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Easy installation of 1,2,3-triazoles or iodo-1,2,3-triazoles onto indole-fused oxazinones via CuAAC-based MCR in the presence of 18-crown-6

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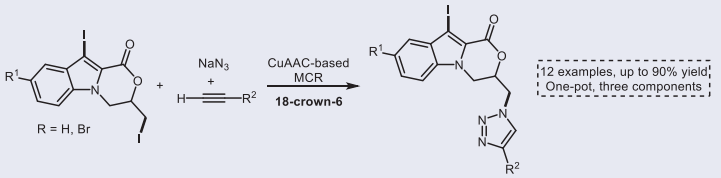
ABSTRACT

An efficient protocol was developed to prepare indole-fused oxazinones using silver nitrate. The latter substrates were subjected to multicomponent reactions in the presence of 18-crown-6, which afforded diverse new heterocycles based on an indole-fused oxazinone-1,2,3-triazole scaffold.

GRAPHICAL ABSTRACT



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KEYWORDS
Azides; click chemistry; iodolactonization; iodotriazoles; multicomponent reactions

Introduction

Polycyclic indole scaffolds constitute the structural core of numerous important classes of molecules that display an extensive range of biological and pharmacological properties.[1] For example HKI 0231A and HKI 0231B have shown the ability to inhibit 3α-hydroxysteroid dehydrogenase, which is a key enzyme in the inflammatory process.[2] More complex polycyclic indole alkaloids, such as vincristine and vinblastine (antitumor agents),[3] have been widely investigated.[4] Triazole-bearing indoles (Fig. 1) have also shown wide-ranging biological activities, such as compound **A** (anti-adipogenic and anti-dyslipidemic activity),[5] molecule **B** (selective inhibitors and inducers of bacterial biofilms),[6] compound **C** (antimicrobial activity),[7] and compound **D** (antifungal agent).[8] In addition, indole-fused oxazinone derivatives are present in a large number

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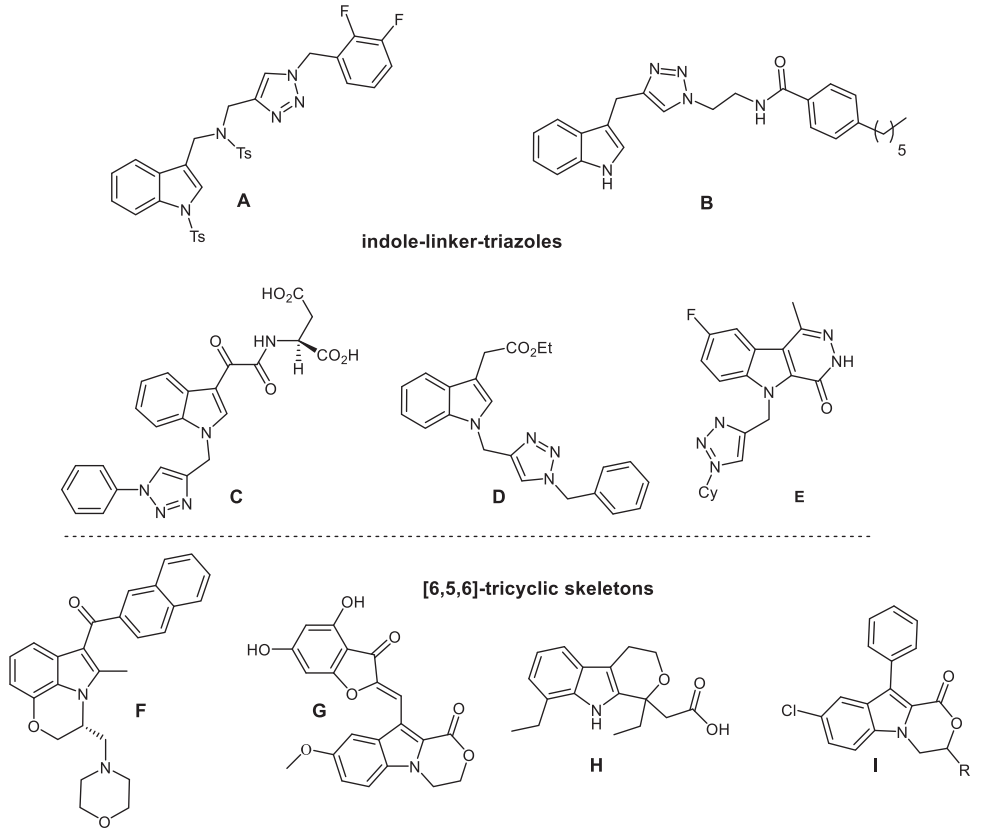


