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A thorough study on the reaction of DMAD with 1-arylaminoimidazole-2-thiones. Expeditious synthesis of imidazo[2,1-*b*][1,3]thiazoles through a novel arylamino rearrangement

Constantinos Neochoritis, Nicolaos Eleftheriadis, Constantinos A. Tsoleridis *, Julia Stephanidou-Stephanatou *

Department of Chemistry, Laboratory of Organic Chemistry, Aristotle University of Thessaloniki, Thessaloniki 54124, Macedonia, Greece

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ABSTRACT

Upon reaction of 1-arylamino-imidazole-2-thiones **1** with dimethyl acetylenedicarboxylate (DMAD) in the presence of 2.2 equiv of sodium hydride, imidazothiazoles **4** were exclusively formed (71–82% yield). However, from the reaction of **1** with DMAD in the absence of base, only the *S*-substituted products **5** were formed as an *E*/Z mixture (53–55%), which could also be converted to **4** with 2.0 equiv of sodium hydride (65–68%). Furthermore, **5a**-*E*/*Z* was converted to arylamino-substituted derivatives **8a** upon reaction with 1.1 equiv of sodium hydride in 78% yield. Formation of **8a** (75% yield) was also possible by reaction of thione **1a** with DMAD in the presence of sodium methoxide in methanol. Substitution on the imidazole 3-NH of thione **1a** leading to **6a**-*Z* was observed either by heating **1a** with DMAD (91%) or by heating the **5a**-*E*/*Z* mixture in benzene (90% yield). Finally, when **5a**-*E* reacted with acetic anhydride the acetylated derivative **7a**-*Z* was the only isolated product (58%). Full assignment of all ^{1}H and ^{13}C NMR chemical shifts has been unambiguously achieved.

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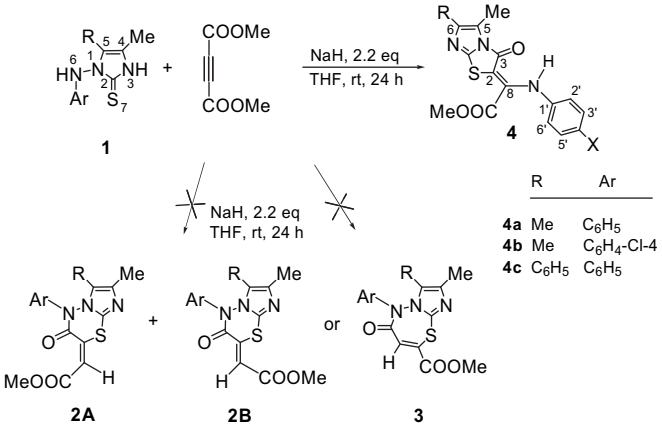
1. Introduction

Imidazoles are scaffolds in highly significant biomolecules including biotin, the essential amino acid histidine, histamine, the pilocarpine,[1] and other terrestrial and marine alkaloids,[2] which have been shown to exhibit interesting biological activities such as antimicrobial, cytotoxic, and anticryptococcal inhibition of nitric oxide synthase.[3] *N*-Aminoimidazoles and *N*-aminoimidazoline thiones have been found to inhibit retroviral replication.[4] Imidazole derivatives also find important applications in other fields, such as polymers,[5] insecticides,[6] antioxidants,[7] photonucleases,[8] and fluorescent dyes.[9] Therefore, considerable interest has been devoted to the development of methods for their elaboration.[10]

2. Results and discussion

Due to the great pharmacological interest in fused imidazoles[11] and as a continuation of our research on new fused imidazoles[12,13] we considered the synthesis of some imidazothiadiazine **2** or imidazothiadiazepine **3** derivatives by using the reaction of suitably substituted imidazole-2-thiones with methyl acetylenedicarboxylate (DMAD, Scheme 1). In order to achieve our goal, 1-arylamino-imidazole-2-thiones[14,15] **1** were selected, since the enhanced reactivity of the sulfur over the 3-NH and 6-NH positions is well documented.[13] We anticipated therefore, that by initial thio-Michael-type addition followed by methanol elimination and cyclization, either **2** or **3** could be formed. However, we found that from the reaction of thiones **1**



Scheme 1. Formation of imidazothiazoles **4**.

* Corresponding authors. Tel.: +30 2310 997831; fax: +30 2310 997679.
E-mail addresses: tsolerid@chem.auth.gr (C.A. Tsoleridis), ioulia@chem.auth.gr (J. Stephanidou-Stephanatou).

