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ARTICLE

Synthesis and Herbicidal Activity of Novel *N*-(2,2,2)-Trifluoroethylpyrazole Derivatives

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A series of novel *N*-(2,2,2)-trifluoroethylpyrazole derivatives were synthesized, and their structures were characterized by IR, mass spectroscopy, ^{1}H NMR, and elementary analysis. The herbicidal activities of target compounds **10a**−**c** and **11a**−**c** were assessed. The bioassay results showed that these pyrazole derivatives exhibited good herbicidal activity. Compound **11a** showed the best pre-emergence herbicidal effects against both dicotyledonous and monocotyledonous weeds with good safety to maize and rape at the dosage of 150 g a.i. ha^{-1} in greenhouse. Field trials indicated that compound **11a** exhibited better herbicidal activity by soil application than the commercial herbicide, metolachlor. Moreover, compound **11a** showed the same level of safety to maize as metolachlor.

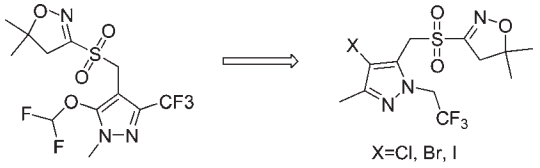
KEYWORDS: *N*-(2,2,2)-Trifluoroethylpyrazole; herbicidal activity; synthesis; safety

INTRODUCTION

Much interest in pyrazole derivatives has been drawn in agrochemicals because of their excellent bioactivity (*1*−*8*). Numerous herbicides such as pyrazolate, pyrazoxyfen, benzofenap, pyraflufen-ethyl, fluazolate, and pyrazosulfuron-ethyl with pyrazole moieties have been commercialized (*9*). Recently, a series of new pyrazole derivatives with potential herbicidal activity have been synthesized by Nakatani et al. (*10*, *11*). The key feature of these compounds is a five- or six-membered heterocycle attached to the 4-position of the pyrazole ring by a thiomethylene or sulfonylmethylene bridge. In the structure−activity relationship (SAR) development around these compounds, the optimal structure with high herbicidal efficacy and selectivity against target species contains a substituted pyrazole, which is attached to a dihydroisoxazole bridged by thiomethylene or sulfonylmethylene. Among them, 3-[[[5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]methyl]sulfonyl]-4,5-dihydro-5,5-dimethylisoxazole (code name KIH-485) is currently under commercial development by Kumiai Chemical Industry Co., Ltd., as a pre-emergence weed control for maize and soybean. The spectrum of weeds controlled by KIH-485 is similar to the acetanilide herbicides such as metolachlor and dimethenamid (*12*−*15*). KIH-485 is a potent inhibitor of very long-chain fatty acids (VLCFAs) biosynthesis, similar to the K3 group of herbicides (*16*). Very long-chain fatty acid elongase (VLCFAE)-inhibiting herbicides have been categorized into the K3 group by the Herbicide Resistance Action Committee, including metolachlor, naproanilide, flufenacet, etc.

To further explore the potential of this class of compounds as herbicide candidates, we developed an idea that dihydroisoxazole is attached to the 5-position of the pyrazole ring linked by thiomethylene or sulfonylmethylene (**Scheme 1**). Moreover, the introduction of trifluoromethyl into *N*-methyl group of pyrazole ring would be expected to improve herbicidal activity due to the intrinsic properties of trifluoromethyl, such as high thermal stability, increased lipophilicity, electronegativity, and relatively small size (*17*). The synthesis and herbicidal activities of these novel pyrazole derivatives are described in this paper.

Scheme 1. Design Strategy for the Target Compounds



KIH-485 **11**

MATERIALS AND METHODS

^{1}H NMR spectra were recorded in $CDCl_3$ with a Bruker DPX300 spectrometer, using tetramethylsilane as an internal standard (performed at China Agricultural University). Elemental analysis (C, H, and N) and electrospray ionization−mass spectrometry (ESI-MS) were performed at the Institute of Chemistry, Chinese Academy of Sciences. IR (KBr) (ν_{max}, cm^{-1}) spectra were recorded on a Nicolet IR200 FT-IR spectrophotometer. Melting points were measured on a WRS-2A melting point apparatus and are uncorrected. The solvents and reagents were used as received or were dried prior to use as needed.

Synthesis. Dihydroisoxazole was synthesized as described in the patent (*18*) (**Scheme 2**). The synthetic route from acetylacetone (**4**) to 4-halo-5-((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonylmethyl)-3-methyl-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole (**11**) is shown in **Scheme 3**.

