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Method

Acid Catalysed Rearrangement of Isobenzofurans to Angularly Fused Phthalides

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An acid catalysed, cascade process for the construction of angularly fused polycyclic phthalides from isobenzofurans under transition metal free conditions has been reported. This process is very general for diverse gem-disubstituted isobenzofuran substrates. Control experiments supported the mechanism as the nucleophilic attack of the carboxylate on to the acid activated furan ring for the simultaneous ring closing-ring opening cascade followed by dehydration. This method serves as a greener alternative for the synthesis of angularly fused polycyclic phthalides.

Introduction

Phthalides (isobenzofuranones) and their derivatives are ubiquitous in bioactive natural products and drugs (Figure 1).[1] They are found to exhibit antibacterial, antiviral and anti-hypertensive activities.[2] They are also employed as versatile building blocks in organic synthesis,[3] for the generation of complex polycyclic systems, e.g., key precursors in the Hauser annulation process.[4] Owing to their importance several synthetic methods have already been developed in literature for the efficient generation of bicyclic as well as polycyclic phthalides. Most of the processes for the synthesis bicyclic phthalides employ the *ortho*-functionalized, aromatic carbonyl derivatives as starting materials.[5]

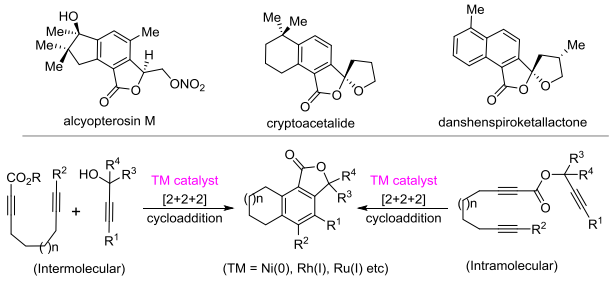
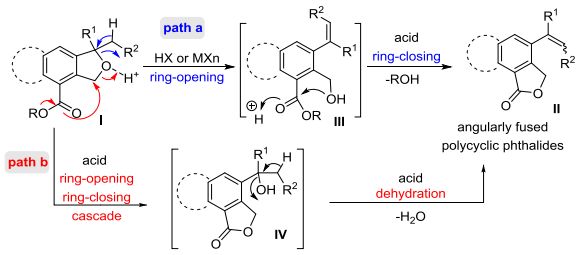


Figure 1 Angularly fused polycyclic phthalide natural products and most commonly used transition metal-catalysed [2+2+2] cycloaddition approach to these frameworks.

Polycyclic phthalides can have either a linear or angular arrangement of the fused rings with respect to the isobenzofuranone moiety. Synthesis of linearly fused polycyclic phthalides and their derivatives is also well documented in literature.[6] In contrast, the synthetic approaches to polycyclic, angularly fused phthalides are very scarce. The commonly employed method is a transition metal [Ni(0), Rh(I), and Ru(I)] catalysed, [2+2+2] cyclotrimerization of alkynes either in an intramolecular or intermolecular fashion (Figure 1).[7] In this method the angular phthalide has been generated from an acyclic precursor. Few other methods involving the generation of the lactone ring as the key step have also been reported.[8] Herein, we designed and developed an acid catalysed, cascade rearrangement process for an efficient generation of angularly fused polycyclic phthalides, from corresponding isobenzofurans. We have also developed a one pot thermal [4+2] cycloaddition followed by acid promoted rearrangement process from acyclic enyne-alkyne precursors.

According to our design (Scheme 1), in presence of an acid (Lewis as well as Brønsted), a linearly fused iso-benzofuran **I** possessing a carboxylate group on the 3[rd]-position of the arene, may involve a rearrangement cascade to generate the angularly fused phthalide **II**. This transformation either may involve a sequential ring opening-ring closing process *via* the hydroxy-ester **III** (path a) or simultaneous ring closing-ring opening process (path b) *via* hydroxy-lactone **IV**. Nevertheless, both the pathways represent a self-relay acid catalysis mechansim.[9]



Scheme 1 Our design for an acid catalysed rearrangement approach to angularly fused phthalides.

