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A Facile Access to 4-Substituted-2-naphthols via a Tandem Friedel–Crafts Reaction: A β-Chlorovinyl Ketone Pathway

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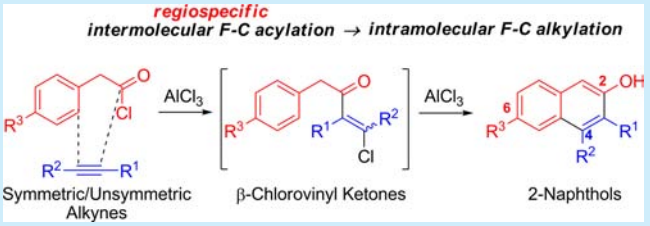
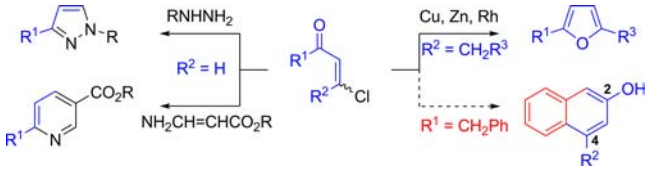
Supporting Information

ABSTRACT: A one-pot synthesis of 2-naphthol derivatives is accomplished using a tandem Friedel–Crafts reaction sequence. The developed methodology allows for a concomitant construction of up to three C–C bonds between readily available alkynes and phenylacetyl chloride derivatives by an intermolecular Friedel–Crafts acylation of alkynes followed by an intramolecular Friedel–Crafts alkylation of β-chlorovinyl ketone intermediates.



β-Chlorovinyl ketones are a class of versatile building blocks, serving as immediate synthetic precursors to various heterocycles such as furans, pyrazoles, and pyridines (Scheme 1).[1]

Scheme 1. Synthetic Utility of β-Chlorovinyl Ketones and Proposed Synthetic Route to 2-Naphthols



Our recent mechanistic study revealed that β-chlorovinyl ketones undergo a facile α-vinyl enolization, leading to [3]cumulenol and alkynyl enol intermediates under mild base conditions using Et_3N.[2] This newly discovered soft α-vinyl enolization of β-chlorovinyl ketones has sparked a renewed interest in their potential as latent nucleophiles[3] as well as electrophiles.[4] With the aim of further exploiting the synthetic utility of β-chlorovinyl ketones, we became interested in the synthesis of 2-naphthol derivatives from β-chlorovinyl ketone intermediates that are readily available from the Friedel–Crafts acylation of alkynes.[5]

The preparation of 2-naphthols is of great importance in synthetic chemistry, as they are frequently used in the synthesis of binaphthyl-containing natural products[6] and their use in asymmetric catalysis.[7] While the electrophilic aromatic substitutions of naphthol derivatives could provide a stepwise introduction of substituents, such methods typically suffer from lengthy synthetic procedures and result in a mixture of isomers.[8] In particular, the synthesis of 4-substituted 2-naphthols is not trivial, considering the multistep synthesis of starting materials that are used in the intramolecular carbocyclization of alkynyl ketones.[9] The electrocyclization of alkynones[10] as well as the [2 + 2] cycloaddition–Dieckmann condensation of ynolate anions provide access to 2-naphthol derivatives;[11] however, these reaction protocols concomitantly introduce an extra substituent at the 3-position. Recently, the group of Kozlowski reported an optimized protocol for the synthesis of 2-naphthol derivatives that possess a hydroxyl group at the 4-position and an ester moiety at the 3-position during the total synthesis of perylenequinone natural products.[12] While the introduction of a methyl group at the 4-position of 2-naphthols was recently accomplished by the group of Feng using a series of palladium-catalyzed Stille coupling and Heck reactions, this method does not allow the introduction of other alkyl and aryl substituents at the 4-position.[13] A recent study by the group of Okuma overcame the synthetic limitation of Feng's protocol by using the reactions of benzyne with 1,3-diketones followed by an intramolecular aldol condensation.[14] However, the Okuma's protocol exhibits modest regioselectivities over the formation of 1-naphthols (1-naphthol/2-naphthol = 2:1 to 1:4) and is limited to the introduction of an aryl group at the 4-position of 2-naphthols.

