4-oxo-but-2-enoic acid ethyl ester (2b, 100 mg, 0.217 mmol), Benzene-1,2-diamine (3a, 25.8 mg, 0.238 mmol), I_2 (11.0 mg, 0.043 mmol) and DMSO (2 mL). Conditions: r.t., 4.5 h. The title compound 4f (50.3 mg, 82% yield) was obtained as grey solid after passing through a short silica gel column chromatography.

mp: 131-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.39 (s, 1H), 8.30 (d, J = 7.6 Hz, 2H), 8.16 (dd, J = 8.4 Hz, 8.0 Hz, 2H), 7.82-7.74 (m, 4H), 7.69 (d, J = 7.6 Hz, 2H), 7.49 (t, J = 7.4 Hz, 2H), 7.40 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 143.2, 143.1, 142.4, 141.6, 140.3, 135.6, 130.3, 129.6, 129.5, 129.1, 128.9, 128.0, 127.9, 127.2.

2-Naphthalen-1-yl--quinoxaline (4g):[24]

The reaction was carried out according to general method B using 2-(Naphthalene-1-carbonyl)-4-naphthalen-1-yl-4-oxo-but-2-enoic acid ethyl ester (2p, 100 mg, 0.244 mmol), Benzene-1,2-diamine (3a, 29.1 mg, 0.269 mmol), I_2 (12.4 mg, 0.048 mmol) and DMSO (2 mL). Conditions: r.t., 4.0 h. The title compound 4g (48.3 mg, 77% yield) was obtained as grey solid after passing through a short silica gel column chromatography.

mp: 135-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.09 (s, 1H), 8.16-8.08 (m, 3H), 7.95-7.88 (m, 2H), 7.78-7.69 (m, 3H), 7.56 (t, J = 7.6 Hz, 1H), 7.50-7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 146.6, 142.2, 141.4, 135.1, 134.1, 131.2, 130.4, 130.2, 130.0, 129.7, 129.3, 128.7, 128.5, 127.2, 126.4, 125.4, 125.1.

2-Thiophen-2-yl--quinoxaline (4h):[24]

The reaction was carried out according to general method B using 4-Oxo-2-(thiophene-2-carbonyl)-4-thiophen-2-yl-but-2-enoic acid ethyl ester (2o, 100 mg, 0.312 mmol), Benzene-1,2-diamine (3a, 37.1 mg, 0.343 mmol), I_2 (15.8 mg, 0.062 mmol) and DMSO (2 mL). Conditions: r.t., 2.5 h. The title compound 4h (54.3 mg, 82% yield) was obtained as yellow crystal after passing through a short silica gel column chromatography.

mp: 114-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.08-8.05 (dd, J = 3.6 Hz, 3.2 Hz, 2H), 7.86 (d, J = 3.6 Hz, 1H), 7.76-7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 7.20 (t, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 142.3, 142.2, 142.1, 141.4, 130.4, 129.8, 129.2, 129.1, 128.5, 127.0.

6-Methyl-2-pheny--quinoxaline and 7-Methyl-2-pheny--quinoxaline (4i):[24]

The reaction was carried out according to general method B using 2-Benzoyl-4-oxo-4-phenyl-but-2-enoic acid ethyl ester (2a, 100 mg, 0.324 mmol), 4-Methyl-benzene-1,2-diamine (3b, 43.6 mg, 0.356 mmol), I_2 (16.5 mg, 0.064 mmol) and DMSO (2 mL). Conditions: r.t., 3.0 h. The title compound 4i (56.4 mg, 79% yield) was obtained as white crystal after passing through a short silica gel column chromatography.

mp: 108-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.28-9.25 (m, 1H), 8.18 (d, J = 7.2 Hz, 2H), 8.05-7.99 (m, 1H), 7.93-7.89 (m, 1H), 7.62-7.50 (m, 4H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 151.1, 143.1, 142.4, 141.6, 140.8, 140.8, 140.2, 140.1, 137.0, 132.6, 131.9, 130.1, 130.0, 129.2, 129.1, 128.6, 128.5, 127.9, 127.5, 127.4, 21.8, 21.8.