Results and discussion

We began our investigation with a linearly fused isonaphthofuran[10] **1a** as the model substrate. When **1a** was treated with 1.2 equiv. of *p*-TSA at RT in CH_2Cl_2, no reaction observed and starting material was recovered after 24 h (Table 1, entry 1). To our delight, increasing the temperature to 55 °C resulted in the formation of the expected angularly fused isonaphthofuranone **2a** in 97% yield after 2.5 h (entry 2). Encouraged by this outcome, we next performed an optimization study to find out the catalytic reaction conditions.

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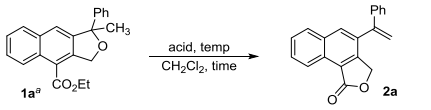
Electronic Supplementary Information (ESI) available: General procedures for the preparation of the compounds and the catalytic reaction; Characterization data including ^1H, ^{13}C NMR spectra, IR and HRMS. See DOI: 10.1039/x0xx00000x

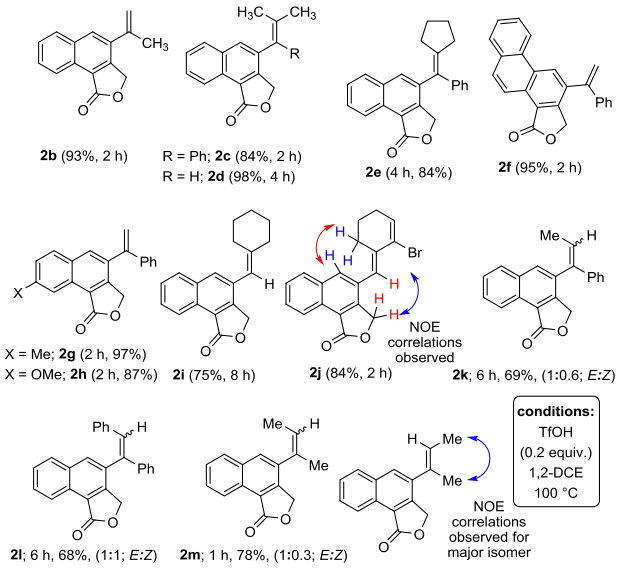


entry	reagent	equiv	temperature (°C)	time (h)	yield(%)[b]
1	*p*-TSA	1.2	0 to rt	24	NR
2	*p*-TSA	1.2	55	2.5	97
3	$MeSO_3H$	1.2	55	18	87
4	TfOH	1.2	0 to rt	1.5	98
5	$FeCl_3$	1.2	55	1	98
6	$BiCl_3$	1.5	55	32	92
7	$AlCl_3$	3	55	28	96
8	$BF_3.Et_2O$	2.4	55	33	96
9	TfOH	0.1	0 to rt	29	58
10	TfOH	0.1	55	50 min	62
11[c]	TfOH	0.1	70	30 min	77
12[c]	TfOH	0.1	100	25 min	85
13[c]	TfOH	0.2	100	20 min	93

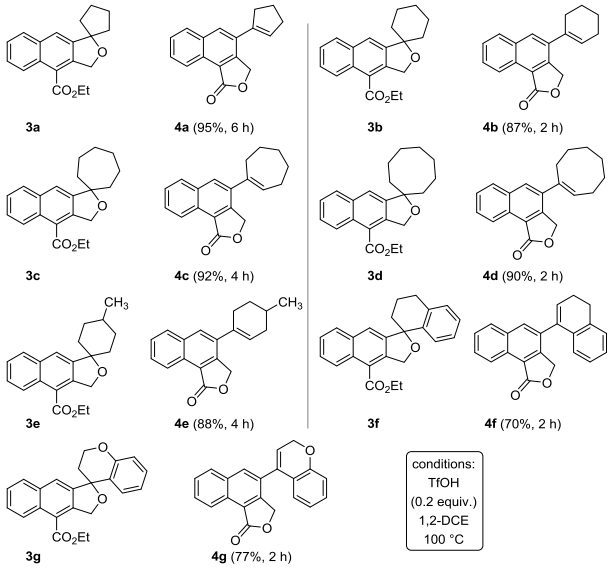
Table 1 Discovery and optimization study. [a] all the reactions were carried out on 0.1 mmol of **1a**; [b] yields after chromatographic purification; [c] solvent is 1,2-DCE; NR: no reaction

