Synthesis of 1,1-Diheteroaryl Ethylenes by a Tandem Appel's Dehydration/Thermal Rearrangement Methodology

Kee-Jung Lee,* Youl Her, and Jong-Gab Jun†

Department of Industrial Chemistry, Hanyang University, Seoul 133-791, Korea
†Department of Chemistry, Hallym University, Chunchon 200-702, Korea
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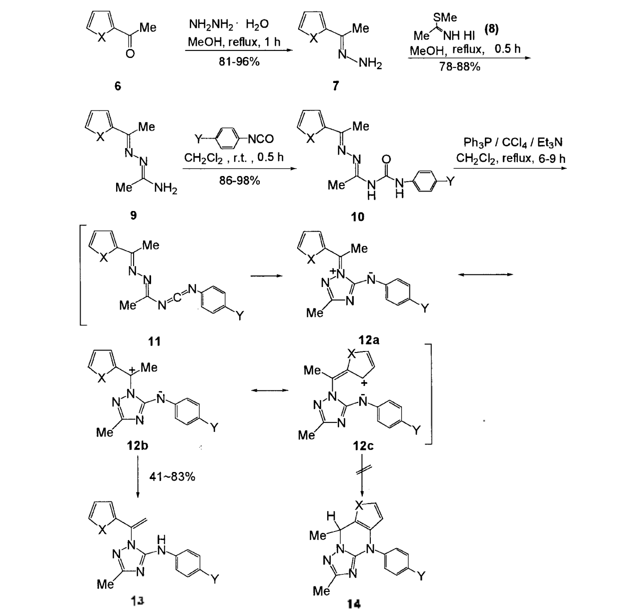
The hydrazones of 2-acetylfuran, 2-acetylthiophene, and 2-acetylpyrrole, were allowed to react with *S*-methylthioacetimidate hydroiodide (**8**) to give azinoureas **10**, and the reaction of **10** with Appel's dehydration conditions (triphenylphosphine/carbon tetrachloride/triethylamine) led to the corresponding azinocarbodiimides **11**, which underwent thermal rearrangement under the reaction conditions to give 1,1-diheteroaryl ethylenes **13**.

Introduction

Vinyl derivatives of five-membered heterocyclic aromatic compounds such as furan, thiophene, and pyrrole appear to be attractive substrates as dienes in the Diels-Alder reaction.[1] The requisite 2-vinylfuran could be prepared by decarboxylation of furylacrylic acid,[2] and 2-vinylthiophene was prepared by dehydration of 2-thienylethanol[3] and 2-vinylpyrrole could be prepared *via* a Wittig reaction from formylpyrroles.[4]

We recently described a new route to 1,2,4-triazole fused heterocycles such as 5,10-dihydro-1,2,4-triazole[5,1-*b*]quinazoline **3**,[5] 7*H*-imidazo[1,2,-*b*] [1,2,4] triazole **4**,[6] and especially monocyclic *N*-α-styryl-5-(phenylamino)-1,2,4-triazole **5**[7] *via* thermal rearrangement of azinocarbodiimide **2**, which was obtained from the corresponding urea **1** using Appel's dehydration method ($Ph_3P/CCl_4/Et_3N$)[8] (Scheme 1).

With our continued interest in the reactions of azine-substituted heterocumulenes to prepare triazole ring systems, we chose to examine the reactions of 2-acetylfuran, 2-acetylthiophene, and 2-acetylpyrrole 1-ureidoethylidenehydrazones **10** with Appel's reagent to see which of the **13** or **14** would be the major product, because either the methyl group or five-membered heterocyclic aromatic ring can participate in the ring forming step (Scheme 2).

