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# A Practical Synthetic Method of *O*-(2-(Pyrazol-1-yl)pyridin-5-yl)methylhydroxylamine as a Component of Modithromycin

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**ABSTRACT:** A practical synthesis of *O*-(2-(pyrazol-1-yl)pyridin-5-yl)methylhydroxylamine was achieved from the inexpensive raw materials, 2-chloro-5-chloromethylpyridine, pyrazole, and acetone oxime, using common reagents such as aq NaOH and sulfuric acid.

## INTRODUCTION

The novel bicyclolide agent modithromycin (**1**, EP-013420, EDP-420, S-013420)[1] was discovered by Enanta Pharmaceuticals and semi-synthesized from erythromycin A 9-oxime (**2**) and two synthetic fragments (**3**, **4**) of the side chain (Scheme 1).[2] To develop modithromycin in Japan, we needed a low-cost and reliable synthetic method by which modithromycin could be prepared on a large scale. We tried to find convenient synthetic methods of **1**.[3] In this paper, we describe developing the synthesis of *O*-(2-(pyrazol-1-yl)pyridin-5-yl)-methylhydroxylamine (**4**) focusing on cost economy, process safety, and selection of common reagents as acids and bases.[3b]

## RESULTS AND DISCUSSION

**Selection of Raw Material and Route.** Retrosynthetic analysis of *O*-substituted hydroxylamine derivative **4** shows that 2-chloro-5-chloromethylpyridine (**7a**) and 2-chloro-5-hydroxymethylpyridine (**7b**) are the best starting materials for the synthesis of hydroxylamine **4** (Scheme 2), because the synthetic routes are convenient and inexpensive. These inexpensive pyridines **7** are widely used as raw materials of chloronicotinyl insecticides which represented nearly 17% of the global insecticide market in 2006.[4]

Two hydroxylamine precursors are typically used to synthesize *O*-substituted hydroxylamine. One of the most conventional precursors is *N*-hydroxyphthalimide derivative **5a**.[5] It is well-known that the phthaloyl moiety, present in **5a**, can be deprotected by hydrazines under mild conditions.[5] However, this protecting group was not suitable to have in the precursor intermediate **6a**, because it might lead to an undesirable cross-reactivity with the pyrazole anion in the nucleophilic substitution process with the chloropyridine. Thus, the phathalimide derivative **5a** was alternatively prepared from the hydroxymethylpyridine **7b** in sequence steps that involved the intermediate **8** with protection, deprotection, and chlorination of the hydroxyl group. As the phthaloyl group involves a lack of atomic economy, we examined other precursors.

Another possible precursor is oximes,[6] the most inexpensive example being acetone oxime derivative **5b**. Fortunately, pyrazole anion **11** does not react with the oxime moiety of **6b** but selectively reacts with the chloride on the pyridine ring of **6b** to give acetone oxime derivative **5b** in good yield. As a result, using acetone oxime as a hydroxylamine precursor offers the most convenient and economical route (Scheme 3).

**Reaction Conditions and Procedure.** After choosing the synthetic route, we examined the reaction conditions and procedure. The selection of reagents for scaling up is determined by reactivity/selectivity, cost, availability, ease of scale-up operations. We tried to develop the reaction using a cheap and convenient reagent. Fortunately, in the presence of aq 48% NaOH,[7] chloromethylpyridine **7a** readily reacted with acetone oxime (**9**) in 1-methyl-2-pyrrolidinone (NMP) at room temperature to give oxime derivative **6b** in good yield.[8] Next, water was added to the reaction mixture to crystallize the oxime derivative **6b**, which was isolated by centrifugation to obtain wet crystals of **6b** without further purification.

Reactions of pyrazole anion **11** with **6b** were examined under various conditions (Table 1). Although amide solvents were superior to toluene and other nonpolar solvents for the reaction rate, in amide solvents pyrazole anion **11** reacted not only with **6b** but also with amide solvents to give a messy reaction mixture (entries 1−3). The pyrazole anion **11** was found to successfully react with **6b** in diethyleneglycol dimethyl ether (diglyme) to give **5b** in good yield (entry 4).

Nonsubstituted pyrazole in the 1-position shows NH acidity. The $pK_a$ value of pyrazole is ∼14 and equals that of water,[9] which led us to examine the preparation of pyrazole anion **11** by 28% sodium methoxide in MeOH and aq 48% NaOH instead of the expensive and hazardous NaH (entries 5−6). As a result, we selected aq 48% NaOH[7] for the preparation of pyrazole sodium salt **11**, although azeotropic dehydration is a time-consuming procedure.

