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# Note

## Environmentally benign approach to imidazole 2-thiones

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An ecofriendly synthesis of some novel 1,4,5-triarylimidazole-2-thiones/1,3,4,5-tetraarylimidazole-2-thiones is described. The reaction involves condensation of benzoin with various readily accessible *N*-substituted thioureas/*N*,*N*′-disubstituted thioureas under microwave over recyclable inorganic solid support. This methodology eliminates the usage of solvent and external catalyst in the reaction step and reduces the reaction time from hours to minutes along with remarkable yield enhancement. In addition versatility of various solid supports as catalyst is also studied.

**Keywords**: Imidazole-2-thione, thiourea, microwave, solid support, montmorillonite K-10 clay

Substituted imidazoles are a class of pharmaceutically important heterocyclic compounds due to the presence of N–C–N grouping[1,2]. They are well known as antiinflammatory agents[3], antimicrobials[4], CNS depressants[5] and as fungicides[6] and herbicides[7]. They also find application in photography as photosensitive compounds[8] as well as emulsion stabilizers[9]. Purines which are imidazopyrimidines are important bases in nucleic acids[10]. Imidazole nucleus also appears in histidine, an important amino acid which is involved in various life processes like ester hydrolysis, acylation and oxygen transport by virtue of its complexing power with iron. Imidazole-2-thiones also have been reported to form stable complexes with iodine[11]. The pharmacological profile is thus the key factor with regard to investigation of title compounds synthesis. We herein report a method that allows the rapid synthesis of *N*-monosubstituted and *N*,*N*′-disubstituted imidazole-2-thiones and does not rely on conventional procedure. Instead our procedure highlights the microwave promoted, solvent-free variation. The functional property of α-hydroxy ketone has been explored. Wider variations by substituting the thiourea have been accommodated quite efficiently.

With the increasing environmental consciousness world wide, the chemical industry is obliged to reexamine the conventional methodologies to seek ways of developing and applying more efficient and environmentally benign strategies that meet the challenges of green chemistry for future sustainable growth. The development of dry media solid supported reactions using microwave make a significant contribution to eco-friendly synthesis.

With a view to explore the reactivity of benzoin and more promising sterically hindered N-substituted thioureas, the biopotential of imidazoles and environmentally benign role of dry-media synthesis[5,12,13] under microwaves, it was thought worthwhile to study the synthetic aspects of substituted imidazoles. Further the role of different inorganic solid supports is studied under MWs for the target molecule synthesis.

### Results and Discussion

A number of methods for the construction of polysubstituted imidazoles have been documented by conventional heating starting from acyloin and thioureas/ammonium thiocyanate[14] or formamidine[10], benzoin/benzil and aldehyde and ammonium acetate[15]. Although these pathways lead to substituted imidazole but they suffer from various drawbacks viz. refluxing for long periods with high boiling solvents, tedious work-up and unsatisfactory yields[13].

We report herein the synthesis of a series of some novel 4,5-diaryl/1,4,5-triaryl/1,3,4,5-tetraaryl-1,3-dihydroimidazole-2-thiones starting from readily accessible reactants, benzoin as a two carbon component and thiourea/*N*-arylthiourea/*N*,*N*′-diarylthiourea as a three atom component. The reaction was first attempted conventionally[10]. Benzoin and thiourea/N-aryl thiourea/*N*,*N*′-diarylthiourea were refluxed in hexanol for 4-6 hrs in the presence of HCl which gave respective imidazole-2-thiones in 50-60% yield. Thus an alternate ecofriendly strategy was sought. With a view to devise a simpler, better and greener route the synthesis was then performed over different solid supports, acidic alumina/ montmorillonite under microwaves. The reactants in appropriate mole ratio were adsorbed over acidic alumina/montmorillonite K-10 clay and were

