Preparation of *O*-Alkylhydroxamic Acids Using 2-Acylpyridazin-3(2*H*)-ones in Water

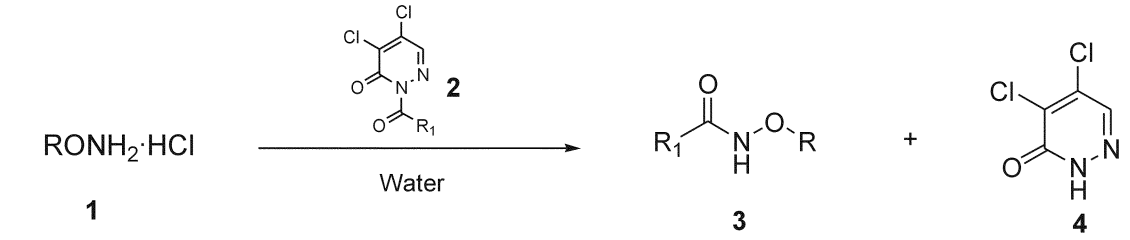
Jeum-Jong Kim, Yong-Dae Park, Su-Dong Cho,[†] Ho-Kyun Kim, Young-Jin Kang, Sang-Gyeong Lee,[‡,*] J. R. Falck,[§] Motoo Shiro,[#] and Yong-Jin Yoon[*]

Department of Chemistry and Environmental Biotechnology National Core Research Center, Gyeongsang National University, Chinju 660-701, Korea
[†]Research Institute of Basic Science, Changwon National University, Changwon 641-773, Korea
[‡]Department of Chemistry and Research Institute of Life Science, Gyeongsang National University, Chinju 660-701, Korea
[§]Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA
[#]Rigaku Corporation, 3-9-12 Matsubara-cho, Akishima-shi, Tokyo 196-8666, Japan
Received June 2, 2004

Key Words : Hydroxamic acid, *O*-Alkylhydroxamic acid, 2-Acyl-4,5-dichloropyridazin-3(2*H*)-ones, Organic reaction in water

Well known to bind with hard metal ions like Zn(II), Fe(III) or Sn(IV),[1-3] hydroxamic acids are key pharmacophores in many important chemotherapeutic agents such as the succinate-based matrix metalloproteinases (MMPs) inhibitors,[1] the class I/II histone deacetylase (HDAC) inhibitors,[2] and iron-containing antibiotics like hydroxamic acid based siderophores and analogues.[4] Methodology for the preparation of functionalized hydroxamic acids has been studied for over a century,[5] *e.g.*, starting from carboxylic acids or their derivatives,[3,6] and *N*-acyloxazolidinones.[7] While some of these methods have attractive features, their general utility is often limited by reagent instability, toxicity, high volatility, use of excess hydroxylamine, high cost and/or difficult purification protocols. There is, consequently, a continuing need for more efficacious procedures for the synthesis of hydroxamic acids from carboxylic acid derivatives. Herein, we report a novel, efficient, convenient and eco-friendly method for the preparation of hydroxamic acids and their derivatives using 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones and *O*-alkylhydroxylamine hydrochlorides in water.

Pyridazin-3(2*H*)-ones are capable of functioning as good leaving groups or activators in synthetic chemistry.[8-10] In our previous reports,[8,9] we demonstrated that 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones are excellent acylating agents



1a: R = $C_6H_5CH_2$-
1b: R = CH_2=$CHCH_2$-
1c: R = CH_3-
1d: R = $(CH_3)_3Si$-

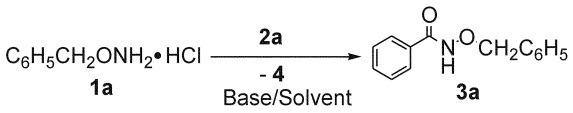
2a: R_1 = C_6H_5-
2b: R_1 = *p*-$CH_3C_6H_4$-
2c: R_1 = *p*-$CH_3OC_6H_4$-
2d: R_1 = 2,4-$Cl_2C_6H_3$-
2e: R_1 = 2-Furyl-
2f: R_1 = CH_3-
2g: R_1 = *n*-C_4H_9-
2h: R_1 = *c*-C_6H_{11}-
2i: R_1 = $C_6H_5CH_2$-
2j: R_1 = (*R,S*)-$C_6H_5CH(CH_3)$-
2k: R_1 = *trans*-C_6H_5CH=CH-
2l: R_1 = (*S*)-$C_6H_5CH_2CH$(NHTs)-

