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1-Arylaminoimidazole-2-thiones as intermediates in the synthesis of imidazo[2,1-*b*][1,3,4]thiadiazines

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

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

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Abstract

The synthesis of the hitherto unknown imidazo[2,1-*b*][1,3,4]thiadiazines **7** in good to very good yields (up to 77%) by using suitable imidazole-2-thione precursors **1** has been described, while *S*-vinylimidazoles **8** and **9** were isolated as by-products. Moreover, the reactivity of the three possible reaction sites of the starting thiones **1** was initially examined by methylation experiments, whereupon the enhanced reactivity of sulfur was proven by the isolation of the methylated derivatives **3** and **4**. By prolonged methylation the imidazolinone **6** is finally formed. Theoretical calculations support the experimental results of alkylation products.

Keywords: Imidazolethiadiazines; Imidazolone; Methylation; Selectivity; *S*-Vinylimidazoles

1. Introduction

Heterocyclic compounds are rich sources of diverse physical, chemical, and biological properties.[1] In medicinal chemistry they are commonly used as templates to design biologically active agents.[2] Moreover, in the past 20 years the drug-discovery process has undergone extraordinary changes and high-throughput biological screening of potential drug candidates has led to an ever increasing demand for novel drug-like compounds.[3] Imidazole is a common structural unit found in many biologically active compounds.[4] Substituted imidazoles have been synthesized by combinatorial fashion on solid supports[5] as well as in the solution phase[6] and are promising scaffolds for drug design.[7] 2-Substituted imidazolines and imidazoles are of increasing interest because of their applications[8] as disinfectants, pharmaceuticals and also because of their applications in supramolecular chemistry—preparation of molecular tectonics through formation of intermolecular hydrogen bonds,[9] formation of helical assembly through triple hydrogen bonds in tris(oxazoline)–tris(imidazoline) benzene,[10] preparation of triple-stranded helices and zigzag chains by coordination with copper(I),[11] synthesis of palladium complexes with pyridine/imidazoline ligands that react readily with carbon monoxide,[12] preparation of supramolecular structures by self assembly using π–π stacking and hydrogen bonding interactions.[13] Recently, it has been reported that *N*-aminoimidazoles and *N*-aminoimidazoline thiones inhibit retroviral replication.[14] In addition, the regioselective synthesis of a series of pyridinyl imidazoles, inhibitors of p38 MAP (mitogen activated protein) kinase, from suitable imidazole-2-thione precursors has been studied.[15,16] Moreover, it is long known that 2,3-dihydroimidazo[2,1-*b*]thiazoles exhibit anti-inflammatory activity,[17] whereas the synthesis of some imidazo[2,1-*b*]thiazolones has been recently reported.[18]

2. Results and discussion

As long as the preparation of new fused imidazole derivatives is of great pharmacological interest, we have considered the synthesis of some imidazo[2,1-*b*][1,3,4]thiadiazines as possible anti-inflammatory drugs by using suitable imidazole-2-thione precursors replacing thus the thiazoline by a thiadiazine ring.

* Corresponding author. Fax: +30 2310 997679.
E-mail address: tsolerid@chem.auth.gr (C.A. Tsoleridis).

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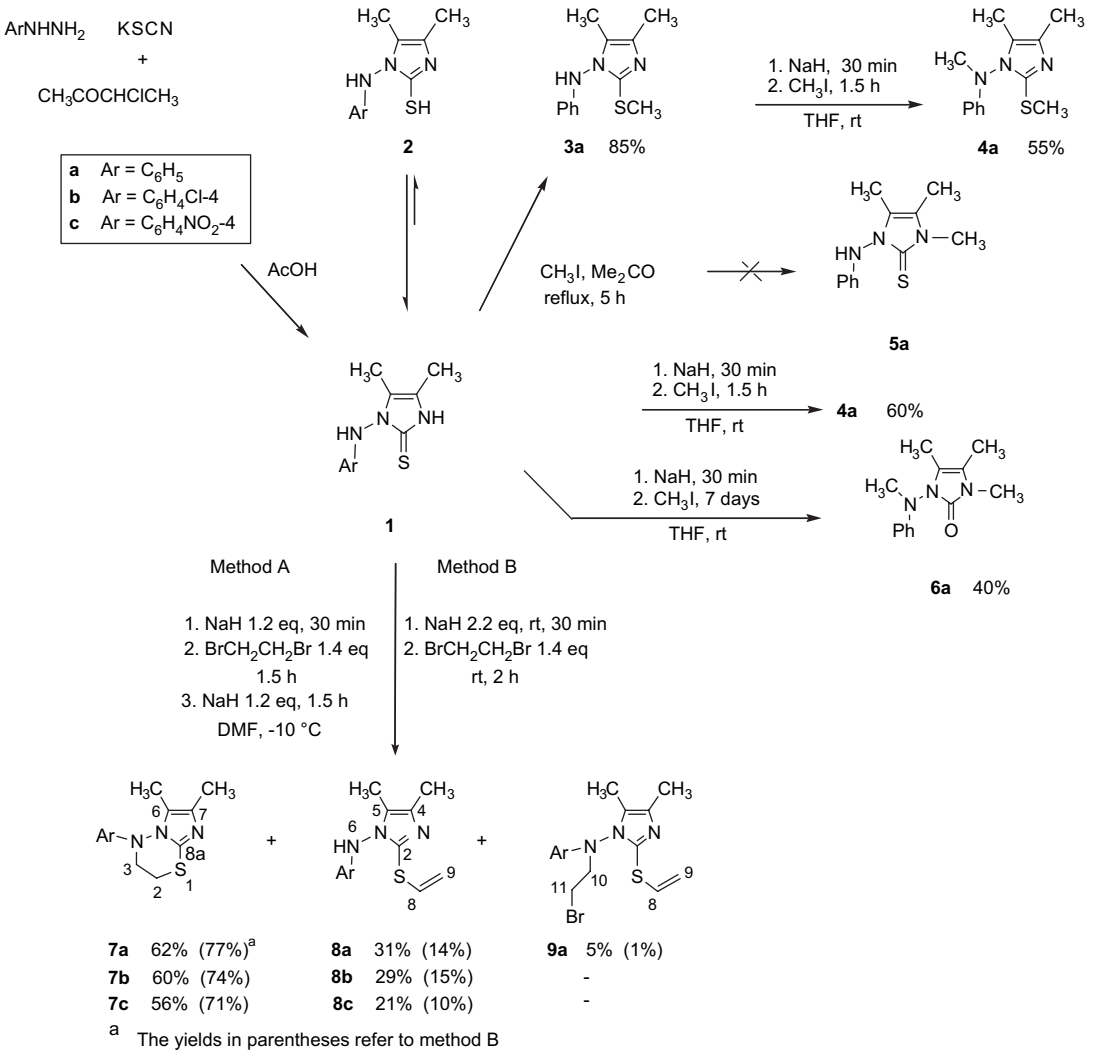
Our synthetic approach is depicted in Scheme 1. 1-Arylamino-4,5-dimethylimidazole-2-thiones **1** were prepared according to a known procedure[14,19] by the reaction of 3-chloro-2-butanone with potassium thiocyanate and arylhydrazines. However, as reported earlier by us[20] a closer inspection of the ^{1}H NMR spectra of compounds **1** indicated a tautomerization between the thione **1** and the thiol **2** (2:1 ratio, $CDCl_3$, ambient temperature). This observation is also supported by theoretical calculations (DFT B3LYP/6-31G*) on the tautomers **1a** and **2a** according to which **1a** is predicted to be more stable than **2a** by 13.47 kcal/mol. Moreover, calculations were carried out for the isomers **3a** and **5a**, whereupon **5a** is favored over its isomer by 10.39 kcal/mol (Table 1).

