Benzotriazol-1-ylalkyl Isocyanides: Versatile Synthons for Preparation of Unsymmetrical Formamidines

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Adducts from benzotriazole, an aldehyde, and formamide are dehydrated to α-(benzotriazol-1-yl)alkyl isocyanides which readily add to secondary amines to form *N'*-(benzotriazol-1-ylalkyl)-*N,N*-dialkylformamidines. The benzotriazolyl group in the latter is displaced by Grignard reagents to yield the corresponding unsymmetrical formamidines.

Formamidines are interesting and important compounds that feature in the biosyntheses of imidazoles and purines, and also in the catabolism of histidine.[1] The *N,N*-dialkyl (often *N*-methyl-*N*-alkyl) derivatives are highly effective acaricides (*e.g.* Amitraz and Chlordimeform[2]). Furthermore, formamidines are reactive synthons for various chemical syntheses.[3]

The chemistry of amidines in general are well documented[3] but usually formamidines are not discussed specifically although few of the general synthetic reactions for amidines can be applied for their preparation. In most routes to formamidines, formation of one of the nitrogen–formyl carbon bonds is the key synthetic step. Thus, treatment of amines (i) with disubstituted (mainly dimethyl) formamides and a 'dehydrating' agent such as PCl_5,[3a] $POCl_3$,[4] $COCl_2$,[5] or tosyl chloride;[6] or (ii) with activated dialkylformamide derivatives such as formamidinium salts (*e.g.*, $Me_3{}^+NCHO{\cdot}MeSO_4{}^-$),[7] dialkoxymethylamines [*e.g.*, $R_2NCH(OR')_2$],[8a,b] DMF aminal esters, [*e.g.*, $(Me_2N)_2CHOBu^t$],[3d] *etc.*, have been used for synthesis of formamidines. Monosubstituted formamides, activated by complexation,[9] or by conversion into imidates (X = OR),[7,10] or into imidoyl chlorides (X = Cl),[11] as well as certain di- or tri-substituted formamidines[3d,7,12] react with amines to form substituted formamidines.

Formimidoylations can be achieved not only by substitutions, but also in the α-addition of an amine to isocyanides (see Equation 1).

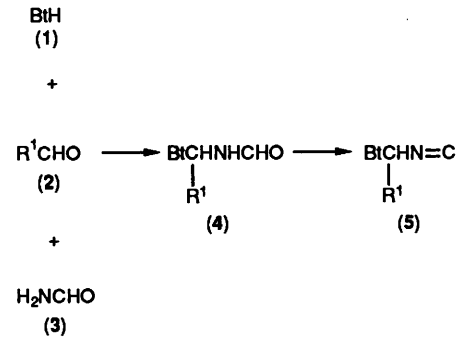
$$RN{=}C + HN\begin{matrix}A^1\\A^2\end{matrix} \longrightarrow RN{=}CHN\begin{matrix}A^1\\A^2\end{matrix} \qquad (1)$$

Aromatic[13] and α,β-unsaturated[14] isocyanides usually do not require special conditions. However, such reactions of aliphatic isocyanides only can be performed in the presence of catalyst and often require elevated temperatures.[15a,16] Although these reactions usually give high yields, the required conditions, as well as the well known, unpleasant odour of the starting isocyanides, are disadvantages, and an attempted application of the method to the formimidoylation of a pterin derivative failed.[17]

Recently benzotriazole (Bt) has been developed in our laboratory as a highly efficient synthetic auxiliary group for various chemical transformations.[18] We now disclose the preparation of isonitriles BtCH(R)N=C [(**5**), Scheme 1], their application to the formimidoylation of amines, and the subsequent nucleophilic displacement of the benzotriazole entity in the resulting formamidines (**6**). Such sequences provide convenient and versatile methods for the preparation of diverse formamidines (**7**).

