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Construction of indazolo[3,2-*a*]isoquinolines *via* [3 + 2] cycloaddition of benzynes†

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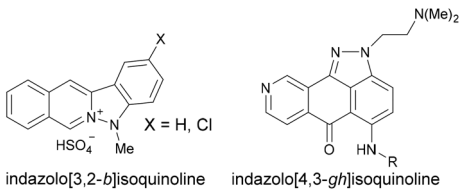
A [3 + 2] annulation protocol for the construction of *N*-substituted indazolo[3,2-*a*]isoquinolines starting from benzynes and *C*,*N*-cyclic azomethine imines was developed. A diverse range of highly functionalized products indazolo[3,2-*a*]isoquinolines featuring an indazole scaffold can be easily accessed *via* a one-step reaction under mild conditions, and they show good anti-proliferative activity on cancer cells.

Introduction

Benzophenanthridine alkaloids are important bioactive natural products. Most of them are known to exhibit potent anti-tumor, anti-inflammatory and bacteriostatic activities.[1] In recent years, many research studies have been carried out on the structure–activity relationship of various substituted benzophenanthridines.[2] Indazolo isoquinoline derivatives have a similar ring system to benzophenanthridine alkaloids, and exhibit diverse biological activities, as shown in previous literature.[3] For example, indazolo[3,2-*a*]isoquinolines have been recognized as an effective DNA intercalator and exhibit anticancer activities.[4] Moreover, indazolo[3,2-*b*]isoquinolines (Scheme 1) have been found to inhibit the reverse transcriptase activity of the Moloney leukaemia enzyme and RNA polymerase.[5] It has been disclosed that indazolo[4,3-*gh*]isoquinolinones (Scheme 1) exhibit cytotoxic/anti-proliferative activity against different cancer cell lines, namely KB/HeLa (cervical carcinoma), SKOV-3 (ovarian carcinoma), and SF-268 (CNS, glioma).[6]

Indazolo[3,2-*a*]isoquinoline compounds have been used in many fields,[7] yet only a few studies on their synthetic strategy have been reported in recent decades.[8] In 1977, the Reddy group[9] reported that the treatment of 1-(2-nitrophenyl)isoquinolines with triethylphosphite gave dihydroindazolo[3,2-*a*]isoquinolines. Subsequent Pt/C hydrogenation furnished indazolo[3,2-*a*]isoquinolines in 62–66% yields (Scheme 2a). A similar result was observed by Stanforth in 1987.[10] In 2005, Kuo and co-workers reported the reaction of 1-(2-nitrophenyl) isoquinolines with $SnCl_2{\cdot}2H_2O$, resulting in indazolo[3,2-*a*]isoquinolines.[11] Up to 77% yield was achieved, yet poor selectivity was demonstrated (Scheme 2b). Then György Hajós reported a multistep approach to obtain fluorescent indazolo [3,2-*a*]isoquinoline-6-amines under microwave irradiation (Scheme 2c).[12] On the basis of previous research studies, exploration of synthetic strategies to obtain a series of structurally diverse indazolo[3,2-*a*]isoquinolines with higher yields and better chemoselectivity is of great interest.

Ever since the discovery of benzynes in the mid-1950s,[13] particularly those which can be generated from the corresponding *o*-(trimethylsilyl)aryl triflates,[14] they have emerged as powerful synthons in organic synthesis.[15] The cycloaddition of benzynes with diazo compounds is an attractive route for the construction of the corresponding heterocyclic compounds.[16] Therefore, on the basis of our previous work on benzyne chemistry,[17] we herein describe a convenient method of using benzyne and *C*,*N*-cyclic azomethine imines to construct indazolo[3,2-*a*]isoquinolines *via* [3 + 2] cycloaddition (Scheme 2d).



indazolo[3,2-*b*]isoquinoline indazolo[4,3-*gh*]isoquinoline

Scheme 1 Examples of indazolo isoquinoline derivatives.