3a: R = $C_6H_5CH_2$-: R_1 = C_6H_5-
3b: R = $C_6H_5CH_2$-: R_1 = *p*-$CH_3C_6H_4$-
3c: R = $C_6H_5CH_2$-: R_1 = *p*-$CH_3OC_6H_4$-
3d: R = $C_6H_5CH_2$-: R_1 = 2,4-$Cl_2C_6H_3$-
3e: R = $C_6H_5CH_2$-: R_1 = 2-Furyl-
3f: R = $C_6H_5CH_2$-: R_1 = CH_3-
3g: R = $C_6H_5CH_2$-: R_1 = $CH_3(CH_2)_3$-
3h: R = $C_6H_5CH_2$-: R_1 = *c*-C_6H_{11}-
3i: R = $C_6H_5CH_2$-: R_1 = $C_6H_5CH_2$-
3j: R = $C_6H_5CH_2$-: R_1 = (*R,S*)-$C_6H_5CH(CH_3)$-
3k: R = $C_6H_5CH_2$-: R_1 = *trans*-C_6H_5CH=CH-
3l: R = $C_6H_5CH_2$-: R_1 = (*S*)-$C_6H_5CH_2CH$(NHTs)-
3m: R = CH_2=$CHCH_2$-: R_1 = *p*-$CH_3OC_6H_4$-
3n: R = CH_3-: R_1 = *p*-$CH_3OC_6H_4$-
3o: R = H-: R_1 = C_6H_5-
3p: R = CH_2=$CHCH_2$-: R_1 = *n*-$CH_3(CH_2)_3$-

Scheme 1

[*]Co-Corresponding Authors. Y.-J. Yoon (yjyoon@nongae.gsnu.ac.kr), S.-G. Lee (leesang@nongae.gsnu.ac.kr)

Table 1. Conversion of *O*-benzylhydroxylamine hydrochloride (**1a**) to *O*-benzylhydroxamide using **2a**[a]



entry	Base (equiv)	solvent	time (min)	**3a** yield (%)[b]
1	Et_3N (1.2)	THF	12	75
2	Et_3N (1.2)	CH_3CN	5	91
3	Et_3N (1.2)	$(Et)_2O$	No reaction	–
4	Et_3N (1.2)	CH_2Cl_2	No reaction	–
5	Et_3N (1.2)	H_2O	10	96
6	K_2CO_3 (1.2)	CH_3CN	35	90
7	NaH (1.2)	CH_3CN	50	94
8	MeONa (1.2)	CH_3CN	20	92
9	Pyridine (1.2)	CH_3CN	63	92
10	–	CH_3CN	No reaction	–
11	–	H_2O	10	96

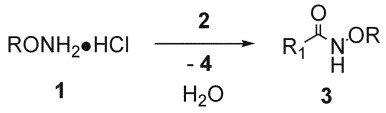
[a]Reactions were carried out at room temperature except for the entries 5, 10 and 11. Entries 5, 10 and 11 were carried out at reflux temperature. [b]Isolated yields. Compound **4** was isolated in quantitative yield.

for amines. Water also is a good solvent for the reaction of 4,5-dichloropyridazin-3(2H)-one.[11] To evaluate the potentiality of 2-acylpyridazin-3(2*H*)-ones for the conversion of *O*-alkylhydroxylamines to hydroxamic acids, we first investigated the reaction of *O*-benzylhydroxylamine hydrochloride (**1a**) with **2a**[8] under various conditions (Table 1).

Treatment of **1a** with **2a** in the presence of Et_3N in tetrahydrofuran, acetonitrile, or water afforded **3a** in 75-96% yield. There was no reaction using methylene chloride or diethyl ether as the solvent.

