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Paper

Photoinduced iodine-mediated tandem dehydrogenative Povarov cyclisation / C–H oxygenation reactions

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We report metal-free, photoinduced aerobic tandem dehydrogenative Povarov cyclisation / C_{sp}^{3} -H oxygenation reactions between *N*-aryl glycine esters and α -substituted styrenes, which efficiently lead to 4,4disubstituted dihydroquinoline-3-ones under mild conditions. The reactions are mediated by iodine along with visible light irradiation, which allows for the *in situ* generation of the essential Brønsted acid HI, to catalyse the key imine [4+2]-cycloaddition.

The direct oxidative C-H functionalisation of organic compounds is a highly attractive strategy for sustainable and targetoriented synthesis, and versatile new synthetic methods have emerged in recent years.¹ As an example, the C_{sp}³–H functionnalisation of amines has attracted much attention, and it has extensively been utilized for the synthesis of polysubstituted amines as well as in the construction of N-heterocyclic compounds. One such protocol is the dehydrogenative Povarov reaction between N-aryl glycines and alkenes (Scheme 1). In these reactions, an amine-to-imine oxidation precedes a pivotal imine [4+2]-cycloaddition, which can be catalysed by a wide range of Brønsted or Lewis acids,² and the consecutive oxidative aromatization leads to substituted quinoline products. Dehydrogenative Povarov reactions have been achieved utilizing metal catalysts like Cu(I) and Cu(II) salts as well as Fe(II) and Au(I) and Au(III) complexes along with DDQ, organic peroxides or O_2 as the stoichiometric oxidants³ (Scheme 1a). Double dehydrogenative variants of the Povarov reaction, including the parallel oxidation of an alkane as the precursor to the alkene 2π component, have also been introduced lately,⁴ as well as first photoredox catalytic protocols.⁵ In 2017, Jia and coworkers reported a dehydrogenative Povarov reaction between N-aryl glycines and α -substituted styrenes, which was accompanied by a subsequent C_{sp}³–H oxygenation. Utilizing a dual catalytic system of a Cu(II) salt along with an aminium radical cation salt in the presence of oxygen, 4,4-disubstituted quinolone-3-ones could be accessed by these tandem functionalisations⁶ (Scheme 1b).

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We recently reported photoinduced and transition metal-free dehydrogenative Povarov reactions, mediated by iodine and visible light under aerobic conditions (Scheme 1c, left).^{7a,b} The initial dehydrogenation of N-aryl glycine esters was followed by regioselective Povarov cyclisations with indoles, and efficient aromatization of the intermediate cycloadducts under the aerobic conditions led to tetracyclic indolo[3,2-c]quinoline products in high yields. In these reactions, atomic iodine, generated by photolysis of a substoichiometric quantity of I₂, effected six consecutive hydrogen abstractions, and the in situgenerated hydrogen iodide (HI) acted as the Brønsted acid catalyst for the key imine [4+2]-cycloaddition. Herein, we report that the same metal-free system of I2 and O2, under blue light irradiation, also efficiently mediates tandem dehydrogenative Povarov cyclisation / C_{sp}³–H oxygenation reactions between Naryl glycines and 1,1-disubstituted alkenes (Scheme 1c, right).











transition metal-free protocols
• photoinduced reactions
• aerobic conditions
• valuable products

Scheme 1. Methods for dehydrogenative Povarov reactions.

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We initially observed that reacting *N*-*p*-toluidinyl glycine ester 1a with α -methylstyrene (2a) in MeCN, in the presence of 10 mol-% of iodine, under O₂ atmosphere and with blue light irradiation, led to full conversion of glycine ester 1a, while the 4,4-disubstituted dihydroquinoline-3-one 3a was produced in 15% yield, conversion of α -methylstyrene (2a) being incomplete at 73% (Table 1, entry 1). Increasing quantities of I_2 and prolonged reaction times both improved the yield of 3a (entries 2-5), even though an extended reaction time with only 20 mol-% of iodine did not lead to a significant increase in yield of 3a despite complete conversion of both substrates, 1a and 2a (entry 3). Using 50 mol-% of I₂ under continuous irradiation for 48 h furnished the desired product 3a in 74% isolated yield (entry 5). Alternative iodine sources such as N-iodosuccinimide (NIS) and iodine monochloride (ICI) also induced the dehydrogenative Povarov cyclisation / oxygenation reaction between 1a, 2a and O₂, however, with lesser efficiency (entries 6 and 7). Tetramethylammonium dichloroiodate⁸ was unsuitable as promoter, leaving glycine ester 1a as well as styrene derivative 2a fully intact (entry 8). Using bromine or NBS at 50 mol-% each, no or hardly any conversion of glycine ester 1a occurred (entries 9 and 10), but these reagents effected the full conversion of α -methylstyrene (2a) into a mixture of unwanted brominated products.

