Res Chem Intermed (2013) 39:2087–2093
DOI 10.1007/s11164-012-0740-5

Crystal structure and mechanistic investigation of the reaction of 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carbonitrile with unsaturated carbonyl compounds

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Received: 24 June 2012 / Accepted: 19 July 2012 / Published online: 4 August 2012

Abstract The crystal structure of 1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-6-ethyl-1*H*-pyrazolo[3,4-b]pyridine-3-carbonitrile was obtained and determined by X-ray crystallography. The reaction mechanism of 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carbonitrile with unsaturated carbonyl compounds was further proposed.

Keywords Pyrazolopyridine · Mechanism · Synthesis · Fipronil

Introduction

Pyrazole and its fused heterocyclic compounds [1, 2] such as pyrazolopyridines are very interesting heterocyclic compounds with wide-ranging biological activities [3, 4]. Some pyrazolo[3,4-b]pyridines have received considerable attention because of the essential roles not only in biological activities but also in fluorescence applications [5, 6], on the basis of their rigid molecular structure. As for 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carbonitrile(APPC), it is the important intermediate in the synthesis of the famous insecticide Fipronil [7, 8], which is a pyrazole insecticide used for insect control worldwide [9]. Meanwhile, the intermediate APPC contains a strong electron-withdrawing group (CN) in its three position, which might lead to its condensation and cycloaddition reactions showing obvious differences from those conventionally reported aminopyrazole compounds. Although our recent work has reported the reaction of intermediate

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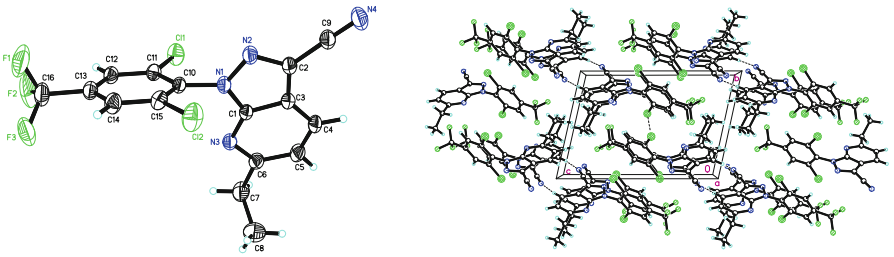


Fig. 1 Crystal structure of (PEPC)

APPC with several α, β-unsaturated aldehydes in acid medium [10], the exact structure characterization and substrate selectivity of α, β-unsaturated carboxyl compounds have not been investigated extensively. In the present work, we further describe the X-ray crystallography of 1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-6-ethyl-1*H*-pyrazolo[3,4-b]pyridine-3-carbonitrile (PEPC) and discuss the possible reaction mechanism by using several α, β-unsaturated carboxyl compounds in place of α, β-unsaturated aldehydes.

Results and discussion

The intermediate APPC, which has three nucleophilic centers including its α-carbon atom (pyrazole) and amino groups to react with electrophiles, is a key intermediate not only for the synthesis of Fipronil but also for the construction of other useful heterocyclic compounds. The synthesis of the crystal compound PEPC was shown in our previous work [10] and its molecular structure was elucidated by X-ray crystallography (Fig. 1; Table 1), which revealed that pyrazolo[3,4-b]pyridine was formed.

In order to investigate the potential reaction activity of intermediate APPC, the effect of the CN group on the product pyrazolopyridine was checked. So, firstly, the CN group of APPC was transformed to an amide group (Compound **3**, Scheme 1), while the further condensation product between compound **3** with acrolein for pyrazolopyridine was not obtained. This indicated that the CN group is necessary for the construction of pyrazolopyridine, which can activate the α-carbon atom of pyrazole. For the reaction of 1,4-benzoquinone(**1**) with intermediate APPC, only the compounds **5** and **6** were obtained, and, interestingly, compound **5** can be further transformed to **6** under a $NaBH_4$/alcohol system. This implies that there is a disproportionation reaction between 1,4-benzoquinone and intermediate APPC.

