Pergamon

Tetrahedron Letters, Vol. 37, No. 21, pp. 3755-3756, 1996
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0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00639-9

Base-promoted Acetal Formation with Phenyl Salicylates.

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Abstract: Base-promoted reaction of phenyl salicylates with aliphatic aldehydes provides the corresponding acetals. Neither methyl salicylate nor aromatic aldehydes participate in this reaction.
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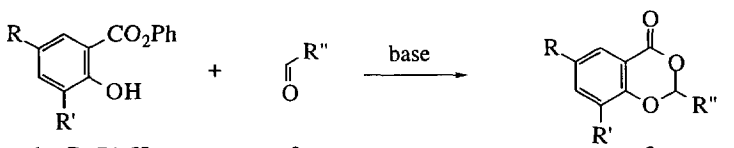
Very recently we demonstrated the ability of aromatic esters of β-hydroxycarboxylic acids (derived from Baylis-Hillman reactions) to form cyclic acetals under base-catalysed conditions.[1] We speculated that esters of 2-hydroxybenzoic acids (i.e. salicylates) might also participate in this process. In this Letter we describe the results of the reactions of several salicylates with a variety of aldehydes (equation (1)).



(1)

1 a R=R'=H
b R=Me R'=H
c R=H R'=Me

2

3

Our first attempt, employing methyl salicylate, returned only starting material. However, switching to the corresponding phenyl ester (**1a**)[2] immediately led to successful reaction (Table).[3] Most reactions were carried out neat except where either, or both, the aldehyde and salicylate were solids. In those cases (entries 1, 9 and 10) a very small volume of chloroform was added to effect solution. The ratio of reactants (salicylate : aldehyde : base = 1 : 5 : 1) follows from our earlier work. From the Table the following points may be noted. Only aliphatic aldehydes reacted under these conditions. No reaction occurred when benzaldehyde (entries 8 and 13) or 4-nitrobenzaldehyde (entry 9) were employed. 1,4-Diazabicyclo[2.2.2]octane (dabco) appeared more effective than triethylamine (compare entries 2 and 3) and was used for the rest of this study. Somewhat surprisingly, pyridine failed to promote this reaction (entry 4). As the size of the aldehyde R increased the reaction became more sluggish (compare entries 2, 5 and 6). Salicylate **1b** is somewhat more reactive than **1a** or **1c** (compare entry 11 with entries 2 and 15). The use of an extremely reactive aldehyde, chloral, led to rapid, efficient acetal formation (entry 7). Finally, paraformaldehyde served well as an equivalent for formaldehyde (entries 1, 14 and 16).

Table. Results from the base-promoted reaction of salicylates with aldehydes.[a]

Entry	Salicylate	R"	Solvent	Reaction Time (d)	Yield (%)
1	**1a**	H[b]	$CHCl_3$[c]	1	81
2	**1a**	Me	neat	2	67
3	**1a**	Me	neat	4	62[h]
4	**1a**	Me	neat	4	n.r.[e,i]
5	**1a**	n-Bu	neat	10	55(61)[d,f]
6	**1a**	i-Pr	neat	10	25(33)[d,f]
7	**1a**	CCl_3	neat	0.08	62
8	**1a**	Ph	neat	5	n.r.[e]
9	**1a**	4-NO_2Ph	$CHCl_3$[c]	5	n.r.[e]
10	**1b**	Me	$CHCl_3$[c]	2	79(88)[d]
11	**1b**	Me	neat	0.6	67(78)[d]
12	**1b**	Et	neat	2	90
13	**1b**	Ph	neat	1	n.r.[e,g]
14	**1b**	H[b]	neat	0.6	83
15	**1c**	Me	neat	2	51(65)[d]
16	**1c**	H[b]	neat	1	56(71)[d]

a. Unless otherwise indicated the reactions were carried out at room temperature, with 1,4-diazabicyclo[2.2.2] octane as base with the following ratio of reactants: (salicylate : aldehyde : dabco = 1 : 5 : 1). b. Paraformaldehyde. c. 0.1 mL of $CHCl_3$ was added to 1 mmol of salicylate. d. Yield in paranthesis based on unrecovered starting material. e. Salicylate recovered unchanged. f. Warming was required to effect solution and hence initiate reaction. g. Heated at 90°C. h. Et_3N used in place of dabco. i. Pyridine used in place of dabco.

This facile process represents one of the very few base-promoted methods for acetal formation.[4] We are currently exploring the use of a wider range of substituted salicylates in this process as well as the efficacy of such salicylate derived acetals as aldehyde protecting groups (especially for the differential protection/deprotection of dialdehydes and keto-aldehydes).[5]

Acknowledgements. E. P. thanks the Australian Agency for International Development for an overseas research scholarship. We are grateful to C.S.I.R.O. (Division of Chemicals and Polymers) for partial financial support.

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3 All new compounds reported here gave satisfactory spectroscopic and combustion analysis.
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(*Received in UK* 22 *February* 1996; *accepted* 3 *April* 1996)