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Reactions of isatin with alkylating agents in basic medium

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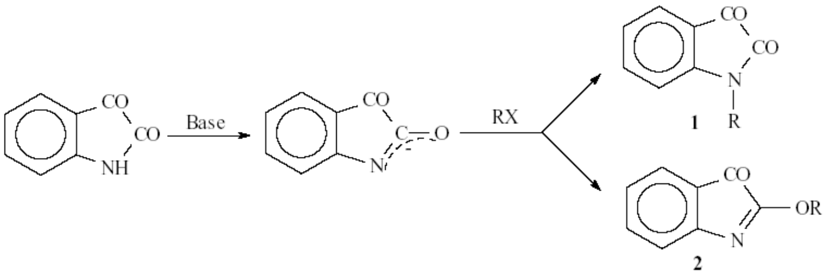
Introduction

N-alkylisatins (**1**) are compounds of great interest as synthetic precursors or intermediates (da Silva *et al*., 2001). Classically *N*-alkylisatins are obtained by reaction of isatin with alkylating agents, especially alkyl halides in the presence of basic agents.

In the reaction isatin anion is generated, which attacks the alkylating agent (Scheme 1). In general, the reaction of isatin with alkyl halides leads mostly to *N*-alkyl derivative when salts of alkaline metals are used as bases (EtONa, K_2CO_3, $CsCO_3$) (Blanco *et al*., 2005). However, due to the ambident anion characteristics this mechanism justifies the possibility of obtaining *O*-alkyl derivatives (**2**) as secondary products.



Scheme 1

Owing to our interest in obtaining isatin derivatives as precursors for synthesis, we studied this kind of reactions by varying the nature of solvents, base, alkylating agent and temperature. Furthermore, results obtained in reactions using conventional heating were compared with those microwave heating.

Methodology

Reactions were carried out in macro or semimicro scales by conventional methods of organic synthesis. In some cases, reactions are optimized using microwaves as energy source. Compounds were purified by chromatographic methods (preparative column or plate, radial chromatography accelerated by centrifugal force using Chromatotron). Products' purity was analysed by thin layer chromatography using chromatofolios. Structure determination was performed on the basis of data from elemental analysis and spectroscopic methods.

Results and discussion

In the reaction of isatin with salts of alkaline metals as bases, *N*-substituted derivatives **1** are obtained when using aprotic polar solvents and moderate temperatures (80-90 °C) (Scheme 2, Table 1).

When alkyl-functionalized halides possessing reactive methylenes (R = CH_2COAr and $CH_2C_6H_4NO_2$) are used, epoxides **3** are isolated in varying amounts according to reaction conditions. These compounds result from an initial aldol-type condensation between isatin through its ketone carbonyl and the reactive methylene of the alkylating agent, and later dehydrohalogenation promoted by the basic agent.

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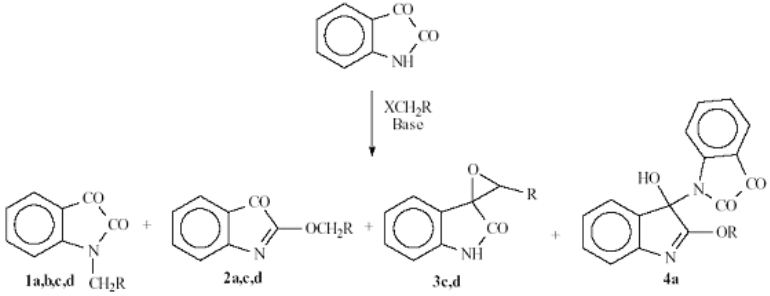

Compounds 1,2,3,4	R
a	CH_2-CH_3
b	CH_2-$CO_2CH_2CH_3$
c	CH_2-CO-C_6H_5
d	CH_2-$C_6H_4NO_2$

Scheme 2

Table 1

RX	Base	T (°C)	Solvent	Products 1 (%)	2 (%)	3 (%)	Others
CH_3CH_2I	K_2CO_3	70-80	DMF or NMP	89	-	-	
	Ag_2CO_3	rt	Benzene	-	-	-	[a]
	Ag_2CO_3	50	Benzene	40	12	-	**4** (33 %)
	Ag_2CO_3	50	Chloroform	26	15	-	**4** (48 %)
$ClCH_2CO_2C_2H_5$/NaI	K_2CO_3	70-80	DMF or NMP	85	-	-	
	Ag_2CO_3	rt	Chloroform	-	-	-	[a]
	Ag_2CO_3	50	Chloroform	36	-	-	[a]
$BrCH_2COC_6H_5$/NaI	K_2CO_3	70	DMF or NMP	66	-	22	
	K_2CO_3	rt	Benzene	-	-	89	[a]
	Ag_2CO_3	rt	Benzene	-	-	-	[a]
	Ag_2CO_3	50	Benzene	58	5	20	$HOCH_2COC_6H_5$
	Ag_2CO_3	50	Chloroform	50	10	35	$HOCH_2COC_6H_5$
$BrCH_2C_6H_4NO_2$/NaI	K_2CO_3	70	DMF or NMP	75		15	$HOCH_2C_6H_4NO_2$
	Ag_2CO_3	rt	Benzene	-	-	-	[a]
	Ag_2CO_3	50	Benzene	40	-	-	$HOCH_2C_6H_4NO_2$
	Ag_2CO_3	50	Chloroform	50	30	-	$HOCH_2C_6H_4NO_2$
	CH_3CH_2ONa	rt	Ethanol	-	-	77	

[a] Non-reacting isatin is recovered.

O-Substituted derivatives **2** are only obtained as minor products by reaction of isatin with an alkyl iodide in the presence of Ag_2CO_3/chloroform or benzene at 50-60 °C. In all cases varying amounts of *N*-alkylated isomer were in addition obtained, and the hydrolysis product of the halogenated derivative among other compounds.

Thus, in the reaction of isatin with ethyl iodide and Ag_2CO_3 in chloroform, product **4** was also isolated, whose formation can be interpreted as a result of obtaining the *O*-ethyl derivative **2**, and later adding isatin anion to the ketonic carbonyl.

The use of microwave irradiation as an alternative energy source is useful only when *N*-substituted derivatives are to be obtained. In these cases reactions are completed quickly, and therefore isolation and purification of reaction products are easier to perform

Note: This study was presented at the "XXVI Congreso Argentino de Química" , San Luis, Argentina, 2006

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