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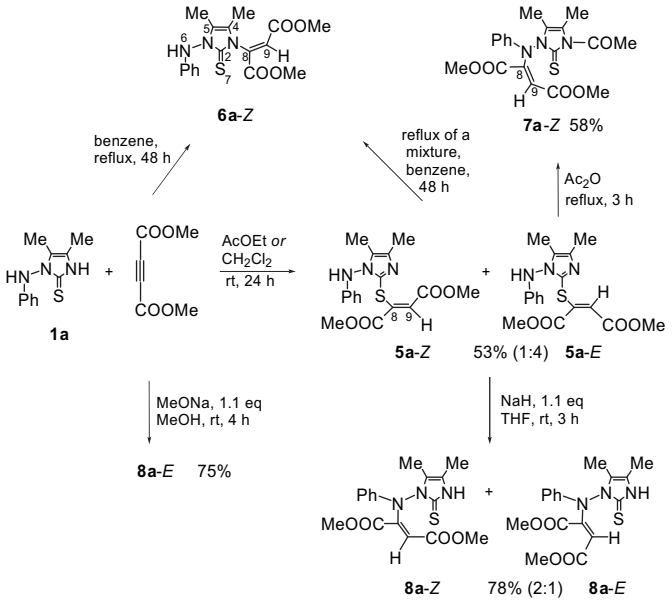
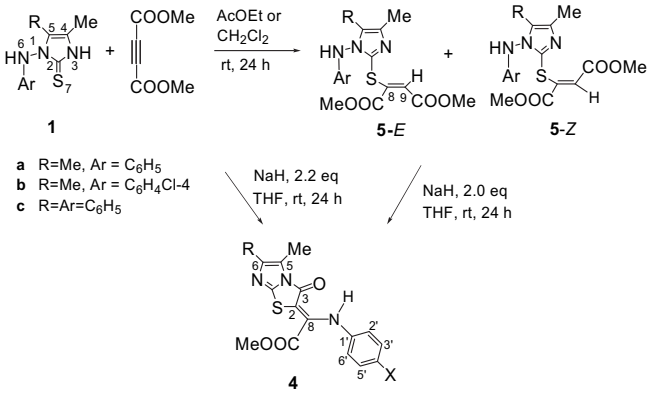
with DMAD in the presence of NaH, imidazothiazoles **4** were exclusively formed.

After this unexpected formation of imidazothiazoles **4**, the reaction between thiones **1** and DMAD was thoroughly investigated and the results are shown in Schemes 2 and 3.



Scheme 2. Reaction conditions for the synthesis of compounds **6a**, **7a** and **8a**.

Initially, upon reaction of **1a** or **1b** with DMAD in ethyl acetate at room temperature for 24 h a ~4:1 mixture of **5**-*E*/**5**-*Z* was formed in good yield (53%, Schemes 2 and 3) through a Michael-type addition reaction. From the reaction mixture, the major *E*-isomer could be isolated upon crystallization. On the contrary, when the reaction was performed with **1c**, **5c**-*Z* containing only traces of **5c**-*E* was isolated (55%). In order to investigate the reaction stereoselectivity, the reaction between **1a** and DMAD was repeated while monitoring the temperature. At −20 °C for 1 h, a stereoselectivity change was observed, namely a ~1:2 **5a**-*E*/**5a**-*Z* isomeric mixture was formed (51% yield). Moreover, the same reaction was attempted using water as solvent, whereupon a 1:3 **5a**-*E*/**5a**-*Z* mixture was

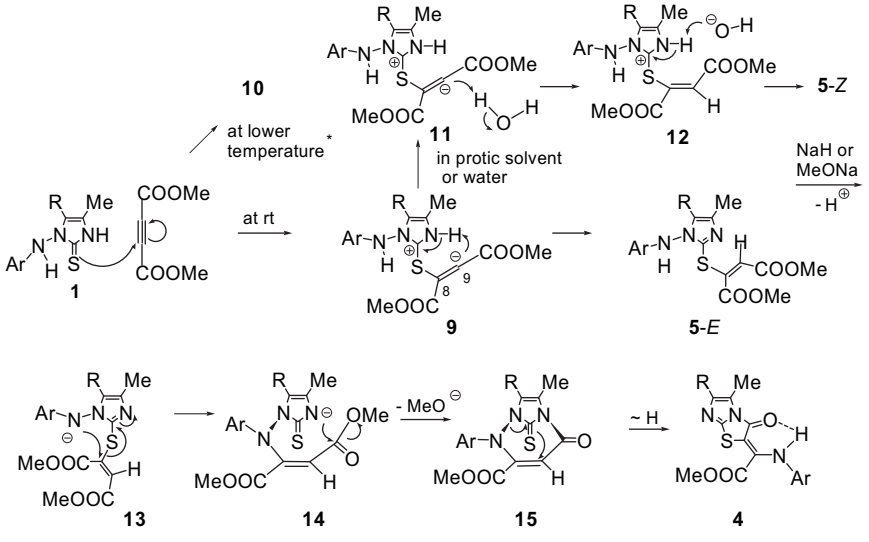


Scheme 3. Cyclization to imidazothiazoles **4.**

isolated in lower yield (29%), most probably due to low solubility of the starting thione in water. The yield was improved to 49% by using a 10% ethanol/water solution. The configuration of **5** is in good agreement with previous results according to which addition is solvent and temperature dependent.[16]

Subsequently, the reaction between **1a** and DMAD was repeated in benzene at reflux for 48 h (Scheme 2), whereupon, instead of the sulfur substituted derivative **5**, the 3-*N*-substituted compound **6a**-*Z* (91% yield) was the only reaction product (Scheme 2). The same product **6a**-*Z* was also formed in 90% yield when **5a** (4:1 *E*/*Z*) was heated in benzene for 48 h, proving the intermediacy of **5** in the formation of **6**. On the contrary, when the imidazolethione **1a** and DMAD were stirred in methanol at ambient temperature in the presence of 1.1 equiv of sodium methoxide for 4 h, reaction on the arylamino nitrogen was observed leading to the formation of the arylamino-substituted derivative **8a**-*E* in 75% yield. Analogously, **8a** was isolated (78% yield) as a 2:1 *Z*/*E* mixture, when a ~4:1 **5a**-*E*/**5a**-*Z* mixture was stirred with 1.1 equiv of sodium hydride in dry THF at ambient temperature for 3 h. Finally, in an attempt to cyclize **5**, reaction of **2a**-*E* with acetic anhydride was studied, whereupon only the 3-acetylated derivative **7a**-*Z* was formed in 58% yield.

Cyclization to imidazothiazoles **4a**–**c** was successful either when a **5**-*Z*/*E* mixture was stirred with 2.0 equiv of sodium hydride in dry THF at ambient temperature for 24 h (65–68% yield), or when



Scheme 4. Plausible mechanism for the formation of compounds **5** and **4**.