Figure 1. Selected biologically active indole-fused oxazinones and indoles incorporating the 1,2,3-triazole moiety.

of bioactive compounds and some representative members of this family are also depicted in Fig. 1. For example, compound **E**,[9] compound **F**,[10] and compound **G**,[11] show anticancer properties. Etodolac **H** is used for the treatment of arthritis,[12] and oxazinoindolones **I** showed anti-inflammatory activity.[13] The aforementioned findings (Fig. 1) gained our attention because of their great importance in biological sciences, and because these structures have rarely been described in the literature.

We envisioned that combining a triazole moiety with the indole fused oxazinones scaffold may lead to potentially bioactive molecules. In the present work, we describe an easy way to install 1,2,3-triazole and iodo-triazole moieties onto indole-fused oxazinones through an efficient CuAAC-based multicomponent reaction in the presence of 18-crown-6 (Fig. 2).

Results and discussion

To achieve our goals, the appropriate cyclization precursors **3a–b** were obtained in two steps starting from ester indoles **1a–b** (Scheme 1). After *N*-alkylation of the latter with allyl bromide, the resulting indole was saponified to **3a–b** in good yields (see SI).

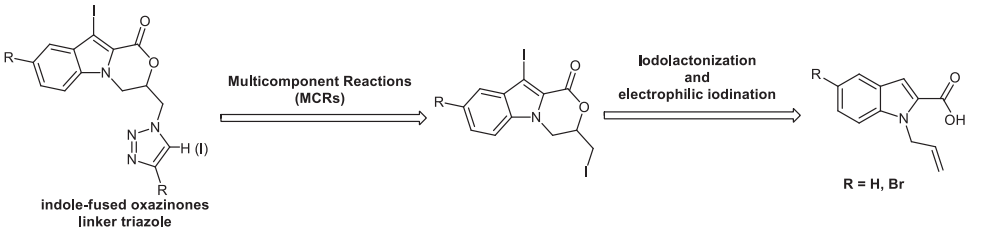
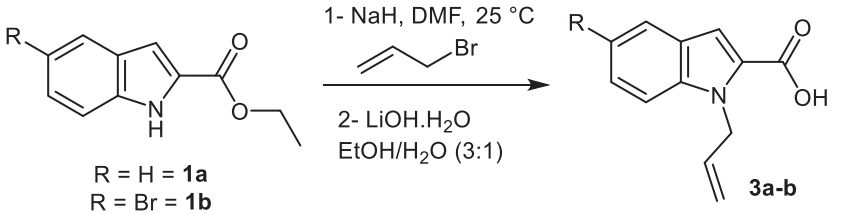
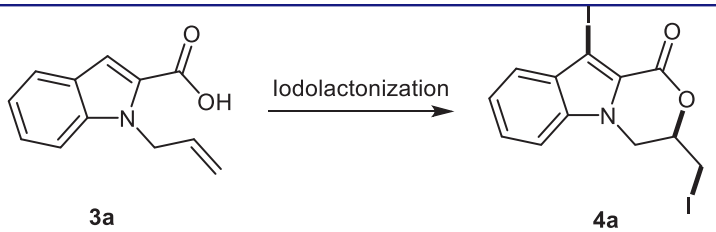


Figure 2. Retrosynthetic strategy for the sequential synthesis of indole-fused oxazinones incorporating the 1,2,3-triazole moiety.



Scheme 1. Preparation of acids **3a**–**b**.

