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Synthesis and biological evaluation of arylhydrazinocyanoacrylates and *N*-aryl pyrazolecarboxylates

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ABSTRACT

A series of arylhydrazino-substituted cyanoacrylates **3** and *N*-aryl pyrazolecarboxylates **6** were synthesized and their bioactivities were evaluated. Though compounds **3** were designed as herbicide, some of them showed fungicidal activity and anti-tumor activity. Some of the compounds **6** exhibited plant growth regulatory activity.

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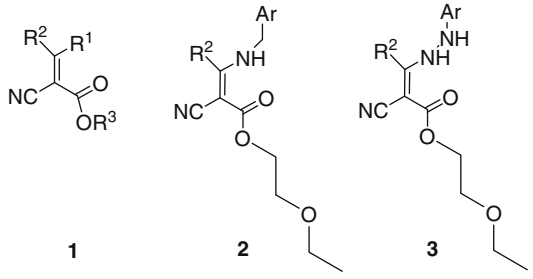
Compounds containing 2-cyanoacrylate skeleton (structure **1**) are of increasing interest because of their herbicidal[1–3], fungicidal[4,5] or antiviral[4–8] activities. In recent years, our group focused on ethoxyethyl 2-cyanoacrylates bearing heteroaryl methyleneamino group (structure **2**), which exhibited excellent herbicidal activities.[1–3] They are photosystem II (PSII) electron transport inhibitors, which displace the native plastoquinone Q_B from its binding site at the PSII reaction center therefore inhibit the growth of weeds by disrupting photosynthetic electron transport. Detailed QSAR study[9,10] revealed that the type of aryl and substituents on it played significant roles on the activity; however, no obvious result was got about methylene moiety between aryl group and atom N. In this Letter we designed structure **3** by replacing arylmethyleneamino moiety with arylhydrazino group in order to study structure-activity relationship. Herein, we report the synthesis of compounds **3** and related compounds with varieties of biological activities.

Compounds **3** were first to be prepared by refluxing arylhydrazines **4** with 3-methylthio or 3-methoxy-2-cyanoacrylate **5** in ethanol, the same procedure as we prepared compounds **2**. The reaction did give products in 40–96% yields. However, the products we got were not expected compounds. Their structures were later determined by crystal X-ray diffraction to be 1-aryl-5-amino-4-pyrazolecarboxylate **6**. (Scheme 1, Table 1 and Fig. 1).



The formation of **6** suggested that compounds **3** were reaction intermediates and could not stay at such harsh condition,[11,12] then a series of reaction conditions were screened to get compounds **3**. It turned out that stirring a mixture of **4** and **5** in ethanol at −10 °C for 30 min gave best reaction conversion and yield of **3**. The product could be filtrated from the reaction mixture, and then purified by silica gel chromatography. However, only phenylhydrazines with one or two substituents at ortho-position afforded acceptable yield of **3**. (Table 2) Crystal of **3i** was got and X-ray structure was drawn in Figure 2. As seen from the figure, the arylhydrazino group and carbonyl group are at the same side of double bond because of the formation of hydrogen bond.

Compounds **3** were tested herbicidal activity with compound **7** as control, a potential herbicide developed by our group previously.[1] The data were listed in Table 3.

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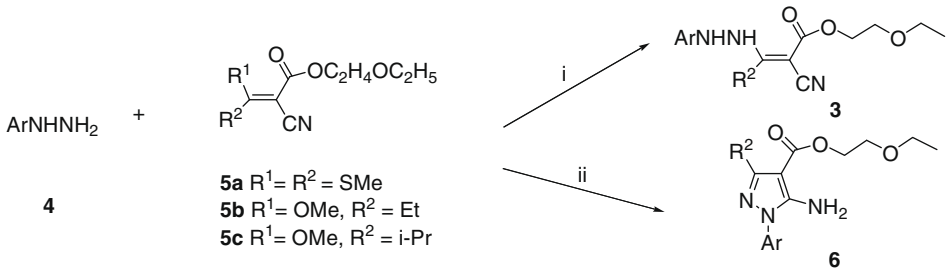


Scheme 1. Reagents and conditions: (i) EtOH, reflux, 1–2 h; (ii) EtOH, −10 °C, 30 min.

