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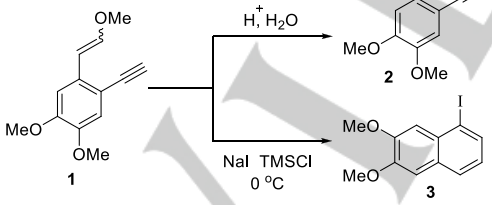
An unprecedented, Lewis acid mediated, metal-free iodoannulation strategy to aromatic iodides

Trisha Banik,[a] Vipul V. Betkekar[a] and Krishna P. Kaliappan*[a]

Abstract: A direct transformation of *ortho*-alkynylated aromatic vinyl ethers to 1-iodonaphthalenes and other iodo-heterocycles under mild Lewis acidic conditions in the presence of iodide as an external nucleophile is reported. The first example of an iodoannulation strategy using a nucleophilic source of iodine, coupled with good to excellent yields, exclusive alpha regioselectivity and a broad substrate scope makes this work an attractive avenue towards the construction of aromatic iodides.

Annulation[1,2] is a process of building rings through creation of a new bond onto a pre-existing cyclic or acyclic system, giving rise to highly complex molecular architecture in one step. Using annulation strategies, formations of rings of all sizes have been developed by a number of synthetic methods over the years. Annulation accompanied by a secondary functionalization on the newly formed cyclic framework adds value to the overall transformation. Introduction of an iodo group during cyclization would lead to the formation of aromatic iodo-compounds in one-pot and this overall process may be termed as "iodoannulation".

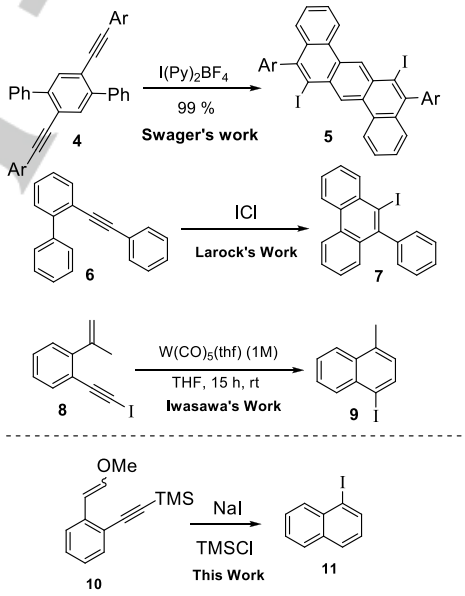
Aryl and heteroaryl iodides are universal precursors and basic building blocks used in chemistry for many important transformations, such as metalation processes,[3,4] nucleophilic aromatic substitutions,[5] and transition-metal catalyzed cross-coupling reactions.[6,7] Iodonaphthalene possesses C-MITOTIC action and also plays an important role in chemical and biological processes especially 1-iodonapthalene is known for its antimicrobial properties.[8] Though ring annulations strategies have been successfully used for the formation of iodoarenes, most of them use either harsh conditions or metal catalysts.[9]



Scheme 1. Preliminary observation

Recently, during the course of an ongoing project in our laboratory on the synthesis of atisane type alkaloids,[10] an attempted hydrolysis of the vinyl ether **1** to its corresponding aldehyde **2** using NaI and TMSCl led to the formation of an unexpected product in excellent yield. Upon careful analysis of this serendipitous product, we concluded that the vinyl ether had undergone an interesting Lewis acid mediated cyclization to produce 6, 7-dimethoxy-1-iodonaphthalene **3**. Once the structure of the newly formed product was confirmed, a survey of existing literature re-established that iodoannulation with good selectivity and generality is a difficult transformation to achieve in the same pot and hence this particular area remains quite unexplored in the synthetic arena. Certainly the incorporation of iodine in the less electron rich nucleus of a naphthalene system was found to be complementary to what is observed for typical aromatic electrophilic iodination on naphthalene derivatives.

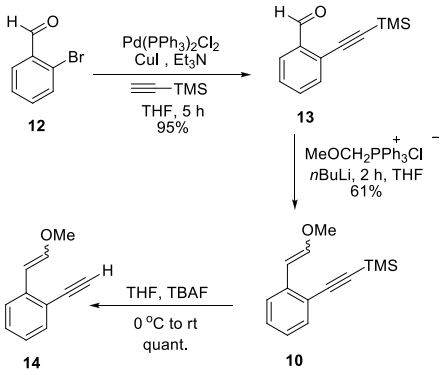
Of the few approaches known for the construction of polycyclic aromatic iodides, each of them proceeds *via* an iodonium ion carbocyclization, which makes the mechanism electrophile induced.



