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Journal of Fluorine Chemistry 127 (2006) 1540–1546
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

Synthesis and bioactivity of novel (3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl containing acrylate and acrylonitrile derivatives

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Received 2 June 2006; received in revised form 10 July 2006; accepted 14 July 2006
Available online 21 July 2006

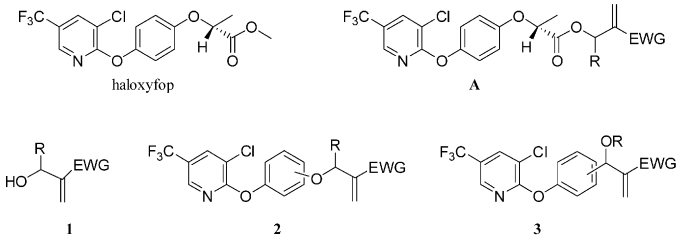
Abstract

Fifteen novel (3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl containing Baylis-Hillman adduct derivatives were designed and synthesized. Evaluation of their biological activities showed that methyl 2-((3-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenoxy)(phenyl)methyl)acrylate (**2g**) exhibited efficient broad-spectrum fungicidal activity, with 100% control of wheat powdery mildew and cucumber downy mildew and 98% control of cucumber anthracnose at 400 g ai/ha. Some of the other title compounds **2**, **3** and two Baylis-Hillman bromide intermediates (**11a**, **11b**) had moderate to good fungicidal activity.

Keywords: Synthesis; Fungicidal activity; (3-Chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl; Baylis-Hillman adduct

1. Introduction

The highly atom-economical Baylis-Hillman reaction has received much attention in recent years because it provides multifunctional molecules **1** (Baylis-Hillman adducts) that are versatile building blocks in organic synthesis [1–4]. Additionally, several Baylis-Hillman adducts possess pronounced biological activities. For example, the Baylis-Hillman adduct 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanenitrile was reported to have molluscicidal activity against *Biomphalaria glabrata* [5,6]. In our earlier work, successful introduction of Baylis-Hillman adduct moieties into haloxyfop, which is a commercial herbicide [7,8], resulted in allyl aryloxy-phenoxy-propionates (compounds **A**) that showed excellent herbicidal activity and safety toward monocotyledonous crops [9]. Continuing our efforts toward discovery of novel lead compounds with simplified structures, the present paper reports on the design and synthesis of α-methylene-β-aryloxy-phenoxy acrylates **2** and their analogs **3** by clipping the chiral propionic acid part of compounds **A**. Compounds **2** and **3** were diversified by modifying the substituents R and the electron-withdrawing groups (EWG), while the (3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl moiety remained unchanged. Evaluation of bioactivities showed that these novel derivatives of Baylis-Hillman adduct **2** and **3** had little herbicidal activity, but exhibited moderate to good fungicidal activity.



EWG = electron-withdrawing group: CO_2Me, CO_2Et, CN.

2. Results and discussion

2.1. Synthesis of 2-(((3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenoxy)methyl)acrylate (2)

Compounds **2a**–**2g** were prepared as illustrated in Schemes 1 and 2, with Baylis-Hillman adducts introduced into structure **2**

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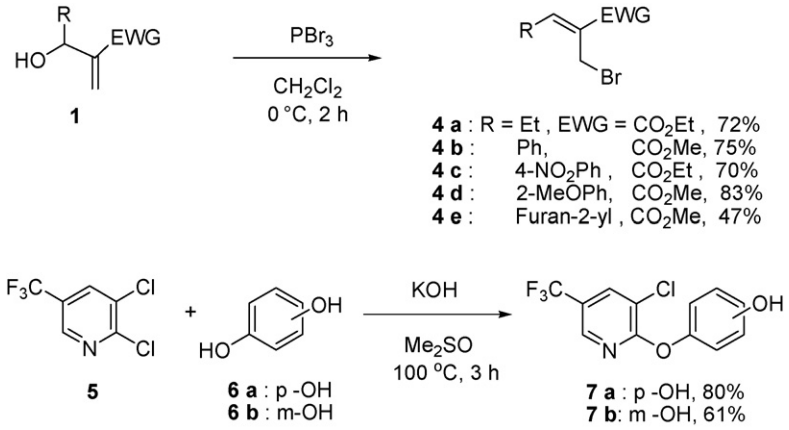
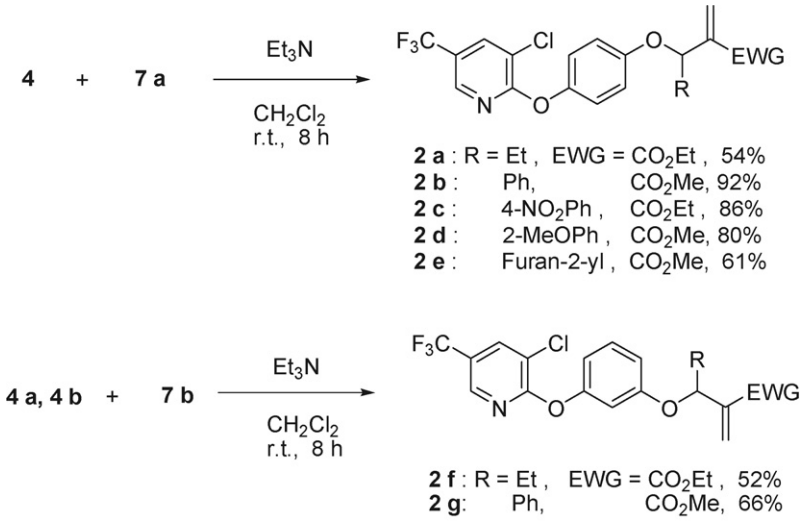
doi:10.1016/j.jfluchem.2006.07.011



Scheme 1.



