SIMPLE METHOD FOR THE PREPARATION OF 1-SUBSTITUTED ISATINS

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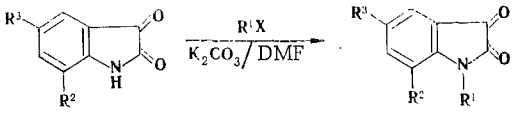
The use of potassium carbonate in dimethylformamide (DMF) makes it possible to carry out the N-alkylation of isatins with alkyl bromides and iodides and acyl chlorides at room temperature and with alkyl chlorides at elevated temperatures (70-80°C) without ring opening. The previously inaccessible N-(2-chloroethyl)-isatins were obtained by alkylation of isatin with 1,2-dichloroethane. The condensation of isatins with 1,3-dichloro-2-butene takes place only at the chlorine atom in the allyl position of the latter.

The direct N-alkylation and N-acylation of isatins, which is usually carried out under severe conditions in the presence of alkalis and metal alkoxides and hydrides [1, 2], has a number of disadvantages. The reaction in alcoholic alkali or in solutions of alkoxides frequently leads to the formation of complex mixtures of compounds, chiefly because of opening of the pyrrole ring. The preparation of isatin salts under the influence of sodium or lithium hydrides in dimethylformamide (DMF) is inconvenient, since it is accompanied by hydrogen evolution and spontaneous heating and requires strict monitoring of the temperature and reaction time in order to avoid decomposition.

We propose a simple method for the preparation of 1-substituted isatins in the presence of potassium carbonate in DMF [3].



I—VIII $R^2=R^3=H$; I $R^1=CH_3$; II $R^1=C_2H_5$; III $R^1=CH_2—CH=CH_2$; IV $R^1=CH_2—C\equiv CH$; V $R^1=H_5C_2OOC—CH_2$; VI $R^1=CH_3CO$; VII $R^1=H_5C_2OOC$; VIII $R^1=CH_2—CH_2—Br$; IX—XXII (see Table 2); X=Cl, Br, I

As a consequence of its high solvating capacity, DMF accelerates the formation of an isatin anion and its subsequent alkylation.

The reaction with dimethyl sulfate, alkyl bromides and iodides, and acyl chlorides takes place in 2-3 h at room temperature and frequently gives the products in quantitative yields (Table 1, I-VIII).

Alkyl chlorides have not been previously used for the alkylation of isatins. The reac-

TABLE 1. Yields of I-VIII

Compound	Alkylating (acylating) agent	Yield, %
I	CH_3I, $(CH_3)_2SO_4$	Quantitative
II	C_2H_5I	81
III	$CH_2=CH—CH_2Br$	95
IV	$HC\equiv C—CH_2Br$	92
V	$H_5C_2OOCCH_2Br$	90
VI	CH_3COCl	88
VII	H_5C_2OOCCl	80
VIII	$BrCH_2CH_2Br$	75