Next, the reactivity of the three possible reaction sites of the molecule, namely the 3-NH, 6-NH, and 7-SH positions was investigated and therefore, theoretical calculations were carried out, according to which the 3-NH or the SH proton abstraction is favored over that of the 6-NH proton, as depicted in Figure 1 and in Table 1. The anions **10** and **11**, which resulted after the proton abstraction from 3-NH or 7-SH are mesomeric forms and therefore they have the same geometry and energy. So, the difference in total energies (ΔE_{total}) between anions **12** and **10** (or **13** and **11**) is 10.49 (or 17.09) kcal/mol, anion **12** being more stable than **13**. Using the atomic charge distribution over **1a** and **2a** as reference, the calculated new atomic charges on the anions reveal that in **10** (or **11**) the negative charge of 3-N atom is decreased by 0.1002 electrons, whereas a small increase is calculated for the anion **11**. For the anion **12** a small decrease, whereas

Table 1
Energy properties of compounds **1a–3a**, **5a** as well as of anionic forms **10–13** calculated at the DFT level (B3LYP/6-31G*)

Compound	E_{total} (au)	ΔE[a]
1a	−989.4327159	0
2a	−989.4112437	13.47[b]
5a	−1028.7455122	0
3a	−1028.7289525	10.39[c]
10, **11**	−988.8707755	0
12	−988.8540585	10.49[d]
13	−988.8435396	17.09[e]

[a] In kcal/mol.
[b] $\Delta E = E_{total\ (2a)} - E_{total\ (1a)}$.
[c] $\Delta E = E_{total\ (3a)} - E_{total\ (5a)}$.
[d] $\Delta E = E_{total\ (12)} - E_{total\ (10)}$.
[e] $\Delta E = E_{total\ (13)} - E_{total\ (10)}$.



Scheme 1. Reaction scheme and conditions for the synthesis of compounds **4–9**.

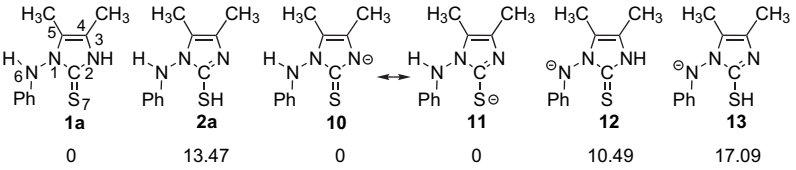


Figure 1. Relative energies (kcal/mol) for the tautomers **1a** and **2a** as well as for their anions **10**–**13** after the abstraction of one proton from the position 3 or 6 or 7 calculated at the DFT level (B3LYP/6-31G*).

for **13** a small increase in electronic charge of 6-N atom is calculated. For the 7-S atom a substantial increase in electronic charge is calculated for all anions, especially for **10** (or **11**) (Table 2). This charge increase can be attributed mainly on charge delocalization on the sulfur atomic orbitals and the stabilization induced by the aromatization of the imidazole ring. Therefore, sulfur alkylation should predominate under mild reaction conditions.

In order to confirm the above results we started studying the methylation reaction on compounds **1**. Upon refluxing **1a** with excess of methyl iodide in acetone for 5 h only the *S*-alkyl product **3a** was isolated in 85% yield, which could be converted to the exocyclic *N*-methyl derivative **4a** by further methylation with sodium hydride and methyl iodide in 55% yield (Scheme 1). Imidazole **4a** was also formed in 60% yield in a one step reaction by methylation of **1a** with sodium hydride and methyl iodide. These experimental results confirm the theoretical predictions.