Hydroxyiminoacetic Acid (2). A mixture of aqueous glyoxylic acid (213 g, 1.44 mol, 50%) and hydroxylamine hydrochloride (100 g, 1.44 mol) was stirred at room temperature overnight. The reaction mixture was

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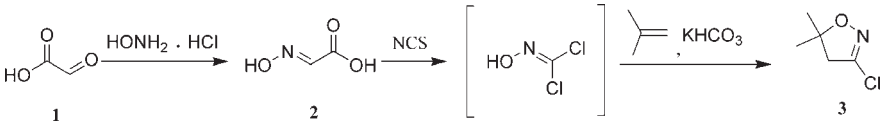
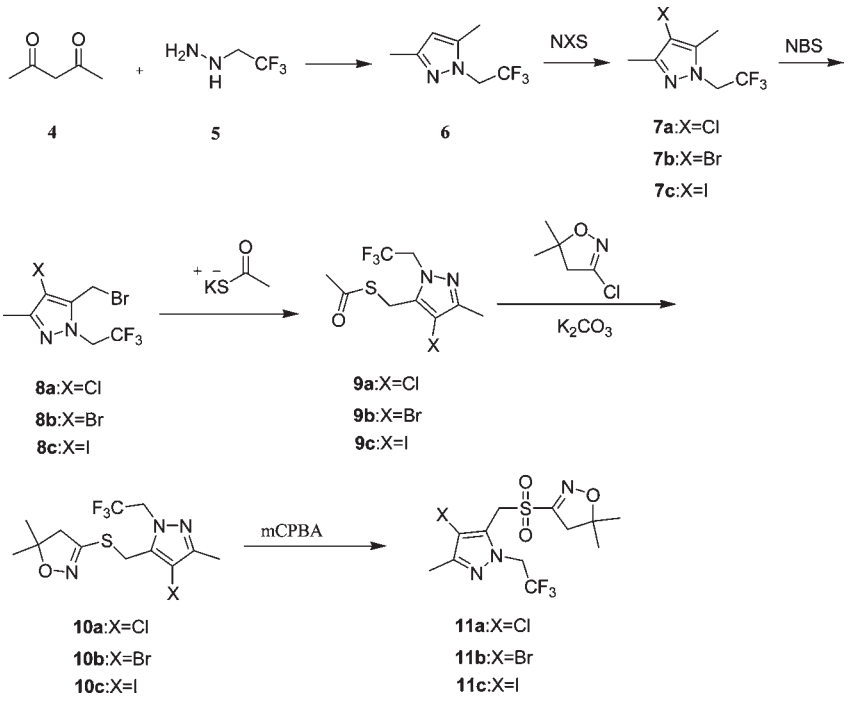
Scheme 2. Synthetic Route of Intermediate Compound **3**



Scheme 3. Synthetic Route of Target Compounds



extracted with diethyl ether, and after it was dried over anhydrous sodium sulfate, the solvent was removed in vacuo. The crude product was recrystallized from acetonitrile to give **2** as colorless crystals (115 g, 89.7% yield).

3-Chloro-5,5-dimethyl-4,5-dihydroisoxazole (3). A mixture of compound **2** (36 g, 0.4 mol) and *N*-chlorosuccinimide (NCS) (108 g, 0.8 mol) in 1,2-dimethoxyethane (500 mL) was refluxed for 1 h. After the mixture was cooled to 5 °C, potassium hydrogen carbonate (148 g, 1.48 mol) and water (18 mL) were added. 2-Methylpropene (45.3 g, 0.8 mol) was then introduced into the suspension over 20 min at 5 °C and sealed. After it was stirred at room temperature for 24 h, the reaction mixture was poured into water (500 mL) and then extracted with hexane (2 × 100 mL). The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to give **3** (19.82 g, 37% yield) as a yellow liquid without further purification. ^{1}H NMR ($CDCl_3$, 300 Hz): δ 1.46 (s, 6H), 2.93 (s, 2H).

3,5-Dimethyl-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole (6). To a solution of acetylacetone (16 mL) in water (100 mL), 2,2,2-trifluoroethylhydrazine (25 g, 70% in water) was added. After it was stirred for 5 min at room temperature, 5 mL of concentrated hydrochloric acid was added and stirred at 60 °C for 1.5 h. The reaction mixture was then treated with 1 N sodium hydroxide solution to slightly basic (pH around 9). After this mixture was extracted with dichloromethane (2 × 100 mL), the combined dichloromethane solution was washed with saturated sodium hydrogen carbonate solution and brine and dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the resulting residue was passed through a short silica gel column, eluting with dichloromethane. After concentration, 36 g of crude desired product was obtained as a light yellow liquid.

4-Chloro-3,5-dimethyl-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole (7a). A mixture of compound **6** (15.6 g, 0.088 mol) and NCS (17.6 g, 0.132 mol) in acetone (500 mL) was irradiated under an ultrasonic wave in a 25−30 °C bath for 8 h. The solution was concentrated, and the resulting residue was passed through a short silica gel column, eluting with dichloromethane, to give the crude product of compound **7a** as an orange liquid (16.85 g).