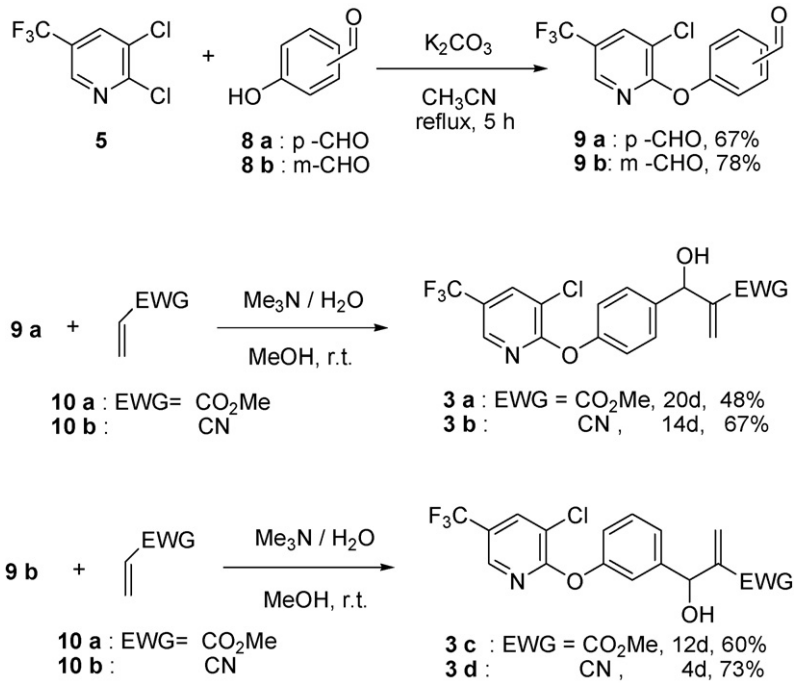
Scheme 2.

at the *para* or *meta* position of the (3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl. First, the Baylis-Hillman adducts **1** were synthesized according to the literature [10], where R was either an alkyl, unsubstituted phenyl, electron withdrawing or donating group substituted phenyl or a furan group, then adducts **1** were brominated by phosphorus tribromide in dichloromethane at 0 °C with clean regioselective as well as stereoselective allylic rearrangement to give (Z)-trisubstituted olefins **4** [11]. Separately, 2,3-dichloro-5-(trifluoromethyl)pyridine (**5**) was readily reacted with hydroquinone (**6a**) or resorcinol (**6b**) to yield corresponding (3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenol **7a** or **7b**, which was then reacted with the allylic bromides **4** in the presence of triethylamine to afford S_N2' products **2a**–**2g** in moderate to good yields [12].

2.2. Synthesis of 2-(((3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl)methyl) acrylate or acrylonitrile (3)

The synthetic routes for compounds **3a**–**3h** were designed as shown in Schemes 3 and 4. Starting material 2,3-dichloro-5-(trifluoromethyl)pyridine (**5**) was refluxed with hydroxybenzaldehydes (**8a**, **8b**) and potassium carbonate in acetonitrile to form (3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)benzaldehydes (**9a**, **9b**) in moderate yields after the usual work up. The *para* substituted benzaldehyde **9a** underwent Baylis-Hillman reaction with methyl acrylate (**10a**) or acrylonitrile (**10b**) catalyzed by aqueous trimethylamine in methanol at room temperature to give the desired β-hydroxy acrylate **3a** or β-hydroxy acrylonitrile **3b** in 48% and 67% yield, respectively. Under the same conditions, *meta* substituted products **3c** and **3d** were obtained in relatively higher yield and shorter time (Scheme 3).

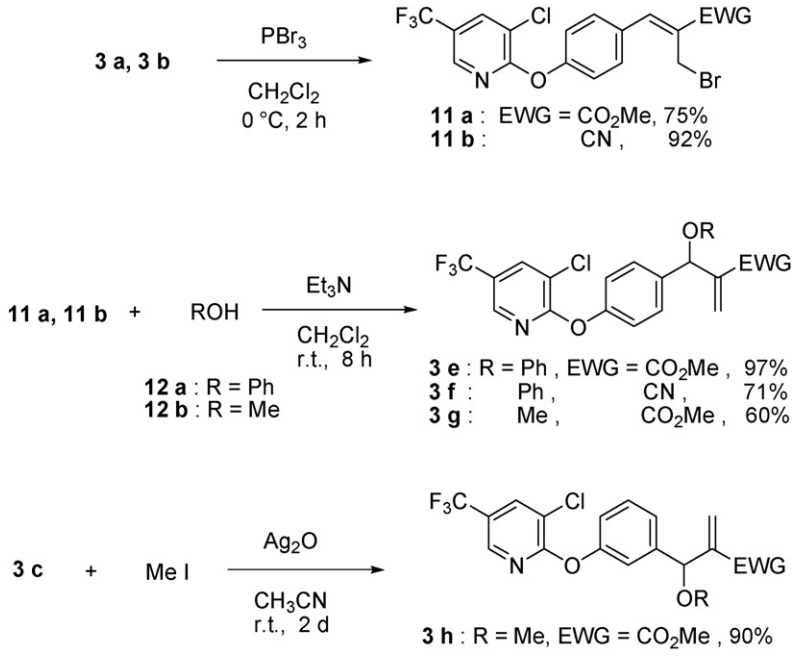
In the design of bioactive molecules, modifying hydrogen bond donor or acceptor groups is interesting because hydrogen bonding generally plays an important role in enzyme inhibition [13,14]. Replacing the hydroxyl group on compounds **3a**–**3d** with an ether bond was expected to result in a marked change in biological activity. Accordingly, etherified products **3e**–**3h** were synthesized through two methods described in Scheme 4. One approach was to convert **3a** and **3b** into (3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl substituted Baylis-Hillman



