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ARTICLE

Designing Tetrahydroimidazo[1,2-*a*]pyridine Derivatives via Catalyst-free Aza-Diels−Alder Reaction (ADAR) and Their Insecticidal Evaluation

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A series of tetrahydroimidazo[1,2-*a*]pyridine derivatives were synthesized by the reaction of 2-vinyl-4,5-dihydroimidazole derivatives with substituted benzylidenemalononitrile via a catalyst-free aza-Diels−Alder reaction. Insecticidal activities of target compounds were tested against pea aphids (*Aphis craccivora*), which showed that activities were strongly influenced by the substituents and their positions. Especially, the introduction of a fluoro group at the 2- position increased activities.

KEYWORDS: Aza-Diels−Alder; catalyst-free; insecticide; biological activities

INTRODUCTION

Insecticide resistance and cross-resistance in target species are common problems in plant protection, which pose a serious threat to insect pest control worldwide (*1*−*4*). Therefore, the exploration of new insecticides has attracted much interest, and numerous novel structures have emerged. For example, flubendiamide and chlorantraniliprole interacted with ryanodine receptors; spirodiclofen, spiromesifen, and spirotetramat performed as inhibitors of lipid biosynthesis; and the N-substituted sulfoximine derivatives appeared as novel neonicotinoids insecticides (*5*−*8*).

As a long-term strategy to explore novel structures, nitromethylene compounds such as **1**, **2**, and **3** were focused on for their high activities. Forming a conjugation system, the nitromethylene moiety plays an important role as a pharmacophore. Derived from compound **1** (**Figure 1**), a series of active compounds **4**, **5**, and **6** were synthesized in our previous work (*9*−*11*). Despite excellent activity, the commercial application of **5** was limited due to its instability. Therefore, further structure modification is urgent. Subsequent study showed the free base of **5**, compound **7**, underwent self-Diels−Alder reaction smoothly, which is one of the reasons for its instability (*12*). The facts inspired us to consider constructing new lead structures via aza-Diels−Alder reactions (ADAR), wherein **7** was regarded as 1-azadiene.

The ADAR is among the most powerful methodologies for the construction of nitrogen-containing six-membered ring compounds, which are key units in medicinal chemistry and agrochemistry and important building blocks in organic synthesis (*13*−*15*). However, the π-electron-deficient system created by the 1-N atom decreased the reactivity of normal $HOMO_{diene}$-controlled cycloadditions. The instability of the enamine product, competitive [2 + 2] imine additions, and imine tautomerization precluded productive [4 + 2] cycloaddition (*16*−*18*). Therefore, ADAR reactions have been subjects of many studies. Previous study of **7** demonstrated that it underwent self-Diels−Alder [4 + 2] cycloaddition efficiently without [2 + 2] addition, whereas the introduced bicyclic system increased the stability obviously. Thus, the program stated in the paper was initiated.

MATERIALS AND METHODS

Chemicals. Sources were as follows: All of the solvents were from Sinopharm Chemical Reagent Co., Ltd.; fluorobenzaldehydes were from Shanghai Weiyuan Fine Fluorine Science and Development Co., Ltd.; and the other chemicals were from Alfa Aesar. The 2-vinyl-4,5-dihydroimidazole derivatives were synthesized according to the method of Shao et al. (*10*). All of the commercial chemicals were of analytical purity.

Instruments. Melting points (mp) were recorded on a Büchi B540 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 (400 MHz) spectrometer with 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.

General Synthetic Procedure for 9. A solution of malononitrile (15 mmol) in ethanol (15 mL) was added dropwise to a solution of aryl aldehyde (15 mmol) in ethanol (15 mL) at room temperature. After stirring for 5 min, piperidine (0.1 mmol) used as catalyst was added. The resulting mixture was stirred for another 2 h, and **8** was obtained as precipitate. Then the reaction of **7** (10 mmol) and **8** (10 mmol) was carried out in ethyl acetate at room temperature and monitored by TLC. After completion, the mixture was filtered, washed with CH_2Cl_2, and dried to afford the desired products.

