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# Electrophile induced branching cascade: a powerful approach to access various molecular scaffolds and their exploration as novel anti-mycobacterial agents†

Cite this: *Chem. Commun.*, 2013, **49**, 10109

Received 16th July 2013,
Accepted 30th August 2013

DOI: 10.1039/c3cc45289a

www.rsc.org/chemcomm

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**Herein we report on the Electrophile Induced Branching Cascade (EIBC), a new technique to produce a variety of biologically important molecular scaffolds. Some compounds exhibit excellent activities against *Mycobacterium smegmatis*.**

In the recent times, a "branching cascade"[1] has been proposed as a new technique of "Diversity Oriented synthesis"[2] for the systematic exploration of chemical space.[3] Recently, we introduced the relay catalytic branching cascade (RCBC) as a new technique for accessing a series of multifunctional polyheterocyclic scaffolds[4] in an efficient manner.[5] In this communication, we report an entirely novel technique; namely, an "electrophile induced branching cascade" (EIBC) to access various molecular scaffolds which have potential for further diversification.

As part of our ongoing interest in DOS, we assumed that a common type of starting material (**X**) would react with several variables (scaffold building agents, SBAs) in the presence of a suitable electrophile ($E^+$) leading to the formation of various molecular scaffolds (Fig. 1). Such an EIBC technique would be synthetically valuable as it would incorporate an electrophile into the polyheterocyclic scaffold and therefore offer clear-cut potential for introduction of further diversity.[6] Unlike our previous report,[5] a major concern was that $E^+$ would react with the electron rich SBAs leading to the formation of electrophile incorporated SBAs which may further react with **X** creating a mixture of products. The products formed have propensity to react again with electrophiles and therefore the overall process can be considered as complicated as it would be difficult to obtain any of the products in good yields. The challenge, therefore, was to search for a suitable $E^+$ source and appropriate reaction conditions which should only give the desired product.

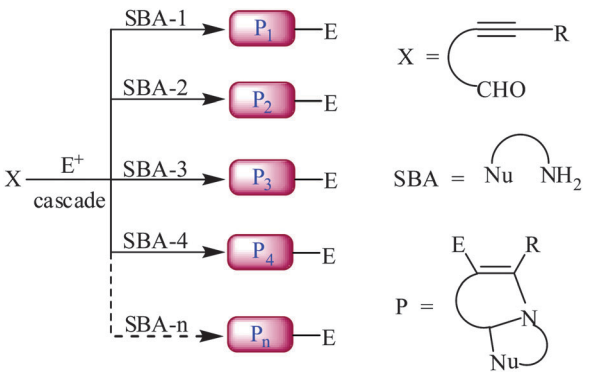


**Fig. 1** Concept of electrophile induced branching cascade (EIBC). X = common type of starting material, SBA = scaffold building agent, P = product, $E^+$ = electrophile.

To the best of our knowledge, there have been no reports on such an EIBC approach leading to diverse electrophile incorporated molecular scaffolds in one-pot operation. Keeping in the mind that the scaffolds of known bioactive small molecules play a key role in guiding the chemist's navigation of biologically relevant chemical space, the strategy was designed in such a way that the accessed compounds would (1) be a hybrid of privileged scaffolds, (2) satisfy the Lipinski "rule of five", (3) have at least one $sp^3$ carbon to attribute the 3D character, (4) have smaller molecular weights, and (5) have the possibility for incorporation of more polar functionalities.

We began to test our hypothesis using 2-(alkynyl)benzaldehydes (**X**) as a common type of starting materials. The SBAs (**1–11**, Fig. 2) were either prepared in the laboratory or purchased from commercial sources.[7] Iodonium ions were considered as a source of electrophiles due to the low electrophilicity of molecular iodine, compared to that of molecular chlorine and bromine, which would enable obtaining the desired product suppressing the formation of side products.[8] The hypothesis, in part, was also based on the fact that $I^+$ is well suited for electrophilic cyclization of alkynes[9] and especially due to the excellent ability of the iodo-group containing product to cross-couple with various nucleophiles

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† Electronic supplementary information (ESI) available. CCDC 928899, 928900 and 929085. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc45289a

