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Unexpected results of a SNAr-reaction. A novel synthetic approach to 1-arylthio-2-naphthols

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Unexpected result of a $S_{N,Ar}$-reaction. A novel synthetic approach to 1-phenylthio-2-hydroxy substituted naphthalenes

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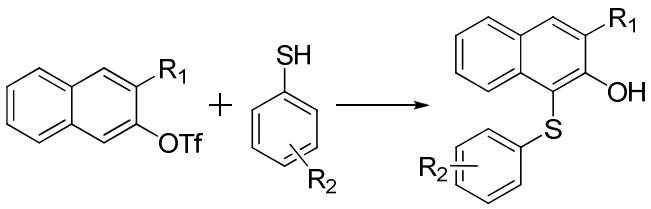
ABSTRACT



1-Phenylthio-2-hydroxy-3-heterocycle substituted naphthalenes were obtained as an unexpected result of a nucleophilic aromatic substitution reaction of 3-(pyridine-3-yl)naphthalene-2-yl trifluoromethanesulfonate with thiophenol. The molecules thus obtained might serve as a new class of inhibitors for cytochrome P450 enzymes and other target classes. Therefore, the scope of the new reaction procedure was examined. The reaction protocol could be applied successfully to various substituted thiophenols.

Cytochrome P450 (CYP) enzymes are a large family of heme-containing enzymes that are present in nearly all forms of life (animals, plants, fungi and bacteria). Most of them act as monooxygenases, catalyzing a variety of reactions such as hydroxylations, epoxidations, *N*- and *O*-dealkylations, and *S*-oxidations. Some CYPs are responsible for the metabolism of xenobiotics. Thus they are able to oxidize different substrates. Other CYPs only convert specific substrates. They catalyze certain steps in the synthesis of secondary metabolites (e.g. in plants), and in the biosynthesis and metabolism of sterols, steroid hormones, and other lipid biomolecules (e.g. in mammals).[1]

Selective inhibition of a single CYP enzyme is a therapeutical option for different diseases as well as a possible mechanism for herbicides or fungicides to block plant or fungi growth. A design concept for non steroidal reversible CYP inhibitors consists of a heterocycle containing a sp^2-hybridized nitrogen, being able to coordinate to the prosthetic heme iron in the active site of the enzyme. The heterocycle is linked to a rather apolar core structure comprising one or more aromatic rings.

In the last years, such inhibitors were developed for different CYP enzymes. Examples are aromatase (CYP19)[2] and CYP17[3] inhibitors for the treatment of breast and prostate cancer, respectively, inhibitors of

aldosterone synthase (CYP11B2)[4,5] which had been proposed as a target for the treatment of several cardiovascular diseases[6] and inhibitors of cortisol synthase (CYP11B1),[7] a target for Cushing's syndrome and metabolic diseases.

In 2008, 3-benzylated 2-pyridylnaphthalenes were also described as inhibitors of human CYP11B2.[4] For further optimization of this compound class, a bioisosteric replacement of the linker Y by a sulfanyl-, sulfinyl- or sulfonyl-bridge X was intended (figure 1).

