

Letter

Iron-Catalyzed Synthesis of Tetrahydronaphthalenes via 3,4-Dihydro-2*H*-pyran Intermediates

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Supporting Information

ABSTRACT: The development of an iron(III)-catalyzed synthetic strategy toward functionalized tetrahydronaphthalenes is described. This approach is characterized by its operational simplicity and is distinct from currently available procedures that rely on [4 + 2]-cycloadditions. Our strategy takes advantage of the divergent reactivity observed for simple aryl ketone precursors to gain exclusive access to tetrahydronaphthalene products (23 examples). Detailed mechanistic investigations identified



pyrans as reactive intermediates that afford the desired tetrahydronaphthalenes in high yields upon iron(III)-catalyzed Friedel-Crafts alkylation.

T etrahydronaphthalenes are key structural motifs in molecules of interest such as biologically active natural products¹ and pharmaceuticals² as well as precursors to functional materials, including optoelectronics³ and organic semiconductors.⁴



B Selected Literature Approaches Based on (4+2)-Cycloadditions:



Figure 1. (A) Divergent reactivity between Brønsted or Lewis acids. (B) Literature procedures for the formation of tetrahydronaphthalenes based on [4 + 2]-cycloadditions.

Consequently, diverse areas of research rely on efficient and economical strategies to synthesize these important building blocks.

Table 1. Reaction Optimization for the Lewis Acid CatalyzedFormation of Tetrahydronaphthalene 12

Ĺ		le (10 solve	vis acid mol %) nt (0.1 M) me, rt		Me Me
entry	Lewis acid	solvent	time (h)	yield ^a (%)	conversion ^{<i>a</i>} (%)
1	Fe(OTf) ₃	DCE	24	23	99
2	Bi(OTf) ₃	DCE	24	48	99
3	GaCl ₃	DCE	24	58	99
4	SnCl ₄	DCE	24	87	99
5	$BF_3 \cdot OEt_2$	DCE	24	87	99
6	AlCl ₃	DCE	24	73	99
7	FeCl ₃	DCE	8	96 ^b	99
8	$FeCl_3$ (5 mol %)	DCE	24	82	99
9	$FeCI_3$ (20 mol %)	DCE	4	61	99
10	FeCl ₃	DCM	4	68	99
11	FeCl ₃	PhMe	4	83	99
12	FeCl ₃	NO_2Me	4	86	99
13 ^c	HCl	DCE	24	0	17
14 ^d	HCl (100 mol %)	DCE	24	0	20
15 ^e	HCl (500 mol %)	DCE	24	0	68

^{*a*}Percent yield and percent conversion determined by ¹H NMR using dimethyl terephthalate as an internal standard. ^{*b*}Isolated yield. ^{*c*}4% (24% brsm) pyran 3 observed. ^{*d*}20% (100% brsm) pyran 3 observed. ^{*e*}35% (52% brsm) pyran 3 observed. ^{*f*}All reactions were performed using 0.113–0.189 mmol of aryl ketone.

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^{*}Conditions: Ketone (1.0 equiv), FeCl₃(10 mol %) in dichloroethane (0.1 M), room temperature, 1–71 h. ^{*a*}Same conditions with two modifications: FeCl₃ (100 mol %) in nitromethane (0.1 M). ^{*b*}Percent yield determined by ¹H NMR using dimethyl terephthalate as an internal standard.

