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A competitive and highly selective 7-, 6- and 5-annulation with 1,3-migration through C–H and N–H – alkyne coupling†

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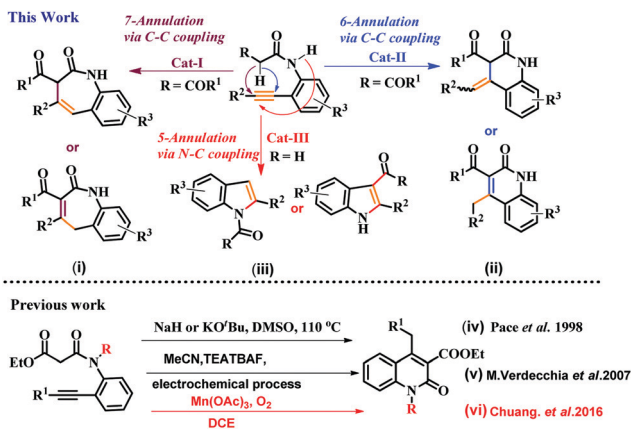
We demonstrated a highly competitive and selective C–C and N–C cross-coupled 7-, 6- and 5-annulation utilizing 2-ethynylanilides to afford functionalized 1*H*-benzo[*b*]azepin-2(5*H*)-ones, 2-quinolinones, and 3-acylindoles in high yield. $ZnCl_2$ was found to be the smart catalyst for 7- and 5-annulation with 1,3-migration through C–H and N–H functionalization, respectively, whereas molecular iodine performed the C–H functionalized 6-annulation with a nonconventional 1,3 H-shift. The mechanism was investigated by intermediate trapping, control, and labeling experiments.

The highly selective C–C and C–N coupled annulation reaction using C–H *vs.* N–H with unsymmetrical alkyne is attractive and challenging because it can deliver a wide range of useful cyclic compounds through the development of cascade cyclization processes using simple, inexpensive and easily prepared substrates. For example, the prime substrate, 2-ethynylanilides (**3**, Scheme 1), can easily be synthesized *in situ* from the readily available 2-(phenylethynyl)aniline (**1**) and ethyl 3-oxo-propionate derivatives (**2**) without employing any catalyst under refluxing toluene. It can easily undergo dual competitive cyclization among C–H and C≡C to produce valuable azepinones (eqn (i)) and quinolinones (eqn (ii)) through 7- and 6-annulation, respectively. On the other hand, an N–H and C≡C coupled 5-annulation will furnish important 3-acyl indoles (eqn (iii)) with the possible migration of the acyl group under catalytic influence. However, selectivity is a big issue for annulation reactions, which may also be overcome using suitable catalysts. More than 20 years back, Pace *et al.* first reported a C–C coupled 6-annulation through C(sp^3)–H and C≡C of anilide (eqn (iv))[1a] using three equivalents of strong base (NaH or KO*t*Bu) at 110 °C in DMSO to obtain quinolinones in a low to moderate yield (30–75%). An electro-chemical approach is reported to convert 2-ethynylanilides (eqn (v)) to quinolones.[1b] The Chuang group established $Mn(OAc)_3$ mediated oxidative radical cyclization of α-substituted *N*-[2-(phenylethynyl)phenyl]acetamides (eqn (vi)).[1c] However, a catalytic synthesis is preferable over a non-catalytic reaction(s). Moreover, the development of smart catalysis is highly desirable to discard the isomeric by-product(s). Thus, we envisaged an expedient cascade catalytic transformation (Scheme 1) of the *in situ* generated *o*-ethynylacetoacetanilides using ethyl benzoyl acetate/*tert*-butyl acetoacetate and *o*-alkynyl anilines to afford the aforementioned heterocycles with excellent selectivity. 1*H*-Benzo[*b*]-azepin-2(5*H*)-one compounds are widely found in numerous natural products and pharmaceuticals including lennoxamine, 2,3,4,5-tetrahydro-1*H*- their syntheses include intramolecular Heck with Pd(II);[2] allylic amination with Ir-[3a,b] Rh-,[3c] Au(I)[3d,f] and Fe(III) or Cu(I)-catalysis;[3g] and the Morita–Baylis–Hillman reaction with phosphine, Pd- and Au-catalyzed ring-expansion approaches.[3h] 2-Quinolinones are found to be antagonists for respiratory disease, an HBV inhibitor for anti-Hepatitis B, and an universal fluorescent marker,[4] and annulation reactions were employed for their synthesis utilizing Pd(II),[5a,f,i] Ag(I),[5d] Au(I),[5g] Ru(II)–Ag(I),[5e] and a few other catalysts.[5b,c,h] 3-Acyl indoles are bioactive natural products and revealed antibiotic (indiacen A and indiacen B) and antidiabetic (MK-0533) activities, and used as important pharmaceuticals, key intermediates, and



Scheme 1 Diverse 7, 6 and 5-annulation reactions of 2-ethynylanilide.

