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Akio MANABE[a], Hirotaka TAKANO[a], Kunihiko FURUZAWA[a], Kazunori YANAGI[b], Yoshio HISADA[a] & Shizuya TANAKA[a]

[a] Agricultural Chemicals Research Laboratory, Sumitomo Chemical Co. Ltd. 4-2-1 Takatsukasa, Takarazuka, Hyogo 665-8555, Japan

[b] Environmental Health Science Laboratory, Sumitomo Chemical Co. Ltd. 4-2-1 Takatsukasa, Takarazuka, Hyogo 665-8555, Japan

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Note

Synthesis and Fungicidal Activity of 1-(α-*tert*-Butylcinnamoyl)imidazoles

Akio MANABE,[1,†] Hirotaka TAKANO,[1] Kunihiko FURUZAWA,[1] Kazunori YANAGI,[2] Yoshio HISADA,[1] and Shizuya TANAKA[1]

[1]*Agricultural Chemicals Research Laboratory, Sumitomo Chemical Co. Ltd., 4-2-1 Takatsukasa, Takarazuka, Hyogo 665-8555, Japan*

[2]*Environmental Health Science Laboratory, Sumitomo Chemical Co. Ltd., 4-2-1 Takatsukasa, Takarazuka, Hyogo 665-8555, Japan*

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Several 1-(α-*tert*-butylcinnamoyl)imidazoles were prepared to examine their fungicidal activity. The (*Z*)-4-chlorocinnamoyl derivative was prepared from (*anti*)-2-*tert*-butyl-3-(4-chlorophenyl)-3-hydroxypropanoic acid by treating with 1,1′-carbonyldiimidazole and a subsequent β-elimination reaction at an elevated temperature. The (*Z*)-isomer of the 4-chlorocinnamoyl derivative showed good fungicidal activity against *Erysiphe graminis* and *Botrytis cinerea* in pot tests, whereas the corresponding (*E*)-isomer derived from the (*Z*)-isomer through photoisomerization was much less active.

Key words: 1-cinnamoylimidazole; β-elimination reaction; geometrical isomer; azole fungicide; fungicidal activity

We have reported in the previous papers[1–2] that a sterically-hindered 1-acyl imidazole compound, *i.e.*, 1-[2-(4-chlorobenzyl)-3,3-dimethylbutanoyl]imidazole was effective for the control of phytopathogenic fungi such as powdery mildew on barley, *Erysiphe graminis* (*E. graminis*), and the gray mold on cucumber, *Botrytis cinerea* (*B. cinerea*). Presumably, like other azole fungicides such as the stylyl triazole fungicide, diniconazole[3] (S-3308; (*E*)-(*RS*)-1-(2,4-dichlorophenyl)-4,4-dimethyl-2-(1*H*-1,2,4-triazol-1-yl)pent-1-en-3-ol), the 1-acyl imidazole compound might show its fungicidal activity by inhibiting ergosterol biosynthesis rather than by acylating reactivity.[2] These findings prompted us to search for fungicidal activity in its cinnamoyl analogues, *i.e.*, 1-(α-*tert*-butylcinnamoyl)imidazoles, sharing the common stylyl moiety with diniconazole. We report in this note their synthesis and fungicidal activity.

The synthetic procedure for 1-[α-(*tert*-butyl)-4-chlorocinnamoyl]imidazole is illustrated in Fig. 1. (*Anti*)-β-hydroxy acid **1a** that was obtained by stereoselective aldol-type addition under ther-