To a solution of pyrazole (**10**) in diglyme were added aq 48% NaOH and toluene, and then the mixture was distilled under reduced pressure to remove toluene and water as an azeotropic mixture. The azeotropic dehydration was repeated until the distillate was clear. The obtained diglyme solution of pyrazole salt **11** was added to the diglyme solution of **6b** which was also dehydrated by azeotropic removal of toluene and water. Then the solvent was exchanged from toluene to

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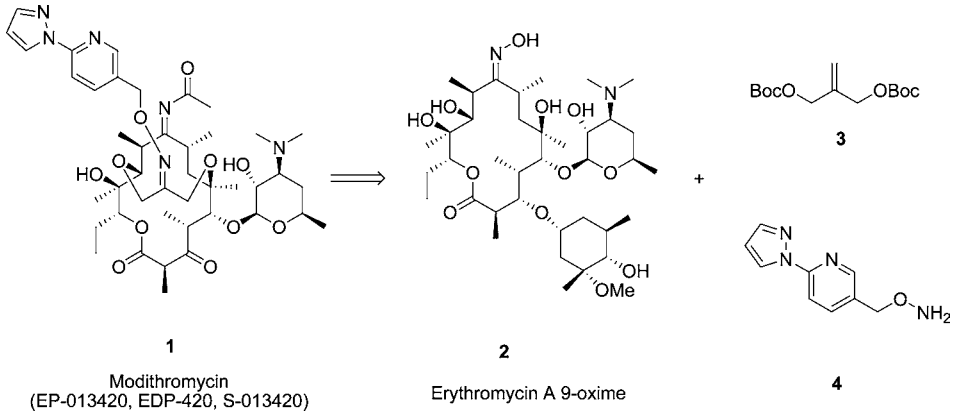
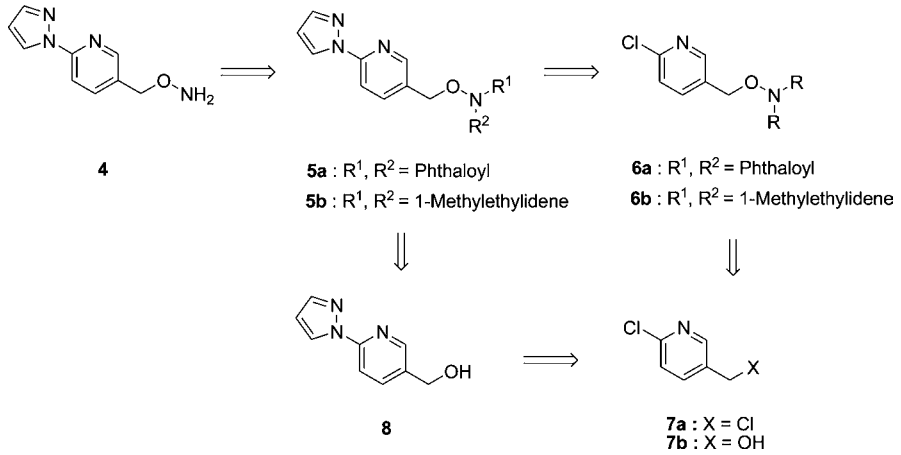
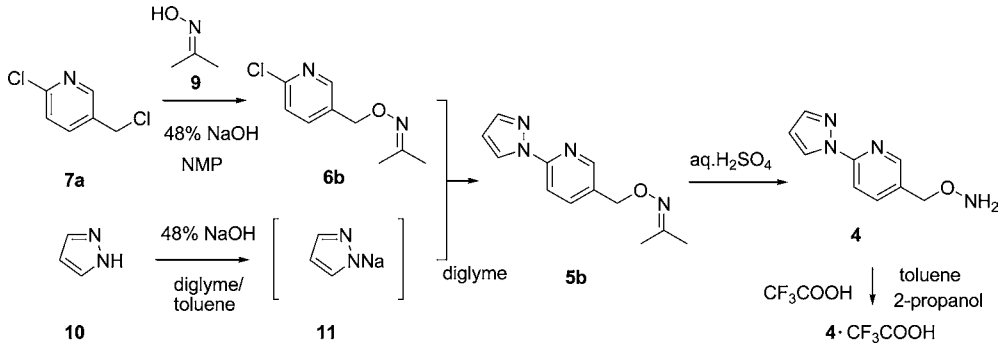
**Scheme 1. Semi-synthesis of modithromycin**




**Scheme 2. Retro-synthetic analysis of *O*-substituted hydroxylamine 4**




**Scheme 3. Synthetic route of *O*-substituted hydroxylamine 4**




diglyme. The obtained anhydrous diglyme solution of **11** and **6b** was heated at 115−135 °C for 13 h to give compound **5b**. After the reaction was completed, water was added to the reaction mixture to crystallize **5b**, which was isolated by centrifugation.

