Facile Route to 1,3-Diazaheterocycle-Fused [1,2*b*]Isoquinolin-1(2*H*)-one Derivatives via Substitution-Cyclization Reactions

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The substitution-cyclization reaction of heterocyclic ketene aminals with polyhalo isophthalonitrile in the presence of *t*-BuOK to form 1,3-diazaheterocycle fused [1,2-*b*]isoquinolin-1(2*H*)-imines, followed by hydrolysis with 1 N HCl, provides a concise and efficient route for the synthesis of highly functional polyhalo 1,3-diazaheterocycle fused [1,2-*b*]isoquinolin-1(2*H*)-ones.

Isoquinolin-1(2*H*)-one derivatives including isoquinolin-1(2*H*)-one and isoquinolin-1(2*H*)-imine possess specific biological activities.[1] These moieties are commonly found in synthetic pharmaceuticals and natural products such as doryphornine,[2] ruprechstyril,[3] dorianine,[4] thalactamine, narciclasine,[5] and lycoricidine.[6] In addition, isoquinolin-1(2*H*)-ones are versatile building blocks for the total synthesis of natural products.[7] Because of their broad range of biological activities[1] and their value as synthetic precursors for pharmaceutical compounds, isoquinolin-1(2*H*)-one derivatives have received increasing interest for many years. Mild and efficient methods to synthesize isoquinolin-1(2*H*)-ones, such as transition metal-catalyzed procedures,[8] have been developed. There are also a variety of classic approaches,[9] including intramolecular oxidation−rearrangement of isoquinolines,[10] the Gabriel−Coleman rearrangement,[11] the Heck coupling reaction,[12] the Bischler−Napieralski reaction,[3] cyclization of isocyanates,[13] the Friedel−Crafts reaction,[14] the addition of carboxamides to alkynes,[15] or carbonyls,[16] Diels−Alder reactions,[17] transformation of isocoumarins or 3-hydroxyphthalides,[1a,18] photochemical reactions,[19] RCM (ring-closing metathesis),[20] and MCR (multicomponent reactions),[21] among others.[22] Although some of these methods are effective for the synthesis of isoquinolones, they usually afford a target compound substituted at the 6- or 7-position with an electron-donating group, such as an alkoxy group, and not all functional groups are tolerated. The introduction of multiple substituents in the isoquinolone ring often requires multistep reactions and complex experimental processes. Procedures to prepare highly functional and diverse isoquinolin- 1(2*H*)-ones are limited, so a general and concise approach to this class of heterocycles that tolerates a wide variety of functional groups is highly desirable.

Heterocyclic ketene aminals (HKAs) are versatile intermediates for the synthesis of a wide variety of fused heterocyclic compounds.[23] These fused heterocyclic structures are frequently found in pharmacophores and play important roles in drug discovery, having found use as herbicides, pesticides,[24] antianxiety agents,[25] antileishmanial agents,[26] and antibacterial drugs.[27]

To explore the biological activity of small *N*-heterocyclic molecules, we have designed and synthesized a compound library of highly functional isoquinolin-1(2*H*)-imines and isoquinolin-1(2*H*)-ones, which may possess potential biological activities and increase the chance to obtain promising leading molecules by further screening and studying on SARs. Furthermore, the halogens and the cyano group may provide handles for ready derivatization, and providing many opportunities to construct more molecule libraries for biological activity screening.

Result and Discussion

To examine the practicality of the projected synthetic route, a set of experiments were carried out using 2-(imidazolidin-2-ylidene)-1-phenyl -ethanone **1a** and 2,4,5,6-tetrachloroisophthalo- nitrile **4a** as model substrates. The mixture composed of a 1:1.1 ratio of **1a** to **4a** were treated with microwave irradiation (MW) in solvent-free conditions (Table 1, entries 1−9). After screening different temperatures and maximum power of microwave irradiation, we found that the optimum reaction conditions to form the product **5a′** were 120 °C for 12 min with a maximum power of 200 W (Table 1, entry 5).

