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Unexpected results of a S_{NAr}-reaction. A novel synthetic approach to 1-arylthio-2-naphthols

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ABSTRACT

1-(Phenylthio)-3-(pyridin-3-yl)-2-naphthol was obtained as an unexpected result of a nucleophilic aromatic substitution reaction of 3-(pyridine-3-yl)naphthalene-2-yl trifluoromethanesulfonate with thiophenol. This observation led to the discovery of an easy to handle method to synthesize 1-arylthio-2-naphthols. It has been revealed that electron withdrawing groups on the aryl thiol promoted the yields and heterocycle substituents at the 3-position of the naphthalene core are tolerable by the reaction. This reaction can thus serve as a corner stone in the structural diversification of 3-heterocycle substituted 1-arylthio-2-naphthols as potential inhibitors of cytochrome P450.

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 an 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 non-polar 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 cancers, respectively. Inhibitors of aldosterone synthase (CYP11B2)[4] and inhibitors of cortisol synthase (CYP11B1)[5] have also been proposed as treatments for several cardiovascular diseases and Cushing's syndrome, respectively.

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

A synthetic route (Scheme 1) was therefore designed for phenylthio-compounds, for example, **4**, which can be further oxidized to other desired products. Firstly, 2-methoxynaphthalene **1** was transformed into the boronic acid via ortho-lithiation[6] and subsequently converted into 3-(3-methoxynaphthalen-2-yl)-pyridine **2** via a Suzuki cross coupling reaction with 3-bromopyridine. After the cleavage of the methyl ether by refluxing in aqueous hydrobromic acid, the resulting alcohol was reacted with triflic anhydride to give **3a** with an overall yield of 52% (four steps). Subsequently, this triflate was supposed to be replaced by thiophenol after refluxing in 1,4-dioxane in the presence of 2.5 mol % $Pd_2(dba)_3$, 5 mol % Xantphos, and 2 equiv of DIPEA as described by Itoh and Mase.[7] However, only unreacted **3a** was recovered after 24 h. Changing the reaction conditions to those of 'classical' nucleophilic aromatic

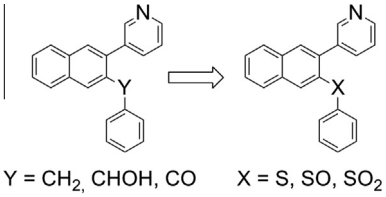

Chart 1. Planned bioisosteric replacement.

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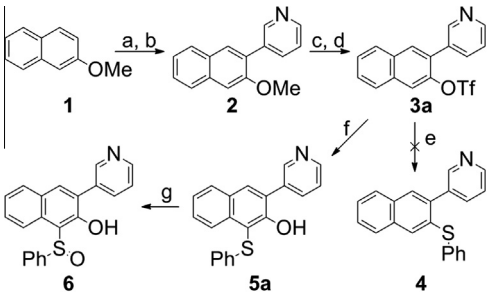


Scheme 1. Reagents and conditions: (a) *n*-BuLi, $B(OMe_3)$, THF, −78 °C; (b) 3-Bromopyridine, $Pd(PPh_3)_4$, toluene/ethanol, aq Na_2CO_3, 90 °C; (c) aq HBr (48%), reflux; (d) Tf_2O, pyridine, DCM, 0 °C; (e) PhSH, *i*-Pr_2NEt, $Pd_2(dba)_3$, Xantphos, dioxane, reflux; (f) PhSH, K_2CO_3, DMF, 100 °C; (g) *m*-CPBA, DCM, rt.

substitution, that is, omission of catalyst, change of solvent from 1,4-dioxane to DMF and replacement of DIPEA by 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** (314.42 $[M+H]^+$). Oxidation with one equivalent of *m*-CPBA yielded product **6** exhibiting a mass of 346.01 $[M+H]^+$. The structures of these two compounds were determined by X-ray diffraction[8] with crystals obtained from dichloromethane. It turned out that the trifluoromethanesulfonyl group was cleaved to expose the phenol group, while the aromatic proton ortho to the trifluoromethanesulfonyl group was displaced by the phenylthio moiety. Other than the desired phenylthio-analogue, compound **5a** (Fig. 1) turns out to be 1-(phenyl-thio)-3-(pyridin-3-yl)-2-naphthol and compound **6** (Fig. 2) is actually 1-(phenylsulfinyl)-3-(pyridin-3-yl)-2-naphthol. Although the compounds are different from the originally designed inhibitors, compound **6** showed potent inhibition of human CYP11B2 with an IC_{50} value of 33 nM, which is in the range of the lead compounds' activity.

