Unequivocal synthesis of substituted thiazolo[3,2-a]benzimidazoles

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Dedicated to Professor Jan Bergman on the occasion of his 80th birthday

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Abstract

An unequivocal route to individual substituted thiazolo[3,2-a]benzimidazole isomers has been developed, involving the acid-catalyzed intramolecular condensation of dialkylacetals with the sulfur atom of benzimidazole-2-thiones. Products are isolated without isomerization, in contrast to several literature methods.

Keywords: Thiazolo[3,2-a]benzimidazoles, unequivocal synthesis, benzimidazole-2-thiones, aminoacetals
Introduction

Thiazolo[3,2-a]benzimidazole (benzo[4,5]imidazo[2,1-b]thiazole) derivatives (1) have received attention over the years due to a variety of biological effects,\textsuperscript{1,2} with the immunomodulator Tilomisole (Wy-18,251) (2),\textsuperscript{3} and the allosteric antagonist of metabotropic glutamate receptor 1 (mGluR1) YM-298198 (3)\textsuperscript{4} having probably received the most attention (Figure 1).\textsuperscript{2}

Figure 1.

As part of a drug development programme we wanted to prepare some 6- and 7-substituted thiazolo[3,2-a]benzimidazole derivatives, but soon found that none of the existing synthetic methods was able to prepare these compounds in an isomerically distinct manner. A standard route to thiazolo[3,2-a]benzimidazoles involves acid-catalyzed ring closure of 2-(acylmethylthio)benzimidazoles,\textsuperscript{1,2,5} but for ring substituted benzimidazoles, two ring-closure routes are available, due to tautomerism of the benzimidazole nitrogens (Scheme 1). Thus the ring-closure of 5-substituted 2-(acylmethylthio)benzimidazoles gives rise to the production of isomeric mixtures of 6- and 7-substituted thiazolo[3,2-a]benzimidazole products.\textsuperscript{6,7}

Scheme 1.
Similarly, 4-substituted 2-(acylmethylthio)benzimidazoles can undergo ring closure to give either 5- or 8-substituted thiazolo[3,2-a]benzimidazole products, although the latter are normally preferred for steric reasons (Scheme 2).

\[
\begin{align*}
\text{R}^4 \quad & \text{SCH(R^2)COR^3} \quad \rightarrow \quad \begin{array}{c}
\text{R}_5 \\
\text{R}_3 \\
\text{R}_2
\end{array} \\
& + \\
\text{R}^3 \quad & \text{N} \quad \text{S} \\
& \text{R}_3 \\
& \text{R}_2
\end{align*}
\]

Scheme 2.

There are some reports in the literature claiming single isomeric products from the ring closure of 5-substituted 2-(acylmethylthio)benzimidazoles,\textsuperscript{9-11} although NMR studies have confirmed that mixtures of both isomeric products are normally obtained.\textsuperscript{6} It is probable that the reports of single products are the result of selective isolation of one isomer, and not of selective synthesis. Several new approaches to the synthesis of thiazolo[3,2-a]benzimidazoles have been reported in recent years,\textsuperscript{12-19} but unfortunately, none of them provides a general route to individual substituted isomers. Therefore, a search for alternative routes that could result in unequivocal formation of individual isomers was initiated.

**Results and Discussion**

It had been reported that 2-methoxy-7-(trifluoromethyl)-2,3-dihydrothiazolo[3,2-a]benzimidazole (4) could be prepared by treatment of the dimethylacetal 5 with boron trifluoride diethyl etherate at room temperature (Scheme 3).\textsuperscript{20} This result was investigated further, and it was found that by using the stronger ring closure conditions of 90% H\textsubscript{2}SO\textsubscript{4} at 100 °C, the analogous 7-(trifluoromethyl)thiazolo[3,2-a]benzimidazole (6) could be obtained, cleanly and in good yield (Scheme 3).

\[
\begin{align*}
\text{CF}_3 \\
\text{N} \\
\text{N} \\
\text{S} \\
\text{OMe} \\
\text{CH}_2\text{Cl}_2, \text{rt}
\end{align*}
\]

\[
\begin{align*}
\text{BF}_3\text{Et}_2\text{O} \\
\text{CF}_3 \\
\text{N} \\
\text{N} \\
\text{S} \\
\text{CH(O\text{Me})}_2 \\
\text{100 °C}
\end{align*}
\]

Scheme 3.

This new route was next investigated for the unequivocal synthesis of other 7-substituted thiazolo[3,2-a]benzimidazoles, starting by reaction of the appropriate 4-substituted-1-halo-2-nitrobenzenes (7a-d) with 2,2-dimethoxyethylamine (aminoacetaldehyde dimethylacetal) (8) (Scheme 4). The resulting 4-substituted-2-nitroaniline derivatives 9a-d were then reduced to the corresponding diamines 10a-d, which normally were not isolated, but treated directly with CS\textsubscript{2} and aqueous KOH in EtOH,\textsuperscript{21} to give the analogous benzimidazole-2-
thiones 11a-d. Ring closure with 90% H$_2$SO$_4$ at 100 °C then gave the desired 7-substituted thiazolo[3,2-α]benzimidazoles 12 (Scheme 4). None of these compounds were previously known, although demethylation of the methoxy derivative 12a with BBr$_3$ did give the 7-hydroxy derivative 12e, which had been reported previously, but without characterization, in a patent.$^{22}$

![Scheme 4](image)

Scheme 4. Synthesis of 7-substituted thiazolo[3,2-α]benzimidazoles

Having established that a variety of 7-substituted thiazolo[3,2-α]benzimidazoles could be synthesized in an unequivocal manner, the synthesis of 5-, 6-, and 8-substituted thiazolo[3,2-α]benzimidazoles was next investigated (Scheme 5). Unfortunately, the reduction and subsequent reaction of the 6-methoxy derivative 13a with CS$_2$ gave an amorphous solid, and not the desired thione 14a, presumably because of steric inhibition of the ring closure step by the adjacent methoxy group. However, no such problem was observed with the less sterically hindered 6-methyl compound 13b which successfully gave both the thione 14b and the thiazolo[3,2-α]benzimidazole 15b. Similarly, the methoxy compounds 13c and 13d and methyl compound 13e, all gave the desired thiones 14c-e and thiazolo[3,2-α]benzimidazoles 15c-e without any problems. Demethylation of 15c then gave the known 6-hydroxy compound 15f.$^{23}$
The synthesis of 3-methylthiazolo[3,2-a]benzimidazoles was also investigated, although it was found that longer reaction times were necessary. Formation of the intermediate 2-alkoxy compounds, analogous to compound 4, did occur rapidly, but the elimination step was much slower. For example, in the ring closure of thione 18 with 90% H$_2$SO$_4$, either the 2-methoxy-2,3-dihydro-compound 19 or the desired product 20 could be isolated, depending on the reaction time (Scheme 6). The $^1$H NMR spectrum of crude 19 showed two isomers in approximate proportions of 77% and 33%. Recrystallization from aqueous MeOH cleanly gave the major component, which was assigned as the trans isomer due to the absence of $3^J$ coupling between the H-2 and H-3 protons. The minor component, which displayed a $3^J$ coupling of 3.5 Hz, was therefore assigned as the cis isomer, although it was never isolated cleanly. Compound 20 had previously been reported as the hydrochloride, although it was probably a mixture of the 6- and 7-benzoyl isomers, due to being produced by a procedure similar to Scheme 1. No evidence to support the 7-isomer structure over the 6-isomer was provided.

