2-Butyl-5-chloro-3*H*-imidazole-4-carbaldehyde as a New Synthon for the Synthesis of Fused Ring Heterocycles *via* Intramolecular 1,3-Dipolar Cycloaddition Reactions

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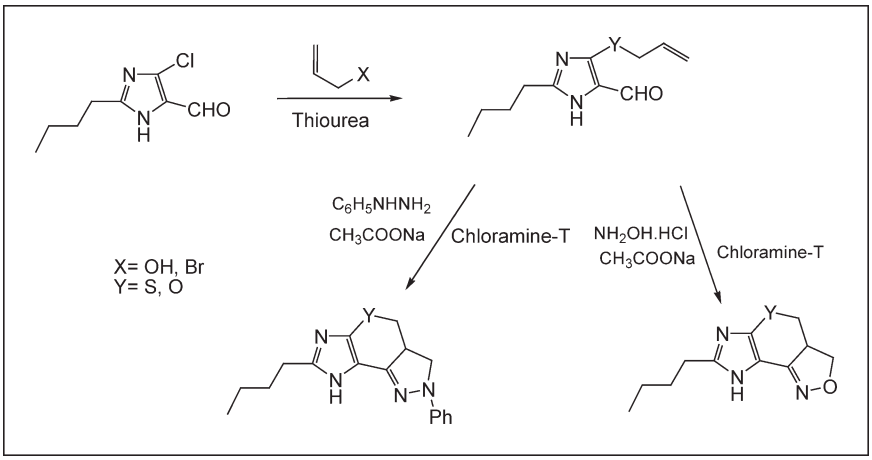

The title compound 2-butyl-5-chloro-3*H*-imidazole-4-carbaldehyde was transformed into tricyclic heterocycles by substituting the chlorine atom by an unsaturated thiolate or alkoxide and then converting aldehyde function into 1,3-dipole. Chloramine-T was used as an efficient reagent for the generation of 1,3-dipoles, which resulted the formation of fused ring heterocycles *via* intramolecular 1,3-dipolar cycloaddition reaction. The method is very useful for the construction of many biologically active fused heterocycles.

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INTRODUCTION

The intramolecular 1,3-dipolar cycloaddition is a powerful method for the construction of fused ring heterocycles [1,2]. In particular intramolecular nitrile oxide cycloaddition results dihydroisoxazole derivatives, which are precursors for γ-amino alcohols, β-hydroxy ketones and derivatives, useful in the synthesis of natural products [3]. Similarly intramolecular nitrile imine cycloaddition results 2-pyrazoline derivatives.

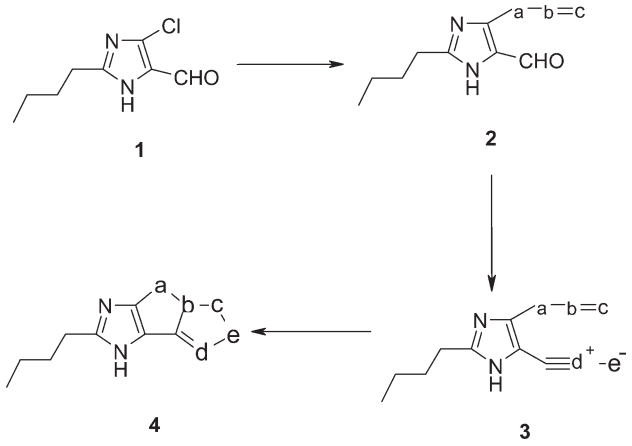
In our previous report, we have used chloramine-T for the generation of nitrile oxide [4], nitrile imine [5], nitroso alkene [6], and azoalkene [7] which are useful intermediates for the synthesis of biologically active 2-isoxazolines, 2-pyrazolines, 1,2-oxazines, and pyridazines, respectively. 2-Butyl-5-chloro-3*H*-imidazole-4-carbaldehyde **1**, a key intermediate for the synthesis of Losartan a nonpeptide angiotensin antagonist, which is an orally active antihypertensive drug [8], and also shows broad spectrum of activity [9–10]. Compounds of these types are interesting starting materials for intramolecular cycloaddition reaction due to the presence of chloro and formyl groups ortho to each other. The chlorine atom can be easily substituted by nucleophiles **2** and the formyl function is suitable for conversion into series of 1,3-dipoles. The final step is the intramolecular cycloaddition of dipole and dipolarophile **3** to give the fused ring system **4** (Scheme 1).

