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A NOVEL SYNTHESIS OF α- AND β-HALONAPHTHALENES *VIA* REGIOSELECTIVE RING CLEAVAGE OF ARYL(*gem*-DIHALOCYCLOPROPYL)METHANOLS AND ITS APPLICATION TO TOTAL SYNTHESIS OF LIGNAN LACTONES, *JUSTICIDIN E* AND *TAIWANIN C*

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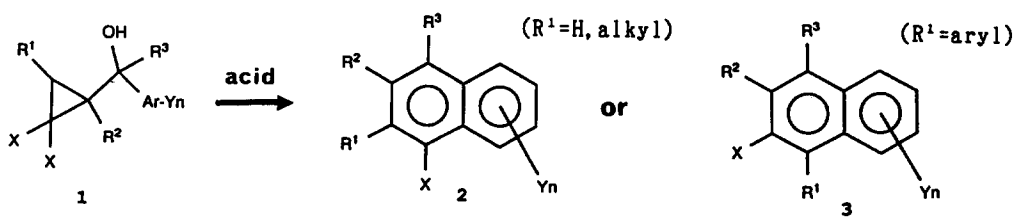
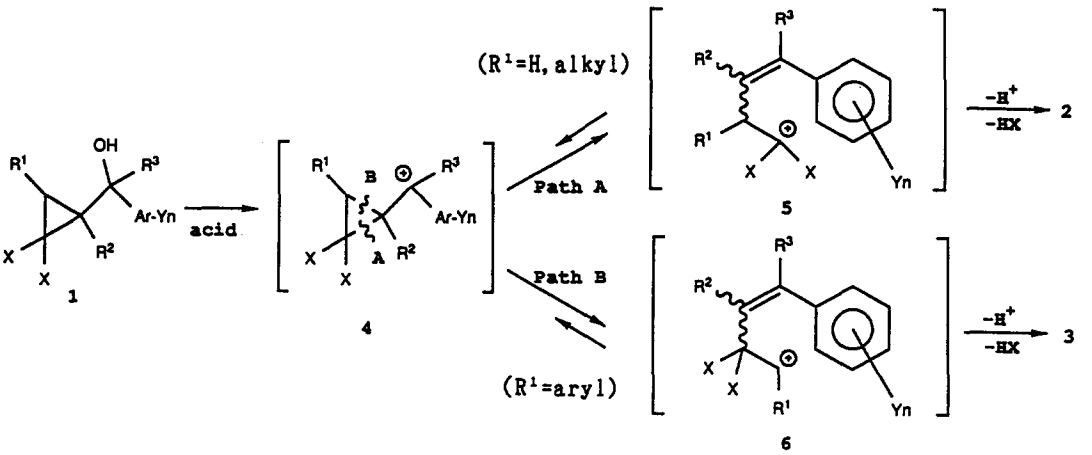
Summary: Acid treatment of two types of aryl(*gem*-dihalocyclopropyl)methanols (ADCM) 1 gave α- and β-halonaphthalenes in good yields with excellent selectivity. With the new method used as the key step, the two title natural lignan lactones were synthesized in seven steps.

Cyclopropylmethanols are well recognized as a class of important precursors in organic synthesis.[1] Although the Nazarov-type cyclopentannulation has been studied extensively,[2] scant attention has been paid to other reactions of *gem*-dihalocyclopropylmethanols which are readily available by dihalocarbene addition to allyl alcohols. During the course of studies on the regioselective isomerization and transformation of chrysanthemic acid derivatives,[3] we focused our attention on the reaction of aryl(*gem*-dihalocyclopropyl)methanol (ADCM) 1[4] system. In this communication, we wish to report a novel synthesis of substituted α- and β- halonaphthalenes 2 and 3 from ADCM 1 wherein two distinctive types of highly regioselective acid-induced cyclopropane-ring-fisson are involved (Scheme I). Application to a total synthesis of natural lignan lactones, *Justicidin E* and *Taiwanin C*[5] is also described (Scheme II).