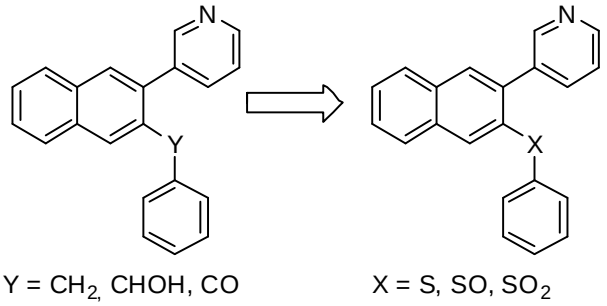
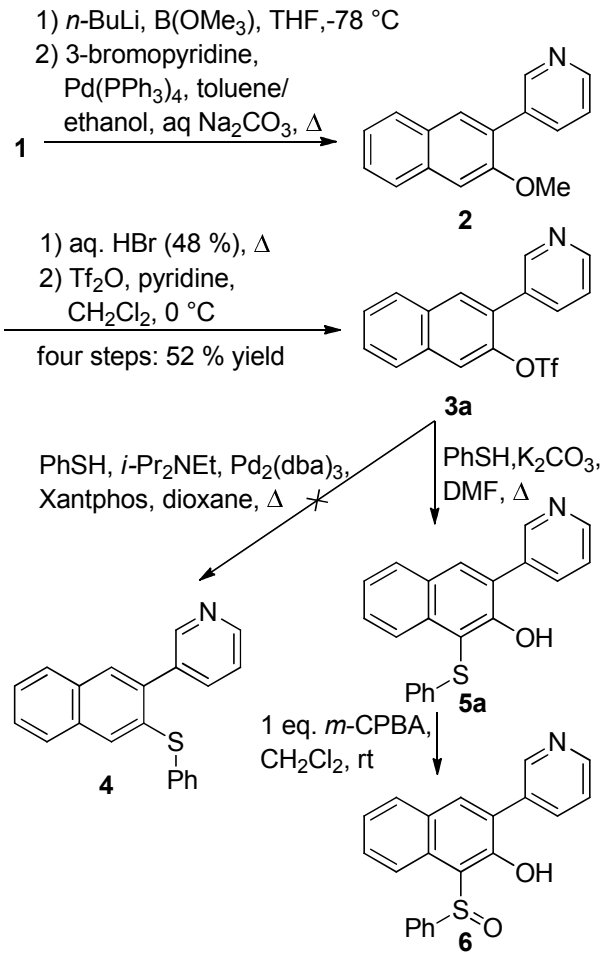


Figure 1. Planned bioisosteric replacement

The synthetic route shown in scheme 1 was designed for phenylthio compounds, e.g. **4**. In the first step, 2-methoxynaphthalene **1** is transformed into the boronic acid via *ortho*-lithiation[8] and subsequently converted into 3-(3-methoxynaphthalen-2-yl)-pyridine **2** via a *Suzuki* cross coupling reaction with 3-bromopyridine as previously described.[9] Cleavage of the methyl ether by refluxing in aqueous hydrobromic acid and reaction of the resulting alcohol with triflate anhydride yields triflate **3a**.[4] In the next step the triflate moiety should be substituted by thiophenol using the conditions for a palladium catalyzed cross coupling reaction of aryl triflates with thiols described by Itoh and Mase.[10] In this publication, aryl triflates should be refluxed with thiophenol in 1,4-dioxane in the presence of 2.5 mol% $Pd_2(dba)_3$, 5 mol% Xantphos, and 2 equivalents of DIPEA. Subsequent oxidation with one or two equivalents *m*-CPBA should yield the corresponding sulfinyl and sulfonyl derivatives.

Triflate **3a** was obtained as described above in four steps in 52 % overall yield. The next step, i.e. the palladium catalyzed nucleophilic substitution reaction of **3a** with thiophenol using the described reaction conditions,[10] unexpectedly yielded mainly unreacted starting material after 24 h. Changing the reaction conditions to "classical" nucleophilic aromatic substitution conditions, i.e. omission of catalyst, change of solvent from 1,4-dioxane to DMF and replacement of DIPEA by a carbonate base such as Cs_2CO_3 or K_2CO_3, resulted in a new product **5a**. ESI-MS showed a mass (*m/z*) of 329.94 $[M + H]^+$ which was not consistent with the calculated mass of substitution product **4** of 314.42 $[M + H]^+$. Oxidation with one equivalent of *m*-CPBA yielded product **6** exhibiting a mass of 346.01 $[M + H]^+$.

Scheme 1. Synthetic route



Determination of the structures by X-ray diffraction revealed that the trifluoromethanesulfonyl group was cleaved and the hydrogen *ortho* to the trifluoromethane-sulfonyl group was displaced by the phenylthio moiety: 1-(phenylthio)-3-(pyridin-3-yl)naphthalen-2-ol **5a** (figure 2) and 1-(phenylsulfinyl)-3-(pyridin-3-yl)-naphthalen-2-ol **6** (figure 3) were obtained.

