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INVESTIGATIONS ON THE REACTIONS OF THIOAMIDES AND RELATED 1,3-DIAZABUTA-1,3-DIENES WITH DIMETHYL ACETYLENEDICARBOXYLATE: SYNTHESIS OF NOVEL FUNCTIONALIZED HETEROCYCLES

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Abstract – The manuscript describes an investigation on the reaction pathways followed in the reactions of variedly substituted thioamides and the corresponding 1,3-diazabuta-1,3-dienes with dimethyl acetylene dicarboxylate. The mechanistic rationales for the reactions pathways followed have been plausibly explicated. The study assumes considerable significance because of the formation of novel functionalized heterocycles.

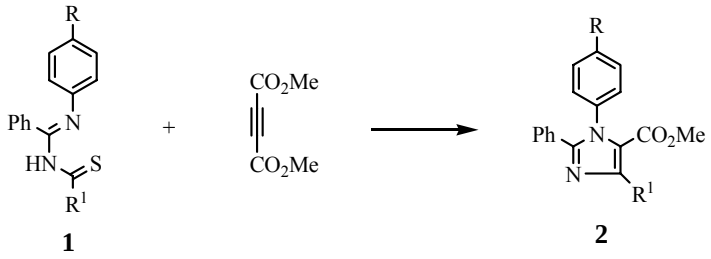
INTRODUCTION

In the last few decades there has been a rapid surge in the synthesis of the compounds containing thioamide moiety because of the remarkable pharmacological potential and diverse range of biological properties such as bactericides, radical scavangers, in congenital hypothyroidism and anticarcinogenic agents etc. possessed by such scaffolds. Simple modifications of the fragments linked up with the thiocarbonyl group or with the thioamide nitrogen atom may give rise to the formation of new reactive centers and thus opens up functionalization possibilities.[1] Much work has been done on the functionalization of thioamides and their use in organic synthesis, including regio- and stereo-selective heterocyclization reactions.[2] Reactions of acetylenic esters with thioamides are known to generate various heterocyclic compounds such as thiazolidinones,[3a] thiazolinones,[3b] thiazonones,[3c] thiazolotriazinediones.[3c] However, the reactions of thioamides with dimethyl acetylenedicarboxylate are studied to a lesser extent. Recently, Bakulev *et al.*

reported the reactions of 5-mercaptazoles and pyridine-2-thiones with DMAD.[3d] Recently, Nakano *et al*. reported the reactions of thioamides with two and five equivalents of DMAD leading to the formation of pyrrole and thiophene derivatives, respectively.[4] As part of our continuing interest in the synthesis of biologically important heterocycles,[5] in a recent communication,[6] we have reported a single pot synthesis of functionalized imidazole derivatives by the reaction of thioamides **1** with DMAD. The present manuscript describes a detailed investigation of the reactions of variedly substituted thioamides with DMAD in order to examine the reaction pathways followed and the nature of the products formed.

RESULTS AND DISCUSSION

A solution of secondary amino-*N*-carbothioic acid (phenyl-*p*-toylimino-methyl) amides popularly known as thioamides **1** (1 mmol) and DMAD (1.2 mmol) was stirred in dry dichloromethane for 2-3hrs at room temperature. Interestingly, these reactions did not yield either the thiazines or any of the heterocyclic compounds like thiazolidinones,[3a] thiazolinones,[3b] thiazinones,[3c] thiazolotriazinediones[3c] etc. as expected based on the literature reports. Instead, the purification of reaction mixture by silica gel chromatography gave the isolated products as imidazoles **2,** characterized on the basis of spectral evidences (Scheme 1).

