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Synthesis of 1-aryl-tetralins and 4-aryl-benzopyrans by sulfoxide-mediated benzylic carbocation cyclizations

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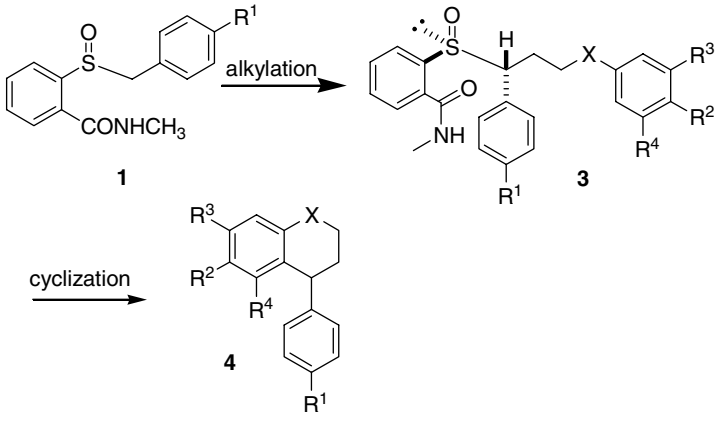
Abstract—An alkylation/cyclization sequence, with both steps mediated by the *ortho*-*N*-methylformamido-phenylsulfinyl function, provided two new C–C bonds and an efficient entry to 1-aryl-tetralins and 4-aryl-benzopyrans. Scope and limits of the process have been studied in detail.

Both aryl-tetralin[1] and benzopyran[2] structural frameworks are widespread in bioactive and natural molecules, such as aryltetralin lignanes, thus representing important synthetic targets. A major challenge is represented by the development of methods suitable for the synthesis of a wide range of differently substituted tetralin and benzopyran skeletons, in order to make available libraries of compounds.[3] We now describe a versatile two-step approach to the title structures, in which a properly functionalized sulfoxide **3** (Scheme 1), obtained by α-carbon alkylation of a benzyl sulfoxide **1**, is used for the generation of a benzyl carbocation intermediate, undergoing cyclization to form a new six-membered ring **4**.

A search in the literature revealed a surprising lack of precedents on the use of similar sulfoxide-based approaches to the target structures.[4]

Recently,[5] we have demonstrated the usefulness of an arylsulfoxide reagent **1a** (Scheme 2) bearing an *ortho*-*N*-methylformamide function for the two-step synthesis (alkylation/Pummerer reaction) of secondary benzyl carbinols and chlorides. We therefore decided to investigate



Scheme 1. Planned synthetic strategy.

Keywords: Sulfoxides; Carbocations; Cyclizations; Alkylations.
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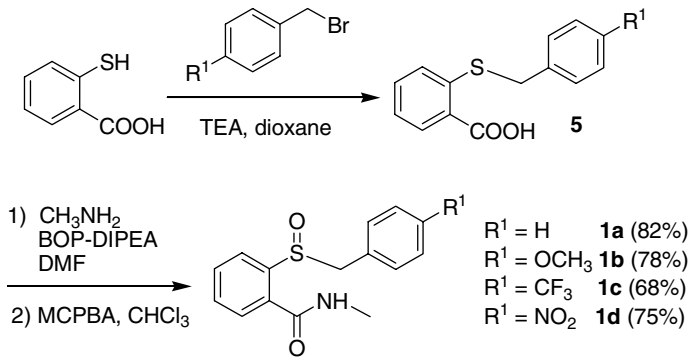
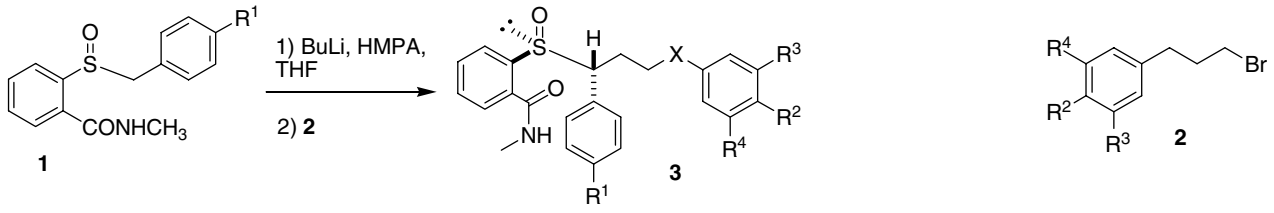


Scheme 2. Synthesis of sulfoxides **1a–d** (in brackets the overall isolated yields).

the suitability of reagents **1a–d** for the synthesis of the target structures.