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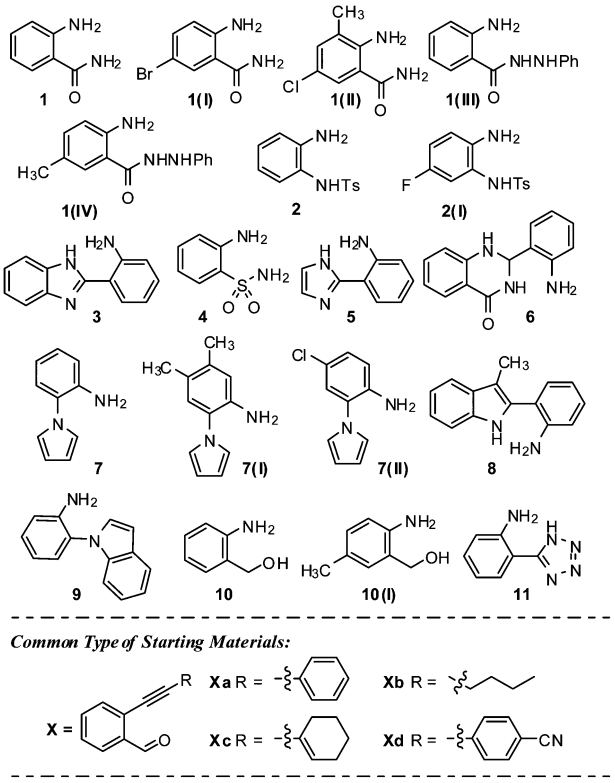


**Fig. 2** Structure of SBAs and common types of starting materials.

much easier than other halo groups. Our preliminary study revealed very discouraging results; as envisioned, a number of products formed in most of the "**X**-SBAs combinations" when iodine alone was used as the source of iodonium ions. A mere change in the reaction conditions such as temperature and solvents did not give the anticipated products in reasonable yields. Moreover, it was found that the reaction conditions suitable for certain kinds of SBAs did not work well for others. We, therefore, carried out detailed investigations and looked for variation in the iodonium ion source, solvents, bases, time, temperature...*etc.* for each and every SBA. Careful optimization studies led us to establish six reaction conditions; those are: (1) $I_2$, DCE, rt, 3 hours (2) $I_2$, $CH_3CN$, rt, 8 hours (3) $I_2$, $K_2CO_3$, $CH_3CN$, rt, 5 hours (4) $I_2$, $K_2CO_3$, DCE, 75 °C, 5 hours (5) *p*-TSA, DCE, rt, 3 hours then $K_2CO_3$, $I_2$, rt, 2 hours and (6) *p*-TSA, DCM, rt, 6 hours then ICl, 0 °C, 2 hours. With the optimized reaction conditions in hand, the scope of the EIBC was then investigated.

