Reactions of 2-Benzyl-5-phenylisoxazolidine-3-thiones with Aromatics in the Presence of Anhydrous Aluminum Chloride: Synthesis of 3-Aryl-*N*-benzyl-3-phenylpropanothiohydroxamic Acids

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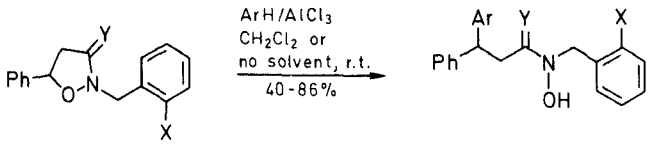
2-Benzyl- and 2-(2-chlorobenzyl)-5-phenylisoxazolidine-3-thiones **1** and 2-benzyl-5-phenylisoxazolidin-3-one **2** react with aromatics such as toluene, biphenyl, *p*-xylene, and chlorobenzene in the presence of anhydrous aluminum chloride, in dichloromethane at room temperature to give 3-aryl-*N*-benzyl-3-phenylpropanothiohydroxamic acids and 3-aryl-*N*-benzyl-3-phenylpropanohydroxamic acids in good yields.

Synthesis of *N*-substituted thiohydroxamic acids has recently attracted much interest because they have not only biological activities such as insecticides,[1-2] and antibiotics[3-4] but also act as excellent metal chelators.[5-6] Although a variety of methods are known for the preparation of thiohydroxamic acids lacking a substituent at nitrogen,[7] only a limited number of methods have been reported for the preparation of *N*-substituted thiohydroxamic acids: one of these is thioacylation of substituted hydroxylamines using *S*-(thiobenzoyl)-thioglycolic acids,[8] thiobenzoyl chloride,[7] or *O*-alkyl thioacetate.[8] However, the availability of the thioacylating agents is more limited. Another method involves the hydrolysis of *N*-acetyl-*N*-alkyl-thiohydroxamic acids[9] which can be synthesized from the reactions of *N*-acetyl-*N*-alkyl-hydroxamic acids with Lawesson's reagent in 10 to 50% yields.

While searching for a novel route to *N*-substituted thiohydroxamic acid, we considered that bond cleavage between oxygen and carbon atoms of isoxazolidine-3-thiones might give the desired compounds. 2-Benzyl-5-phenylisoxazolidine-3-thione (**1a**, X = H) and 2-(*o*-chlorobenzyl)-5-phenylisoxazolidine-3-thione (**1b**, X = Cl) were readily synthesized from the reactions of the corresponding isoxazolidin-3-ones **2** with phosphorus pentasulfide in benzene at reflux temperature. We have found that the thiones **1** react with aromatics such as toluene, biphenyl, *p*-xylene, and chlorobenzene in the presence of anhydrous aluminum chloride in dichloromethane at room temperature to give 3-aryl-*N*-benzyl-3-phenylpropanothiohydroxamic acids **3b–3e** and **3g–3i** in good yields. In all the cases, no structural isomers were detected.

When the thiones **1** were treated with anhydrous aluminum chloride in benzene, *N*-benzyl-3,3-diphenylpropanothiohydroxamic acids **3a** and **3f** were also obtained in good yields. However, the reactions depend on the concentration of aluminum chloride. That is, when the mole ratio of aluminum chloride to **1b** (X = Cl) in benzene was 1:1, no reaction occurred even at reflux temperature and **1b** (X = Cl) was quantitatively recovered. When the mole ratio of aluminum chloride to **1b** (X = Cl) was over 2:1, the reaction proceeded smoothly to give the product **3f** either at reflux or room temperature although longer reaction time was required at room temperature. Similarly, **1a** (X = H) was recovered quantitatively when a 1:1 mole ratio of aluminum chloride to