Existing reports to access this structural motif often utilize Brønsted or Lewis acid catalyzed [4 + 2]-cycloaddition reactions of o-alkynyl(oxo)-benzenes 5 with alkenes 6,⁵ or isochromene acetals 8 with vinyl boronates 9 (Figure 1B).⁶ We herein present a mild and efficient strategy for the synthesis of tetrahydronaphthalenes 4 which was inspired by mechanistic insights obtained during our previous studies toward the synthesis of 3,4-dihydro-2H-pyrans 2 from aryl ketones 1 bearing α -carbonyl substituents.⁷ The corresponding α -arylated analogs of 1 exhibit divergent reactivity upon Brønsted or Lewis acid catalysis resulting in either the preferential formation of pyrans 3 or the exclusive formation of tetrahydronaphthalenes 4 depending on the choice of activation (Figure 1A). Divergent reactivity of the same substrate upon Lewis acid or Brønsted acid catalysis has recently been recognized as an attractive strategy to rapidly access molecular diversity.⁸ Subsequent mechanistic investigations aimed at the optimization of this transformation identified pyrans 3 as reactive intermediates which undergo FeCl₃-catalyzed⁹ Friedel-Crafts alkylation resulting in the exclusive formation of tetrahydronaphthalenes 4 in high yields. The strategy described herein provides a mild reaction protocol to access functionalized tetrahydronaphthalenes relying on iron as an environmentally benign metal catalyst and complements current synthetic approaches.

Following the discovery of divergent reactivity utilizing FeCl_3 , we then investigated the suitability of other Lewis acids. When aryl ketone 11 was converted using catalytic amounts of $\text{Fe}(\text{OTf})_3$, the corresponding tetrahydronaphthalene 12 was obtained in

23% yield with full conversion of the substrate (entry 1, Table 1). The use of $Bi(OTf)_3^{10}$ resulted in increased yields of 48% while catalytic quantities of GaCl₃ further improved the yield of 12 to 58% (entries 2 and 3, Table 1). Both SnCl₄ and BF₃·Et₂O resulted in the formation of tetrahydronaphthalene 12 in comparable yields of 87% while AlCl₃, a more potent Lewis acid, formed 12 in diminished yields of 73% (entries 4-6, Table 1). Catalytic amounts of FeCl₃ proved superior and gave rise to the desired tetrahydronaphthalene in 96% yield in an overall shorter reaction time of 8 h (entry 7). Furthermore, the evaluation of various solvents with FeCl₃ provided diminished reactivity, as dichloromethane, toluene, and nitromethane resulted in 68%, 83%, and 86% yield, respectively (entries 10–12, Table 1). Overall, 10 mol % of FeCl₃ in dichloroethane provided optimal reaction conditions. Importantly, orthogonal reactivity of aryl ketone 11 was observed upon treatment with 10 mol %, 100 mol %, and 500 mol % of HCl, which resulted in the exclusive formation of the corresponding pyran product (3, Figure 1A) (entries 13–15). The optimized reaction conditions for the synthesis of tetrahydronaphthalenes proved applicable to a variety of electronically differentiated aryl ketone substrates (Scheme 1). Electron-deficient aryl ketones incorporating nitro, halogen and nitrile functionalities were converted to the corresponding products 17-18 and 21-22 in yields up to 96% (Scheme 1). In comparison, electron-neutral substrates bearing phenyl (12) and biphenyl (15) groups performed equally well and formed the desired products in yields up to 96% (Scheme 1). Additionally,

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electron-rich aryl ketones bearing hydroxyl, acetate, and methoxy substitution were tolerated under the optimized reaction conditions and gave rise to the corresponding tetrahydronaphthalenes 25, 26, and 33 in up to 66% yield (Scheme 1). Thiopheneand furan-containing substrates proved viable and resulted in the formation of the desired products 19 and 23 in 64% and 56% yield, respectively. Cinnamyl-derived aryl ketones were also identified as suitable substrates for this transformation, tolerating a wide range of electron-rich and electron-deficient substituents in up to 99% yield (16, 20, 28, 29, and 34, Scheme 1). Importantly, aryl ketones bearing bromine or triflate substituents, which would enable subsequent functionalization via cross-coupling reactions, led to the desired tetrahydronaphthalene products in excellent yields of up to 98% (13 and 14, Scheme 1). Furthermore, the corresponding tetrahydronaphthalene products such as 16 undergo facile oxidation to the polyaromatic scaffold 35 in 82% yield upon treatment with DDQ (Figure 2). Notably, this sequence provides



Figure 2. Oxidation of tetrahydronaphthalene 16 to give rise to functionalized naphthalene 35.

