Polyaromatic Compounds

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Tandem Ring Expansion of Alkenyl Benzocyclobutenol Derivatives into Substituted Naphthols**

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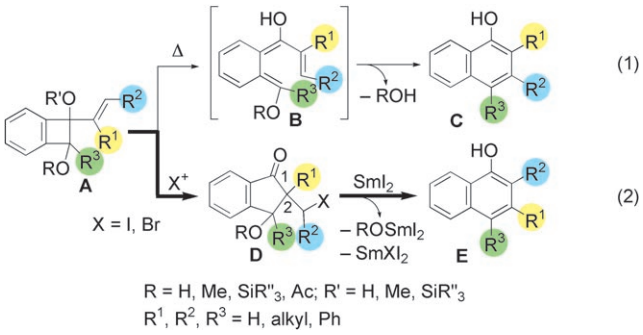
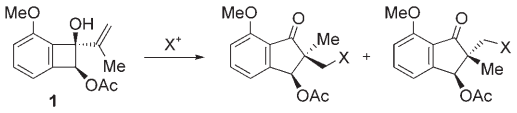
In our continuing studies on the synthesis of polyaromatic compounds,[1] we previously reported thermal conversion of alkenyl benzocyclobutene **A** into functionalized naphthol **C** by tandem electrocyclic reactions [Eq. (1)].[2] We report



herein a process that is capable of converting the same starting material **A** into *isomeric* naphthol **E** [Eq. (2)]. The process involves two successive ring enlargements (**A**→**D**→**E**): the halonium ion (X^+) induces ring expansion of alkenyl benzocyclobutene **A** (four-membered ring) to indanone **D** (five-membered ring), and SmI_2 promotes expansion of **D** to naphthol **E** (six-membered ring) with concomitant elimination of $ROSmI_2$.

This tandem 4→5→6 ring-enlargement process starts with the 4→5 ring enlargement triggered by the halogenation of diol derivative **1** (Table 1).[3] When alcohol **1** was treated with ICl (1.5 equivalents) in THF (0°C→RT), the ring enlargement occurred smoothly to give iodomethyl indanone **2a** in 90% yield as a mixture of stereoisomers (Table 1, entry 1).[4] An NOE study showed that the major product of **2a** has the *cis* configuration with respect to the iodomethyl and the acetoxy groups. Similarly, bromination of **1** was also effective (1.5 equivalents NBS, CH_2Cl_2, −78→−10°C) and gave bromomethyl indanone **2b** in quantitative yield (Table 1, entry 2).

Table 1: 4→5 Ring enlargement triggered by the halogenation of diol derivative **1**.

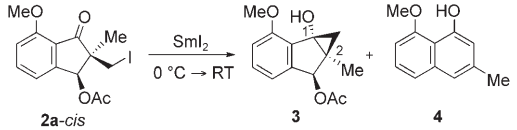


Entry	Conditions	Yield [%]	*cis*/*trans*
1	ICl, THF, 0°C→RT	90	1.6:1
2	NBS, CH_2Cl_2, −78→−10°C	quant.	3.2:1

Ac = acetyl, NBS = *N*-bromosuccinimide.

The second step, 5→6 ring enlargement, is the intramolecular Barbier-type reaction of halomethyl indanone and subsequent Grob fragmentation[5] of the resulting cyclopropanol intermediate (Table 2).[6]

Table 2: 5→6 Ring enlargement by an intramolecular Barbier-type reaction and subsequent Grob fragmentation of halomethyl indanone **2**.



Entry	Conditions	*t* [h]	Yield of **3** [%]	Yield of **4** [%]
1	THF/HMPA[a]	8	15[d]	78
2	THF/HMPA,[a] $BF_3{\cdot}Et_2O$[b]	2.5	–	82
3	CH_3CN[c]	4	–	79

[a] 11–14% HMPA. [b] 2.0–2.5 equivalents. [c] SmI_2 in CH_3CN. [d] Cyclopropanol **3** has the *trans* configuration with respect to the hydroxy and acetoxy groups on the five-membered ring. HMPA = hexamethyl phosphoramide.