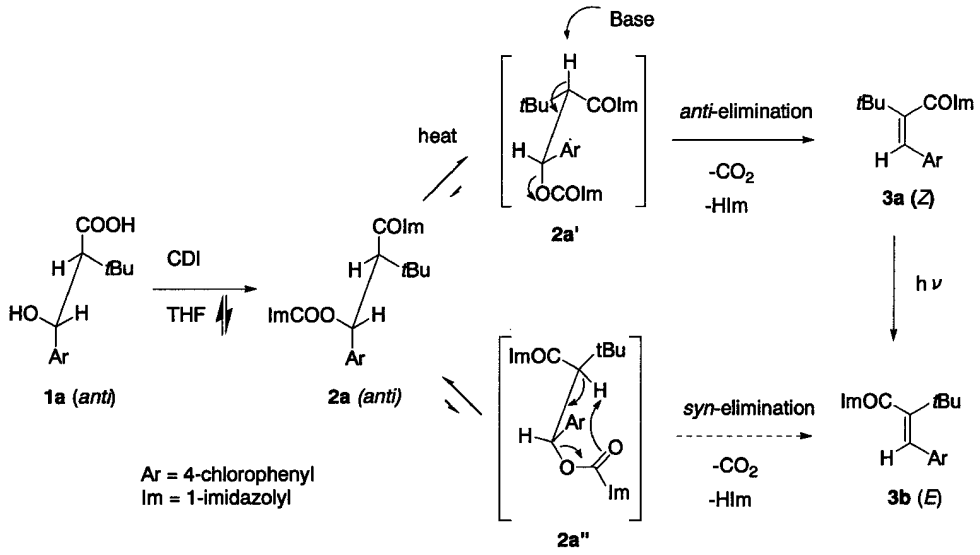


Fig. 1. Synthesis of 1-[α-(*tert*-Butyl)-4-chlorocinnamoyl]imidazole.

† To whom correspondence should be addressed. Fax: +81-797-74-2129; E-mail: manabe@sc.sumitomo-chem.co.jp

Abbreviations: *E. graminis*, *Erysiphe graminis*; *B. cinerea*, *Botrytis cinerea*; CDI, 1,1′-carbonyldiimidazole; THF, tetrahydrofuran

modynamic control[4] was reacted with 3.5 equivalents of 1,1′-carbonyldiimidazole (CDI) in tetrahydrofuran (THF) under reflux to give diimidazole derivative **2a** in a 69% yield. Since the reaction is considered to have proceeded with retention of the configuration at two asymmetric carbon atoms, **2a** should have the *anti* configuration like **1a**. When **2a** was heated at 190–200°C, a *β*-elimination reaction took place with the loss of carbon dioxide and imidazole to give desired cinnamoyl imidazole **3a** having the *Z* configuration in a 42% yield as the main product. Its chemical structure (**3a**), including the *Z* configuration of the double bond, was confirmed by an X-ray structural analysis. The molecular structure of **3a** is shown Fig. 2. As shown in Fig. 1, since (*anti*)- diimidazole **2a** gave mainly (*Z*)-product **3a**, the *β*-elimination reaction may be characterized as involving *anti*-elimination rather than pyrolytic *syn*-elimination: the necessary conformation of **2a″** leading to (*E*)-product **3b** was presumably destabilized in this reaction by steric interaction between the bulky *tert*-butyl group and the 4-chlorophenyl group. Each of the other (*Z*)-cinnamoyl derivatives **3c-3g** (Table 1) was prepared in a similar way by an analogous procedure. On the other hand, corresponding (*E*)-derivative **3b** was obtained by photoisomerization of (*Z*)-derivative **3a** under irradiation by sunlight in acetone.

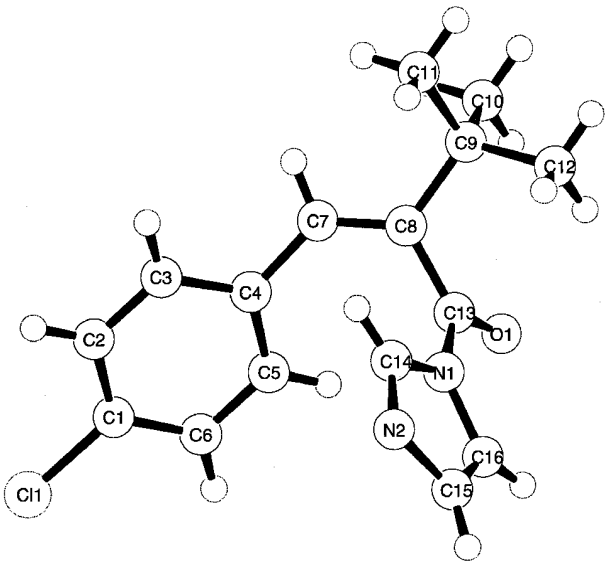


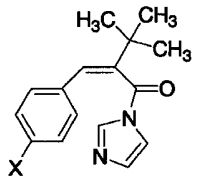
Fig. 2. Molecular Structure of 3a Determined by an X-ray Analysis.

