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Application of Organolithium and Related Reagents in Synthesis. Part XXVIII [1]. Synthesis Strategies Based on Aromatic Metallation: A Conversion of Benzoic Acids into Arylthiomethyl Aromatic Carboxylic Acids

Adam Bieniek, Jan Epsztajn*, and **Mieczysław W. Płotka**

Department of Organic Chemistry, Institute of Chemistry, University of Łódź, 90-136 Łódź, Narutowicza 68, Poland

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Summary. A convenient two step protocol preparation of *ortho*-phenylthiomethyl aromatic carboxylic acids from aromatic carboxylic acids anilides is reported. The phenylthiolation of phthalides with benzenethiol as a key step is described.

Keywords. Lithiation; Secondary benzamides; Phthalides; *ortho*-Phenylthiomethylaromatic carboxylic acids.

Introduction

In the past few years attention has been focussed on the synthesis of *ortho*-arylthiomethyl aromatic carboxylic acids as key starting materials for the preparation of numerous heterocyclic compounds including physiologically active products, for example, dibenzo[*b*,*c*]thiepine series showing neuroleptic [2, 3], antidepressant [4], and antiinflammatory [5, 6] activity.

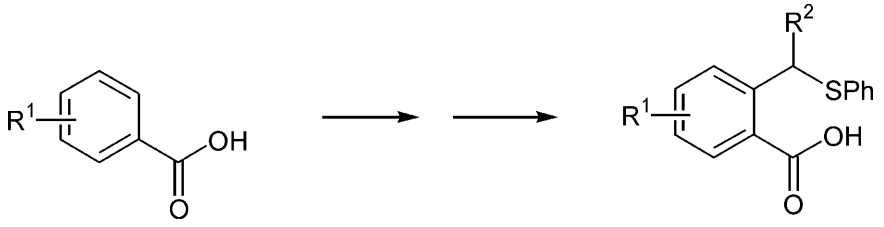
This prompted us to examine a methodology for the synthesis of these systems. In particular, our attention focussed on the development of a general synthetic route for the preparation of *ortho*-arylthiomethylbenzoic acids. Available methods for the preparation of *ortho*-phenylthiomethylbenzoic acids generally require one of the following techniques. The most common approach involves the lateral lithiation of *ortho*-alkylated benzoic acids or their masked derivatives [7] and a subsequent

* Corresponding author. E-mail: epsztajn@krysia.uni.lodz.pl

reaction with bisulfides. However, this methodology often requires a multistep preparation of starting materials. Literature suggests that the most attractive route could be the reaction of esters or lactones with thiols [8] in the presence of *Lewis* acids. Yet, in the case of phthalides this process failed. On the other hand, it has been shown [2–4, 9] that unsubstituted phthalides reacted with benzenethiols in the presence of base to yield *ortho*-phenylthiomethylbenzoic acids.

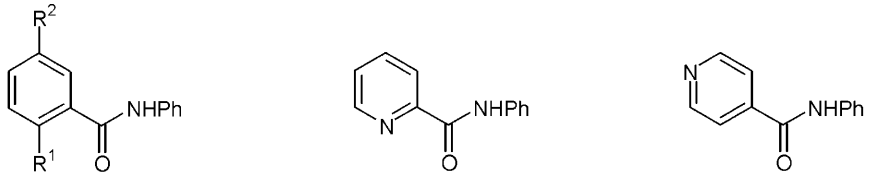
Results and Discussion

Our aim was to extend the scope of this idea to the synthesis of new *ortho*-arylthiomethylbenzoic acids (**B**) ($R^2 \neq H$) and we report here the results obtained with a series of 3-substituted phthalides. This method provides an efficient synthesis sequence as a general strategy for the transformation of aromatic carboxylic acids (**A**) into *ortho*-arylthiomethyl aromatic carboxylic acids (**B**) ($R^2 \neq H$) (Scheme 1) by means of a two-step protocol starting from benzoic acid anilides **1**, **2**, and **3**.