Indanone **2a**-*cis* was used for the initial model study, which revealed several sets of suitable conditions. Upon treatment of **2a**-*cis* with SmI_2 (0.1M in THF) in THF/HMPA, the starting material was quickly consumed, thereby giving naphthol **4** in 78% yield and a sizable amount of cyclopropanol **3** (Table 2, entry 1).[7] Monitoring of the reaction by TLC showed the initial formation of cyclopropanol **3**, which was gradually consumed to give naphthol **4**. The process is rationalized by selective cleavage of the C1−C2 bond and elimination of samarium acetate. Although prolonged reaction time and/or higher reaction temperature was incapable of driving the in situ conversion of cyclopropanol **3** to the final product **4**, we were pleased to find that the conversion was facilitated by the presence of $BF_3{\cdot}Et_2O$ (Table 2, entry 2) or by the use of CH_3CN *as the solvent* (Table 2, entry 3), thus giving naphthol **4** in high yield.[8,9]

With these results in hand, we attempted to carry out the two consecutive reactions *in one pot*, which proved to be successful. Thus, alcohol **1** was treated with ICl (1.4 equiv-

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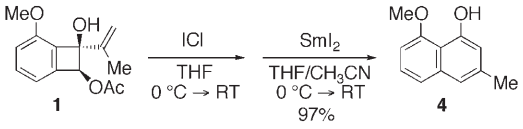
alents) in THF at 0 °C, and the reaction was stirred for 40 minutes at room temperature. The reaction mixture was again chilled to 0 °C, and 3.4 equivalents of SmI_2 (0.07 M in CH_3CN) was added. Subsequent stirring at room temperature for four hours cleanly gave naphthol **4** as the sole product in 97 % yield [Eq. (3)]. The almost quantitative yield in this

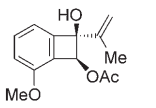
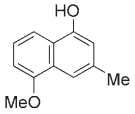
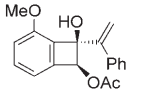
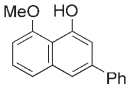
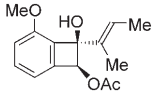
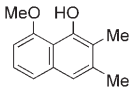
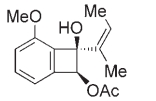
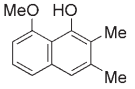
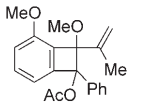
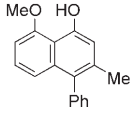


(3)

particular instance implies that both isomers of the initially formed indanones **2a**-*cis* and **2a**-*trans* took part in the second 5→6 ring enlargement. Importantly, this one-pot procedure gave a higher yield of **4** than the overall yield by the reactions that were performed separately.

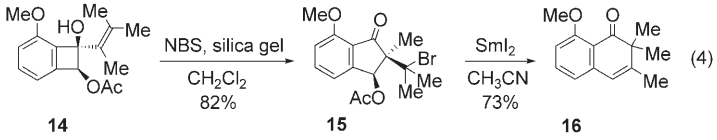
Table 3 shows the application of this one-pot protocol to various substrates. Under the same conditions, the reaction of compound **5**, isomeric to **1**, also proceeded smoothly (Table 3, entry 1). Likewise, the reaction of α-styryl alcohol **6** gave naphthol **11** in 96 % yield (Table 3, entry 2). The reactions worked well with substrates **7** and **8**, which have one additional methyl group at the β position of the olefin with *E* or *Z* geometry, and afforded the tetrasubstituted naphthalene **12** in high yields (Table 3, entries 3 and 4).[10] Arylated substrate **9**[11] also underwent smooth ring expansion to give 78 % yield of aryl naphthalene **13** (entry 5).

Table 3: One-pot preparation of substituted naphthols.

Entry	Benzocyclobutene[a]	Product	Yield [%]
1		**5** 	**10** 85
2		**6** 	**11** 96
3		**7** 	**12** 88
4		**8** 	**12** 77
5		**9** 	**13** 78

[a] Conditions: ICl, THF, 0 °C→RT (20–40 minutes), then SmI_2 in CH_3CN, 0 °C→RT (1.5–4 hours).

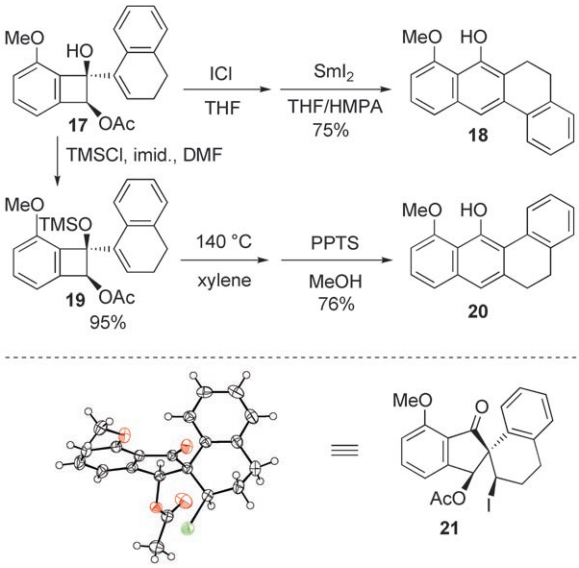
Furthermore, the process of successive ring enlargement proved to be applicable to substrates with more highly substituted olefinic moieties [Eq. (4)]. Treatment of **14** with NBS in the presence of silica gel[12] gave the bromoisopropyl