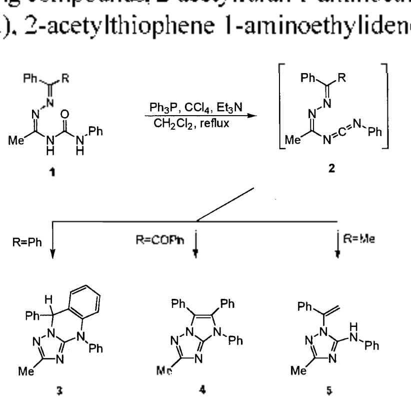


6,7,9	X	10,11,13	X	Y	10,11,13	X	Y	10,11,13	X	Y
a	O	a_1	O	H	b_1	S	H	c_1	NH	H
b	S	a_2	O	Cl	b_2	S	Cl	c_2	NH	Cl
c	NH	a_3	O	MeO	b_3	S	MeO	c_3	NH	MeO

Scheme 2

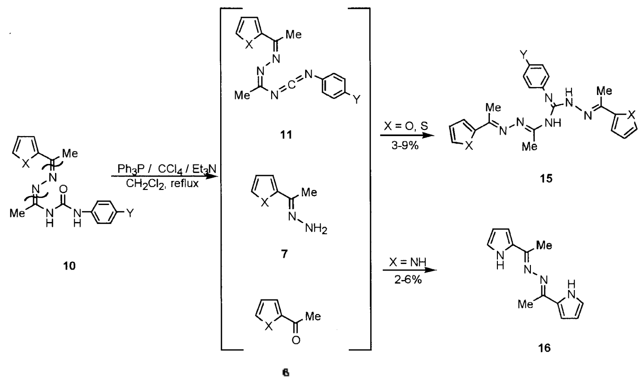
Results and Discussion

The starting compounds, 2-acetylfuran 1-aminoethylidenehydrazone (**9a**), 2-acetylthiophene 1-aminoethylidenehydraone



Scheme 1

(**9b**), and 2-acetylpyrrole 1-aminoethylidenehydrazone (**9c**) were obtained by the reaction of known *S*-methylthioacetimidate hydroiodide (**8**)[9] with 2-acetylfuran hydrazone (**7a**), 2-acetylthiophene hydrazone (**7b**), and 2-acetylpyrrole hydrazone (**7c**) in methanol at reflux temperature in 78-88% yield, respectively. The ureas **10** were produced by the reactions of hydrazones **9** with aryl isocyanates in dichloromethane at room temperature in 86-98% yield. Although thin layer chromatography (tlc) showed one spot (silica gel, ethyl acetate-hexane, 1 : 1), ^1H NMR spectrum showed a mixture of two isomers[10] and the ratio based on ^1H NMR peak of NH protons were 2.0-2.6 : 1 for the furylureas **10a₁-a₃**, 4.4-22 : 1 for the thienylureas **10b₁-b₃**, and 1.3-2.1 : 1 for the pyrrolylureas **10c₁-c₃**. Treatment of ureas **10** with triphenylphosphine, carbon tetrachloride, and triethylamine in dichloromethane at reflux temperature for 6-9 h smoothly afforded



10,15	X	Y	10,15	X	Y
a_1	O	H	b_1	S	H
a_2	O	Cl	b_2	S	Cl
a_3	O	MeO	b_3	S	MeO

Scheme 3

the 1-(1-heteroaryl)-5-(*N*-substituted amino)-1,2,4-triazoles **13** as a major product. The transformation may have occurred *via* a proton abstraction from the methyl group[7] by the exocyclic nitrogen anion in the resonance structure **12b**. 1,2,4-Triazole fused heterocycle **14** was not found at all. Presumably the small contribution of resonance form **12c** having destruction of aromatic ring prohibited production of **14**.

Instead, guanidines **15** and azine **16** were isolated as a minor product in the case of furyl- and thienylureas **10a₁-b₃** and pyrrolylureas **10c₁-c₃**, respectively. The probable mechanism for the formation of **15** and **16** is shown in Scheme 3. The reaction of the presumed intermediate, azinocarbodiimides **11**, with hydrazone **7** gave guanidines **15** and the reaction of hydrazone with 2-acetylpyrrole afforded azine **16**, which were obtainable by the partial hydrolysis of ureas under the Appel's conditions. The reason why the furyl- and thienylureas **10a₁-b₃** produce only the guanidine derivatives **15** and pyrrolylureas **10c₁-c₃** produce only the azine **16** is not clear yet.

In summary, we have worked out a simple method for the synthesis of 1,1-diheteroaryl ethylenes **13** from azinoureas **10**. Further studies into the preparation of other heterocycles for use as dienes in Diels-Alder reaction are underway.