Compounds **7b**,**c** were synthesized using similar procedure by treating compound **6** with *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS), respectively.

5-(Bromomethyl)-4-chloro-3-methyl-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole (8a). To a solution of compound **7a** (16.85 g, 0.08 mol) in carbon tetrachloride (300 mL) were added NBS (15.57 g, 0.087 mol) and a catalytic amount of benzoyl peroxide (0.1 g). After it was refluxed for 0.5 h, the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated, and the resulting mixture was poured into water, followed by extraction with dichloromethane. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1/20) to give compound **8a** (21.4 g) as a yellow liquid. Compounds **8b**,**c** were synthesized via the same procedures accordingly. Compound **8a**, 62.5% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.28 (s, 3H, CH_3), 4.43 (s, 2H, CH_2Br), 4.60 (dd, 2H, CH_2CF_3, J = 8.2, 8.3 Hz). Compound **8b**, 59.5% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.26 (s, 3H, CH_3), 4.44 (s, 2H, CH_2Br), 4.62 (dd, 2H, CH_2CF_3, J = 8.2, 8.3 Hz). Compound **8c**, 60.3% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.25 (s, 3H, CH_3), 4.47 (s, 2H, CH_2Br), 4.78 (dd, 2H, CH_2CF_3, J = 8.3, 8.3 Hz).

***s*-{4-Chloro-3-methyl-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole-5-yl}-methyl Ethanethioate (9a).** To a solution of compound **8a** (21.4 g, 0.083 mol) in anhydrous ethanol (300 mL), potassium thioacetate (14.2 g, 0.124 mol) was added. After it was stirred at room temperature for 4 h, the solvent was removed in vacuo, and the residue was poured into water, followed by extraction with dichloromethane. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1/18) to give compound **9a** (11.4 g) as a yellow liquid. Compounds **9b**,**c** were synthesized via the same procedures accordingly. Compound **9a**, 54.3% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.21 (s, 3H, $COCH_3$), 2.37 (s, 3H, CH_3), 4.13 (s, 2H), 4.82 (dd, 2H, CH_2CF_3, J = 9.0, 8.3 Hz). Compound **9b**, 55.8% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.21 (s, 3H, $COCH_3$), 2.37 (s, 3H, CH_3), 4.13 (s, 2H),

4.83 (dd, 2H, CH_2CF_3, J = 8.5, 8.4 Hz). Compound **9c**, 50.7% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.22 (s, 3H, $COCH_3$), 2.37 (s, 3H, CH_3), 4.15 (s, 2H), 4.87 (dd, 2H, CH_2CF_3, J = 8.4, 8.3 Hz).

4-Chloro-5-((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)thiomethyl)-3-methyl-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole (10a). A mixture of compound **9a** (11.4 g, 0.04 mol), compound **3** (5.34 g, 0.04 mol), and potassium carbonate (8.28 g, 0.06 mol) in anhydrous ethanol (250 mL) was refluxed for 8 h. The reaction mixture was cooled and then poured into water. The product was extracted with ethyl acetate, and the organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1/10) to give compound **10a** (7.98 g) as colorless crystals. Compounds **10b**,**c** were synthesized via the same procedures accordingly. Compound **10a**, 58.0% yield; mp, 77−78 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.40 [s, 6H, $C(CH_3)_2$], 2.23 (s, 3H, CH_3), 2.77 (s, 2H, CCH_2C), 4.26 (s, 2H, SCH_2), 4.92 (dd, 2H, CH_2CF_3, J = 8.4, 8.3 Hz). IR (KBr, cm^{-1}): 673.0, 1263.4, 2972.0. Anal. calcd for $C_{12}H_{15}ClF_3N_3OS$: C, 42.17; H, 4.42; N, 12.29. Found: C, 42.18; H, 4.48; N, 12.22. Compound **10b**, 55.4% yield; mp, 75−77 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 [s, 6H, $C(CH_3)_2$], 2.24 (s, 3H, CH_3), 2.78 (s, 2H, CCH_2C), 4.26 (s, 2H, SCH_2), 4.96 (dd, 2H, CH_2CF_3, J = 9.0, 8.5 Hz). IR (KBr, cm^{-1}): 669.6, 1271.1, 2996.3. Anal. calcd for $C_{12}H_{15}BrF_3N_3OS$: C, 37.32; H, 3.91; N, 10.88. Found: C, 37.29; H, 3.82; N, 10.91. Compound **10c**, 59.6% yield; mp, 77−78 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 [s, 6H, $C(CH_3)_2$], 2.24 (s, 3H, CH_3), 2.77 (s, 2H, CCH_2C), 4.26 (s, 2H, SCH_2), 4.96 (dd, 2H, CH_2CF_3, J = 8.4, 8.5 Hz). IR (KBr, cm^{-1}): 669.6, 1271.0, 2992.1. Anal. calcd for $C_{12}H_{15}IF_3N_3OS$: C, 33.27; H, 3.49; N, 9.70. Found: C, 33.29; H, 3.50; N, 9.66.