Scheme 3.

bromides **11a** and **11b** by treatment with phosphorus tribromide. Then the bromides **11a** and **11b** were reacted with phenol (**12a**) or methanol (**12b**) to afford the corresponding ethers **3e**, **3f** and **3g**. The highest yield (97%) was obtained when brominated acrylate **11a** was reacted with phenol, while reaction with methanol yielded moderately (60%). The alternative synthetic strategy was to react **3c** with iodomethane in the presence of silver oxide in acetonitrile to give β-methoxyl acrylate **3h** in good yield (90%).

All synthesized compounds were characterized by IR, ^{1}H NMR and elemental analyses. Most of the title compounds **2** and **3** were further confirmed by ^{13}C NMR, ^{19}F NMR and mass spectra. The ^{19}F NMR spectrum of title compounds showed a singlet (chemical shift is around −62.0 ppm) and ^{13}C NMR showed a quartet (chemical shift is around 122.8 ppm and coupling constant is around 270 Hz), both of which correspond to a trifluoromethyl group. In addition, two single peaks (δ = 5.70–6.60) in the ^{1}H NMR spectrum of compounds **2** and **3**



Scheme 4.

indicated the presence of an end-ene group. All spectra and data were consistent with the assigned structures.

2.3. Biological activities

The biological activities of fifteen target compounds **2**, **3** and two Baylis-Hillman bromides **11a** and **11b** were evaluated in the greenhouse according to the literature [15,16]. Among the compounds **2**, the most active was **2g**, where R was an unsubstituted phenyl and the Baylis-Hillman adduct moiety was at the *meta* position of the (3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl. Compound **2g** exhibited significant broad-spectrum fungicidal activity, with 100% control of wheat powdery mildew and cucumber downy mildew (CDM) and 98% control of cucumber anthracnose at 400 g ai/ha, where 100% is complete control of the fungus. Neither change in the position of the substituent (**2b**), introduction of an electron withdrawing or donating group to the phenyl (**2c**, **2d**) nor replacement of the phenyl group with an alkyl (**2a**, **2f**) or heterocycle (**2e**) resulted in any promising activity (all activity was below 50%).

Hydroxyl containing compounds **3a**–**3d** possessed pronounced fungicidal activity. Compounds **3a** and **3c** gave 80% and 70% control of CDM at 400 g ai/ha. Compound **3b** and the (3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl substituted Baylis-Hillman bromides (**11a**, **11b**) were effective against rice blast at a very low rate of 25 g ai/ha, with 85%, 80% and 100% control, respectively. In contrast, none of the etherified products **3e**–**3h** showed fungicidal activity, though **3h** possessed insecticidal activity, with 70% control of *Tetranychus cinnabarinus* at 600 g ai/ha. Based on the dramatic loss of fungicidal activity with etherifying of the hydroxyl group of **3**, it was presumed that the hydroxyl was an important functional group in the structure **3**.

3. Conclusion

The title compounds **2** and **3** were designed, synthesized by Baylis-Hillman reaction and their structures were confirmed. Some of these compounds and their bromide intermediates (**11a**, **11b**) had moderate to good fungicidal activity. Among them, 2-((3-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenoxy)(phenyl)methyl)acrylate (**2g**) showed potent broad-spectrum fungicidal activity. These novel (3-chloro-5-(trifluoromethyl) pyridin-2-yloxy)phenyl containing Baylis-Hillman adduct derivatives **2** and **3** are versatile multifunctional molecules that could easily be modified and used as lead compounds for further study.

4. Experimental

Melting points were determined on a Buchi melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were performed on a Mercury 300 (Varian, 300 MHz) spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. ^{19}F NMR spectra were obtained on the Mercury 300 (Varian, 300 MHz) spectrometer using CCl_3F as an internal standard. Infrared spectra were recorded with a PE-983G instrument (Perkin-Elmer). Mass spectra (GC–MS) were obtained on an MD-800 (Fisons) instrument. Combustion analyses for elemental composition were made with an EA 1106 analyzer (Fisons). All reactions were monitored by TLC. All chemicals and reagents were purchased from standard commercial suppliers.

4.1. General procedure for the preparation of (3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)benzaldehyde (*9a*, *9b*)

A mixture of 2,3-dichloro-5-(trifluoromethyl)pyridine (**5**, 2.16 g, 10 mmol), hydroxybenzaldehyde (**8a** or **8b**, 1.83 g, 15 mmol), and 2.07 g powdered anhydrous K_2CO_3 in 30 mL acetonitrile was refluxed for 5 h in a nitrogen atmosphere with stirring. The reaction product was allowed to cool and filtered. The filtrate was evaporated to dryness. The residue was extracted with ethyl acetate and water, and then the organic layer was washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography to give compound **9a** or **9b**.