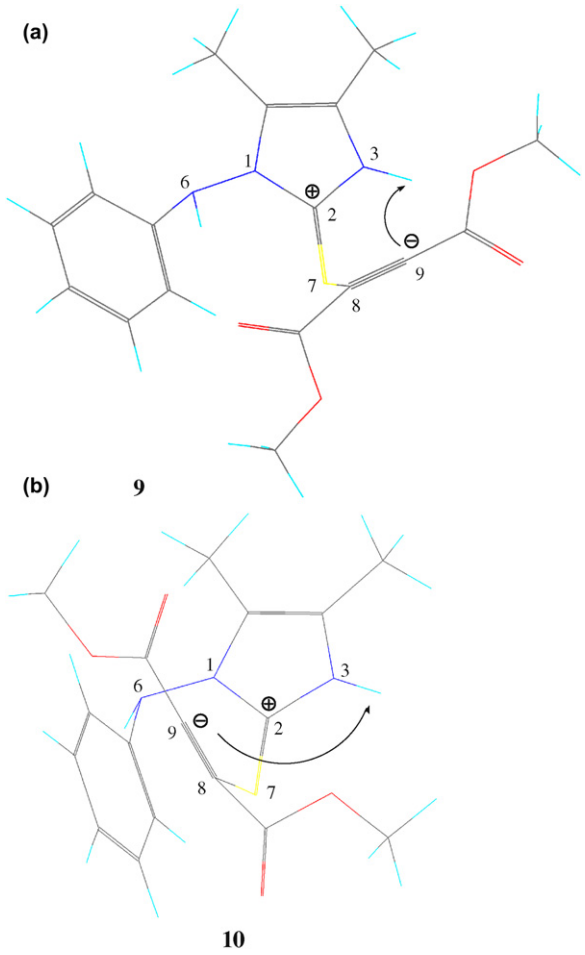


Figure 1. (a) At room temperature fast rotation about C2-S7 and S7-C8 bonds favors conformation **9** leading to **5a**-*E* isomer. (b) At lower temperatures conformation **10** is stabilized by electronic interactions of C9-ester group with nitrogen atoms N1 and N6 leading to **5a**-*Z* isomer (AM1).

thiones **1a–c** were allowed to react with DMAD in the presence of 2.2 equiv of sodium hydride for 24 h (71–82% yield), proving thus that cyclization to **4** proceeds through initial formation of **5**.

For the formation of **5** and **4** the following mechanistic scheme can be proposed (Scheme 4). Initially, by the reaction of thiones **1** with DMAD a mixture of *Z*- and *E*-substituted derivatives **5** is formed. In an attempt to explain the regiospecificity of acetylenedicarboxylate addition to the thione sulfur, we assume that after initial formation of **9** or **10** (Fig. 1), 3-NH hydrogen abstraction is the most probable pathway and the negatively charged acetylenedicarboxylate moiety is supposed to be still linear and the C2–S–C8 angle about 100°. At room temperature, fast rotation about the C2–S7 and S7–C8 bonds favors conformation **9** leading to **5**-*E* isomers. On the contrary, at lower temperatures the favored conformation **10** could be stabilized by secondary electronic interactions of C9-ester group with nitrogen atoms N1 and N6 leading to **5**-*Z* isomers. In the case of a C5-phenyl substituent the electron density as well as the HOMO coefficient of S-7 are decreased (Table 1, AM1)[17] leading at ambient temperature almost exclusively to a product with *Z*-configuration. Finally, in protic solvents or in water it is believed that intermediate **11** could be more easily protonated by abstracting a solvent hydrogen forming intermediate **12** and subsequently **5**-*Z*. Although it is well known that Michael-type amine and thione addition to acetylenic esters leads to *E*/*Z* isomeric mixtures, no attempt has been made until now to explain this stereospecificity.[16]

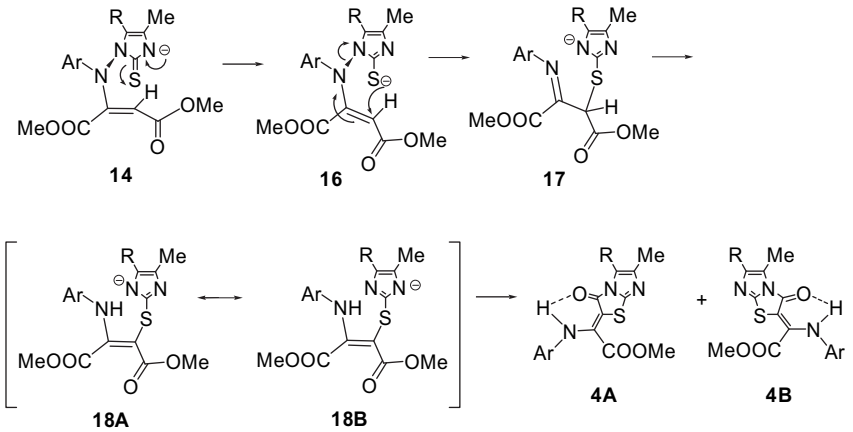
Table 1
Electron densities and HOMO coefficients on sulfur in compounds **1a–c** (AM1)

Compound	S-7 HOMO P_z coefficient	Charge q_{net} (electrons)
1a	−0.6506	−0.2612
1b	−0.6491	−0.2563
1c	−0.6213	−0.2555

Concerning the formation of **4**, reaction of **5** with sodium hydride furnishes the anion **13**. Migration of the carbomethoxy-vinyl group to the 6-arylamino nitrogen results in formation of **14**, from which subsequent ring closure to **15** can occur. Finally, formation of the isolated imidazothiazoles **4** is feasible through nitrogen–nitrogen bond fission, formation of a new thiazole ring and 1,3-H migration. Thus, as a result, for the formation of the end products **4**, an arylamino group migration from thione position 1 to the acetylenedicarboxylate moiety of **4** takes place. An alternative plausible mechanism for the formation of **4** (Scheme 5) involving N1–N6 bond fission and formation of the tautomeric intermediate mixture **18A** and **18B** through **16** and **17** could also be proposed. However, in this case the final product would be a **4A**, **4B** mixture. Since, in the case of the asymmetrically substituted thione **1c** only one isomer of **4c** was formed this mechanism should be excluded.