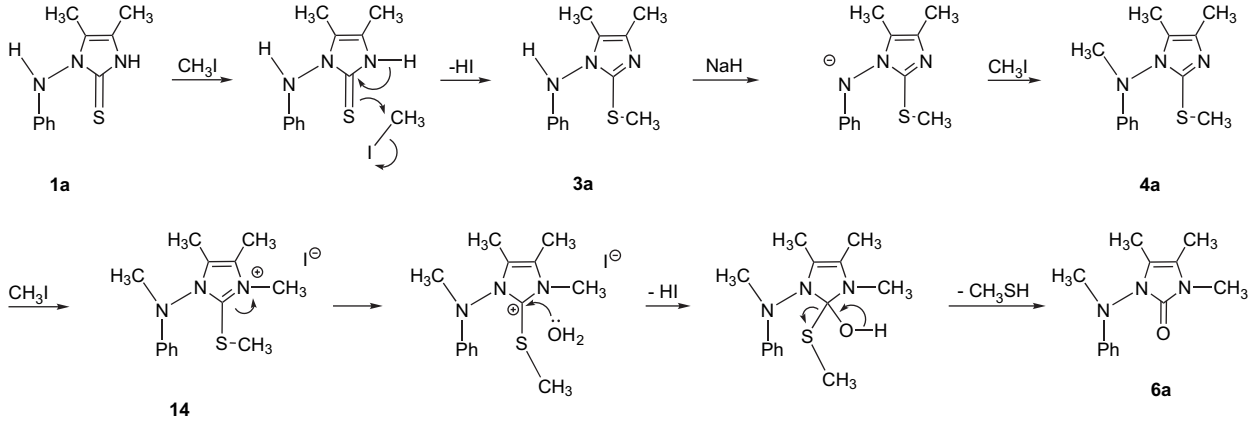
However, the use of an excess of sodium hydride and methyl iodide in combination with prolonged reaction times leads to the formation of the hydrolysis product, the imidazolone **6a**, which was isolated in 40% yield. Most probably, the reaction proceeds through initial formation of **4a**, from which upon further methylation **14** could be formed. By subsequent hydrolysis during the workup procedure compound **6a** is formed, as depicted in Scheme 2.

Having in hand the above methylation results it could be rather safely predicted that the target imidazo[2,1-*b*]-[1,3,4]thiadiazines could be synthesized from thiazolones **1** by using 1,2-dibromoethane. Indeed, compounds **7a**–**7c** were synthesized in good yield (56–62%) by the cyclization of thiones **1a**–**1c** with sodium hydride and 1,2-dibromoethane (Method A, Scheme 1), along with the *S*-vinyl derivatives **8a**–**8c** (21–31% yield) and the *N*-2-bromoethyl-*S*-vinyl compound **9a** (5% yield), increasing thus the overall reaction yield to 77–96%. However, the yield of the thiadiazines **7**

Table 2
Net charge distribution over some atoms of compounds **1a** and **2a** in neutral as well as for their anions **10**–**13** calculated at the DFT level (B3LYP/6-31G*)

Compound	Atomic net charge q_{net} ($\times 10^4$ electrons)									
	1	2	3	Δq[a]	4	5	6	Δq[b]	7	Δq[c]
1a	−3680	3429	−6365		2758	2892	−5116		−3306	
2a	−3620	2545	−4814		1750	3005	−5228		−243	
10	−3680	2879	−5363	−1002	1865	2836	−5154		−5545	2239
11	−3680	2879	−5363	549	1865	2836	−5154		−5545	5302
12	−3474	3645	−6408		2723	2858	−5044	−72	−4659	1353
13	−3223	2547	−5340		1753	2875	−5297	69	−687	444

[a] $\Delta q_{(10)}=q_{(1a)}-q_{(10)}$, $\Delta q_{(11)}=q_{(2a)}-q_{(11)}$.
[b] $\Delta q_{(12)}=q_{(1a)}-q_{(12)}$, $\Delta q_{(13)}=q_{(2a)}-q_{(13)}$.
[c] $\Delta q_{(10)}=q_{(1a)}-q_{(10)}$, $\Delta q_{(11)}=q_{(2a)}-q_{(11)}$, $\Delta q_{(12)}=q_{(1a)}-q_{(12)}$, $\Delta q_{(13)}=q_{(2a)}-q_{(13)}$.



Scheme 2. Plausible mechanism for the synthesis of compounds **3a** and **4a** and for the formation of compound **6a**.

was considerably increased (71–77%) at the expense of the by-products by initial addition of 2.2 equiv of sodium hydride followed after 30 min by dropwise addition of the 1,2-dibromoethane (Method B).

3. Structure assignments

The assigned molecular structures of all new compounds are based on rigorous spectroscopic analysis including IR, NMR (^{1}H, ^{13}C, DEPT, COSY H–H, NOESY H–H, HETCOR C–H and COLOC C–H), MS, and elemental analysis data.

Concerning compound **3a** the methyl protons resonating at δ 2.87 have long range C–H (COLOC) correlation with the quaternary carbon at 144.5 ppm (C-2) via $^3J_{CH}$, whereas both methyl protons at δ 2.15 and at δ 2.44 have COLOC correlation with the quaternary carbons at 125.4 and 128.4 ppm, via $^2J_{CH}$ and $^3J_{CH}$, being the C-5 and C-4, respectively. The NHPh proton resonating at δ 8.31 shows COLOC correlations with C-1′ and C-2′, and also NOESY correlation spot with the methyl protons at δ 2.15 proving thus that methyl is set on C-5. The intensities of the COLOC correlation spots are higher between C(5)–CH_3(5) and C(4)–CH_3(4) than the correlations between C(5)–CH_3(4) and C(4)–CH_3(5) proving thus that $^2J_{CH}$ is closer to the optimized value of 10 Hz than the $^3J_{CH}$ (Fig. 2). This observation can be used as evidence for the assignment of the methyl signals of 4,5-dimethylimidazoles.

The structure of compound **6a** was deduced from the spectral data presented in Section 5, as well from the COLOC correlations depicted in Figure 2. The mass spectrum (m/z=231) and elemental analysis are in accord with the molecular formula $C_{13}H_{17}N_3O$. The more downfield carbon signal at 151.6 ppm is assigned to the ureido carbonyl group that gives in IR a strong double absorption at 1702 and 1690 cm^{-1}.