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**Scheme 5.** Synthesis of 5-, 7-, and 8-substituted thiazolo[3,2-a]benzimidazoles

13a; R$^6$ = OMe, R$^3$ = R$^5$ = H
13b; R$^6$ = Me, R$^3$ = R$^5$ = H
13c; R$^5$ = OMe, R$^3$ = R$^6$ = H
13d; R$^3$ = OMe, R$^5$ = R$^6$ = H
13e; R$^3$ = Me, R$^5$ = R$^6$ = H
14a; R$^7$ = OMe, R$^4$ = R$^6$ = H
14b; R$^7$ = Me, R$^3$ = R$^5$ = H
14c; R$^5$ = OMe, R$^4$ = R$^7$ = H
14d; R$^4$ = OMe, R$^6$ = R$^7$ = H
14e; R$^4$ = Me, R$^6$ = R$^7$ = H
15a; R$^5$ = Me, R$^6$ = R$^8$ = H
15b; R$^5$ = Me, R$^6$ = R$^8$ = H
15c; R$^6$ = OMe, R$^5$ = R$^8$ = H
15d; R$^6$ = OMe, R$^5$ = R$^8$ = H
15e; R$^8$ = Me, R$^5$ = R$^8$ = H
15f; R$^8$ = OH, R$^5$ = R$^8$ = H

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**Scheme 6.** Ring closure of thione 18 with 90% H$_2$SO$_4$.
Attempts to extend the acetal procedure to the synthesis of 3-phenylthiazolo[3,2-α]benzimidazole derivatives were not successful, with long reaction times being required, which resulted in mixtures of products being obtained, from which the desired compounds could not be isolated in synthetically useful yields.

Conclusions

An efficient route for the unequivocal synthesis of individual substituted thiazolo[3,2-α]benzimidazole isomers has been developed, with both 3-unsubstituted, and 3-alkylthiazolo[3,2-α]benzimidazoles able to be prepared. Single isomeric products are isolated cleanly, in contrast to the results from several literature methods.

Experimental Section

General. Elemental analyses were performed by the Microchemical Laboratory, University of Otago, Dunedin, New Zealand. Melting points were determined on an Electrothermal IA9100 melting point apparatus and are as read. NMR spectra were obtained on a Bruker Avance 400 spectrometer at 400 MHz for proton spectra, and 100 MHz for carbon spectra, referenced to Me₄Si or solvent resonances. Low-resolution atmospheric pressure chemical ionization (APCI) mass spectra were measured for methanol solutions on an Agilent Technologies 6120 Quadrupole LC/MS connected to an Agilent Technologies 1260 Infinity autosampler. High-resolution mass spectra were obtained with organic solutions on an Agilent Technologies 6500 Series quadrupole time-of-flight (Q-TOF) LC/MS system. Thin-layer chromatography was carried out on aluminium-backed silica gel plates (Merck 60 F254), with visualization of components by UV light (254 nm). Column chromatography was carried out on silica gel, (Merck 230 - 400 mesh) unless otherwise stated. Tested compounds were >95% purity, as determined by combustion analysis, or by HPLC conducted on an Agilent 1100 system, using a reversed-phase C8 column with diode array detection.

7-(Trifluoromethyl)thiazolo[3,2-α]benzimidazole (6). A mixture of 1-chloro-2-nitro-4-(trifluoromethyl)benzene (2.256 g, 10 mmol) and 2,2-dimethoxyethylamine (8) (2.31 g, 22 mmol) in DMSO (10 mL) was stirred at room temperature overnight. Dilution with water gave a yellow solid which was collected by filtration, and dried, to give N-(2,2-dimethoxyethyl)-2-nitro-4-(trifluoromethyl)aniline (2.76 g, 94%): mp (from aq. MeOH) 51-53 °C. ¹H NMR (CDCl₃): δH 8.47 (dd, J 1.8, 0.6 Hz, 1H), 8.37 (br s, 1H), 7.63 (dd, J 9.0, 2.2 Hz, 1H), 6.97 (d, J 9.0 Hz, 1H), 4.65 (t, J 5.4 Hz, 1H), 3.49 (t, J 5.4 Hz, 2H), 3.46 (s, 6H). ¹³C NMR (CDCl₃): δC 146.9 (C), 132.3 (q, JCF 4.1 Hz, CH), 132.8 (q, JCF 4.1 Hz, CH), 123.8 (q, JCF 270.8 Hz, CF₃), 118.0 (q, JCF 34.4 Hz, C-4), 114.8 (CH), 102.2 (CHO₂), 54.6 (CH₃O), 45.0 (CH₂). MS m/z 263.1 (100%) (M-OMe)⁺, m/z 295.1 (80%) (M+H)⁺.

A solution of N-(2,2-dimethoxyethyl)-2-nitro-4-(trifluoromethyl)aniline (2.38 g, 8 mmol) in EtOH (50 mL) was hydrogenated over 5% Pd on carbon, and filtered through celite to remove the catalyst. CS₂ (4 mL) andaq. KOH (2.5 g in 20 mL H₂O) were added, and the mixture was heated under gentle reflux for 2 h. After removal of the EtOH, the mixture was diluted with water, and neutralized with HOAc to give 1,3-dihydro-1-(2,2-
dimethoxyethyl)-5-(trifluoromethyl)-2H-benzimidazole-2-thione. All 1H and 13C NMR data (in CDCl3) were recorded at 300 and 75 MHz, respectively, with TMS as internal standard. HRMS (ESI) was performed on a Bruker Daltonics MicroMass Q-Tof II instrument. Analytical data (alcohol) were obtained by flash chromatography on silica, eluting with hexanes/EtOAc.

A solution of 5 (0.306 g, 1 mmol) in a mixture of water (5 g) and conc. H2SO4 (45 g) was heated at 100 °C for 30 min and poured into ice-water. The mixture was diluted with aq. NH3, and extracted with EtOAc to give 6 as a white solid (199 mg, 82 %). mp (from i-Pr2O) 200-203 °C. 1H NMR (CDCl3): δH 8.03 (br s, 1H, NH), 7.62 (d, J = 3.0 Hz, 1H, H-3), 7.16 (dd, J = 9.3, 3.1 Hz, 1H, H-5), 6.85 (d, J = 9.3 Hz, 1H, H-6), 4.62 (t, J = 5.5 Hz, 1H, CH2), 3.80 (s, 3H, CH3O), 3.45 (s, 6H, 2 x CH3O), 3.44 (t, J = 5.5 Hz, 2H, CH2N). 13C NMR (CDCl3): δC 150.0 (C), 141.2 (C), 131.5 (C), 127.3 (CH, C-5), 115.5 (CH, C-6), 107.4 (CH, C-3), 102.5 (CH, CH2O), 56.0 (CH3O), 54.2 (2 x CH3O). HRMS (ESI): found m/z 243.0821 (M+), calcd for C10H6F3N2S: 243.0198.

