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ARTICLE

Synthesis, Crystal Structure, and Insecticidal Activities of Highly Congested Hexahydroimidazo[1,2-*a*]pyridine Derivatives: Effect of Conformation on Activities†

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A series of hexahydroimidazo[1,2-*a*]pyridine derivatives were designed and synthesized through aza-Diels−Alder reactions and evaluated for insecticidal activities. Compounds **6a**−**d** with *endo*-conformation were endowed with excellent insecticidal activities against cowpea aphid (*Aphis craccivora*) and armyworm (*Pseudaletia separata* Walker), whereas *exo*-compounds **7a**−**d** showed only low activities against cowpea aphid. The difference in activities between the *endo*- and *exo*-conformations indicated that conformation was the determinant of life or death of the insects for these compounds.

KEYWORDS: Diels−Alder reaction; insecticide; conformation; activities

INTRODUCTION

Synthetic insecticides have played an essential role not only in modern agricultural pest management but also in the control of infectious diseases transmitted by insect vectors and microorganisms (*1*, *2*). Due to the ability of insects to rapidly develop resistance and the desire to have compounds with less mammalian and environmental toxicity, the discovery of novel active molecules with ideal properties has been the focus of intense research for decades and continues to be an active area of research today.

Discovering insecticides with novel structures or mode of actions is one of the effective resistance-management tactics. In our effort to find novel insecticides previously, a series of neonicotinoids **1** (**Figure 1**) with nitro-conjugated systems that exhibited high insecticidal activities against cowpea aphid (*Aphis craccivora*), armyworm (*Pseudaletia separata* Walker), *Nephotettix bipunctatus* (Fabricius), and small brown rice planthopper (*Laodelphasx striatellus*) were synthesized (*3*). Subsequently, free base **2** was obtained by neutralizing the hydrochloric salts **1** with triethylamine (TEA). Unexpectedly, it was found that compounds **2** were unstable and could lead to the formation of two new hexahydroimidazo[1,2-*a*]pyridine isomers via self-Diels−Alder reaction, and further bioassays indicated that these two isomers showed different insecticidal activities against cowpea aphid and armyworm. Concurrent with our studies at this time, we reported that hexahydroimidazo[1,2-*a*]pyridine derivatives were potential insecticidal molecules (*4*). On the basis of the above observations, it was reasoned that the Diels−Alder reaction might be an another way to construct hexahydroimidazo[1,2-*a*]pyridine derivatives. Therefore, as an extension of our previous study and part of our agrochemistry program aimed at the discovery of novel insecticides, we report herein the synthesis and insecticidal activities of highly congested hexahydroimidazo[1,2-*a*]pyridine derivatives constructed by aza-Diels−Alder reactions.

MATERIALS AND METHODS

Instrumentation and Chemicals. Melting points (mp) were recorded on Büchi B540 apparatus (Büchi Labortechnik AG, Flawil, Switzerland) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 (400 MHz) spectrometer with $CDCl_3$ or DMSO-d_6 as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. High-resolution mass spectra were recorded under electron impact (70 eV) condition using a MicroMass GCT CA 055 instrument. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F254), and spots were visualized with ultraviolet (UV) light. X-ray diffraction was performed with a Bruker Smart 1000. The HPLC system was an Agilent 1100 series with a diode array detector (DAD), and the column was a Zorbax RX-C18 (5 μm, 4.6 mm × 250 mm). Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Yields were not optimized. All reactions were carried out under a protective atmosphere of drying nitrogen or utilizing a calcium chloride tube.

Synthetic Procedures. Compounds **4a**−**d** were synthesized according to our previously reported methods (*3*).

General Synthetic Procedure for 6a−d and 7a−d. *Method 1:* To a stirring mixture of compound **4a** (**4b**, **4c**, or **4d**) (2.5 mmol) in acetonitrile (30 mL) was added TEA, and the pH value of the mixture was adjusted to 7−8 to give **5a** (**5b**, **5c**, or **5d**). The resulting mixture was further stirred at room temperature, and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with dichloromethane/acetone (v/v 4:1) to afford target products **6a** and **7a** (**6b** and **7b**, **6c** and **7c**, or **6d** and **7d**).

Method 2 (*One-Pot Procedure*): To a mixture of compound **3** (1.02 g, 4.0 mmol) were added five-membered aromatic aldehydes (4.1 mmol),

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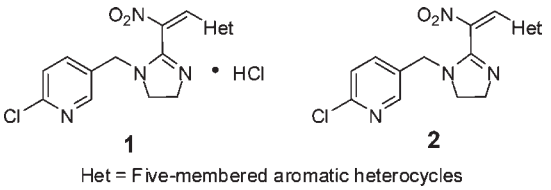


Figure 1. Neonicotinoids with nitro-conjugated system.

acetonitrile (20 mL), and 0.15 mL of concentrated hydrochloric acid. The reaction was carried out at room temperature, and the progress of the reaction was monitored by TLC. After the disappearance of compound **3**, TEA was added and the pH value of the mixture was adjusted to 7−8. Without purification, the resulting mixture continued stirring at room temperature, and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with dichloromethane/acetone (v/v 4:1) to afford target products **6a**−**d** and **7a**−**d**.

