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Note

Synthesis of 2,2,4,4-Tetramethyl-*N*,*N*′-bis(2,6-dimethylphenyl)cyclobutane-1,3-diimine, a Unique Compound from *Arundo donax*, and Its Analogues to Test Their Antifeedant Activity Against the Boll Weevil, *Anthonomus grandis*

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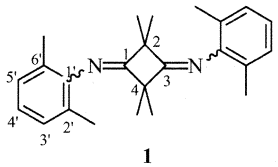
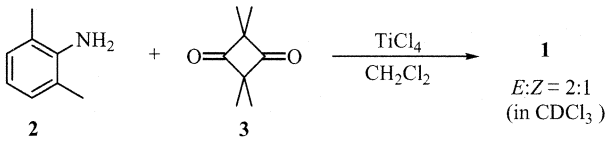
2,2,4,4-Tetramethyl-*N*,*N*′-bis(2,6-dimethylphenyl) cyclobutane-1,3-diimine (1), which was isolated from the Thai plant *Arundo donax* as an antifeedant against the boll weevil (*Anthonomus grandis*), and its analogues (9–13) were synthesized and shown to possess no remarkable antifeedant activity of practical interest.

Key words: *Arundo donax*; cyclobutanes; imines; NMR spectroscopy; phytochemistry

In 1993, Miles *et al.* isolated a crystalline compound with the molecular formula $C_{24}H_{30}N_2$ from the aerial part of the Thai plant, *Arundo donax*.[1] Its structure was resolved by an X-ray crystallographic analysis as 2,2,4,4-tetramethyl-*N*,*N*′-bis(2,6-dimethylphenyl)cyclobutane-1,3-diimine (**1**).[1] In addition, they reported it to show 54% inhibition of feeding against the boll weevil, *Anthonomus grandis*, at a dosage of 0.5 mg.[1] The unique structure of **1**, as well as its antifeedant activity, aroused interest among chemists, and indeed it was referred to in Harbone's authoritative review on chemical ecology.[2] We became interested in synthesizing **1** and its analogues so as to evaluate their antifeedant activity against the boll weevil, a notorious cotton pest in the U.S.A. At the start of the work, we believed **1** to be a new natural product according to Miles *et al.*[1] It turned out, however, that **1** has been known since 1974 as reported by Barker and Rosamond, who synthesized **1** in the course of their study on ketenimines.[3] Nevertheless, we continued our work, because the structure **1** is quite unusual as a natural product.

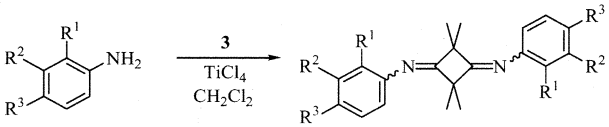


1



2 **3**

Scheme 1.



4–8 **9–13**

Starting anilines	R^1	R^2	R^3	Resulting diimines	(yield)	*E*:*Z* (in $CDCl_3$)
4	Me	H	Me	**9**	(76%)	2.2:1
5	Me	Me	H	**10**	(86%)	2.1:1
6	Me	H	H	**11**	(79%)	2.0:1
7	H	H	Me	**12**	(70%)	2.3:1
8	H	H	H	**13**	(65%)	2.1:1

Scheme 2.

The synthesis of **1** was carried out in the conventional manner shown in Scheme 1. Titanium(IV) chloride-catalyzed imine formation[4] between 2,6-dimethylaniline (**2**) and 2,2,4,4-tetramethylcyclobutane-1,3-dione (**3**) smoothly furnished **1**. Similarly, five analogues (**9–13**) of **1** were synthesized as shown in Scheme 2 by starting from **3** and arylamines **4–8**. Diimines **1** and **9–13** were all obtained as crystals in 63–86% yields based on **3**.

