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One-Pot Synthesis of Substituted Tetrahydrocyclobuta[*a*]naphthalenes by Domino Aldol Condensation/Olefin Migration/Electrocyclization

Meng-Yang Chang,* Ming-Hao Wu, and Yeh-Long Chen

Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan

mychang@kmu.edu.tw

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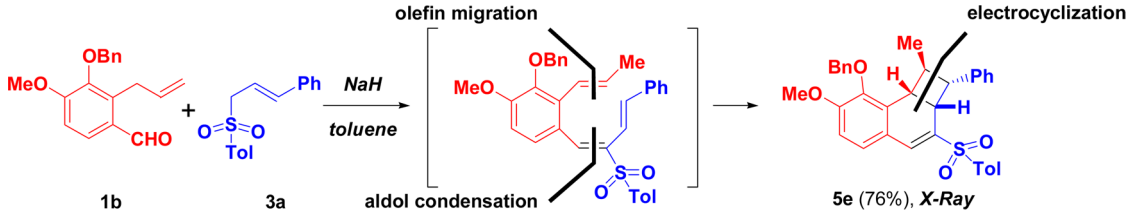
ABSTRACT



A facile one-pot synthetic route for preparing the novel benzofused tricyclic skeleton of 1,2,2a,8b-tetrahydrocyclobuta[*a*]naphthalenes 5 is developed. The route was realized by a NaH-mediated tandem aldol condensation/olefin migration/electrocyclization of *o*-allylbenzaldehydes 1 with cinnamyl sulfones 3 in good yields.

The domino reaction is a useful synthetic tool for constructing diversified frameworks; it has been successfully applied to different synthetic fields.[1] Most notably, it has been found that a one-pot, well- designed reaction sequence is the key combination to shortening reaction time and increasing synthetic efficiency. Because the synthetic approaches for domino types are currently in vogue, many catalyst-mediated one-pot reactions have been developed.[2]

In continuation of our recent investigation on the structure of *o*-allylbenzaldehyde **1A** for synthesizing benzannulated molecules (e.g., homoisotwistanes **2A** and tetrahydroanthracen-9-ones **2B**) using the facile condensation/cycloaddition strategy;[3,4] a one-pot synthetic route for preparing tricyclic benzofused tetrahydrocyclobuta[*a*]naphthalenes **2C** was studied. As shown in Scheme 1, the *o*-allyl functional group plays an important role in enabling different carbon−carbon bond formations to be useful substituent during the tandem sequence. The introduction of an *o*-allyl substituent is expected to shorten the synthetic step of targets by utilizing a simple tandem design without transition metal manipulation. The cyclobutanated naphthalene and its carbon allotropes have received considerable attention from theorists and synthetic chemists, because they can be used as the spacer or building blocks for functionalized organic electrical materials and potential agents.[5] However, only limited methods are known

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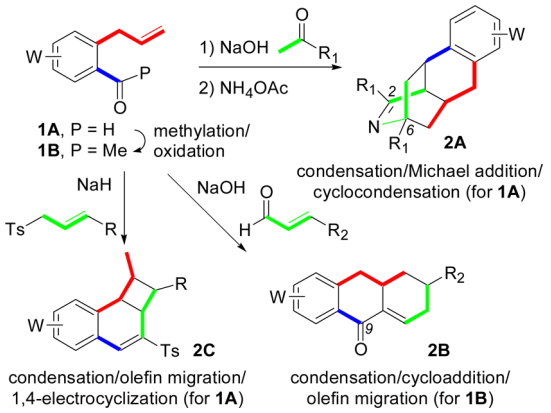
for establishing core structures, including the Birch reduction of biphenylene, thermolyic rearrangement of tetrahydrobiphenylene, photolytic irradiation of homobenzotropilidene and metal complex-mediated cross-coupling routes.[6] New routes with this specific substitution pattern are needed.

Scheme 1. Application of *o*-Allylbenzaldehyde **1A**



To trigger the one-pot tandem synthesis of 1,2,2a, 8b-tetrahydrocyclobuta[*a*]naphthalenes **5**, *o*-allylbenzaldehyde **1a** and cinnamyl sulfone **3a** were chosen as the starting substrates in the investigation of the one-pot and domino aldol condensation/olefin migration/intramolecular electrocyclization under various basic conditions (see Table 1). Compound **1a** can be prepared from isovanillin or 3-hydroxybenzaldehyde via a three-step procedure of O-allylation, Claisen rearrangement and O-alkylation.[3,4] Compound **3a** was prepared from the nucleophilic substitution of cinnamyl chloride with toluenesulfinic sodium salt. Next, when we initially employed NaH as the base for the intermolecular aldol reaction of compounds **1a** and **3a** in refluxing toluene, compound **5a** was obtained at a 75% yield.

