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Facile Synthesis of 2-Alkylthio-3-amino-4 *H*-imidazol-4-ones and 2*H*-Imidazo[2,1-*b*]-1,3,4-thiadiazin-6(7*H*)-ones via *N*-Vinylic Iminophosphorane

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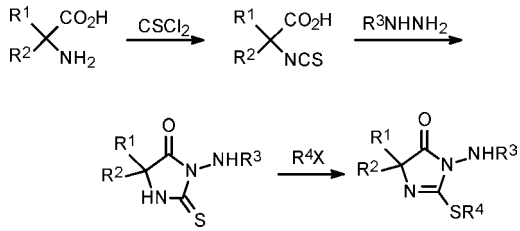
ABSTRACT: *2-Alkylthio-3-amino-4H-imidazol-4-ones* **5** *were synthesized by S-alkylation of 2-thioxo-3-amino-4-imidazolidinones* **4**, *which were obtained via cyclization of isothiocyanates* **2** *with hydrazine hydrate.* **5l–n** *reacted with* Ph_3P, C_2Cl_6, *and* NEt_3 *to give 2H-imidazo[2,1-b]-1,3,4-thiadiazin- 6(7H)-ones* **7a–c** *in good yields.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:76–80, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20069

INTRODUCTION

Derivatives of 4*H*-imidazol-4-one have shown good biological activities, especially those with 2-alkylthio-3-amino substituent [1–3]. Efforts to discover new biologically active derivatives are reflected by the still important number of publications and patents devoted to the subject [4–8]. For example, some 2-alkylthio substituted 4*H*-imidazol-4-ones show significant antifungal and antibacterial activities [5,6], whereas others exhibited good antitumor and antiviral activities [7,8]. However, most of the 2-alkylthio-3-aminoimidazolones reported are of the 5,5-disubstituted type and were generally synthesized from corresponding α-amino acetic acid [1,2] (Eq. (1)). Unfortunately, 5-arylmethylene-2-alkylthio-3-aminoimidazolones cannot be prepared by this general method for the corresponding starting material needed would be unstable vinyl amino acetic acids.



(1)

The introduction of a thiadiazine ring to the imidazolone system is expected to influence the biological activities significantly, however, there are few reports on synthesis of 2*H*-imidazo[2,1-*b*]-1,3,4-thiadiazin-6(7*H*)-ones [9]. The aza-Wittig reactions of iminophosphoranes have received increased attention in view of their utility in the synthesis of nitrogen heterocyclic compounds [10,11]. The reaction of iminophosphoranes with carbon disulfide, which was known since last century [12], has been successfully utilized in synthesis of some heterocycles including imidazolones [13–15]. Recently, we are also interested in the synthesis of biologically active imidazolones via tandem aza-Wittig reaction [16–18]. Here we wish to report a new efficient

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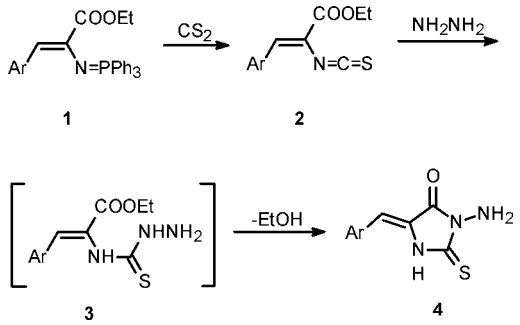
synthesis of 5-arylmethylene-2-alkylthio-3-amino-imidazolones and 2*H*-imidazo[2,1-*b*]-1,3,4-thiadiazin-6-(7*H*)-ones from the stable vinyliminophosphorane **1**.

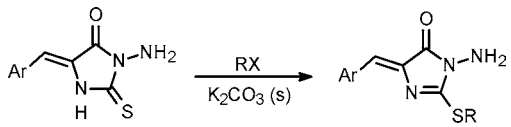
RESULTS AND DISCUSSION

The easily accessible vinyliminophosphorane **1** reacted with carbon disulfide to give vinyl isothiocyanate **2**, which were allowed to react with hydrazine to give 3-amino-2-thioxo-4-imidazolidinones **4** in 70–94% yields. The formation of **4** can be rationalized in terms of an initial nucleophilic addition of hydrazine to give the thiourea intermediate **3** which cyclizes to give **4** (Eq. (2)). The crystal color of **4** is yellow, and other results of preparation of **4** from**1** are listed in Table 1. Although reactions of vinyl isocyanate **2** with alkanethiols, alkanols, secondary and primary amine have been reported [19], there is no report about the reaction of vinyl isocyanate **2** with hydrazine.