The ^{1}H-NMR spectrum of **1** has been examined at either 60 MHz[2] or 200 MHz[1] in previous works. The ^{13}C-NMR spectrum of **1** was measured at 50 MHz, and only six signals were recorded without their full assignment.[1] Our own NMR observations on **1** at 500 MHz (proton) or at 125 MHz (carbon) are summarized in Tables 1 and 2. The notable feature in

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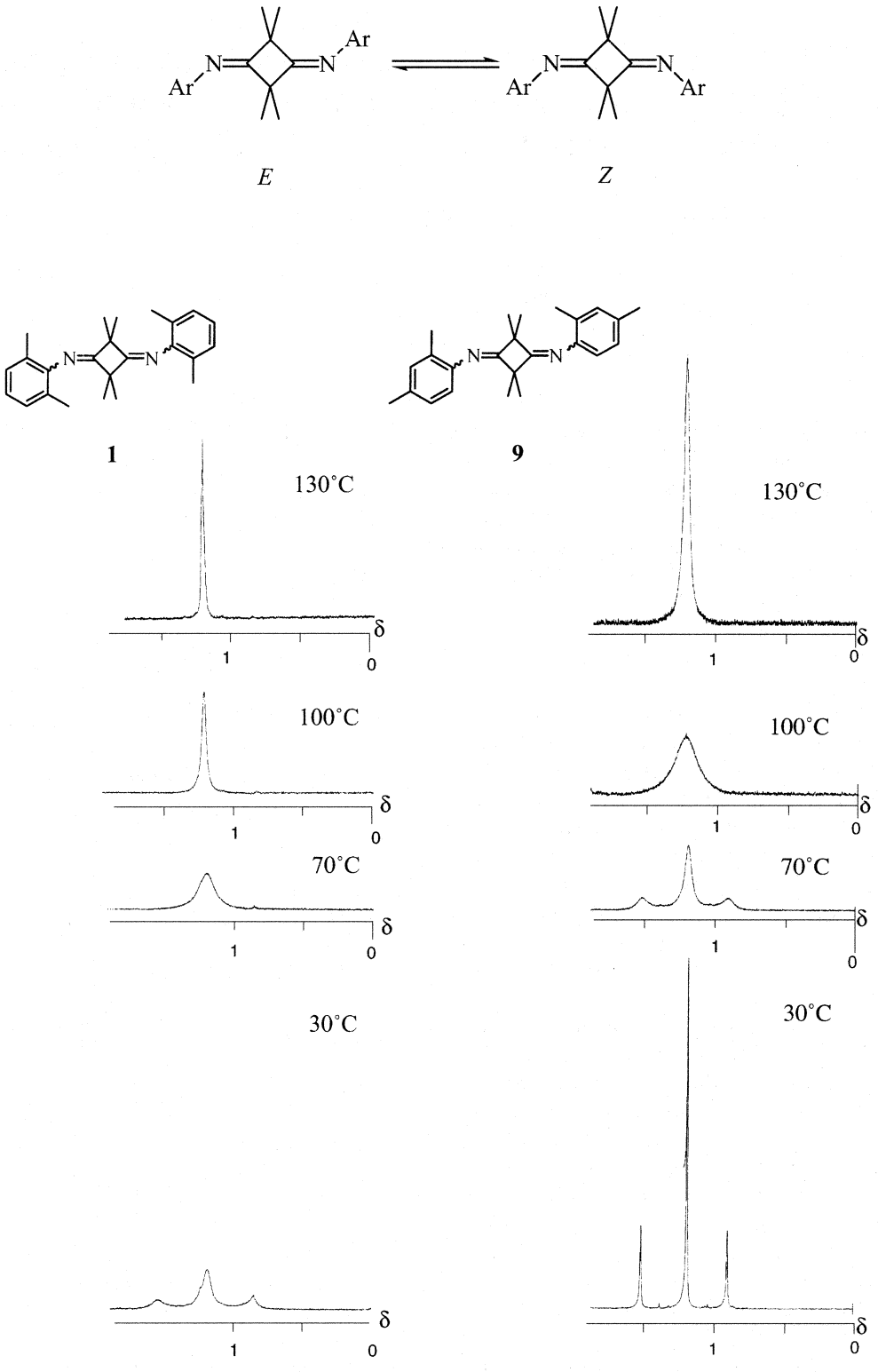

Fig. 1.

