

MAOS versus conventional synthesis of 4,5-di- and 3,4,5-triphenylimidazole-2-thione and their derivatives

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Dedicated to Prof. Atta-ur-Rahman on his 65th birthday

Abstract

Microwave-Assisted Organic Synthesis (MAOS) of 4,5-di- and 3,4,5-triphenylimidazole (**1**) and (**2**) has been achieved by reaction of benzoin with ammonium thiocyanate and phenylthiourea, respectively. Reaction of **1** and **2** with chloroacetic acid and ethyl chloroacetate afforded the respective mercaptoacetic acid derivatives. Dehydrative cyclization of (4,5-diphenylimidazol-2-yl)mercaptoacetic acid (**4**) gave 5,6-diphenyl-2,3-dihydroimidazo[2,1-*b*]thiazol-3-one (**5**) by action of acetic anhydride under MW irradiation. Hydrazinolysis of the thiazolone **5**, esters **6** and **7** gave **8** and **9**, respectively, whose condensation with aldehydes and isatin gave the respective hydrazones. MW irradiation led to higher yields in much less time than conventional methods. Selectivity and/or reactivity encountered during the reactions have been theoretically investigated by using the AM1 method for calculating the relative stabilities, charge densities, dipole moments and electronic energies of reactants and their tautomers.

Keywords: Imidazole; imidazo[2,1-*b*]thiazolone; isatin; MAOS; microwave irradiation; AM1 semiempirical calculation

Introduction

Microwave (MW) energy is well known to induce reduction in time of various reactions, yield enhancement and cleaner chemistry. Recently, this energy has been widely used as an alternative to conventional heating to a number of research programs and development processes,¹ whereby microwave-assisted organic synthesis (MAOS) become a fashion in organic chemistry. On the other hand, imidazoles possess important biological, pharmacological and therapeutic activities.²⁻⁵ Substituted 2-thioimidazoles are present in compounds that have antiasthmatic,⁶ antiinflammatory,⁷ antiulcerative,⁸ antithrombotic,⁹ fungicidal¹⁰ and herbicidal¹¹ activities. As

part of an ongoing program directed to the use of MW irradiation in the synthesis of heterocyclic compounds in our laboratories,¹²⁻¹⁷ we report herein a comparative study of the MAOS and conventional heating for the synthesis of 4,5-di- and 3,4,5-triphenyl imidazole derivatives.

