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Facile Synthesis of 2-Alkylthio-5-phenylmethylene-4H-imidazol-4-ones

Yong Sun[1] and Ming-Wu Ding[2]

[1]*Department of Chemistry, Yunyang Teachers College, Danjiangkou Hubei 442700, People's Republic of China*

[2]*Institute of Organic Synthesis, Central China Normal University, Wuhan Hubei 430079, People's Republic of China*

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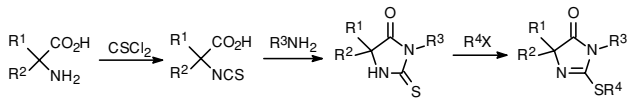
ABSTRACT: *2-Alkylthio-5-phenylmethylidene-4H-imidazol-4-ones* **4** *were synthesized by S-alkylation of 2-thioxo-3-alkyl(aryl)-4-imidazolidinones* **3**, *which were obtained via cyclization of isothiocyanates* **2** *with aliphatic(aromatic) primary amines.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:348–351, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10160

INTRODUCTION

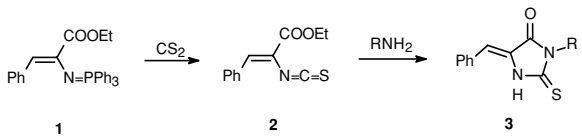
4H-Imidazol-4-ones are important heterocycles having biological and pharmaceutical activities [1–3], and some 2-alkylthioimidazolones show significant fungicidal activities [4–6]. However, most of the 2-alkylthioimidazolones reported are of the 5,5-disubstituted type and are generally synthesized from corresponding α-amino acetic acid [6,7] (Eq. (1)). Unfortunately, 5-arylmethylene-2-alkylthioimidazolones cannot be prepared by this general method for the corresponding starting material needed would be unstable vinyl amino acetic acids. Recently, we were interested in the synthesis of biologically active imidazolones via tandem aza-Wittig reaction [8–10]. Herein we report a new efficient synthesis of 5-arylmethylene-2-alkyl(aryl)thioimidazolones from the stable vinyliminophosphorane **1**.



(1)

RESULTS AND DISCUSSION

The easily accessible vinyliminophosphorane **1** reacted with carbon disulfide to give vinyl isothiocyanate **2**. The reaction of **2** with aliphatic primary amines took place smoothly at room temperature to give 2-thioxo-4-imidazolidinones **3** in 75–96% yields. The reaction of **2** with aromatic primary amines had to be carried out in refluxing acetonitrile in the presence of potassium carbonate (Eq. (2)). The crystal color of **3** is yellow, and other data of the preparation of **3** are listed in Table 1.



1 **2** **3**

(2)

S-Alkylation of **3e** with alkyl halides in presence of potassium carbonate provided 2-alkylthio-5-phenylmethylidene-4H-imidazol-4-ones **4** in 65–98%

Correspondence to: Yong Sun; e-mail: sunyong6111@sina.com.
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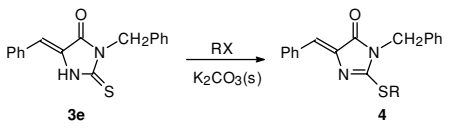
TABLE 1 Preparation of 3-Substituted-2-thioxo-4-imidazolidinones **3** from Vinyl Isothiocyanate **2**

	R	*Formula*	*Condition*	*Yield (%)*[a]	*mp (°C)*
3a	Me	$C_{11}H_{10}N_2OS$	rt/30 min	75	207–208
3b	*i*-Bu	$C_{14}H_{16}N_2OS$	rt/10 min	84	154–155
3c	*n*-C_5H_{11}	$C_{15}H_{18}N_2OS$	rt/15 min	91	98–99
3d	*n*-C_8H_{17}	$C_{18}H_{24}N_2OS$	rt/10 min	83	81–82
3e	$PhCH_2$	$C_{17}H_{14}N_2OS$	rt/10 min	96	228–229
3f	CH_2CH_2OH	$C_{12}H_{12}N_2O_2S$	rt/50 min	79	105–107
3g	3-Me-Ph	$C_{17}H_{14}N_2OS$	80°C/2 h	50	181–182
3h	3-Cl-2-Me-Ph	$C_{17}H_{13}N_2OClS$	80°C/3 h	52	200–201
3i	4-EtO-Ph	$C_{18}H_{16}N_2O_2S$	80°C/2 h	79	195–196