4.1.1. 4-(3-Chloro-5-(trifluoromethyl)pyridin-2-yloxy)benzaldehyde (*9a*)

Yield 67% of white solid: mp 44–46 °C; IR (KBr) ν: 3070, 2830, 1700, 1590, 1460, 1320, 1205, 850 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.03 (s, 1H, CHO), 8.29 (s, 1H, Ar–H), 8.03 (s, 1H, Ar–H), 7.99 (d, 2H, J = 8.4 Hz, Ar–H), 7.36 (d, 2H, J = 8.4 Hz, Ar–H); Anal. Calcd. (%) for $C_{13}H_7ClF_3NO_2$: C, 51.76; H, 2.34; N, 4.64. Found: C, 51.64; H, 2.39; N, 4.58.

4.1.2. 3-(3-Chloro-5-(trifluoromethyl)pyridin-2-yloxy)benzaldehyde (*9b*)

Yield 78% of white solid: mp 110–112 °C; IR (KBr) ν: 3070, 2830, 1700, 1585, 1460, 1325, 1130, 810 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.04 (s, 1H, CHO), 8.27 (s, 1H, Ar–H), 8.02 (s, 1H, Ar–H), 7.82 (d, 1H, J = 7.8 Hz, Ar–H), 7.71 (s, 1H, Ar–H), 7.64 (t, 1H, J = 7.8 Hz, Ar–H), 7.47 (d, 1H, J = 7.8 Hz, Ar–H); Anal. Calcd. (%) for $C_{13}H_7ClF_3NO_2$: C, 51.76; H, 2.34; N, 4.64. Found: C, 51.71; H, 2.27; N, 4.53.

4.2. General procedure for the preparation of Baylis-Hillman adducts (*3a*–*3d*)

A solution of 3 mmol substituted benzaldehyde (**9a** or **9b**), 4 mmol 33% aqueous trimethylamine and 9 mmol methyl acrylate (or acrylonitrile) in 10 mL methanol was stirred at room temperature for an appropriate time. When the reaction was completed as indicated by TLC, the reaction mixture was extracted with dichloromethane. The organic layer was washed with water, dried over $MgSO_4$ and evaporated to dryness. The residue was purified by silica gel column chromatography to give compounds **3a**–**3d**.

4.2.1. Methyl 2-((4-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl)(hydroxy)methyl)acrylate (*3a*)

Yield 48% of colorless oil: IR (KBr) ν: 3480, 3070, 2960, 1715, 1600, 1460, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ:

8.26–8.27 (m, 1H, Ar–H), 7.98 (d, 1H, J = 1.8 Hz, Ar–H), 7.47 (dd, 2H, J = 6.9, 1.8 Hz, Ar–H), 7.16 (dd, 2H, J = 6.9, 1.8 Hz, Ar–H), 6.37 (s, 1H, C=CH_2), 5.89 (s, 1H, C=CH_2), 5.61 (s, 1H, CH), 3.76 (s, 3H, OCH_3), 3.06 (br, 1H, OH); Anal. Calcd. (%) for $C_{17}H_{13}ClF_3NO_4$: C, 52.66; H, 3.38; N, 3.61. Found: C, 52.64; H, 3.21; N, 3.57.

*4.2.2. 2-((4-(3-Chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl)(hydroxy)methyl)acrylonitrile (**3b**)*

Yield 67% of colorless oil: IR (KBr) ν: 3440, 3080, 2230 (CN), 1600, 1505, 1460, 920, 855 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.25–8.26 (m, 1H, Ar–H), 8.00 (d, 1H, J = 2.1 Hz, Ar–H), 7.50 (dd, 2H, J = 6.6, 2.1 Hz, Ar–H), 7.22 (dd, 2H, J = 6.6, 2.1 Hz, Ar–H), 6.17 (d, 1H, J = 1.2 Hz, C=CH_2), 6.09 (d, 1H, J = 1.2 Hz, C=CH_2), 5.37 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 160.9, 153.1, 142.4 (q, $^3J_{CF}$ = 5 Hz), 136.6, 136.5 (q, $^3J_{CF}$ = 3 Hz), 130.1, 128.0, 126.0, 122.7 (q, $^1J_{CF}$ = 271 Hz, CF_3), 122.7 (q, $^2J_{CF}$ = 33 Hz), 122.1, 119.4, 117.3 (CN), 73.6; Anal. Calcd. (%) for $C_{16}H_{10}ClF_3N_2O_2$: C, 54.18; H, 2.84; N, 7.90. Found: C, 54.26; H, 3.03; N, 7.79.