both the ^{1}H- and ^{13}C-NMR spectra of **1** is the shape of the signals due to the methyl groups at C-2 and C-4, which suggested the existence of reversible isomerization between (*E*)-**1** and (*Z*)-**1**. To study this phenomenon, the ^{1}H-NMR (500 MHz) spectra of **1** and **9** were measured in DMSO-d_6 at different temperatures (Fig. 1). In the case of **1**, three broad signals were observed at 30°C for the methyl protons at C-2 and C-4, which then coalesced to give a broad signal at 70°C, and finally a 12-proton singlet was observed at 130°C. This implies that, at 30°C both (*E*)- and (*Z*)-**1** could be observed, while at 130°C,

Table 1. ^{1}H-NMR Data for **1** (in $CDCl_3$)

	δ at 60 MHz[2)]	δ at 200 MHz[1)]	δ at 500 MHz (present work)
2-Me, 4-Me	1.27 (br)	1.25 (br)	0.94 (br), 1.30 (br.s), 1.67 (br)
Ar-Me	2.08 (s)	2.10 (s)	2.13 (s)
Ar-H	6.5–7.2 (m)	7.00 (m)	6.90 (br), 6.97 (br.s)

Table 2. ^{13}C-NMR Data for **1** and **9–13** (in $CDCl_3$)

	1	**9**	**10**	**11**	**12**	**13**
Ar-Me	18.0	17.6 (2-), 20.8 (4-)	13.8 (2-), 20.1 (3-)	17.7	20.7, 20.8	—
2-, 4-Me	20.7, 22.0, 23.0	23.2, 23.3, 23.4	23.1, 23.2, 23.3	23.1, 23.2, 23.3	23.2, 24.2, 24.8	23.2, 24.1, 24.7
C-2, C-4	59.9	57.7, 59.9	57.7, 59.9, 62.7	57.8, 60.0	57.5, 60.1, 63.3	57.2, 57.6, 60.2
C-2′	125.6	133.0, 133.1	125.4, 125.7	127.1, 127.4	119.4, 119.6	119.5, 119.6
C-3′	127.7	132.8	137.1	130.1	128.9, 129.0	128.4, 128.5
C-4′	123.2	126.9, 127.2	125.2, 125.4	123.8, 123.9	132.9, 133.1	123.5, 123.8
C-5′	127.7	126.2, 126.3	125.0, 125.1	125.7, 125.8	128.9, 129.0	128.4, 128.5
C-6′	125.6	118.8, 118.9	116.9, 117.0	118.9, 119.0	119.4, 119.6	119.5, 119.6
C-1′	147.0	145.1, 145.7	147.5, 148.1	147.6, 148.3	146.5, 147.1	149.0, 149.7
C=N	181.1	181.2, 181.7	180.8, 181.3	181.1, 181.6	181.2, 182.4	181.8, 182.4

the isomerization between them was rapid enough to show a coalesced sharp singlet. In the case of **9** at 30°C, the signals due to the methyl groups at C-2 and C-4 were observed as three sharp singlets, and even at 70°C, three broad signals were apparent. This means that **1** isomerized much more easily between (*E*)- and (*Z*)-**1** than **9** due to the severe steric repulsion between the methyl groups at C-2 or C-4 and those at C-2′ or C-6′. In the case of **9**, there must be a higher energy barrier to retard the isomerization between (*E*)- and (*Z*)-**9**.

Miles *et al.* did not describe the ^{13}C-NMR signals due to C-2, C-4, C-1′ and C=N of **1**, the low intensities of these signals preventing this. In our ^{13}C-NMR measurement at 125 MHz, we could observe them as shown in Table 2, in which the assignments of the signals in the ^{13}C-NMR spectra of **1** and **9–13** are summarized. These assignments were made possible by ^{13}C-^{1}H COSY measurements.

Finally, the bioactivity of diimines **1** and **9–13** was assessed by research staff at Sumitomo Chemical Co., Ltd. None of them showed any remarkable insecticidal, antibacterial or herbicidal activity. The antifeedant activity of **1** and **9–13** was tested by using adult boll weevils (*Anthonomus grandis*) as the test insect. To our disappointment, none of them exhibited any definite antifeedant activity. At concentrations of 31.25–125 ppm, they seemed to show very weak antifeedant activity (27.3–61.5% feeding inhibition), but at 500 ppm, they seemed even to stimulate feeding.

In conclusion, none of synthesized diimines **1** and **9–13** can be considered as a practical antifeedant against the boll weevil by using it alone in the absence of a certain synergist.

