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First catalytic hetero-Diels–Alder reaction of imidazole-2-thiones and *in silico* biological evaluation of the cycloadducts

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ABSTRACT

The Lewis acid-catalyzed Diels–Alder reactions of suitably substituted imidazole-2-thiones with dienes were studied. It was found that the electron density of the imidazole core influenced the reaction, since electron withdrawing groups led to the novel spiro-derivatives **2** whereas electron donating groups gave rise to the sulfur substituted imidazole derivatives **6**. The reaction conditions were optimized and full assignment of all ¹H and ¹³C NMR chemical shifts has been unambiguously achieved. *In silico* evaluation of the cycloadducts by means of molecular modeling in three different proteins and calculation of ADME-Tox properties was performed.

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1. Introduction

Thiones and especially imidazole-2-thiones are privileged scaffolds with a strong and diverse presence in many biologically active compounds or drugs.^{1–6} Imidazole-2-thiones were previously found to exhibit antibacterial and antitumor activity, inhibit different protein targets e.g., MMP-13, CCR2 receptor whereas methimazole is already a commercially available antithyroid drug (Fig. 1).^{1–6}

Furthermore, thiones have been known to participate efficiently as dienophiles in Diels–Alder reactions.^{7,8} The breadth of reactions available to manipulate the carbon–sulfur bond (e.g., desulfurization, elimination or Pummerer rearrangement) make cycloadditions of such dienophiles leading to dihydrothiapyrans a powerful method to form carbon–carbon bonds.⁹ Moreover thiocarbonyl compounds as well as their cycloaddition products, the dihydrothiapyrans, have already been used in the synthesis of natural or bioactive products^{10–16} in particular thiosugars.^{17,18} Unfortunately, the use of thiocarbonyl dienophiles in synthesis is limited perhaps because the level of regioselectivity observed with unsymmetrical 1,3-dienes is not always useful and often difficult to predict.^{7,8,10–12} It is worth mentioning that in the last few years, research has been focused on catalyzed thia-Diels–Alder reactions,

Fig. 1. Thione/thiol derivatives present in various biologically and pharmaceutically active compounds.

since a Lewis or Brønsted acid catalyst affords a more reactive heterodienophile activating the thiocarbonyl group by lowering the LUMO dienophile energy, therefore reducing the activation energy of the process. This methodology has been applied particularly in dithioesters.¹⁹

It is documented that the nature and pattern of the substituents on the thione greatly influences the regiochemical outcome of their

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Diels–Alder reactions.⁷ Electron-deficient substituents render the sulfur electrophilic^{20–23} and thus enlarge sulfur's orbital coefficient in the lowest unoccupied molecular orbital (LUMO).

In the present work, we describe a study of the reactivity of suitably substituted imidazole-2-thiones of biological interest^{24–26} as heterodienophiles in catalytic thia-Diels–Alder reactions activated by Lewis acids. Moreover *in silico* biological evaluation of the corresponding cycloadduct is provided.

2. Results and discussion

Two types of imidazole-2-thiones, the *N*-aryl-substituted structure **1a**²⁴ bearing electron withdrawing substituents in the 4,5-position and the *N*-arylamino-substituted structure **5**^{25,27,28} were synthesized and subsequently employed for a study concerning hetero thia-Diels–Alder reactions. Initially, the reactivity of the imidazole-2-thione **1a** towards the reactive unfunctionalized 1,3-dimethylbutadiene was examined whereupon, no reaction was observed in the case of uncatalyzed reactions even with harsher conditions or microwave irradiation. Only after the addition of the Lewis acids ZnCl₂ or BF₃·Et₂O the reaction precedes successfully, the yield of the product and also the reaction time depending on the nature and the amount of the catalyst (Table 1). It was found that the yield of products **2** was optimized by using microwave irradiation along with 4.0 equiv of BF₃·Et₂O at 90 °C for only 5 min (entry 5).

Table 1
Optimization of thia hetero-Diels–Alder reaction conditions involving 4,5-dicarboxy ethyl-substituted imidazole-2-thiones

Entry	Catalyst (eq)	Conditions	Yield (%) cycloadduct 2a
1	—	Reflux, 24 h	—
2	—	MW, 90 °C/5 min	—
3	BF ₃ ·Et ₂ O (2.5)	Reflux, 48 h	15
4	BF ₃ ·Et ₂ O (4.0)	Reflux, 2 h	20
5	BF ₃ ·Et ₂ O (4.0)	MW, 90 °C/5 min	57
6	ZnCl ₂ (4.0)	Reflux, 24 h	12

Having established the optimized conditions between thione **1a** and 2,3-dimethylbutadiene, we proceeded to the reaction of the imidazole–thione derivatives **1b–j** yielding the desired cycloadducts in moderate to good yields, 57–85% (Scheme 1). We synthesized a small series of these spiro compounds consisting of different substituents on the phenyl ring, varying from electron donating to electron withdrawing groups. To the best of our knowledge, it is the first time that a thia hetero Diels–Alder of imidazole-thiones is reported.

Suspecting that the electron density of the imidazole plays crucial role for the Diels–Alder reaction, we replaced the carboxy ethyl moiety on 4- and 5-position of the imidazole core with phenyl rings.²⁹ In that case the cycloaddition under the optimized conditions with the 1,3-dimethylbutadiene did not take place affording compound **3** (Fig. 2). Next, the cycloaddition reaction was repeated with commercially available dienes, 1-acetoxybutadiene, 1-trimethylsilyloxybutadiene and 1-methoxy-3-trimethylsilyloxybutadiene but unfortunately in all attempts, the Diels–Alder cycloadducts were not isolated. Unexpectedly, the reaction of **1a** either with 1-trimethylsilyloxybutadiene or 1-methoxy-3-trimethylsilyloxybutadiene compound **4** was isolated, after reflux for 4 days, as the only reaction product in 31% and 26%, respectively. It seems that the initially formed spiro-cycloaddition product was

Scheme 1. Hetero Diels–Alder reactions with dienes affording the spiro-cycloaddition products.

