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Alternating Iodonium-Mediated Reaction Cascades Giving Indole- And Quinoline-Containing Polycycles

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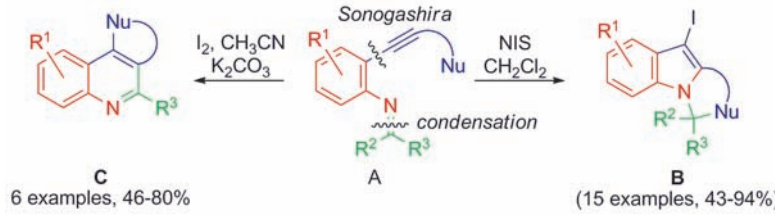
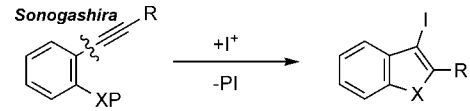
ABSTRACT



A simple two-step convergent protocol gives direct access to synthetic intermediate A from ortho-iodoanilines. Intermediate A can be treated with NIS in CH_2Cl_2 to induce novel iodonium mediated domino reaction cascade, which provides direct access to ring-fused indole compounds B. Simply by changing the reaction conditions, this protocol can be directed down an alternative domino reaction cascade to give various ring fused quinoline compounds C.

Iodocyclization has emerged as an effective protocol in the preparation of a variety of carbocyclic and heterocyclic ring systems.[1–5] For example, indoles[2] and their O,[3] S,[4] and Se[5] isosteres **2** are readily prepared from phenylacetylenes **1** (Scheme 1). The facile preparation of compounds **1** through

Scheme 1



1a X = N-Alkyl, P = Alkyl
1b X = NH, N-C(O)R, P = H
1c X = O, P = H
1d X = S, P = Alkyl
1e X = Se, P = Alkyl

2a X = N-Alk
2b X = NH, N-C(O)R
2c X = O
2d X = S
2e X = Se

Sonogashira coupling and the versatility of the iodo group in **2** to further substitution, as well as the established capacity to perform these reactions on solid phases, make this an extremely powerful method for the construction of these heterocycles.[2–5]

In this current study, we have sought to further extend the utility of this process by exploring the use of an *N*-(*o*-alkynylphenyl)imines **3** in iodocyclization. In particular, we were interested in the possibility of trapping the intermediate iminium ion **4** with a tethered nucleophile (Nu), so as to

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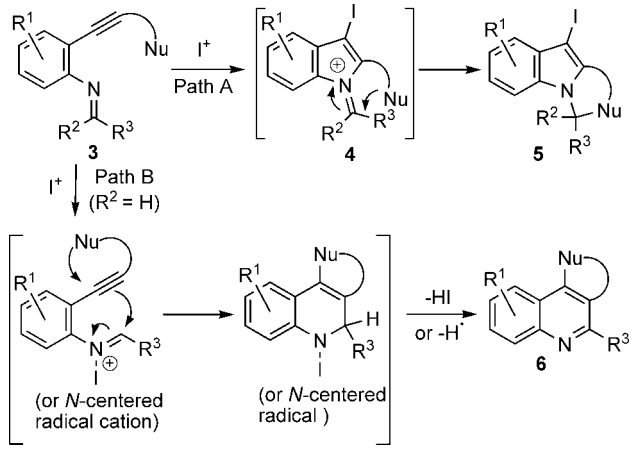
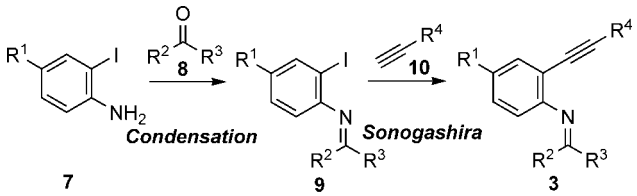
Scheme 2



give ring-fused indole product **5** in a novel tandem reaction process (Path A, Scheme 2). A fascinating discovery has been made in the course of this study, where a simple modification of the reaction conditions employed in the iodocyclization leads to an alternative reaction path giving ring-fused quinoline products **6** (Path B, Scheme 2).[6]

For the purpose of our investigation, we prepared a series of *N*-(*o*-alkynylphenyl)imines **3** (Scheme 3). These were