1 2 3 4 (2)

S-Alkylation of **4** with alkyl halides in the presence of solid potassium carbonate provided 2-alkylthio-3-amino-4*H*-imidazol-4-ones **5** in 63–88% yields. With alkylating reagents such as MeI, the alkylation could be carried out at room temperature. With other reagents, the alkylation had to be carried out at 50–60°C (see Table 1) (Eq. (3)). The crystal color of **5** is light yellow, and other results of alkylation of **4** to **5** are listed in Table 1.



4 5 (3)

The structures of **4** and **5** have been characterized spectroscopically, and their data are listed in Table 2. For example, the ^{1}H NMR spectral data in **5a** show the signals of =CH, $-NH_2$, and $-SCH_3$ at 6.96 ppm, 4.18 ppm, and 2.66 ppm as single absorption, respectively. The chemical shift of aryl hydrogens is 7.37–8.17 ppm with multiple absorption. In the IR spectral data of **5a**, the stretching resonance peaks of N–H appear at 3327 and 3216 cm^{-1}, whereas the stretching resonance peak of imidazolone C=O appears at 1712 cm^{-1}. The stretching resonance of C=C shows relatively strong absorption at about 1627 cm^{-1} due to resonance effect. The MS spectrum of **5a** shows molecule ion peak at *m/z* 233 with 80% abundance.

TABLE 1 Preparation of 2-Thioxo-4-imidazolidinones **4**, 4*H*-Imidazol-4-ones **5**, and 2*H*-Imidazo[2,1-*b*]-1,3,4-thiadiazin-6(7*H*)-ones **7**

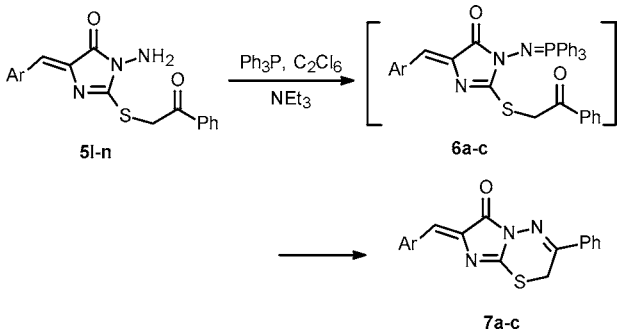
	Ar	*RX*	*Formula*	*Conditions*	*Yield (%)*	*Mp (°C)*
4a	Ph		$C_{10}H_9N_3OS$	rt/20 min	91	228–230
4b	4-$MeOC_6H_4$		$C_{11}H_{11}N_3O_2S$	rt/30 min	94	174–176
4c	4-ClC_6H_4		$C_{10}H_8ClN_3OS$	rt/10 min	77	254–255
4d	2-Furfuryl		$C_8H_7N_3O_2S$	rt/10 min	70	238–240
5a	Ph	MeI	$C_{11}H_{11}N_3OS$	rt/3 h	71	163–164
5b	4-$MeOC_6H_4$	MeI	$C_{12}H_{13}N_3O_2S$	rt/3 h	84	187–188
5c	2-Furfuryl	MeI	$C_9H_9N_3O_2S$	rt/3 h	88	182–183
5d	4-ClC_6H_4	MeI	$C_{11}H_{10}ClN_3OS$	rt/3 h	63	231–233
5e	Ph	EtBr	$C_{12}H_{13}N_3OS$	50°C/5 h	72	128–129
5f	Ph	*n*-PrBr	$C_{13}H_{15}N_3OS$	60°C/5 h	86	113–114
5g	Ph	$BrCH_2C{\equiv}CH$	$C_{13}H_{11}N_3OS$	50°C/5 h	72	165–166
5h	Ph	$BrCH_2COOMe$	$C_{13}H_{13}N_3O_3S$	60°C/3 h	85	186–187
5i	4-$MeOC_6H_4$	$BrCH_2COOMe$	$C_{14}H_{15}N_3O_4S$	60°C/3 h	65	181–182
5j	2-Furfuryl	$BrCH_2COOMe$	$C_{11}H_{11}N_3O_4S$	60∘C/5 h	64	114–116
5k	4-ClC_6H_4	$BrCH_2COOMe$	$C_{13}H_{12}ClN_3O_3S$	60°C/5 h	67	183–184
5l	Ph	$PhCOCH_2Br$	$C_{18}H_{15}N_3O_2S$	60°C/5 h	73	201–202
5m	4-$MeOC_6H_4$	$PhCOCH_2Br$	$C_{19}H_{17}N_3O_3S$	60°C/5 h	74	209–210
5n	2-Furfuryl	$PhCOCH_2Br$	$C_{16}H_{13}N_3O_3S$	60°C/5 h	69	196–197
7a	Ph		$C_{18}H_{13}N_3OS$	rt/1 h	82	216–217
7b	4-$MeOC_6H_4$		$C_{19}H_{15}N_3O_2S$	rt/1 h	86	225–226
7c	2-Furfuryl		$C_{16}H_{11}N_3O_2S$	rt/1 h	73	221–222

