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SYNTHESIS OF C(2)HALOMETHYL SUBSTITUTED DERIVATIVES OF 2,3-DIHYDRO-1,3-BENZOXAZ-4-ONES

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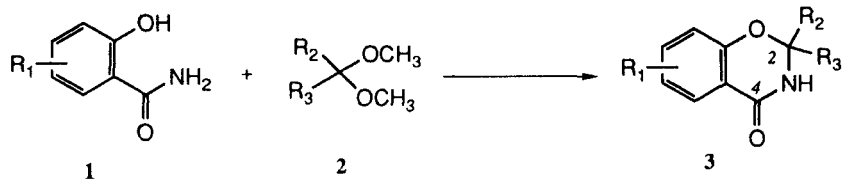
In the pursuit of biologically active compounds we required as a key intermediate 2,3-dihydro-1,3-benzoxaz-4-ones having a halomethylene moiety at C(2), i.e. **3** (R_2= H or alkyl, R_3=CH_2X). The standard procedure for the preparation of this class of compounds is the condensation of salicylamide derivatives **1** with the proper aldehydes[1-5] and ketones[5,6]. Usually, hydrochloric acid or sulphuric acid is used as catalyst and the water formed is cocommittently removed using a dehydrating agent or by azeotropic destillation[7]. These procedures did not serve our purpose as the required α-substituted aldehyde or ketone as such is unstable under the conditions employed. Here we report that employment of acetals and ketals **2** affords the desired compound **3**; yields are appreciable when the proper reaction conditions are used.



1 2 3

Scheme 1

Table 1 2,3-Dihydro-1,3-benzoxaz-4-ones **3** prepared by condensation of salicylamides **1** and acetals or ketals **2**

entry	product	R_1	R_2	R_3	yield (%)	mp °C	ref yield (mp)	crystal[d] solvent
1	**3A**	H	H	$ClCH_2$	5[a]			
2	**3A**	H	H	$ClCH_2$	18	142		A/C
3	**3A**	H	H	$ClCH_2$	29[b]	142		A/C
4	**3A**	H	H	$ClCH_2$	53 [c]	142		A/C
5	**3B**	5-Cl	H	$ClCH_2$	63	182		D
6	**3C**	H	H	Ph	95	170	57(168)[5]	A
7	**3D**	H	CH_3	CH_3	90	138	47(135)[5]	B/C
8	**3E**	H	CH_3	$BrCH_2$	93	144		B

a) The reaction was performed in DMF and the yield was determined by ^1H NMR.

b) Calcium chloride was added to the chloroform solution.

c) Methanol formed during the condensation was removed *via* distillation.

d) A = EtOH, B = Hexane, C = EtOAc, D = $CHCl_3$.

Reaction of salicylamide (**1**, R_1=H) and 2-chloroacetaldehyde dimethyl acetal (**2**, R_2=H, R_3=CH_2Cl) in refluxing chloroform in the presence of a catalytic amount of concentrated surphuric acid yielded the expected product **3A**[8] in 18% yield (entry 2, Table 1). When this reaction was performed in DMF as solvent at 90 °C, the yield dropped considerably (entry 1). Improvement of this yield could be achieved by

addition of $CaCl_2$ to the chloroform solution for removal of the methanol formed (entry 3). The procedure of choice appeared to be the removal of methanol by distillation along with chloroform at ambient temperature while fresh chloroform was added dropwise to balance the volume of the solution. In such a fashion, the desired product **3A** was obtained as a crystalline solid after aqueous workup (entry 4). In a similar manner, the compounds **3B**[8] and **3C** were prepared in fair to good yields (entries 5 and 6, resp.). Employment of the respective ketals gave the corresponding products **3D** and **3E**[8] in good yields (entries 7 and 8, resp.).

Experimental

Typical procedure for the synthesis of **3A**: a suspension of salicylamide **1**, R_1=H (68 g) and 2-chloroacetaldehyde dimethylacetal **2**, R_2=H, R_3=CH_2Cl (64 g) in 800 mL of chloroform in the presence of 15 mL of concentrated sulphuric acid was refluxed for 12 h. Then, the chloroform was distilled together with the methanol formed, while fresh solvent was being added dropwise to keep the volumn of the reaction mixture constant. The resulting mixture was refluxed for another 12 h. The solvent was removed *in vacuo* after which the residue was slowly poured out under vigorous stirring into a cold aqueous 2 N potassium hydroxide solution. Filtration and removal of H_2O under reduced pressure gave 101 g of solid which was crystallized in a mixture of EtOAc and EtOH to afford 52.5 g (53 %) of the desired products **3A**.

In summary, the previously observed condensation of **1** with aldehydes and ketones to yield **3** has been extented using acetals or ketals **2**. This allows the synthesis of **3** having halomethyl substituents at C(2). As expected, ketals **2D** and **2E** and the aromatic acetal **2C** reacted faster and furnished higher yields than their aliphatic aldehyde counterparts **2A** and **2B**.

References and Notes

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7) Polyphosphate esters have been used to function as catalyst as well as dehydrating agent, see: Irvine, J. L.; Piantadosi, C. *Synthesis* **1972**, 568.

8) The chemical structure was confirmed by IR, NMR, MS spectra and equivalent weights.

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