The preparation of racemic sulfoxides **1** (Scheme 2) started with S-alkylation of thiosalicylic acid by benzyl bromides, affording the *ortho*-carboxy sulfides **5**, which were transformed into the corresponding amides by coupling with CH_3NH_2, and oxidized with MCPBA to **1a–d** in good overall isolated yields.

The 1-Br-3-arylpropyl substrates **2** (see Scheme 3 and Table 1) were either commercially available (**2a**,**b**,**h**) or prepared according to known methodologies.[6,7]



Scheme 3. Alkylation of racemic **1**.

Table 1. Alkylation of lithiated racemic **1a–d** with **2a–h**

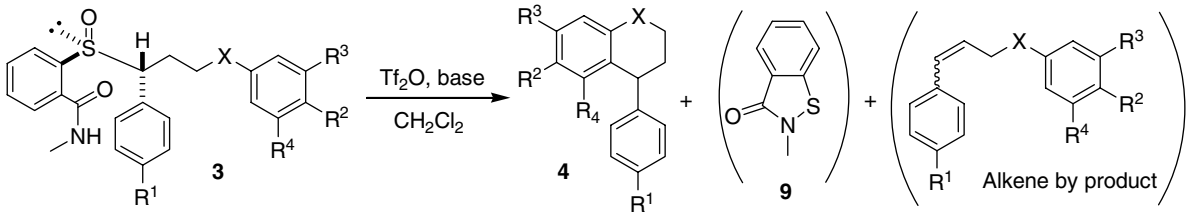
Entry	Substrate	1-Br-3-Aryl derivatives	Product	R^1	R^2	R^3	R^4	X	dr	Yield (%)
1	**1a**	**2a**	**3a**	H	H	H	H	CH_2	93:7	74
2	**1a**	**2a**	**3a**	H	H	H	H	CH_2	93:7	88[a]
3	**1a**	**2b**	**3b**	H	H	H	H	O	88:12	60
4	**1a**	**2c**	**3c**	H	OCH_3	H	H	CH_2	97:3	85
5	**1a**	**2d**	**3d**	H	OCH_3	Cl	H	CH_2	99:1	94
6	**1a**	**2e**	**3e**	H	OCH_3	OCH_3	OCH_3	CH_2	>98:2	65
7	**1a**	**2f**	**3f**	H	H	Br	H	CH_2	—	n.d.[b]
8	**1a**	**2g**	**3g**	H	CN	H	H	CH_2	>98:2	95
9	**1b**	**2a**	**3h**	OCH_3	H	H	H	CH_2	93:7	78
10	**1b**	**2a**	**3h**	OCH_3	H	H	H	CH_2	89:11	83[a]
11	**1b**	**2b**	**3i**	OCH_3	H	H	H	O	85:15	85
12	**1b**	**2d**	**3j**	OCH_3	OCH_3	Cl	H	CH_2	90:10	90
13	**1b**	**2e**	**3l**	OCH_3	OCH_3	OCH_3	OCH_3	CH_2	98:2	88
14	**1c**	**2a**	**3m**	CF_3	H	H	H	CH_2	89:11	51[c]
15	**1c**	**2a**	**3m**	CF_3	H	H	H	CH_2	29:71	65[d]
16	**1c**	**2c**	**3n**	CF_3	OCH_3	H	H	CH_2	98:2	45[c]
17	**1c**	**2c**	**3n**	CF_3	OCH_3	H	H	CH_2	42:58	77[d]
18	**1c**	**2c**	**3n**	CF_3	OCH_3	H	H	CH_2	95:5	51[c]
19	**1c**	**2d**	**3o**	CF_3	OCH_3	Cl	H	CH_2	64:46	79[d]
20	**1d**	**2a**	**3p**	NO_2	H	H	H	CH_2	—	n.d.[b]
21	**1a**	**2h**	**3q**	H	H	H	H	C=O	—	n.r.[e]

[a] Reactions performed at −30 °C.
[b] Not determined: a complex mixture of products and starting material was obtained.
[c] Reactions stopped after 2 h (−70 °C → −20 °C).
[d] Reactions stopped after 330 min (−70 °C → rt).
[e] No reaction: deprotonation in α to the carbonyl is faster than substitution.

