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Sequential and Regioselective Friedel-Crafts Reactions of *gem*-Dihalocyclopropanecarbonyl Chlorides with Benzenes for the Synthesis of 4-Aryl-1-naphthol Derivatives

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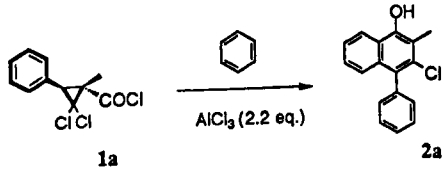
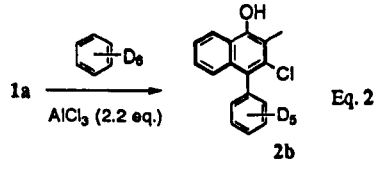
Abstract: Two types of novel, sequential and regioselective Friedel-Crafts reactions of *gem*-dihalocyclopropanecarbonyl chlorides with benzenes proceeded in a one-pot manner; *E*-3-aryl-2,2-dihalo-cyclopropanecarbonyl chlorides reacted with substituted benzenes to afford 4-aryl-3-halo-1-naphthols, while 2,2-dichlorocyclopropanecarbonyl chlorides were transformed into 4-aryl-1-naphthols in benzene or *p*-xylene. Both annulations involved alternative and highly regioselective cyclopropane ring-openings.

Synthetic methodology based on the characteristic properties of cyclopropanes has grown widely in the past two decades and has continuously been developed.[1] Annulations utilizing ring expansions of cyclopropanes are recognized as a representative example.[1c-e] During our continuing synthetic studies on new reactions utilizing *gem*-dihalocyclopropyl compounds,[2] we report here two types of novel, sequential and regioselective Friedel-Crafts (F-C) reactions of *gem*-dihalocyclopropanecarbonyl chlorides with benzenes to give various 4-aryl-1-naphthols, which are attracting attention as the basic skeleton of several biologically active lignan-type natural products and pharmaceuticals.[3]

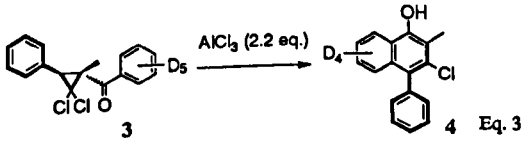
One of the sequential F-C reactions involved an intramolecular cyclization of *E*-3-aryl-2,2-dihalo-cyclopropanecarbonyl chlorides **1**, followed by intermolecular coupling with substituted benzenes giving 4-aryl-3-halo-1-naphthols **2**. As an example, *E*-2,2-dichloro-1-methyl-3-phenylcyclopropanecarbonyl chloride (**1a**)[4] with benzene in the presence of $AlCl_3$ (2.2 eq.; being optimized) gave 3-chloro-2-methyl-4-phenyl-1-naphthol (**2a**)[5] in 52% yield (Eq. 1).



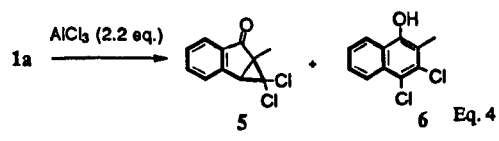
1a **2a** Eq. 1



2b Eq. 2



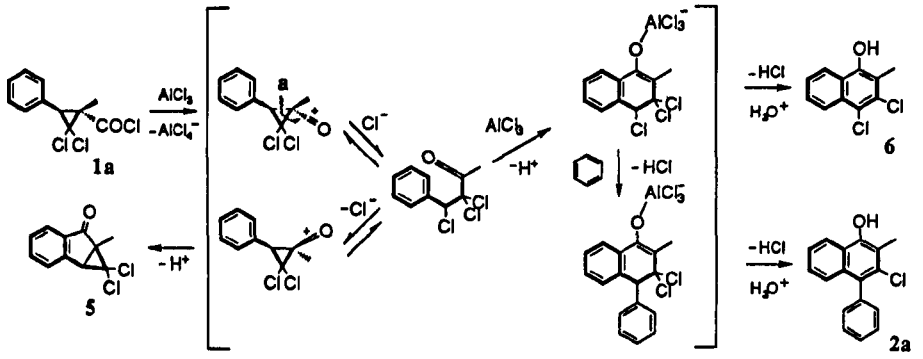
3 **4** Eq. 3



5 **6** Eq. 4

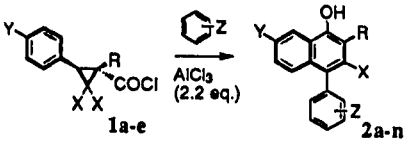
To clarify this reaction mechanism, we confirmed that the identical reaction of **1a** using C_6D_6 in the place of benzene gave 4-C_6D_5-naphthol **2b** (Eq. 2).[6] In clear contrast, the C_6D_5-substituted ketone **3**,[7] which is the postulated intermediate in the case that intermolecular F-C acylation initially occurred, mainly afforded an