Experimental Section

All reagents and solvents were reagent grade or were purified by standard methods before use and the reactions were routinely carried out under an inert atmosphere. Silica gel 60 (70-230 mesh ASTM) used for column chromatography was supplied by E. Merck. Analytical thin layer chromatography (tlc) was performed on silica gel with fluorescent indicator coated on aluminium sheets. Melting points were taken using an Electrothermal melting point apparatus and are uncorrected. Microanalyses were obtained using a Carlo Erba EA 1180 element analyzer. The ^{1}H and ^{13}C NMR spectra were measured on a Gemini 300 spectrometer. All chemical shifts are reported in parts per million (δ) relative to tetramethylsilane.

The *S*-methylthioacetimidate hydroiodide (**8**) was prepared following the literature procedure.[9]

2-Acetylfuran hydrazone (7a). A solution of 2-acetylfuran (**6**, 4.40 g, 40 mmol) and hydrazine monohydrate (8.01 g, 160 mmol) in methanol (40 mL) was stirred at reflux temperature for 1 h. After cooling, the solution was concentrated to dryness, and the residual material was dissolved in water, and extracted with dichloromethane (50 mL×2). The organic layer was separated, dried with magnesium sulfate, concentrated to dryness, and crystallized from petroleum ether to give the product **7a**; yield 4.02 g (81%); mp 48-50 °C; ^{1}H NMR ($CDCl_3$): δ 2.03 (s, 3H, CH_3), 5.38 (br s, 2H, NH_2), 6.39 (dd, 1H, *J*=3.3, *J*=0.9, aromatic), 6.48 (d, 1H, *J*=3.3, aromatic), 7.39 (d, 1H, *J*=0.9, aromatic). Anal. Calcd. for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.22; H, 6.66; N, 22.77.

2-Acetylthiophene hydrazone (7b). 2-Acetylthiophene hydrazone (**7b**) was prepared in 96% yield from 2-acetylthiophene (**6b**) for 1 h by the aforementioned procedure, mp 68-69 °C; ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H, CH_3), 5.23 (br s, 2H, NH_2), 6.97-7.21 (m, 3H, aromatic). Anal. Calcd. for $C_6H_8N_2S$: C, 51.39; H, 5.75; N, 19.98; S, 22.87. Found: C, 51.45; H, 5.63; N,20.27; S, 22.45.

2-Acetylpyrrole hydrazone (7c). 2-Acetylpyrrole hydrazone (**7c**) was prepared in 95% yield from 2-acetylpyrrole for 1 h by the aforementioned procedure, mp 85-87 °C; ^{1}H NMR ($CDCl_3$): δ 2.04 (s, 3H, CH_3), 5.08 (s, 2H, NH_2), 6.17 (m, 1H, aromatic), 6.32 and 6.75 (s, each 1H, aromatic), 9.45 (br s, 1H, NH). Anal. Calcd. for $C_6H_9N_3$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.84; H, 7.75; N, 34.07.

2-Acetylfuran 1-aminoethylidenehydrazone (9a). To a solution of *S*-methylthioacetimidate hydroiodide (**8**) (8.68 g, 48 mmol) in methanol (150 mL) was added 2-acetylfuran hydrazone (**7a**, 4.96 g, 40 mmol) and this solution was stirred at reflux temperature for 0.5 h. After cooling, the solution was concentrated to dryness, and the residual material was dissolved in dichloromethane (300 mL) and washed with 10% sodium hydrogen carbonate solution (200 mL). The organic layer was separated, dried with magnesium sulfate, concentrated to dryness, and crystallized from ethyl acetate-petroleum ether to give the product **9a**; yield 5.74 g (87%); mp 74-76 °C; ^{1}H NMR ($CDCl_3$): δ 2.10 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 5.42 (br s, 2H, NH_2), 6.45 (m, 1H, aromatic), 6.74 (d, 1H, aromatic), 7.47 (s, 1H, aromatic). Anal. Calcd. for $C_8H_{11}N_3O$: C, 58.16; H, 6.71; N, 25.44. Found: C, 58.02; H, 6.35; N, 25.65.