7-Methoxythiazolo[3,2-a]benzimidazole (12a). A mixture of 4-fluoro-3-nitroanisole (7a) (1.71 g, 10 mmol) and 2,2-dimethoxyethylanime (8) (2.31 g, 22 mmol) in DMSO (12 mL) was stirred at room temperature overnight, and diluted with water. The mixture was neutralized with acetic acid, concentrated, and diluted with water, to give 1,3-dihydro-1-(2,2-dimethoxyethyl)-5-methoxy-2H-benzimidazole-2-thione (11a) as white crystals (1.60 g, 60 %): mp 132-133 °C (from aq. MeOH). 1H NMR (CDCl3): δH 12.71 (br, 1H, exchangeable with D2O, NH), 7.28 (d, J = 8.8 Hz, 1H, H-7), 6.79 (dd, J = 8.8, 2.4 Hz, 1H, H-6), 6.70 (d, J = 2.4 Hz, 1H, H-4), 4.75 (t, J = 5.5 Hz, 1H, CH2O), 4.27 (d, J = 5.5 Hz, 2H, CH2N), 3.76 (s, 3H, CH3O), 3.29 (s, 6H, 2 x CH3O). Anal. calcd for C10H15N2O5S (268.33): C, 53.71; H, 6.01; N, 10.44. Found: C, 53.39; H, 6.29; N, 10.24.

A solution of 9a (2.56 g, 10 mmol) in MeOH was hydrogenated over Pd/C, and after filtration to remove the catalyst, the solution was treated with an excess of Cs2 and aqueous KOH as for the synthesis of 5. After being heated under gentle reflux for 1 h, the mixture was neutralized with acetic acid, concentrated, and diluted with water, to give 1,3-dihydro-1-(2,2-dimethoxyethyl)-5-methoxy-2H-benzimidazole-2-thione (11a) as white crystals (1.60 g, 60 %): mp 132-133 °C (from aq. MeOH). 1H NMR (CDCl3): δH 12.71 (br, 1H, exchangeable with D2O, NH), 7.28 (d, J = 8.8 Hz, 1H, H-7), 6.79 (dd, J = 8.8, 2.4 Hz, 1H, H-6), 6.70 (d, J = 2.4 Hz, 1H, H-4), 4.75 (t, J = 5.5 Hz, 1H, CH2O), 4.27 (d, J = 5.5 Hz, 2H, CH2N), 3.76 (s, 3H, CH3O), 3.29 (s, 6H, 2 x CH3O). Anal. calcd for C10H15N2O5S (268.33): C, 53.71; H, 6.01; N, 10.44. Found: C, 53.39; H, 6.29; N, 10.24.

7-Aminotheiazolo[3,2-a]benzimidazole (12b). A mixture of 1-chloro-2,4-dinitrobenzene (7b) (10.13 g, 5 mmol), 2,2-dimethoxyethylanime (8) (12.6 g, 6 mmol), and Et3N (15 g, 0.306 g, 1 mmol) in DMSO (50 mL) at room temperature was stirred for 5 min, acidified with acetic acid, diluted with water, and extracted with EtOAc, to give N-(2,2-dimethoxyethyl)-2,4-dinitroanilnine (9b) as a yellow oil (13.6 g, 100 %): mp 61-62 °C (from EtOH).
NMR [(CD$_3$)$_2$SO]: \( \delta_h \) 8.85 (d, J 2.7 Hz, 1H, H-3), 8.74 (br, 1H, NH), 8.26 (dd, J 9.6, 2.7 Hz, 1H, H-5), 7.30 (d, J 9.7 Hz, 1H, H-6), 4.66 (t, J 5.2 Hz, 1H, CH$_2$O), 3.56 (t, J 5.4 Hz, 2H, CH$_2$N), 3.35 (s, 6H, 2 x CH$_3$O). Anal. calcd for C$_{10}$H$_{13}$N$_2$O$_2$ (271.23): C, 44.28; H, 4.83; N, 15.49. Found: C, 44.45; H, 4.56; N, 15.70.

A solution of 9b (5.43 g, 20 mmol) in MeOH was hydrogenated over Pd/C, and after filtration to remove the catalyst, the resulting solution was treated with excess Cs$_2$KOH as for above examples. After being heated under gentle reflux for 1h, the mixture was acidified with acetic acid, and concentrated. Aqueous NaHCO$_3$ was added, and the mixture was extracted with EtOAc to give 5-amino-1,3-dihydro-1-(2,2-dimethoxyethyl)-2H-benzimidazole-2-thione (11b) as a white solid (3.1 g, 61 %): mp 202-204 °C (from MeOH). $^1$H NMR [(CD$_3$)$_2$SO]: \( \delta_h \) 12.31 (br s, 1H, NH), 7.03 (d, J 8.5 Hz, 1H, H-7), 6.44 (dd, J 8.5, 2.0 Hz, 1H, H-6), 6.40 (d, J 1.8 Hz, 1H, H-4), 5.02 (br, 2H, NH$_2$), 4.74 (t, J 5.5 Hz, 1H, CH$_2$O), 4.19 (d, J 5.5 Hz, 2H, CH$_2$N), 3.28 (s, 6H, 2 x CH$_3$O). Anal. calcd for C$_{11}$H$_{15}$N$_2$O$_2$ (253.32): C, 52.16; H, 5.97; N, 16.59; S, 12.66. Found: C, 52.36; H, 6.24; N, 16.72; S, 12.90.

A solution of 11b (1.01 g, 4 mmol) in 90 % H$_2$SO$_4$ was heated at 100 °C for 5 min, cooled, and poured onto ice. The resulting solution was made basic with aqueous ammonia, and extracted with EtOAc, to give 12b as a white solid (0.74 g, 98 %): mp 219-221 °C (from aq. MeOH). $^1$H NMR [(CD$_3$)$_2$SO]: \( \delta_h \) 8.21 (d, J 4.5 Hz, 1H, H-3), 7.61 (d, J 8.4 Hz, 1H, H-5), 7.13 (d, J 4.5 Hz, 1H, H-2), 6.78 (d, J 2.0 Hz, 1H, H-8), 6.57 (dd, J 8.6, 2.0 Hz, 1H, H-6), 4.95 (br s, 2H, NH$_2$). $^{13}$C NMR [(CD$_3$)$_2$SO]: \( \delta_c \) 155.3 (C), 149.3 (C), 145.3 (C), 122.1 (C), 119.8 (CH), 111.1 (CH), 109.8 (CH), 109.6 (CH), 101.5 (CH). Anal. calcd for C$_{3}$H$_{7}$N$_{3}$S (189.24): C, 57.12; H, 3.73; N, 22.21. Found: C, 57.23; H, 3.87; N, 22.51.

**Thiazolo[3,2-a]benzimidazole-7-carboxylic Acid (12c).** A mixture of 4-chloro-3-nitrobenzoic acid (7c) (5.04 g (25 mmol), 2,2-dimethoxyethane (8) (7.90 g, 75 mmol) and Et$_3$N (4 mL) in DMSO (30 mL) was heated at 100 °C for 14 h, acidified with acetic acid, and diluted with water, to give 4-[2-(2-dimethoxyethyl)amino]-3-nitrobenzoic acid (9c) as a white solid (6.21 g, 92 %): mp 187-189.5 °C (from MeOH). $^1$H NMR [(CD$_3$)$_2$SO]: \( \delta_h \) 12.92 (br, 1H, CO$_2$H), 8.61 (d, J 2.1 Hz, 1H, H-2), 8.44 (t, J 5.5 Hz, 1H, NH), 7.97 (dd, J 9.1, 2.0 Hz, 1H, H-6), 7.19 (d, J 9.1 Hz, 1H, H-5), 4.66 (t, J 5.2 Hz, 1H, CH$_2$O), 3.56 (t, J 5.4 Hz, 2H, CH$_2$N), 3.35 (s, 6H, 2 x CH$_3$O). Anal. calcd for C$_{11}$H$_{14}$N$_2$O$_6$ (270.24): C, 48.89; H, 5.22; N, 10.37. Found: C, 49.05; H, 5.20; N, 10.61.

