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Efficient Access to Methyl-1-hydroxy-2-naphthoates and Heterocyclic Analogues

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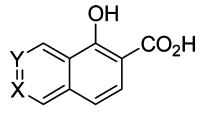
Supporting Information

ABSTRACT: We report the synthesis of methyl-1-hydroxy-2-naphthoate derivatives and heterocyclic analogues using a two-step approach. This short route employs a Heck coupling of a 2-halo-benzoate with methyl 3-butenoate followed by a Dieckmann cyclization, yielding the 1-hydroxynaphthalene-2-carboxylic acid derivatives in the multigram scale.

INTRODUCTION

Medicinal chemistry programs typically require rescaffolding and decoration of initial-hit series to improve their properties, such as biological activity, solubility, and ADME profile. To this end, a rapid and efficient synthesis of the scaffold is an important asset for the program, both as it enables a rapid exploration of the structure−activity relationship, and as a prerequisite for the rapid supply of larger quantities for the further advancement of the compounds into preclinical and clinical development. Along these lines, we investigated the efficient rescaffolding of 1-hydroxynaphthalene-2-carboxylic acid as a central scaffold of a recent CXCR2 lead series (Scheme 1).[1]

Scheme 1. Examples of Methyl-1-hydroxy-2-naphthoates and Heterocyclic Analogues



1

1a: X, Y = CH > 1000 hits
1b: X = N; Y = CH > 10 hits
1c Y = N; X = CH > 7 hits
1d X = C-F; Y = CH > 2 hits

While a simple SciFinder search for 1-hydroxynaphthalene-2-carboxylic acid itself returns more than 1000 references, the synthetic access to even simple derivatives such as halogenated derivatives is described only with multistep sequences, including the route used at Sanofi for the preparation of the first CXCR2 inhibitors.[1] The chemical community has recently risen to the surprisingly unmet challenge with efforts toward the synthesis of substituted naphthalenes[2] being the focus of several recent publications.[3,4] These efforts highlight the importance of naphthalene as a synthetic building block as well as the fact that an efficient synthetic access to many derivatives is lacking—surprising as this may be if one takes into consideration that naphthalene chemistry formed the core of many of the commodities that were the foundation of the synthetic dye industry over 150 years ago. Recent approaches to derivatives of **1** are centered on several different strategies which are dominated by C−H activation strategies.[5] We add to these recent developments by reporting a highly efficient, short access to 1-hydroxynaphthalene-2-carboxylic acid derivatives starting from readily available starting materials using simple and scalable chemistry.

RESULTS AND DISCUSSION

Synthetic approaches that begin by building up the aromatic part of the molecule promise to deliver flexible options of allowing many substitutions in the naphthalene. Following this strategy, the original access described by Sanofi[1] commenced with a Sonogashira reaction between an aryl bromide **2** and butyne-1-ol (Scheme 2). The resulting acetylene **3** was first reduced to **4** followed by a subsequent oxidation of the alcohol **4** which yielded **5**.

Intramolecular Friedel−Crafts acylation of **5** followed by carboxylation yielded tetrahydro-1-oxonaphthalene-2-carboxylate **7**. DDQ oxidation furnished the annulated salicylic acid **8** in less than 6% overall yield. This chemistry fits the purpose of allowing an initial exploration of the chemical space—nevertheless, the sequence requires multiple oxidation state adjustments and is thus inherently lengthy, time-consuming, and costly.

Our new synthetic strategy is almost trivial, albeit to the best of our knowledge not described in the literature. It consists of a Heck reaction between an ortho brominated methyl benzoate **9** and butenoate **10**, as exemplified in Scheme 3 for the preparation of **8**. Methyl-3-butenoate **10** can be obtained by standard esterification procedures from the commodity vinyl acetic acid and is available commercially.[6] The product resulting from the Heck coupling is subjected to base to induce a Dieckmann condensation resulting directly in the desired **8**. In summary, the key retrosynthetic consideration avoids the highly unproductive and unnecessary oxidation adjustment that plagues the known routes.