Replacement of Et_3N with sodium hydride, potassium carbonate, sodium methoxide or pyridine in acetonitrile afforded **3a** in 90-94% yield. Notably, reaction of **1a** with **2a** without base in water, but not acetonitrile, smoothly generated hydroxamide **3a** in quantitative yield. The unexpected efficiency of this transformation may be due in part to the ability of the hydroxylamine hydrochloride to improve the solubility of **2a** in water.

Table 2. Preparation of *O*-substituted-hydroxamic acids **1** using **2** in refluxing H_2O



Entry	**3**	time (min)	yield (%)[a]
1	**b**	20	99
2	**c**	10	94
3	**d**	10	94
4	**e**	15	92
5	**f**	15	91
6	**g**	10	92
7	**h**	15	95
8	**i**	15	88
9	**j**	30	95
10	**k**	15	95
11	**l**	30	87
12	**m**	15	94
13	**n**	20	97
14	**o**	35	92[b]
15	**p**	20	82

[a]Isolated yields. Compound **4** was isolated in quantitative yield. [b]$(Me)_3SiONH_2$ was used as compound **1**.

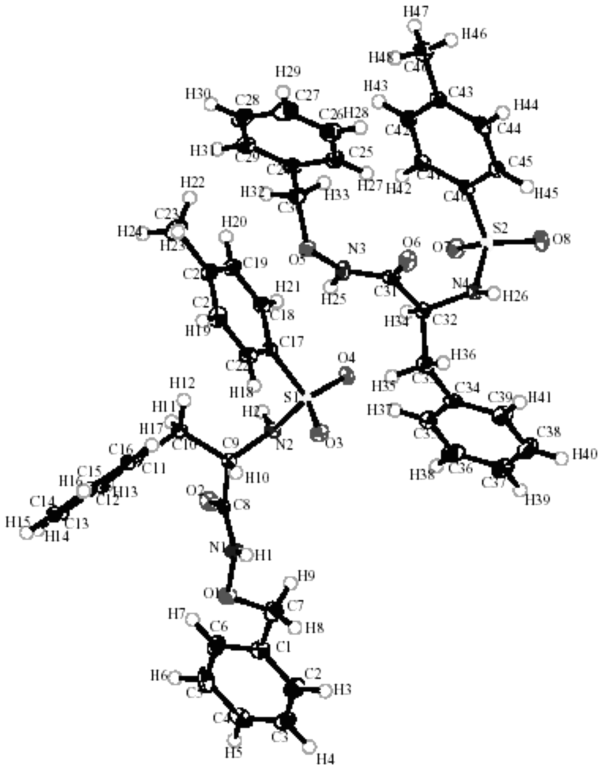


Figure 1. ORTEP for compound **3l**.

Since water as the reaction medium offers many important advantages from the point of view of green chemistry and economics,[12] we determined the scope of the conversion of **1** into **3** in refluxing water. Reactions of *O*-alkylhydroxylamine hydrochlorides **1** with 2-acyl (or aroyl)pyridazin-3(2*H*)-ones **2** in refluxing water gave the corresponding *O*-alkylhydroxamides **3** in excellent yields (Table 2). *N*-Tosyl-protected amino acid derivative **2l** reacted cleanly to give only hydroxamic acid **3l** in good yield (Entry 11, Table 2) without affecting the amino functionality. Furthermore, no racemization of the α-chiral center was observed by X-ray analysis. Reaction of silylated-hydroxylamine **1d** with **2a** in water afforded the hydroxamic acid **3o** directly in excellent yield (Entry 14, Table 2). However, reaction of hydroxylamine hydrochloride with **2a** in water gave a mixture of unknown compounds. In all the cases, any unreacted 4,5-dichloropyridazin-3(2*H*)-one could be recovered quantitatively.

In conclusion, we have developed an efficient, mild, inexpensive and eco-friendly procedure for the *N*-acylation of hydroxylamines using 2-acyl(or aroyl)pyridazin-3(2*H*)-

ones **2** to give hydroxamic acids **3**. A wide variety of hydroxylamines can be used in the amidation process and proceeds without racemization.