Concerning the imidazothiadiazines **7**, the structure of compound **7b** will be analyzed. The mass spectrum (m/z= 279/281) and elemental analysis are in accord with the molecular formula $C_{13}H_{14}ClN_3S$. The proton NMR spectrum showed the presence of two methyl groups at δ 1.90 (C-6) and δ 2.15 (C-7) having COLOC correlation spots with both quaternary carbons at 122.5 ppm (C-6) and 130.9 ppm (C-7). There are also two methylene groups at δ 2.99 (t, J=5.3 Hz) and δ 3.98 (br s) with their carbons resonating at 20.6 and 51.7 ppm, respectively. The methylene group at δ 3.98 being in the vicinity of the phenyl group appears as a broad signal, whereas the second methylene protons show COLOC correlation spot with the quaternary carbon at 130.5 ppm (C-8a), confirming thus their position (Fig. 2).

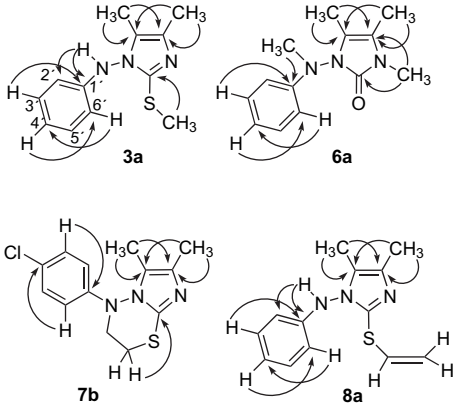


Figure 2. Long range correlations (COLOC) between protons and carbons via $^2J_{CH}$ and $^3J_{CH}$ in compounds **3a**, **6a**, **7b**, and **8a**.

For the vinyl substituted compounds **8**, **8a** will be analyzed. The mass spectrum (m/z=245) and elemental analysis were in accord with the molecular formula $C_{13}H_{15}N_3S$. The proton NMR spectrum showed the presence of two methyl groups at δ 2.07 (on C-5, 126.9 ppm) and δ 2.21 (on C-4, 132.7 ppm). Concerning the vinyl group, the H-8 proton appears as doublet of doublets at δ 6.53 (J_{cis}=9.5 Hz, J_{trans}=16.7 Hz, on C-8, 128.6 ppm), whereas the two H-9 protons appear as doublet of doublets at δ 5.75 (J_{trans}=16.7 Hz, J_{gem}=0.4 Hz) and δ 5.79 (J_{cis}=9.5 Hz, J_{gem}=0.4 Hz) with their carbon resonating at 116.4 ppm.

In Figure 2 the COLOC (long range via $^2J_{CH}$ and $^3J_{CH}$ couplings) C–H correlations for compounds **3a**, **6a**, **7b**, and **8a** are depicted.

4. Conclusion

In summary, the methylation of 1-phenylamino-4,5-dimethylimidazole-2-thiones has been studied and the results are in agreement with the results of theoretical calculations according to which the 3-position proton is more acidic than the NHAr proton. Furthermore, by prolonged methylation an imidazolinone is formed as the only reaction product. More important, the target synthesis of the hitherto unknown pharmacologically interesting imidazo[2,1-*b*][1,3,4]thiadiazines in very good yields by using suitable imidazole-2-thione precursors has been achieved.

5. Experimental

5.1. General procedure

Melting points were measured on a Kofler hot-stage and are uncorrected. Column chromatography was carried out using Merck silica gel (70–230 mesh). Petroleum ether refers to the fraction boiling between 60 and 80 °C. IR Spectra: Perkin–Elmer 1600 series FTIR spectrophotometer, ν in cm^{-1}. NMR spectra were recorded on a Bruker AM 300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively, using $CDCl_3$ as solvent. The chemical shifts are expressed in δ values (ppm) relative to TMS as internal standard for ^{1}H (0.00 ppm) or to $CDCl_3$ (77.05 ppm) for ^{13}C NMR spectra. Coupling constants ^nJ are reported in hertz. Low-resolution electron impact mass spectra (EIMS) were obtained on a 6890N GC/MS instrument (Agilent Technology), m/z (rel intensity in %); ionization energy 70 eV. Elemental analyses performed with a Perkin–Elmer 2400-II CHN analyzer. Geometries were optimized and Mulliken net atomic charges were computed at the Density Functional Theory (DFT, B3LYP/6-31G level) in vacuo as implemented in the Gaussian 03 package.[21]

5.2. Synthesis of compounds **1** and **3**

5.2.1. 1,3-Dihydro-4,5-dimethyl-1-phenylamino-2H-imidazole-2-thione (**1a**)

The compound was synthesized in 70% yield according to a known procedure.[19,20] Mp 229–231 °C (lit.[19] 230–232 °C).

5.2.2. 1-[(4-Chlorophenyl)amino]-1,3-dihydro-4,5-dimethyl-2H-imidazole-2-thione (**1b**)

The compound was synthesized in 70% yield according to a known procedure.[19] Mp 226–228 °C. IR (cm^{-1}) 3208, 3190 (NH), 3092, 2920, 2726, 1670, 1596. ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ 1.98 (s, 3H, 4-CH_3), 2.08 (s, 3H, 5-CH_3), 3.12 (br s, 0.41H, 2-SH), 6.58 (d, J=12.0, 2H, H-2′,6′), 7.14 (d, J=12.0, 2H, H-3′,5′), 8.15 (br s, 1H, NH), 11.9 (br s, 0.59H, 3-NH). ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ 8.0 (4-CH_3), 9.4 (5-CH_3), 114.7 (C-2′,6′), 117.8 (C-5), 122.5 (C-4), 125.2 (C-4″), 128.9 (C-3′,5′), 145.7 (C-1′), 159.8 (C-2). EIMS: 253/255 ($M^{+\bullet}$, 100), 237/239 (20), 220/22 (20), 211/213 (12), 185 (30), 170 (15), 127 (25). Anal. Calcd for $C_{11}H_{12}ClN_3S$ (253.75): C, 52.07; H, 4.77; N, 16.56. Found: C, 51.99; H, 4.67; N, 16.33.