For the possible mechanism of cycloadduct **5**, the formation of intermediate **A** was first proposed. After the olefin migration of *o*-allylbenzaldehyde on intermediate **A**, intermediate **B** with a (*E*,*Z*,*E*)-triene motif exhibited a stronger repulsion with steric hindrance than did intermediate **C**. For intermediate **C**, the orientation of the *o*-styrenyl group and the sulfonyl group on the central alkene was *trans-configured* to one another (*E*-orientation). Under thermal conditions, the preferred intermediate **C** with a fully (*E*,*E*,*E*)-conjugated skeleton advanced an intramolecular cascade stereospecific 8π-electrocyclic conrotatory ring closure to generate two adjacent stereogenic centers with *trans*-configuration on intermediate **D**.[7] After the sequential formation of a 6π-electrocyclic disrotatory ring closure on intermediate **D**, two contiguous *cis*-stereogenic centers were also formed via the cyclooctatriene system.

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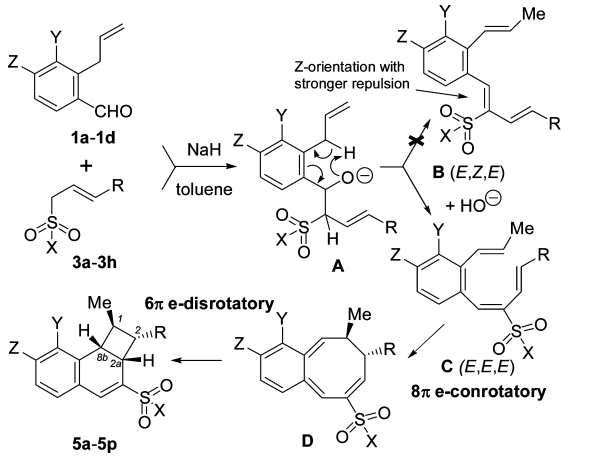
Table 1. One-Pot Synthetic Route toward 1,2,2a, 8b-Tetrahydrocyclobuta[*a*]naphthalenes **5**[a,b]



entry	aldehydes **1** (Y, Z)	sulfones **3** (X, R)	products **5** yield (%)
1	**1a**, MeO, MeO	**3a**, Tol, Ph	**5a**, 75
2	**1a**, MeO, MeO	**3b**, Tol, 4-FPh	**5b**, 82
3	**1a**, MeO, MeO	**3c**, Tol, 3,4-CH_2O_2Ph	**5c**, 80
4	**1a**, MeO, MeO	**3d**, Tol, 4-MeOPh	**5d**, 78
5	**1b**, BnO, MeO	**3a**, Tol, Ph	**5e**, 76
6	**1b**, BnO, MeO	**3b**, Tol, 4-FPh	**5f**, 84
7	**1b**, BnO, MeO	**3c**, Tol, 3,4-CH_2O_2Ph	**5g**, 78
8	**1b**, BnO, MeO	**3d**, Tol, 4-MeOPh	**5h**, 80
9	**1c**, *c*-C_5H_9O, MeO	**3a**, Tol, Ph	**5i**, 75
10	**1c**, *c*-C_5H_9O, MeO	**3b**, Tol, 4-FPh	**5j**, 79
11	**1c**, *c*-C_5H_9O, MeO	**3c**, Tol, 3,4-CH_2O_2Ph	**5k**, 84
12	**1c**, *c*-C_5H_9O, MeO	**3d**, Tol, 4-MeOPh	**5l**, 80
13	**1d**, MeO, H	**3a**, Tol, Ph	**5m**, 84
14	**1b**, BnO, MeO	**3e**, Ph, Ph	**5n**, 87
15	**1b**, BnO, MeO	**3f**, Me, Ph	**5o**, 79
16	**1b**, BnO, MeO	**3h**, Tol, Me	**5p**, 84
17	**1a**, MeO, MeO	**3g**, Tol, H	complex

[a] The reactions were run on a 0.3 mmol scale with skeletons **1** and **3** in toluene (10 mL). [b] The product was >95% pure as determined by ^{1}H NMR analysis.