1-((6-Chloropyridin-3-yl)methyl)-7-(furan-2-yl)-8-nitro-5-phenyl-2,3,5,7-tetrahydroimidazo[1,2-a]pyridine-6,6(1H)-dicarbonitrile ***9e****:*. yield, 64%; mp 178.9−179.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.41−3.54 (m, 2H), 3.82−3.88 (m, 1H), 3.97−4.05 (m, 1H), 4.82 (d, J = 15.6 Hz, 1H), 4.89 (s, 1H), 4.92 (d, J = 15.6 Hz, 1H), 5.62 (s, 1H), 6.47 (d, J = 3.2 Hz, 1H), 6.52 (dd, J_1 = 2.0 Hz, J_2 = 3.2 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.53 (s, 5H),

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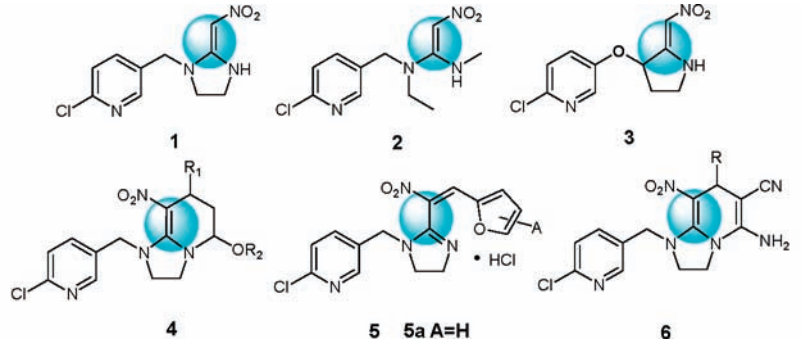
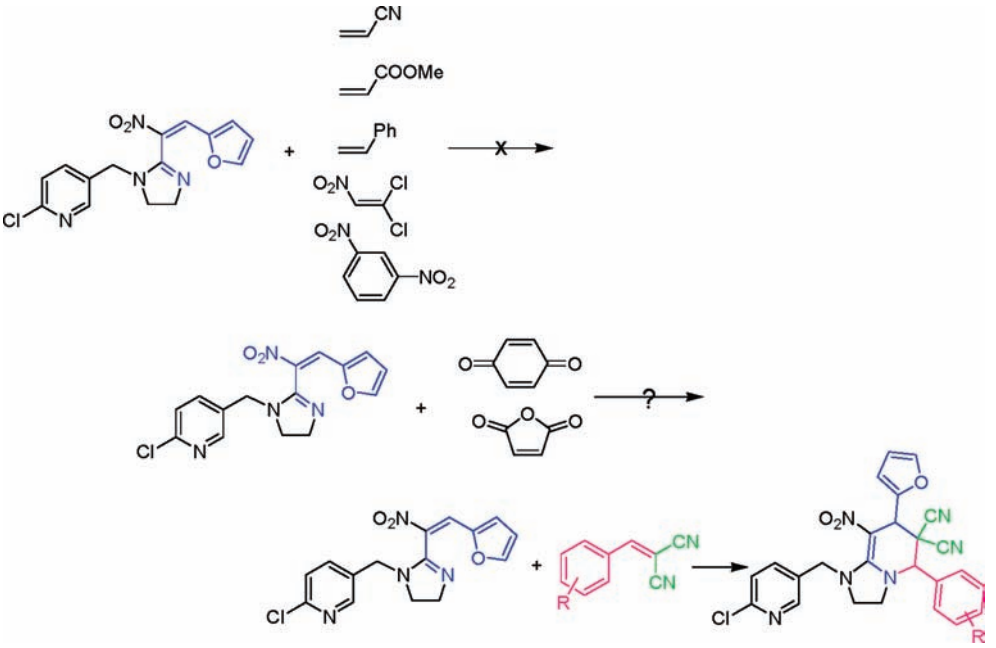


Figure 1. Nitromethylene compounds.