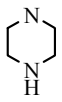


a. R = Me, R^1 = NMe_2

b. R = Me, R^1 = 

c. R = Me, R^1 = 

d. R = Me, R^1 = 

e. R = Me, R^1 = 

f. R = H, R^1 = NMe_2

g. R = H, R^1 = 

h. R = H, R^1 = 

i. R = H, R^1 = 

j. R = H, R^1 = 

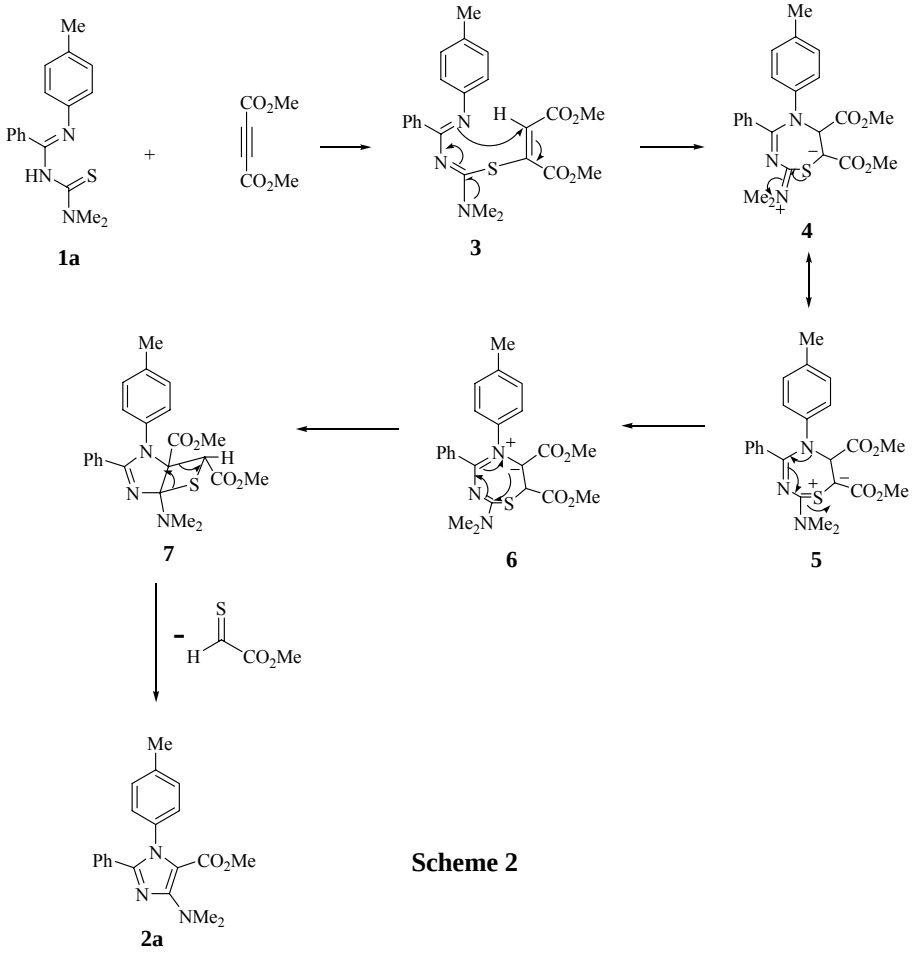
k. R = Cl, R^1 = NMe_2

l. R = Cl, R^1 = 

Scheme 1

The ^{1}H NMR spectrum of compound **2a**, for example, characterized as 5-dimethylamino-2-phenyl-3-*p*-tolyl-3*H*-imidazole-4-carboxylic acid methyl ester, exhibited singlets at δ 3.08 (6*H*) and 3.63 (3*H*) corresponding to the -NMe_2 and the -OMe protons, respectively, and a multiplet for the aromatic protons at δ 7.06-7.35 (9*H*). The ^{13}C NMR spectrum exhibited signals at δ 21.2 (CH_3), 42.7 (NMe_2), 50.7 (OMe), 158.6 (-C=N) and 160.3 (-C=O) ppm. Its IR spectrum showed a carbonyl absorption at 1689 cm^{-1} whilst the mass spectrum exhibited a molecular ion peak [M^+] at *m/z* = 335 for $C_{20}H_{21}O_2N_3$. The structure was unambiguously established with the help of x-ray crystallographic studies. The ORTEP diagram of **2a** is shown in the Figure 1 and the crystal data for the structure refinement of **2a** has been provided in the experimental. The crystal structure studies exhibit that in the five-membered imidazole ring system the C5-N1, C2-C3 distances are 1.327(3) Å and 1.397(3) Å, respectively indicating the double bond character in these bonds. The angles inside the five member ring are in the range 104.9(2)° for C2-C3-N4 and 111.4(2)° for N4-C5-N1. The average value of these five angles is 107.98°. The bond distance of 1.192(3) Å between C22-O23 corresponds to a normal C=O bond.

A plausible mechanism underlying the formation of the imidazole derivatives is shown in Scheme 2.[6]



Scheme 2

The sulfur atom of thioamide being nucleophilic attacks one of the acetylenic carbons of DMAD to form and intermediate **3**, which undergoes intramolecular cyclization to give thiocarbonyl ylide **5** *via* another intermediate **4**. Thiocarbonyl ylide **5** is then converted to thermodynamically more stable azomethine ylide **6**, which after intramolecular cyclization leads to the formation of bicyclic intermediate **7**. This bicyclic intermediate being unstable dissociates to give imidazole **2** after the facile elimination of a thioaldehyde molecule.

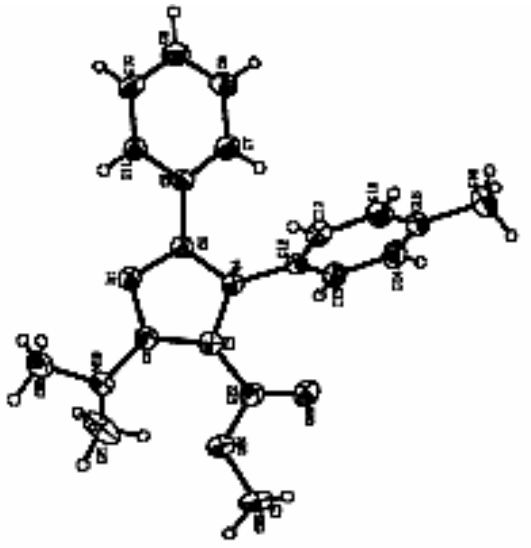
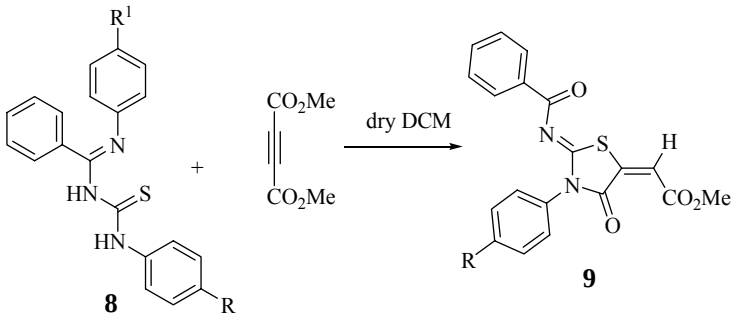


Figure 1. ORTEP Diagram of 2a

Thus, the reactions of thioamides **1** with DMAD have provided a single-pot and exclusive synthetic route leading to novel imidazole derivatives *via* a cyclic azomethine ylide intermediate. Imidazoles are a common integral of a large number of natural products and pharmacologically active molecules.[7] The prevalence and prominence of this component makes methods, which expedite their preparation, highly valuable. The method reported herein assumes significance because of the regio-specific introduction of latent amine and carbomethoxy (-CO_2Me) groups, which are amenable to further elaboration through N-C and N-heteroatom bond formation thereby leading to the concise syntheses of purine analogues. Such poorly represented functionalized imidazoles having latent/masked amine functionality are nevertheless the potential pre-constructed heterocyclic precursors in the succinct synthesis of purine analogues,[8a] interesting insecticides,[8b] alkaloids[8c] and other natural products.[8d]

In view of the interesting synthetic and mechanistic chemistry followed in the above reactions, it was thought worthwhile to extend these studies to the reactions of thioamides **8** obtained by replacing the secondary amine moiety at the thiocarbonyl carbon of **1** with primary arylamine function. Accordingly, the treatment of a solution of thioamide **8** (1 mmol) with DMAD (1.2 mmol) in dry dichloromethane at room

temperature for 15-18 h resulted in the formation of products which were characterized as (4-Oxo-2-benzoylimino-3-aryl-thiazolidin-5-ylidene)-acetic acid methyl ester derivatives **9** on the basis of analytical data and spectral evidences (Scheme 3). The ^{1}H NMR spectra of the products showed the absence of one of the methoxy group and presence of a characteristic olefinic/vinylic proton. Their elemental analyses showed the presence of sulfur.

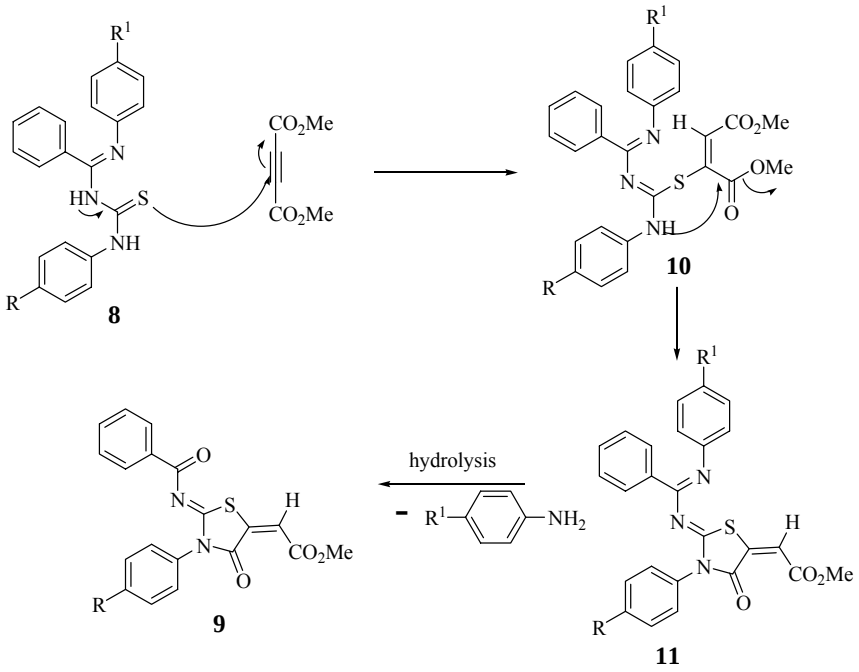


a. R = Me, R^1 = H
b. R = Me, R^1 = Me
c. R = H, R^1 = Me
d. R = H, R^1 = H
e. R = Me, R^1 = Cl

