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TETRAHEDRON

Efficient Synthesis of N^1- or N^3- Substituted Thieno[2,3-*d*]imidazol-2-ones

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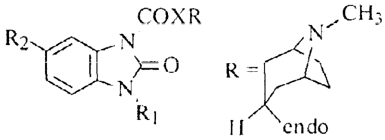
Abstract: - N^1- or N^3-substituted thieno[2,3-*d*]imidazol-2-one derivatives are selectively obtained after N-alkylation of thiaisatoic anhydrides followed by formation of the N-substituted aminocarbonyl azides and Curtius rearrangement. © 1999 Elsevier Science Ltd. All rights reserved.

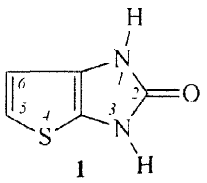
The benzimidazolone derivatives having the general formula :



$R_1 = C_2H_5$; $R_2 = H$; X = NH BIMU 1
$R_1 = iPr$; $R_2 = H$; X = NH BIMU 8
$R_1 = H$; $R_2 = H$; X = NH Itasetron (DAU 6215)
$R_1 = H$; $R_2 = OCH_3$; X = O DAU 6285

are potent and effective ligands of serotonin receptors and acting as either 5-HT$_3$ or 5-HT$_4$ agonists or antagonists[1-3]. Among them, the endo-azabicycloalkyl derivatives BIMU 1, BIMU 8, itasetron (DAU 6215), DAU 6285 are of interest as potential therapeutic agents.

As part of a medicinal chemistry research program aiming to study new thiophene bioisosteres of heterocyclic compounds of therapeutic interest[4,5], we report a new and efficient synthesis of thieno[2,3-*d*]imidazol-2-one **1** starting from thiaisatoic anhydrides **2** and **3**.



1

Compound **1** was previously prepared by Binder et al.[6] and Huddleston et al.[7] who subjected various aminothiophene carbonylazides to Curtius rearrangement. Huddleston et al. prepared 3-amino-2-thiophenecarbonylazide **4** from the corresponding carbonylhydrazide[7] and Binder et al. used only N-acylated aminocarbonylazides obtained from the corresponding carboxylic acids[6]. In these papers, thienoimidazolone **1** was only identified as a reaction product without study of its reactivity. Searching for a new direct methodology to

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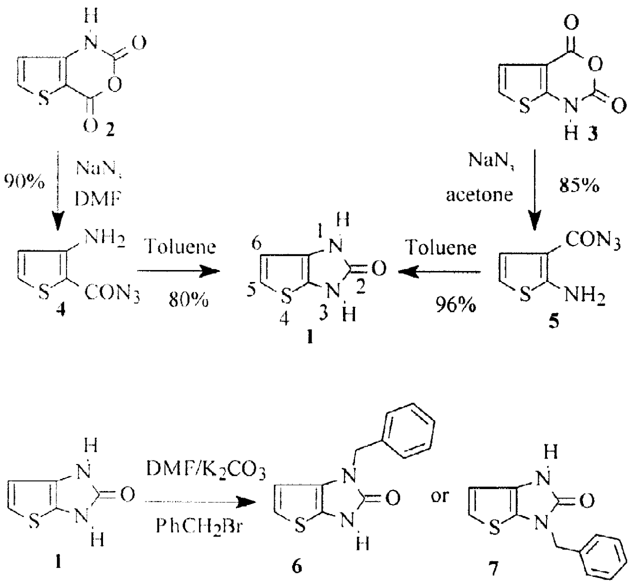
produce the unsubstituted *o*-aminothiophenecarbonylazides **4** and **5**, we found that treatment of thiaisatoic anhydride **2** (in DMF at 50°C) and **3** (in acetone at room temperature) with sodium azide led to the high yield formation of 3-amino-2-thiophenecarbonylazide **4** (90%) and 2-amino-3-thiophenecarbonylazide **5** (85%), respectively. These two compounds were then submitted to a Curtius rearrangement in refluxing toluene to give the identical product **1** in 80% and 96% yields, respectively (Scheme 1).