2-Acetylthiophene 1-aminoethylidenehydrazone (9b). 2-Acetylthiophene 1-aminoethylidenehydrazone (**9b**) was prepared in 78% yield from 2-acetylthiophene hydrazone (**7b**) for 0.5 h by the aforementioned procedure, mp 76-78 °C; ^{1}H NMR ($CDCl_3$): δ 2.06 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 5.34 (br s, 2H, NH_2), 6.97-7.29 (m, 3H, aromatic). Anal. Calcd. for $C_8H_{11}N_3S$: C, 53.01; H, 6.12; N, 23.18; S, 17.69. Found: C, 52.69; H, 6.47; N, 23.06; S, 17.32.

2-Acetylpyrrole 1-aminoethylidenehydrazone (9c). 2-Acetylpyrrole 1-aminoethylidenehydrazone (**9c**) was prepar-ed in 88% yield from 2-acetylpyrrole hydrazone (**7c**) for 0.5 h by the aforementioned procedure, mp 148-149 °C; ^{1}H NMR ($CDCl_3$): δ 2.02 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 5.28 (br s,

Table 1. 1-Ureidoethylidenehydrazones **10** Prepared

Compound	Yield (%)	mp (°C)	^{1}H NMR (DMSO-d$_6$) δ[a]				Analyses (%) Calcd./(Found)				Ratio[d]
			Two CH$_3$[b]	aromatic[c]	Two NH[b]	others	C	H	N	S	
10a$_1$	88	190-192	2.27, 2.35 (2.30, 2.43)	6.62-7.85	9.67, 11.61 (9.14, 9.86)		63.36 (63.56)	5.67 (5.88)	19.71 (19.77)		2.3/1
10a$_2$	91	197-199	2.26, 2.34 (2.30, 2.43)	6.62-7.85	9.74, 11.69 (9.15, 10.00)		56.52 (56.51)	4.74 (4.89)	17.58 (17.54)		2.0/1
10a$_3$	91	183-185	2.27, 2.34 (2.31, 2.44)	6.62-7.84	9.61, 11.50 (9.10, 9.67)	3.74(OCH$_3$)	61.13 (61.33)	5.77 (6.12)	17.83 (17.98)		2.6/1
10b$_1$	86	195-196	2.26, 2.45 (2.40, 2.42)	7.02-7.68	9.68, 11.58 (8.91, 9.86)		59.97 (60.04)	5.37 (5.36)	18.65 (18.68)	10.67 (10.23)	4.5/1
10b$_2$	98	206-208	2.31, 2.50 (2.46, 2.48)	7.17-7.68	9.82, 11.73 (8.99, 10.07)		53.80 (53.42)	4.52 (4.55)	16.73 (16.35)	9.58 (9.25)	4.4/1
10b$_3$	95	197-200	2.27, 2.45 (2.41, 2.43)	6.93-7.64	9.66, 11.49 (8.87, 9.73)	3.76(OCH$_3$)	58.16 (58.17)	5.49 (5.54)	16.96 (16.90)	9.71 (9.42)	22/1
10c$_1$	93	196-197	2.31, 2.31 (2.28, 2.40)	6.13-6.18, 6.60- 6.64, 6.91-7.55	9.50, 11.75 (9.30, 9.54)	11.15(NH)	63.58 (63.50)	6.05 (6.42)	24.71 (25.00)		1.7/1
10c$_2$	87	197-199	2.31, 2.31 (2.27, 2.40)	6.13-6.18, 6.61- 6.64, 6.92-7.59	9.57, 11.84 (9.46, 9.57)	11.16(NH)	56.69 (56.92)	5.08 (5.35)	22.04 (22.34)		1.3/1
10c$_3$	86	189-190	2.29, 2.30 (2.27, 2.39)	6.11-6.18, 6.60- 6.63, 6.88-7.46	9.44, 11.60 (9.11, 9.49)	11.15(NH), 3.73(OCH$_3$)	61.32 (61.56)	6.11 (6.42)	22.35 (22.73)		2.1/1

[a] Parentheses values are minor compounds. [b] All singlets. [c] Values are both isomers. [d] Ratios based on 300 MHz ^{1}H NMR of NH proton.

2H, NH$_2$), 6.20 (s, 1H, aromatic), 6.51 (d, 1H, aromatic), 6.79 (s, 1H, aromatic), 9.78 (br s, 1H, NH). Anal. Calcd. for $C_8H_{12}N_4$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.18; H, 7.75; N, 34.19.