For but-3-en-2-one (**2**), we checked its reaction activity for condensation with APPC and found that pyrazolopyridine compound **7** was formed, which indicated that ketenes (such as **2**) may proceed via the reaction procedure differently from substituted α, β-unsaturated aldehydes. As for 2-methylpent-2-enal (**9**), the minor (5 %) product **11** was isolated by careful silica gel chromatography. The proposed reaction pathway for intermediate APPC with unsaturated carbonyl compounds is further shown in Scheme 2. The reaction may proceed via three different reaction procedures, such as

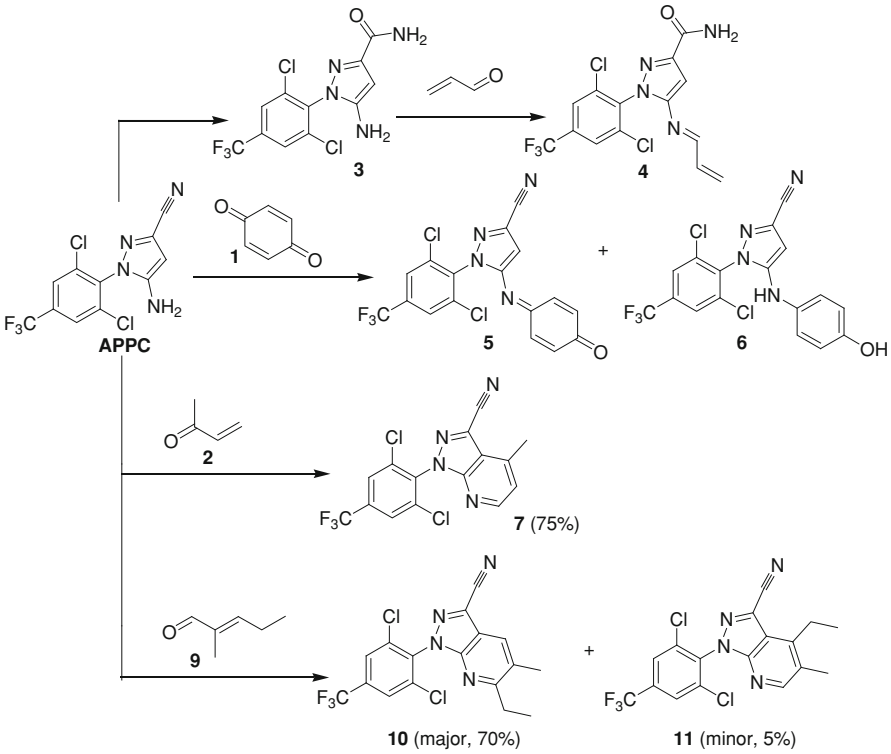
Table 1 The crystal data and structure refinements for PEPC

Compound	PEPC
Empirical formula	$C_{16}H_9Cl_2F_3N_4$
Formula weight	385.17
Temperature (K)	293 (2)
Crystal system	Triclinic
Space group	P-1
a (Å)	7.1348 (10)
b (Å)	9.1199 (12)
c (Å)	13.2736 (18)
α (°)	102.507 (2)
β (°)	90.291 (2)
γ (°)	92.404 (2)
Volume ($Å^3$)	842.4 (2)
Z	2
Absorption coefficient (mm^{-1})	0.422
F (000)	388
Crystal size (mm^3)	0.505 × 0.482 × 0.407
Theta range for data collection (°)	4.579–54.717
h/k/l	−8,8/−8,11/−16,16
Goodness-of-fit on F^2	1.044
Final *R* indices [$I > 2\sigma(I)$]	$R = 0.0533$, $wR\ (F_2) = 0.1490$
R indices (all data)	$R_{factor} = 0.0643$, $wR_{factor} = 0.1573$