Scheme 3



9a R^1 = H, R^2 = R^3 = NMe_2, 84%
9b R^1 = R^2 = H, R^3 = NMe_2, 99%
9c R^1 = R^2 = H, R^3 = Ph, 85%
9d R^1 = H, R^2 = Ph, R^3 = Ph, 92%
9e R^1 = H, R^2 = OMe, R^3 = Ph, 91%
9f R^1 = H, R^2 = R^3 = PMP, 69%
9g R^1 = R^2 = H, R^3 = PMP, 95%
9h R^1 = R^2 = H, R^3 = Tol, 88%
9i R^1 = H, R^2 = H, R^3 = OEt, 99%
9j R^1 = Me, R^2 = R^3 = Ph, 79%

PMP = 4-methoxyphenyl
Tol = 4-methylphenyl

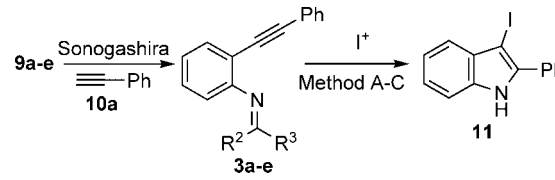
conveniently prepared by condensation of *o*-iodoanilines **7** with ketones or aldehydes **8** to give *N*-(*o*-iodophenyl)imines **9**,[7] followed by Sonogashira coupling of **9** with acetylenes **10** [1.2 equiv of acetylene, 3 mol% $PdCl_2(PPh_3)_2$, 8 mol% CuI, THF/Et_3N] to give **3**. Most of the imines **3** were sensitive to hydrolysis and protocyclization; accordingly, the crude reaction mixtures were generally used in the iodocyclization step (Tables 1 and 2).

We initially evaluated the capacity of *N*-(*o*-alkynylphenyl)imines **3**, bearing a non-nucleophilic R^4 group to undergo

(6) For an alternative approach to chemoselective indole and quinoline formation, see ref 2d.

(7) Imine **9a** was prepared via nucleophilic substitution of the corresponding iminium chloride as described in the Supporting Information.

Table 1. Iodocyclization of *N*-(*o*-Alkynylphenyl)imines **3** Derived from Phenylacetylene



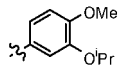
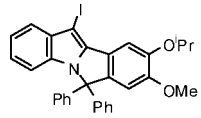
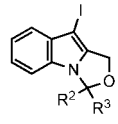
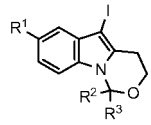
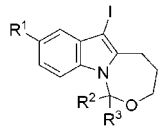
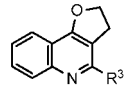
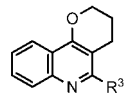
entry	**3**	method[a]	yield (%) of **11** from **9**
1	**3a** (R^2 = R^3 = NMe_2)	A	31[b]
2	**3b** (R^2 = H, R^3 = NMe_2)	A	78[b]
3	**3c** (R^2 = H, R^3= Ph)	A/B/C	0[c]
4	**3d** (R^2 = R^3 = Ph)	B	70
5	**3d** (R^2 = R^3 = Ph)	C	62
6	**3e** (R^2 = OMe, R^3 = Ph)	B	36
7	**3e** (R^2 = OMe, R^3 = Ph)	C	71

[a] Method A: I_2, CH_2Cl_2; Method B: I_2, K_2CO_3, CH_3CN; Method C: NIS, CH_2Cl_2. [b] Additional step to cleave the imine portion (5 M KOH, CH_2Cl_2) was required. [c] Decomposition was observed, formation of benzaldehyde was observed in all reactions.

iodocyclization. This reaction was evaluated using different *N*-(*o*-iodophenyl)imines **9a**−**e**, which were coupled to phenylacetylene **10a** and the resulting crude products **3a**−**e** subjected to iodocyclization under different conditions (Table 1). The dimethylamino substituted imines, **3a** and **3b**, gave very stable iminium ions after iodocyclization (Method A: I_2, CH_2Cl_2); these required an additional cleavage step [5 M KOH(aq)] to give the N−H indole product **11** (31 and 78%, respectively). Of the other imines trialed, **3c**−**e** (entries 3−7), only iodocyclization of **3d** (Method B: I_2, K_2CO_3, CH_3CN) and **3e** (Method C: NIS, CH_2Cl_2) gave good yields of **11** (Table 1 entries 4 and 7, respectively). In these cases, the N−H indole **11** was obtained directly, due to rapid *in situ* hydrolysis of the iminium ions formed during the iodocyclization. As such, they complement the use of *N*-tosyl and *N*-BOC derivatives of *o*-alkynylanilines **1b**, in activating these substrates toward iodocyclization to give protected N−H indoles **2** (X = NH) (Scheme 1).[2b,c] In view of the availability of these alternative procedures, we did not further study this reaction but turned to our main objective of trapping the iminium ion **4** with an internal nucleophile to give **5** (Scheme 2).