Notably, the *C*-arylation product **5a′** was attained exclusively in most cases. This is ascribed to the stronger nucleophilicity of the α-carbon than that of the nitrogen atom,[23] and the electronic effect of the ortho- and para-cyano groups. The 2-site of the aryl ring in **4a** was deactivated as a result of the steric effect of the two ortho-cyano groups, thus leading to nucleophilic attack specifically at the 4-positon of the aromatic ring.[28]

After extensive optimization of the cyclocondensation reaction conditions for **5a′**, we found that the two steps could

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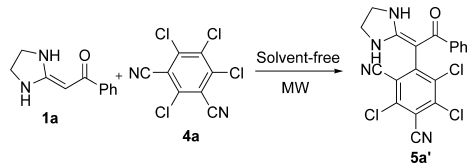
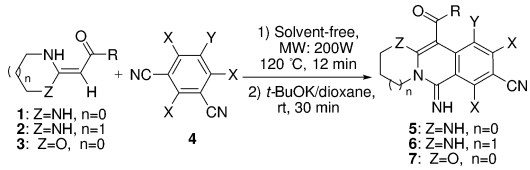
Table 1. Reaction of HKAs **1a** with Polyhalo-isophthalonitrile **4a** in Solvent-Free Environment under Microwave Irradiation



entry	power	*T* (°C)	time (min)	yield (%)[a]
1	MW/170 W	110	12	70
2	MW/170 W	120	12	88
3	MW/170 W	130	12	86
4	MW/200 W	110	12	70
5	MW/200 W	120	12	89
6	MW/200 W	130	12	84
7	MW/230 W	110	12	71
8	MW/230 W	120	12	87
9	MW/230 W	130	12	80

[a] Isolated yield based on HKAs **1a**.

Table 2. Substitution−cyclization Synthesis of Polyhalo-1,3-diazaheterocycle-Fused 1,2-Dihydroiso-quinolin-imines **5**−**7**



entry	**1**	**4**	X	Y	R	**5**−**7**	yield[a] (%)
1	**1a**	**4a**	Cl	Cl	Ph	**5a**	89
2	**1a**	**4b**	F	Cl	Ph	**5b**	90
3	**1a**	**4c**	F	F	Ph	**5c**	94
4	**1b**	**4a**	Cl	Cl	*p*-CH_3OPh	**5d**	79
5	**1b**	**4b**	F	Cl	*p*-CH_3OPh	**5e**	84
6	**1b**	**4c**	F	F	*p*-CH_3OPh	**5f**	89
7	**1c**	**4a**	Cl	Cl	*p*-ClPh	**5g**	80
8	**1c**	**4b**	F	Cl	*p*-ClPh	**5h**	84
9	**1c**	**4c**	F	F	*p*-ClPh	**5i**	91
10	**1d**	**4a**	Cl	Cl	CH_3	**5j**	81
11	**1d**	**4b**	F	Cl	CH_3	**5k**	83
12	**1d**	**4c**	F	F	CH_3	**5l**	90
13	**1e**	**4a**	Cl	Cl	OEt	**5m**	91
14	**1e**	4b	F	Cl	OEt	**5n**	94
15	**1e**	**4c**	F	F	OEt	**5o**	92
16	**2a**	**4a**	Cl	Cl	Ph	**6a**	82
17	**2a**	**4b**	F	Cl	Ph	**6b**	85
18	**2a**	**4c**	F	F	Ph	**6c**	92
19	**2b**	**4a**	Cl	Cl	*p*-CH_3OPh	**6d**	83
20	**2b**	**4b**	F	Cl	*p*-CH_3OPh	**6e**	85
21	**2b**	**4c**	F	F	*p*-CH_3OPh	**6f**	92
22	**2c**	**4a**	Cl	Cl	*p*-ClPh	**6g**	82
23	**2c**	**4b**	F	Cl	*p*-ClPh	**6h**	87
24	**2c**	**4c**	F	F	*p*-ClPh	**6i**	87
25	**2d**	**4a**	Cl	Cl	*p*-CH_3Ph	**6j**	84
26	**2d**	**4b**	F	Cl	*p*-CH_3Ph	**6k**	83
27	**2d**	**4c**	F	F	*p*-CH_3Ph	**6l**	90
28	**3a**	**4a**	Cl	Cl	Ph	**7a**	84
29	**3a**	**4b**	Cl	F	Ph	**7b**	88
30	**3a**	**4c**	F	F	Ph	**7c**	94
31	**3b**	**4a**	Cl	Cl	*p*-CH_3OPh	**7d**	86
32	**3b**	**4b**	Cl	F	*p*-CH_3OPh	**7e**	92
33	**3b**	**4c**	F	F	*p*-CH_3OPh	**7f**	96