A screen of several reaction conditions for the Heck reaction revealed that high conversion can be achieved by using a method previously reported by Fu.[7] The product of this reaction is a complex and variable mixture of E/Z isomers of both the styrenic

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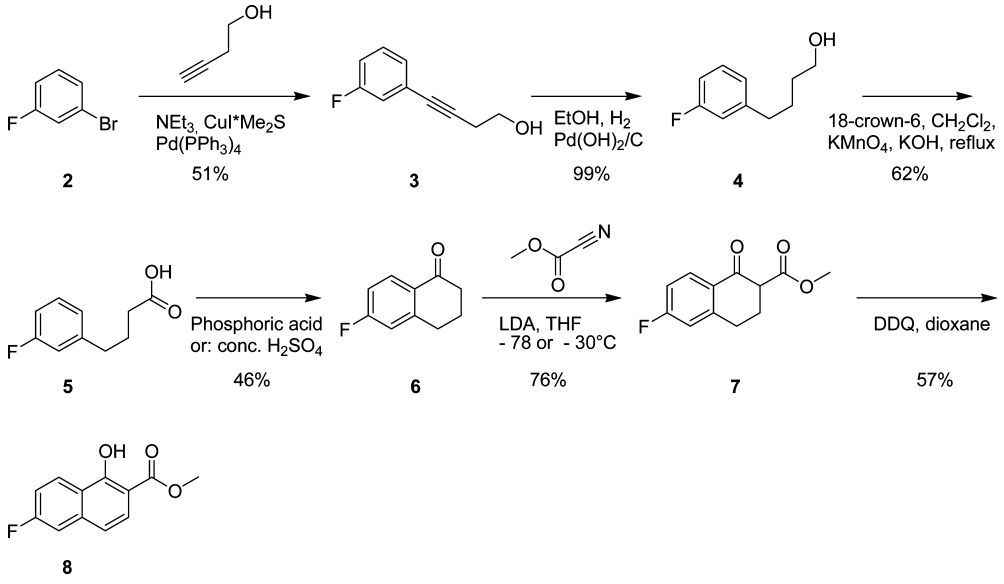
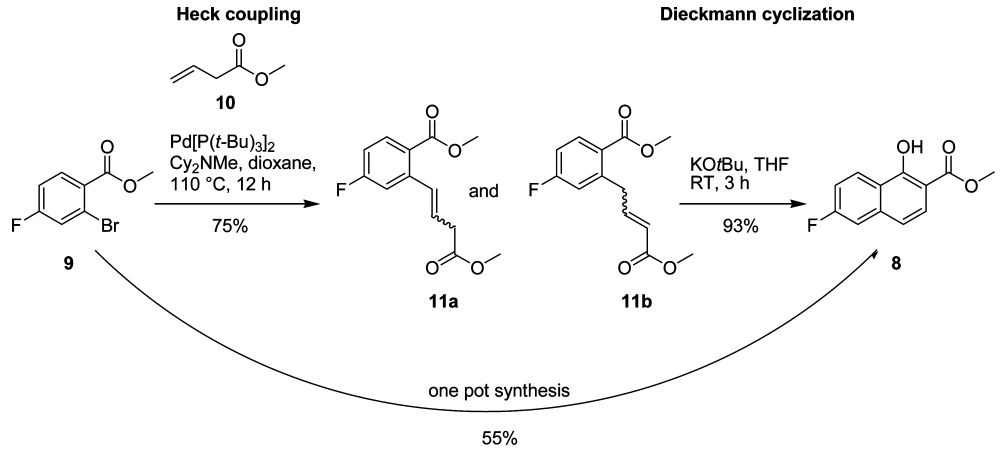
Scheme 2. Medicinal Chemistry Route to Methyl-1-hydroxy-2-naphthoate Derivatives



Scheme 3. Development of a New Route to Methyl-1-hydroxy-2-naphthoate Derivatives



11a and acrylic **11b** double bond isomers. Fortunately, this mixture is inconsequential for the following steps (vide infra), so that the Heck coupling product was not fully characterized. NMR analysis of the crude reaction product of **11a/b** shows only linear Heck product (see Supporting Information NMR of crude **11a/b**). Thus, either no isomerization of methyl 3-butenoate to methyl 2-butenoate takes place, or methyl 2-butenoate did not participate in the Heck reactions.[8]

The second synthetic step consists of a Dieckmann cyclization of the Heck product. The initial screening of mild reaction conditions combined with a simple workup indicated that sterically hindered bases such as potassium *tert*-butoxide or sodium *tert*-pentoxide result in high yields (>90% by LCMS) within 3 h in THF at room temperature.

