Simple and Efficient Microwave Assisted N-Alkylation of Isatin

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Abstract: We present herein the results of microwave promoted N-alkylations of isatin (1) with different alkyl, benzyl and functionalized alkyl halides. Reactions were carried out under different conditions, always employing methodologies compatible with MW assisted chemistry. Generation of isatin anion employing diverse bases and solvents or using the preformed isatin sodium salt was tested. The best results were achieved using K₂CO₃ or Cs₂CO₃ and a few drops of N,N-dimethylformamide or N-methyl-2-pyrrolidinone. These reactions present noteworthy advantages over those carried out employing conventional heating.

Keywords: Isatin, N-alkylation, microwave irradiation, conventional heating, isatin sodium salt.

Introduction

N-alkylation of isatin (1, Scheme 1) reduces the lability of the isatin nucleus towards bases, while maintaining its typical reactivity. Thus, N-substituted isatins 2 have been frequently used as intermediates and synthetic precursors for the preparation of a wide variety of heterocyclic compounds [1, 2]. In addition, properly functionalized N-alkyl isatins present different biological activities [1], and in recent years compounds showing potent cytotoxicity in vitro [3], antiviral activity [4] and potent and selective caspase inhibition [5] have been reported, among others.
As part of our ongoing investigations, we needed to use a series of isatinacetic acid derivatives. This fact led us to explore synthetic methods to obtain $N$-alkylisatins 2 (Scheme 1). Literature procedures include: a) direct synthesis from $N$-alkylanilines and b) $N$-alkylation of isatin. Direct synthesis involves tedious multistep processes which usually give $N$-alkylisatins in low to moderate overall yields [6]. $N$-Alkylation of isatin (1) is usually carried out generating the highly conjugated isatin anion (1') [7] with different bases, followed by treatment with appropriate alkylation agents, generally alkyl halides or sulphates (Scheme 1). These methods had been extensively reviewed [1,8] and include the use of bases such as NaOH, NaH, CaH$_2$ and K$_2$CO$_3$ in different solvents. Synthesis of $N$-functionalized isatins using a parallel synthesis employing a polymer supported strong base for the deprotonation step has been recently reported [9].

Scheme 1. Synthetic route for $N$-substituted isatins 2.

Though some of the above mentioned methods provide good yields of $N$-alkylisatins, they generally present drawbacks related to: a) the base lability of the isatin nucleus [10], b) use of hazardous reagents such as metal hydrides, which require anhydrous solvents, c) use of aprotic organic solvents with high water solubility and high boiling points, leading to complex workups, d) use of carcinogenic solvents in some cases and e) side reactions due to the presence of keto-carbonyls (i.e. reductions when metallic hydrides are used, aldolisation when K$_2$CO$_3$ in acetone is employed). Besides, reaction times are in general lengthy, with consequent formation of by-products, and hence low yields and difficulties in product isolation.

Our interest in this type of reactions prompted us to test the use of microwave (MW) irradiation as an alternative energy source. MW heating has gained popularity in the last decades as it remarkably accelerates a wide variety of reactions and minimizes thermal decomposition of the products. Since the initial work of Gedye [11] and Giguere [12], a rapidly increasing number of reports and reviews have been published demonstrating the importance of such methodology [13]. However, to the best of our knowledge, the potential of this method has not been exploited yet for the type of reactions of interest in this case [14].

We present herein results of MW assisted synthesis of $N$-alkylisatins 2 by $N$-alkylation of isatin (1) with different alkyl, benzyl and functionalized alkyl halides (Scheme 1, Table 1) and their comparison with those obtained under conventional heating. Reactions were carried out under different conditions, always employing methodologies compatible with MW assisted chemistry.
**Results and Discussion**

We initially examined reactions under “dry” conditions [16], irradiating the mixture of neat reactants, either generating isatin anion (1') in situ (Method A) or employing the pre-formed sodium isatin salt (Na'1) (Method B). In all cases decomposition of reactants or recovery of unreacted starting material was observed. On the other hand, results improved notably when some drops of a polar aprotic solvent, enough to humidify the reaction mixture, are added, giving a polar mixture that is more prone to MW absorption [17]. This is a fundamental requirement in the case where the sodium salt of isatin or alkylating agents with high melting point (i.e.: N-methyl-N-phenylchloroacetamide) are used.