Experimental

Melting point (mp) data were measured with a Yanaco MP-S3 instrument and are uncorrected values. IR data were measured with a Perkin Elmer 1640 instrument, and NMR data with a Jeol JNM-LA500 instrument (500 MHz and 125 MHz for ^{1}H and ^{13}C, respectively). TMS at $\delta_H = 0.00$ and $CHCl_3$ at $\delta_H = 7.26$ were used as internal standards for ^{1}H-NMR; for ^{13}C-NMR, $CDCl_3$ at $\delta_C = 77.0$ was used.

2,2,4,4 - Tetramethyl - N,N′ - bis (2,6 - dimethyl - phenyl)cyclobutane-1,3-diimine (1). To a stirred and ice-cooled solution of **3** (0.500 g, 3.57 mmol) and 2,6-dimethylaniline (**2**, 6.50 g, 53.6 mmol) in dry CH_2Cl_2 (20 ml) was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (4.3 ml, 4.3 mmol) under argon. The mixture was stirred and gently warmed to room temp., before being heated under reflux for 24 h at 50–60°C (bath temp.). The reaction mixture was filtered through Celite. The resulting filtrate was successively washed with water, 0.1 M NaOH, 0.1 M HCl and brine, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a residue, which was recrystallized from hexane/$CHCl_3$ (1:8) to afford 0.78 g of **1** (63%) as colorless prisms, mp 176–178°C. IR ν_{max} (KBr) cm^{-1}: 3015 (w, aromatic C-H), 2960 (s, C-H), 2920 (s), 2860 (m), 1695 (s, C=N), 1680 (vs, C=N), 1590 (m), 1450 (s), 1370 (m), 1350 (m), 1250 (m), 1210 (s), 1155 (m), 1110 (m), 1050 (s), 845 (m), 760 (vs), 735 (m). ^{1}H-NMR ($CDCl_3$) δ: 0.94, 1.30, 1.67 (total 12H, br.s×3, 2-, 4-CH_3), 2.13 (total 12H, s, aromatic CH_3), 6.90, 6.97 (total 6H, br.s×2, 3′-, 4′-, 5′-H). ^{13}C-NMR ($CDCl_3$) δ: 18.0 (aromatic CH_3), 20.7, 22.0, 23.0 (br, 2-, 4-CH_3), 59.9 (br, C-2, C-4), 123.2 (C-4′), 125.6 (C-2′, C-6′), 127.7 (C-3′, C-5′), 147.0 (br, C-1′), 181.1 (br,

C=N). *Anal.* Found: C, 83.30; H, 8.86; N, 8.00%. Calcd. for $C_{24}H_{30}N_2$: C, 83.19; H, 8.73; N, 8.08%.

2,2,4,4 - Tetramethyl - N,N' - bis(2,4 - dimethyl - phenyl)cyclobutane-1,3-diimine (9). In the same manner as that just described (the reaction time was 18 h), **3** (0.500 g, 3.57 mmol) and 2,4-dimethylaniline (**4**, 4.40 g, 35.7 mmol) were converted to 0.95 g (76%) of **9** as colorless prisms, mp 166°C IR ν_{max} (KBr) cm^{-1}: 3010 (w, aromatic C-H), 2965 (s, C-H), 2920 (s), 2860 (m), 1685 (vs, C=N), 1490 (s), 1450 (s), 1370 (m), 1360 (m), 1240 (m), 1220 (s), 1165 (m), 1145 (m), 1110 (m), 1050 (s), 850 (m), 810 (vs), 685 (m), 570 (m), 495 (m). ^{1}H-NMR ($CDCl_3$) δ: 1.01, 1.29, 1.58 (total 12H, s×3, 2-, 4-CH_3), 2.11, 2.13 (total 6H, s×2, 2-aromatic CH_3), 2.25, 2.29 (total 6H, s×2, 4-aromatic CH_3), 6.54, 6.61 (total 2H, d×2, J=7.5 Hz, 6'-H), 6.84, 6.91 (total 2H, d, J=7.5 Hz, 5'-H), 6.95, (total 2H, s, 3'-H). ^{13}C-NMR ($CDCl_3$) δ: 17.6 (aromatic CH_3), 20.8 (aromatic CH_3), 23.2, 23.3, 23.4 (C-2, C-4 CH_3), 57.7, 59.9 (C-2, C-4), 118.8, 118.9 (C-6'), 126.2, 126.3 (C-5'), 126.9, 127.2 (C-4'), 132.8 (C-3'), 133.0, 133.1 (C-2'), 145.1, 145.7 (C-1'), 181.2, 181.7 (C=N). *Anal.* Found: C, 83.00; H, 8.63; N, 7.95%. Calcd. for $C_{24}H_{30}N_2$: C, 83.19; H, 8.73; N, 8.08%.

