

SHORT COMMUNICATION

SOLVENT FREE SYNTHESIS OF N-ALKYLATED IMINO INDOLINE-2-ONE DERIVATIVES UNDER MICROWAVE IRRADIATION

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ABSTRACT. The solvent-free microwave-assisted syntheses of N-alkyl isatin Schiff base derivatives are reported. These isatin derivatives are obtained as a result of the condensation of an isatin compound with a benzyl halide and an aniline derivatives using microwave irradiation condition in high yield and short reaction time.

KEY WORDS: Microwave, Isatin derivatives, Solvent free, Combinatorial synthesis

INTRODUCTION

Microwave-assisted organic synthesis (MAOS) is a new method for synthesis and methodology in formation of new organic compounds. This technique is based on application of microwave irradiation that absorbed by chemical bonds and lead to chemical transformations. Use of microwave irradiation rather than conventional heating leads to higher product in shorter reaction time, which in many cases are in the range of second or minute, that is very attractive than the conventional heating procedure in reflux condition.

Synthesis of new bioactive molecules has been a very interest in organic chemistry. In this regard, development of new compounds and especially small structures lead to very high attention for pharmaceutical chemists. This is because growing requirements to introducing of different structures for evaluating of compounds in drug discovery attempts.

Isatin is a natural product found in a number of plants including those of the genus *Isatis* [1]. It has also been found as a metabolic derivative of adrenaline in humans [2]. Moreover, it has been demonstrated that isatin found at higher levels in patients involved with neuro pathological conditions and also proved to be a competitive MAO-B inhibitor [3, 4]. Various derivatives of isatin are known to possess a range of pharmacological properties including antiprotozoal [5, 6], anti glycation [7], anticonvulsant and sedative-hypnotic [8, 9], anti-inflammatory [10], antibacterial and anti-fungal [11] activities. Thus isatin is a biologically validated starting point for the design and synthesis of chemical libraries directed at these targets [12]. Due to the privileged nature of isatin, libraries designed and synthesized around the basic structure of this scaffold may yield medicinally active compounds with high hit rates [13, 14].

The use of microwave energy in organic synthesis has attracted growing interest in the past few years. Initially, it was applied to the synthesis of organic compounds in solvent or without the solvent [15-17]. In recent years, few synthesis methods have reported the use of microwave reactions for synthesis of organic and organometallic compounds [18, 19].

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In continuation to our interest in synthesis of new biologically active compounds, here, we report the synthesis of some Schiff bases and N-alkylated Isatin derivatives in good yields and short time in solvent free and microwave irradiation condition [20, 21].

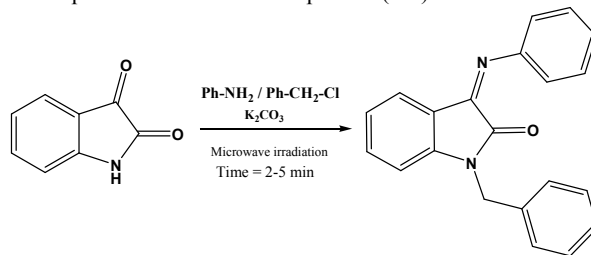
EXPERIMENTAL

Instruments and materials. All compounds were purchased and solvents were purified by standard methods. Infrared spectra were recorded on a Shimadzu model 420 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker spectrometer operated at 300 MHz. ^1H and ^{13}C NMR spectra were referenced to external SiMe_4 . Melting points were measured on an Electro thermal 9100 melting point apparatus. We used a Micro synthesis Millstone laboratory microwave oven using a 400 Watts WestPoint microwave operating at 3.67 GHz.

