Tetrahedron Letters 51 (2010) 2144–2147

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient synthesis of (*Z*)- and (*E*)-methyl 2-(methoxyimino)-2-phenylacetate

Yong-Jin Wu [a,*], Stella Huang [b], Alicia Ng [c], Qi Gao [d], S. Roy Kimura [e], David R. Langley [e]

[a] Department of Neuroscience Chemistry, Research and Development, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492, USA
[b] Analytical Research and Development, Research and Development, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492, USA
[c] Bioanalytical and Discovery Analytical Sciences, Research and Development, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492, USA
[d] Analytical Research and Development, Bristol-Myers Squibb Company, 1 Squibb Drive, New Brunswick, NJ 08901, USA
[e] Department of Computer-Aided Drug Design, Research and Development, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492, USA

ARTICLE INFO

Article history:
Received 15 January 2010
Revised 4 February 2010
Accepted 12 February 2010
Available online 19 February 2010

ABSTRACT

Direct oximation of 2-oxo-2-phenylacetate (**3**) gave the (*Z*)-methyl 2-(methoxyimino)-2-phenylacetate (**1**) in 71% yield, while the *E* oxime **2** was prepared from **3** in 65% yield via oxime isomerization of 2-(methoxyimino)-2-phenylacetic acid (**5**). Computational studies suggest that the isomerization of **5** is thermodynamically driven, while the direct oximation of ketoester **3** is kinetically controlled.

Alkyloximes are valuable intermediates in organic synthesis and are found in a variety of drugs on the market, including fluvoxamine (antidepressant), oxiconazole (antifungal), gemifloxacin (antibacterial), and cefetamet (antibacterial) (Fig. 1).

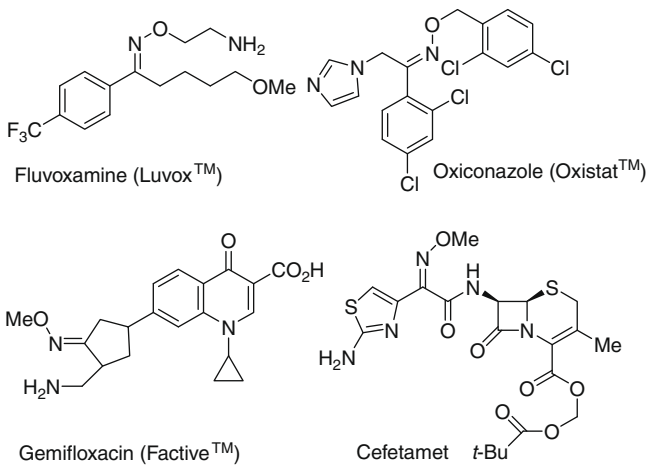


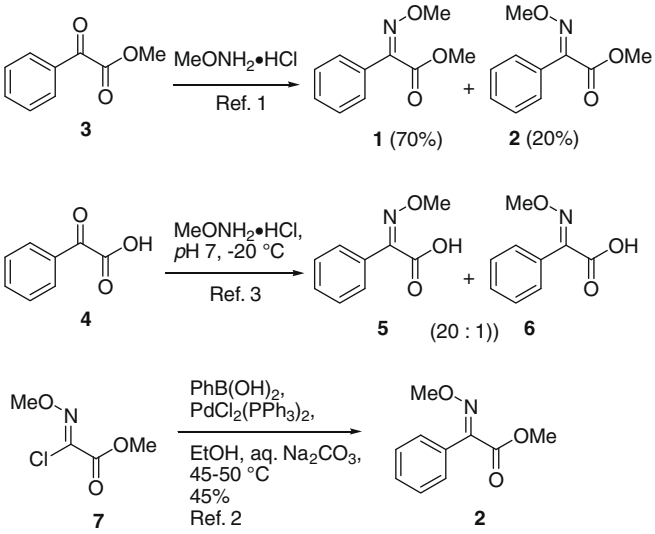
Figure 1.

In a recent medicinal chemistry program, we desired to have easy access to both (*Z*)- and (*E*)-methyl 2-(methoxyimino)-2-phenylacetate **1** and **2**. A simple approach to these compounds involves oximation of 2-oxo-2-phenylacetate (**3**) with methoxyamine hydrochloride as demonstrated by Uda et al. (Scheme 1).[1] Thus, the treatment of **3** with methoxyamine hydrochloride afforded the two oxime isomers **1** and **2** in 70% and 20% yields, respectively. We carried out this reaction on a multigram scale and obtained similar yields of both isomers. The method did allow us to deliver a sizable amount of the major *Z* isomer **1** for our medicinal chemistry program, but we were unable to scale up a sufficient quantity of the minor *E* isomer **2**. Oxime **2** can also be prepared in moderate yield via a palladium-catalyzed cross-coupling reaction of phenylboronic acid with (*Z*)-methyl 2-chloro-2-(methoxyimino)acetate (**7**) as described by Ziegler et al. (Scheme 1).[2] As chloride **7** is not readily available, this method has limited application for our purpose. We also looked into the oximation of 2-oxo-2-phenylacetic acid (**4**) with methoxyamine hydrochloride as the oxime acid **6** can be converted to its methyl ester **2**, but again, the *E* isomer was formed as a very minor product (**5**:**6** = 20:1) when oximation of **4** was carried out in methanol at pH 7 and −20 °C as reported recently by Tsukiyama and Sato (Scheme 1).[3] Therefore, there is still a need to develop efficient methods for the preparation of the *E* oximes of 2-arylacetates. This Letter describes a practical synthesis of the *E* oxime **2** via oxime isomerization.

