Studying the Synthesis of 4-*tert*-Butyl-1,3-dihydroimidazol-2-ones and Their Corresponding Thiones

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4-*tert*-Butyl-1,3-dihydroimidazol-2-ones and 1,3-dihydroimidazol-2-thiones were synthesized from 1-amino-3,3-dimethylbutanone and subjected to alkylation reactions. The latter compounds were S-alkylated with iodoacetamide under alkaline conditions. The N^1,N^3-unsubstituted derivative was iodinated and subsequently alkylated with alkylation reagents which previously have been used for the synthesis of anti-HIV active imidazoles. Unfortunately, the present products were devoid of activity against HIV.

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1,3-Dihydroimidazol-2-ones are used as cardiotonic agents [1-4] and 1-substituted 1,3-dihydroimidazole-2-thione derivatives are used for the treatment of thyroid disorder [5], arthritis [6,7] and cardiovascular disorders [8,9]. 1-Substituted 1*H*-imidazole derivatives are used as HIV-1 reverse transcriptase inhibitors [10,11]. In addition, anti-inflammatory activities [12] and, more recently, antioxidant properties [13] have been reported as well. In the present report, we are exploring the chemistry of *tert*-butyl substituted imidazoles which could be possible intermediates for the synthesis of imidazole derivatives with potential activity against HIV. We found *tert*-butyl derivatives interesting because an ethyl or an isopropyl group seems to be a prerequisite for activity against HIV of both AG1549 (5-(3,5-dichlorophenyl)thio-4-isopropyl-1-(4-pyridyl)methyl-1*H*-imidazol-2-ylmethyl carbamate) [11] and in SJ-3366 (1-(3-cyclopenten-1-yl)-methyl-6-(3,5-dimethylbenzoyl)-5-ethyl-2,4-pyrimidinedione) [14].

α-Aminoketone hydrochlorides were heated with potassium cyanate to give 4-alkyl-1,3-dihydroimidazol-2-ones **1a,b** as previously described by Lawson [15] for **1a** and by Jackman *et al* [16] for **1b**. Compound **1b** was silylated by the action of *N*,*O*-bis-(trimethylsilyl)acetamide (BSA) and followed by N^3-alkylation of **1b** with ethoxymethyl chloride to afford monoalkylated imidazolone **2** and dialkylated imidazolone **3**. The silylation step induced protection at the N^1 position of **1b** rather than N^3 due to steric hindrance of the *tert*-butyl group. In this way the lone pair at N^3 of **1b** was available for attack on the alkylating reagent. An alternative explanation for the formation of **2** could be *via* dealkylation of **3** at the least hindered site (Scheme 1). Assignment of the structure of compound **2** was confirmed by NOE. Irradiation of NCH_2O showed 4.7% NOE in $(CH_3)_3C$, and no NOE in H-4 was observed.

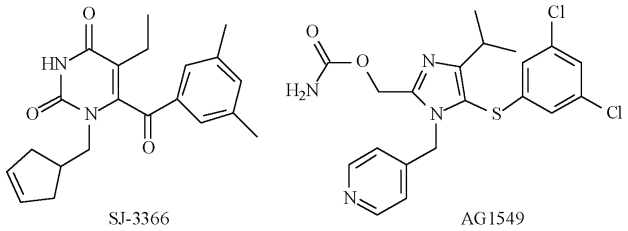
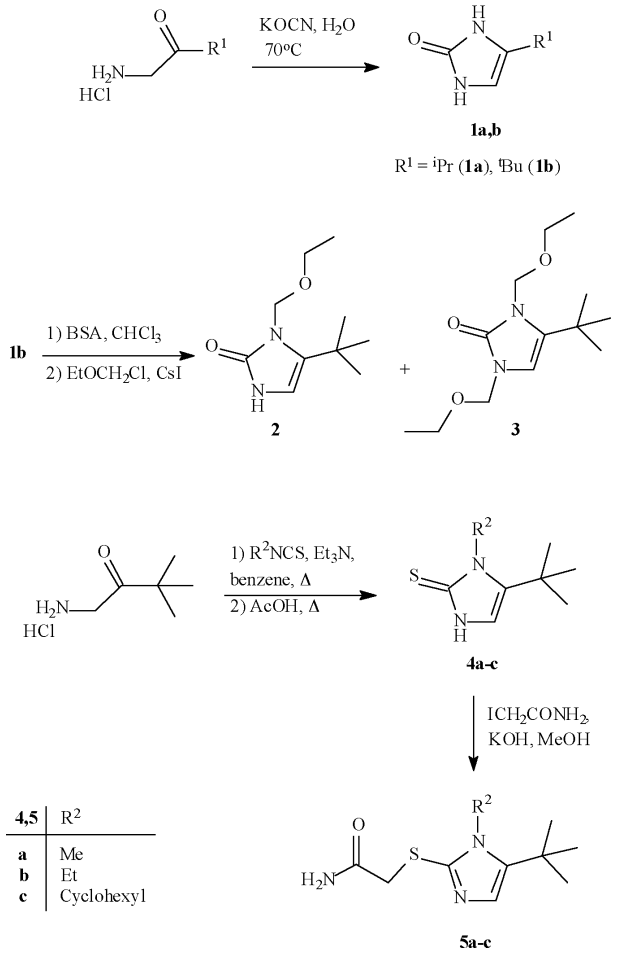


Figure 1. Chemical Structure of SJ-3366 and AGI 549.