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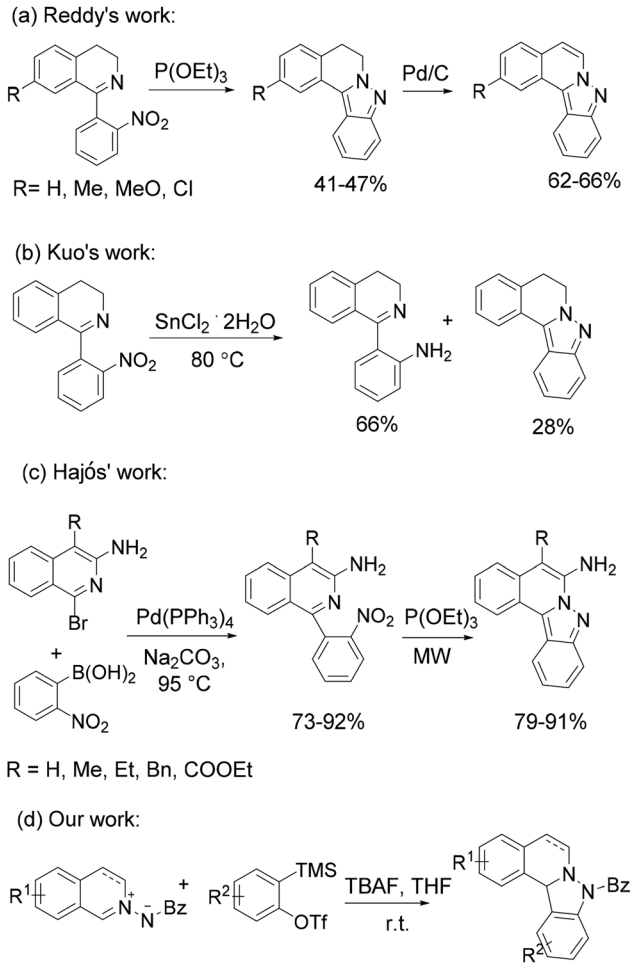
†Electronic supplementary information (ESI) available: Detailed experimental procedures, characterization data, copies of NMR spectra for all previously unknown products, and 2D ^{1}H–^{1}H NOESY spectra of **3l**, **4b**, **4d** and **4f**. See DOI: 10.1039/c9ob01878f

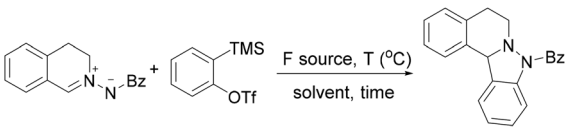


Scheme 2 Approaches a–d to synthesize indozolo[3,2-*a*]isoquinolines.

Results and discussion

Firstly, the reaction of *C*,*N*-cyclic azomethine imines **1a** with the benzyne precursor **2a** was selected as the model reaction.[18] As shown in Table 1, the target product indazolo[3,2-*a*]isoquinoline (**3a**) was generated when 1.2 or 2.0 equivalents of the benzyne precursor were used and TBAF was utilized as the fluoride source (Table 1, entries 1 and 2). It was observed that the amount of **2a** used affected the yield of **3a**. To our delight, the yield of **3a** was improved obviously to 91% when the amount of benzyne precursor **2a** was increased to 3.0 equivalents (Table 1, entry 3). Further increase of the loading of **2a** to 4.0 equivalents led to no obvious change in the yield of **3a** (Table 1, entry 4). Meanwhile, two other fluoride sources KF/18-C-6 and CsF were tested, and they both gave **3a** in moderate yields (Table 1, entries 5 and 6). It is presumed that the release rate of benzyne did not match well with the reaction under these conditions. Then the effect of temperature on the reaction was investigated. Product **3a** was isolated in 85% yield at 0 °C (Table 1, entry 7), and the reaction carried out at 40 °C gave 88% of **3a** (Table 1, entry 8). Logically, the conditions described in entry 3 (Table 1) were chosen as the suitable reaction conditions.

