Tetrahedron Letters 50 (2009) 4781–4784

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of tricyclic and tetracyclic sultones by Pd-catalyzed intramolecular cyclization

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ARTICLE INFO

Article history:
Received 2 May 2009
Revised 4 June 2009
Accepted 8 June 2009
Available online 11 June 2009

Keywords:
Sulfonate
Pd-catalyst
Cyclization
Sultone

ABSTRACT

A new efficient synthesis of aromatic six-membered ring sultones by the implementation of ligand-free Pd-catalyzed intramolecular cyclization of aromatic sulfonates derived from various bromo phenols and naphthols is described.

Sultones **1** are the internal esters of hydroxy sulfonic acids and are the sulfur analogues of lactones. Some representative structures of sultones are depicted in Figure 1. The first sultone 1,8-naphthosultone was analyzed in 1887 by Schultz,[1] who credited C. Mensching for having discovered it. This compound was studied by Erdmann,[2] who confirmed the structure and coined the term 'sultone'.

The biological activities of sultones are concerned with toxicological,[3] skin sensitization[4,5] and antiviral properties.[6] Sultones are synthetically useful heterocycles which can react with a variety of compounds to introduce the alkylsulfonic acid function, and therefore used as sulfoalkylating agents.[7] Over the past several years, sultones have emerged as valuable heterocyclic intermediates that offer novel possibilities for stereoselective transformation. There have been several new developments for the synthesis of sultones which have also been applied in the total synthesis of natural products. For example, Wolinsky and Solas reported the use of camphenesultone for the total synthesis of β-santalol.[8] Metz et al. have succeeded in developing the stereoselective synthesis of 1,10-*seco*-eudesmanolide ivangulin starting from 2-acetylfuran by means of intramolecular Diels–Alder reaction of a furan-derived vinylsulfonate, a radical cyclization onto a dienylsultone, and a reductive cleavage of a sultone as key steps.[9] They have also synthesized macrodiolide antibiotic pamamycin-607

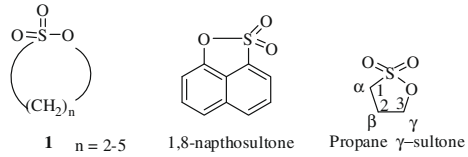

Figure 1. Some representative structure of sultones.

from a sultone.[10] A further synthetic application of sultone as a key intermediate for the synthesis of (−)-myltaylenol has been described by Winterfeldt and co-workers.[11]

We undertook a target to establish a short and efficient route for the synthesis of aromatic sultones. The most common procedure for the synthesis of aromatic sultones involves an elimination reaction of the corresponding hydroxy sulfonic acid derivatives, using concentrated sulfuric acid,[12] phosphorous pentachloride,[13] or phosphorus oxychloride.[14,15] Hanson and Kemp[16] have synthesized polycyclic aromatic sultones by treatment of *ortho* aryl phenols with thionyl chloride and aluminum chloride, followed by adjustment of sulfur oxidation state. Polycyclic aromatic sultones have also been synthesized from diazotized amino sulfonic acids and esters with powdered copper[17,18] and some of the reactions lead only to mixtures of products. Drozd and Saks[19] have reported the preparation of aromatic 6-membered ring sultones by the reaction of phenyl vinylsulfonate with various phenols. There are some classical cyclization approaches available for synthesizing sultones such as the Diels–Alder reaction.[20–22] However, a number of

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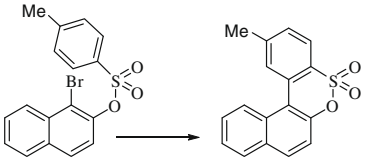
doi:10.1016/j.tetlet.2009.06.028

transition metal-catalyzed approaches to sultones have come to light, including the use of Rh-,[23] Ru-,[24–27] and a few examples of Pd-catalyzed reactions.[28] Recently we have published the synthesis of polycyclic sultams by Pd-catalyzed intramolecular coupling reaction.[29] Our continuous interest in the development of biologically important heterocycles based on Pd-chemistry,[30] prompted us to undertake a study to develop a new efficient route for the synthesis of polycyclic sultones via ligand-free Pd-catalyzed intramolecular coupling reaction.

For this purpose the required precursors **3a–g** were prepared in 90–95% yields by tosylation of the substrates **2a–g** using *p*-TsCl and pyridine at 80 °C for 4–5 h. The substrates **2a–g** were in turn prepared in 70–75% yields by bromination of various phenols **1a–f** using NBS in acetonitrile for 1–2 h at rt (Scheme 1).

