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Highly regioselective, electrophile induced cyclizations of 2-(prop-1-ynyl)benzamides†

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We report an electrophile promoted, highly regioselective (~100%) synthesis of 5-membered haloimidiates from 2-(1-alkynyl)benzamides under metal free conditions. The steric bulk in association with neighbouring group assistance at the propargylic carbon of an alkyne has been employed as the dictating factor to achieve the regioselectivity. A very broad structural diversity has been observed for propargylic alcohols and acetates, and for amide functional groups. Control experiments supported the role of the steric bulk as well as neighbouring group assistance from the oxygen atom of the substituent for the observed high regioselectivity.

Introduction

Recently, the electrophile activated cyclizations of alkynes in particular halocyclizations have been found to be versatile methods for the generation of structurally divergent carbocyclic as well as heterocyclic systems.[1] These strategies have already been well utilized for the synthesis of various biologically privileged heterocyclic scaffolds such as benzofurans,[2a] furans,[2b,c] benzothiophenes,[2d] indoles,[2e,f] carbazoles,[2g] quinolines,[2h,i] isoxazoles,[2j] pyrroles,[2k] *etc.*[2l,m]

The 2-(1-alkynyl)benzamide units **1** are highly versatile intermediates for the diversity oriented synthesis of structurally novel heterocyclic systems. This system can in principle undergo regioselective as well as chemoselective cyclizations such as *5-exo-dig vs. 6-endo-dig* cyclizations, using either a nitrogen (N) or oxygen (O) atom as the nucleophile (Fig. 1a).[3] Various transition metal promoted, chemo- and regioselective cyclizations of 2-(1-alkynyl)benzamide **1** have been developed for the selective synthesis of two types of imidates **2** or **3** (*via* *O*-nucleophilicity)[3a,b] or isoquinolinones[3c,d] **4** or isoindolinones[3e–h] **5** (*via* *N*-nucleophilicity). In this context, Larock *et al.* reported transition metal free, electrophilic cyclizations of 2-(1-alkynyl)benzamides **1**.[4] This method exhibits high chemoselectivity towards cyclization through the oxygen-centre, but the regioselectivity is poor. Always variable amounts of a mixture of both regioisomeric products, 6-membered as well as 5-membered imidates **6** and **7** *via 6-endo-dig* and *5-exo-dig* cyclizations, respectively, were observed. There was no 100% selectivity towards a particular type of imidate, except in entries 23 and 24 in Table 2, where a 6-membered imidate was the sole product and the reason for this was not clear. With this background, herein we reported metal free, halonium ion promoted cyclizations of 2-(1-alkynyl)benzamides **1** for the highly chemo- and regioselective (~100%) synthesis of 5-membered haloimidates.

In continuation of our ongoing interest on the unconventional functionalization of alkynes, propargylic alcohols and

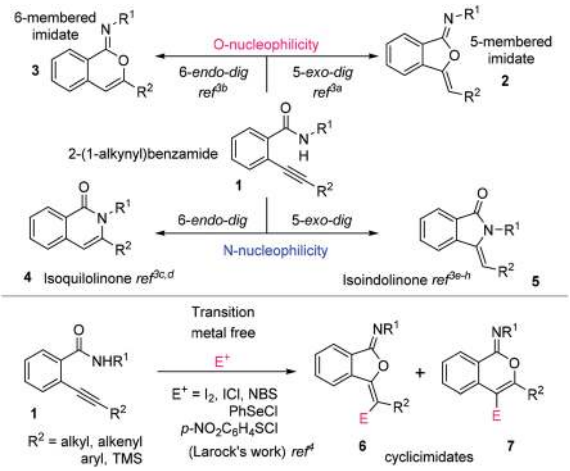

Fig. 1 (a) Transition metal promoted intramolecular cyclizations of 2-(1-alkynyl)benzamides and (b) metal free, electrophile activated cyclizations of 2-(1-alkynyl)benzamides (Larock's work).

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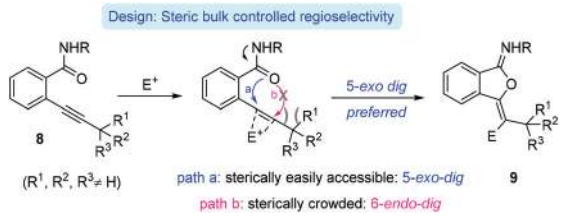
†Electronic supplementary information (ESI) available: General procedures for the preparation of the compounds and the catalytic reaction; characterization data including ^{1}H, ^{13}C NMR spectra, IR and HRMS. CCDC 1589065. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ob00434j



Scheme 1 Our design for a steric bulk directed, regioselective synthesis of 5-membered haloimidates.

their derivatives,[5] we chose to explore the reactivity of 2-(1-alkynyl)benzamides **1** under metal free conditions. In organic synthesis, the steric bulk of the substituents plays a key role in the regio- as well as stereoselectivity of any particular reaction.[6] Inspired by this approach, we envisioned that keeping a sterically bulky (mostly tertiary) carbon on the terminus of the alkyne of 2-(1-alkynyl)benzamide **8**, *i.e.*, at the propargylic position, might prevent the halonium (X^+) activated *6-endo-dig* process and provide access exclusively to the 5-membered haloimidates **9**, through *5-exo-dig* cyclization (Scheme 1).