Motivated by the significant limitations in the preparation of 4-substituted-2-naphthols combined with our strong interests in the design of multifaceted chiral catalysts such as BINOLs, we investigated the potential use of β-chlorovinyl ketones as immediate synthetic precursors to 2-naphthol derivatives. Previously, we observed the formation of 2-naphthol derivative **4a** as a byproduct during the preparation of β-chlorovinyl ketones **3a** using the Friedel–Crafts alkylation of alkynes with phenylacetyl chloride **2a** (Scheme 2). While the reaction at 0 °C resulted in the preferential formation of a 4:1 mixture of (*E*)- and (*Z*)-β-chlorovinyl ketones **3a**, the emergence of 2-naphthol derivative **4a** as a major product was evident upon increasing the reaction temperature to 23 °C. Thus, a simple change of reaction temperature led to the *exclusive* formation of 4-substituted-2-naphthanol **4a** in 73% yield. To confirm the intermediacy of **3a** in the subsequent intramolecular Friedel–

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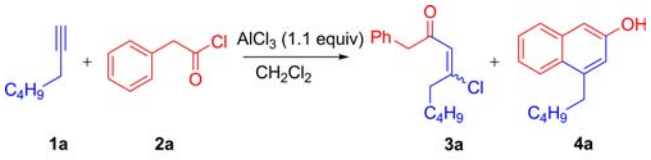
Scheme 2. One-Pot Synthesis of 4-Pentyl-2-naphthol



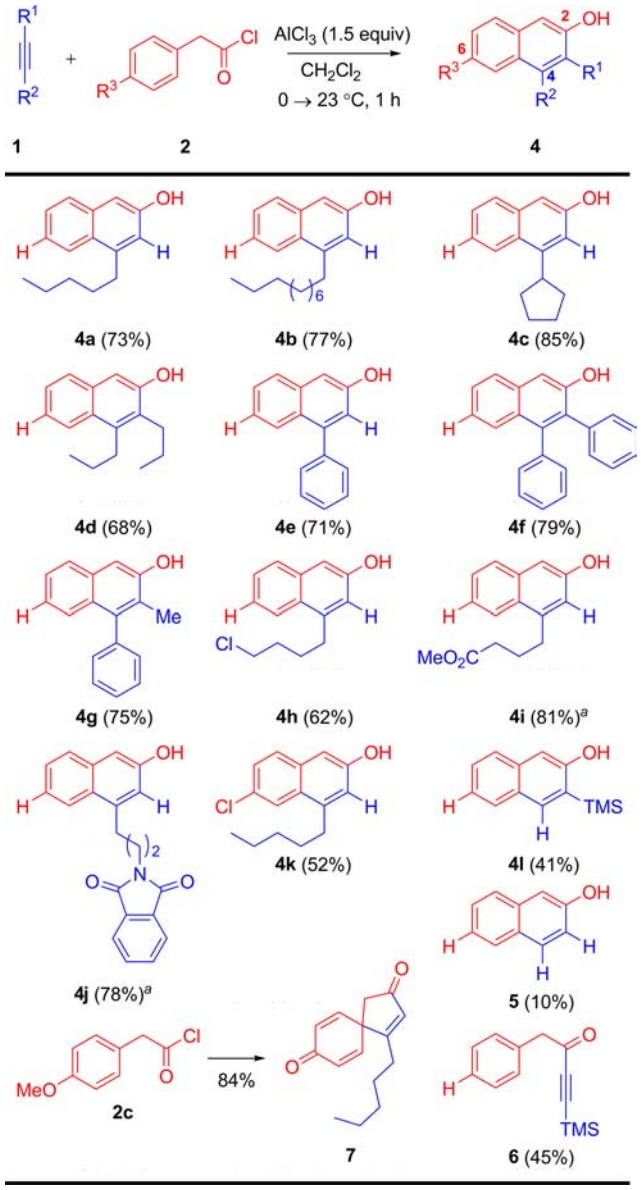
entry	conditions	yield (%) 3a	4a
1	0 °C, 0.5 h	52 (*E*/*Z* = 4:1)	13
2	0 → 23 °C, 1 h	15	61
3	0 → 23 °C, 1 h ($AlCl_3$ 1.5 equiv)	0	73
		3a	4a
4	0 → 23 °C, 2 h ($AlCl_3$ 0.2 equiv)	> 95%	
5	0 → 23 °C, 1 h ($AlCl_3$ 0.4 equiv)	> 95%	

Crafts alkylation, we subjected a mixture of **3a** under the identical reaction conditions where a clean formation of 2-naphthol derivative **4a** was observed (**3a** and **4a**).[15] The use of two commercially available starting materials, alkyne and phenylacetyl chloride, is a significant advantage from the synthetic point of view, in addition to its operational simplicity (i.e., one pot, short reaction time, and high yielding process).