$MeSO_3H$ (1.2 equiv.) at 55 °C, provided the product **2a** in 87% yield (entry 3). With a stronger acid i.e., TfOH (1.2 equiv., entry 4) the reaction was faster (1.5 h) and high yielding for **2a** (98%) even at 0 °C to RT. Next, we employed various Lewis acids. In case of $FeCl_3$ (1.2 equiv.) the reaction was faster (1 h) and afforded 98% yield of the **2a** at 55 °C (entry 5). Other Lewis acids (entries 6-8) $BiCl_3$ (1.5 equiv., 28 h, 92%), $AlCl_3$ (3 equiv., 28 h, 96%) and $BF_3.OEt_2$ (2.4 equiv., 33 h, 96%) also promoted the reaction very smoothly and efficiently but took longer reaction times even with higher amounts of acids. We next performed this reaction with lower amounts of TfOH to find out the possibility for a catalytic transformation (entries 9-13). The reaction was slower and less efficient (29 h; 58%) with 0.1 equiv. at RT. As the temperature increases from 55 to 100 °C, the reaction rate and efficiency (62 to 85%) also increased. Next performing the reaction with 0.2 equiv. of TfOH resulted in 93% of **2a** within 20 min at 100 °C (entry 13) and we chose this as an optimized condition for the designed cascade rearrangement.

Next, we performed a scope study for substrates for the generation of structurally diverse, angularly fused polycyclic phthalides. Initially, various substituents such as methyl-methyl, ethyl-phenyl, isopropyl-phenyl, benzyl-phenyl, cycloalkyl-phenyl, attached at the α-carbon position of linearly fused isobenzofuran (Scheme 2) were employed. All these substrates **1b-j** smoothly underwent the cascade rearrangement under standard reaction conditions to afford the corresponding angularly fused phthalides **2b-j** in excellent yields (68-97%). The geometry of the *exo*-olefin present in product **2j** was assigned by NOESY (see supporting information for details). Interestingly, in case of Et-Ph and Bn-Ph substrates **1k** & **1l**, a (1:0.6) and (1:1) mixture of *E*:*Z*-isomers **2k** and **2l** were obtained respectively.[11] We also employed an isobenzofuran **1m** carrying an unsymmetric quaternary centre (ethyl,methyl). Here, we have exclusively isolated the products (E/Z-isomers; 3:1) **2m** obtained *via* the elimination occuring through ethyl group instead from methyl group. The configuration across the olefin was confirmed by the NOE correlations obseved for two methyl groups present in the major isomer. It supports the major compound as *E*-olefin and minor as the *Z*-isomer.



Scheme 2 Substrate scope study



Scheme 3 Substrate scope study of spiroisonaphthofurans

Subsequently, we also employed spiro-fused isobenzofurans **3a-g** under standard reaction conditions (Scheme 3). There was no ring size effect observed, when employed isobenzofurans **3a-e** containing various spiro-cycloalkanes (cyclopentane to cyclooctane). All these substrates yielded the corresponding angularly fused phthalides **4a-e** in excellent yields (70-95%). In addition, tetraline and chromane spiro-fused iso-bezofurans **3f** and **3g** were also efficiently converted to the corresponding products **4f** and **4g**.

At this juncture, we envisioned an opportunity to extend this strategy for the synthesis of highly functionalized angularly fused phthalides by incorporating a cyclopropane ring at the α-carbon of the isobenzofuran framework. According to our design (Figure 2), the cyclopropane ring of **5** can be opened-up

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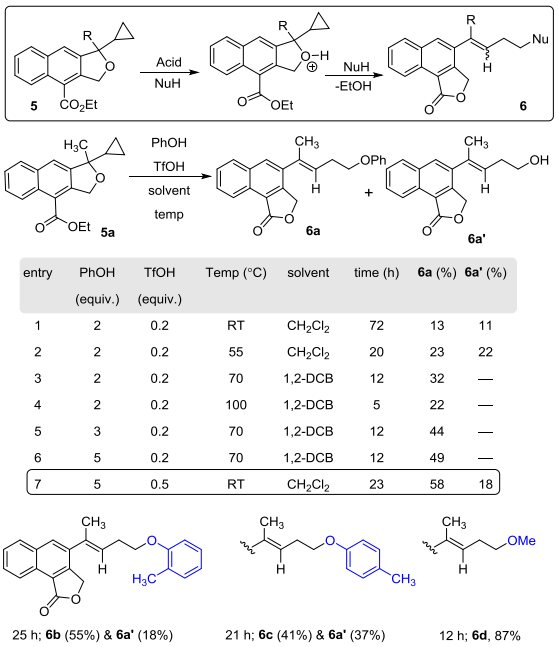
during the rearrangement process and the corresponding carbocation can be further trapped by various nucleophiles in a 1,3-fashion to give functionalized benzophthalides **6**. Initially, we focused our attention to perform the reaction by employing external nucleophiles to open the cyclopropane ring in the presence of CF_3SO_3H (the counterion ^-OTf is non-nucleophilic) (Figure 2).