Scheme 2. Earlier reports on iodoannulation

Intramolecular electrophilic cyclization of diarylated acetylenes utilizing electrophilic iodine source such as $I(py)_2BF_4$ has been reported by Swager[11] and Barluenga.[12] Later on Larock and co-workers used ICl or I_2 to simplify the iodine source.[13] In 2002, Iwasawa and co-workers reported the transformation of pre-iodinated terminal alkynes to 1-iodonaphthalene derivatives by using an expensive route *via* tungsten mediated 6π-electrocyclization (Scheme 2).[14] During the preparation of our manuscript, Kwon and co-workers published the synthesis of β–silylalkenyl triflates *via* an alkenyl carbocation intermediate,[15] where the weakly nucleophilic triflate only quenches the highly reactive vinylic carbocation intermediate. There are only a handful of reports where such annulations are driven by

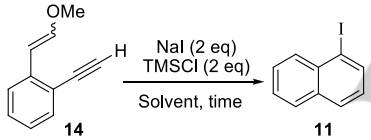
nucleophiles, but in most cases these are internal nucleophiles already embedded in the system.[16] This prompted us to develop our serendipitous observation into a more general methodology for the synthesis of polycyclic aromatic iodides. To the best of our knowledge, till date there are no reports known for iodoannulations using external nucleophilic iodine source.



Scheme 3. Synthesis of (alkynyl)aryl vinyl ethers

Herein, we report a versatile method for the synthesis of polycyclic aromatic iodides in high yields under mild reaction conditions using vinylated phenyl acetylenes and NaI as a nucleophilic source in the presence of a mild Lewis acid TMSCl. The fact that this cyclization is driven by a nucleophile makes this method mechanistically different from the existing ones.

Table 1. Optimization of iodoannulation



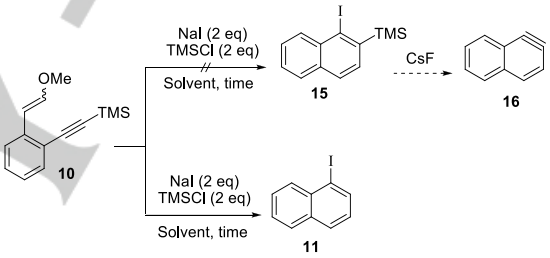
Entry	Solvent	Temp.	Time	Isolated Yield
1	CH_3CN	rt	36 h	48%
2	CH_3CN[a]	rt	48 h	31%
3	THF	rt	24 h	-
4	DMSO	rt	24 h	Trace
5	DMF	rt	24 h	-
6	DCE	rt	24 h	-
7	Toluene	rt	36 h	44%
8	**Toluene**	**reflux**	**2.5 h**	**83%**
9	**CH_3CN**	**reflux**	**2.5 h**	**87%**

[a] KI used instead of NaI

In order to standardize the reaction conditions in general, we chose the unfunctionalized system, 1-ethynyl-2-(2-methoxyvinyl)benzene **14** as our test substrate. For the preparation of the same, 2-bromobenzaldehyde **12** was converted to the corresponding TMS-alkyne **13** by Sonogashira coupling, which in turn was homologated to enol ether **10** using (methoxymethyl)triphenylphosphonium chloride. Once compound **10** was formed, the terminal TMS group was removed with TBAF to obtain the terminal alkyne (Scheme 3).

At the outset of our studies, we treated our test substrate **14** with NaI in presence of TMSCl. Unlike the electron rich substrates, the unsubstituted alkynyl vinyl ether provided a moderate yield of 48% in CH_3CN. Replacement of the iodide source with KI reduced the yield to 31%. Polar aprotic solvents like THF, DMSO, DMF or DCE did not provide any significant product formation even after 24 h. Non-polar solvent like toluene at room temperature yielded 44% of the iodoannulated product. However refluxing temperatures in toluene and acetonitrile improved the yield significantly to 83% and 87% respectively and also reduced the reaction time considerably.

Table 2. Attempted preparation of aryne precursors

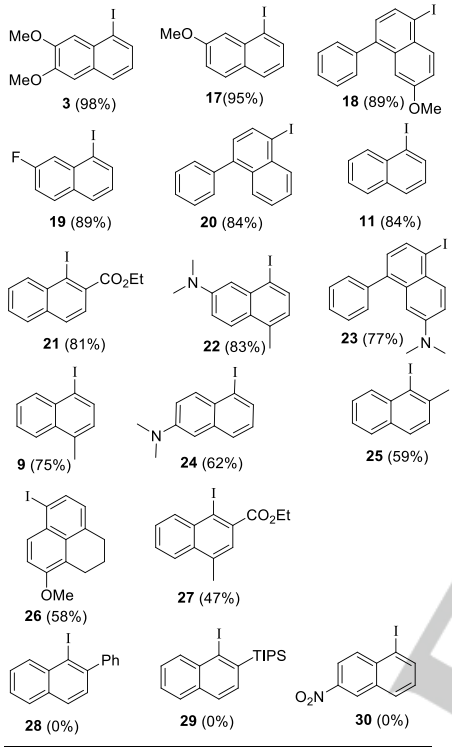


Entry	Solvent	Temp.	Time	Isolated Yield
1	CH_3CN	Rt	3.5 h	84%
2	Toluene	Rt	4 h	79%

