Brief Report

Experimental and theoretical investigation of the reaction of a 3-amidothiophene derivative with various carbonyl compounds

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S Supplementary material

The reactions of a 3-amidothiophene derivative, which is a partial structure of penthiopyrad, with various carbonyl compounds were investigated. Depending on the carbonyl compound that was used as a reactant, different products (alkenes and bis-products) were obtained from the attack of the carbon at the 2-position of the 3-amidothiophene on the carbonyl compounds. Density functional theory (DFT) calculations revealed that dehydration conditions were important for the first carbonyl addition to shift the reaction toward the product, as the products are more unstable than reactants other than aldehyde. The DFT calculations also suggested that the relative stability of the alkenyl state determined whether the second bis-product formation would proceed; *i.e.*, the relatively unstable disubstituted alkene led to bis-products, and the stable trisubstituted or conjugated alkene yielded alkenyl products.

Keywords: Penthiopyrad, 3-aminothiophene, alkenylation, DFT calculations.

Introduction

Penthiopyrad (**1**; Fig. 1) is an SDHI (succinate dehydrogenase inhibitor) fungicide that was discovered, developed, and launched by Mitsui Chemicals Agro, Inc., and exhibits high activity against various plant pathogens classified as Ascomycetes and Basidiomycetes.^{1–3)} In order to develop and launch pesticides, it is necessary to develop a manufacturing method that can be industrialized. Penthiopyrad has a pyrazole carbonyl moiety and a thiophene amine moiety to which a 1,3-dimethylbutyl group is bonded at the 2-position of the thiophene ring. Pyrazole carboxylic acid was a known compound at the time penthiopyrad was discovered.⁴⁾ However, the thiophene amine with a 1,3-dimethylbutyl group was a novel compound, and it became an industrialization challenge to efficiently and selectively introduce this unique second-

ary alkyl group at the 2-position of the thiophene ring.

The research group of Francis Outurquin and Claude Paulmier has examined methods for synthesizing various 2-alkyl-3-aminothiophenes from 3-aminothiophene, various aldehydes, catalytic amounts of *p*-toluenesulfonic acid, and selenophenol.⁵⁾ However, these methods were limited to the introduction of primary alkyl groups, and it was known that bis(3-amino-2-thienyl)methane derivatives (bis-products) were obtained when the reaction was carried out without selenophenol as a reductant. The same group synthesized 3-amino-2-isopropylthiophene *via* the same reaction systems using acetone as an electrophile and selenophenol.⁶⁾ However, the reactions using ketones other than acetone as electrophiles were not reported in their results. Furthermore, the group reported that some types of 3-amino-2-primary alkenylthiophene derivatives could be synthesized from 3-aminothiophene derivatives, including amide compounds and aldehyde; however, the reactants for these reactions were limited to α -branched aldehydes, and the resulting products were limited to 2-primary alkenylthiophenes.⁷⁾ Thus, they did not provide general synthetic methods to introduce secondary alkyl groups or alkenyl groups that could be applied to the manufacturing method for penthiopyrad.

We executed a project to develop a large-scale production process for penthiopyrad. This research resulted in the development

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Fig. 1. Production scheme for penthiopyrad, a broad spectrum fungicide.

of synthetic methods for introducing secondary alkenyl groups into 3-aminothiophene or its derivatives at the 2-position of the thiophene ring, which could be converted to 2-secondary alkyl-3-aminothiophene derivatives.^{8–10} This method could be used to synthesize penthiopyrad from a 3-amidothiophene derivative (**2**) and methyl isobutyl ketone (**3a**) in a few steps (Fig. 1).

In this study, in order to investigate the variations and limitations of these reactions, we examined the reactions of compound **2** with various carbonyl compounds under acidic conditions. Furthermore, we investigated the reaction mechanism of 3-amidothiophene with various carbonyl compounds (ketone or aldehyde) using density functional theory (DFT).