path A, path B, and path C. Path A has been reported in our previous work [10], which may include the Michael adduct and disproportionation reaction. Paths B and C might be involved in C–C or C–N condensation reactions, intramolecular Diels–Alder reaction, and aromatization [11]. In path B, the addition of α-carbon atom of pyrazole (APPC) to α, *β*-unsaturated carboxyl compounds formed unstable intermediate **8**, which can be converted into main product pyrazolopyridine(C–C), e.g. product **7**. Similarly, in path C, compound pyrazolopyridine(C–N) was obtained by the C–N condensation reaction of APPC and α, *β*-unsaturated carboxyl compounds with the formation of a key intermediate Schiff base, which is stable in the case of AcOH as catalyst [10], but unstable in the case of HCl as catalyst with minor product **11** being formed. Therefore, it is easy to obtain several kinds of pyrazolo[3,4-b]pyridine derivatives with electron-withdrawing group (CN) through changing the different α, *β*-unsaturated carboxyl compounds and the corresponding acid catalyst.

Conclusions

In summary, the crystal structure of 1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-6-ethyl-1*H*-pyrazolo[3,4-b]pyridine-3-carbonitrile (PEPC) and the reaction mechanism

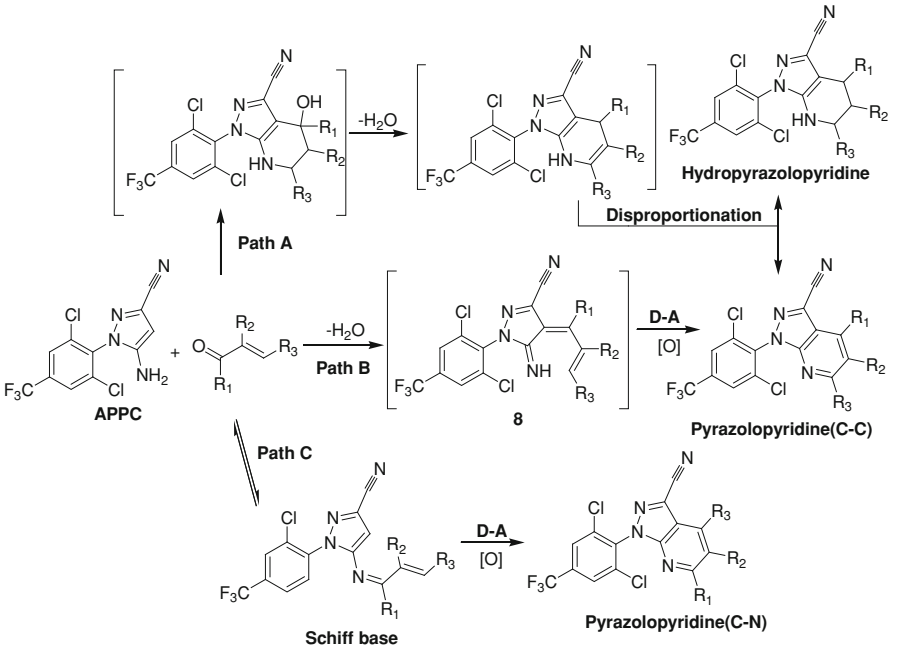


Scheme 1 The reaction of APPC with several α, β-unsaturated carboxyl compounds

of 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carbonitrile with unsaturated carbonyl compounds are further proposed. Our group is actively engaged in developing the easily accessible pyrazolo[3,4-b]pyridine derivatives to explore their reactivity and synthetic applications. Further development of pyrazolo[3,4-b]pyridine-based heterocyclic compounds and the exploration of their application in heterocyclic chemistry and intermediate research are in progress in our group.