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TABLE 2. 1-Alkylisatins

Compound	R^1	R^2	R^3	mp, °C	Found, %				Empirical formula	Calc., %				Yield, %
					C	H	Br (Cl)	N		C	H	Br (Cl)	N	
IX	$-CH_2-CH=C(Cl)-CH_3$	H	H	111—112	61,0	4,3	15,6	5,9	$C_{12}H_{10}ClNO_2$	61,2	4,3	15,4	5,9	96
X	$-CH_2-CH=C(Cl)-CH_3$	H	CH_3	131—132	62,3	5,0	14,5	5,7	$C_{13}H_{12}ClNO_2$	62,5	4,8	14,2	5,6	91
XI	$-CH_2-CH=C(Cl)-CH_3$	H	CH_3O	112—113	58,7	4,6	13,4	5,4	$C_{13}H_{12}ClNO_3$	58,8	4,6	13,3	5,3	65
XII	$-CH_2-CH=C(Cl)-CH_3$	H	Cl	119—120	53,4	3,4	26,3	5,1	$C_{12}H_9Cl_2NO_2$	53,3	3,4	26,3	5,2	70
XIII	$-CH_2-CH=C(Cl)-CH_3$	H	Br	125—126	46,0	3,1	37,0	4,7	$C_{12}H_9BrClNO_2$	45,8	2,9	36,7	4,5	67
XIV	$-CH_2-CH=C(Cl)-CH_3$	CH_3	H	114—115	62,4	4,8	14,4	5,8	$C_{13}H_{12}ClNO_2$	62,5	4,8	14,2	5,6	70
XV	$-CH_2-CH=C(Cl)-CH_3$	H	NO_2	154—155	51,4	3,2	12,5	9,8	$C_{12}H_9ClN_2O_4$	51,4	3,2	12,6	10,0	71
XVI	$-CH_2-CH=C(Cl)-CH_3$	CH_3	NO_2	145—147	52,9	3,6	12,3	9,4	$C_{13}H_{11}ClN_2O_4$	53,0	3,8	12,0	9,5	65
XVII	$-CH_2-CH_2-Cl$	H	H	111—112	57,4	3,9	17,1	6,6	$C_{10}H_8ClNO_2$	57,3	3,9	17,0	6,7	80
XVIII	$-CH_2-CH_2-Cl$	H	CH_3	125—127	59,3	4,7	15,8	6,5	$C_{11}H_{10}ClNO_2$	59,1	4,5	15,9	6,3	80
XIX	$-CH_2-CH_2-Cl$	CH_3	H	108—109	59,3	4,5	15,7	6,3	$C_{11}H_{10}ClNO_2$	59,1	4,5	15,9	6,3	85
XX	$-CH_2-CH_2-Cl$	H	Cl	114—116	49,5	3,1	29,4	5,6	$C_{10}H_7Cl_2NO_2$	49,2	2,9	29,1	5,7	67
XXI	$-CH_2-CH_2-Cl$	H	Br	138—140	41,8	2,4	40,1	4,9	$C_{10}H_7BrClNO_2$	41,6	2,4	40,0	4,8	67
XXII	$-CH_2-CH_2-Cl$	H	NO_2	141—143	47,3	2,7	14,2	11,0	$C_{10}H_7ClN_2O_4$	47,2	2,8	13,9	11,0	33

TABLE 3. Spectral Characteristics of the 1-Alkylisatins

Compound	IR spectrum, cm^{-1}		UV spectrum, λ_{max}, nm (log ε)
	α-CO	β-CO	
IX	1750	1735	213,5 (4,28); 247 (4,32); 303 (3,33); 428 (2,67)
X	1748	1724	217 (4,31); 251 (4,51); 304 (3,88); 510 (2,78)
XI	1740	1723	216 (4,44); 257 (4,48); 309 (3,32); 510 (2,78)
XII	1739		212,5 (4,48); 251 (4,38); 301,5 (3,49); 438 (2,41)
XIII	1755	1725	215 (4,38); 2,54 (4,62); 305 (3,54); 439 (2,42)
XIV	1740	1718	219 (4,31); 248 (4,44); 315 (3,65); 436 (2,75)
XV	1759		207 (4,49); 255 (4,20); 336 (4,26)
XVI	1755	1740	214 (4,42); 260 (3,68); 335 (4,18)
XVII	1728		213 (4,18); 244 (4,34); 251 (4,27); 301 (3,45); 420 (2,70)
XVIII	1746	1743	216 (4,14); 249 (4,33); 255 (4,26); 303 (3,41); 435 (2,71)
XIX	1745	1758	218 (4,17); 248 (4,30); 253 (4,26); 312 (3,56); 427 (2,78)
XX	1753		213 (4,26); 2,51 (4,15); 256 (4,12); 300 (3,15); 435 (2,41)
XXI	1745		215 (4,29); 253 (4,18); 257 (4,16); 301 (3,18); 436 (2,48)
XXII	1760		209 (4,26); 326 (4,06)

tion is readily realizable when the chlorine atom is replaced by an iodine atom via the Finkelstein reaction; however, this method cannot be used in the preparation of 1-chloroalkylisatins.