CHEMISTRY

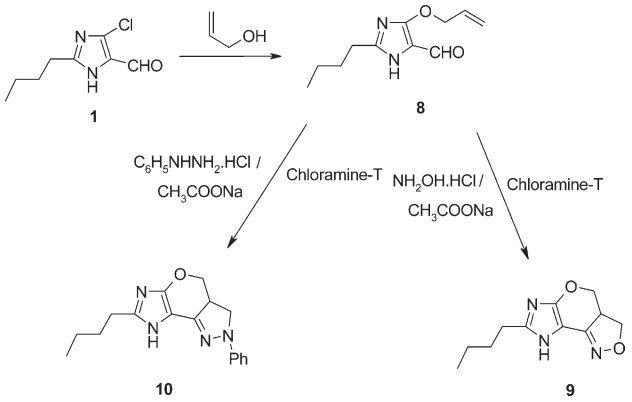
The starting compound 2-butyl-5-chloro-3*H*-imidazole-4-carbaldehyde was synthesized by literature procedure [9]. Substitution of chloro group with allyl thiols furnished 2-butyl-5-(allylsulfanyl)imidazole-4-carbaldehyde. This compound could be transformed into the tricyclic heterocycles by converting the aldehyde function into 1,3-dipoles (Scheme 2). Similarly, substitution with allyl alcohol furnished the 2-butyl-5-(allyloxyl)imidazole-4-carbaldehyde which could be transformed into corresponding tricyclic heterocycles by converting the aldehyde function into 1,3-dipoles (Scheme 3).

The aldehyde **5** was converted into the oxime and then oxidized with chloramine-T to give nitrile oxide,

Scheme 1



Scheme 3

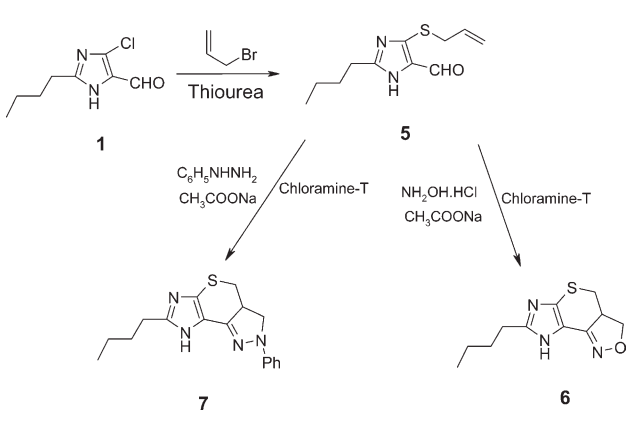


which undergoes intramolecular cycloaddition to form dihydroisoxazole **6**. The aldehyde **5** was converted to phenyl hydrazone and then oxidized with chloramine-T to give nitrile imine, which on intramolecular cycloaddition results pyrazole derivative **7**. The aldehyde **5** was prepared by substituting chloro group of aldehyde **1** with allyl thiol, generated by basic decomposition of the allyl isothiourea salt. Similarly, compounds **9** and **10** are synthesized to form aldehyde **1** by substituting chloro group with allyl alcohol.

RESULTS AND DISCUSSION

^{1}H NMR, ^{13}C NMR, IR, and elemental analyses characterized all the synthesized compounds. ^{1}H NMR of aldehyde **5** showed a doublet at δ 3.89 for two protons due to CH_2S group and two multiplets at δ 4.9–5.02 and 5.62–5.71 are due to vinylic CH_2 and vinylic CH groups, respectively. Aldehydic proton was observed at δ 9.63 and a broad singlet at δ 11.7 is due to NH group of imidazole ring. ^{13}C NMR showed peak at δ 116.2 and 131.9 due to vinylic CH_2 and vinylic CH groups, respectively. The aldehydic carbon was observed at δ 184.2.