When 3-isopropoxy-4-methoxyphenylacetylene **10b** was coupled to **9d** under Sonogashira conditions (see above) and the crude product **3f** subject to iodocyclization under using Method C (NIS, CH_2Cl_2), the cocyclized product isoindolo[2,1-*a*]indole **5a** was obtained in a reasonable overall yield of 52% from **9d** (Table 2, entry 1). This two-step coupling cocyclization reaction sequence was next investigated using a range of different *N*-(*o*-iodophenyl)imines **9c**, **9d**, and **9f**−**j** and hydroxyl-containing acetylenes **10c**−**e** (Table 2, entries 2−17). Iodocyclization of the crude coupling products **3g**−**u** gave the ring fused indoles **5b**−**p** in moderate to excellent yields from the respective *N*-(*o*-iodophenyl)imine

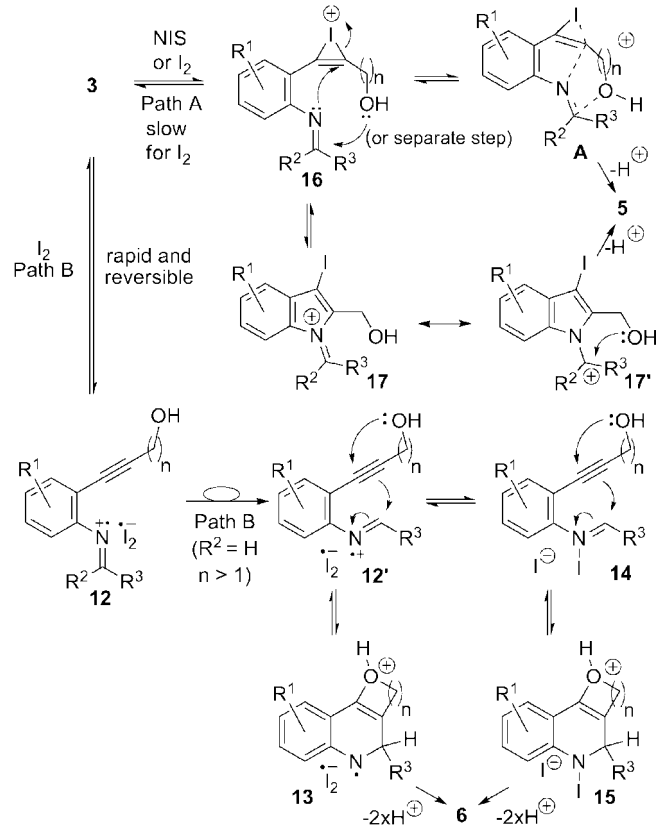
Table 2. Iodonium Induced Tandem Cyclization of **3**