[a]Isolated yields based on vinyliminophosphorane **1**.

yields. With alkylating reagents such as RI and $BrCH_2COR$, the alkylation could be carried out at room temperature. With other reagents, the alkylation had to be carried out at 50–60°C (Eq. (3)). The crystal color of **4** is light yellow, and other data of the alkylation of **3e** are listed in Table 2.



3e **4** (3)

The structures of **3** and **4** have been characterized spectroscopically, and their data are listed in Tables 3 and 4, respectively. For example, the ^1H NMR spectral data in **4a** show the signals of =CH, $-CH_2Ph$, and $-SCH_3$ at $\delta = 6.96$, 4.77, and 2.68 ppm as single absorption. The chemical shift of aryl hydrogen multiplets is 8.13–7.21 ppm. In the IR spectra of **4a**, the strong stretching mode absorption of imidazolone C=O appear at 1712 cm^{-1}. The stretching mode of C=C shows relatively strong absorption at about 1635 cm^{-1} because of resonance effect. The MS spectrum of **4a** shows molecule ion peak at *m/z* 308 with 87% abundance.

EXPERIMENTAL

Melting points are uncorrected. MS were measured on a HP5988A spectrometer. IR were recorded on a PE-983 infrared spectrometer as KBr pellets. NMR were recorded in $CDCl_3$ on a Varian XL-200 spectrometer and resonances are given relative to TMS. Elemental analyses were taken on a Perkin-Elmer 2400 CHN Elementary Analysis Instrument. CS_2 is poisonous and a good hood should be used.

Preparation of Vinyliminophosphorane **1**

Vinyliminophosphorane **1** was prepared by the Staudinger reaction of vinyl azide and triphenyl phosphine according to [11], m.p. 148–150°C (Lit. [11] m.p. 149°C).

Preparation of 3-Alkyl-2-thioxo-4-imidazolidinones **3a–f** *from Vinyl Isothiocyanate* **2**

To a solution of vinyliminophosphorane **1** [12] (2.25 g, 5 mmol) in dry methylene chloride (15 ml) was added excess carbon disufide (5 ml). After the reaction mixture was refluxed for 28 h, the solvent was removed under reduced pressure and ether/petroleum ether (1:2, 20 ml) was added to precipitate triphenylphosphine sulfide, which was removed by filtration. The filtrate was evaporated to give isothiocyanate **2**, which was used directly without further purification. To a solution of crude **2** in

TABLE 2 Alkylation of **3e** to 2-Alkylthio-4H-imidazol-4-ones **4**

	RX	*Formula*	*Condition*	*Yield (%)*[a]	*mp (°C)*
4a	MeI	$C_{18}H_{16}N_2OS$	rt/3 h	90	127–128
4b	EtBr	$C_{19}H_{18}N_2OS$	50°C/3 h	90	112–113
4c	*n*-PrBr	$C_{20}H_{20}N_2OS$	60°C/3 h	95	97–98
4d	*n*-BuBr	$C_{21}H_{22}N_2OS$	50°C/3 h	81	83–84
4e	*i*-BuBr	$C_{21}H_{22}N_2OS$	60°C/4 h	65	83–85
4f	*n*-$C_6H_{13}Br$	$C_{23}H_{26}N_2OS$	50°C/3 h	67	54–55
4g	$PhCH_2Cl$	$C_{24}H_{20}N_2OS$	50°C/2 h	87	141–142
4h	$ClCH_2CN$	$C_{19}H_{15}N_3OS$	50°C/2 h	88	156–158
4i	$PhCOCH_2Br$	$C_{25}H_{20}N_2O_2S$	rt/2 h	95	180–181
4j	$ClCH_2CONH_2$	$C_{19}H_{17}N_3O_2S$	50°C/2 h	85	202–203
4k	$BrCH_2COOMe$	$C_{20}H_{18}N_2O_3S$	rt/2 h	95	144–145
4l	$ClCH_2COOEt$	$C_{21}H_{20}N_2O_3S$	50°C/2 h	98	113–114
4m	$BrCH_2CH_2COOEt$	$C_{22}H_{22}N_2O_3S$	50°C/3 h	69	79–81
4n	$BrCH(CH_3)COOEt$	$C_{22}H_{22}N_2O_3S$	60°C/2 h	76	108–109