[a] Yield of isolated product from reaction on a 1 mmol scale.

be carried out in an efficient general process to afford a 1,3-diazaheterocycle fused [1,2-*b*]isoquinolin- 1(2*H*)-imine **5a**. Following microwave treatment of a mixture composed of a 1:1.1 ratio of HKA **1a** to polyhalo isophthalonitrile **4a**, then addition of 1.1 equiv. of *t*-BuOK at room temperature

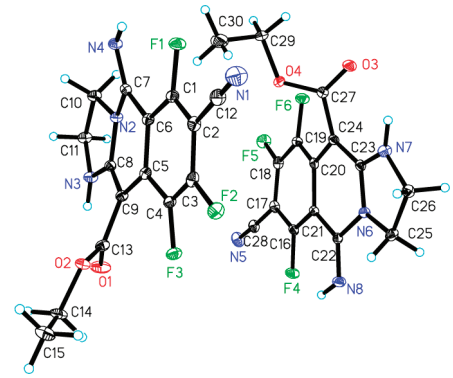


Figure 1. X-ray crystal structure of **5o**.

for 30 min was optimal for the formation of isoquinolin-1(2*H*)-imine **5a** in an excellent isolated yield of 89% (Table 2, entry 1).

These results stimulated us to further explore the utility and scope of the present protocol by using various HKAs **1**−**2** with a range of halogenated isophthalonitriles **4**, as shown in Table 2. As a result, this methodology was found to be applicable to a diverse set of HKAs, with various substituents and rings (**1a**−**e**, **2a**−**d**), and polyhalogen isophthalonitriles (**4a**−**c**), producing the corresponding cyclocondensation products. The reactions took only 12 min at 120 °C under microwave irradiation in solvent-free conditions. The *C*-arylated intermediates were directly treated with *t*-BuOK without further purification.

To explore the scopes and limitations of this method, The *N*,*O*-acetals **3a** and **3b** were used as substrates to react with polyhalo isophthalonitriles **4a**−**c** (Table 2, entries 28−33). The results showed that these reactions proceed smoothly under the same conditions.

The results in Table 2 demonstrate that HKAs and *N*,*O*-acetals, with various substituents and different ring-sizes, were all good substrates for the reaction. The reactions were straightforward and gave very good to excellent overall yields. It is worth mentioning that the structure of the polyhalo isophthalonitrile **4** has an obvious influence on the reaction. The reactivity of **4** varied with the electron-withdrawing properties of the groups X and Y, with the reactivity of polyhalo isophthalonitrile under the typical conditions was found to be **4c** > **4b** > **4a** (Table 2, entries 1−33).

To verify the structure of the product 1,3-diazaheterocycle fused 1,2-dihydroiso- quinolin-imine, **5o** was selected as a representative compound and characterized by X-ray crystallography as shown in Figure 1 (CCDC 736001).[29]

A proposed mechanism for the two-step reaction is depicted in Scheme 1. HKAs **1** and **2** react with polyhalo isophthalonitrile **4** possibly via an aza-ene[23d] and S_NAr mechanism to form **12** after imine−enamine tautomerization. Addition of base allows an addition cyclization step to form the final product **5** or **6**.

Finally, polyhalo [1,2-*b*]isoquinolin-1(2*H*)-imines **5** and **6** were hydrolyzed under acid cataly zed under acid catalysis

Scheme 1. Proposed Mechanism for the Substitution−Cyclization Reaction of HKAs **1** and **2** and Polyhalo-isophthalonitrile **4**

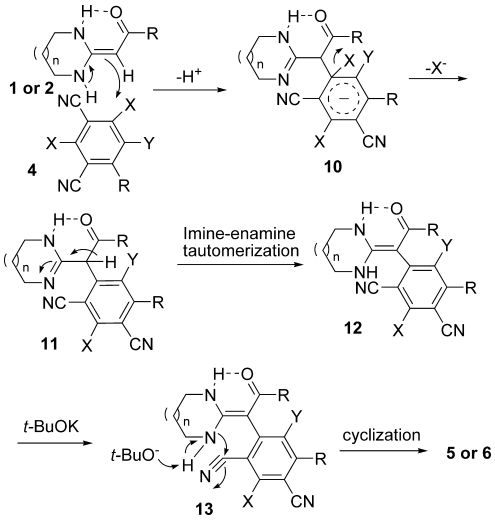
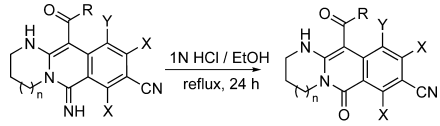