Table 1 Screening optimal conditions[a]



1a 2a 3a

Entry	**2a** (equiv.)	Time (h)	*T* (°C)	F⁻/solvent	**3a** yield[b] (%)
1	1.2	5	r.t.	TBAF/THF	36
2	2.0	5	r.t.	TBAF/THF	42
3	3.0	5	r.t.	TBAF/THF	91
4	4.0	5	r.t.	TBAF/THF	90
5	3.0	5	r.t.	KF/18-C-6/THF[c]	46
6	3.0	5	r.t.	CsF/MeCN[c]	57
7	3.0	5.5	0	TBAF/THF	85
8	3.0	4	40	TBAF/THF	88

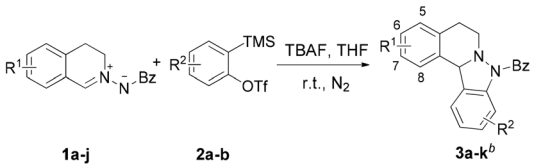
[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), F source (0.8 mmol, 4.0 equiv.), and solvent (1.2 mL). [b] Isolated yield. [c] 2.0 mL of solvent was used. r.t. = room temperature.

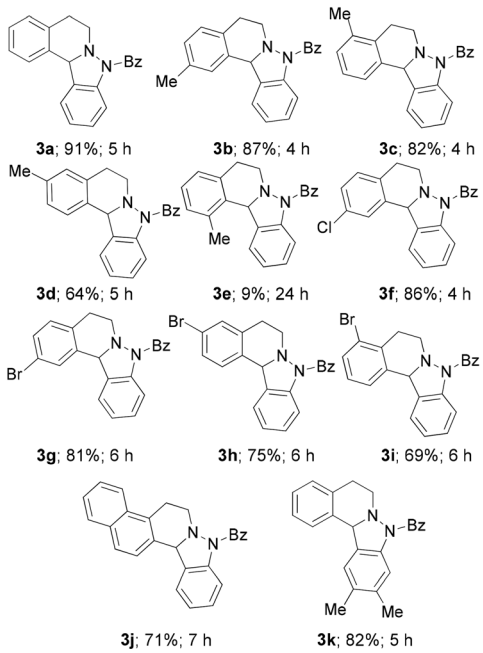
With the optimal conditions in hand (Table 1, entry 3), we then explored the generality of this [3 + 2] cycloaddition reaction. As shown in Table 2, various *C*,*N*-cyclic azomethine imines were prepared and reacted with benzyne precursors, furnishing the desired products (**3a–3l**) in moderate to good yields. As for azomethine imine **1e** with the methyl group at the 8-position, only 9% of **3e** (Table 2) was isolated, even with a prolonged reaction time. We speculated that it was probably due to the methyl steric hindrance preventing the reaction partners from coming together. Besides, comparing the effects of different substituents on the 7-position, the methyl substituent of azomethine imine **1b** was found to give the corresponding product **3b** (Table 2) in 87% yield. The halogen substituted *C*,*N*-cyclic azomethine imines also afforded the corresponding compounds in good yields (Table 2, **3f–i**). Therefore, the reaction of chloride- and bromide-substituted *C*,*N*-cyclic azomethine imines (**1f** and **1g**) furnished higher yields of the corresponding products (**3f** and **3g**). In addition, azomethine imine **1j** with a naphthalenyl moiety could also be smoothly converted into the corresponding product **3j** with satisfactory yield (71%). Also, the reaction of 4,5-dimethyl benzyne precursor **2b** with *C*,*N*-cyclic azomethine imine **1a** was studied. The corresponding indazolo[3,2-*a*]isoquinoline product **3k** was successfully isolated in 82% yield.

Considering that indazolo isoquinolines are important compounds for anti-cancer activities,[19] the debenzoylation reaction of **3a** was further explored in the presence of $LiBHEt_3$ (Scheme 3). Gratifyingly, 5,6-dihydroindazolo[3,2-*a*]isoquinolines **4a** were obtained in a perfect yield of 90%.