3. Structure assignments of the new compounds

The assigned molecular structures of the new compounds **4**, **5**, **6**, **7** and **8** were based on rigorous spectroscopic analysis including IR, NMR (^{1}H, ^{13}C, H–H COSY, H–H NOESY, HETCOR and COLOC), MS and



Scheme 5. Alternative plausible mechanism for the formation of compounds **4** leading to an isomeric mixture and therefore excluded.

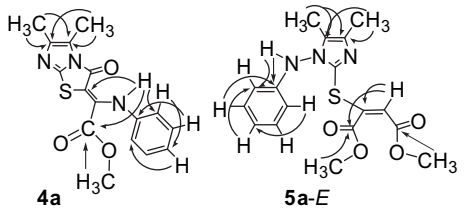


Figure 2. COLOC correlations observed in compounds **4a** and **5a**-*E*.

elemental analysis data. In Figure 2 the COLOC correlations of protons with carbons via ^{2}J and ^{3}J coupling for compounds **4a** and **5a**-*E* are depicted.

Concerning the identification of the various isolated compounds of high diagnostic value is the substantial chemical shift difference between the 3- and 6-NH protons, which resonate at δ ~11.9 and ~6.9, respectively. The 4- and 5-methyl group carbon chemical shifts are also of diagnostic value, since in a thione ring they resonate at δ 9.4 and 8.5, whereas in a thiol at δ 13.3 and 8.5, respectively. Furthermore, the carbomethoxy-vinyl proton chemical shifts for *E*-isomers are found between 5.0–5.7 ppm, whereas those for *Z*-isomers between 6.5–7.0 ppm in agreement with *E*- and *Z*-configurations of dimethyl citraconate and dimethyl mesaconate, where the vinyl proton resonates at δ 5.87 and δ 6.68, respectively.[18] Another characteristic feature of *E*-, *Z*-isomers is the $^{3}J_{CH}$ coupling constant. As depicted in Figure 3, a value of $^{3}J_{CH}$ of 11.0 Hz is found

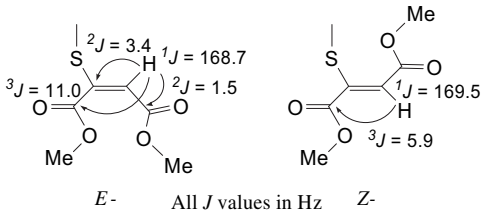


Figure 3. $^{1}J_{CH}$,$^{2}J_{CH}$ and $^{3}J_{CH}$ coupling constants measured in **5a**-*E* and **5a**-*Z*.

in **5a**-*E* isomer approximately twice the value of 5.9 Hz found in **5a**-*Z* isomer, in accordance with the literature.[19] Finally, concerning compounds **4**, the proposed *E*-configuration of the exocyclic vinyl group was based on the low-field resonance of the NH proton at 10.44–10.58 ppm, due to hydrogen bonding with the adjacent carbonyl oxygen. This hypothesis is also supported by the fact that **4**-*E* isomer is calculated to be energetically favored by ~3.5 kcal/mol (AM1) over its **4**-*Z* counterpart. In Figure 4 a global lower energy molecular model for **5a**-*E* isomer calculated by AM1 in accordance with NMR data is represented.

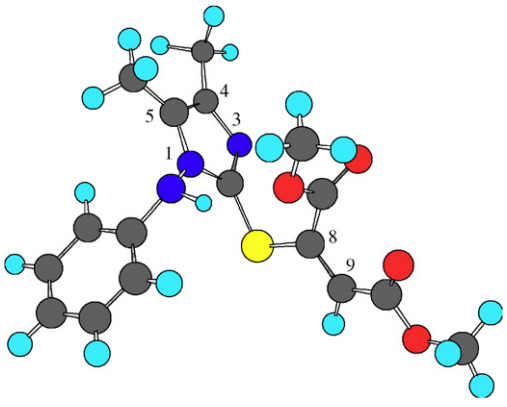


Figure 4. Global lower energy conformation of **5a**-*E* calculated by AM1 in accordance with NMR data.

4. Conclusion

In conclusion, we have achieved the synthesis of new imidazo[2,1-*b*][1,3]thiazoles through a novel arylamino rearrangement. Furthermore, the substituent, solvent, and temperature dependent Michael-type addition reaction of DMAD to 1-arylaminoimidazole-2-thiones was thoroughly investigated. The stereospecificity of the reaction between thiones and acetylenedicarboxylates leading to formation of *E*/*Z* isomeric mixtures was also studied and it was established that at room temperature formation of **5**-*E* isomers is favored, whereas at lower temperatures *Z*-isomers are the predominated ones.

