Tetrahedron Letters 53 (2012) 2514–2517

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Reaction of isatin with alkylating agents with acidic methylenes

María S. Shmidt [a], Isabel A. Perillo [a], Mercedes González [b], María M. Blanco [a,*]

[a] Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956 (1113) Buenos Aires, Argentina
[b] Facultad de Ciencias, Universidad de la República, Iguá 4225, 11400 Montevideo, Uruguay

ARTICLE INFO

Article history:
Received 6 February 2012
Revised 29 February 2012
Accepted 2 March 2012
Available online 11 March 2012

Keywords:
Isatin
N- and *O*-Alkyl derivatives
Epoxyindoles
Rearrangement
4-Quinolinones

ABSTRACT

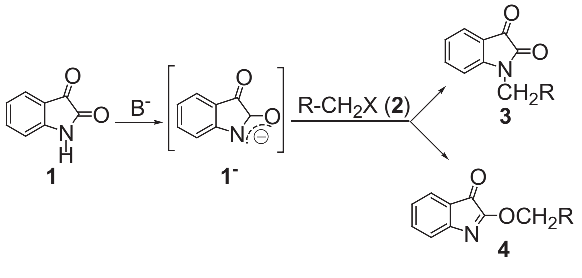
The reaction of isatin (**1**) with different alkyl halides **2** and alkaline carbonates in aprotic polar solvents leads mainly to *N*-alkyl derivatives **3**. The use of alkylating agents that have acidic methylenes leads to competitive formation of the corresponding epoxide **5**. The formation of **5** is favored by low-polarity solvents at low temperatures and strong bases. Epoxides **5c, d** obtained using NaEtOH/EtOH at 0–5 °C are transformed into the corresponding 4-quinolinones **6** at higher temperatures. The use of Ag$_2$CO$_3$ allows obtaining compounds **3** as major products, along with varying amounts of labile *O*-alkyl derivatives **4** and dimerization products.

Isatin (2,3-dihydro-2,3-dioxo-1*H*-indole) **1** is a polyfunctional nitrogen heterocycle, whose behavior in alkylation reactions promoted by bases is strongly dependent on the reaction conditions and nature of the alkylating agent **2**.[1] Due to the ambident character of the anion of the amide (**1**$^-$), the use of alkali metal salts as bases leads mainly to *N*-alkyl derivatives **3**,[2] whereas, the use of silver salts leads to O-alkylated regioisomers **4**[1] (Scheme 1). This result is consistent with the assumption made by Kornblum in which the silver ion polarizes the C-halogen bond of the alkyl halides, enhancing the development of the carbocation character in the transition state. The greater binding affinity for the atom that has the higher electron density would thus lead preferably to the *O*-alkyl derivative.[3] Similar conclusions arise from the application of the HSAB principle.[4]

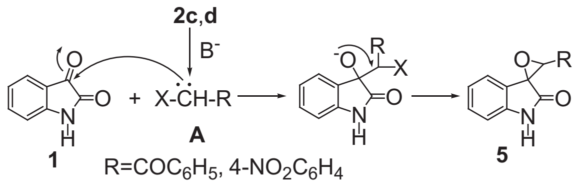
On the other hand, the formation of the epoxyoxindole **5** is often the main product[5] when the alkylating agent has an acidic α-proton (such as phenacyl and nitrobenzyl halides) (Scheme 2). Its formation is interpreted as the result of a Darzens condensation,[6] which involves the generation of the conjugated base of the alkyl halide (**A**), the nucleophilic attack to the β-keto carbonyl, and the final displacement of the ion halide by an anionic oxygen attack (Scheme 2). As a consequence of this reaction, the formation of *N*-phenacyl isatins has been proved to be difficult,[7] and different synthetic strategies have been used to improve yields.[8]

Our interest in the use of N-substituted derivatives of isatin **3**[9] as synthetic precursors prompted us to study alkylation reactions of isatin (**1**) to determine the influence of the alkylating agent and the reaction conditions (type of base, solvent, temperature) on them.