Scheme 1. Synthesis Route Exploration



7.69 (d, J = 1.6 Hz, 1H), 7.83 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 8.39 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 42.3, 44.2, 48.2, 49.5, 51.3, 61.2, 99.4, 111.1, 111.4, 112.7, 113.0, 124.5, 129.0, 129.5, 130.9, 131.7, 131.9, 139.7, 144.7, 148.5, 149.8, 150.0, 157.5. HRMS (ES+) calcd for $C_{25}H_{19}N_6O_3{}^{35}ClNa$ (M + Na)$^+$: 509.1105. Found: 509.1119. Calcd for $C_{25}H_{19}N_6O_3{}^{37}ClNa$ (M + Na)$^+$: 511.1075. Found: 511.1073.

Biological Assay. All compounds were dissolved in acetone and diluted with 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.

The insecticidal activities of title compounds against pea aphids (*Aphis craccivora*) were tested according to a previously reported procedure (*9*, *19*). Tender shoots of soybean with 40−60 healthy apterous adults were dipped in diluted solutions of the chemicals containing Triton X-100 (0.1 mg L^{-1}) for 5 s, the superfluous fluid was removed, and the shoots were placed in the conditioned room (25 ± 1 °C, 50% relative humidity). Water containing Triton X-100 (0.1 mg L^{-1}) was used as control. Mortality was assessed after 24 h; the control mortality was 4.1%. Each treatment had three repetitions, and the data were corrected and subjected to probit analysis using SPSS software.

RESULTS AND DISCUSSION

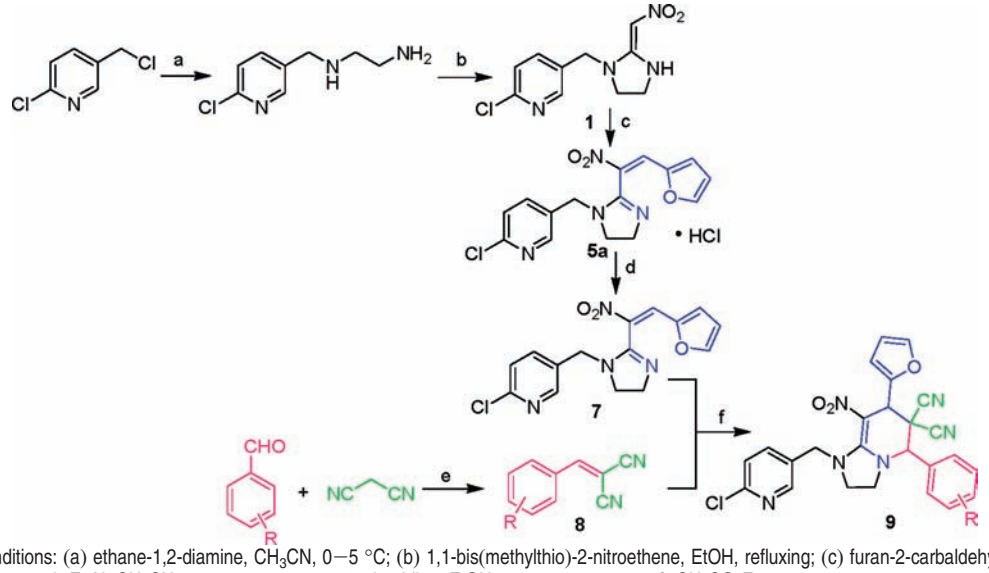
Synthesis. The ADAR investigation of **7** with electron-deficient dienophile started from styrene, methyl acrylate, acrylonitrile, 1,1-dichloro-2-nitroethene, and 1,3-dinitrobenzene. However, no reaction occurred even in the presence of Lewis acid either at room temperature or at refluxing conditions. Then, furan-2,5-dione and 1,4-benzoquinone were tried, but still no target [4 + 2] products were obtained (**Scheme 1**). Finally, benzylidenemalononitrile was applied for its strong electron-deficient ability. To our delight, the reaction proceeded successfully at room temperature in the absence of catalyst.