Table 1. Reaction optimization.

Ĺ	1a (2.0 equiv.)	+ 2a (1.0 equiv.)	- conditions - O ₂ , MeCN hv (450±50 nm) r.t.		OEt OBa
 #	reagent (mol-%)	time [h]	conv. 1a [%] ^[a]	conv. 2a [%] ^[a]	yield 3a [%] ^[b]
1	I ₂ (10)	24	100	73	15
2	I ₂ (20)	24	100	81	50
3	I ₂ (20)	48	100	100	54
4	I ₂ (50)	24	100	85	53
5	I ₂ (50)	48	100	100	74 (74 ^[c])
6	NIS (50)	48	100	100	50
7	ICI (50)	48	0	100	44
8	Me ₄ N ⁺ ICl ₂ ⁻ (50)	48	0	0	0
9	Br ₂ (50)	48	0	100	0
 10	NBS (50)	48	12	100	0

Reactions were performed on 0.10 mmol scale of **2a**, irradiation with 36 W blue compact fluorescent lamps (CFL), $\lambda = (450\pm50)$ nm. [a] Conversion determined by ¹H NMR spectroscopic analysis. [b] Yield determined by ¹H NMR spectroscopy against CH₂Br₂ as internal standard. [c] Yield of isolated product after chromatography.

A number of 3,4-dihydroquinoline-3-ones **3** could readily be synthesized under the optimized reaction conditions (Figure 1). Utilizing *p*-toluidinyl glycine ester **1a** in combination with various α -alkylstyrenes, full conversion of the alkenes **2** was observed in all cases and products **3a-3f** could be obtained in yields ranging from 59-74%. 1,1-Diarylethenes also were suitable 2π -components, leading to the 4,4-diarylated compounds **3g** and **3h** with 47% and 48% yield, respectively. Upon variation of the *N*-aryl glycine ester component, we found that both donor and acceptor substituents on the aromatic ring diminished the product **3i-3l** were isolated in moderate yields

of 23-33% after 48 h.⁹ In addition, *N*-Phenyl glycine, **1** f as well as the 4-trifluoromethylphenyl and the 3-pyridyl derivatives **1** g and **1h** were unsuitable reaction partners. While compound **1** f partially underwent aromatic iodination under the reaction conditions, the electron-deficient amines **1** g and **1h** did not undergo the initial dehydrogenation to the corresponding imines. Further, the use of non-conjugated alkenes like e.g. limonene **(4)** was unsuccessful.



 $\label{eq:Figure 1. Reaction scope. Yields after chromatography. Conditions: 1 (0.20 mmol), 2 (0.10 mmol), I_2 (50 mol-%), MeCN (0.03 M), O_2, hv (450\pm50) nm, r.t., 48 h.$

The diminished yields in the reactions leading to compounds 3g and 3h can partially be attributed to the fact that conversion of the alkene component 2 was incomplete even after a reaction time of 48 h, evidently as a result of a less efficient and somewhat slower [4+2]-cycloaddition. In addition, the 1,1diaryl-substituted ethenes partially underwent oxidative C,Ccleavage to the corresponding benzophenones which could be isolated as byproducts in these reactions. Another origin of the decreased reaction selectivity in some cases became evident in reaction of *p*-anisidinyl glycine ester **1i** with α -methylstyrene **2a**. While 3,4-dihydroquinoline-2-carboxy-late 3m was isolated in a moderate yield of 28%, the rearranged 4-methyl-3phenylquinoline 5 was generated in 23% yield (Scheme 2a). The same rearrangement was observed in several other reactions, however, the corresponding products were formed in small quantities (<5%) only. Their formation can be rationalised by the generation of an intermediate azaallyl radical 6 followed by an intramolecular 1,2-aryl shift via the spirocyclohexadienyl radical 7 and a succeeding benzylic radical 8 which undergoes a final dehydrogenation to 5.6,10 In addition to 1,1-disubstituted styrenes, β -methylstyrene (9) could also be employed in the dehydrogenative Povarov reaction with glycine ester 1a, leading Published on 24 August 2020. Downloaded by Goteborgs Universitet on 8/24/2020 9:41:34 PM.