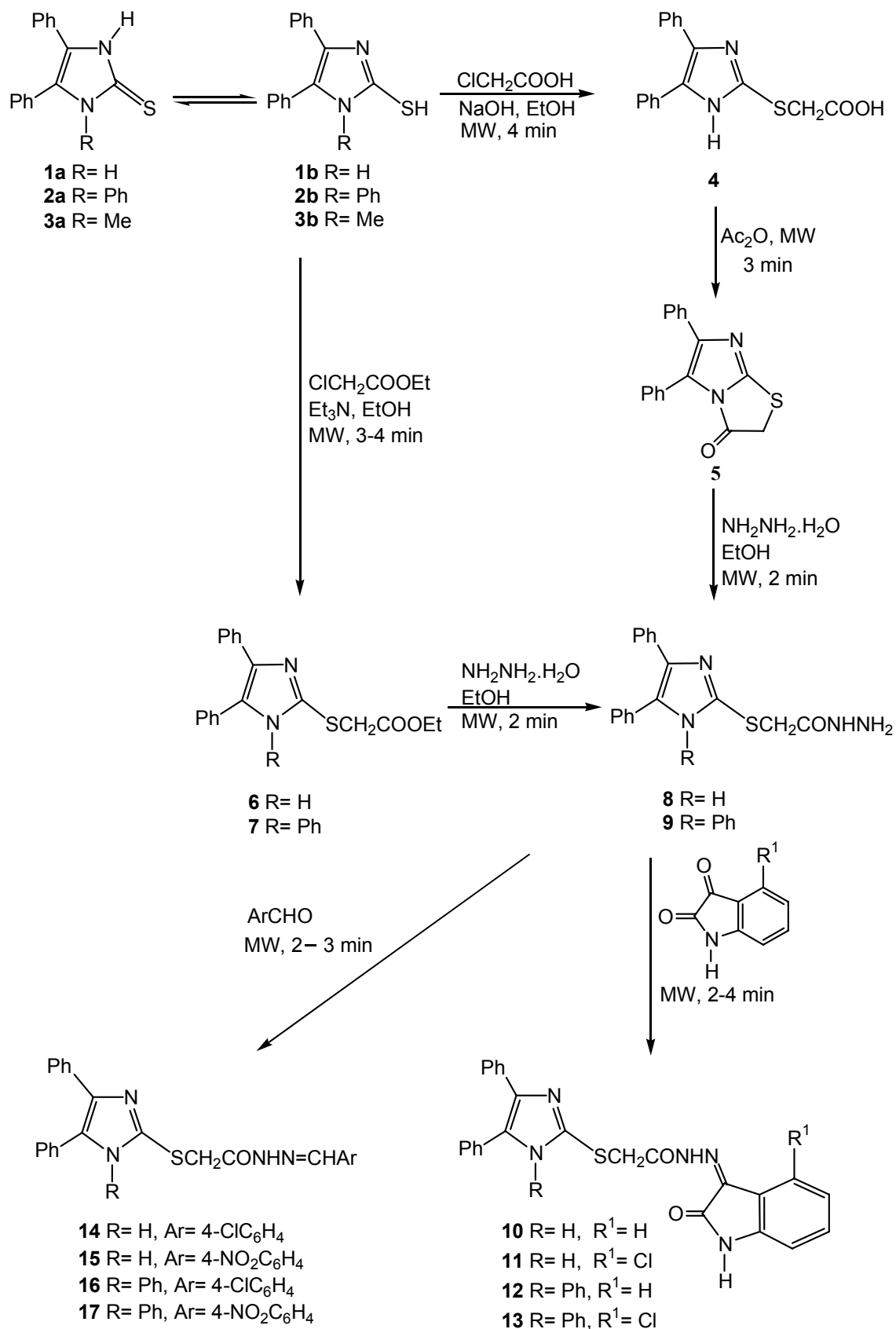
Result and Discussion

Microwave irradiation (MWI) of a mixture of benzoin with ammonium thiocyanate or phenylthiourea in MW oven for 3-4 min gave 4,5-di- and 3,4,5-triphenyl imidazole (**1**) and (**2**) in 91 and 94% yield, respectively. Compounds **1** and **2** were conventionally obtained from the reactants by fusion at 165-170 °C¹⁸ and boiling in hexanol,¹⁹ respectively. The ¹H NMR spectrum of **1** showed the presence of only one singlet at down field indicating that **1a** may be the possible tautomers, but that of **2** may not lead decisively to the particular tautomers (see later). Alkylation of **1** with chloroacetic acid in aqueous sodium hydroxide under MWI for 4 min afforded (4,5-diphenylimidazol-2-yl)mercaptoacetic acid (**4**) in 91% yield; conventional heating required 3 h.²⁰ Cyclization of **4** to the respective 5,6-diphenyl-2,3-dihydroimidazo[2,1-*b*]thiazol-3-one (**5**) was carried out by irradiation in acetic anhydride in a closed Teflon vessel for 3 min, instead of 1 h under conventional boiling.²¹ Carboethoxymethylation of **1** and **2** with ethyl chloroacetate in presence of triethylamine under MWI for 3-4 min gave the respective esters **6** and **7** in 98 and 94% yield; conventional heating required 2-3 h to give 86 and 82% yield of **6** and **7**, respectively. Nucleophilic attack of hydrazine on the carbonyl-amide of the thiazolone ring in **5** has been also proceeded by MWI for 2 min to afford the corresponding acid hydrazide **8** in 99% yield. Alternatively, the hydrazides **8** and **9** were synthesized by treatment of **6** and **7** with hydrazine hydrate in ethanol under MWI for 2-3 min to give 99 and 98% yield, respectively. The IR spectra of **6** and **7** showed a characteristic absorption bands at 1737 and 1739 cm⁻¹; respectively for the ester carbonyl group which did not exist in **8** or **9**, but amide absorption was instead appeared at 1664 and 1661 cm⁻¹, respectively. The ¹H NMR spectra of **6** and **7** showed a triplet at δ 1.31 and 1.28 due to CH₃, a singlet at δ 3.70 and 4.01 due to SCH₂ and a quartet at δ 4.25 and 4.23 due to CH₂ groups, respectively. The phenyl protons and the imidazolyl NH group were also assigned.