*4.2.3. Methyl 2-((3-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl)(hydroxy)methyl)acrylate (**3c**)*

Yield 60% of colorless oil: IR (KBr) ν: 3450, 3080, 2960, 1720, 1460, 1325, 1070, 965 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.25–8.26 (m, 1H, Ar–H), 7.98 (d, 1H, J = 1.8 Hz, Ar–H), 7.43 (t, 1H, J = 7.8 Hz, Ar–H), 7.30 (d, 1H, J = 7.8 Hz, Ar–H), 7.22 (s, Ar–H), 7.11 (d, 1H, J = 7.8 Hz, Ar–H), 6.37 (s, 1H, C=CH_2), 5.87 (s, 1H, C=CH_2), 5.59 (s, 1H, CH), 3.75 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 166.5, 161.0, 152.7, 143.6, 142.4 (q, $^3J_{CF}$ = 5 Hz), 141.5, 136.3 (q, $^3J_{CF}$ = 3 Hz), 129.6, 126.5, 123.9, 122.8 (q, $^1J_{CF}$ = 270 Hz, CF_3), 122.4 (q, $^2J_{CF}$ = 33 Hz), 120.9, 119.8, 119.3, 72.6, 51.9; ^{19}F NMR (282 MHz, CCl_3F) δ: −62.0 (s, CF_3); Anal. Calcd. (%) for $C_{17}H_{13}ClF_3NO_4$: C, 52.66; H, 3.38; N, 3.61. Found: C, 52.78; H, 3.31; N, 3.41.

*4.2.4. 2-((3-(3-Chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl)(hydroxy)methyl)acrylonitrile (**3d**)*

Yield 73% of colorless oil: IR (KBr) ν: 3440, 3070, 2900, 2230 (CN), 1590, 1460, 1320, 1070, 920 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.21–8.22 (m, 1H, Ar–H), 8.00 (d, 1H, J = 1.8 Hz, Ar–H), 7.48 (t, 1H, J = 7.8 Hz, Ar–H), 7.31 (d, 1H, J = 7.8 Hz, Ar–H), 7.23–7.24 (m, 1H, Ar–H), 7.16–7.19 (m, 1H, Ar–H), 6.11 (d, 1H, J = 1.2Hz, C=CH_2), 6.05 (d, 1H, J = 1.2 Hz, C=CH_2), 5.31 (s, 1H, CH), 2.90 (br, 1H, OH); Anal. Calcd. (%) for $C_{16}H_{10}ClF_3N_2O_2$: C, 54.18; H, 2.84; N, 7.90. Found: C, 53.95; H, 3.01; N, 7.81.

*4.3. General procedure for the preparation of Baylis-Hillman bromides (**4a–4e, 11a, 11b**)*

To a stirred solution of 5 mmol Baylis-Hillman adduct (**1**, **3a**, **3b**) in 10 mL dry dichloromethane was added dropwise a solution of PBr_3 (1.381 g, 5 mmol, in 10 mL dry CH_2Cl_2) at 0 °C over 50 min. The reaction was allowed to stir for 2 h at the same temperature. The reaction mixture was poured into ice water and extracted with dichloromethane. The organic layers were combined, washed with water, dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel column chromatography to give the Baylis-Hillman bromides (**4a–4e**, **11a**, **11b**).

*4.3.1. (Z)-methyl 3-(4-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl)-2-(bromomethyl)acrylate (**11a**)*

Yield 75% of white solid: mp 86–88 °C; IR (KBr) ν: 3080, 2960, 1720, 1600, 1465, 1500, 1330, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.29–8.30 (m, 1H, Ar–H), 8.02 (d, 1H, J = 2.4 Hz, Ar–H), 7.84 (s, 1H, Ar–CH=C), 7.69 (d, 2H, J = 8.7 Hz, Ar–H), 7.29 (d, 2H, J = 8.7 Hz, Ar–H), 4.42 (s, 2H, CH_2Br), 3.90 (s, 3H, OCH_3); Anal. Calcd. (%) for $C_{17}H_{12}BrClF_3NO_3$: C, 45.31; H, 2.68; N, 3.11. Found: C, 45.53; H, 2.77; N, 3.07.

*4.3.2. (Z)-3-(4-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl)-2-(bromomethyl)acrylonitrile (**11b**)*

Yield 92% of white solid: mp 98–100 °C; IR (KBr) ν: 3080, 2920, 2220 (CN), 1595, 1460, 1205, 1175, 920 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.28–8.29 (m, 1H, Ar–H), 8.01 (d, 1H, J = 2.4 Hz, Ar–H), 7.91 (d, 2H, J = 6.9 Hz, Ar–H), 7.28 (d, 2H, J = 6.9 Hz, Ar–H), 7.23 (s, 1H, Ar–CH=C), 4.24 (s, 2H, CH_2Br); Anal. Calcd. (%) for $C_{16}H_9BrClF_3N_2O$: C, 46.02; H, 2.17; N, 6.71. Found: C, 46.26; H, 2.30; N, 6.64.

*4.4. General procedure for the preparation of **2a–2g** and **3e, 3f, 3g***

A mixture of 2.5 mmol Baylis-Hillman bromide (**4a–4e**, **11a**, **11b**) and 2.5 mL triethylamine in 5 mL dry dichloromethane was stirred at room temperature for 15 min. Then 2.75 mmol (3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenol (**7a**, **7b**), phenol (**12a**) or methanol (**12b**) was added. The mixture was allowed to react 8 h at room temperature. After that, the reaction mixture was diluted with 2N HCl and extracted with CH_2Cl_2. The combined organic layer was washed with aqueous $NaHCO_3$ solution and water, dried over $MgSO_4$, and evaporated to dryness. The crude product was purified by silica gel column chromatography to give the title compounds **2a–2g** and **3e**, **3f**, **3g**.