A mixture of 9c (5.40 g, 20 mmol) and KOH (1.5 g) in aqueous MeOH was hydrogenated over Pd/C, and after filtration to remove the catalyst, the resulting solution was treated with an excess of Cs$_2$ and KOH as for previous examples. After being heated at gentle reflux over night, the reaction mixture was concentrated, filtered through celite, and acidified with acetic acid, to give 2,3-dihydro-1-(2,2-dimethoxyethyl)-2-thioxo-1H-benzimidazole-5-carboxylic acid (11c) as a white solid (4.02 g, 59 %): mp 248 °C (dec) (from MeOH). $^1$H NMR [(CD$_3$)$_2$SO]: \( \delta_h \) 13.10 (br s, 1H, NH), 12.92 (br, 1H, CO$_2$H), 7.82 (dd, J 8.3, 1.5 Hz, 1H, H-6), 7.70 (d, J 1.4 Hz, 1H, H-4), 7.47 (d, J 8.4 Hz, 1H, H-7), 4.77 (t, J 5.4 Hz, 1H, CH$_2$O), 4.35 (d, J 5.4 Hz, 2H, CH$_2$N), 3.30 (s, 6H, 2 x CH$_3$O). Anal. calcd for C$_{11}$H$_{14}$N$_2$O$_4$ (282.31): C, 51.05; H, 5.00; N, 9.92. Found: C, 51.14; H, 4.84; N, 10.02.

A suspension of 2,3-dihydro-1-(2,2-dimethoxyethyl)-2-thioxo-1H-benzimidazole-6-carboxylic acid (11c) (2.82 g, 1 mmol) in 90 % H$_2$SO$_4$ (100 mL) was heated at 100 °C for 10 min to give a clear solution. After cooling, the solution was poured onto ice, and aqueous ammonia was added until the mixture was just basic. After filtration, the solution was acidified with acetic acid, to give 12c as a white solid (2.13 g, 98 %): mp 307-309 °C (from MeOH). $^1$H NMR [(CD$_3$)$_2$SO]: \( \delta_h \) 13.00 (br, 1H, CO$_2$H), 8.47 (d, J 4.6 Hz, 1H, H-3), 8.28 (br s, 1H, H-8), 8.11 (d, J 8.4 Hz, 1H, H-5), 7.92 (dd, J 8.4, 1.3 Hz, 1H, H-6), 7.39 (d, J 4.6 Hz, 1H, H-2). $^{13}$C NMR [(CD$_3$)$_2$SO]: \( \delta_c \) 167.7 (C), 158.1 (C), 147.3 (C), 132.2 (C), 125.8 (C), 121.7 (CH), 120.0 (CH), 119.4 (CH), 112.8 (CH), 111.4 (CH). Anal. calcd for C$_{11}$H$_{10}$N$_2$O$_5$ (282.23): C, 55.04; H, 2.77; N, 12.84. Found: C, 55.09; H, 2.85; N, 13.00.
7-Benzoylthiazolo[3,2-a]benzimidazole (12d). A mixture of 4-chloro-3-nitrobenzenone (7d) (5.23 g, 20 mmol) and 2,2-dimethoxyethyamine (8) (5.26 g, 50 mmol) in DMSO (50 mL) was heated at 100 °C overnight. After treatment with aqueous acetic acid, to hydrolyze imine byproducts, the solution was diluted with water to give 4-[(2,2-dimethoxyethyl)amino]-3-nitrobenzenone (9d) as a yellow solid (6.11 g, 93%). mp 98-99.5 °C (from MeOH). 1H NMR [(CD3)2SO]: δH 8.57 (t, J 5.5 Hz, 1H, NH), 8.44 (d, J 2.1 Hz, 1H, H-2), 7.95 (dd, J 9.0, 2.1 Hz, 1H, H-6), 7.73-7.65 (m, 3H, H-2′, 4′, 6′), 7.58 (t, J 7.5 Hz, 2H, H-3′, 5′), 7.29 (d, J 9.2 Hz, 1H, H-5), 4.68 (t, J 5.2 Hz, 1H, CHO2), 3.61 (t, J 5.5 Hz, 2H, CH2N), 3.37 (s, 6H, 2 x CH3O). Anal. calcd for C27H18N2O5 (330.34): C, 61.81; H, 5.49; N, 8.48. Found: C, 61.97; H, 5.64; N, 8.75.

A mixture of 9d (4.95 g, 15 mmol), Fe powder (5.04 g, 60 mmol) and HOAc (1 mL) in 65% aqueous EtOH (150 mL) was heated under reflux for 30 min. Excess aq. NH3 was added and the mixture was boiled to coagulate Fe salts. The mixture was filtered through celite, washing with EtOH. Removal of the EtOH under vacuum, and extraction with EtOAc gave 3-amino-4-[(2,2-dimethoxyethyl)amino]benzophenone (10d) as a red oil (4.50 g, 100%). 1H NMR [(CD3)2SO]: δH 7.61-7.54 (m, 3H, H-2′, 4′, 6′), 7.49 (t, J 6.7 Hz, 2H, H-3′, 5′), 7.12 (d, J 2.0 Hz, 1H, H-2), 6.99 (dd, J 8.3, 2.0 Hz, 1H, H-6), 6.54 (d, J 8.4 Hz, 1H, H-5), 5.40 (t, J 5.7 Hz, 1H, NH), 4.86 (br s, 2H, NH2), 4.56 (t, J 5.4 Hz, 1H, CHO2), 3.36 (s, 6H, 2 x CH3O) 3.28 (t, J 5.5 Hz, 2H, CH2N).

A mixture of crude 10d (4.5 g, 15 mmol), CS2 (2.3 g, 30 mmol) and KOH (2.0 g, 36 mmol) in 80% aqueous EtOH (100 mL) was heated under gentle reflux for 1 h and cooled. Neutralization with acetic acid then gave 5-benzoyl-1,3-dihydro-1-(2,2-dimethoxyethyl)-2H-benzimidazole-2-thione (11d) as a white solid (4.83 g, 94%). mp 170-180 °C (from MeOH). 1H NMR [(CD3)2SO]: δH 13.11 (br s, 1H, NH), 7.74-7.50 (m, 4H), 4.80 (t, J 5.4 Hz, 1H, CHO2), 4.38 (d, J 5.4 Hz, 2H, CH2N), 3.32 (s, 6H, 2 x CH3O). Anal. calcd for C18H18N2O3S (342.41): C, 63.14; H, 5.30; N, 8.18; S, 9.36. Found: C, 63.05; H, 5.04; N, 8.27; S, 9.30.

A solution of 11d (2.0 g, 5.8 mmol) in 90% H2SO4 (100 mL) was heated at 100 °C for 5 min, cooled, and poured onto ice. After being made basic with conc. aq. NH3 solution, the mixture was extracted with EtOAc, to give 12d as a white solid (1.58 g, 97%). mp 162-163 °C (from MeOH). 1H NMR [(CD3)2SO]: δH 8.51 (d, J 4.6 Hz, 1H), 8.17 (d, J 8.4 Hz, 1H), 8.02 (d, J 1.1 Hz, 1H), 7.79-7.68 (m, 4H), 7.59 (t, J 7.5 Hz, 2H), 7.42 (d, J 4.6 Hz, 1H).