This interesting unexpected S_{NAr}-reaction provides a novel synthetic approach to 1-arylthio-2-naphthols. Since the reported methods to synthesize this class of compounds either employed expensive catalyst $VO(acac)_2$[9a] or involved complicated photochemistry,[9b] our approach is apparently cheaper and easier to handle. More importantly, this approach and the route shown in Scheme 1 are suitable for the synthesis of 3-aryl substituted 1-phenylthio-2-naphthols, which are rarely reported. The only example in the literature, to the best of our knowledge, is 3,4-bis(4-methoxyphenyl)-1-(*p*-tolylsulfinyl)-2-naphthol[10] prepared via a palladium-catalyzed annulation, which is obviously not feasible for structural diversification.

Encouraged by these advantages, we further optimized the reaction conditions and investigated the reaction scope[11] before initiating an extensive synthetic program and subsequent screening of this new compound class for biological activity. Various bases (including K_2CO_3, NaH, K_3PO_4, and Et_3N) and different solvents (e.g., DMF, DMSO, THF, and 1,4-dioxane) were employed to

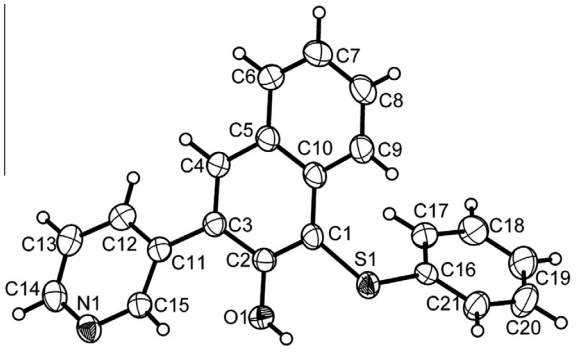


Figure 1. X-ray structure of compound **5a**.

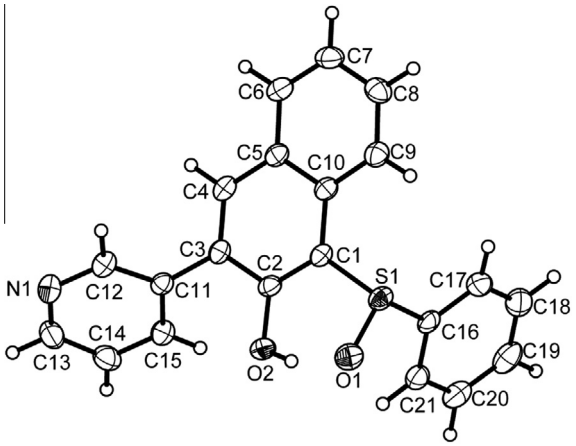


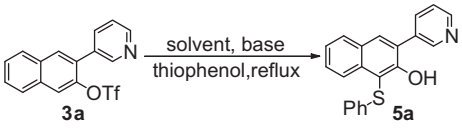
Figure 2. X-ray structure of compound **6**.

explore the influence on the conversion of **3a**–**5a** (Table 1). It turned out that the use of Et_3N, THF, and 1,4-dioxane did not achieve the reaction, whereas K_3PO_4 in DMF or NaH in DMSO led to low yields (22%). In contrast, K_2CO_3 or NaH in DMF gave similar high yields (73–79%).

Furthermore, triflate **3a** was treated with various thiophenols in the presence of K_2CO_3 in DMF (Table 2). Both thiophenols with electron donating (OMe, entries 2–4) and electron withdrawing groups (CF_3, entries 5–7) resulted in the desired products. Nevertheless, CF_3 analogues generally presented higher yields (around 85%) compared to the OMe ones (yields ranging from 34% to 62%). Thiophene-2-thiol, in contrast, only gave a modest yield of 34%. Employment of aliphatic thiols (cyclohexanethiol, entries 9 and 10) or other nucleophiles, such as phenol (entry 11) and aniline (entry12) did not yield the desired products. Replacement of the substituent at the 3-position of the naphthalene core (3-pyridyl) by a bulkier 4-isoquinolinyl (**3b**, entry 13) or removal of it to H (**3c**, entry 15) gave similar yields of around 60% when reacted with thiophenol. 4-Isoquinolinyl triflate **3b** even showed a higher yield of 71% (entry 14) compared to 3-pyridyl triflate **3a** (42%, entry 3) when treated with 3-methoxybenzenethiol. However, after the triflate core was altered to benzene, no reaction occurred (entry 16). Moreover, using mesylates instead of the corresponding triflates was also attempted, however, this procedure did not yield the desired products.