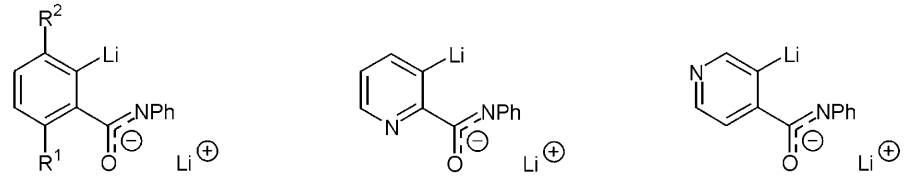


A **B**

Scheme 1



1 **2** **3**



4 **5** **6**

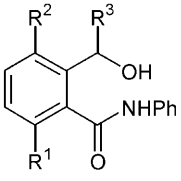
For **1** and **4**:

a	$R^1 = R^2 = H$	
b	$R^1 = Cl$;	$R^2 = H$
c	$R^1 = H$;	$R^2 = Cl$
d	$R^1 = H$;	$R^2 = OMe$

Scheme 2

We have reported in a series of recent studies [10] that the secondary carboxamide moiety provides an excellent possibility for the regiospecific synthesis of 3-substituted phthalides, which are key starting materials here. Therefore, phthalides **10**, **11**, and **12** were obtained by lithiation of anilides **1**, **2**, and **3** using BuLi in *THF* [10] followed by the reaction of the generated bis-(*N*- and *C*-*ortho*) lithiated anilides **4**–**6** with aldehydes. Thus, upon acid-driven cyclization the formed hydroxymethyl products **7**–**9** yielded the corresponding phthalides **10**–**12** without isolation.

In the next step the *Protiva* [9] procedure was used for the synthesis of the desired *ortho*-arylthiomethyl aromatic carboxylic acids **13**–**15** by the treatment of **10**–**12** with benzenethiol. It was expected that the reaction of 3-substituted phthalides with benzenethiol would provide the desired aromatic carboxylic acids.



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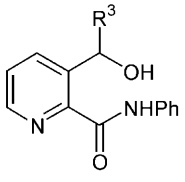

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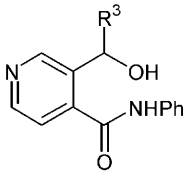

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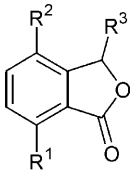

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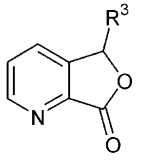

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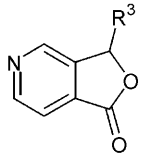

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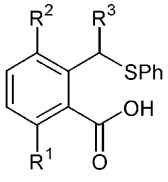

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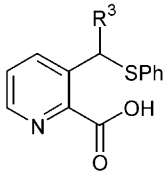

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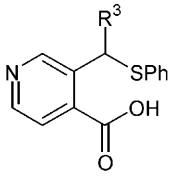

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For **7**, **10**, and **13**:	**a**	$R^1 = H$	$R^2 = H$	$R^3 = C_6H_4OMe$-*p*
	b	$R^1 = Cl$	$R^2 = H$	$R^3 = C_6H_4OMe$-*p*
	c	$R^1 = Cl$	$R^2 = H$	$R^3 = C_6H_4OMe$-*o*
	d	$R^1 = Cl$	$R^2 = H$	$R^3 = Me$
	e	$R^1 = H$	$R^2 = Cl$	$R^3 = C_6H_4OMe$-*p*
	f	$R^1 = H$	$R^2 = Cl$	$R^3 = Me$
	g	$R^1 = H$	$R^2 = OMe$	$R^3 = C_6H_4OMe$-*o*

For **8**, **9**, **11**, **12**, **14**, and **15**: $R^3 = C_6H_4OMe$-*o*

Scheme 3

Table 1. Reaction of phthalides **10–12** with benzenethiol

Phthalide	Product	Yield/%
10a	**13a**	33
10b	**13b**	51
10c	**13c**	58
10d	**13d**	57
10e	**13e**	trace
10f	**13f**	trace
10g	**13g**	trace
11	**14**	15
12	**15**	67

However, phthalide **10a**, when reacted with benzenethiol in the presence of potassium carbonate, furnished the corresponding 2-phenylthiobenzylbenzoic acid **13a**.