5.2.3. 1,3-Dihydro-4,5-dimethyl-1-[(4-nitrophenyl)amino]-2H-imidazole-2-thione (**1c**)

The compound was synthesized in 71% yield according to a known procedure.[19] Mp 262–264 °C (lit.[19] 275–280 °C). ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ 1.98 (s, 3H, 4-CH_3), 2.10 (s, 3H, 5-CH_3), 6.66 (d, J=8.8, 2H, H-2′,6′), 8.08 (d, J=8.8, 2H, H-3′,5′), 9.53 (s, 1H, NH), 12.03 (br s, 1H, 3-NH). ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ 8.0 (4-CH_3), 9.4 (5-CH_3), 111.8 (C-2′,6′), 118.2 (C-5), 122.3 (C-4), 125.7 (C-3′,5′), 140.4 (C-4′), 152.9 (C-1′), 160.8 (C-2). EIMS: 264 ($M^{+\bullet}$, 100), 248 (15), 234 (15), 217 (18), 207 (50), 185 (30), 128 (27). Anal. Calcd for $C_{11}H_{12}N_4O_2S$ (264.31): C, 49.99; H, 4.58; N, 21.20. Found: C, 49.94; H, 4.79; N, 21.43.

5.2.4. 1-Anilino-4,5-dimethyl-2-methylthio-1H-imidazole (**3a**)

The compound was synthesized in 80% yield according to a known procedure.[19] Mp 197–199 °C (lit.[19] 198 °C). ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H, 5-CH_3), 2.44 (s, 3H, 4-CH_3), 2.87 (s, 3H, SCH_3), 6.59 (d, J=9.0, 2H, H-2′,6′), 6.90–6.96 (m, 1H, H-4′), 7.20–7.26 (m, 2H, H-3′,5′), 8.31 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ 7.6 (5-CH_3), 9.6 (4-CH_3), 15.2 (SCH_3), 112.5 (C-2′,6′), 121.8 (C-4′), 125.4 (C-5), 128.4 (C-4), 129.1 (C-3′,5′), 143.9 (C-1′), 144.5 (C-2). EIMS: 233 ($M^{+\bullet}$, 100), 141 (73).

5.3. Synthesis of compound **4**

5.3.1. 2-Methylthio-N-phenyl-N,4,5-trimethyl-1H-imidazole-1-amine (**4a**)

*5.3.1.1. Method A from **3a**.* To a suspension of compound **3a** (0.116 g, 0.5 mmol) in dry tetrahydrofuran (20 mL) at 0 °C sodium hydride (0.030 g of 60% in oil, 1.2 mmol) was added. Salt formation was allowed to proceed at ambient temperature for 30 min, methyl iodide (0.285 g, 2.0 mmol) was then added and the solution was stirred for 1.5 h. Water was added, the organic layer was washed with water, dried (Na_2SO_4), and concentrated. The methylated product was crystallized, by the addition of petroleum ether, as a yellow solid in 55% yield. Mp 78–80 °C (CH_2Cl_2–pet. ether). ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 3H, 5-CH_3), 2.18 (s, 3H, 4-CH_3), 2.47 (s, 3H, S-CH_3), 3.35 (s, 3H, N-CH_3), 6.46 (d, J=9.0, 2H, H-2′,6′), 6.86–6.91 (m, 1H, H-4′), 7.21–7.27 (m, 2H, H-3′,5′). ^{13}C NMR ($CDCl_3$) δ 8.4 (5-CH_3), 13.1 (4-CH_3), 15.0 (S-CH_3), 39.8 (N-CH_3), 112.1 (C-2′,6′), 120.1 (C-4′), 124.5 (C-5), 129.4 (C-3′,5′), 132.7 (C-4), 141.5 (C-2), 147.7 (C-1′). EIMS: 247 (M^+, 100), 232 (7), 200 (35), 191 (25), 141 (100). Anal. Calcd for $C_{13}H_{17}N_3S$ (247.36): C, 63.12; H, 6.93; N, 16.99. Found: C, 63.34; H, 6.89; N, 16.83.

*5.3.1.2. Method B from **1a**.* To a suspension of compound **1a** (0.110 g, 0.5 mmol) in dry tetrahydrofuran (10 mL) at 0 °C sodium hydride (0.036 g of 60% in oil, 1.5 mmol) was added. Salt formation was allowed to proceed at ambient temperature for 30 min, methyl iodide (0.43 g, 3.0 mmol) was then added and the solution was stirred for 1.5 h. The reaction mixture was worked up as above and compound **4a** was obtained in 60% yield.

5.4. Synthesis of compound **6a**

5.4.1. 1,3-Dihydro-1-(methyl(phenyl)amino)-3,4,5-trimethyl-2H-imidazole-2-one (**6a**)

To a suspension of compound **1a** (0.116 g, 0.5 mmol) in dry tetrahydrofuran (20 mL) at 0 °C sodium hydride (0.048 g of 60% in oil, 2.0 mmol) was added. Salt formation was allowed to proceed at ambient temperature for 30 min, methyl iodide (0.57 g, 4.0 mmol) was then added and the solution was stirred for seven days. Water was added, the organic layer was washed with water, dried (Na_2SO_4), and concentrated. The imidazolone was crystallized, by the addition of methylene chloride and petroleum ether, as a white solid in 40% yield. Mp 200–202 °C (CH_2Cl_2–pet. ether). IR (cm^{-1}) 1702, 1690 (C=O). ^{1}H NMR ($CDCl_3$) δ 1.89 (q, J=0.9, 3H, 5-CH_3), 2.02 (q, J=0.9, 3H, 4-CH_3), 3.19 (s, 3H, 3-CH_3), 3.34 (s, 3H, PhN-CH_3), 6.57–6.62 (m, 2H, H-2′,6′), 6.81–6.87 (m, 1H, H-4′), 7.20–7.25 (m, 2H, H-3′,5′). ^{13}C NMR ($CDCl_3$) δ 7.7 (5-CH_3), 8.9 (4-CH_3), 27.3 (3-CH_3), 39.7 (PhN-CH_3), 112.1 (C-4), 112.3 (C-2′,6′), 114.2 (C-5), 119.6 (C-4′), 129.2 (C-3′,5′), 149.0 (C-1′), 151.6 (C=O). EIMS: 231 (M^+, 100), 189(50), 173 (39), 159 (40). Anal. Calcd for $C_{13}H_{17}N_3O$ (231.29): C, 67.51; H, 7.41; N, 18.17. Found: C, 67.59; H, 7.47; N, 18.13.