4-Chloro-5-((5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonylmethyl)-3-methyl-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole (11a). A mixture of compound **10a** (7.98 g, 0.023 mol) and *m*-chloroperbenzoic acid (12.4 g, 0.057 mol, 80%) in dichloromethane (250 mL) was stirred at room temperature for 24 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with an aqueous sodium hydrogen sulfite, sodium hydrogen carbonate, and brine and dried over anhydrous sodium sulfate. The solution was concentrated, and the solid residue was washed with hexane to afford compound **11a** as a colorless solid (6.86 g). Compounds **11b**,**c** were synthesized via the same procedures accordingly. Compound **11a**, 79.3% yield; mp, 167−169 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.50 [s, 6H, $C(CH_3)_2$], 2.28 (s, 3H, CH_3), 3.00 (s, 2H, CCH_2C), 4.76 (s, 2H, SCH_2), 4.96 (dd, 2H, CH_2CF_3, J = 8.4, 8.3 Hz). IR (KBr, cm^{-1}): 640.5, 1143.5, 1341.3, 2976.6. ESI-MS $[M + Na]^+$ 396. Anal. calcd for $C_{12}H_{15}ClF_3N_3O_3S$: C, 38.56; H, 4.04; N, 11.24. Found: C, 38.60; H, 4.06; N, 11.20. Compound **11b**, 69.5% yield; mp, 158−160 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.51 [s, 6H, $C(CH_3)_2$], 2.28 (s, 3H, CH_3), 2.99 (s, 2H, CCH_2C), 4.76 (s, 2H, SCH_2), 4.97 (dd, 2H, CH_2CF_3, J = 8.4, 8.4 Hz). IR (KBr, cm^{-1}): 640.0, 1137.4, 1341.5, 2973.5. ESI-MS $[M + Na]^+$ 440. Anal. calcd for $C_{12}H_{15}BrF_3N_3O_3S$: C, 34.46; H, 3.62; N, 10.05. Found: C, 34.50; H, 3.51; N, 9.99. Compound **11c**, 76.5% yield; mp, 156−159 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.50 [s, 6H, $C(CH_3)_2$], 2.27 (s, 3H, CH_3), 2.99 (s, 2H, CCH_2C), 4.76 (s, 2H, SCH_2), 4.97 (dd, 2H, CH_2CF_3, J = 8.4, 8.4 Hz). IR (KBr, cm^{-1}): 644.7, 1125.3, 1340.1, 2974.4. ESI-MS $[M + Na]^+$ 487. Anal. calcd for $C_{12}H_{15}IF_3N_3O_3S$: C, 30.98; H, 3.25; N, 9.03. Found: C, 30.88; H, 3.21; N, 9.11.

Inhibitory Effect of Compounds 10a−c and 11a−c on the Growth of Weed Roots and Shoots. A mixture of agar powder (8 g) and distilled water (1 L) was heated to melt and then cooled down to 40−50 °C. The solution (0.2 mL) containing 10 g/L (acetone as solvent) testing compound and melting agar (19.8 mL) was mixed, and this mixture was added into plastic cups (Ø10 cm). The agar plate without test compound was used as an untreated control. The seeds of *Echinochloa crusgalli* L., *Digitaria sanguinalis* L., and *Portulaca oleracea* L. were put on the surface of the agar plate. The cups were covered with glass lids, and the cultivations were kept at 25 ± 1 °C, 50−55% relative humidity, and 12 h in the light and 12 h in the dark alternatively for 7 days. The experiments were conducted in three replicates. The lengths of root and shoot were measured after 7 days of treatment, and the growth inhibitory rate related to untreated control was determined. The commercial herbicide metolachlor was used as the positive control.