(4)

indanone **15**, which was smoothly converted into the corresponding ketone **16** by the Barbier reaction. ICl was ineffective in this case and gave only a complex mixture of products, presumably because of the instability of the intermediary tertiary alkyl iodide.

The process is applicable to the synthesis of natural-product-like structures, such as angucycline-type tetracycle **18** (Scheme 1).[13] After treatment of compound **17**,[11] which has



Scheme 1. Divergent sSynthesis of isomeric tetracyles **18** and **20**. Lower left: molecular structure of **21**; thermal ellipsoids set at 50 % probability (O red, I green). PPTS = pyridinium *p*-toluenesulfonate; imid. = imidazole.

a dihydronaphthalene substituent, with ICl (THF, 0 °C→RT, 0.5 hours), the reaction was warmed to 40 °C, and HMPA and subsequently SmI_2 (0.1 M in THF, 10 minutes) were added to afford the angular tetracycle **18**[11] in 75 % yield. It should be noted that this one-pot reaction proceeded smoothly even though the intermediates that are involved should have highly strained polycyclic structures.

It is thus interesting to note the X-ray structure of spiroketone **21**[14] (the major isomer), which was obtained by interception of the above process at the initial iodination stage (92 % yield, major/minor 2.4:1). The structure is intriguing in relation to the synthesis of polycyclic natural products containing a spiro center.[15] The stereoselectivity of the iodination was enhanced to 5.6:1 by employing $BnMe_3N^+ICl_2^-$ as the iodinating agent.

This process constitutes one of the two complementary processes that allow divergent syntheses of isomeric polyaromatic compounds from a single starting material. Indeed, the

isomeric angular tetracycle **20**[11] was accessible from the same alcohol **17** in high yield by silylation, thermolysis, and desilylation of the initially formed ring-expanded product [see Eq. (1)].

In summary, we have described a facile synthesis of substituted polyaromatic compounds by successive ring expansion of alkenyl benzocyclobutenes. Further studies are currently in progress.

Experimental Section

General experimental procedures for the synthesis of naphthols (one-pot procedure): A solution of acetate **1** (121 mg, 0.489 mmol) in THF (2.0 mL) was added to a solution of ICl (114 mg, 0.702 mmol) in THF (1.5 mL) at 0 °C. The reaction was stirred for 40 min at room temperature. SmI_2 (0.07 M in CH_3CN, 24 mL, 1.7 mmol) was added to the reaction mixture at 0 °C, and the temperature raised to room temperature. After 4 h, the reaction was quenched with saturated aqueous NH_4Cl. The products were extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 9:1) to give naphthol **4** (89.3 mg, 97.0 %).

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Keywords: halogenation · polyaromatic compounds · reductive coupling · ring expansion · strained molecules

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[7] When the reaction was performed without HMPA, the yield of **4** decreased to 46 % and was accompanied by cyclopropanol **3** (16 %).

[8] This 5→6 ring enlargement was applicable to the bromo substrate **2b** (SmI_2 in THF/HMPA, $BF_3{\cdot}Et_2O$), giving naphthalene **4** in 48 % yield.

[9] Concentration of SmI_2 in CH_3CN was 0.07 M (iodometric titration); recently, solvent effects of SmI_2-mediated reactions were reported: a) B. Hamann, J.-L. Namy, H. B. Kagan, *Tetrahedron* **1996**, *52*, 14225 – 14234; b) P. R. Chopade, T. A. Davis, E. Prasad, R. A. Flowers II, *Org. Lett.* **2004**, *6*, 2685 – 2688.

[10] Previously, we reported the thermolysis of alkenyl benzocyclobutenes that have alkyl groups at the β position of the olefin with *Z* geometry, whereby mainly a 1,7-hydrogen shift occurred to give the ring-opened 1,3-diene derivatives as the major products; see references [2c] and [2d].

[11] For details, see the Supporting Information.

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[14] CCDC-611287 (**21**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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