1a Y = S, X = H
1b Y = S, X = Cl
2a Y = O, X = H
2b Y = O, X = Cl

3a-n

3	X	Y	Ar	3	X	Y	Ar
a	H	S	Ph	**h**	Cl	S	4-PhC_6H_4
b	H	S	4-MeC_6H_4	**i**	Cl	S	2,5-$Me_2C_6H_3$
c	H	S	4-PhC_6H_4	**j**	H	O	Ph
d	H	S	2,5-$Me_2C_6H_3$	**k**	H	O	4-MeC_6H_4
e	H	S	4-ClC_6H_4	**l**	H	O	4-PhC_6H_4
f	Cl	S	Ph	**m**	H	O	2,5-$Me_2C_6H_3$
g	Cl	S	4-MeC_6H_4	**n**	H	O	4-ClC_6H_4

1a (X = H) was used at either temperature but a two-fold increase amount of aluminum chloride gave **3a** in 83% yield at either temperature. Consequently a 2:1 mole ratio of aluminum chloride to **1** was applied to the other reactions at room temperature. Similarly, **2a** (X = H) gave 3-aryl-*N*-benzyl-3-phenylpropanohydroxamic acids **3j–3n** under the same conditions. The reaction conditions and yields of 3-aryl-*N*-benzyl-3-phenylpropanothiohydroxamic acids **3a–3i** and 3-aryl-*N*-benzyl-3-phenylpropanohydroxamic acids **3j–3n** are collected in Table 1, and analytical and spectroscopic data are summarized in Table 2.

Table 1. Reaction Conditions and Yields of 3-Aryl-*N*-benzyl-3-phenylpropanothiohydroxamic Acids **3a–3i** and 3-Aryl-*N*-benzyl-3-phenylpropanohydroxamic Acids **3j–3n** Prepared

Substrate	1 or 2 (mmol)	$AlCl_3$ (mmol)	ArH (mmol)	CH_2Cl_2 (mL)	Time (min)	Product	Yield (%)[b]
1a	0.25	0.55	benzene[a]		25	**3a**	83
1a	0.35	0.94	toluene (7.52)	15	30	**3b**	79
1a	0.33	0.81	biphenyl (0.83)	15	270	**3c**	78
1a	0.25	0.87	*p*-xylene (5.06)	15	60	**3d**	76
1a	0.47	2.20	chlorobenzene (10.82)	10	240	**3e**	86
1b	0.33	0.80	benzene[a]		30	**3f**	80
1b	0.47	1.15	toluene (9.39)	20	30	**3g**	78
1b	0.30	0.72	biphenyl (0.73)	15	150	**3h**	74
1b	0.43	1.08	*p*-xylene (8.16)	20	120	**3i**	83
2a	1.01	2.13	benzene[a]		30	**3j**	56
2a	1.04	2.38	toluene (2.35)	10	30	**3k**	63
2a	1.25	2.62	biphenyl (2.40)	10	30	**3l**	65
2a	1.21	2.62	*p*-xylene (2.37)	10	30	**3m**	62
2a	1.30	2.92	chlorobenzene (2.66)	10	120	**3n**	40

[a] Benzene (10 mL) was used as a nucleophile and a solvent.
[b] Yield of isolated compounds.

In the meantime, reaction of **1b** (X = Cl) with anisole under the similar conditions did not proceed at all and **1b** (X = Cl) was recovered quantitatively. However, by refluxing for 1 hour, only 2-(2-*o*-chlorobenzyl)-5-phenylisoxazolidin-3-one (**2b**, X = Cl) was isolated in 39% yield.

Arylations with aromatics promoted by aluminum chloride at the ring carbon 5 of **1** are particularly valuable for the synthesis of *N*-substituted 3-aryl-3-phenylpropanothiohydroxamic acids, otherwise unavailable by reported methods.[7-9] Our method has the additional advantage of using readily available reactants.