Scheme 3

The ^{1}H NMR spectrum of compound **9a**, for example, characterized as (2-benzoylimino-4-oxo-3-*p*-tolyl-thiazolidin-5-ylidene)-acetic acid methyl ester, exhibited a singlet at δ 3.91 (3*H*) corresponding to the -OMe protons and a singlet characteristic of a vinylic proton at δ 7.06 (1*H*). The signals for the carbonyl carbons appeared at δ 164.9, 165.4 and 176.9 ppm, in its ^{13}C NMR spectrum. The IR spectrum of **9b** showed three carbonyl absorption at 1615, 1719 and 1731 cm^{-1} respectively, whilst the mass spectrum exhibited a molecular ion peak [M^+] at *m/z* = 380 for $C_{20}H_{16}O_4N_2S$. The assigned structure was unambiguously established with the help of X-ray crystallographic studies (ORTEP diagram, Figure 2)[9] and the crystal data for the structure refinement of **9a** has been provided in the experimental.

A plausible mechanism underlying the formation of thiazolidinone derivatives **9** is shown in the **Scheme 4**. It is assumed that sulfur being a strong nucleophile attacks one of the acetylenic carbons of DMAD to give a 1:1 adduct, which undergoes N-H proton migration to generate **10**. Intramolecular cyclization of **10** after the facile elimination of a molecule of CH_3OH yields **11**. The iminic nitrogen of the product thus formed **11**, by some obscure mechanism, undergoes hydrolysis eventually to form the final product **9,** after the elimination of primary amine (Path I, Scheme 4).



Scheme 4

Thus the reactions of thioamides **1** and **8** with DMAD resulted in the unprecedented formation of imidazoles and thiazolidin-5-ylidene-acetic acid methyl esters, respectively, of significant synthetic and pharmaceutical value.[10]

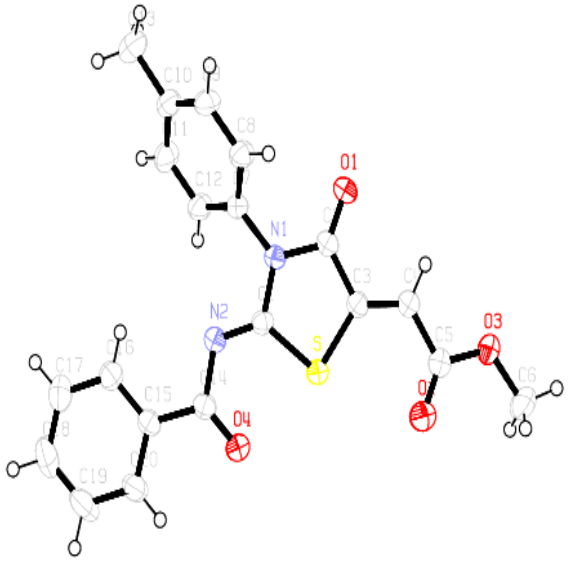
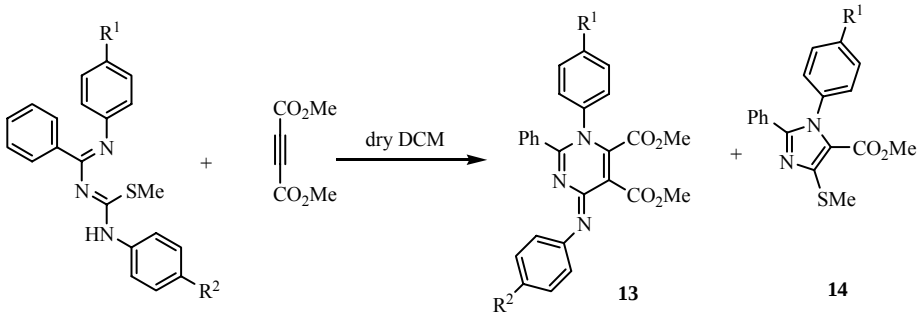


Figure 2. ORTEP Diagram of 9a

As a part of our continued interest in the chemistry of 1,3-diazabuta-1,3-dienes,[11] we have also explored the reactions of diazabutadienes **12** with DMAD. The present work also describes an unprecedented reaction pathway and a thorough rationalization of the reaction mechanism followed in these reactions.

Thus, a solution of diazabutadiene **12** (4 mmol) and DMAD (4.2 mmol) in dry dichloromethane was allowed to stir at r.t. for 15-18 h. The completion of the reaction was ensured with the help of TLC. The crude reaction mixture on separation by silica gel column chromatography gave products **13** and **14** as shown in Scheme 5. The products **13** and **14** were characterized as dihydropyrimidine-4,5-dicarboxylic esters and imidazoles, respectively on the basis of spectral evidences and analytical data. The compound **13a**, for example, characterized as 2-Phenyl-6-phenylimino-3-*p*-tolyl-3,6-dihydro-pyrimidine-4,5-dicarboxylic acid dimethyl ester. It exhibited a singlet at δ 2.43 corresponding to methyl protons, two singlets at δ 3.59 and 3.62 corresponding to methoxy protons (2 × OMe), two doublets at δ7.05 and 7.24 (J = 7.4 Hz) for two sets of two protons each of *p*-tolyl group and a multiplet at δ 7.32-7.53 corresponding to the aromatic protons (10H) in its ^{1}H NMR spectrum. Its mass spectrum exhibited molecular ion peak [M^+] at m/z = 453. The signals in its ^{13}C NMR spectrum also attest to the assigned structure. On the other hand, the compound **14a**, analyzed for $C_{19}H_{18}O_2N_2S$, exhibited three singlets at 2.41, 2.72 and 3.75 corresponding to methyl (3H), thiomethyl (3H) and methoxy protons (3H). Its mass spectrum exhibited a molecular ion peak [M^+] at m/z = 338.