5. Experimental

5.1. General

Melting points were measured on a Kofler hot–stage and are uncorrected. Column chromatography was carried out using Merck silica gel. TLC was performed using precoated silica gel glass plates 0.25 mm containing fluorescent indicator UV_{254} purchased from Macherey–Nagel, using a 3:1 mixture of petroleum ether/ethyl acetate. Petroleum ether refers to the fraction boiling between 60 and 80 °C. NMR spectra were recorded at room temperature on a Bruker AM 300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively, using $CDCl_3$ as solvent. Chemical shifts are expressed in δ values (ppm) relative to TMS as internal standard for ^{1}H and relative to TMS (0.00 ppm) or to $CDCl_3$ (77.05 ppm) for ^{13}C NMR spectra. Coupling constants ^{n}J are reported in Hz. Second order ^{1}H spectra in the aromatic region, where it was possible, were analysed by simulation.[20] IR spectra were recorded on a Perkin–Elmer 1600 series FTIR spectrometer and are reported in wave numbers (cm^{-1}). Low-resolution electron impact mass spectra were recorded on a 6890 N LC/MS system (Agilent Technology) and elemental analyses performed with a Perkin–Elmer 2400-II CHN analyzer in the Laboratory of Organic Chemistry, University of Thessaloniki. Structural assignments of the derived compounds were established by analysis of their IR, MS and NMR spectra (^{1}H, ^{13}C, DEPT, H–H COSY, H–H NOESY, HETCOR and COLOC).

5.2. General procedure for the reaction of thiones (1a–c) with dimethyl acetylenedicarboxylate

A reaction mixture of thione **1** (1.0 mmol) and dimethyl acetylenedicarboxylate (0.22 g, 1.1 mmol) in ethyl acetate (20 mL), was stirred at ambient temperature until thione **1** was consumed completely (followed by TLC, approximately 24 h). From the reaction mixture the solvent was distilled off in vacuo and the resulting residue was either crystallized (**5a**–**b**) or subjected to column chromatography on silica gel using petroleum ether/AcOEt (7:1) as eluent, slowly increasing the polarity up to 4:1 to give the isolated product (**5c**):

*5.2.1. Dimethyl 2-[(1-anilino-4,5-dimethyl-1H-imidazol-2-yl)thio]-but-2-enedioate (**5a**).* Yellow solid (0.191 g, 53% yield), as a mixture of *E*- and *Z*-isomers in a ~4:1 ratio. From this mixture crystallization of the major *E*-isomer was possible from ether.

Major isomer **5a**-*E*: mp 135–137 °C. IR (Nujol) ν_{max}: 3208, 3182 (br), 3118, 1742, 1718 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3H, 5-CH_3), 2.23 (s, 3H, 4-CH_3), 3.67 (s, 3H, 8-OCH_3), 3.70 (s, 3H, 9-OCH_3), 5.87 (s, 1H, 9-H), 6.48 (ddd, *J*=7.7, 2.0, 1.0 Hz, 2H, 2′,6′-H), 6.93 (tt, *J*=6.9, 1.0 Hz, 1H, 4′-H), 7.10 (br s, 1H, NH), 7.23 (ddd, *J*=7.7, 6.9, 2.0 Hz, 2H,

3′,5′-H).[19] ^{13}C NMR ($CDCl_3$) δ 8.6 (5-CH_3), 13.3 (4-CH_3), 52.1 (9-OCH_3), 53.3 (8-OCH_3), 112.7 (C-2′,6′), 116.6 (C-9), 121.7 (C-4′), 129.5 (C-2)[†], 129.5 (C-3′,5′), 129.7 (C-5), 134.8 (C-4), 146.3 (C-1′), 147.1 (C-8), 163.8 (9-CO), 165.8 (8-CO). MS (LCMS) *m*/*z* (%) 360 (100, M^+). Anal. calcd for $C_{17}H_{19}N_3O_4S$ (361.42): C, 56.50; H, 5.30; N, 11.63. Found: C, 56.37; H, 5.15; N, 11.48.

Minor isomer **5a**-*Z*: After isolation of **5a**-*E* some NMR data of the *minor isomer* **5a**-*Z* were also deduced: ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H, 5-CH_3), 2.17 (s, 3H, 4-CH_3), 3.65 (s, 3H, 8-OCH_3), 3.72 (s, 3H, 9-OCH_3), 6.53 (s, 1H, 9-H), 6.55 (d, *J*=8.9 Hz, 2H, 2′,6′-H), 6.91–6.93 (m, 1H, 4′-H), 7.21–7.23 (m, 2H, 3′,5′-H), 7.29 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 8.4 (5-CH_3), 13.2 (4-CH_3), 52.0 (9-OCH_3), 53.4 (8-OCH_3), 112.8 (C-2′,6′), 116.4 (C-9), 121.5 (C-4′), 127.9 (C-5), 129.4 (C-3′,5′), 129.5 (C-2), 133.7 (C-4), 145.9 (C-1′), 146.2 (C-8), 164.8 (9-CO), 165.1 (8-CO).

*5.2.2. Dimethyl 2-({1-[(4-chlorophenyl)amino]-4,5-dimethyl-1H-imidazol-2-yl}thio)but-2-enedioate (**5b**).* Yellow solid (0.214 g, 54%), as a mixture of the *E*- and *Z*-isomer in a 4:1 ratio. From this mixture crystallization of the major *E*-isomer was possible from ether.