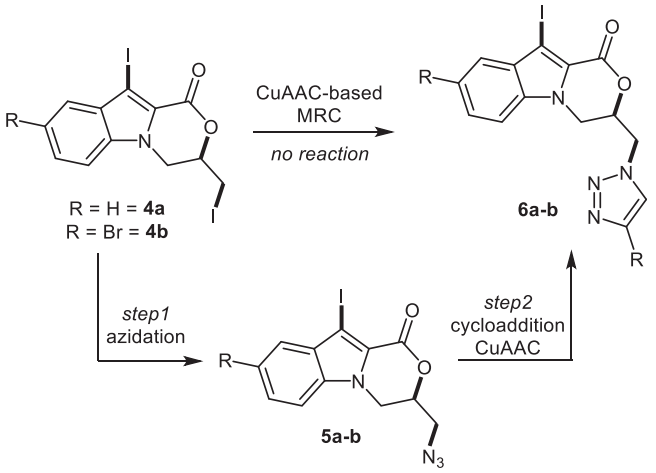
Table 1. Optimization of Iodolactonization.



Entry	Electrophile (equiv)	Temp (°C)	Base (equiv)	Solvent (ratio)	Additif (equiv)	Yield[a] (%)
1	I_2 (3)	70	$NaHCO_3$ (3)	$CHCl_3/H_2O$ (1/3)	–	84
2	NIS (2.3)	−20	$NaHCO_3$ (3)	CH_2Cl_2	2,6-lutidine	81
3	ICl (3)	70	$NaHCO_3$ (3)	CH_2Cl_2	–	54
4	NBS (3)	70	$NaHCO_3$ (3)	CH_2Cl_2	–	–[b]
5	I_2 (3)	70	K_2CO_3 (3)	$CHCl_3/H_2O$ (1/3)	–	80
6	I_2 (3)	70	Na_2CO_3 (3)	$CHCl_3/H_2O$ (1/3)	–	80
7	I_2 (3)	70	KOH (3)	$CHCl_3/H_2O$ (1/3)	–	80
8	I_2 (3)	25	NaH (2)	CH_2Cl_2	–	88
9	I_2 (3)	25	NaH (2)	CH_2Cl_2	$AgNO_3$ (0.5)	99
10	I_2 (3)	25	NaH (2)	CH_2Cl_2	$AgNO_3$ (1)	96[c]
11	I_2 (3)	25	NaH (2)	CH_2Cl_2	$AgNO_3$ (1.5)	96

[a]Isolated yields after column chromatography.
[b]Starting material, no bromolactonization was observed.
[c]30 min time of reaction.

For the iodocyclization reaction, other workers[14] reported that the use of I_2 and $NaHCO_3$ at 70 °C afforded the products 4a in 84% yield while using NIS and lutidine gave the desired compound **4a** in 81% yield (Table 1, entries 1 and 2). For our part, we wished to reexamine this iodocyclization reaction. Firstly, we tested the efficacy of different sources of electrophilic iodine, such as ICl and NIS instead of I_2 without changing other factors (Table 1, entries 3 and 4), but we observed a decrease in the yield of the desired product 4a. We then evaluated the effect of different bases on the

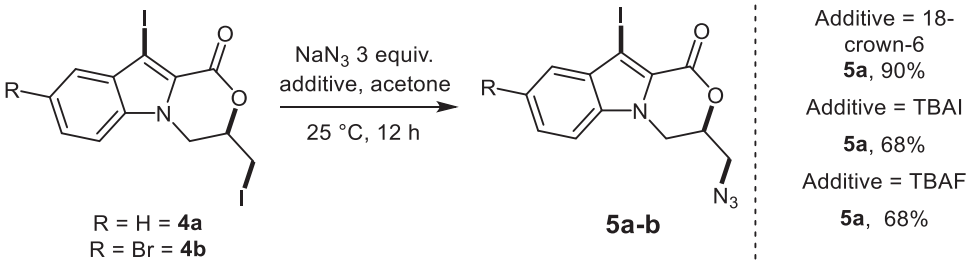


Scheme 2. Synthetic routes towards triazole-bearing oxazinoindolones.

iodine-mediated electrophilic cyclization of 3a (Table 1, entries 5–8). The results showed that sodium hydride was the most effective base at room temperature (Table 1, entry 8). To optimize the reaction conditions, we tested the addition of $AgNO_3$, and this effectively improved the conversion to reach 99% of the desired product (Table 1, entry 9). An increase in the quantity of the latter additive from 0.5 to 1 equiv reduced the reaction time from 2 h to 30 min, but the yield was not improved (Table 1, entries 10 and 11). Compound **4b** was also obtained in good yield (95%) under the same conditions. This protocol displayed higher yields and lower reaction times than that previously reported by Joseph and coworkers.[14]