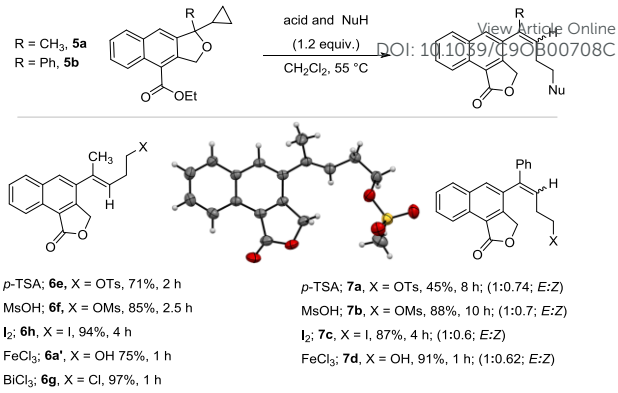
entry	PhOH (equiv.)	TfOH (equiv.)	Temp (°C)	solvent	time (h)	**6a** (%)	**6a'** (%)
1	2	0.2	RT	CH_2Cl_2	72	13	11
2	2	0.2	55	CH_2Cl_2	20	23	22
3	2	0.2	70	1,2-DCB	12	32	—
4	2	0.2	100	1,2-DCB	5	22	—
5	3	0.2	70	1,2-DCB	12	44	—
6	5	0.2	70	1,2-DCB	12	49	—
7	5	0.5	RT	CH_2Cl_2	23	58	18

25 h; **6b** (55%) & **6a'** (18%) 21 h; **6c** (41%) & **6a'** (37%) 12 h; **6d**, 87%

Figure 2 Design, optimization and scope study for functionalised angularly fused phthalides *via* cyclopropane ring-opening with phenols and methanol

The compound **5a** upon subjection to standard reaction conditions in presence of phenol (2 equiv.), offered the phenol trapped product **6a** (13%) along with hydroxyl trapped product **6a'** (11%). After screening various temperatures, equiv., of acid and phenol (entries 2-7), we found that, phenol (5 equiv.), TfOH (50 mol%) and RT in CH_2Cl_2 (entry 7, Table 2) as the best condition to obtain the phenol trapped product **6a** in good yield. We also employed three different nucleophiles such as *o*-cresol, *p*-cresol and methanol. All these reagents gave the corresponding products **6b-d** (55%, 41% and 87% respectively) along with 18%, 37% and 0% of **6a'** respectively.

Next, the dual (simultaneous catalytic as well as nucleophilic) behaviour of several acids,[12] where their counterions are good nucleophiles to trap the carbocation, have also been tested (Scheme 4). Accordingly, when we treated the substrate **5a** (methyl-cyclopropyl) with acids such as *p*-TSA (1.2 equiv.), MsOH (1.2 equiv.), and $BiCl_3$ (1.5 equiv.) in CH_2Cl_2 at 55 °C; the corresponding counter ions (tosylate, mesylate and chloride respectively) have efficiently trapped the carbocation to provide access to angularly fused benzophthalides **6e-g** in excellent yields. Interestingly, when the reaction was employed with $FeCl_3$ (1.2 equiv.), the hydroxyl trapped compound **6a'** was obtained as the sole product in 75% yield.



p-TSA; **6e**, X = OTs, 71%, 2 h
MsOH; **6f**, X = OMs, 85%, 2.5 h
I_2; **6h**, X = I, 94%, 4 h
$FeCl_3$; **6a'**, X = OH 75%, 1 h
$BiCl_3$; **6g**, X = Cl, 97%, 1 h