TABLE 2 The Elemental Analysis, IR, MS, and ^{1}H-NMR Data of **4**, **5**, and **7**

	Anal. %, (Calc.)	*IR (cm^{-1})*	*MS (m/z, %)*	*^{1}H-NMR ($CDCl_3$, δ)*
4a[a]	C, 54.71 (54.78); H, 4.02 (4.14); N, 19.25 (19.16)	3316, 3288, 1711, 1613	219 (M^+, 69), 188 (11), 190 (25), 147 (99), 132 (100)	5.22 (s, 2H, NH_2), 6.64 (s, 1H, =CH), 7.40–7.78 (m, 5H, Ar-H), 12.24 (s, 1H, NH)
4b[a]	C, 53.18 (53.00); H, 4.55 (4.45); N, 16.84 (16.86)	3321, 3211, 1681, 1595	249 (M^+, 93), 218 (14), 190 (25), 147 (99), 132 (100)	3.82 (s, 3H, OCH_3), 5.20 (s, 2H, NH_2), 6.68 (s, 1H, =CH), 6.87–7.72 (m, 4H, Ar-H), 12.20 (s, 1H, NH)
4c[a]	C, 47.27 (47.34); H, 3.22 (3.18); N, 19.61 (16.56)	3323, 3274, 1713, 1607	255 (24), 253 (M^+, 62), 222 (10), 194 (31), 89 (100)	5.22 (s, 2H, NH_2), 6.63 (s, 1H, =CH), 7.48–7.80 (m, 4H, Ar-H), 12.28 (s, 1H, NH)
4d[a]	C, 45.84 (45.93); H, 3.16 (3.37); N, 20.15 (20.08)	3328, 3246, 1723, 1651	209 (M^+, 77), 178 (8), 150 (30), 107 (100)	5.20 (s, 2H, NH_2), 6.55 (s, 1H, =CH), 6.68–7.88 (m, 3H, Ar-H), 11.90 (s, 1H, NH)
5a	C, 56.68 (56.63); H, 4.69 (4.75); N, 18.05 (18.01)	3327, 3216, 1712, 1627	233 (M^+, 80), 216 (12), 116 (62), 89 (100)	2.66 (s, 3H, SCH_3), 4.18 (s, 2H, NH_2), 6.96 (s, 1H, =CH), 7.37–8.17 (m, 5H, Ar-H)
5b	C, 54.80 (54.74); H, 4.97 (4.98); N, 15.88 (15.96)	3321, 3215, 1701, 1631	263 (M^+, 89), 248 (16), 146 (48), 89 (100)	2.67 (s, 3H, SCH_3), 3.86 (s, 3H, OCH_3), 4.17 (s, 2H, NH_2), 6.94–8.15 (m, 5H, Ar-H, and =CH)
5c	C, 48.36 (48.42); H, 4.11 (4.06); N, 18.85 (18.82)	3323, 3212, 1701, 1621	223 (M^+, 85), 206 (14), 106 (39), 89 (100)	2.65 (s, 3H, SCH_3), 4.20 (s, 2H, NH_2), 6.92 (s, 1H, =CH), 6.58–7.59 (m, 3H, Ar-H)
5d	C, 49.25 (49.35); H, 3.81 (3.76); N, 15.67 (15.69)	3332, 3206, 1706, 1626	267 (M^+, 40), 269 (14), 150 (17), 89 (100)	2.67 (s, 3H, SCH_3), 4.17 (s, 2H, NH_2), 6.89 (s, 1H, =CH), 7.37–8.11 (m, 4H, Ar-H)
5e	C, 58.23 (58.28); H, 5.38 (5.30); N, 16.96 (16.99)	3343, 3277, 1710, 1634	247 (M^+, 2), 202 (3), 160 (4), 116 (100)	1.51 (s, 3H, $J = 7.2$ Hz, CH_3), 3.29 (q, 2H, $J = 7.2$ Hz, SCH_2), 4.16 (s, 2H, NH_2), 6.95 (s, 1H, =CH), 7.37–8.16 (m, 5H, Ar-H)
5f	C, 59.87 (59.75); H, 5.78 (5.79); N, 16.14 (16.08)	3340, 3263, 1724, 1631	261 (M^+, 55), 219 (95), 160 (26), 75 (100)	1.10–1.92 (m, 5H, CH_2CH_3), 3.26 (t, 2H, $J = 7.2$ Hz, SCH_2), 4.16 (s, 2H, NH_2), 6.95 (s, 1H, =CH), 7.37–8.17 (m, 5H, Ar-H)