*4.4.1. Ethyl 2-((4-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenoxy)(ethyl)methyl)acrylate (**2a**)*

Yield 54% of pale yellow oil: IR (film) ν: 3070, 2980, 1715, 1610, 1505, 1460, 1400, 1320 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.27 (qd, 1H, $^4J_{HF}$ = 0.9 Hz, $^4J_{HH}$ = 2.1 Hz, Ar–H), 7.96 (qd, 1H, $^4J_{HF}$ = 0.6 Hz, $^4J_{HH}$ = 2.1 Hz, Ar–H), 7.03 (dd, 2H, J = 6.9, 2.4 Hz, Ar–H), 6.91 (dd, 2H, J = 6.9, 2.4 Hz, Ar–H), 6.31 (s, 1H, C=CH_2), 5.86 (s, 1H, C=CH_2), 5.04 (dd, 1H, J = 7.2, 3.6 Hz, CH), 4.27 (q, 2H, J = 7.2 Hz, OCH_2), 1.83–1.96 (m, 1H, CH_2), 1.76–1.82 (m, 1H, CH_2), 1.34 (t, 3H, J = 7.2 Hz, O–CH_2CH_3), 1.03 (t, 3H, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 165.9, 161.4 (q, $^4J_{CF}$ = 1 Hz), 155.5, 146.2, 142.6 (q, $^3J_{CF}$ = 4 Hz), 140.1, 136.1 (q, $^3J_{CF}$ = 3 Hz),

125.6, 122.9 (q, $^1J_{CF}$ = 270 Hz, CF_3), 122.3, 122.2 (q, $^2J_{CF}$ = 33 Hz), 119.17, 116.4, 76.8, 60.9, 29.0, 14.1, 9.8; GC–MS, *m/z* (%): 429 ($[M]^+$, 27%), 431 ($[M + 2]^+$, 9%), 383, 340, 326, 199, 180 (100%), 115, 91; Anal. Calcd. (%) for $C_{20}H_{19}ClF_3NO_4$: C, 55.89; H, 4.46; N, 3.26. Found: C, 55.79; H, 4.63; N, 3.17.

*4.4.2. Methyl 2-((4-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenoxy)(phenyl)methyl)acrylate (**2b**)*

Yield 92% of colorless oil: IR (KBr) *ν*: 3060, 2950, 1720, 1460, 1400 1320, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ*: 8.25 (d, 1H, *J* = 1.8 Hz, Ar–H), 7.95 (d, 1H, *J* = 1.8 Hz, Ar–H), 7.44–7.47 (m, 2H, Ar–H), 7.31–7.39 (m, 3H, Ar–H), 7.04 (d, 2H, *J* = 9.3 Hz, Ar–H), 6.97 (d, 2H, *J* = 9.3 Hz, Ar–H), 6.42 (s, 1H, CH), 6.13 (s, 1H, C=CH_2), 5.99 (s, 1H, C=CH_2), 3.76 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) *δ*: 165.8, 161.3, 155.2, 146.4, 142.4 (q, $^3J_{CF}$ = 5 Hz), 140.0, 138.6, 136.1 (q, $^3J_{CF}$ = 3 Hz), 128.5, 128.2, 127.3, 126.3, 122.8 (q, $^1J_{CF}$ = 270 Hz, CF_3), 122.3, 121.9 (q, $^2J_{CF}$ = 33 Hz), 119.0, 116.7, 77.8, 51.9; ^{19}F NMR (282 MHz, CCl_3F) *δ*: −62.0 (s, CF_3); Anal. Calcd. (%) for $C_{23}H_{17}ClF_3NO_4$: C, 59.56; H, 3.69; N, 3.02. Found: C, 59.69; H, 3.80; N, 2.86.

*4.4.3. Ethyl 2-((4-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenoxy)(4-nitrophenyl)methyl)acrylate (**2c**)*

Yield 86% of pale yellow oil: IR (KBr) *ν*: 3080, 2990, 1715, 1610, 1460, 1325, 1190, 915 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ*: 8.21–8.25 (m, 3H, Ar–H), 7.96 (qd, 1H, $^4J_{HF}$ = 0.6 Hz, $^4J_{HH}$ = 2.1 Hz, Ar–H), 7.67 (dd, 2H, *J* = 6.9, 2.4 Hz, Ar–H), 7.06 (d, 2H, *J* = 9.3 Hz, Ar–H), 6.96 (d, 2H, *J* = 9.3 Hz, Ar–H), 6.48 (s, 1H, CH), 6.21 (s, 1H, C=CH_2), 6.09 (s, 1H, C=CH_2), 4.20–4.24 (m, 2H, OCH_2), 1.28 (t, 3H, *J* = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) *δ*: 165.1, 161.3, 154.7, 147.0, 146.2, 142.5 (q, $^3J_{CF}$ = 5 Hz), 139.4, 136.3 (q, $^3J_{CF}$ = 3 Hz), 128.2, 127.0, 123.8, 122.9 (q, $^1J_{CF}$ = 270 Hz, CF_3), 122.7, 119.2, 116.9, 61.3, 14.1; ^{19}F NMR (282 MHz, CCl_3F) *δ*: −62.1 (s, CF_3); Anal. Calcd. (%) for $C_{24}H_{18}ClF_3N_2O_6$: C, 55.13; H, 3.47; N, 5.36. Found: C, 55.20; H, 3.29; N, 5.32.