The hydrazone derivatives **10-17** were prepared in 90-98%, via the irradiation under MW for 2-3 min of **8** and **9** with isatin, 4-chloroisatin, 4-chloro and 4-nitrobenzaldehydes; conventional heating gave 80-88%. The structures of the new synthesized hydrazones were elucidated from their elemental and spectral analyses. Thus, their IR spectra showed characteristic absorption bands at 1625-1688 cm⁻¹ for the carbonyl-amide groups. The ¹H NMR spectra of hydrazones **10-17** in DMSO-d₆ solution showed the presence of two singlets characteristic for SCH₂ protons at δ 4.02-4.15 and 4.36-4.53 in a ratio varying from 1 to 1-2.3, respectively. Moreover the hydrazone NH proton resonated as two singlets at δ 11.62-12.64 and 11.80-13.45, respectively with the same ratio. This pairing of signals might be attributed to the different steric arrangement of hydrazone functionality in the geometric syn and anti isomers

resulting from the hindered rotation of azomethine linkage. This explanation has been deduced from the absence of such pairing in hydrazides **8** and **9**. This isomerism may cause a difference in hydrogen bonding with DMSO-*d*₆. However, for similar analogues such pairing was explained by the presence of hydrogen bonding between amide N-H and S atom.¹⁸

The imidazole ring was found to exist in thione-thiol equilibrium due to the mobility of the NH proton where the C-2 flanked between the two nitrogen atoms and can be linked to a mercapto or thione group (Scheme 1).²² Theoretical studies on the tautomerism in unsubstituted 2-mercaptoimidazole using the three semiempirical calculation methods (AM1, MNDO and PM3) has shown that the thiol form was more stable than the thione form.²³ We have attempted to study theoretical approach to predict the tautomerism in di- and triphenyl-2-mercaptoimidazoles **1** and **2** and its effect on regioselectivity of alkylation. This was performed by considering the theoretical calculations for **1** and **2** by means of semiempirical AM1 methods which were carried out with MOPAC7 program package.²⁴ The heat of formation, dipole moment, highest occupied molecular orbital energies E_{HOMO} , lowest unoccupied molecular orbital energies E_{LUMO} and the charge density on imidazole heteroatoms as well as the relative stability of the tautomers of **1-3** have been taken into account (Table 1).



Scheme 1

Table 1. Calculated (AM1) heat of formation (Kcal.mol⁻¹), dipole moments (μ , Debye), HOMO orbital energies (E_{HOMO} , eV), LUMO orbital energies (E_{LUMO} , eV), charge density on imidazole heteroatoms and relative stability (Kcal.mol⁻¹) for the reactant tautomers

Tautomer No	Heat of Formation (ΔH_f) Kcal.mol ⁻¹	Dipole moment Debye	E_{HOMO} eV	E_{LUMO} eV	Charge Density on imidazole heteroatoms	Relative Stability ⁱ (RS) Kcal.mol ⁻¹
1a	103.617	6.425	-8.003	-0.676	(S) -0.266	-0.629
					(N1) -0.236	
					(N3) -0.236	
1b	104.246	2.305	-8.119	-0.318	(S) 0.177	
					(N1) -0.144	
					(N3) -0.175	
2a	146.329	5.929	-7.962	-0.464	(S) -0.256	0.152
					(N1) -0.238	
					(N3) -0.137	
2b	146.177	3.239	-8.053	-0.162	(S) 0.195	
					(N1) -0.099	
					(N3) -0.147	
3a	109.453	6.229	-7.948	-0.469	(S) -0.277	-16.187
					(N1) -0.234	
					(N3) -0.182	
3b	127.640	3.176	-7.861	-0.050	(S) 0.756	
					(N1) 0.028	
					(N3) -0.154	

ⁱRS = $\Delta H_f(\text{thione}) - \Delta H_f(\text{thiol})$; minus sign indicates that thione is more stable and vice versa.