Using ethyl chloroacetate as alkylating agent, we optimized reaction conditions by testing several parameters such as different bases and solvents. The best results were obtained employing K$_2$CO$_3$ or Cs$_2$CO$_3$ in N,N-dimethylformamide (DMF) or N-methyl-2-pyrrolidinone (NMP). Results obtained with different alkyl halides are shown in Table 2. Employing low or medium power settings full conversions are achieved in a few minutes and moderate to high yields of compounds 2 are obtained. The use of NMP is specially important when poorly reactive halides are employed (see entry 19). We also observed that, in general, the use of Cs$_2$CO$_3$ as the base facilitates the workup, but yields are lower in some cases (see entries 5 and 17).

In experiments carried out under conventional heating we encounter longer reaction times and lower yields. As an example, using K$_2$CO$_3$/DMF, the cinnamyl derivative 2e was obtained in high yield in two minutes, whereas under classical heating four hours were required (Entry 8). Furthermore, to reach satisfactory yields high amounts of solvent are required, thus making product isolation most difficult.

**Table 1. N-Substituted isatins 2.**

| Comp | R   | Comp | R               |
|------|-----|------|-----------------|
| 2a   | Me  | 2g   | CH$_2$CO$_2$Et  |
| 2b   | Et  | 2h   | CH(CO$_2$Et)$_2$|
| 2c   | n-Bu| 2i   | CH$_2$CONH-i-Pr |
| 2d   | CH$_2$Ph | 2j | CH$_2$CON(Me)Ph |
| 2e   | CH$_2$CH=CHP | 2k | CH$_2$(CH$_2$)$_2$CO$_2$Et |
|      | h   |      |                 |
| 2f   | CH$_2$CH$_2$Br | 2l | CH$_2$COPh      |
MW promoted reaction of isatin and equimolecular amounts of ethylene bromide lead to a moderate yield of N-(2-bromoethyl)isatin (2f, Entry 10), while when a three-fold ratio of isatin to ethylene bromide is employed the bis derivative, 1,2-di(1-isatinyl)ethane, was obtained in acceptable yield (Entry 11).

