Sixth International Conference
South-West University
Faculty of Mathematics & Natural Sciences
Blagoevgrad, Bulgaria 10 - 14 June, 2015

SYNTHESIS OF 2-FLUOROMETHYL-7-(ARYLSULFANYLMETHYL)NAPHTHALENES

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Abstract. Starting from the readily available 2,7-bis(bromomethyl)naphthalene, two 2-fluoromethyl-7-(arylsulfanylmethyl) naphthalene derivatives were prepared in four steps. It was found that direct, partial treatment of 2,7-bis(bromomethyl)naphthalene with thiophenoxide could not be controlled and the major product was bis thiophenoxy derivative. The key synthetic intermediate was 2-bromomethyl-7-fluoromethylnaphthalene, which gave the final products, 2-fluoromethyl-7-(phenylsulfanylmethyl)naphthalene and 2-fluoromethyl-[(4-bromophenyl) sulphanylmethyl]naphthalene, when treated with the corresponding thiophenoxides under phase transfer catalytic conditions. The structure of the final products and the key intermediate was established by ^{1}H NMR, ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis.

Keywords: 2-fluoromethyl-7-(phenylsulfanylmethyl)naphthalene, 2-fluoromethyl-[(4-bromophenyl)sulfanylmethyl]naphthalene, synthesis

Introduction

In the course of our study on preparative methods for chiral sulfoxides based on asymmetric oxidation of aryl sulfides, we needed several arylmethyl phenylsulfides. In particular were trying to probe the effect of certain halogen substituenys on certain catalysts used for the asymmetric oxidation and the decision was made to prepare 2-fluoromethyl-7-(arylsulfanylmethyl) naphthalene derivatives. Even though that there are many procedures for the synthesis of such arylmethyl phenyl sulfides (Cremlyn, 1996; Rayner, 1995; Yin & Pidgeon, 1997; Herriott & Picker, 1975; Khurana & Sahoo, 1992) the introduction of fluoromethyl group presents a challenge. Logical and readily available starting material for accomplishing this is 2,7-bis(bromomethyl)naphthalene, which could be conveniently prepared by double benzylic bromination published in the literature (Ried & Bodem, 1958). Initially, a "straightforward" approach was pursued, *i.e*. treatment of 2,7-bis(bromomethyl)naphthalene with 1 equivalent of thiophenoxide, followed by fluorine/bromine halogen exchange. Unfortunately, it was found that the

reaction of 2,7-bis(bromomethyl)naphthalene with thiophenoxide could not be controlled and the major product was bis thiophenoxy derivative. Another approach was to partially hydrolyze the 2,7-bis(bromomethyl)naphthalene, **1**, to isolate the corresponding bromoalcohol, [7-(bromomethyl)-2-naphthyl]methanol (Minami et al., 2005), and then replace the hydroxyl group with fluorine. In this case also it was difficult to control the partial hydrolysis. Herein we would like to report the synthetic approach towards two 2-fluoromethyl-7-(arylsulfanylmethyl) naphthalene derivatives, via four steps using 2-bromomethyl-7-fluoromethyl (**3**) naphthalene as the key intermediate.

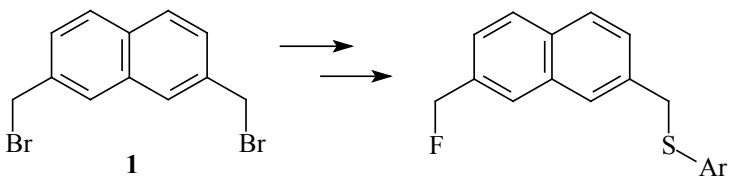

Fig. 1. Multistep synthesis of 2-fluoromethyl-7-(arylsulfanylmethyl)naphthalene derivatives starting from 2,7-bis(bromomethyl)naphthalene, **1**

Materials and methods

The chemicals and reagents were obtained from commercial suppliers and were used without further purification. Melting points were determined using Thomas-Hoover capillary mp apparatus and were uncorrected. NMR spectra were recorded on Bruker DRX-400 spectrometer (400 MHz for proton) in deuterated chloroform ($CDCl_3$) and were reported in ppm with respect to tetramethylsilane (2 drops per 100 g $CDCl_3$). Preparative flash chromatography (Still et al., 1978; Bogdanov, 2014) was performed using Merck silica gel 60 (230-400 mesh) and TLC was carried out using Merck pre-coated plates (60 F_{254}, 250 μm).The EI mass spectra were obtained using GC-MS instrument (HP 6890 GC coupled with MS HP-5MS, capillary column, 30m, 0.25 mm i.d., 0.25 μm film thickness). 2,7-bis(bromomethyl)naphthalene (**1**) (Reid & Bodem, 1958) and [7-fluoromethyl)-2-naphthyl]methanol (**2**) [8] were prepared according to literature procedures.