5.5. General procedure for the reaction of thiones (**1a–1c**) with 1,2-dibromoethane (method A)

To a suspension of compound **1a** (0.5 mmol) in dry dimethylformamide (5 mL) at −10 °C sodium hydride (0.015 g of 60% in oil, 0.62 mmol) was added. Salt formation was allowed to proceed for 30 min, 1,2-dibromoethane (0.14 g, 0.7 mmol)

was then added and the reaction mixture was stirred for 1.5 h at −10 °C. Sodium hydride (0.015 g of 60% in oil, 0.62 mmol) was again added to this solution at −10 °C and the reaction mixture was stirred for another 1.5 h. Dilution of the solution with 40 mL ice-water precipitated the products. The crude product mixture was subjected to column chromatography on silica gel using petroleum ether/EtOAc (3:1) as eluent, to give in order of elution.

*5.5.1. From compound **1a***

*5.5.1.1. 1-[(N-2-Bromoethyl)-(N-phenyl)]amino-4,5-dimethyl-2-(vinylthio)-1H-imidazole (**9a**).* Colorless crystals, yield 0.018 g, 5%. Mp 77–79 °C. ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3H, 5-CH_3), 2.21 (s, 3H, 4-CH_3), 3.57 (t, J=8.3, 2H, H-10), 3.97–4.21 (m, 2H, H-11), 5.36 (d, J_{cis}=9.5, 1H, H-9), 5.38 (d, J_{trans}=16.6, 1H, H-9), 6.41 (d, J=9.0, 2H, H-2′,6′), 6.62 (dd, J_{cis}=9.5, J_{trans}=16.6, 1H, H-8), 6.90–6.95 (m, 1H, H-4′), 7.22–7.28 (m, 2H, H-3′,5′). ^{13}C NMR ($CDCl_3$) δ 8.7 (5-CH_3), 13.3 (4-CH_3), 27.5 (C-11), 55.3 (C-11), 116.4 (C-9), 116.6 (C-2′,6′), 121.0 (C-4′), 125.4 (C-5), 128.6 (C-8), 129.7 (C-3′,5′), 134.1 (C-4), 137.8 (C-2), 146.5 (C-1′). Anal. Calcd for $C_{15}H_{18}BrN_3S$ (352.29): C, 51.14; H, 5.15; N, 11.93. Found: C, 51.01; H, 5.22; N, 11.78.

*5.5.1.2. 4,5-Dimethyl-1-N-phenylamino-2-(vinylthio)-1H-imidazole (**8a**).* White solid in 31% yield. Mp 140–142 °C. IR (cm^{-1}) 3470 (NH). ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H, 5-CH_3), 2.21 (s, 3H, 4-CH_3), 5.75 (dd, J=16.7, 0.4, 1H, H_{trans}-9), 5.79 (dd, J=9.5, 0.4, 1H, H_{cis}-9), 6.53 (dd, J=16.7, 9.5, 1H, H-8), 6.50–6.54 (m, 2H, H-2′,6′), 6.90–6.96 (m, 1H, H-4′), 7.10 (br s, 1H, NH), 7.19–7.25 (m, 2H, H-3′,5′). ^{13}C NMR ($CDCl_3$) δ 8.3 (5-CH_3), 12.9 (4-CH_3), 112.8 (C-2′,6′), 116.4 (C-9), 121.8 (C-4′), 126.9 (C-5), 128.6 (C-8), 129.5 (C-3′,5′), 132.7 (C-4), 137.2 (C-2), 146.2 (C-1′). EIMS: 245 (M^+, 70), 153 (100). Anal. Calcd for $C_{13}H_{15}N_3S$ (245.34): C, 63.64; H, 6.16; N, 17.13. Found: C, 63.48; H, 6.27; N, 17.00.

*5.5.1.3. 6,7-Dimethyl-4-phenyl-3,4-dihydro-2H-imidazo[2,1-b][1,3,4]thiadiazine (**7a**).* White solid in 62% yield. Mp 135–137 °C. ^{1}H NMR ($CDCl_3$) δ 1.90 (s, 3H, 6-CH_3), 2.17 (s, 3H, 7-CH_3), 2.99 (t, J=5.5, 2H, H-2), 4.00 (br s, 2H, H-3), 6.65–6.70 (m, 2H, H-2′,6′), 7.00–7.07 (m, 1H, H-4′), 7.26–7.33 (m, 2H, H-3′,5′). ^{13}C NMR ($CDCl_3$) δ 7.5 (6-CH_3), 12.7 (7-CH_3), 20.5 (C-2), 51.6 (C-3), 117.7 (C-2′,6′), 122.6 (C-6), 123.5 (C-4′), 129.5 (C-3′,5′), 130.5 (C-7), 130.6 (C-8a), 147.5 (C-1′). EIMS: 245 (M^+, 23), 211 (90), 210 (100), 200 (20), 187 (60), 128 (40). Anal. Calcd for $C_{13}H_{15}N_3S$ (245.34): C, 63.64; H, 6.16; N, 17.13. Found: C, 63.78; H, 6.25; N, 17.30.