Experimental Section

General Remarks. Reagent and solvents were used as received from commercial sources. TLC was performed on plates coated with silica gel (silica gel 60 F_{254}, Merck). The spots were located by UV light. Open-bed chromatography was carried out on silica gel (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent. Melting points were determined with a capillary apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer with chemical shift values reported in units (ppm) relative to an internal standard (TMS). IR spectra were obtained on a IR spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240C. X-Ray diffraction data were obtained with a Rigaku AFC7R diffractometer with filtered Mo-Kα radiation and a rotating anode generator.

General Procedure. A mixture of *O*-alkylhydroxylamine hydrochloride **1** (1.26 mmol), and 2-acyl-4,5-dichloro-pyridazin-3(2*H*)-ones **2**[13] (1.38 mmol) in water (15 mL) was refluxed with stirring until **2** disappeared. After cooling to room temperature, the reaction mixture was extracted with methylene chloride (4 × 50 mL). The organic extracts were dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure, and the residue was purified via silica gel column chromatography using CH_2Cl_2/diethyl ether (10 : 1, v/v) to afford the corresponding *O*-alkylhydroxamic acids **3** in good to excellent yields. All products were fully characterized on the basis of spectral (IR, ^{1}H and ^{13}C NMR) and elemental analytical data. Data for some selected compounds;

***N*-Benzyloxypentanamide** (**3g**): oil. IR (KBr): 3200, 2980, 2880, 1660, 1500, 1460, 1370, 1270, 1210, 1100, 1050, 970, 910, 750 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.37 (s, NH, D_2O exchangeable), 7.36 (s, Ar-5H), 4.87 (s, 2H), 2.05 (t, 2H, J = 7.07 Hz), 1.63-1.51 (m, 2H), 1.37-1.25 (m, 2H), 0.87 (t, 3H, J = 7.29 Hz). ^{13}C NMR ($CDCl_3$): δ 13.7, 22.3, 27.5, 33.9, 78.0, 128.5, 128.6, 129.2, 135.4, 171.4. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 68.48; H, 8.40; N, 6.73. Elution solvent for the column = CH_2Cl_2 : diethyl ether (10 : 1, v/v); R_f = 0.20 (CH_2Cl_2 : diethyl ether = 9 : 1, v/v).

(*R*,*S*)-*N*-Benzyloxy-2-phenylpropanamide (**3j**): mp. 117-118 °C. IR (KBr): 3200, 3070, 3030, 2980, 2930, 2880, 1660, 1500, 1450, 1370, 1210, 1180, 1060, 1020, 930, 740, 690 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.91 (s, NH, D_2O exchangeable), 7.31-7.21 (m, Ar-10H), 4.76 (s, 2H), 3.47-3.41 (q, 1H, J = 6.97 Hz), 1.44 (d, 3H, J = 6.91 Hz). ^{13}C NMR ($CDCl_3$) δ 18.2, 43.8, 77.9, 127.2, 127.5, 128.4, 128.6, 128.7, 129.3, 135.1, 140.5, 172.0. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.45; H, 6.80; N, 5.40. Elution solvent for the column = CH_2Cl_2 : diethyl ether (10 : 1, v/v); R_f = 0.62 (CH_2Cl_2 : diethyl ether = 9 : 1, v/v).

***N*-Benzyloxy-(*S*)-3-phenyl-2-(4-methylphenylsulfonyl-amino)propanamide** (**3l**): mp. 97-98 °C. IR (KBr): 3260, 3050, 2960, 2880, 1660, 1500, 1460, 1330, 1160, 1090, 750, 700, 670, 550 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.36 (s, NH, D_2O exchangeable), 7.50 (d, Ar-2H, J = 8.30 Hz), 7.34-7.28 (m, Ar-5H), 7.15-7.11 (m, Ar-5H), 6.95 (d, Ar-2H, J = 5.97 Hz), 5.57 (d, NH, J = 7.96 Hz, D_2O exchangeable), 4.70 (dd, 2H, J = 10.90 Hz), 3.91 (dd, 1H, J = 7.40, 7.42 Hz), 2.97-2.78 (m, 2H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 21.5, 38.4, 56.4, 78.4, 127.0, 128.5, 128.7, 129.3, 129.8, 134.8, 135.2, 143.8, 168.0. Anal. Calcd for $C_{23}H_{24}N_2O_4S$: C, 65.07; H, 5.70; N, 6.60; S, 7.55. Found: C, 65.49; H, 5.78; N, 6.67; S, 7.48. Elution solvent for the column = CH_2Cl_2 : diethyl ether (5 : 1, v/v); R_f = 0.56 (CH_2Cl_2 : diethyl ether = 5 : 1, v/v).