General procedure for the synthesis of N-alkylated imino isatin derivatives

Typical procedure for preparation of (Z)-1-benzyl-3-(phenylimino)indolin-2-one. A mixture of isatin (0.735 g, 5 mmol), K_2CO_3 (0.13 g, 9.42 mmol), benzyl chloride (0.630 g, 5 mmol), aniline (0.525 g, 5 mmol) and CH_3CN (3 mL) contained in a 100 mL beaker placed in the microwave oven (Scheme 1). The beaker was covered with a stem less funnel and subjected to irradiation in condition as shown in Scheme 1 (operated in 150 W). The residue was allowed to cool to room temperature and cold water (5 mL) was added. The precipitate thus obtained was filtered off and washed with water. Recrystallizing with the hot ethanol gave pure and high yielded products.

This procedure was performed for other compounds (**2-8**).



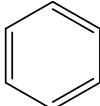
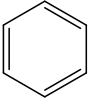
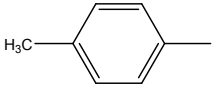
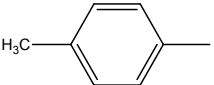
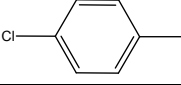
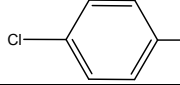


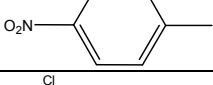
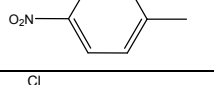
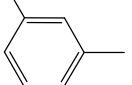
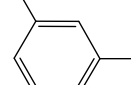
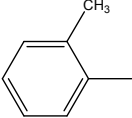
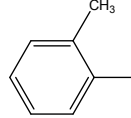
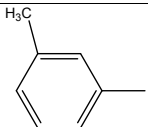
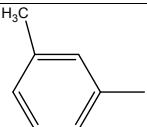
Scheme 1. Synthesis of N-alkylated isatin Schiff base derivatives.

Characteristic data for synthesized compounds

(Z)-1-Benzyl-3-(phenylimino)indolin-2-one (1). m.p. 170–173 °C. IR (KBr, cm^{-1}): 3200, 3120, 1730, 1650, 850. ^1H NMR (300 MHz, DMSO-d_6 , ppm): 7.21–7.67 (m, 14H, Ph), 4.34 (s, 2H, $-\text{CH}_2-$). ^{13}C NMR (DMSO-d_6 , 300 MHz, ppm): 46, 118, 120, 122, 123, 125, 127, 129, 130, 131, 133, 134, 135, 138, 157, 160, 170. 167 (C=O), 165 (C=N), 118–155 (Ph). Found, %: C: 84.99, H: 6.18, N: 4.56, O: 5.19. $\text{C}_{22}\text{H}_{17}\text{NO}$ calculated, %: C: 84.92, H: 6.18, N: 4.62, O: 5.12.

(Z) (4-Methyl)-1-benzyl-3-(4-methylphenylimino)indolin-2-one (2). m.p. 168–172 °C. IR (KBr, cm^{-1}): 3230, 3150, 1730, 1650, 850. ^1H NMR (300 MHz, DMSO-d_6 , ppm): 7.25–7.56 (m, 12H, Ph), 4.27 (s, 2H, $-\text{CH}_2-$), 2.11 (s, 3H, $-\text{CH}_3$), 2.23 (s, 3H, $-\text{CH}_3$). ^{13}C NMR (DMSO-d_6 , 300 MHz, ppm): 24, 26, 46, 118, 120, 122, 123, 125, 127, 129, 130, 131, 133, 134, 135, 138, 157, 160, 170. Found, %: C: 84.99, H: 6.18, N: 4.56, O: 5.19. $\text{C}_{24}\text{H}_{21}\text{NO}$ calculated, %: C: 84.92, H: 6.18, N: 4.62, O: 5.12.

Table 1. Synthesis of new indolin-2-one derivatives under microwave condition.