The relative stability (**RS**) calculations from gas phase AM1 method for the diphenylimidazole favored the predominance of the thione form **1a** over the thiol form **1b** with relative stability energy (-0.629 Kcal.mol⁻¹). In contrast, the thiol form **2b** in triphenylimidazole has been found to be more stable over the thione form **2a** with relative stability energy (0.152 Kcal.mol⁻¹) (Table 1). However, the value of **RS** for **2** is less than that of **1**.

The predominance of the thiol form in compound **2** can be due to the electron withdrawing effect of the phenyl group on N-3, which has affected the charge density distribution on imidazole heteroatoms; the electron density was found to be shifted towards the nitrogen atom bearing the phenyl group, and hence stabilizes the thiol form. Further evidence of the effect of substituents on thiol-thione tautomerism was obtained by the study of N-methyl-4,5-phenyl-2-mercaptoimidazole **3**, where the thione form was found to be more predominant than thiol form with relative stability **RS** (-16.187 Kcal.mol⁻¹) (Table 1).

On the other hand, the charge density on imidazole heteroatoms (Table 1) has been mainly localized on the sulfur atom. These results explain the higher reactivity of the sulfur atom towards the electrophilic attack than nitrogen atoms, presumably due to the gain of higher nucleophilic properties and lower electronegativity of the sulfur atom.²² Accordingly the theoretical calculations agreed with the experimental results and the alkylation of **1** or **2** with ethyl chloroacetate in the presence of triethylamine as a basic catalyst has been directed the carboxymethylation to the S atom.

Conclusions

The synthesis of thioimidazole derivatives was successfully carried out by applying an environmental friendly and time saving protocol.

The AM1 semiempirical study were in agreement with the experimental data where the thione form in 4,5-diphenylimidazole-2-thione **1a** was found to be the predominant form, while the thiol form **2b** was the predominant one.

Experimental Section

General Procedures. Melting points were determined with a Melt-Temp apparatus and are uncorrected. TLC was performed on Baker-Flex silica gel using ethyl acetate-hexane as developing solvents, and the spot were detected by UV light absorption. Irradiation was done in a domestic microwave oven EM-230M (800 watt output power). IR spectra were recorded with Perkin-Elmer 1430 spectrometer. ¹H NMR spectra were recorded on Jeol spectrometer (500 MHz). Chemical shifts δ are given in ppm relative to the signal for TMS as internal standard. The elemental analyses were performed by the microanalysis unit in the Faculty of Science, Cairo University.

4,5-Diphenylimidazole-2-thione (1). A mixture of benzoin (2.5 mmol) and ammonium thiocyanate (5 mmol) was irradiated by MW for 3 min, then allowed to cool and treated with water (10 ml). The solid was filtered and recrystallized from ethanol to give colorless crystals. mp 308 °C (lit. >300 °C); ¹⁸ IR: 3456 (NH), 1595 (C=C), 1203 (C=S) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 7.26-7.32 (m, 10H, Phenyl protons), 12.52 (s, 2H, 2NH, deuterium oxide-exchangeable).

3,4,5-Triphenylimidazole-2-thiol (2). Method A. A mixture of benzoin (2.5 mmol) and phenylthiourea (5 mmol) was fused at 165-175 °C for 1h, then allowed to cool and treated with water (10 ml). The solid was filtered and recrystallized from ethanol, to give pale yellow crystals. mp 309-310 °C.