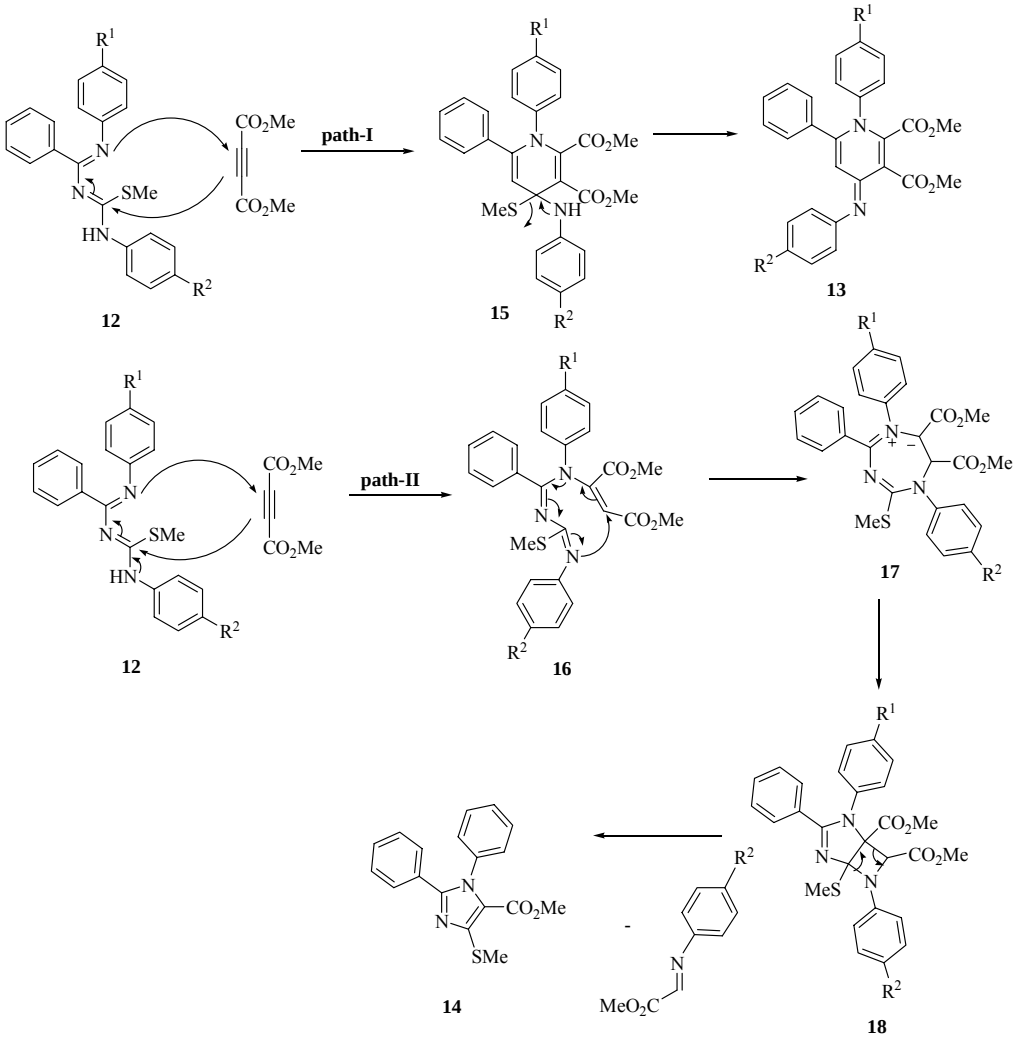


a. R^1 = Me, R^2 = H
b. R^1 = H, R^2 = Me
c. R^1 = Me, R^2 = Me
d. R^1 = Me, R^2 = Cl
e. R^1 = H, R^2 = H
f. R^1 = H, R^2 = Cl

Scheme 5

The most plausible mechanism underlying the formation of the products **13** and **14** is depicted in the Scheme 6. The formation of the product **13** can be explained *via* path I which involves the nucleophilic attack of N-1 of the diazadiene resulting in the formation of a cyclic adduct **15** which then underwent the elimination of methyl thio group to form the adduct **13**. The formation of **14** can be explained by the initial nucleophilic attack of N-1 of the diazadiene at the acetylenic carbon of DMAD to form 1:1 adduct, which undergoes NH proton migration to form **16** (path-II). Intramolecular cyclization of **16** generates azomethine ylide **17**. This azomethine ylide undergoes further intramolecular cyclization to form an unstable bicyclic

intermediate **18**, which after the loss of an imine forms the desired imidazole **14** as shown in the Scheme 6.



Scheme 6

EXPERIMENTAL

GENERAL REMARKS

Melting points were determined by open capillary method using Veego Precision Digital Melting Point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Shimadzu D-8001 spectrophotometer. ^{1}H NMR spectra were recorded in deuterochloroform with Brucker AC-E 200 (200MHz) and AC-E 300 (300MHz) spectrometers using TMS as internal standard. Chemical shift values are expressed as δ (ppm) downfield from TMS and *J* values are in Hz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, q: quartet and br: broad peak. ^{13}C-NMR spectra were also recorded on a Brucker AC- 200E (50.4 MHz) or Brucker AC-300E (75.0 MHz) spectrometers in a deuterochloroform using TMS as internal standard. Mass spectra were recorded on Shimadzu

GCMS-QP-2000 mass spectrometer. Elemental analyses were performed on Heraus CHN-O-Rapid Elemental Analyzer. Column chromatography was performed on a silica gel (60-120) mesh or Harrison Research Chromatotron using 2 mm plates (Silica gel 60 PF254).

STARTING MATERIALS

All the thioamides **1** and **8** were prepared by reported procedures.[12a] All the dienes **1** were prepared by reported procedures.[12b] Dimethyl acetylenedicarboxylate (DMAD) was commercially available. Dichloromethane (CH_2Cl_2) dried over *di*-phosphorous pentoxide and stored over molecular sieve (4Å).

General procedure for the reaction of thioamides 1 and DMAD

A solution of thioamides **1** (4 mmol) and DMAD (4.2 mmol) in dry CH_2Cl_2 was stirred at rt for about 4-5 h. The progress of the reaction was checked with the help of TLC monitoring. After the completion of the reaction, the mixture was concentrated under *vacuo* and the crude reaction mixture thus obtained was chromatographed on 60-120-mesh silica gel to yield imidazoles **2** [eluent:: 1 : 5 = EtOAc : hexane]. The products were recrystallized from 1 : 2 = CH_2Cl_2 : hexane.

5-Dimethylamino-2-phenyl-3-*p*-tolyl-3*H*-imidazole-4-carboxylic acid methyl ester (2a):

White crystalline solid; mp 139-140 ^oC, Yield: 71%; IR (KBr) ν_{max} : 1689 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 2.38 (s, 3H,-CH_3), 3.08 (s, 6H, -$N(CH_3)_2$, 3.63 (s, 3H, -OCH_3), 7.06-7.35 (m, 9H, arom); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 21.2 (-CH_3), 42.7 (-$N(CH_3)_2$), 50.7 (-OCH_3), 108.7, 127.8, 127.9, 128.7, 128.9, 129.2, 129.9, 135.6, 138.2, 148.1, 158.6 (-C=N) and 160.3 (-C=O); MS: *m/z* 335; Anal. Calcd for $C_{20}H_{21}O_2N_3$: C, 71.64; H, 6.27; N, 12.54. Found: C, 71.59; H, 6.30; N, 12.61%.