Fig. 2. Isolated imidazole derivatives with different substitution pattern during hetero Diels–Alder with trimethylsilyloxybutadiene derivatives.

desialylated on the chromatography column and then degraded to give finally compound **4**.

In continuation of the above investigation, the BF₃·Et₂O catalyzed reaction under microwave irradiation was carried out with the arylamino substituted thiones **5** and 1,3-dimethylbutadiene whereupon in all cases (Scheme 2) the sulfur substituted imidazole derivatives **6** were isolated in good yields analogously to compound **3**.

- a: X = R¹ = R² = H
 b: X = H, R¹ = Me, R² = H
 c: X = Cl, R¹ = Me, R² = H
 d: X = Cl, R¹ = Me, R² = -COCH₃

Scheme 2. Reactions of imidazole–thiones **2** with 1,3-dimethylbutadiene.

We believe that the substitution pattern of the imidazole ring plays an important role on the reaction. Increasing or decreasing the electron density of the heterocycle, which subsequently affects the C–S bond can lead to the cycloaddition or not. The cycloadditions in our case can be characterized as normal electron demand hetero Diels–Alder reactions since we have a diene, which does not contain a heteroatom and an electron deficient dienophile due to the presence of the heteroatom.³⁰ Thus, the HOMO (donor-orbital) of the 2,3-dimethylbutadiene reacts with the LUMO (acceptor-orbital) of the C=S. Electron withdrawing groups on the dienophile, such as the thione **1** with the carboxy ethyl groups in the 4,5-position, reduce the π -electron density and allow better flow of electrons to this orbital. Therefore, the atoms of the C=S bond become more electrophilic, which means a better dienophile for the hetero Diels–Alder reaction. The use of Lewis acid lowers the LUMO dienophile energy even further contributing to the reduction of activation energy of the reaction.

The formation of compounds **3** and **6**, even in the case of the N–COCH₃ substituted thione (**5d**), can be attributed to the reduced electrophilicity of C-2 of thiones **5** on account of the electron donating substituents according to the aforementioned hypothesis. The two types of thiones that examined, **1** and **5**, were subjected to energy minimization using DFT calculations and afterwards the partial charges were calculated (Supplementary data). Indeed, comparing the C-2 on the two thiones (Fig. 3), there is a distinct decrease on the electrophilicity on the thione **5** (Fig. 3B) from 0.583 to 0.382 elementary charge units (q), which can give a plausible explanation to reaction's mechanism.

Fig. 3. Calculated partial charges on selected atoms of the employed thiones after energy minimization.

2.1. Structure assignments of the new compounds

The assigned molecular structures of the new compounds **2**, **3**, **4** and **6** were based on rigorous spectroscopic analysis including NMR (¹H, ¹³C, H–H COSY, H–H NOESY, HETCOR and COLOC), MS and elemental analysis data. In Fig 4 the COLOC correlations of protons with carbons via ²J and ³J coupling for compounds **2a** and **4** are depicted.

Fig. 4. COLOC correlations observed via ²J and ³J coupling for compounds **2a**, **4** and **6b**.

Concerning the identification of the spiro-derivatives **2**, the derivative **2a** was studied. The proton NMR spectrum showed the presence of two carboxy ethyl groups, and of the imidazole 3-NH proton, at $\delta \sim 1.81$. In addition, the 8- and 9-methyl group

protons were observed at δ 1.62 (C-9) and δ 1.64 (C-8), respectively. Two more methylene singlets at δ 3.92 and δ 1.66 with their carbons resonating at 38.0 ppm and 20.4 ppm, respectively, were observed. The methylene group protons at δ 3.92 being in the vicinity of the sulfur atom showed COLOC correlations with the quaternary spiro carbon at 121.6 ppm, and C-9 and C-8 carbons whereas the second methylene group protons showed COLOC correlations also with the quaternary spiro carbon (Fig. 4).

For compound **4**, there is a correlation ²J_{CH} of C(2) of the methylene group next to sulfur with the quaternary carbon C-6 at 148.0 ppm (the chemical shift for the corresponding carbon in the case of the spiro compound **2a** is at 121.6 ppm) and with the adjacent methylene group CH₂(3). Moreover, correlations appear of ³J_{CH} with the CH₂(4) and CH₂(5), illustrating the ring opening of the imidazole core (Fig. 4).

Concerning compound **6b**, the two imidazole ring methyl group protons, which appear at δ 2.08 and 2.20, respectively, have COLOC correlations with the quaternary carbons at 126.0 and 132.4 ppm being the C-5 and C-4, respectively, via ²J_{CH} and ³J_{CH}. The NHPH proton resonating at δ 8.31 shows COLOC correlations with C-1' and C-2', and also a NOESY correlation with the methyl protons at δ 2.15 proving thus its position at C-5. The intensities of the COLOC correlations are higher between C(5)–CH₃(5) and C(4)–CH₃(4) than the correlations between C(5)–CH₃(4) and C(4)–CH₃(5) proving thus that ²J_{CH} > ³J_{CH}. This observation has been used as evidence for the assignment of the methyl signals of 4,5-dimethylimidazoles.

2.2. In silico biological evaluation of the cycloadducts 2

The cycloadducts **2**, due to the number of hydrogen donor or acceptor atoms^{31,32} that are consisted and their 'locked' conformation without the thione–thiol tautomerism,³³ could be further evaluated for any potential biological activity.

Very often, *in silico* evaluation (also known as computational therapeutics or computational pharmacology) is the first approach to assess new compounds for a specific target. It plays an important role in drug discovery and contributes significantly to a faster first selection of the compounds as potential drug candidates.³⁴

Our two-pronged strategy for this kind of evaluation is based on molecular modeling, which explores the three-dimensional protein structures and performs computational calculation to predict binding models of potential inhibitors³⁵ and the *in silico* calculation of the ADME-Tox properties, which was proved to give a very good estimation to the experimental values.^{36–38} Thus, ADME-Tox prediction of the compound **2a** was performed followed by computationally evaluation for its interaction with possible biological targets.