Experimental

Commercially available reagents 1,4-benzoquinone (**1**), but-3-en-2-one (**2**), 2-methylpent-2-enal (**9**) and APPC were bought and used without further purification. Solvents were treated prior to use according to the standard methods. Melting points were taken on a micro-melting point apparatus made in Beijing and were uncorrected. ^{1}H NMR spectra were recorded with a Bruker WP-500SY (400 MHz) spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. Infrared spectra were measured on KBr disks using a Nicolet FT-IR-20SX instrument. High resolution mass spectra were obtained on a MicroMass GCT CA 055 spectrometer. Analytical thin-layer chromatography (TLC) was carried out on precoated plated (silica gel 60_{F254}), and spots were visualized with ultraviolet light. Crystals were



Scheme 2 Proposed reaction pathways

obtained by slow evaporation from ethanol solutions of the pure compound PEPC. A colorless single crystal of suitable size was selected for X-ray diffraction analysis. Data were collected on a Bruker Smart and the unit cell dimensions were obtained by least-squares refinement.

General synthesis of intermediates and the target compounds

*5-Amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamide (**3**)*

A solution of 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carbonitrile (3.20 g, 0.01 mol), hydrogen peroxide solution (27.5 %, 2 ml) and ammonia (2 ml) in acetonitrile (20 ml) was stirred for 5 h at room temperature. Then, the solution was added 30 ml water, and extracted with chloroform (30 ml × 3). The organic layer was dried over Na_2SO_4. The solvent was concentrated to afford the crude product **3**, which was directly used in the next step. GC–MS: 338 $[M]^+$, 320, 213, 143.

*(E)-5-(Allylideneamino)-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamide (**4**)*

A solution of 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carboxamide (**3**, 3.38 g, 0.01 mol), acrolein (1.12 g, 0.02 mol) and 3 drops HCl in

acetonitrile (20 ml) was refluxed for the required reaction time, according to TLC (PE:EA = 8:1). The mixture was cooled to room temperature and the solution was added to 30 ml water, and extracted with chloroform (30 ml × 3). The organic layer was dried over Na_2SO_4. The solvent was concentrated and the residue was purified by silica gel chromatography to afford the white solid **4,** yield 70 %; mp 157.3–164.2 °C; IR (KBr); *v* 3,435, 3,358, 3,148, 1,707, 1,664, 1,305, 1,128, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.03 (d, 2H, $J = 12$ Hz, CH_2), 6.52 (m, 1H, CH), 6.79 (s, 2H, NH_2), 6.88 (s, 1H, pyrazole), 7.74 (s, 2H, ArH), 8.32 (d, $J = 9.1$ Hz, 1H, CH). EIMS, *m/z* (%): 376 $[M]^+$ (15.77), 361 (29.18), 358 (100.00), 334 (22.27), 298 (35.38), 296 (66.47), 280 (6.30), 271 (26.97), 213 (29.51), 178 (10.79), 143 (8.63), 66 (8.33), 39 (13.42). HRMS Calcd for $C_{14}H_9N_4OF_3Cl_2$: 376.0106. Found: 376.0114.

*Synthesis of target compounds **5** and **6***

A solution of 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carbonitrile (3.20 g, 0.01 mol), 1,4-benzoquinone (1.08 g, 0.01 mol) and 3 drops HCl in acetonitrile (20 ml) was refluxed for the required reaction time, according to TLC (PE:EA = 8:1). The mixture was cooled to room temperature and the solution was added to 30 ml water, and extracted with chloroform (30 ml × 3). The organic layer was dried over Na_2SO_4. The solvent was concentrated and the residue was purified by silica gel chromatography to afford the white solids **5** and **6**.

*1-(2,6-Dichloro-4-(trifluoromethyl)phenyl)-5-(4-oxocyclohexa-2, 5-dienylideneamino)-1H-pyrazole-3-carbonitrile (**5**)*

mp 157.2–158.6 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 6.61 (s, 1H, CH), 6.65–6.74 (m, 2H, *p*-benzoquinone), 7.07–7.11 (dd, $J_1 = 2.8$ Hz, $J_2 = 10.4$ Hz, 1H, *p*-benzoquinone), 7.52–7.55 (dd, $J_1 = 2.8$ Hz, $J_2 = 10.4$ Hz, 1H, *p*-benzoquinone), 7.76 (s, 2H, ArH).