Results and discussion

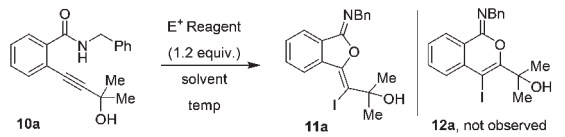
To test our hypothesis, we chose a dimethylpropargylic alcohol containing *o*-benzamide **10a** as the model substrate. When **10a** was treated with *N*-iodosuccinimide (NIS, 1.2 equiv.) in THF at RT (Table 1, entry 1), the expected 5-membered iodoimidate **11a** *via 5-exo-dig* cyclization was isolated in 42% yield after 30 min. There was no detection of the *6-endo-dig* product **12a**. Pleased by this result and in order to improve the yield of **11a**, we next performed this reaction in various solvents keeping the amount of NIS (1.2 equiv.) constant. In all the solvents screened, such as ethyl acetate, carbon tetrachloride, chloroform, acetonitrile, methanol, toluene, acetone, 1,2-dichloroethane (1,2-DCE) and dichloromethane (entries 2–10), the substrate **10a** underwent a smooth cyclization to yield the iodoimidate **11a** in very good yields (68–95%). None of these solvents gave any traces of the corresponding 6-membered imidate **12a**.

Next, the reaction was performed at elevated temperatures (55, 80 and 100 °C; entries 11–13) employing 1,2-DCE as the solvent. We observed reduced reaction times and yields of the product **11a** as the temperature increased. When iodine was employed as the electrophile (entry 14) in CH_2Cl_2, the yield of **11a** was 86%. With *N*-bromosuccinimide (NBS), the reaction was relatively slower (30 min) to yield the corresponding 5-membered bromoimidate **13a** in 79% yield. When we performed the reaction at elevated temperatures with NBS, a decrease in yields of **13a** was observed.[7] Hence, for the regioselective synthesis of the corresponding 5-membered haloimidates, we chose the optimized conditions shown in entries 9, 10 and 15.

Having the best conditions in hand, we turned our attention to evaluate the scope of this transformation (Scheme 2). Structurally divergent, cyclic and acyclic propargylic alcohols **10b–h** were employed. All these substrates **10b–h** were found to be compatible under standard reaction conditions and resulted in the formation of the corresponding highly functionalized iodoimidates **11b–h** in excellent yields (up to 98%) within short reaction times (15–30 min). To unambiguously confirm the regio- and stereoselective formation of the 5-membered iodoimidate, a single crystal X-ray diffraction analysis for compound **11d** was also performed.[8]

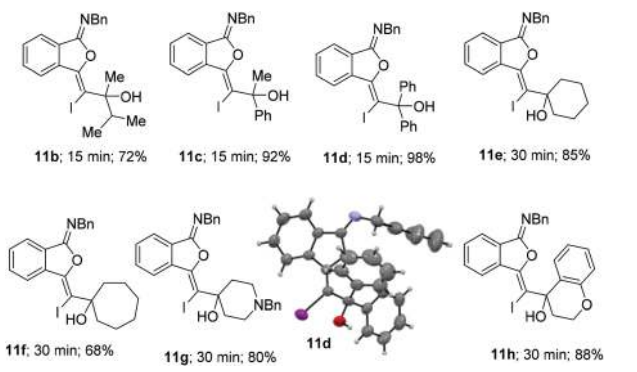
Subsequently, various amides **14a–h** possessing divergent aliphatic amines, electron rich as well as electron poor anilines, and 3,5-disubstituted anilines were also employed against the *gem*-dimethylpropargylic alcohol (Scheme 3). Though the electronic properties of the nitrogens are varyingly different, all the amides gave excellent yields (up to 95%) of the corresponding iodoimidates **15a–h**. However, for none of

