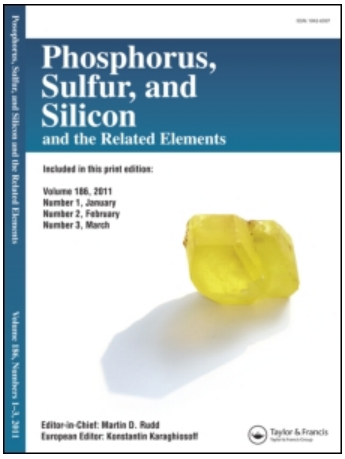

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SYNTHESIS AND FUNGICIDAL ACTIVITIES OF 2-BENZOTHIAZOLYLTHIO-SUBSTITUTED 4H-IMIDAZOL-4-ONES AND 4(3H)-QUINAZOLINONES

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SYNTHESIS AND FUNGICIDAL ACTIVITIES OF 2-BENZOTHIAZOLYLTHIO-SUBSTITUTED 4H-IMIDAZOL-4-ONES AND 4(3H)-QUINAZOLINONES

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*4H-Imidazol-4-ones **4** or 4(3H)-quinazolinones **8** were synthesized by base catalytic reactions of 2-mercaptobenzothiazole with carbodiimides **2** or **6**, respectively, which were obtained via aza-Wittig reaction of iminophosphorane **1** or **5** with aromatic isocyanates. **4** and **8** exhibited fungicidal activity.*

Keywords: 4H-Imidazol-4-ones; aza-Wittig reaction; fungicidal activities; quinazolinones; synthesis

INTRODUCTION

4H-Imidazol-4-ones and 4(3H)-quinazolinones are important heterocycles having good biological and pharmaceutical activities. Some derivatives of 2-alkylthioimidazolones and 2-alkylthioquinazolinones were found to show good fungicidal or antitumor activities.[1–7] Recently, we became interested in synthesis of imidazolones and quinazolinones, some of them having shown potential fungicidal activities.[8–12] Here we wish to report further the synthesis and fungicidal activity of some new derivatives of 2-benzothiazolylthio-substituted 4H-imidazol-4-ones and 4(3H)-quinazolinones, which were not easily accessible by routine synthetic method.

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TABLE I Preparation of 4H-imidazol-4-ones **4** and 4(3H)-quinazolinones **8**

Compound	Ar^1	Ar^2	Ar	Reaction time (h)	Yield (%)[a]
4a	Ph	Ph		3	38
4b	Ph	4-Cl-C_6H_4		2	46
4c	Ph	4-CH_3-C_6H_4		3	41
4d	4-Cl-C_6H_4	Ph		3	40
4e	4-Cl-C_6H_4	4-Cl-C_6H_4		2	34
4f	4-Cl-C_6H_4	4-CH_3-C_6H_4		3	43
4g	2-Furfuryl	4-Cl-C_6H_4		2	40
4h	2-Furfuryl	4-CH_3-C_6H_4		3	42
8a			Ph	12	56
8b			4-Me-C_6H_4	12	55

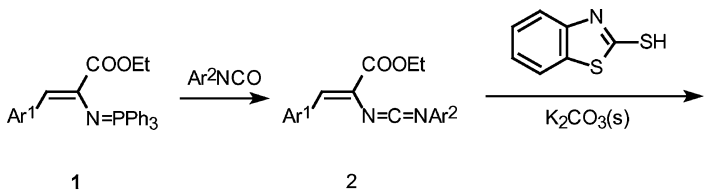
[a]Isolated yields based on iminophosphophorane used.

RESULTS AND DISCUSSION

The easily accessible vinyliminophosphorane **1** reacted with aromatic isocyanates to give carbodiimides **2**, which were allowed to react with 2-mercaptobenzothiazole in presence of catalytic solid potassium carbonate to give the imidazolones **4** at 50 ~ 60°C in moderate yields (see Table I).

The structure of **4** has been characterized spectroscopically. For example, the ^{1}H NMR spectral data in **4c** show the signals of —CH_3 at 2.29 ppm as single absorption. The chemical shift of alkenyl hydrogen is overlapped with the signals of Ar-H (8.19–7.01). In the IR spectral data of **4c**, the strong stretching resonance peak of imidazolone C=O appears at 1723 cm^{-1}. The stretching resonance of C=C shows relatively strong absorbtion at about 1643 cm^{-1} due to resonance effect. The stretching resonance of C=N shows strong absorbtion at about 1555 cm^{-1}. The mass spectrum of **4c** shows molecule ion peak at m/z 427 with 29% abundance.