Screening in Greenhouse Conditions. The seeds of test plants were planted (0.6 cm depth) in plastic pots (200 cm^2) containing clay loam soil. Each test compound was dissolved in dimethylsulfoxide to give a 10 g/L solution. Aqueous suspensions, prepared by diluting an emulsifiable concentrate with water (containing 0.1% Tween 80) to a specified concentration, were sprayed onto the surface of the soil using a microsprayer at 1 day after planting. The plastic pots were placed at 22−25 °C in a greenhouse. The fresh weights of aerial plant parts were measured 20 days later, and the percentage of inhibition relative to water-sprayed controls was calculated. Commercial herbicide metolachlor was used as the positive control. Three replicates were performed for each concentration. Monocotyledonous weeds such as *E. crusgalli* L. and *D. sanguinalis* L. were used for the preliminary herbicidal screening test of compounds **10a−c** and **11a−c** at the dosage of 600 g a.i. ha^{-1}. Four different kinds of weeds such as *D. sanguinalis* L., *Eleusine indica* L., *E. crusgalli* L., and *P. oleracea* L. were used for the advanced herbicidal screening test of compound **11a**, and the treatment dosages were 600, 300, and 150 g a.i. ha^{-1}. Maize (*Zea mays* L. var. SHEN DAN 17) and rape (*Brassica campestris* L. var. JING GUAN 1) were used for evaluating the crop selectivity of compound **11a**.

Field Trial. Field experiments were conducted in the experimental field at Nankai University in July, 2009. The soil was a loam soil with a composition of 1.1−1.3% organic matter, and the pH of the soil was 7.8−8.3. The experimental design area of plot was 20 m^2, and four replicates were performed for each concentration. The maize variety SHEN DAN 17 was planted on July 9. The compound **11a** was formulated as a 20% suspension concentrate. Pre-emergence herbicide applications were made to the soil surface within 24 h after maize planting at the dosages of 300, 400, 600, and 800 g a.i. ha^{-1}. The fresh weights of aerial plant parts were measured 30 days later, and the percentage of inhibition relative to water-sprayed control was calculated. Commercial herbicide 72% metolachlor EC (1404 g a. i. ha^{-1}) was used as the positive control to compound **11a**. Visual evaluations of crop injury were assessed on a scale of 0−100%, with 0 representing no crop injury and 100 representing complete maize death.

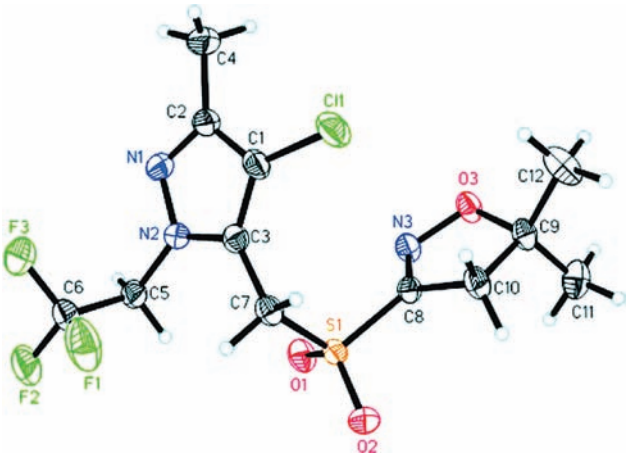
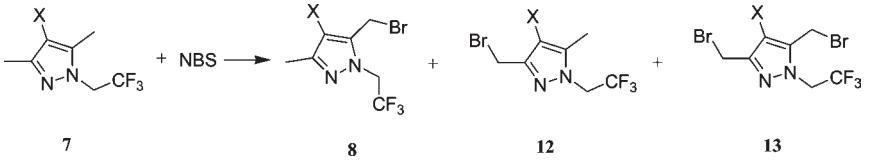


Figure 1. Crystal structure of compound **11a**.

Scheme 4. Selective Bromination toward Intermediate **8**



7 8 12 13

RESULTS AND DISCUSSION

Synthesis. A series of *N*-(2,2,2)-trifluoroethylpyrazole derivatives were synthesized including eight intermediates, **7a**−**c**, **8a**−**c**, and **9b**,**c**, and six target compounds, **10a**−**c** and **11a**−**c**. The structures of these compounds were confirmed by ^{1}H NMR. The target compounds were further confirmed by IR, MS, and elementary analysis. Compounds **11a**,**b** were recrystallized by slow evaporation from the acetone as solvent, and to confirm the structures of these kinds of compounds, their single crystals were analyzed by X-ray diffraction crystallography (*19*, *20*). The corresponding structure of compound **11a** was shown in **Figure 1**. In the synthesis of dihydroisoxazole, the intermediate dichloroxime was not isolated. The crude compound was used directly for the next step due to its unstability. During the preparation of the target compounds **11a**−**c**, the synthesis of the intermediates **8a**−**c** was the key reaction, which is a free radical substitution reaction. Both methyl groups at the 3-position and 5-position on pyrazole ring could be possibly substituted by bromine to generate monosubstituted products **8**, **12**, and the bis-substituted product **13** (**Scheme 4**). To our delight, the bromination of compounds **7a**−**c** provided the desirable regioisomers **8a**−**c** as the major products in excellent isolated yields. Although it was difficult to assign the structure of compound **8** by simple ^{1}H NMR analysis, the structure of compound **8** was inferred from the final targets, while the final target **11a** was confirmed by single-crystal X-ray diffraction analysis.