As shown in Fig. 3, a wide array of SBAs (amino-aromatics, amino-alcohols, diamines, *etc.*) participated smoothly in the reaction leading to a powerful EIBC approach for the synthesis of the iodo-group containing polyheterocyclic scaffolds in moderate to good yields. The reaction of 2-(phenylethynyl)benzaldehyde (**Xa**) with 2-aminobenzamide (**1**) and its derivatives **1(I)**, **1(II)**, **1(III)**, **1(IV)** under the reaction condition-1 afforded cyclization products **1a**, **1b**, **1c**, **1d** and **1e** in 92%, 89%, 84%, 84% and 83% yields, respectively (branch-1). Similar results were observed with the substrate **Xc** and 2-aminobenzamide derivative **1(III)** to get the product **1f** in 81% yield. The SBA, monoprotected 1,2-diamino benzene **2**, when treated with **Xa** and **Xc** under the reaction condition-1, delivered the required products **2a** and **2b** in 72 and 68% yields (branch-2). Fluorine substituted SBA-**2(I)** also worked well with **Xa** under the same reaction conditions to get product **2c** in 65% yield. It should be noted that the protection of one of the amine nitrogens on 1,2-diaminobenzene proved to be essential. As shown in branch-3, the substrate, 2-alkynylbenzaldehydes **Xa**, **Xb** and **Xc** reacted well with 2-(aminophenyl)benzimdazole (**3**) under the reaction condition-6 to give desired benzoimadazoquinazolines **3a**, **3b** and **3c** in 75, 71 and 62% yields, respectively. The excellent reaction profiles observed with the SBA 2-aminobenzenesulphonamide (**4**) and 2-alkynylbenzaldehydes **Xa**, **Xd** and **Xc** affording the cyclization products **4a**, **4b** and **4c** in 80%, 87% and 78% yields, respectively (branch-4). The SBA-5, 2-(aminophenyl)imadazole found to be react efficiently under the reaction condition-6 with **Xa**, **Xb** and **Xc** to produce imadazoquinazolines **5a**, **5b** and **5c** in 84%, 62% and 75% yields, respectively (branch-5). The SBA-6 afforded the expected quinazolines **6a** and **6b** in moderate yields after reaction with **Xa** and **Xc** under the reaction condition-1 (branch-6). Gratifyingly, the pyrrole based SBA derivatives **7**, **7(I)** and **7(II)** also worked well with **Xa** under the reaction condition-5 to afford the fused ring products **7a**, **7b** and **7c**; albeit, in low yields (branch-7). To further explore the generality and scope of EIBC, indole based SBAs were examined to deliver the indole fused heterocyclic scaffolds. For instance the desired indoloquinazolines **8a**, **8b** and **8c** were obtained in 48–64% yields from SBA-8 and 2-alkynylbenzaldehydes **Xa**, **Xb** and **Xc** under the reaction condition-4 (branch-8). The other indole based SBA, 2-amino-*N*-phenylindole (**9**) reacted with 2-alkynylbenzaldehydes **Xa** and **Xb** under the reaction condition-2 to deliver the products **9a** and **9b** in moderate yields (branch-9). The SBA, 2-aminobenzylalcohol (**10**) when treated with **Xa** and **Xb** under the reaction condition-3 to afford the desired oxazinoisoquinolines **10a** and **10b** in 74% and 63% yields (branch-10). The methyl derivative of SBA **10(I)** afforded the product **10c** in 66% yield after reaction with **Xa**. The tetrazoquinazolines **11a** and **11b** were obtained in 64% and 62% yields; respectively, when 5-(2-aminophenyl)-tetrazole (**11**) reacted with **Xa** and **Xd** under the reaction condition-6 (branch-11). The structure of products **1b**, **1e** and **5c** was unequivocally confirmed by using X-ray crystallography.[7] A product accessed through one of the branches was transformed to more functionalised scaffolds by metal catalysed cross-coupling reactions.[7] It should be noted that each scaffold has several privileged structures embedded within it.[7] One of the branches of present EIBC (branch 1) has been made enantioselective (90% ee) under the catalysis of chiral Brønsted acid under the realm of iodine induced cyclization.[7] Some of the compounds accessed through EIBC; especially, **7a**, **7b**, and **8a** showed excellent activity against *Mycobacterium smegmatis* (MIC = 11.15, 6.14 and 7.70, respectively) in a reference to isoniazid (MIC = 15.25) and rifampicin (MIC = 1.87) with minimum cytotoxicity.[7]

In summary, we have developed electrophile induced branching cascade (EIBC) as an interesting and a very direct approach for the efficient generation of a library of drug-like polyheterocycles. One of the branches of the present EIBC has been made enantioselective indicating the possibility of enantioselective EIBC. The screening results are found to be very promising as some compounds are

 