Table 1
Compounds **6** synthesized from **4** and **5**[a]

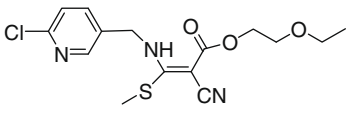
Compound	Ar	R^2	Yield[b]
6a	Phenyl	SMe	96
6b	Phenyl	Et	62
6c	Phenyl	*i*-Pr	53
6d	4-Cl-phenyl	SMe	80
6e	4-Cl-phenyl	Et	63
6f	4-Cl-phenyl	*i*-Pr	68
6g	4-NO_2-phenyl	SMe	75
6h	4-NO_2-phenyl	Et	75
6i	4-NO_2-phenyl	*i*-Pr	40
6j	4-Me-phenyl	SMe	50
6k	4-Me-phenyl	*i*-Pr	74
6l	2,4-Cl_2-phenyl	SMe	86
6m	2,4-Cl_2-phenyl	*i*-Pr	62
6n	2,4-Me_2-phenyl	SMe	63

[a] Characterization of compounds **6** can be found in Supplementary data.
[b] Separated yields.

Table 2
Compounds **3** synthesized from **4** and **5**[a]

Compound	Ar	R^2	Yield[b]
3a	2,4-Cl_2-phenyl	Et	29
3b	2,4-Cl_2-phenyl	*i*-Pr	31
3c	2,3-Cl_2-phenyl	Et	35
3d	2,3-Cl_2-phenyl	*i*-Pr	20
3e	2,4,5-Cl_3-phenyl	Et	32
3f	2,4,5-Cl_3-phenyl	*i*-Pr	30
3g	2,6-Cl_2-phenyl	Et	30
3h	2,6-Cl_2-phenyl	*i*-Pr	31
3i	2,4,6-Cl_3-phenyl	Et	31
3j	2,4,6-Cl_3-phenyl	*i*-Pr	29

[a] Characterization of compounds **6** can be found in Supplementary data.
[b] Separated yields.



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As shown in Table 3, all the compounds **3** had no obvious herbicidal reactivity compared to arylmethyleneamino-substituted cyanoacrylate **7**. We had mentioned that compounds **2** (including

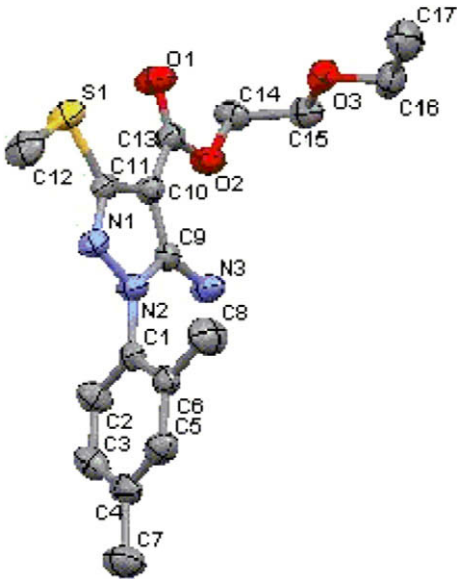

Figure 1. X-ray diagram of compound **6n**. Crystallographic data for **6n** has been deposited in the Cambridge Crystallographic Data Center (CCDC 725099).

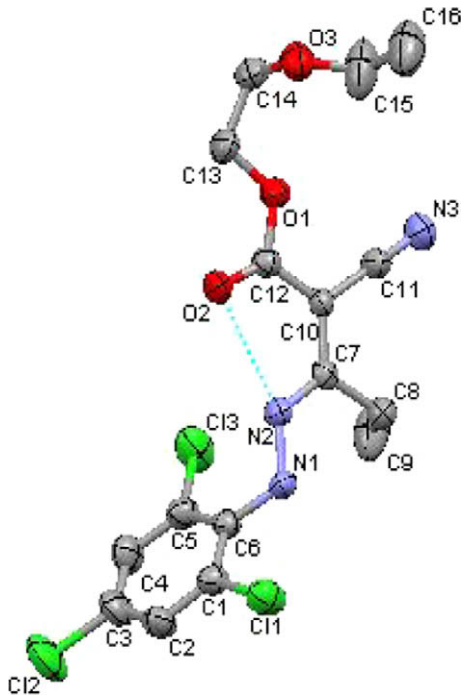

Figure 2. X-ray diagram of compound **3i**. Crystallographic data for **3i** has been deposited in the Cambridge Crystallographic Data Center (CCDC 715100).