1-((6-Chloropyridin-3-yl)methyl)-6-(1-((6-chloropyridin-3-yl)methyl)-4,5-dihydro-1H-imidazol-2-yl)-5,7-di(furan-2-yl)-6,8-dinitro-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine ***6a****:* yield, 31%; yellow powder; mp, 120.1−121.6 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 8.34 (d, J = 2.4 Hz, 1H, Py−**H**), 8.29 (d, J = 2.4 Hz, 1H, Py−**H**), 7.76 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H, Py−**H**), 7.69 (dd, J_1 = 2.4 Hz, J_2 = 8.0 Hz, 1H, Py−**H**), 7.66 (d, J = 1.2 Hz, 1H, furan−**H**), 7.57 (d, J = 1.2 Hz, 1H, furan−**H**), 7.52 (d, J = 8.4 Hz, 1H, Py−**H**), 7.44 (d, J = 8.0 Hz, 1H, Py−**H**), 6.52 (d, J = 3.2 Hz, 1H, furan−**H**), 6.45 (dd, J_1 = 2.0 Hz, J_2 = 3.2 Hz, 1H, furan−**H**), 6.38 (dd, J_1 = 2.0 Hz, J_2 = 3.0 Hz, 1H, furan−**H**), 6.23 (d, J = 3.2 Hz, 1H, furan−**H**), 6.01 (s, 1H, furan−C**H**), 5.68 (s, 1H, furan−C**H**), 4.86 (d, J = 15.6 Hz, 1H, Py−C**H**), 4.75 (d, J = 15.6 Hz, 1H, Py−C**H**), 4.16 (d, J = 15.2 Hz, 1H, Py−C**H**), 4.04 (d, J = 14.8 Hz, 1H, Py−C**H**), 3.66−3.87 (m, 3H, N−C**H**$_2$C**H**$_2$−N), 3.48−3.56 (m, 1H, N−C**H**$_2$C**H**$_2$−N), 3.19−3.28 (m, 1H, N−C**H**$_2$C**H**$_2$−N), 3.07−3.17 (m, 2H, N−C**H**$_2$C**H**$_2$−N), 2.64−3.03 (m, 1H, N−C**H**$_2$C**H**$_2$−N); ^{13}C NMR (100 Mz, DMSO-d_6) δ 157.5, 156.5, 150.0, 149.9, 149.8, 149.7, 149.6, 145.9, 144.9, 143.6, 139.6, 139.6, 132.2, 132.0, 124.8, 124.5, 113.9, 111.2, 111.1, 109.1, 101.6, 89.1, 57.3, 52.1, 51.4, 51.1, 48.9, 48.2, 48.1, 41.8. HRMS (ES+) calcd for $C_{30}H_{26}N_8O_6{}^{35}Cl_2Na$ (M + Na)$^+$, 687.1250; found, 687.1256; calcd for $C_{30}H_{26}N_8O_6{}^{35}Cl^{37}ClNa$ (M + Na)$^+$, 689.1221; found, 689.1217; calcd for $C_{30}H_{26}N_8O_6{}^{37}Cl_2Na$ (M + Na)$^+$, 691.1191; found, 691.1221.

1-((6-Chloropyridin-3-yl)methyl)-6-(1-((6-chloropyridin-3-yl)methyl)-4,5-dihydro-1H-imidazol-2-yl)-6,8-dinitro-5,7-di(thiophen-2-yl)-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine ***6b****:* yield, 26%; yelllow powder; mp, 169.7−170.4 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 8.40 (d, J = 2.4 Hz, 1H, Py−**H**), 8.18 (d, J = 2.4 Hz, 1H, Py−**H**), 7.79 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H, Py−**H**), 7.56−7.59 (m, 2H, Py−**H** and thiophene−**H**), 7.43−7.51 (m, 3H, Py−**H** and thiophene−**H**), 7.06 (d, J = 2.8 Hz, 1H, thiophene−**H**), 6.99 (dd, J_1 = 3.6 Hz, J_2 = 5.2 Hz, 1H, thiophene−**H**), 6.93−6.95 (m, 1H, thiophene−**H**), 6.89 (d, J = 3.6 Hz, 1H, thiophene−**H**), 6.21 (s, 1H, thiophene−C**H**), 5.89 (s, 1H, thiophene−C**H**), 4.85 (d, J = 15.6 Hz, 1H, Py−C**H**), 4.76 (d, J = 15.6 Hz, 1H, Py−C**H**), 3.74−3.91 (m, 5H, N−C**H**$_2$C**H**$_2$−N and Py−C**H**), 3.62−3.71 (m, 1H, N−C**H**$_2$C**H**$_2$−N), 3.38−3.57 (m, 2H, N−C**H**$_2$C**H**$_2$−N), 3.13−3.20 (m, 1H, N−C**H**$_2$C**H**$_2$−N), 2.93−2.96 (m, 1H, N−C**H**$_2$C**H**$_2$−N); ^{13}C NMR (100 Mz, DMSO-d_6) δ 158.1, 157.8, 151.2, 150.0, 149.9, 149.8, 149.6, 146.8, 144.9, 142.6, 139.9, 139.7, 132.8, 131.9, 124.6, 124.6, 111.4, 111.1, 110.8, 109.2, 102.6, 94.3, 54.6, 52.4, 52.0, 50.9, 49.5, 48.5, 47.3, 42.8. HRMS (ES+) calcd for $C_{30}H_{26}N_8O_4S_2{}^{35}Cl_2Na$ (M + Na)$^+$, 719.0793; found, 719.0781; calcd for $C_{30}H_{26}N_8O_4S_2{}^{35}Cl^{37}ClNa$ (M + Na)$^+$, 721.0764; found, 721.0771; calcd for $C_{30}H_{26}N_8O_6{}^{37}Cl_2Na$ (M + Na)$^+$, 723.0734; found, 723.0739.