Major isomer (E): mp 139–141 °C; IR (Nujol) ν_{max}: 3172 (br), 1740, 1717 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H, 5-CH_3), 2.22 (s, 3H, 4-CH_3), 3.67 (s, 3H, 8-OCH_3), 3.71 (s, 3H, 9-OCH_3), 5.89 (s, 1H, 9-H), 6.43 (d, *J*=8.9 Hz, 2H, 2′,6′-H), 7.18 (d, *J*=8.9 Hz, 2H, 3′,5′-H), 7.44 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 8.6 (5-CH_3), 13.1 (4-CH_3), 52.0 (9-OCH_3), 53.4 (8-OCH_3), 113.9 (C-2′,6′), 116.8 (C-9), 126.6 (C-4′), 129.5 (C-2), 129.5 (C-3′,5′), 129.6 (C-5), 134.9 (C-4), 144.9 (C-1′), 145.2 (C-8), 163.8 (9-CO), 165.1 (8-CO). MS (LCMS) *m*/*z* (%) 396/398 (100, M^++1). Anal. calcd for $C_{17}H_{18}ClN_3O_4S$ (395.86): C, 51.58; H, 4.58; N, 10.61. Found: C, 51.69; H, 4.56; N, 10.39.

Minor isomer (*Z*): After isolation of **5b**-*E* the NMR data of the *minor isomer* **5b**-*Z* were also deduced: ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H, 5-CH_3), 2.17 (s, 3H, 4-CH_3), 3.65 (s, 3H, 8-OCH_3), 3.72 (s, 3H, 9-OCH_3), 6.51 (d, *J*=8.9, 2H, 2′,6′-H), 6.54 (s, 1H, 9-H), 7.17 (d, *J*=8.9 Hz, 2H, 3′,5′-H), 7.47 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 8.4 (5-CH_3), 13.1 (4-CH_3), 52.0 (9-OCH_3), 53.2 (8-OCH_3), 112.8 (C-2′,6′), 116.4 (C-9), 121.5 (C-4′), 127.9 (C-5), 128.5 (C-2), 129.4 (C-3′,5′), 134.0 (C-4), 145.8 (C-8), 146.6 (C-1′), 164.8 (8-CO), 165.1 (9-CO).

*5.2.3. Dimethyl (2Z)-2-[(1-anilino-4-methyl-5-phenyl-1H-imidazol-2-yl)thio]but-2-enedioate (**5c**).* Yellow solid (0.233 g, 55%), mp 126–128 °C, was isolated only as the *Z*-isomer. IR (Nujol) ν_{max}: 3174 (br), 1732, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H, 4-CH_3), 3.67 (s, 3H, 8-OCH_3), 3.72 (s, 3H, 9-OCH_3), 6.58 (d, *J*=7.7 Hz, 2H, 2′,6′-H), 6.61 (s, 1H, 9-H), 6.90 (t, *J*=7.3 Hz, 1H, 4′-H), 7.15–7.22 (m, 2H, 3′,5′-H), 7.24 (br s, 1H, NH), 7.33–7.37 (m, 5H, 4-Ph).^{13}C NMR ($CDCl_3$) δ 14.2 (4-CH_3), 52.1 (9-OCH_3), 53.5 (8-OCH_3), 113.1 (C-2′,6′), 122.7 (C-9), 121.6 (C-4′), 128.0 (C-4″), 128.3 (C-2″,6″), 128.4 (C-2), 128.6 (C-5), 129.2 (C-3″,5″), 129.4 (C-3′,5′), 132.0 (C-4), 135.7 (C-1″), 145.1 (C-1′), 147.0 (C-8), 164.8 (9-CO), 165.0 (8-CO). MS (LCMS) *m*/*z* (%) 424 (100, M^++1). Anal. calcd for $C_{22}H_{21}N_3O_4S$ (423.48): C, 62.40; H, 5.00; N, 9.92. Found: C, 62.47; H, 4.95; N, 9.78.

5.3. Reaction of thione 1a with DMAD in benzene at reflux

A reaction mixture of thione **1a** (1.0 mmol) and DMAD (0.22 g, 1.1 mmol) in benzene (20 mL), was heated at reflux until thione was consumed completely (followed by TLC, approximately 48 h). The solvent was distilled off in vacuo and the resulting residue was subjected to column chromatography on silica gel using petroleum ether/AcOEt (5:1) as eluent, slowly increasing the polarity up to 1:1 to give only.

[†] Revealed after the acquisition of the C–H coupled spectrum.

*5.3.1. Dimethyl (2E)-2-(3-anilino-4,5-dimethyl-2-thioxo-2,3-dihydro-1H-imidazol-1-yl)but-2-enedioate (**6a**-Z).* Yellowish oil in 91% yield; IR (neat) ν_{max}: 3161 (br), 1750, 1712 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3H, 6-CH_3), 2.14 (s, 3H, 5-CH_3), 3.75 (s, 3H, 9-OCH_3), 3.88 (s, 3H, 8-OCH_3), 6.70–6.74 (m, 2H, 2′,6′-H), 6.92 (br s, 1H, NH), 6.94–7.01 (m, 1H, 4′-H), 7.27 (s, 1H, 9-H), 7.26–7.29 (m, 2H, 3′,5′-H). ^{13}C NMR ($CDCl_3$) δ 8.5 (5-CH_3), 9.3 (4-CH_3), 52.6 (9-OCH_3), 53.6 (8-OCH_3), 114.2 (C-2′,6′), 119.6 (C-4), 122.3 (C-4′), 123.3 (C-5), 129.4 (C-3′,5′), 129.8 (C-9), 135.8 (C-8), 145.8 (C-1′), 162.1 (C-2), 162.4 (8-CO), 162.9 (9-CO). MS (LCMS) *m*/*z* (%) 362 (100, M^++1). Anal. calcd for $C_{17}H_{19}N_3O_4S$ (361.42): C, 56.50; H, 5.30; N, 11.63. Found: C, 56.71; H, 5.25; N, 11.78.