Dihaloalkanes with one chlorine atom also cannot be used because it is replaced by the more active halogen under the influence of the KBr (KI) formed during the reaction. Thus, judging from the mass-spectral data, in an attempt to synthesize 1-(γ-chloropropyl)isatin from isatin and 1-bromo-3-chloropropane we obtained a mixture of the desired product with 1-(γ-bromopropyl)isatin. This may apparently explain the inaccessibility of 1-chloroalkylisatins, which were obtained by an indirect method, viz., by exchange of the hydroxy group in 1-(hydroxyalkyl)isatins for a chlorine atom by the action of thionyl chloride [4, 5].

The use of K_2CO_3/DMF and raising the reaction temperature made it possible to obtain 1-chloroalkylisatins by direct alkylation of isatins with dichloroalkanes (Table 2).

The structures of the previously described compounds were confirmed by comparison with the literature data and genuine samples.

The IR spectra of the 1-alkylisatins contain two intense absorption bands of C_2=O and C_3=O groups, which are sometimes overlapped. Four maxima are usually observed in the UV spectra (Table 3), and the fragmentation that is characteristic for isatins is observed in the mass spectra [5].

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in alcohol were recorded with a Specord UV-vis spectrophotometer. The mass spectra were obtained with an MKh-1320 mass spectrometer with introduction of the substances into the ion source; the source temperature was 60°C, and the ionizing voltage was 70 eV at an emission current of 50 μA.

To monitor the alkylation samples were selected periodically and diluted with water, and the diluted samples were acidified and extracted with ether or ethyl acetate. The extracts were analyzed by thin-layer chromatography (TLC) on Silufol in benzene–acetone (4:1), chloroform–acetone (9:1), and chloroform–petroleum ether–acetone (9:5:1) systems. 5-Methylisatin, 7-methylisatin [6], 5-methoxyisatin [7], 5-nitroisatin, and 5-nitro-7-methylisatin [5] were obtained by the described methods.

Isatin was recrystallized from water, and 5-bromoisatin was recrystallized from dioxane. Commercial-grade DMF (without special purification) and finely ground anhydrous potassium carbonate were used.

Alkylation and Acylation. A 0.1-mole sample of the corresponding isatin was dissolved in 40 ml of DMF, 0.15 mole of potassium carbonate was added, and 0.12 mole of the corresponding halide was then added dropwise with stirring. After 2 h, the reaction mass was poured into 400 ml of ice water. In the synthesis of IX-XXI the mixture was heated at 50°C for 3 h and poured into 15% sodium chloride solution with the addition of 0.15 mole of HCl. The precipitate was separated, washed with water, and dried successively in air and *in vacuo* over $CaCl_2$. The aqueous filtrate was extracted with benzene, and the extract was dried over anhydrous Na_2SO_4. Evaporation gave an additional quantity of the substance. Where necessary, the product was crystallized from ethanol.

N-(2-Chloroethyl)isatin. A 7.35-g (0.05 mole) sample of isatin was dissolved in 50 ml of DMF, 17.25 g (0.125 mole) of potassium carbonate and 98.9 g (1 mole) of 1,2-dichloroethane were added to the solution with stirring, and the mixture was heated at 80°C with stirring for 5 h. It was then poured into 500 ml of water containing 13 ml of concentrated HCl, and the organic layer was separated. The aqueous layer was extracted with 1,2-dichloroethane (three 100-ml portions), and the combined extracts were washed with water and dried over Na_2SO_4. The solvent was removed, and the precipitate was crystallized from ethanol to give 8.46 g (80%) of a product with mp 111–112°C. Mass spectrum (m/z): 209 (M^+), 181, 153, 180/182, 151/152, 146, 132, 105, 104, 77. Other examples are given in Table 2.

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