*1-(2,6-Dichloro-4-(trifluoromethyl)phenyl)-5-(4-hydroxyphenylamino)-1H-pyrazole-3-carbonitrile (**6**)*

mp 190.1–190.9 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 4.76 (s, 1H, OH), 5.08 (s, 1H, NH), 6.78 (d, $J = 8.9$ Hz, 2H, ArH), 6.94 (d, $J = 8.9$ Hz, 2H, ArH), 7.79 (s, 2H, ArH); EIMS, *m/z* (%): 412 $[M]^+$ (100), 377 (5.23), 342 (11.81), 212 (3.89), 178 (3.81), 119 (10.95). HRMS Calcd for $C_{17}H_9N_4OF_3Cl_2$: 412.0106. Found: 412.0106.

*1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-methyl-1H-pyrazolo[3,4-b]pyridine-3-carbonitrile (**7**)*

A solution of 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carbonitrile (3.20 g, 0.01 mol), but-3-en-2-one (1.68 g, 0.02 mol) and 3 drops HCl in acetonitrile (20 ml) was refluxed for the required reaction time, according to TLC (PE:EA = 8:1). The mixture was cooled to room temperature and the solution was added to 30 ml water, and extracted with chloroform (30 ml × 3). The organic

layer was dried over Na_2SO_4. The solvent was concentrated and the residue was purified by silica gel chromatography to afford the white solid **7**: yield 75 %; mp 153.2–153.9 °C; IR (KBr): ν 2,239, 1,583, 1,310, 1,171, 1,128, 831, 785, 565 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.91 (s, 3H, CH_3), 7.22 (d, $J = 4.5$ Hz, 1H, pyridine), 7.82 (s, 2H, ArH), 8.52 (d, $J = 4.6$ Hz, 1H, pyridine); EIMS, *m/z* (%): 370 $[M]^+$ (6.45), 337 (17.33), 335 (100.00), 300 (5.22), 283 (7.02), 248 (3.11), 213 (3.24), 178 (3.17), 143 (3.32), 78 (2.88), 51 (3.57). HRMS Calcd for $C_{15}H_7N_4F_3Cl_2$: 370.0000. Found: 370.0005.

*1-(2,6-Dichloro-4-(trifluoromethyl)phenyl)-6-ethyl-5-methyl-1H-pyrazolo [3,4-b]pyridine-3-carbonitrile (**11**)*

The procedure and the target compound **10** were reported in [10]. The target compound **11** was isolated by silica gel chromatography to afford the white solid, yield 5 %; mp 158.5–159.0 °C; IR (KBr): ν 3,043, 2,239, 1,592, 1,579, 1,310, 1,124, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (t, $J = 7.6$ Hz, 3H), 2.49 (s, 3H), 3.23 (m, 2H), 7.82 (s, 2H), 8.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.8, 150.2, 146.2, 136.5, 136.0, 134.4, 134.1, 127.9, 126.1, 126.0, 123.5, 120.8, 120.0, 115.9, 113.3, 22.3, 15.3, 14.2; EIMS, *m/z* (%): 398 $[M]^+$ (24.34), 363 (100), 348 (13.13), 336 (8.23); HRMS Calcd for $C_{17}H_{11}N_4F_3Cl_2$: 398.0313; Found: 398.0313.

Acknowledgments We are grateful for financial support from the Science Foundation of Shanghai Institute of Technology (YJ2010-49), the Opening Fund of Shanghai Key Laboratory of Chemical Biology (No. SKLCB-2011-08), and the National Natural Science Foundation of China (Grant No. 20972050, No. 21172148 and No. 21005049).

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