[a]Isolated yields based on 2-thioxo-4-imidazolidinone **3e**.

TABLE 3 Elemental Analysis, IR, MS, and ^{1}H NMR Data of 2-Thioxo-4-imidazolidinones **3**

	Anal. % (Calc.)	*IR (cm^{-1})*	*MS (m/z, %)*	*^{1}H-NMR ($CDCl_3$, δ)*
3a	C, 60.81 (60.55) H, 4.78 (4.59) N, 13.11 (12.84)	3248 1705 1647	218 (M^+, 4), 201 (100), 183 (94), 167 (52), 152 (56), 116 (53), 108 (82)	3.34 (s, 3H), 6.72 (s, 1H), 7.08–8.11 (m, 5H), 8.81 (s, 1H)
3b	C, 64.60 (64.62) H, 6.21 (6.15) N, 11.04 (10.77)	3254 1708 1649	260 (M^+, 21), 227 (3), 203 (30), 160 (17), 117 (100), 89 (26)	0.96 (d, 6H), 2.29 (m, 1H), 3.72 (d, 2H), 6.68 (s, 1H), 7.23–7.44 (m, 5H), 8.81 (s, 1H)
3c	C, 65.93 (65.69) H, 6.86 (6.57) N, 10.41 (10.22)	3257 1706 1647	274 (M^+, 2), 241 (13), 218 (19), 203 (2), 117 (81), 89 (88), 73 (100)	0.93 (t, 3H), 1.27–1.75 (m, 6H), 3.88 (t, 2H), 6.68 (s, 1H), 7.23–7.42 (m, 5H), 8.82 (s, 1H)
3d	C, 68.41 (68.35) H, 7.83 (7.59) N, 9.05 (8.86)	3253 1707 1648	316 (M^+, 6), 283 (100), 203 (10), 160 (18), 117 (43), 90 (11)	0.87 (t, 3H), 1.25–1.70 (m, 12H), 3.87 (t, 2H), 6.67 (s, 1H), 7.23–7.43 (m, 5H), 8.82 (s, 1H)
3e	C, 69.55 (69.39) H, 5.03 (4.76) N, 9.79 (9.52)	3250 1704 1643	294 (M^+, 97), 265 (8), 261 (21), 203 (4), 148 (52), 117 (64), 91 (100)	5.08 (s, 2H), 6.71 (s, 1H), 7.00–7.81 (m, 5H), 8.71 (s, 1H)
3f	C, 58.29 (58.06) H, 5.10 (4.84) N, 11.56 (11.29)	3445 3259 1711 1650	248 (M^+, 3), 230 (3), 203 (2), 160 (6), 117 (30), 89 (29), 44 (100)	2.48 (s, 1H), 3.88 (t, 2H), 4.11 (t, 2H), 6.71 (s, 1H), 7.23–7.45 (m, 5H), 8.83 (s, 1H)
3g	C, 69.66 (69.39) H, 5.01 (4.74) N, 9.78 (9.52)	3234 1747 1644	294 (M^+, 16), 265 (2), 189 (10), 148 (17), 116 (73), 102 (24), 89 (100)	2.38 (s, 3H), 6.79 (s, 1H), 7.12–7.58 (m, 9H), 9.00 (s, 1H)
3h	C, 62.38 (62.10) H, 4.25 (3.96) N, 8.49 (8.52)	3229 1747 1645	328 (M^+, 90), 313 (30), 295 (98), 232 (73), 117 (99), 89 (94), 32 (100)	2.19 (s, 3H), 6.81 (s, 1H), 7.05–7.47 (m, 8H), 9.23 (s, 1H)
3i	C, 66.66 (66.67) H, 5.15 (4.94) N, 8.92 (8.64)	3225 1746 1643	324 (M^+, 100), 295 (34), 291 (8), 237 (19), 180 (67), 160 (65), 117 (97)	1.43 (t, 3H), 4.04 (q, 2H), 6.78 (s, 1H), 6.93–7.43 (m, 9H), 9.14 (s, 1H)