2-Acetylfuran 1-ureidoethylidenehydrazones 10a$_1$-a$_3$, 2-Acetylthiophene 1-ureidoethylidenehydrazones 10b$_1$-b$_3$, and 2-Acetylpyrrole 1-ureidoethylidenehydrazones 10c$_1$-c$_3$; General Procedure. To a stirred solution of 1-aminoethylidenehydrazone **9** (20 mmol) in dichloromethane (50 mL) was added isocyanate (22 mmol) at room temperature. After stirring for 0.5 h at ambient temperature, the precipitated solid was separated by filtration, washed with ether and dried in vacuo to give **10** (Table 1).

3-Methyl-1-(1-furylethenyl)-5-(*N*-substituted amino)-1,2,4-triazoles 13a$_1$-a$_3$, 3-Methyl-1-(1-thienylethenyl)-5-(*N*-substituted amino)-1,2,4-triazoles 13b$_1$-b$_3$, and 3-Methyl-1-(1-pyrrolylethenyl)-5-(*N*-substituted amino)-1,2,4-triazoes 13c$_1$-c$_3$; General Procedure. To a stirred suspension of the

Table 2. 1,1-Diheteroaryl Ethylenes **13** Prepared

Compound	Reaction Time (h)	Yield[a] (%)	Mp (°C)	^{1}H NMR (CDCl$_3$) δ					Analyses (%) Calcd./(Found)			
				CH$_3$[b]	=CH$_2$[b]	NH[b]	aromatic[c]	others[b]	C	H	N	S
13a$_1$	6	63	119-121	2.36	5.39, 5.91	6.43	6.29-6.30, 6.41-6.43, 6.97-7.02, 7.29-7.49		67.65 (67.45)	5.30 (5.61)	21.04 (21.11)	
13a$_2$	6	83	116-118	2.34	5.36, 5.88	6.53	6.27-6.29, 6.41-6.42, 7.20-7.48		59.90 (60.16)	4.36 (4.59)	18.63 (18.81)	
13a$_3$	7	76	107-109	2.31	5.35, 5.84	6.49	6.28-6.29, 6.40-6.41, 6.80-6.83, 7.34-7.43	3.74(OCH$_3$)	64.85 (65.19)	5.44 (5.77)	18.91 (18.86)	
13b$_1$	8	58	108-110	2.39	5.42, 5.76	6.24	7.00-7.45		63.81 (63.58)	5.00 (5.39)	19.84 (19.45)	11.36 (11.78)
13b$_2$	8	60	99-100	2.39	5.42, 5.76	6.23	7.02-7.41		56.86 (57.14)	4.14 (4.27)	17.69 (17.35)	10.12 (9.85)
13b$_3$	7	55	107-109	2.36	5.41, 5.74	6.10	6.84-7.35	3.78(OCH$_3$)	61.51 (61.40)	5.16 (5.40)	17.94 (17.55)	10.26 (10.01)
13c$_1$	8	68	195-197	2.31	5.21, 5.42	6.49	6.14[b], 6.23-6.26, 6.80-6.81, 6.95-7.32	9.88(NH)	67.90 (68.10)	5.70 (6.01)	26.40 (26.06)	
13c$_2$	9	41	198-199	2.31	5.22, 5.45	6.51	6.20[b], 6.27-6.28, 6.86[b], 7.19-7.30	9.61(NH)	60.10 (60.25)	4.71 (4.35)	23.37 (23.71)	
13c$_3$	7	73	192-194	2.31	5.21, 5.45	6.50	6.08[b], 6.23-6.26, 6.80-6.83, 7.23-7.26	3.76(OCH$_3$), 9.57(NH)	65.06 (64.78)	5.80 (6.15)	23.72 (23.41)	

[a] Yield of pure isolated product. [b] All singlets. [c] Multiplets.

