Organic LETTERS

Letter

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Skeletally Diverse Synthesis of Indole-Fused Diazocine and Diazepine Frameworks by One-Pot, Two-Component Cascade Reaction

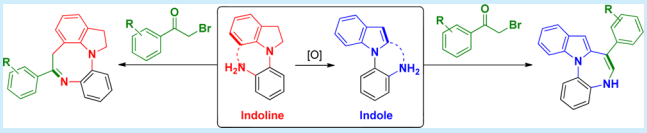
Tushar Ulhas Thikekar,[†] Manikandan Selvaraju,[†] and Chung-Ming Sun*[,†,‡]

[†]Department of Applied Chemistry, National Chiao-Tung University, 1001 Ta-Hseuh Road, Hsinchu 300-10, Taiwan

[‡]Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, 100 Shih-Chuan First Road, Kaohsiung 807-08, Taiwan

Supporting Information

ABSTRACT: An expeditious and novel strategy has been explored for the synthesis of structurally diverse indole-fused diazocine and diazepine derivatives. A substrate-based diversification approach of methyl-3-aminoindole/indoline benzoates coupled with the Pictet−Spengler reaction and three different reaction cascades furnished indolodiazepine and indoloquinoxalines. The formation of indolodiazocines proceeds through an initial condensation followed by intramolecular alkylation.



Indole represents one of the most versatile and important classes of heterocycles which occupy a pivotal position in medicinal and organic chemistry because of their unique structural and interesting biological properties.[1,2] In particular, indoles fused with other heterocycles have shown significant biological applications. Diazepines and diazocines are seven-and eight-membered rings of nitrogen-containing heterocycles found in many natural products. Among those, the indole-fused diazepines act as kinase inhibitors and antidepressant agents.[3,4] Over the years, many medicinal chemists synthesized a variety of compounds by installing various active groups to the indole/indoline moieties through a new synthetic strategy. These heterocycles have potential utility in the fields of biology, pesticides, and medicinal chemistry.[5,6] Some examples of biologically important diazepines and diazocines are shown Figure 1.

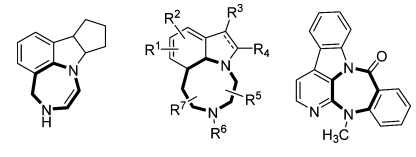


Figure 1. Biologically important compounds containing fused indolodiazepine and indolodiazocine.

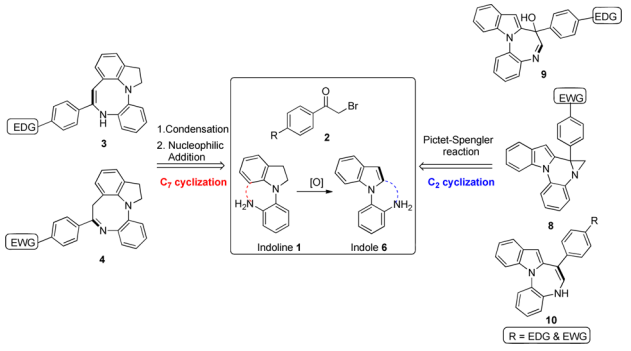
Their diverse biological activities and synthetic applications have stimulated substantial interest in the study of these important heterocycles. Surprisingly, the literature contains only a few reports describing the synthesis of indole-fused diazepines. Further, the combination of indoline fused with diazocine is not yet documented. Typical molecular constructions of indole-fused azepine fall into two steps: Pictet−Spengler reaction of tryptamines with pyruvates, followed by skeletal rearrangement via aziridine formation. Kuehne et al. reported the Pictet−Spengler reaction of tryptamine with methylchloro pyruvate for the formation of indoloazepine.[7] Similarly, Flatt and co-workers demonstrated the stepwise synthesis of azepinoindoles through ring expansion of carbolines obtained by the reaction of tryptamine with bromopyruvates.[8] Hence, a convenient and novel strategy for an efficient construction of these scaffolds is highly desirable.