Table 1 Reaction optimization study

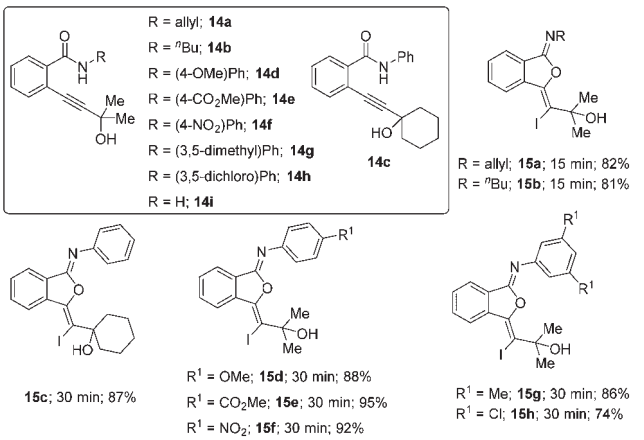


Entry[a]	Reagent	Solvent	Temp. (°C)	Time (min)	Yield (%)
1	NIS	THF	RT	30	42
2	NIS	EtOAc	RT	15	68
3	NIS	CCl_4	RT	15	70
4	NIS	$CHCl_3$	RT	15	72
5	NIS	CH_3CN	RT	15	82
6	NIS	MeOH	RT	15	84
7	NIS	Toluene	RT	15	86
8	NIS	Acetone	RT	15	89
9	NIS	1,2-DCE	RT	15	95
10	NIS	CH_2Cl_2	RT	15	95
11	NIS	1,2-DCE	55	10	91
12	NIS	1,2-DCE	80	5	87
13	NIS	1,2-DCE	100	5	86
14	I_2	CH_2Cl_2	RT	15	86
15	NBS	CH_2Cl_2	RT	30	79

[a] In all of the above cases, the starting compound **10a** was completely consumed.



Scheme 2 Scope study of propargylic alcohols. Reaction conditions: NIS (1.2 equiv.), RT, CH_2Cl_2, 15–30 min.

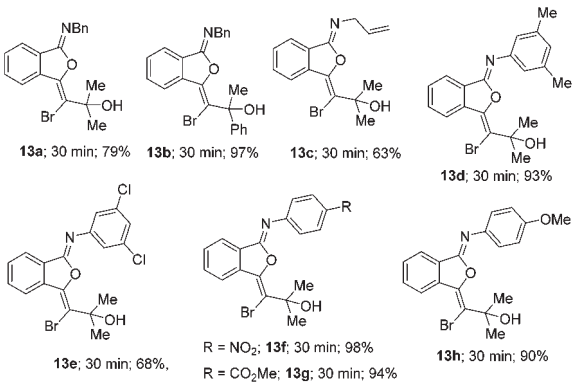


Scheme 3 Scope study of amides (amines). Reaction conditions: NIS (1.2 equiv.), RT, CH_2Cl_2, 15–30 min.

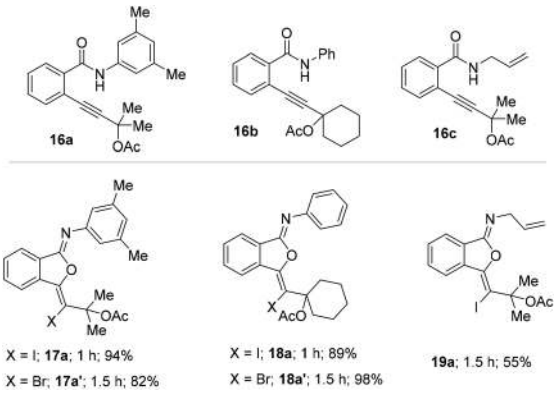
the substrates, the competitive six-membered product was observed. We had also employed a substrate **14i** possessing a free $CONH_2$ (*i.e.*, unsubstituted amide) under standard reaction conditions. Surprisingly, the starting compound **14i** was consumed with time, but no identifiable products were observed.

Next, we extended this transformation to employ NBS as the electrophilic bromonium ion source, against electronically variable amides and propargylic alcohols (Scheme 4). In all the cases, the reaction was clean and smooth to yield the corresponding bromoimidates **13a–h** in excellent yields (up to 98%). The reactions were found to be slower in comparison with their iodonium counterparts (Schemes 2 and 3).

We have further employed this strategy with various *tert*-propargylic acetates against different benzamides **16a–c.** Both iodonium as well as bromonium ion promoted cyclizations were efficient and highly selective towards the corresponding 5-membered haloimidates **17a–19a, 17a′** and **18a′.** In none of the cases, the competitive *6-endo-dig* products were observed (Scheme 5).



Scheme 4 Employing *N*-bromosuccinimide as the electrophilic source. Reaction conditions: NIS (1.2 equiv.), RT, CH_2Cl_2, 15–30 min.