Next, we examined the reactivity of the di-iodinated indole **4a** via CuAAC-based MCR in order to obtain the desired triazole compound **6a**. Various one-pot multicomponent syntheses of 1,2,3-triazoles starting from organic halides have been reported in the literature. We first examined the reaction of di-iodinated indole **4a** according to a literature procedure for an analogous transformation.[15] In our case, the starting di-iodinated indole **4a** was reacted with sodium azide and phenyl acetylene at 50 °C in $EtOH/H_2O$ for 15 h, in the presence of copper iodide. Under these conditions, no desired product **6a** was formed. Although we tested various conditions by changing the solvents, copper catalysts, base and temperature used for this one-pot two-step sequence, no successful combination was found.

To access the desired compound **6a**, a two-step strategy for the click reaction was adopted (Scheme 2). Di-iodinated precursor **4a** was subjected to nucleophilic substitution to introduce the azide group under conditions similar to those already employed for related substrates.[16] Preliminary experiments were carried out using sodium azide in $MeOH/H_2O$ at room temperature. Only a complex mixture of products was obtained, so different reaction conditions were tested. Initially, we screened the solvent used for the substitution of 4a to form the azide **5a**, and found that the use of aprotic solvents DMF, acetone and MeCN gave the desired product in only low yield (30%). An increase in the quantity of NaN_3 from 3 to 6 equivalents did not improve the yield of the reaction, and in all cases the isolated yield of the desired product 5a did not exceed 40%. We also found that increasing the temperature from 25 °C to 55 °C gave only a mixture



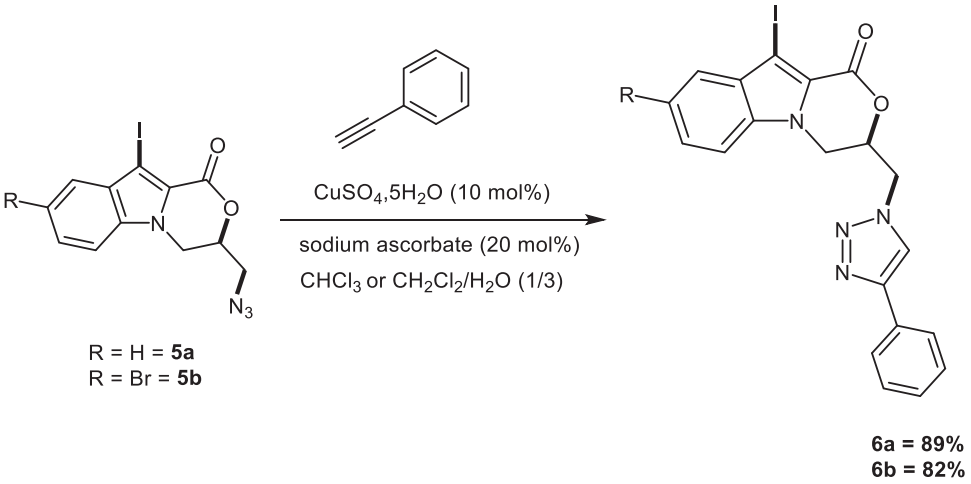
Scheme 3. Optimization of the reaction between indole-fused oxazinones **4a**–**b** and sodium azide.

of products and no desired product **5a** was isolated. However, the use of phase transfer agents proved to be crucial to improve the outcome of the reaction (Scheme 3).[17] We found that the best phase transfer agent was 18-crown-6 rather than TBAI or TBAF. Further investigation showed that increasing the amount of additive reduced the reaction time but did not give better yields. Significantly, the protocol was also tolerant of the di-iodinated precursor **3b** to furnish the product **4b** in 88% yield.

This success in the synthesis of **5a**–**b** led us to investigate cycloaddition (CuAAC) reactions of the azide for building systems bearing a 1,2,3-triazole moiety. Traditional approaches for the synthesis of 1,2,3-triazoles starting from an azide precursor have been reported in the literature.[18] A first attempt with $CuSO_4{\cdot}5H_2O$ (10 mol%), sodium ascorbate (20 mol%) and phenylacetylene (1.5 equiv) in toluene:H_2O (3:1) at room temperature provided the corresponding product with a moderate yield (53%). After testing different solvents, we found that by using chlorinated solvents, such as CH_2Cl_2 or $CHCl_3$, the products **6a**–**b** could be obtained in higher yields (89% and 82% respectively) (Scheme 4).