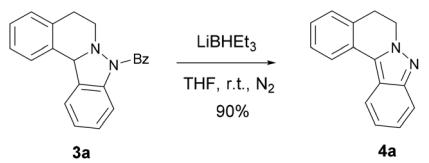
To disclose the regioselectivity of this [3 + 2] cycloaddition, nonsymmetric benzyne precursors were used. As expected, the reaction of **2c** with *C*,*N*-cyclic azomethine imine **1a** afforded regioisomers **3l** and **3l′** in a 1 : 1.2 ratio (Scheme 4, eqn (1)). The structure of product **3l** was confirmed by the NOESY study, which indicated that the methyl group was on the same

Table 2 Reaction scope of *C,N*-cyclic azomethine imines and benzynes[a]

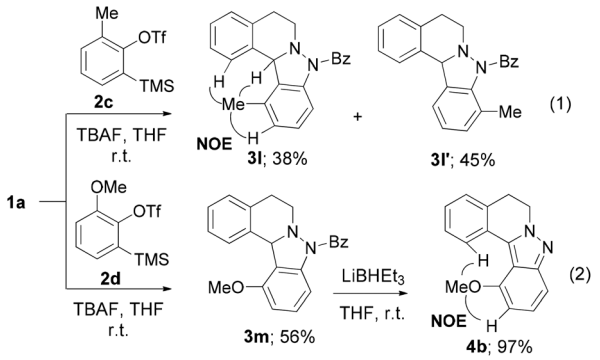




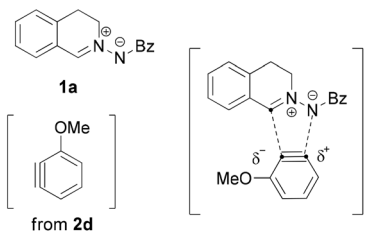
[a] Reaction conditions: **1a–1j** (0.2 mmol, 1.0 equiv.), **2a–2b** (0.6 mmol, 3.0 equiv.), TBAF (0.8 mmol, 4.0 equiv.), and THF (1.2 mL), at room temperature, under a nitrogen atmosphere. [b] Isolated yield.



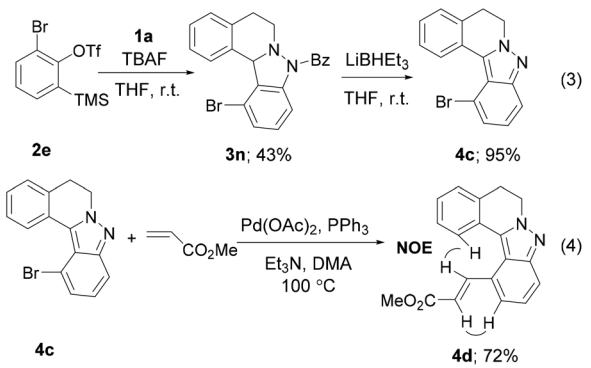
Scheme 3 Debenzoylation of compound **3a**.



Scheme 4 Reaction scope of nonsymmetric benzyne precursors **2c** and **2d**.



Scheme 5 The electronic effect of the reaction of **1a** and **2d**.

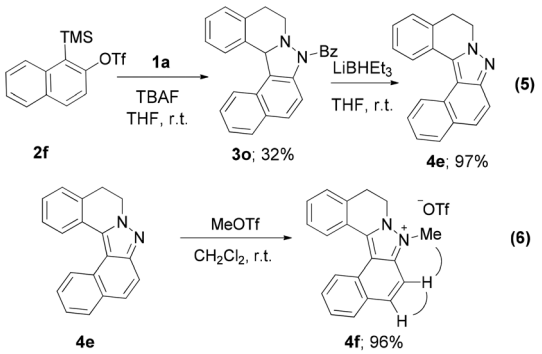


Scheme 6 Reaction scope of nonsymmetric benzyne precursor **2e** and the NOESY study of the Heck coupling product **4c**.

side of the isoquinoline moiety. To our surprise, the reaction of 3-methoxyl benzyne precursor **2d** gave the sole regioisomer **3m** (56%, Scheme 4, eqn (2)). The observed excellent regioselectivity may be attributed to the electron induced effect of the methoxyl group.[20] As demonstrated in Scheme 5, when **1a** came close to the *o*-methoxy benzyne in the reaction, the isoquinoline moiety and the methoxyl group on the same side were favoured. After debenzoylation of **3m** under $LiBHEt_3$ conditions, the structure of product **4b** could be confirmed by the NOESY study (Scheme 4, eqn (2)).