The C–C bond-forming reaction of lithiated sulfoxides **1a–d** with bromides **2a–g** took place in good to excellent yields (Scheme 3 and Table 1), with few exceptions. In the optimized protocol, treatment of benzyl sulfoxide **1a** with 2.1 equiv of *n*-BuLi, in the presence of 5 equiv of HMPA (THF, −78 °C), followed by addition of alkyl bromides **2a–g** afforded the products **3a–g** with good to excellent yields and high diastereoselectivity.[8]

All the reactions occurred with nearly complete site-selectivity in favor of the C-alkylation. The stereochemistry of the main diastereomers was confidentially assigned on the basis of a previous study on the C-alkylation of **1a**.[4] Benzyl sulfoxide **1a** afforded very good yields of the α-alkyl products **3a–g** (entries 1–8), except for the *m*-Br-derivative **3f** (entry 7), owing to the unexpected formation of complex reaction mixtures. Furthermore, no reaction was observed with the β-Br ketone **2h** (entry 21), because α-deprotonation of the carbonyl group was faster than the C–C bond forming. Excellent results, both in terms of yields and diastereoselectivity, were obtained with the electron rich, and therefore highly nucleophilic, α-lithiated *p*-MeO-Bn sulfoxide **1b** (entries 9–13), and good results were achieved even with the electron poor *p*-CF_3-benzyl sulfoxide **1c** (entries 14–19), whereas the nitro sulfoxide **1d** (entry 20) produced a complex reaction mixture. It is worth noting that performance of the reactions at higher temperatures (−30 to −20 °C) led to higher yields (entries 10, 14, 16, and 18), but also to partial epimerization of the products, which became very relevant with the *p*-CF_3 substrate **1c** at rt (entries 15, 17, and 19).[9]

The cyclization step (Scheme 4 and Table 2) was performed by treatment of sulfoxides **3a–o** with triflic anhydride in DCM, in the presence of a base, preferably 3 equiv of TMP or 1.5 equiv of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), at −78 °C for less than 5 min. DTBMP was preferentially used with *p*-methoxy sulfoxides **3h–l** (entries 10–17), since it allowed to suppress the β-elimination of the sulfinyl group observed with TMP.[10] Five and 3 equiv of Tf_2O were used with TMP and DTBMP, respectively.[11] The reactions took place in very good yields with a wide range of substrates, affording the corresponding 4-aryl-benzopyrans **4b** and **4h** (entries 4 and 15) and 1-aryl-tetralins (all of the other entries in Table 2), failing only in the case of **3g** (R^2 = CN, entries 8–9), which is deactivated toward



Scheme 4. Synthesis of 1-aryltetralines and 4-arylbenzopyrans **4**.

Table 2. Synthesis of 1-aryltetralines and 4-arylbenzopyrans **4**

Entry	Substrate	Product	R^1	R^2	R^3	R^4	X	*T* (°C)	Base (equiv)	Yield (%)
1	**3a**	**4a**	H	H	H	H	CH_2	0	TMP (3)	78
2	**3a**	**4a**	H	H	H	H	CH_2	−78	TMP (3)	75
3	**3a**	**4a**	H	H	H	H	CH_2	−78 → rt	TMP (1.5)	37[a]
4	**3b**	**4b**	H	H	H	H	O	−78	TMP (3)	63
5	**3c**	**4c**	H	OCH_3	H	H	CH_2	−78	TMP (3)	95
6	**3d**	**4d**	H	OCH_3	Cl	H	CH_2	−78	TMP (3)	85[b]
7	**3e**	**4e**	H	OCH_3	OCH_3	OCH_3	CH_2	−78	TMP (3)	70
8	**3g**	**4f**	H	CN	H	H	CH_2	−78	TMP (3)	—[d]
9	**3g**	**4f**	H	CN	H	H	CH_2	−78	DTBMP (3)	—[d]
10	**3h**	**4g**	OCH_3	H	H	H	CH_2	0	TMP (3)	n.d.[a,c]
11	**3h**	**4g**	OCH_3	H	H	H	CH_2	−20	TMP (3)	n.d.[a,c]
12	**3h**	**4g**	OCH_3	H	H	H	CH_2	−78	TMP (3)	n.d.[a,c]
13	**3h**	**4g**	OCH_3	H	H	H	CH_2	−78	DTBMP (3)	41
14	**3h**	**4g**	OCH_3	H	H	H	CH_2	−78	DTBMP (1.5)	70
15	**3i**	**4h**	OCH_3	H	H	H	O	−78	DTBMP (1.5)	85
16	**3j**	**4i**	OCH_3	OCH_3	Cl	H	CH_2	−78	DTBMP (1.5)	88[b]
17	**3l**	**4j**	OCH_3	OCH_3	OCH_3	OCH_3	CH_2	−78	DTBMP (1.5)	89
18	**3m**	**4l**	CF_3	H	H	H	CH_2	0	TMP (3)	80
19	**3n**	**4m**	CF_3	OCH_3	H	H	CH_2	0	TMP (3)	77
20	**3o**	**4n**	CF_3	OCH_3	Cl	H	CH_2	−78	TMP (3)	45[b]
21	**3o**	**4n**	CF_3	OCH_3	Cl	H	CH_2	0	TMP (3)	85[b]

