Abstract: A metal-free, photoinduced aerobic tandem amine
dehydrogenation/Povarov cyclization/aromatization reaction
between N-aryl glycine esters and indoles leads to tetracyclic
11H-indolo[3,2-c]quinolines under mild conditions and with
high yields. The reaction can be performed by using molecular
iodine along with visible light, or by combining an organo-
photoredox catalyst with a halide anion. Mechanistic stud-
ies reveal that product formation occurs through a combina-
tion of radical-mediated oxidation steps with an iminium ion
or N-haloiminium ion [4+2]-cycloaddition, and the N-hetero-
cyclic products constitute new analogues of the antiplasmo-
dial natural alkaloid isocryptolepine.

Introduction

The Povarov reaction (i.e., the aza-Diels–Alder reaction of
imines with electron-rich alkenes) is a classical and versatile
method for the synthesis of polysubstituted tetrahydroquino-
lines,[1] and the pivotal imine [4+2]-cycloaddition can be cata-
lyzed by a range of Brensted or Lewis acids.[2] In recent years,
dehydrogenative Povarov reactions have been developed
(Scheme 1a), in which an amine-to-imine oxidation precedes
the imine [4+2]-cycloaddition, followed by aromatization to
quinoline products. These protocols typically involve the use
of metal catalysts like CuI and CuII salts as well as FeII and AuI
and AuIII complexes, along with 2,3-dichloro-5,6-dicyano-1,4-
benzoquinone (DDQ), organic peroxides, or O2 as the stoichi-
ometric oxidants.[3] A thermal double dehydrogenative variant
of the Povarov reaction, including the parallel oxidation of an
alkane as the precursor to the alkene 2 component, has also
been introduced,[4] and Huo et al. remarkably could achieve
such a process using the metal-free system of CBr4 and PPh3
(Scheme 1b).[5] In the arena of photochemistry, Li and Zhang
developed a dual photoredox and Lewis acid catalyzed dehy-
drogenative Povarov reaction between glycinic esters and sty-
renes (Scheme 1c),[6] and later they also demonstrated the use

Scheme 1. Methods for the tandem dehydrogenative Povarov/aromatization reaction.\[\text{NHPi} = \text{N-hydroxyphthalimid, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TBHP = tert-butyl hydroperoxide, PC = photoredox catalyst.}\]
of Eosin Y as an organic photocatalyst for the dehydrogenation of glycine esters in the Brønsted acid mediated cycloaddition with dihydrofuran.[8] A single example of an aerobic photoinduced Cu^2+ mediated reaction has also been reported.[9]

We report here the tandem amine dehydrogenation/iminolysis[4+2]-cycloaddition/ aromatization of glycine esters with indoles. We developed two photoinduced aerobic and metal-free variants of this reaction, either using I_2 with blue light irradiation, or employing a system combining an organic photoredox catalyst with a source of halide anion X^- and visible light (Scheme 1d). 11H-Indolo[3,2-c]quinoline products were obtained under mild conditions and with yields up to 99%. These tetracyclic compounds possess the core structure of the natural alkaloid isocryptolepine from the West African flowering plant Cryptolepis sanguinolenta, which shows antimalarial activity against Plasmodium falciparum.[10] Therefore, new derivatives of isocryptolepine have been of ongoing interest in medicinal chemistry research.[11]