5g	C, 60.74 (60.68); H, 4.24 (4.31); N, 16.46 (16.33)	3331, 3286, 2220, 1704, 1622	257 (M^+, 72), 241 (77), 160 (62), 116 (100)	2.31 (s, 1H, C≡CH), 4.04 (s, 2H, SCH_2), 4.18 (s, 2H, NH_2), 6.99 (s, 1H, =CH), 7.41–8.17 (m, 5H, Ar-H)
5h	C, 53.41 (53.60); H, 4.37 (4.50); N, 14.54 (14.42)	3348, 3277, 1742, 1714, 1631	291 (M^+, 100), 260 (45), 231 (74), 147 (96)	3.81 (s, 3H, OCH_3), 4.01 (s, 2H, SCH_2), 4.19 (s, 2H, NH_2), 6.97 (s, 1H, =CH), 7.40–8.12 (m, 5H, Ar-H)
5i	C, 53.55 (53.33); H, 4.85 (4.70); N, 13.03 (13.08)	3347, 3275, 1742, 1713, 1634	321 (M^+, 56), 290 (13), 262 (38), 147 (100)	3.80 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.01 (s, 2H, SCH_2), 4.18 (s, 2H, NH_2), 6.93–8.10 (m, 5H, Ar-H and =CH)
5j	C, 46.87 (46.97); H, 3.90 (3.94); N, 15.06 (14.94)	3338, 3262, 1746, 1715, 1636	281 (M^+, 100), 250 (11), 222 (50), 106 (64)	3.79 (s, 3H, OCH_3), 4.00 (s, 2H, SCH_2), 4.20 (s, 2H, NH_2), 6.94 (s, 1H, =CH), 6.59–7.58 (m, 3H, Ar-H)
5k	C, 47.80 (47.93); H, 3.62 (3.71); N, 12.97 (12.90)	3348, 3277, 1745, 1710, 1633	325 (M^+, 100), 293 (14), 266 (62), 147 (92)	3.80 (s, 3H, OCH_3), 4.00 (s, 2H, SCH_2), 4.20 (s, 2H, NH_2), 6.90 (s, 1H, =CH), 7.37–8.06 (m, 4H, Ar-H)
5l[a]	C, 64.23 (64.08); H, 4.56 (4.48); N, 12.33 (12.45)	3327, 3269, 1713, 1696, 1634	337 (M^+, 66), 319 (99), 232 (65), 105 (100)	4.88 (s, 2H, SCH_2), 5.47 (s, 2H, NH_2), 6.77 (s, 1H, =CH), 6.95–8.18 (m, 10H, Ar-H)
5m[a]	C, 62.17 (62.11); H, 4.58 (4.66); N, 11.56 (11.44)	3318, 3278, 1711, 1698, 1635	367 (M^+, 60), 349 (64), 335 (49), 262 (57), 105 (100)	3.77 (s, 3H, OCH_3), 4.83 (s, 2H, SCH_2), 5.30 (s, 2H, NH_2), 6.89–8.07 (m, 10H, Ar-H, and =CH)
5n[a]	C, 58.48 (58.70); H, 4.16 (4.00); N, 12.76 (12.84)	3312, 3277, 1710, 1636	327 (M^+, 47), 309 (58), 265 (43), 105 (100)	4.86 (s, 2H, SCH_2), 5.44 (s, 2H, NH_2), 6.98 (s, 1H, =CH), 6.63–8.14 (m, 8H, Ar-H)
7a	C, 67.62 (67.69); H, 4.16 (4.10); N, 13.04 (13.16)	1734, 1634, 1512, 1201	319 (M^+, 100), 291 (23), 175 (59), 116 (90)	4.04 (s, 2H, SCH_2), 7.23 (s, 1H, =CH), 7.43–8.16 (m, 10H, Ar-H)
7b	C, 65.24 (65.31); H, 4.28 (4.33); N, 12.15 (12.03)	1725, 1635, 1597, 1256	349 (M^+, 83), 321 (18), 175 (29), 146 (100)	3.87 (s, 3H, OCH_3), 4.03 (s, 2H, SCH_2), 7.20 (s, 1H, =CH), 6.95–8.15 (m, 9H, Ar-H)
7c	C, 62.17 (62.12); H, 3.64 (3.58); N, 13.48 (13.58)	1721, 1635, 1499, 1240	309 (M^+, 92), 281 (28), 175 (69), 117 (100)	4.03 (s, 2H, SCH_2), 6.60–7.89 (m, 9H, Ar-H, and =CH)