1-((6-Chloropyridin-3-yl)methyl)-6-(1-((6-chloropyridin-3-yl)methyl)-4,5-dihydro-1H-imidazol-2-yl)-5,7-bis(5-methylfuran-2-yl)-6,8-dinitro-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine ***6c****:* yield, 56%; yelllow powder; mp, 113.7−114.5 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 8.36 (d, J = 2.4 Hz, 1H, Py−**H**), 8.31 (d, J = 2.4 Hz, 1H, Py−**H**), 7.77 (dd, J_1 = 2.4 Hz, J_2 = 8.2 Hz, 1H, Py−**H**), 7.71 (dd, J_1 = 2.4 Hz, J_2 = 8.2 Hz, 1H, Py−**H**), 7.53 (d, J = 8.0 Hz, 1H, Py−**H**), 7.43 (d, J = 8.2 Hz, 1H, Py−**H**), 6.37 (d, J = 3.2 Hz, 1H, furan−**H**), 6.01−6.04 (m, 2H, furan−**H**), 5.95−5.96 (m, 1H, furan−**H**), 5.92 (s, 1H, furan−C**H**), 5.61 (s, 1H, furan−C**H**), 4.89 (d, J = 15.6 Hz, 1H, Py−C**H**), 4.74 (d, J = 15.6 Hz, 1H, Py−C**H**), 4.16 (d, J = 14.8 Hz, 1H, Py−C**H**), 4.05 (d, J = 14.8 Hz, 1H, Py−C**H**), 3.73−3.87 (m, 2H, N−C**H**$_2$C**H**$_2$−N), 3.62−3.69 (m, 1H, N−C**H**$_2$C**H**$_2$−N), 3.49−3.58 (m, 1H, N−C**H**$_2$C**H**$_2$−N), 3.25−3.31 (m, 1H, N−C**H**$_2$C**H**$_2$−N), 3.11−3.19 (m, 2H, N−C**H**$_2$C**H**$_2$−N), 3.02−3.07 (m, 1H, N−C**H**$_2$-C**H**$_2$−N), 2.22 (s, 3H, furan−C**H**$_3$), 2.16 (s, 3H, Furan−C**H**$_3$); ^{13}C NMR (100 Mz, DMSO-d_6) δ 157.6, 156.5, 153.5, 152.1, 150.0, 149.9, 149.8, 149.6, 148.0, 144.0, 139.8, 139.6, 132.3, 132.0, 124.8, 124.5, 114.8, 110.0, 107.3, 107.1, 101.7, 89.1, 57.2, 52.1, 51.5, 50.9, 48.8, 48.2, 48.1, 41.9, 13.7, 13.6. HRMS (ES+) calcd for $C_{32}H_{30}N_8O_6{}^{35}Cl_2$ (M + H)$^+$, 693.1699; found, 693.1716; calcd for $C_{32}H_{30}N_8O_6{}^{35}Cl^{37}Cl$ (M + H)$^+$, 695.1740.

1-((6-Chloropyridin-3-yl)methyl)-6-(1-((6-chloropyridin-3-yl)methyl)-4,5-dihydro-1H-imidazol-2-yl)-5,7-bis(5-methylthiophen-2-yl)-6,8-dinitro-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine ***6d****:* yield, 38%; yellow powder; mp, 132.8−134.4 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 8.39 (d, J = 2.4 Hz, 1H, Py−**H**), 8.19 (d, J = 2.4 Hz, 1H, Py−**H**), 7.76 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H, Py−**H**), 7.58 (dd, J_1 = 2.4 Hz, J_2 = 8.2 Hz, 1H, Py−**H**), 7.50 (d, J = 8.2 Hz, 1H, Py−**H**), 7.46 (d, J = 8.2 Hz, 1H, Py−**H**), 6.84 (d, J = 3.6 Hz, 1H, thiophene−**H**), 6.67−6.68 (m, 2H, thiophene−**H**), 6.59 (d, J = 2.5 Hz, 1H, thiophene−**H**), 6.07 (s, 1H, N−C**H**$_2$C**H**$_2$−N), 5.81 (s, 1H, thiophene−C**H**), 4.92 (d, J = 15.6 Hz, 1H, Py−C**H**), 4.74 (d, J = 15.6 Hz, 1H, Py−C**H**), 3.78−3.92 (m, 4H, Py−C**H** and N−C**H**$_2$C**H**$_2$−N), 3.76 (d, J = 15.6 Hz, 1H, Py−C**H**), 3.62−3.71 (m, 1H, N−C**H**$_2$C**H**$_2$−N), 3.42−3.56 (m, 2H, N−C**H**$_2$C**H**$_2$−N), 3.12−3.20 (m, 1H, N−C**H**$_2$-C**H**$_2$−N), 2.93−3.00 (m, 1H, N−C**H**$_2$C**H**$_2$−N), 2.36 (s, 6H, thiophene−C**H**$_3$); ^{13}C NMR (100 Mz, DMSO-d_6) δ 158.5, 156.5, 150.0, 150.0, 149.9, 149.5, 142.3, 139.8, 139.6, 139.5, 138.3, 132.9, 132.1, 131.8, 129.9, 127.5, 125.4, 125.2, 124.7, 124.5, 104.7, 94.7, 59.6, 51.8, 51.4, 50.6, 49.0, 48.4, 47.9, 42.4, 15.5, 15.4. HRMS (ES+) calcd for $C_{32}H_{31}N_8O_4S_2{}^{35}Cl_2$ (M + H)$^+$, 725.1287; found, 725.1308; calcd for $C_{32}H_{31}N_8O_4S_2{}^{35}Cl^{37}Cl$ (M + H)$^+$, 727.1257; found, 727.1286; calcd for $C_{32}H_{31}N_8O_4S_2{}^{37}Cl_2$ (M + H)$^+$, 729.1228; found, 729.1259.