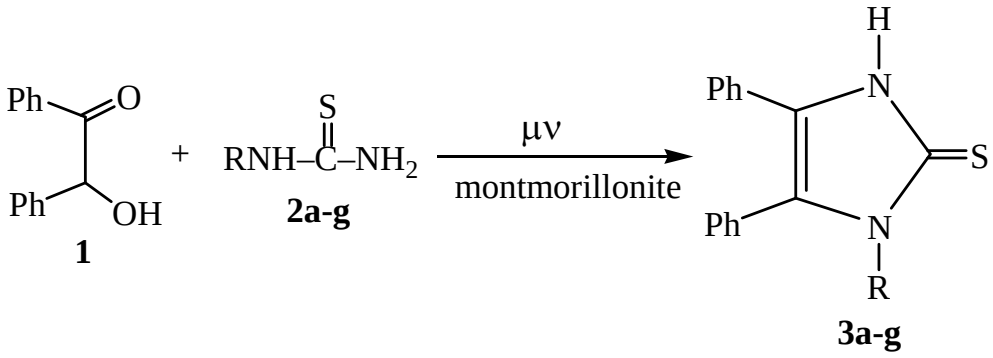
irradiated under microwave to afford *N*-aryl/*N,N'*-diaryl imidazole-2-thione derivatives in 72-92% yields **(Scheme I/Scheme II)**. The inorganic solid support used acted as energy transfer medium and catalyst as well eliminating the addition of HCl to facilitate the reaction. Decreased reaction times along with considerable yield enhancement were realised because of the increased reactivity of the reactants in solid state with large surface area especially when coupled with microwave as compared to conventional procedure **(Table I)**. Of the two solid supports, montmorillonite was observed to be better in terms of yield and reaction time.

The title compounds were characterised on the basis of elemental analyses and spectral data. In IR, bands at 1678 $cm^{-1}$ and 3379 $cm^{-1}$ due to C=O str. and O–H str. respectively disappeared in the products **(3a-g)** and **(5a-e)** and bands at 1660-1670 and 1208-1213 $cm^{-1}$ due to C=C and C=S respectively appeared in **(3a-g)** and **(5a-e)** whereas a band at ~ 3300 $cm^{-1}$ appeared in **(3a-g)** due to N–H str. in the IR spectra. In $^1$H NMR spectra, a singlet at δ 6.03 due to CH and at δ 4.62 due to OH of benzoin disappeared in the products **(3a-g)** and **(5a-e)** whereas a broad singlet between δ 7.98-8.34 due to N–H appeared in **(3a-g)**. Appearance of molecular ion peaks in the mass spectral fragmentation further confirmed the formation of the proposed products. The elemental analysis data (C, H and N) were also same with a variation of ± 0.4% from calculated values.

## Experimental Section

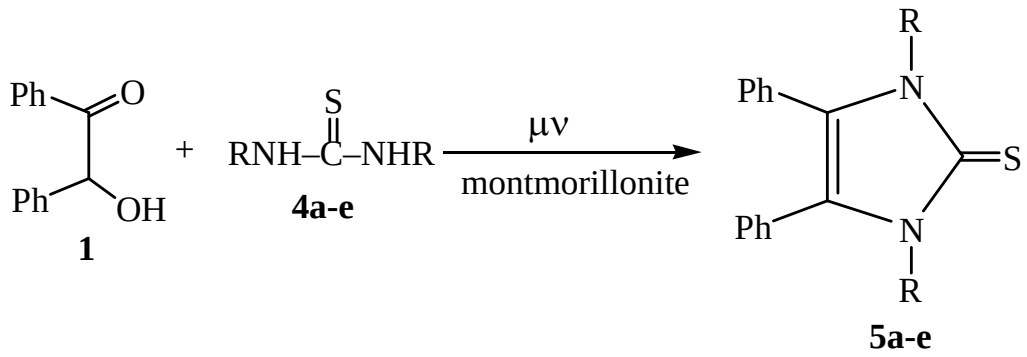
Melting points were determined on a Thomas Hoover melting point apparatus and were uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR-1710 spectrophotometer. $^1$H NMR spectra were recorded on a FT-NMR Hitachi R-600 (300 MHz) instrument using TMS as an internal standard (chemical shifts in δ, ppm). EI mass spectra were recorded on a JEOL-JHS-DX 303 mass spectrometer at 70 eV. Elemental analyses were performed using a Heraeus CHN Rapid Analyser. Purity of compounds was checked through TLC, over silica-gel-coated Al plates (Merk) using iodine for revelation of spots. Microwave irradiation was carried out in a Kenstar microwave oven, Model No. OM9925E (2450 MHz, 800 W). Temperature of the reaction was measured through an AZ, Mini Gun Type, Non-contact IR Thermometer Model No. 8868.