The ease of the conditions allows for a simple scale-up to larger amounts; 50 g of compound **8** were prepared via Dieckmann cyclization of the crude Heck product. The two-step procedure produced **8** in an overall yield of 65% after recrystallization of **8**, highlighting the practicality and utility of this approach for the preparation of substituted derivatives of 1-hydroxynaphthalen-2-carboxylate.

As a further operational simplification, we decided to investigate a one-pot synthesis. In this case, the Heck reaction mixture was evaporated to remove excess methyl 3-butenoate **10**. The residue was subsequently converted via the established Dieckmann condensation using one additional equivalent of potassium *tert*-butoxide on account for the presence of the Cy_2NMe hydrobromide. The resulting **8** was obtained in a slightly lower yield and purity (55%, 90% purity).

Given the wide availability of 2-bromo benzoates and their heterocyclic relatives, it was tempting to extend the chemistry described above to further derivatives. Indeed, the reaction proved to be very versatile leading to the synthesis of several heterocyclic derivatives (Table 1).

The reaction is very general and amenable to various substitution patterns. Both naphthalene derivatives and heterocyclic analogues (**8**, **13**, **15**, **17**, **19**, and **21**) are accessible in good-to-excellent yield using the procedures previously optimized. The 16% yield of **19** is the result of the low reactivity of 2-chloro-pyridine derivatives in Heck reactions. All compounds were prepared on a multigram scale, indicating that further scale-up is expected to be possible.

■ CONCLUSIONS

In summary, the straightforward combination of a Heck reaction between **9** and **10**, followed by a Dieckmann condensation,

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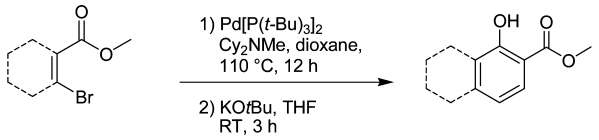
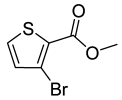
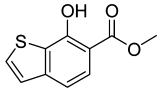
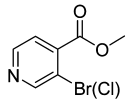
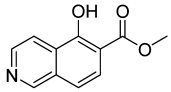
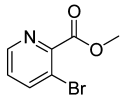
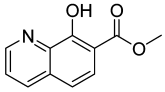
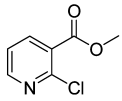
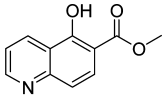
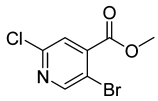
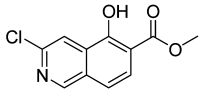
Table 1. List of Compounds Prepared



Starting material		Product		Overall yield
12		13		61%
14		15		65% from Br 62% from Cl
16		17		67%
18		19		16%
20		21		68%

constitutes a rapid access to methyl-1-hydroxy-2-naphthoate derivatives and heterocyclic analogues. The chemistry is both short and efficient, but at the same time also highly variable, thus allowing the preparation of analogues. We believe that this type of work is a good example for the importance of synthetic chemistry in the drug discovery process, enabling both a rapid access to chemical space and the preparation of larger amounts of material, enabling the full assessment of the resulting compounds as suitable drug candidates. This concept is certainly not limited to the given examples and should prove valuable for the preparation of further analogues.

EXPERIMENTAL SECTION

Synthesis of 6-Fluoro-2-(methoxycarbonyl)-1-hydroxynaphthalene (8). Methyl 2-bromo-4-fluorobenzoate **9** (81 g, 0.35 mol), methyl 3-butenoate **10** (52.2 g, 1.5 equiv, 0.52 mol), and *N,N*-dicyclohexylmethylamine (150 g, 160 mL, 2.2 equiv, 0.76 mol) were dissolved in dioxane (800 mL), and the solution was thoroughly degassed with argon. Fluoroboric acid tri-*tert*-butylphosphine adduct (0.03 equiv., 2.8 g, 10 mmol) were added, and the solution was heated to 50 °C. After 10 min tris(dibenzylideneacetone)dipalladium(0) (3.18 g, 0.01 eq., 3.48 mmol) was added, and the reaction mixture was stirred overnight at 110 °C. For workup dioxane was removed under reduced pressure, and the residue was taken up in ethyl acetate. The solution was then filtered through a small glass frit with silica gel, and the silica gel was washed with ethyl acetate. The combined organic phase was washed twice with 1 N HCl, saturated $NaHCO_3$, and water. The solvent was then removed under reduced pressure, and the residue was dried under high vacuum to yield the crude Heck product **11a/b**.