Results and Discussion

Initially, we observed that reacting p-anisidinyl glycine ester 1a with N-Boc-indole (2a) (Boc = tert-butoxycarbonyl) in the presence of small amounts of molecular iodine and oxygen under blue light irradiation led to the aromatic N-Boc-protected 11H-indolo[3,2-c]quinoline-6-carboxylate 4a in a mixture with the Boc-deprotected derivative 4a', and the reaction was subsequently optimized as shown in Table 1, method A (see also Table S1, Supporting Information). Using 10 mol% of I_2 in MeCN under air led to a combined yield of cycloadducts 4a,4a' of 38% after 48 h (Table 1, entry 1). When the same reaction was performed in the dark, the dihydro-11H-indolo[3,2-c]quinoline 3a was formed in 12% yield along with 5% of product 4a. The intermediacy of 3a in the reaction was soon confirmed because its conversion to 4a,4a' increased with prolonged reaction time. Increasing quantities of I_2 and oxygen both improved the yields of 4a and 4a' (Table 1, entries 3–5), and using 50 mol% of I_2 under O_2 atmosphere fully converted indole 2a within 48 hours, to give compound 4a in a high yield of 70% after chromatography, along with 22% of its Boc-deprotected congener 4a'. Br_2 could be used in place of I_2 (Table S1, Supporting Information); however, this resulted in lesser conversion and a markedly decreased selectivity. Under the optimum conditions, no conversion occurred in the absence of I_2 and just 14% in the absence of O_2, whereas in the case of p-anisidinyl glycine ester 1a, some product formation was also observed in the dark, which can be attributed to the particular ease of antioxidation of the highly electron-rich substrate 1a. By comparison, the analogous dark reaction of the much less activated p-toluidinyl glycine ester 1b gave only trace amounts of the corresponding product 4b (<5%) (Table S1, Supporting Information). Employing N-tosylindole (2b) in the reaction with 1a under the optimum conditions, none of the corresponding indolo[3,2-c]quinolines could be detected. Using N-acetylindole (2c), its cycloadducts were formed in only 14% combined yield, whereas 1H-indole (2d) underwent decomposition to undefined products (entry 6).

We subsequently aimed at developing an alternative photoorganocatalytic variant of the reaction (Table 1, method B), which potentially would allow replacement of I_2 by the iodine anion. Although Fukuzumi’s catalyst[12] along with a catalytic quantity of tetrabutylammonium iodide (TBAI) under O_2 in MeCN slowly converted glycine ester 1a to the corresponding imine (56% conversion after 48 h), no cycloaddition products were detected (entry 7). The same reaction with the triphenylpyrylium (TPP^+·) cation as the organic photocatalyst gave a similar result, however, with quantitative conversion of 1a to the imine. Using 1 mol% of TPP-BF_4, and 10 mol% of TBAI in the protic solvent mixture of hexafluoroisopropanol (HFIP) and dichloroethane (DCE), conditions similar to those previously used by Muñiz et al. for photocatalytic Hofmann–Löffler-type reactions,[13] glycine ester 1a and N-Boc-indole (2a) were converted into the Boc-deprotected aromatic cycloadduct 4a' with 48% yield after 48 h (Table 1, entry 9). After further experimentation (Table 1, entries 10 and 11 and Table S1, Supporting Information), the best conditions were using 1 mol% of

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TPP-BF₄ with irradiation for 72 h, to give 4a’ as the major product with 52% yield, accompanied by 10% of N-Boc-protected compound 4a. To generate a single product, the reaction mixture was subsequently treated with trifluoroacetic acid (TFA), to furnish compound 4a’ in an isolated yield of 55% after chromatography. Using glycine ester 1a, a maximum conversion of indole 2a of 74% was obtained under these conditions; however, in the case of p-toluidinyl-substituted 1b, we demonstrated that despite incomplete conversion of 2a of 80% (Table 1, entry 12), an isolated yield as high as 75% for compound 4b’ could be achieved. Further, we found that tetra-n-butylammonium bromide (TBABr) could be used in place of TBAI (Table S1, Supporting Information).

The scope of the visible-light-mediated tandem dehydrogenative Povarov/aromatization reaction is depicted in Scheme 2. Using method A, various donor-substituted N-aryl glycine esters 1a–1f were employed in the reaction giving rise to clean and quantitative conversion of N-Boc-indole (2a) in all cases. The indolo[3,2-c]quinoline products 4a–4f were isolated in high yields of 59–85%, along with minor quantities of their N-deprotected analogues 4a’–4f (9–35%), which were readily separated by column chromatography. Using method B, compounds 4a’–4f were obtained in 55–75% yield after treatment of the crude product mixtures with TFA. Notably, the N-phenyl glycine ester 1g did not provide the products 4g,4g’ under the conditions of method A (aromatic iodination of the aniline ring occurred), but using method B, derivative 4g’ was prepared in 37% yield. Further, acceptor-substituted glycine esters like the 4-trifluoromethylphenyl and 4-cyanophenyl derivatives 1h and 1i did not react when employed under conditions A. However, by using the photocatalyst TPP-BF₄ with a halide anion, this limitation could be overcome. Thus, product 4h’ was formed in 17% yield with TPP+/TBAI, and with a significantly improved yield of 52% with TBABr in place of TBAI.

