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Application of organolithium and related reagents in synthesis. Part 25: Novel specific synthesis of the 4-arylisochroman-3-acetic acids via conversion of benzoic acids†

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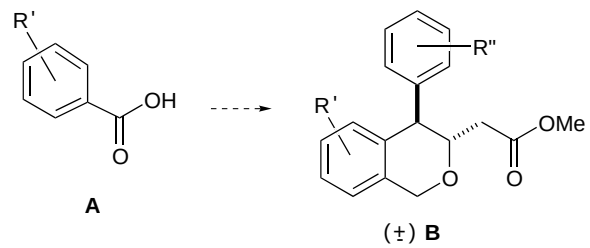
Abstract—The transformation of the benzanilides **1** into 4-arylisochroman-3-acetic acids **8** applying the following sequence of reactions is described. At first, the 3-arylphthalides **3** were obtained via metallation [*n*-BuLi] of benzanilides **1** and subsequent treatment of the generated bis-lithiated anilides **2** with aromatic aldehydes. Next, the 3-arylphthalides **3** were reduced [$LiBH_4$] to phthalanes **5** and then, via reductive metallation [$Li/C_{10}H_8$] and reaction of the generated bis-lithiated species **6** with dimethylformamide, 3-hydroxy-4-arylisochromans **7** were produced. In the final step the isochromans **7** were treated with 1-methoxy-1-trimethylsilyloxyethene in the presence of titanium tetrachloride and furnished 4-arylisochromans-3-acetic acid methyl esters **8** as *trans* stereoisomers (Ψ-e/e).

In the past few years we have witnessed tremendous activity directed towards the synthesis of the benzo[*c*]pyrans, because some members of this family have been found in nature and shown to possess a variety of biological properties.[1–10] This is the motive of the widespread interest in their synthesis. In particular, our attention has been focused on obtaining a synthetic methodology for 3,4-disubstituted isochromans in which a carboxymethyl group is attached at C-3. The position and nature of that substituent is characteristic for the benzo[*c*]pyran antibiotics.[1–10]

The reported available methods for the preparation of this system generally require multi-step sequences.[11–18] Most of them appeared to be unsatisfactory both in yield and generality.

We now wish to report a methodology, which provides access to a new and efficient regio- and diastereoselective synthetic sequence as a general strategy for transformation of aromatic carboxylic acids (**A**) into the desired 3,4-disubstituted isochromans (**B**), in a four-step protocol, starting from benzoic acid anilides (**1**) (Scheme 1).



Scheme 1.

In a series of recent studies we have reported[19–22] that the secondary carboxamide moiety provides an excellent possibility for the regioselective synthesis of 3-arylphthalides, which are the key starting materials here.

Therefore, 3-arylphthalides were obtained by the lithiation of benzoic acid anilides (**1**) using *n*-BuLi in THF,[19,21] followed by the reaction of the generated bis (*N*- and *C-ortho*) lithiated anilides (**2**) with aromatic aldehydes (Scheme 2). Upon acid cyclization, the *ortho* hydroxyarylmethyl intermediates, gave the corresponding phthalides (**3**).

The treatment of the phthalides (**3**) with lithium borohydride[23,24] produced the corresponding diols (**4**), which after the usual acidic aqueous work-up furnished the desired phthalanes (**5**).

Keywords: benzanilides; metallations; isochromans.