| Entry | Cpd. [a] | Reagents | Base | Solvent | Microwave min/watts | Yield (%) | Conventional heating h/ºC yield (%) |
|-------|----------|----------|------|---------|---------------------|-----------|----------------------------------|
| 1     | 2a       | 1        | IMe [b] | K₂CO₃ | DMF 3/300           | 95        | 1/70 80                          |
| 2     | 2b       | 1        | IEt [b] | K₂CO₃ | DMF 3/300           | 90        | 1.30/70 78                       |
| 3     | 2c       | 1        | Br-nBu | K₂CO₃ | DMF 3/400           | 90        | 2/70 85                          |
| 4     | 2c       | Na¹⁻    | Br-nBu | -      | DMF 5/500           | 69        |                                  |
| 5     | 2d       | 1        | ClICH₂Ph | K₂CO₃ | DMF [c] 5/200       | 96        | 1/120 82                         |
| 6     | 2d       | Na¹⁻    | ClICH₂Ph | -     | DMF 5/400           | 66        |                                  |
| 7     | 2d       | Na¹⁻    | ClICH₂Ph | -     | 4/700 [d] 62 [e]    |           |                                  |
| 8     | 2e       | 1        | BrCH₂CH=CHPh | K₂CO₃ | DMF [c] 2/200       | 86        | 4/70 62                          |
| 9     | 2e       | Na¹⁻    | BrCH₂CH=CHPh | -     | DMF 3/300           | 67        |                                  |
| 10    | 2f       | 1        | BrCH₂CH₂Br | K₂CO₃ | DMF 2/200           | 50 [f]   | 2/70 40 [g]                      |
| 11    | 2f       | 1        | BrCH₂CH₂Br | [h]   | K₂CO₃ 3/300         | 15 [i]   |                                  |
| 12    | 2g       | 1        | ClICH₂CO₂Et | K₂CO₃ | DMF [c] 3/200       | 76        | 2/85 68                          |
| 13    | 2h       | 1        | Br(CH₂CO₂Et)₂ | K₂CO₃ | DMF 3/200           | 55 [j]   | 4/70 25                          |
| 14    | 2i       | 1        | ClICH₂CONH₂-Pr | K₂CO₃ | DMF 4/200           | 86        | 2/90 81                          |
| 15    | 2i       | Na¹⁻    | ClICH₂CONH₂-Pr | -     | DMF 4/300           | 58        |                                  |
| 16    | 2i       | Na¹⁻    | ClICH₂CONH₂-Pr | -     | 10/400 [d] 44 [e]   |           |                                  |
| 17    | 2j       | 1        | ClICH₂CON(Me)Pₙ | K₂CO₃ | NMP [k] 3/200       | 94        | 2/90 83                          |
| 18    | 2j       | Na¹⁻    | ClICH₂CON(Me)Pₙ | -     | DMF 5/300           | 43        |                                  |
| 19    | 2k       | 1        | Cl(CH₂)₂CO₂Et | K₂CO₃ | NMP 4/400           | 56 [l]   | 3/120 38                         |
| 20    | 2k       | Na¹⁻    | Cl(CH₂)₂CO₂Et | -     | DMF 6/500           | 28        |                                  |
| 21    | 2k       | Na¹⁻    | Cl(CH₂)₂CO₂Et | -     | 8/800 [d] [m,e]     |           |                                  |
| 22    | 2l       | 1        | BrCH₂COPh | K₂CO₃ | DMF 7/160           | 53 [n]   | 2/70 22 [o]                      |
| 23    | 2l       | Na¹⁻    | BrCH₂COPh | -     | DMF 4/320           | 62 [p]   |                                  |

[a] Melting points and literature data are presented in Experimental section; [b] a four-fold ratio of alkyl iodide to isatin was used. [c] 93% when Cs₂CO₃ is used as base; employing NMP as the solvent similar yields were obtained; [d] reactions were conducted with intermittent heating alternating irradiation (1 min) and cooling (1 min) periods until the required irradiation time was met; [e] yields do not improve employing tetrabutylammonium bromide as PTC. [f] 16% of 1,2-di(1-isatinyl)ethane was also obtained; [g] 20% of 1,2-di(1-isatinyl)ethane was also obtained; [h] A three-fold ratio of isatin to ethylene bromide was used; [i] 60% of 1,2-di(1-isatinyl)ethane was obtained; [j] 15% of isatin was recovered; when higher powers or longer times are used the yield of 2h diminished and important amounts of compound 2g were obtained; [k] 72% when Cs₂CO₃ is used as base; [l] 35% when DMF is used as solvent; [m] traces of 2k, decomposition products and unreacted isatin were detected by TLC; [n] 30% of epoxide 3 was obtained; [o] 45% of epoxide 3 was obtained; [p] 22% of epoxide 3 was obtained.
Reaction of isatin with phenacyl bromide, either under conventional heating or in the MW promoted reaction, leads to \(N\)-substituted derivative 2l in acceptable yields, although the MW procedure provided the best results (Entry 22). Variable amounts of epoxide 3 (Scheme 2), resulting from addition of the halomethylketone anion (A) onto the isatin \(\beta\)-carbonyl and further cyclization were obtained as a side product [18].

MW promoted \(N\)-alkylation of isatin using the preformed sodium salt (\(Na^+\)1) requires higher power to complete the reactions, but the yields do not surpass 70% (entries 4, 6, 9, 15, 18 and 20). In the reaction with phenacyl bromide, the method facilitates work up and improves yields by minimizing epoxide formation (Entry 23). Absence of an excess of base which would make carbanion A formation difficult, accounts for such results (Scheme 2).

As an alternative, techniques combining MW irradiation with the use of isatin sodium salt supported on mineral surfaces under solvent free conditions were used (Method C), an eco-friendly methodology which had received attention in recent years [16]. Under such conditions, high powers were required. In order to avoid reactant and product decomposition, reactions were conducted with intermittent heating. This method was designed to avoid overheating of reactants, according to Varma et al., when a household microwave oven is employed. [19] However, yields did not exceed 62 %, and could not be improved using phase transfer catalysis (Entries 7, 16 and 21).