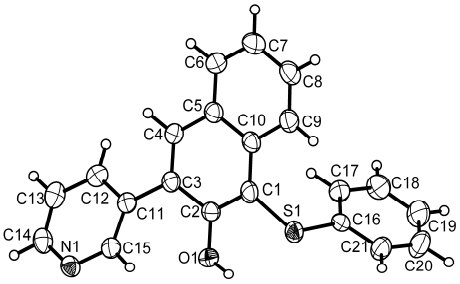


Figure 2. X-ray structure of compound **5a**.

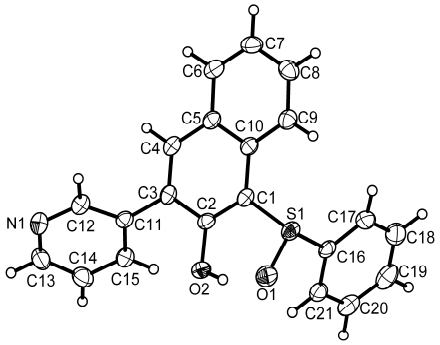
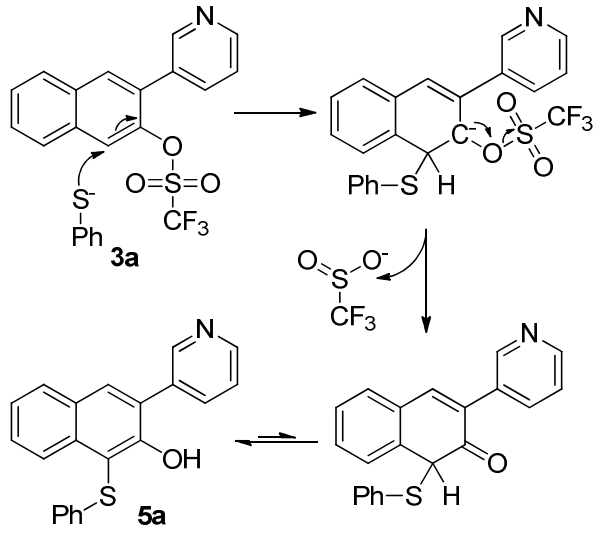


Figure 3. X-ray structure of compound **6**.

In the literature, only few examples of similar but not exactly the same 1-phenylthio-2-hydroxy-3-aryl-substituted naphthalenes or related compounds could be found. For example, Tsukamoto and Kondo reported on 3,4-bis(4-methoxyphenyl)-1-(*p*-tolylsulfinyl)naphthalen-2-ol prepared by a palladium-catalyzed annelation[11] and Xu and Moore described 3-methoxy-2-phenyl-4-(phenylthio)naphthalen-1-ol synthesized by a thermolytic rearrangement of a cyclobutenone.[12]

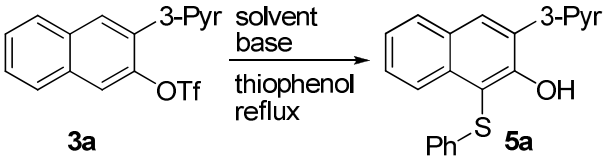
A hypothetical mechanism for this untypical nucleophilic substitution reaction is depicted in scheme 2. Reaction of thiophenol with carbonate generates thiophenolate which could be added *ortho* to the triflate. Subsequently, trifluoromethanesulfinate could be eliminated yielding a ketone, which is converted by rearomatization to the phenolic product observed in the crystal structure due to the tautomeric equilibrium.

Scheme 2. Proposed mechanism for the addition of thiophenol to triflate **3a**



Before starting an extensive synthetic program and screening this new compound class for biological activity, the reaction conditions were optimized (Table 1). The optimal reaction conditions found utilize sodium hydride as base and DMF as solvent. For a more convenient procedure in most of the following reactions, potassium carbonate was used.