It is interesting that the sole regioisomer **3n** was obtained in 43% yield with the utilization of the *o*-bromo substituted benzyne precursor **2e** (Scheme 6, eqn (3)). The Heck coupling reaction of the debenzoylated product **4c** with methyl acrylate was subsequently conducted, so that the structure of product **4d** could be studied by the NOESY analysis (Scheme 6, eqn (4)). The NOESY analysis of **4d** showed that the β-H of olefin hydrogen was related to the triplet of the phenyl ring. Therefore, it is confirmed that the bromine substituent of **3n** is on the same side of the isoquinoline moiety.

Furthermore, the 1,2-naphthalyne precursor **2f** was also used and it successfully afforded the sole regioisomer product **3o** in 32% yield (Scheme 7, eqn (5)). This may be attributed to the higher steric hindrance of the naphthalene ring. Debenzoylation of **3o** followed by the reaction with methyl trifluoro-methanesulfonate afforded *N*-methyl triflate **4f**. The

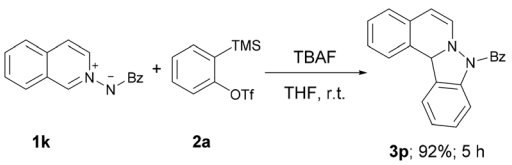


Scheme 7 Reaction scope of nonsymmetric benzyne precursor **2f** and the NOESY study of product **4f**.

NOESY study of **4f** indicated that the naphthalene ring was on the same side of the isoquinoline moiety (Scheme 7, eqn (6)).

To further explore the [3 + 2] cycloaddition, it is proposed that the addition of the conjugated structure may also yield the corresponding product under the same conditions. Thus, isoquinolinium imide **1k** was employed to react with the benzyne precursor **2a**. The reaction proceeded smoothly under the optimal conditions and afforded the target product **3p** in excellent yield (92%, Scheme 8).

After obtaining a series of indazolo[3,2-*a*]isoquinolines (**3** and **4**), we mainly investigated their anti-proliferative activities on human NSCLC NCI-H460[6] and colon carcinoma cells HCT-116[17c] using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay.[21] As shown in Table 3, the anti-proliferative activities of **3a**, **3p** and **4a** were demonstrated. The concentration of the compound that inhibited 50% (IC_{50}) of cell viability after 48 h was calculated by non-linear regression (GraphPad Prism™).[22] Compound **3p** showed good inhibitory activity on NCI-H460 (IC_{50} = 163.5 μmol L^{-1}), but weak cytotoxicity on HCT-116. The apoptosis rate of NCI-H460 was fast when the concentration of compound **3p** was between 0 and 100 μmol L^{-1} (Fig. 1). It was interesting to observe that **4a** exhibited excellent anti-proliferative activities



Scheme 8 Reaction of *N*-benzoyl isoquinolinium imide **1l** with the benzyne precursor **2a**.

Table 3 Anti-proliferative activities on NCI-H460 and HCT-116 (IC_{50}/μM)

Compound	NCI-H460	HCT-116
3a	412.9	1476
3p	163.5	1463
4a	218.9	126.9

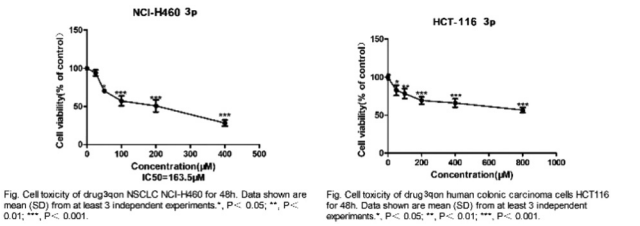


Fig. Cell toxicity of drug3qon NSCLC NCI-H460 for 48h. Data shown are mean (SD) from at least 3 independent experiments.*, P< 0.05; **, P< 0.01; ***, P< 0.001.