As shown in Table 1, (*Z*)-4-chloro derivative **3a** showed good activity against *E. graminis* and *B. cinerea* in pot tests. In marked contrast, corresponding (*E*)-isomer **3b** was much less active against both fungi, suggesting the significance of the stereochemistry in eliciting the fungicidal activity of this class of compounds. In this context, it is interesting to note that the geometrical isomer-fungicidal activity relationship is different between the cinnamoyl imidazoles (**3a** *vs.* **3b**) and the stylyl triazoles (diniconazole *vs.* its less active geometrical isomer); *i.e.*, in more active **3a**, the phenyl ring and the imidazolylcarbonyl moiety are *cis*, while in more active diniconazole, the phenyl and triazolyl rings are *trans*.[3] The bromo (**3d**) and cyano (**3f**) analogues of **3a** also showed good activity comparable to that of **3a**, while the trifluoromethyl (**3e**), methyl (**3g**) and unsubstituted (**3c**) analogues were less active.

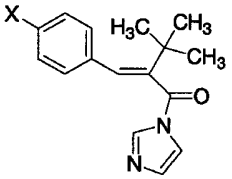
Experimental

Melting point (mp) data were determined with Yanagimoto micro melting point apparatus and are

Table 1. 1[(*α*-(*tert*-Butyl)-4-substituted-cinnamoyl]imidazoles and Their Fungicidal Activity against *Erysiphe graminis* and *Botrytis cinerea*



Z



E

Compound						Preventive activity	
No.	X	*Z*/*E*	mp (°C)	^{1}H-NMR ($CDCl_3$/TMS) *δ* (ppm)		pED_{50}[a]	
				t-Bu	2-Position of imidazole	*E. graminis*	*B. cinerea*
3a	Cl	*Z*	95.5–96.5	1.31	7.82	5.92	4.82
3b	Cl	*E*	111.5–112.5	1.20	8.24	3.52	2.92
3c	H	*Z*	88–89	1.31	7.87	4.17	3.40
3d	Br	*Z*	111–111.5	1.29	7.82	5.96	4.63
3e	CF_3	*Z*	74–74.5	1.31	7.84	4.19	3.04
3f	CN	*Z*	134–135	1.32	7.80	5.89	4.40
3g	Me	*Z*	79–80	1.28	7.63	3.92	3.43

a) Negative logarithm of the molar concentration required for 50% control in pot tests.

uncorrected. Proton (^{1}H) NMR spectra were measured with a Hitachi R-24B (60 MHz) spectrometer or JEOL JNM-AL400 spectrometer.

(Anti)-2-tert-butyl-3-(4-chlorophenyl)-3-hydroxypropanoic acid (1a). To a stirred solution of diisopropylamine (40.48 g) in dry THF (200 ml) was added dropwise butyllithium (1.6 M in hexane, 250 ml) at below 0°C. After stirring at 0°C for 10 min, *tert*-butylacetic acid (20.91 g) in dry THF (50 ml) was added dropwise at below 0°C, and the mixture was stirred at room temperature for 1 hr. To the mixture was added 4-chlorobenzaldehyde (25.30 g) in dry THF (50 ml) at −50°C. The mixture was allowed to rise to room temperature, and stirred for 2 days. The resulting mixture was poured into ice-cooled water and acidified with HCl aq. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layer was dried and concentrated. The residue was triturated with acetonitrile-hexane to give a solid, which was recrystallized from acetonitrile to give **1a** (10.20 g, 21%), mp165–166°C (its (*syn*)- isomer has been reported to have a melting point of 194–195°C[4]). Anal.Found: C, 60.82; H, 6.77; Cl, 13.73%. Calcd. for $C_{13}H_{17}O_3Cl$: C, 60.82; H, 6.77; Cl, 13.81%. ^{1}H-NMR (400 MHz)δ(acetone-d_6/TMS): 1.06 (9H, s), 2.64 (1H, *J*=*4.8 Hz*, d), 5.04 (1H, *J*=*4.8 Hz*, d), 7.3–7.45 (4H, m)

(Anti)-1-(4-chlorophenyl)-2-(1-imidazolylcarbonyl)-3,3-dimethylbutyl imidazole-1-carboxylate (2a). A mixture of **1a** (8.99 g) and CDI (19.73 g) in THF (100 ml) was heated under reflux for 4 hr while stirring. After evaporating the solvent, the residue was diluted with ether, washed with water, dried and concentrated. The residue was chromatographed on silica gel (eluent, hexane-acetone (1:1,v/v)) to give **2a** (9.7 g, 69%), mp 69–71°C. Anal. Found: C, 59.50; H, 5.37; N, 13.70%. Calcd. for $C_{20}H_{21}N_4O_3Cl$: C, 59.93; H, 5.28; N, 13.98%. ^{1}H-NMR (60 MHz)δ($CDCl_3$/TMS): 1.02 (9H, s), 3.53 (1H, *J*=*8 Hz*, d), 6.30 (1H, *J*=*8 Hz*, d), 6.98 (1H, s), 7.09 (1H, s), 7.12(1H, s), 7.37 (4H, s), 7.46 (1H, s), 7.87 (1H, s), 8.13 (1H, s). IR ν_{max} (nujol) cm^{-1}: 1758 (C=O), 1728 (C=O)

