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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 K_2CO_3 or Cs_2CO_3 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.

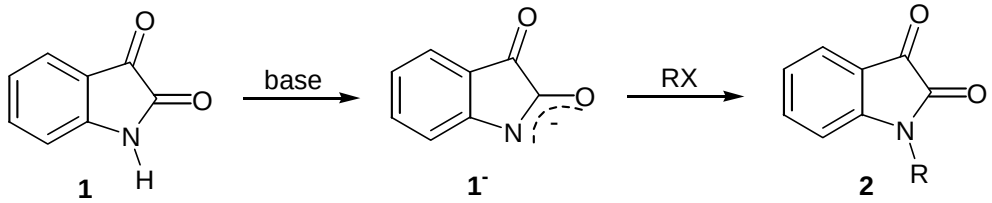
Keywords: Isatin, *N*-alkylation, microwave irradiation, conventional heating, isatin sodium salt.

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 alkylating 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_2CO_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**.

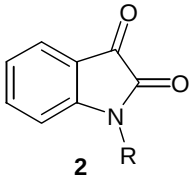


Though some of the above mentioned methods provide good yields of *N*-alkylisatins, they generally present drawbacks related to: a) the base lability of the isatin nucleus [10], b) use of hazardous reagents such as metal hydrides, which require anhydrous solvents, c) use of aprotic organic solvents with 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_2CO_3 in acetone is employed). Besides, reaction times are in general lenghty, 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 potentialy 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.

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



2

Comp.	R	Comp.	R
2a	Me	**2g**	CH_2CO_2Et
2b	Et	**2h**	$CH(CO_2Et)_2$
2c	*n*-Bu	**2i**	CH_2CONH*i*-Pr
2d	CH_2Ph	**2j**	$CH_2CON(Me)Ph$
2e	CH_2CH=CHPh	**2k**	$CH_2(CH_2)_2CO_2Et$
2f	CH_2CH_2Br	**2l**	CH_2COPh

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_2CO_3 or Cs_2CO_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_2CO_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_2CO_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.

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).

Table 2. Reaction times and yields for isatin *N*-alkylation under MW irradiation and conventional heating.

Entry	Cpd. [a]	Reagents		Base	Solvent	Microwave		Conventional heating	
						min/watts	Yield (%)	h/ºC	yield (%)
1	**2a**	**1**	IMe [b]	K_2CO_3	DMF	3/300	95	1/70	80
2	**2b**	**1**	IEt [b]	K_2CO_3	DMF	3/300	90	1.30/70	78
3	**2c**	**1**	Br-*n*Bu	K_2CO_3	DMF	3/400	90	2/70	85
4	**2c**	Na^+**1**$^-$	Br-*n*Bu		DMF	5/500	69		
5	**2d**	**1**	$ClCH_2Ph$	K_2CO_3	DMF [c]	5/200	96	1/120	82
6	**2d**	Na^+**1**$^-$	$ClCH_2Ph$	-	DMF	5/400	66		
7	**2d**	Na^+**1**$^-$ /Al_2O_3	$ClCH_2Ph$	-	-	4/700 [d]	62 [e]		
8	**2e**	**1**	$BrCH_2CH{=}CHPh$	K_2CO_3	DMF [c]	2/200	86	4/70	62
9	**2e**	Na^+**1**$^-$	$BrCH_2CH{=}CHPh$	-	DMF	3/300	67		
10	**2f**	**1**	$BrCH_2CH_2Br$	K_2CO_3	DMF	2/200	50 [f]	2/70	40 [g]
11	**2f**	**1**	$BrCH_2CH_2Br$ [h]	K_2CO_3	DMF	3/300	15 [i]		
12	**2g**	**1**	$ClCH_2CO_2Et$	K_2CO_3	DMF [c]	3/200	76	2/85	68
13	**2h**	**1**	$BrCH(CO_2Et)_2$	K_2CO_3	DMF	3/200	55 [j]	4/70	25
14	**2i**	**1**	$ClCH_2CONH$*i*-Pr	K_2CO_3	DMF	4/200	86	2/90	81
15	**2i**	Na^+**1**$^-$	$ClCH_2CONH$*i*-Pr	-	DMF	4/300	58		
16	**2i**	Na^+**1**$^-$ /Al_2O_3	$ClCH_2CONH$*i*-Pr	-	-	10/400 [d]	44 [e]		
17	**2j**	**1**	$ClCH_2CON(Me)Ph$	K_2CO_3	NMP [k]	3/200	94	2/90	83
18	**2j**	Na^+**1**$^-$	$ClCH_2CON(Me)Ph$	-	DMF	5/300	43		
19	**2k**	**1**	$Cl(CH_2)_3CO_2Et$	K_2CO_3	NMP	4/400	56 [l]	3/120	38
20	**2k**	Na^+**1**$^-$	$Cl(CH_2)_3CO_2Et$	-	DMF	6/500	28		
21	**2k**	Na^+**1**$^-$ /Al_2O_3	$Cl(CH_2)_3CO_2Et$	-	-	8/800 [d]	[m,e]		
22	**2l**	**1**	$BrCH_2COPh$	K_2CO_3	DMF	7/160	53 [n]	2/70	22 [o]
23	**2l**	Na^+**1**$^-$	$BrCH_2COPh$	-	DMF	4/320	62 [p]		