*4.4.4. Methyl 2-((4-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenoxy)(2-methoxyphenyl)methyl)acrylate (**2d**)*

Yield 80% of white solid: mp 83–84 °C; IR (KBr) *ν*: 3080, 2960, 1730, 1320, 1190, 1070, 1030, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ*: 8.25 (d, 1H, *J* = 2.4 Hz, Ar–H), 7.95 (d, 1H, *J* = 2.4 Hz, Ar–H), 7.39–7.43 (m, 1H, Ar–H), 7.28–7.34 (m, 1H, Ar–H), 6.90–7.04 (m, 6H, Ar–H), 6.56 (s, 1H, C=CH_2), 6.40 (s, 1H, C=CH_2), 5.73 (s, 1H, CH), 3.85 (s, 3H, Ar–OCH_3), 3.77 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) *δ*: 166.3, 161.4 (q, $^4J_{CF}$ = 1 Hz), 156.7, 155.8, 146.3, 142.6 (q, $^3J_{CF}$ = 4 Hz), 139.8, 136.1, 129.4, 127.9, 127.1, 126.5, 122.9 (q, $^1J_{CF}$ = 270 Hz, CF_3), 122.2, 122.0 (q, $^2J_{CF}$ = 33 Hz), 120.7, 119.2, 116.8, 110.7, 72.1, 55.5, 52.0; ^{19}F NMR (282 MHz, CCl_3F) *δ*: −62.1 (s, CF_3); Anal. Calcd. (%) for $C_{24}H_{19}ClF_3NO_5$: C, 58.37; H, 3.88; N, 2.84. Found: C, 58.19; H, 4.02; N, 2.74.

*4.4.5. Methyl 2-((4-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenoxy)(furan-2-yl)methyl)acrylate (**2e**)*

Yield 61% of pale yellow solid: mp 107–109 °C; IR (KBr) *ν*: 3070, 2960, 1710, 1460, 1320, 1070, 1020, 915, 820, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ*: 8.26–8.27 (m, 1H, Ar–H), 7.96 (d, 1H, *J* = 2.1 Hz, Ar–H), 7.43–7.44 (m, 1H, Ar–H), 6.99–7.09 (m, 4H, Ar–H), 6.17–6.51 (m, 5H, Ar–H, C=CH_2, CH), 3.79 (s, 3H, OCH_3); Anal. Calcd. (%) for $C_{21}H_{15}ClF_3NO_5$: C, 55.58; H, 3.33; N, 3.09. Found: C, 55.63; H, 3.28; N, 3.20.

*4.4.6. Ethyl 2-((3-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenoxy)(ethyl)methyl)acrylate (**2f**)*

Yield 52% of pale yellow oil: IR (film) *ν*: 3070, 2980, 1715, 1590, 1460, 1400, 1325, 1130, 960, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ*: 8.29 (d, 1H, *J* = 2.1 Hz, Ar–H), 7.97 (d, 1H, *J* = 2.1 Hz, Ar–H), 7.29 (t, *J* = 8.1 Hz, 1H, Ar–H), 6.69–6.80 (m, 3H, Ar–H), 6.30 (s, 1H, C=CH_2), 5.85 (s, 1H, C=CH_2), 5.04–5.07 (m, 1H, CH), 4.25 (q, 2H, *J* = 7.2 Hz, OCH_2), 1.81–1.94 (m, 1H, CH_2), 1.65–1.77 (m, 1H, CH_2), 1.31 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3), 1.01 (t, 3H, *J* = 7.2 Hz, CH_2CH_3); Anal. Calcd. (%) for $C_{20}H_{19}ClF_3NO_4$: C, 55.89; H, 4.46; N, 3.26. Found: C, 55.74; H, 4.42; N, 3.11.

*4.4.7. Methyl 2-((3-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenoxy)(phenyl)methyl)acrylate (**2g**)*

Yield 66% of pale yellow oil: IR (KBr) *ν*: 3070, 2960, 1720, 1590, 1130, 1065, 970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ*: 8.25 (d, 1H, *J* = 2.4 Hz, Ar–H), 7.96 (d, 1H, *J* = 2.4 Hz, Ar–H), 7.25–7.45 (m, 5H, Ar–H), 6.72–6.86 (m, 4H, Ar–H), 6.40 (s, 1H, CH), 6.15 (s, 1H, C=CH_2), 5.98 (s, 1H, C=CH_2), 3.73 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) *δ*: 165.9, 160.9 (q, $^4J_{CF}$ = 1 Hz), 158.6, 153.6, 142.6 (q, $^3J_{CF}$ = 4 Hz), 139.8, 138.4, 136.2 (q, $^3J_{CF}$ = 3 Hz), 129.9, 128.5, 128.2, 127.3, 122.8 (q, $^1J_{CF}$ = 270 Hz, CF_3), 122.4 (q, $^2J_{CF}$ = 34 Hz), 119.3, 114.2, 113.2, 109.7, 77.5, 52.0; ^{19}F NMR (282 MHz, CCl_3F) *δ*: −62.0 (s, CF_3); GC–MS, *m/z* (%): 463 ($[M]^+$, 11%), 465 ($[M + 2]^+$, 4%), 431, 404, 368, 288, 223, 180 (98%), 152, 91, 77, 59 (100%); Anal. Calcd. (%) for $C_{23}H_{17}ClF_3NO_4$: C, 59.56; H, 3.69; N, 3.02. Found: C, 59.75; H, 3.81; N, 3.17.