Scheme 2. Probable mechanism for the synthesis of epoxide 3.

Conclusions

We have developed a simple and efficient MW assisted synthesis of \(N\)-alkylisatins 2 by \(N\)-alkylation of isatin (1) using a household oven. The procedure involves the use of \(K_2CO_3\) or \(Cs_2CO_3\) and a few drops of DMF or NMP, and is a general one for reactions with alkyl, benzyl and functionalized alkyl halides of different reactivity. The use of MW irradiation offers many advantages over conventional heating: it remarkably decreases reaction times, requires less solvent, thus facilitating reaction workups, and increases yields.

Experimental

General

Melting points were taken on a Büchi capillary apparatus and are uncorrected. The \(^1\)H- and \(^13\)C-NMR spectra were recorded on a Bruker MSL 300 MHz spectrometer. DMSO-d6 was used as the
solvent, and the standard concentration of the samples was 20 mg/mL. Chemical shifts are reported in ppm (δ) relative to TMS as an internal standard. Splitting multiplicities are reported as singlet (s), broad signal (bs), doublet (d), double doublet (dd), triplet (t), double triplet (dt), quartet (q), and multiplet (m). MS (electron impact) were performed on a Shimadzu QP-1000 instrument at 70 eV. High resolution spectra were obtained with a Shimadzu AutoSpec three sector (EBE) mass spectrometer (Waters, Milford, MA, USA) at a scan rate of 1 scan/4 sec, operating with variable magnetic field at 8000 resolving power (10% valley definition) using perfluorokerosene (PFK) as reference compound. TLC analyses were carried out on Silica gel 60 F 254 using chloroform:methanol (9:1) as solvent. Preparative thin layer separations (PLC) were carried out by centrifugally accelerated radial chromatography using a Chromatotron model 7924T. The rotors were coated with Silica Gel 60 PF254 and the layer thickness was 2 mm. Chloroform and increasing percentages of methanol were used as eluent. Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures. Reactions with reagents solid or high boiling point under MW irradiation were conducted in a domestic MW oven (BGH 16260) employing open vessels. Adaptation for reflux heating [20] was used when volatile alkylating agents were employed.

General procedure for synthesis of compounds 2 employing conventional heating

A mixture of isatin (I, 147 mg, 1 mmol), potassium carbonate (1.82 mg, 1.3 mmol), the corresponding alkyl halide (1.1 mmol) and DMF (5 mL) was heated in an oil bath at appropriate temperature and monitored by TLC. When the reaction was completed, the reaction mixture was poured into ice-water. If the product crystallized, the resulting solid was filtered, washed with water and purified by recrystallization or by chromatographic methods. If not, the suspension was extracted with chloroform and the organic layer was washed with water, and then dried and concentrated in vacuo affording compounds 2. Details of the reactions (temperature, times and yields) are listed in Table 2. Using either higher temperatures or smaller amounts of solvent, the yields diminish.

General procedures for synthesis of compounds 2 employing MW irradiation

Method A: Generating the isatin anion (I) in situ

Reaction conditions were selected using ethyl chloroacetate as alkylating agent. Na2CO3, K2CO3, Cs2CO3, CaH2, TEA, LiOH, NMM, NaOEt were tested as bases. The following polar aprotic solvents were evaluated: DMF, DMA, HMPT, MeCN, DMSO and NMP. The best results were obtained using K2CO3 or Cs2CO3 and a few drops of DMF or NMP. The following general procedure was employed: an intimate mixture of isatin (I, 147 mg, 1 mmol), the appropriate alkyl halide (1.1 mmol), base (1.3 mmol) and some drops of the corresponding solvent (giving a slurry at room temperature) was exposed to MW irradiation. The reaction mixture was cooled to room temperature and mixed thoroughly with ice-water. Compounds 2 were isolated following the procedure indicated above. Solvents, powers, times and yields are listed in Table 2 (entries 1-3, 5, 8, 10-14, 17, 19 and 22).
Method B: Employing preformed isatin sodium salt