Usually acetone oximes are hydrolyzed on a laboratory scale by hydrochloric acid,[6] which generates volatile hydrogen chloride and causes the threat of rusting if used in the plant. To avoid rusting, nonvolatile sulfuric acid was used instead of hydrochloric acid. Acetone oxime **5b** was hydrolyzed in aqueous sulfuric acid at reflux by removing acetone to obtain **4**.

**Safety Assessment of Hydroxylamine Derivatives.** Because hydroxylamine derivatives are high-energy compounds,[10] their handling was evaluated with respect to thermal stability by DSC (Table 2). The decomposition energies of the hydroxylamine derivatives greatly depend on the material of the DSC pans (entries 5−9). Therefore, to prevent the decomposition reaction, contamination with metal ion must be avoided. Furthermore, it was found that hydroxylamine **4** in aqueous sulfuric acid, the hydrolytic reaction mixture of **5b** and sulfuric acid, had considerable exothermic energy with a considerable low onset at 160 °C (entry 7). The hydroxylamine **4** in aqueous sulfuric acid must be exposed to heat aging at reflux for long periods of time to complete the hydrolysis of **5b**.

The potential instability of the hydroxylamine **4** in aqueous sulfuric acid was examined using an advanced reactive system screening tool (ARSST) on a sample of the reaction mixture, which showed that the hydroxylamine **4** in aqueous sulfuric acid


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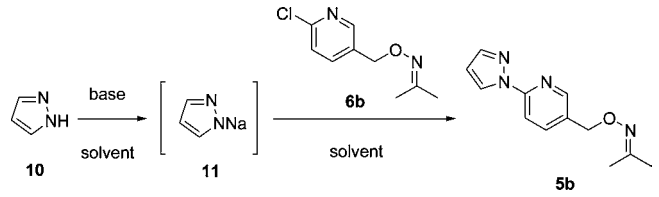
**Table 1. Preparation of pyrazole anion 11 and reaction of 11 with 6b**




| entry | base | solvents | results[a] yields of **5b** |
|---|---|---|---|
| 1 | 55% NaH[b] | toluene | slow |
| 2 | 55% NaH[b] | DMF | messy |
| 3 | 55% NaH[b] | NMP | messy |
| 4 | 55% NaH[b] | diglyme | 88% |
| 5 | 28% NaOMe in MeOH[c] | diglyme | 75% |
| 6 | aq 48% NaOH[d] | diglyme | 80% |

[a]Pyrazole anion **11** was reacted with chloropyridine **6b** at 120 °C for 7 h. [b]Dispersion in mineral oil. [c]Salt **11** was prepared by distillation to remove MeOH. [d]Salt **11** was prepared by distillation to remove $H_2O$.

**Table 2. Thermal analysis study of hydroxylamine derivatives by DSC**

| entry | cmpds | decomposition-onset temp [°C] | decomposition energy [J/g] | materials of pan |
|---|---|---|---|---|
| 1 | **9** | >200 | – | aluminum |
| 2 | **6b** | 283 | 274 | stainless steel |
| 3 | reaction mixture of **6b** with pyrazole | 214 | 36 | stainless steel |
| 4 | **5b** | >300 | – | gold |
| 5 | **4**·1/2$H_2SO_4$ | 241 | 454 | stainless steel |
| 6 | **4**·1/2$H_2SO_4$ | 216 | 637 | aluminum |
| 7 | **4** in aq $H_2SO_4$ (Reaction mixture of hydrolyzed **5b**) | 160 | 229 | gold |
| 8 | **4**·$CF_3COOH$ | 246 | 168 | stainless steel |
| 9 | **4**·$CF_3COOH$ | 179 | 1143 | aluminum |

is stable at 30−220 °C. A 5-g sample of the reaction mixture was loaded into the ARSST 10-mL glass test cell, which was sealed in a 350-mL vessel and pressurized with 410 psi nitrogen. The sample was heated from 30 to 220 °C at 2 °C/min polynomial control condition. Figure 1 and Figure 2 show the temperature and pressure profiles from the ARSST.