ADME-Tox properties from compound **2a** were calculated using Qikprop from Maestro software (Schrödinger Suite). As it was shown, a high majority of the calculated properties of compound **2a** e.g., the dipole moment, the hydrophobic and hydrophilic SASA (Solvent Accessible Surface Area) or the electron affinity, are in the range of 95% of commercially available drugs. In addition, no violation to any of the Lipinski and Jorgensen rules was predicted and also a high solubility in different solvents was estimated (see Supplementary data).

Furthermore, molecular modeling studies were performed due to the fact that compound **2a** presents a drug-like scaffold, as it consists of a spiro thioimidazole ring combined with a very interesting substitution pattern. The compound consists of two carboxy ethyl groups and a sulfur, which can interact with hydrogen donors, an –NH group which can interact with hydrogen acceptor and finally a hydrophobic part for possible lipophilic interactions (Fig. 5A). Compound **2a** was docked in three different proteins in order to investigate potential interactions. Two of the targeted proteins were chosen based on the high similarity of the previously

Fig. 5. A) Potential interactions of compound **2a**. Binding of compound **2a** in the catalytic site of B) MMP-13 protein, C) Aggrecanase-2 and D) h-15-LOX-1 after molecular modeling studies.

described inhibitors and our newly synthesized compound **2a**. MMP-13 and Aggrecanase-2 are zinc containing enzymes in which, derivatives of imidazole-2-thiones⁶ and thiosemicarbazides,³⁹ respectively, exhibit inhibition. The third protein was selected as an example of exploring the interactions of the substitution pattern of the compound **2a**. Human 15-LOX-1 (h-15-LOX-1) is an iron containing enzyme and indole-based inhibitors with similar substitution pattern were very recently described.⁴⁰ Molecular docking of the compound **2a** in the catalytic site of the proteins followed by energy minimization was performed using MOE software. The poses with the highest docking score were selected to provide the final binding model of the compound **2a** in the active site of the corresponding protein. In MMP-13 protein (PDB: 830C) an important interaction between the sulfur of the compound and the zinc of the enzyme was observed along with the formation of a hydrogen bond between **Glu223** with the $-NH$ group and an interaction between **His187** with the 4-carboxy ethyl group (Fig. 5B). A similar interaction between the sulfur and the zinc was also observed when the compound was docked in Aggrecanase-2 (PDB: 3B8Z). In addition, a hydrogen bond between **Gly380** with the $-NH$ group and an interaction between **Gly372** with the 4-carboxy ethyl group (Fig. 5C) was identified. Finally, when the compound **2a** was docked in the active site of h-15-LOX-1 (PDB: 1LOX), gave a strong interaction between iron and the carboxy ethyl group and formed two hydrogen bonds between the **Glu357** with the $-NH$ group and **Gln548** with the sulfur (Fig. 5D). It seems that indeed the substitution pattern, including the NH and the two carboxy ethyl groups from the imidazole core along with the sulfur, plays an essential role. We could argue, based on this initial *in silico* evaluation that our cycloadducts **2** could serve as starting point for further evaluation and proceed to *in vitro* studies.

3. Conclusion

In conclusion, we have investigated a hetero thia-Diels–Alder reactions by using two types of imidazole-2-thiones, the *N*-aryl-substituted structure **1** bearing electron withdrawing substituents in the 4,5-positions and the *N*-arylamino-substituted structure **5**. We confirmed that the reaction outcome is greatly related to the nature of the thione substituents. Electron-deficient substituents render the sulfur electrophilic and thus enable the Diels–Alder reaction giving the spiroderivatives whereas electron donating

groups deactivated the C–S bond and result to sulfur substituted imidazole derivatives. Initial *in silico* evaluation showed prominent results and in near future *in vitro* results will be described.

4. Experimental

4.1. General

Column chromatography was carried out using Merck silica gel. TLC was performed using precoated silica gel glass plates 0.25 mm containing fluorescent indicator UV₂₅₄ 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 ¹H and 75 MHz for ¹³C, respectively, using CDCl₃ as solvent. Chemical shifts are expressed in δ values (ppm) relative to TMS as internal standard for ¹H and relative to TMS (0.00 ppm) or to CDCl₃ (77.05 ppm) for ¹³C NMR spectra. Coupling constants nJ are reported in Hz. Second order ¹H spectra in the aromatic region, where it was possible, were analyzed by simulation.⁴¹ Low-resolution electron impact mass spectra were recorded on a 6890N LC/MS system (Agilent Technology) and elemental analyses performed with a Perkin–Elmer 2400-II CHN analyzer. Structural assignments of the derived compounds were established by analysis of their MS and NMR spectra (¹H, ¹³C, DEPT, H–H COSY, H–H NOESY, HETCOR and COLOC).

4.2. General procedure for the reaction of thiones (1a–d) with dimethylbutadiene

A reaction mixture of thione **1** (1.0 mmol), 2,3-dimethylbutadiene (2.0 mmol) and BF₃·Et₂O (4.0 mmol) in dichloromethane (20 mL), was refluxed until thione **1** was consumed completely (followed by TLC, approximately 2 h). To the reaction mixture was added water, the organic layer separated, washed with water, dried with Na₂SO₄, the solvent was distilled off *in vacuo* and the resulting residue was subjected to column chromatography on silica gel using petroleum ether/AcOEt (10:1) as eluent, slowly increasing the polarity up to 7:1 to give the isolated products (**2** and **3**).

Analogously a mixture of thione **1** (1.0 mmol), 2,3-dimethylbutadiene (2.0 mmol) and BF₃Et₂O (4.0 mmol) was subjected to MW irradiation at 90 °C, for 5 min.