A hypothetical mechanism for this atypical nucleophilic substitution reaction is proposed in Scheme 2. Thiophenol was first

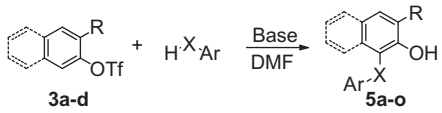
Table 1
Optimization of reaction conditions[a]



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]

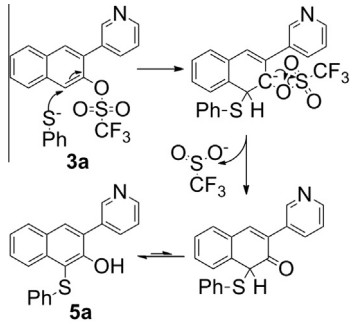
[a] Conditions: 0.5 mmol base, 0.3 mmol thiophenol, 0.25 mmol **3a**, 2 ml solvent, 100 °C, 1 h.
[b] Yields after purification by flash-chromatography on silica gel (0.5% methanol in DCM), purity >95%.
[c] No product was detected by TLC and LC–MS (ESI).

Table 2
Investigation of the reaction scope[a]



Entry	Triflate	Core	R	Ar	X	Base	Product	Yield[b] (%)
1	**3a**	Naphthalene	3-Pyridyl	Ph	S	K_2CO_3	**5a**	73
2	**3a**	Naphthalene	3-Pyridyl	2-OMe-Ph	S	K_2CO_3	**5b**	34
3	**3a**	Naphthalene	3-Pyridyl	3-OMe-Ph	S	K_2CO_3	**5c**	42
4	**3a**	Naphthalene	3-Pyridyl	4-OMe-Ph	S	K_2CO_3	**5d**	62
5	**3a**	Naphthalene	3-Pyridyl	2-CF_3-Ph	S	K_2CO_3	**5e**	83
6	**3a**	Naphthalene	3-Pyridyl	3-CF_3-Ph	S	K_2CO_3	**5f**	82
7	**3a**	Naphthalene	3-Pyridyl	4-CF_3-Ph	S	K_2CO_3	**5g**	85
8	**3a**	Naphthalene	3-Pyridyl	2-Thienyl	S	K_2CO_3	**5h**	34
9	**3a**	Naphthalene	3-Pyridyl	*c*-Hexyl	S	K_2CO_3	**5i**	0[c]
10	**3a**	Naphthalene	3-Pyridyl	*c*-Hexyl	S	NaH	**5i**	0[d]
11	**3a**	Naphthalene	3-Pyridyl	Ph	O	NaH	**5j**	0[d]
12	**3a**	Naphthalene	3-Pyridyl	Ph	NH	NaH	**5k**	0[d]
13	**3b**	Naphthalene	4-Isoquinolinyl	Ph	S	K_2CO_3	**5l**	64
14	**3b**	Naphthalene	4-Isoquinolinyl	3-OMe-Ph	S	K_2CO_3	**5m**	71
15	**3c**	Naphthalene	H	Ph	S	NaH	**5n**	58
16	**3d**	Benzene	3-Pyridyl	Ph	S	NaH	**5o**	0[d]

[a] Reactions were carried out with triflate (1 equiv), base (2 equiv), and nucleophile (1.2 equiv) in DMF at 100 °C for 0.5–3 h.
[b] Yield of isolated products (purity >95%).
[c] 3-(Pyridin-3-yl)-2-naphthol was isolated in 72% yield.
[d] No product was detected by TLC and LC–MS (ESI).



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

deprotonated by the base before the nucleophilic attack to the *ortho*-position of the triflate. Subsequently, trifluoromethanesulfinate was eliminated yielding a ketone, which was converted into the phenolic compound via rearomatization due to the tautomeric equilibrium.

In conclusion, an easy to handle method to synthesize 1-arylthio-2-naphthols via the nucleophilic substitution of aryl thiol to 2-naphthol triflate was discovered. This method facilitated the preparation of 3-heterocycle substituted 1-arylthio-2-naphthols, which are potential CYP11B2 inhibitors.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.111.

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8. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 936616–936617. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.Uk.
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11. *Procedure A:* (Used for all reactions in Table 1, and entries 10–12, 15 and 16 in Table 2) The utilized base (0.5 mmol, 2 equiv) was suspended in 1 ml solvent under an atmosphere of nitrogen. Nucleophile (0.3 mmol, 1.2 equiv) and triflate (0.25 mmol, 1 equiv) dissolved in 1 ml solvent were added. The mixture was stirred at 100 °C for 1 h before cooling to rt. Subsequently it was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and the solvents were removed under reduced pressure. The products were obtained by flash chromatography on silica gel (CH_2Cl_2/methanol 99.5:0.5).

Procedure B: (Used for entries 2–9, 13 and 14 in Table 2) Dry potassium carbonate (2 equiv) and the corresponding thiol (1.2 equiv) were added to a solution of triflate (1 equiv) in dry DMF under an atmosphere of nitrogen. The mixture was stirred at 100 °C for 0.5–3 h and subsequently cooled to room temperature before water was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ before the solvents were removed under reduced pressure. The products were obtained after purification by flash chromatography on silica gel (petroleum ether/ethyl acetate or CH_2Cl_2/methanol mixtures).