Discussion

α-(Benzotriazol-1-yl)alkyl isocyanides (**5a–d**) were prepared as shown in Scheme 1. Benzotriazole (**1**), formamide (**3**) and the appropriate aldehyde (**2**), [paraformaldehyde for (**4a**)] were treated in refluxing toluene under Dean-Stark conditions, similar to the method applied previously for higher amides,[18c] to give the formamides (**4a–d**) in good yields (Table 1). Compounds (**4a–d**) were characterized by their ^1H, ^{13}C NMR and IR spectra and C,H,N analyses. Dehydration of the formamide derivatives (**4**) with $POCl_3$ in the presence of Et_3N or $Pr^i{}_2NH$ resulted in the isocyanides (**5a–d**) in good yields (Table 2). Application of other dehydrating methods, such as tosyl chloride,[6] or thionyl chloride and base,[19] or triphenylphosphine and carbon tetrachloride,[20] were less advantageous. The isocyanide structure is confirmed by the strong IR absorption band at 2132 cm^{-1}, and by the ^{13}C signal of the isocyanato carbon at δ = 161–163 ppm.[21] Chemical shifts and multiplicities of the ^1H NMR signal of CH_2 or CH(R) attached to benzotriazole, are also very indicative of the product structure. Isocyanide (**5a**) is solid and can be recrystallized. Physical data of the compound were identical to the published values.[22] Isocyanides (**5b–d**) are oils; they were characterized by their IR, NMR and high resolution mass spectra (Tables 2–4) and used for further transformations in the crude state.



Scheme 1.

Although aliphatic isocyanides are reported to remain unchanged when treated with primary or secondary amines without a catalyst even at temperatures as high as 120 °C,[15a] when the isocyanides (**5**) are treated with cyclic secondary amines without any catalyst at 20 °C they give high yields of amidines (**6**) (Table 5). Three equivalents of the amine were used in general for this reaction; however, treatment of the isonitriles (**5a**) and (**5c**) with 1.1 equivalent of piperidine also yielded the formamidines (**6a**) and (**6d**), respectively, in high yield. The work-up procedure is simple and gives the solid products in a practically pure state.

Compounds (**6a–d**) were characterized by their spectra and C,H,N analyses or high resolution mass spectra. The singlet of

Table 1. Synthesis of the 1-(1-formylaminoalkyl)benzotriazoles (**4**).

Compd.	R^1	Yield (%)	Recryst. solvent	M.p. (°C)	Formula	Analysis (%) Required C	H	N	Found C	H	N
(**4a**)	H	63	EtOH	138–139[a]	$C_8H_8N_4O$	54.5	4.6	31.8	54.2	4.4	32.0
(**4b**)	Pr	87		*b*	$C_{11}H_{14}N_4O$	218.116 76			218.116 82[c]		
(**4c**)	Pr^i	92	Hexane–Et_2O	93–95	$C_{11}H_{14}N_4O$	60.5	6.5	25.7	60.4	6.0	25.8
(**4d**)	Ph	77	EtOH	141–142	$C_{14}H_{12}N_4O$	66.7	4.8	22.2	66.7	4.7	22.4

[a] Lit.,[21] m.p. 146–147 °C. [b] Oil, b.p. 95–100 °C/0.5 mmHg. [c] Molecular mass, determined by high resolution mass spectroscopy.

Table 2. Synthesis of the α-(benzotriazol-1-yl)alkyl isocyanides (**5**).

Compd.	R^1	Yield (%)	M.p. (°C)	Formula	Accurate molecular mass Required	Found (HRMS)
(**5a**)	H	66	104–106[a]	$C_8H_6N_4$		
(**5b**)	Pr	64	Oil	$C_{11}H_{12}N_4$	200.106 20	200.106 66
(**5c**)	Pr^i	72	25–28	$C_{11}H_{12}N_4$	200.106 20	200.106 63
(**5d**)	Ph	77	Oil	$C_{14}H_{10}N_4$	234.090 55	234.090 12

[a] Lit.[21] m.p. 103–106 °C.

Table 3. ^1H NMR chemical shifts of the 1-(1-formylaminoalkyl)benzotriazoles (**4**)[a] and benzotriazol-1-ylalkyl isocyanides (**5**).[c]

Compd.	Bt (m,4 H) δ	BtCH(R^1) δ	m	H	R^1 δ	m	H	CHO (s) δ	NH δ	m
(**4a**)	7.2–8.2	6.2	d	2				8.2	9.2–9.4	s
(**4b**)	7.2–8.4	6.9	q	1	0.9	t	3	8.5	9.3	d
					1.1–1.8	m	2			
					2.5	q	2			
(**4c**)	7.2–8.4[b]	6.5	t	1	0.7	d	3	8.6	*b*	
					1.2	d	3			
					2.2–3.2	m	1			
(**4d**)	7.6–8.2	8.3	s	1	7.5	s	5	8.6	10.2	d
(**5a**)	7.3–8.3	6.3	s	2						
(**5b**)	7.2–8.4	6.5	t	1	1.1	t	3			
					1.2–2.2	m	2			
					2.5	q	2			
(**5c**)	7.2–8.4	6.3	d	1	0.8	d	3			
					1.4	d	3			
					2.4–3.2	m	1			
(**5d**)	7.2–8.1	7.8	s	1	7.4–7.5	m	5			