4.2.1. Diethyl 8,9-dimethyl-1-phenyl-6-thia-1,4-diazospiro[4.5]deca-2,8-diene-2,3-dicarboxylate (2a). Yellow oil (0.229 g, 57% yield), ¹H NMR (CDCl₃) δ 1.07 (3H, t, ³J_{HH}=7.1 Hz, OCH₂CH₃), 1.39 (3H, t, ³J_{HH}=7.1 Hz, OCH₂CH₃), 1.81 (1H, br s, NH), 1.62 (3H, s, 9-CH₃), 1.66 (3H, s, 8-CH₃), 1.67 (2H, s, 10-CH₂), 3.92 (2H, s, 7-CH₂), 4.13 (2H, q, J=7.1 Hz, OCH₂CH₃), 4.41 (2H, q, J=7.1 Hz, OCH₂CH₃), 7.20–7.30 (2H, m, *o*-ArH), 7.47–7.51 (3H, m, *m*, *p*-ArH). ¹³C NMR (CDCl₃) δ 13.7 (OCH₂CH₃), 14.3 (OCH₂CH₃), 18.0 (8-CH₃), 20.4 (10-CH₂), 20.9 (9-CH₃), 38.0 (7-CH₂), 61.4 (OCH₂CH₃), 61.5 (OCH₂CH₃), 121.6 (5-C), 127.2 (2,6-C phenyl), 129.2 (3,5-C phenyl), 129.4 (2-C), 129.6 (4-C phenyl), 131.5 (9-C), 135.3 (1-C phenyl), 136.0 (3-C), 148.6 (8-C), 159.4 (CO ester), 162.5 (CO ester). MS (LCMS) *m/z* (%) 402 (100, M⁺), 320 (93%, M⁺–82, *retro* Diels–Alder). Anal. calcd for C₂₁H₂₆N₂O₄S (402.507): C, 62.66; H, 6.51; N, 6.96. Found: C, 62.37; H, 6.45; N, 6.78.

4.2.2. Diethyl 8,9-dimethyl-1-(*p*-tolyl)-6-thia-1,4-diazospiro[4.5]deca-2,8-diene-2,3-dicarboxylate (2b). Colorless oil (0.300 g, 72% yield), ¹H NMR (CDCl₃) δ 1.11 (3H, t, ³J_{HH}=7.1 Hz, OCH₂CH₃), 1.38 (3H, t, ³J_{HH}=7.1 Hz, OCH₂CH₃), 1.55 (1H, br s, NH), 1.62 (3H, s, 9-CH₃), 1.65 (3H, s, 8-CH₃), 1.67 (2H, s, 10-CH₂), 2.41 (3H, s, phenyl-CH₃), 3.92 (2H, s, 7-CH₂), 4.14 (2H, q, J=7.1 Hz, OCH₂CH₃), 4.40 (2H, q,

$J=7.1$ Hz, OCH_2CH_3), 7.14 (2H, d, $J=8.0$ Hz, *o*-ArH), 7.26 (2H, d, $J=8.0$ Hz, *m*-ArH). ^{13}C NMR (CDCl_3) δ 13.8 (OCH_2CH_3), 14.3 (OCH_2CH_3), 18.1 (9-CH₃), 20.5 (10-CH₂), 20.9 (8-CH₃), 21.3 (phenyl-CH₃), 38.0 (7-CH₂), 61.3 (OCH_2CH_3), 61.5 (OCH_2CH_3), 119.8 (2-C), 121.8 (5-C), 127.1 (2,6-C phenyl), 129.9 (3,5-C phenyl), 131.4 (9-C), 132.8 (1-C phenyl), 136.1 (3-C), 139.9 (4-C phenyl), 148.9 (8-C), 159.6 (CO ester), 162.7 (CO ester). MS (LCMS) m/z (%) 439 (85%, $\text{M}^+ + \text{Na}$), 417 (100, $\text{M}^+ + 1$). Anal. calcd for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_4\text{S}$ (416.534): C, 63.44; H, 6.78; N, 6.73. Found: C, 63.49; H, 6.56; N, 6.39.

4.2.3. Diethyl 1-(4-chlorophenyl)-8,9-dimethyl-6-thia-1,4-diazaspiro[4.5]deca-2,8-diene-2,3-dicarboxylate (2c). Colorless oil (0.292 g, 67%), ^1H NMR (CDCl_3) δ 1.14 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, OCH_2CH_3), 1.39 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, OCH_2CH_3), 1.81 (1H, br s, NH), 1.63 (3H, s, 9-CH₃), 1.66 (3H, s, 8-CH₃), 1.68 (2H, s, 10-CH₂), 3.94 (2H, s, 7-CH₂), 4.17 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.41 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 7.24 (2H, d, $J=8.5$ Hz, *o*-ArH), 7.47 (2H, d, $J=8.5$ Hz, *p*-ArH). ^{13}C NMR (CDCl_3) δ 13.4 (OCH_2CH_3), 13.9 (OCH_2CH_3), 17.7 (9-CH₃), 20.1 (10-CH₂), 20.6 (9-CH₃), 37.6 (7-CH₂), 61.1 (OCH_2CH_3), 61.2 (OCH_2CH_3), 121.2 (5-C), 127.6 (2-C), 128.3 (2,6-C phenyl), 129.6 (3,5-C phenyl), 131.3 (9-C), 133.4 (4-C phenyl), 135.4 (1-C phenyl), 136.3 (3-C), 148.5 (8-C), 158.7 (CO ester), 162.1 (CO ester). MS (LCMS) m/z (%) 459/461 (100%, $\text{M}^+ + \text{Na}^+$), 437/439 (70%, $\text{M}^+ + \text{H}$). Anal. calcd for $\text{C}_{21}\text{H}_{25}\text{ClN}_2\text{O}_4\text{S}$ (436.95): C, 57.72; H, 5.77; N, 6.41. Found: C, 57.57; H, 5.905; N, 6.58.