7) are a kind of PSII electron transport inhibitors and they can bind with D1 protein at the PSII reaction center. The methylene moiety between aryl and atom N in structure **2** allows aryl group to rotate to a proper position, therefore making the molecular binding more tightly with the protein. However, when methylene moiety is changed to NH, aryl group in structure **3** cannot rotate freely be-

Table 3
Herbicidal activities of compounds **3**, **6** and **7** (1.5 kg/ha, percent inhibition, %)[a]

Compound	Postemergence treatment				Preemergence treatment			
	Rape	Amaranth pigweed	Alfalfa	Hairy crabgrass	Rape	Amaranth pigweed	Alfalfa	Hairy crabgrass
3a	0	18.0	0	0	0	0	0	0
3b	1.6	3.9	7.5	17.9	0	0	0	3.8
3c	4.3	15.6	3.3	5.4	0	5.9	0	0
3d	0.2	22.7	5.1	16.1	0	0	0	0
3e	0	15.6	4.7	0	0	5.9	0	3.8
3f	5.0	20.3	3.7	0	0	5.9	0	0
3g	11.1	22.7	2.3	0	5.3	8.8	0	0
3h	2.3	15.6	1.4	0	9.9	0	0	0
3i	0	13.3	5.6	1.8	0	8.8	0	00
3j	0	13.3	21.0	17.9	0	0	0	0
6a	53.6	32.0	38.3	0	0	10.0	0	0
6b	61.5	0	0	0	0	0	0	0
6c	58.8	0	0	0	15.0	0	0	0
6d	0	0	0	0	0	0	0	0
6e	0	0	0	0	0	0	0	0
6f	26.4	0	0	0	40.0	0	0	0
6g	0	0	38.3	0	0	0	0	0
6h	15.0	0	0	0	0	0	0	0
6i	0	0	0	0	0	0	0	0
6j	52.7	38.0	0	0	10.0	0	0	0
6k	40.70	0	20.0	0	15.0	0	0	0
6l	0	0	0	0	30.0	0	0	0
6m	0	0	16.6	0	0	0	0	0
6n	24.1	0	0	0	0	0	0	0
7	100	100	55.3	54.1	47.6	32.4	3.6	18.8

[a] Assay method and procedure were described in Supplementary data.

cause p-π conjugation exists between N1 and the aromatic ring (Fig. 1, the bond length of C6–N1 in compound **3i** is 1.40 Å, shorter than normal C–N single bond, which is 1.47 Å), therefore compounds **3** cannot bind with the protein as tightly as compound **7**. Thus, compounds **3** could not effectively inhibit electron transport thereby did not show any herbicidal effect. Compounds **6** were also tested but did not exhibit any herbicidal activity.

Compounds **3** and **6** were also evaluated if they have fungicidal activities, plant growth regulatory activity or anti-tumor activity because similar structures were found to have varieties of bioactivity.[13–19] As shown in Table 4, compounds **3a**, **3b**, **3c and 3d** exhibited good antifungal activity against *Physalospora piricola*. Compounds **3a** and **3b** also showed moderate activity against *Cercospora arachidicola*. Most of the compounds **6** gave moderate fun-

Table 4
Fungicidal activities (50 mg/L) and plant growth regulatory activities (10 mg/L) of compounds **3** and **6**. (percent inhibition, %)[a]

Compound	Fungicidal activities					Regulatory activities
	G. zeae	*A. solani*	*C. arachidicola*	*P. piricola*	*C. cucumerinum*	
3a	28.6	40.0	51.5	76.0	38.9	−5.2
3b	4.8	40.0	51.5	73.3	22.2	−27.8
3c	14.4	20.0	24.2	65.3	13.9	−12.7
3d	14.4	35.0	36.4	66.7	25.0	72.9
3e	9.6	10.0	21.3	36.0	13.9	−39.0
3f	14.4	10.0	18.2	26.7	16.7	−1.5
3g	0	10.0	24.4	24.0	0	−6.0
3h	4.8	10.0	0	10.7	0	−6.0
3i	19.2	25.0	15.5	46.7	22.2	−16.5
3j	4.8	10.0	18.2	6.7	8.3	−2.2
6a	42.2	8.0	41.2	0	12.7	50.4
6b	46.7	20.0	35.3	1.3	18.2	46.3
6c	46.7	32.0	20.6	32.0	1.8	46.3
6d	37.8	20.0	26.5	36.0	23.6	66.6
6e	53.3	0	41.2	38.7	14.5	111.3
6f	44.4	0	23.5	33.3	23.6	38.2
6g	51.1	8.0	11.8	13.3	12.7	54.4
6h	11.1	8.0	39.2	40.0	36.4	5.6
6i	46.7	16.0	44.1	46.7	40	21.9
6j	46.7	28.0	35.3	22.7	20	66.6
6k	51.1	12.0	20.6	13.3	40	21.9
6l	42.2	16.0	47.1	46.7	32.7	17.8
6m	26.7	28.0	44.1	9.3	30.9	−2.4
6n	46.7	8.0	35.3	9.3	10.9	42.2
Difenoconazole[b]	100	100	100	100	100	—
IAA[c]	—	—	—	—	—	>150