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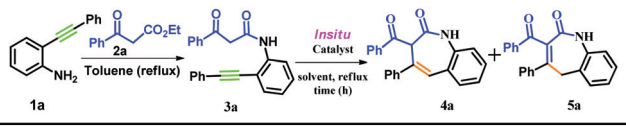
synthons.[6] Traditional procedures to furnish 3-acyl indoles involved mainly through acylation of N-protected indoles *via* Friedel–Crafts,[7a] carbonylative 3-acylation,[7b] and a few others.[7c,d] Zinc chloride[8] and molecular iodine[9] emerged as useful catalysts in organic synthesis because they are inexpensive, readily available, less toxic, environmentally benign, and above all, they have diverse catalytic activities.

We initiated the annulation reaction of *in situ* generated 3-oxo-3-phenyl-*N*-(2-(phenylethynyl)phenyl)propanamide (**3a**) from 2-(phenylethynyl)aniline (**1a**) and ethyl benzoyl acetate (**2a**) under refluxing toluene. The annulation reaction was screened employing 10 mol% of potential catalysts such as $FeCl_3$, $RuCl_3$, and $Pd(OAc)_2$, which could not furnish the 7-annulated product(s), **4a** and/or **5a** even after 24 h (entries 1–3, Table 1). To our delight, the construction of isomeric 3-benzoyl-4-phenyl-1*H*-benzo[*b*]azepin-2(5*H*)-one (**5a**) was detected (5–15%) with catalysts CuCl and $Cu(OTf)_2$ (entries 4 and 5). The yield was moderately improved (40%, entry 6) by the use of $Zn(OAc)_2$. Screening of Zn(II)-salts such as $Zn(OTf)_2$, ZnI_2, $ZnBr_2$, and $ZnCl_2$ led to a significant improvement in the yield (40–70%, entries 7–10) along with the formation of **4a** (10–15%). Gratifyingly, an excellent yield (**5a**, 90%, entry 11) was obtained upon enhancing the catalyst loading of $ZnCl_2$ from 10 to 20 mol% with the subsidized by-product **4a** (3%). However, no further improvement in the yield (**5a**) was observed upon using more amount of the catalyst (entry 12). The 7-annulation reaction did not occur at room temperature (entry 13), and the desired product (**5a**) was formed only in 60% yield along with 20% of **4a** (entry 14) at moderate temperature (80 °C). The role of the catalyst was confirmed as the reaction did not occur in the absence of $ZnCl_2$ (entry 15). A brief survey of the solvent (entries 16–20) revealed that the formation of the by-product (**4a**) was enhanced in the case of xylene, dioxane, and THF (entries 16, 17 and 21). The yield of **5a** was reduced (40–60%) upon using DMSO, DMF, and MeCN, along with an enhanced yield of the by-product (**4a**, 20%, entries 18–20). Thus, toluene was found to be the best reaction medium for the 7-annulation process (entry 11). The viability of our strategy for large scale synthesis of azepinone was validated in gram-scale synthesis (86%, entry 22).