When the intramolecular coupling reaction was carried out with the substrate **3a** using the concept of Jeffery's protocol[31] in the presence of $Pd(OAc)_2$ as catalyst in dry *N,N*-dimethylformamide, KOAc as base, and TBAB as additive at 100 °C for 1 h under nitrogen atmosphere, the starting materials underwent total decomposition showing no significant spot on TLC. Therefore, we performed a series of experiments where sequential changes were made to the catalyst, base, and solvent. When the catalyst was changed to $Pd(PPh_3)_2Cl_2$, the starting material was decomposed and in case of $PdCl_2$, no change was observed on TLC. However, when we used $Pd(PPh_3)_4$, the reaction proceeded smoothly and was completed within 1 h. Among several solvents examined, DMF gave the best result. The effect of base was also studied, and KOAc was found to be superior to Et_3N. Here, it is important to note that the additive plays an important role in the Pd-catalyzed cyclization. The reaction did not occur in the absence of TBAB. Using this optimized condition [$Pd(PPh_3)_4$/TBAB/KOAc/DMF/100 °C] **3a**[32] was successfully cyclized to afford the sultone **10a**[33] in 88% yield. The optimization results are summarized in Table 1.

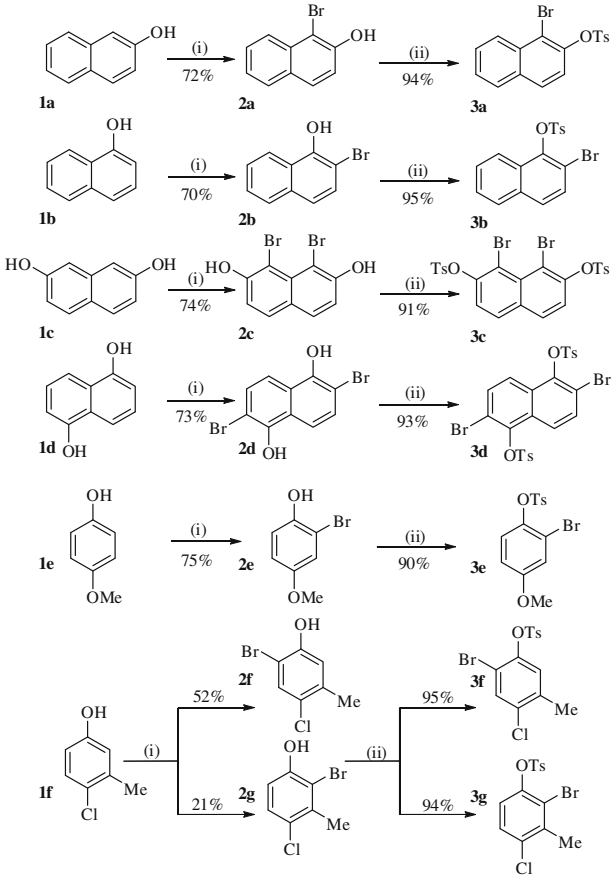
Table 1
Optimization of the palladium-catalyzed cyclization[a] of **10a** from **3a**