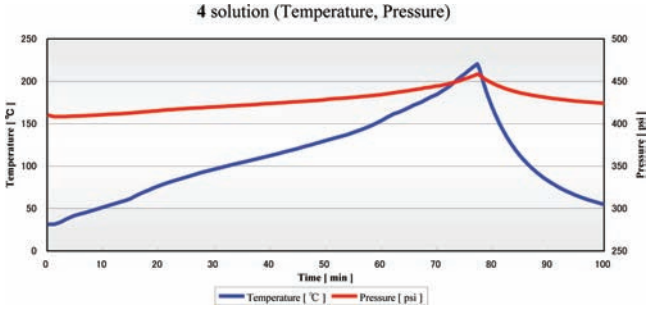



**Figure 1.** Temperature and pressure profile for **4** in aqueous sulfuric acid determined with ARSST.

To enhance the safety of the hydrolytic reaction of **5b**, we adopted distillation under reduced pressure for the following three reasons. Lowering the operation temperature by reducing

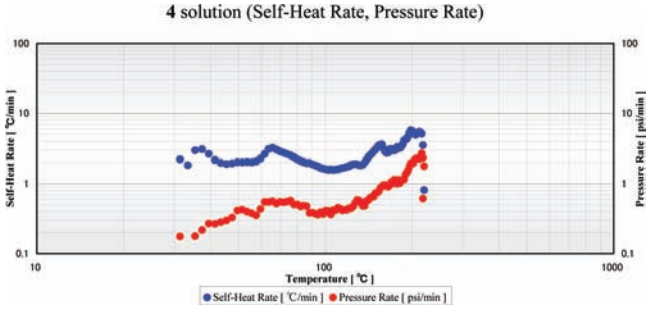



**Figure 2.** Temperature rate and pressure rate profile for **4** in aqueous sulfuric acid determined with ARSST.

pressure, can suppress the decomposition reaction of **4**. If the decomposition reaction occurs, boiling at the heat of the decomposition reaction can be suppressed by raising the pressure. Moreover, if the capacity of the condenser is enough to cool the heat of the decomposition reaction, accidents can be avoided.

On a laboratory scale (1 L), **5b** was hydrolyzed with aqueous sulfuric acid at reflux by removing acetone to obtain **4**.[11] In the case of production in a plant, twice the appropriate amount of ethanol was added to a two-phase mixture of **5b** and aqueous sulfuric acid to increase the affinity of the two phases. The two-phase mixture was then distilled under reduced pressure at 70−100 °C for 9 h, with continuous addition of water to maintain volume of the mixture, to obtain **4**.

The obtained hydroxylamine **4** was used to prepare the bridge oxime of modithromycin **1**, which has an *E*-oxime configuration.[2b] Other researchers in our company found that the highest *E*/*Z* ratio (7/1) of **1** could be achieved by using trifluoroacetic acid for the acid-catalyzed oximation reaction.[3a] Thus, a trifluoroacetic acid salt of hydroxylamine **4** became one of the starting materials for modithromycin **1** synthesis.

## ■ CONCLUSION

We have developed a convenient, economical, and safe synthetic method of **4** starting from the inexpensive compound **7a** and using common and operator-friendly reagents (aq 48% NaOH and sulfuric acid). Use of this method led to the successful manufacturing of hydroxylamine **4**·$CF_3COOH$ by our outsourcing companies on a 33−36 kg/lot scale.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## EXPERIMENTAL SECTION

**General.** The $^{1}H$ and $^{13}C$ NMR spectra were measured on a Varian Gemini 300 MHz FT NMR spectrometer and/or Varian Inova 500 MHz FT NMR spectrometer. The FT-IR spectra were recorded on a Bruker Vertex 70 spectrometer. Mp was measured on Büchi melting point apparatus B-545. DSC measurements were run on a Perkin-Elmer Pyris 1 and a Mettler Toledo DSC 822e, and the scanning rate was 10 °C/min, with a temperature range up to 300 °C.