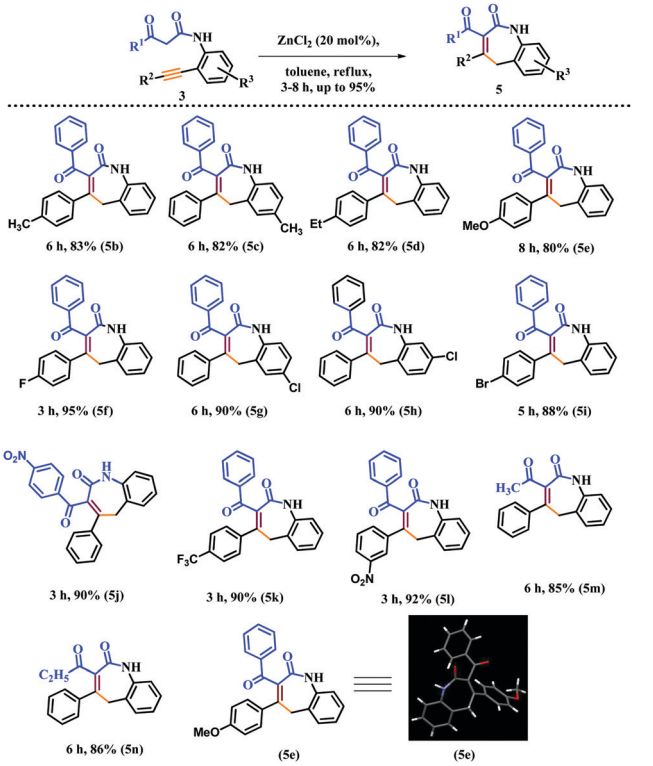
The scope of the new method was explored by utilizing several *in situ* prepared *o*-ethynylacetoacetanilide derivatives (Scheme 2). A number of substrates bearing electron-donating substituents (R_2 = Me, Et, and OMe) and electron-withdrawing substituents (R_2 = F, Cl, Br, NO_2, and CF_3) worked well in this cascade reaction under the developed conditions to obtain the corresponding azepinones (**5a–l**) in excellent yields (82–95%). Interestingly, in the case of electron withdrawing substituents at the aromatic residue of the alkyne moiety, the reaction led to a comparatively higher yield than that bearing electron donating substituents. Again, the *o*-ethynylanilides (**3m**, **n**) obtained from *tert*-butyl acetoacetate and ethyl propionylacetate, respectively, furnished the corresponding azepinones **5m** and **5n** in 85–86% yield without changing the reaction conditions. However, the outcomes of the 7-annulation reactions led us to conclude that the cascade cyclization is independent of electronic influence exerted by the carbonyl residue. The structure of all the new azepinones (**5a–o**) was unambiguously established with NMR, FTIR and ESI-MS spectroscopy and also single crystal XRD analyses of compound **5e**.[10a]

Table 1 Development of the 7-annulation reaction[a]



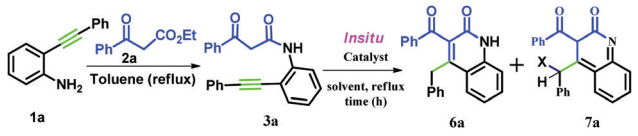
Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield[b] (%) 4a	5a
1	$FeCl_3$(10)	Toluene	Reflux	24	—	NR[c]
2	$RuCl_3$(10)	Toluene	Reflux	24	—	NR[c]
3	$Pd(OAc)_2$(10)	Toluene	Reflux	24	—	ND[d]
4	CuCl(10)	Toluene	Reflux	24	—	5
5	$Cu(OTf)_2$(10)	Toluene	Reflux	24	—	15
6	$Zn(OAc)_2$(10)	Toluene	Reflux	8		40
7	$Zn(OTf)_2$(10)	Toluene	Reflux	8	—	40
8	ZnI_2(10)	Toluene	Reflux	12	15	50
9	$ZnBr_2$(10)	Toluene	Reflux	12	15	50
10	$ZnCl_2$(10)	Toluene	Reflux	10	10	70
11	**$ZnCl_2$(20)**	**Toluene**	**Reflux**	**6**	**3**	**90**
12	$ZnCl_2$(30)	Toluene	Reflux	5	2	90
13	$ZnCl_2$(20)	Toluene	rt	24	ND	ND
14	$ZnCl_2$(20)	Toluene	80	6	20	60
15	—	Toluene	Reflux	12	ND	ND
16	$ZnCl_2$(20)	Xylene	120	8	30	60
17	$ZnCl_2$(20)	Dioxane	120	12	35	50
18	$ZnCl_2$(20)	DMSO	120	12	20	55
19	$ZnCl_2$(20)	DMF	120	20	20	50
20	$ZnCl_2$(20)	CH_3CN	Reflux	18	20	40
21	$ZnCl_2$(20)	THF	Reflux	12	30	60
22[e]	$ZnCl_2$(20)	Toluene	Reflux	8	5	88

[a] Reactions were carried out using 1 mmol of **3a** in the presence of 10 mol% of catalysts. [b] Yields of **4a** and **5a** after purification by column chromatography. [c] No reaction. [d] Not detected. [e] Gram scale synthesis of **1a** (5.5 mol%, 1 g), **2a** (5 mol%, 0.96 g), 20 mol% $ZnCl_2$.



Scheme 2 Synthesis of functionalized azepinones.