13C NMR [(CD3)2SO]: δC 195.6 (CO), 158.3 (C), 147.0 (C), 137.7 (C), 132.2 (CH), 132.1 (C), 132.0 (C), 129.5 (2 x CH), 128.4 (2 x CH), 122.2 (CH), 120.8 (CH), 119.4 (CH), 112.9 (CH), 111.6 (CH). Anal. calcd for C16H10N2OS (278.33): C, 69.05; H, 3.62; N, 10.06. Found: C, 69.05; H, 3.68; N, 10.21.

7-Hydroxythiazolo[3,2-a]benzimidazole (12e).22 A mixture of 7-methoxythiazolo[3,2-a]benzimidazole (12a) (0.204 g, 1 mmol) and BBr3 (1 M in CH2Cl2, 4 mL, 4 mmol) in CH2Cl2 (20 mL) was heated under reflux for 5 h, and the solvent was removed. The residue was mixed with ice-water, and neutralized with aqueous NaHCO3, to give 12e as a white solid (0.14 g, 74%). mp 294-296 °C (from aq. MeOH). 1H NMR [(CD3)2SO]: δH 9.27 (s, 1H, OH), 8.28 (d, J 4.5 Hz, 1H, H-3), 7.75 (d, J 8.7 Hz, 1H, H-5), 7.19 (d, J 4.5 Hz, 1H, H-2), 6.97 (d, J 2.1 Hz, 1H, H-8), 6.74 (dd, J 8.7, 2.3 Hz, 1H, H-6). 13C NMR [(CD3)2SO]: δC 156.2 (C), 154.1 (C), 149.0 (C), 123.5 (C), 119.4 (CH, C-3), 111.4 (CH, C-5), 110.4 (CH, C-2), 110.0 (CH, C-6), 103.1 (CH, C-8). Anal. calcd for C9H8N2OS (190.22): C, 56.83; H, 3.18; N, 14.73. Found: C, 56.94; H, 3.29; N, 14.95.

5-Methylthiazolo[3,2-a]benzimidazole (15b). A mixture of 2-fluoro-3-nitrotoluene (1.55 g, 1 mmol), 2,2-dimethoxyethyamine (8) (1.26 g, 1.2 mmol), and DIEPA (1.55 g, 1.2 mmol) in DMSO (10 mL) was stirred at 100 °C for 4 h, cooled, acidified with acetic acid, diluted with water, and extracted with EtOAc, to give N-(2,2-dimethoxyethyl)-2-methyl-6-nitroaniline (13b) (2.30 g, 96%). 1H NMR (CDCl3): δH 7.88 (dd, J 8.4, 1.1 Hz, 1H, H-
A solution of crude 13b (2.30 g, 0.96 mmol) in EtOH (50 mL) was hydrogenated over 5% Pd on C, and filtered through celite to remove the catalyst. A solution of KOH (0.56 g, 10 mmol) in H₂O (10 mL) and CS₂ (0.76 g, 10 mmol) were added and the mixture was heated under gentle reflux overnight. After being concentrated, the solution was diluted with water and neutralized with HOAc to give 1-(2,2-dimethoxyethyl)-4-methyl-1,3-dihydro-2H-benzimidazole-2-thione (14b) as a white solid (1.645 g, 68%). mp from MeOH 210-212 °C. ¹H NMR [(CD₃)₂SO]: δH 12.84 (br, 1H, NH), 7.07-7.01 (m, 2H), 6.96-6.92 (m, 1H), 4.80 (t, J 5.6 Hz, 1H, CHO₂), 4.51 (d, J 5.6 Hz, 2H, CH₂N), 3.29 (s, 6H, 2 x CH₃O), 2.64 (s, 3H, CH₃). MH⁺ 241.2

A solution of 14b (0.252 g, 1 mmol) in a mixture of H₂SO₄ (45 g) and H₂O (5 g) was heated at 100 °C for 30 min, and poured into ice-water. Neutralization with aq NH₃ and extraction with EtOAc gave 15b as a white solid (91 mg, 48%). mp (from aq. MeOH) 171-173 °C. ¹H NMR (CDCl₃): δH 7.84 (d, J 4.6 Hz, 1H, H-3), 7.62 (d, J 8.2 Hz, 1H, H-8), 7.25 (dd, J 8.1, 7.5 Hz, 1H, H-7), 7.02 (dt, J 7.3, 0.8 Hz, 1H, H-6), 6.78 (d, J 4.6, 1H, H-2), 2.72 (s, 3H, CH₃).

¹³C NMR (CDCl₃): δC 151.7 (C), 148.5 (C), 129.5 (C), 123.7 (CH, C-7), 122.5 (CH, C-6), 121.6 (C), 119.5 (CH, C-3), 117.1 (CH, C-8), 110.5 (CH, C-2), 18.1 (CH₃). HRMS (ESI): found m/z 189.0481 (M+H)⁺, calcd for C₁₀H₆N₂S: 189.0481.

6-Methoxythiazolo[3,2-a]benzimidazole (15c). A mixture of 3-fluoro-4-nitroanisole (1.71 g, 10 mmol), 2,2-dimethoxyethylamine (8) (2.11 g, 20 mmol) in DMSO (12 mL), was stirred at room temperature for 1 h and diluted with water, to give N-(2,2-dimethoxyethyl)-5-methoxy-2-nitroaniline (13c) as a yellow solid (2.42 g, 94%): mp 76-78 °C (from MeOH). ¹H NMR (CDCl₃): δH 8.37 (br, 1H, NH), 8.15 (d, J 9.5 Hz, 1H, H-3), 6.26 (dd, J 9.5, 2.6 Hz, 1H, H-4), 6.19 (d, J 2.5 Hz, 1H, H-6), 4.65 (t, J 5.5 Hz, 1H, CHO₂), 3.86 (s, 3H, CH₃O), 3.46 (s, 6H, 2 x CH₃O), 3.42 (t, J 5.4 Hz, 2H, CH₂N). Anal. calcd for C₁₁H₁₆N₂O₅ (256.26): C, 51.56; H, 6.29; N, 10.93. Found: C, 51.74; H, 6.54; N, 11.10.

A solution of 13c (2.30 g, 9 mmol) in MeOH was hydrogenated over Pd/C, and after filtration to remove the catalyst, the solution was treated with an excess of CS₂ and aqueous KOH. After being heated under gentle reflux for 1 h, the mixture was concentrated, diluted with water, and acidified with HOAc, to give 1,3-dihydro-1-(2,2-dimethoxyethyl)-6-methoxy-2H-benzimidazole-2-thione (14c) as a white solid (2.0 g, 83%): mp 127-129 °C (from MeOH). ¹H NMR [(CD₃)₂SO]: δH 12.67 (br, 1H, NH), 7.07 (d, J 8.7 Hz, 1H, H-4), 6.99 (d, J 2.3 Hz, 1H, H-7), 6.78 (dd, J 8.6, 2.3 Hz, 1H, H-5), 4.78 (t, J 5.4 Hz, 1H, CHO₂), 4.30 (d, J 5.5 Hz, 2H, CH₂N), 3.78 (s, 3H, CH₃O), 3.31 (s, 6H, 2 x CH₃O). Anal. calcd for C₁₂H₁₆N₂O₅·0.75H₂O (281.84): C, 51.13; H, 6.33; N, 9.94. Found: C, 50.86; H, 5.77; N, 9.91.