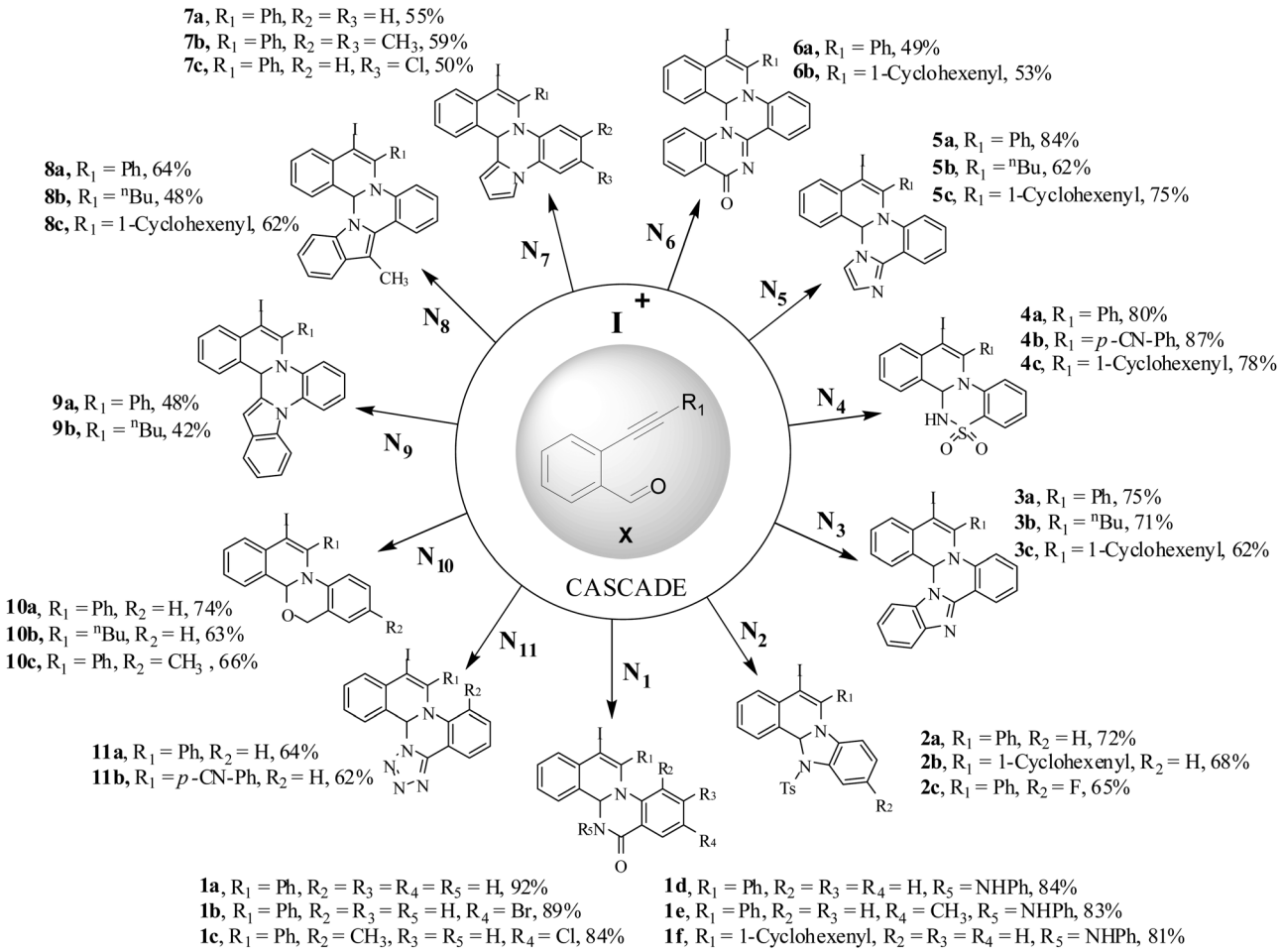


**Fig. 3** Generation of focused library *via* electrophile induced branching cascade. Reaction conditions: SBA (1 eq.), 2-alkynylbenzaldehyde (1 eq.) Condition 1: $I_2$ (3 eq.), DCE, rt, 3 hours (for $N_1$, $N_2$, $N_4$, $N_6$). Condition 2: $I_2$ (3 eq.), $CH_3CN$, 8 hours (for $N_9$). Condition 3: $I_2$ (1.8 eq.), $K_2CO_3$ (2 eq.), $CH_3CN$, rt, 5 hours (for $N_{10}$). Condition 4: $I_2$ (1.8 eq.), $K_2CO_3$ (2 eq.), DCE, 75 °C, 5 hours (for $N_8$). Condition 5: *p*-TSA (0.05 eq.), DCE, rt, 3 hours the $K_2CO_3$ (1.2 eq.), $I_2$ (1.1 eq.), 2 hours (for $N_7$). Condition 6: *p*-TSA (0.05 eq.), DCM, rt, 6 hours then ICl (1.1 eq.), 0 °C, 2 hours (for $N_3$, $N_5$, $N_{11}$). Note: $N_{1,2\ldots11}$ represents the branch number generated from corresponding SBAs.

highly selective against *Mycobacterium smegmatis.* Further efforts to test these compounds against *Mycobacterium tuberculosis* and SAR studies are currently underway in our laboratories.

NTP and RU gratefully acknowledge financial support from MoES, ORGIN, OSDD and SMILE projects.

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