As alkylating agents, we used alkyl halides (**2**, R–CH$_2$–X) containing methylene groups with different reactivity: ethyl iodide (**2a**), ethyl chloroacetate, 4-nitrobenzyl bromide, and phenacyl chloride, which, according to the conditions, could lead to



Scheme 1.



Scheme 2.

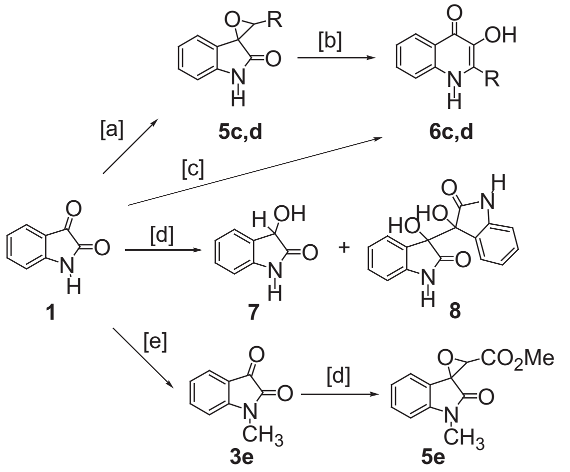
---

* Corresponding author.
E-mail address: mblanco@ffyb.uba.ar (M.M. Blanco).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.03.010

Table 1
Structure of the compounds which were attempted to prepare

Compounds **2–6**	R
a	CH_3
b	CO_2CH_3
c	$4\text{-}NO_2C_6H_4$
d	COC_6H_5



Scheme 3. Reagents and conditions: (a) **2c**,**d**, NaOEt/EtOH, 5–10 °C. (b) NaOEt/EtOH, 20–25 °C. (c) **2c**,**d**, NaOEt/EtOH, 20–25 °C. (d) **2b**, NaOEt/EtOH, 0–5 °C. (e) ICH_3/K_2CO_3/DMF, 50 °C.

compounds **3–5** (Table 1). To minimize the differences due to the reactivity of the halogen, the reactions of chlorides or bromides were carried out in the presence of catalytic amounts of NaI, generating the corresponding iodides **2b–d** in situ[10] (Table 1). As bases, we used alkaline carbonates, NaOEt and Ag_2CO_3.

Results are presented in Table 2. The reaction of isatin (**1**) with alkylating agents **2a–c** and K_2CO_3 as base in DMF at 70–80 °C led to the corresponding N-substituted derivatives **3a–c** with good yields (74–89%) (entries 1, 4, 7). With NMP, the results were similar. Instead, using Cs_2CO_3, the by-products increased and the workup was more difficult.

On the other hand, in the reaction of **1** with phenacyl iodide (**2d**) (K_2CO_3/DMF), the yield of N-alkyl derivative **3d** was lower (66%) due to the competitive formation of epoxyoxindole **5d** (3′-benzoylspiro[2-oxoindoline-3,2′-oxirane], 22%) (entry 18). This reaction is strongly dependent on the working conditions. Thus, the yield of **3d** improves (75%) when the reaction was carried out under microwave irradiation. Using conventional heating in low-polarity solvents (benzene, chloroform, reflux temperature), epoxide **5d** was isolated as the main product (40–52%) together with smaller amounts of **3d** (ca. 20%) (entries 21 and 23). Working at room temperature, independently of the nature of the solvent, epoxide **5d** was obtained with excellent yields (ca. 90%) (entries 19, 20, 22).

According to the accepted mechanism (Scheme 2), the formation of epoxide **5** requires the generation of carbanion **A**, which in turn depends on the methylene acidity of the alkyl halide and the strength of the base. Given that the order of the acidity of the alkyl halides is **2a** <**2b** <**2c** <**2d**, it is justified that with the less reactive ones (**2a**, **b**) it was not possible to obtain the corresponding epoxides