*4.4.8. Methyl 2-((4-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl)(phenoxy)methyl)acrylate (**3e**)*

Yield 97% of pale yellow oil: IR (KBr) *ν*: 3070, 2920, 1720, 1460, 1325, 1135, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ*: 8.27–8.28 (m, 1H, Ar–H), 7.98 (d, 1H, *J* = 2.4 Hz, Ar–H), 7.54 (d, 2H, *J* = 8.7 Hz, Ar–H), 7.23–7.28 (m, 2H, Ar–H), 7.16 (d, 2H, *J* = 8.7 Hz, Ar–H), 6.92–6.97 (m, 3H, Ar–H), 6.41 (s, 1H, CH), 6.19 (s, 1H, C=CH_2), 6.04 (s, 1H, C=CH_2), 3.77 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) *δ*: 166.4, 161.3 (q, $^4J_{CF}$ = 1 Hz), 157.8, 152.9, 143.0 (q, $^3J_{CF}$ = 4 Hz), 140.4, 136.8, 136.7 (q, $^3J_{CF}$ = 3 Hz), 131.8, 129.9, 129.3, 126.8, 123.2 (q, $^1J_{CF}$ = 270 Hz, CF_3), 123.0 (q, $^2J_{CF}$ = 34 Hz), 122.8, 121.9, 121.8, 119.9, 116.3, 77.0, 52.4; ^{19}F NMR (282 MHz, CCl_3F) *δ*: −62.1 (s, CF_3); Anal. Calcd. (%) for $C_{23}H_{17}ClF_3NO_4$: C, 59.56; H, 3.69; N, 3.02. Found: C, 59.52; H, 3.90; N, 3.19.

*4.4.9. 2-((4-(3-Chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl)(phenoxy)methyl)acrylonitrile (**3f**)*

Yield 71% of pale yellow oil: IR (KBr) ν: 3080, 2940, 2240 (CN), 1600, 1500, 1460, 1400, 1325, 1170, 1070, 920, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.26–8.27 (m, 1H, Ar–H), 7.99 (d, 1H, $J = 2.1$ Hz, Ar–H), 7.55 (d, 2H, $J = 6.9$ Hz, Ar–H), 7.28–7.38 (m, 4H, Ar–H), 6.96–7.10 (m, 3H, Ar–H), 6.11 (m, 2H, CH, C=CH_2), 5.73 (s, 1H, C=CH_2); Anal. Calcd. (%) for $C_{22}H_{14}ClF_3N_2O_2$: C, 61.33; H, 3.28; N, 6.50. Found: C, 61.57; H, 3.32; N, 6.44.

*4.4.10. Methyl 2-((4-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl)(methoxy)methyl)acrylate (**3g**)*

Yield 60% of colorless oil: IR (KBr) ν: 3080, 2960, 1720, 1600, 1505, 1460, 1325, 1135, 1095, 960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.27 (s, 1H, Ar–H), 7.98 (s, 1H, Ar–H), 7.43 (dd, 2H, $J = 6.6$, 1.8 Hz, Ar–H), 7.14 (dd, 2H, $J = 6.6$, 1.8 Hz, Ar–H), 6.36 (s, 1H, C=CH_2), 5.97 (s, 1H, C=CH_2), 5.17 (s, 1H, CH), 3.73 (s, 3H, CO_2CH_3), 3.36 (s, 3H, OCH_3); Anal. Calcd. (%) for $C_{18}H_{15}ClF_3NO_4$: C, 53.81; H, 3.76; N, 3.49. Found: C, 53.94; H, 3.83; N, 3.40.

*4.5. Preparation of methyl 2-((3-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)phenyl)(methoxy)methyl)acrylate (**3h**)*

Dry silver oxide (556 mg, 2.4 mmol) was added gradually under stirring to **3c** (242 mg, 0.6 mmol) and iodomethane (317 mg, 2.4 mmol) in 10 mL acetonitrile. After stirring at room temperature for 2 days, dry diethyl ether was added. The precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography to afford 217 mg **3h** as pale yellow oil, yield 90%. IR (KBr) ν: 3070, 2930, 1720, 1460, 1320, 1135, 1095, 805 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.25–8.26 (m, 1H, Ar–H), 8.97 (d, 1H, $J = 2.4$ Hz, Ar–H), 7.37–7.42 (m, 1H, Ar–H), 7.27–7.29 (m, 1H, Ar–H), 7.20–7.21 (m, 1H, Ar–H), 7.09–7.12 (m, 1H, Ar–H), 6.34 (s, 1H, C=CH_2), 5.94 (s, 1H, C=CH_2), 5.18 (s, 1H, CH), 3.71 (s, 3H, CO_2CH_3), 3.35 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 166.0, 161.0 (q, $^4J_{CF} = 1$ Hz), 152.7, 142.4 (q, $^3J_{CF} = 4$ Hz), 141.8, 140.8, 136.1 (q, $^3J_{CF} = 3$ Hz), 129.3, 125.2, 124.7, 122.8 (q, $^1J_{CF} = 270$ Hz, CF_3), 122.3 (q, $^2J_{CF} = 33$ Hz), 120.9, 120.4, 119.2, 80.3, 57.0, 51.6; GC–MS, m/z (%): 401 ($[M]^+$, 44%), 403 ($[M + 2]^+$, 14%), 388, 354 (100%), 300, 180, 145, 115 (54%), 91, 75; Anal. Calcd. (%) for $C_{18}H_{15}ClF_3NO_4$: C, 53.81; H, 3.76; N, 3.49. Found: C, 53.73; H, 3.58; N, 3.45.

Acknowledgement

We thank the National Pesticide Engineering Research Center of China (Shenyang) for funding this work.

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