Table 1. Optimization of reaction conditions.[a]



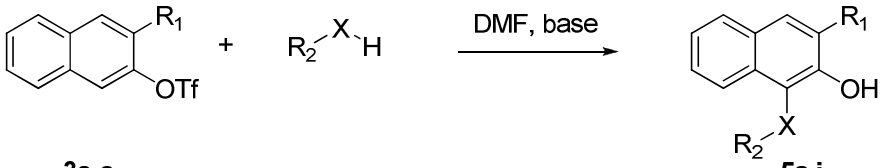
entry	base	Solvent	yield (%)[b]
1	K_2CO_3	DMF	73
2	NaH	DMF	79
3	K_3PO_4	DMF	22
4	NEt_3	DMF	0[c]
5	NaH	DMSO	22
6	NaH	THF	0[c]
7	NaH	1,4-dioxane	0[c]

[a] Conditions: 0.5 mmol base, 0.3 mmol thiophenol, 0.25 mmol **3a**, 2 ml solvent, 100 °C, 1 h. [b] Yields after purification by flash-chromatography on silica gel (0.5 % methanol in CH_2Cl_2), LC > 95 %. [c] No product was detectable by TLC and LC-MS (ESI).

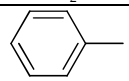
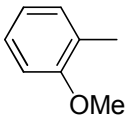
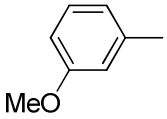
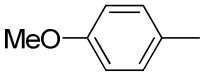
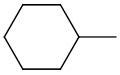
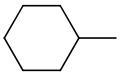
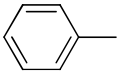
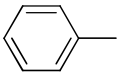
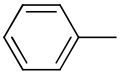
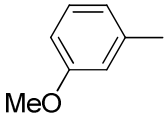
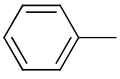
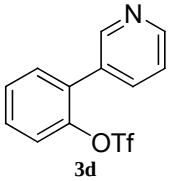
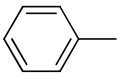
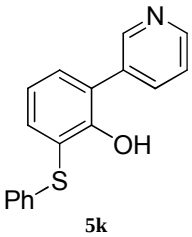
In the next step the scope of the substitution reaction was explored with regard to potential nucleophiles as well as structurally different variants of the former used triflate **3a** (Table 2). For methoxy-substituted thiophenols (entries 2-4) the conversion proceeded in moderate yields (34-62 %). Using cyclohexanethiol as example for an aliphatic thiol (entry 5) only hydrolysis of the triflate was observed, thus 3-(pyridin-3-yl)naphthalen-2-ol was obtained in 72 % yield. The use of sodium hydride instead of carbonate as base did not yield the desired product **5e**, either (entry 6). Coupling reactions with other

nucleophiles, i.e. phenol or aniline, were not successful. This leads to the assumption, that the reaction scope excludes “harder” nucleophiles than thiophenol. The introduction of an isoquinoline moiety instead of a pyridine did not affect the reaction. In the examples, acceptable yields (entry 9: 64 % and entry 10: 71 %) were obtained. An interesting observation was that a substitution of the naphthalene core in 3-position was not necessary and that the reaction proceeded smoothly for 2-naphthyl triflate **3c** yielding the *o*-hydroxyl substituted coupling product **5j** (entry 11) thus providing a new synthetic access to this type of compounds. A limitation of the reaction scope is shown by entry 12. No product was obtained in case of phenyl triflate **3d**, thus the annulated ring system (i.e. naphthalene) seems to be mandatory for the reaction.

Table 2. Investigation of the reaction scope.[a]



3a-c **5a-j**

entry	triflate	R_1	R_2	X	base	product	yield (%)[b]
1	**3a**	3-pyridine		S	K_2CO_3	**5a**	73
2	**3a**	3-pyridine		S	K_2CO_3	**5b**	34
3	**3a**	3-pyridine		S	K_2CO_3	**5c**	42
4	**3a**	3-pyridine		S	K_2CO_3	**5d**	62
5	**3a**	3-pyridine		S	K_2CO_3	**5e**	0[c]
6	**3a**	3-pyridine		S	NaH	**5e**	0[d]
7	**3a**	3-pyridine		O	NaH	**5f**	0[d]
8	**3a**	3-pyridine		NH	NaH	**5g**	0[d]
9	**3b**	4-isoquinoline		S	K_2CO_3	**5h**	64
10	**3b**	4-isoquinoline		S	K_2CO_3	**5i**	71
11	**3c**	H		S	NaH	**5j**	58
12	 **3d**			S	NaH	 **5k**	0[d]