A solution of 14c (1.34 g, 5 mmol) in 85% H₂SO₄ (50 mL) was heated at 100 °C for 30 min, cooled, and poured onto ice. The resulting aqueous solution was filtered through celite and made basic with aqueous ammonia, to give a precipitate, which was collected and dried. Chromatography on alumina, eluting with CH₂Cl₂/EtOAc (9:1) gave 15c as a white solid (0.37 g, 36%): mp 137-139 °C (from MeOH). ¹H NMR (CDCl₃): δH 7.67 (d, J 8.9 Hz, 1H, H-8), 7.62 (d, J 4.6 Hz, 1H, H-3), 7.14 (d, J 2.4 Hz, 1H, H-5), 7.01 (dd, J 8.9, 2.5 Hz, 1H, H-7), 6.79 (d, J 4.6 Hz, 1H, H-2), 3.90 (s, 3H, CH₃O). ¹³C NMR (CDCl₃): δC 155.6 (C), 155.4 (C), 143.1 (C), 130.0 (C), 120.0 (CH, C-8), 117.4 (CH, C-3), 112.8 (CH, C-7), 110.8 (CH, C-2), 94.5 (CH, C-5), 56.2 (CH₃O). MS m/z 205.1 (M+H)⁺. Anal. calcd for C₁₀H₈N₂O₅ (204.25): C, 58.80; H, 3.95; N, 13.72. Found: C, 58.98; H, 4.01; N, 13.86.
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8-Methoxythiazolo[3,2-α]benzimidazole (15d). A mixture of 3-fluoro-2-nitroanisole (3.42 g, 20 mmol) and 2,2-dimethoxyethylamine (8) (4.21 g, 40 mmol) in DMSO (20 mL) was heated at 60 °C for 6 h, cooled and diluted with water. Extraction with EtOAc gave N-(2,2-dimethoxyethyl)-3-methoxy-2-nitroaniline (13d) as red oil, which solidified on standing (4.85 g, 95%). mp 36-38 °C (from i-Pr2O). 1H NMR (CDCl3): δH 7.24 (t, J 8.4 Hz, 1H, H-5), 6.38 (d, J 8.5 Hz, 1H), 6.30 (d, J 8.3 Hz, 1H), 6.10 (br, 1H, NH), 4.56 (t, J 5.6 Hz, 1H, CHO2), 3.87 (s, 3H, CH3O), 3.42 (s, 6H, 2 x CH3O), 3.31 (t, J 5.5 Hz, 2H, CH2N). 13C NMR (CDCl3): δC 155.1 (C), 143.8 (C), 133.6 (CH, C-5), 128.2 (C), 105.4 (CH), 102.4 (CHO2), 100.3 (CH), 56.6 (CH3O), 54.3 (2 x CH3O), 45.3 (CH2). MS m/z 257.2 (M+H)+.

A solution of 13d (1.024 g, 4 mmol) in EtOH (50 mL) was hydrogenated over 5% Pd on C, and filtered through celite. CS2 (2 mL) and KOH (1.6 g in 10 mL H2O) were added and the mixture was heated under reflux for 4 h. The solution was concentrated, diluted with water and neutralized with HOAc to give 1-(2,2-dimethoxyethyl)-4-methoxy-1,3-dihydro-2H-benzimidazole-2-thione (14d) as a white solid (0.58 g, 54%). mp 179-181 °C (from aq. MeOH). 1H NMR (CDCl3): δH 12.99 (s, 1H, NH), 7.12 (t, J 8.1 Hz, 1H, H-6), 6.99 (d, J 7.9 Hz, 1H), 6.81 (d, J 8.1 Hz, 1H), 4.78 (t, J 5.5 Hz, 1H, CHO2), 4.28 (d, J 5.5 Hz, 2H, CH2N), 3.88 (s, 3H, CH3O), 3.28 (s, 6H, 2 x CH3O). 13C NMR (CDCl3): δC 168.1 (C), 143.9 (C), 134.4 (C), 123.0 (CH), 120.1 (C), 105.0 (CH), 103.3 (CHO2), 101.4 (CH), 55.8 (CH3O), 54.3 (2 x CH3O), 45.8 (CH2). MS m/z 269.1 (M+H)+.

A solution of 14d (0.268 g, 1 mmol) in a mixture of H2SO4 (45 g) and H2O (5 g) was heated at 100 °C for 30 min, and poured into ice-water. After neutralization with aq. NH3 the mixture was extracted with EtOAc to give 15d as a white solid (78 mg, 38%). mp (from aq. MeOH) 166-168 °C. 1H NMR (CDCl3): δH 7.64 (d, J 4.6 Hz, 1H, H-3), 7.26 (dd, J 8.1, 0.9 Hz, 1H), 7.18 (t, J 8.0 Hz, 1H, H-6), 6.81 (dd, J 8.0, 0.6 Hz, 1H), 6.80 (d, J 4.6 Hz, 1H, H-2), 4.05 (s, 3H, CH3O). 13C NMR (CDCl3): δC 155.4 (C), 150.9 (C), 138.7 (C), 130.9 (C), 121.8 (CH), 117.7 (CH-C3), 111.3 (CH, C-2), 104.4 (CH), 103.4 (CH), 56.1 (CH3O). HRMS (ESI): found m/z 205.0432 (M+H)+, calcd for C10H12N2OS: 205.0430.

8-Methylthiazolo[3,2-α]benzimidazole (15e). A mixture of 3-fluoro-2-nitrotoluene (3.10 g, 20 mmol) and 2,2-dimethoxyethylamine (8) (4.60 g, 44 mmol) in DMSO (10 mL) was heated at 100 °C overnight. Dilution with water and extraction with EtOAc gave N-(2,2-dimethoxyethyl)-3-methyl-2-nitroaniline (13e) as an orange oil which solidified on standing (4.82 g, 100%). mp (from i-Pr2O) 38-39 °C. 1H NMR (CDCl3): δH 7.22 (t, J 8.0 Hz, 1H, H-5), 6.67 (d, J 8.5 Hz, 1H), 6.56 (d, J 7.4 Hz, 1H), 6.48 (br, 1H, NH), 4.58 (t, J 5.6 Hz, 1H, CHO2), 3.43 (s, 6H, 2 x CH3O), 3.33 (t, J 5.5 Hz, 2H, CH2N), 2.46 (s, 3H, CH3). 13C NMR (CDCl3): δC 143.5 (C), 136.7 (C), 135.5 (C), 133.3 (CH), 119.8 (CH), 111.4 (CH), 102.4 (CHO2), 54.3 (CH3O), 45.3 (CH2), 21.3 (CH3). MS m/z 241.2 (M+H)+.