A solution of sodium (0.8 g) in absolute ethanol (16 mL) was added to isatin (6 g) suspended in absolute ethanol (24 mL), the mixture being well shaken to avoid caking. The violet-black isatin sodium salt (Na\(^+\)I\(^-\)) was collected, well washed with alcohol and finally with benzene until the washings were colourless and then dried. An intimate mixture of isatin sodium salt (Na\(^+\)I\(^-\)) (169 mg, 1 mmol), the appropriate alkyl halide (1.1 mmol) and some drops of the corresponding solvent was exposed to MW irradiation and the reaction products isolated as was indicated in the method A. Solvents, powers, times and yields are given in Table 2 (entries 4, 6, 9, 15, 18, 20 and 23).

Method C: Employing supported reagents

To a solution of isatin sodium salt (Na\(^+\)I\(^-\), 169 mg, 1 mmol) in the minimum amount of water, neutral alumina (400 mg) was added. The mixture was evaporated with a rotary evaporator and the solid was dried 1 h at 110ºC. The corresponding alkyl halide (1.1 mmol) was adsorbed onto isatin on alumina and the mixture was irradiated by microwave in a Pyrex beaker (15 mL). After cooling at room temperature, the mixture was extracted with dichloromethane. The product was purified after evaporation of the solvent. Powers, times and yields are listed in Table 2 (Entries 7, 16 and 21).

Physical properties of compounds 2

Compounds 2a-j and 2l are described in literature. Melting points for these and other compounds are as follows: 1a, 131ºC, lit. [21] 129-130ºC; 2b, 86ºC, lit. [21] 86-87ºC; 2c, isolated as an oil, lit. [22] 36ºC; 2d, 131ºC, lit. [23] 132ºC; 2e, 137ºC, lit. [24] 137-139ºC; 2f, 131ºC, lit. [22] 131ºC; 2g, 117ºC, lit. [25]116-118ºC; 2h, 96ºC, lit. [21] 95-96ºC; 2i, 193ºC, lit. [26] 193-195ºC; 2j, 188ºC, lit. [26] 188-189ºC; 2l, 140-142, lit. [27] 144-145ºC. Spectral properties of compounds 2a, 2b, 2d, 2f-j and 2l were similar to those reported in literature indicated above. Data that was not found in the literature was as follows:

\( \text{N-(n-Butyl)isatin (2c): } \) 

\( ^1\text{H-NMR } \delta: 7.60\text{ (d, H-4, 7.4 Hz), 7.55\text{ (t, H-6, 7.4 Hz), 7.10\text{ (t, H-5, 7.4 Hz),}\) } \)

\( 6.89\text{ (d, H-7, 7.4 Hz), 3.71\text{ (t, NCH}_2\text{, 7.3 Hz), 1.67 and 1.40\text{ (m, CH}_2\text{-CH}_2\text{) and 0.95\text{ (t, CH}_3\text{, 7.1 Hz);\) } \) } \)

\( ^{13}\text{C-NMR } \delta: 188.0\text{ (C-3), 158.9\text{ (C-2), 148.9\text{ (C-7a), 138.0\text{ (C-6), 126.3 and 123.6\text{ (C-4,5), 121.0\text{ (C-3a), 116.3\text{ (C-7), 48.1\text{ (NCH}_2\text{, 29.2\text{ (N-CH}_2\text{-CH}_2\text{, 19.4\text{ (CH}_2\text{-CH}_3\text{) and 13.6\text{ (CH}_3\text{); EIMS } m/z: 203\text{ (M}^+\text{, 41%)}, 132\text{ (100%)}.\) }}\) } \) } \)

\( \text{N-Cinnamylisatin (2e): } \) 