First, the reaction of an ADCM (1a) with $BF_3 \cdot OEt_2$ (1.0 equiv.) at room temperature was found to give 1-chloro-3-methylnaphthalene in 62% yield as a sole product. Encouraged by this result, we next tried the reaction with other ADCM (1b~1j) and obtained the corresponding 1-chloro- or 1-bromonaphthalenes using suitable acids as summarized in Table 1 (entries 1~17).



Scheme I

A plausible reaction pathway is illustrated in Scheme I (path A). Benzyl cation 4 initially formed rearranges into homoallyl cation 5 through regioselective bond-A cleavage.[6] The (Z)-form of the homoallyl cation of 5 undergoes intramolecular Friedel-Crafts reaction with the phenyl group to afford the corresponding 1-chloro- or 1-bromonaphthalenes.[7] When substrate 1b (R^3=Ph) was used, the reaction took place spontaneously (reaction time <5 min.) to give 1-phenyl-2-methyl-4-chloronaphthalene quantitatively, since the homoallyl cation intermediate may orient itself toward the phenyl group (entry 5). From the substrate 1c (R^2=H), (*E*)-1,1-dichloro-4-phenyl-1,3-butadiene was formed predominantly (about 30 %) through the (*E*)-intermediate of 5.[7] $SnCl_4$ and $BF_3 \cdot OEt_2$ were found to be effective catalysts for the substrates bearing substituents (Y_n) on phenyl group (entries 10~17). These reactions being carried out in a diluted solution (about 1×10^{-2} M), we needed to add molecular sieves 4A to circumvent an undesirable intermolecular oligomerization and the formation of (*E*)-4-aryl-1,1,1-trichloro-3-butenes.

In contrast, the reaction of 2,2-dihalo-1-methyl-3-phenylcyclopropyl(phenyl)-methanol (1k[8], 1l) in CF_3CO_2H was found to give 1-phenyl-2-halo-3-methyl-naphthalene *via* regioselective cleavage of bond-B (Scheme I, path B). Clearly, benzyl cation intermediate 6 rather than 5 was formed due to the higher stability of the cation compared with dihalorocarbinyl cation (entries 18, 19).

A typical procedure for the preparation of 2 is as follows (entry 5): To a stirred solution of (2,2-dichloro-1-methylcyclopropyl)diphenylmethanol (307 mg, 1.0 mmol) in 1,2-dichloroethane (2 ml) was added $BF_3 \cdot OEt_2$ (142 mg, 1.0 mmol) at room temperature, and the mixture was allowed to stand for 1 h. After usual work up, 252 mg (100%) of 1-chloro-3-methyl-4-phenylnaphthalene[9] was obtained.

To demonstrate the utility of the present reaction, we present the total synthesis of two lignan lactones, *Justicidine E* and *Taiwanin C*[5] wherein the

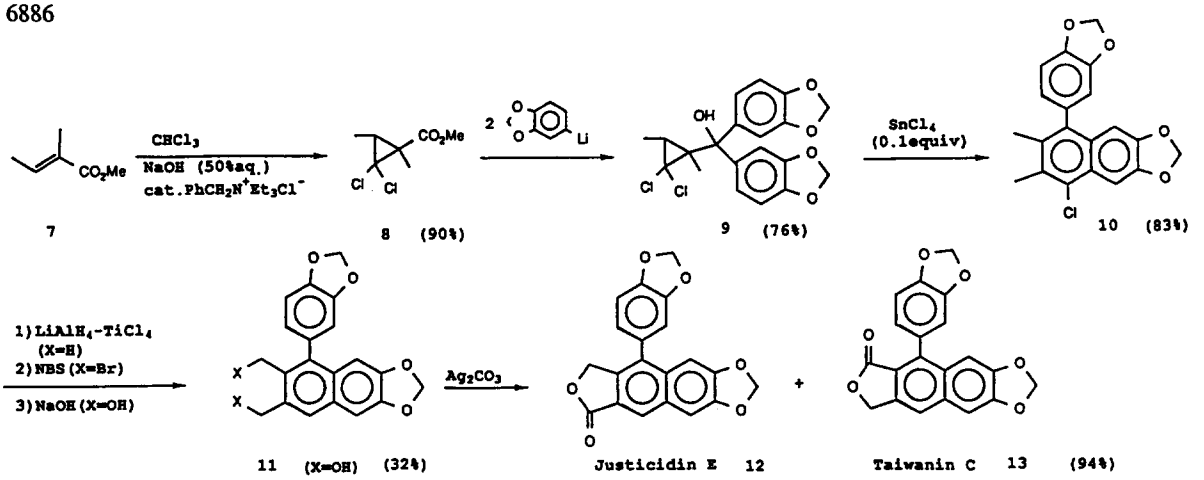
Table 1. Synthesis of α- and β-halonaphthalenes 2 and 3 from aryl(*gem*-dihalocyclopropyl)methanols (ADCM) 1.[a)]