A solution of 13e (2.40 g, 1 mmol) in EtOH (50 mL) was hydrogenated over 5% Pd on C, and filtered through celite. CS2 (5 mL) and KOH (2.5 g in 10 mL H2O) were added and the mixture was heated under reflux for 3 h. The solution was concentrated, diluted with water abd neutralized with HOAc to give 1-(2,2-dimethoxyethyl)-4-methyl-1,3-dihydro-2H-benzimidazole-2-thione (14e) as a white solid (2.306 g, 91%). mp (from aq. MeOH) 171-174 °C. 1H NMR [(CD3)2SO]: δH 12.89 (s, 1H), 7.20 (d, J 8.0 Hz, 1H), 7.08 (t, J 7.8 Hz, 1H, H-6), 6.97 (d, J 7.5 Hz, 1H), 4.79 (t, J 5.5 Hz, 1H, CHO2), 4.30 (d, J 5.5 Hz, 2H, CH2N), 3.29 (s, 6H, 2 x CH3O), 2.39 (s, 3H, CH3). MS m/z 253.2 (M+H)+.

A solution of 14e (0.505 g, 0.2 mmol) in a mixture of H2SO4 (45 g) and H2O (5 g) was heated at 100 °C for 30 min, and poured into ice-water. After neutralization with aq. NH3 the mixture was extracted with EtOAc to give 15e as a white solid (0.318 g, 84%). mp (from aq. MeOH) 150-152 °C. 1H NMR (CDCl3): δH 7.64 (d, J 4.6 Hz, 1H, H-3), 7.48 (dd, J 6.8, 2.2 Hz, 1H, H-6), 7.19-7.14 (m, 2H, H-5, 7), 6.78 (d, J 4.6 Hz, 1H, H-2), 2.70 (s, 3H, CH3).
13C NMR (CDCl3): δC 156.2 (C), 147.8 (C), 129.4 (C), 129.3 (C), 124.1 (CH), 121.0 (CH), 117.8 (CH, C-3), 110.8 (CH, C-2), 107.9 (CH, C-6), 17.1 (CH3). HRMS (ESI): found m/z 189.0480 (M+H)+, calcd for C10H9N2S: 189.0481.

6-Hydroxythiazolo[3,2-α]benzimidazole (15f).23 A mixture of 6-methoxythiazolo[3,2-α]benzimidazole (0.23 g, 1.13 mmol) and BBr3 (1M in CH2Cl2, 4 mL, 4 mmol) in CH2Cl2 (20 mL) was heated under reflux for 6 h, and the solvent was removed. The residue was then mixed with ice-water, and neutralized with aqueous ammonia, to give 15f as a white solid (0.17 g, 79 %). mp 94 °C (from aq. MeOH) (lit.23 mp > 280 °C). 1H NMR [(CD3)2SO]: δH 9.39 (s, 1H, OH), 8.27 (d, J 4.6 Hz, 1H, H-3), 7.45 (d, J 8.7 Hz, 1H, H-8), 7.32 (d, J 2.3 Hz, 1H, H-5), 7.18 (d, J 4.6 Hz, 1H, H-2), 6.83 (dd, J 8.8, 2.4 Hz, 1H, H-7). 13C NMR [(CD3)2SO]: δC 154.1 (C), 152.3 (C), 141.3 (C), 130.0 (C), 119.1 (CH, C-3), 118.7 (CH, C-8), 112.8 (CH, C-7), 110.7 (CH, C-2), 97.0 (CH, C-5). Anal. calcd for C10H8N2OS (190.22): C, 56.83; H, 3.18; N, 14.73. Found: C, 56.73; H, 3.11; N, 14.85.

1,1-Dimethoxy-2-propylamine26 (16). A mixture of 1,1-dimethoxycacetone (23.6 g, 0.2 mol) and benzylamine (21.4 g, 0.2 mol) in toluene (100 mL) was heated under reflux with a Dean-Stark condenser until water evolution ceased. The toluene was removed under vacuum and the residue was dissolved in EtOH (100 mL). The solution was treated with NaBH4 (3.78 g, 0.1 mol) and the resulting mixture was heated under reflux for 30 min. After cooling, acetic acid was added to destroy excess NaBH4 and the solvent was removed under vacuum. The residue was made basic with aqueous ammonia, and extracted with CH2Cl2. Elution through alumina with CH2Cl2 gave N-benzyl-1,1-dimethoxy-2-propylamine25 as an oil (36.8 g, 88 %): 1H NMR (CDCl3): δH 7.34-7.30 (m, 4H, ArH), 7.26-7.21 (m, 1H, ArH), 4.14 (d, J 6.3 Hz, 1H, CHO2), 3.89 (d, J 13.1 Hz, 1H, benzyl CH), 3.70 (d, J 13.2 Hz, 1H, benzyl CH), 3.38 (s, 3H, CH3O), 3.35 (s, 3H, CH3O), 2.84 (pentet, J 6.3 Hz, 1H, CHN), 1.82 (br s, 1H, NH), 1.10 (d, J 6.5 Hz, 3H, CH3). 13C NMR (CDCl3): δC 140.4 (C), 128.4 (2 x CH), 128.1 (2 x CH), 126.8 (CH), 107.9 (CHO2), 54.7 (CH3O), 54.5 (CH3O), 53.5 (CHN), 51.1 (CH2N), 14.9 (CH3).

Hydrogenation of the above amine over 10% Pd on carbon in MeOH, gave 1,1-dimethoxy-2-propylamine26 (16) as an oil: 1H NMR (CDCl3): δH 3.98 (d, J 6.0 Hz, 1H, CHO2), 3.43 (s, 3H, CH3O), 3.40 (s, 3H, CH3O), 3.01 (pentet, J 6.4 Hz, 1H, CHN), 1.67 (s, 2H, NH2), 1.09 (d, J 6.6 Hz, 3H, CH3).

trans-7-Benzoyl-2-methoxy-3-methyl-2,3-dihydrothiazolo[3,2-α]benzimidazole (19). A mixture of 4-chloro-3-nitrobenzophenone (7d) (2.62 g, 10 mmol), (15.4 g, 13 mmol) and Et3N (2 mL) in DMSO (30 mL) was heated at 100 °C for 14 h. The mixture was diluted with water and acetic acid, and extracted into EtOAc. The organic layer was washed with aqueous Na2CO3 solution, dried, and the solvent was removed, to give (17) as a yellow solid (3.1 g, 90 %): mp 92-94 °C (from i-PrOH). 1H NMR [(CD3)2SO]: δH 8.57 (d, J 8.5 Hz, 1H, NH), 8.44 (d, J 2.1 Hz, 1H, H-2), 7.95 (dd, J 9.2, 2.0 Hz, 1H, H-6), 7.73-7.65 (m, 3H, H-2’,4’,6’), 7.57 (t, J 7.5 Hz, 2H, H-3’,5’), 7.33 (d, J 9.3 Hz, 1H, H-5), 4.49 (t, J 3.9 Hz, 1H, CHO2), 4.17 (m, 1H, CHN), 3.43 (s, 3H, CH3O), 3.42 (s, 3H, CH3O), 1.22 (d, J 6.6 Hz, 3H, CH3). Anal. calcd for C18H18N2O5 (344.37): C, 62.78; H, 5.85; N, 8.13. Found: C, 62.96; H, 6.12; N, 8.16.