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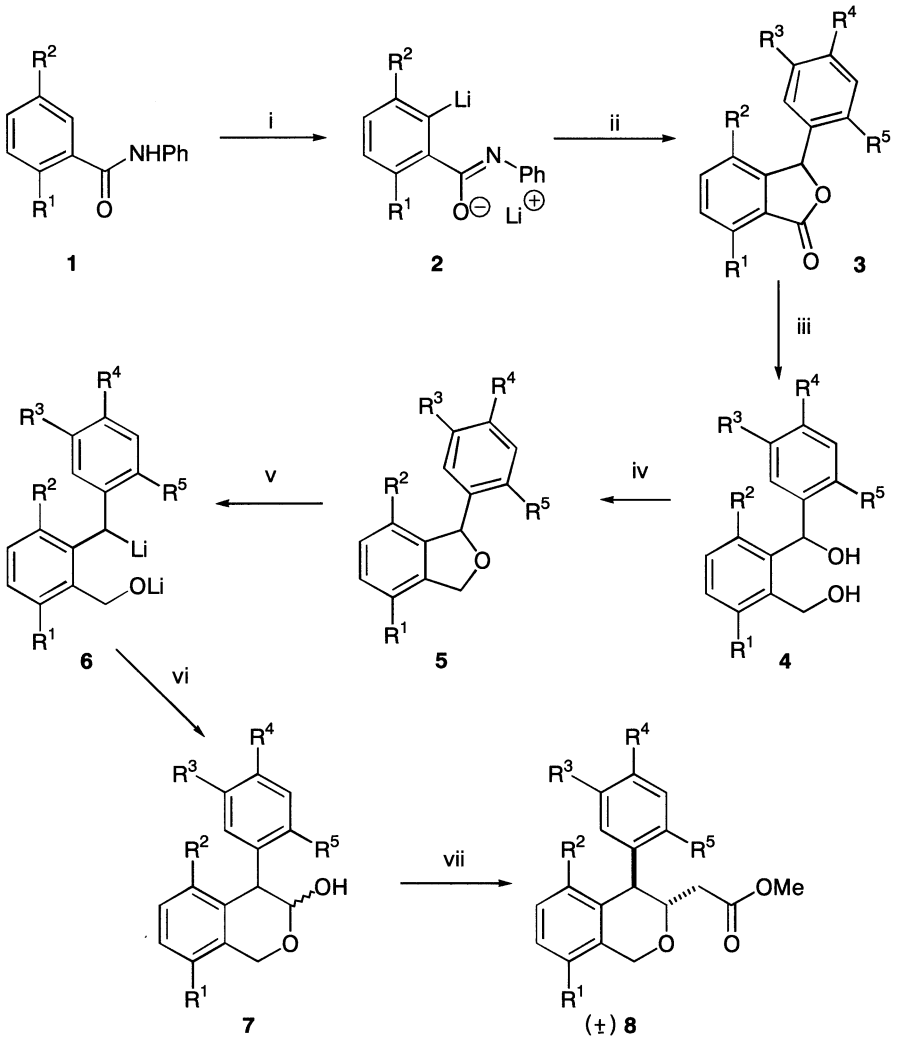

	R^1	R^2	R^3	R^4	R^5
a	H	-OMe	H	-OMe	H
b	H	-OMe	-OMe	H	H
c	H	-OMe	-OMe	H	-OMe
d	-OMe	H	-OMe	H	-OMe

i	BuLi/THF
ii	Ar-CHO/THF
iii	$LiBH_4$/THF
iv	HCl/aq
v	$Li/C_{10}H_8$/THF
vi	$HCONMe_2$(DMF)/THF
vii	$CH_2=C(OMe)OSiMe_3/TiCl_4/CH_2Cl_2$

Scheme 2.

The phthalanes (**5**) were converted into the bis-lithiated species (**6**) via reductive-lithiation[25–28] ($Li/C_{10}H_8$ in THF), which after reaction with dimethylformamide (DMF) gave the 3-hydroxy-4-arylisochromans (**7**) as a mixture of anomers. The structures of the crystallized (ethanol) isochromans (**7**) exemplified by compounds (**7a**) and (**7d**) were determined by X-ray crystallography,[29] which indicated that they were diastereoisomers (Ψ-a/a). The proton NMR data in DMSO-d_6 indicated that the *trans* isomers predominated. On the other hand, in $CDCl_3$ the spectroscopic data showed that both anomers were present and that their ratio varied with time.

In the final step, the Mukaiyama procedure[30–34] was used for the introduction of the carboxymethyl group at the 3-position of the isochroman skeleton.

It was expected that the reaction of the 3-hydroxyisochromans (**7**) with 1-methoxy-1-trimethylsilyloxyethene would provide an effective route for the desired benzo[*c*]pyran-3-acetic acid methyl esters (**8**). In reality, 3-hydroxyisochromans (**7**) when reacted with 1-methoxy-1-trimethylsilyloxyethene in the presence of titanium tetrachloride furnished the corresponding 4-arylisochroman-3-acetic acid methyl esters (**8**). The proton NMR data suggests that the compounds formed

Table 1. Detailed yields (%) of the conversion **1→8**

	1→3	3→5	5→7	7→8
a	68	94	74	81
b	67	88	70	80
c	75	92	72	83
d	68	96	68	80

are *trans* isomers (Ψ-e/e). The coupling constant of the hydrogen atoms (Ψ-a/a) ranged between 6.4 and 9.2 Hz.[35] The structure of the isochromans **8**, exemplified by compound **8c** was confirmed by X-ray crystallography.[29] The formation of the *trans* isomers is most probably due to the fact that the approach trajectory of the incoming nucleophile, is opposite to the aryl substituents of the oxonium cation generated from the 3-hydroxy-4-arylisochromans (**7**).

Overall yields for the regio- and diastereotransformation of the starting benzoic acid anilides (**1**) into benzo[*c*]pyran-3-acetic acids methyl esters (**8**) are about 40% (Table 1).

In conclusion, we have shown a novel general strategy for the preparation of the 3,4-disubstituted isochromans. The procedure is particularly useful because of its efficiency, ready availability of the starting materials and ease of operation, as well as its applicability to the synthesis of important natural products.

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