TABLE 4 Elemental Analysis, IR, MS, and ^{1}H NMR Data of 2-Alkylthio-4H-imidazol-4-ones **4**

	Anal. % (Calc.)	*IR (cm^{-1})*	*MS (m/z, %)*	*^{1}H-NMR ($CDCl_3$, δ)*
4a	C, 70.41 (70.13) H, 5.45 (5.19) N, 9.36 (9.09)	1712 1635	308 (M^+, 87), 293 (8), 275 (31), 218 (73), 203 (22), 117 (80), 91 (100)	2.68 (s, 3H), 4.77 (s, 2H), 6.96 (s, 1H), 7.21–8.13 (m, 10H)
4b	C, 70.06 (70.81) H, 5.88 (5.59) N, 8.99(8.70)	1712 1636	322 (M^+, 87), 294 (27), 289 (11), 200 (9), 116 (21), 91 (100)	1.46 (t, 3H), 3.30 (q, 2H), 4.74 (s, 2H), 6.94 (s, 1H), 7.20–8.11 (m, 10H)
4c	C, 71.19 (71.43) H, 6.22 (5.95) N, 8.58 (8.33)	1711 1634	336 (M^+, 79), 308 (5), 303 (28), 294 (94), 148 (64), 116 (75), 91 (100)	1.05 (t, 3H), 1.84 (m, 2H), 3.26 (t, 2H), 4.74 (s, 2H), 6.93 (s, 1H), 7.19–8.12 (m, 10H)
4d	C, 72.23 (72.00) H, 6.57 (6.29) N, 8.27 (8.00)	1713 1636	350 (M^+, 42), 321 (3), 317 (16), 303 (60), 294 (80), 116 (50), 91 (100)	0.97 (t, 3H), 1.48 (m, 2H), 1.79 (m, 2H), 3.29 (t, 2H), 4.75 (s, 2H), 6.94 (s, 1H), 7.20–8.13 (m, 10H)
4e	C, 72.25 (72.00) H, 6.54 (6.29) N, 8.23 (8.00)	1713 1635	350 (M^+, 50), 335 (7), 317 (15), 294 (65), 261 (50), 116 (63), 91 (100)	1.04 (d, 6H), 2.10 (m, 1H), 3.18 (d, 2H), 4.75 (s, 2H), 6.93 (s, 1H), 7.18–8.12 (m, 10H)
4f	C, 70.27 (70.02) H, 7.11 (6.88) N, 7.69 (7.41)	1711 1637	378 (M^+, 93), 349 (10), 345 (31), 331 (40), 294 (100), 289 (80), 90 (99)	0.89 (t, 3H), 1.35–1.82 (m, 8H), 3.28 (t, 2H), 4.76 (s, 2H), 6.94 (s, 1H), 7.21–8.10 (m, 10H)
4g	C, 74.96 (75.00) H, 5.01 (5.21) N, 7.55 (7.29)	1712 1636	384 (M^+, 89), 350 (6), 293 (53), 206 (40), 160 (44), 116 (48), 91 (100)	4.53 (s, 2H), 4.74 (s, 2H), 6.98 (s, 1H), 7.20–8.15 (m, 15H)
4h	C, 68.20 (68.47) H, 4.25 (4.50) N, 12.50 (12.61)	2253 1715 1637	333 (M^+, 69), 300 (10), 293 (29), 188 (41), 160 (27), 116 (54), 91 (100)	4.01 (s, 2H), 4.73 (s, 2H), 7.07 (s, 1H), 7.20–8.10 (m, 10H)

(Continued)