an alternative synthetic strategy to current approaches toward functionalized naphthalenes **35** which often rely on gold-catalyzed benzannulation reactions of *o*-alkynyl(oxo)benzenes **5**.¹¹

Subsequent studies focused on the elucidation of the reaction mechanism. During our evaluation of various Lewis acids, we observed the formation of a new compound after short reaction times. However, prolonged reaction times led to the isolation of the corresponding tetrahydronaphthalenes as the sole products, suggesting the intermediacy of this compound in the reaction. Subsequent efforts focused on the isolation of this reactive intermediate, which was later identified as the corresponding pyran **36**. To validate this result, pyran **36** was prepared independently and subjected to the optimized reaction conditions (Figure 3). After



Figure 3. Evidence for intermediacy of 36. Conditions: (a) Percent yield and percent conversion determined by ¹H NMR using dimethyl terephthalate as an internal standard. (b) 36 does not form 11 or 12 under 1.0 equiv of HCl in 0.1 M DCE after 24 h.

1 h, a mixture of aryl ketone 11 and tetrahydronaphthalene 12 was observed in a 2:1 ratio, respectively, suggesting that the formation of pyran 36 is reversible under Lewis acid catalysis. This hypothesis was further validated when the reaction was quenched after 5 h, resulting in the formation of tetrahydronaphthalene 12 in 83% yield as the exclusive reaction product. Subsequent NMR experiments provided additional support for the formation of pyran 36 as a reactive intermediate (Figure 4). The distribution of starting material 11, pyran 36, and tetrahydronaphthalene product





Figure 4. (A) Monitoring conversion of aryl ketone **11** to product **12** via intermediate **36**. (B) Distribution of **11**, **12**, and **36** as determined by percent yield using ¹H NMR with dimethyl terephthalate as an internal standard. (C) Relevant sections of the ¹H NMR spectra after 0 min, 30 min, 6 h, and 7 h.

12 was monitored at different time points when ketone 11 was subjected to the optimized reaction conditions (Figure 4A,B). Within the first 2 h of the transformation, the majority of starting material 11 was consumed, and a high concentration of pyran 36 was observed. As the reaction progressed, the concentration of pyran 36 decreased as the concentration of tetrahydronaphthalene 12 increased. Figure 4C shows the changing composition of substrate 11, pyran 36 and product 12 in the reaction mixture after 0 min, 30 min, 6 h, and 7 h. Based on these mechanistic insights, we propose the following mechanism for the synthesis of tetrahydronaphthalenes (Figure 5). Activation of aryl ketone 37 upon coordination of the Lewis acid leads to initial enolization of the carbonyl to provide 38, which can subsequently protonate the alkene subunit to form carbocation 39. The resulting carbocation 39 can either be trapped with the oxygen functionality of the iron-enolate 39 to result in pyran 40 or undergo Friedel-Crafts



Figure 5. Mechanistic hypothesis for the FeCl₃-catalyzed formation of tetrahydronaphthalenes.

alkylation with the pendant aromatic moiety to from carbocation **41**. Our experimental observations suggest that under Lewis acidic conditions pyran **40** forms initially. However, the reversibility of this step ultimately leads to the formation of tetrahydronaphthalene **42** following Friedel–Crafts alkylation and rearomatization. In comparison, Brønsted acid catalysis does not mediate the desired reaction pathway and provides pyrans **40** as products.

In summary, we have developed a mild and catalytic method for the synthesis of tetrahydronaphthalenes bearing a variety of electronically distinct substituents. Mechanistic investigations suggest the role of intermediate 3,4-dihydro-2*H*-pyrans in the FeCl₃-catalyzed synthesis of tetrahydronaphthalenes. This transformation illustrates the ability of aryl ketones to be selectively converted into 3,4-dihydro-2*H*-pyran or tetrahydronaphthalene products by the use of either a Brønsted or Lewis acid catalyst.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03367.

Experimental details and spectroscopic data for all intermediates, reactants, and products (PDF)

Accession Codes

CCDC 1589086 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The authors declare no competing financial interest.

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