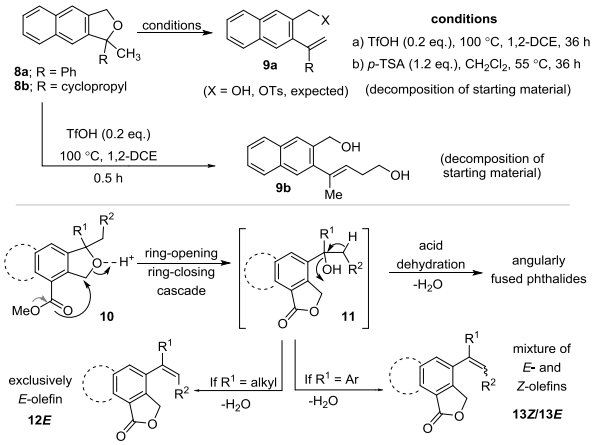
p-TSA; **7a**, X = OTs, 45%, 8 h; (1:0.74; *E*:*Z*)
MsOH; **7b**, X = OMs, 88%, 10 h; (1:0.7; *E*:*Z*)
I_2; **7c**, X = I, 87%, 4 h; (1:0.6; *E*:*Z*)
$FeCl_3$; **7d**, X = OH, 91%, 1 h; (1:0.62; *E*:*Z*)

Scheme 4 Scope study for cyclopropyl-isobenzofurans and ORTEP diagram for compound **6f**

We also used iodine (I_2, 1.2 equiv.) as an electrophilic promoter and the *in situ* generated iodide (I^-) as the nucleophile to generate the alkyl iodide **6h** in excellent yield (94%). In all the above cases, the *E*-isomer was isolated as the exclusive product and no traces of the corresponding *Z*-isomers were obtained. Surprisingly, when we employed the phenyl-cyclopropyl substrate **5b** with all four acids, an inseparable mixture of *E:Z* isomers of corresponding benzophthalide products **7a-d** were obtained in good yields. A single crystal X-ray diffraction analysis for compound **6f**, unambiguously confirmed the presence of angularly fused benzophthalide framework.[13]

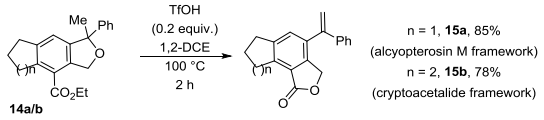
After describing a good substrate scope, we performed few control experiments (Scheme 5) to get insights into the mechanism and to differentiate between two proposed pathways (path a & b, Scheme 1). Accordingly, treatment of a linear isobenzofruan **8a** (which lacks ester group)[10] under standard conditions resulted in decomposition of starting material after 36 h, instead of giving compound **9a** *via* ring opening reaction. Similarly, the isobenzofuran **8b** possessing a cyclopropyl and lacks the ester group also resulted in decomposition, upon subjection to standard reaction conditions.

These observations suggested that, the ester group is necessary for a smooth ring (furan) opening process. Hence, this rules out the pathway a, and supports pathway b (Scheme 1) as the possible mechanism i.e., the ester might involve in the nucleophilic attack on to the acid activated furan ring for the simultaneous ring closing-ring opening cascade followed by the acid promoted dehydration. Since, the TfOH is acting as the catalyst for both the transformations, the overall process resemebles the self-relay catalysis.[9] In pathway b, after the initial ring opening-ring closing cascade of **10**, the dehydration of resultant tertiary alcohol **11** is dependent on the nature of the group present at carbinol carbon. When R^1 = alkyl; an exclusive formation of more stable *E*-olefin **12*E*** (see Scheme 5) is observed. On the other hand, in case of R^1 = aryl; a mixture of both *E*- and *Z*-olefins **13*E*** and **13*Z*** (as evidenced in Scheme 2 and 4) are observed.



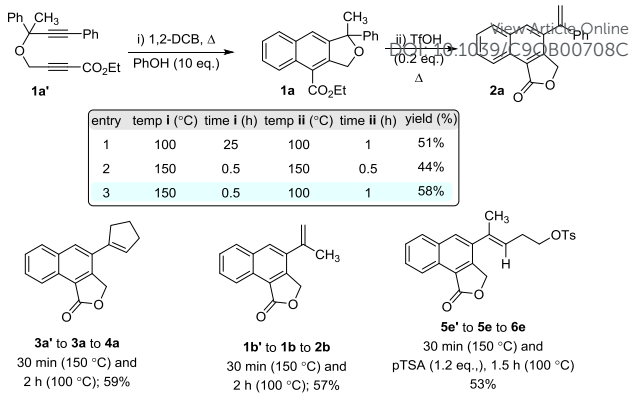
Scheme 5 a) Control experiments; b) possible mechanism

We have also extended this methodology for the synthesis of simple phthalides. Accordingly, isobenzofurans **14a** and **14b** were subjected to standard reaction conditions (Scheme 6). Both substrates underwent smooth rearrangement to yield the corresponding phthalides **15a** and **15b** in excellent yields (85% and 78% respectively) after 2 h. These two phthalide structures **15a** and **15b** represent the tricyclic frameworks present in bioactive natural products alcyopterosin M and cryptoacetalide respectively (see Figure 1).