The use of catalytic amount of solid K_2CO_3 gave moderate yields of **4**. The best reaction time was 2–3 h (Table I). Although the reactivity of the carbodiimides **2** was different with respect to substituent on the benzene ring, the reaction was carried out at 50–60°C. The formation of **4** can be rationalized in terms of an initial nucleophilic addition of 2-mercaptobenzothiazole under potassium carbonate to give the intermediates **3**, which directly cyclize to give **4**.



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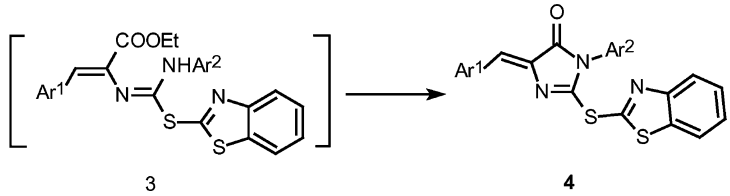
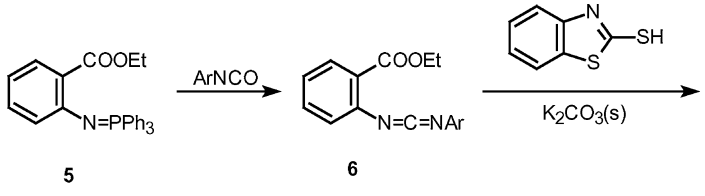


3 4

The above method was also successively applied to synthesize 2-(2-benzothiazolylthio)-4(3H)-quinazolinone **8**. Iminophosphorane **5** reacted with aromatic isocyanates to give carbodiimides **6**, which was allowed to react with 2-mercaptobenzothiazole in the presence of solid potassium carbonate to give **8**. Moderate yields of **8** were obtained when catalytic solid potassium carbonate was used with overnight, stirring at 50∼60°C (Table I). The structure of **8** has been characterized spectroscopically. For example, the ^{1}H NMR spectrum data in **8a** showed the signals of 8-H in quinazolinone ring at 8.38 ppm as a double absorption and other Ar-H at 7.88–6.85 ppm as multiple absorptions. In the IR spectral data of **8a**, the strong stretching resonance peak of quinazolinone C=O appears at 1689 cm^{-1}. The MS spectrum of **8a** shows molecule ion peak at m/z 387 with 73% abundance. The formation of **8** can be rationalized in terms of an initial nucleophilic addition of 2-mercaptobenzothiazole in the presence of solid potassium carbonate to give the intermediate **7**, which directly cyclized to give **8**.



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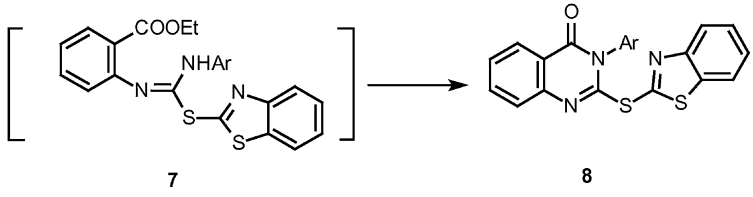

7 8

TABLE II The Fungicidal Activities of 4H-imidazol-4-ones **4** and quinazolinones **8** (50 mg/l, relative inhibition %)

Compound	*Fusarium oxysporum*	*Gibberella zeae*	*Cercospora beticola sacc*	*Physalospora piricola*	*Pellicularia sasakii*
4a	33	50	37	33	71
4b	44	56	71	47	64
4c	33	61	37	67	82
4d	67	44	43	67	82
4e	44	72	51	67	87
4f	72	78	72	87	93
4g	83	56	54	73	82
4h	17	0	31	73	82
8a	94	94	50	80	89
8b	38	27	34	60	74

The biological activities of **4** and **8** were investigated, and the results showed that they exhibited moderate-to-good fungicidal activities. For example, **8a** showed 94% inhibition of *Fusarium oxysporum* and *Gibberella zeae* in 50 mg/l (see Table II).

EXPERIMENTAL

Melting points were uncorrected. MS were measured on a Finnigan Trace MS spectrometer. IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. NMR were recorded in $CDCl_3$ on a Varian Mercury 400 or 200 spectrometer, and resonances are given in ppm (δ) relative to TMS. Elementary analyses were taken on a Perkin-Elmer CHN 2400 elementary analysis instrument.