Entry	Ph	Ph	Time (min)	Yield (%)	m.p. (°C)
1			2	90	170-172
2			2	92	168-170
3			3	88	165-168
4			3	90	177-179
5			4	90	172-174
6			5	90	158-160
7			3	88	180-182
8			3	92	173-175

(*Z*) (4-Chloro)-1-benzyl-3-(4-chlorophenylimino)indolin-2-one (**3**). m.p. 165-169 °C. IR (KBr, cm^{-1}): 3200, 3120, 1690, 1650, 1400, 960, 850. ^1H NMR (300 MHz, DMSO-d_6 , ppm): 7.37-7.68 (m, 12H, Ph), 4.11 (s, 2H, $-\text{CH}_2-$). ^{13}C NMR (DMSO-d_6 , 300 MHz, ppm): 46, 119, 121, 122, 123, 125, 127, 129, 130, 131, 134, 135, 136, 138, 157, 160, 170. Found, %: C: 49.40, H: 3.92, N: 3.75, O: 4.28. $\text{C}_{22}\text{H}_{15}\text{Cl}_2\text{NO}$ calculated, %: C: 69.49, H: 3.98, N: 3.68, O: 4.21.

(*Z*) (4-Hydroxi)-1-benzyl-3-(4-hydroxyphenylimino)indolin-2-one (**4**). m.p. 177-182 °C. IR (KBr, cm^{-1}): 3300, 3240, 2970, 1630, 1600, 1400, 960, 850. ^1H NMR (300 MHz, DMSO-d_6 , ppm): 7.21-7.57 (m, 12H, Ph), 5.23-5.32 (s, 2H), 4.11 (s, 2H, $-\text{CH}_2-$). ^{13}C NMR (DMSO-d_6 , 300 MHz, ppm): 46, 118, 120, 122, 123, 125, 127, 129, 130, 131, 133, 134, 135, 153, 157, 165, 168. Found, %: C: 76.91, H: 5.08, N: 4.92, O: 14.1. $\text{C}_{22}\text{H}_{17}\text{NO}_3$ calculated, %: C: 76.95, H: 4.99, N: 4.08, O: 13.98.

(*Z*) (4-Nitro)-1-benzyl-3-(4-nitrophenylimino)indolin-2-one (**5**). m.p. 172-175 °C. IR (KBr, cm^{-1}): 3210, 2925, 1630, 1600, 1545, 1400, 960, 850. ^1H NMR (300 MHz, DMSO-d_6 , ppm): 7.36-7.67 (m, 12H, Ph), 4.23 (s, 2H, $-\text{CH}_2-$). ^{13}C NMR (DMSO-d_6 , 300 MHz, ppm): 45, 116, 121, 122, 123, 125, 127, 129, 130, 131, 133, 134, 135, 138, 150, 166, 172. Found, %: C: 65.73, H: 3.71, N: 10.55, O: 19.90. $\text{C}_{22}\text{H}_{15}\text{N}_3\text{O}_5$ calculated, %: C: 65.83, H: 3.77, N: 10.47, O: 19.93.

(*Z*) (3-Chloro-4-methyl)-1-benzyl-3-(3-chloro-4-methylphenylimino)indolin-2-one (**6**). m.p. 158-162 °C. IR (KBr, cm^{-1}): 3210, 2925, 1630, 1600, 1545, 1400, 960, 850. ^1H NMR (300 MHz, DMSO-d_6 , ppm): 7.17-7.45 (m, 10H, Ph), 4.34 (s, 2H, $-\text{CH}_2-$), 2.54 (s, 6H, CH_3). ^{13}C NMR (DMSO-d_6 , 300 MHz, ppm): 21, 23, 44, 118, 120, 122, 123, 125, 127, 129, 130, 131, 133, 134, 136, 139, 152, 164, 173. Found, %: C: 49.41, H: 3.93, N: 3.73, O: 4.28. $\text{C}_{22}\text{H}_{15}\text{Cl}_2\text{NO}$ calculated, %: C: 69.49, H: 3.98, N: 3.68, O: 4.21.