Scheme 2



^{1}H NMR of isoxazoline **6** showed multiplet at δ 2.92–2.98 for one proton due to CH group. A multiplet at δ 3.15–3.23 is due to CH_2S group and a multiplet at δ 3.92–4.01 is due to CH_2 group of isoxazoline ring. ^{13}C NMR showed doublet at δ 33.3 due to CH group. A triplet at δ 44.4 may be due to carbon of CH_2S group and triplet at δ 63.3 is due to CH_2 group of isoxazoline ring. All other substituents are observed in the expected region. The moderate yield of 67% is obtained starting from aldehyde **5** because the intermediate impure oxime was taken directly for next step without purification. The yield of isoxazoline **6** can be improved by purifying the oxime.

^{1}H NMR of pyrazoline **7** showed multiplet at δ 2.85–2.92 for one proton due to CH group. A doublet was observed at δ 3.10 is due to CH_2S group and a multiplet at δ 3.86–3.92 is due to CH_2 group of pyrazolines ring. The aromatic protons are observed in the region δ 6.85–7.12. In ^{13}C NMR a triplet at δ 32.5 may be due to carbon of CH_2S group and a triplet at δ 56.1 may be due to CH_2 group of isoxazoline ring. A doublet at δ 46.9 indicates the presence of CH group. All other substituents are observed in the expected region. The moderate yield of 65% is obtained starting from aldehyde **5**. The yield of pyrazoline **7** can be improved by purifying the intermediate phenyl hydrazone.

^{1}H NMR of aldehyde **8** showed a doublet at δ 4.79 for two protons due to CH_2O group and two multiplets at δ 5.22–5.31 and 5.60–5.69 are due to vinylic CH_2 and vinylic CH groups, respectively. Aldehydic proton was observed at δ 9.89 and a broad singlet at δ 11.59 is due to NH group of imidazole ring. ^{13}C NMR showed peak at δ 117.0 and 134.9 due to vinylic CH_2 and vinylic CH groups, respectively. The aldehydic carbon was observed at δ 182.1.

^{1}H NMR of isoxazoline **9** showed multiplet at δ 2.96–3.0 for one proton due to CH group. A doublet δ 4.16 is due to CH_2O group and a multiplet at δ 3.96–4.04 is due to CH_2 group of isoxazoline ring. ^{13}C NMR showed doublet at δ 44.3 due to CH group. A triplet at δ 73.3 may be due to carbon of CH_2O group and triplet at δ 62.1 is due to CH_2 group of isoxazoline ring. All other substituents are observed in the expected region.

^{1}H NMR of pyrazoline **10** showed multiplet at δ 2.80–2.86 for one proton due to CH group. A multiplet at δ 3.76–3.83 is due to CH_2 group of pyrazolines ring. A doublet was observed at δ 4.22, which is due to OCH_2 group. The aromatic protons are observed in the region δ 6.85–7.12. ^{13}C NMR showed doublet at δ 44.2 due to CH group. A triplet at δ 52.1 may be due to CH_2 group of isoxazoline ring and a triplet at δ 71.3 is due to OCH_2 group. All other substituents are observed in the expected region.

CONCLUSIONS

In conclusion, we have demonstrated that 2-butyl-5-chloro-3*H*-imidazole-4-carbaldehyde can be used for intramolecular 1,3-dipolar cycloaddition by substituting chloro group with unsaturated nucleophiles and converting the aldehyde function into 1,3-dipole. Chloramine-T is found to be an efficient reagent for the generation of 1,3-dipole. Other compounds possessing a halogen and aldehyde group at ortho position are also potential candidates for carrying out similar reactions.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AM 300 MHz spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were measured on Jeol 400 (100 MHz) instrument. The chemical shifts are expressed in δ and following abbreviations were used, s = singlet, d = doublet, t = triplet, and m = multiplet. Infrared (IR) spectra were recorded on Shimadzu 8300 IR spectrometer. Elemental analyses were obtained on a Vario-EL instrument. Thin layer chromatography (TLC) was done with precoated silica gel G plates.