\( ^1\text{H-NMR } \delta: 7.63\text{ (d, H-4, 7.7 Hz), 7.56\text{ (t, H-6, 7.7 Hz), 7.37-7.24\text{ (m, H}_6\text{H}_5\text{), 7.12\text{ (t, H-5, 7.7 Hz), 6.96\text{ (d, H-7, 7.7 Hz), 7.68\text{ (d, CH=CH-C}_8\text{H}_8\text{, 15.9 Hz), 6.18\text{ (td, CH}_2\text{-CH=CH, 15.9 and 6.2 Hz), 4.5\text{ (d, NCH}_2\text{, 6.2 Hz);}\) } \) } \)

\( ^{13}\text{C-NMR } \delta: 190.0\text{ (C-3), 158.3\text{ (C-2), 150.7 (C-7a), 138.3 (C-6), 135.7 (Cipso-C}_8\text{H}_8\text{), 134.0 (CH}_2\text{-CH=CH, 128.7 (Cm-C}_8\text{H}_8\text{), 128.2 (Cp-C}_8\text{H}_8\text{, 126.5 (Co-C}_8\text{H}_8\text{), 125.4 and 123.8 (C-4,5), 121.4 (CH=CH-C}_8\text{H}_8\text{, 118.6 (C-3a), 110.8 (C-7) and 42.2 (NCH}_2\text{; EIMS } m/z: 263 (M}^+\text{, 26%), 146 (100%).\) }}\)
N-(3-Ethoxycarbonylpropyl)isatin (2k): isolated as an oil; $^1$H-NMR $\delta$: 7.67 (d, H-4, 7.3 Hz), 7.57 (t, H-6, 7.3 Hz), 7.14 (t, H-5, 7.3 Hz), 6.98 (d, H-7, 7.3 Hz), 4.10 (q, OCH$_2$, 7.1 Hz), 3.77 (t, NCH$_2$, 7.3 Hz), 2.40 (t, COCH$_2$, 7.3 Hz), 2.00 (m, CH$_2$, 7.3 Hz) and 1.25 (t, CH$_3$, 7.1 Hz); $^{13}$C-NMR $\delta$: 186.5 (C-3), 156.9 (C-2), 149.1 (C-7a), 136.4 (C-6), 125.9 and 124.3 (C-4,5), 122.2 (C-3a), 118.6 (C-7), 59.6 (OCH$_2$), 46.1 (NCH$_2$), 31.5 (CH$_2$-CO), 22.6 (N-CH$_2$-CH$_2$), and 13.9 (CH$_3$); EIMS $m/z$: 261 (M$^+$, 52%), 132 (100%); HMRS: Calcd. for C$_{14}$H$_{15}$NO$_4$: 261.100108; Experimental: 261.100452.

Acknowledgements

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References and Notes

1. (a) Sumpter, W.C. The chemistry of isatin. Chem. Rev. 1944, 34, 393-434; (b) Popp, F.D. The chemistry of isatin. Adv. Heterocyclic Chem. 1975, 18, 1-58; (c) da Silva, J.F.M.; Garden, S.J.; da C. Pinto, A. The chemistry of isatin: a review from 1975 to 1999. J. Braz. Chem. Soc. 2001, 12, 273-324.

2. Some recent examples: (a) Bursavich, M.G.; Gilbert, A. M.; Lombardi, S.; Georgiadis, K.E.; Reifenberg, E.; Flannery, C. R. Morris, E.A. 5′-Phenyl-3'H-spiro[indoline-3,2'[1,3,4]thiadiazol]-2-one inhibitors of ADAMTS-5 (Aggrecanase-2). Bioorg. Med. Chem. Lett. 2007, 17, 5630-5633; (b) Jarrahpour, A.; Khalili, D. Synthesis of some mono- and bis-spiro-β-lactams of benzylisatin. Tetrahedron Lett. 2007, 48, 7140-7143; (c) Basavaiah, D.; Reddy, K.R. Simple and One-Pot Protocol for Synthesis of Indene-spiro-oxindoles Involving Tandem Prins and Friedel-Crafts Reactions. Org. Lett. 2007, 9, 57-60.

3. Vine, K.L.; Locke, J.M.; Ranson, M.; Pyne, S.G.; Bremner, J.B. An Investigation into the Cytotoxicity and Mode of Action of Some Novel N-Alkyl-Substituted Isatins. J. Med. Chem. 2007, 50, 5109-5117, and references cited therein.