***N*-Hydroxybenzamide** (**3o**): mp. 102 °C. IR (KBr): 3350, 3075, 2825, 1660, 1620, 1580, 1520, 1460, 1310, 1240 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 11.23 (s, NH, D_2O exchangeable), 9.05 (s, OH, D_2O exchangeable), 7.78-7.74 (m, Ar-2H), 7.53-7.42 (m, Ar-3H). ^{13}C NMR (DMSO-d_6): δ 126.8, 128.3, 131.1, 136.6, 164.2. Anal. Calcd for $C_7H_7NO_2$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.25; H, 5.34; N, 10.48. Elution solvent for the column = ethyl acetate : *n*-hexane (1 : 1, v/v); R_f = 0.1 (ethyl acetate : *n*-hexane = 1 : 1, v/v).

X-Ray Data for 3l: A colorless needle crystal of $C_{23}H_{24}N_2O_4S$ having approximate dimensions of 0.40 × 0.08 × 0.04 mm was mounted in a loop. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-Kα radiation. Indexing was performed from 3 oscillations that were exposed for 18 seconds. The crystal-to-detector distance was 127.40 mm. Cell constants and an orientation matrix for data collection corresponded to a primitive monoclinic cell with dimensions: a = 14.04(1) Å, b = 5.259(5) Å, b = 96.99(4)°, c = 28.41(3) Å, V = 2080(3) Å^3. For Z = 4 and F.W. = 424.51, the calculated density is 1.35 g/cm^3. Based on the systematic absences of: 0k0: k ± 2n packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be: $P2_1$ (#4).

The data were collected at a temperature of -180 ± 1 °C to a maximum 2θ value of 59.9°. A total of 107 oscillation images were collected. A sweep of data was done using ω scans from 130.0 to 190.0° in 2.0° step, at χ = 45.0° and ϕ = 270.0°. The exposure rate was 180.0 [sec./°]. A second sweep was performed using w scans from 0.0 to 154.0° in 2.0° step, at χ = 45.0° and ϕ = 90.0°. The exposure rate was 180.0 [sec./°]. The crystal-to-detector distance was 127.40 mm. Readout was performed in the 0.100 mm pixel mode.

Data Reduction; Of the 23317 reflections that were collected, 9994 were unique (R_{int} = 0.042); equivalent reflections were merged. The linear absorption coefficient, μ, for Mo-Kα radiation is 1.9 cm^{-1}. An empirical absorption correction was applied which resulted in transmission factors ranging from 0.856 to 0.993. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement; The structure was solved by direct methods[14] and expanded using Fourier techniques[15]. The non-hydrogen atoms were refined aniso-

tropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement[16] on F^2 was based on 9994 observed reflections and 590 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of: $R1 = \Sigma ||Fo|-|Fc||/\Sigma|Fo| = 0.036$; $wR2 = [\Sigma(w (Fo^2-Fc^2)^2)/\Sigma w(Fo^2)^2]^{1/2} = 0.067$.

The standard deviation of an observation of unit weight[17] was 1.07. A Sheldrick weighting scheme was used. Plots of $\Sigma w(|Fo|-|Fc|)^2$ versus |Fo|, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.78 and -0.68 $e^-/Å^3$, respectively. The flack parameter[18] is 0.04(4) and The friedel pairs is 3385.