Synthesis of structurally complex and highly functionalized heterocyclic skeletons is a challenging goal in modern organic chemistry. Cascade reactions, which are defined as multiple bond formations in a single step with a sequence of reactions, are one of the most promising approaches.[9] These processes avoid the isolation and purification of intermediates, maximizing the yield of the final product and minimizing solvent waste with high atom-economy. The attractive features of these cascade reactions are the formation of several C−C, C−N bonds for rapid access to fused and complex polycyclic skeletons. In continuation of our earlier work on the synthesis of indole fused nitrogen heterocycles,[10] we aimed to carry out an unconventional Pictet−Spengler reaction on 2-(1*H*-indol-1-yl)aniline/2-(indolin-1-yl)aniline with α-bromo ketones, as shown in Scheme 1. In this present work, we were surprised to find that the reactivity patterns were completely altered by the reaction conditions and substituents on substrates. The tunable reactivity of these scaffolds allowed us to design two different cyclization reactions with α-bromo ketones **2**. It is proposed that indole **6** will undergo cyclization at the C2 position, whereas indoline **1** will cyclize at C7 to create two different, new molecular entities. 2-(1*H*-Indol-1-yl)aniline **6** successfully underwent the Pictet−Spengler cyclization which

Received: December 7, 2015

DOI: 10.1021/acs.orglett.5b03481
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of Skeletally Diverse Indole/Indoline Fused Diazocines and Diazepines



on further reaction to furnish three novel heterocycles under three different reaction conditions. To our surprise, 2-(indolin-1-yl)aniline **1** performed condensation followed by intramolecular C-alkylation to deliver compounds **3** or **4** instead the expected Pictet−Spengler reaction.

The key aspect of our new approach is the construction of quaternary sp^3 carbon atoms in fused ring systems, which disrupts the one-dimensional planarity of the scaffolds. Increasing the saturation may create several conformations which can act as a suitable substrate in drug discovery to design several high affinity ligands by creation of diverse chemical space.[11]

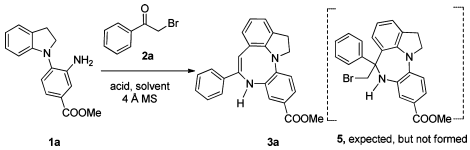
Our studies began with the preparation of a key substrate, methyl 3-amino-4-(indolin-1-yl)benzoate **1a**, from 4-fluoro-3-nitrobenzoic acid by sequential reactions such as esterification, nucleophilic substitution with indoline, and nitro reduction.[10c] Then, we carried out an unconventional Pictet−Spengler reaction on compound **1a** with α-bromo acetophenone **2a** in the presence of TFA (1 equiv) in refluxing chloroform (Table 1, entry 1). To our surprise, the possible Pictet−Spengler product **5** was not observed, and a serendipitous formation of **3a** was isolated in 20% yield with the remaining of starting material **1a**. Careful analysis of the proton NMR reveals the participation of all starting material in the isolated product and the absence of $-CH_2Br$ protons. Similarly, the mass analysis did not show the bromo pattern corresponding to the expected product **5**. Hence, we reasoned that the product **3a** is obtained by stepwise condensation followed by intramolecular C-alkylation. Under these reaction conditions, a high reaction selectivity toward aromatic substitution is observed instead of Pictet−Spengler reaction on imine carbon.

Interestingly, the proton NMR spectra of **3g** shows two conformers which are non-interconverting on the NMR time scale at ambient temperature. This conformational behavior is further supported by varying temperature studies as shown in Figures 3 and 4 (Supporting Information). Although the anticipated product was not obtained, this unprecedented formation of indolo-fused diazocine **3** might be more rewarding, as there are no previous reports on such a convenient one-pot synthesis of new molecules from these readily available starting materials. Hence, we aimed to generalize this outcome by carrying out optimization studies with various acid catalysts and solvents as shown in Table 1. No reaction was observed when TCT (trichlorotriazine) or *p*-TSA was employed as an acid catalyst. A survey of various solvents such as DMSO, DMF, and acetonitrile showed the same results with very little conversion to the desired product. Increasing the amount of TFA (3equiv) in refluxing chloroform improved the reaction yield up to 38%.

However, a higher yield of 88% was obtained when the reaction was carried out in a sealed vessel at 80 °C in chloroform for 4 h (entry 11). Further increase in TFA or temperature did not improve the reaction yield. Thus, we concluded that the optimum conditions for this cyclization is the employment of 3 equiv of TFA in chloroform in a sealed tube at 80 °C for 4 h.