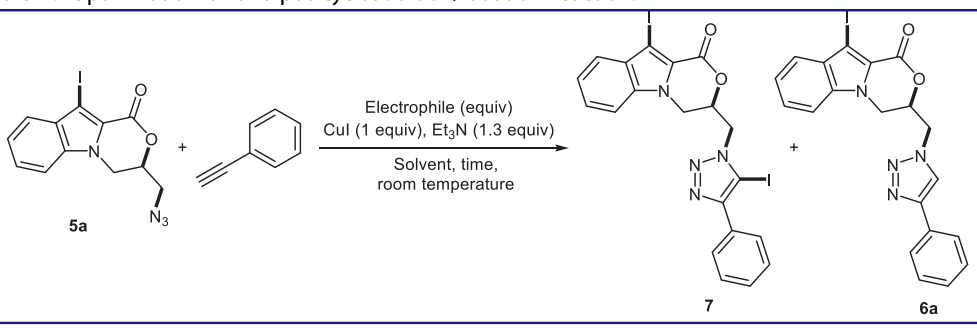
In keeping with our efforts to examine the reactivity of **5a**, we attempted to synthesize 5-iodotriazole **7** through a simple one-pot cycloaddition/iodination reaction. Initially, we tested this reaction under conditions previously defined by our group (Table 2, entry 1).[19] This protocol gave the desired product **7** in 55% yield and with a 27/73 ratio of **6a/7**, respectively. To increase the selectivity of the reaction, we examined a range of solvents, catalysts, and reaction times. The use of I_2 or NBS as an electrophilic trapping reagent did not give better results than ICl (Table 2, entries 2 and 3). Next, we screened other organic solvents (Table 2, entry 4 and 5). The use of chlorinated solvents, such as CH_2Cl_2 or $CHCl_3$, improved the yield of this one pot reaction but always gave a mixture of **7** and the mono-iodinated compound **6a** (85:15). The addition of catalysts, such as NaI or LiI was unsuccessfully tested (Table 2, entries 6 and 7). We therefore turned our attention to the reaction duration, and it appeared that extended reaction times increased the yield of the side product **6a** (Table 2, entries 8–11). The best result in terms of yield and selectivity was obtained when the reaction time was limited to 48–50 h (Table 2, entries 8 and 9).

Multicomponent reactions are chemical processes which represent an economically useful way to synthesize a large number of potentially bioactive molecules by combining several reaction steps in a single operation. For example, various MCR syntheses of 1,2,3-triazoles have been published in the past decade starting from organic halides, sodium azide, and terminal alkynes. Our preliminary results showed that 1,2,3-triazoles could be obtained in very good yields only in the presence of 18-crown-6 starting from



Scheme 4. 1,3-Dipolar cycloaddition between **5a**–**b** and phenylacetylene.