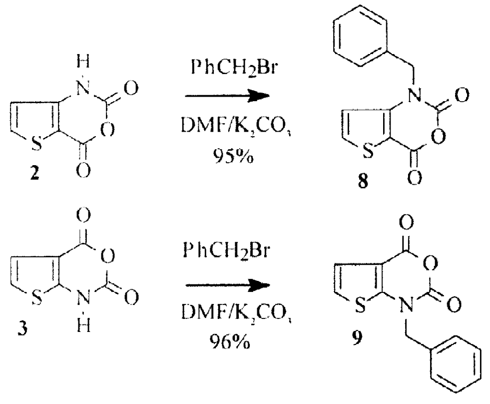
Scheme 1

Alkylation of **1** by treatment with benzyl bromide at room temperature in DMF gave a sole N-alkylated product whose structure could not be elucidated from analytical data. In order to determine whether N^1- or N^3-substitution had taken place, we developed unequivocal syntheses of the two positional isomers **6** and **7** from the corresponding anhydrides **2** and **3**, respectively.

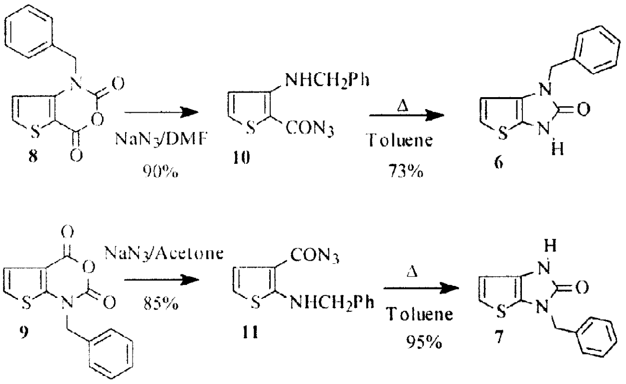
N-alkylation of anhydrides **2** and **3** were performed with benzyl bromide in DMF and led to the corresponding N-benzylated anhydrides **8** and **9** in high yields (Scheme 2). Treatment of **8** or **9**, respectively, with sodium azide as mentioned above gave the 3-benzylamino-2-thiophenecarbonylazide **10** or its isomer **11**. Subsequent Curtius rearrangement of these compounds led to 1-benzyl-thienoimidazolone **6** and 3-benzyl thienoimidazolone **7**, respectively, in 73 and 95% yield (Scheme 3).

Analytical data of **6** and **7** demonstrated that the product of alkylation of **1** with benzyl bromide was the 3-benzylthienoimidazolone **7**. The high regioselectivity of alkylation of the thienoimidazolone **1** could find an explanation in the proximity of the sulfur atom with the nitrogen atom in position 3. The electron inducting effect of the sulfur atom would increase the acidity of the proximal nitrogen atom thus driving the alkylation to the N^3 position.

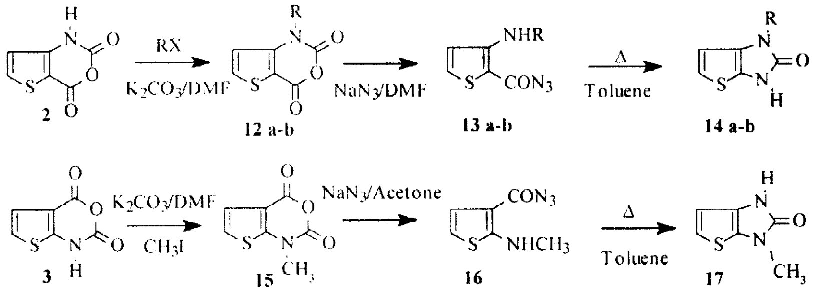
In the same way we synthesized N^1-methyl and N^1-ethyl thieno[2,3-*d*]imidazol-2-ones **14a-b** and N^3-methyl thieno[2,3-*d*]imidazol-2-one **17** (Scheme 4).



Scheme 2



Scheme 3



a: R=CH$_3$; b: R=C$_2$H$_5$

overall yields: **14a**: 44% ; **14b**: 21% ; **17**: 54%

Scheme 4

We have here described a facile synthesis of N^1- and N^3- substituted thieno[2,3-*d*]imidazol-2-ones in good yields. This work can allow the development of new strategies to prepare various thiophene derivatives with potential pharmacological interest. By this method, we are now studying the synthesis of substituted thienoimidazolones in order to prepare thia-analogues in the BIMU and DAU series.