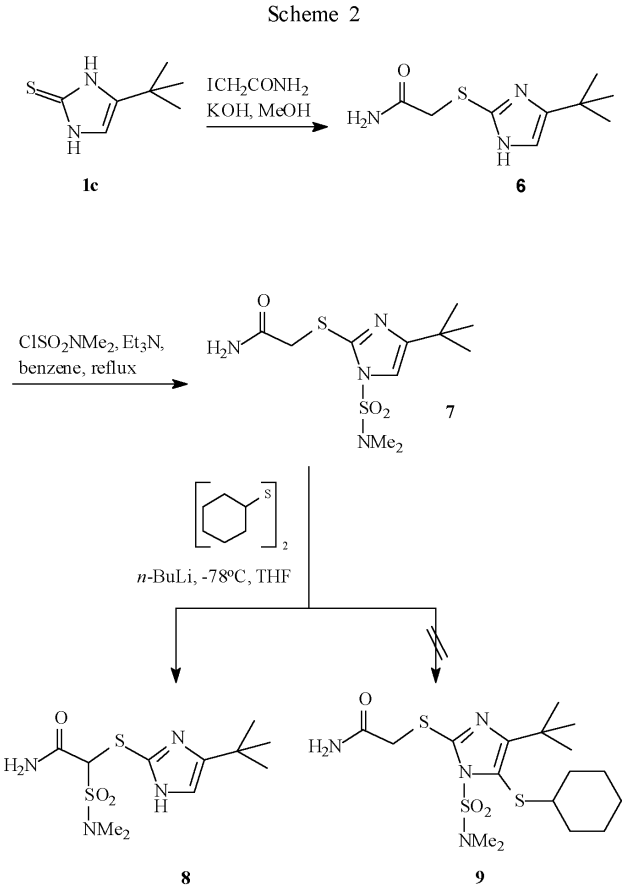
1-Alkyl-5-*tert*-butyl-1,3-dihydroimidazole-2-thiones **4a-c** were obtained by condensation of 1-amino-3,3-dimethylbutan-2-one hydrochloride with aliphatic isothiocyanate derivatives (methyl, ethyl, and cyclohexyl, respectively). Compound **4a** has previously been prepared by Doney and Altland [17] by the same synthetic procedure. The potassium salt of compounds **4a-c** were treated with 2-iodoacetamide to afford 2-(1-alkyl-5-*tert*-butyl-1*H*-imidazol-2-ylsulfanyl)acetamides **5a-c** (Scheme 1). This is an effective way to prepare N^1,S-dialkylated-1*H*-dihydroimidazol-2-thiones **5a-c** which have a substituent in the 2-position with some resemblance to the one in AG1549.

2-[(4-*tert*-Butyl-1*H*-imidazol-2-yl)thio]acetamide **6** was synthesized by reaction of the potassium salt of the commercial available 4-*tert*-butyl-1,3-dihydroimidazole-2-thione **1c** with 2-iodoacetamide in methanol. Compound **6** was coupled with dimethylsulfamoyl chloride to get 2-[(4-*tert*-butyl-1-dimethylsulfamoyl-1*H*-imidazol-2-yl)thio]acetamide **7**. It was attempted to introduce a cyclohexylthio substituent to the 5-position of **7** by lithiation with *n*-butyl lithium at –78° followed by addition of cyclohexyl disulfide. However, the product was elucidated to be

Scheme 1



Scheme 2



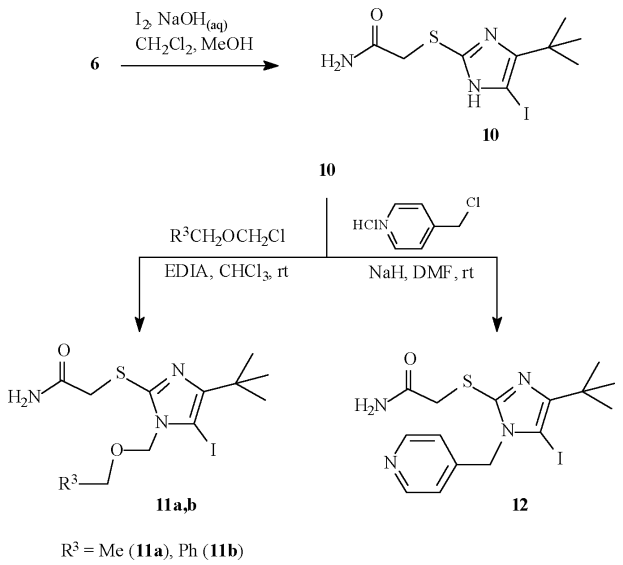
2-[(4-*tert*-butyl-1*H*-imidazol-2-yl)thio]-2-dimethylsulfamoylacetamide **8** and not the desired 2-[(4-*tert*-butyl-5-cyclohexylsulfanyl-1-dimethylsulfamoyl-1*H*-imidazol-2-yl)thio]acetamide **9** (Scheme 2). Both tautomers of compound **8** were observed in ^{1}H-nmr and ^{13}C-nmr where double signals were observed for nearly all the atoms. In all other cases with tautomeric structures in this investigation, the tautomerisation in the imidazole ring resulted in line broadening and/or disappearance of imidazole carbons in ^{13}C-nmr.

Phase transfer iodination of compound **6** by treatment with a mixture of methylene chloride, aqueous sodium hydroxide and methanol followed by addition of iodine solution in methanol and methylene chloride afforded 2-[(4-*tert*-butyl-5-iodo-1*H*-imidazol-2-yl)thio]acetamide (**10**). Coupling of compound **10** with ethoxy (or benzyloxy) methyl chloride in the presence of *N*-ethyldiisopropylamine (EDIA) as a bulky base gave N^{1} substituted 2-[(4-*tert*-butyl-5-iodo-1*H*-imidazol-2-yl)thio]acetamides **11a,b** as the sole product due to steric hindrance of the *tert*-butyl group. Formation of sodium salt of compound **10** was obtained by its treatment with sodium hydride in anhydrous dimethylformamide under ice cooling. By portionwise addition of 4-pyridylmethyl chloride hydrochloride to the salt of **10**, 2-[(4-*tert*-butyl-5-iodo-1-(pyridin-4-ylmethyl)-1*H*-imidazol-2-yl)thio]acetamide (**12**) was formed (Scheme 3). It was clear that steric hindrance of the *tert*-butyl group at the 4-position inhibited coupling at the 3-position of the imidazole ring

The sodium salt of 3,5-dimethylthiophenol was treated with compound **11b** in dimethylformamide in order to introduce the 3,5-dimethylphenylthio group in the 5-position of the imidazole ring. The products separated from the reaction mixture using column chromatography were elucidated to be 2-[(1-benzyloxymethyl-4-*tert*-butyl-1*H*-imidazol-2-yl)thio]acetamide (**13**), 1-benzyloxymethyl-4-*tert*-butyl-1,3-dihydroimidazole-2-thione (**14**), and 2,2-bis-(3,5-dimethylphenylthio)acetamide (**15**) and not the desired substitution product (Scheme 4).