Crystal data and structure refinement for 2a (JS04):

CCDC 235730; Empirical formula:$C_{20}H_{21}N_3O_2$; Formula Weight: 335.40; Temperature: 293(2) K; Wavelength: 0.71073 Å; Crystal system: Monoclinic; Space group: $P2_1$; Unit cell dimensions: a= 5.9295(6) Å, a=90^o, b=10.0750(10) Å, b=92.603(2)^o, c=14.9191(15) Å, g=90^o; Volume:890.34(15) $Å^3$; Z:2; Density(calculated): 1.251 Mg/m^3; Absorption coefficient: 0.082 mm^{-1}; F(000):356; Theta range for data collection: 2.44 to 28.03^o; Index ranges: -7<=h<7,-13<=k<=13,-19<=l<=17 Reflection collected: 5480 Independent reflections: 3626[R(int)=0.0164] Completeness to theta: 28.03^o 95.6%; Refinement method: Full-matrix least-squares on F^2; Data/restraints/parameters:3626/1/230; Goodness-of-fit on F^2: 1.031; Final R indices [I>2sigma(I)]; R1=0.0482, wR2=0.1183; R indices (all data):R1=0.0565,wR2=0.1245; Absolute structure parameter:2.0 (17); Largest diff. peak and hole: 0.170 and -0.205 e.$Å^{-3}$

2-Phenyl-5-pyrrolidin-1-yl-3-*p*-tolyl-3*H*-imidazole-4-carboxylic acid methyl ester (2b):

White crystalline solid; mp 160-161 ^{o}C, Yield: 72 %; IR (KBr) ν_{max} : 1719 cm^{-1} ; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 1.88-1.92 (m, 4H, -CH_2-CH_2-), 2.35 (s, 3H, -CH_3); 2.99-3.02 (m, 2H, -N-CH_2-), 3.34-3.37 (m, 2H, -N-CH_2-), 3.60 (s, 3H, OCH_3), 7.07 (d, *J* = 8.0 Hz, 2H, ArH), 7.18 (d, *J* = 8.0 Hz, 2H, ArH), 7.23-7.33 (m, 5H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 21.1 (-CH_3), 25.1 (CH_2-CH_2), 47.5 (-N(CH_2)$_2$), 50.7 (-OCH_3), 110.7, 127.8, 128.0, 128.7, 128.8, 129.4, 129.7, 134.2, 138.5, 147.9, 157.9 (-C=N) and 160.1 (-C=O); MS: *m/z* 361; Anal. Calcd for $C_{22}H_{23}O_2N_3$: C, 73.11; H, 6.41; N, 11.63. Found: C, 73.18; H, 6.38; N, 11.67%.

5-Morpholin-4-yl-2-phenyl-3-*p*-tolyl-3*H*-imidazole-4-carboxylic acid methyl ester (2c):

White crystalline solid; mp 142-143 ^{o}C, Yield: 70%; IR (KBr**)** ν_{max} : 1721 cm^{-1} ; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 2.35 (s, 3H, -CH_3); 3.46-3.51 (m, 4H, -CH_2-N-CH_2-); 3.60 (s, 3H, -OCH_3); 3.87-3.91 (m, 4H, -CH_2-O-CH_2-); 7.06-7.33 (m, 9H, arom); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 21.3 (-CH_3), 30.9 (-CH_2-N-CH_2-), 50.8 (-OCH_3), 67.0 (-CH_2-O-CH_2), 110.1, 127.7, 128.0, 128.9, 129.0, 129.4, 129.7, 135.5, 138.4, 147.9, 157.7 (-C=N) and 160.0 (-C=O); MS: *m/z* 377; Anal. Calcd for $C_{22}H_{23}O_3N_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 69.95; H, 6.27; N, 11.20%.

2-Phenyl-5-piperidin-1-yl-3-*p*-tolyl-3*H*-imidazole-4-carboxylic acid methyl ester (2d):

Light yellow crystalline solid; mp 167-168 ^{o}C, Yield: 75 %; IR (KBr) ν_{max} : 1725 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 1.65 (brs, 6H, -CH_2-CH_2-CH_2-), 2.34 (s, 3H, -CH_3); 2.98-3.02 (m, 2H, -N-CH_2-), 3.15-3.19 (m, 2H, -N-CH_2-), 3.67 (s, 3H, OCH_3), 7.08 (d, *J* = 8.0 Hz, 2H, ArH), 7.16 (d, *J* = 8.0 Hz, 2H, ArH), 7.21-7.35 (m, 5H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 20.9 (-CH_3), 25.9 (CH_2), 27.8 (-CH-CH_2-), 47.5 (-N(CH_2)$_2$), 50.9 (-OCH_3), 108.9, 127.7, 128.1, 128.7, 128.8, 128.9, 129.5, 135.2, 138.5, 148.1, 157.9 (-C=N) and 163.2 (-C=O); MS: *m/z* 375; Anal. Calcd for $C_{23}H_{25}O_2N_3$: C, 73.57; H, 6.71; N, 11.19. Found: C, 73.62; H, 6.66; N, 11.25%.

2-Phenyl-5-piperazin-1-yl-3-*p*-tolyl-3*H*-imidazole-4-carboxylic acid methyl ester (2e):

Light yellow crystalline solid; mp 175-176 ^{o}C, Yield: 78 %; IR (KBr) ν_{max} : 1689 cm^{-1} ; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 1.55-1.58 (m, 6H, -CH_2-CH_2-CH_2-), 2.34 (s, 3H, -CH_3); 2.82-3.09 (m, 2H, -CH_2-N-CH_2-), 3.24-3.52 (m, 2H, -CH_2-N-CH_2-), 3.69 (s, 3H, OCH_3), 7.04 (d, *J* = 8.7 Hz, 2H, ArH), 7.15 (d, *J* = 8.7 Hz, 2H, ArH), 7.22-7.35 (m, 5H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 20.9 (-CH_3), 25.1 (CH_2-CH_2), 26.2 (CH_2), 51.1 (OCH_3), 53.9 (CH_2-N-CH_2-), 110.5, 122.3, 123.4, 126.8, 128.4, 133.8, 134.2, 137.9, 146.9, 147.8, 158.0 (C=N), 160.2 (C=O); MS: *m/z*: 376. Anal. Calcd for $C_{22}H_{24}O_2N4$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.21; H, 6.45; N, 14.86%.

5-Dimethylamino-2,3-diphenyl-3*H*-imidazole-4-carboxylic acid methyl ester (2f):

White crystalline solid; mp 177-178 ^{o}C, Yield: 73 %; IR (KBr) ν_{max} : 1699 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 3.06 (s, 6H, -N(CH_3)$_2$, 3.61 (s, 3H, -OCH_3), 7.05-7.33 (m, 10H, arom); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 42.9 (-N(CH_3)$_2$), 50.7 (-OCH_3), 108.6, 127.2, 127.7, 128.5, 128.8, 129.2, 129.7, 134.9, 138.5, 148.2, 158.7 (-C=N) and 162.7 (-C=O); MS: m/z 321; Anal. Calcd for $C_{19}H_{19}O_2N_3$: C, 71.01; H, 5.96; N, 13.08. Found: C, 71.10; H, 6.02; N, 13.00%.