1-((6-Chloropyridin-3-yl)methyl)-6-(1-((6-chloropyridin-3-yl)methyl)-4,5-dihydro-1H-imidazol-2-yl)-5,7-di(furan-2-yl)-6,8-dinitro-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine ***7a****:* yield, 25%; yellow powder; mp, 177.5−178.0 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 8.40 (d, J = 2.4 Hz, 1H, Py−**H**), 8.25 (d, J = 2.4 Hz, 1H, Py−**H**), 7.86 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H, Py−**H**), 7.73 (d, J = 1.2 Hz, 1H, furan−**H**), 7.65 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H, Py−**H**), 7.50−7.54 (m, 2H, Py−**H**), 7.36 (d, J = 0.8 Hz, 1H, furan−**H**), 6.50 (dd, J_1 = 2.0 Hz, J_2 = 3.2 Hz, 1H, furan−**H**), 6.40 (d, J = 3.2 Hz, 1H, furan−**H**), 6.38 (s, 1H, furan−C**H**), 6.27 (dd, J_1 = 2.0 Hz, J_2 = 3.2 Hz, 1H, furan−**H**), 6.02 (d, J = 3.2 Hz, 1H, furan−**H**), 5.99 (s, 1H, furan−C**H**), 4.84 (d, J = 15.6 Hz, 1H, Py−C**H**), 4.78 (d, J = 15.6 Hz, 1H, Py−C**H**), 4.15 (d, J = 14.8 Hz, 1H, Py−C**H**), 4.00−4.07 (m, 1H, N−C**H**$_2$C**H**$_2$−N), 3.84−3.91 (m, 3H, N−C**H**$_2$C**H**$_2$−N and Py−C**H**), 3.62−3.70 (m, 2H, N−C**H**$_2$C**H**$_2$−N), 3.21−3.31 (m, 1H, N−C**H**$_2$C**H**$_2$−N), 3.00−3.12 (m, 2H, N−C**H**$_2$C**H**$_2$−N); ^{13}C NMR (100 Mz, DMSO-d_6) δ 158.3, 156.7, 150.0, 149.9, 149.9, 149.5, 140.8, 139.8, 139.5, 135.6, 132.0, 131.8, 129.8, 129.1, 127.6, 127.2, 127.0, 126.3, 124.7, 124.6, 104.6, 94.5, 54.6, 52.4, 52.0, 50.9, 49.4, 48.4, 47.3, 42.8. HRMS (ES+) calcd for $C_{30}H_{27}N_8O_6{}^{35}Cl_2$ (M + H)$^+$, 665.1431; found, 665.1423; calcd for $C_{30}H_{27}N_8O_6{}^{35}Cl^{37}Cl$ (M + H)$^+$, 667.1401; found, 667.1400; calcd for $C_{30}H_{27}N_8O_6{}^{37}Cl_2$ (M + H)$^+$, 669.1372; found, 669.1397.

1-((6-Chloropyridin-3-yl)methyl)-6-(1-((6-chloropyridin-3-yl)methyl)-4,5-dihydro-1H-imidazol-2-yl)-6,8-dinitro-5,7-di(thiophen-2-yl)-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine ***7b****:* yield, 32%; yellow powder; mp, 150.3.7−151.3 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 8.44 (d, J = 2.0 Hz, 1H, Py−**H**), 8.30 (d, J = 2.0 Hz, 1H, Py−**H**), 7.90 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H, Py−**H**), 7.70 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H, Py−**H**), 7.63 (d, J = 5.0 Hz, 1H, thiophene−**H**), 7.52−7.56 (m, 2H, Py−**H**), 7.24−7.26 (m, 1H, thiophene−**H**), 7.15 (d, J = 3.0 Hz, 1H, thiophene−**H**), 7.05 (dd, J_1 = 3.6 Hz, J_2 = 5.0 Hz, 1H, thiophene−**H**), 6.78 (dd, J_1 = 3.6 Hz, J_2 = 5.0 Hz, 1H, thiophene−**H**), 6.55 (d, J = 3.2 Hz, 1H, thiophene−**H**), 6.53 (s, 1H, thiophene−C**H**), 6.25 (s, 1H, thiophene−C**H**), 4.92 (d, J = 15.6 Hz, 1H, Py−C**H**), 4.79 (d, J = 15.6 Hz, 1H, Py−C**H**), 4.37 (d, J = 14.4 Hz, 1H, Py−C**H**), 4.05−4.12 (m, 1H, N−C**H**$_2$C**H**$_2$−N), 3.97 (d, J = 14.4 Hz, 1H, Py−C**H**), 3.78−3.92 (m, 2H, N−C**H**$_2$C**H**$_2$−N), 3.65−3.73 (m, 2H, N−C**H**$_2$C**H**$_2$−N), 3.13−3.22 (m, 1H, N−C**H**$_2$C**H**$_2$−N), 2.99−3.09 (m, 2H, N−C**H**$_2$C**H**$_2$−N); ^{13}C NMR (100 Mz, DMSO-d_6) δ 156.8, 155.8, 148.5, 148.4, 148.4, 148.3, 141.3, 138.4, 138.3, 133.7, 131.1, 130.3, 128.0,