[a] Reactions were carried out with 1 equivalent of triflate **3a-d**, 2 equivalents of base and 1.2 equivalents of nucleophile in DMF at 100 °C for 0.5-3 h. [b] Yield of isolated pure (LC > 95 %) material. [c] 3-(Pyridin-3-yl)naphthalen-2-ol was isolated in 72 % yield. [d] No product (LC < 5 %) was detectable by TLC and LC-MS (ESI).

In summary, we discovered a simple reaction pathway to synthesize *ortho*-hydroxyl substituted 1-(phenylthio)-naphthalenes and trisubstituted 1-phenylthio-2-hydroxy-3-hetrocycle substituted naphthalenes.

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Supporting Information Available: Experimental details and characterization data for all compounds. X-ray crystallographic data for **5a** and **6** and copies of ^{1}H NMR and ^{13}C NMR spectra for **3b**, **5a**-**5d**, and **5h**-**5j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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References

(1) (a) Omura, T. Biochem. *Biophys. Res. Commun.* **1999**, *3*, 690. (b) Estabrook, R. W. *Drug Metab. Dispos.* **2003**, *12*, 1461.

(2) (a) Le Borgne, M.; Marchand, P.; Duflos, M.; Delevoye-Seiller, B.; Piessard-Robert, S.; Baut, G. L.; Hartmann, R. W.; Palzer, M. *Arch. Pharm. (Weinheim)* **1997**, *5*, 141. (b) Gobbi, S.; Cavalli, A.; Rampa, A.; Belluti, F.; Piazzi, L.; Paluszcak, A.; Hartmann, R. W.; Recanatini, M.; Bisi, A. *J. Med. Chem.* **2006**, *15*, 4777.

(3) (a) Hille, U. E.; Hu, Q.; Vock, C.; Negri, M.; Bartels, M.; Müller-Vieira, U.; Lauterbach, T.; Hartmann, R. W. *Eur. J. Med. Chem.* **2009**, *7*, 2765. (b) Hutschenreuter, T. U.; Ehmer, P. B.; Hartmann, R. W. *J. Enzyme Inhib. Med. Chem.* **2004**, *1*, 17.

(4) Lucas, S.; Heim, R.; Negri, M.; Antes, I.; Ries, C.; Schewe, K. E.; Bisi, A.; Gobbi, S.; Hartmann, R. W. *J. Med. Chem.* **2008**, *19*, 6138.

(5) Lucas, S.; Heim, R.; Ries, C.; Schewe, K. E.; Birk, B.; Hartmann, R. W. *J. Med. Chem.* **2008**, *24*, 8077.

(6) (a) Ehmer, P. B.; Bureik, M.; Bernhardt, R.; Müller, U.; Hartmann, R. W. *J. Steroid Biochem. Mol. Biol.* **2002**, *2*, 173. (b) Hartmann, R. W.; Müller, U.; Ehmer, P. B. *Eur. J. Med. Chem.* **2003**, *4*, 363.

(7) Hille, U. E.; Zimmer, C.; Vock, C. A.; Hartmann, R. W. *ACS Med. Chem. Lett.* **2010**, *in press*.

(8) Chowdhury, S.; Georghiou, P. E. *J. Org. Chem.* **2002**, *19*, 6808.

(9) Voets, M.; Antes, I.; Scherer, C.; Müller-Vieira, U.; Biemel, K.; Barassin, C.; Marchais-Oberwinkler, S.; Hartmann, R. W. *J. Med. Chem.* **2005**, *21*, 6632.

(10) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *24*, 4587.

(11) Tsukamoto, H.; Kondo, Y. *Org. Lett.* **2007**, *21*, 4227.

(12) Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1989**, *17*, 4024.