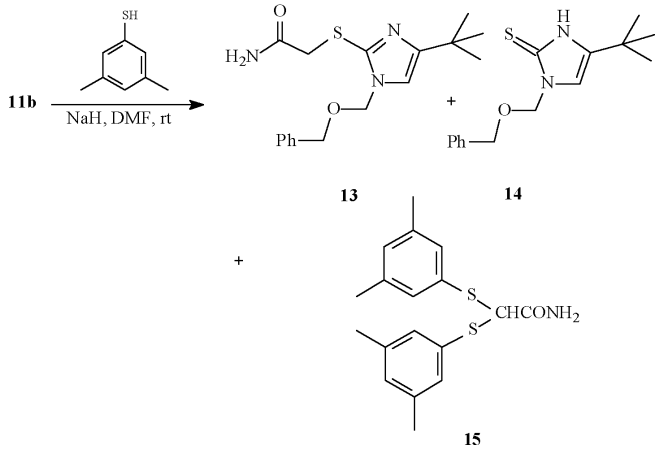
It is believed that a deiodination reaction of **11b** takes place by a nucleophilic attack of sulfide on iodine forming a 3,5-dimethylphenyl sulfenyliodide that in turn is believed to be an iodination reagent. Iodination can then take place in the α-position of the acetamide side chain

Scheme 3



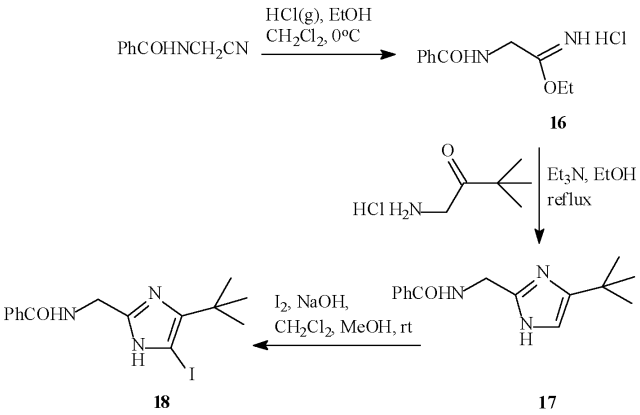
because an anion here easily can be formed due to the neighboring sulfur atom. A series of subsequent reaction will then lead to the main compound **15**.

Scheme 4



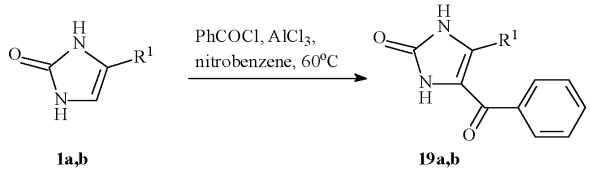
Benzoylaminoacetonitrile was prepared by treatment of aminoacetonitrile with benzoyl chloride in pyridine under ice cooling as described by Goldberg and Kelly [18]. Benzoylaminoacetonitrile was converted to ethyl 2-benzoylaminoacetamidate hydrochloride (**16**) by passing hydrogen chloride gas through a solution of benzoylaminoacetonitrile and absolute ethanol in methylene chloride under ice cooling [19]. Refluxing compound **16** with 1-amino-3,3-dimethylbutan-2-one hydrochloride and triethylamine in ethanol afforded *N*-(4-*tert*-butyl-1*H*-imidazol-2-ylmethyl)benzamide (**17**). Phase transfer iodination of compound **17** furnished *N*-(4-*tert*-butyl-5-iodo-1*H*-imidazol-2-ylmethyl)benzamide (**18**). Lithiation of compound **18** by *n*-butyl lithium at –78° followed by addition of cyclohexyl disulfide was tried, but the isolated product was compound **17** (Scheme 5).

Scheme 5



4-Alkyl-1,3-dihydroimidazol-2-ones **1a,b** were acylated by benzoyl chloride under the Friedel-Crafts conditions using nitrobenzene as a solvent and aluminum chloride as a catalyst to furnish 5-alkyl-4-benzoyl-1,3-dihydroimidazol-2-ones **19a,b** (Scheme 6). The yield of the reaction in the case of isopropyl group was higher than that of *tert*-butyl group due to the steric hindrance of the *tert*-butyl group. This seems so far to be the only route for synthesizing 4-*tert*-butyl substituted imidazole derivatives with an aryl containing substituent in the 5-position. Further work is progress of utilizing such compounds as intermediates in the synthesis of potential anti-HIV compounds.

Scheme 6



The test for activity against HIV-1 was performed in MT4 cell cultures infected with wild type HIV-1 (strain IIIB) using the assay as previously described [20]. The compounds were inactive at 100μM or inactive at subtoxic concentrations.

EXPERIMENTAL

NMR spectra were recorded on a Varian Gemini 2000 NMR spectrometer at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C with TMS as an internal standard. EI mass spectra were recorded on a Finnigan MAT SSQ 710. The progress of the reactions was monitored by TLC (analytical silica gel plates $60F_{254}$). The silica gel (0.040x0.063 mm) used for column chromatography was purchased from Merck. Microanalyses were carried out at Microanalytical Department, Chemical Laboratory II at the University of Copenhagen, Denmark.

5-*tert*-Butyl-1-ethoxymethyl-1,3-dihydroimidazol-2-one (**2**) and 4-*tert*-Butyl-1,3-bis(ethoxymethyl)-1,3-dihydroimidazol-2-one (**3**).

To a solution of compound **1b** (0.7 g, 5 mmoles) in chloroform (20 ml) under nitrogen atmosphere, was added *N,O*-bis-(trimethylsilyl)acetamide (4.3 ml, 17.5 mmoles). The mixture was stirred at room temp. for 0.5 hour, then ethoxymethyl chloride (0.7 ml, 7.5 mmoles) and cesium iodide (2 g, 7.5 mmoles) were added dropwise and the mixture was stirred for 3 hours. The reaction was quenched by addition of a saturated solution of sodium carbonate (10 ml), the mixture was filtered, the two layers were separated and the aqueous phase was further extracted with chloroform (20 ml). The chloroform phases were dried with sodium sulfate and the solvent was removed under reduced pressure. The residual products were chromatographed on a column of silica gel with methanol:chloroform (1:10, v/v) to afford compounds **2** and **3**.

5-*tert*-Butyl-1-ethoxymethyl-1,3-dihydroimidazol-2-one (**2**).