Preparation of 2-bromomethyl-7-fluoromethylnaphthalene (3)

To a mixture of [7-fluoromethyl)-2-naphthyl]methanol (0. , 2 mmol) in dichloromethane (5 mL), phosphorous tribromide (0.190, mL, 2.0 mmol) was added dropwise at 25 °C. The resulting clear solution was stirred at ambient temperature for 1 hour. The excess of phosphorous tribromide was quenched with dropwise addition of methanol

(1 mL) and argon was bubbled for 3 min to remove the generated hydrogen bromide. The mixture was diluted with dichloromethane (10 mL) and poured over water. The layers were separated and the organic layer was washed with water and then brine. Drying over sodium sulphate and removal of solvent gave an off-white solid. The desired product was isolated by flash chromatography, eluting with 10% dichloromethane in hexanes, as a white solid weighing 0.342 g (68%). mp 90-92 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): 7.92 - 7.78 (m, 4 H), 7.53 (d, J = 8.4 Hz, 1 H), 7.49 (d, $^{2}J_{H-F}$ = 47.7 Hz, 2 H), 4.66 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): 135.99 (C), 134.66 (C), 134.60 (C), 130.20 (C), 130.12 (C), 128.87(CH), 128.92 (CH), 128.53 (CH), 128.22 (CH), 127.62, (CH), 126.83 (CH), 126.76 (CH), 125.83 (CH), 125.79 (CH), 85.59 (CH_2), 83.93 (CH_2), 34.00 (CH_2); **EI-MS** (*m*/*z*, relative intensity): 254 (M^+ + 2, 7%), 252 (M^+, 7%), 174 (16%), 173 (M^+ - Br, 100%);

Calcd. for $C_{12}H_{10}BrF$, C 56.94% H 3.98%. Found: C, 56.78%; H, 4.04%.

Preparation of 2-fluoromethyl-7-(arylsulfanylmethyl) naphthalene derivatives

A mixture of 2-bromomethyl-7-fluoromethylnaphthalene, (0.395 mmol), 3:1 (v/v) dichloromethane/acetonitrile (4 mL), 1 M NaOH (4 mL), and corresponding thiophenol (0.443 mmol) and tetraethylammonium bromide (TEAB) (0.025 mmol) was lowered into a oil bath at 60 °C and was vigorously stirred for 6 hours under nitrogen atmosphere. The mixture was cooled to room temperature, the layers were separated and the organic layer was washed with 1M sodium hydroxide, water and brine. Drying over sodium sulfate and removal of solvent *in vacuo* afforded yellow solid, which was recrystallized from benzene/hexane (cooling at -20 ˚C for 16 hours).

2-fluoromethyl-7-(phenylsulfanylmethyl)naphthalene (4a)

(0.054g, 48%) mp 102-104 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): 7.82 (d, J = 8.4 Hz, 1 H), 7.78 (d, J = 8.4 Hz, 1 H), 7.72 (s, 1H), 7.66 (s, 1H), 7.48 (d, J = 8.4 Hz, 1 H), 7.44 (d, J = 8.4 Hz, 1 H), 7.30-7.14 (m, 5H), 5.50 (d, $^{2}J_{H-F}$ = 47.7 Hz, 2 H), 4.25 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): 136.20, 135.82, 134.22, 133.19, 132.70, 130.31, 129.08, 128.44, 128.37, 127.83, 127.76, 126.74, 126.72, 126.64, 125.15, 125.11, 85.73, 84.07, 39.57; **EI-MS** (*m*/*z*, relative intensity): 283 (M^+ + 1, 3%), 282 (M^+, 14%), 174 (14%), 173 (M^+ - SPh, 100%);

Calcd. for $C_{18}H_{15}FS$, C 76.56% H 5.35%. Found: C, 76.64%; H, 5.22%.

2-fluoromethyl-[(4-bromophenyl)sulfanylmethyl]naphthalene (4b)

(0.087 g, 61%) mp 126-127 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): 7.84 (d, J = 8.4 Hz, 1 H), 7.80 (d, J = 8.4 Hz, 1 H), 7.74 (s, 1H), 7.66 (s, 1H), 7.49-7.44 (m, 2H), 7.34 (d,

J = 8.4 Hz, 2 H), 7.15 (d, J = 8.4 Hz, 2 H), 5.52 (d, $^{2}J_{H\text{-}F}$ = 47.7 Hz, 2 H), 4.24 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): 135.58, 135.47, 134.57, 134.40, 133.36, 130.31, 132.94, 132.92, 132.32, 132.12, 128.69, 128.66, 127.99, 127.87, 126.88, 126.81, 125.47, 125.42, 120.95, 85.89, 84.24, 39.81; **EI-MS** (*m*/*z*, relative intensity): 362 (M^+ + 2, 5%), 360 (M^+, 5%), 281 (9%) 174 (12%), 173 (M^+ - *p*BrSPh, 100%);

Calcd. for $C_{18}H_{14}BrFS$, C 59.84% H 3.91%. Found: C 59.96%; H 3.80%.