In the case of 4-cyanophenyl glycine ester 1i, the best result was achieved by using the photocatalyst along with tetrabuty-
lammonium chloride (TBACl), to furnish product 4i' in 54 % yield. In addition to N-Boc-indole (2a), N-Boc-5-bromoindole (2e) as well as the 5- and 7-methoxylated N-Boc-indoles 2f and 2g were used, giving rise to polysubstituted indolokinolines 4j–4l'. Further, 2-methyl-N-Boc-indole (2h) was successfully employed, leading to the cycloadducts 4m and 4n with 59 and 31 % yields, respectively, but using I2 only. Finally, benzo- 
furan (5) was identified as another viable 2π component, to generate the benzofuro[2,3-c]quinoline-6-carboxylates 6a–6c in yields of 42–94 %, and the observed reversal of regioselectivity in these cycloaddition reactions was unambiguously confirmed by the single-crystal X-ray structure of compound 6c.[13]

Again, products 6a–6c were accessible only under the conditions of method A. We further attempted to use N-Boc-pyrrrole (7) and benzothiophene (8) in the reaction; however, no cycloaddition occurred and both substrates were mostly recovered. The reaction between glycine ester 1a and 5-cyano-N-Boc-

indole (2i) was also not feasible.

With regard to the reaction mechanism, we conducted the control experiments summarized in Scheme 3. The reaction to form products 4a,4a' starting from glycine ester 1a and N-Boc-indole (2a) could also be promoted by N-iodosuccinimide (NIS) with blue light irradiation, whereas almost no conversion occurred in the dark, which proved the contribution of radical intermediates (Scheme 3a). Additionally, the standard reaction between 1a and 2a using I2 was largely quenched in the presence of an equimolar amount of 2,2,6,6-tetramethylpiperidine-N-oxide (TEMPO) (Scheme 3b). Although no cycloaddition occurred, 56 % of the imine 9a was formed, indicating its role as a key intermediate. The same experiment under the conditions of method B also showed radical quenching, even though to a slightly lesser extent (compare with Table 1, entry 11).

Imine 9a, derived from glycine ester 1a by dehydrogena-
tion, was generally present in all crude reaction mixtures as evident from NMR spectroscopic analysis. When glycine ester 1a was reacted alone, imine 9a was generated exclusively, both under the conditions of methods A and B. As shown in Scheme 3c (and Table S2, Supporting Information), we reacted imine 9a with indole 2a under various conditions. Although irradiation of imine 9a in MeCN under O2 with indole 2a alone gave no conversion, its reactions under both conditions of methods A and B delivered the products 3a, 4a, and 4a'. In order to establish which species actually activates imine 9a in the [4+2]-cycloaddition, we added hydroiodic acid (HI), NIS as well as I2, to find that the cycloaddition occurred in all cases, even in the dark. These results showed that the imine could be activated by a number of alternative pathways, including protonation by HI to the iminium ion (9-H)* as well as N-iodination with NIS or I2 to give the N-iodoiminium ion (9·I)+, and possibly also by halogen bonding activation of 9 in a complex 9·I2 under these model conditions.[14]

However, when using HI, NIS, and I2 under irradiation, a further significant increase in conversion was observed, which proved an additional strong contribution of light-induced radical pathways in the subsequent oxidation steps to the final products 4a,4a'. Finally, in order to rule out a conceivable reac-tion pathway consisting of a tandem cross-dehydrogenative coupling (CDC) between glycine ester 1a and indole, followed by 6π-electron cyclization and aromatization, we subjected the independently prepared CDC products 10a and 10b to the typical conditions of method A (Scheme 3d). These reactions however did not generate products 3 and 4,4', but the deeply rearranged[15] 6H-indolo[2,3-b]quinoline-11-carboxylates 11a and 11b were formed as the only products and isolated in moderate yields of 38 and 48 %, respectively; their constitution being confirmed by single-crystal X-ray analysis of product 11b.[13]