Table 1. Inhibition of Compound **10a**−**c** and **11a**−**c** on the Growth of Weed Roots and Shoots at 100 mg/L

	relative inhibition (%)					
	E. crusgalli[a]		*D. sanguinalis*		*P. oleracea*	
compd	shoot	root	shoot	root	shoot	root
metolachlor	88 ab[b]	80 bc	88 bc	92 b	62 a	74 b
10a	88 ab	89 d	93 d	98 c	54 a	75 b
10b	88 ab	86 cd	93 d	97 c	54 a	80 b
10c	89 b	86 cd	91 cd	98 c	62 a	81 b
11a	84 ab	62 a	82 a	89 a	54 a	63 a
11b	81 a	74 b	85 ab	88 a	62 a	80 b
11c	84 ab	63 a	84 a	90 ab	62 a	75 b

[a] *E. crusgalli, Echinochloa crusgalli* L.; *D. sanguinalis, Digitaria sanguinalis* L.; *P. oleracea, Portulaca oleracea* L. [b] The treatments were grouped into statistically distinct classes by applying analysis of variance (ANOVA) at $P = 0.05$ based on Fisher's LSD.

Table 2. Herbicidal Effect of Compounds **10a**−**c** and **11a**−**c** on Fresh Weights against Monocotyledonous Weeds at 600 g a.i. ha^{-1} in Greenhouse Conditions

	relative inhibition (%)	
compd	*E. crusgalli*[a]	*D. sanguinalis*
metolachlor	66 a[b]	38 a
10a	81 ab	54 a
10b	82 bc	74 bc
10c	100 c	54 ab
11a	100 c	100 d
11b	100 c	79 c
11c	100 c	90 cd

[a] *E. crusgalli, Echinochloa crusgalli* L.; *D. sanguinalis, Digitaria sanguinalis* L. [b] The treatments were grouped into statistically distinct classes by applying ANOVA at $P = 0.05$ based on Fisher's LSD.

Growth Inhibition of Weed Roots and Shoots. As shown in **Table 1**, compounds **10a**−**c** and **11a**−**c** inhibited root and shoot elongation of the germinated seed of weeds. Germination itself was not strongly inhibited by these compounds. At 3 days after treatment, the shoots and roots of the monocotyledonous weeds were etiolated, followed by withering. The inhibitory activity against *P. oleracea* L. showed no significant difference between the metolachlor and the compounds synthesized.

Herbicidal Activity in Greenhouse Conditions. It can be seen from **Table 2** that all of the compounds showed better herbicidal activities against monocotyledonous weeds in pre-emergence treatment at the dosage of 600 g a.i. ha^{-1} than metolachlor. When the linker was sulfonylmethylene, the corresponding molecules (**11a**−**c**) had a higher inhibition rate for *E. crusgalli* L. and *D. sanguinalis* L. It was also found that when the substituent was chlorine at the 4-position of the pyrazole ring, the corresponding compound **11a** exhibited the best herbicidal activity. The herbicidal activity of compound **11a** was further evaluated in a greenhouse (**Table 3**). Compound **11a** showed excellent inhibitory activity against both dicotyledonous and monocotyledonous weeds, especially for monocotyledonous weeds even at a reduced rate of 150 g a.i. ha^{-1}.

Field Trial. Compound **11a** held excellent herbicidal activity against monocotyledonous and dicotyledonous weeds in field trials. At 15 days after soil treatment, the injury symptoms against monocotyledonous weeds included leaf browning and necrosis. Dicotyledonous weeds exhibited severe symptoms of leaf crinkling and etiolating. As shown in **Table 4**, experimental data showed that compound **11a** achieved more than 95% of an inhibition rate against monocotyledonous weeds at 30 days after soil treatment, and there was no significant difference between the different dosages of compound **11a** and metolachlor. The inhibition rates of the fresh weights against *P. oleracea* L. reached 80, 85, 95, and 100% at the different dosages of 300, 400, 600, and 800 g a.i. ha^{-1}, respectively. However, compound **11a** showed a weak effect to perennial weeds *Convolvulus arvensis* L.