EXPERIMENTAL SECTION

General. Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were taken with a Genesis Series FTIR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JEOL Lambda 400 spectrometer. Chemical shifts are expressed in parts per million downfield from TMS as the internal standard. Mass spectra (MS) were recorded on a JEOL JMS GCMate spectrometer at a ionizing potential of 70 eV. Elemental analyses were performed at the "Institut de Recherche en Chimie Organique Fine" (Rouen). Reaction times were monitored by thin-layer chromatography (TLC) until no starting material was observed. TLC were performed on 0.2-mm precoated plates of silica gel 60 F-264 (Merck). Visualization was made with ultraviolet light. All solvents and reagents were purchased from Acros and Aldrich Chimie and used without further purification.

2,3-dihydro-1H-thieno[2,3-d]imidazol-2-one (1). The azide **4** or **5** (2 g, 12 mmol) was dissolved in toluene (10 ml) and refluxed until starting material has disappeared (5 hours). The imidazolone crystallised on cooling and was collected by filtration. Yield : 80% from **4**, 96% from **5** (m.p. 256°C, Lit[6, 7]: 257 °C). IR (KBr, cm^{-1}) 3100-2750; 1708; 1652; 1261; 1099; 823; 729. ^{1}H NMR (DMSO-d$_6$) δ: 6.75 (d, 1H, 6-CH, *J*=5.1 Hz); 6.88 (d, 1H, 5-CH, *J*=5.1 Hz); 10.57 (s, 1H, NH); 10.66 (s, 1H, NH). ^{13}C NMR (DMSO-d$_6$) δ: 111.6; 114.8; 121.6; 127.3; 157.6.

1H-Thieno[3,2-d][1,3]oxazine-2,4-dione (2), 2-thiaisatoic anhydride and *1H-thieno[2,3-d][1,3]oxazine-2,4-dione (3), 3-thiaisatoic anhydride* were prepared from methyl 3-aminothiophene-2-carboxylate and ethyl 2-aminothiophene-3-carboxylate as described[5], or obtained from Syntheval SA, Caen-France.

3-aminothiophene-2-carbonylazide (4). 2-Thiaisatoic anhydride **2** (5 g, 30 mmol) was dissolved in DMF (100 ml), sodium azide (2.9 g, 45 mmol) was added to the solution and the reaction mixture was heated at 50°C for two hours. After cooling, the solution was poured in water and extracted twice with diethyl ether. The organic layer was washed with water, dried with $MgSO_4$, treated with charcoal and evaporated to dryness to give **4** as a pale yellow powder (4.4 g, 90%, m.p. 126 °C). The azide **4** was used without further purification. IR (cm^{-1}) 3436; 3328; 2127; 1630. ^{1}H NMR (DMSO-d6) δ: 6.62 (d, 1H, 4-CH, *J*=5.3 Hz); 7.07 (broad, 2H, NH_2); 7.64 (d, 1H, 5-CH, *J*=5.3 Hz).

2-aminothiophene-3-carbonylazide (5). 3-Thiaisatoic anhydride **3** (5 g, 30 mmol) was dissolved in acetone. Sodium azide (3.9 g, 60 mmol) in minimum water was then added to the solution. After 1 hour at room temperature, the solvent was evaporated in *vacuo* and the residue was treated with water (50 ml). The precipitate was filtered, washed with diethyl ether (10 ml) and dried to give **5** (4.2 g, 85%, m.p. 158 °C). **5** was used without further purification. IR (cm^{-1}) 3420; 3320; 2130; 1688. ^{1}H NMR ($CDCl_3$) δ: 6.15 (d, 1H, *J*=5.8 Hz); 6.34 (broad, 2H, NH_2); 6.85 (d, 1H, *J*=5.8 Hz).

1-benzyl-2,3-dihydro-1H-thieno[2,3-d]imidazol-2-one (6). Using the same procedure as described for **1**, starting from azide **10** (2 g, 7.8 mmol) and heating for 5 hours, the imidazolone **6** crystallised on cooling. **6** was filtered and washed with diethyl ether (1.3 g, 73%, m.p. 200 °C (ethyl acetate / n-hexane)). IR (cm^{-1}) 3110, 3025, 1670, 1505, 1384, 1074, 735. ^{1}H NMR (DMSO-d_6) δ 4.32 (s, 2H); 6.78 (d, 1H, *J*=5.2 Hz); 6.90 (d, 1H, *J*=5.2 Hz); 7.24-7.31 (m, 5H); 11.00 (broad, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 45.1; 111.3; 115.2; 120.4; 127.5; 127.7; 128.6; 128.8; 137.5; 156.3. Anal. Calcd for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16. Found: C, 62.21; H, 4.25; N, 11.92.