Method B. A mixture of benzoin (2.5 mmol) and phenylthiourea (5 mmol) was irradiated by MW for 4 min, then allowed to cool and treated with water (10 ml). The solid was filtered and recrystallized from ethanol, to give **2** as pale yellow crystals. mp 312 °C; IR :1594 (C=C),

1260 (C=S) cm^{-1} ; $^1\text{H NMR}$ (DMSO- d_6) δ 7.22-7.24 (m, 15H, Phenyl protons), 12.97 (s, 1 H, SH, deuterium oxide-exchangeable).

(4,5-Diphenylimidazol-2-yl)mercaptoacetic acid (4). A mixture of **1** (1 mmol), chloroacetic acid (1 mmol) and aqueous sodium hydroxide (5 ml, 2 N) in ethanol (5 ml) was irradiated by MW for 4 min in a closed Teflon vessel. The solution was cooled, filtered and acidified with dil. HCl. The precipitate was filtered off and recrystallized from ethanol to give colorless plates. mp 214 °C (lit. 215-216 °C).²⁰

5,6-Diphenyl-2,3-dihydroimidazo[2,1-b]thiazol-3-one (5). A mixture of **4** (1 mmol) and acetic anhydride (5 ml) was irradiated by MW for 3 min in a closed Teflon vessel. The reaction mixture was poured into ice water. The product was recrystallized from ethanol to give brown needles. mp 209-210 °C (lit. 206-208 °C).²¹

General procedure for the preparation of compounds 6-7. Method A. A mixture of **1** or **2** (1 mmol), triethylamine (1 mmol) and ethyl chloroacetate (1.1 mmol) in ethanol (10 ml) was refluxed for 2-3 h. Ethanol was removed under reduced pressure, and the products were recrystallized from ethanol to give **6** and **7**.

Method B. A mixture of **1** or **2** (1 mmol), triethylamine (1 mmol) and ethyl chloroacetate (1.1 mmol) in ethanol (5 ml) was irradiated by MW for 3-4 min in a closed Teflon vessel. The reaction was processed as described above to give **6** and **7** (Table 2).

Ethyl (4,5-diphenylimidazol-2-yl)mercaptoacetate (6). This compound was obtained as colorless crystals, mp 192-193 °C; IR: 3495 (NH), 1737 (CO), 1602 (C=N) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 1.31 (t, 3H, CH_2CH_3 , $J = 7.7$ Hz), 3.70 (s, 2H, SCH_2), 4.25 (q, 2H, CH_2CH_3), 7.25-7.49 (m, 10H, phenyl protons), 10.48 (s, 1H, NH, deuterium oxide-exchangeable). Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$: C, 67.43; H, 5.36; N, 8.28. Found: C, 67.11; H, 5.55; N, 8.20.

Ethyl (4,5,6-triphenylimidazol-2-yl)mercaptoacetate (7). This compound was obtained as colorless crystals, mp 222-223 °C; IR: 1739 (CO), 1595 (C=N) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 1.28 (t, 3H, CH_2CH_3 , $J = 7.7$ Hz), 4.01 (s, 2H, SCH_2), 4.23 (q, 2H, CH_2CH_3), 7.09-7.53 (m, 15H, phenyl protons). Anal. Calcd for $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$: C, 72.44; H, 5.35; N, 6.76. Found: C, 72.57; H, 5.75; N, 6.84.

General procedure for the preparation of 8-9. Method A. A mixture of **6** or **7** (1 mmol) and hydrazine hydrate (2.5 mmol) in ethanol (10 ml) was refluxed for 6 h. After cooling to room temperature, ice water was added and the precipitate was recrystallized from ethanol to give **8** and **9** (Table 2).

Method B. A mixture of **5**, **6** or **7** (1 mmol) and hydrazine hydrate (2.5 mmol) in ethanol (5 ml) was irradiated by MW for 2-3 min in a closed Teflon vessel. The reaction mixture was cooled and processed as described above to give **8** and **9** (Table 2).