127.7, 125.2, 124.7, 124.1, 123.2, 123.1, 102.8, 98.5, 95.6, 54.5, 50.8, 50.0, 49.5, 47.9, 47.4, 45.4, 41.0. HRMS (ES+) calcd for $C_{30}H_{27}N_8O_4S_2{}^{35}Cl_2$ $(M + H)^+$, 697.0974; found, 697.0972; calcd for $C_{30}H_{27}N_8O_4S_2{}^{35}Cl^{37}Cl$ $(M + H)^+$, 699.0944; found, 699.0949; calcd for $C_{30}H_{27}N_8O_6{}^{37}Cl_2$ $(M + H)^+$, 701.0948; found, 701.0972; calcd for $C_{30}H_{26}N_8O_4S_2{}^{35}Cl_2Na$ $(M + Na)^+$, 719.0793; found, 719.0798; calcd for $C_{30}H_{26}N_8O_4S_2{}^{35}Cl^{37}ClNa$ $(M + Na)^+$, 721.0764; found, 721.0781; calcd for $C_{30}H_{26}N_8O_6{}^{37}Cl_2Na$ $(M + Na)^+$, 723.0734; found, 723.0765.

1-((6-Chloropyridin-3-yl)methyl)-6-(1-((6-chloropyridin-3-yl)methyl)-4,5-dihydro-1H-imidazol-2-yl)-5,7-bis(5-methylthiophen-2-yl)-6,8-dinitro-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine **7d**: yield, 29%; yellow powder; mp, 136.6−138.0 °C; ^{1}H NMR (400 Mz, DMSO-d_6) δ 8.44 (d, J = 2.4 Hz, 1H, Py−**H**), 8.31 (d, J = 2.4 Hz, 1H, Py−**H**), 7.89 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H, Py−**H**), 7.71 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H, Py−**H**), 7.53−7.57 (m, 2H, Py−**H**), 6.96 (d, J = 3.4 Hz, 1H, thiophene−**H**), 6.73 (dd, J_1 = 1.0 Hz, J_2 = 3.4 Hz, 1H, thiophene−**H**), 6.44 (dd, J_1 = 1.0 Hz, J_2 = 3.4 Hz, 1H, thiophene−**H**), 6.41 (s, 1H, thiophene−C**H**), 6.29 (d, J = 3.4 Hz, 1H, thiophene−**H**), 6.13 (s, 1H, thiophene−C**H**), 4.90 (d, J = 15.6 Hz, 1H, Py−C**H**), 4.81 (d, J = 15.6 Hz, 1H, Py−C**H**), 4.35 (d, J = 14.6 Hz, 1H, Py−C**H**), 4.04−4.11 (m, 1H, N−C**H**$_2$C**H**$_2$−N), 3.96 (d, J = 14.6 Hz, 1H, Py−C**H**), 3.80−3.92 (m, 2H, N−C**H**$_2$C**H**$_2$−N), 3.64−3.71 (m, 2H, N−C**H**$_2$C**H**$_2$−N), 3.18−3.27 (m, 1H, N−C**H**$_2$C**H**$_2$−N), 2.98−3.09 (m, 2H, N−C**H**$_2$C**H**$_2$−N), 2.41 (s, 3H, thiophene−C**H**$_3$), 2.31 (s, 3H, thiophene−C**H**$_3$); ^{13}C NMR (100 Mz, DMSO-d_6) δ 158.4, 157.2, 150.1, 149.9, 149.9, 149.8, 142.5, 140.0, 140.0, 139.9, 138.6, 132.7, 132.7, 132.0, 129.7, 126.1, 125.1, 124.7, 124.6, 124.6, 104.3, 97.0, 56.3, 52.4, 51.6, 51.0, 49.7, 49.0, 46.9, 42.8, 15.5, 15.4. HRMS (ES+) calcd for $C_{32}H_{31}N_8O_4S_2{}^{35}Cl_2$ $(M + H)^+$, 725.1287; found, 725.1280; calcd for $C_{32}H_{31}N_8O_4S_2{}^{35}Cl^{37}Cl$ $(M + H)^+$, 727.1257; found, 727.1256; calcd for $C_{32}H_{31}N_8O_4S_2{}^{37}Cl_2$ $(M + H)^+$, 729.1228; found, 729.1243.