[a] Mixture with the olefin by-product formed by β-elimination of the sulfinyl group.
[b] As a single regioisomer.
[c] Not determined.
[d] Only the formation of alkene by-products via elimination of the sulfinyl group was obtained, in 76% (entry 7) and 37% yield (entry 8).

intramolecular electrophilic substitution. In that case, elimination of the sulfinyl group became competitive and was the only observed outcome. Satisfactorily, both electron-donating (such as OMe, entries 10–17) and -withdrawing substituents R^1 (such as CF_3, entries 18–21) appear to be compatible with the reaction, although in the latter case the optimized reaction temperature was higher (0 °C).

Concerning the mechanism, it is very likely that the cyclization takes place through a benzyl carbocation formed by action of Tf_2O on the sulfinyl moiety of **3**, which undergoes a fast electrophilic cyclization with the aromatic ring originally belonging to the 1-Br-3-arylpropyl derivatives **2**, affording the title compounds **4**.[12]

In summary, we have developed a very effective two-step approach to a large array of structurally diverse 1-aryl-tetralins and 4-aryl-benzopyrans, exploiting the synthetic potential of *ortho*-*N*-methylformamido-phenylsulfoxides **1**. We are currently investigating an enantioselective version of the process starting from enantiopure **1**, which could be feasible thanks to the high diastereoselectivity of the α-carbon alkylation step, as well as its application to the synthesis of more complex, biologically important structures.

Acknowledgment

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8. *Synthesis of compounds* **3**. To a cooled solution of **1** (1.83 mmol, 500 mg) and dry HMPA (9.15 mmol, 1.60 mL) in dry THF (29 mL), a 2.5 M solution of *n*-BuLi (3.85 mmol, 1.54 mL) was added drop-wise at −70 °C and under Ar atmosphere. After 10 min, at −78 °C bromide **2** (2.01 mmol) was added. After the reaction was complete (TLC monitoring), saturated aqueous NH_4Cl was added, the temperature raised to rt, and the solution extracted with AcOEt. The collected organic layers were dried on anhydrous Na_2SO_4, filtered, and the solvent evaporated in vacuo. The residue was purified by flash-chromatography to give **3**.
9. In fact, diastereomerically pure **3n**, obtained according to entry 16 (Table 1), epimerized quantitatively when treated with *n*-BuLi/HMPA in THF at 0 °C.
10. (a) When *p*-MeO sulfoxides **3h–l** were kept in $CDCl_3$ solution at 305 K, a 1:1:2 mixture of the corresponding cyclized product **4**, olefin by-product arising by β-elimination of the sulfinyl group, and 2-methyl-benzo[*d*]isothiazol-3-one co-product **9** (Scheme 4) was formed spontaneously in few hours, as detected by NMR analysis.; (b) *Synthesis of compounds* **4**. To a cooled solution of **3** (1 equiv) and a base (TMP or DTBMP, 3 equiv or 1.5 equiv, see Table 2) in dry DCM (0.1 M solution), neat Tf_2O (5 or 3 equiv, respectively) was added under nitrogen at −78 or 0 °C (see Table 2). After less than 5 min, the reaction was diluted with a 1 N HCl aqueous solution, the temperature raised to rt, and the mixture extracted with DCM. The collected organic layers were washed with a $NaHCO_3$ saturated aqueous solution, dried on anhydrous Na_2SO_4, filtered, and the solvent evaporated in vacuo. The crude was purified by flash chromatography affording pure **4**.
11. Less equivalent of TMP (Table 2, entry 3) or more equivalent of DTBMP (entry 13) led to a drop of yields.
12. Although we failed to isolate sulfur-containing reaction co-products sufficiently pure for allowing a reliable structure assignment, we believe that in analogy with previously studied Pummerer-type reactions involving *ortho*-*N*-methylformamido-phenylsulfoxides **1** (Ref. 5), 2-methyl-benzo[*d*]isothiazol-3-one **9** (Scheme 4) is formed in the reaction. In order to learn more about this issue, a $CDCl_3$ solution of pure **9** was treated, in an NMR tube, with an excess of Tf_2O, which resulted in a complete and immediate conversion of the substrate to a complex mixture of products. This suggests that the same event occurs in the cyclization process.