(Z)-1-[α-(tert-butyl)-4-chlorocinnamoyl]imidazole (3a). (*Anti*)-diimidazole **2a** (48.23 g) was heated at 190–200°C while stirring until the gas (carbon dioxide) evolution ceased. After cooling, the mixture was dissolved in ether, washed twice with water, dried and concentrated. The residue was chromatographed on silica gel (eluent, hexane-acetone (5:1, v/v)) to give a solid, which was recrystallized from diisopropyl ether to give **3a** (14.6 g, 42%), mp 95.5–96.5°C. Anal. Found: C, 66.84; H, 5.99; N, 9.71; Cl, 12.38%. Calcd. for $C_{16}H_{17}N_2OCl$: C, 66.55; H, 5.93; N, 9.70; Cl, 12.28%. ^{1}H-NMR (60 MHz) δ($CDCl_3$/TMS): 1.31 (9H, s), 6.81 (1H, s), 6.91 (1H, m), 7.12 (4H, s), 7.32 (1H, m), 7.82 (1H, s). IR ν_{max} (nujol) cm^{-1}: 1697 (C=O).

Compounds **3c-3g** were prepared by a similar method to that just described.

X-ray analysis. A single crystal of **3a**, which had been obtained by recrystallization from diisopropyl ether, was monoclinic, space group *C2/c*, with a=33.303 (4) Å, b=6.047 (1) Å, c=16.492 (2) Å, β=112.80 (1)°, V=3061.4 Å^3, and d_{calcd}=1.253 g cm^{-3} for Z=8 ($C_{16}H_{17}N_2OCl$, mol. wt.=288.78). The intensity data were measured by an Enraf-Nonius CAD 4 diffractometer with Cu K_α radiation. The structure was resolved by the direct method and refined by the full-matrix least-squares method. The final discrepancy indices are R=0.040 and R_w=0.058.

(E)-1-[α-(tert-butyl)-4-chlorocinnamoyl]imidazole (3b). (*Z*)-derivative **3a** (1.0 g) was placed in a Pyrex glass flask and dissolved in acetone (500 ml). After allowing the resulting solution to stand for 20 hr under irradiation with sunlight, the solvent was evaporated. The residue was crystallized from diisopropyl ether to give (*E*)-derivative **3b** (0.24 g, 24%), mp111.5–112.5°C. Anal. Found: C, 66.43; H, 5.83; N, 9.66; Cl, 12.35%. Calcd. for $C_{16}H_{17}N_2OCl$: C, 66.55; H, 5.93; N, 9.70; Cl, 12.28%. ^{1}H-NMR (60 MHz) δ($CDCl_3$/TMS): 1.20 (9H, s), 6.80 (1H, s), 7.15–7.50 (5H, m), 7.60 (1H, m), 8.24 (1H, s). IR ν_{max} (nujol) cm^{-1}: 1700 (C=O).

The preventive activity of compounds **3a-3g** against a) powdery mildew on wheat, *E. graminis*, and b) gray mold on cucumber, *B. cinerea*, was determined by pot tests.

a) A plastic pot was filled with sandy loam soil, and wheat (var., Norin No. 73) was sown and cultivated in a greenhouse. Each of the test compounds in the form of an emulsifiable concentrate was diluted with water and foliar-sprayed on to the young seedlings in the first true leaf stage to run-off. The seedlings were cultivated in a greenhouse for one day and inoculated with the spores of *E. graminis*. The seedlings were cultivated for 10 days more in the greenhouse, and the controlling activity was examined.

b) A plastic pot was filled with sandy loam soil, and cucumber (var., Sagamihanjiro) was sown and cultivated in a greenhouse. Each of the test compounds in the form of an emulsifiable concentrate was diluted with water and foliar-sprayed on to the young seedlings in the cotyledonous stage to run-off. The seedlings were cultivated in the greenhouse for one day and inoculated with agar gel containing *B. cinerea*. The seedlings were cultivated at 20°C for 4 days more in humid and dark conditions, and the controlling activity was examined.

The preventive activity was evaluated by measur-

ing the degree of fungal infection of the controlled *vs*. untreated control, and is expressed as the $p\mathrm{ED}_{50}$ value, the negative logarithm of the molar concentration required for 50% control.

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