[a] Assay method and procedure were described in Supplementary data.
[b] Commercial fungicidal agent.
[c] Indole-3-acetic acid, commercial plant growth regulatory agent.

Table 5
Anti-tumor activities of compounds **3** and **6**[a]

Compound	Leukemia HL-60 cell				Liver cancer BEL-7402 cell			
	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-4}	10^{-5}	10^{-6}	10^{-7}
3a	57.2	0	0	0	0	0	0	0
3b	73.2	17.6	6.0	0	45.9	6.5	4.3	5.3
3c	69.4	50.0	26.8	21.2	55.3	24.9	12.1	11.6
3d	48.8	36.2	28.7	24.3	49.1	19.0	15.1	14.7
3e	80.4	7.3	11.8	8.3	94.5	0	0	0
3f	81.1	1.5	23.4	7.1	96.9	0	0	0
3g	80.4	72.4	35.9	4.3	79.8	54.6	17.1	11.5
3h	73.4	21.4	7.7	0	45.1	17.3	9.5	7.6
3i	84.3	36.6	23.1	2.5	95.9	3.6	3.9	0
3j	80.3	20.8	0	0	84.3	9.0	12.7	5.2
6a	10.6	0.6	6.8	4.3	49.0	0	0	0
6g	28.5	22.3	0	2.4	48.4	4.2	0	5.5
6h	41.5	13.1	1.3	0.8	45.2	0	0	0
6i	10.0	27.8	9.0	0	48.6	10.7	6.2	0
6l	56.1	16.9	8.4	4.3	46.7	0	0	0
6m	56.8	11.8	4.4	4.4	45.6	4.2	0	5.5
6n	43.5	49.9	21.0	9.4	32.9	0	0	0

Percent inhibition (%) in different concentration of compounds.
[a] Assay method and procedure were described in Supplementary data.

gicidal activity against *Gibberella Zeae*. For plant growth regulatory activity, most of the compounds **3** exhibited inhibited-growth activity whereas compound **3d** showed accelerated-growth regulatory activity as high as 72.9%. Compounds **6** showed much different activities depending on the structure, of which **6e** gave the highest activity (111%). To our pleasure, most of the compounds **3** and two of compounds **6** also showed good anti-tumor activity at concentration of 10^{-4} mol/L. Compound **3g** still remained moderate anti-tumor activity for both leukemia HL-60 cell and liver cancer BEL-7402 cell at the concentration 10^{-5} mol/L (Table 5).

In summary, arylhydrazino-substituted cyanoacrylates **3** and *N*-aryl pyrazolecarboxylates **6** were synthesized from arylhydrazine and 3-methylthio (or 3-methoxy)-2-cyanoacrylate **5** in different reaction conditions. Though there is structural similarity between compounds **3** and **2**, **3** did not exhibit any herbicidal activity. But at the optional screening of bioactivities, some of the compounds **3** showed fungicidal activity and anti-tumor activity, and some of the compounds **6** exhibited good plant growth regulatory activity. These result deserved further investigation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.04.048.