5.4. Isomerization of 2a (mixture *E*/*Z*) in benzene at reflux

A solution of thione **2a** (4:1 mixture *E*/*Z*) (1.0 mmol) in benzene (20 mL) was heated at reflux until compound **2a** was consumed completely (followed by TLC, approximately 48 h). The solvent was distilled off in vacuo and the resulting residue was subjected to column chromatography on silica gel using petroleum ether/AcOEt (5:1) as eluent, slowly increasing the polarity up to 1:1 to give only **6a**-*Z*, in 90% yield.

5.5. Reaction of thione 1a with DMAD in the presence of sodium methoxide

To a suspension of compound **1a** (1.0 mmol) in dry methanol (10 mL) at 20 °C, sodium (1.1 mmol) was added, the mixture was stirred for 10 min, DMAD (1.0 mmol) was then added and the reaction mixture was stirred for 4 h at 20 °C. Dilution of the reaction mixture with 40 mL ice resulted to precipitation of the product which was rinsed with ether to give the *dimethyl* (*2E*)-*2*-[*4,5-dimethyl-2-thioxo-2,3-dihydro-1H-imidazol-1-yl*(*phenyl*)*amino*]*but-2-enedioate* (**8a**-E).

Yield 75%; mp 178–180 °C. IR (Nujol) ν_{max}: 3424 (br), 1746, 1709 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3H, 5-CH_3), 2.10 (s, 3H, 4-CH_3), 3.67 (s, 3H, 8-OCH_3), 3.78 (s, 3H, 7-OCH_3), 5.13 (s, 1H, 9-H), 7.23–7.25 (m, 1H, 4′-H), 7.33–7.36 (m, 2H, 3′,5′-H), 7.48 (d, *J*=7.7, 2H, 2′,6′-H), 11.9 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 8.4 (5-CH_3), 9.4 (4-CH_3), 51.5 (8-OCH_3), 53.2 (7-OCH_3), 96.6 (C-9), 124.0 (C-2′,6′), 127.4 (C-4′), 129.4 (C-3′,5″), 141.0 (C-1′), 149.5 (C-8), 161.1 (C-2), 166.6 (8-CO), 163.5 (7-CO). MS (LCMS) *m*/*z* (%) 362 (100, M^++1). Anal. calcd for $C_{17}H_{19}N_3O_4S$ (361.42): C, 56.50; H, 5.30; N, 11.63. Found: C, 56.38; H, 5.21; N, 11.48.

5.6. Isomerization of 5a in the presence of sodium hydride

To a suspension of compound **5a** (1.0 mmol of *E*/*Z* 4:1 mixture) in dry THF (15 mL) at 20 °C sodium hydride (60% in oil, 1.1 mmol) was added under argon. The reaction mixture was stirred for 3 h at room temperature. After dilution of the solution with 40 mL ice–water the product precipitated. The crude product mixture was subjected to column chromatography on silica gel using petroleum ether/EtOAc (3:1) as eluent, to give the *dimethyl 2*-[*4,5-dimethyl-2-thioxo-2,3-dihydro-1H-imidazol-1-yl*(*phenyl*)*amino*]*but-2-enedioate* (**8a**) as a 2:1 mixture of isomers *E*/*Z* in 78% yield.

5.7. Formation of (2*E*)-2-[(arylamino)(methoxycarbonyl)-methylene]-5,6-dimethylimidazo[2,1-*b*][1,3]thiazol-3(2*H*)-one (4)

*5.7.1. Method A. From the reaction of thiones **1** with DMAD. General procedure.* To a suspension of compound **1** (1.0 mmol) in dry tetrahydrofuran (15 mL) at 20 °C, sodium hydride (60% in oil, 2.2 mmol) was added under argon. Salt formation was allowed to proceed for 30 min, DMAD (1.0 mmol) was then added and the

reaction mixture was stirred at for 24 h at room temperature. Dilution of the solution with 40 mL ice–water precipitated the product. The crude product mixture was subjected to column chromatography on silica gel using petroleum ether/EtOAc (5:1) as eluent, to give the purified imidazothiazoles **4**.

*5.7.1.1. (2E)-2-[(Anilino)(methoxycarbonyl)methylene-5,6-dimethylimidazo[2,1-b][1,3]thiazol-3(2H)-one (**4a**).* Isolated as a white solid in 74% yield, mp 159–161 °C.IR (Nujol)ν_{max}: 1713, 1661 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.17 (s, 3H, 6-CH_3), 2.44 (s, 3H, 5-CH_3), 3.73 (s, 3H, OCH_3), 6.98 (d, J=7.8 Hz, 2H, 2′,6′-H), 7.18 (t, J=7.4 Hz, 1H, 4′-H), 7. 31–7.37 (m, 2H, 3′,5′-H), 10.54 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 8.6 (5-CH_3), 12.6 (6-CH_3), 53.2 (OCH_3), 104.3 (C-2), 120.7 (C-5), 121.4 (C-2′,6′), 125.4 (C-4′), 129.4 (C-3′,5′), 139.8 (C-1′), 141.7 (C-6), 142.6 (C-8), 146.5 (C-7a), 162.6 (C-3), 163.2 (8-CO). MS (LCMS) m/z (%) 368 (100, M^++K). Anal. calcd for $C_{16}H_{15}N_3O_3S$ (329.37): C, 58.34; H, 4.59; N, 12.76.Found: C, 58.53; H, 4.42; N, 12.88.