The compound was obtained as white crystals. Yield 0.08 g (8%); mp 83–84°; ^{1}H-nmr ($CDCl_3$): δ 1.12 (t, 3H, CH_3CH$_2$, *J* = 7.1 Hz), 1.23 (s, 9H, $(CH_3)_3C$), 3.54 (q, 2H, CH_3CH_2, *J* = 7.1 Hz), 5.17 (s, 2H, NCH_2O), 5.92 (s, 1H, H-4), 10.41 (brs, 1H, NH); ^{13}C-nmr ($CDCl_3$): δ 14.97 (CH_3CH_2), 29.58 ($(CH_3)_3C$), 31.15 ($(CH_3)_3C$), 63.66 (CH_3CH_2O), 71.14 (NCH_2O), 103.68 (C-4), 132.61 (C-5),156.56 (C-2); EI MS: *m/z* 198 (M^+).

4-*tert*-Butyl-1,3-bis(ethoxymethyl)-1,3-dihydroimidazol-2-one (**3**).

The compound was obtained as an oil. Yield 0.2 g (15%); ^{1}H-nmr ($CDCl_3$): δ 1.17–1.25 (m, 6H, 2 × CH_3CH$_2$O), 1.32 (s, 9H, $(CH_3)_3C$), 3.54–3.65 (m, 4H, 2 × CH_3CH_2O) 5.01 (NCH_2O), 5.25 (NCH_2O), 6.08 (s, 1H, H-5); ^{13}C-nmr ($CDCl_3$): δ 14.85 (CH_3CH_2O), 14.95 (CH_3CH_2O), 29.50 ($(CH_3)_3C$), 31.20 ($(CH_3)_3C$), 63.86 (CH_3CH_2O), 64.24 (CH_3CH_2O), 71.52 (NCH_2O), 72.72 (NCH_2O), 105.49 (C-5), 132.78 (C-5), 156.28 (C-2); EI MS: *m/z* 256 (M^+).

General Procedure for Preparation of 1-Alkyl-5-*tert*-butyl-1,3-dihydroimidazole-2-thiones **4b,c**.

A mixture of 1-amino-3,3-dimethylbutan-2-one hydrochloride (3.03 g, 20 mmoles), isothiocyanate derivative (ethyl, and cyclohexyl) (20 mmoles), and triethylamine (2.8 ml, 20 mmoles) in dry benzene (20 ml) was refluxed for 3 hours. The solvent was removed under reduced pressure, and acetic acid (20 ml) was added to the residual material and the mixture was refluxed for 2 hours. The solvent was concentrated to 5 ml, then water (30 ml) was added and the solid product formed was collected, washed with ether (30 ml), and dried to afford compounds **4b,c**.

5-*tert*-Butyl-1-ethyl-1,3-dihydroimidazole-2-thione (**4b**).

This compound was obtained as white crystals. Yield 1.1 g (30%); mp 160–162°; ^{1}H-nmr (DMSO-d_6): δ 1.19–1.28 (m, 12H, $(CH_3)_3C$ and CH_3CH$_2$), 4.09 (q, 2H, CH_3CH_2, *J* = 6.3 Hz), 6.53 (s, 1H, H-4), 11.93 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 13.50 (CH_3CH_2), 29.45 ($(CH_3)_3C$), 30.63 ($(CH_3)_3C$), 40.11 (CH_2N), 109.68 (C-4), 137.90 (C-5); EI MS: *m/z* 184 (M^+).

Anal. Calcd. for $C_9H_{16}N_2S•0.25H_2O$ (188.81): C, 57.25; H, 8.54; N, 14.84. Found: C, 57.23; H, 8.62; N, 14.72.

5-*tert*-Butyl-1-cyclohexyl-1,3-dihydroimidazole-2-thione (**4c**).

This compound was obtained as white crystals. Yield 4.1 g (86%); mp 198–200°; ^{1}H-nmr ($CDCl_3$): δ 1.18–1.46 (m, 13H, $(CH_3)C$ and H_{cy}), 1.66–1.96 (m, 4H, H_{cy}), 3.36–3.48 (m, 2H, H_{cy}), 4.13–4.24 (m, 1H, H_{cy}), 6.41 (s, 1H, H-4), 11.81 (s, 1H, NH); ^{13}C-nmr ($CDCl_3$): δ 24.81, 26.39, 27.88, 58.35 (C_{cy}), 29.68 ($(CH_3)C$), 30.93 ($(CH_3)C$), 109.95 (C-4), 139.51 (C-5), 159.20 (C=S); EI MS: *m/z* 238 (M^+).

Anal. Calcd. for $C_{13}H_{22}N_2S•0.25H_2O$ (242.9): C, 64.28; H, 9.13; N, 11.53. Found: C, 64.68; H, 9.37; N, 11.65.

General Procedure for Preparation of 2-[(1-Alkyl-5-*tert*-butyl-1-methyl-1*H*-imidazol-2-yl)thio]acetamides **5a-c**.

To a solution of potassium hydroxide (0.28 g, 5 mmoles) in methanol (15 ml), compound **4a-c** (1.3 g, 5 mmoles) was added and the mixture was stirred for 0.5 hour. 2-Iodoacetamide (0.93 g, 5 mmoles) was added to the reaction mixture, and the reaction was stirred at room temp. for an additional hour. The solvent was removed under reduced pressure, water (25 ml) was added to the residual material. The solid product was collected and recrystallized from ethanol/water to give **5a-c**.

2-[(5-*tert*-Butyl-1-methyl-1*H*-imidazol-2-yl)thio]acetamide (**5a**).

This compound was obtained as white crystals. Yield 0.68 g (60%); mp 94–96°; ^{1}H-nmr ($CDCl_3$): δ 1.35 (s, 9H, $(CH_3)_3C$), 3.63 (s, 2H, CH_2S), 3.68 (s, 3H, CH_3N), 5.79 (brs, 1H, *H*NH), 6.77 (s, 1H, H-4), 8.46 (brs, 1H, HN*H*); ^{13}C-nmr ($CDCl_3$): δ 29.33 ($(CH_3)_3C$), 31.01 ($(CH_3)_3C$), 33.03 (CH_2S), 35.95 (CH_3N), 124.43 (C-4), 142.36 (C-5), 142.68 (C-2), 172.14 (C=O). EI MS: *m/z* 227 (M^+).

Anal. Calcd. for $C_{10}H_{17}N_3OS$ (227.32): C, 52.84; H, 7.54; N, 18.48. Found: C, 52.35; H, 7.57; N, 18.25.