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to 3-methyl-4-phenyl-substituted quinoline carboxylate **10** in 65% yield (Scheme 2b). 2,3-Dihydrofuran (**11**) was another suitable 2π -component, to give the δ -lactone-fused quinoline **12** after cycloaddition, acid-induced ring-opening and intramolecular transesterification (Scheme 2c).^{11,4d}



Scheme 2. a) Reaction leading to the rearranged 3,4-disubstituted quinoline 5. b) Reaction between 1a and β -methylstyrene (9). c) Reaction between 1a and 2,3-dihydrofuran (11).

Control experiments aimed at elucidating the reaction mechanism are depicted in Scheme 3. When N-p-toluidinyl glycine ester 1a was irradiated alone, under the typical reaction conditions, imine 13a was formed quantitatively within 48 h (Scheme 3a). The reaction between imine 13a and α methylstyrene (2a) in the presence of light, O2 and iodine produced compound 3a in 74% yield, just as observed when employing glyine ester 1a (Scheme 3b). No reaction occurred in the absence of I_2 , O_2 or visible light (Scheme 3c). When the reference reaction between 1a and 2a was conducted in the presence of one equivalent of TEMPO, radical adduct 14 was formed as confirmed by ESI-TOF mass spectrometry (Scheme 1d). Consistent with the above observations and previous reports,6,7a,12 we propose a reaction mechanism as shown in Scheme 4. Photolysis of molecular iodine generates atomic iodine, which abstracts a methylene hydrogen atom from glycine ester 1, to give α -amino radical 15 and hydrogen iodide (HI). Trapping of 15 with oxygen gives peroxyl radical 16, which reacts with substrate 1 in a chain propagation step, generating hydroperoxide 17. Elimination of hydrogen peroxide (H_2O_2) produces imine 13, which undergoes a Brønsted acid-catalysed Povarov cyclisation with styrene derivative 2, mediated by the in situ-generated HI. The HI catalyst can be reoxidised to I₂ by H₂O₂.¹³ Cycloadduct **18** is dehydrogenated to 3,4-dihydroquinoline intermediate 19 by atomic iodine, again generating

HI. Another hydrogen abstraction from **19** by l⁻ leads to azaally radical **20**, which adds a second molecule of OQ.1ATAPPRETORNAM propagation step between peroxyl radical **21** and glycine ester **1** gives hydroperoxide **22**, which, under elimination of water, is converted into product **3**. Overall, the Brønsted acid catalyst HI, which drives the [4+2]-cycloaddition, is generated *in situ* by this method, while five H-abstraction steps are effected by atomic iodine. Since just 50 mol-% of I₂ are employed, corresponding to one equivalent of reactive iodine atoms, the reaction can be classified as catalytic in iodine. This is also confirmed by the entries 6 and 7 in Table 1, where NIS and ICI were employed as promoters in 50 mol-% quantity each.







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Conclusions

lodine, in the presence of oxygen and under visible light irradiation, efficiently mediates the metal-free tandem Povarov cyclisation / C_{sp}³–H oxygenation dehydrogenative reaction between N-aryl glycine esters and styrenes, to afford differentially substituted dihydroguinoline-3-ones in moderate to high yields. A substoichiometric quantity of 50 mol-% of I2 allows for the consecutive abstraction of five hydrogen atoms, and thus the reaction can be regarded as catalytic in iodine. Moreover, the essential Brønsted acid catalyst to mediate the pivotal imine [4+2]-cycloaddition is readily generated in situ during the course of the multistep reaction. Future investigations are necessary to overcome intrinsic limitations of the present method, such as the lack of reactivity of electrondeficient N-arylglycine esters like 1g and 1h in the initial dehydrogenation event.

Experimental

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General procedure for the synthesis of compounds 3. In a 10 mL crimp cap vial, N-aryl glycine ester 1 (typically 0.20 mmol) and styrene derivative 2 (typically 0.10 mmol) were dissolved in MeCN (3.50 mL per 0.10 mmol of 2). I₂ (50 mol-%) was added, the vial was sealed and fitted with an O2-balloon (septum pierced by needle). The mixture was irradiated between two blue CFL lamps (2×18 W, 450 \pm 50 nm) with rapid stirring for 48 h. The mixture was poured into $NaHCO_3$ aq. and $Na_2S_2O_3$ aq. followed by extraction with EtOAc (3×). The combined organic layers were dried with Na₂SO₄, filtered and evaporated to dryness. Column chromatography (silica gel) furnished product 3.

Conflicts of interest

There are no conflicts to declare.

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TOC graphic



Visible light and iodine mediate dehydrogenative imine [4+2]cycloaddition / C-H oxygenation reactions to furnish highly functionalised 3-quinolones under metal-free conditions.

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amine dehydrogenation \rightarrow imine [4+2]-cycloaddition \rightarrow C–H oxygenation