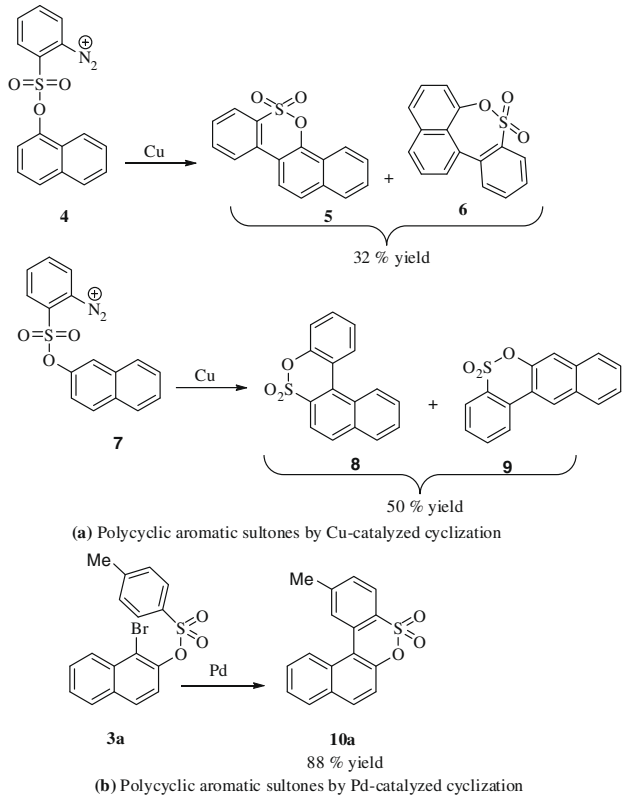
3a **10a**

Entry	Catalyst	Base	Solvent	Time (h)	Yield (%)
1[b]	$Pd(PPh_3)_4$	KOAc	DMF	1	88
2[b]	$Pd(OAc)_2$	KOAc	DMF	1	Decomposition
3[b]	$Pd(OAc)_2$	Et_3N	DMF	4	NR
4[b]	$Pd(PPh_3)_4$	Et_3N	DMF	6	44
5	$Pd(OAc)_2$	Ag_2CO_3	DMF	3	NR
6[b]	$Pd(OAc)_2$	CS_2CO_3	DMF	1	Decomposition
7[b]	$Pd(PPh_3)_2Cl_2$	KOAc	DMF	1	Decomposition
8[b]	$PdCl_2$	KOAc	DMF	3	NR
9	$Pd(OAc)_2$	Et_3N	MeCN	3	NR
10[b]	$Pd(OAc)_2$	KOAc	1,4-Dioxane	1	Decomposition
11	$Pd(PPh_3)_4$	KOAc	DMF	1	NR
12[b]	$Pd(PPh_3)_4$	KOAc	1,4-Dioxane	3	<5

NR—no reaction.
[a] All reactions were carried out at 100 °C and the amount of catalyst used in the reaction was 10 mol %.
[b] TBAB was used as an additive.

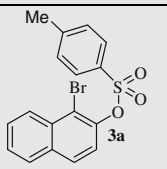
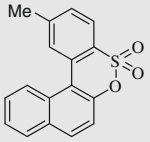
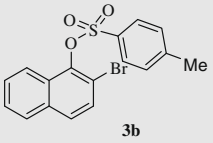
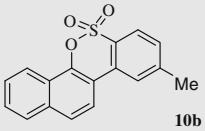
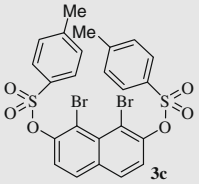
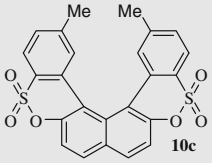
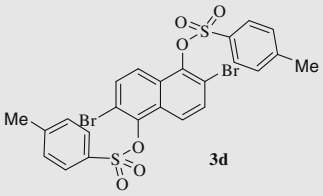
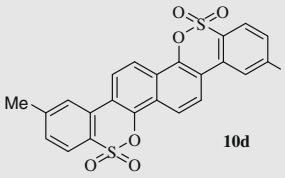
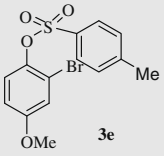
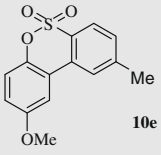
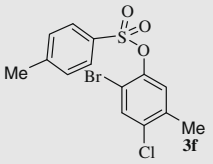
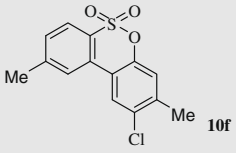
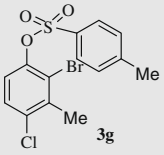
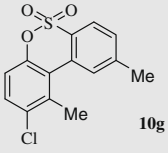


Scheme 1. Synthesis of sultone precursors. Reagent and conditions: (i) NBS, CH_3CN, rt, 1–2 h (ii) *p*-TsCl, pyridine, 80 °C, 4–5 h.



Scheme 2. Comparison of Cu- and Pd-catalyzed cyclization for the synthesis of sultones.

Table 2
Polycyclic sultones

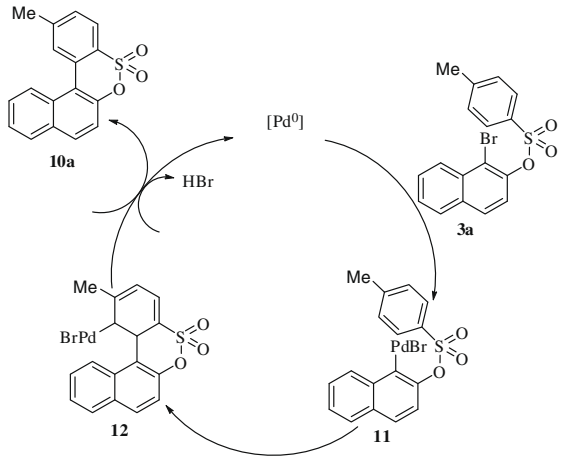
Entry	Sultone precursor	Sultone	Time (h)	Yield (%)
1	 **3a**	 **10a**	1	88
2	 **3b**	 **10b**	2.5	71
3	 **3c**	 **10c**	2	79
4	 **3d**	 **10d**	1.5	78
5	 **3e**	 **10e**	1	90
6	 **3f**	 **10f**	1.5	84
7	 **3g**	 **10g**	1.5	83