Result and discussion

The successful strategy was to introduce, the less reactive, benzylic fluoride first, by controllable halogen exchange of 2,7-bis(bromomethyl)-naphthalene (**1**). Once the fluoroalcohol (**2**) is obtained, using standard chemistry it can be converted to the key intermediate 2-bromomethyl-2-fluoromethylnaphthalene (**3**). During the second step it is important to quench PBr_3 with methanol and remove the hydrogen bromide by bubbling argon or nitrogen. This intermediate (**3**) is quite valuable because it is stable, it is obtainable with high purity and the naphthylic bromide can be substituted with wide variety of nucleophiles.

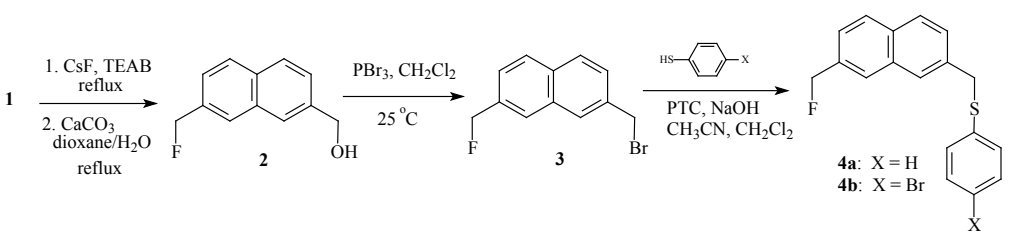

Fig. 2. Multistep synthesis of 2-fluoromethyl-7-(phenylsulfanylmethyl)-naphthalene (**4a**) and 2-fluoromethyl-[(4-bromophenyl)sulfanylmethyl]naphthalene (**4b**)

The reaction **3** with thiophenol(s) under phase-transfer conditions, in the presence of TEAB gave the desired products **4a** and **4b** respectively in moderate yields (48% and 61%). For reproducible results and higher yields it is best the reactions to be performed with degassed solutions under argon atmosphere. This is necessary in order to to avoid the oxidation of the thiophenols to diaryldisulfides (Cremlyn, 1996). The structures of the new compounds, **3**, **4a** and **4b**, were unambiguously determined by spectroscopic methods (^{1}H NMR, ^{13}C NMR and MS). It is important for the obtained products to be free of diaryldisulfides because they are undesirable interference if further oxidation studies of **4a** and **4b** to the corresponding sulfoxides are carried out. The synthesis presented

herein can be extended to other thiophenols and phenols to obtain various arylmethyl phenyl sulfides and arylmethyl phenyl ethers.

Acknowledgement. The author expresses deep gratitude to Dr. Pshemak Maslak (Pennsylvania State University, USA) for his help and valuable advices and to Dr. Alan Benesi and Dr. Robert Minard from Pennsylvania State University, USA for their help with the acquisition of NMR and mass spectra.

REFERENCES

Bogdanov, J. (2014). [7-(fluoromethyl)-2-naphthyl]methanol. *Molbank, 2014,* Issue 1, M818.

Cremlyn, R.J. (1996). *An introduction to organosulfur chemistry.* New York: Wiley.

Herriot, A.W. & Picker, D. (1975). The phase-transfer synthesis of sulphides and diacetales. *Synthesis, 1975,* 447-448.

Khurana, J.M. & Sahoo, P.K. (1992). Chemoselective alkylation of thiols: a detailed investigation of reactions of thiols with halides. *Synthesis Communications, 22,* 1691-1702.

Minami, A., Uchida, R., Eguchi, T. & Kakinuma, K. (2005). Enzymatic approach to unnatural glycosides with diverse aglycon scaffolds using glycosyktransferase VinC. *J. Amer. Chem. Soc., 127,* 6148-6149.

Rayner, C.M. (1995). Synthesis of thiols, sulphides, sulfoxides and sulfones. *Contemp. Organic Synthesis, 2,* 409-440.

Ried, W. & Bodem, H. (1958). Charakteristische Derivate der Di- und Trimethyl-naphthaline. *Chem. Ber., 91,* 1981-1982.

Still, W.C., Kahn, M. & Mitra, A. (1978). Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem., 43,* 2923-2925.

Yin, J. & Pidgeon, C. (1997). Simple and efficient method for preparation of unsymmetrical sulphides. *Tetrahedron Lett., 38,* 5953-5954.

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