[a] In $CDCl_3/(CD_3)_2SO$ with Me_4Si as the reference. [b] NH signal overlaps with benzotriazole signals. [c] In $CDCl_3$ with Me_4Si as the reference.

Table 4. ^{13}C NMR chemical shifts (δ) of the 1-(1-formylaminoalkyl)benzotriazoles (**4**)[a] and α-(benzotriazol-1-yl)alkyl isocyanides (**5**).[b]

Compd.	Bt signals C-3a	C-4	C-5	C-6	C-7	C-7a	BtCH	R^1	CHO	N=C
(**4a**)	144.6	126.4	118.1	109.8	123.0	131.1	48.2		160.8	
(**4b**)	146.0	128.4	120.0	110.9	125.0	133.3	61.0	13.8, 19.2, 36.3	161.9	
(**4c**)	145.2	127.9	119.5	110.0	124.4	133.2	65.9	18.6, 18.8, 32.7	161.4	
(**4d**)	144.2	126.1	118.0	108.9	122.6	130.6	61.8	124.9, 127.2, 124.4, 134.2	159.6	
(**5a**)	146.1	128.9	120.4	108.8	124.9	131.7	52.3			163.3
(**5b**)	147.3	128.4	120.4	109.6	124.7	131.3	66.3	12.7, 18.0, 36.7		162.3
(**5c**)	146.7	128.9	120.9	110.3	125.2	131.5	72.9	18.1, 19.0, 34.5		163.5
(**5d**)	147.1	128.9	120.9	110.7	125.2	131.1	69.3	126.1, 129.7, 124.8, 130.8		164.8

[a] In $CDCl_3/(CD_3)_2SO$ with Me_4Si as the reference. [b] In $CDCl_3$ with Me_4Si as the reference.

Table 5. Synthesis of the *N,N*-dialkyl-*N'*-(benzotriazol-1-yl)alkylformamidines (**6**).

Compd.	R^1	R^2NR^2	Yield (%)	Recryst. solvent	M.p. (°C)	Formula	Analysis (%) Required C	H	N	Found C	H	N
(**6a**)	H	Piperidino	79	Et_2O	99–102	$C_{13}H_{17}N_5$	64.2	7.0	28.8	64.3	7.1	29.2
(**6b**)	H	Morpholino	92	Et_2O	116–119	$C_{12}H_{15}N_5O$	58.8	6.2	28.6	58.7	6.2	28.5
(**6c**)	H	Pyrrolidinyl	89	Et_2O	125–128	$C_{12}H_{15}N_5$	62.9	6.6	30.5	62.6	6.6	30.8
(**6d**)	Pr^i	Piperidino	99	Oil		$C_{16}H_{23}N_5$	286.2029			286.2034[a]		

[a] Molecular mass ($M + 1^+$), determined by high resolution mass spectroscopy.

Table 6. ^1H NMR chemical shifts of the *N,N*-dialkyl-*N'*-(benzotriazol-1-yl)alkylformamidines (**6**).[a]

Compd.	Bt (m, 4 H) δ	$BtCH_2$ (s, 2 H) δ	N=CH (s, 1 H) δ	R^2NR^2 δ	m	H
(**6a**)	7.3–8.1	6.0	7.6	1.4–1.8	m	6
				3.0–3.6	br s	4
(**6b**)	7.3–8.2	6.1	7.7	3.2–3.5	m	4
				3.5–3.9	m	4
(**6c**)	7.3–8.2	6.0	7.9	1.7–2.0	m	4
				3.2–3.5	br s	4
(**6d**)[b]	7.0–8.2	5.5[c]	8.1	2.6–3.8	m	4
				1.0–1.8	m	6

[a] In $CDCl_3$ with Me_4Si as the reference. [b] Pr^i signals: 2.0–2.6 (m, 1 H), 1.0 (br s, 3 H), and 0.8 (br s, 3 H). [c] (m, 1 H).

