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SYNTHESIS OF 6-AMYLSALICYLIC ACID FROM 3-ANISALDEHYDE : CONVERSION OF PHTHALIDE TO THIOPHTHALIDE BY ALUMINUM HALIDE-BUTANETHIOL

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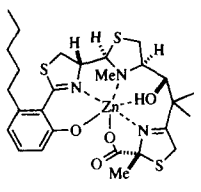
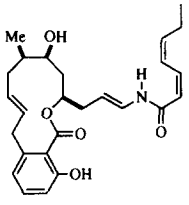
Abstract: The Lewis acid-promoted reaction of 3-butyl-7-methoxyphthalide with butanethiol gave the thiophthalide, which was converted to 6-amylsalicylic acid by alkaline hydrolysis and successive desulfurization by Raney Ni.

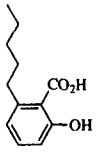
6-Alkylsalicylic acids are components of marine-derived natural products such as micacocidin A (**1**),[1] produced by *Pseudomonas* sp. Lot 57-250, and salicylihalamide A (**2**),[2] isolated from the sponge *Haliclona* sp. Here, we describe an efficient synthesis of 6-amylsalicylic acid (**3**),[1c] a key intermediate of micacocidin A.



micacocidin A (1)



salicylihalamide A (2)



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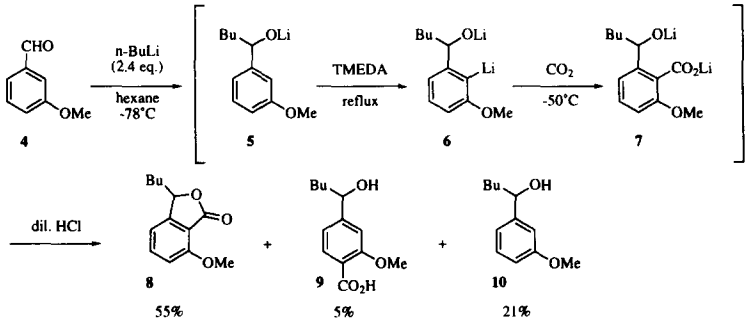
The 1, 2-addition of an *n*-butyl group to 3-anisaldehyde (**4**) and successive *ortho*-selective lithiation followed by carboxylation were performed in one pot to give 3-butyl-7-methoxyphthalide (**8**) in 55% yield (Scheme1). Since the hydrogenolysis of **8** to 6-amylsalicylic acid was unsuccessful, we chose stepwise conversion. First, nucleophilic ring opening of phthalide by thiol, promoted by Lewis acid, was investigated. Fujita and co-workers have reported the nucleophilic cleavage of several γ-butyrolactones to the corresponding butylthiocarboxylic acids, though, the reactivity of phthalide was quite low.[3] We found that the methoxy group of **8** was cleanly cleaved by aluminum chloride (5.0 eq.) promoted displacement of butanethiol at room temperature to give the phenol **12**.

Scheme 1



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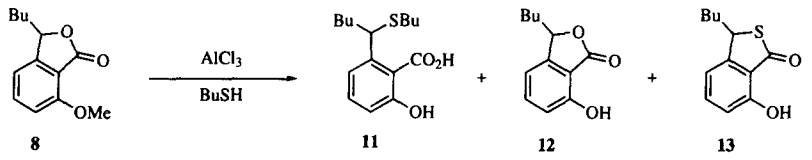
Benzylic cleavage of **12** to give the desired butylthiocarboxylic acid (**11**) did not take place under these conditions. However, at a higher temperature (120°C), a less polar product than **12** was obtained in good yield, and it was identified as the thiophthalide (**13**) by means of spectroscopic analyses (Scheme 2).[5] The negative ion FAB MS of the crude reaction mixture indicated the presence of a trace amount of **11**, suggesting that **11'** is a possible intermediate of **13** (Scheme 3). It is plausible that the initial displacement of alkanethiol at the sterically hindered benzylic center proceeded in Sn 1 fashion under relatively drastic condition.[5] The reaction of 3-butylphthalide with $AlCl_3$-butanethiol also gave the corresponding thiophthalide in moderate yield. However, in the cases of both **6** and 3-butylphthalide, the use of thiophenol instead of butanethiol resulted in complete decomposition, giving none of the desired thiophthalides. Since β-elimination pathway is not possible with thiophenol, the following mechanism is proposed (Scheme 3).

Scheme 2

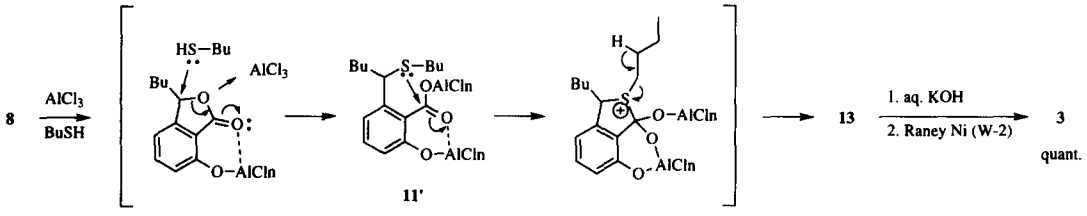


8 **11** **12** **13**

temperature	time	sulfide* **11**	phthalide **12**	thiophthalide **13** (yield %)
r. t.	12 h	trace	quant.	0
120°C	6 h	trace	0	68

*detected by negative ion FAB MS.

Scheme 3



The conversion of the thiophthalide to **3** proceeded quantitatively by alkaline hydrolysis (aq. KOH (6 eq.), reflux, 80 min) followed by desulfurization with Raney Ni (W-2, rt, 2 h) in ethanol and acidification (c. HCl). This method should provide easy access to a variety of 6-alkyl salicylic acids.

Acknowedgment

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References and Notes

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4. Node, M., Nishide, K., Fuji, K., Fujita, E. *J. Org. Chem.*, **1980**, *45*, 4275.
5. Aluminum bromide appeared to be less effective than aluminum chloride.