Table 3. Hydrolysis of Isoquinolin-1(2*H*)-imines



entry	no.	*n*	X	Y	R	yield (%)[a]
1	**8a**	0	Cl	Cl	Ph	73
2	**8b**	0	F	Cl	Ph	77
3	**8c**	0	F	F	Ph	82
4	**8d**	0	F	Cl	*p*-CH_3OPh	78
5	**8e**	0	F	F	*p*-CH_3OPh	81
6	**8f**	0	F	Cl	*p*-ClPh	74
7	**8g**	0	F	F	*p*-ClPh	85
8	**8h**	0	Cl	Cl	OEt	74
9	**8i**	0	F	Cl	OEt	79
10	**8j**	0	F	F	OEt	86
11	**9a**	1	F	Cl	Ph	79
12	**9b**	1	F	F	*p*-CH_3OPh	83
13	**9c**	1	F	Cl	*p*-ClPh	80
14	**9d**	1	F	F	*p*-CH_3Ph	86

[a] Yield of isolated product from reaction on a 1 mmol scale.

to produce the polyhalo [1,2-*b*] isoquinolin-1(2*H*)-ones **8** and **9** in 73−86% yield as shown in Table 3.

Conclusion

In summary, this study offers a novel procedure for the synthesis of highly functional polyhalo 1,3-diazahetero-cycle fused [1,2-*b*]iso-quinolin-1(2*H*)-one derivatives. By using different types of HKAs and polyhalo isophthalonitriles, we could obtain novel libraries of isoquinolinimines and -ones that make the method suitable for combinatorial and parallel synthesis in drug discovery. As a result, a library of 1,3-diazaheterocycle fused [1,2-*b*]iso -quinolin-1(2*H*)-one derivatives was rapidly constructed using the present protocol. The title compounds **5**−**7** were screened in vitro cytotoxic activity on K562, HL60, A431, HepG2,and Skov-3 cell lines using MTT (3-(4,5-dimethyl- thiazol-2-yl)-2,5-diphenyltetrazolium bromide) colorimetric assay. Among the series compounds, **5c**, **5n**, **5o**, **6b**,and **7c** were found to possess excellent cellular cytotoxicity with IC_{50} values lower than 3.4 μg/mL against the above five human tumor cell lines, making its more active than cisplatin except the HepG2 cell line. Consequently, this concise process presented herein has great potential to be applied to parallel synthesis in drug discovery.

Experimental Section

General Procedure for the Synthesis of 5−7. A dry mortar was charged with HKAs **1**−**3** (1 mmol) and polyhalo isophthalonitrile **4** (1.1 mmol). The mixture was mixed at room temperature by vigorously grinding with a pestle for a few minutes (∼1−2 min). The mixture was placed in a microwave tube and irradiated in a microwave reactor (Discover), with control of power and temperature by infrared detection, at 120 °C for 12 min (maximum power 200 W). After it was cooled, the resulting mixture was transferred to a 50 mL flask, and dissolved in 25 mL of -dioxane, and addition of *t*-BuOK (1.5 mmol). Stirring at room temperature, the reaction process was monitored by TLC. After completion, the reaction mixture was poured into 60 mL of water and filtered to obtain the crude products, which were purified by column chromatography (petrol/ethyl acetate = 1:3, v/v) on silica-gel to give the desired products **5**−**7**, for example, 1,3-diazaheterocycle-fused [1,2-*b*]iso- quinolin-1(2*H*)-imine **5a** as a yellow solid (0.37 g, 89%): mp 216−219 °C; IR (KBr) (ν_{max}, cm^{-1}) 3378, 2224, 1598, 1248, 1078, 806, 636; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.35 (br. s, 1H, NH), 8.70 (br, 1H, NH), 7.50 (d, J = 7.3 Hz, 2H, PhH), 7.46 (d, J = 7.3 Hz, 1H, PhH), 7.32 (t, J = 7.3 Hz, 2H, PhH), 4.10−4.00 (m, 2H, NCH_2), 3.82 (t, J = 8.5 Hz, 2H, NCH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 189.8, 157.0, 151.8, 143.3, 141.2, 137.4, 134.7, 132.0, 128.7, 128.0, 125.7, 117.9, 114.7, 108.3, 89.0, 45.3, 43.5; HRMS (TOF ES^+) *m*/*z* calcd for $C_{19}H_{12}Cl_3N_4O^+$ [M^+], 417.0071; found, 417.0069. Compound **7a**: yellow solid (0.352 g, 84%); mp 244−246 °C; IR IR (KBr) (ν_{max}, cm^{-1}) 3422, 3270, 2239, 1624, 1435, 1357, 1065, 963, 750; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.38 (br. s, 1H, NH), 7.32 (d, J = 6.9 Hz, 1H, PhH), 7.25 (t, J = 7.1 Hz, 2H, PhH), 7.13 (d, J = 7.2 Hz, 2H, PhH), 4.56 (t, J = 8.2 Hz, 2H, OCH_2), 3.91 (br s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.7, 167.7, 148.6, 141.5, 140.8, 138.7, 136.4, 130.8, 128.7, 128.1, 118.0, 114.9, 114.9, 113.6, 88.1, 69.4, 44.6; HRMS (TOF ES^-) *m*/*z* calcd for $C_{19}H_9Cl_3N_3O_2^-$ [M^-], 415.9766; found, 415.9765.