2-[(5-*tert*-Butyl-1-ethyl-1*H*-imidazol-2-yl)thio]acetamide (**5b**).

This compound was obtained as white crystals. Yield 0.7 g (58%); mp 103–105°; ^{1}H-nmr ($CDCl_3$): δ 1.32–1.39 (m, 12H, $(CH_3)_3C$ and CH_3CH$_2$), 3.65 (s, 2H, CH_2S), 4.09 (q, 2H, CH_3CH_2, *J* = 7.2 Hz), 5.76 (brs, 1H, *H*NH), 6.70 (s, 1H, H-4), 8.62 (brs, 1H, HN*H*); ^{13}C-nmr ($CDCl_3$): δ 15.95 (CH_3CH_2), 30.03 ($(CH_3)_3C$), 31.14 ($(CH_3)_3C$), 35.89 (CH_3CH_2), 40.37 (CH_2S), 124.36 (C-4), 141.98 (C-2 and C-5), 172.39 (C=O); EI MS: *m/z* 241 (M^+).

Anal. Calcd. for $C_{11}H_{19}N_3OS$ (241.35): C, 54.74; H, 7.93; N, 17.40. Found: C, 54.73; H, 8.04; N, 17.35.

2-[(5-*tert*-Butyl-1-cyclohexyl-1*H*-imidazol-2-yl)thio]acetamide (**5c**).

This compound was obtained as white crystals. Yield 1.13 g (77%); mp 182–184°; ^{1}H-nmr (DMSO-d_6): δ 1.09–1.44 (m, 13H, $(CH_3)_3C$ and H_{cy}), 1.66–1.88 (m, 4H, H_{cy}), 2.26–2.38 (m, 2H, H_{cy}), 3.78 (s, 1H, CH_2S), 6.60 (s, 1H, H-4), 7.12 (brs, 1H, *H*NH),

7.69 (brs, 1H, HN*H*); ^{13}C-nmr (DMSO-d_6): δ 24.63, 25.67, 30.36, 55.58 (C_{cy}), 29.77 ((*C*H$_3$)$_3$C), 30.63 ((CH$_3$)$_3$*C*), 37.04 (CH$_2$S), 123.54 (C-5), 139.66 (C-2), 141.38 (C-4), 169.50 (C=O);. EI MS: *m/z* 295 (M$^+$).

Anal. Calcd. for $C_{15}H_{25}N_3OS$ (295.44): C, 60.98; H, 8.53; N, 14.22. Found: C, 60.91; H, 8.59; N, 14.24.

2-[(4-*tert*-Butyl-1*H*-imidazol-2-yl)thio]acetamide (**6**).

To a solution of potassium hydroxide (0.56 g, 10 mmoles) in methanol (15 ml), compound 4-*tert*-butyl-1,3-dihydroimidazole-2-thione **1c** (1.56 g, 10 mmoles) was added and the mixture was stirred for 0.5 hour. 2-Iodoacetamide (1.86 g, 10 mmoles) was added to the reaction mixture and the reaction was stirred at room temperature for an additional hour. The solvent was removed under reduced pressure, and water (25 ml) was added to the residual material and the solid product formed was collected and recrystallized from ethanol/water to give compound **6**.

The compound was obtained as white crystals. Yield 1.34 g (63%); mp 145–147°; ^{1}H-nmr (DMSO-d_6): δ 1.19 (s, 9H, (CH$_3$)$_3$C), 3.63 (s, 2H, CH$_2$S), 6.69 (brs, 1H, H-5), 7.17 (s, 1H, *H*NH), 7.76 (brs, 1H, HN*H*), 11.96 (brs, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 29.83 ((*C*H$_3$)$_3$C), 36.66 (CH$_2$S), 137.56 (C-2), 170.12 (C=O); EI MS: *m/z* 213 (M$^+$).

Anal. Calcd for $C_9H_{15}N_3OS \cdot 0.25H_2O$ (217.81): C, 49.63; H, 7.17; N, 19.70. Found: C, 49.83; H, 6.96; N, 19.34.

2-[(4-*tert*-Butyl-1-dimethylsulfamoyl-1*H*-imidazol-2-yl)thio]-acetamide (**7**).

To a mixture of compound **6** (0.53 g, 2.5 mmoles) and triethylamine (0.35 ml, 2.5 mmoles) in toluene (20 ml), dimethylsulfamoyl chloride (0.26 ml, 2.5 mmoles) in toluene (5 ml) was added dropwise. The mixture was stirred at room temp. for 1 hour followed by refluxing for 5 hours. After cooling to room temp., water (30 ml) was added to the reaction mixture and the two layers were separated. The organic layer was dried over sodium sulfate, and the solvent was removed under reduced pressure. The residual material was chromatographed on a column of silica gel with CH$_2$Cl$_2$:EtOAc (1:1, v/v) to afford compound **7**.

The compound was obtained as white crystals. Yield 0.38 g (48%); mp 120–122°; ^{1}H-nmr (CDCl$_3$): δ 1.24 (s, 9H, (CH$_3$)$_3$C), 2.95 (s, 6H, (CH$_3$)$_2$N), 3.77 (s, 2H, CH$_2$S), 5.84 (brs, 1H, *H*NH), 6.95 (s, 1H, H-5), 7.81 (brs, 1H, HN*H*); ^{13}C-nmr (CDCl$_3$): δ 29.36 ((*C*H$_3$)$_3$C), 31.89 ((CH$_3$)$_3$*C*), 35.09 (CH$_2$S), 38.54 ((CH$_3$)$_2$N), 114.54 (C-5), 143.34 (C-4), 151.81 (C-2), 171.88 (CONH$_2$); HiResMALDI *m/z* 321.1049 (M+H$^+$. $C_{11}H_{20}N_4O_3S_2$) requires 321.1055.

2-[(4-*tert*-Butyl-1*H*-imidazol-2-yl)thio]-2-dimethylsulfamoyl-acetamide (**8**).