The scope and limitation of the reaction were next studied to understand, in particular, the influence of the substituents presenting on α-bromo acetophenones (Scheme 2). We found that the final outcome of the reaction is significantly dependent

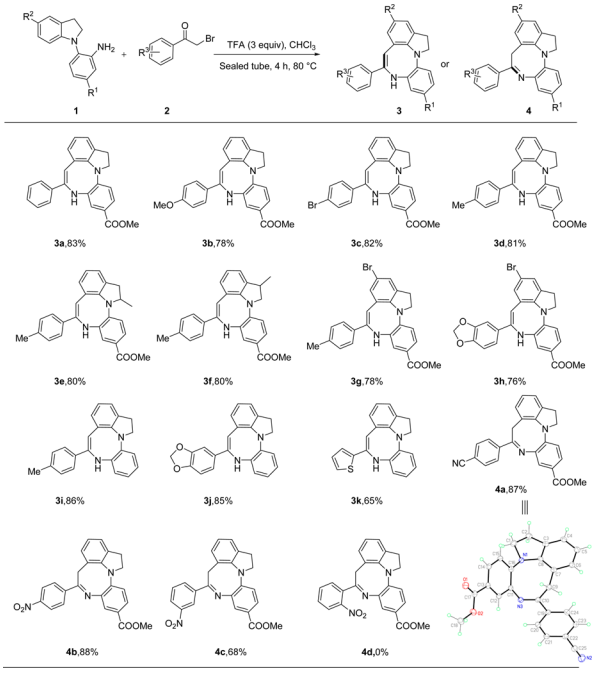
Table 1. Effect of Different Reaction Parameters on the Preparation of Indolodiazocines 3a[a]



entry	acid (equiv)	solvent	temp (°C)	time (h)	yield[b] (%)
1	TFA (1)	$CHCl_3$	reflux	24	20
2	TCT (1)	DMSO	80	24	NR[c]
3	TCT (1)	$CHCl_3$	reflux	24	NR
4	PTSA (1)	$CHCl_3$	reflux	24	NR
5	PTSA (1)	DMF	80	24	NR
6	TFA (3)	DMF	80	24	10
7	TFA (3)	CH_3CN	reflux	24	20
8	PTSA (1)	CH_3CN	reflux	24	NR
9	TFA (3)	$CHCl_3$	reflux	24	38
10	TFA (6)	$CHCl_3$	reflux	12	45
11[d]	**TFA (3)**	**$CHCl_3$**	**80**	**4**	**88**

[a]The reaction was performed in the presence of **1a** (0.25 mmol) and **2a** (0.25 mmol) and acid catalyst in solvent (2 mL). [b]Isolated yield. [c]NR = no reaction. [d]Reaction performed in sealed tube.

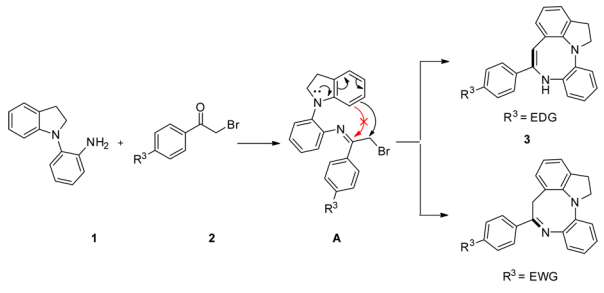
Scheme 2. Synthesis of Indolo-Fused Diazocines 3 or 4



DOI: 10.1021/acs.orglett.5b03481
Org. Lett. XXXX, XXX, XXX−XXX

on the electronic nature of substituents attached directly on the aromatic rings of α-bromo acetophenones. Two different types of product formation were observed under these conditions. Aryl rings bearing R^3 electron-donating groups furnished compounds **3a**–**k**, whereas products **4a**–**d** were obtained when the R^3 groups are electron-withdrawing. For example, electron-donating substituents as well as thiophene **3k**, an electron-rich heterocycle, favor the formation of enamines **3**, whereas the electron-deficient cyano and nitro groups favor the formation of **4**. However, α-bromo ketone possessing a nitro substituent at the ortho position did not deliver the product **4d** due to steric effects. In general, all of the substituents are well-tolerated under the same conditions and delivered the products with satisfactory yields. As shown in Scheme 2, the structure of one of the representative compounds **4a** is elucidated by X-ray single-crystal analysis. On the basis of experimental observation, a plausible mechanism is depicted in Scheme 3.