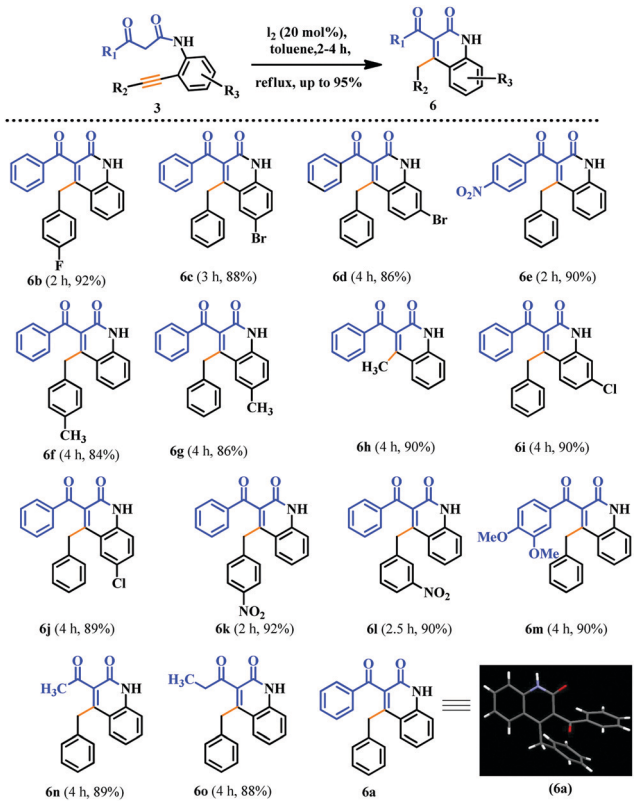
Table 2 Evaluation of the 6-annulation reaction[a]



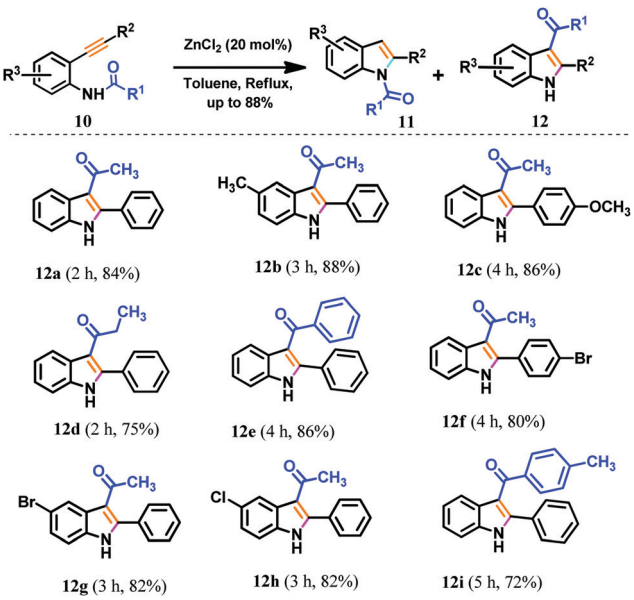
Entry	Catalyst (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%) 6a[b]	7a
1	NIC[c] (10)	Toluene	Reflux	12	NR[d,e]	—
2	HI (10)	Toluene	Reflux	12	NR[d]	—
3	IPy_2BF_4 (10)	Toluene	Reflux	6	57	Trace[f]
4	NaI, $PhI(OAc)_2$ (10)	Toluene	Reflux	8	NR	Trace
5	TBAI, $PhI(OAc)_2$ (10)	Toluene	Reflux	8	ND	Trace
6	I_2 (10)	Toluene	Reflux	5	90	ND[g]
7	**I_2 (20)**	**Toluene**	**Reflux**	**3**	**95**	**ND**
8	I_2 (40)	Toluene	Reflux	2	77	Trace
9	I_2 (15)	THF	Reflux	12	61	Trace
10	I_2 (15)	DMSO	Reflux	12	48	Trace

[a] Reaction developed using 1 mmol of **3a** in the presence of 0.15 mmol of catalysts taken in toluene at ambient temperature. [b] Yield after purification by column chromatography. [c] *N*-Iodosuccinimide. [d] No reaction. [e] Complete recovery of **3a**. [f] X = I. [g] Not detected.