*5.5.2. From compound **1b***

*5.5.2.1. 4,5-Dimethyl-1-N-(4-chlorophenyl)amino-2-(vinylthio)-1H-imidazole (**8b**).* White solid in 29% yield. Mp 135–137 °C. ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H, 5-CH_3), 2.21 (s, 3H, 4-CH_3), 5.26 (d, J_{trans}=16.7, 1H, H-9), 5.31 (d, J_{cis}=9.6, 1H, H-9), 6.44 (d, J=8.8, 2H, H-2′,6′), 6.48 (dd, J_{cis}=9.6, J_{trans}=16.7, 1H, H-8), 6.63 (br s, 1H, NH), 7.19 (d, J=8.8, 2H, H-3′,5′). ^{13}C NMR ($CDCl_3$) δ 8.4 (5-CH_3), 13.3 (4-CH_3), 114.0 (C-2′,6′), 116.0 (C-9), 126.4 (C-4′), 126.7 (C-5), 128.9 (C-8), 129.5 (C-3′,5′), 133.6 (C-4), 136.6 (C-2), 144.90 (C-1′). EIMS: 279/281 (M^+, 70), 153 (100), 126/128 (15), 94 (40). Anal. Calcd for $C_{13}H_{14}ClN_3S$ (279.79): C, 55.81; H, 5.04; N, 15.02. Found: C, 55.99; H, 5.12; N, 14.93.

*5.5.2.2. 6,7-Dimethyl-4-(4-chlorophenyl)-3,4-dihydro-2H-imidazo[2,1-b][1,3,4]thiadiazine (**7b**).* White solid in 60% yield. Mp 141–143 °C. ^{1}H NMR ($CDCl_3$) δ 1.90 (s, 3H, 6-CH_3), 2.15 (s, 3H, 7-CH_3), 2.99 (t, J=5.3, 2H, H-2), 3.98 (br s, 2H, H-3), 6.62 (d, J=8.9, 2H, H-2′,6′), 7.26 (d, J=8.9, 2H, H-3′,5′). ^{13}C NMR ($CDCl_3$) δ 7.5 (6-CH_3), 12.8 (7-CH_3), 20.6 (C-2), 51.7 (C-3), 119.0 (C-2′,6′), 122.5 (C-6), 128.7 (C-4′), 129.6 (C-3′,5′), 130.5 (C-8a), 130.9 (C-7), 146.1 (C-1′). EIMS: 279/281 (M^+, 85), 237/239 (50), 223/225 (45), 184/186 (15), 169/171 (100), 137/139 (30). Anal. Calcd for $C_{13}H_{14}ClN_3S$ (279.79): C, 55.81; H, 5.04; N, 15.02. Found: C, 55.72; H, 5.07; N, 15.13.

*5.5.3. From compound **1c***

*5.5.3.1. 4,5-Dimethyl-1-N-(4-nitrophenyl)amino-2-(vinylthio)-1H-imidazole (**8c**).* White solid in 21% yield. Mp 86–88 °C. IR (cm^{-1}) 3470 (NH), 1504 (NO_2 as), 1330 (NO_2 sym). ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H, 5-CH_3), 2.21 (s, 3H, 4-CH_3), 5.27 (d, J_{trans}=17.1, 1H, H-9), 5.32 (d, J_{cis}=9.4, 1H, 9-H), 6.47 (dd, J_{cis}=9.4, 1H, 8-H), 6.55 (d, J=9.2, 2H, H-2′,6′), 7.4 (br s, 1H, NH), 8.15 (d, J=9.2, 2H, H-3′,5′). ^{13}C NMR ($CDCl_3$) δ 8.3 (5-CH_3), 13.2 (4-CH_3), 111.8 (C-2′,6′), 116.5 (C-9), 126.1 (C-3′,5′), 126.9 (C-5), 128.5 (C-8), 134.1 (C-4), 136.9 (C-2), 142.1 (C-4′), 151.4 (C-1′). EIMS: 290 (M^+, 78), 153 (100). Anal. Calcd for $C_{13}H_{14}N_4O_2S$ (290.34): C, 53.78; H, 4.86; N, 19.30. Found: C, 53.62; H, 4.75; N, 19.41.

*5.5.3.2. 6,7-Dimethyl-4-(4-nitrophenyl)-3,4-dihydro-2H-imidazo[2,1-b][1,3,4]thiadiazine (**7c**).* White solid in 56% yield. Mp 228–230 °C. ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3H, 6-CH_3), 2.18 (s, 3H, 7-CH_3), 3.15 (br s, 2H, H-2), 4.20 (br s, 2H, H-3), 6.80 (d, J=9.0, 2H, H-2′,6′), 8.20 (d, J=9.0, 2H, H-3′,5′). ^{13}C NMR ($CDCl_3$) δ 7.6 (6-CH_3), 12.9 (7-CH_3), 22.4 (C-2), 50.9 (C-3), 116.4 (C-2′,6′), 122.7 (C-6), 125.8 (C-3′,5′), 131.2 (C-8a), 131.7 (C-7), 143.0 (C-4′), 152.7 (C-1′). EIMS: 290 (M^+, 78), 258 (30), 248 (31), 234 (30), 180 (100). Anal. Calcd for $C_{13}H_{14}N_4O_2S$ (290.34): C, 53.78; H, 4.86; N, 19.30. Found: C, 53.91; H, 4.62; N, 19.41.

*5.6. General procedure for the reaction of thiones (**1a–1c**) with 1,2-dibromoethane (method B)*

To a suspension of compound **1** (0.5 mmol) in dry dimethylformamide (50 mL) sodium hydride (0.27 g of 60% in oil, 1.13 mmol) was added. Salt formation was allowed to proceed for 30 min at rt, 1,2-dibromoethane (0.132 g, 0.7 mmol) in dry dimethylformamide (5 mL) was then added dropwise

and the reaction mixture was stirred at ambient temperature for 2 h. Dilution of the solution with 40 mL ice-water precipitated the products. The crude product mixture was subjected to column chromatography on silica gel using petroleum ether/EtOAc (3:1) as eluent, to give in order of elution.