As shown in the experimental results of the Frontier molecular orbital theory,[8] a tricyclic skeleton of tetrahydrocyclobuta[*a*]naphthalene **5** was isolated as a sole isomer. Several tricyclic benzannulated compounds **5b**–**p** were efficiently constructed in good yields (75–87%) by the above-mentioned one-pot facile, efficient and cascade reaction of four *o*-allylbenzaldehydes **1a**–**d** (Y/Z = H, OMe, OBn, OC_5H_9) and eight cinnamyl sulfones **3a**–**f** and **3h** (X = R = Me/Ar). The results clearly show benzaldehyde component of skeleton **1** must be electron-rich and the sulfonyl substituent of skeleton **3** with electron-withdrawing

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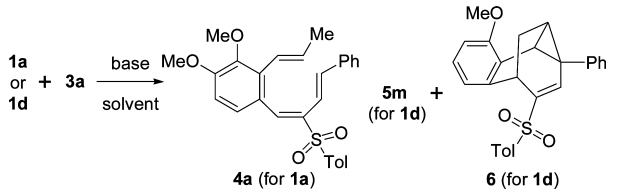
group also play a key factor to initiate the formation of skeleton **5** via the delocalized electron push−pull conjugated relationship. However, NaH-mediated treatment of compound **1a** with compound **3g** in refluxing toluene provided a complex mixture due to the relative equilibrium of carbanion in compound **3g**, producing a competitive nucleophilic substitution between α-attack (S_N2) and γ-attack (S_N2'). Furthermore, the structure of compound **5e** was determined by single-crystal X-ray crystallography.[9]

Table 2. Reaction Conditions of Compounds **3a** and **1a** or **1d**[a,b]

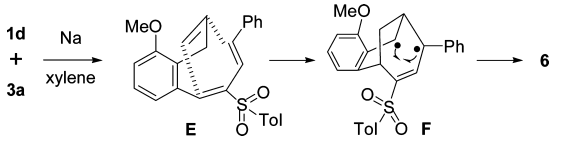


entry	substrate (**1a**, **1d**/**3a**), base (equiv), solvent (mL), temp (°C), time (h)	products **4a**/**5m**/**6** yield (%)
1	**1a**/**3a**, NaH (10), THF, 25, 20	65/–/–
2	**1a**/**3a**, NaH (10), THF, 67, 6	71/–/–
3	**1a**/**3a**, NaH (10), THF, 67, 20	80/–/–
4	**1a**/**3a**, *t*-BuOK (10), THF, 67, 20	67/–/–
5	**1a**/**3a**, LDA (1.0 M, 10), THF, 67, 20	65/–/–
6	**1d**/**3a**, Na (25), xylene (10), 139, 20	–/46/30

[a] The reactions were run on a 0.3 mmol scale with **1a** or **1b** and **3a** in THF or xylene (10 mL). [b] The product was >95% pure as determined by ^{1}H NMR analysis.

Changing the base to NaH, *t*-BuOK, or LDA (from 25 to 67 °C) in THF for the reaction of compound **1a** and **3a** (see Table 2), we found that compound **4a** was obtained with a range of yields from 65−80% via a process of aldol condensation and olefin migration (an interrupted Julia olefination). Under the refluxing THF conditions with different bases, no skeleton for compound **5a** was observed. According to these phenomena, we envisioned that the refluxing temperature of the reaction solvent is a key factor controlling the formation of intramolecular electrocyclization, and affecting the distribution of the product. Furthermore, when the base and solvent were replaced with Na (10 equiv) and xylene (10 mL) in the one-pot domino reaction of compound **1d** with **3a**, the isolated yield of the compound **5m** was decreased to 46% and the unexpected compound **6** was isolated at a 30% yield. This is an interesting phenomenon for the formation of compound **6**.