Table 2
Reaction of isatin with alkylating agents with acidic methylenes

Entry	RI[a]	Base	Conditions (h, °C)	Solvent	**3** (%)	**4** (%)	**5** (%)	Others (%)
1	**2a**	K_2CO_3	2, 70–80[b]	DMF	89	–	–	–
2	**2a**	Ag_2CO_3	24, 50[b]	C_6H_6	40	12	–	**9** (13)
3	**2a**	Ag_2CO_3	24, 50	$HCCl_3$	26	15	–	**9** (18)
4	**2b**	K_2CO_3	2, 70–80[b]	DMF	88	–	–	–
5	**2b**	NaOEt	24, 0–5	EtOH	–	–	–	**7** (15), **8** (22)[c,d]
6	**2b**	Ag_2CO_3	24, 50[b]	$HCCl_3$	36	–	–	[e]
7	**2c**	K_2CO_3	1, 80	DMF	74	–	–	$HOCH_2(4\text{–}NO_2C_6H_4)$ (8)[c]
8	**2c**	K_2CO_3	24, 20–25	DMF	62	–	–	[c]
9	**2c**	K_2CO_3	48, 20–25	C_6H_6	40	–	15	[c]
10	**2c**	K_2CO_3	1, 80	C_6H_6	87	–	–	–
11	**2c**	K_2CO_3	24, 20–25	$HCCl_3$	55	–	–	[c]
12	**2c**	K_2CO_3	2, 70	$HCCl_3$	92	–	–	–
13	**2c**	NaOEt	6, 5–10	EtOH	–	–	95	–
14	**2c**	NaOEt	0.5, 70	EtOH	–	–	56	**6c** (32)
15	**2c**	NaOEt	24, 20–25	EtOH	–	–	5	**6c** (90)
16	**2c**	Ag_2CO_3	24, 50[b]	C_6H_6	40	–	–	$HOCH_2(4\text{–}NO_2C_6H_4)$ (14)[e]
17	**2c**	Ag_2CO_3	24, 50[b]	$HCCl_3$	50	30	–	$HOCH_2(4\text{–}NO_2C_6H_4)$ (10)[e]
18	**2d**	K_2CO_3	1, 80	DMF[f]	66	–	22	–
19	**2d**	K_2CO_3	2, 20–25	DMF	–	–	92	–
20	**2d**	K_2CO_3	24, 20–25	C_6H_6	–	–	89	–
21	**2d**	K_2CO_3	2, 80	C_6H_6	20	–	40	[e]
22	**2d**	K_2CO_3	3, 20–25	$HCCl_3$	–	–	90	[c]
23	**2d**	K_2CO_3	2, 70	$HCCl_3$	23	–	52	[e]
24	**2d**	NaOEt	2, 0–5	EtOH	–	–	99	–
25	**2d**	NaOEt	4, 20–25	EtOH	–	–	10	**6d** (73)
26	**2d**	NaOEt	1, 70	EtOH	–	–	–	**6d** (76)
27	**2d**	Ag_2CO_3	24, 50[b]	C_6H_6	40	–	20	$HOCH_2COC_6H_5$ (6)[e]
28	**2d**	Ag_2CO_3	24, 50[b]	$HCCl_3$	50	–	35	$HOCH_2COC_6H_5$ (6)[e]

[a] Compounds **2b–d** were generated in situ from the corresponding chlorides or bromides and catalytic amounts of NaI.
[b] No reaction was observed at 25 °C after 24 h.
[c] Unreacted isatin was recovered.
[d] At higher temperature complex mixtures of decomposition products were obtained.
[e] Mixtures of colored products were obtained.
[f] 15 mL of DMF were used.

5, whereas with the most reactive one, phenacyl iodide (**2d**), the yields were generally high (entries 19, 20, 22).

The influence of the base is observed in the reactions with the nitrobenzyl halide **2c**, a compound with intermediate methylene acidity. In this case, using K_2CO_3 at different temperatures in different solvents, mainly *N*-alkyl derivative **3c** was obtained (entries 7–12). In contrast, when the reaction was carried out at 5–10 °C in EtO^-/EtOH, a considerably stronger base, epoxide **5c** (3′-(4-nitrophenyl)spiro[2-oxoindoline-3,2′-oxirane]) was obtained in excellent yields (95%) (Scheme 3) (entry 13). As the temperature or the reaction time increased, the yield of **5c** decreased (entries 14 and 15) with the simultaneous appearance and increase in the yield of a compound of mp 370–372 °C. By bi-dimensional heteronuclear correlation spectra, the structure of the product was established as 1,4-dihydro-3-hydroxy-2-(4-nitrophenyl)-4-oxoquinoline (**6c**). The best yields of **6c** were obtained after 24 h at 20–25 °C (entry 15).