Fig. Cell toxicity of drug3qon human colonic carcinoma cells HCT116 for 48h. Data shown are mean (SD) from at least 3 independent experiments.*, P< 0.05; **, P< 0.01; ***, P< 0.001.

Fig. 1 Cell toxicity of **3p** on NCI-H460 and HCT-116.

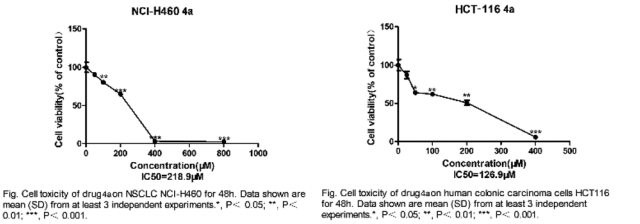
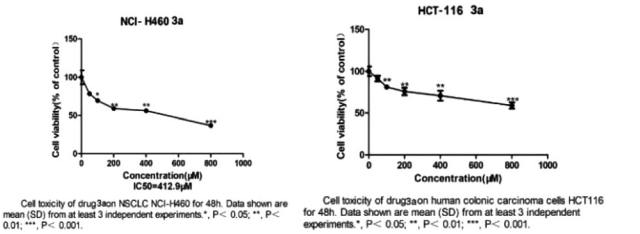


Fig. Cell toxicity of drug4aon NSCLC NCI-H460 for 48h. Data shown are mean (SD) from at least 3 independent experiments.*, P< 0.05; **, P< 0.01; ***, P< 0.001.

Fig. Cell toxicity of drug4aon human colonic carcinoma cells HCT116 for 48h. Data shown are mean (SD) from at least 3 independent experiments.*, P< 0.05; **, P< 0.01; ***, P< 0.001.

Fig. 2 Cell toxicity of **4a** on NCI-H460 and HCT-116.



Cell toxicity of drug3aon NSCLC NCI-H460 for 48h. Data shown are mean (SD) from at least 3 independent experiments.*, P< 0.05; **, P< 0.01; ***, P< 0.001.

Cell toxicity of drug3aon human colonic carcinoma cells HCT116 for 48h. Data shown are mean (SD) from at least 3 independent experiments.*, P< 0.05; **, P< 0.01; ***, P< 0.001.

Fig. 3 Cell toxicity of **3a** on NCI-H460 and HCT-116.

on two kinds of cancer cells, and showed a better effect on HCT-116 (IC_{50} = 126.9 μmol L^{-1}). Both cancer cell lines were almost dead when the concentration of **4a** reached 400 μmol L^{-1} (Fig. 2). We speculated that the structural change of the dihydroisoquinoline moiety might be responsible for the increased bioactivity. Compound **3a** was found to show weak inhibitory activity on both the cancer cell lines (Fig. 3).

Conclusions

In summary, we have developed a benzyne-based strategy for the synthesis of indazolo[3,2-*a*]isoquinolines. *Via* this one-step approach, a diverse range of highly functionalized isoquinolines featuring an indazole scaffold can be easily obtained in moderate to good yields with high regioselectivity under mild conditions. Furthermore, debenzoylation reaction could smoothly furnish indazolo isoquinolines in excellent yields. Good proliferative activities were observed towards cancer cell lines NCI-H460 and HCT-116. This novel synthetic approach provides an efficient access to indazolo[3,2-*a*]isoquinoline derivatives with biological activity.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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22 Measurement of the cellular cytotoxic/anti-proliferative activity is based on the MTT assay. The cells were seeded in the respective growth medium recommended by the supplier in 125 μL per 96 well and were grown for 24 h at 37 °C/5% CO_2. Cell numbers were adapted for each cell line to generate signals in the linear detection range under the experimental conditions applied. After 48 h of compound incubation at 37 °C/5% CO_2, 200 μL of the new culture medium and 20 μL of 0.5% MTT storage liquid were added for an additional 4 h. After adding 100 μL of DMSO per hole and rapidly oscillating for 60 s, using an enzyme labeling instrument , the absorbance values were detected at 492 nm and 630 nm. The cell survival rate was calculated according to the absorbance value. The difference in cell viability between different concentrations was detected by Student's *t*-test.