4.2.4. Diethyl 1-(4-bromophenyl)-8,9-dimethyl-6-thia-1,4-diazaspiro[4.5]deca-2,8-diene-2,3-dicarboxylate (2d). Colorless oil (0.336 g, 72%), ^1H NMR (CDCl_3) δ 1.14 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, OCH_2CH_3), 1.39 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, OCH_2CH_3), 1.58 (1H, br s, NH), 1.63 (3H, s, 9-CH₃), 1.65 (3H, s, 8-CH₃), 1.68 (2H, s, 10-CH₂), 3.97 (2H, s, 7-CH₂), 4.16 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.41 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 7.15 (2H, d, $J=8.5$ Hz, *o*-ArH), 7.61 (2H, d, $J=8.5$ Hz, *p*-ArH). ^{13}C NMR (CDCl_3) δ 13.8 (OCH_2CH_3), 14.2 (OCH_2CH_3), 18.1 (9-CH₃), 20.5 (10-CH₂), 20.9 (8-CH₃), 38.1 (7-CH₂), 61.5 (OCH_2CH_3), 61.6 (OCH_2CH_3), 121.6 (5-C), 127.6 (2-C), 129.0 (2,6-C phenyl), 132.6 (3,5-C phenyl), 131.7 (9-C), 133.4 (4-C phenyl), 134.4 (1-C phenyl), 137.0 (3-C), 148.5 (8-C), 149 (8-C), 159.3 (CO ester), 162.7 (CO ester). MS (LCMS) m/z (%) 481/483 (70%, $\text{M}^+ + \text{H}$), 503/505 (100%, $\text{M}^+ + \text{Na}^+$). Anal. calcd for $\text{C}_{21}\text{H}_{25}\text{BrN}_2\text{O}_4\text{S}$ (482.07): C, 52.39; H, 5.23; N, 5.82. Found: C, 52.25; H, 5.12; N, 5.71.

4.2.5. Diethyl 1-(3-methoxyphenyl)-8,9-dimethyl-6-thia-1,4-diazaspiro[4.5]deca-2,8-diene-2,3-dicarboxylate (2e). Yellow oil (0.259 g, 60% yield), ^1H NMR (CDCl_3) δ 1.11 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, OCH_2CH_3), 1.39 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, OCH_2CH_3), 1.63 (3H, s, 9-CH₃), 1.66 (3H, s, 8-CH₃), 1.68 (2H, s, 10-CH₂), 3.82 (3H, s, OCH_3), 3.93 (2H, s, 7-CH₂), 4.15 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.40 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 6.81 (1H, m, *o*-ArH), 6.85 (1H, d, $J=7.8$ Hz, *o*-ArH), 7.02 (1H, d, $J=8.4$ Hz, *p*-ArH), 7.38 (1H, t, $J=8.0$ Hz, *m*-ArH). ^{13}C NMR (CDCl_3) δ 13.9 (OCH_2CH_3), 14.4 (OCH_2CH_3), 18.2 (8-CH₃), 20.6 (10-CH₂), 21.0 (9-CH₃), 38.1 (7-CH₂), 55.6 (OCH_3), 61.5 (OCH_2CH_3), 61.7 (OCH_2CH_3), 113.1 (6-C phenyl), 115.5 (2-C phenyl), 119.4 (4-C phenyl), 121.7 (5-C), 128.8 (2-C), 130.1 (3-C phenyl), 131.6 (9-C), 135.9 (1-C phenyl), 136.3 (3-C), 148.7 (8-C), 159.6 (4-C phenyl), 160.2 (CO ester), 162.6 (CO ester). MS (LCMS) m/z (%) 433.28 ($\text{M}^+ + \text{H}$), 351.14 (*retro Diels–Alder*), 455.24 ($\text{M}^+ + \text{Na}$).

4.2.6. Diethyl 8,9-dimethyl-1-(3-phenoxyphenyl)-6-thia-1,4-diazaspiro[4.5]deca-2,8-diene-2,3-dicarboxylate (2f). Yellow oil (0.380 g, 77% yield), ^1H NMR (CDCl_3) δ 1.14 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, OCH_2CH_3), 1.37 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, OCH_2CH_3), 1.63 (3H, s, 9-CH₃), 1.65 (3H, s, 8-CH₃), 1.66 (2H, s, 10-CH₂), 3.90 (2H, s, 7-CH₂), 4.16 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.38 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 6.89 (1H, s, *o*-ArH), 7.00 (1H, m, *m*-ArH), 7.06 (2H, d, $J=8.1$ Hz, *o*-PhH), 7.11–7.17 (m, 2H, *p*, *o*-ArH), 7.36 (2H, t, $J=8.0$ Hz, *m*-PhH), 7.41 (1H, t, $J=8.1$ Hz, *p*-PhH). ^{13}C NMR (CDCl_3) δ 13.9 (OCH_2CH_3), 14.3 (OCH_2CH_3), 18.2 (8-

CH₃), 20.6 (10-CH₂), 21.1 (9-CH₃), 38.3 (7-CH₂), 61.6 (OCH_2CH_3), 61.8 (OCH_2CH_3), 117.3 (6-C phenyl), 119.6 (2,6-C OPh), 119.6 (4-C OPh), 121.7 (3-C phenyl), 123.3 (5-C), 124.4 (2-C phenyl), 129.8 (1-C phenyl), 130.1 (3,5-C OPh), 130.4 (4-C phenyl), 130.5 (2-C), 131.8 (9-C), 136.4 (3-C), 148.7 (8-C), 156.2, (1-C OPh), 158.3 (5-C phenyl), 159.4 (CO ester), 162.5 (CO ester). MS (LCMS) m/z (%) 495.27 ($\text{M}^+ + \text{H}$), 413.16 (*retro Diels–Alder*), 517.26 ($\text{M}^+ + \text{Na}$).