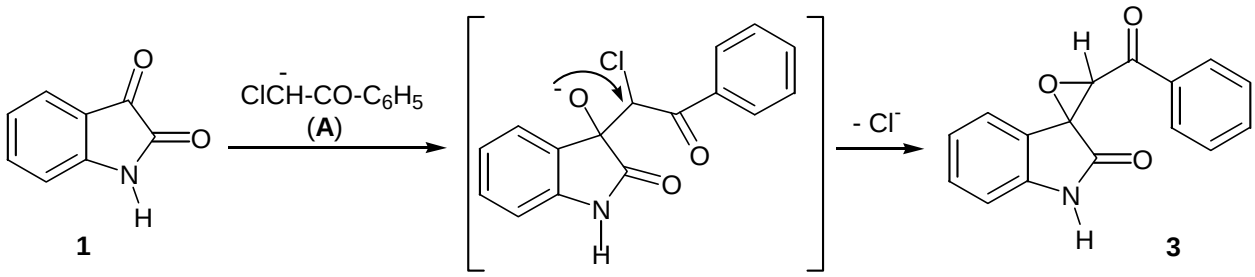
[a] Melting points and literature data are presented in Experimental section; [b] a four-fold ratio of alkyl iodide to isatin was used. [c] 93% when Cs_2CO_3 is used as base; employing NMP as the solvent similar yields were obtained; [d] reactions were conducted with intermittent heating alternating 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 were used the yield of **2h** diminished and important amounts of compound **2g** were obtained; [k] 72% when Cs_2CO_3 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 halometylketone anion (**A**) onto the isatin β-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-d_6 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 MS Shimadzu QP-1000 instrument at 70 eV. High resolution spectra were obtained with a model VG 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 PF_{254} 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 (**1**, 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* ($\mathbf{1}^-$) *in situ*

Reaction conditions were selected using ethyl chloroacetate as alkylating agent. Na_2CO_3, K_2CO_3, Cs_2CO_3, CaH_2, 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 K_2CO_3 or Cs_2CO_3 and a few drops of DMF or NMP. The following general procedure was employed: an intimate mixture of isatin (**1**, 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^+**1**$^-$) 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^+**1**$^-$) (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^+**1**$^-$, 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:

N-(n-Butyl)isatin (**2c**): ^{1}H-NMR δ: 7.60 (d, H-4, 7.4 Hz), 7.55 (t, H-6, 7.4 Hz), 7.10 (t, H-5, 7.4 Hz), 6.89 (d, H-7, 7.4 Hz), 3.71 (t, NCH_2, 7.3 Hz), 1.67 and 1.40 (m, CH_2-CH_2) and 0.95 (t, CH_3, 7.1 Hz); ^{13}C-NMR δ: 188.0 (C-3), 158.9 (C-2), 148.9 (C-7a), 138.0 (C-6), 126.3 and 123.6 (C-4,5), 121.0 (C-3a), 116.3 (C-7), 48.1 (NCH_2), 29.2 (N-CH_2-*C*H_2), 19.4 (*C*H_2-CH_3) and 13.6 (CH_3); EIMS *m/z*: 203 ($M^{+\cdot}$, 41%), 132 (100%).

N-Cinnamylisatin (**2e**): ^{1}H-NMR δ: 7.63 (d, H-4, 7.7 Hz), 7.56 (t, H-6, 7.7 Hz), 7.37-7.24 (m, H_{C6H5}), 7.12 (t, H-5, 7.7 Hz), 6.96 (d, H-7, 7.7 Hz), 7.68 (d, CH=C*H*-C_6H_5, 15.9 Hz), 6.18 (td, CH_2-C*H*=CH, 15.9 and 6.2 Hz), 4.5 (d, NCH_2, 6.2 Hz); ^{13}C-NMR δ: 190.0 (C-3), 158.3 (C-2), 150.7 (C-7a), 138.3 (C-6), 135.7 (C*ipso*-C_6H_5), 134.0 (CH_2-*C*H=CH), 128.7 (C*m*-C_6H_5), 128.2 (C*p*-C_6H_5), 126.5 (C*o*-C_6H_5), 125.4 and 123.8 (C-4,5), 121.4 (CH=*C*H-C_6H_5), 118.6 (C-3a), 110.8 (C-7) and 42.2 (NCH_2); EIMS *m/z*: 263 ($M^{+\cdot}$, 26%), 146 (100%).

N-(3-Ethoxycarbonylpropyl)isatin (**2k**): isolated as an oil; ^{1}H-NMR δ: 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 δ: 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 ($M^{+\cdot}$, 52%), 132 (100%); HMRS: Calcd. for $C_{14}H_{15}NO_4$: 261.100108; Experimental: 261.100452.

Acknowledgements

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