Crop Safety. It was reported that KIH-485 provided good efficacy on both grass and broadleaf weed species with excellent selectivity in maize, wheat, and soybean (*12*−*16*). Compound **11a** showed comparable herbicidal activity in greenhouse conditions and field trials. As shown in **Table 3**, compound **11a** demonstrated good safety to maize and rape, showing less than 2% growth inhibition to maize and 12% growth inhibition to rape in

Table 3. Herbicidal Activity and Selectivity of Compound **11a** in Greenhouse Conditions

		relative inhibition (%)					
compd	dosage (g a.i. ha^{-1})	*D. sanguinalis*[a]	*E. indica*	*E. crusgalli*	*P. oleracea*	*Z. mays*	*B. campestris*
metolachlor	150	43 ± 6.3	84 ± 0.4	25 ± 1.1	36 ± 0.4	1 ± 2.0	0
	300	76 ± 2.0	98 ± 3.8	39 ± 1.6	57 ± 1.3	2 ± 1.7	9 ± 1.9
	600	90 ± 0.8	97 ± 0.4	50 ± 1.6	60 ± 0.8	2 ± 2.8	11 ± 1.8
11a	150	86 ± 2.2	97 ± 2.7	100	70 ± 1.5	0	7 ± 1.6
	300	97 ± 2.3	99 ± 0.6	100	97 ± 0.3	0	12 ± 0.9
	600	100	100	100	99 ± 1.4	1 ± 1.6	11 ± 2.4

[a] *D. sanguinalis, Digitaria sanguinalis* L.; *E. indica, Eleusine indica* L.; *E. crusgalli, Echinochloa crusgalli* L.; *P. oleracea, Portulaca oleracea* L.; *Z. mays, Zea mays* L.; *B. campestris, Brassica campestris* L.

Table 4. Herbicidal Activity and Safety of Compound **11a** in a Maize Field at 30 Days after Soil Treatment

		relative inhibition (%)						crop injury[c]
compd	dosage (g a.i. ha^{-1})	*D. sanguinalis*[a]	*E. crusgalli*	*E. indica*	monocotyledonous	*P. oleracea*	*C. arvensis*	*Z. mays*
11a	300	95	100	97	97 a[b]	80	14	0
	400	98	100	98	98 a	85	16	0
	600	100	100	98	99 a	95	27	0
	800	100	100	99	100 a	100	40	0
metolachlor	1404	95	100	99	98 a	100	47	0

[a] *D. sanguinalis, Digitaria sanguinalis* L.; *E. crusgalli, Echinochloa crusgalli* L.; *E. indica, Eleusine indica* L.; *P. oleracea, Portulaca oleracea* L.; *C. arvensis, Convolvulus arvensis* L.; *Z. mays, Zea mays* L. [b] The treatments were grouped into statistically distinct classes by applying ANOVA at $P = 0.05$ based on Fisher's LSD. [c] Crop Injury, where 0 indicates no visible effect and 100 indicates complete death of maize.

greenhouse conditions. In field trials, compound **11a** also showed the same level of safety to maize as the commercial herbicide metolachlor, and no visible injury was observed to the aerial parts of maize (**Table 4**). A moderate selectivity was detected between the inhibition of VLCFAEs from maize and the KIH-485-sensitive plants. However, this weak selectivity could not explain the selectivity in growth inhibition between maize and KIH-485-sensitive plants. Other factors, such as detoxification of KIH-485 by glutathione *S*-transferase, might be involved in the observed selectivity as referred according to the report of document (*16*). The inhibition of VLCFAEs and the detoxification of glutathione *S*-transferase might also be factors to the selectivity of compound **11a** between crop and weed.

In summary, a series of *N*-(2,2,2)-trifluoroethylpyrazole derivatives were synthesized, and their herbicidal activities were evaluated. The herbicidal tests showed that when the dihydroisoxazole was attached to the 5-position of the *N*-(2,2,2)-trifluoroethylpyrazole ring linked by thiomethylene or sulfonylmethylene, the corresponding compounds presented good herbicidal activities. Especially compound **11a** possessed excellent herbicidal activity and selectivity to maize and rape and deserved further studies on its biological efficacy, crop safety, and toxicity as the herbicide candidate in a maize field.

ABBREVIATIONS USED

VLCFAs, very long-chain fatty acids; VLCFAE, very long-chain fatty acid elongase; NCS, *N*-chlorosuccinimide; NBS, *N*-bromosuccinimide; NIS, *N*-iodosuccinimide.

LITERATURE CITED

(1) Shiga, Y.; Okada, I.; Fukuchi, T. Synthesis and acaricidal activity of *N*-(1,3,4-thiadiazol-2-yl)pyrazole-5-carboxamides and *N*-(1,3,4-thiadiazol-2-yl)thiazole-5-carboxamides. *J. Pestic. Sci.* **2003**, *28*, 310–312.

(2) Shiga, Y.; Okada, I.; Ikeda, Y.; Takizawa, E.; Fukuchi, T. Insecticidal activity of *N*-acy-*N*-(4-aryloxybenzyl)pyrazole-5-carboxamides. *J. Pestic. Sci.* **2003**, *28*, 313–314.

(3) Ohno, R.; Watanabe, A.; Matsukawa, T.; Ueda, T.; Sakurai, H.; Hori, M.; Hirai, K. Synthesis and herbicidal activity of new pyrazole-4-carboxamide derivatives. *J. Pestic. Sci.* **2004**, *29*, 15–26.