Table 2. Analytical and ^{1}H-NMR Data of **3** Prepared

Compound	mp (°C)	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
3a	92–93 (hexane)	$C_{22}H_{21}NOS$ (347.4)	3.43 (d, 2H, J = 8, CH_2C=S), 4.57 (s, 2H, $CH_2C_6H_5$), 4.93 (t, 1H, J = 8, $CHCH_2$), 7.00–8.33 (m, 15H$_{arom}$), 11.00 (s, 1H, OH)
3b	90–91 (hexane)	$C_{23}H_{23}NOS$ (361.4)	2.30 (s, 3H, CH_3), 3.41 (d, 2H, J = 8, CH_2C=S), 4.60 (s, 2H, $CH_2C_6H_5$), 4.83 (t, 1H, J = 8, $CHCH_2$), 7.01–7.37 (m, 14H$_{arom}$), 10.93 (s, 1H, OH)
3c	137–138 (hexane)	$C_{28}H_{25}NOS$ (423.5)	3.38 (d, 2H, J = 8, CH_2C=S), 4.53 (s, 2H, $CH_2C_6H_5$), 4.88 (t, 1H, J = 8, $CHCH_2$), 6.72–7.63 (m, 19H$_{arom}$), 10.82 (s, 1H, OH)
3d	133–134 (hexane)	$C_{24}H_{25}NOS$ (375.5)	2.19 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 3.41 (d, 2H, J = 8, CH_2C=S), 4.54 (s, 2H, $CH_2C_6H_5$), 5.01 (t, 1H, J = 7, $CHCH_2$), 6.97–7.37 (m, 13H$_{arom}$), 10.94 (s, 1H, OH)
3e	58–59 (hexane)	$C_{22}H_{20}ClNOS$ (381.9)	3.36 (d, 2H, J = 8, CH_2C=S), 4.63 (s, 2H, $CH_2C_6H_5$), 4.89 (t, 1H, J = 8, $CHCH_2$), 6.87–7.52 (m, 14H$_{arom}$), 9.92 (s, 1H, OH)
3f	112–113 (CCl_4/hexane)	$C_{22}H_{20}ClNOS$ (381.9)	3.43 (d, 2H, J = 8, CH_2C=S), 4.65 (s, 2H, $CH_2C_6H_5$), 4.90 (t, 1H, J = 8, $CHCH_2$), 7.00–7.53 (m, 14H$_{arom}$), 9.88 (s, 1H, OH)
3g	liquid	$C_{23}H_{22}ClNOS$ (395.9)	2.30 (s, 3H, CH_3), 3.41 (d, 2H, J = 8, CH_2C=S), 4.68 (s, 2H, $CH_2C_6H_5$), 4.81 (t, 1H, J = 8, $CHCH_2$), 7.02–7.39 (m, 13H$_{arom}$), 10.96 (s, 1H, OH)
3h	liquid	$C_{28}H_{24}ClNOS$ (458.0)	3.46 (d, 2H, J = 8, CH_2C=S), 4.72 (s, 2H, $CH_2C_6H_5$), 4.91 (t, 1H, J = 8, $CHCH_2$), 7.02–7.63 (m, 18H$_{arom}$), 10.98 (s, 1H, OH)
3i	liquid	$C_{24}H_{24}ClNOS$ (409.9)	2.21 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.41 (d, 2H, J = 7, CH_2C=S), 4.49 (d, 1H, J = 18, $CH_2C_6H_5$), 4.76 (d, 1H, J = 18, $CH_2C_6H_5$), 5.00 (t, 1H, J = 7, $CHCH_2$), 6.99–7.36 (m, 12H$_{arom}$), 10.96 (s, 1H, OH)
3j	107–108 (CCl_4/hexane)	$C_{22}H_{21}NO_2$ (331.4)	3.23 (d, 2H, J = 8, CH_2C=O), 4.60 (s, 2H, $CH_2C_6H_5$), 4.67 (t, 1H, $CHCH_2$), 6.83–7.43 (m, 15H$_{arom}$), 10.92 (s, 1H, OH)
3k	liquid	$C_{23}H_{23}NO_2$ (345.4)	2.30 (s, 3H, CH_3), 3.27 (d, 2H, J = 8, CH_2C=O), 4.73 (s, 2H, $CH_2C_6H_5$), 4.73 (t, 1H, $CHCH_2$), 6.87–7.57 (m, 14H$_{arom}$), 9.67 (s, 1H, OH)
3l	118–119 (hexane)	$C_{28}H_{25}NO_2$ (407.5)	3.30 (d, 2H, J = 8, CH_2C=O), 4.70 (s, 2H, $CH_2C_6H_5$), 4.77 (t, 1H, $CHCH_2$), 7.05–7.70 (m, 19H$_{arom}$), 9.52 (s, 1H, OH)
3m	liquid	$C_{24}H_{25}NO_2$ (359.5)	2.20 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.28 (d, 2H, J = 8, CH_2C=O), 4.70 (s, 2H, $CH_2C_6H_5$), 4.93 (t, 1H, $CHCH_2$), 6.92–7.43 (m, 13H$_{arom}$), 9.47 (s, 1H, OH)
3n	65–66 (hexane)	$C_{22}H_{20}ClNO_2$ (365.9)	3.22 (d, 2H, J = 8, CH_2C=O), 4.43 (s, 2H, $CH_2C_6H_5$), 4.63 (t, 1H, $CHCH_2$), 6.79–7.43 (m, 14H$_{arom}$), 9.28 (s, 1H, OH)