2,2,4,4 - Tetramethyl - N,N' - bis (2,3 - dimethyl - phenyl)cyclobutane-1,3-diimine (10). In the same manner as that already described (the reaction time was 18 h), **3** (0.500 g, 3.57 mmol) and 2,3-dimethylaniline (**5**, 4.40 g, 35.7 mmol) were converted to 1.10 g (86%) of **10** as colorless prisms, mp 126–127°C IR ν_{max} (KBr) cm^{-1}: 3065 (w, aromatic C-H), 2965 (s, C-H), 2925 (s), 2860 (m), 1680 (vs, C=N), 1580 (s), 1455 (s), 1375 (m), 1360 (m), 1250 (s), 1190 (w), 1170 (w), 1150 (w), 1055 (s), 845 (m), 780 (s), 760 (s), 720 (s). ^{1}H-NMR ($CDCl_3$) δ: 0.97, 1.28, 1.61 (total 12H, s×3, 2-, 4-CH_3), 2.06, 2.08 (total 6H, s×2, 2-aromatic CH_3), 2.24, 2.28 (total 6H, s×2, 3-aromatic CH_3), 6.52, 6.59 (total 2H, d×2, J=7.5 Hz, 6'-H), 6.84, 6.90 (total 2H, d×2, J=7.5 Hz, 4'-H), 6.94, 7.01 (total 2H, t×2, J=7.5 Hz, 5'-H). ^{13}C-NMR ($CDCl_3$) δ: 13.8 (2-aromatic CH_3), 20.1 (3-aromatic CH_3), 23.1, 23.2, 23.3 (2-, 4-CH_3), 57.7, 59.9, 62.7 (C-2, C-4), 116.9, 117.0 (C-6'), 125.0, 125.1 (C-5'), 125.2, 125.4 (C-4'), 125.4, 125.7 (C-2'), 137.1 (C-3'), 147.5, 148.1 (C-1'), 180.8, 181.3 (C=N). *Anal.* Found: C, 82.97; H, 8.54; N, 7.95%. Calcd. for $C_{24}H_{30}N_2$: C, 83.19; H, 8.73; N, 8.08%.

2,2,4,4 - Tetramethyl - N,N' - bis (2 - methyl - phenyl)cyclobutane-1,3-diimine (11). In the same manner (the reaction time was 18 h), **3** (0.500 g, 3.57 mmol) and 2-methylaniline (**6**, 4.00 g, 35.7 mmol) were converted to 0.90 g (79%) of **11** as colorless prisms, mp 150°C IR ν_{max} (KBr) cm^{-1}: 3065 (w, aromatic C-H), 3020 (w), 2960 (s, C-H), 2920 (s), 2860 (m), 1675 (vs, C=N), 1600 (m), 1575 (m), 1480 (m), 1455 (s), 1375 (m), 1360 (m), 1230 (s), 1190 (m), 1160 (w), 1110 (m), 1055 (s), 755 (vs), 725 (vs). ^{1}H-NMR ($CDCl_3$) δ: 1.01, 1.30, 1.61 (total 12H, s×3, 2-, 4-CH_3), 2.15, 2.16 (total 6H, s×2, aromatic CH_3), 6.65, 6.72 (total 2H, d×2, J=7.5 Hz, 6'-H), 6.73–7.15 (total 6H, m, 3'-, 4'-, 5'-H). ^{13}C-NMR ($CDCl_3$) δ: 17.7 (aromatic CH_3), 23.1, 23.2, 23.3 (2-, 4-CH_3), 57.8, 60.0 (C-2, C-4), 118.9, 119.0 (C-6'), 123.8, 123.9 (C-4'), 125.7, 125.8 (C-5'), 127.1, 127.4 (C-2'), 130.1 (C-3'), 147.6, 148.3 (C-1'), 181.1, 181.6 (C=N). *Anal.* Found: C, 82.89; H, 8.42; N, 8.68%. Calcd. for $C_{22}H_{24}N_2$: C, 82.97; H, 8.23; N, 8.80%.