The preparation of obtained derivatives is outlined in **Scheme 2**. Starting from 2-chloro-5-chloromethylpridine and ((5-chloropyridin-2-yl)-methyl)-ethane-1,2-diamine, **1** and intermediate **5a** were obtained following the procedure reported previously (*9*, *20*). Treatment of **5a** in acetonitrile by triethylamine (TEA) afforded its free base **7**. The formation of **8** was via Knoevenagel condensation reaction of malononitrile and appropriate aromatic aldehyde. Further reaction of **7** and **8** completed within 30 min and precipitated compounds **9** except **9l**, which had to be purified by column chromatography. Nevertheless, attempts to synthesize the corresponding products by using aliphatic aldehydes were unsuccessful.

Initially, various solvents, including polar and nonpolar ones, were employed to enlarge the solvent's scope in our system. The particular [4 + 2] cycloaddition reactions were found to exhibit little solvent dependency on the yield and reaction rate. Ethyl acetate was ultimately chosen as it slightly increased the yield. Then, different catalysts were introduced to evaluate their effects on the reaction. However, the introduction of $AlCl_3$, DNBA, CSA, TSOH, CH_3COOH, CCl_3COOH, BF_3, and piperidine made little difference.

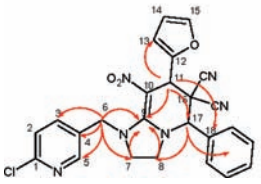
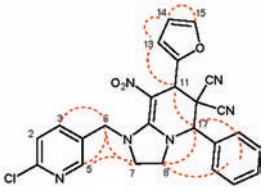
The mild conditions prompted us to extend the scope of this reaction. To evaluate the novel analogues and describe the

Scheme 2. [a] Preparation of Designed Compounds



[a] Reagents and conditions: (a) ethane-1,2-diamine, CH_3CN, 0−5 °C; (b) 1,1-bis(methylthio)-2-nitroethene, EtOH, refluxing; (c) furan-2-carbaldehyde, concentrated HCl, CH_3CN, room temperature; (d) Et_3N, CH_3CN, room temperature; (e) piperidine, EtOH, room temperature; (f) CH_3CO_2Et, room temperature.

Table 1. NMR Data and HMBC and NOESY Correlations of Compound **9e**

	HMBC		HMBC	NOESY
	HMBC			NOESY
				
atom no.	δ_H (m, *J* in Hz)	δ_C	HMBC (δ_H to δ_C)	NOESY
1		150.0		
2	7.50 (d, 8.0)	124.5	1, 3, 4, 5	3, 5
3	7.83 (dd, 2.4, 8.4)	139.7	1, 5, 6	2, 5, 6
4		131.7		
5	8.39 (d, 2.4)	149.8	1, 2, 3, 4, 6	2, 3, 6, 7
6	4.82 (d, 15.6), 4.92 (d, 15.6)	51.3	3, 4, 5, 7, 9	3, 5, 7
7	3.82−3.88 (m), 3.97−4.05 (m)	49.5	8, 9	5, 6, 8
8	3.41−3.54 (m)	48.2	7, 9	7, 17
9		157.5		
10		99.4		
11	5.62 (s)	42.3	9, 10, 12, 13, 16, 17	13, 17
12		148.5		
13	6.47 (d, 3.2)	111.1	12, 14, 15, 16	11, 14, 15
14	6.52 (dd, 2.0, 3.2)	111.4	12, 13, 15	13, 15
15	7.69 (d, 1.6)	144.7	12, 13, 14	13, 14
16		44.2		
17	4.89 (s)	61.2	8, 9, 11, 16, 18	8, 11
18		131.9		
Ph-H	7.53 (s)	129.0	16, 17, 18	8, 17
		129.5		
		130.9		

substituents' influence on bioactivity, an additional 21 aromatic aldehydes with electron-withdrawing groups or electron-donating ones were used as substrates. The electron-withdrawing group at the dienophile shortened reaction time and increased reaction yield. When an electron-donating group was introduced, reaction rates slowed, accompanied with apparent self-addition of **7**, which occurred prior to the reaction of **7** with **8**, especially when *N*,*N*-dimethyl groups were introduced. Little improvement was observed when **7** was added stepwise.