2,3-Diphenyl-5-pyrrolidin-1-yl-3*H*-imidazole-4-carboxylic acid methyl ester (2g):

White crystalline solid; mp 156-157 ^{o}C, Yield: 75 %; IR (KBr) ν_{max} : 1705 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 1.86-1.91 (m, 4H, -CH_2-CH_2-), 2.97-3.02 (m, 2H, -N-CH_2-), 3.30-3.34 (m, 2H, -N-CH_2-), 3.59 (s, 3H, OCH_3), 7.02-7.35 (m, 10H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 25.6 (CH_2-CH_2), 47.5 (CH_2-N-CH_2), 50.7 (-OCH_3), 109.9, 127.5, 127.9, 128.5, 128.9, 129.2, 129.5, 135.2, 138.2, 147.7, 157.7 (-C=N) and 160.2 (-C=O); MS: *m/z* 347; Anal. Calcd for $C_{21}H_{21}O_2N_3$: C, 72.60; H, 6.09; N, 12.10. Found: C, 72.67; H, 6.02; N, 12.15%.

5-Morpholin-4-yl-2,3-diphenyl-3*H*-imidazole-4-carboxylic acid methyl ester (2h):

White crystalline solid; mp 165-166 ^{o}C, Yield: 72 %; IR (KBr) ν_{max} : 1719 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 3.44-3.46 (m, 4H, -CH_2-N-CH_2-); 3.62 (s, 3H, -OCH_3); 3.81-3.87 (m, 4H, -CH_2-O-CH_2-); 7.07-7.38 (m, 10H, arom); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 35.2 (-CH_2-N-CH_2-), 50.7 (-OCH_3), 66.9 (-CH_2-O-CH_2), 110.0, 127.9, 128.2, 128.7, 128.9, 129.3, 129.7, 135.4, 138.6, 148.1, 157.9 (-C=N) and 160.3 (-C=O); MS: *m/z* 363; Anal. Calcd for $C_{21}H_{21}O_3N_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.48; H, 5.76; N, 11.62%.

2,3-Diphenyl-5-piperidin-1-yl-3*H*-imidazole-4-carboxylic acid methyl ester (2i):

Light yellow crystalline solid; mp 184-185 ^{o}C, Yield: 73 %; IR (KBr) ν_{max} : 1715 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 1.59 (brs, 6H, -CH_2-CH_2-CH_2-), 3.00-3.05 (m, 2H, -CH_2-N-), 3.19-3.31 (m, 2H, -CH_2-N-), 3.61 (s, 3H, OCH_3), 7.02-7.39 (m, 10H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 25.5 (CH_2), 27.9 (-CH_2-CH_2-), 51.2 (OCH_3), 53.9 ((CH_2-N-CH_2-), 110.1, 128.2, 128.5, 128.7, 128.8, 128.9, 129.3, 135.7, 138.9, 148.8, 158.1 (-C=N) and 160.4 (-C=O); MS: *m/z* 361; Anal. Calcd for $C_{22}H_{23}O_2N_3$: C, 73.11; H, 6.41; N, 11.63. Found: C, 73.14; H, 6.44; N, 11.60%.

2,3-Diphenyl-5-piperazin-1-yl-3*H*-imidazole-4-carboxylic acid methyl ester (2j):

Yield: 78 %; IR (KBr) ν_{max} : 1689 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 1.53-1.58 (m, 6H, -CH_2-CH_2-CH_2-), 2.81-3.11 (m, 2H, -CH_2-N-), 3.23-3.50 (m, 2H, -CH_2-N-), 3.68 (s, 3H, OCH_3), 7.11-7.23 (m, 6H, ArH), 7.25-7.34 (m, 4H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 24.9 (CH_2-CH_2), 26.1 (CH_2), 51.4 (OCH_3), 53.8 (CH_2-N-CH_2-), 110.6, 121.9, 123.5, 124.8, 125.7, 125.9, 127.4, 129.7, 135.3, 146.7, 159.2

(C=N), 160.3 (C=O); MS: *m/z*: 362. Anal. Calcd for $C_{22}H_{24}O_2N4$: C, 69.59; H, 6.12; N, 15.46. Found: C, 69.61; H, 6.11; N, 15.45%.

3-(4-Chlorophenyl)-5-dimethylamino-2-phenyl-3*H*-imidazole-4-carboxylic acid methyl ester (2k):

White crystalline solid; mp 179-180 ^oC, Yield: 79 %; IR (KBr) ν_{max} : 1720 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 3.05 (s, 6H, $-N(CH_3)_2$), 3.63 (s, 3H, $-OCH_3$), 6.98-7.35 (m,9H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 42.6 ($-N(CH_3)_2$), 50.8 (OCH_3), 109.9, 125.8, 127.1, 127.9, 128.8, 129.1, 130.2, 134.5, 139.1, 148.3, 158.6 (-C=N) and 160.3 (-C=O); MS: *m/z* 355; Anal. Calcd for $C_{19}H_{18}ClN_3O_2$: C, 64.10; H, 5.01; Cl, 9.87; N, 11.89. Found: C, 64.15; H, 5.08; Cl, 9.94; N, 11.83%.

3-(4-Chlorophenyl)-2-phenyl-5-pyrrolidin-1-yl-3*H*-imidazole-4-carboxylic acid methyl ester (2l):

White crystalline solid; mp 171-172 ^oC, Yield: 80 %; IR (KBr) ν_{max} : 1721 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 1.84-1.90 (m, 4H, $(-CH_2)_2$), 2.95-3.00 (m, 2H, $-NCH_2$), 3.31-3.35 (m, 2H, $-NCH_2$), 3.63 (s, 3H, OCH_3), 6.99-7.36 (m, 9H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 25.7 ($(-CH_2)_2$), 47.8 ($-N(CH_2)$, 50.9 (OCH_3), 110.9, 126.8, 127.1, 127.8, 129.1, 130.6, 133.8, 134.7, 138.9, 148.4, 158.5 (-C=N), 160.4 (-C=O); MS: *m/z* 381; Anal. Calcd for $C_{21}H_{20}ClN_3O_2$: C, 66.05; H, 5.28; Cl, 9.28; N, 11.00. Found: C, 66.11; H, 5.32; Cl, 9.22; N, 11.08%.

General procedure for the reaction of thioamides 8 and DMAD

A solution of thioamides **8** (4 mmol) and DMAD (4.2 mmol) in dry CH_2Cl_2 was stirred at rt for about 15-18 h. The progress of the reaction was checked with the help of TLC monitoring. After the completion of the reaction, the mixture was concentrated under *vacuo* and the crude reaction mixture thus obtained was subjected to column chromatography on 60-120-mesh silica gel. The thiazolidinone derivatives **9** were obtained from 1 : 4 = EtOAc : hexane and were recrystallized from 3 : 10 = CH_2Cl_2 : hexane.