General procedure for the synthesis of N-substituted thioureas and N,N'-disubstituted thioureas




| | R |
|---|---|
| **3a** | Hydrogen |
| **3b** | Phenyl |
| **3c** | 3-Chloro-4-fluorophenyl |
| **3d** | 4-Chlorophenyl |
| **3e** | 4-Methoxyphenyl |
| **3f** | 3-Methylphenyl |
| **3g** | 4-Nitrophenyl |

**Scheme I**




| | R |
|---|---|
| **5a** | Phenyl |
| **5b** | 4-Chlorophenyl |
| **5c** | Furfuryl |
| **5d** | 4-Methoxyphenyl |
| **5e** | 3-Methylphenyl |

**Scheme II**

**Table I** — Comparison of the reaction times and yields for the compounds **3a-g**, **5a-e**

| Compd No. | Conventional Yield (%)/Time (hrs) | Microwave[a] | | | | m.p., °C |
|---|---|---|---|---|---|---|
| | | Acidic Alumina | | Montmorillonite K-10 Clay | | |
| | | Yield (%) | Time (min) | Yield (%) | Time (min) | |
| **3a** | 46/4 | 72 | 4.8 | 85 | 3.0 | 272-274[18] |
| **3b** | 50/35 | 72 | 5.0 | 77 | 3.5 | 180-182 |
| **3c** | 45/3.5 | 71 | 6.0 | 82 | 4.0 | >300 |
| **3d** | 52/5 | 70 | 5.5 | 80 | 4.5 | 340-342[19] |
| **3e** | 55/4 | 74 | 3.8 | 90 | 2.0 | 288-291 |
| **3f** | 56/3.5 | 73 | 6.5 | 92 | 5.0 | 279-281[19] |
| **3g** | 53/4.5 | 78 | 3.8 | 88 | 2.0 | 256-258 |
| **5a** | 55/5 | 67 | 7.2 | 80 | 6.0 | 248-249[20] |
| **5b** | 56/6 | 69 | 7.3 | 80 | 5.5 | 300-301 |
| **5c** | 52/5 | 80 | 3.5 | 91 | 1.5 | 282-284 |
| **5d** | 39/5 | 70 | 6.2 | 84 | 4.0 | 266-267 |
| **5e** | 48/5 | 70 | 6.3 | 83 | 4.5 | 291-293 |

[a] Microwave heating (800 W, 120-130°C)

These were prepared according to literature methods[16,17] modified with microwave irradiations.

**General procedure for the synthesis of 4,5-diaryl/1,4,5-triaryl/1,3,4,5-tetraaryl-1, 3-dihydro-imidazole-2-thiones (3a-g) and (5a-e) (conventional method)**

A mixture of benzoin (1 mmole), thiourea/*N*-arylthiourea/*N*,*N'*-diarylthiourea (1 mmole), *n*-hexanol 10 mL and HCl few drops was refluxed for the specified time **(Table I)**. Upon completion of reaction, the reaction mixture was kept overnight. The solid which appeared was filtered, washed repeatedly with ether, dried and recrystallized from ethanol/ methanol to give the products as pale yellow to brown crystals.

**General procedure for the synthesis of 4,5-diaryl/1,4,5-triaryl/1,3,4,5-tetraaryl-1, 3-dihydro-imidazole-2-thiones (3a-g) and (5a-e) (microwave assisted method)**

A mixture of benzoin (1 mmole) and *N*-thiourea/*N*-arylthiourea/*N*,*N'*-diarylthiourea (1mmole) was dissolved in a solution of chloroform and ethanol (3:1 v/v) to which 20 g of solid support acidic alumina/ montmorillonite K-10 clay was added. The reaction mixture was stirred thoroughly, dried in air, kept in an alumina bath and subjected to MWI (800 W) for a

specified time **(Table I)**. On completion of reaction, as examined by TLC (at an interval of 30 s), the product was extracted into ethanol (3 × 15 mL). Recovering the solvent under reduced pressure gave the required product which was recrystallised from aqueous methanol.