[a] Satisfactory microanalyses obtained: C ± 0.26, H ± 0.21, N ± 0.15.

All solvents were dried by standard methods. $AlCl_3$ was obtained from Aldrich and P_4S_{10} was from E. Merck. 2-Benzyl-5-phenylisoxazolidin-3-ones **2a, b** were prepared according to the literature method.[10] Column chromatography was performed on Kiesel gel 60 (70–230 mesh) from E. Merck. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H-spectra were measured on Bruker AC 80 Spectrometer. Mass spectra were measured on VG 12-250 Mass Spectrometer. Microanalyses were performed by Korea Research Institute of Chemical Technology, Dae Jeon, Korea.

2-Benzyl-5-phenylisoxazolidine-3-thiones 1a,b; General Procedure:
A stirred solution of 2-benzyl-5-phenylisoxazolidin-3-ones **2a** or **2b** (10 mmol) and P_4S_{10} (20 mmol) in dry benzene (50 mL) is refluxed for 1 h, followed by the addition of water (100 mL). The organic layer is separated, washed with water (2 × 20 mL), dried ($MgSO_4$), and evaporated to dryness. The residue is chromatographed on a silica gel column (10 × 2 cm), eluting with benzene (100 mL) to give **1a** or **1b**

1a (X = H): Yield: 92%; mp 83–84°C (hexane).

$C_{16}H_{15}NOS$ (269.4) calc. C 71.34 H 5.61 N 5.20 S 11.90
found 71.18 5.63 5.18 11.61

MS (70 eV): m/z = 269 (M^+).

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.46 (dd, 1H, J = 18, 9 Hz, CH_2C=S), 3.84 (dd, 1H, J = 18, 9 Hz, CH_2C=S), 5.17 (d, 1H, J = 14 Hz, $CH_2C_6H_5$), 5.45 (d, 1H, J = 14 Hz, $CH_2C_6H_5$), 5.57 (t, 1H, J = 9 Hz, $CHCH_2$), 7.22–7.75 (m, 10H$_{arom}$).

1b (X = Cl): Yield: 85%; liquid

$C_{16}H_{14}ClNOS$ (303.8) calc. C 63.26 H 4.65 Cl 11.67 N 4.61 S 10.55
found 63.09 4.58 11.55 4.59 10.39

MS (70 eV): m/z = 303 (M^+).

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.47 (dd, 1H, J = 17,9 Hz, CH_2C=S), 3.83 (dd, 1H, J = 17, 9 Hz, CH_2C=S), 5.40 (s, 2H, $CH_2C_6H_5$), 5.57 (t, 1H, J = 9 Hz, $CHCH_2$), 7.03–7.67 (m, 9H$_{arom}$).

Reaction of 1a,b or 2a with Aromatics; General Procedures:
In the following general procedures, in each case consult Table 1 for quantities of reactants, solvents, reaction times and yields.

Reaction of 1a,b or 2a with $AlCl_3$ in Benzene; General Procedure:
To a solution of **1a, b** or **2a** in benzene is added anhydrous $AlCl_3$. The mixture is stirred at r.t. until **1** had disappeared on TLC and then quenched with water (100 mL), extracted with CH_2Cl_2 (3×25 mL), dried ($MgSO_4$), and evaporated to dryness. The residue is chromatographed on a silica gel column (8×2 cm), eluting with benzene (100 mL) to give **3a**, **3f**, and **3j** (Table 1).