Neutral atom scattering factors were taken from Cromer and Waber.[19] Anomalous dispersion effects were included in Fcalc;[20] the values for Df' and Df'' were those of Creagh and McAuley.[21] The values for the mass attenuation coefficients are those of Creagh and Hubbell.[22] All calculations were performed using the CrystalStructure[23,24] crystallographic software package.

Acknowledgments. This work was supported by a grant from the Korea Science and Engineering Foundation (KOSEF) to the Environmental Biotechnology National Core Research Center (grant #: R15-2003-012-02001-0).

References and Footnotes

1. (a) For a review: Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735. (b) Caldarelli, M.; Habermann, J.; Ley, S. V. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 2049.
2. (a) Finnin, M. S.; Donigian, J. R.; Cohen, A.; Richon, V. M.; Rifkind, R. A.; Marks, P. A.; Breslow, R.; Pavletich, N. P. *Nature* **1999**, *401*, 188. (b) Miller, T. A.; Witter, D. J.; Belvedere, S. *J. Med. Chem*. **2003**, *46*, 5097. (c) Kim, D. K.; Lee, J. Y.; Kim, J. S.; Ryu, J. H.; Choi, J. Y.; Lee, J. W.; Im, G. J.; Kim, T. K.; Seo, J. W.; Park, H. J.; Yoo, J.; Park, J. H.; Kim, T. U.; Bang, Y. J. *J. Med. Chem*. **2003**, *46*, 5745. (d) Lu, Q.; Yang, Y.-T.; Chen, C.-S.; Davis, M.; Byrd, J. C.; Etherton, M. R. *J. Med. Chem*. **2004**, *47*, 467.
3. (a) Roosenberg II, J. M.; Miller, M. J. *J. Org. Chem*. **2000**, *65*, 4833. (b) Gaspar, M.; Granzina, R.; Bodor, A.; Farkas, E.; Santos, M. A. *J. Chem. Soc. Dalton Trans*. **1999**, 799. (c) Lin, Y.-M.; Miller, M. J. *J. Org. Chem*. **1999**, *64*, 7451. (d) Wang, Q. X.; Phanstiel IV, O. *J. Org. Chem*. **1998**, *63*, 1491. (e) Xu, Y.; Miller, M. J. *J. Org. Chem*. **1998**, *63*, 4314. (f) Sakamoto, T.; Li, H.; Kikugawa, Y. *J. Org. Chem*. **1996**, *61*, 8496.
4. (a) Miller, M. J. *Chem. Rev.* **1989**, *89*, 1563. (b) Bergeron, R. J.; Wiegand, J.; McManis, J. S.; Perumal, P. T. *J. Med. Chem.* **1991**, *34*, 3182.
5. Sandler, S. P.; Karo, W. In *Organic Functional Group Preparations*, Vol. III; Academic Press: New York, 1972; p 406.
6. (a) Koshiti, N.; Reddy, G. V.; Jacobs, H.; Gopalan, A. *Synth. Commun*. **2002**, *32*, 3779. (b) Bailen, M. A.; Chinchilla, R.; Dodsworth, D. J.; Najera, C. *Tetrahedron Lett*. **2001**, *42*, 5013. (c) Fray, M. J.; Burslm, M. F.; Dicknson, R. P. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 567. (d) Dankwardt, S. M.; Billedeau, R. J.; Lawley, L. K.; Abbot, S. C.; Martin, R. L.; Chan, C. S.; Van Wart, H. E.; Walker, K. A. M. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2513. (e) Nikam, S. S.; Kronberg, B. E.; Johnson, D. R.; Doherty, A. M. *Tetrahedron Lett*. **1995**, *36*, 197. (f) Altenburger, J. M.; Mioskowski, C.; d'Orchymont, H.; Schirlin, D.; Schalk, C.; Tarnus, C. *Tetrahedron Lett.* **1992**, *33*, 5055. (g) Pirrung, M. C.; Chang, J. H. L. *J. Org. Chem*. **1995**, *60*, 8084. (h) Barlaam, B.; Harmon, A.; Maudet, M. *Tetrahedron Lett.* **1998**, *39*, 7865. (i) Ando, W.; Tsumaki, H. *Synth. Commun*. **1983**, *13*, 1053. (j) Lee, B. H.; Miller, M. J. *J. Org. Chem.* **1983**, *48*, 24. (k) King, F. D.; Pike, S.; Walton, D. R. M. *J. Chem. Soc. Chem. Commun*. **1978**, 351.