isomeric naphthol **4** (28%) (Eq. 3).[8] In the controlled reaction without benzene, the tricyclic ketone **5** (21%)[9] and dichloronaphthol **6** (22%)[10] were obtained as major products (Eq. 4). Both of these by-products, **5** and **6**, could be detected only in trace amounts in the presence of benzene. Treatment of **5** under the identical conditions (in the presence of benzene/$AlCl_3$) resulted in only the recovery of **5**. These results would indicate that during this sequential F-C reaction, intramolecular cyclization precedes intermolecular coupling with another benzene as shown in scheme 1. Heavy lines in these equations indicate backbones of the starting 2,2-dichloro-3-phenylcyclopropane moiety. It is noted that the bond **a** cleavage proceeded with high regioselectivity, which resulted in the selective synthesis of **2**. Table 1 lists the results of the synthesis of various 4-aryl-3-halo-1-naphthols **2**.



Scheme 1

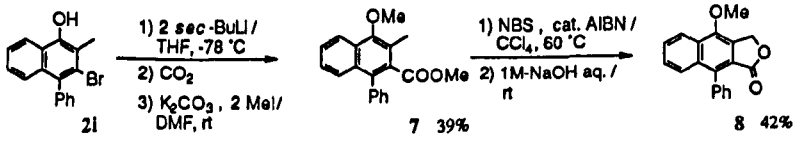
Table 1



Substrate	(X	Y	R)	Z	Product	Yield/%
1a	(Cl	H	Me)	H	**2a**	52
				D_6	**2b**	50
				Me	**2c**[a]	56
				Cl	**2d**[b]	81
				Br	**2e**[c]	64
				1-Me, 2-Cl, 6-Cl	**2f**[d]	60
				1-Cl, 4-Cl	**2g**	47
1b	(Cl	H	H)	Cl	**2h**[e]	51
1c	(Br	H	Me)	H	**2i**	47
				Cl	**2j**[f]	72
1d	(Cl	Cl	Me)	H	**2k**	48
				1-Me, 2-Cl, 6-Cl	**2l**[d]	44
1e	(Cl	OMe	Me)	H	**2m**	23
				1-Me, 2-Cl, 6-Cl	**2n**[d]	30

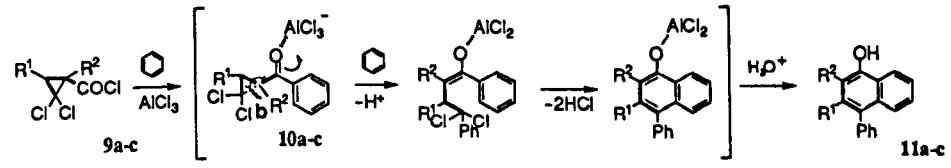
a) *p-/o-* (*vs.* Z)= 10/1. b) *p-/o-* (*vs.* Z) = 2/1. c) *p-/o-* (*vs.* Z)= 3.5/1. d) Exclusively *m-* (*vs.* 1-Me in Z). e) *p-/o-* (*vs.* Z) = 2/1. f) *p-/o-* (*vs.* Z) = 2/1. These ratio were determined by the integration of ^1H NMR (400 MHz).

Following the demonstration utilizing 4-aryl-3-halo-1-naphthols **2**, a derivatization of bromonaphthol **2i** toward a kind of lignan lactone **8**[11] *via* ester **7**[12] is illustrated in scheme 2.



Scheme 2

Another sequential F-C reaction involved the intermolecular acylation of 2,2-dihalocyclopropanecarbonyl chlorides **9a-c** with one benzene molecule giving ketones **10a-c**, a successive intermolecular trap by another benzene molecule, and a final intramolecular cyclization (Scheme 3). It is noted that these reactions spontaneously took place to give 4-phenyl-1-naphthols **11a-c**[13] with a highly regioselective bond b-cleavage, which resulted in the selective synthesis of **11a-c** (Table 2, entries 1-3). In the case using *p*-xylene, the desired reaction also proceeded to give **11d**[14] (Table 2, entry 4). To confirm this reaction mechanism, we examined the reaction of intermediary ketones **10c-f**[15] which were alternatively prepared. Expectedly, several ketones **10c-f** gave 4-aryl-1-naphthols **11c, e-k**[16] under the identical conditions, wherein a variety of **11** were obtained, since different substituted benzenes could be stepwise incorporated (Table 3).