**4,5-Diphenyl-1,3-dihydroimidazole-2-thione(3a).** IR (Nujol): 3318 (NH), 1662 (C=C), 1209 (C=S) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 8.20 (brs, 2H, NH), δ 7.14-8.09 (m, 10H, Ar); MS, *m/z*: 252 ($M^+$). Anal. Calcd. for $C_{15}H_{12}N_2S$: C, 71.42; H, 4.76; N, 11.11; S, 12.69. Found: C, 71.19; H, 4.28; N, 10.91; S, 12.47.

**1,4,5-Triphenyl-1,3-dihydroimidazole-2-thione (3b).** IR (Nujol): 3318 (NH), 1662 (C=C), 1210 (C=S) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 8.13 (brs, IH, NH), 7.38-8.06 (m, 15H, Ar-H); MS, *m/z*: 328 ($M^+$). Anal. Calcd. for $C_{21}H_{16}N_2S$: C, 76.82; H, 4.87; N, 8.53; S, 9.75. Found: C, 76.41; H, 4.32; N, 8.16; S, 9.05.

**1-(3-Chloro-4-fluorophenyl)-4,5-dihydrophenyl-1,3-dihydroimidazole-2-thione (3c).** IR (Nujol): 3312 (NH), 1660 (C=C), 1211 (C=S) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.98 (brs, IH, NH), 7.4-7.8 (m, 10H, Ar-H), 7.1-7.3 (m, 3H, N-phenyl-H); MS, *m/z*: 380.5 ($M^+$). Anal. Calcd for $C_{21}H_{14}N_2SCl$ F: C, 66.22; H, 3.67; N, 7.35; S, 8.40. Found: C, 65.93; H, 3.23; N, 7.16; S, 8.03.

**1-(4-Chlorophenyl)-4,5-diphenyl-1,3-dihydro-imida-zole-2-thione (3d).** IR (Nujol): 3310 (NH), 1660 (C=C), 1210 (C=S) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 8. 15 (brs, 1H, NH), 7.51-8.02 (m, 10H, Ar-H), 7.22-7.41 (m, 4H, N-phenyl-H); MS, *m/z*: 362.5 ($M^+$). Anal. Calcd. for $C_{21}H_{15}N_2SCl$: C, 69.51; H, 4.13; N, 7.72; S, 8.82. Found: C, 68.93, H, 3.79; N, 7.26; S, 8.17.

**1-(4-Methoxyphenyl)-4,5-diphenyl-1,3-dihydro-imidazole-2-thione (3e).** IR (Nujol): 3315 (NH), 1661 (C=C), 1210 (C=S) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 8.12 (brs, 1H, NH), 7.56-8.00 (m, 10H, Ar-H), 7.24-7.56 (m, 4H, N-phenyl-H), 3.41 (s, 3H, $OCH_3$); MS, *m/z*: 358 ($M^+$). Anal. Calcd. for $C_{22}H_{18}N_2$ SO: C 73.74; H, 5.02; N, 7.82; S, 8.93. Found: C, 73.33, H, 4.89; N, 7.24; S, 8.46.

**1-(3-Methylphenyl)-4,5-diphenyl-1,3-dihydro-imidazole-2-thione (3f).** IR (Nujol): 3318 (NH), 1662 (C=C), 1208 (C=S) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): 7.99 (brs, 1H, NH), 7.71-7.90 (m, 10H, Ar-H), 7.44-7.59 (m, 4H, N-tolyl-H), 2.53 (S, 3H, $CH_3$); MS, *m/z*: 342 ($M^+$). Anal. Calcd. for $C_{22}H_{18}N_2S$: C, 77.19; H, 5.26; N, 8.18; S, 9.35. Found C, 76.64; H, 4.89; N, 7.78; S, 9.13.