Materials and methods

1. Synthesis of compounds

All commercially available reagents were purchased from commercial sources and used as received. The reactions were monitored using thin-layer chromatography (TLC) with a precoated silica gel plate. Melting points (mps.) were determined by using a local hot-stage melting-point apparatus and are uncorrected. IR spectra were measured using a JASCO FT-IR-7300 spectrometer. ¹H-NMR spectra were measured using a JEOL JNM-Λ400 FT-NMR system at 400 MHz, with tetramethylsilane as the internal standard. MSs were run on a Micromass Quattro II with APC ionization. Analytical data for each compound shown below are provided in supplemental materials.

1.1. Mixture of (Z)- and (E)-1-methyl-N-(2-(4-methylpent-2-en-2-yl)thiophen-3-yl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (**4a**) and 1-methyl-N-(2-(4-methylpent-1-en-2-yl)thiophen-3-yl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (**4'a**)

1-Methyl-N-(3-thienyl)-3-(trifluoromethyl)pyrazole-4-carboxamide⁸⁾ **2** (20.0 g, 72.7 mmol), methyl isobutyl ketone (MIBK) **3a** (21.9 g, 218.2 mmol), and a catalytic amount of *p*-toluenesulfonic acid monohydrate (1.0 g) were added to toluene (160 mL), and the resulting mixture was refluxed (112°C) with stirring for 8 hr, while the water that was produced during the reaction was extracted using a Dean–Stark apparatus. After cooling to 50°C, the reaction mixture was washed with a saturated sodium hydrogen carbonate solution and dried over sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified *via* silica gel column chromatography (eluent: hexane/ethyl acetate=6/4) to obtain mixture **4a** (24.1 g, *E:Z*=47:53, 93% yield) as a white solid. A small amount of the exomethylene compound **4'a** was present in the mixture.

1.2. Mixture of (Z)- and (E)-N-(2-(but-2-en-2-yl)thiophen-3-yl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (**4b**) and N-(2-(but-1-en-2-yl)thiophen-3-yl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (**4'b**)

1-Methyl-N-(3-thienyl)-3-(trifluoromethyl)pyrazole-4-carboxamide **2** (2.2 g, 8.0 mmol), methyl ethyl ketone (MEK) **3b** (2.3 g, 32.0 mmol), and a catalytic amount of *p*-toluenesulfonic acid monohydrate (0.2 g) were added to toluene (20 mL), and the resulting mixture was refluxed (105°C) with stirring for 3 hr, while the water that was produced during the reaction was extracted using the Dean–Stark apparatus. After cooling to 50°C, the reaction mixture was washed with a saturated sodium hydrogen carbonate solution and dried over sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified *via* silica gel column chromatography (eluent: hexane/ethyl acetate=6/4) to obtain mixture **4a** (1.7 g, *E:Z*=44:55, 64% yield) as a colorless oil. A small amount of the exomethylene compound **4'b** was present.

1.3. N-(2-(cyclohex-1-en-1-yl)thiophen-3-yl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (**4c**)

We obtained **4c** as a white solid (1.8 g, 63% yield) using a method similar to that in 1. 2.

1.4. 1-Methyl-N-(2-(1-phenylvinyl)thiophen-3-yl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (**4d**)

We obtained **4d** as a colorless oil (0.3 g, 11% yield) using a method similar to that in 1. 2.

1.5. N,N'-(propane-2,2-diylbis(thiophene-2,3-diyl))bis(1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide) (**5e**)

1-Methyl-N-(3-thienyl)-3-(trifluoromethyl)pyrazole-4-carboxamide **2** (2.2 g, 8.0 mmol), acetone **3e** (4.6 g, 80.0 mmol), and *p*-toluenesulfonic acid monohydrate (0.2 g) were added to toluene (20 mL), and the resulting mixture was refluxed (80°C) with stirring for 3 hr under azeotropic conditions using the Dean–Stark apparatus. After cooling to 50°C, the reaction mixture was washed with a saturated sodium hydrogen carbonate solution and dried over sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified *via* silica gel column chromatography (eluent: hexane/ethyl acetate=1/1→3/7) to obtain **5e** (1.5 g, 64% yield) as a colorless solid.