(4) Vicentini, C. B.; Mares, D.; Tartari, A.; Manfrini, M.; Forlani, G. Synthesis of pyrazole derivatives and their evaluation as photosynthetic electron transport inhibitors. *J. Agric. Food Chem.* **2004**, *52*, 1898–1906.

(5) Vicentini, C. B.; Romagnoli, C.; Andreotti, E.; Mares, D. Synthetic pyrazole derivatives as growth inhibitors of some phytopathogenic fungi. *J. Agric. Food Chem.* **2007**, *55*, 10331–10338.

(6) Li, H. B.; Zhu, Y. Q.; Song, X. W.; Hu, F. Z.; Liu, B.; Li, Y. H.; Niu, Z. X.; Liu, P.; Wang, Z. H.; Song, H. B.; Zou, X. M.; Yang, H. Z. Novel protoporphyrinogen oxidase inhibitors: 3*H*-pyrazolo[3,4-d]-[1,2,3]triazin-4-one derivatives. *J. Agric. Food Chem.* **2008**, *56*, 9535–9542.

(7) Ouyang, G. P.; Cai, X. J.; Chen, Z.; Song, B. A.; Bhadury, P. S.; Yang, S.; Jin, L. H.; Xue, W.; Hu, D. Y.; Zeng, S. Synthesis and antiviral activities of pyrazole derivatives containing an oxime moiety. *J. Agric. Food Chem.* **2008**, *56*, 10160–10167.

(8) Ouyang, G. P.; Chen, Z.; Cai, X. J.; Song, B. A.; Bhadury, P. S.; Yang, S.; Jin, L. H.; Xue, W.; Hu, D. Y.; Zeng, S. Synthesis and antiviral activity of novel pyrazole derivatives containing oxime esters group. *Bioorg. Med. Chem.* **2008**, *16*, 9699–9707.

(9) Hirai, K.; Uchida, A.; Ohno, R. *Herbicide Classes in Development*; Boger, P., Hirai, K., Wakabyashi, K., Eds.; Springer-Verlag: Heidelberg, Germany, 2002; pp 179−289.

(10) Nakatani, M.; Ito, M.; Miyazaki, M. Pyrazole derivatives and process for the production thereof. U.S. Patent 7256298, 2007.

(11) Nakatani, M.; Kugo, R.; Miyazaki, M.; Kaku, K.; Fujinaml, M.; Ueno, R.; Takahashi, S. Isoxazoline derivative and herbicide comprising the same as active ingredient. U.S. Patent 7238689, 2007.

(12) Steele, G. L.; Porpiglia, P. J.; Chandler, J. M. Efficacy of KIH-485 on Texas Panicum (*Panicum texanum*) and selected broadleaf weeds in corn. *Weed Technol.* **2005**, *19*, 866–869.

(13) Geier, P. W.; Stahlman, P. W.; Frihauf, J. C. KIH-485 and S-metolachlor efficacy comparisons in conventional and no-tillage corn. *Weed Technol.* **2006**, *20*, 622–626.

(14) King, S. R.; Ritter, R. L.; Hagood, E. S.; Menbere, H. Control of acetolactate synthase-resistant shattercane (*Sorghum bicolor*) in field corn with KIH-485. *Weed Technol.* **2007**, *21*, 578–582.

(15) Sikkema, P. H.; Robinson, D. E.; Nurse, R. E.; Soltani, N. Preemergence herbicides for potential use in pinto and small red Mexican bean (*Phaseolus vulgaris*) production. *Crop Prot.* **2008**, *27*, 124–129.

(16) Tanetani, Y.; Kaku, K.; Kawai, K.; Fujioka, T.; Shimizu, T. Action mechanism of a novel herbicide, pyroxasulfone. *Pestic. Biochem. Physiol.* **2009**, *95*, 47–55.

(17) Welch, J. T. Tetrahedron report number 221: Advances in the preparation of biologically active organofluorine compounds. *Tetrahedron.* **1987**, *43*, 3123–3197.

(18) Boehmer, J. E.; Mclachlan, M. M. W. Herbicidal isoxazoline compounds. WO Patent 2007096576, 2007.

(19) Ma, H. J.; Zhao, Q. F.; Mei, X. D.; Ning, J. 4-Chloro-5-[(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl-methyl]-3-methyl-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole. *Acta Crystallogr., Sect. E* **2009**, *65*, o2567.

(20) Ma, H. J.; Zhao, Q. F.; Mei, X. D.; Ning, J. 4-Bromo-5-[(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)sulfonyl-methyl]-3-methyl-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole. *Acta Crystallogr., Sect. E* **2009**, *65*, o2702–o2703.

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