3-benzyl-2,3-dihydro-1H-thieno[2,3-d]imidazol-2-one (7). In the same way as described for **6**, **7** was obtained from azide (**11**) (0.75 g, 2.9 mmol) by refluxing in toluene (7 ml) for 5 hours. Filtration gave **7**: (0.64 g, 95%, m.p. 186 °C (2-PrOH)). IR (cm^{-1}) 3120, 1673, 1453, 1359, 1088, 823, 722. ^{1}H NMR ($CDCl_3$) δ 4.88 (s, 2H); 6.79 (d, 1H, *J*=5 Hz); 6.88 (d, 1H, *J*=5 Hz); 7.30-7.37 (m, 5H); 10.92 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 45.7; 111.6; 115.7; 122.9; 125.6; 127.8; 128.1; 128.7; 136.1; 156.2. Anal. Calcd for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16. Found: C, 62.74; H, 4.35; N, 12.24.

1-benzyl-1H-thieno[3,2-d][1,3]oxazine-2,4-dione (8). 2-Thiaisatoic anhydride **2** (10 g, 59 mmol) was dissolved in DMF (60 ml), K_2CO_3 (10 g, 72 mmol) and benzyl bromide (7 ml, 60 mmol) were added. The mixture was allowed to stand at room temperature for 30 min and poured in water to give a white precipitate. It was filtered, washed with water and diethyl ether to give **8**. (14 g, 91%, m.p. 160 °C (ethyl acetate/n-hexane)). IR (cm^{-1}) 3119, 1763, 1716, 1562, 1475, 989, 766. ^{1}H NMR (DMSO-d_6) δ: 5.19 (s, 2H), 7.23 (d, 1H, *J*=5.3 Hz), 7.28-7.39 (m, 5H), 8.26 (d, 1H, *J*=5.3 Hz). ^{13}C NMR (DMSO-d_6) δ: 49.5, 107.5, 117.8, 127.1, 127.7, 128.7, 135.4, 139.9, 149.3, 149.7, 154.3; Anal. Calcd for $C_{13}H_9NO_3S$: C, 60.22; H, 3.50; N, 5.40. Found: C, 59.93; H, 3.42; N, 5.72.

1-benzyl-1H-thieno[2,3-d][1,3]oxazine-2,4-dione (9). The procedure was the same as described for **8**, starting from the anhydride **3** (10 g, 59 mmol). Yield (14.7 g, 96%, m.p. 142 °C). IR (cm^{-1}) 1791, 1721, 1548, 1504, 1273. ^{1}H NMR (DMSO-d_6) δ: 5.12 (s, 2H); 7.21 (d, 1H, *J*=5.6 Hz); 7.26 (d, 1H, *J*=5.6 Hz); 7.29-7.44 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 51.7; 111.1; 119.5; 123.3; 127.5; 128.1; 128.7; 133.9; 148.4; 154.2; 157.1; Anal. Calcd for $C_{13}H_9NO_3S$: C, 60.22; H, 3.50; N, 5.40. Found: C, 60.35; H, 3.52; N, 5.55.

3-benzylaminothiophene-2-carbonylazide (10). A mixture of **8** (5 g, 19.4 mmol) and sodium azide (2.5 g 39 mmol) was heated in DMF (50 ml) at 55 °C for two hours. Water was then added to the reaction mixture until a precipitate formed. The mixture was extracted twice with diethyl ether. The organic layer was washed twice with water and evaporated to dryness to give **10** as a pale yellow powder. (4.5 g, 90% m.p. 110 °C). **10** was used without further purification. IR (cm^{-1}) 3375, 2156, 1638, 1393, 1263, 934, 761, 669. ^1H NMR ($CDCl_3$) δ: 4.59 (d, 2H, *J*=6 Hz); 6.83 (d, 1H, *J*=5.5 Hz); 7.36 (m, 5H); 7.78 (d, 1H, *J*=5.5 Hz); 7.91 (broad, 1H, NH).

2-benzylaminothiophene-3-carbonylazide (11). Compound **9** (1 g, 3.9 mmol) was dissolved in acetone (10 ml) and sodium azide (0.5 g, 7.8 mmol) dissolved in minimum water was added. The mixture was stirred at room temperature for one hour. Acetone was evaporated under reduced pressure and the residue taken up in water. The precipitate was filtered and dried. **11** was used without further purification. (0.85 g, 85%, m.p. 106 °C). IR (cm^{-1}) 3345, 1632, 1540, 1517, 1393,1225, 1071, 682. ^1H NMR (DMSO-d_6) δ 4.48 (d, 2H, *J*=6 Hz); 6.35 (d, 1H, *J*=5.8 Hz); 6.81 (d, 1H, *J*=5.8 Hz); 7.25-7.34 (m, 5H); 8.71 (t, 1H, NH, *J*=6 Hz).