On the basis of our observations, we propose the mecha-nism depicted in Scheme 4. Under the conditions of method A, photolysis of I2 generates the iodine radical I+, which abstracts a hydrogen atom from glycine ester 1, to give HI and the α-amino radical 12, which is trapped by O2. The resulting peroxyl radical can react with another molecule of glycine ester 1 in a chain propagation step.[16] Elimination of H2O2 from hydroperoxide 13 gives the imine 9, which undergoes a Bronsted acid mediated [4+2]-cyclization with HI followed by 1,4-hydrogen shift, and a fast oxidation mediated by I+ and O2 leads to the dihydroquinoline 3. The regeneration of the I2 catalyst can occur through the reaction between HI and H2O2.[17] Converse-
ly, using TPP⁺ and X⁻ (method B), photoelectron transfer (PET) between the excited-state catalyst (E*$_{\text{red}}$ = +2.55 V vs. the standard calomel electrode (SCE)\textsuperscript{[17]} and glycine esters 1 (E$_{\text{ra}}$ ranging from +0.82 to +1.59 V vs. SCE\textsuperscript{[18]} generates the radical cation 14, which can react with superoxide to give the imine 9. In the protic medium, the major product-forming pathway similarly is the acid-mediated [4+2]-cycladdition and oxidation to 3; however, control experiments showed that the presence of the halide ion X⁻ contributes to 30–35% of total conversion to products 3 and 4 (Table S1, Supporting Information), indicating the existence of a second minor reaction pathway. We propose that PET between PC* andHX generates X$_{\text{PC*}}$\textsuperscript{[19, 20]} which in the presence of trace amounts of H$_2$O gives hypohalite,\textsuperscript{[21]} to convert imine 9 into the N-haloiminium ion 14. The subsequent [4+2]-cycladdition followed by elimination of HX leads to intermediate 3. The final comparatively slow oxidation of 3 gives the aromatic product 4, which undergoes N-Boc-de-protection by HX, the rate of which depends on the actual acid concentration under the reaction conditions A or B. Generally, the protic medium of method B also facilitates an autoxidative product formation in the case of highly electron-rich glycine esters like 1a or 1b; this is however much less pronounced for less activated and acceptor-substituted systems. In the presence of TPP⁺, all incident light is absorbed by the photocatalyst.

The orientation of the C3-nucleophilic indole 2 and imine 9 in the [4+2]-cycladdition is polarity-matched, yet it also avoids a steric clash between the N-Boc-group of the indole and the carboxethoxy function of the imine; such steric hindrance does not occur in cycladditions with benzofuran (5), which reacts through a regioisomeric orientation, which is also in agreement with its higher charge density at C2.\textsuperscript{[22]} The failure of benzofuran (5) to undergo the imine [4+2]-cycladdition under conditions B likely results from a competing photoelectron transfer to the excited photocatalyst (E$_{\text{ra}}$ of 5 = +1.20 V vs. SCE\textsuperscript{[22]} impeding further conversion, and which evidently does not occur with N-Boc-indole (2a).

Conclusion

We developed two metal-free protocols for the photoinduced aerobic tandem amine dehydrogenation/Povarov cyclization/ aromatization reaction between N-aryl glycine esters and indoles as well as benzofuran, to furnish the corresponding aromatic [4+2]-cycladducts with high selectivity and yield. The indolo[3,2-c]quinoline products resemble new analogues of the antimalarial natural alkaloid isocryptolepine, and thus they may be of value in medicinal research.

Experimental Section

Typical procedures: synthesis of compounds 4b and 4b’

**Method A:** In a 10 mL crimp cap vial, N-aryl glycine ester 1b (40.2 mg, 208 μmol) and N-Boc-indole (2a, 22.6 mg, 104 μmol) were dissolved in MeCN (3.50 mL). I$_2$ (13.2 mg, 52.0 μmol) was added, and the vial was sealed and fitted with an O$_2$-balloon (with the septum pierced by a needle). The mixture was irradiated between two blue CFL lamps (2 × 18 W, 450 ± 50 nm) with rapid stirring for 48 h. The mixture was poured into NaHCO$_3$ (aq) and Na$_2$S$_2$O$_4$ (aq) followed by extraction with EtOAc (3 × 10 mL). The combined organic layers were dried with Na$_2$SO$_4$, filtered, and evaporated to dryness. Column chromatography (silica, Et$_2$O/heptane 1:1) furnished compounds 4b (35.8 mg, 85%) and 4b’ (4.4 mg, 14%).

