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Synthesis of functionalized 3-chloro-1-naphthols via Friedel–Crafts acylation of vinyl chlorides

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Friedel–Crafts type cyclization of vinyl chlorides was developed into a general method for the synthesis of functionalized naphthols. The chloro functional group contained within these products allowed for further elaboration via cross-coupling reactions, leading to increased structural complexity.

Introduction

The Friedel–Crafts acylation of arenes is a thoroughly established technique for the synthesis of aromatic ketones.[1–8] Intramolecular acylation with alkenes as nucleophiles has also proven highly useful in the formation of ring-systems.[9–14] While previous studies demonstrated the use of electron enriched alkenes as efficient nucleophiles, few Friedel–Crafts acylation reactions with electron deficient alkene species have been reported. As part of a continuing effort to develop efficient approaches to functionalized organic intermediates, we recently became interested in the use of alternative nucleophilic components to the commonly used arene ring. In particular, we sought to investigate the use of electron deficient vinyl chlorides as the nucleophilic component in intramolecular Friedel–Crafts acylation reactions. Herein, we disclose the results from our work in this area, which demonstrate the utility of intramolecular Friedel–Crafts acylation of vinyl chlorides for the synthesis of various functionalized naphthols.

Results and discussion

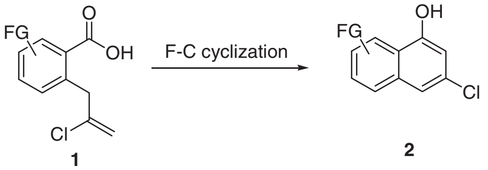
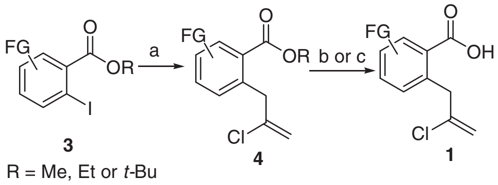


Figure 1. Access to naphthols via vinyl chloride Friedel–Crafts acylation.

Figure 1 depicts the basic process that we set out to develop into a general method for the preparation of naphthols. To our knowledge, there are no literature examples of the direct synthesis of naphthols via this kind of vinyl chloride Friedel–Crafts reaction. Furthermore, the potential to generate naphthol products bearing a chloro-group in a 1,3-relationship to a hydroxy was attractive since this type of disubstituted naphthalene is difficult to prepare by other means.[15]

Numerous reports from the Knochel group have established the utility of Mg–I exchange for the preparation of functionalized aromatic compounds.[16–19] Using this technology, it was possible to access various functionalized substrates containing the desired vinyl chloride and carboxylic acid subunits in convenient fashion via quenching of aryl-MgX species with 2-chloro-3-iodopropene in the presence of a Cu catalyst (Scheme 1).[20] This reaction



Scheme 1. Synthesis of chloroallyl Friedel–Crafts cyclization substrates via Mg–I exchange chemistry. (a) *i*-PrMgCl/THF, CuCN·2LiCl, 2-chloro-3-iodopropene. (b) 10% NaOH, MeOH. (c) TFA, CH_2Cl_2.

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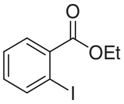
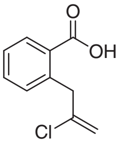
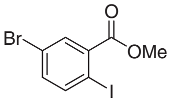
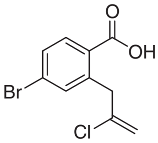
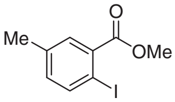
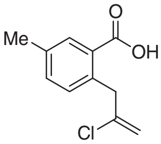
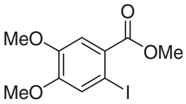
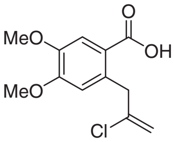
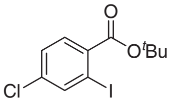
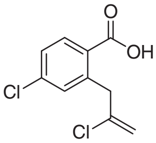
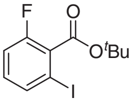
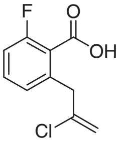
sequence with methyl or ethyl ester **4** normally afforded modest yields of substituted benzoic acids due to formation of allene by-products during basic hydrolysis via an E_{1cb} pathway (Table 1, entries 1–4). Alternative alkylation and acidic hydrolysis of *t*-butyl analogues could improve the overall yields (entries 5 and 6).

Intramolecular Friedel–Crafts acylation reactions using these substrates was initially processed in two separated steps of acid chloride formation and intramolecular Friedel–Crafts acylation. However, isolation of acid chloride intermediates sometimes cost a significant reduction of yields for the final product. Improved results were obtained with conducting the two-step sequence in one pot fashion by treating the intermediate acid chloride in-situ with $AlCl_3$. Reactions normally gave a mixture of dichloroketone **5** and desired chloronaphthol **2**. Upon being subject to longer reaction time or a basic workup, dichloroketone can be converted to the desired chloronaphthol product completely. As shown in Table 2, substrates bearing different functional groups display the same reactivity.