Table 7. ^{13}C NMR chemical shifts (δ) of the *N,N*-dialkyl-*N'*-(benzotriazol-1-yl)alkylformamidines (**6**).[a]

Compd.	Bt signals C-3a	C-4	C-5	C-6	C-7	C-7a	$BtCH_2$	N=CH	R^2NR^2
(**6a**)	132.6	123.6	110.4	119.5	126.9	146.1	68.1	156.8	41–45 (b). 25.5, 24.4
(**6b**)	133.8	124.4	110.8	120.3	127.8	147.0	68.1	157.0	43–45 (b), 67.0
(**6c**)	133.1	123.5	110.2	119.3	126.8	146.0	67.7	154.6	44–50 (b), 24.6
(**6d**)[b]	132.0	123.0	113.0	119.3	126.2	147.0	88.2	155.6	45–52 (b), 24.5–28.0 (b), 24.6

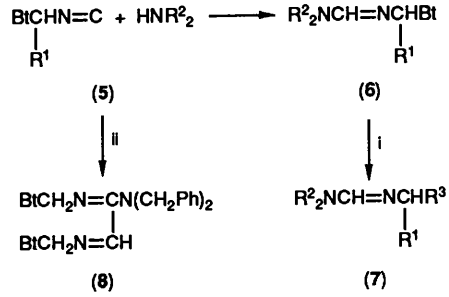
[a] In $CDCl_3$ with Me_4Si as the reference. [b] Pr^i signals: 18.5, 18.9, and 34.9.

the formamidine CH around 7.3 ppm in the ^1H NMR spectra (Table 6), the N=C–N absorption in the IR spectra (1 630–1 640 cm^{-1}) and the formamidine carbon signal in the ^{13}C NMR spectra in 150–157 ppm region (Table 7) are the most characteristic spectral data for identification of compounds (**6a–d**).

Owing to the known restricted rotation of formamidines,[23] the ^1H NMR signals of the α and β CH_2 groups of the formamidine products from cyclic secondary amines are broadened at room temperature. At a low temperature (−30 °C), separation of the rotamer signals can be observed: the ^{13}C NMR spectrum of the formamidine (**6a**) shows clearly separated α, α′ and β, β′ carbon resonances of piperidine ring (δ 49.9, 42.6, 26.0, and 24.4 ppm, respectively); the ^1H NMR spectrum shows two singlets (δ 3.4 and 3.2 ppm) for protons on the α and α′ carbons and an overlapping signal (1.55 ppm) for the four protons on the β and β′ carbons.

Surprisingly, from the treatment of the isonitrile (**5a**) with dibenzylamine, the bis-adduct (**8**) (Scheme 2) was obtained in 68% yield. Similar reaction products are obtained in the treatment of phenyl isocyanide with both phenol and naphthols.[15c]

The formamidines (**6**) were transformed by displacing the benzotriazole group using different Grignard reagents to unsymmetrical formamidines (**7**) (Table 8). These compounds



Scheme 2. *Reagents:* i, R^3MgBr; ii, $HN(CH_2Ph)_2$. For precise structures of (**6**) and (**7**) see Tables 5 and 8. $R^2{}_2N$ = piperidino, morpholino, or pyrrolidinyl; Bt = benzotriazolyl; R^1 = H or Pr^i; R^3 = Ph, vinyl, or *p*-tolyl.

were characterized by ^{13}C, ^1H, IR spectra and high resolution mass spectra or as the corresponding picrate or chloride salts. The singlet of the formamidine CH around 7.3 ppm (Table 9), the formamidine carbon signal at 153–156 ppm (Table 10) and N=CH–N absorption in the IR spectra (1 630–1 640 cm^{-1}) are the most characteristic spectral data for the identification of compounds (**7a–f**). As for the formamidines (**6**), in compounds (**7a–f**), broadening of proton and carbon signals of α and β

Table 8. Synthesis of the *N,N'*-dialkyl-*N'*-alkylformamidines (**7**).