[a] ^{1}H NMR were recorded in DMSO-d_6.

When **5l–n** were treated with triphenylphosphine, hexachloroethane, and triethylamine, the color of the reaction mixture quickly turned red and 2*H*-imidazo[2,1-*b*]-1,3,4-thiadiazin-6(7*H*)-ones **7a–c** were obtained in 73–86% yields (Eq. (4)). Presumably, the conversion of **5l–n** into **7a–c** involves initial transformation of **5l–n** into the iminophosphoranes **6a–c** as reactive intermediates, which easily undergo intramolecular aza-Wittig reaction to give **7a–c**.



(4)

The structures of **7** have been characterized spectroscopically, and their data are listed in Tables 2. For example, the ^{1}H NMR spectral data in **7a** show the signals of =CH and $-CH_2S-$ at 7.23 ppm and 4.04 ppm as single absorption with disappearing of NH_2 absorption. The chemical shift of aryl hydrogens is 7.43–8.16 ppm with multiple absorption. In the IR spectral data of **7a**, the stretching resonance peaks of imidazolone C=O and C=C appear at 1734 and 1634 cm^{-1} respectively with disappearing of NH_2 absorption. The MS spectrum of **7a** shows molecule ion peak at *m*/*z* 319 with 100% abundance.

EXPERIMENTAL

Melting points were uncorrected. MS were measured on a Finnigan Trace MS spectrometer. IR spectra were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Varian Mercury 400 spectrometer and resonances are given in ppm (δ) relative to TMS. Elementary analyses were taken on a Vario EL III elementary analysis instrument.

Preparation of 3-Amino-2-thioxo-4-imidazolidinones **4**

To a solution of vinyliminophosphorane **1** [20–22] (5 mmol) in dry methylene chloride (15 mL) was added excess carbon disulfide (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 that 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 CH_3CN (15 mL) was added hydrazine hydrate (0.35 g, 6 mmol, 85%). The mixture was allowed to stir for 10–30 min at room temperature and the precipitated solid was collected by filtration and washed with water and ethanol, recrystallized from methylene chloride/petroleum ether to give 3-amino-2-thioxo-4- imidazolidinone **4**.

Preparation of 2-Alkylthio-3-amino-4H-imidazol-4-ones **5** *by S-Alkylation of* **4**

A mixture of **4** (4 mmol), alkyl halide (5 mmol), and solid potassium carbonate (1.11 g, 8 mmol) in CH_3CN (30 mL) was stirred for 3–5 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-3-amino-4*H*-imidazol-4-ones **5**.

Preparation of 2H-Imidazo[2,1-b]-1,3,4-thiadiazin-6(7H)-ones **7a–c** *by Intramolecular Aza-Wittig Reaction*

To a mixture of imidazolone **5l–n** (3 mmol), PPh_3 (1.05 g, 4 mmol) and C_2Cl_6 (0.95 g, 4 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise NEt_3 (0.81 g, 8 mmol) at room temperature. The color of the reaction mixture quickly turned red. After the solution was stirred for 1 h. The solvent was removed under reduced pressure and the residue was recrystallized from EtOH to give 2*H*-imidazo[2,1-*b*]-1,3,4-thiadiazin-6(7*H*)-ones **7a–c**.

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