4. Zhou, L.; Liu, Y.; Zhang, W.; Wei, P.; Huang, C.; Pei, J.; Yuan, Y.; Lai, L. Isatin Compounds as Noncovalent SARS Coronavirus 3C-like Protease Inhibitors. J. Med. Chem. 2006, 49, 3440-3443 and references cited therein.

5. (a) Chu, W.; Rothfuss, J.; d’Avignon, A.; Zeng, C.; Zhou, D.; Hotchkiss, R.S.; Mach, R.H. Isatin Sulfonyamide Analogs Containing a Michael Addition Acceptor: A new Class of Caspase 3/7 Inhibitors. J. Med. Chem. 2007, 50, 3751-3755 and references cited therein; (b) Kopka, K.; Faust, A.; Keul, P.; Wagner, S.; Breiholz, H.-J.; Höltke, C.; Schober, O.; Schäfers, M.; Levkau, B. 5-Pyrolidinylsulfonyl Isatins as a Potential Tool for the Molecular Imagin of Caspases in Apoptosis. J. Med. Chem. 2006, 49, 6704-6715 and references cited therein.

6. For some examples: (a) Baiocchi, L.; Giannangeli, M.; Rossi, V.; Ambrogi, V.; Grandolini, G.; Perioli, L. Synthesis and antimicrobial activity of some new indolo[2,1-b]quinazolin-6(12H)ones Il Farmaco 1993, 48, 487-501; (b) Meth-Cohn, O.; Goon, S. Synthetic Applications of Umpoled Vilsmeier Reagents. A new Simple One-Pot Route to Isatins from Formanilides. Tetrahedron Lett. 1996, 37, 9381-9384.
7. Casey, L. A.; Galt, R.; Page; M. I. The Mechanisms of Hydrolysis of the β-Lactam Isatin and its Derivatives. *J. Chem. Soc. Perkin Trans. 2* 1993, 23-28.

8. Garden, S.J.; Torres, J.C.; da Silva, L.E.; Pinto, A.C. A Convenient Methodology for the N-Alkylation of Isatin Compounds. *Synth. Commun.* 1998, 28, 1679-1689.

9. Shuttleworth, S.J.; Nasturica, D.; Gervais, C.; Siddiqui, M.A.; Rando, R.F.; Lee, N. Parallel Synthesis of Isatin-Based Serine Protease Inhibitors. *Bioorg. Med. Chem. Lett.* 2000, 10, 2501-2504.

10. Torisawa *et al.* developed a mild base combination of CuCO\(_3/\)Cs\(_2\)CO\(_3\) for N-alkylation of the labile 5-nitroisatin: Torisawa, Y.; Nishi, T.; Minamikawa, J.-I. An Efficient Conversion of 5-Nitroisatin Into 5-Nitroindole Derivative. *Bioorg. Med. Chem. Lett.* 2001, 11, 829-832.

11. Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. The Use of Microwave Ovens for Rapid Organic Synthesis. *Tetrahedron Lett.* 1986, 27, 279-282.

12. Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. Application of Commercial Microwave ovens to Organic Synthesis. *Tetrahedron Lett.* 1986, 27, 4945-4948.

13. Relevant reviews of microwave assisted reactions: (a) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. Microwave assisted organic synthesis –a review. *Tetrahedron* 2001, 57, 9225-9283; (b) Kappe, C.O. Controlled Microwave Heating in Modern Organic Synthesis. *Angew. Chem. Int. Ed.* 2004, 43, 6250-6284; (c) Bose, A.K.; Manhas, M.S.; Ganguly, S.N.; Sharma, A.H.; Banik, B.K. MORE Chemistry for Less Pollution: Applications for Process Development. *Synthesis* 2002, 1578-1591; (d) Xu, Y.; Guo, Q.-X. Synthesis of Heterocyclic Compounds under Microwave Irradiation. *Heterocycles* 2004, 63, 903-974.

14. N-Benzylolation of isatin under MW irradiation employing the salt of isatin generated from isatin and K\(_2\)CO\(_3\) in water and irradiating at high power to eliminate the solvent was reported in 2004 [15]. However, our attempts to reproduce this reaction failed, and a change of the red isatin solution to yellow as the result of the ring cleavage in aqueous basic media was observed [7].