**Method B:** In a 10 mL crimp cap vial, N-aryl glycine ester 1b (44.1 mg, 228 μmol), N-Boc-indole (2a, 24.8 mg, 114 μmol), TBAI (4.2 mg, 11.0 μmol), and TPP·BF$_4$ (0.5 mg, 1.0 μmol) were dissolved in DCE (1.90 mL) and HFIP (1.90 mL). The vial was sealed and fitted with an O$_2$-balloon (with the septum pierced by a needle). The mixture was irradiated between two blue CFL lamps (2 × 18 W, 450 ± 50 nm) with rapid stirring for 72 h. TFA (169 μL, 2.21 mmol) was added, and the mixture was stirred at 50 °C for 6 h. The mixture was poured into NaHCO$_3$ (aq) and Na$_2$S$_2$O$_4$ (aq) followed by extraction with EtOAc (3 ×). The combined organic layers were dried with Na$_2$SO$_4$, filtered, and evaporated to dryness. Column chromatography (silica, Et$_2$O/heptane 1:1) furnished compounds 4b’ (26.0 mg, 75%).

**Compound 4b:** Colorless solid; m.p. 103 °C; R$_f$ = 0.57 (Et$_2$O/heptane 1:1); 1H NMR (600 MHz, CDCl$_3$), δ = 1.56 (t, J = 7.2 Hz, 3H, CH$_3$), 1.72 (s, 9H, tBu), 2.62 (s, 3H, Ar-CH$_3$), 4.70 (q, J = 7.2 Hz, 2H, CH$_2$), 7.45 (ddd, J$_1$ = 1.1 Hz, J$_2$ = 7.2, 8.2 Hz, 1H, 8-H), 7.54–7.60 (m, 2H, 3-H, 9-H), 8.07 (s, 1H, 1-H), 8.21 (dt, J = 0.9 Hz, J = 8.4 Hz, 1H, 10-H), 8.23 (d, J = 8.6 Hz, 1H, 4-H), 8.44 ppm (d, J = 1.0 Hz, J = 7.9 Hz, 1-H, 7-H); 13C NMR (150 MHz, CDCl$_3$), δ = 14.5 (q, CH$_3$), 22.4 (q, Ar-CH$_3$), 28.1 (q, tBu), 62.6 (s, CH$_3$), 85.8 (s, tBu), 114.4 (d, C-10), 111.7 (s, C-6a), 119.1 (s, C-4a), 123.0 (s, C-6b), 123.4 (d, C-7), 123.6 (d, C-1) 124.0 (d, C-8), 127.7 (d, C-9), 130.8 (d, C-4), 131.2 (d, C-3), 136.9 (s, C-2), 140.3 (s, C-10a), 141.1 (s, C-11a), 144.2 (s, C-6), 146.9 (s, C-11b), 150.9 (s, NCO), 167.1 ppm (s, CO$_2$R); IR: δ = 2980, 2935 (–C=H, –C=H), 1740 (CO), 1250 (C=C), 1150, 1095, 750 cm$^{-1}$; HRMS (ESI+): m/z calcd C$_{13}$H$_9$N$_3$O$_4$ [M+H]$: 450.1809$, found: 450.1825.

**Compound 4b’:** Colorless solid; m.p. 276 °C (dec.); R$_f$ = 0.57 (Et$_2$O/heptane 3:1); 1H NMR (600 MHz, D$_2$Dacetonate), δ = 1.50 (t, J = 7.2 Hz, 3H, CH$_3$), 2.62 (s, 3H, Ar-CH$_3$), 4.62 (d, J = 7.1 Hz, 2H, CH$_2$), 7.35 (ddd, J = 1.1 Hz, J = 7.1, 8.2 Hz, 1H, 8-H), 7.52 (ddd, J = 8.4

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**Scheme 4. Proposed mechanism.**

[Image]
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Conflict of interest

The authors declare no conflict of interest.

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