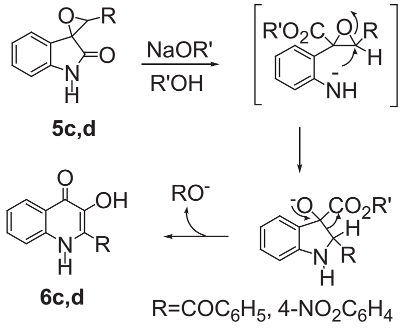
The origin of compound **6c** could be interpreted as the result of the N-substitution of isatin generating **3c** and its subsequent alkoxide induced ring open-ring closing rearrangement.[9] However, by monitoring the reaction at room temperature (TLC, Cl_2CH_2:MeOH (4.7:0.3), we observed the appearance of the epoxide **5c** (*Rf*: 0.55) after 2 h of reaction.

At 5 h, we began detecting **6c** (*Rf*: 0.30), which increased in intensity as isatin (**1**) and epoxide **5c** decreased. At 24 h, **6c** was the main product together with traces of epoxide **5c**. Neither **3c** nor any other intermediate product was detected at any time. On the other hand, the reaction of **5c** with EtO^-/EtOH under similar conditions slowly led to **6c** only, whereas **3c** under the same conditions led to a complex mixture of products. These results indicate that, under our working conditions, **5c** is a precursor of hydroxyquinolinone **6c** (Scheme 3).

The reaction of isatin (**1**) with phenacyl halide **2d** in EtO^-/EtOH showed a behavior similar to that of the previous case, producing epoxide **5d** and hydroxyquinolinone **6d** according to the conditions, although in this case, the rearrangement **5d**→**6d** was even faster. Thus, at 0–5 °C in 2 h, the yield of epoxide **5d** was practically quantitative (entry 24), whereas at 20 °C in 4 h or at 70 °C in 1 h, good yields of **6d** were obtained (entries 25 and 26).

A possible mechanism for the alkoxide-promoted rearrangement **5**→**6** is shown in Scheme 4. This mechanism involves the initial attack of the alkoxide with cleavage of the lactam and generation of an anionic nitrogen. This, in turn, induces the opening of the oxirane ring. Finally, the expansion of the pentagonal ring would result from a 1,2-intramolecular migration of a carbon of the ring to the ester carbonyl, with displacement of RO^-.

The **5d**→**6d** rearrangement would be favored by the carbanionic character that can be acquired by the migratory carbon due to the stability conferred by the electron acceptor group (COC_6H_5 or 4-$NO_2C_6H_4$). The **5d**→**6d** rearrangement would be faster than **5c**→**6c** due to the greater acceptor effect of the electrons of COC_6H_5 with respect to 4-$NO_2C_6H_4$ and therefore the greater carbanionic character that would be acquired by the migratory carbon.



Scheme 4.

Unlike the behavior of halides **2c**, **d** in the reactions of alkylation in the presence of alkoxide, using the haloester **2b**, it was not possible to isolate the corresponding epoxide. The reaction at 0–5 °C for 24 h leads to dioxindole **7** (2,3-dihydro-3-hydroxy-2-oxo-1*H*-indole, 15%), isatide **8** (2,2′,3,3′-tetrahydro-3,3′-dihydroxy-2,2′-dioxo-[3,3′-bi-1*H*-indole], 22%) and decomposition products (entry 5) (Scheme 3). The presence of dioxindole **7** can be explained by the carbonyl reductive ability of sodium alkoxides.[9] On the other hand, the presence of isatide **8** is probably the result of the condensation of isatin **1** with dioxindole **7** in the reaction medium.[1a]