1.6. N,N'-((3-methylbutane-1,1-diyl)bis(thiophene-2,3-diyl))bis(1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide) (**5f**)

1-Methyl-N-(3-thienyl)-3-(trifluoromethyl)pyrazole-4-carboxamide **2** (2.2 g, 8.0 mmol), 3-methylbutanal **3f** (0.76 g,

8.8 mmol), and *p*-toluenesulfonic acid monohydrate (0.2 g) were added to dichloromethane (11 mL), and the resulting mixture was stirred at room temperature for 4 hr. The reaction mixture was washed with a saturated sodium hydrogen carbonate solution and dried over sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified *via* silica gel column chromatography (eluent: hexane/ethyl acetate = 4/6 → 2/8) to obtain **5f** (2.2 g, 87% yield) as a white solid.

2. Computational procedures

The reaction mechanism of the first carbonyl addition reaction and the second bis-product formation was investigated using DFT with ketones (acetone, MEK, and acetophenone) or acetaldehyde as a substitute for 3-methylbutanal. In the DFT calculations, the pyrazole group was modeled by a methyl group, and HCl was used as a catalytic acid instead of *p*-toluenesulfonic acid. The structures corresponding to the reactants, transition states (TSs), intermediates, and products for the model reactions were optimized using the GAUSSIAN-09 computational package.¹¹⁾ All of the calculations were performed at the B3LYP level using a 6–31+G (d) basis set.^{12–14)} Frequency calculations were performed to estimate the zero-point vibrational energies and the thermochemical parameters. The thermodynamic properties and relative Gibbs free energies for the reaction profiles were calculated at 298.15 K and 1 atm. The solvation effect was evaluated using an implicit description of toluene *via* the solvent model density (SMD) method.¹⁵⁾ The reaction paths (Figs. 2 and 3) were calculated in the gas phase, and the solvation energy was added later, whereas the other structures shown in Table 2 and described in the text (**2**, **3b**, **4b**, and H₂O) were optimized in a toluene solvent using the SMD model. The synchronous transit-guided quasi-Newton method was used to obtain the TSs.¹⁶⁾ Intrinsic reaction coordinate calculations were performed to confirm that the TSs were properly connected to the reactants and products.¹⁷⁾

Results and discussion

1. Reaction of 3-amidothiophene with various carbonyl compounds

The results of the reactions of the 3-amidothiophene derivative (**2**) with various carbonyl compounds (**3a–f**) in the presence of *p*-toluenesulfonic acid are summarized in Table 1. With the exception of 3-methylbutanal (**3f**), these reactions were conducted under toluene reflux and azeotropic conditions using a Dean–Stark apparatus. The reaction with **3f** proceeded at room temperature.

When ketones other than acetophenone (**3d**) or acetone (**3e**) were used as reactants, *N*-(2-alkenyl-3-thienyl)carboxamide derivatives were obtained at moderate or good yields. A mixture of β -substituted alkenyl compounds and exomethylene compounds was obtained when MIBK (**3a**) or MEK (**3b**) was used as a reactant. The ratio of *E*:*Z* in the β -substituted alkenyl compounds was approximately 1:1, and a small amount of exomethylene compound was produced in both cases. When **3d** was used as a reactant, a poor yield was obtained, and the other reactant (**2**)

remained in the reaction mixture. When **3e** was used as a reactant, a bis-product (**5e**) from two amidothiophenes and acetone was obtained at a moderate yield instead of a compound with an isopropenyl group at the 2-position of the thiophene ring. A similar bis-product (**5f**) was obtained at a high yield under milder reaction conditions using an aldehyde (**3f**) as a reactant, and this result is consistent with the previous report.⁷⁾