Preparation of 4H-imidazol-4-ones 4

To a solution of vinyliminophosphorane **1**[12] (5 mmol) in dry methylene dichloride (15 ml) was added aromatic isocyanate (5 mmol) under nitrogen at room temperature. After the reaction mixture was standing for 3–6 h the solvent was removed under reduced pressure, and ether/petroleum ether (1:2, 20 ml) was added to precipitate triphenylphosphine oxide. Filtered, the solvent was removed to give carbodiimide **2**, which was used directly without further purification.

To a solution of **2** prepared above in CH_3CN (30 ml) was added 2-mercaptobenzothiazole (0.84 g, 5 mmol) and catalytic solid K_2CO_3 (0.05 g). The reaction mixture was stirred for 2–3 h at 50–60°C and then filtered. The filtrate was condensed, and the residual was recrystallized

from methylene dichloride/petroleum ether to give 4H-imidazolin-4-ones **4**.

2-(2-benzothiazolylthio)-3-phenyl-5-phenylmethylene-4H-imidazol-4-one (4a)

Yellow crystals, m.p. 174–176°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20–7.02 (m, 15H, Ar-H and =CH); IR (cm^{-1}), 1722, 1654, 1558, 1269; MS (m/z, %), 413 (M^+, 4), 247 (11), 191 (99), 117 (100). Elemental Anal. Calcd. for $C_{23}H_{15}N_3OS_2$: C, 66.81; H, 3.66; N, 10.16. Found: C, 66.65; H, 3.71; N, 10.14.

2-(2-benzothiazolylthio)-3-(4-chlorophenyl)-5-phenylmethylene-4H-imidazol-4-one (4b)

Yellow crystals, m.p. 253–255°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19–7.07 (m, 14H, Ar-H and =CH); IR (cm^{-1}), 1727, 1643, 1548, 1296; MS (m/z), 449 (23), 447 (M^+, 65), 414 (38), 303 (60), 281 (80), 250 (77), 166 (92), 116 (100). Elemental Anal. Calcd. for $C_{23}H_{14}ClN_3OS_2$: C, 61.67; H, 3.15; N, 9.38. Found: C, 61.71; H, 3.23; N, 9.27.

2-(2-benzothiazolylthio)-3-(4-methylphenyl)-5-phenylmethylene-4H-imidazol-4-one (4c)

Yellow crystals, m.p. 233–235°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19–7.01 (m, 14H, Ar-H and =CH), 2.29 (s, 3H, CH_3); IR (cm^{-1}), 1723, 1643, 1555, 1302; MS (m/z), 427 (M^+, 29), 283 (25), 261 (90), 250 (72), 166 (41), 115 (100). Elemental Anal. Calcd. for $C_{24}H_{17}N_3OS_2$: C, 67.42; H, 4.01; N, 9.83. Found: C, 67.61; H, 3.95; N, 9.91.

2-(2-benzothiazolylthio)-3-phenyl-5-(4-chlorophenylmethylene)-4H-imidazol-4-one (4d)

Yellow crystals, m.p. 224–225°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15–7.13 (m, 14H, Ar-H and =CH); IR (cm^{-1}), 1726, 1644, 1553, 1246; MS (m/z), 449 (24), 447 (M^+, 71), 414 (14), 312 (47), 281 (88), 269 (81), 165 (100), 149 (98). Elemental Anal. Calcd. for $C_{23}H_{14}ClN_3OS_2$: C, 61.67; H, 3.15; N, 9.38. Found: C, 61.42; H, 3.06; N, 9.52.

2-(2-benzothiazolylthio)-3-(4-chlorophenyl)-5-(4-chlorophenylmethylene)-4H-imidazol-4-one (4e)

Yellow crystals, m.p. 245–247°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14–7.06 (m, 13H, Ar-H and =CH); IR (cm^{-1}), 1730, 1643, 1554, 1236; MS (m/z), 483 (29), 481 (M^+, 42), 448 (14), 348 (13), 315 (51), 284 (58), 166 (100). Elemental Anal. Calcd. for $C_{23}H_{13}Cl_2N_3OS_2$: C, 57.27; H, 2.72; N, 8.71. Found: C, 57.04; H, 2.81; N, 8.78.