Scheme 3

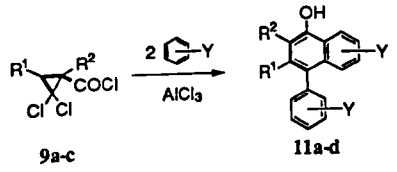


Table 2

Substrate	(R^1	R^2)	Y	Product	Yield/%
9a	(H	H)	H	11a	38[a]
9b	(Me	Me)	H	11b	40[b]
9c	(H	Me)	H	11c	58[a]
9c	(H	Me)	1-Me, 4-Me	11d[c]	44[a]

a) $AlCl_3$ (2.2 eq.) was used. b) $AlCl_3$ (3.3 eq.) was used c) 2,5,8-Trimethyl-1-naphthol (~10%) was contained as a by-product.

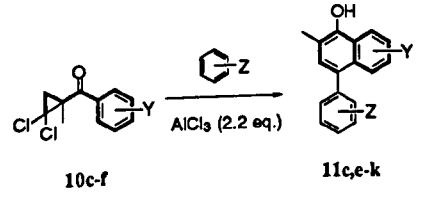


Table 3

Substrate	(Y)	Z	Product	Yield/%
10c	(H)	H	11c	56
10c	(H)	1-Me, 2-Cl, 6-Cl	11e[a]	48
10d	(4-Cl)	H	11f	52
10d	(4-Cl)	1-Me, 2-Cl, 6-Cl	11g[a]	23
10e	(4-Me)	H	11h	32
10e	(4-Me)	1-Me, 2-Cl, 6-Cl	11i[a]	23
10f	(3-Me)	H	11j[b]	55
10f	(3-Me)	1-Me, 2-Cl, 6-Cl	11k[a)b)]	43

a) Exclusively *m*- (*vs.* 1-Me in Z). b) Exclusively 7-methyl compound.

In conclusion, compared with a known analogous annulation for the synthesizing tetralones from 2-arylcyclopropyl aryl ketones,[17] and with our previous report on the preparation of α- and β-halonaphthalenes from aryl(*gem*-dihalocyclopropyl)methanol,[2a] the present sequential F-C reactions proceed more straightforwardly (in a one-pot manner) *via* significantly different mechanisms. The variation in these annulations unequivocally owes to the high degree of site-selectivity in the ring-openings (bonds a and b)[18] which is one of the characteristics of the *gem*-dihalocyclopropanes.