Reaction of 1a,b or 2a with Aromatics in the Presence of $AlCl_3$ in CH_2Cl_2; General Procedure:
Arene is added to a solution of **1a, b** or **2a** in CH_2Cl_2 in the presence of anhydr. $AlCl_3$. The mixture is stirred at room temperature until **1a, b** or **2a** had disappeared on TLC and quenched with water (100 mL), extracted with CH_2Cl_2 (3×25 mL), dried ($MgSO_4$), and evaporated to dryness. The residue is chromatographed on a silica gel column (8×2 cm). Compounds **3b** and **3e** are obtained by elution with benzene (100 mL). Compound **3c** is obtained by elution with benzene (100 mL) after the mixture of biphenyl and unknown compounds are eluted with CCl_4 (120 mL). Compounds **3d, 3g, 3h**, and **3i** are obtained by the elution with benzene (100 mL) after an unknown mixture is removed by the elution with hexane (160 mL).

Reaction of 1b (X = Cl) with Anisole in the Presence of $AlCl_3$ in CH_2Cl_2:
Anisole (0.995 g, 9.20 mmol) is added to a solution of **1b** (X = Cl; 0.095 g, 0.33 mmol) in CH_2Cl_2 (15 mL) containing $AlCl_3$ (0.249 g, 3.99 mmol). The mixture is refluxed for 1 h and quenched with water (100 mL), extracted with CH_2Cl_2 (3×25 mL), dried ($MgSO_4$), and evaporated to dryness. The residue is chromatographed on a silica gel column (8×2 cm). Elution with benzene (100 mL), followed by Et_2O (100 mL) gave **2b** (X = Cl); yield: 0.035 g (0.13 mmol, 39%)

$C_{16}H_{14}ClNO_2$	calc.	C 66.79	H 4.90	Cl 12.32	N 4.87
(287.7)	found	67.16	4.38	12.23	4.83

MS (70 eV) $m/z = 287$ (M^+).
IR (KBr): $\nu = 1708\ cm^{-1}$ (C=O).
^{1}H-NMR ($CDCl_3$/TMS): $\delta = 2.92$ (dd, 1H, $J = 16$, 10 Hz, CH_2C=O), 3.10 (dd, 1H, $J = 16$, 8 Hz, CH_2C=O), 4.70 (d, 1H, $J = 16$ Hz, $CH_2C_6H_5$), 5.03 (d, 1H, $J = 16$ Hz, $CH_2C_6H_5$), 5.40 (dd, 1H, $J = 10$, 8 Hz, $CHCH_2$), 7.00–7.67 (m, 9 H_{arom}).

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(1) Oyama, H.; Kitaori, K.; Morita, T.; Moriyama, S.; Uchiyama, T. *Japn Patent (Jpn. Kokai Tokkyo Koho)* 61109795 (1986), Hokko Chemical Industry Co., Ltd.; *C.A.* **1986**, *105*, 227011.
(2) D'Silva, T.D.J. *US Patent* 4568671 (1986), Union Carbide Corp.; *C.A.* **1986**, *104*, 163746.
(3) Egawa, Y.; Umino, K.; Ito, Y.; Okuda, T. *J. Antibiot.* **1971**, *24*, 124.
(4) Ito, Y.; Umino, K.; Sekiquchi, T.; Miyagishima, T.; Egawa, Y. *J. Antibiot.* **1971**, *24*, 131.
(5) Mitchell, A.F.; Murray, K.S.; Newman, P.J.; Clark, P.E. *Aust. J. Chem.* **1977**, *30*, 2439.
(6) Murray, K.S.; Newman, P.J.; Gatehouse, B.M.; Taylor, D. *Aust. J. Chem.* **1978**, *31*, 983.
(7) Walter, W.; Schaumann, E. *Synthesis* **1971**, 111.
(8) Coates, R.M.; Firsan, S.J. *J. Org. Chem.* **1986**, *51*, 5198.
(9) Prabhaker, S.; Lobo, A.M.; Santos, M.A.; Rzepa, H.S. *Synthesis* **1984**, 829.
(10) Chang, J.H. *US Patent* 4692182 (1987), FMC Corp.: *C.A.* **1988**, *108*, 6000.