Considering that the lability of the isatin nucleus against bases was one of the factors that hindered the reaction, we used *N*-methylisatin (**3e**) as substrate. The reaction of this compound with the haloester **2b** under similar conditions led to the corresponding epoxyester **5e** in good yield (77%) (Scheme 3). This result is similar to that obtained by Baiocchi, thus confirming that the N-substituted isatins are excellent substrates for the Darzens condensation.[11]

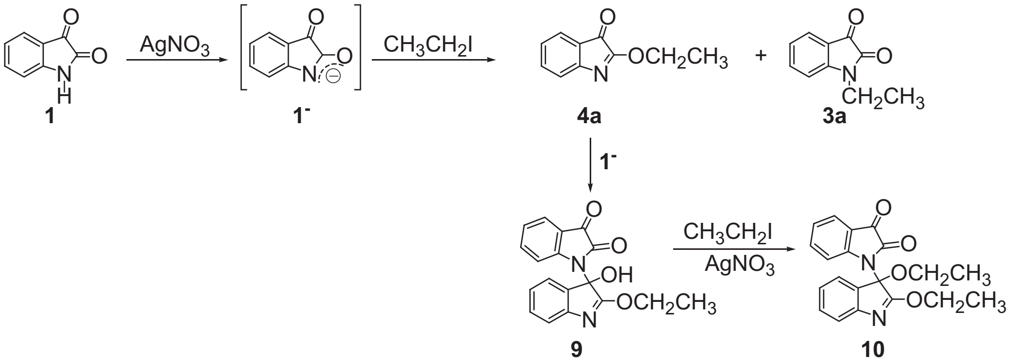
In order to promote the formation of the *O*-alkyl regioisomers **4**, we used Ag_2CO_3 as base, an agent that showed high regioselectivity in the alkylation of 2-quinolones.[12] When the alkylation of isatin (**1**) was attempted with halides **2a–d** at room temperature in benzene or chloroform, unreacted starting material was recovered in all cases. On the other hand, the reaction with ethyl iodide (**2a**) at 50 °C led to a mixture of derivatives N- and O-substituted **3a** and **4a** together with a third product (entries 2, 3, and Scheme 5). The HRMS of this compound corresponds to the molecular formula $C_{18}H_{14}N_2O_4$ and coincides with that of the 'ethyl isatoide' described by Heller and Benade.[13] Finally, the structure was established on the basis of the ^1H and ^{13}C NMR correlation experiments and the compound was identified as 2-ethoxy-3-(2,3-dihydro-2,3-dioxo-1*H*-indolyl)-3-hydroxy-3*H*-indole (**9**).

The formation of **9** can be interpreted as the result of obtaining the *O*-ethyl derivative **4a** and subsequent addition of the anion of isatin to the β-keto carbonyl (Scheme 5). Monitoring this reaction by TLC, using CH_2Cl_2 as eluent, initial formation of **4a** (25% after 6 h of reaction) together with significant amounts of unreacted isatin **1** was observed. At longer reaction times, there is a decrease of **4a** and the appearance of **3a** and **9**, which are the main products after 24 h of reaction (entry 2). By prolonging the heating, compound **4a** disappears, and a complex mixture of colored products is obtained from which compound **10** (2,3-diethoxy-3-(2,3-dihydro-2,3-dioxo-1*H*-indolyl)-3*H*-indole), along with **3a** and **9**, was isolated. Compound **10** may be considered the result of the O-ethylation of **9** in the basic medium of the reaction (Scheme 5).

During storing or chromatographic isolation of **4a**, its partial transformation into **9**, among other products, was observed. These results are consistent with the instability described for the *O*-alkyl isatins **4** against hydrolysis[14] generating the isatin anion ($\mathbf{1}^-$) and the subsequent formation of **9** as described above.