To obtain more insight into this problem, we decided to investigate to what extent the fixation of substituents in the close neighbourhood to the centre of the reaction could affect the transformation of the phthalides upon their treatment with benzenethiol into *ortho*-phenylthiomethyl aromatic carboxylic acids. The results of the reactions are reported in Table 1.

The only products obtained from the reaction were the corresponding *ortho*-phenylthiomethyl aromatic carboxylic acids **13–15** together with the recovered phthalides **10–12**.

The observed yields indicated that the tested thiolation of phthalides was significantly affected by the substituents surrounding the reaction centre. In the case of phthalides **10a–d**, **11**, and **12** in which the substituent at the position 4 of the phthalide nucleus (''*peri*'' to the reaction centre) is not larger than a hydrogen atom, the thiolation gave good yields. The presence of the *ortho*-methoxy group at the 3-phenyl ring of phthalides **10c**, **11**, and **12** did not produce any change in the yields. On the other hand, when the hydrogen atom at position 4 of the phthalide nucleus was replaced by a methoxy group or chlorine (**10e**, **10f**, and **10g**) the reaction gave a complex mixture in which the desired products **13e–g** were present in low yields ($\sim 5\%$) as was determined by ^{1}H NMR spectroscopy. This may be attributed to the steric hindrance of the S_N2-type nucleophilic attack by thiophenolate. This is in good agreement with the behaviour of lactones in the reaction with nucleophilic systems [8].

In summary, we present a versatile synthetic method for the preparation of *ortho*-phenylthiomethyl aromatic carboxylic acids **B**. The synthesis involves: (i) successive conversion of aromatic carboxylic acids anilides **1–3** *via* the directed lithiation–electrophilic substitution (aldehydes) sequence into phthalides **10–12** and (ii) their transformation *via* thioarylation into the desired *ortho*-(phenylthiomethyl) aromatic carboxylic acids **13–15**.

Experimental

Melting points were determined using a *Boetius* hot-stage apparatus and are uncorrected. IR spectra were recorded on NEXUS FT-IR (KBr pellets). ^{1}H-NMR spectra were obtained by means a Varian

Gemini-200 using *TMS* as an internal standard. The homogeneity of the compounds was checked by thin-layer chromatography on silica gel plate (60 F254, Merck). Column chromatography was carried out on silica gel (Kieselgel 60, Merck). Elementar analysis gave satisfactory results.

The starting phthalides **10**, **11**, and **12** were prepared *via* metallation (BuLi) of the corresponding benzanilides, as well as picolinic- and isonicotinicanilide, and subsequent reaction of the bis-lithiated anilides with aldehydes [10, 11].

General Procedure for the Preparation of Substituted 2-Phenylthiomethylbenzoic Acids and 3-Phenylthiomethylisonicotinic Acid

A mixture of 4 mmol of corresponding phthalide and 4 mmol of benzenethiol was heated to 110°C and treated over 2 min with 6 mmol of anhydrous K_2CO_3. The mixture was stirred for 5 min and heated to 125°C without stirring for 1 h. The melt was diluted with 7.5 cm^3 hot H_2O, the undissolved fraction was filtered off and the filtrate was acidified with conc. HCl. After cooling to 10°C the crude product was filtered or extracted with $CHCl_3$. Then it was purified by column chromatography and (or) recrystallized.

2-[(4-Methoxyphenyl)-phenylthiomethyl]-benzoic Acid (**13a**, $C_{21}H_{18}O_3S$)

The yellowish solid was column chromatographed (silica gel, chloroform) to give colourless crystals (33%); mp 116–118°C (benzene:*n*-hexane 1:1); IR (KBr): $\bar{\nu} = 2999$ (COOH), 1686 (C=O), 1254 (ArOMe) cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 11.80$–10.80 (br. s., COOH), 8.20–7.80 (m, 2 Ar–H), 7.60–6.60 (m, n Ar–H + n′ CH), 3.70 (s, OMe) ppm.