***O*-(2-Chloropyridin-5-yl)methyl Acetone Oxime (6b).** Under nitrogen atmosphere, into a solution of 2-chloro-5-chloromethylpyridine (**7a**) (30.0 kg, 185 mol) and acetone oxime (**9**) (15.3 kg, 210 mol) in NMP (61.8 kg) and water (7.5 kg), was added aq 48% NaOH (17.1 kg, 205 mol) dropwise at 27−40 °C for 1 h with stirring. After reaction completion, the reaction mixture was cooled to 13−17 °C. The seed crystals of **6b** were added; then water (253.5 kg) was added at 13−17 °C for 150 min with stirring. The obtained slurry was separated by centrifugation, and the crystals of **6b** were washed twice with water (120 kg). The obtained wet crystals of **6b** were used in the next reaction without further purification. The yield was estimated at ∼87% by HPLC analysis.

***6b:*** mp 38.9−39.0 °C. $^{1}H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.86 (3H, s), 1.87 (3H, s), 5.03 (2H, s), 7.30 (1H, d, $J$ = 8.1 Hz), 7.64 (1H, dd, $J$ = 2.3 and 8.1 Hz), 8.36 (1H, d, $J$ = 2.3 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 15.7, 21.7, 71.6, 123.7, 132.7, 138.3, 149.0, 150.4, 155.8. IR ($CHCl_3$) 3025, 2994, 1590, 1462, 1213, 1106, 1075, 1020 $cm^{-1}$. Anal. Calcd for $C_9H_{12}ClN_2O$: C, 54.42; H, 5.58; Cl, 17.85; N, 14.10. Found: C, 54.06; H, 5.42; Cl, 17.46; N, 14.09.

***O*-(2-(Pyrazol-1-yl)pyridin-5-yl)methyl Acetone Oxime (5b).** A mixture of the wet crystals **6b** (33.2 kg) and toluene (104 kg) was distilled under reduced pressure at 40−80 °C until 52 kg of toluene was removed by the distillation; toluene (52 kg) was added and distilled under reduced pressure. The above distillation was repeated until the distillate was clear. The dehydration was verified by a Karl Fischer titration test until the water content of toluene solution of **6b** was 0.1% or less.

Under nitrogen atmosphere, a mixture of pyrazole (14.4 kg), diethyleneglycol dimethyl ether (diglyme, 85.1 kg), 48% aq NaOH (16.4 kg), and toluene (52 kg) was distilled under reduced pressure at 40−80 °C. After 26 kg of distillate was removed by the distillation, toluene (26 kg) was added and then distilled under reduced pressure. The above distillation was repeated until the distillate was clear and the water content of diglyme solution of **11** was 0.2% or less.

The dehydrated toluene solution of **6b** was added to the diglyme solution of **11**, the combined solution was distilled under reduced pressure until the toluene content was 2% or less. Diglyme was added to adjust the volume of the solution to 102 L. The obtained diglyme solution was heated with stirring at 115−135 °C for 13 h.

After the reaction completion, the reaction mixture was cooled at 20 °C, and water (90 kg) was added dropwise for 20 min at 20−30 °C. After the beginning of crystallization, the slurry was stirred for 30 min at 20 °C, water (135 kg) was added dropwise for 30 min at 20−30 °C, and then the obtained slurry was cooled at −5 °C for 30 min. After completion of crystallization, the slurry was separated by centrifugation, and the obtained crystals were washed with 60 kg of water at 3−5 °C. The obtained wet crystals of **5b** were used in the next reaction with an activated carbon treatment. The yield was estimated at ∼92% by HPLC analysis.

***5b:*** mp 60.8−60.9 °C. $^{1}H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.87 (3H, s), 1.88 (3H, s), 5.08 (2H, s), 6.46 (1H, dd, $J$ = 1.5 and 2.7 Hz), 7.72−7.75 (1H, m), 7.81 (1H, dd, $J$ = 2.3 and 8.7 Hz), 7.96 (1H, dd, $J$ = 0.6 and 8.7 Hz), 8.38−8.42 (1H, m), 8.56 (1H, dd, $J$ = 0.6 and 2.7 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 15.7, 21.8, 72.0, 107.5, 111.8, 126.7, 131.4, 138.5, 141.7, 147.4, 150.8, 155.5.