2,2,4,4 - Tetramethyl - N,N' - bis (4 - methylphenyl) cyclobutane-1,3-diimine (12). In the same manner (the reaction time was 7 h), **3** (0.500 g, 3.57 mmol) and 4-methylaniline (**7**, 4.00 g, 35.7 mmol) were converted to 0.80 g (70%) of **12** as colorless prisms, mp 204–205°C IR ν_{max} (KBr) cm^{-1}: 3025 (w, aromatic C-H), 2965 (s, C-H), 2925 (s), 2860 (m), 1680 (vs, C=N), 1605 (m), 1500 (s), 1445 (m), 1375 (m), 1360 (m), 1270 (w), 1225 (s), 1110 (m), 1060 (s), 860 (m), 810 (vs), 780 (m), 720 (m), 680 (m), 560 (m). ^{1}H-NMR ($CDCl_3$) δ: 1.05, 1.29, 1.54 (total 12H, s×3, 2-, 4-CH_3), 2.28, 2.32 (total 6H, s×2, aromatic CH_3), 6.69, 6.76 (total 4H, d×2, J=8.0 Hz, 2'-, 6'-H), 7.03, 7.08 (total 4H, d×2, J=8.0 Hz, 3'-, 5'-H). ^{13}C-NMR ($CDCl_3$) δ: 20.7, 20.8 (aromatic CH_3), 23.2, 24.2, 24.8 (2-, 4-CH_3), 57.5, 60.1, 63.3 (C-2, C-4), 119.4, 119.6 (C-2', C-6'), 128.9, 129.0 (C-3', C-5'), 132.9, 133.1 (C-4'), 146.5, 147.1 (C-1'), 181.2, 182.4 (C=N). *Anal.* Found: C, 83.06; H, 8.24; N, 8.75%. Calcd. for $C_{22}H_{24}N_2$: C, 82.97; H, 8.23; N, 8.80%.

2,2,4,4 - Tetramethyl - N,N' - diphenylcyclobutane - 1,3-diimine (13). In the same manner (the reaction time was 7 h), **3** (0.500 g, 3.57 mmol) and aniline (3.30 g, 35.7 mmol) were converted to 0.67 g (65%) of **13** as colorless prisms, mp 140°C IR ν_{max} (KBr) cm^{-1}: 3060 (w, aromatic C-H), 2970 (s, C-H), 2920 (s), 2860 (m), 1695 (vs), 1680 (vs), 1590 (s), 1485 (s), 1450 (m), 1445 (m), 1375 (m), 1360 (m), 1275 (m), 1225 (s), 1055 (s), 905 (m), 845 (m), 760 (vs), 720 (vs), 700 (vs), 580 (m), 500 (m). ^{1}H-NMR ($CDCl_3$) δ: 1.05, 1.29, 1.56 (total 12H, s×3, CH_3), 6.77, 6.80 (total 4H, d×2, J=7.5 Hz, 2'-, 6'-aromatic H), 7.02, 7.08 (total 4H, t×2, J=8.0 Hz, 3'-, 5'-H), 7.24, 7.29 (total 2H, t×2, J=7.5 Hz, 4'-H). ^{13}C-NMR ($CDCl_3$) δ: 23.2, 24.1, 24.7 (2-, 4-CH_3), 57.2, 57.6, 60.2 (C-2, C-4), 119.5, 119.6 (C-2', C-6'), 123.5, 123.8 (C-4'), 128.4, 128.5 (C-3', C-5'), 149.0, 149.7 (C-1'), 181.8, 182.4 (C=N). *Anal.* Found: C, 82.63; H, 7.83; N, 9.51%. Calcd. for $C_{20}H_{18}N_2$: C, 82.72; H, 7.64; N, 9.65%.

Acknowledgments

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