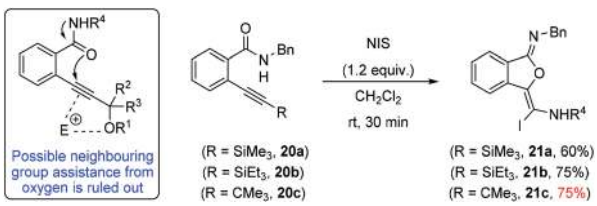


Scheme 5 Extension to propargylic acetates. Reaction conditions: NIS (1.2 equiv.), RT, CH_2Cl_2, 15–30 min.

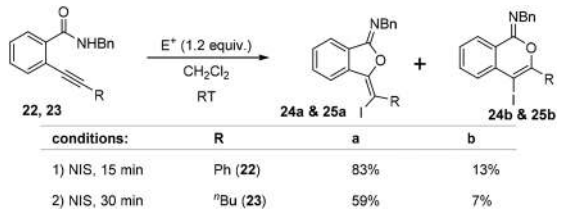
In order to verify any possibility of neighbouring group assistance from the Lewis basic (nucleophilic) oxygen of either a hydroxyl or acetate group in the observed regioselectivity, we have performed this reaction with 2-(alkynyl)benzamides **20a–c** which lack the oxygen atom. Delightfully, the reactions were clean with both trimethylsilylethyne **20a** and triethylsilylethyne **20b** under standard reaction conditions, and resulted in an exclusive formation of the respective 5-membered iodoimidates **21a** and **21b** in good yields. On the other hand, in the case of **20c**, which is carrying a *tert*-butyl group, the 5-membered iodoimidate **21c** was isolated as a major product (75% yield) along with a very minor amount (3% yield) of a mixture of two products including possibly the 6-membered iodoimidate (see the ESI for ^{1}H-NMR†). This suggests that there may possibly be a neighbouring group assistance (from the oxygen atom of the hydroxyl or acetoxy group) in addition to the steric bulk of the propargylic carbon in controlling the observed regioselectivity (Scheme 6).

Subsequently, we also subjected 2-(1-alkynyl)benzamides **22** and **23** possessing phenyl and *n*-butyl groups (smaller in size), respectively, on the terminus of the alkyne to standard reaction conditions. Agreeably, in both cases, a mixture of *5-exo-dig* and *6-endo-dig* products **24a** and **24b** (6.4 : 1) and **25a** and **25b** (8.5 : 1), respectively, was isolated. This observation supports the need for a tertiary carbon (*i.e.*, steric bulk) and the neighbouring group assistance at the propargylic position to induce the selectivity towards the *5-endo-dig* cyclization (Scheme 7).

Finally, we converted one of the iodo-imidates **11a** into a highly conjugated, hybrid-polyheterocyclic system **26** employ-

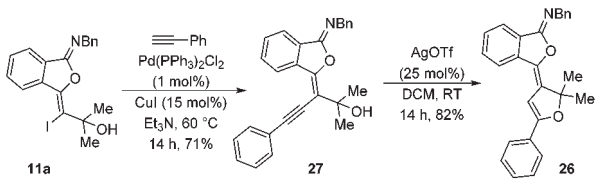


Scheme 6 Control experiments.



conditions:	R	a	b
1) NIS, 15 min	Ph (**22**)	83%	13%
2) NIS, 30 min	^{n}Bu (**23**)	59%	7%

Scheme 7 Testing the standard reaction conditions of substrates locking tertiary propargylic carbons and co-ordinating atoms.



Scheme 8 Preparation of a furanyl-imidate hybrid-heterocyclic framework.

ing a two-step protocol (Scheme 8). The Sonogashira coupling of **11a** with phenylacetylene followed by a *5-endo-dig* cyclization of the resulting homopropargylic alcohol **27** in the presence of Ag(I) gave the furanylidine-isobenzofuran derivative **26** in excellent yield (67% for two steps).

Conclusions

In conclusion, we have developed a metal free process for the highly regioselective (~100%) synthesis of 5-membered haloimidates from 2-(1-alkynyl)benzamides. We employed the steric bulk in association with neighbouring group assistance of the substituent present at the propargylic carbon of an alkyne as the directing factor to achieve the regioselectivity. A very broad structural generality has been seen in terms of propargylic alcohols, propargylic acetates, and amide functional groups. Control experiments revealed the fact that the steric bulk and neighbouring group assistance from the hydroxyl or acetate functionality are responsible for the observed regioselectivity.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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7 When we employed *N*-chlorosuccinimide as the electrophilic source, there was no reaction observed. At elevated temperatures, a slow decomposition of the starting materials to unidentifiable products was observed.

8 Crystallographic data information for iodoimidate **11d** has been deposited with the Cambridge Crystallographic Data Centre with CCDC 1589065. Further details are given in the ESI.†