X-ray Diffraction Analysis. Compound **7b** was recrystallized by slow evaporation from a mixture of acetone and dichloromethane to afford a suitable single crystal. Yellow blocks of **7b** (0.347 mm × 0.184 mm × 0.053 mm) were mounted on a quartz fiber. Cell dimensions and intensities were measured at 293 K on a Bruker SMART CCD area detector diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å); θ_{max} = 25.50; 17868 measured reflections; 6387 independent reflections (R_{int} = 0.0949). Data were corrected for Lorentz and polarization effects and for absorption (T_{min} = 0.8234 and T_{max} = 1.0000). The structure was solved by direct methods using SHELXS-97 (*5*); all other calculations were performed with Bruker SAINT system and Bruker SMART programs (*6*). Full-matrix least-squares refinement based on F^2 using the weight of $1/[\sigma^2(F_o^2) + (0.1512)^2 + 7.2988P]$ gave final values of R = 0.1140, ωR = 0.2933, and GOF (F) = 1.053 for 454 variables and 3123 contributing reflections. Maximum shift/error = 0.0000(3) and max/min residual electron density = 0.579/−0.843 e Å^{-3}. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter.

Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. All compounds were dissolved in *N*, *N*-dimethylformamide (AP, Shanghai Chemical Reagent Co., Ltd., Shanghai, China) and diluted with distilled water containing Triton X-100 (0.1 mg L^{-1}) to obtain series concentrations of 500.0, 250.0, and 125.0 mg L^{-1} and others for bioassays. For comparative purposes, imidacloprid were tested under the same conditions.

Insecticidal Test for Cowpea Aphid (*Aphis craccivora*). The activities of insecticidal compounds against cowpea aphid were tested by leaf-dip method according to our previously reported procedure (*7*, *8*). The horsebean plant leaves with 40−60 apterous adults were dipped in diluted solutions of the chemicals containing Triton X-100 (0.1 mg L^{-1}) for 5 s, and the excess dilution was sucked out with filter paper; the burgeons were placed in the conditioned room (25 ± 1 °C, 50% RH). Water containing Triton X-100 (0.1 mg L^{-1}) was used as control. The mortality rates were evaluated 24 h after treatment. Each treatment had three repetitions, and the data were adjusted and subjected to probit analysis as before.

Insecticidal Test for Armyworm (*Pseudaletia separata Walker*). The activities of insecticidal compounds against armyworm were tested using previously reported procedures (*9*, *10*). The insecticidal activity against armyworm was tested by foliar application. Individual corn (*Zea mays*) leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the compound solution and exposed to dry. The dishes were infested with 10 second-instar larvae and placed in the conditioned room. The mortality rates were evaluated 48 h after treatment. Each treatment had three repetitions, and the data were adjusted and subjected to probit analysis as before.

Insecticidal Test for Brown Planthopper (*Nilaparvata lugens*). The activities against brown planthopper were tested by Otsuka Chemical Co., Ltd. (Japan). Insecticidal compounds were diluted to a series of concentrations with acetone. Chemical solution, 2.5 mL each, was drenched into the soil of rice seedling post (pot size = 3 × 3 × 4 cm). After the solution was drenched into the soil, each seedling (4 plants/plastic cup) was covered with a plastic cup, and the 8 second-instar larvae of the brown rice planthopper were released into the plastic cup. The controls used acetone instead of insecticide solution. The plastic cup was kept in a greenhouse (25 ± 2 °C). The mortality of planthopper was determined in two replications after 6 days. The data were adjusted and subjected to probit analysis as before.

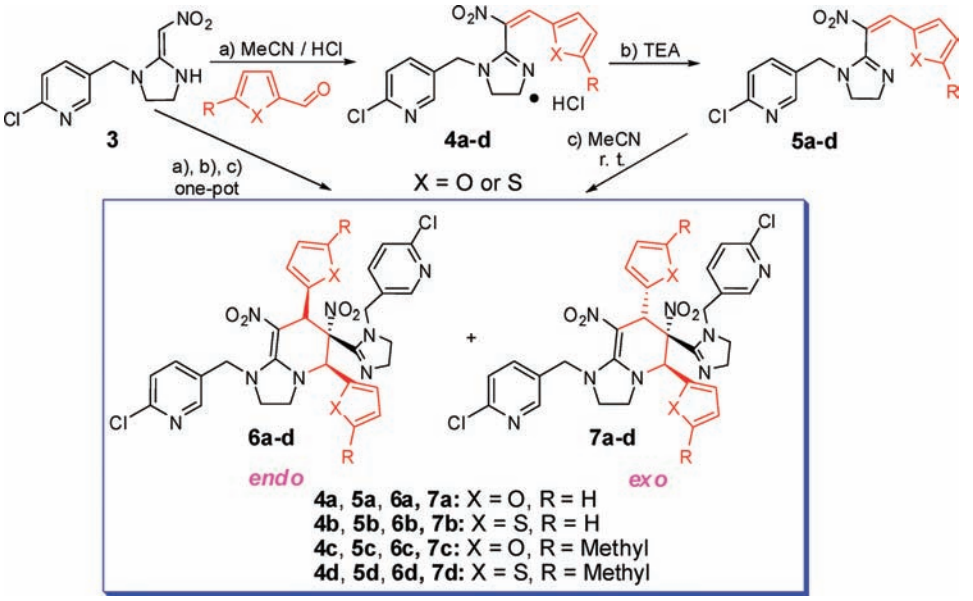
RESULTS AND DISCUSSION

Synthesis. The synthetic route of the target compounds is summarized in **Scheme 1**. According to the procedure reported previously (*11*), intermediate **3** was conveniently synthesized by a two-step process. Compound **3** could readily react with five-membered aromatic aldehydes catalyzed by concentrated hydrochloric acid at room temperature, furnishing 2-alkenyl-4,5-dihydroimidazole derivatives **4a**−**d** as the sole products. Compounds **4a**−**d** were obtained as hydrochloric acid salts.