General Procedure for the Hydrolysis Reaction. Polyhalo[1,2-*b*]isoquinolin-1(2*H*)-imines **5**−**6** (1 mmol) were suspended in 20 mL of ethyl alcohol, and 10 mL of 1N aqueous hydrochloric acid, and stirred at reflux for 24 h. The mixture was cooled to room temperature, neutralized with a saturated solution of Na_2CO_3 to a pH of 8−9, and then EtOAc (30 mL) was added. The organic phase was washed with water (10 mL × 3), dried over Na_2SO_4, concentrated, and purified by flash column chromatography, to afford polyhalo [1,2-*b*]isoquinolin-1(2*H*)-ones **8** and **9** in 73−86% yield. Compound **8a**: yellow solid (0.305 g, 73%); mp >300 °C; IR (KBr) (ν_{max}, cm^{-1}) 3371, 2228, 1630, 1301, 1180, 1004, 735; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (s, 1H, NH), 7.57−7.37 (m, 5H, PhH), 4.19−4.09 (m, 2H, NCH_2), 3.81−3.71 (m, 2H, NCH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 191.7, 162.7, 157.0, 154.1, 144.3, 140.5, 138.0, 132.7, 128.9, 128.4, 124.8, 116.1, 114.8,

108.3, 90.3, 44.5, 43.0; HRMS (TOF ES$^+$) *m/z* calcd for $C_{19}H_{10}Cl_3N_3O_2$ [M], 416.9839; found, 416.9845. Compound **9a**: Yellow solid (0.316 g, 79%). Mp 271−273 °C; IR (KBr) (ν_{max}, cm^{-1}) 3437, 2233, 1594, 1285, 1112, 927, 852, 784; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.23 (br, 1H, NH), 7.50 (d, J = 7.3 Hz, 2H, PhH), 7.59 (t, J = 7.3 Hz, 1H, PhH), 7.36 (t, J = 7.3 Hz, 2H, PhH), 4.00−3.96 (m, 2H, NCH_2), 3.45−3.41 (m, 2H, NCH_2), 2.06−2.00 (m, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 192.7, 163.1 (d, J = 275.0 Hz), 159.0 (d, J = 251.3 Hz), 157.0, 151.8, 143.3, 141.1, 132.6, 129.0, 128.8, 110.0, 108.4 (d, J = 16.3 Hz), 104.9, 91.0, 84.6, 40.7, 38.1, 19.1; ^{19}F NMR (470 MHz, DMSO-d_6) δ −100.4 (d, J = 4.7 Hz, 1F), −103.6 (d, J = 4.7 Hz, 1F); HRMS (TOF ES$^-$) *m/z* calcd for $C_{20}H_{11}ClF_2N_3O_2^-$ [M$^-$], 398.0513; found, 398.0511.

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Supporting Information Available. Experimental details and characterization data including ^{1}H, ^{13}C, and ^{19}F NMR for all new compounds (**5**−**9**). This information is available free of charge via the Internet at http://pubs.acs.org.

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(29) CCDC 736001 contain the supplementary crystallographic data for compound **5o**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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