A solution of (17) (3.0 g, 8.7 mmol) in 65 % aqueous EtOH was reduced with Fe powder as for the reduction of 9d, to give crude 3-amino-[N-(1,1-dimethoxy-2-propyl)amino]benzophenone (2.7 g). 1H NMR [(CD3)2SO]: δH 7.60-7.55 (m, 3H, H-2’,4’,6’), 7.49 (t, J 7.5 Hz, 2H, H-3’,5’), 7.12 (d, J 2.0 Hz, 1H, H-2), 6.98 (dd, J 8.3, 2.0 Hz, 1H, H-6), 6.57 (d, J 8.5 Hz, 1H, H-5), 5.08 (d, J 8.2 Hz, 1H, NH), 4.85 (br s, 2H, NH2), 4.32 (t, J 4.6 Hz, 1H, CHO2), 3.78-3.72 (m, 1H, CHN), 3.36 (s, 3H, CH3O), 3.34 (s, 3H, CH3O), 1.14 (d, J 6.5 Hz, 3H, CH3).

Crude diamino product was treated with an excess of CS2 and aqueous KOH in MeOH, as for the synthesis of 11d. After being heated under gentle reflux for 1 h, the reaction mixture was concentrated, diluted with
water, cooled, and acidified with acetic acid, to give an oil, which was extracted into EtOAc. Chromatography on silica, eluting with CH$_2$Cl$_2$/EtOAc (9:1), gave 5-benzoyl-1,3-dihydro-1-(1,1-dimethoxy-2-propyl)-2H-benimidazole-2-thione (18) (2.7 g, 87%): mp 151-152.5 °C (from aq. MeOH). $^1$H NMR [(CD$_3$)$_2$SO]: $\delta$H 13.10 (br s, 1H, NH), 7.79-7.72 (m, 3H, 3 x ArH), 7.68 (t, $J$ 7.4 Hz, 1H, ArH), 7.59-7.55 (m, 3H, 3 x ArH), 7.51 (d, $J$ 1.3 Hz, ArH), 5.42 (m, 1H, CHN), 4.38 (m, 1H, CH$_2$O), 3.41 (s, 3H, CH$_3$O), 3.21 (s, 3H, CH$_3$O), 1.48 (d, $J$ 5.5 Hz, 3H, CH$_3$). Anal. calcld for C$_{19}$H$_{20}$N$_2$O$_3$S: C, 64.02; H, 4.14; N, 9.58. Found: C, 64.16; H, 4.80; N, 9.64.

A solution of 18 (0.20 g, 0.56 mmol) in 90 % H$_2$SO$_4$ (10 mL) was heated at 100 °C for 5 min, cooled, and poured onto ice. The solution was made basic with conc. ammonia solution to give a white solid which was collected by filtration and recrystallized from aqueous MeOH to give 19: mp 136-137 °C. $^1$H NMR (CDCl$_3$): $\delta$H 8.06 (dd, $J$ 1.5, 0.5 Hz, 1H, H-8), 7.82-7.78 (m, 3H, H-6, 2’, 6’), 7.60-7.55 (m, 1H, H-4’), 7.50 (m, 2H, H-3’, 5’), 7.32 (dd, $J$ 8.4, 0.5 Hz, 1H, H-5), 5.56 (s, 1H, H-2), 4.80 (q, $J$ 6.8 Hz, 1H, H-3), 3.48 (s, 3H, CH$_3$O), 1.52 (d, $J$ 6.8 Hz, 3H, CH$_3$). $^{13}$C NMR (CDCl$_3$): $\delta$C 196.8 (CO), 157.7 (C), 148.6 (C), 138.5 (C), 136.1 (C), 132.2 (CH, C-4’), 131.8 (C), 130.2 (CH, C-2’, 6’), 128.4 (CH, C-3’, 5’), 124.7 (CH, C-6), 122.3 (CH, C-8), 108.5 (CH, C-5), 100.9 (CH, C-2), 59.7 (CH, C-3), 57.0 (CH$_3$O), 17.0 (CH$_3$). MS m/z 325.1 (M+H)$^+$. Anal. calcld for C$_{18}$H$_{16}$N$_2$O$_2$S (324.40): C, 66.65; H, 4.97; N, 8.64 Found: C, 67.02; H, 5.05; N, 8.74.

7-Benzoyl-3-methylthiazolo[3,2-$\alpha$]benzimidazole (20). A solution of 5-Benzoyl-1,3-dihydro-1-(1,1-dimethoxy-2-propyl)-2H-benimidazole-2-thione (18) (0.20 g, 0.56 mmol) in 90 % H$_2$SO$_4$ (10 mL) was heated at 100 °C for 3 h, cooled, and poured onto ice. After being made basic with conc. ammonia solution, the mixture was extracted with EtOAc. Chromatography on alumina, eluting with CH$_2$Cl$_2$ gave 7-benzoyl-3-methylthiazolo[3,2-$\alpha$]benzimidazole (20): mp 122-123.5 °C (from aq. MeOH). $^1$H NMR [(CD$_3$)$_2$SO]: $\delta$H 8.13 (d, $J$ 8.4 Hz, 1H, H-5), 8.01 (d, $J$ 1.4 Hz, 1H, H-8), 7.76-7.72 (d, $J$ 7.5 Hz, 2H, H-2’, 6’), 7.72-7.68 (m, 2H, H-6, H-6, 4’), 7.59 (br t, $J$ 7.5 Hz, 2H, H-3’, 5’), 6.97 (d, $J$ 1.3 Hz, 1H, H-2), 2.78 (d, $J$ 1.1 Hz, 3H, CH$_3$). $^{13}$C NMR [(CD$_3$)$_2$SO]: $\delta$C 195.5 (s, CO), 158.4 (C), 147.1 (C), 137.7 (C), 132.4 (C), 132.2 (CH), 131.7 (C), 130.1 (C), 129.5 (2 x CH), 128.4 (2 x CH), 121.9 (CH), 120.6 (CH), 111.4 (CH), 106.6 (CH), 13.7 (CH$_3$). Anal. calcld for C$_{17}$H$_{12}$N$_2$OS (292.36): C, 69.84; H, 4.14; N, 9.58. Found: C, 70.03; H, 3.99; N, 9.45.

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Supplementary Material

Copies of $^1$H NMR spectra are available in the supplementary material associated with this paper.

References
[https://doi.org/10.3987/REV-88-391](https://doi.org/10.3987/REV-88-391)

[https://doi.org/10.3390/molecules15063775](https://doi.org/10.3390/molecules15063775)

[https://doi.org/10.1021/jm00226a016](https://doi.org/10.1021/jm00226a016)

[https://doi.org/10.1124/jpet.105.087171](https://doi.org/10.1124/jpet.105.087171)

[https://doi.org/10.1139/v67-471](https://doi.org/10.1139/v67-471)


[https://doi.org/10.3987/COM-03-S(P)27](https://doi.org/10.3987/COM-03-S(P)27)


[https://doi.org/10.1002/adsc.201900909](https://doi.org/10.1002/adsc.201900909)

[https://doi.org/10.1039/C8CC09122F](https://doi.org/10.1039/C8CC09122F)

[https://doi.org/10.1002/adsc.201800393](https://doi.org/10.1002/adsc.201800393)

[https://doi.org/10.1021/acs.joc.7b00162](https://doi.org/10.1021/acs.joc.7b00162)

[https://doi.org/10.1002/ajoc.201600042](https://doi.org/10.1002/ajoc.201600042)

[https://doi.org/10.1016/j.tetlet.2014.04.070](https://doi.org/10.1016/j.tetlet.2014.04.070)

[https://doi.org/10.1039/c2ob26211h](https://doi.org/10.1039/c2ob26211h)


https://doi.org/10.1021/op400184f

https://doi.org/10.1021/jo00321a010