2-Butyl-5-chloro-3*H*-imidazole-4-carbaldehyde 1 [7]. The aldehyde **1** was synthesized by literature procedure [9]. ^{1}H NMR $CDCl_3$: δ 0.92 (t, J = 7.5 Hz, 3H, CH_3), 1.32 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 2.61 (t, J = 7.5 Hz, 2H, CH_2), 9.32 (s, 1H, CHO), 11.89 (bs, 1H, NH). ^{13}C NMR $CDCl_3$: δ 13.2 (q), 23.2 (t), 28.1 (t), 30.1 (t), 128.2 (s), 144.1 (s), 158.8 (s), 179.2 (d). IR (KBr pellets cm^{-1}) ν 3409, 3070, 2969, 2827, 1672, 1459. Anal. Calcd for $C_8H_{11}ClN_2O$: C, 51.48; H, 5.94; N, 15.01%. Found: C, 51.38; H, 5.98; N, 15.10%.

5-Allylsulfanyl-2-butyl-3*H*-imidazole-4-carbaldehyde 5. A solution of allyl bromide (4.87 g, 40.24 mmol) and thiourea (3.08 g, 40.52 mmol) in ethanol (50 mL) were refluxed for 1 h. Ethanolic NaOH solution (3.2 g, 50 mL) was then added and the reaction mass was refluxed for 1 h. The aldehyde **1** (5.0 g, 26.9 mmol) was added to the mixture, which was then refluxed for 2 h. Ethanol was removed under vacuum and the residue was extracted with diethyl ether (2 × 50 mL), washed with water, dried (Na_2SO_4), and the solvent was removed to give crude oil which was purified by column chromatography (chloroform:ethyl acetate, 7:3) to give **5** as a pale yellow oil (4.10 g, 68%). ^{1}H NMR $CDCl_3$: δ 0.94 (t, 3H, CH_3), 1.33 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 2.60 (t, 2H, CH_2), 3.89 (d, 2H, CH_2S), 4.9–5.02 (m, 2H, vinylic CH_2), 5.62 (m, 1H,vinylic CH), 9.63 (s, 1H, CHO), 11.70 (bs, 1H, NH). ^{13}C NMR $CDCl_3$: δ 13.4 (q), 23.0 (t), 28.4 (t), 32.1 (t), 39.2 (t), 118.2 (t), 131.9 (d), 139.8 (s), 147.2 (s), 157.8 (s), 181.2 (d). IR (KBr pellets cm^{-1}) ν 3410, 2949, 2816, 1669, 1461. Anal. Calcd. for $C_{11}H_{16}N_2OS$: C, 58.90; H, 7.19; N, 12.49%. Found: C, 58.96; H, 7.10; N, 12.44%.

7-Butyl-3a,4-dihydro-3*H*,8*H*-2-oxa-5-thia-1,6,8-triaza-as-indacene 6. A solution of aldehyde **5** (2.0 g, 8.92 mmol) in ethanol (20 mL) was warmed with aqueous $NH_2OH.HCl$ (0.92 g 13.33 mmol) and CH_3COONa (1.10 g, 13.40 mmol) for 1 h. Ethanol was removed under vacuum and the residue was extracted with ethyl acetate (2 × 25 mL), washed with water, dried (Na_2SO_4), and the solvent was removed. The resultant residue was dissolved in ethanol (20 mL), chloramine-T (3.0 g, 10.67 mmol) was added, and the mixture was warmed under vigorous stirring for 2–3 h. Ethanol was removed under vacuum and the residue was extracted with diethyl ether (2 × 25 mL), washed with 1*N* NaOH (2 × 25 mL), washed with water, dried (Na_2SO_4), and the solvent was removed. The residue left behind was purified by column chromatography (chloroform:ethyl acetate, 7:3) to give **6** as a pale yellow oil (1.41 g, 67%). ^{1}H NMR $CDCl_3$: δ 0.92 (t, 3H, CH_3), 1.32 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 2.61 (t, 2H, CH_2), 2.92–2.98 (m, 1H, CH), 3.15–3.23 (m, 2H, CH_2), 3.92–4.01 (m, 2H, CH_2), 11.79 (bs, 1H, NH). ^{13}C NMR $CDCl_3$: δ 13.0 (q), 23.4 (t), 28.4 (t), 32.5 (t), 33.3 (d), 44.4 (t), 69.3 (t), 111.3 (s), 136.2 (s), 148.8 (s), 156.1 (s). IR (KBr pellets cm^{-1}) ν 3416, 2981, 1590, 1421, 1220, 1151. Anal. Calcd. for $C_{11}H_{15}N_3OS$: C, 55.67; H, 6.37; N, 17.71%. Found: C, 55.59; H, 6.41; N, 17.78%.