2-(2-benzothiazolylthio)-3-(4-methylphenyl)-5-(4-chlorophenylmethylene)-4H-imidazol-4-one (4f)

Yellow crystals, m.p. 243–245°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14–7.00 (m, 13H, Ar-H and =CH), 2.30 (s, 3H, CH_3); IR (cm^{-1}), 1732, 1645, 1556, 1240; MS (m/z), 463 (20), 461 (M^+, 58), 428 (10), 312 (47), 295 (73), 284 (73), 165 (81), 149 (100). Elemental Anal. Calcd. for $C_{24}H_{16}ClN_3OS_2$: C, 62.40; H, 3.49; N, 9.10. Found: C, 62.53; H, 3.41; N, 9.27.

2-(2-benzothiazolylthio)-3-(4-chlorophenyl)-5-(2-furfurylidene)-4H-imidazol-4-one (4g)

Yellow crystals, m.p. 150°C decomposed, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75–7.06 (m, 11H, Ar-H and =CH), 6.63–6.61 (m, 1H, Furyl-4-H); IR (cm^{-1}), 1717, 1639, 1548, 1251; MS (m/z), 439 (18), 437 (M^+, 52), 303 (52), 268 (38), 240 (61), 166 (100). Elemental Anal. Calcd. for $C_{21}H_{12}ClN_3O_2S_2$: C, 57.60; H, 2.76; N, 9.60. Found: C, 57.51; H, 2.94; N, 9.44.

2-(2-benzothiazolylthio)-3-(4-methylphenyl)-5-(2-furfurylidene)-4H-imidazol-4-one (4h)

Yellow crystals, m.p. 181°C decomposed, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73–7.00 (m, 11H, Ar-H and =CH), 6.63–6.61 (m, 1H, Furyl-4-H), 2.29 (s, 3H, CH_3); IR (cm^{-1}), 1715, 1641, 1554, 1246; MS (m/z), 417 (M^+, 53), 283 (50), 268 (38), 240 (32), 166 (100). Elemental Anal. Calcd. for $C_{22}H_{15}N_3O_2S_2$: C, 63.29; H, 3.62; N, 10.06. Found: C, 63.44; H, 3.72; N, 9.93.

Preparation of 4(3H)-quinazolinones 8

To a solution of iminophosphorane **5**[10] (2.12 g, 5 mmol) in dry methylene dichloride (15 ml) was added aromatic isocyanate (5 mmol) under nitrogen at room temperature. After the reaction mixture stood for 12 h at 0–5°C the solvent was removed under reduced pressure, and ether/petroleum ether (1:2, 20 ml) was added to precipitate triphenylphosphine oxide. After filtering, the solvent was removed to give carbodiimide **6**, which was used directly without further purification. To the solution of **6** prepared above in CH_3CN (15 ml) was added 2-mercaptobenzothiazole (0.84 g, 5 mmol) and catalytic solid K_2CO_3 (0.05 g). The mixture was stirred for 12 h at 50–60°C and filtered. The filtrate was condensed and the residual was recrystallized from methylene dichloride/petroleum ether to give quinazolinones **8**.

2-(2-benzothiazolylthio)-3-phenyl-4(3H)-quinazolinone (8a)

White crystals, m.p. 173–175°C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.38 (d, $J = 7.5$ Hz, 1H, 8-H), 7.88–6.85 (m, 12H, Ar-H); IR (cm^{-1}), 1689, 1587, 1452, 1250; MS (m/z, %), 387 (M^+, 73), 310 (24), 253 (52), 221 (97), 146 (100). Elemental Anal. Calcd. for $C_{21}H_{13}N_3OS_2$: C, 65.10; H, 3.38; N, 10.84. Found: C, 65.26; H, 3.31; N, 10.92.

2-(2-benzothiazolylthio)-3-(4-methylphenyl)-4(3H)-quinazolinone (8b)

White crystals, m.p. 182–184°C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.38 (d, $J = 7.5$ Hz, 1H, 8-H), 7.85–6.87 (m, 11H, Ar-H), 2.15 (s, 3H, CH_3); IR (cm^{-1}), 1680, 1589, 1452, 1255; MS (m/z, %), 401 (M^+, 61), 368 (6), 252 (81), 166 (100), 118 (96). Elemental Anal. Calcd. for $C_{22}H_{15}N_3OS_2$: C, 65.81; H, 3.77; N, 10.47. Found: C, 65.58; H, 3.65; N, 10.58.

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