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A Highly-Efficient Synthesis of Benzoxazine-2,4-diones.

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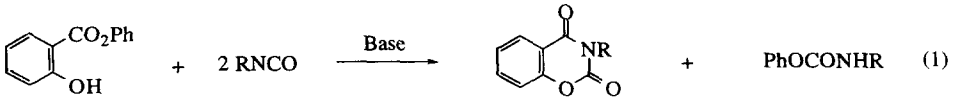
Abstract: Base-promoted reaction of salicylate esters with isocyanates provides a highly efficient route to benzoxazine-2,4-diones. © 1998 Elsevier Science Ltd. All rights reserved.

Substituted benzoxazine-2,4-diones have attracted interest from synthetic chemists recently due to their potential in pharmacology[1,2] and photography.[3] Several methods have been reported for the preparation of these heterocycles.[2,4-10] In this Letter we describe a new, very efficient process for preparing benzoxazine-2,4-diones from a variety of salicylate-type esters (equation (1)). By analogy with our work on the synthesis of oxo-acetals derived from phenyl salicylates,[11] it appeared that it should be possible to prepare benzoxazine-2,4-diones by reacting phenyl salicylate with isocyanates (equation (1)). Initially we examined this reaction using combinations of bases (including pyridine, triethylamine, potassium carbonate) and solvents (including diethyl ether, chloroform and tetrahydrofuran). Even in the presence of 4-(N,N-dimethylamino)pyridine the reactions were incomplete either at room temperature or after extended heating. However, when the reactions were carried out in either dimethylformamide or dimethylsulfoxide the reactions proceeded to completion in excellent yields at room temperature or with heating (Table).



1 **2** **3**

Because of the success of this reaction in either DMF or DMSO several salicylate-type phenyl esters[12] (**1a** - **c** and **4**) were reacted with selected isocyanates providing, respectively, benzoxazine-2,4-diones **3aa** - **ad**, **3b**, **3c** and **5a** - **c**. Most reactions in DMF gave very high yields at room temperature. For phenyl salicylate itself, reaction times ranged from 40 to 45 hours for i-propyl and n-butylisocyanates (entries 1 and 2) to approximately 3 days for cyclohexyl and phenylisocyanates (entries 4 and 5). Reaction times were considerably shorter in DMSO (compare entry 2 with 3 and 5 with 6) whilst maintaining high yields. Phenylisocyanate also reacted under these conditions, however the yields were relatively poor (entries 5 and 6). Aqueous acidic workup, followed by chromatographic separation of the product from the carbamate by-product, was usually carried out. In each case purification by direct crystallisation of the crude reaction

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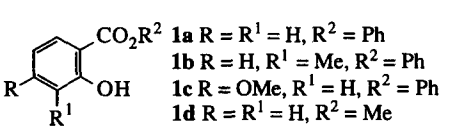
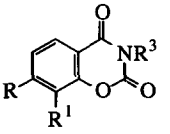
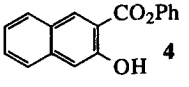
product (rather than chromatography) from ethanol was also possible although the yields were typically ~20% lower. Under these conditions even the reaction of methyl salicylate, **1d**, which had failed to react in our previous report,[11] proceeded in excellent yield (entry 9). Very good results were also obtained using only a catalytic amount of DMAP and no triethylamine (see entries 1-4). Reaction times were longer and heating was necessary. If lower temperatures are required then the inclusion of triethylamine is recommended. Reactions run without triethylamine or DMAP present were much slower although some product was obtained after several days.



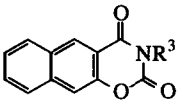
1a R = R^1 = H, R^2 = Ph
1b R = H, R^1 = Me, R^2 = Ph
1c R = OMe, R^1 = H, R^2 = Ph
1d R = R^1 = H, R^2 = Me



3aa R = R^1 = H, R^3 = i-Pr
3ab R = R^1 = H, R^3 = n-Bu
3ac R = R^1 = H, R^3 = Cyclohexyl
3ad R = R^1 = H, R^3 = Ph
3b R = R^1 = Me, R^3 = n-Bu
3c R = OMe, R^1 = H, R^3 = n-Bu



4



5a R^3 = i-Pr
5b R^3 = n-Bu
5c R^3 = Cyclohexyl

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

Entry	Salicylate	RNCO (R)	Solvent	Product	Reaction Time (h)[b,c]	Yield (%)[b,c,d]
1	**1a**	i-Pr	DMF	**3aa**[2]	45 (4) {10}	97 (86) {79}
2	**1a**	n-Bu	DMF	**3ab**[2]	40 (2) {4}	98 (80) {89}
3	**1a**	n-Bu	DMSO	**3ab**[2]	12 {4}	98 {88}
4	**1a**	Cyclohexyl	DMF	**3ac**[9]	72 (21) {46}	97 (82) {73}
5	**1a**	Ph	DMF	**3ad**	43 (3d)	43 (51)
6	**1a**	Ph	DMSO	**3ad**	3d	42
7	**1b**	n-Bu	DMF	**3b**[e]	(6)	(53)
8	**1c**	n-Bu	DMF	**3c**[e]	(2.5)	88
9	**1d**	n-Bu	DMF	**3ab**[2]	(6)	96
10	**4**	i-Pr	DMF	**5a**[e]	(3.5)	(50)
11	**4**	n-Bu	DMF	**5b**[e]	1	(66)
12	**4**	Cyclohexyl	DMF	**5c**[e]	24	(28)

a. Reactions were carried out at room temperature, with 1 equiv. of Et_3N and 0.1 equiv. DMAP. b. Numbers in parantheses refer to reactions carried out as in (a) but with heating at 80°C. c. Numbers in curled parantheses, ie {}, refer to reactions carried out out as in (b) but without Et_3N and with only a catalytic amount of DMAP. d. Isolated yields after chromatography on silica gel. e. All new compounds gave satisfactory spectroscopic and elemental analysis.

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