4.2.7. Diethyl 8,9-dimethyl-1-(*m*-tolyl)-6-thia-1,4-diazaspiro[4.5]deca-2,8-diene-2,3-dicarboxylate (2g). Yellow oil (0.287 g, 69% yield), ^1H NMR (CDCl_3) δ 1.09 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, OCH_2CH_3), 1.39 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, OCH_2CH_3), 1.62 (3H, s, 9-CH₃), 1.65 (3H, s, 8-CH₃), 1.67 (2H, s, 10-CH₂), 2.40 (3H, s, CH₃), 3.92 (2H, s, 7-CH₂), 4.14 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.40 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 7.06–7.07 (2H, m, *o*, *o*-ArH), 7.29 (1H, d, $J=7.4$ Hz, *p*-ArH), 7.35 (1H, t, $J=8.0$ Hz, *m*-ArH). ^{13}C NMR (CDCl_3) δ 13.8 (OCH_2CH_3), 14.3 (OCH_2CH_3), 18.1 (8-CH₃), 20.5 (10-CH₂), 21.0 (9-CH₃), 21.3 (Ar-CH₃), 38.1 (7-CH₂), 61.4 (OCH_2CH_3), 61.6 (OCH_2CH_3), 121.7 (5-C), 124.2 (6-C phenyl), 127.7 (2-C phenyl), 128.8 (2-C), 129.1 (4-C phenyl), 130.5 (3-C phenyl), 131.5 (9-C), 135.2 (1-C phenyl), 135.7 (3-C), 139.6 (5-C phenyl), 148.5 (8-C), 159.5 (CO ester), 162.5 (CO ester). MS (LCMS) m/z (%) 417.23 ($\text{M}^+ + \text{H}$), 335.19 (*retro Diels–Alder*), 439.22 ($\text{M}^+ + \text{Na}$).

4.2.8. Diethyl 8,9-dimethyl-1-(*o*-tolyl)-6-thia-1,4-diazaspiro[4.5]deca-2,8-diene-2,3-dicarboxylate (2h). Yellow oil (0.337 g, 81% yield), ^1H NMR (CDCl_3) δ 1.04 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, OCH_2CH_3), 1.40 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, OCH_2CH_3), 1.62 (3H, s, 9-CH₃), 1.66 (3H, s, 8-CH₃), 1.68 (2H, s, 10-CH₂), 2.08 (3H, s, CH₃), 3.96 (2H, s, 7-CH₂), 4.10 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.41 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 7.14 (1H, d, $J=7.8$ Hz, *o*-ArH), 7.28 (1H, t, $J=7.9$ Hz, *m*-ArH), 7.34 (1H, d, $J=7.3$ Hz, *m*-ArH), 7.40 (1H, t, $J=7.5$ Hz, *p*-ArH). ^{13}C NMR (CDCl_3) δ 13.7 (OCH_2CH_3), 14.3 (OCH_2CH_3), 17.5 (8-CH₃), 18.2 (10-CH₂), 20.6 (9-CH₃), 21.0 (Ar-CH₃), 37.8 (7-CH₂), 61.5 (OCH_2CH_3), 61.6 (OCH_2CH_3), 121.6 (5-C), 127.0 (2-C phenyl), 127.8 (2-C), 128.0 (3-C phenyl), 128.2 (9-C), 130.3 (5-C phenyl), 133.1 (4-C phenyl), 131.8 (3-C), 134.5 (1-C phenyl), 136.3 (6-C phenyl), 149.0 (8-C), 159.1 (CO ester), 162.5 (CO ester). MS (LCMS) m/z (%) 417.23 ($\text{M}^+ + \text{H}$), 335.19 (*retro Diels–Alder*), 439.22 ($\text{M}^+ + \text{Na}$).

4.2.9. Diethyl 1-(3,4-dimethylphenyl)-8,9-dimethyl-6-thia-1,4-diazaspiro[4.5]deca-2,8-diene-2,3-dicarboxylate (2i). Yellow oil (0.366 g, 85% yield), ^1H NMR (CDCl_3) δ 1.12 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, OCH_2CH_3), 1.39 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, OCH_2CH_3), 1.62 (3H, s, 9-CH₃), 1.66 (3H, s, 8-CH₃), 1.67 (2H, s, 10-CH₂), 2.29 (3H, s, CH₃), 2.31 (3H, s, CH₃), 3.92 (2H, s, 7-CH₂), 4.16 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.39 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 6.99 (1H, d, $J=7.9$ Hz, *o*-ArH), 7.01 (1H, s, *o*-ArH), 7.21 (1H, d, $J=7.9$ Hz, *p*-ArH). ^{13}C NMR (CDCl_3) δ 13.9 (OCH_2CH_3), 14.4 (OCH_2CH_3), 18.2 (8-CH₃), 19.8 (10-CH₂), 20.0 (9-CH₃), 20.6 (Ar-CH₃), 21.1 (Ar-CH₃), 38.1 (7-CH₂), 61.5 (OCH_2CH_3), 61.6 (OCH_2CH_3), 121.8 (5-C), 124.5 (6-C phenyl), 128.1 (2-C phenyl), 128.8 (2-C), 130.4 (3-C phenyl), 131.6 (9-C), 133.0 (1-C phenyl), 135.8 (3-C), 138.0 (5-C phenyl), 138.6 (4-C phenyl), 148.9 (8-C), 159.8 (CO ester), 162.8 (CO ester). MS (LCMS) m/z (%) 431 ($\text{M}^+ + \text{H}$), 349 (*retro Diels–Alder*).