Subsequently, free bases **5a**−**d** were obtained by neutralizing hydrochloric salts **4a**−**d** with triethylamine. Compounds **5a**−**d** were unstable when dissolved in acetonitrile at room temperature and led to the formation of two new products, respectively. Structure elucidation by their spectroscopic data revealed the two products were stereoisomers **6a**−**d** or **7a**−**d**, apparently formed by aza-Diels−Alder (ADA) reaction between two molecules of **5a**, **5b**, **5c**, or **5d**. The establishment of the stereochemistry of diastereomers **6b** and **7b** was made possible by X-ray crystallographic analysis (**Figure 2**) and *cis*-principle of Diels−Alder reactions that the stereochemistry of substituents in the starting material is retained in the product (*12*, *13*). The ^{1}H NMR spectra of **6b** and **7b** are almost the same, the only difference between them being the chemical shift values. Because the two protons (δ 6.21 and 5.89 for **6b**, δ 6.53 and 6.25 for **7b**) in the tetrapyridine ring gave a single peak in ^{1}H NMR, it can be judged that **6b** and 7b are not the regioisomers, but the diastereomers. The cycloaddition reactions of compound **5a**, **5b**, and **5d** exhibited moderate endo diastereoselectivities (*endo*/*exo* = 76:24, 59:41, and 63:37, respectively, **Table 1**), which was determined by HPLC analysis of unpurified reaction mixtures. However, the cycloaddition reaction of compound **5c** exhibited a higher *endo* diastereoselectivity (*endo*/*exo* = 88:12); the amount of **7c** obtained was too low to supply the structure analysis data. The ADA reactions described above had the following notable features: (i) The C═C—C═N part in compounds **5a**−**d** served as both 1-azadiene and dienophile. (ii) Although common 1-azadienes had inherent low reactivity and high propensity to decompose and were resistant to undergoing normal $HOMO_{diene}$-controlled ADA reactions (*14*−*19*), the 1-azadiene described here had moderate reactivity to react with itself, and the products were stable enough. (iii) The reaction required only simple workup procedures, mild conditions, and no catalyst.

The latter observation proved that Diels−Alder adducts **6a**−**d** and **7a**−**d** could also be acquired from **3** by a convenient, one-pot operation. Because the ADA reaction is among the most powerful and convergent strategies for the construction of piperidine rings (*19*, *20*), application of this unprecedented one-pot sequential reaction might be a flexible strategy for rapid

Scheme 1. Synthesis of Highly Congested Hexahydroimidazo[1,2-*a*]pyridine Derivatives **6a**−**d** and **7a**−**d**



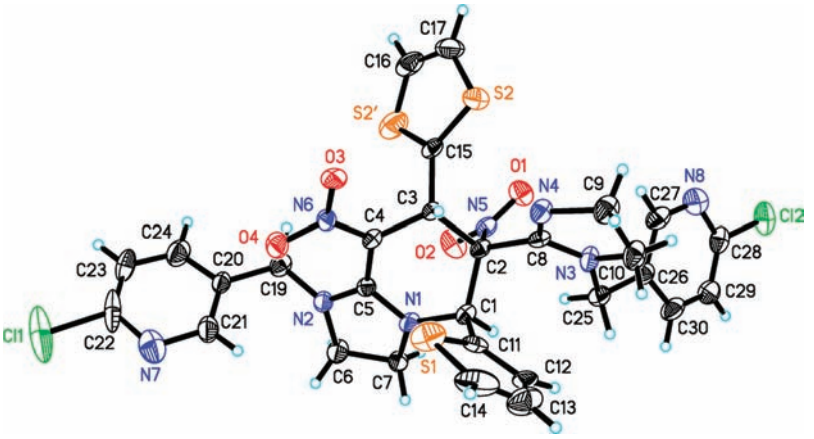


Figure 2. ORTEP view showing the atom-labeling scheme with thermal ellipsoids drawn at 30% probability for compound **7b**.

Table 1. Cycloaddition Diastereoselectivity of Compounds **5a**−**d**

entry	compd	*endo*/*exo*[a]
1	**5a**	76:24
2	**5b**	59:41
3	**5c**	88:12
4	**5d**	63:37

[a] Determined by HPLC.

construction of highly congested hexahydroimidazo[1,2-*a*]pyridine derivatives, which are valuable structures of biologically molecules (*21*, *22*). In addition to the potential of this approach to the generation of hexahydroimidazo[1,2-*a*]pyridine derivatives, it is a rare example of intermolecular ADA reaction between the same C═C—C═N systems (*14*).

Crystal Structure Analysis. To provide more evidence for the proposed molecular structure and establish the conformation of the target compounds, X-ray crystallography analysis of compound **7b** was performed. The structure of **7b** was unambiguously confirmed as shown in **Figure 2**.