Scheme 6 Synthesis of frameworks of bioactive natural products

Finally, to improve the synthetic efficiency of this cascade rearrangement, we also designed and developed a one pot strategy for the synthesis of angular phthalides directly from the corresponding enyne-alkyne precursors, without the isolation of isobenzofuran product after the tetradehydro Diels-Alder (TDDA) reaction (Table 2).[14] The substrate **1a'** upon heating at 100 °C in 1,2-DCB and phenol (10 equiv.), smoothly underwent the [4+2]cycloaddition reaction. After completion of **1a'** (25 h), TfOH (20 mol%) was added to the reaction mixture and then continued the heating for 30 min at same temperature (entry 1, Table 1) to give the phthalide **2a** in 51% overall yield. Increase in the reaction temperature to 150 °C resulted in decreased yield (44%) of **2a** (entry 2). Next, we performed the TDDA reaction of **1a'** at 150 °C followed by the rearrangement reaction of the resultant **1a** at 100 °C (entry 3). This combination gave an improved yield of **2a** (58%). Subsequently, two more substrates **3a'** and **1b'** were subjected to this one pot strategy, employing the conditions of entry 3 (Table 2). The overall yields obtained were good for the corresponding angular phthalides **4a** (59%) and **2b** (57%). A cyclopropyl containing substrate **5e'** has also been efficiently employed in this one pot strategy using pTSA to generate the phthalide **6e** (53%). This one pot methodology represents an exact alternative strategy to the metal catalysed [2+2+2] cycloaddition approaches for the angular phthalides (see Figure 1).



entry	temp **i** (°C)	time **i** (h)	temp **ii** (°C)	time **ii** (h)	yield (%)
1	100	25	100	1	51%
2	150	0.5	150	0.5	44%
3	150	0.5	100	1	58%

Table 2 One pot TDDA-skeletal rearrangement process

Conclusions

In conclusion, we have designed and developed an acid catalyzed, cascade process for the construction of angularly fused polycyclic phthalides from isobenzofurans. This process found to exhibit a very broad scope for various *gem*-disubstituted isobenzofuran substrates. Including the cyclopropane as one of the substituent and trapping the carbocation by various external nucleophiles provided structurally diverse angularly fused phthalide frameworks. Control experiments supported the mechanism as the nucleophilic attack of the carboxylate on to the acid activated furan ring for the simultaneous ring closing-ring opening cascade followed by dehydration. This metal free approach for the angularly fused polycyclic phthalides can serve as a greener alternative.

Acknowledgements

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13 X-ray diffraction analysis data for **6f** has been deposited with the Cambridge Crystallographic Data Centre with CCDC1846904. Further details are given in the Supporting Information (Table 1).

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Method

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Acid Catalysed Rearrangement of Isobenzofurans to Angularly Fused Phthalides

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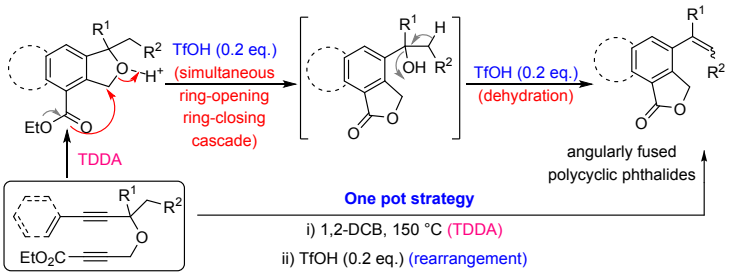

An acid catalysed, cascade process for the construction of angularly fused polycyclic phthalides from isobenzofurans *via* a simultaneous ring closing-ring opening cascade has been reported. This approach serves as a greener alternative for the angularly fused polycyclic phthalides.