(4,5-Diphenylimidazol-2-yl)mercaptoacetic acid hydrazide (8). This compound was obtained as colorless crystals, mp 164-165 °C (lit. 162-163 °C).²⁵

(4,5,6-Triphenylimidazol-2-yl)mercaptoacetic acid hydrazide (9). This compound was obtained as colorless crystals, mp 118-120 °C; IR: 3284-3494 (NH), 1661 (C=O) cm^{-1} . $^1\text{H NMR}$ (DMSO- d_6) δ (ppm) 3.79 (s, 2H, SCH_2), 3.89 (s, 2H, NH_2 , deuterium oxide-exchangeable), 7.08-

7.50 (m, 15H, phenyl protons), 9.87 (s, 1H, NH, deuterium oxide-exchangeable). Anal. Calcd for $C_{23}H_{20}N_4OS$: C, 68.98; H, 5.03; N, 13.99. Found: C, 68.65; H, 5.36; N, 13.59.

General procedure for the preparation of compounds 10-17. Method A. A mixture of **8** or **9** (1 mmol) and carbonyl compounds (1.1 mmol) in ethanol (25 ml) with drops of acetic acid was refluxed for 4-6 h. The product obtained was collected and recrystallized from ethanol.

Method B. A mixture of **8** or **9** (1 mmol) and carbonyl compounds (1.1 mmol) in ethanol (5 ml) with drops of acetic acid was irradiated for 2-3 min by MW in a closed Teflon vessel. The product was recrystallized from ethanol. They were identical to that obtained above.

Isatin [(4,5-diphenylimidazol-2-yl)mercaptoacetyl]hydrazone (10). This compound was obtained as orange crystals, mp 286-288 °C; IR: 3169 (br, NH), 1712 (C=O, isatin), 1688 (C=O, hydrazide), 1620 (C=N) cm^{-1} ; 1H NMR (DMSO- d_6) δ 4.12 (s, 0.6H, SCH₂), 4.36 (s, 1.4H, SCH₂), 6.87-7.43 (m, 14H, Ar-H), 11.31 (s, 1H, imidazole NH, deuterium oxide-exchangeable), 12.49 (s, 0.7H, CONH, deuterium oxide-exchangeable), 13.30 (s, 0.3H, CONH, deuterium oxide-exchangeable), 12.69 (s, 1H, indole NH, deuterium oxide-exchangeable). Anal. Calcd for $C_{25}H_{19}N_5O_2S$: C, 66.21; H, 4.22; N, 15.44. Found: C, 66.01; H, 4.54; N, 15.04.

4-Chloroisatin [(4,5-diphenylimidazol-2-yl)mercaptoacetyl]hydrazone (11). This compound was obtained as orange crystals, mp 268 °C; IR: 3163 (br NH), 1720 (C=O, isatin), 1684 (C=O, hydrazide), 1619 (C=N) cm^{-1} ; 1H NMR (DMSO- d_6): δ 4.10 (s, 0.8H, SCH₂), 4.40 (s, 1.2H, SCH₂), 6.88-7.49 (m, 13H, Ar-H), 11.21 (s, 1H, imidazole NH, deuterium oxide-exchangeable), 12.58 (s, 0.8H, CONH, deuterium oxide-exchangeable), 13.34 (s, 0.2H, CONH, deuterium oxide-exchangeable), 12.66 (s, 1H, indole NH, deuterium oxide-exchangeable). Anal. Calcd for $C_{25}H_{18}N_5O_2SCl$: C, 61.54; H, 3.72; N, 14.35. Found: C, 61.27; H, 3.90; N, 13.90.

Isatin [(4,5,6-triphenylimidazol-2-yl)mercaptoacetyl]hydrazone (12). This compound was obtained as orange crystals, mp 164-166 °C; IR: 3484 (NH), 1709 (C=O, isatin), 1645 (C=O, hydrazide), 1625 (C=N) cm^{-1} ; 1H NMR (DMSO- d_6) δ : 4.12 (s, 1H, SCH₂), 4.52 (s, 1H, SCH₂), 6.93-7.53 (m, 19H, Ar-H), 11.30 (s, 1H, indole NH, deuterium oxide-exchangeable), 12.64 (s, 0.5H, CONH, deuterium oxide-exchangeable), 13.45 (s, 0.5H, CONH, deuterium oxide-exchangeable). Anal. Calcd for $C_{31}H_{23}N_5O_2S$: C, 70.30; H, 4.38; N, 13.22. Found: C, 70.39; H, 4.65; N, 12.93.