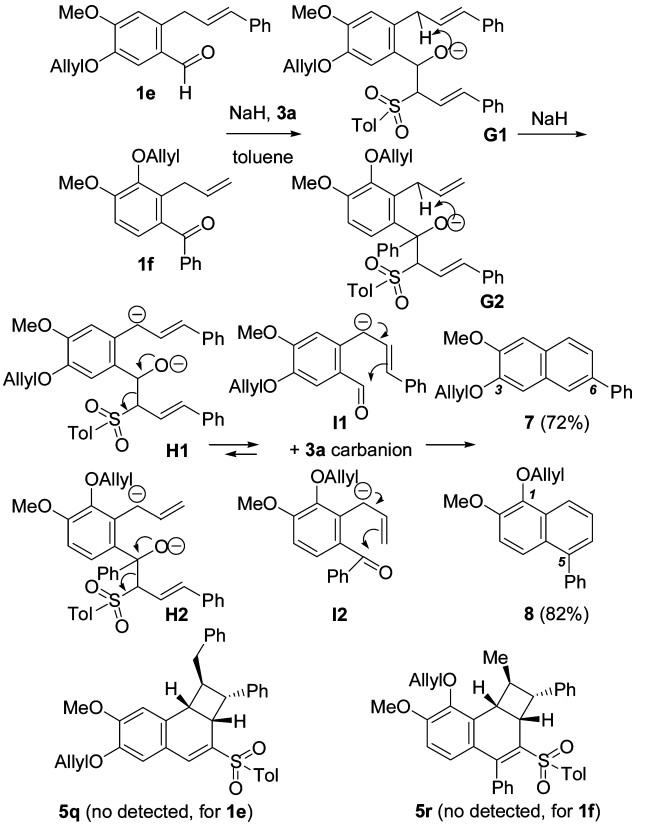
Scheme 2. Possible Mechanism



The proposed mechanism was shown in Scheme 2.[10] The tetracyclic bridged structural framework of compound **6** with a three-membered ring was established by a one-pot cascade reaction, including the following: (i) an intermolecular aldol condensation of compound **1d** with **3a**, (ii) an intramolecular 6π-electrocyclization of intermediate **E**, (iii) sequential generation of benzylic diradicals, and (iv) followed by a self-coupling of two benzylic radicals on intermediate **F**. The structure of compound **6** was determined by single-crystal X-ray crystallography.[9]

In the next work, the one-pot NaH-mediated reaction of compounds **1e**,**f** and **3a** in refluxing toluene was examined, as shown in Scheme 3. However, two skeletons of 1-allyloxy-6-phenylnaphthalene **7** (72%) and 3-allyloxy-5-phenylnaphthalene **8** (82%) were isolated as the sole products, and no desired tricyclic compounds **5q**,**r** were detected.[11] The exact skeleton of compound **7** was determined by single-crystal X-ray crystallography.[9] A plausible explanation for the efficient formation of compound **7** or **8** could be that intermediate **G1** or **G2** was generated first via an intermolecular NaH-mediated nucleophilic substitution of compounds **1e** (benzaldehyde) or **1f** (benzophenone) with the carbanion of compound **3a**. Then, an intramolecular proton exchange of intermediate **G1** or **G2** occurred. Furthermore, excess NaH deprotonated the hydroxyl group to form dianion intermediate **H1** or **H2**. After removal of compound **3a**, compound **7** or **8** was accomplished by an intramolecular cyclodehydration of the carbanion of intermediate

Scheme 3. Synthesis of Compounds **7** and **8**



I1 or **I2**. For the reaction mechanism of compound **7**, we envisioned that the stable carbanion of intermediate **I1** was easily delocalized on the 1,3-diarylpropene system such that it was not easy to trigger the occurrence of aldol condensation. At this stage, the oxy-anion could easily eliminate fragment **3a**. In the mechanism of compound **8**, when the carbanion of intermediate **I2** had not yet proceeded to aldol condensation, the oxy-anion on the quaternary carbon center was preferred to eliminate fragment **3a**. Therefore, by changing the substituent from allyl to styryl group (for **1e**) and replacing the group of aldehyde with phenylketone (H → Ph, for **1f**), a one-pot NaH-mediated tandem cyclodehydration of compounds **1e** and **1f** with compound **3a** provided the one-pot synthetic route toward a naphthalene skeleton at good yields.

To extend this one-pot domino protocol for the application of cinnamyl azide (**3i**) or cinnamyl nitrile (**3j**),[12] we found that complex mixture was observed for the reaction of compounds **1a** and **3i** or **3j**.[13] From the results, we envisioned that the sulfonyl group should be the key substituent affecting aldol condensation.

In summary, we have successfully presented a synthetic method for producing a tricyclic skeleton of 1,2,2a,8b-tetrahydrocyclobuta[*a*]naphthalene **5**, which involves a one-pot intermolecular aldol condensation/olefin migration/intramolecular electrocyclization of *o*-allylbenzaldehydes **1** with cinnamyl sulfones **3**. The substituent effect of skeletons **1** and **3** and various reaction conditions were well-investigated. The one-pot synthetic route of a naphthalene skeleton was also examined. The structures of key products were confirmed by X-ray crystal analysis. The one-pot synthetic approach begins with simple starting materials and reagents, and provides a potential methodology for the synthetic research. Considering the utility of these polycyclic benzofused compounds, the development of these general synthetic approaches of *o*-allylbenzaldehydes is significant.

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Supporting Information Available. Experimental data and scanned photocopies of ^{1}H and ^{13}C NMR spectral data are provided. This information is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(9) CCDC 934886 (**5e**), 934884 (**6**), and 923281 (**7**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

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(13) No condensation products were observed for the NaH-mediated reaction of compound **1a** with **3i** or **3j**.