Entry	Substrate	X	R^1	R^2	R^3	Y_n	acid (equiv.)	Product 2 (%)	Product 3 (%)
1	1a	Cl	H	Me	H	H	$BF_3 \cdot OEt_2$ (1.0)	62	0
2	1a	Cl	H	Me	H	H	$SnCl_4$ (1.0)	55	0
3	1a	Cl	H	Me	H	H	$TiCl_4$ (1.0)	35	0
4	1a	Cl	H	Me	H	H	CF_3CO_2H[b)]	77	0
5	1b	Cl	H	Me	Ph	H	$BF_3 \cdot OEt_2$ (1.0)	100	0
6	1c	Cl	Me	H	Ph	H	$SnCl_4$ (1.0)	22	0
7	1c	Cl	Me	H	Ph	H	CF_3CO_2H[b)]	0	0
8	1d	Cl	Et	Me	Ph	H	$BF_3 \cdot OEt_2$ (1.0)	86	0
9	1d	Cl	Et	Me	Ph	H	$SnCl_4$ (1.0)	85	0
10[c)]	1e	Cl	H	Me	H	p-MeO	$BF_3 \cdot OEt_2$ (1.0)	43[d)]	0
11[c)]	1e	Cl	H	Me	H	p-MeO	CF_3CO_2H[b)]	28[d)]	0
12[c)]	1e	Cl	H	Me	H	p-MeO	$SnCl_4$ (1.0)	62[d)]	0
13[c)]	1f	Cl	H	Me	H	o-MeO	$BF_3 \cdot OEt_2$ (1.0)	66[e)]	0
14[c)]	1g	Cl	H	Me	H	p-Me	$SnCl_4$ (1.0)	65[d)]	0
15[c)]	1h	Cl	H	Me	H	p-Cl	$SnCl_4$ (1.0)	27[d)]	0
16[c)]	1i	Cl	H	Me	H	p-NHAc	$SnCl_4$ (1.0)	39[d)]	0
17[c)]	1j	Br	H	Me	H	p-Me	$SnCl_4$ (1.0)	82[d)]	0
18	1k	Cl	Ph	Me	H	H	CF_3CO_2H[b)]	0	78
19	1l	Br	Ph	Me	H	H	CF_3CO_2H[b)]	0	64

a) These reactions were carried out in 1,2-dichloroethane at room temperature for 1h～24h unless noted otherwise. b) Used as solvent. c) Diluted conditions (about $1X10^{-2}$ M) in the presence of molecular sieves 4A. d) 1-Halo-3-methyl-7-substituted (Y_n) naphthalenes were obtained as a sole regioisomer. e) 1-Chloro-3-methyl-5-methoxynaphthalene was obtained as a sole regioisomer.