4-Chloroisatin [(4,5,6-triphenylimidazol-2-yl)mercaptoacetyl]hydrazone (13). This compound was obtained as orange crystals, mp 148-149 °C; IR: 3217 (NH), 1708 (C=O, isatin), 1678 (C=O, hydrazide), 1619 (C=N) cm^{-1} ; 1H NMR (DMSO- d_6) δ 4.15 (s, 1H, SCH₂), 4.53 (s, 1H, SCH₂), 6.94-7.58 (m, 18H, Ar-H), 11.41 (s, 1H, indole NH, deuterium oxide-exchangeable), 12.57 (s, 0.5H, CONH, deuterium oxide-exchangeable), 13.42 (s, 0.5H, CONH, deuterium oxide-exchangeable). Anal. Calcd for $C_{31}H_{22}N_5O_2SCl$: C, 66.01; H, 3.93; N, 12.42. Found: C, 65.98; H, 4.23; N, 12.26.

4-Chlorobenzylidene [(4,5-diphenylimidazol-2-yl)mercaptoacetyl] hydrazone (14). This compound was obtained as yellow crystals, mp 118-119 °C (lit. 120-121 °C).¹⁸

4-Nitrobenzylidene [(4,5-diphenylimidazol-2-yl)mercaptoacetyl] hydrazone (15). This compound was obtained as yellow crystals, mp 126-128 °C (lit. 124-126 °C).¹⁸

4-Chlorobenzylidene [(4,5,6-triphenylimidazol-2-yl)mercaptoacetyl] hydrazone (16). This compound was obtained as yellow crystals, mp 208-209 °C; IR: 3172 (NH), 1672 (C=O, hydrazide), 1598 (C=N) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 4.02 (s, 0.8H, SCH₂), 4.41 (s, 1.2H, SCH₂), 7.10-8.70 (m, 20H, Ar-H, HC=N), 11.62 (s, 0.6H, CONH, deuterium oxide- exchangeable), 11.80 (s, 0.4H, CONH, deuterium oxide- exchangeable). Anal. Calcd for C₃₀H₂₃N₄OSCl: C, 68.89; H, 4.43; N, 10.71. Found: C, 68.48; H, 4.54; N, 10.37.

4-Nitrobenzylidene [(4,5,6-triphenylimidazol-2-yl)mercaptoacetyl] hydrazone (17). This compound was obtained as yellow crystals, mp 238-240 °C; IR: 3185 (NH), 1673 (C=O, hydrazide), 1582 (C=N) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 4.04 (s, 0.8H, SCH₂), 4.43 (s, 1.2H, SCH₂), 7.90-8.30 (m, 20H, Ar-H, HC=N), 11.84 (s, 0.4H, CONH, deuterium oxide-exchangeable), 12.10 (s, 0.6H, CONH, deuterium oxide-exchangeable). Anal. Calcd for C₃₀H₂₃N₅O₃S: C, 67.53; H, 4.34; N, 13.12. Found: C, 67.95; H, 4.62; N, 13.34.

Table 2. Comparative data of conventional and MW methods for the synthesis of compounds 1-16

Compound No.	Conventional method		Microwave method	
	Time (h)	Yield%	Time (min)	Yield%
1	1.0	77	3.0	91
2	1.0	87	4.0	94
4	3.0	89	4.0	91
5	1.0	86	3.0	92
6	2.0	86	3.0	98
7	3.0	82	4.0	94
8ⁱ	1.0	90	2.0	99
8ⁱⁱ	6.0	88	2.0	99
9	6.0	86	3.0	98
10	6.0	82	3.0	94
11	4.0	80	2.0	98
12	4.0	84	2.5	96
13	5.0	82	3.0	98
14	6.0	86	2.0	92
15	6.0	84	2.5	90
16	6.0	82	3.0	90
17	4.0	88	2.0	96

i. Prepared from **5**; ii. Prepared from **6**.

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