2. Investigation of the reaction mechanism using DFT

2.1. The first carbonyl addition reaction

A plausible reaction mechanism for the first carbonyl addition reaction is shown in Fig. 2. We prepared four initial conformations with different relative orientations between aminothiophene and the ketone or aldehyde reactant (**R-1**). The catalytic acid, HCl, mainly interacted with the carbonyl group in the initial state. The first TSs (**TS-1**) were obtained from the initial four conformations. We selected the TS structures with the lowest energy for the following calculations of the reaction profiles. At **TS-1**, the cationic carbon atom in the carbonyl group was electrophilically attacked by the anionic carbon at the 2-position of the thiophene ring. After aminothiophene was added to the carbonyl group, the hydrogen atom at the 2-position of the thiophene ring was extracted by a chloride anion with relatively low activation energies (**TS-2**). The following torsional rotation of the hydroxy group provided a hydrogen bond between the hydroxy group and the hydrogen atom in HCl (**TS-3**). The hydroxy group that was activated by HCl spontaneously dissociated *via* an E1-like mechanism in our model with relatively high activation energies (**TS-4**). The intermediate after the dehydration reaction was in a chlorine-bound state (covalent state, **P-1**), where the bond distance between the chlorine and carbon atom was longer than that of the standard bond. This long distance implied reversible dissociation of the chlorine atom. In fact, the dissociation of the chlorine atom occurred with low activation energies (**TS-5**) and resulted in an ionic state (**P-2**) except for acetaldehyde. In the final step, a dissociated chloride anion extracted a proton from an aliphatic carbon atom to form an alkene (alkene state, **P-3**). In the case of acetaldehyde, a dissociated chloride anion extracted the proton without forming a stable ionic state.

The first C–C bond formation (**TS-1**) was the rate-limiting step for all of the compounds except for acetaldehyde, for which the dehydration step (**TS-4**) was the rate-limiting step. The activation free energies for the rate-limiting step were in qualitative agreement with the yields, *i.e.*, using acetophenone as a reactant resulted in low yields, using acetone and MEK as reactants resulted in moderate or high yields, and using acetaldehyde as a reactant resulted in high yields. The type of carbonyl reactant affected the activation energy of the formation of the first C–C bond. The activation energy was increased when the electron-donating substituents lowered the cationicity of carbonyl carbon in the reactants.

Table 1. Reaction products for *N*-(3-thienyl)-carboxamide derivative (**2**) and various carbonyl compounds under acidic conditions

Entry	Carbonyl compound	Product	Yield (%) ^{a)}
1	3a		93 ^{b)}
2	3b		64 ^{b)}
3	3c		63
4	3d		11
5	3e		64
6	3f		87

^{a)} Isolated yield calculated after chromatographic purification. ^{b)} Yield calculated from mixture containing *E/Z* mixture (**4a** or **4b**) and exomethylene compound (**4'a** or **4'b**)

2.2. Effect of dehydration conditions on the first carbonyl addition reaction

An unexpected result was that the final products or intermediates in the first carbonyl addition reaction were less stable than the reactants except for the acetaldehyde intermediate. To further confirm the stability of the products, we calculated the Gibbs free energy change between the reactants (**2**+**3b**) and the products (**4b**+H₂O). In this thermodynamic calculation, the interactions between molecules were completely neglected for both the reactants and the products, which may be a valid assumption under dilute conditions. The products (**4b**+H₂O) were less stable than the reactants (**2**+**3b**) by 59.6 kJ/mol, indicating that the first carbonyl addition reaction using ketones did not proceed under equilibrium conditions. This result appeared to be inconsistent with our experimental results that alkenyl products or bis-products were obtained at moderate or high yields.

We speculated that a small portion of the reactant formed a dehydrated product, and the generated water molecule was removed from the system under azeotropic reflux conditions in toluene. The eliminated water shifted the reaction toward the product, although the Gibbs free energy of the product was higher than that of the reactant. The DFT calculations suggested that only the aldehyde did not require dehydrated conditions because the product (**P-1**) was more stable than the reactant (**R-1**; Fig. 2), which was consistent with the experimental observation that the bis-product was produced without the use of dehydrated conditions only when 3-methylbutanal was used as a reactant.

2.3. Relative stability of products in the first carbonyl addition reaction

As shown in Fig. 2, three products (covalent, ionic, and alkene states) could be mutually converted at low activation ener-

Fig. 2. Computed relative Gibbs free energy diagram for carbonyl addition reaction (kJ/mol).

gies. Therefore, it is possible that these three states were equilibrated. To understand the relative stabilities in the absence of water, the relative stability of the products in toluene was evaluated using DFT calculations (Table 2). The covalent state was the most stable when acetone and acetaldehyde were used as reactants. When acetophenone was used as a reactant, conjugation with a phenyl group made the ionic and alkene states more stable than the covalent state. MEK exhibited different stabilities depending on the position of the double bond. The covalent state was the most stable when a disubstituted double bond

was formed, whereas the alkene state was the most stable when a trisubstituted double bond was formed. The difference in the stabilities of the double bonds coincided with Zaitsev's rule for E1-elimination reactions. The DFT calculations indicated that MEK and acetophenone produced stable alkene states, whereas acetone and acetaldehyde produced covalent states in the first carbonyl addition reaction.