The one-pot synthesis of 4-substituted-2-naphthols from the reaction of alkynes and phenylacetyl chloride derivatives is general. Thus, terminal alkynes with an aliphatic as well as aryl substituent smoothly underwent the desired cyclization process to provide 2-naphthol derivatives in good to excellent yields (Scheme 3).[16] In addition, various functional groups were tolerated under the reaction conditions; however, the use of trimethylsilyl acetylene resulted in the formation of 3-(trimethylsilyl)-2-naphthol **4l**, 2-naphthol **5**, and alkynyl ketone **6** due to the low regioselectivity of the Friedel–Crafts acylation of trimethylsilyl acetylene. Thus, it is reasonable to assume that the trimethylsilyl acetylene does not lead to the regioselective *β*-chlorovinyl ketone intermediates, the key requirement for accessing to 4-substituted-2-naphthols, under our Friedel–Crafts acylation conditions.[17] Interestingly, the use of disubstituted alkynes resulted in the regioselective formation of **4g**, allowing an access to 3,4-disubstituted-2-naphthol due to the regioselective formation of *β*-chlorovinyl ketone intermediates.[18] The investigation into the electronic effect of phenylacetyl chloride derivatives revealed low reactivity for the electron-deficient phenylacetyl chloride derivative (**2b**, R^3 = Cl). Consistently, the use of an electron-rich phenylacetyl chloride derivative (**2c**, R^3 = OMe) displayed a fast reaction rate but led to the formation of a spiro[4.5]decane **7** in 84% yield.[19]

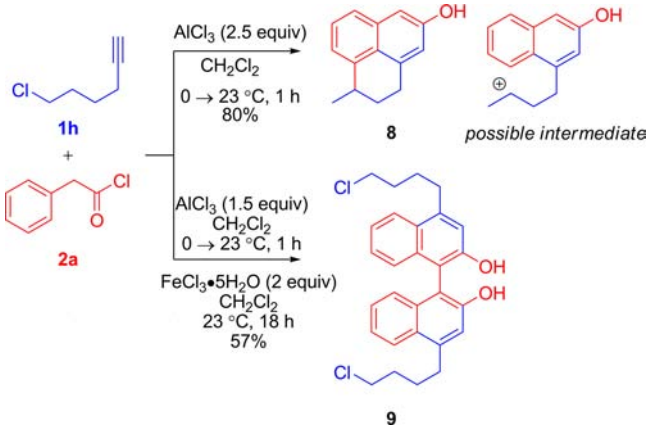
The amount of $AlCl_3$ employed in this tandem Friedel–Crafts reaction sequence can be increased to promote another C–C bond formation. Thus, the use of 2.5 equiv of $AlCl_3$ on substrate **1h** led to the formation of 2,3-dihydro-1*H*-phenalene **8** in 80% yield, presumably via the intermediacy of a secondary carbocation (Scheme 4). Additionally, the synthetic access to 1,1′-bi-2-naphthols from the tandem Friedel–Crafts reaction sequence can be demonstrated. Thus, quenching the reaction mixture after complete consumption of phenylacetyl chloride derivative **2a** using water followed by the treatment of the organic layer with $FeCl_3$ resulted in the formation of BINOL derivative **9** in 57% yield over a two-step sequence. This

Scheme 3. Scope of the One-Pot Synthesis of Substituted 2-Naphthols



[a]Use of 2.2 equiv of $AlCl_3$.

Scheme 4. Application to Other Aryl Compounds



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synthetic route to BINOL derivatives significantly improves regioselectivity as well as chemical efficiency compared to other existing synthetic approaches to BINOL derivatives.[7]

In summary we discovered a tandem Friedel−Crafts reaction sequence that readily allows the synthesis of substituted 2-naphthol derivatives through the regioselective formation of β-chlorovinyl ketone intermediates. While there are a few commercially available phenylacetyl chloride derivatives, the utilization of two readily available starting materials greatly broadens the structural diversity of 2-naphthol derivatives that might be useful in further synthetic modifications to more valuable chemical entities. Consequently, we are currently investigating the synthetic utility of 4-substituted-2-naphthols, and our results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) We did not observe any significant rate difference between (*E*)- and (*Z*)-β-chlorovinyl ketones, as the reactions were complete within 1 h for both stereoisomers. The use of a catalytic amount of $AlCl_3$ (i.e., 10−40 mol%) is sufficient in inducing the intramolecular Friedel−Crafts alkylation of (*E*)/(*Z*)-β-chlorovinyl ketones at 0−23 °C.

(16) In most cases the intermediacy of β-chlorovinyl ketones has been confirmed by either NMR monitoring of the reaction mixtures or isolation of intermediates.

(17) Our effort to isolate β-chlorovinyl ketone intermediates from the reaction of trimethylsilyl acetylene was not successful. Previously, Juteau and coworkers at Merck Frost Canada reported the synthesis of 3-(triisopropylsilyl)-2-naphthols under similar reaction conditions using triisopropylsilyl acetylene; see: Juteau, H.; Gareau, Y.; Lachance, H. *Tetrahedron Lett.* **2005**, *46*, 4547.

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