In general, alkylation of isatin (**1**) in the presence of Ag_2CO_3 with iodides **2b–d** led to complex mixtures of compounds that probably result from reactions such as those indicated in Scheme 5 (entries 6, 16, 17, 26, 27). The expected *O*-alkyl derivative **4c** was isolated only in low yields using $HCCl_3$ as solvent (entry 17). In other cases the corresponding N-substituted compounds **3** were the main products. Several attempts to increase the yields of *O*-alkyl derivatives **4** failed. Shorter reaction times and a lower reaction temperature allowed recovering abundant unreacted isatin (**1**). Increasing the temperature or using MW, the yield of the corresponding *N*-alkyl derivatives **3** and the formation of dimerization products increased.

In summary, herein we have presented the results of alkylation reactions of isatin in basic media. These reactions allow obtaining



Scheme 5.

N-and O-substituted derivatives **3** and **4**, respectively, as well as epoxides **5** that result from the addition of alkyl halide to the β-carbonyl of isatin. The course of the reactions depends on the acidity of the methylene attached to the halogen and the reaction conditions, especially the strength of the base, the nature of the solvent and the reaction temperature. The use of MW was only relevant for N-alkylation reactions which require moderately high temperatures. The use of MW irradiation performing these alkylating reactions is not appropriate since low temperatures are required to obtain compounds **4** and **5**.

Acknowledgments

This work was financially supported by the Universidad de Buenos Aires and the Agencia Nacional de Promoción Científica y Tecnológica.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.010.

References and notes

1. (a) Sumpter, W. C. *Chem. Rev.* **1944**, *34*, 393–434; (b) Popp, F. D. *Adv. Heterocycl. Chem.* **1975**, *18*, 1–58; (c) da Silva, J. F. M.; Garden, S. J.; da C. Pinto, A. *J. Braz. Chem. Soc.* **2001**, *12*, 273–324.
2. Shmidt, M. S.; Reverdito, A. M.; Kremenchuzky, L.; Perillo, I. A.; Blanco, M. M. *Molecules* **2008**, *13*, 831–840.
3. Kornblum, N.; Smiley, R. A.; Blackwood, R. K.; Iffland, D. C. *J. Am. Chem. Soc.* **1955**, *77*, 6269–6280.
4. Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827–1836.
5. (a) Ainley, A. D.; Robinson, R. *J. Chem. Soc.* **1934**, 1508–1520; (b) Black, D. S. C.; Wong, L. C. H. *J. Chem. Soc., Chem. Commun.* **1980**, 200; (c) Kikumoto, R.; Kobashi, T. *Tetrahedron* **1966**, *22*, 3337–3343.
6. Ballester, M. *Chem. Rev.* **1955**, *55*, 283–300.
7. Matesic, L.; Locke, J. M.; Bremner, J. B.; Pyne, S. G.; Skropeta, D.; Ranson, M.; y Vien, K. L. *Bioorg. Med. Chem.* **2008**, *16*, 3118–3124.
8. (a) Rekhter, M. A. *Chem. Heterocycl. Compd.* **2005**, *41*, 1119–1120; (b) Zhungieto, G. I.; Gorgos, V. I.; Rekhter, M. A.; Korpan, A. I. *Izv. Akad. Nauk Mold. SSR, Ser. Biol. Khim. Nauk* **1980**, 61–67. *Chem. Abstr.* **1980**, *93*, 239138; (c) Rekhter, M. A. *Chem. Heterocycl. Compd.* **1993**, *29*, 548–552; (d) Rekhter, M. A. *Chem. Heterocycl. Compd.* **1999**, *35*, 1165–1166.
9. Blanco, M. M.; Dal Maso, M.; Shmidt, M. S.; Perillo, I. A. *Synthesis* **2007**, 829–834.
10. The results presented in this study are similar to those obtained using alkyl iodides prepared in situ employing the method of Rekhter.[8a]
11. Baiocchi, L.; Giannangeli, M. *J. Heterocycl. Chem.* **1988**, *25*, 1905–1909.
12. Morel, A. F.; Larghi, E. L.; Selvero, M. M. *Synlett* **2005**, 2755–2758.
13. Heller, G.; Benade, W. *Ber.* **1922**, *55*, 1006–1014.
14. Cox, E. G.; Goodwin, T. H.; Wagstaff, A. I. *Proc. R. Soc. London A* **1936**, *157*, 399–411. and references cited therein.