2.4. The second bis-product formation

A plausible reaction mechanism for the second bis-product formation is shown in Fig. 3. The initial state of the sec-

Fig. 3. Computed relative Gibbs free energy diagram for second dimerization (kJ/mol).

Table 2. Computed relative Gibbs free energy differences (kJ/mol)

R ₁ /R ₂	covalent	ion	alkene
H/Me	0	14.5	9.6
Me/Me	0	12.4	-11.9
H/Et	0	12.4	2.6
H/Ph	0	-5.7	-18.5
H/H	0	12.2	19.7

ond bis-product formation (**R-2**) was set as the covalent state (**P-1**) in Fig. 2 by replacing the water molecule with 3-acetamidothiophene. The first TS (**TS-7**) was the dissociation of a chloride anion by 3-acetamidothiophene at relatively low activation energies. The chloride anion was stabilized by two hydrogen bonds in the intermediate state (**I-4**). In the next TS for C–C bond formation (**TS-8**), a carbocation was electrophilically attacked by the carbon atom at the 2-position of the thiophene ring. After 3-acetamidothiophene was added to the carbocation, the proton at the 2-position of the thiophene ring was extracted by a chloride anion with relatively small activation energies (**TS-9**). The final product (**P-5**) was generated by the transfer of HCl to the carbonyl group to form a hydrogen bond *via* a few local minimums.

2.5. Key factors that determine the type of product

With the exception of acetophenone, the activation energies for the rate-limiting step in the second bis-product formation were smaller than those for the first addition reaction. In addition, all of the final products (**P-5**) in the second reaction were more stable than the reactants (**R-2**). These results indicated that the second bis-product formation could proceed under the same conditions as the first reaction. Because the bis-product formation step is expected to be in equilibrium under dehydration conditions, the most stable state will be the product. The bis-products of acetophenone and MEK (**P-5**) are only 1.4 and 1.1 kJ/mol more stable than the reactants of the covalent states (**R-2**) (see Fig. 3), whereas the alkene states of acetophenone and MEK are 18.5 and 11.9 kJ/mol more stable than the covalent states (Table 2). These DFT calculations indicated that MEK and acetophenone were the most stable in the alkenyl states and yielded alkenyl products. Meanwhile, the covalent states of acetaldehyde and acetone are 19.6 and 9.6 kJ/mol more stable than those of the alkene states (Table 2), suggesting that the covalent reactants of acetaldehyde and acetone undergo a bis-product formation reaction. This conclusion, which was based on the DFT calculations, was consistent with the experimental data. Our DFT calculations proposed that the stability of formed alkene states determined the products; *i.e.*, the unstable disubstituted alkene yielded bis-products, and the stable trisubstituted or conjugated alkene remained in alkene states. Therefore, in the production of

penthiopyrad, the formation of stable trisubstituted alkene was suggested to be a key factor for obtaining the alkenyl product without selenophenol as a reductant.

Conclusion

In summary, we reported the reaction of 3-amidothiophene with a ketone or an aldehyde. Experimental and DFT studies revealed that (i) dehydration conditions during synthesis were important for the first carbonyl addition reaction to proceed using a ketone, (ii) the alkenyl product was obtained when a trisubstituted or conjugated stable alkene was formed, and (iii) the bis-product was obtained when an unstable disubstituted alkene formed in the first reaction. Our findings are useful for understanding the detailed reaction mechanism by which different products are generated depending on the reactant for the same reaction system. The obtained alkenyl compounds are expected to be applicable on an industrial production scale to synthesize novel compounds such as pharmaceuticals and agrochemicals.

Electronic supplementary materials

The online version of this article contains supplementary material (Analytical data), which is available at <https://www.jstage.jst.go.jp/browse/jpestics/>

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