Compound **7** (0.32 g, 1 mmole) was dissolved in tetrahydrofuran (20 ml) under nitrogen atmosphere, and the solution was cooled to –78°. *n*-Butyl lithium (1.8 ml, 4 mmoles) was added to the solution at –78°. The mixture was stirred for 0.5 hour at –78°, then cyclohexyl disulfide (0.69 g, 3 mmoles) was added dropwise at –78°. The mixture was left to reach room temp. and the reaction was quenched with water (10 ml). The reaction mixture was filtered and ether (30 ml) was added to the filtrate before separating the two layers. The organic layer was dried over sodium sulfate. The solvents were removed under reduced pressure and the residual material was chromatographed on a column of silica gel with CH$_2$Cl$_2$:MeOH (15:1, v/v) to afford compound **8**.

The compound was obtained as white crystals. Yield 0.1 g (30%); mp 185–187°; ^{1}H-nmr (DMSO-d_6): δ 1.21 (s, 9H, (CH$_3$)$_3$C), 1.22 (s, 9H, (CH$_3$)$_3$C), 2.77 (s, 6H, (CH$_3$)$_2$N), 2.81 (s, 6H, (CH$_3$)$_2$N), 5.45 (s, 1H, CHS), 5.59 (s, 1H, CHS), 6.68 (s, 1H, H-5), 6.88 (s, 1H, H-5), 7.63 (brs, 2H, *H*NH), 8.02 (brs, 1H, HN*H*), 8.06 (brs, 1H, HN*H*), 12.17 (s, 1H, NH), 12.26 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 29.56, 30.06 ((*C*H$_3$)$_3$C), 30.23, 31.53 ((CH$_3$)$_3$*C*), 37.35, 37.54 ((CH$_3$)$_2$N), 68.63, 68.88 (CHS), 112.55, 123.51 (C-5), 134.18, 143.03 (C-4), 152.41 (C-2), 164.07, 171.50 (CONH$_2$); EI MS: *m/z* 320 (M$^+$).

Anal. Calcd for $C_{11}H_{20}N_4O_3S_2 \cdot 0.6H_2O$ (331.24): C, 39.89; H, 6.45; N, 16.91. Found: C, 39.66; H, 6.00, N, 16.62.

2-[(4-*tert*-Butyl-5-iodo-1*H*-imidazol-2-yl)thio]acetamide (**10**).

To a solution of sodium hydroxide (0.6 g, 15 mmoles) in water (15 ml) were added methylene chloride (15 ml) and compound **6** (3.2 g, 15 mmoles). A solution of iodine (3.84 g, 15 mmoles) in methylene chloride (15 ml) and methanol (10 ml) was added dropwise under ice cooling. After 15 min. the mixture was filtered and the precipitated material was washed with ether (30 ml) and dried to give a pure solid of compound **10**.

The compound was obtained as white crystals. Yield 2.9 g (57%); mp 158–160°; ^{1}H-nmr (DMSO-d_6): δ 1.33 (s, 9H, (CH$_3$)$_3$C), 3.68 (s, 2H, CH$_2$S), 7.23 (brs, 1H, *H*NH), 7.66 (s, 1H, HN*H*), 12.09 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 29.67 ((*C*H$_3$)$_3$C), 36.38 (CH$_2$S), 169.91 (C=O). EI MS: *m/z* 339 (M$^+$).

Anal. Calcd for $C_9H_{14}IN_3OS$ 0.25H$_2$O (343.70): C, 31.45; H, 4.25; N, 12.23. Found: C, 31.13; H, 3.87; N, 11.81.

General Procedure for Preparation of 2-[(1-Alkoxymethyl-4-*tert*-butyl-5-iodo-1*H*-imidazol-2-yl)thio]acetamide (**11a,b**).

Compound **10** (1.36 g, 4 mmoles) was dissolved in methylene chloride (20 ml) under nitrogen atmosphere. *N*-Ethyldiisopropylamine (EDIA) (0.72 ml, 4 mmoles) was added to the reaction mixture followed by addition of ethoxy or benzyloxy methyl chloride (4 mmoles). The reaction mixture was stirred for 3 hours at room temp. and quenched with water (20 ml). Methylene chloride (30 ml) was added and the two layers were separated. The organic layer was dried using sodium sulfate, and the solvent was removed under reduced pressure. The residual material was chromatographed on a column of silica gel with ethyl acetate to afford compounds **11a,b**.

2-[(4-*tert*-Butyl-1-ethoxymethyl-5-iodo-1*H*-imidazol-2-yl)thio]acetamide (**11a**).

The compound was obtained as white crystals. Yield 1.14 g (72%); mp 95–97°; ^{1}H-mnr (CDCl$_3$): δ 1.21 (t, 3H, C*H*$_3$CH$_2$, *J* = 7.0 Hz), 1.40 (s, 9H, (CH$_3$)$_3$C), 3.54 (q, 2H, CH$_3$C*H*$_2$, *J* = 7.0 Hz), 3.63 (s, 2H, CH$_2$S), 5.31 (s, 1H, NCH$_2$O), 5.69 (brs, 1H, *H*NH), 8.68 (brs, HN*H*); ^{13}C-mnr (CDCl$_3$): δ 14.84 (*C*H$_3$CH$_2$), 29.83 ((*C*H$_3$)$_3$C), 32.94 ((CH$_3$)$_3$*C*), 36.42 (CH$_2$S), 64.46 (CH$_3$*C*H$_2$O), 65.82 (C-5), 75.71 (NCH$_2$O), 142.94 (C-4), 152.40 (C-2), 172.20 (C=O); EI MS: *m/z* 397 (M$^+$).

Anal. Calcd. for $C_{12}H_{20}IN_3OS$ (397.27): C, 36.28; H, 5.07; N, 10.58. Found: C, 36.53; H, 5.05; N, 10.35.

2-[(1-Benzyloxymethyl-4-*tert*-butyl-5-iodo-1*H*-imidazol-2-yl)thio]acetamide (**11b**).

The compound was obtained as white crystals. Yield 1.38 g (75%); mp 104–106°; ^{1}H-mnr (CDCl$_3$): δ 1.39 (s, 9H, (CH$_3$)$_3$C), 3.59 (s, 2H, CH$_2$S), 4.58 (s, 2H, C*H*$_2$Ph), 5.36 (s, 2H, NCH$_2$O),

5.67 (s, 1H, *H*NH), 7.26-7.35 (m, 5H, Ph), 8.62 (s, 1H, HN*H*); ^{13}C-nmr ($CDCl_3$): δ 29.83 ((*C*H$_3$)$_3$C), 32.94 ((CH$_3$)$_3$*C*), 36.36 (CH$_2$S), 65.72 (C-5), 70.78 (*C*H$_2$Ph), 75.38 (NCH$_2$O), 127.59, 128.02, 128.44, 136.52 (C$_{arom}$), 143.08 (C-4), 152.64 (C-2), 172.14 (C=O); EI MS: *m/z* 459 (M$^+$).