(2-Benzoylimino-4-oxo-3-phenylthiazolidin-5-ylidene)acetic acid methyl ester (9a):

Creamish white crystalline Solid; mp 162-163 ^oC, Yield: 78 %; IR (KBr) ν_{max} : 1610, 1703, 1730 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 3.94 (s, 3H, OCH_3), 7.13 (s, 1H, vinylic), 7.31-7.47 (m, 4H, ArH), 7.54-7.68 (m, 4H, ArH), 8.04-8.08 (m, 2H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 52.7 (OCH_3), 120.6, 127.8, 128.5, 129.3, 130.4, 133.6, 134.2, 134.7, 136.9, 141.1, 158.2 (C=N), 164.2 (C=O), 165.5 (C=O) and 185.2 (C=O); MS: *m/z* 366; Anal. Calcd for $C_{19}H_{14}N_2O_4S$: C, 62.28; H, 3.85; N, 7.65; S, 8.75. Found: C, 62.35; H, 3.88; N, 7.71; S, 8.69 %.

Crystal data and structure refinement for 9a:

Empirical formula: $C_{20}H_{16}N_2O_4S$; Formula weight: 380.41; Temperature: 293(2) K; Wavelength: 0.71069 Å; Crystal system: Monoclinic; Space group: $P2_1/n$; Unit cell dimensions: a = 12.919(5) Å; a=

90°.000(5)°; b = 7.461(5); b=97.520(5)°; c = 19.034(5) Å; g = 90.000(5)°; Volume: 1818.9(15) $Å^3$; Z: 4; Density (calculated) 1.389 mg/m^3; Absorption coefficient: 0.207 mm^{-1}; F (000) : 792; Crystal size: 0.4 × 0.3 × 0.3 mm; Theta range for data collection: 1.80 to 25.00°; Limiting indices: 0<=h<=15, 0<=k<=8, -22<=1<=22; Reflections collected: 3338 / 3188 [R(int) = 0.0417; Completeness to theta: 25.00° 99.6 %; Absorption corrections: None; Refinement method: Full-matrix least squares on F^2; Data / restraints / parameters: 3188 / 0 / 245; Goodness-of-fit on F^2 : 1.155; Final R indices [I>2sigma(I)]: R1 = 0.0454, wR2 = 0.1322; R indices (all data): R1 = 0.0660, wR2 = 0.1557; Extinction coefficient: 0.049 (4); Largest diff. peak and hole: 0.357 and -0.255 e.$Å^{-3}$

(2-Benzoylimino-4-oxo-3-*p*-tolylthiazolidin-5-ylidene)acetic acid methyl ester (9b):

Light yellow crystalline solid; mp 238-239 °C, Yield: 75 %; IR (KBr) ν_{max} : 1615, 1717, 1731 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 2.26 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 7.06 (s, 1H, vinylic), 7.27 (d, *J* = 8.0 Hz, 2H, ArH), 7.37 (d, *J* = 8.0 Hz, 2H, ArH), 7.40-7.52 (m, 3H, ArH), 8.03 (m, 2H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 21.2 (CH_3), 52.9 (OCH_3), 123.2, 124.7, 129.0, 129.7, 131.5, 133.5, 134.5, 134.7, 136.2, 139.4, 148.9, 164.2, 165.4 and 179.9; MS: *m/z* 380; Anal. Calcd for $C_{20}H_{16}N_2O_4S$: C, 63.14; H, 4.24; N, 7.36; S, 8.43. Found: C, 63.21; H, 4.19; N, 7.44; S, 8.35 %.

[2-Benzoylimino-3-(4-chlorophenyl)-4-oxo-thiazolidin-5-ylidene]acetic acid methyl ester (9e):

White solid; mp 226-227 °C, Yield: 75 %; IR (KBr) ν_{max} : 1625, 1712, 1735 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 3.88 (s, 3H, OCH_3), 7.13 (s, 1H, vinylic), 7.17-7.35 (m, 5H, ArH), 7.39-7.53 (m, 4H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 52.3 (OCH_3), 120.6, 126.8, 129.1, 130.8, 132.4, 134.9, 135.2, 137.2, 142.1, 151.2, 165.4, 166.2 and 178.8; MS: *m/z* 400; Anal. Calcd for $C_{19}H_{13}ClN_2O_4S$: C, 56.93; H, 3.27; Cl, 8.84; N, 6.99; S, 8.00. Found: C, 56.99; H, 3.19; Cl, 8.92 N, 7.04; S, 8.07%

General procedure for the reaction of 2-methyl-1,3-diaryl-isothioureas 13 and DMAD

A solution of 2-methyl-1,3-diaryl-isothioureas **13** (4 mmol) and DMAD **2** (4.2 mmol) in dry CH_2Cl_2 was stirred at rt for about 15-18 h. The progress of the reaction was checked with the help of TLC monitoring. After the completion of the reaction, the mixture was concentrated under *vacuo* and the crude reaction mixture thus obtained was subjected to column chromatography on 60-120-mesh silica gel. The imidazoles **14** and **15** were obtained from 1 : 50 and 1 : 10 EtOAc : hexane. The products **14** and **15** were recrystallized from dichloromethane-hexane (2:1) and EtOAc-hexane (1:5).

2-Phenyl-6-phenylimino-3-*p*-tolyl-3,6-dihydropyrimidine-4,5-dicarboxylic acid dimethyl ester (13a):

Red crystalline solid; mp 175-176 °C, Yield: 30 %; IR (KBr) ν_{max} : 1623 and 1716 cm^{-1}; ^1H NMR (200

MHz; $CDCl_3$; Me_4Si) : δ 2.43 (s, 3H, CH_3), 3.59 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 7.05 (d, *J* = 7.2 Hz, 2H, ArH), 7.24 (d, *J* = 7.4 Hz, 2H, ArH), 7.32-7.51 (m, 8H, ArH), 7.53-7.62 (m, 2H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 21.3 (CH_3), 51.9 (OCH_3), 53.2 (OCH_3), 102.6, 123.0, 127.9, 128.2, 128.8, 129.9, 130.0, 130.5, 132.2, 135.1, 138.2, 139.4, 144.7, 147.9, 154.3, 163.3, 165.1 and 168.4; MS: *m/z* 453; Anal. Calcd for $C_{27}H_{23}O_4N_3$: C, 71.51; H, 5.11; N, 9.27. Found: C, 71.59; H, 5.06; N, 9.32 %.