entry	imine 9	R^4 in 10 and 3	method[a]	product	yield(%) from 9
1	**9d**	 **10b, 3f**	C	 **5a**	52
		 -CH_2OH			
2	**9d**	**10c, 3g**	C	**5b** ($R^2 = R^3$ = Ph)	63
3	**9c**	**10c, 3h**	B/C	**5c** (R^2 = H, R^3 = Ph)	0[b]
		 -$(CH_2)_2OH$			
4	**9d**	**10d, 3i**	C	**5d** (R^1 = H, $R^2 = R^3$ = Ph)	94
5	**9d**	**10d, 3i**	B	**5d** (R^1 = H, $R^2 = R^3$ = Ph)	67
6	**9j**	**10d, 3j**	C	**5e** (R^1 = Me, $R^2 = R^3$ = Ph)	70
7	**9f**	**10d, 3k**	C	**5f** (R^1 = H, $R^2 = R^3$ = PMP)	54
8	**9c**	**10d, 3l**	C	**5g** ($R^1 = R^2$ = H, R^3 = Ph)	62
9	**9g**	**10d, 3m**	C	**5h** ($R^1 = R^2$ = H, R^3 = PMP)	43
10	**9i**	**10d, 3n**	C	**5i** ($R^1 = R^2$ = H, R^3 = OEt)	51
		 -$(CH_2)_3OH$			
11	**9d**	**10e, 3o**	C	**5j** R^1 = H, $R^2 = R^3$ = Ph	69
12	**9j**	**10e, 3p**	C	**5k** (R^1 = Me, $R^2 = R^3$ = Ph)	62
13	**9f**	**10e, 3q**	C	**5l** (R^1 = H, $R^2 = R^3$ = PMP)	61
14	**9c**	**10e, 3r**	C	**5m** ($R^1 = R^2$ = H, R^3 = Ph)	75
15	**9g**	**10e, 3s**	C	**5n** ($R^1 = R^2$ = H, R^3 = PMP)	52
16	**9h**	**10e, 3t**	C	**5o** ($R^1 = R^2$ = H, R^3 = Tol)	73
17	**9i**	**10e, 3u**	C	**5p** ($R^1 = R^2$ = H, R^3 = OEt)	60
		 -$(CH_2)_2OH$			
18	**9c**	**10d, 3l**	B	**6a** (R^3 = Ph)	80
19	**9g**	**10d, 3m**	B	**6b** (R^3 = PMP)	48
20	**9h**	**10d, 3v**	B	**6c** (R^3 = Tol)	72
21	**9i**	**10d, 3n**	B	**6d** (R^3 = OEt)	0[b]
		 -$(CH_2)_3OH$			
22	**9c**	**10e, 3r**	B	**6e** (R^3 = Ph)	61
23	**9g**	**10e, 3s**	B	**6f** (R^3 = PMP)	46
24	**9h**	**10e, 3t**	B	**6g** (R^3 = Tol)	59

[a] Method B: I_2, K_2CO_3, wet CH_3CN; Method C: NIS, CH_2Cl_2. [b] Decomposition of starting material was observed.

9 (43−94%). Only in the case of the phenylaldimine **3h** did the cyclization reaction fail, giving a complex mixture (Table 2, entry 3).

Scheme 4



During our investigations into these cocyclizations reactions, we also employed Method B. Sonogashira coupling **9d** to **10d** followed by direct iodocyclization of the crude product **3i** using Method B gave the same pyrano fused indole **5c** as that obtained using Method C, albeit in lower yield (67%) (compare entries 4 and 5 in Table 2). However, application of Method B to the phenyl-*N*-(*o*-alkynylphenyl)imine **3l**, obtained from coupling **9c** to **10d**, did not give the pyranoindole **5g** obtained using Method C but gave the furanoquinoline **6a** in an excellent yield (80%) (compare entries 8 and 18 in Table 2). This product has resulted from an oxidative cocyclization reaction (Path B, Scheme 2). The use of Method B to give a ring fused quinoline was extended to other systems involving aldimines **9g**−**i** (R^2 = H) and hydroxyalkynes **10d** and **10e** to give moderate to good yields (46−72%) of the furano- and pyrano-fused quinolines over the two steps (entries 19, 20, and 22−24). In no case was the corresponding indole compound formed as a byproduct of this reaction. The ethoxy substituted *N*-(*o*-alkynylphenyl)imine **3n** failed to give the ring-fused quinoline product **6d** but instead underwent rapid decomposition. Attempted iodocyclization of the *N*-(*o*-propynolphenyl)phenylimine **3h** using Method B also failed to give either quinoline or indole **5c** using Method B but underwent decomposition under the reaction conditions (Table 1, entry 3).

On the basis of observations made during this study, we have made a number of tentative mechanisitic proposals (Scheme 4). The propensity for the iodocyclization of

aldimines **3** ($R^2 = H$) using either I_2 or NIS to give either **5** or **6**, respectively, may arise out of the greater bias of I_2, relative to NIS, to activate the imine in **3** to electrophilic cyclization than it does the alkyne. Rapid and reversible single electron extraction from **3** by I_2 gives **12**. Rotamer **12′** then undergoes a concerted cocyclization reaction to give **13**. Alternatively, **12** may first convert to the *N*-iodoiminium ion **14** and then cocyclize to give **15**. Intermediate **14**/**15** then loses 2 equivalents of HI giving **6**. The HI is sequestered by the K_2CO_3 present in the reaction mixture (Method B).