Anal. Calcd. for $C_{17}H_{22}IN_3OS$ (459.35): C, 44.45; H, 4.83; N, 9.15. Found: C, 45.06; H, 4.76; N, 8.92.

2-[(4-*tert*-Butyl-5-iodo-1-pyridin-4-ylmethyl-1*H*-imidazol-2-yl)thio]acetamide (**12**).

Compound **10** (1.36 g, 4 mmoles) was dissolved in dimethylformamide (15 ml), sodium hydride (0.35 g, 8 mmoles) was added to the solution portionwise under ice cooling. After stirring for 0.5 hour, 4-pyridylmethyl chloride hydrochloride (1.7 g, 10 mmoles) was added portionwise to the reaction mixture under ice cooling, and the reaction mixture was left to be stirred at room temp. for 4 hours. The solvent was removed under reduced pressure and the residual material was treated with water (30 ml) and filtered. The precipitate was dried and chromatographed on a column of silica gel with EtOAc:MeOH (20:1, v/v) to give compound **12**.

The compound was obtained as white crystals. Yield 0.9 g (52%); mp 135–137°; ^{1}H-mnr ($CDCl_3$): δ 1.42 (s, 9H, (CH$_3$)$_3$C), 3.57 (s, 2H, CH$_2$S), 5.19 (s, 2H, CH$_2$N), 5.77 (s, 1H, *H*NH), 6.94 (d, 2H, H$_{py}$, *J* = 6.0 Hz), 8.58 (d, 2H, H$_{py}$, *J* = 6.0 Hz), 8.64 (s, 1H, HN*H*); ^{13}C-mnr ($CDCl_3$): δ 29.79 ((*C*H$_3$)$_3$C), 32.99 (CH$_3$)$_3$*C*), 36.56 (CH$_2$S), 66.46 (C-5), 121.29, 144.38, 150.26 (C$_{py}$), 142.15 (C-4), 153.13 (C-2), 171.87 (C=O); EI MS: *m/z* 430 (M$^+$).

Anal. Calcd for $C_{15}H_{19}IN_4OS$ (430.31): C, 41.87; H, 4.45; N, 13.02. Found: C, 42.13; H, 4.39; N, 12.69.

2-[(1-Benzyloxymethyl-4-*tert*-butyl-1*H*-imidazol-2-yl)thio]-acetamide (**13**), 1-Benzyloxymethyl-4-*tert*-butyl-1,3-dihydroimidazole-2-thione (**15**) and 2,2-Bis(3,5-dimethylphenylthio)-acetamide (**14**).

3,5-Dimethylthiophenol (0.13 ml, 1 mmole) was dissolved in dimethylformamide (10 ml), and sodium hydride (44 mg, 1 mmole) was added to the solution portionwise under ice cooling. After stirring for 0.5 hour, compound **11b** (0.46 g, 1 mmole) was added portionwise to the reaction mixture under ice cooling, and the reaction mixture was left to be stirred at room temp. for 4 hours. The solvent was removed under reduced pressure and the residual material was treated with water (20 ml) and filtered. The precipitate was dried and chromatographed on a column of silica gel with CH_2Cl_2:EtOAc (6:1, v/v) to furnish compounds **13, 14** and **15**.

2-[(1-Benzyloxymethyl-4-*tert*-butyl-1*H*-imidazol-2-yl)thio]-acetamide (**13**).

The compound was obtained as an oil. Yield 50 mg (15%); ^{1}H-nmr ($CDCl_3$): δ 1.65 (s, 9H, (CH$_3$)$_3$C), 3.52 (s, 2H, CH$_2$S), 4.43 (s, 2H, C*H*$_2$Ph), 5.18 (s, 2H, NCH$_2$O), 5.73 (brs, 1H, *H*NH), 6.66 (s, 1H, H-5), 7.20-7.29 (m, 5H, Ph), 8.75 (brs, 1H, HN*H*); ^{13}C-nmr ($CDCl_3$): δ 29.78 ((*C*H$_3$)$_3$C), 31.78 ((CH$_3$)$_3$*C*), 36.29 (CH$_2$S), 70.63 (O*C*H$_2$Ph), 74.69 (NCH$_2$O), 115.17 (C-5), 127.75, 128.10, 128.48, 136.35 (C$_{arom}$), 141.16 (C-4), 152.71 (C-2), 172.45 (C=O); MS HiResMALDI *m/z* 334.1576 (M+H$^+$.$C_{17}H_{23}N_3O_2S$) requires 334.1583.

1-Benzyloxymethyl-4-*tert*-butyl-1,3-dihydro-imidazol-2-thione (**14**).

The compound was obtained as white crystals. Yield 50 mg (18%); mp 110–112°; ^{1}H-nmr ($CDCl_3$): δ 1.29 (s, 9H, (CH$_3$)$_3$C), 4.68 (s, 2H, C*H*$_2$Ph), 5.52 (s, 2H, NCH$_2$O), 6.47 (s, 1H, H-5), 7.27-7.38 (m, 5H, Ph), 11.71 (brs, 1H, NH); ^{13}C-nmr ($CDCl_3$): δ 29.29 ((*C*H$_3$)$_3$C), 30.50 ((CH$_3$)$_3$*C*), 71.43 (O*C*H$_2$Ph), 75.39 (NCH$_2$O), 110.99 (C-5), 127.88, 127.89, 128.38, 137.19 (C$_{arom}$), 139.59 (C-4), 161.43 (C-2); EI MS: *m/z* 276 (M$^+$).

2,2-Bis(3,5-dimethylphenylthio)acetamide (**15**).

The compound was obtained as white crystals.Yield 120 mg (36%); mp 138–140°; ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 12H, 4 × CH$_3$), 4.79 (s, 1H, CH), 5.67 (brs, 1H, *H*NH), 6.39 (brs, 1H, HN*H*), 6.92 (s, 2H, Ph), 7.08 (s, 4H, Ph); ^{13}C-nmr ($CDCl_3$): δ 21.15 (4 × CH$_3$), 58.03 (CH), 129.81, 130.27, 132.39, 138.85 (C$_{arom}$), 170.26 (C=O); EI MS: *m/z* 331 (M$^+$).