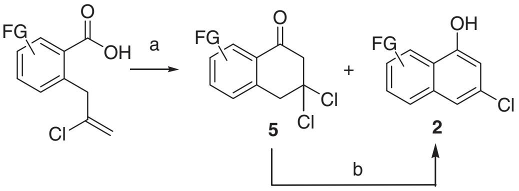
Several methodologies have been developed to functionalize unprotected chloro-phenols or naphthols via C–C or C–X (X = O, N, or S) bond formations.[21] To further demonstrate the principal possibility of the application of 3-chloronaphthol in organic synthesis, we elaborated one example of Pd-catalyzed C–N bond formation at 3rd position of naphthols, as shown in the Scheme 2. With steric bulky *t*-butyl Xphos ligand, hydroxy group was tolerated under an amination condition.[21e] 3-morpholine substituted naphthol can be directly derived from the chloro-precursor in a high yield.

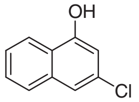
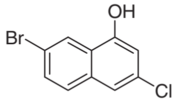
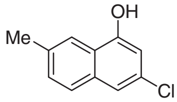
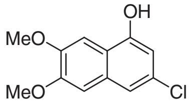
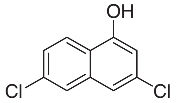
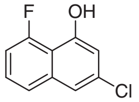
Table 1
Synthesis of chloroallyl benzoic acid substrates

Entry	Iodo ester	Benzoic acids	Yield[a] (%)
1			67
2			64
3			69
4			73
5			92
6			83

[a] Isolated yield of analytically pure material over two steps.

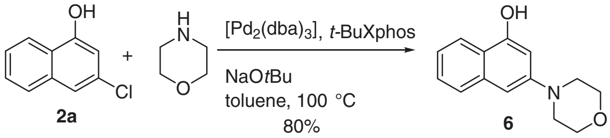
Table 2
Synthesis of functionalized chloronaphthols[a]



Entry	Benzoic acids	Yield[b] (%)
1	 **2a**	89
2	 **2b**	92
3	 **2c**	93
4	 **2d**	83
5	 **2e**	83
6	 **2f**	83

[a] Carboxylic acid (1.0 equiv), oxalyl chloride (1.5 equiv), cat. DMF, and $AlCl_3$ (2.0 equiv).

[b] Isolated yield of analytically pure material.



Scheme 2. Elaboration of functionalized chloronaphthols via C–N bond formations.

Conclusion

In summary, we have described the facile synthesis of 3-chloro-1-naphthols from readily available starting materials by an intramolecular Friedel–Crafts acylation of vinyl chloride. The *meta*-substitution pattern produced using this chemistry is not readily achievable through alternative approaches. Moreover, the resultant aryl chloride functionality was demonstrated to be a useful synthetic handle to access to multisubstituted naphthalene system via cross-coupling chemistry.

Experimental section

Typical experimental procedure for 2-(2-chloroallyl)-benzoic acid formation **1**: A dry, N_2 flushed 25 mL round-bottomed flask, equipped with a magnetic stirring bar, was charged with aryl iodide **3** (1 mmol) in anhydrous THF (5 mL), and cooled to −40 °C. *i*-PrMgCl (2 M in THF, 2 mmol) was slowly added. After 0.5 h, CuCN·2LiCl (premixed CuCN and 1 M LiCl in THF) (0.1 mmol) was added. After 5 min, at the same temperature, 2-chloro-3-iodo-propene (2 mmol) was added and the reaction mixture allowed to warm to rt. The reaction mixture was quenched with sat. NH_4Cl (20 mL) and extracted with MTBE (2 × 20 mL). The combined organic fractions were washed with brine (10 mL), then dried over Na_2SO_4, and concentrated in vacuo. The crude product was used in the next step after a silica plug treatment or without further purification.

At rt, to a solution of ester **4** from the last step (1 mmol) in MeOH (10 mL) was added 10% NaOH (5 mL). After 20 h, the reaction was acidified with concentrated HCl to pH 2. After removing most of MeOH, the reaction was extracted with MTBE (2 × 20 mL). Organic layers were separated, combined, and washed with brine (20 mL). The organic extract was concentrated in vacuo and the crude product was purified by recrystallization from a mixture of hexanes and EtOAc.

In a case of *t*-butyl ester hydrolysis, at rt, to a solution of *t*-butyl ester (1 mmol) in CH_2Cl_2 (5 mL) was added TFA (10 mmol). After 16 h, the reaction was quenched by H_2O and extracted with MTBE (2 × 20 mL). Organic layers were separated, combined, and washed with brine (20 mL). The organic extract was concentrated in vacuo and TFA/H_2O was removed by azeotrope of toluene. Crude product was purified by recrystallization from a mixture of hexanes and EtOAc.

Typical experimental procedure for Friedel–Crafts cyclization of vinyl chloride to afford 3-chloro-1-naphthol **2**: At rt, to acid (1 mmol) in CH_2Cl_2 (5 mL) was added two drops of DMF and oxalyl chloride (2 mmol) slowly. After 10 min, aluminum chloride (2 mmol) was added. The reaction was stirred for 15 min. The reaction was quenched by 1 N HCl (10 mL) and MTBE (20 mL). After phase cut, organic layer was concentrated to half volume and heptane (10 mL) was added. Organic solution was washed with 10% NaOH (2 × 20 mL). Aqueous layers were combined and acidified to pH 2, and then extracted with MTBE (2 × 20 mL). Organic layers were separated, washed with water (20 mL), and brine (20 mL) and dried with Na_2SO_4. After removal of solvent, crude product was purified by flash chromatography.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.011.

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