We envisioned that an iodonaphthalene derivative with a TMS group intact at the 2-position would be an ideal aryne precursor[17, 18] and in order to achieve this, we carried out the reaction with the terminal TMS group intact in the vinyl ether. Unfortunately the TMS group proved to be too labile under these reaction conditions and we obtained the same 1-iodonaphthalene **11**, but in lesser reaction times and at room temperature.

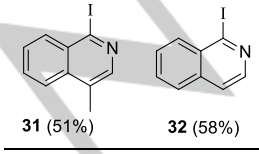
So, even though we could not achieve the synthesis of our desired aryne precursor by this route, it was a blessing in disguise as it reduced one step in the preparation of our iodoannulated precursors. The TMS-protected alkyne **10** provided 1-iodonaphthalene with a yield of 79% in toluene, while acetonitrile yielded 84%, which were very much comparable to our earlier conditions (Table 1, Entries 8 and 9). We decided to compromise the small decrease in yield, in order to accommodate the other advantages of a lesser reaction time and much milder conditions.

With the optimized reaction condition in hand (Entry 2, Table 2), the scope of this interesting transformation was examined. It is worth mentioning that electron rich aromatic nuclei afforded very good yields, whilst substrates with electron withdrawing groups like $-NO_2$ failed to furnish the desired product at all. Electron withdrawing groups attached on the terminal position of the alkyne reacted well, while methyl substituted alkynes returned moderate results. However, bulky alkyne substituents like TIPS or Ph failed to provide the iodonaphthalenes, presumably due to steric issues.



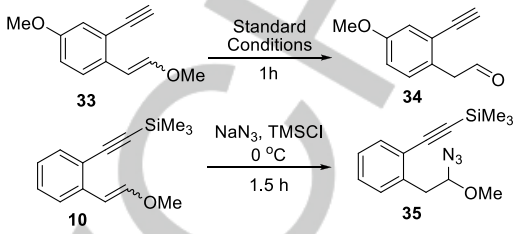
Scheme 4. Substrate scope for iodoannulation

We also explored the scope of α-substituted vinyl ethers derived from acetophenone or benzophenone derivatives to afford the 1,4-disubstituted naphthalenes with equally efficient results. Substituted alkynes attached to ketone derivatives provided the 1,2,4-trisubstituted naphthalenes, although in poor yields, probably due to the highly congested nature of the intermediates. The test substrate was iodoannulated in gram scale with reproducible yield, which establishes the scalability of the method.



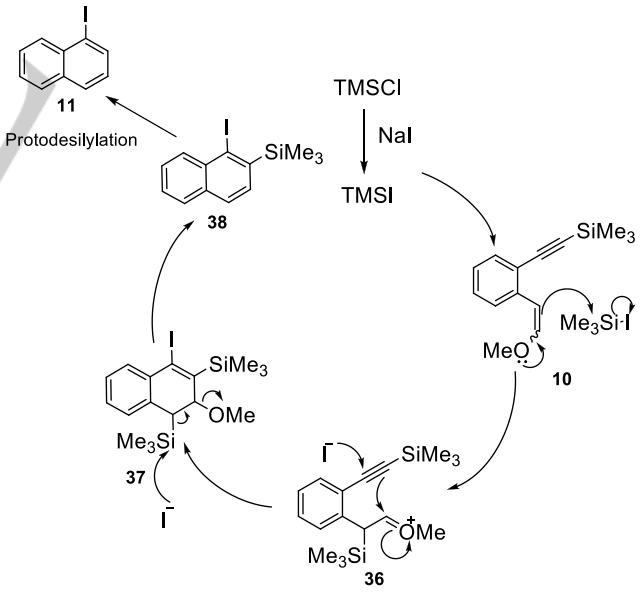
Scheme 5. Iodoannulation leading to isoquinoline derivatives

An extension of our method was envisaged by replacing the alkyne with a nitrile group in few of our vinyl ether substrates. This furnished 1-iodoisoquinolene[19] under the standard conditions, which happens to be a privileged scaffold in heterocyclic chemistry (Scheme 4).