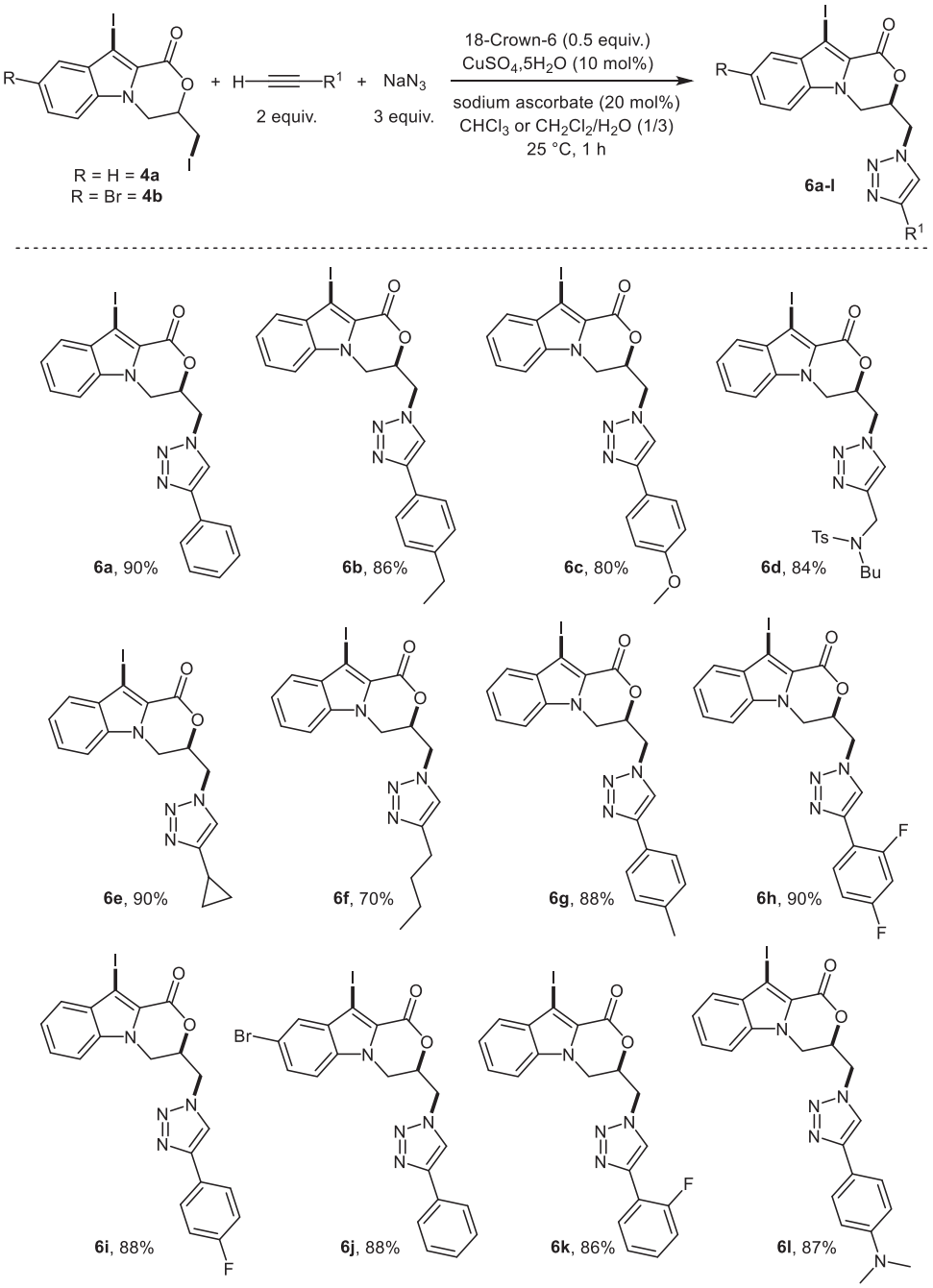
Table 2. Optimization of one-pot cycloaddition/iodation reaction.



Entry	Electrophile (equiv)	Solvent	Time0 (h)	Ratio (7/6a)[a]	Yield of 7 (%)[b]
1	ICl (1.2)	THF	60	(73/27)	55
2	NBS (1.2)	THF	60	–	–[c]
3	I_2 (1.2)	THF	60	(71/29)	46
4	ICl (1.2)	$CHCl_3$	60	(85/15)	74
5	ICl (1.2)	CH_2Cl_2	60	(88/12)	70
6	ICl (1.2))	$CHCl_3$	60	(88/12)	72[d]
7	ICl (1.2)	$CHCl_3$	60	(88/12)	74[e]
8	ICl (1.2)	$CHCl_3$	50	(90/10)	77
9	ICl (1.2)	$CHCl_3$	48	(93/7)	76
10	ICl (1.2)	$CHCl_3$	40	(95/5)	60
11	ICl (1.2)	$CHCl_3$	72	(66/34)	53