**1-(4-Nitrophenyl)-4,5-diphenyl-1,3-dihydro-imidazole-2-thione (3g)**. IR (Nujol): 3322 (NH), 1662 (C=C), 1211 (C=S) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 8.34 (brs, 1H, NH), 7.62-8.28 (m, 10H, Ar-H), 7.43-7.59 (m, 4H, N-phenyl-H); MS, *m/z*: 373 ($M^+$). Anal. Calcd. for $C_{21}H_{15}N_3SO_2$: C, 67.56; H, 4.02; N, 11.26; S, 8.57. Found: C, 67.27; H, 3.63; N, 10.98; S, 8.14.

**1,3,4,5-Tetraphenyl-1,3-dihydroimidazole-2-thione (5a)**. IR (Nujol): 1663 (C=C), 1212 (C=S) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.23-7.85 (m, 20H, Ar-H); MS, *m/z*: 404 ($M^+$). Anal. Calcd. for $C_{27}H_{20}N_2$ S: C, 80.19, H, 4.95; N, 6.93; S, 7.92. Found: C, 79.41; H, 4.32; N, 6.73; S, 7.14.

**1,3-Di-(4-Chlorophenyl)-4,5-diphenyl-1,3-dihydroimidazole-2-thione (5b).** IR (Nujol): 1663 (C=C), 1210 (C=S) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): 7.55-7.93 (m, 10H, Ar-H), 7.26-7.52 (m, 8H, N-phenyl-H); MS, *m/z*: 473 ($M^+$). Anal. Calcd. for $C_{27}H_{18}N_2Cl_2S$: C, 68.49; H, 3.80; N, 5.91; S, 6.76. Found: C, 68.02; H, 3.21; N, 5.44; S, 6.23.

**1,3-Difurfuryl-4,5-diphenyl-1,3-dihydroimidazole-2-thione (5c).** IR (Nujol): 1658 (C=C); 1211 (C=S) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.63-8.21 (m, 10H, Ar-H), 7. 35-7.67 (m, 6H, N-furfuryl-H); MS, *m/z*: 352 ($M^+$). Anal. Calcd. for $C_{23}H_{16}N_2S$: C, 78.40; H, 4.54; N, 7.95; S, 9.09. Found: C, 77.93; H, 4.16; N, 7.32; S, 8.75.

**1,3-Di(4-methoxyphenyl)-4,5-diphenyl-1,3-dihydro-imidazole-2-thione (5d).** IR (Nujol): 1661 (C=C), 1210 (C=S) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.65-8.21 (m, 10H, Ar-H), 7.22-7.51 (m, 8H, N-phenyl-H), 3.44 (s, 6H, $CH_3O$); MS, *m/z*: 464 ($M^+$). Anal. Calcd. for $C_{29}H_{24}N_2O_2S$: C, 75.00; H, 5.17; N, 6.03; S, 6.89. Found: C, 74.64; H, 4.83; N, 5.62; S, 6.23.

**1,3-Di-(3-methylphenyl)-4,5-diphenyl-1,3-dihydroimidazole-2-thione (5e).** IR (Nujol): 1660 (C=C), 1211 (C=S) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.41-7.82 (m, 10H, Ar-H), 7.12-7.23 (m, 8H, N-tolyl-H), 2.44 (s, 6H, $CH_3$). MS, *m/z*: 432 ($M^+$). Anal. Calcd. for $C_{29}H_{24}N_2S$: C, 80.55; H, 5.55; N, 6.48; S, 7.40. Found C, 80.24; H, 5.19; N, 6.17; S, 6.99.

## Conclusion

In conclusion, we have described the synthesis of substituted imidazole-2-thiones from benzoin and substituted thioureas. A novel, facile and an efficient

MW assisted modification of a conventional reaction has been introduced that allows the rapid assembly of structurally diverse imidazole-2-thiones. The advantages of this eco-friendly and safe protocol include a simple reaction set-up, good product yield, recyclability of catalytic support short reaction time and above all, elimination of high boiling solvent and hydrochloric acid from the reaction step.

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