2-[(4-Methoxyphenyl)-phenylthiomethyl]-6-chlorobenzoic Acid (**13b**, $C_{21}H_{17}ClO_3S$)

The crude acid was taken up with $CHCl_3$ and dried over $MgSO_4$. The solvent was removed to give a pale brown solid. White crystals (51%); mp 141–143.5°C (EtOH); IR (KBr): $\bar{\nu} = 3360$ (COOH), 1740 (C=O), 1250 (ArOMe) cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 7.70$–6.70 (m, n Ar–H + n′ COOH), 6.30 (s, CH), 3.80 (s, OMe) ppm.

2-[(2-Methoxyphenyl)-phenylthiomethyl]-6-chlorobenzoic Acid (**13c**, $C_{21}H_{17}ClO_3S$)

The crude product was extracted with $CHCl_3$ and dried over $MgSO_4$. The solvent was removed and the residue was washed with CCl_4. White crystals (58%); mp 161–163°C (EtOH); IR (KBr): $\bar{\nu} = 3350$ (COOH), 1750 (C=O), 1240 (ArOMe) cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 7.60$–6.70 (m, n Ar–H, n′ CH, COOH), 3.90 (s, OMe) ppm.

2-(Methylphenylthiomethyl)-6-chlorobenzoic Acid (**13d**, $C_{15}H_{13}ClO_3S$)

Extraction with $CHCl_3$ gave a colourless oil, which solidified. The crude product was washed with *n*-hexane. White crystals (57%); mp 95–97°C (EtOH); IR (KBr): $\bar{\nu} = 2980$ (COOH), 1740 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 7.60$–6.60 (m, n Ar–H, COOH), 5.50 (q, $J = 7$ Hz, CH), 1.60 (d, $J =$ 7 Hz, Me) ppm.

3-[(2-Methoxyphenyl)phenylthiomethyl]-isonicotinic Acid (**15**, $C_{20}H_{17}NO_3S$)

White crystals (67%); mp 228–229°C (EtOH); IR (KBr): $\bar{\nu} = 3425$ (COOH), 1720 (C=O), 1250 (ArOMe) cm^{-1}; ^{1}H-NMR (CF_3COOH): $\delta = 9.30$–9.00 (d, $J = 5$ Hz, Py–H-2), 8.85–8.65 (d, $J = 6$ Hz, Py–H-6), 8.43–8.16 (d, $J = 6$ Hz, Py–H-5), 7.83–6.93 (m, 9 Ar–H), 6.83 (s, CH), 3.73 (s, –OMe) ppm.

3-(2-Methoxyphenyl)-phenylthiomethylpicolinic Acid (**14**, $C_{20}H_{17}NO_3S$)

A mixture of sodium thiophenolate prepared from 4 mmol benzenethiol and 1 cm^3 of a methanolic solution of MeONa (4 mol/dm^3), 6 mmol of the corresponding phthalide, 7 mmol NaCl and 12.5 cm^3 dry xylene was refluxed under Ar for 1 h. Then it was cooled to room temperature and left overnight. The solvent was evaporated under reduced pressure. The insoluble material was filtered off, and the filtrate was adjusted with conc. HCl to *pH* 4–5. The resulting solid was collected by filtration and purified by crystallisation from ethanol to give the acid as pale yellow crystals (15%); mp 193–196°C; IR (KBr): $\bar{\nu} = 2477$ (NH^+), 1580 and 1415 (COO^-) cm^{-1}; ^{1}H-NMR (*DMSO-d*$_6$): $\delta = 8.48$ (dd, $J_1 = 3$ Hz, $J_2 = 1.5$ Hz, Py–H-6), 7.96 (dd, $J_1 = 6.5$ Hz, $J_2 = 1.5$ Hz, Py–H-4), 7.60–7.43 (m, Py–H-5, Ar–H), 7.32–7.12 (m, N–H, Ar–H), 7.10–6.88 (m, 2 Ar–H), 6.82 (s, CH), 3.71 (s, OMe) ppm.

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