Here it is relevant to mention that Schetty has synthesized similar type polycyclic sultones by the treatment of the diazotized solution of α-naphthol and β-naphthol esters of *o*-aminobenzenesulfonic acid (**4** and **7**) with sodium acetate, followed by copper powder to yield an inseparable mixture of isomers in 32 and 50% yields, respectively.[18] It is worthy to note that our method affords selectively one isomer in excellent yield (Scheme 2).

The substrates **3b–g** when treated under the aforesaid optimized conditions afforded the corresponding sultones **10b–g** in excellent yields. The results are summarized in Table 2.

The proposed mechanism for this Pd-catalyzed cyclization for the synthesis of sultone is shown in Scheme 3. Initially oxidative addition of compound **3** to palladium may form aryl palladium intermediate **11**. Complex **11** may then be added to the double bond to give a σ-alkyl palladium intermediate **12** followed by β-hydrogen elimination from intermediate **12** to provide sultone **10**.

In conclusion, we have developed a short and efficient method for the construction of tri- and tetracyclic sultones by a Pd-catalyzed, ligand-free intramolecular coupling reaction.



Scheme 3. Plausible mechanism.

Acknowledgments

We thank DST (New Delhi) and CSIR (New Delhi) for financial assistance. One of us S.M. is thankful to DST (New Delhi) and D.G. is grateful to CSIR (New Delhi) for fellowships.

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31. Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287.
32. *Compound* **3a**: white solid, mp 108–110 °C, yield 94%. IR (KBr, cm^{-1}) ν_{max}: 2923, 1351; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.44 (s, 3H), 7.30 (d, 2H, J = 8.2 Hz), 7.47 (d, 1H, J = 9.2 Hz), 7.52 (t, 1H, J = 7.2 Hz), 7.59 (t, 1H, J = 7.2 Hz), 7.79 (d, 2H, J = 8.3 Hz), 7.83 (d, 2H, J = 7.0 Hz), 8.18 (d, 1H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.8, 116.1, 121.7, 126.9, 127.5, 128.0, 128.1, 128.2, 128.7, 129.0, 129.9, 130.1, 132.6, 132.9, 145.1, 145.8; HRMS: calcd for $C_{17}H_{13}BrO_3S$: 398.9667 [M+Na], 400.9540 [M+2+Na]. Found: 398.9666 [M+Na], 400.9666 [M+2+Na].
33. *General procedure for the synthesis of sultones* **10**(**a**–**g**) *by the Pd-catalyzed cyclization reaction*: A mixture of **3a** (300 mg, 0.79 mmol), tetrabutylammonium bromide (308 mg, 0.96 mmol), and dry potassium acetate (214 mg, 2.19 mmol) was taken in dry *N,N*- dimethylformamide (6 mL) under nitrogen atmosphere. $Pd(PPh_3)_4$ (17.8 mg, 0.079 mmol) was added and the reaction mixture was stirred at 100 °C for 1 h. The reaction mixture was cooled and water (25 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the organic layer was washed with water (2 × 25 mL), followed by brine (25 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography using ethyl acetate: petroleum ether (1:9) to afford the product **10a**. The other substrate **3(b–g)** was similarly treated to give products **10(b–g)**.
Compound **10a**: White solid, mp 196–198 °C, yield 85%. IR (KBr, cm^{-1}) ν_{max}: 1382, 1192; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.55 (s, 3H), 7.42 (dd, 2H, J = 8.9, 2.8 Hz), 7.56 (t, 1H, J = 7.4), 7.65 (t, 1H, J = 7.3), 7.92 (dd, 2H, J = 9.2, 2.2 Hz), 7.97 (d, 1H, J = 7.9 Hz), 8.04 (s, 1H), 8.54 (d, 1H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 22.1, 117.6, 118.3, 124.5, 125.1, 126.1, 128.1, 129.2, 129.3, 129.6, 129.7, 130.6, 131.5, 132.0, 132.5, 144.0, 147.9; HRMS: Calcd for $C_{17}H_{12}O_3S$: 319.0405 [M+Na]. Found: 319.0405 [M+Na].