***O*-(2-(Pyrazol-1-yl)pyridin-5-yl)methylhydroxylamine Trifluoroacetic Acid Salt (4·$CF_3COOH$).** Under nitrogen atmosphere, a slurry of the obtained wet **5b** (35.5 kg), activated carbon (1.7 kg), and ethyl acetate (30.7 kg) was stirred for 30 min at 20−30 °C. Then heptane (186 kg) was added, and the slurry was stirred for 30 min. The slurry was filtered, and the removed activated carbon was washed three times with mixed solutions of ethyl acetate (10 kg) and heptane (62 kg). The obtained filtrate and rinse were combined and concentrated under reduced pressure at 30−80 °C until the ethyl acetate and heptane content was as little as possible.

A mixture of the concentrated residue, ethanol (26 kg), water (157 kg), and sulfuric acid (43 kg) was distilled under reduced pressure (0.005−0.007 MPa) at 70−100 °C for 60 min. Ethanol (26 kg) and water (22 kg) were added, and the distillation was continued for 8 h at 70−90 °C under reduced pressure (0.001−0.005 MPa), while adding water to maintain the volume of the mixture.

After the reaction completing, the reaction mixture was cooled to 60 °C, and toluene (57.2 kg) and water (66 kg) were added and stirred at 55−65 °C. The toluene layer was separated to remove insoluble material in the aqueous layer. To the separated aqueous layer, toluene (85.7 kg) and 48% NaOH (72.8 kg) were added at 15−35 °C with stirring; the mixture was filtered with Celite (1.7 kg) and washed with toluene (5.7 kg).

Layers were separated, and the aqueous layer was extracted with toluene (42.9 kg). The combined toluene layer was dehydrated by distillation under reduced pressure at 40−80 °C with addition of toluene until the distillate was clear, and the water content of the toluene solution of **4** was 0.5% or less. Toluene was added to adjust the weight of the solution of **4** to 170 kg.

To a solution of trifluoroacetic acid (3.44 kg), 2-propanol (2.6 kg), and toluene (11.4 kg), the obtained toluene solution of **4** was added dropwise at 20−30 °C, and then toluene (40 kg) was added. The slurry was cooled at 0 °C for 30 min, filtered, and washed with a solution of 2-propanol (0.3 kg) and toluene (11 kg). The obtained wet 4·$CF_3COOH$ was dried under reduced pressure at 25−55 °C to afford 36.1 kg of 4·$CF_3COOH$ (77.0% yield) .

***4 $CF_3COOH$:*** mp 112.6−112.7 °C dec. $^{1}H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 4.99 (2H, s), 6.60 (1H, dd, $J$ = 0.9 and 1.5 Hz), 7.85 (1H, t, $J$ = 0.9 Hz), 7.95−8.10 (2H, m), 8.48−8.52 (1H, m), 8.64 (1H, dd, $J$ = 0.6 and 1.5 Hz). Anal. Calcd for $C_9H_{10}N_4O·C_2HF_3O_2$: C, 43.43; H, 3.64; F, 18.73; N, 18.42. Found: C, 43.45; H, 3.71; F, 18.69; N, 18.55. FAB-MS (NBA) $m/z$ 191 $[M + H]^+$. FAB-MS (NBA + Na) $m/z$ 213 $[M + Na]^+$.

***4 1/2 $H_2SO_4$:*** mp 188.6−189.2 °C dec. $^{1}H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 4.85 (2H, s), 6.59 (1H, dd, $J$ = 1.8 and 2.4 Hz), 7.83 (1H, dd, $J$ = 0.6 and 1.5 Hz), 7.94 (1H, dd, $J$ = 0.8 and 8.5 Hz), 8.00 (1H, dd, $J$ = 2.4 and 8.5 Hz), 8.467 (1H, d, $J$ = 1.5 Hz), 8.62 (1H, dd, $J$ = 0.8 and 2.4 Hz). Anal. Calcd for $C_9H_{10}N_4O·1/2H_2SO_4$: C, 45.18; H, 4.63; N, 23.42; S, 6.70.


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Found: C, 45.09; H, 4.70; N, 23.31; S, 6.75. FAB-MS (NBA) $m/z$ 191 $[M + H]^+$. FAB-MS (NBA + Na) $m/z$ 213 $[M + Na]^+$.

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## REFERENCES


(1) (a) Scorneaux, B.; Arya, A.; Polemeropoulos, A.; Lillard, M.; Han, F.; Amsler, K.; Sonderfan, A.; Wang, G., Wang, Y.; Peng, Y.; Xu, G.; Kim, H.; Lien, T.; Phan, L. T., Or, Y. S. *Abstract No. F-1191*; 43rd Annual ICAAC, Chicago, IL, September 2003. (b) McAlpine, J. B.; Yagisawa, M. Antibacterials for the Treatment of Gram Positive Infections. *Annu. Rep. Med. Chem.* **2005**, *40*, 301−322.