*5.6.1. From compound **1a***

Compound **9a** in 1% yield; compound **8a** in 14% yield and compound **7a** in 77% yield.

*5.6.2. From compound **1b***

Compound **8b** in 15% yield and compound **7b** in 74% yield.

*5.6.3. From compound **1c***

Compound **8c** in 10% yield and compound **7c** in 71% yield.

References and notes

1. Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. *Chem. Rev.* **2004**, *104*, 2777–2812.
2. Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*; John Wiley-VCH: New York, NY, 1997.
3. Coleman, C. M.; MacElroy, J. M. D.; Gallagher, J. F.; O'Shea, D. F. *J. Comb. Chem.* **2002**, *4*, 87–93.
4. Blakeney, J. S.; Reid, R. C.; Le, G. T.; Fairlie, D. P. *Chem. Rev.* **2007**, *107*, 2960–3041.
5. (a) Tortolani, D. R.; Biller, S. A. *Tetrahedron Lett.* **1996**, *37*, 5687–5690; (b) Gelens, E.; Koot, W. J.; Menge, W. M.; Ottenheijm, H. C.; Timmerman, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1935–1938; (c) Kondo, Y.; Komine, T.; Sakamoto, T. *Org. Lett.* **2000**, *2*, 3111–3113; (d) Lee, H. B.; Balasubramanian, S. *Org. Lett.* **2000**, *2*, 323–326.
6. (a) Blass, B. E.; Huang, C. T.; Kawamoto, R. M.; Li, M.; Liu, S.; Portlock, D. E.; Rennells, W. M.; Simmons, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1543–1545; (b) Boger, D. L.; Dechantsreiter, M. A.; Ishii, T.; Fink, B. E.; Hedrick, M. P. *Bioorg. Med. Chem.* **2000**, *8*, 2049–2057; (c) Boger, D. L.; Fink, B. E.; Hedrick, M. P. *J. Am. Chem. Soc.* **2000**, *122*, 6382–6394; (d) Hamper, B. C.; Jerome, K. D.; Yalamanchili, G.; Walker, D. M.; Chott, R. C.; Mischke, D. A. *Biotechnol. Bioeng.* **2000**, *71*, 28–37.
7. (a) Xu, J.; Yang, Z.; Dammermann, W.; Zhang, L.; Guse, A. H.; Zhang, L.-H. *J. Med. Chem.* **2006**, *49*, 5501–5512; (b) Abdel-Meguid, S. S.; Metcalf, B. W.; Carr, T. J.; Demarsh, P.; Desjarlais, R. L.; Fisher, S.; Green, D. W.; Ivanoff, L.; Lambert, D. M.; Murthy, K. H. M.; Petteway, S. R.; Pitts, W. J.; Tomaszek, T. A.; Winborne, E.; Zhao, B. G.; Dreyer, G. B.; Meek, T. D. *Biochemistry* **1994**, *33*, 11671–11677; (c) Thompson, S. K.; Murthy, K. H. M.; Zhao, B.; Winborne, E.; Green, D. W.; Fisher, S. M.; Desjarlais, R. L.; Tomaszek, T. A.; Meek, T. D.; Gleason, J. G.; Abdelmeguid, S. S. *J. Med. Chem.* **1994**, *37*, 3100–3107.
8. Testard, A.; Picot, L.; Fruitier-Arnaudin, I.; Piot, J.-M.; Chabane, H.; Domon, L.; Thiery, V.; Besson, T. *J. Enzyme Inhib. Med. Chem.* **2004**, *19*, 467–473.
9. (a) Mann, S. *Nature* **1993**, *365*, 499–505; (b) Hosseini, M. W. *Coord. Chem. Rev.* **2003**, *240*, 157–166; (c) Hosseini, M. W. *Acc. Chem. Res.* **2005**, *38*, 313–323; (d) Wuest, J. D. *Chem. Commun.* **2005**, 5830–5837.
10. Nam, S. R.; Kim, H.-J.; Sakamoto, S.; Yamaguchi, K.; Hong, J.-I. *Tetrahedron Lett.* **2004**, *45*, 1339–1342.
11. Huang, X.-C.; Zhang, J.-P.; Lin, Y.-Y.; Chen, X.-M. *Chem. Commun.* **2005**, 2232–2234.
12. Bastero, A.; Ruiz, A.; Claver, C.; Milani, B.; Zangrando, E. *Organometallics* **2002**, 5820–5829.
13. Cheruzel, L. E.; Mashuta, M. S.; Buchanan, R. M. *Chem. Commun.* **2005**, 2223–2225.
14. Lagoja, I. M.; Pannecouque, C.; Van Aerschot, A.; Witvrouw, M.; Debyser, Z.; Balzarini, J.; Herdewijn, P.; De Clercq, E. *J. Med. Chem.* **2003**, *46*, 1546–1553.
15. Laufer, S. A.; Kotschenreuther, D.; Wagner, G. K. *J. Org. Chem.* **2003**, *68*, 4527–4530.
16. Laufer, S. A.; Wagner, G. K.; Kotschenreuther, D. A.; Albrecht, W. *J. Med. Chem.* **2003**, *46*, 3230–3244.
17. Lantos, I.; Bender, P. E.; Razgaitis, K. A.; Sutton, B. M.; DiMartino, M. J.; Griswold, D. E.; Walz, D. T. *J. Med. Chem.* **1984**, *27*, 72–75.
18. El Ashry, E. S. H.; Rashed, N.; Awad, L. F.; Ramadan, E.; Abdel-Maggeed, S. M.; Rezki, N. *ARKIVOC* **2007**, *vii*, 30–40.
19. Schantl, J. G.; Lagoja, I. M. *Heterocycles* **1997**, *4*, 691–700.
20. Neochoritis, C.; Tsoleridis, C. A.; Stephanidou-Stephanatou, J. *ARKIVOC* **2007**, *xv*, 101–111.
21. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Peterson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, Y. C.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Rev. B.02*; Gaussian: Pittsburgh, PA, 2003.