(*Z*) (2-Methyl)-1-benzyl-3-(2-methylphenylimino)indolin-2-one (**7**). m.p. 180-184 °C. IR (KBr, cm^{-1}): 3170, 2920, 1630, 1545, 1400, 983, 850. ^1H NMR (300 MHz, DMSO-d_6 , ppm): 7.17-7.45 (m, 10H, Ph), 4.34 (s, 2H, $-\text{CH}_2-$), 2.34 (s, 6H, CH_3). ^{13}C NMR (DMSO-d_6 , 300 MHz, ppm): 22, 25, 48, 119, 121, 122, 123, 125, 127, 129, 130, 131, 133, 134, 135, 137, 155, 165, 171. Found, %: C: 84.96, H: 6.20, N: 4.55, O: 5.21. $\text{C}_{24}\text{H}_{21}\text{NO}$ calculated, %: C: 84.92, H: 6.18, N: 4.62, O: 5.12.

(*Z*) (3-Methyl)-1-benzyl-3-(3-methylphenylimino)indolin-2-one (**8**). m.p. 173-177 °C. IR (KBr, cm^{-1}): 3170, 2920, 1630, 1545, 1400, 983, 850. ^1H NMR (300 MHz, DMSO-d_6): 7.17-7.45 (m, 10H, Ph), 4.34 (s, 2H, $-\text{CH}_2-$), 2.20 (s, 3H, $-\text{CH}_3$), 2.12 (s, 3H, $-\text{CH}_3$). ^{13}C NMR (DMSO-d_6 , 300 MHz, ppm): 21, 23, 47, 119, 121, 122, 123, 125, 127, 129, 130, 131, 133, 134, 134, 137, 155, 166, 173. Found, %: C: 84.98, H: 6.19, N: 4.55, O: 5.17. $\text{C}_{24}\text{H}_{21}\text{NO}$ calculated, %: C: 84.92, H: 6.18, N: 4.62, O: 5.12.

RESULTS AND DISCUSSION

Reaction of isatin with benzyl chloride and aryl amines was investigated under microwave irradiation in solvent free condition. As shown in Scheme 1, aromatic amine and benzyl chloride derivatives could be reacted with isatin to the synthesis of corresponding N-alkylated imino isatin derivatives in excellent yields. The results showed that under this condition, reaction times reduced to less than 5 minute compare to other conventional heating methods that products are formed in several minutes [1-4]. Advantages of microwave irradiation in these cases are in terms of simple application, good yield, no side product formation, have short reaction time and a diversity of bioactive molecules that can be synthesis with this method. Isatin and aromatic amines and benzyl halides are very versatile compounds based on simplicity and suitability. In our research on synthesis processes, it has been found that they are very applicable organic molecules for microwave synthesis. This is because they are having polar bonds and therefore, are polar material. These are the best conditions for effective conversion of microwave energy to the dielectric heating mechanism. We used a very small amount of solvents (acetonitrile) as a polar solvent that have a dipole moment and can efficiently absorb the electromagnetic energy of microwave irradiation. They have an ability to absorb the microwave energy, this resulting in turn in a very rapid and homogeneous heating. Consequently, they display very strong specific microwave effects, with significant improvements in temperature homogeneity and heating rates, enabling faster reactions and less degradation of final products when compared to classical heating. We noticed that the reaction times in this study were 2-5 minutes. These times are better than other products that formed with classical heating methods. Also the yields of products were improved as compared with classical heating methods [22, 23].

CONCLUSION

In conclusion, it has been found that isatin is a very suitable starting material for synthesis of novel organic compounds. Some of the advantages of our application of this method, are the easy handling, simple work-up, short reaction times, and excellent yields of the products that make this protocol a useful addition to available procedures for the synthesis of isatin derivatives. In this paper, we reported a procedure where the reaction is performed in microwave irradiation, in order to prevent problems connected with conventional heating (cost, handling, safety, pollution, and decreases in reactivity by dilution of the reactants).

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