4.2.10. Diethyl 8,9-dimethyl-1-(5,6,7,8-tetrahydronaphthalen-1-yl)-6-thia-1,4-diazaspiro[4.5]deca-2,8-diene-2,3-dicarboxylate (2j). Yellow oil (0.292 g, 64% yield), ^1H NMR (CDCl_3) δ 1.04 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, OCH_2CH_3), 1.40 (3H, t, $^3J_{\text{HH}}=7.1$ Hz, OCH_2CH_3), 1.62 (3H, s, 9-CH₃), 1.67 (3H, s, 8-CH₃), 1.69 (2H, s, 10-CH₂), 1.71–1.79 (4H, m, naphthyl), 2.32–2.35 (2H, m, naphthyl), 2.83 (2H, m, naphthyl), 3.95 (2H, s, 7-CH₂), 4.10 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.41 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 6.95 (1H, d, $J=7.3$ Hz, *o*-ArH), 7.18 (1H, t, $J=7.3$ Hz, *m*-ArH), 7.20 (1H, d, $J=7.3$ Hz, *p*-ArH). ^{13}C NMR (CDCl_3) δ 13.8 (OCH_2CH_3), 14.3 (OCH_2CH_3), 18.1 (8-CH₃), 20.6 (10-CH₂), 21.0 (9-CH₃), 22.5 (naphthyl), 22.7 (naphthyl), 24.7 (naphthyl), 29.5

(naphthyl), 37.7 (7-CH₂), 61.4 (OCH₂CH₃), 61.4 (OCH₂CH₃), 121.8 (5-C), 125.1 (2-C phenyl), 125.9 (3-C phenyl), 128.1 (2-C), 131.1 (4-C phenyl), 131.5 (9-C), 134.3 (1-C phenyl), 135.3 (5-C phenyl), 136.2 (3-C), 139.1 (6-C phenyl), 148.8 (8-C), 159.2 (CO ester), 162.7 (CO ester). MS (LCMS) *m/z* (%) 457 (M⁺+H), 375 (retro Diels–Alder).

4.2.11. 2[(2,3-Dimethylbut-2-en-yl)thio]-1,4,5-triphenyl-1H-imidazole (3). Yellow solid (0.291 g, 71% yield), ¹H NMR (CDCl₃) δ 1.62 (3H, s, 3'-CH₃), 1.62 (3H, s, 4'-CH₃), 1.64 (3H, s, 2'-CH₃), 3.84 (2H, s, 1'-CH₂), 7.07–7.32 (13H, m, ArH), 7.52–7.57 (2H, m, ArH). ¹³C NMR (CDCl₃) δ 17.9 (2'-CH₃), 20.3 (3'-CH₃), 20.9 (4'-CH₃), 38.9 (1'-CH₂), 122.9, 126.6, 127.3, 127.9, 128.1, 128.3, 128.4, 128.8, 130.3, 130.7, 130.8, 131.2, 134.5, 136.3, 138.9 (2-C), 143.5 (1-C phenyl). MS (LCMS) *m/z* (%) 411 (50%, M⁺+1). Anal. calcd for C₂₇H₂₆N₂S (410.57): C, 78.98; H, 6.38; N, 6.82. Found: C, 78.77; H, 6.47; N, 6.74.

4.2.12. Diethyl 2-(phenylamino)-3-((Z)-(tetrahydro-2H-thiopyran-2-ylidene)amino)maleate (4). A reaction mixture of thione **1** (1.0 mmol), 1-trimethylsilyloxybutadiene (or 1-methoxy-3-trimethylsilyloxybutadiene) (2.0 mmol) and BF₃·Et₂O (4.0 mmol) in tetrahydrofuran (20 mL), was refluxed until thione **1** was consumed completely (followed by TLC, approximately 4 days). To the reaction mixture water was added, the organic layer was separated, washed with water, dried with Na₂SO₄, the solvent was distilled off in vacuo and the resulting residue was subjected to column chromatography on silica gel using petroleum ether/AcOEt (3:1) as eluent to give the isolated product (**4**).

Colorless oil (0.125 g, 31% yield), ¹H NMR (CDCl₃) δ 1.07 (3H, t, ³J_{HH}=7.1 Hz, OCH₂CH₃), 1.39 (3H, t, ³J_{HH}=7.1 Hz, OCH₂CH₃), 2.90 (1H, br s, NH), 1.63 (2H, q, 5-CH₂), 1.84 (2H, q, 4-CH₂), 3.22 (2H, dd, 3-CH₂), 3.71 (2H, t, 6-CH₂), 4.13 (2H, q, J=7.1 Hz, OCH₂CH₃), 4.40 (2H, q, J=7.1 Hz, OCH₂CH₃), 7.25–7.30 (2H, m, o-ArH), 7.47–7.53 (3H, m, m, p-ArH). ¹³C NMR (CDCl₃) δ 13.6 (OCH₂CH₃), 14.1 (OCH₂CH₃), 25.9 (4-CH₂), 30.9 (5-CH₂), 31.4 (3-CH₂), 61.4 (6-CH₂), 61.4 (OCH₂CH₃), 61.5 (OCH₂CH₃), 127.1 (2,6-C phenyl), 128.6 (2'-C), 129.3 (3,5-C phenyl), 129.8 (4-C phenyl), 135.1 (1-C phenyl), 135.7 (3'-C), 148.5 (2-C), 159.2 (CO ester), 162.3 (CO ester). MS (LCMS) *m/z* (%) 402 (100, M⁺). Anal. calcd for C₂₁H₂₆N₂O₄S (402.16): C, 62.66; H, 6.51; N, 6.96. Found: C, 62.10; H, 6.45; N, 7.10.

4.3. General procedure for the reaction of arylamino–thiones (5a–d) with dimethylbutadiene

A reaction mixture of thione **1** (1.0 mmol), 2,3-dimethylbutadiene (2.0 mmol) and BF₃·Et₂O (2.0 mmol) in dichloromethane (20 mL), was refluxed until thione **1** was consumed completely (followed by TLC, approximately 24 h). To the reaction mixture water was added, the organic layer was separated, washed with water, dried with Na₂SO₄, the solvent was distilled off in vacuo and the resulting residue was subjected to column chromatography on silica gel using petroleum ether/AcOEt (3:1) as eluent, slowly increasing the polarity up to 1:1 to give the isolated product (**6**).

Analogously a mixture of thione **1** (1.0 mmol), 2,3-dimethylbutadiene (2.0 mmol) and BF₃·Et₂O (2.0 mmol) in chloroform (20 mL), was subjected to MW irradiation at 90 °C, for 5 min.