2-(4-Methoxy-phenyl)-6-methyl--quinoxaline and 2-(4-Methoxy-phenyl)-6-methyl--quinoxaline (4j):

The reaction was carried out according to general method B using 2-(4-Methoxy-benzoyl)-4-(3-methoxy-phenyl)-4-oxo-but-2-enoic acid ethyl ester (2e, 100 mg, 0.271 mmol), 4-Methyl-benzene-1,2-diamine (3b, 13.7 mg, 0.298 mmol), I_2 (11.2 mg, 0.054 mmol) and DMSO (2 mL). Conditions: r.t., 3.0 h. The title compound 4j (55.0 mg, 81% yield) was obtained as yellow solid after passing through a short silica gel column chromatography.

mp: 121-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24-9.21 (m, 1H), 8.18-8.13 (m, 2H), 8.02-7.96 (m, 1H), 7.89-7.86 (m, 1H), 7.60-7.53 (m, 1H), 7.07 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 161.4, 151.4, 150.8, 142.8, 142.1, 141.1,140.8, 139.6, 132.5, 131.4, 129.5, 128.9, 128.9, 128.8, 128.5, 128.2, 127.9, 114.6, 55.4, 21.8, 21.8. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{15}N_2O$: 251.1184; found: 251.1201.

2-(3-Chloro-phenyl)-pyrazine (6):

To a solution of 2-(3-Chloro-benzoyl)-4-(3-chloro-phenyl)-4-oxo-but-2-enoic acid ethyl ester (2j, 100 mg, 0.265 mmol) in DMSO (3 mL), Ethane-1,2-diamine (5, 17.5 mg, 0.291 mmol), I_2 (13.5 mg, 0.05 mmol) and K_2CO_3 (44 mg, 0.318 mmol) was added at room temperature and heated at 80 ^oC for 8 h. After completion, the reaction mixture was allowed to cool to room temperature and quenched with sodium thiosulfate water and ethyl acetate. The organic phase was separated, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel column chromatography using hexane / ethyl acetate as eluent. The title compound 6 (36.4 mg, 72% yield) was obtained as light yellow solid after passing through a short silica gel column chromatography.

mp: 92-94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (s, 1H), 8.58 (dd, J = 2.0, 1.6 Hz, 1H), 8.48 (d, J = 2.4 Hz, 1H), 7.98 (s, 1H), 7.83-7.81(m, 1H), 7.39-7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 144.3, 143.6, 142.2, 138.1, 135.3, 130.3, 130.0, 127.2, 124.9. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_7ClN_2Na$: 213.0195; found: 213.0198.

(9,9a-Dihydro-4aH-β-carbolin-1-yl)-(4-methoxy-phenyl)-methanone (8):[21]

To a solution of 2-(4-Methoxy-benzoyl)-4-(4-methoxy-phenyl)-4-oxo-but-2-enoic acid ethyl ester (2j, 100 mg, 0.271 mmol) in DMSO (3 mL), Tryptamine (7, 47.8 mg, 0.298 mmol), and $Cu(OAc)_2.H_2O$ (16.3 mg, 0.081 mmol) was added at room temperature and heated at 80 ^oC for 6 h. After completion, the reaction mixture was allowed to cool to room temperature and quenched with water and ethyl acetate. The organic phase was separated, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel column chromatography using hexane / ethyl acetate as eluent. The title compound 8 (62.4 mg 76% yield) was obtained as light brown solid after passing through a short silica gel column chromatography.

mp: 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.48 (s, 1H), 8.63 (d, J = 5.2 Hz, 1H), 8.48 (d, J = 7.0 Hz, 2H), 8.21-8.18 (m, 2H), 7.64-7.63 (m, 2H), 7.39-7.35 (m, 1H), 7.07 (dd, J = 2.0, 2.0 Hz, 2H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 163.3, 141.0, 137.8, 137.3, 137.0, 133.8, 131.6, 130.3, 129.2, 121.8, 120.9, 120.6, 118.2, 113.4, 112.0, 55.5.

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