Scheme 6. Evidences for oxonium ion formation

A couple of important observations provided us a lead towards elucidating a plausible mechanism of the annulation reaction (Scheme 6). When we stopped the reaction after 1 h, aldehyde **34** was isolated which suggested a predictable hydrolysis of the vinyl ether **33** under Lewis acidic conditions, *via* an intermediate oxonium ion. So the first step of our cyclization process should be the formation of the oxonium ion catalyzed by the *in situ* generated TMSI, thereby generating intermediate **36**. Another independent experiment with a hard nucleophile like sodium azide resulted in the direct quenching of the oxonium ion to provide the azido-ether **35** (Scheme 6).

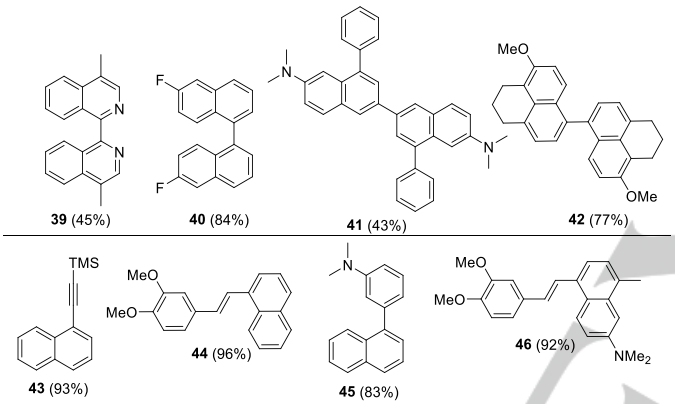


Scheme 7. Plausible mechanism for iodoannulation protocol

This led us to believe that a softer nucleophile like iodide would quench the oxonium ion indirectly by a relay nucleophilic attack on the internal carbon of the triple bond, which would in turn complete the ring formation through a 6-*exo*-trig type cyclization

to generate intermediate 37. This process is analogous to Prins type cyclization,[20] where the oxonium ion is quenched by the triple bond and the newly formed carbocation is stabilized by β-stabilizing effect of silicon. Finally a second equivalent of iodide aromatizes the ring by elimination of –OMe and TMS groups to generate the silylated iodonaphthalene 38, which undergoes protodesilylation to provide our desired 1-iodonaphthalene 11 *in situ* (Scheme 7). As we have used dry CH_3CN, freshly dried NaI and distilled TMSCl, chances of HI being formed during the reaction is minimal. This eliminates an alternative possibility of our reaction being driven by a strong Bronsted acid like HI.

To further extend the scope of our iodoannulated products, a few self-coupling reactions were performed with our iodoannulated products which led to the formation of some interesting binaphthyl compounds, which have enormous scope in the field of asymmetric synthesis as axially chiral ligands.



Scheme 8. Coupling products obtained from the iodoannulated derivatives

Some well known coupling reactions like Suzuki coupling, Heck coupling and Sonogashira coupling utilizing our iodonaphthalene derivatives with various coupling partners were carried out, which furnished some interesting polyaromatic compounds with excellent yield and a broad scope (Scheme 8).

Conclusion

In conclusion, we have reported a direct transformation of 2-alkynylated aromatic vinyl ethers to various aromatic iodides, which are useful substrates for various coupling reactions. Arising from a serendipitous observation, the reaction conditions were carefully optimized to synthesize a wide number of 1-iodonaphthalene derivatives with good to excellent yields, employing a mild and scalable condition at room temperature. Exclusive alpha-regioselectivity irrespective of substituents was observed in the less electron rich nucleus of the naphthalene derivatives, which is contrary to what occurs in aromatic electrophilic iodination.

In addition, iodinated derivatives of isoquinoline were also synthesized which have immense value in the construction of various biologically active moieties. The scope of this method has been further extended by carrying out various coupling reactions on our aromatic iodo-compounds to provide a wide range of polyaromatic scaffolds, which are not always easily accessible. Mechanistically, the reaction is driven by the Lewis acid mediated formation of an oxonium ion followed by relay quenching of the same by iodide ion, *via* a nucleophile mediated 6-*exo*-trig cyclization. To the best of our knowledge, this is the first example of such a nucleophile mediated iodoannulation strategy and it holds a lot of potential towards the construction of 1-aromatic iodides and their derivatives.

Experimental Section

Please check the supporting information.

Acknowledgements

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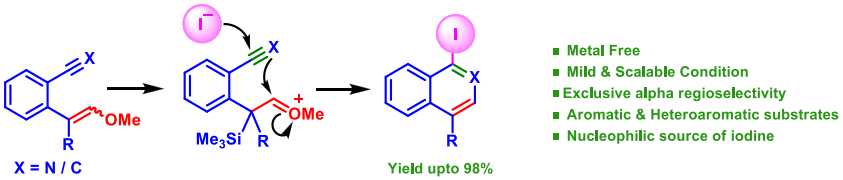

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