1-methylthieno[3,2-d][1,3]oxazine-2,4-dione (12a). In the same way as described for **8**, starting from **2** (5 g, 30 mmol) in DMF (20ml), methyl iodide (2.8 ml; 45 mmol) and K_2CO_3 (4.9 g, 36 mmol) were added and the mixture was stirred at room temperature for 30 min. After dilution with water until a precipitate formed, filtration gave **12a**: (4.5 g, 83%, m.p. 189 °C (ethyl acetate / n-hexane)). IR (cm^{-1}) 3102, 1763, 1723, 1707, 1565, 1480, 1015, 776. ^1H NMR (DMSO-d_6) δ 3.45 (s, 3H); 7.33 (d, 1H, *J*=5.3 Hz); 8.31 (d, 1H, *J*=5.3 Hz). ^{13}C NMR (DMSO-d_6) δ 33.6; 106.7; 117.8; 139.8; 149.0; 150.6; 154.5. Anal. Calcd for $C_7H_5NO_3S$: C, 45.90; H, 2.75; N, 7.65. Found: C, 45.72; H, 2.87; N, 7.68.

1-ethylthieno[3,2-d][1,3]oxazine-2,4-dione (12b). In the same way as described for **8**, starting from **2** (10 g, 59 mmol) in DMF (50ml), ethyl iodide (4.8 ml; 120 mmol) and K_2CO_3 (9.9 g, 72 mmol) were added and the mixture was stirred at room temperature for 2 hours. After dilution with water, filtration gave **12b** (6.75 g, 58%, m.p. 156 °C (ethyl acetate / n-hexane)) IR (cm^{-1}) 3101, 1760, 1710, 1563, 1474, 1279, 1097, 983, 773. ^1H NMR (DMSO-d_6) δ 1.21 (t, 3H, *J*=7 Hz); 3.98 (q, 2H, *J*=7 Hz); 7.38 (d, 1H, *J*=5.3 Hz); 8.33(d, 1H, *J*=5.3 Hz). ^{13}C NMR (DMSO-d_6) δ 12.6; 42.0; 107.1; 117.5; 140.0; 148.6; 149.6; 154.5. Anal. Calcd for $C_{12}H_{10}N_2OS$: C, 45.90; H, 2.75; N, 7.65. Found: C, 45.72; H, 2.87; N, 7.68.

3-methylaminothiophene-2-carbonylazide (13a). In the same way as described for **10**, starting from **12a** (2.5 g, 14 mmol) in DMF (40ml). sodium azide (1.33 g, 20 mmol) was added and the mixture was stirred at 50 °C for 3 hours. Extraction gave **13a** (2 g, 80%, m.p. 97 °C) and was used without further purification. IR

(KBr, cm^{-1}) 3380, 2121, 1628, 1569, 1383, 1227, 995, 760. ^{1}H NMR (CDCl$_3$) δ 2.95 (d, 3H, *J*=5.1 Hz); 6.55 (d, 1H, *J*=5.5 Hz); 7.10 (broad, 1H, NH); 7.34 (d, 1H, *J*=5.5 Hz).

3-ethylaminothiophene-2-carbonylazide (13b). In the same way as described for **10, starting from 12b** (1 g, 5.1 mmol) in DMF (20 ml), sodium azide (0.49 g, 7.6 mmol) was added and the mixture was stirred at 50°C for 3 hours. Extraction gave **13b** (0.57g, 57%, oil) and was used without further purification. IR (cm^{-1}) 3358, 2972, 2128, 1634, 1567, 1395, 1226, 955, 762. ^{1}H NMR (CDCl$_3$) δ 1.28 (t, 3H, *J*=7.2 Hz); 3.34 (q, 2H, *J*=7.2 Hz), 6.61 (d, 1H, *J*=5.5 Hz); 7.19 (broad, 1H, NH); 7.39 (d, 1H, *J*=5.5 Hz).