References and notes

1. Wang, Q.; Sun, H.; Cao, H.; Cheng, M.; Huang, R. *J. Agric. Food Chem.* **2003**, *51*, 5030.
2. Wang, Q.; Li, H.; Li, Y.; Huang, R. *J. Agric. Food Chem.* **2004**, *52*, 1918.
3. Liu, Y.; Cai, B.; Li, Y.; Song, H.; Huang, R.; Wang, Q. *J. Agric. Food Chem.* **2007**, *55*, 3011.
4. Li, H.; Diao, Y.; Wang, J.; Chen, C.; Ni, J.; Zhou, M. *Crop Prot.* **2008**, *27*, 90.
5. Lv, Y.; Wang, X.; Song, B.; Yang, S.; Yan, K.; Xu, G.; Bhadury, P. S.; Liu, F.; Jin, L.; Hu, D. *Molecules* **2007**, *12*, 965.
6. Song, B.; Zhang, H.; Wang, H.; Yang, S.; Jin, L.; Hu, D.; Pang, L.; Xue, W. *J. Agric. Food Chem.* **2005**, *53*, 7886.
7. Long, N.; Cai, X.; Song, B.; Yang, S.; Chen, Z.; Bhadury, P. S.; Hu, D.; Jin, L.; Xue, W. *J. Agric. Food Chem.* **2008**, *56*, 5242.
8. Chen, Z.; Wang, X.; Song, B.; Wang, H.; Bhadury, P. S.; Yan, K.; Zhang, H.; Yang, S.; Jin, L.; Hu, D.; Xue, W.; Zeng, S.; Wang, J. *Bioorg. Med. Chem.* **2008**, *16*, 3076.
9. Han, X.; Liu, Y.; Liu, Y.; Lai, L.; Huang, R.; Wang, Q. *Chin. J. Chem.* **2007**, *25*, 1135.
10. Liu, Y.; Wei, D.; Zhu, Y.; Liu, S.; Zhang, Y.; Zhao, Q.; Cai, B.; Li, Y.; Song, H.; Liu, Y.; Wang, Y.; Huang, R.; Wang, Q. *J. Agric. Food Chem.* **2008**, *56*, 204.
11. Cernuchova, P.; Vo-Thanh, G.; Milata, V.; Loupy, A.; Jantova, S.; Theiszova, M. *Tetrahedron* **2005**, *61*, 5379.
12. Guerrini, G.; Ciciani, G.; Cambi, G.; Bruni, F.; Selleri, S.; Melani, F.; Montali, M.; Martini, C.; Ghelardini, C.; Norcini, M.; Costanzo, A. *Bioorg. Med. Chem.* **2008**, *16*, 4471.
13. Ouyang, G.; Chen, Z.; Cai, X.; Song, B.; Bhadury, P. S.; Yang, S.; Jin, L.; Xue, W.; Hu, D.; Zeng, S. *Bioorg. Med. Chem.* **2008**, *16*, 9699.
14. Farag, A. M.; Mayhoub, A. S.; Barakat, S. E.; Bayomi, A. H. *Bioorg. Med. Chem.* **2008**, *16*, 881.
15. Bouabdallah, I.; M'Barek, L. A.; Zyad, A.; Ramdani, A.; Zidane, I.; Melhaoui, A. *Nat. Prod. Res.* **2006**, *20*, 1024.
16. Bernardino, A. M. R.; Gomes, A. O.; Charret, K. S.; Freitas, A. C. C.; Machado, G. M. C.; Canto-Cavalheiro, M. M.; Leon, L. L.; Amaral, V. F. *Eur. J. Med. Chem.* **2006**, *41*, 80.
17. Park, H.; Lee, K.; Park, S.; Ahn, B.; Lee, J.; Cho, H.; Lee, K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3307.
18. Goldstein, D. M.; Alfredson, T.; Bertrand, J.; Browner, M. F.; Clifford, K.; Dalrymple, S. A.; Dunn, J.; Freire-Moar, J.; Harris, S.; Labadie, S. S.; La Fargue, J.; Lapierre, J. M.; Larrabee, S.; Li, F.; Papp, E.; McWeeney, D.; Ramesha, C.; Roberts, R.; Rotstein, D.; San Pablo, B.; Sjogren, E. B.; So, O.-Y.; Talamas, F. X.; Tao, W.; Trejo, A.; Villasenor, A.; Welch, M.; Welch, T.; Weller, P.; Whiteley, P. E.; Young, K.; Zipfel, S. *J. Med. Chem.* **2006**, *49*, 1562.
19. Abadi, A. H.; Eissa, A. A. H.; Hassan, G. S. *Chem. Pharm. Bull.* **2003**, *51*, 838.