Scheme 3. Plausible Mechanism for the Unexpected Formation 3 or 4

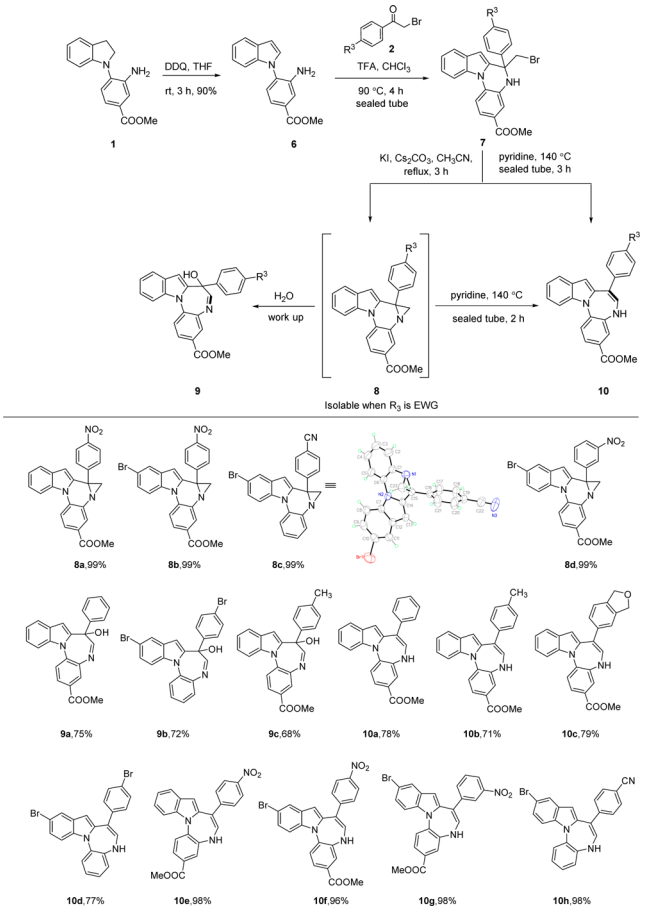


This domino transformation begins with the condensation of 2-(indolin-1-yl)aniline **1** with α-halo ketone **2** to give intermediate **A**, which will undergo intramolecular alkylation at electron-rich C7 to deliver the unexpected indolo-fused diazocine analogues **3** or **4** with respect to the substituents.

Creation of diverse libraries with various molecular scaffolds is an ideal goal in drug discovery research. Hence, the indoline moiety present in compound **1** gave ample opportunity for further diversification. The oxidation of indoline to its corresponding indole **6** was achieved with DDQ as shown in Scheme 4. The obtained 2-(1*H*-indol-1-yl)aniline **6** could act as a suitable substrate for modified Pictet–Spengler reaction with α-bromo ketones under acid conditions to furnish indolo quinoxaline **7** (Scheme 4). The obtained indolo quinoxaline **7** was further treated with potassium iodide and cesium carbonate in acetonitrile under reflux conditions for 3 h. Interestingly, this reaction furnished a new kind of heterocycle **9** possessing hydroxyl group at quaternary carbon (when R^3 = H). The structure of representative compound **9a** is unequivocally confirmed by X-ray crystallography as shown in Figure 2. The compound exhibit attractive 3D-shapes due to the obvious sp^3 character in the skeleton. The indole-fused seven membered diazepine ring is twisted and hence makes the molecule nonplanar.

The formation of **9** can be rationalized by the initial formation of aziridine **8** which undergoes ring-opening reaction on aqueous workup to give indole-fused diazepine **9**. However, addition of water as a cosolvent did not deliver the observed product **9**. In a further study, we tried to isolate the aziridine intermediate **8** to understand the original source of hydroxyl group in compound **9**. Herein, we observed that the electronic

Scheme 4. Synthesis of Indole-Fused Azirinoquinoxalines 8 and Diazepines 9 or 10



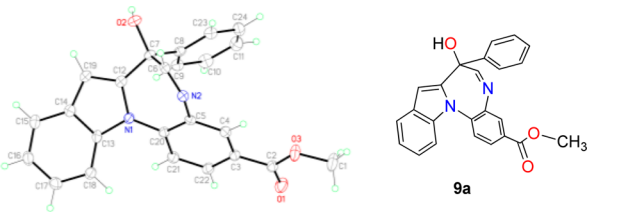


Figure 2. ORTEP diagram of compound **9a**.