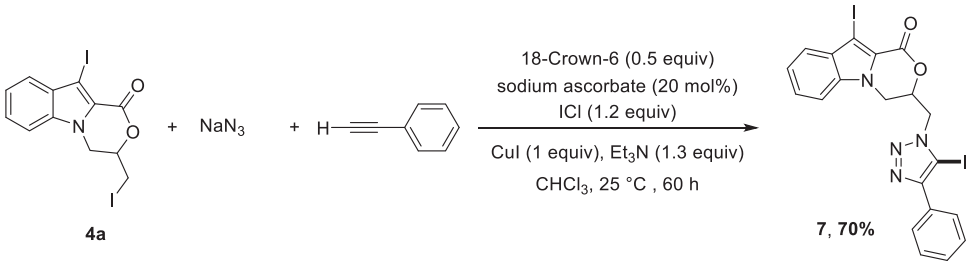
[a]Ratios were measured via ^{1}H NMR.
[b]Isolated yields.
[c]Degradation.
[d]Addition of 20 mol% of LiI.
[e]Addition of 20 mol% of NaI.

the corresponding **4a** through the classical two-step route.[20] With this knowledge in hand, we re-attempted the one-pot process for the two previously defined steps to prepare the substrate **6a**–**b** from the organic halides **4a**–**b**. Pleasingly, this time the multicomponent reaction worked well in the presence of 18-crown-6, and the desired 1,2,3-triazoles **6a**–**b** were obtained in 90 and 88% yield, respectively. Using the optimized



Scheme 5. Synthesis of triazole-bearing oxazinoindolones through a CuAAC one-pot procedure.

conditions, we then focused on exploring the scope of this reaction with various alkynes and sodium azide. The corresponding indole-fused oxazinone-1, 2, 3-triazole scaffolds **6a–l** were isolated in good to excellent yields (see SI). As shown in Scheme 5, both electron-withdrawing and electron-donating groups can be successfully incorporated in the alkyne component, without substantially altering the one-pot process' efficiency.



Scheme 6. One-pot azidation/cycloaddition/iodation reaction.

We have also shown that iodo-triazole **7** could efficiently be obtained via a simple one-pot cycloaddition/iodination reaction starting from azido-indole-fused oxazinones. We supposed that indole-fused oxazinone **4a** could be converted into iodotriazole **7** in the presence of 18-crown-6 *via* a MCR process (Scheme 6). In this context, indole-fused oxazinone **4a**, phenylacetylene, sodium azide and ICl reacted in the presence of copper iodide, 18-crown-6 and Et_3N as base. Under these conditions, the desired iodo-triazole **7** was obtained in 76% yield as a major product but mixed with 5% of **6a**. It was found that 18-crown-6 is indispensable for this multicomponent click reaction. This one-pot reaction led to the isolation of the desired iodo-triazole **7** with a better yield than in the two-step sequence (70%).

Conclusions

In summary, we have developed a new protocol to prepare indole-fused oxazinones. We have also demonstrated that these gave access to a novel series of heterocyclic derivatives based on triazole and indole-fused oxazinones, prepared using CuAAC based multicomponent reactions. Further investigations concerning the resulting products **6a–i** are ongoing in our laboratory, and an evaluation of their biological activity is underway at the Lilly platform.

Experimental

General procedure for the synthesis of ethyl 1-Allyl-5-bromo-1H-indole-2-carboylate (2b)

In a two-necked round bottom flask, NaH 60% (44 mg, 1.1 mmol, 1.1 equiv.) was dissolved in DMF (6 mL). Compound **1b** (1 mmol, 1 equiv.) in DMF (3 mL) was added dropwise at 0 °C under argon. The mixture was stirred for 30 min at room temperature. A solution of allyl bromide (145.2 mg, 1.2 mmol, 1.2 equiv.) in DMF (3 mL) was added dropwise at 0 °C. After 4 h of stirring at room temperature, the mixture was hydrolyzed by aqueous NH_4Cl (20 mL), extracted by diethyl ether (6 × 10 mL), and the organic phases were washed with brine (3 × 10 mL), dried over $MgSO_4$ and concentrated under vacuum.

General procedure for the synthesis of indole-2-carboxylic acids 3

In a round bottom flask, NaOH 12% (240 mg, 6 mmol, 3 equiv.) was slowly added to a solution of indole ester **2a–b** (2 mmol, 1 equiv.) in ethanol (6 mL). The mixture was

stirred at 45 °C for 3 h, cooled to 0 °C and acidified with HCl (1 M) to obtain pH = 1. The resulting precipitate was filtered and washed with hexane.