TABLE 4 Continued

	Anal. % (Calc.)	*IR (cm^{-1})*	*MS (m/z, %)*	*^{1}H-NMR ($CDCl_3$, δ)*
4i	C, 73.03 (72.82) H, 5.11 (4.85) N, 7.07 (6.80)	1716 1699 1638	412 (M^+, 13), 380 (4), 307 (21), 294 (5), 116 (12), 105 (79), 91 (100)	4.75 (s, 2H), 4.82 (s, 2H), 6.91 (s, 1H), 7.06–8.06 (m, 15H)
4j	C, 65.24 (64.96) H, 5.11 (4.84) N, 12.25 (11.97)	3317 3271 1714 1679 1634	351 (M^+, 20), 307 (9), 294 (19), 215 (9), 148 (15), 116 (21), 91 (100)	3.90 (s, 2H), 4.78 (s, 2H), 5.08 (s, 2H), 6.70 (s, 1H), 7.04–7.99 (m, 10H)
4k	C, 65.79 (65.57) H, 5.11 (4.92) N, 7.88 (7.65)	1734 1713 1636	366 (M^+, 64), 333 (41), 307 (46), 293 (53), 188 (62), 160 (59), 91 (100)	3.75 (s, 3H), 4.01 (s, 2H), 4.77 (s, 2H), 6.96 (s, 1H), 7.21–8.08 (m, 10H)
4l	C, 66.02 (66.32) H, 5.11 (5.26) N, 7.10 (7.37)	1738 1713 1635	380 (M^+, 64), 347 (18), 335 (19), 307 (53), 293 (51), 188 (64), 91 (100)	1.28 (t, 3H), 4.01 (s, 2H), 4.21 (q, 2H), 4.79 (s, 2H), 6.96 (s, 1H), 7.21–8.06 (m, 10H)
4m	C, 66.96 (67.00) H, 5.85 (5.58) N, 7.40 (7.11)	1745 1712 1633	394 (M^+, 57), 361 (36), 349 (32), 321 (40), 303 (19), 294 (58), 91 (100)	1.25 (t, 3H), 2.91 (t, 2H), 3.53 (t, 2H), 4.15 (q, 2H), 4.74 (s, 2H), 6.96 (s, 1H), 7.21–8.10 (m, 10H)
4n	C, 66.87 (67.00) H, 5.80 (5.58) N, 7.34 (7.11)	1741 1713 1636	394 (M^+, 86), 361 (31), 349 (22), 321 (32), 293 (91), 188 (50), 91 (100)	1.24 (t, 3H), 1.68 (d, 3H), 4.18 (q, 2H), 4.60–4.86 (m, 3H), 6.95 (s, 1H), 7.20–8.09 (m, 10H)

CH_3CN (15 ml) was added RNH_2 (5 mmol). The mixture was allowed to stand for 10–50 min at room temperature and the precipitated solid was collected and washed with water and ethanol, recrystallized from methylene chloride/petroleum ether to give 3-alkyl-2-thioxo-4-imidazolidinone **3a–f**.

Preparation of 3-Aryl-2-thioxo-4-imidazolidinones **3g–i** *from Vinyl Isothiocyanate* **2**

To the solution of **2** in CH_3CN (15 ml) was added $ArNH_2$ (5 mmol) and solid potassium carbonate (0.05 g). The mixture was stirred for 2–3 h at refluxing temperature and filtered; the filtrate was then evaporated in vacua and the residue was recrystallized from methylene chloride/petroleum ether to give 3-aryl-2-thioxo-4-imidazolidinone **3g–i**.

Preparation of 2-Alkylthio-4H-imidazol-4-ones **4** *by S-Alkylation of* **3e**

A mixture of **3e** (1.18 g, 4 mmol), alkyl halide (5 mmol), and solid potassium carbonate (1.11 g, 8 mmol) in CH_3CN (30 ml) was stirred for 2–4 h at room temperature or 50–60°C and filtered, the filtrate was condensed and the residue was recrystallized from methylene chloride/petroleum ether to give 2-alkylthio-4H-imidazol-4-ones **4**.

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