Compd.	R^2NR^2	R^3	R^1	Yield (%)	Formula	Accurate molecular mass (HRMS) Required	Found
(**7a**)	Piperidino	Ph	H	80	$C_{13}H_{18}N_2$	*a*	
(**7b**)	Morpholino	Ph	H	82	$C_{12}H_{16}N_2O$	204.126 25	204.125 25
(**7c**)	Pyrrolidinyl	Ph	H	79	$C_{12}H_{16}N_2$	188.131 35	188.131 83
(**7d**)	Piperidino	*p*-MeC_6H_4	H	62	$C_{14}H_{20}N_2$	216.162 65	216.162 62
(**7e**)	Piperidino	vinyl	H	76	$C_9H_{16}N_2$	152.131 35	152.130 12
(**7f**)	Piperidino	Ph	Pr^i	53[b]	$C_{16}H_{24}N_2$	*c*	

[a] Characterized as picrate, m.p. 136–137 °C (lit.[17] m.p. 139 °C). [b] Yield of the isolated HCl salt, m.p. 230–232 °C. [c] Characterized by ^{13}C and ^1H NMR spectroscopy.

Table 9. ^1H NMR chemical shifts of the formamidines (**7**).[a]

	R^2			R^3CH_2N		N=CHN		R^3		
Compd.	δ	m	H	δ	m	δ	m	δ	m	H
(**7a**)	1.4–1.8	br s	6	4.5	s	7.6	s	7.2–7.6	br s	5
	3.2–3.6	br s	4							
(**7b**)	3.2–3.4	m	4	4.4	s	7.3	s	7.1–7.3	br s	5
	3.5–3.6	m	4							
(**7c**)	1.8–1.9	m	4	4.4	s	7.7	s	7.0–7.5	m	5
	3.4–3.5	m	4							
(**7d**)	1.6–1.8	br s	6	4.5	s	7.7	s	2.3	s	3
	3.4–3.6	br s	4					7.1–7.2	m	2
								7.2–7.4	m	2
(**7e**)	1.3–1.8	br s	6	4.0	br s	7.8	s	5.9–6.1	m	1
	3.4–3.7	br s	4					5.1–5.3	m	2
(**7f**)[b]	1.6–1.8	br s	6	4.15[c]	t	8.2	d	7.2–7.5	m	3
	3.4–3.7	m	2					7.6–7.8	m	2
	4.1–4.4	m	2							

[a] In $CDCl_3$ with Me_4Si as the reference. [b] Run as the hydrochloride. Pr^i signals: 0.8 (d, 3 H), 1.2 (d, 3 H), and 2.7–2.9 (m, 1 H); NH signal: 10.5 (t, 1 H). [c] (1 H).

Table 10. ^{13}C NMR chemical shifts (δ) of the *N,N*-dialkyl-*N'*-alkylformamidines (**7**).[a]

Compd.	R^2	R^3CN	N=CHN	R^3
(**7a**)	47.3, 26.0, 25.1	59.1	155.7	126.8, 127.9, 128.6, 142.1
(**7b**)	45.8, 66.5	59.4	154.8	126.3, 127.3, 128.1, 141.5
(**7c**)	47.4, 24.9	57.8	152.8	126.5, 127.6, 128.2, 141.1
(**7d**)	48.1, 25.4, 20.1	54.9	154.5	127.8, 129.0, 129.2, 136.3
(**7e**)	48.1, 25.3, 23.7	52.9	154.2	116.6, 135.3
(**7f**)[b]	23.6, 25.3, 26.7	71.9	153.6	128.3, 129.1, 129.7, 140.8
	48.2, 53.8			

[a] In $CDCl_3$ with Me_4Si as the reference. [b] Pr^i signals: 20.3, 21.1, and 32.7.

positions of the secondary amine entity was observed. This method proves to be very amenable to variation and represents a new method for the preparation of *N,N*-dialkyl and *N'*-alkyl unsymmetrical formamidines.

Experimental

M.p.s were determined with a capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 283B grating spectrometer. Proton NMR spectra were recorded on a Varian EM 360L (60 MHz) spectrometer and carbon NMR on Varian XL 200 (50 MHz) spectrometer. High resolution mass spectra were recorded on an AEI MS-30 mass spectrometer.

General Procedure for the Preparation of the Formamides (**4**).—Benzotriazole (5.95 g, 0.05 mol), the appropriate aldehyde (0.167 mol) and formamide (20 ml, 0.5 mol) in toluene (20 ml) were refluxed, and the water formed was removed using a Dean-Stark trap.