Table 3. Guanidines **15** Prepared

Compound	Reaction Time (h)	Yield[a] (%)	Mp (°C)	^{1}H NMR ($CDCl_3$) δ three CH_3[b]	aromatic[c]	two NH[b]	others[b]	Analyses (%) Calcd./(Found) C	H	N	S
15a₁	6	2	161-163	2.43(6H), 2.44	6.48-7.76	9.15, 11.35		64.60 (64.58)	5.68 (6.03)	21.52 (21.27)	
15a₂	6	7	188-189	2.40(6H), 2.43	6.47-7.70	9.11, 11.40		59.36 (58.98)	4.98 (5.23)	19.78 (19.43)	
15a₃	7	3	167-169	2.41(6H), 2.44	6.47-7.67	9.13, 11.20	3.81(OCH_3)	62.84 (62.51)	5.75 (5.72)	19.99 (19.65)	
15b₁	8	8	178-180	2.42, 2.51(6H)	7.03-7.75	9.11, 11.30		59.69 (60.02)	5.25 (5.59)	19.88 (19.53)	15.17 (14.80)
15b₂	8	3	203-205	2.41, 2.48(6H)	7.04-7.69	9.07, 11.37		55.19 (54.79)	4.63 (4.67)	18.39 (18.03)	14.03 (14.12)
15b₃	7	6	192-194	2.42, 2.49(6H)	6.88-7.67	9.10, 11.17	3.81(OCH_3)	56.39 (56.12)	5.16 (5.30)	17.93 (18.12)	13.68 (13.60)

[a] Yield of pure isolated product. [b] All singlets. [c] Multiplets.

Table 4. ^{13}C NMR Data of 1,1-Diheteroaryl Ethylenes **13**

Compound	^{13}C NMR ($CDCl_3$/TMS) δ
13a₁	14.3, 110.7, 111.8, 117.6, 122.4, 129.1, 132.8, 138.8, 143.7, 144.2, 148.4, 151.3, 158.7
13a₂	14.2, 110.7, 111.8, 118.9, 128.9, 132.7, 137.5, 143.7, 144.2, 145.1, 148.3, 151.0, 158.6
13a₃	14.1, 55.1, 110.4, 111.6, 114.1, 120.1, 132.1, 132.7, 143.4, 144.0, 148.4, 152.1, 155.2, 158.4
13b₁	14.4, 110.9, 117.7, 122.5, 127.4, 127.5, 127.9, 129.2, 136.5, 137.8, 138.9, 151.4, 158.9
13b₂	14.3, 118.7, 119.2, 127.3, 127.7, 128.0, 128.8, 129.3, 136.3, 137.5, 137.6, 150.9, 158.8
13b₃	14.4, 55.5, 110.7, 114.4, 120.2, 127.3, 127.4, 127.9, 132.2, 136.6, 137.9, 152.1, 155.5, 158.8
13c₁	14.3, 105.5, 109.8, 109.9, 117.8, 120.6, 122.4, 125.7, 129.0, 134.4, 138.8, 151.2, 158.7
13c₂	14.3, 105.6, 110.0, 110.1, 118.9, 120.7, 125.5, 127.3, 129.0, 134.3, 137.4, 150.8, 158.8
13c₃	14.2, 55.5, 105.2, 109.7, 114.3, 120.2, 120.5, 121.6, 125.8, 132.1, 134.5, 151.9, 155.4, 158.6

urea **10** (3.0 mmol) in dichloromethane (30 mL) was added triphenylphosphine (1.18 g, 4.5 mmol), carbon tetrachloride (1.16 mL, 12 mmol), and triethylamine (0.63 mL, 4.5 mmol) and the mixture was heated to reflux temperature for the time indicated in Table 2. After cooling to room temperature the reaction mixture was partitioned between water and dichloromethane (15 mL×2), and combine each other, and the solvent was removed after drying over magnesium sulfate. The residue was chromatographed on silica gel column and eluted with hexane-ethyl acetate 4 : 1 to give **13** as a white solid after crystallization from petroleum ether (Table 2 and Table 4).

In the case of furyl-, and thienylureas **10a₁-b₃**, guanidine **15** was eluted first during chromatography, and in the case of pyrrolylureas **10c₁-c₃**, all azine **16** was obtained first during chromatography in 2.2 and 6% yields, respectively; mp 205-206 °C; ^{1}H NMR ($CDCl_3$): 2.32 (s, 3H, CH_3), 6.26 (s, 1H, aromatic), 6.59(d, J=1.7, 1H, aromatic), 6.90 (s, 1H, aromatic), 9.37 (s, 1H, NH). Anal. Calcd. For $C_{12}H_{14}N_4$: C, 67, 26; H, 6.59; N, 26.15. Found: C, 67.31 ; H, 6.86; N, 26.05.

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