1-methyl-2,3-dihydro-1H-thieno[2,3-d]imidazol-2-one (14a). In the same way as described for **1**, starting from the azide **(13a)** (2 g, 11 mmol) gave the crystalline imidazolone on cooling. Recrystallisation from ethyl acetate/n-hexane gave **14a** (1.1 g, 65%, m.p. 202 °C). IR (cm^{-1}) 3116, 1673, 1431, 1382, 1073, 999, 735, 616. ^{1}H NMR (DMSO-d$_6$) δ 3.26 (s, 3H); 6.94 (s, 2H), 10.84 (s, 1H, NH). ^{13}C NMR (DMSO-d$_6$) δ 28.4; 111.1; 115.0; 119.9; 129.9; 156.5. Anal. Calcd for $C_6H_6N_2OS$: C, 46.74; H, 3.92; N, 18.17. Found: C, 47.16; H, 3.86; N, 17.83.

1-ethyl-2,3-dihydro-1H-thieno[2,3-d]imidazol-2-one (14b). The azide **13b** (0.57 g, 2.9 mmol) was dissolved in toluene (7 ml) and the mixture was refluxing for 5 hours. Toluene was evaporated under reduced pressure and the residue triturated in petroleum ether (30ml). After filtration, recrystallisation from ethyle acetate/n-hexane gave **14b** (0.32g, 65%, m.p. 120°C). IR (cm^{-1}) 3121, 2970, 1669, 1505, 1377, 1076, 897, 739, 614. ^{1}H NMR (DMSO-d$_6$) δ 1.21 (t, 3H, *J*=7.2 Hz); 3.75 (q, 2H, *J*=7.2 Hz), 6.91 (d, 1H, *J*=5.2 Hz); 6.94 (d, 1H, *J*=5.2 Hz); 10.80 (s, 1H, NH). ^{13}C NMR (DMSO-d$_6$) δ 14.1; 36.4; 111.0; 114.8; 120.2; 128.6; 155.8. Anal. Calcd for $C_7H_8N_2OS$: C, 49.98; H, 4.79; N, 16.65. Found: C, 50.12; H, 4.87; N, 16.68.

1-methyl-1H-thieno[2,3-d][1,3]oxazine-2,4-dione (15). In the same way as described for **8**, starting from anhydride **3** (5g, 30mmol) in DMF (30ml), methyl iodide (1.9 ml, 30 mmol) was added and the mixture was stirred at room temperature for 1 hour. After dilution with water until a precipitate formed, filtration gave **15** (4.1 g, 76%, m.p. 190 °C). IR (cm^{-1}) 3107; 1771; 1731; 1548, 1506, 1290. ^{1}H NMR (CDCl$_3$) δ 3.58 (s, 3H); 6.94 (d, 1H, *J*=5.7 Hz); 7.33 (d, 1H, *J*=5.7 Hz). ^{13}C NMR (CDCl$_3$) δ 35.3; 111.0; 117.5; 124.9; 148.1; 153.8; 157.8. Anal. Calcd for $C_7H_5NO_3S$: C, 45.90; H, 2.75; N, 7.65. Found: C, 45.72; H, 2.87; N, 7.68.

2-methylaminothiophene-3-carbonylazide (16). Using the same procedure as for **11**, starting from **16** (5 g, 27 mmol) in acetone (50ml) gave azide **16** (4.2 g, 85%, m.p. 103 °C) IR (cm^{-1}) 3356; 2145; 1631; 1552;

1516; 1390; 1231; 1061; 682. ^{1}H NMR ($CDCl_3$) δ 3.06 (d, 3H, *J*=5.1 Hz); 6.15 (d, 1H, *J*=5.8 Hz); 6.91 (d, 1H, *J*=5.8 Hz); 7.88 (broad, 1H, NH).

3-methyl-2,3-dihydro-1H-thieno[2,3-d]imidazol-2-one (17). Using the same procedure as described for **7**, starting from azide **16** (5 g, 27 mmol) gave **17** which crystallised on cooling. Filtration and washing with diethyl ether gave **17** (84% yield; m.p. 200 °C). IR (cm^{-1}) 3116; 1680. ^{1}H NMR ($CDCl_3$) δ 3.44 (s, 3H, CH_3); 6.83 (dd, 2H, HC=CH, *J*=5 Hz); 10.83 (broad, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 29.3; 112.1; 114.9; 125.4; 125.5; 157.8. Anal. Calcd for $C_6H_6N_2OS$: C, 46.74; H, 3.92; N, 18.17. Found: C, 47.03; H, 3.94; N, 18.23.

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