7. Sibi, M. P.; Hasegawa, H.; Ghorpade, S. R. *Org. Lett*. **2002**, *4*, 3343.
8. Kang, Y. J.; Chung, H. A.; Kim, J. J.; Yoon, Y. J. *Synthesis* **2002**, 733.
9. Park, Y. D.; Kim, J. J.; Chung, H. A.; Kweon, D. H.; Cho, S. D.; Lee, S. G.; Yoon, Y. J. *Synthesis* **2003**, 560.
10. (a) Park, Y. D.; Kim, H. K.; Kim, J. J.; Cho, S. D.; Kim, S. K.; Shiro, M.; Yoon, Y. J. *J. Org. Chem*. **2003**, *68*, 9113. (b) Kim, H. K.; Park, Y. D.; Kim, J. J.; Lee, M. H.; Chung, H. A.; Kweon, D. H.; Cho, S. D.; Yoon, Y. J. *Bull. Korean Chem. Soc*. **2003**, *24*, 1655. (c) Kim, J. J.; Park, Y. D.; Lee, W. S.; Cho, S. D.; Yoon, Y. J. *Synthesis* **2003**, 1517. (d) Kweon, D. H.; Kim, H. K.; Kim, J. J.; Chung, H. A.; Lee, W. S.; Kim, S. K.; Yoon, Y. J. *J. Heterocyclic Chem.* **2002**, *39*, 203.
11. Chung, H. A.; Kweon, D. H.; Kang, Y. J.; Park, J. W.; Yoon, Y. J. *J. Heterocyclic Chem*. **1999**, *36*, 905.
12. (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blakie Academic and Professional: London, 1998. (b) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. Manabe, K.; Kobayasi, S. *Chem.-Eur. J*. **2002**, *8*, 4094. (c) Corma, A.; Garcia, H. *Chem. Rev.* **2003**, *103*, 4307.
13. Compound **2** was prepared by literature method.[8]
14. SIR97: Altomare, A.; Burla, M.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **1999**, *32*, 115.
15. DIRDIF99: Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; de Gelder, R.; Israel, R.; Smits, J. M. M. *The DIRDIF-99 Program System*, Technical Report of the Crystallography Laboratory; University of Nijmegen: The Netherlands, 1999.
16. Least Squares function minimized: $\Sigma w(F_o^2-F_c^2)^2$ where w = Least Squares weights.
17. Standard deviation of an observation of unit weight: $[\Sigma w(F_o^2-F_c^2)^2/(N_o-N_v)]^{1/2}$ where: N_o = number of observations, N_v = number of variables.
18. Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876-881.
19. Cromer, D. T.; Waber, J. T. *International Tables for X-ray Crystallography*, Vol. IV; The Kynoch Press: Birmingham, England, 1974; Table 2.2 A.
20. Ibers, J. A.; Hamilton, W. C. *Acta Crystallogr.* **1964**, *17*, 781.
21. Creagh, D. C.; McAuley, W. J. *International Tables for Crystallography*, Vol C; Wilson, A. J. C., Ed.; Kluwer Academic Publishers: Boston, 1992; pages 219-222, Table 4.2.6.8.
22. Creagh, D. C.; Hubbell, J. H. *International Tables for Crystallography*, Vol C; Wilson, A. J. C., Ed.; Kluwer Academic Publishers: Boston, 1992; pages 200-206, Table 4.2.4.3.
23. *CrystalStructure 3.6.0*: Crystal Structure Analysis Package; Rigaku and Rigaku/MSC: 9009 New Trails Dr. The Woodlands, TX 77381, USA, 2000-2004.
24. Watkin, D. J.; Prout, C. K.; Carruthers, J. R.; Betteridge, P. W. *CRYSTALS*, Issue 10; Chemical Crystallography Laboratory: Oxford, UK, 1996.