Anal. Calcd. for $C_{18}H_{21}NOS_2$ (331.49): C, 65.22; H, 6.39; N, 4.23. Found: C, 64.78; H, 6.39; N, 4.29.

N-(4-*tert*-Butyl-1*H*-imidazol-2-ylmethyl)benzamide (**17**).

A mixture of compound **16** (4.85 g, 20 mmoles), 1-amino-3,3-dimethylbutan-2-one hydrochloride (3.03 g, 20 mmoles), and triethylamine (5.6 ml, 40 mmoles) was refluxed in ethanol (30 ml) for 6 hours. The reaction mixture was cooled to room temp. and the solvent was removed under reduced pressure. The residue was treated with water (50 ml) and extracted with ether (3 x 25 ml). The ether extracts were dried (sodium sulfate), and concentrated to 10 ml. Petroleum ether (50 ml) was added to the concentrated solution and the solid product formed was collected and dried to furnish compound **17**.

The compound was obtained as white crystals. Yield 1.6 g (31%); mp 168–170°; ^{1}H-nmr ($CDCl_3$): δ 1.24 (s, 9H, (CH$_3$)$_3$C), 4.58 (d, 2H, C*H*$_2$NH, *J* = 5.4 Hz), 6.61 (s, 1H, H-5), 7.26?7.47 (m, 3H, Ph), 7.93 (d, 2H, Ph, *J* = 7.5 Hz), 9.56 (brs, 1H, NH); ^{13}C-nmr ($CDCl_3$): δ 30.12 ((*C*H$_3$)$_3$C), 30.85 ((CH$_3$)$_3$*C*), 37.43 (CH$_2$), 127.44, 128.34, 131.56, 133.65 (C$_{arom}$), 145.59 (C-2), 169.01 (CONH); EI MS: *m/z* 257 (M$^+$).

Anal. Calcd for $C_{15}H_{19}N_3O$•0.15H_2O (260.04): C, 69.28; H, 7.48; C, 16.16. Found: C, 69.27; H, 7.34; N, 15.93.

N-(4-*tert*-Butyl-5-iodo-1*H*-imidazol-2-ylmethyl)benzamide (**18**).

To a solution of sodium hydroxide (0.2 g, 5 mmoles) in water (10 ml) was added methylene chloride (10 ml) and compound **17** (1.3 g, 5 mmoles). A solution of iodine (1.28 g, 5 mmoles) in methylene chloride (10 ml) and methanol (5 ml) was added dropwise under ice cooling. After 15 min. the mixture was filtered, and the precipitated material was washed with ether (20 ml) and dried to give a pure solid of compound **18**.

The compound was obtained as white crystals. Yield 0.85 g (44%); mp 215–217°; ^{1}H-nmr ($CDCl_3$): δ1.36 (s, 9H, (CH$_3$)$_3$C), 4.45 (d, 2H, C*H*$_2$NH, *J* = 5.1 Hz), 7.44?7.56 (m, 3H, Ph), 7.90 (d, 2H, Ph, *J* = 6.9 Hz), 8.87 (t, 1H, CH$_2$N*H*, *J* = 5.1 Hz); ^{13}C-nmr ($CDCl_3$): δ 29.77 ((*C*H$_3$)$_3$C), 30.31 ((CH$_3$)$_3$*C*), 36.46 (CH$_2$), 77.01 (C-5), 127.26, 128.18, 131.21, 137.99 (C$_{arom}$), 133.98 (C-4), 145.25 (C-2), 165.97 (CONH); EI MS: *m/z* 383 (M$^+$).

Anal. Calcd for $C_{15}H_{18}IN_3O$ (283.23): C, 47.01; H, 4.73; N, 10.96. Found: C, 46.86; H, 4.62; N, 10.76.

5-Alkyl- 4-benzoyl-1,3-dihydroimidazol-2-ones **19a,b**.

Benzoyl chloride (0.6 g, 5 mmoles) was added dropwise to a mixture of anhydrous aluminum chloride (1.33 g, 10 mmoles), 4-alkyl-1,3-dihydroimidazol-2-one **1a,b** (5 mmoles) in nitrobenzene (10 ml) over 15 min. The mixture was stirred for 6 hours at 60–65° and then poured onto ice (100 g). The resulting solid was

collected, washed with water and ether (20 ml) and recrystallized from ethanol/water to give compounds **19a,b**.

4-Benzoyl-5-isopropyl-1,3-dihydroimidazol-2-one (**19a**).

The compound was obtained as white crystals. Yield 0.4 g (35%); mp 254–256°; ^{1}H-nmr (DMSO-d_6): δ 1.05 (d, 6H, $(CH_3)_2CH$, J = 6.8 Hz), 2.56 (hept., 1H, $(CH_3)_2CH$, J = 6.8 Hz), 7.47–7.61 (m, 5H, Ph), 10.31 (s, 1H, NH), 11.01 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 20.98 ($(CH_3)_2CH$), 24.63 ($(CH_3)_2CH$), 117.24, 127.66, 128.29, 131.46, 139.61 (C-4, C_{arom}), 141.06 (C-5), 153.27 (C-2), 183.93 (*C*OPh); EI MS: *m/z* 230 (M^+).

Anal. Calcd. for $C_{13}H_{14}N_2O_2 \cdot 0.3H_2O$ (235.67): C, 66.25; H, 6.24; N, 11.89. Found: C, 66.21; H, 5.98; N, 11.60.

4-Benzoyl-5-*tert*-butyl-1,3-dihydroimidazol-2-one (**19b**).

The compound was obtained as white crystals. Yield: 0.2 g (16%); mp 215–217°; ^{1}H-nmr (DMSO-d_6): δ 1.25 (s, 9H, $(CH_3)_3C$), 7.48–7.72 (m, 5H, Ph), 10.14 (s, 1H, NH), 10.66 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 28.85 ($(CH_3)_3C$), 31.91 ($(CH_3)_3C$), 115.79, 128.44, 128.96, 132.51, 138.56 (C-4, C_{arom}), 139.42 (C-5), 152.41 (C-2), 186.11 (*C*OPh); EI MS: *m/z* 244 (M^+).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$ (244.30): C, 68.83; H, 6.60; N, 11.47. Found: C, 68.78; H, 6.59; N, 11.51.

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