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References and Notes

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2. (a) Seko, S.; Tanabe, Y.; Suzukamo, G. *Tetrahedron Lett.*, **1990**, *31*, 6883. (b) Tanabe, Y.; Nishii, Y. Wakimura, K. *Chem. Lett.*, **1994**, 1757. (c) Tanabe, Y.; Wakimura, K.; Nishii, Y.; Muroya, Y. *Synthesis*, in press.
3. Ogiku, T.; Yoshida, S.; Ohmizu, H.; Iwasaki, T. *J. Org. Chem.*, **1995**, *60*, 4585. References cited therein.
4. Acyl chlorides **1** were prepared according to the reported method; Nishii, Y.; Matsumura, H.; Muroya, Y.; Tsuchiya. T.; Tanabe, Y. *Biosci. Biotech. Biochem.*, **1995**, *59*, 1355.
5. General procedure of synthesis of **2**: To a stirred solution of an acyl chloride **1** (1.0 mmol) and a substituted benzene (1.2 mmol) in 1,2-dichloroethane (5.0 ml) was added $AlCl_3$ (2.2 mmol) at 0-5 °C, and the mixture was stirred at rt for 10 h. Usual work up and purification with silica-gel column chromatography (hexane/ether=8:1~5:1) gave 4-aryl-1-naphthols **2**. **2a**: Colorless crystals, mp 85-88 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.52 (3H, s), 5.32 (1H, brs, -OH), 7.22-7.38 (4H, m), 7.40-7.55 (4H, m), 8.14 (1H, d, J = 7.4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.5, 115.6, 121.0, 122.9, 125.1, 125.3, 126.7, 127.4, 127.9, 128.3, 128.6, 130.7, 130.9, 132.3, 133.5, 138.6, 148.8; IR (KBr) 3532, 3484, 1576, 1520, 1506 cm^{-1}; MS *m/z* 268 (M^+). ^1H NMR peaks in the range of δ 8.0-8.3 are characteristic of 8-position in 4-arylnaphthol derivatives whose assignments were supported by NOESY measurement between H (8-position) and -OH.
6. **2b**: Colorless crystals, mp 110-112 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.51 (3H, s), 5.32 (1H, brs, -OH), 7.24-7.54 (3H, m), 8.12 (1H, d, J = 7.38 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 115.5, 122.8, 126.3, 127.3, 127.4, 128.2, 128.3, 130.6, 130.7, 130.8, 132.3, 138.5, 138.6, 148.7; IR (KBr) 3532, 3492, 1558, 1462 cm^{-1}.
7. Ketone **3** was prepared by coupling reaction of acyl chloride **1a** with C_6D_5MgBr (1.0 equiv.) at 0-5 °C-rt for 4 h in 65% yield. **3**: Colorless oil; ^1H NMR (90 MHz, $CDCl_3$) δ 1.44 (3H, s), 3.58 (1H, s), 7.27-7.48 (5H, m); IR (neat) 1686, 1244, 1157 cm^{-1}.
8. **4**: Amorphous solid; ^1H NMR (400 MHz, $CDCl_3$) δ 2.51 (3H, s), 5.32 (1H, brs, -OH), 7.20-7.35 (2H, m), 7.40-7.55 (3H, m); IR (KBr) 3532, 3492, 1578, 1502 cm^{-1}
9. **5**: Colorless oil, ^1H NMR (400 MHz, $CDCl_3$) δ 1.72 (3H, s), 3.20 (1H, s), 7.40-7.45 (1H, m), 7.54-7.62 (2H, m), 7.70 (1H, d, J = 7.7 Hz); IR (neat) 1725, 1620, 1303 cm^{-1}; MS *m/z* 226 (M^+).
10. **6**: Red crystals, mp 118-120 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.50 (3H, s), 5.27 (1H, brs, -OH), 7.50-7.62 (2H, m), 8.10 (1H, d, J = 8.8 Hz), 8.21 (1H, d, J = 8.5 Hz); IR (KBr) 3374, 1586, 1263 cm^{-1}; MS *m/z* 226 (M^+).
11. **8**: Light yellow crystals, mp 181-184 °C; a new lactone compound: ^1H NMR (400 MHz, $CDCl_3$) δ 4.19 (3H, s), 5.31 (2H, s), 7.33-7.40 (2H, m), 7.45-7.54 (4H, m), 7.60-7.71 (1H, m), 7.75 (1H, d, J = 8.05 Hz), 8.35 (1H, d, J = 8.31 Hz); IR (KBr) 2922, 1760, 1361 cm^{-1}.
12. **7**: Colorless oil, ^1H NMR (90 MHz, $CDCl_3$) δ 2.45 (3H, s), 3.50 (3H, s), 3.96 (3H, s), 7.20-7.70 (8H, m), 8.05-8.27 (1H, m).
13. General procedure of synthesis of **11a-c**: To a stirred solution of an acyl chloride **9** (1.0 mmol) in benzene (5 ml) was added $AlCl_3$ (2.2 mmol) at 0-5 °C, and the mixture was stirred at room temperature for 10 h. After a similar work up in the case preparing **2**, 4-phenyl-1-naphthols **11a-c** were obtained. **11c**: Brown crystals; mp 73-75 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.17 (3H, s), 5.46 (1H, brs, -OH), 6.77 (1H, s), 7.24-7.54 (8H, m), 8.15 (1H, d, J = 11.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 111.1, 121.3, 122.7, 124.1, 126.1, 126.3, 126.8, 128.3, 130.7, 131.2, 133.4, 134.1, 139.7, 150.4; IR (KBr) 3441, 1597, 1233 cm^{-1}; MS *m/z* 234 (M^+).
14. **11d**: Amorphous solid; ^1H NMR (400 MHz, $CDCl_3$) δ 1.84 (3H, s), 1.95 (3H, s), 1.96 (3H, s), 2.34 (3H, s), 2.98 (3H, s), 5.23 (1H, brs, -OH), 6.68 (1H, s), 6.92 (1H, s), 7.00-7.20 (4H, m).
15. Ketones **10c-f** were prepared by coupling reaction of acyl chloride **9c** with the corresponding ArMgBr (1.0 equiv.) at 0-5 °C-rt for 4 h in 52-61% yields.
16. **11e**: Light yellow crystals; mp 126-127 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.14 (3H, s), 2.60 (3H, s), 5.57 (1H, brs, -OH), 6.79 (1H, s), 7.04 (1H, d, J = 8.1 Hz), 7.20 (1H, d, J = 8.0 Hz), 7.34-7.44 (2H, m), 7.41 (1H, d, J = 8.1 Hz), 8.21 (1H, d, J = 8.3 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 20.3, 110.9, 121.6, 122.8, 124.3, 125.1, 126.7, 127.5, 128.2, 130.0, 133.3, 133.9, 134.2, 134.9, 136.2, 137.4, 151.1; IR (KBr) 3280, 1600, 1390 cm^{-1}.
17. Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 2920.
18. A similar reason for the enhancement of high regioselectivity was described in Ref. 2a.

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