5-Methylsulfanyl-2-phenyl-3-*p*-tolyl-3*H*-imidazole-4-carboxylic acid methyl ester (14a):

White crystalline solid; mp 160-161 ^oC, Yield: 32 %; IR (KBr) ν_{max} : 1717 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 2.41 (s, 3H, CH_3), 2.72 (s, 3H, SCH_3), 3.75 (s, 3H, OCH_3), 7.10 (d, *J* = 8.0 Hz, 2H, ArH), 7.20 (d, *J* = 8.0 Hz, 2H, ArH), 7.23-7.27 (m, 3H, ArH), 7.37 (d, 2H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 17.9 (SCH_3), 20.9 (CH_3), 51.3, 127.4, 127.7, 127.8, 128.2, 128.4, 128.9, 129.1, 129.2, 129.6, 133.2, 141.5 and 165.5; MS: *m/z* 338; Anal. Calcd for $C_{19}H_{18}O_2N_2S$: C, 67.43; H, 5.36; N, 8.28; S, 9.48. Found: C, 67.48; H, 5.30; N, 8.32; S, 9.40 %.

2,3-Diphenyl-6-*p*-tolylimino-3,6-dihydropyrimidine-4,5-dicarboxylic acid dimethyl ester (13b):

Red crystalline solid; Yield: 35 %; IR (KBr) ν_{max} : 1627 and 1721 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 2.39 (s, 3H, CH_3), 3.57 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 7.02 (d, *J* = 8.0 Hz, 2H, ArH), 7.21 (d, *J* = 8.0 Hz, 2H, ArH), 7.35-7.52 (m, 10H, ArH), ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 21.5 (CH_3), 52.1 (OCH_3), 53.1 (OCH_3), 104.5, 123.2, 127.7, 128.1, 128.7, 129.8, 129.9, 130.2, 132.5, 135.2, 138.5, 139.7, 144.9, 148.0, 154.2, 161.1, 165.3 and 168.5; MS: *m/z* 453; Anal. Calcd for $C_{27}H_{23}O_4N_3$: C, 71.51; H, 5.11; N, 9.27. Found: C, 71.58; H, 5.05; N, 9.33 %.

5-Methylsulfanyl-2,3-diphenyl-3*H*-imidazole-4-carboxylic acid methyl ester (14b):

White crystalline solid; mp 144-145 ^oC, Yield: 30 %; IR (KBr) ν_{max} : 1719 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 2.77 (s, 3H, SCH_3), 3.80 (s, 3H, OCH_3), 7.09-7.24 (m, 4H, ArH); 7.30-7.52 (m, 6H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 18.5 (SCH_3), 51.1, 127.2, 127.5, 127.7, 128.1, 128.2, 128.7, 129.1, 129.5, 134.7, 139.0, 142.5 and 165.5; MS: *m/z* 324; Anal. Calcd for $C_{18}H_{16}O_2N_2S$: C, 66.64; H, 4.97; N, 8.64; S, 9.88. Found: C, 66.70; H, 4.91; N, 8.70; S, 9.93 %.

2-Phenyl-3-*p*-tolyl-6-*p*-tolylimino-3,6-dihydropyrimidine-4,5-dicarboxylic acid dimethyl ester (14c):

Brown crystalline solid; mp 152-153 ^oC, Yield: 38 %; IR (KBr) ν_{max} : 1625 and 1717 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 2.26 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.55 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 6.92 (d, *J* = 8.0 Hz, 2H, ArH), 6.94 (d, *J* = 8.0 Hz, 2H, ArH), 7.23-7.50 (m, 9H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 20.9 (CH_3), 21.3 (CH_3), 52.1 (OCH_3), 53.5 (OCH_3), 104.7, 123.1, 127.8, 128.1, 128.7, 129.7, 130.1, 130.2, 132.1, 135.7, 138.2, 139.5, 141.8, 147.9, 152.2, 161.1, 165.2 and 168.4; MS: *m/z* 467;

Anal. Calcd for $C_{28}H_{25}O_4N_3$: C, 71.93; H, 5.39; N, 8.99. Found: C, 72.01; H, 5.31; N, 8.90 %.

6-(4-Chlorophenylimino)-2-phenyl-3-*p*-tolyl-3,6-dihydropyrimidine-4,5-dicarboxylic acid dimethyl ester (13d):

Red crystalline solid; mp 135-136 ^oC, Yield: 35 %; IR (KBr) ν_{max} 1623 and 1730: cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 2.41 (s, 3H, CH_3), 3.57 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 6.96 (d, *J* = 6.6 Hz, 2H, ArH), 7.18 (d, *J* = 6.6 Hz, 2H, ArH), 7.26-7.38 (m, 4H, ArH), 7.39-7.48 (m, 5H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 20.9 (CH_3), 52.5 (OCH_3), 53.2 (OCH_3), 102.5, 123.2, 127.7, 128.2, 128.5, 129.8, 130.3, 130.5, 132.1, 135.5, 138.4, 139.2, 142.9, 147.7, 153.7, 158.5, 164.9 and 167.5; MS: *m/z* 487; Anal. Calcd for $C_{27}H_{22}O_4N_3Cl$: C, 66.46; H, 4.54; N, 8.61; Cl, 7.27. Found: C, 66.52; H, 4.60; N, 8.67; Cl, 7.32 %.

2,3-Diphenyl-6-phenylimino-3,6-dihydropyrimidine-4,5-dicarboxylic acid dimethyl ester (13e):

Dark red crystalline solid; mp 154-155 ^oC, Yield: 35 %; IR (KBr) ν_{max} : 1627 and 1731 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 3.59 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 6.91-7.32 (m, 10H, ArH), 7.35-7.44 (m, 5H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 52.2 (OCH_3), 53.1 (OCH_3), 102.2, 123.0, 127.5, 128.1, 128.8, 129.2, 129.7, 130.2, 132.0, 135.1, 137.7, 138.2, 142.9, 146.9, 153.1, 158.4, 165.1 and 167.9; MS: *m/z* 439; Anal. Calcd for $C_{26}H_{21}N_3O_4$: C, 71.06; H, 4.82; N, 9.56. Found: C, 71.11; H, 4.78; N, 9.62; %.

6-(4-Chlorophenylimino)-2,3-diphenyl-3,6-dihydropyrimidine-4,5-dicarboxylic acid dimethyl ester (13f):

Brown crystalline solid; mp 183-185 ^oC, Yield: 37 %; IR (KBr) ν_{max} : 1621 and 1719 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$; Me_4Si) : δ 3.56 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 7.01-7.15 (m, 5H, ArH), 7.26-7.38 (m, 4H, ArH), 7.39-7.48 (m, 5H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si) δ 52.4 (OCH_3), 53.1 (OCH_3), 104.4, 123.5, 127.9, 128.4, 128.7, 129.9, 130.1, 130.3, 132.0, 135.4, 138.2, 139.1, 144.1, 147.2, 153.7, 159.5, 165.4 and 168.0; MS: *m/z* 473; Anal. Calcd for $C_{26}H_{20}ClN_3O_4$: C, 65.89; H, 4.25; Cl, 7.48; N, 8.87. Found: C, 65.94; H, 4.29; N, 8.92; Cl, 7.41 %.

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