Table 2. Insecticidal Activities of Compounds **9a**−**v** and Imidacloprid (IMI) against Pea Aphid

compd	R	mortality (%), 500 mg L^{-1}	LC_{50} (mmol L^{-1})
9a	4-NO_2	0	nt[a]
9b	4-OCF_3	0	nt
9c	4-CN	0	nt
9d	4-OCH_3	0	nt
9e	H	0	nt
9f	2-F-5-CH_3	73.9	nt
9g	2,4-diCl	85.9	nt
9h	3-Br	75.8	nt
9i	2-F-4-Cl	56.7	nt
9j	2-Cl-4-Br	0	nt
9k	3-NO_2	0	nt
9l	4-$N(CH_3)_2$	0	nt
9m	3-CN	0	nt
9n	2-CH_3-5-F	0	nt
9o	2-F-5-CF_3	100	0.11260
9p	2-CF_3-4-Cl	100	0.08719
9q	2-F-4-CH_3	100	0.00552
9r	2,3-diF	48.8	nt
9s	3-Cl-4-OCF_3	0	nt
9t	3-F-4-CF_3	96.8	0.08738
9u	4-F	64.21	nt
9v	4-CH_3	0	nt
IMI			0.03502[b]

[a] nt, not tested. [b] Data from Shao et al. (*10*).

The structures of the title compounds were well characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. The two single peaks around δ 5.0 and 5.7 in the ^{1}H NMR spectra of all compounds showed that the structure of the target compounds was the way we illustrated. Moreover, heteronuclear and homonuclear chemical shift correlation experiments (HMBC, HMQC, COSY, and NOESY) were performed to confirm the assignments of the ^{13}C NMR spectrum and to assign all signals of the ^{1}H NMR spectrum. A complete assignment of the proton signals and selected HMBC and NOESY correlations of compound **9e** is shown in **Table 1**.

Bioassay. The insecticidal activities of compounds **9a**−**v** were evaluated against pea aphid (*Aphis craccivora*) as reported before (*9*). Results are depicted in **Table 2**.

As shown in **Table 2**, half of the compounds exhibited moderate to high activities against pea aphids. Activities varied significantly depending upon the types and patterns of substituents on the benzene ring. Among monosubstituted derivatives, compared to nonsubstituent compound (**9e**), substituents were unfavorable to activities except for halogen (e.g., **9h**, **9u**). Among multisubstituted compounds, 2-fluoro-4-methyl (**9q**) was most prominent in increasing activity, whereas 2-fluoro-5-trifluoromethyl (**9o**), 2-trifluoromethyl-4-chloro (**9p**), and 3-fluoro-4-trifluoromethyl (**9t**) also significantly increased activities. For the effect of substituted position, it was observed that the introduction of a fluoro group at the 2- position was beneficial for activities. Especially, the compound with a 2-fluoro-4-methyl group (**9q**) showed potency comparable to that of imidacloprid.

In conclusion, a series of tetrahydroimidazo[1,2-*a*]pyridine derivatives were designed and synthesized via catalyst-free aza-Diels−Alder reaction. The mild experimental conditions, short reaction time, and wide substrate generality represent the notable features of this procedure. Applications of the [4 + 2] cycloaddition reactions of the 2-vinyl-4,5-dihdroimidozole derivatives are in progress as are additional studies to define their full [4 + 2] cycloaddition scope, and the results of such studies will be reported in due course. The bioactivities were evaluated against pea aphids. It was found that some of the compounds showed high activities; activities were significantly influenced by the substituents and their positions. Especially, the introduction of a fluoro group at the 2-position increased activities.

Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and HRMS data of compounds **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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