The residue was taken up in anhydrous THF (800 mL), and the solution was cooled to 5 °C. Potassium *tert*-butoxide (54 g, 485 mmol, 1.4 equiv) was added, and the solution was allowed to warm to room temperature; the stirring was continued for 2 h. For work up the reaction had been quenched/neutralized by addition of aqueous 2 N HCl (1.4 equiv). The reaction mixture was reduced in volume under reduced pressure, and the residue was taken up in ethyl acetate. The organic layer was washed twice with water. The solvent was removed under high vacuum, and the residue was crystallized from ethanol to yield **8** (50 g, 65%) as a colorless solid.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00280.

^{1}H and ^{13}C NMR spectra of compound **8**, **13**, **15**, **17**, **19**, and **21** and general procedure for the synthesis (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Knieps, S.; Dedio, J.; Heitsch, H.; Czechtizky, W.; Grueneberg, S.; Shimshock, S.; Kosley, R. W.; Lanter, C.; Li, H. Sher, R.; Weichsel, A. Fused Bicyclic Carboxamide Derivatives for uses as CXCR2 Inhibitors in the Treatment of Inflammation. WO2006069656, 2006. (b) Hachtel, S.; Dedio, J.; Shimshock, S.; Lanter, C. Inhibitors of CXCR2. WO2008000407, 2008. Hachtel, S.; Dedio, J.; Pernerstorfer, J.; Shimshock, S.; Lanter, C.; Kosley. R. W. CXCR2 Antagonists WO2008000408. 2008. (c) Hachtel, S.; Dedio, J.; Defossa, E.; Grueneberg, S.; Heitsch, H.; Bock, W.; Chen, C.; Kosley. R.; Kung, C.-Y.; Patek, M.; Sher, R.; Shimshock, S.; Weichsel, A. New CXCR2 Inhibitors. WO2008000409, 2008. (d) Hachtel, S.; Dedio, J.; Pernerstorfer, J.; Shimshock, S.; Lanter, C. CXCR2 Inhibitors.-WO2008000410, 2008.

(2) Ding, W.; Pu, J.; Zhang, C. *Synthesis* **1992**, *1992*, 635−637.

(3) Jeon, I.; Mangion, I. K. *Synlett* **2012**, *23*, 1927−1930 and references cited therein..

(4) Brenneman, J. B.; Ginn, J. D.; Lowe, M. D.; Sarko, C. R.; Tasber, E.; Zhang, Z. WO2014039434, 2014.

(5) (a) Youn, S. W.; Kim, S. B.; Jagdale, A. *J. Am. Chem. Soc.* **2012**, *134*, 11308−11311. (b) Yang, Y.; Lin, Y.; Rao, Y. *Org. Lett.* **2012**, *14*, 2874−2877. (c) Cui, L.-Q.; Dong, K. L.; Zhang, C. *Org. Lett.* **2011**, *13*, 6488−6491. (d) Huang, X.; Xue, J. *J. Org. Chem.* **2007**, *72*, 3965−3968. (e) Jiang, H.; Cheng, Y.; Zhang, Y.; Yu, S. *Org. Lett.* **2013**, *15*, 4884−4887.

(6) (a) Esteban, G.; López-Sánchez, M. A.; Martinez, M. E.; Plumet, J. *Tetrahedron* **1998**, *54*, 197−212. (b) Alcock, S. G.; Baldwin, J. E.; Bohlmann, R.; Harwood, L. M.; Seeman, J. I. *J. Org. Chem.* **1985**, *50*, 3526−3535.

(7) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989−7000.

(8) We are aware that dioxane is not an ideal solvent for large-scale work and is generally easily replaced by performing the reaction with, e.g., THF under a slight pressure, but the convenience of the high boiling point of dioxane outweighed the disadvantages for this stage of development.

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