15. El Ashry, E.S.H.; Ramadan, E.S.; Abdel Hamid, H.M.; Hagar, M. Microwave Irradiation for Acceleration each Step for the Synthesis of 1,2,4-Triazino[5,6b]indole-3-thiols and their derivatives from Isatin and 5-Chloroisatin. *Synlett* 2004, 723-725.

16. Solvent-free reactions represent eco-friendly approaches, recognized by their simplicity, manipulative ease of the operation, increased safety and economic advantages due to the absence of solvent. Some reviews: (a) Bougrin, K.; Loupy, A.; Soufiaoui, M. Microwave Assisted Solvent-free Heterocyclic Synthesis. *J. Photochem. Photobiol. C: Photochem. Rev.* 2005, 6, 139-167; (b) Varma, R.S. Solvent-free Accelerated Organic Syntheses using Microwaves. *Pure Appl. Chem.* 2001, 73, 193-198.

17. Vidal, T.; Petit, A.; Loupy, A.; Gedye, R.N. Re-examination of Microwave-Induced Synthesis of Phthalimides. *Tetrahedron* 2000, 56, 5473-5478.

18. Epoxide formation in the reaction of isatin with phenacyl halides in basic medium is the result of the presence of an acidic α-proton in the alkylating agent. This is a well-known reaction, producing the epoxide as the main product under certain conditions: (a) Ainley, A.D.; Robinson, R. The Epindoline Group. Part I. Trial of Various Methods for the Synthesis of Epindolidiones. *J. Chem. Soc.* 1934, 1508-1520; (b) Black, D.S.C.; Wong, L.C.H. A Simple Synthesis of-2-Acyl Indoles from Isatins. *J. Chem. Soc., Chem. Comun.* 1980, 200.
19. Varma, R. S.; Dahiya, R. An Expeditious and Solvent Free Synthesis of 2-Amino-Substituted Isoflav-3-enes Using Microwave Irradiation. *J. Org. Chem.* **1998**, *63*, 8038-8041.

20. Kingston, H.M.; Haswell, S. J. *Microwave –Enhanced Chemistry*; American Chemical Society: Washington DC, 1997; p. 25.

21. Esmaili, A.E.; Bodaghi, A. New and efficient one-pot synthesis of functionalized-spirolactones mediated by vinyltriphenylphosphonium salts. *Tetrahedron* **2003**, *59*, 1169-1171.

22. Bauer, D.J.; Sadler, P.W. 1-Substituted Isatin-thiosemicarbazones, their Preparation and Pharmaceutical Preparations Containing them. *Brit. Pat.* 975357, **1964**; [*Chem. Abstr.* **1965**, *62*, 6462c].

23. Majumdar, K.C.; Kundu, A. K.; Chatterjee, P. 1-Alkylisatins via Aldol-Retro-aldol Condensation. *J. Chem. Res. (S)* **1996**, *460-461*.

24. Brittain, D. R.; Wood, R. Pharmaceutical Spiro-hydantoin Derivatives. *Eur. Pat. Appl. EP* 66378; [*Chem. Abstr.* **1983**, *98*, 179379d].

25. Muthusamy, S.; Arulananda Babu, S.; Nethaji, M., A Facile Regioselective Construction of Spiro epoxi-bridged tetrahydropyranona Frameworks. *Tetrahedron* **2003**, *59*, 8117-8127.

26. Blanco, M.M.; Dal Maso, M.; Shmidt, M.S.; Perillo, I.A. Reaction of Isatin-1-acetamides with Alkoxides: Synthesis of Novel 1,4-Dihydro-3-hydroxy-4-oxo-2-quinolinecarboxamides. *Synthesis* **2007**, *829-834*.

27. Rekhter, M.A. Direct N-Alkylation of Isatin by Halomethyl Ketones, *Chem. Heterocycl. Comp.* **2005**, *41*, 1119-1120.

*Sample Availability:* Samples of the compounds are available from the authors.

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