construction of 4-aryl-1-chloro-2,3-dimethylnaphthalene skelton is used as the key step (Scheme Ⅱ). Methyl angelate (7) was converted in 68% overall yield to the alcohol 9 through dichlorocarbene addition followed by the treatment with 3,4-methylenedioxyphenyllithium (two equiv.) at -78℃. Alchol 9 was treated with 0.1 equiv. of $SnCl_4$[10)] in 1,2-dichloroethane in the presence of molecular sieves 4A at room temperature for 30 min to afford the desired 4-aryl-1-chloro-2,3-dimethylnaphthalene 10 in 83% yield. $LiAlH_4$-$TiCl_4$ removal[11)] of the chlorine atom in 10, followed by bromination of methyl groups with *N*-bromosuccinimide and the successive treatment with 10% NaOH aqueous solution, gave the diol 11 in overall 68 % yield. Finally, oxidation of 11 by $AgCO_3$-Celite followed by separation[5e)] gave *Justicidine E* (12) and *Taiwanin C* (13) (12/13=5/1), respectively in 17% overall yield from 7.

Further investigation of the synthesis of heteroaromatics is now in progress.



Scheme II

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References and Notes

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2) T. Hiyama, M. Tsukanaka, and H. Nozaki, *J. Am. Chem. Soc.*, 96, 3713 (1974).
3) a) G. Suzukamo, *J. Synth. Org. Chem. Jpn.*, 40, 930 (1982). b) G. Suzukamo, M. Fukao, and M. Tamura, *Tetrahedron* Lett., 25, 1595 (1984). c)G. Suzukamo, M. Fukao, and T. Nagase, *Chem. Lett.*, 1799 (1984). c) Y. Sakito, and G. Suzukamo, *ibid.*, 621 (1986).
4) For the preparation of ADCM 1 following three methods are available: (1) Friedel-Crafts acylation of substituted benzenes with (*gem*-dihalocyclopropyl)-acetyl chlorides followed by reduction of the carbonyl group; (2) dichlorocarbene addition to allylic alchols or the corresponding THP ethers[2] followed by oxidation of the *gem*-dihalocyclopropylmethanols to the aldehydes and successive treatment with arylmagnesium bromide or aryllithium; (3) [for the preparation of diaryl(*gem*-dihalocyclopropyl)methanols] dichlorocarbene addition to α-alkyl-α,β-unsaturated esters followed by treatment with two equiv. of arylmagnesium bromide or aryllithium.
5) Previous syntheses: a) T. L. Holmes, and R. Stevenson, *J. Chem. Soc.*, (C), 2091 (1971). b) T. L. Holmes, and R. Stevenson, *J. Org. Chem.*, 36, 3450 (1971). c) E. Block, and R. Stevenson, *ibid.*, 36, 3453 (1971). d) B. J. Arnold, S. M. Mellows, and P. G. Sammes, *J. Chem. Soc. Perkin 1*, 1266 (1973). e) Z. Horii, M. Tsujiuchi, K. Kanai, and T. Momose, *Chem. Pharm. Bull.*, 25, 1803 (1977).
6) Regioselectivity of the cleavage of *gem*-dihalocyclopropylmethanols has been studied: F. T. DeWeese, D. E. Minster, J. T. Nosovitch, Jr., and M. G. Rudel, *Tetrahedron*, 42, 239 (1986).
7) Although thermodynamically stable (*E*)-intermediate 5 may form predominantly, it would isomerize to a (*Z*)-intermediate to some extent *via* the benzyl cation 4. (*E*)-4-Aryl-1,1,1-trihalo-3-butenes and (*E*)-4-aryl-1,1-dichloro-1,3-butadienes were detected as by-products derived from the (*E*)-intermediate.
8) Colorless crystals: mp 112-115 ℃; ^{1}H NMR ($CDCl_3$) 2.25 (3H, s), 7.00-8.00 (10H, m); MS (70 eV) *m/z* 252 (M^+).
9) Colorless crystals: mp 87-87.5℃; ^{1}H NMR ($CDCl_3$) 2.20 (3H, s), 7.00-7.60 (9H, m), 8.15-8.35 (1H, m; proton of 8-position of naphthalene); MS (70 eV) *m/z* 252 (M^+).
10) A catalytic amount of $SnCl_4$ was sufficient for the reaction of this substrate 9.
11) T. Mukaiyama, M. Hayashi, and K. Narasaka, *Chem. Lett.*, 291 (1973).

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