*5.7.1.2. (2E)-2-{[(4-Chlorophenyl)amino](methoxycarbonyl)-methylene}-5,6-dimethylimidazo[2,1-b][1,3]thiazol-3(2H)-one (**4b**).* Isolated as a white solid (71% yield), mp 169–171 °C. IR (Nujol) ν_{max}: 1725, 1679 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.17 (s, 3H, 6-CH_3), 2.43 (s, 3H, 5-CH_3), 3.76 (s, 3H, OCH_3), 6.91 (d, J=8.7 Hz, 2H, 2′,6′-H), 7.30 (d, J=8.7 Hz,, 2H, 3′,5′-H), 10.44 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 8.6 (5-CH_3), 12.7 (6-CH_3), 53.4 (OCH_3), 105.9 (C-2), 120.8 (C-5), 122.7 (C-2′,6′), 129.5 (C-3′,5′), 130.8 (C-4′), 138.6 (C-1′), 141.8 (C-6)[‡], 141.9 (C-8)[†], 146.6 (C-7a), 162.7 (3-CO), 163.1 (COOMe). MS (LCMS) m/z (%) 364/366 (100, M^++1). Anal. calcd for $C_{16}H_{14}ClN_3O_3S$ (363.82): C, 52.82; H, 3.88; N, 11.55. Found: C, 52.67; H, 3.92; N, 11.68.

*5.7.1.3. (2E)-2-[Anilino(methoxycarbonyl)methylene]-5-methyl-6-phenylimidazo[2,1-b][1,3]thiazol-3(2H)-one(**4c**).* Isolated as a white solid (82% yield), mp 175–177 °C.IR (Nujol)ν_{max}: 3244, 3025, 2945, 1713, 1679 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.73 (s, 3H, 5-CH_3), 3.72 (s, 3H, OCH_3), 6.99 (d, J=7.8 Hz, 2H, 2′,6′-H), 7.18 (t, J=7.5 Hz, 1H, 4′-H), 7.27–7.32 (m, 1H, 4″-H), 7. 31–7.36 (m, 2H, 3′,5′-H), 7.39–7.44 (m, 2H, 3″,5″-H), 7.68 (d, J=7.5 Hz, 2H, 2″,6″-H), 10.58 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 9.9 (5-CH_3), 53.2 (OCH_3), 104.0 (C-2), 121.4 (C-5), 121.5 (C-2′,6′), 125.5 (C-4′), 127.4 (C-2″,6″), 127.5 (C-4″), 128.5 (C-3″,5″), 129.4 (C-3′,5′), 133.6 (C-1″), 139.7 (C-1′), 142.9 (C-8), 144.6 (C-6), 147.2 (C-7a), 163.0 (C-3), 163.1 (COOMe). MS (LCMS) m/z (%) 392 (100, M^++1). Anal. calcd for $C_{21}H_{17}N_3O_3S$ (391.44): C, 64.43; H, 4.38; N, 10.73.Found: C, 64.51; H, 4.22; N, 10.75.

*5.7.2. Method B. From Dimethyl 2-[(1-arylamino-4-methyl-5-methyl(or phenyl)-1H-imidazol-2-yl)thio]but-2-enedioate (**5**-E/Z).* To a suspension of **5**-*E*/*Z*(1.0 mmol) in dry tetrahydrofuran (15 mL) at 20 °C sodium hydride (60% in oil, 2.0 mmol) was added under argon. The reaction mixture was stirred for 24 h at room temperature. Dilution of the solution with 40 mL ice–water precipitated the product. The crude product mixture was subjected to column chromatography on silica gel using petroleum ether/EtOAc (5:1) as eluent to give the purified imidazothiazoles **4**. Compound **4a** was obtained in 68% yield, **4b** in 67% yield and **4c** in 65% yield.

5.8. Reaction of 5a-*E* with acetic anhydride

A solution of **5a**-*E* (1.0 mmol) in acetic anhydride (10 mL) was heated at reflux for 3 h. The reaction mixture was then washed repeatedly with water; the remainder was dried and subjected to column chromatography on silica gel using petroleum ether/EtOAc (3:1 up to 1:1) as eluent, to give the purified product.

*5.8.1. Dimethyl 2-[3-acetyl-4,5-dimethyl-2-thioxo-2,3-dihydro-1H-imidazol-1-yl(phenyl)amino]but-2-enedioate **7**-Z.* Yellow solid, 0.234 g (58%), mp 160–162 °C; IR (Nujol) ν_{max}: 1740, 1707 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.96 (s, 3H, 5-CH_3), 2.07 (s, 3H, 4-CH_3), 2.18 (s, 3H, $COCH_3$), 3.75 (s, 3H, 8-OCH_3), 3.89 (s, 3H, 7-OCH_3), 7.21–7.23 (m, 1H, 4′-H), 7.30 (s, 1H, 9-H), 7.29–7.35 (m, 2H, 3′,5′-H), 7.55–7.57 (m, 2H, 2′,6′-H). ^{13}C NMR ($CDCl_3$) δ 8.7 (4-CH_3), 9.3 (5-CH_3), 22.5 (3-CH_3), 52.6 (8-OCH_3), 53.6 (7-OCH_3), 121.1 (C-5), 121.4 (C-4), 122.9 (C-2′,6′), 126.5 (C-4′), 128.9 (C-3′,5′), 130.0 (C-9), 135.5 (C-8), 139.4 (C-1′), 162.6 (8-CO), 161.9 (7-CO), 164.3 (C-2), 170.9 (3-CO). MS (LCMS) m/z (%) 404 (100, M^++1). Anal. calcd for $C_{19}H_{21}N_3O_5S$ (403.45): C, 56.56; H, 5.25; N, 10.42.Found: C, 56.66; H, 5.06; N, 10.38.

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[‡] These assignments may be interchanged.