In the crystal structure of **7b**, the C(5)—N(2), C(5)—N(1), and C(8)—N(3) bond lengths, 1.333(8), 1.333(8), and 1.359(8) Å, respectively, are shorter than the typical C—N single bond (1.47 Å) but close to C═N (1.33 Å) (*23*, *24*). The short C—N bonds indicated the delocalization of the lone-pair electrons on the amines to C(4)—C(5) or C(8)—N(4) double bond. The C(8)—N(4) double bond, 1.269(8) Å, is shorter than the normal one. The bond lengths of C(2)—NO_2 and C(4)—NO_2 are 1.533(8) and 1.370(8) Å, respectively, whereas typical C—NO_2 (C—N in C—NO_2) is 1.49 Å. The torsion angles of C(2)—C(3)—C(4)—N(6) and N(5)—C(2)—C(3)—C(4) were 162.5(5)° and 88.4(6)°, respectively. The tetrahydropyridine ring adopted a half-chair conformation. Two thiophene rings pointed in opposite directions, and the two nitro groups were also oriented in opposite directions. The S2 atom in the thiophene ring was disordered.

Bioassay. The insecticidal activities against cowpea aphid and armyworm of the title compounds were investigated using imidacloprid as a control, and the results are presented in **Table 2**. Compounds **6a**−**d** with *endo*-conformation displayed excellent insecticidal activities against cowpea aphid. Compounds **6a** (LC_{50} = 0.00443 mmol L^{-1}), **6c** (LC_{50} = 0.00131 mmol L^{-1}), and **6d** (LC_{50} = 0.00379 mmol L^{-1}) were endowed with the most potent activities; they were 8-, 26-, and 9-fold more active than imidacloprid (LC_{50} = 0.03502 mmol L^{-1}), respectively. The LC_{50} value of compound **6b** was 0.04675 mmol L^{-1}, which was comparable to that of imidacloprid. Against armyworm, compounds **6a**−**d** also exhibited high insecticidal activities, whereas the activities of imidacloprid were weak, which implied that these compounds

Table 2. Insecticidal Activities of Compounds **6a**−**d**, **7a**−**b**, and **7d** and Imidacloprid against Cowpea Aphid (*Aphis craccivora*) and Armyworm (*Pseudaletia separata* Walker)

	Aphis craccivora		*Pseudaletia separata* Walker	
compd	motality (%, 500 mg L^{-1})	LC_{50} (μmol L^{-1})	motality (%, 500 mg L^{-1})	LC_{50} (μmol L^{-1})
6a	100	4.43	100	26.52
6b	100	46.75	100	44.09
6c	100	1.31	100	42.97
6d	100	3.79	100	27.90
7a	87.0	nt[a]	0	nt
7b	85.6	nt	0	nt
7d	100	nt	0	nt
imidacloprid	100	35.02	100	125.49

[a] Not tested.

Table 3. Insecticidal Activities of Compound **6a** and Imidacloprid against Imidacloprid-Resistant Brown Planthoppper (*Nilaparvata lugens*)

strain	compd	LC_{50} (μmol L^{-1})	toxic ratio[a]
sensitive	**6a**	1.07	1.62
	imidacloprid	1.73	1.00
resistant	**6a**	3.76	10.32
	imidacloprid	38.82	1.00

[a] Toxic ratio is defined as the ratio of imidacloprid's LC_{50} value for baseline toxicity to the compounds' LC_{50} value.

displayed broader spectrum activities than imidacloprid. Interestingly, compounds **7a**, **7b**, and **7d** with *exo*-conformation exhibited low insecticidal activities (87.0, 85.6, and 100% mortality, respectively) at the dosage of 500 mg L^{-1}, and they were devoid of activities against armyworm.

The results shown in **Table 2** revealed that hexahydroimidazo-[1,2-*a*]pyridine derivatives might be used as new lead compounds for insecticide development. From the results above, it is noteworthy that *endo*-compounds showed high activities against cowpea aphid and armyworm, whereas *exo*-compounds showed only low activities against cowpea aphid. The results further indicated that small differences between the structures could lead to large differences in the overall activities. Surprisingly, the insecticidal activities of compound **6a** against imidacloprid-resistant brown planthopper were 10-fold higher than that of imidacloprid based on the value of LC_{50} (**Table 3**). These results increase our databank of insecticidal activities of hexahydroimidazo[1,2-*a*]pyridine derivatives for further structure−activity relationship (SAR) studies.

In summary, a series of highly congested hexahydroimidazo-[1,2-*a*]pyridine derivatives were designed and synthesized through aza-Diels−Alder reactions and evaluated for insecticidal activity. Meanwhile, a convenient and efficient procedure for the rapid construction of highly congested hexahydroimidazo[1,2-*a*]pyridine derivatives through aza-Diels−Alder reactions was developed. The procurement of hexahydroimidazo[1,2-*a*]pyridine derivatives can also be achieved though a simple, one-pot procedure. The preliminary bioassays indicated that some of the hexahydroimidazo[1,2-*a*]pyridine derivatives exhibited excellent insecticidal activities against cowpea aphid and armyworm. Interestingly, *endo*-derivatives showed higher insecticidal activities than *exo*-derivatives, which demonstrated that the *endo*-conformation was a more suitable conformation for insecticidal activities in these compounds. These results brought forward a new and unexplored scaffold as novel insecticides. Further studies on the structural optimization and mode of action of this scaffold are in progress and will be reported in due course.

Supporting Information Available: CIF data. This material is available free of charge via the Internet at http://pubs.acs.org.

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