General procedure for the synthesis of iodoindole-fused oxazinones 4

In a round bottom flask containing carboxylic acid **3** (1.11 mmol) and 25 mL of CH_2Cl_2, we added sodium hydride (88 mg, 2.22 mmol), iodine (845 mg, 3.33 mmol) and silver nitrate (94 mg, 0.55 mmol). The mixture was stirred overnight at room temperature. The medium was hydrolyzed by saturated solution of $Na_2S_2O_3$ (30 mL) then extracted by dichloromethane (3 × 25 mL). The organic phase was washed with NaCl (3 × 10 mL), dried over $MgSO_4$ and concentrated under vacuum to give the products **4a**–**b**. Spectroscopic data of known compound **4a** are identical to those reported previously.[14]

General procedure for the synthesis of azides 5

A mixture of the appropriate **4a**–**b** (0.76 mmol), sodium azide (148 mg, 2.28 mmol), 18-crown-6 (100 mg, 0.38 mmol) and acetone (20 mL) was stirred at room temperature until completion of the reaction (TLC). The solvents were evaporated under reduced pressure, and the mixture was then poured into water, extracted with CH_2Cl_2 (3 × 40 mL), dried ($MgSO_4$), and concentrated in vacuum. The crude product was purified by silica gel chromatography using PE/EtOAc (1:4) mixture as eluent.

General procedure for the synthesis of triazoles 6

Starting from azide 5

Finely powdered $CuSO_4$, 5 H_2O (10 mol%) and sodium ascorbate (20 mol%) were slowly added to a stirred solution of **5** (0.8 mmol) and appropriate terminal alkyne (1.2 mmol) in $H_2O/CHCl_3$ (3:1 = 22.5 mL/7.5 mL) at 0–10 °C. The mixture was then warmed to room temperature and stirred until completion (TLC). The mixture was filtered, concentrated and diluted with water (30 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with H_2O and then with brine, dried over $MgSO_4$ and concentrated in vacuum. The crude products were purified by flash chromatography on silica gel (EtOAc:PE = 4:1) to afford the pure triazoles **6a** and **6c**–**l**.

Starting from bis-iodine 4

Sodium azide (148 mg, 2.28 mmol) and 18-crown-6 (100 mg, 0.38 mmol) were added to a solution of compound **4** (0.76 mmol) in H_2O:$CHCl_3$ (3:1 = 22.5 mL/7.5 mL), and the suspension was stirred for 30 min. The mixture was then degassed at 0 °C and terminal alkyne (4.0 mmol), sodium ascorbate (641 mg, 4.0 mmol) and $CuSO_4 \cdot 5\,H_2O$ (76 mg, 0.4 mmol) were successively added. The mixture was stirred overnight. The reaction was quenched by the addition of an aqueous saturated NH_4Cl solution. After being stirred for further 15 min, the mixture was filtered through a Celite pad. The aqueous phase

was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was then purified by flash chromatography on silica gel (EtOAc:PE = 4:1) giving compounds **6a** and **6b**.

General procedure for the synthesis of triazole 7

Starting from azide 5

A mixture of azide **5a** (1 mmol), terminal alkyne (1.3 mmol), Et_3N (1.2 mmol), $CHCl_3$ (100 mL), ICl (195 mg, 1.2 mmol), and CuI (190 mg, 1 mmol) was stirred at room temperature under an argon atmosphere for 48 h. The solvent was removed by distillation under reduced pressure and the crude residue was purified by flash chromatography over silica gel ($CHCl_3$:MeOH = 88:12) to afford the pure desired triazole product **7**.

Starting from bis-iodine 4

Compound **4a**–**b** (0.76 mmol) was dissolved in $CHCl_3$ (20 mL). Sodium azide (148 mg, 2.28 mmol) and 18-crown-6 (100 mg, 0.38 mmol) were then added to the solution and the suspension was stirred for 30 min. The mixture was then degassed at 0 °C and terminal alkyne (4.0 mmol), Et_3N (125 µL, 0.92 mmol), CuI (145 mg, 0.76 mmol) and ICl (148 mg, 0.91 mmol) were successively added. The mixture was stirred at room temperature under an argon atmosphere for 60 h. The reaction mixture was quenched by the addition of an aqueous saturated NH_4Cl solution and stirred for further 15 min. The mixture was filtered through a pad of Celite. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by flash chromatography on silica gel (EtOAc:PE = 4:1).

Disclosure statement

No potential conflict of interest was reported by the authors.

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