7-Butyl-2-phenyl-2,3a,4,8-tetrahydro-3*H*-5-thia-1,2, 6,8-tetraaza-as-indacene 7. A solution of aldehyde **5** (2.0 g, 8.92 mmol) in ethanol (20 mL) was warmed with aqueous phenyl hydrazine hydrochloride (1.93 g, 13.40 mmol) and CH_3COONa (1.10 g, 13.41 mmol) for 1 h. The reaction mass was cooled and the solid formed was filtered. The solid was dissolved in ethanol (20 mL), chloramine-T (3.0 g, 10.67 mmol) was added, and the mixture was warmed under vigorous stirring for 2–3 h. Ethanol was removed under vacuum and the residue was extracted with diethyl ether (2 × 25 mL), washed with 1*N* NaOH (2 × 25 mL), washed with water, dried (Na_2SO_4), and the solvent was removed. The residue left behind was purified by column chromatography (chloroform:ethyl acetate, 8:2) to give **7** as a yellow oil (1.81 g, 65%). ^{1}H NMR $CDCl_3$: δ 0.95 (t, J = 7.5 Hz, 3H, CH_3), 1.35 (m, 2H, CH_2), 1.69 (m, 2H, CH_2), 2.65 (t, J = 7.5 Hz, 2H, CH_2), 2.85–2.92 (m, 1H, CH), 3.10–3.15 (d, 2H, CH_2), 3.86–3.92, (m, 2H, CH_2), 6.85–6.95 (m, 3H, ArH), 7.12 (t, 2H, ArH),

11.77 (bs, 1H, NH). ^{13}C NMR $CDCl_3$: δ 13.1 (q), 23.6 (t), 28.9 (t), 30.7 (t), 32.5 (t), 46.9 (d), 56.1 (t), 110.3 (s), 112.9 (d), 118.1 (d), 119.9(s), 129.8 (d), 134.1 (s), 144.8 (s), 151.1 (s), 153.6 (s). IR (KBr pellets cm^{-1}) ν 3411, 3012, 2956, 1643, 1319, 1014. Anal. Calcd. for $C_{17}H_{20}N_4S$: C, 65.35; H, 6.45; N, 17.93%. Found: C, 65.45; H, 6.40; N, 17.90%.

5-Allyoxy-2-butyl-3*H*-imidazole-4-carbaldehyde 8. A mixture of aldehyde **1** (5 g, 26.9 mmol), allyl alcohol (2.34 g, 40.3 mmol), and potassium *tert*-butoxide (3.61 g, 32.23 mmol) in tetrahydrofuran (50 mL) were stirred at room temperature for 4 h. The reaction mass was diluted with diethyl ether (25 mL) and the solid was filtered. The filtrate was evaporated and the residue was purified by column chromatography (chloroform:ethyl acetate, 7:3) to give **8** as a pale yellow oil (4.02 g, 72%). ^{1}H NMR $CDCl_3$: δ 0.92 (t, J = 7.5 Hz, 3H, CH_3), 1.30 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 2.65 (t, J = 7.5 Hz, 2H, CH_2), 4.79 (d, J = 7.0 Hz, 2H, CH_2S), 5.22–5.41 (m, 2H, vinylic CH_2), 5.60–5.69 (m, 1H, vinylic CH), 9.89 (s, 1H, CHO), 11.59 (bs, 1H, NH). ^{13}C NMR $CDCl_3$: δ 13.8 (q), 23.0 (t), 28.4 (t), 32.1 (t), 76.2 (t), 118.2 (t), 122.2 (s), 134.9 (d), 149.8 (s), 155.8 (s), 182.1 (d). IR (KBr pellets cm^{-1}) ν 3422, 2959, 2856, 1669, 1641, 1215. Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 63.44; H, 7.74; N, 13.45%. Found: C, 63.49; H, 7.70; N, 13.40%.