4.3.1. 2[(2,3-Dimethylbut-2-en-1-yl)thio]-N-phenyl-1H-imidazol-1-amine (6a). Yellow solid (0.218 g, 80% yield), ¹H NMR (CDCl₃) δ 1.56 (3H, s, 3'-CH₃), 1.65 (3H, s, 4'-CH₃), 1.69 (3H, s, 2'-CH₃), 3.67 (2H, s, 1'-CH₂), 7.11 (1H, br s, NH), 6.52–6.60 (2H, m, o-ArH), 6.91–6.98 (1H, m, p-ArH), 7.11 (1H, s, 4-H), 7.19–7.24 (2H, m, m-ArH), 7.25 (1H, s, 5H MS (LCMS) *m/z* (%) 274 (100, M⁺). ¹³C NMR (CDCl₃) δ 17.9 (2'-CH₃), 20.1 (3'-CH₃), 20.9 (4'-CH₃), 38.9 (1'-CH₂), 113.4 (2,6-C phenyl), 122.2 (4-C phenyl), 122.5 (5-C), 122.9 (2'-C), 128.3 (4-C), 129.5 (3,5-C phenyl), 130.8 (3'-C), 130.9 (2-C), 146.7 (1-C phenyl). Anal.

calcd for C₁₅H₁₉N₃S (273.396): C, 65.90; H, 7.00; N, 15.37. Found: C, 65.77; H, 7.08; N, 15.24.

4.3.2. 2[(2,3-Dimethylbut-2-en-yl)thio]-4,5-dimethyl-N-phenyl-1H-imidazol-1-amine (6b). Yellow solid (0.256 g, 85% yield), ¹H NMR (CDCl₃) δ 1.45 (3H, s, 3'-CH₃), 1.63 (3H, s, 4'-CH₃), 1.65 (3H, s, 2'-CH₃), 2.08 (3H, s, 5-CH₃), 2.20 (3H, s, 4-CH₃), 3.48 (2H, s, 1'-CH₂), 6.95 (1H, br s, NH), 6.49 (2H, d, J=8.6 Hz, o-ArH), 6.87–6.94 (1H, m, p-ArH), 7.17–7.24 (2H, m, m-ArH). ¹³C NMR (CDCl₃) δ 8.4 (8-CH₃), 13.1 (4-CH₃), 17.9 (2'-CH₃), 20.0 (3'-CH₃), 20.8 (4'-CH₃), 39.9 (1'-CH₂), 112.8 (2,6-C phenyl), 121.5 (4-C phenyl), 123.1 (2'-C), 126.0 (5-C), 129.4 (3,5-C phenyl), 130.5 (3'-C), 132.5 (4-C), 139.0 (2-C), 146.8 (1-C phenyl). MS (LCMS) *m/z* (%) 301 (50%, M⁺), 268 (100, M⁺–33). Anal. calcd for C₁₇H₂₃N₃S (301.45): C, 67.73; H, 7.69; N, 13.94. Found: C, 67.77; H, 7.57; N, 13.84.

4.3.3. N-(4-Chloro-phenyl)-2-[(2,3-dimethylbut-2-en-1-yl)thio]-4,5-dimethyl-1H-imidazol-1-amine (6c). Yellow solid (0.291 g, 87% yield), ¹H NMR (CDCl₃) δ 1.44 (3H, s, 3'-CH₃), 1.62 (3H, s, 4'-CH₃), 1.63 (3H, s, 2'-CH₃), 2.05 (3H, s, 5-CH₃), 2.16 (3H, s, 4-CH₃), 3.51 (2H, s, 1'-CH₂), 6.46 (2H, d, J=8.7 Hz, o-ArH), 7.15 (2H, d, J=8.7 Hz, m-ArH), 7.73 (1H, br s, NH). ¹³C NMR (CDCl₃) δ 8.2 (8-CH₃), 13.5 (4-CH₃), 17.7 (2'-CH₃), 19.8 (3'-CH₃), 20.8 (4'-CH₃), 39.5 (1'-CH₂), 113.7 (2,6-C phenyl), 122.8 (2'-C), 125.7 (5-C), 125.6 (4-C phenyl), 129.1 (3,5-C phenyl), 130.3 (3'-C), 132.5 (4-C), 139.3 (2-C), 145.5 (1-C phenyl). MS (LCMS) *m/z* (%) 336/338 (100, M⁺+1). Anal. calcd for C₁₇H₂₂ClN₃S (335.89): C, 60.79; H, 6.60; N, 12.51. Found: C, 60.87; H, 6.57; N, 12.34.

4.3.4. N-[2-[(2,3-Dimethylbut-2-en-yl)thio]-4,5-dimethyl-1H-imidazol-1-yl]-N-phenylacetamide (6d). Yellow solid (0.298 g, 79% yield), ¹H NMR (CDCl₃) δ 1.54 (3H, s, 3'-CH₃), 1.60 (3H, s, 4'-CH₃), 1.60 (3H, s, 2'-CH₃), 1.90 (3H, br s, COCH₃), 1.98 (3H, s, 5-CH₃), 2.11 (3H, s, 4-CH₃), 3.70 (2H, br s, 1'-CH₂), 7.11 (1H, m, p-ArH), 7.24–7.26 (4H, m, o-m-ArH). ¹³C NMR (CDCl₃) δ 8.0 (8-CH₃), 12.9 (4-CH₃), 17.7 (2'-CH₃), 20.2 (3'-CH₃), 20.6 (4'-CH₃), 21.7 (COCH₃), 38.3 (1'-CH₂), 122.1 (2,6-C phenyl), 130.7 (4-C phenyl), 123.5 (2'-C), 125.9 (5-C), 128.7 (3,5-C phenyl), 121.2 (3'-C), 133.4 (4-C), 139.9 (2-C), 140.7 (1-C phenyl), 170.1 (CO). MS (LCMS) *m/z* (%) 377 (100%, M⁺). Anal. calcd for C₁₉H₂₆N₃OS (377.13): C, 60.38; H, 6.40; N, 11.12. Found: C, 60.30; H, 6.31; N, 11.09.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at <http://dx.doi.org/10.1016/j.tet.2016.02.034>.

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