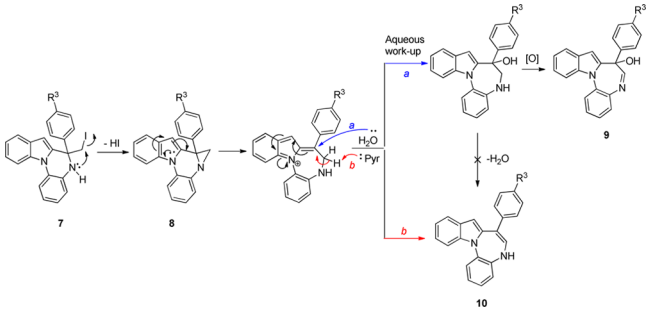
nature of R^3 plays a crucial role on the stability of the aziridine intermediate. We were able to isolate the aziridines **8a**–**d** only when the R^3 is an electron-withdrawing substituent. As shown in Scheme 4, the structure of aziridine **8c** is elucidated by X-ray single-crystal analysis. All efforts to isolate compound **8** possessing electron-donating R^3 groups were unsuccessful, and they furnished only compound **9** directly.

In addition, the reaction of isolated aziridine **8a** with water as a cosolvent under the optimized conditions did not proceed to the expected product **9**. Hence, the driving force for the formation of hydroxyl-substituted product could be the substituent-aided stability of the aziridine ring. The presence of an electron-withdrawing group at the para position of the aromatic ring stabilized the highly strained aziridine ring, whereas ring-opening of aziridine was observed during the aqueous workup if there is an electron-donating group at the para position. Treatment of the isolated aziridines **8** in pyridine at 140 °C in a sealed tube for 2 h underwent skeletal

DOI: 10.1021/acs.orglett.5b03481
Org. Lett. XXXX, XXX, XXX–XXX

rearrangement to indole-fused diazepines **10**. Delighted with this observation, we evaluated the possibility of performing the whole transformation in a one-pot, two-step domino fashion without isolation of the aziridine intermediate **8**. To our delight, treatment of Pictet− Spengler product **7** with pyridine at 140 °C in a sealed tube for 3 h furnished compound **10** directly. In this transformation, the reaction condition plays a crucial role as both the electron-donating and -withdrawing substituents (R^3) deliver the seven-membered products with satisfactory yields. Hence, three different unique heterocycles were formed exclusively depending on the electronic nature of the substituents and the reaction conditions as depicted in Scheme 4. On the basis of experimental observation, a plausible mechanism is depicted in Scheme 5. To gain insight into the

Scheme 5. Plausible Mechanism for the Formation of Indole Fused Azirinoquinoxalines 8 and Diazepines 9 or 10



reaction mechanism, a few control experiments were conducted. To elucidate the conversion of compound **7** to **10**, a one-pot reaction for the synthesis of **10** was carried out (Scheme 4), and the formation of compound **8** was observed after 1 h.

This experiment strongly confirmed that this cyclization could be rationalized to proceed through an initial intramolecular N-alkylation to generate aziridines **8** followed by ring expansion under basic conditions to diazepines **10**. To confirm further, the isolated intermediate **8** was successfully converted to **10** in refluxing pyridine for 24 h or under a sealed tube at 140 °C for 2 h. To account for the formation of **9**, a tandem aziridine formation followed by a ring-opening mechanism was proposed (Scheme 5). Initial intramolecular N-alkylation of **7** in the presence of KI and Cs_2CO_3 in acetonitrile to furnish aziridine **8**. Further, it underwent ring-opening reaction with the water molecule during the aqueous workup, aided by the electronic effect of the substituent on α-bromo ketones. It is noteworthy to mention that oxidation to imine formation is favored over the dehydration to enamine.

In summary, we have disclosed an efficient method for the construction of several undocumented indole-fused diazepines and diazocines through a substrate-based diversification approach. Employment of four different reactions such as Pictet−Spengler cyclization, aziridine ring formation, skeletal rearrangement, and hydroxylation yielded these novel heterocycles. The selectivity of product formation was dictated by the substituents and reaction conditions. This strategy provides straightforward access to a library of compounds with privileged structures that are of immense interest in drug discovery. Further study on the reaction scope and their biological application is still underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03481.

Experimental details plus spectroscopic and other data for compounds (PDF)
X-ray data for **4a** (CIF)
X-ray data for **8c** (CIF)
X-ray data for **9a** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cmsun@mail.nctu.edu.tw.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Science Council of Taiwan for financial support and the authorities of the National Chiao Tung University for providing laboratory facilities. This study was particularly supported by the "Centre for bioinformatics research of aiming for the Top University Plan" of the National Chiao Tung University and Ministry of Education, Taiwan.

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DOI: 10.1021/acs.orglett.5b03481
Org. Lett. XXXX, XXX, XXX−XXX