The fact that the diphenylimine **3i** gave the pyrano indole **5d** under both conditions, Methods B and C (Table 2, entries 4 and 5), probably arises from a much reduced capacity of the activiated imine **12** to achieve the conformation required for cyclization (**12′**/**14**) due to increased steric interference. Accordingly, in this case, the reaction flux is directed through Path A, where I_2 acts as an electrophile upon the alkyne.

When Method C is employed, the cyclization proceeds through Path A, irrespective of the nature of R^2 (i.e., for aldimines and other imines). It is proposed that, relative to iodine, NIS acts more effectively as an electrophilic π-acid upon the alkyne than it does as an oxidant upon the imine, directing the reaction flux through Path A. In Path A, **3** is initally converted into the cationic intermediate **16**. Intramolecular attack by the imine in **16** gives **17**, which cyclizes through its canonical form **17′** to give **5**. Alternatively, **16** may give **5** through an asynchronous, concerted reaction process, transition state **A**.

Although the stepwise cyclization of **16** through **17**/**17′** could be used to explain both the monocyclization and cocyclization reactions to give indoles, it does not fully explain the pattern of results obtained in this work. We were struck by the fact that, despite numerous attempts, we were unable to use Methods B or C to convert aldimine **3c** to **11** (Table 1, entry 3), or aldmine **3h** to **5c** (Table 2, entry 3), yet all other aldimines **3l**,**m**,**n**,**r**,**s**,**t**,**v** bearing a tethered hydroxyl groups ($n = 2$ or 3) cyclized quite efficiently to give **5** (Method C) or **6** (Method B). The reactions involving **3c** and **3h** (Methods A−C) all gave a complex mixture of products. We conclude from this that aldimines **3** ($R^2 = H$) are generally unstable under the reaction conditions but that reversible formation of reactive intermediates **12**, **14**, and **16** does occur at a rate faster than decomposition. In the presence of an appropriately tethered nucleophile ($n > 1$), these intermediates rapidly undergo cocyclization through concerted transition states **A** or **12′**/**14** to give **5** or **6**, respectively. In both cases (**A** and **12′**/**14**), the nucleophile assists cyclization by providing a lower energy pathway to cocyclization than a stepwise process. In the case of **A**, this may be further assisted by the direct development of aromaticity in the transition state (indole formation) relative to the transition state leading to the azafulvene intermediate **17**.

Transition states **A** and **12′**/**14** are not available to **3c** because it lacks a nucleophile. In the case of **3h**, transition state **A** ($n = 1$) is disfavored by Baldwin's rules as it involves a 5-endotrigonal cyclization.[8] The 6- and 7-endotrigonal cyclizations that attend the cocyclization of **3l**,**m**,**n**,**r**,**s**,**t**,**v** through transistion state **A** ($n = 2$ or 3) are all favored under Baldwin's rule. The ring strain in the transition state of **12′**/**14** ($n = 1$) going to **13**/**15** prevents conversion of **3h** to a quinoline **6**.

More highly substituted imines ($R^{2/3} \neq H$) are sufficiently stable to the reaction conditions such that cyclization of **16** to form **17** can occur. Traping of **17**/**17′** by reaction with water or an internal nucleophile then gives **11** or **5** (e.g., Table 1 entries 4−7 and Table 2 entries 1−2, respectively). If **17**/**17′** had formed in the case of the aldimines **3** ($R^2 = H$) then cyclization of **3h** would be expected to proceed at least as efficiently as the other hydroxyl-containing aldimines **3** ($n = 2$ or 3).

In summary, a concise, convergent protocol combining *o*-iodoanilines **7**, ketones (or aldehydes) **8** and alkynes **10** has been devised that provides for ready access to *N*-(*o*-alkynylphenyl)imines **3**, which can be cyclized to give either ring-fused indoles **5** or quinolines **6** (**8** is an aldehyde) through divergent iodonium induced reaction cascades (Path A and B, Scheme 2). Formation of **6** most likely involves a concerted cocyclization process (**12′**/**14**), whereas formation of **5** may be stepwise (**17**/**17′**) or concerted (**A**) depending on the nature of the nucleophile.

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Supporting Information Available: General experimental procedures and all spectral data for the isolated starting materials and final products. This material is available free of charge via the Internet at http://pubs.acs.org.

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