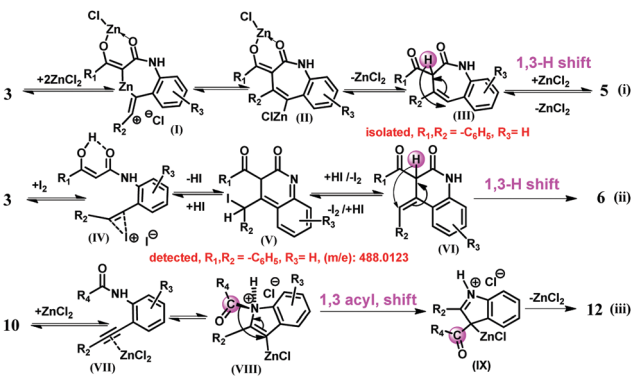
Next, we hypothesized the catalytic C–C coupled selective 6-annulation (Table 2) of the same substrate (**3a**) and the cyclization reaction was examined to furnish quinolinone (**6a**) and/or the isomeric product (**7a**) tactfully to restrict 7-annulation. To suppress the 7-annulation reaction, our initial experiments for **3a** began with iodine-based nonmetallic catalysts (10 mol%, Table 2). No reaction occurred with *N*-iodosuccinimide (10 mol%) even in refluxing toluene (entry 1, Table 2). On the other hand, HI could not transform **3a** into **6a** or **7a** at all (entry 2) *via* activation of the alkyne moiety. To our delight, $IPy2BF_4$ facilitated the formation of the quinolinone derivative (**6a**) in a moderate yield (57%) along with a trace of **7a** (entry 3), and the existence of **7a** (X = I) was detected by recording mass spectrometry of the product mixture (ESI†). Attempts were made to generate nascent iodine using $PhI(OAc)_2$ in combination with NaI, or TBAI formation of the desired product was not detected (entries 4 and 5). Gratifyingly, treatment of **3a** with inexpensive molecular iodine (10 mol%) at ambient temperature led the reaction to completion within 5 h to furnish the desired 2-quinolinone (**6a**) in a high yield (90%, entry 6). The yield was further improved to 95% upon enhancement of the catalyst loading to 20 mol% (entry 7). However, a further increase of molecular iodine (40 mol%) showed a detrimental effect on the yield of the product **6a** from 95% to 77% (entry 8) along with the generation of the by-product **7a**, which was not detected in the previous two experiments (entries 6 and 7). The yield (**6a**) was reduced (48–61%) upon screening the



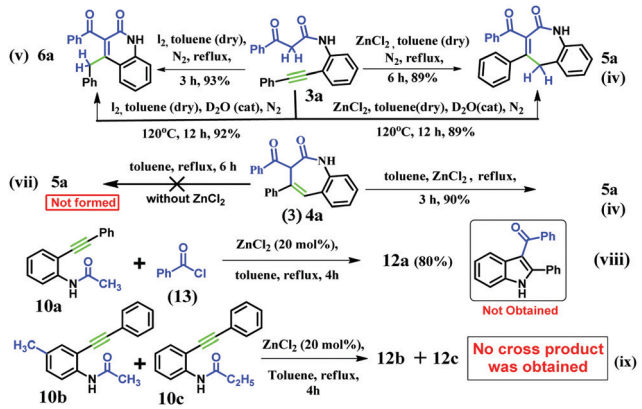
Scheme 3 Scope for direct synthesis of functionalized 2-quinolinones.



Scheme 4 Synthesis of indoles through 5-annulation.



Scheme 5 Plausible mechanistic pathways.



Scheme 6 Control experiments.

6-annulation reaction with polar solvents such as THF and DMSO (entries 9 and 10).

On the basis of the developed reaction conditions, we scrutinized the validation of the reaction employing a wide variety of *in situ* generated *o*-ethynylanilides (**3**, Scheme 3), and it was observed that electronically rich and poor substrates worked well in this reaction to obtain quinolinone derivatives **6a–o** in a high yield (84–95%). The quinolinone derivatives were characterized by FTIR, NMR and ESI MS spectroscopy, and also the structural elucidation of **6a** through single-crystal XRD analyses.[10b]

To understand the role of C–H, relatively less acidic C–H was employed by changing the substrate to *N*-acetyl-2-phenylethynyl anilines (**10a**, Scheme 4) instead of **3**, and a 5-annulation reaction occurred through N–C coupling using the $ZnCl_2$ catalyst under the same reaction conditions. Valuable 3-acyl-2-aryl indoles (**12a**) were easily produced in a high yield (84%). The substrate scope of the rapid (2–4 h) reaction was also verified to obtain 3-acyl indoles (**12a–i**) in a good yield (72–88%). Interestingly, 1,3-acyl and 1,3-benzoyl group migration was observed,[11] and the other possible products (**11**) were found in traces only when R1 = Ph (**12e** and **12i**).

The plausible mechanism (ESI†) for $ZnCl_2$ catalysed 7- and 5-annulation with 1,3-migration and I_2 tuned 6-annulation with nonconvensional 1,3 H-shift are displayed in Scheme 5 along with intermediate trapping, control, and labeling experiments (Scheme 6).

In conclusion, we discovered diverse catalytic 5-, 6- and 7-cyclization processes with a concerted 1,3-migration to achieve three valuable heterocycles from 2-ethynyl anilides with excellent selectivity, yield and operational simplicity, which will find considerable application in synthetic chemistry and the allied branches of science and medicinal chemistry.

Conflicts of interest

There are no conflicts to declare.

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