Work-up procedure for compounds (**4b**) *and* (**4c**). The reaction mixture was diluted with water (30 ml) and ethyl acetate (30 ml). The aqueous layer was extracted with ethyl acetate (30 ml). The combined organic layers were washed with water, saturated aqueous sodium carbonate (×3), and again with water. After drying ($MgSO_4$) the solvent was removed under reduced pressure to give a yellow oil.

Work-up procedure for compounds (**4a**) *and* (**4d**). Brine (60 ml; 27%) was added to the reaction mixture to precipitate the product. The product was kept in the refrigerator overnight, the solid was filtered off and washed with water and ether. Analytical samples were obtained by recrystallization (solvents are given in Table 1).

General Procedure for the Preparation of the Isocyanides (**5**) *from the Formamides* (**4**).—The formamide derivative (**4**) (0.1

mol) was dissolved in dichloromethane (100 ml), and then di-isopropylamine (0.27 mol) was added. Phosphorus oxychloride (0.11 mol) was added dropwise at 0 °C to the stirred mixture. Stirring was continued for 1 h at 0 °C, and, for the sparingly soluble formamide (**4d**), for 8–10 h at room temperature. Aqueous sodium carbonate (100 ml; 20%) was added slowly. After stirring at 20 °C for 1 h, dichloromethane (50 ml) and water (100 ml) were added. The organic layer was washed with water (3 × 50 ml), dried (Na_2SO_4) and evaporated, resulting in compound (**5a**) as a yellow solid, compound (**5c**) as a pale yellow solid and compound (**5d**) as a brown solid; a light brown oil was obtained for compound (**5b**).

General Procedure for the Preparation of the Formamidines (**6**).—The isocyanide (**5**) (0.03 mol) was added in small portions to a stirred amine (0.1 mol) at room temperature. After the mixture had been stirred for a further 2 h, ether (30 ml) was added, the precipitating product was filtered off and washed with ether to give the amidines (**6a–c**).

Preparation of the Formamidine (**6d**).—The isocyanide (**5c**) (1.0 g, 5 mmol) was added in small portions to stirred piperidine (0.47 g, 5.5 mmol) at room temperature. After 2 h the mixture became viscious and non-stirrable. Isopropyl ether (5 ml) was added, and the stirring was continued until the IR absorption band of the isocyanide (2 132 cm^{-1}) completely disappeared (1 week). Removal of the solvent and piperidine under reduced pressure yielded the formamidine (**6d**), which was characterized by NMR and high resolution mass spectra.

General Procedure for the Treatment of the Formamidines (**6**) *with Grignard Reagents*.—The commercial ethereal solution of a Grignard reagent (0.011 mol) was added dropwise to a solution of a formamidine (**6**) (0.01 mol) in THF (50 ml). The reaction mixture was stirred for 2 h, and then refluxed for a further 2 h, after which it was poured into a beaker containing crushed ice (10 g) and HCl (10 ml, 3 mol l^{-1}). Extraction with diethyl ether (50 ml, then 2 × 20 ml) removed benzotriazole. The aqueous layer was then treated with 20% aqueous NaOH to raise the pH to 7. Compound (**7f**) precipitated as the hydrochloride salt, and was filtered off, washed with cold water and ether. For the other amidines the pH was increased to 8. Extraction with methylene dichloride (5 × 20 ml) and washing the organic layer with 20% aqueous NaOH, drying (Na_2SO_4) and removal of the solvent, yielded the crude unsymmetrical formamidines (**7**).

Procedure for the Formation of Product (**8**).—Benzotriazolylmethyl isocyanide (4.70 g, 0.03 mol) was added in small portions to dibenzylamine (19.73 g, 0.11 mol), and the reaction mixture was stirred overnight. Diethyl ether (50 ml) was added and a pale green solid precipitated (5.23 g, 68%); m.p. 71–72 °C (fine white needles from diethyl ether) (Found: C, 70.3; H, 5.3; N, 24.7. $C_{30}H_{27}N_9$ requires C, 70.17; H, 5.26; N, 24.56%); $\delta_H(CDCl_3)$ 4.4 (4 H, s), 6.3 (2 H, s), 6.6 (2 H, s), 7.0–7.9 (17 H, m), and 8.0–8.4 (2 H, m).

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