7-Butyl-3a,4-dihydro-3*H*,8*H*-2,5-dioxa-1,6,8-triaza-as-indacene 9. A solution of aldehyde **8** (1.0 g, 4.80 mmol) in ethanol (10 mL) was warmed with aqueous $NH_2OH.HCl$ (0.50 g 7.24 mmol) and CH_3COONa (0.60 g, 7.30 mmol) for 1 h. Ethanol was removed under vacuum and the residue was extracted with ethyl acetate (2 × 10 mL), washed with water, dried (Na_2SO_4), and the solvent was removed. The resultant residue was dissolved in ethanol (10 mL), chloramine-T (1.62 g, 5.76 mmol) was added, and the mixture was warmed under vigorous stirring for 2–3 h. Ethanol was removed under vacuum and the residue was extracted with diethyl ether (2 × 20 mL), washed with 1*N* NaOH (2 × 25 mL), washed with water, dried (Na_2SO_4), and the solvent was removed. The residue left behind was purified by column chromatography (chloroform:ethyl acetate, 7:3) to give **9** as a pale yellow oil (0.65 g, 61%). ^{1}H NMR $CDCl_3$: δ 0.92 (t, 3H, CH_3), 1.32 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 2.61 (t, 2H, CH_2), 2.96–3.0 (m, 1H, CH), 3.92–4.04 (m, 2H, CH_2), 4.16 (d, 2H, CH_2), 11.80 (bs, 1H, NH). ^{13}C NMR $CDCl_3$: δ 13.0 (q), 23.4 (t), 29.4 (t), 31.5 (t), 44.3 (d), 58.4 (t), 73.3 (t), 109.3 (s), 136.2 (s), 149.8 (s), 157.1 (s). IR (KBr pellets cm^{-1}) ν 3410, 2952, 1638, 1598, 1220, 1100. Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99%. Found: C, 59.61; H, 6.89; N, 19.04%.

7-Butyl-2-phenyl-2,3a,4,8-tetrahydro-3*H*-5-oxa-1,2,6, 8-tetraaza-as-indacene 10. A solution of aldehyde **8** (1.0 g, 4.8 mmol) in ethanol (10 mL) was warmed with aqueous phenyl hydrazine hydrochloride (1.03 g, 7.15 mmol) and CH_3COONa (0.60 g, 7.31 mmol) for 1 h. The reaction mass was cooled and the solid formed was filtered. The solid was dissolved in ethanol (10 mL), chloramine-T (1.62 g, 5.76 mmol) was added, and the mixture was warmed under vigorous stirring for 2–3 h. Ethanol was removed under vacuum and the residue was extracted with diethyl ether (2 × 20 mL), washed with 1*N* NaOH (2 × 25 mL), washed with water, dried (Na_2SO_4), and the solvent was removed. The residue left behind was purified by column chromatography (chloroform:ethyl acetate, 8:2) to give **10** as a yellow oil (0.90 g, 63%). ^{1}H NMR $CDCl_3$: δ 0.93 (t, J = 7.5 Hz, 3H, CH_3), 1.33 (m, 2H, CH_2), 1.66 (m, 2H, CH_2), 2.64 (t, J = 7.5 Hz, 2H, CH_2), 2.88–2.93 (m, 1H, CH), 3.86–3.92 (m, 2H, CH_2), 4.08–4.15, (m, 2H, CH_2), 6.90–7.05 (m, 3H, ArH), 7.24 (t, 2H, ArH), 11.75 (bs, 1H, NH). ^{13}C NMR $CDCl_3$: δ 13.2 (q), 23.8 (t), 29.2 (t), 30.9 (t), 44.2 (d), 52.4 (d), 71.3 (t), 114.3 (s), 112.0 (d), 117.4 (d), 129.2 (d), 132.1 (s), 144.8 (s), 149 (s), 153.1 (s). IR (KBr pellets cm^{-1}) ν 3396, 3026, 2990, 1635, 1235. Anal. Calcd. for $C_{17}H_{20}N_4O$: C, 68.90; H, 6.80; N, 18.90%. Found: C, 68.99; H, 6.71; N, 18.84%.

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