(2) (a) Revill, P.; Bolos, J.; Serradell, N. *Drugs Future* **2006**, *31*, 479. (b) Xu, G.; Tang, D.; Gai, Y.; Wang, G.; Kim, H.; Chen, Z.; Phan, Ly T.; Or, Y. S.; Wang, Zhe. *Org. Process Res. Dev.* **2010**, *14*, 504.

(3) (a) Kabaki, M.; Takeo, M.; Yokota, Y.; Shimomoto, A.; Osaki, M.; Ooe, M.; Goda, S. It is unpublished data that modithromycin was synthesized from erythromycin A 9-oxime in 25% total yield in the third campaign. (b) Shimizu, S.; Hakogi, T. PCT Int. WO/2006/068102, June 2006. (c) Osato, H.; Kabaki, M.; Shimizu, S. *Org. Process Res. Dev.* **2011**, *15*, 581.

(4) (a) Jeschke, P.; Nauen, R. *Pest Manage. Sci.* **2008**, *64*, 1084. (b) Latli, B.; D'Amour, K.; Casida, J. E. *J. Med. Chem.* **1999**, *42*, 2227. (c) Zhang, N.; Tomizawa, M.; Casida, J. E. *J. Med. Chem.* **2002**, *45*, 2832. (d) Sun, C.; Jin, J.; Zhu, J.; Wanga, H.; Yang, D.; Xing. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3301.

(5) (a) Schumann, E. L.; Heinzelman, R. V.; Greig, M. E.; Veldkamp, W. *J. Med. Chem.* **1964**, *7*, 329. (b) Martin, D. G.; Schumann, E. L.; Veldkamp, W.; Keasling, H. *J. Med. Chem.* **1965**, *8*, 456. (c) Hamor, G. H.; Rubessa, F. *J. Med. Chem.* **1972**, *15*, 470. (d) Koyama, J.; Sugita, T.; Suzuta, Y.; Irie, H. *Chem. Pharm. Bull.* **1983**, *31*, 2601. (e) Kolasa, T.; Gunn, D. E.; Bhatia, P.; Woods, K. W.; Gane, T.; Stewart, A. O.; Bouska, J. B.; Harris, R. R.; Hulkower, K. I.; Malo, P. E.; Bell, R. L.; Carter, G. W.; Brooks, C. D. W. *J. Med. Chem.* **2000**, *43*, 690.

(6) (a) Truitt, P.; Holst, E. H.; Robbins, M. *J. Am. Chem. Soc.* **1952**, *74*, 3956. (b) Gilon, C.; Knobler, Y.; Sheradsky, T. *Tetrahedron* **1967**, *23*, 4441. (c) Cannon, J. G.; Mulligan, P. J.; Garst, J. E. *J. Med. Chem.* **1973**, *16*, 287. (d) Bajwa, B. S.; Acton, N.; Brossi, A. *Heterocycles* **1983**, *20*, 839.

(7) Anderson, N. G. *Practical Process Research and Development*; Academic Press: San Diego, CA, 2000; p 59.

(8) Under the reaction conditions, **7a** was hydrolyzed to **7b**, which subsequently reacted with next **7a** and resulted in 2% yield of di[(2-chloropyridin-5-yl)methyl]ether (by HPLC analysis). The ether was easily removed by crystallization of **6b**.

(9) (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2003; p 181. (b) Abboud, J. L. M.; Sraidi, K.; Abraham, M. H.; Taft, R. W. *J. Org. Chem.* **1990**, *55*, 2230.

(10) (a) Boyles, D. C.; Curran, T. T.; Parlett, R. V. IV *Org. Process Res. Dev.* **2002**, *6*, 230. (b) Hett, R.; Krähmer, R.; Vaulont, I.; Leschinsky, K.; Snyder, J. S.; Kleine, P. H. *Org. Process Res. Dev.* **2002**, *6*, 896. (c) Mendiola, J.; Rincón, J. A.; Mateos, C.; Soriano, J. F.; de Frutos, o.; Niemeier, J. K.; Davis, E. M. *Org. Process Res. Dev.* **2009**, *13*, 263.

(11) The preliminary experiment using the actually used materials was conducted prior to the scale-up as a quality test.