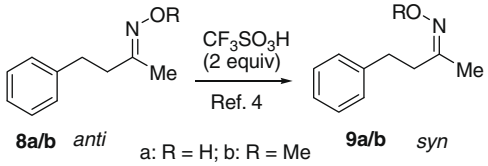
At the outset of this program, we wondered if the *E* oxime ester **2** can be prepared from the *Z* isomer **1** by means of isomerization, and not surprisingly, we observed no appreciable formation of **2** when **1** was subjected to a variety of thermal and acidic conditions. The lack of isomerization is consistent with the literature finding that *O*-alkyloximes rarely isomerize under standard conditions, while hydroxyloximes can undergo facile isomerization. For example, Narasaka reported that oxime **8a** isomerizes quickly upon exposure to trifluoromethanesulfonic acid, but no isomerization is observed with the corresponding *O*-methyloxime **8b** under the same conditions (Scheme 2).[4]

* Corresponding author. Tel.: +1 203 677 7485; fax: +1 203 677 7702.
E-mail address: yong-jin.wu@bms.com (Y.-J. Wu).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.02.073



Scheme 1.

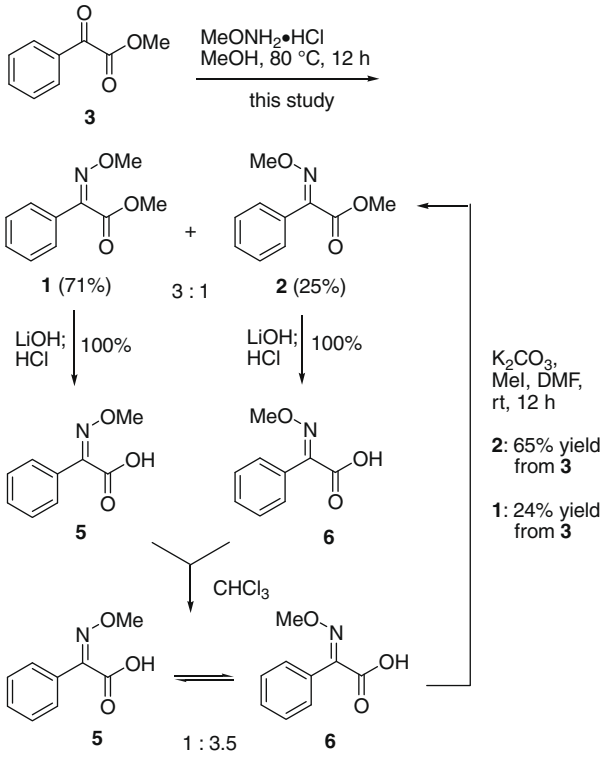


R	Time	*anti*/*syn*
H	<20 min	2 : 1
Me	12 h	100 : 0

Scheme 2.

We next turned our attention to the isomerization of oxime acids **5** and **6** (Scheme 3). These acids were prepared in quantitative yields from their corresponding esters upon treatment with aqueous lithium hydroxide in THF followed by neutralization with 1 N aqueous hydrochloric acid. Under these conditions, no isomerization occurred. Both oxime acids were very stable at room temperature as white solids presumably due to intermolecular hydrogen bonding interactions as observed in the X-ray crystal structures (data not shown). However, when dissolved in an organic solvent such as chloroform, dichloromethane, and methanol at room temperature for 6–12 h, both **5** and **6** isomerized to the same mixture of **5** and **6** in a 1:3.5 ratio as shown in the ^{1}H NMR spectrum of the equilibrium mixture (Fig. 2). This ratio remained unchanged with an addition of acid (e.g., hydrochloric acid) or use of polar solvents (e.g., methanol) or at higher temperature (e.g., 80 °C). Under basic conditions such as aqueous 1 N lithium hydroxide, both **5** and **6** showed no detectable isomerization. Thus, the isomerization observed with both **5** and **6** is most likely self-acid-catalyzed.

The observation that oxime acids **5** and **6** readily isomerize led to an efficient preparation of the *E* oxime **2**. Thus, ketoester **3** was treated with methoxyamine hydrochloride in methanol at 80 °C for 12 h to give a 3:1 mixture of **1** and **2**. This crude mixture was hydrolyzed with lithium hydroxide and then neutralized with 1 N hydrochloric acid. The resulting 3:1 mixture of **5** and **6** was dissolved in chloroform and the ratio changed to 1:3.5 after overnight at room temperature. The solvent was removed, and the residue was treated with potassium carbonate and methyl iodide in DMF to afford **2** and **1** in 65% and 24% overall yields, respectively, from **3**. We have utilized this equilibration method to scale up multigram quantities of oxime **2**.



Scheme 3.

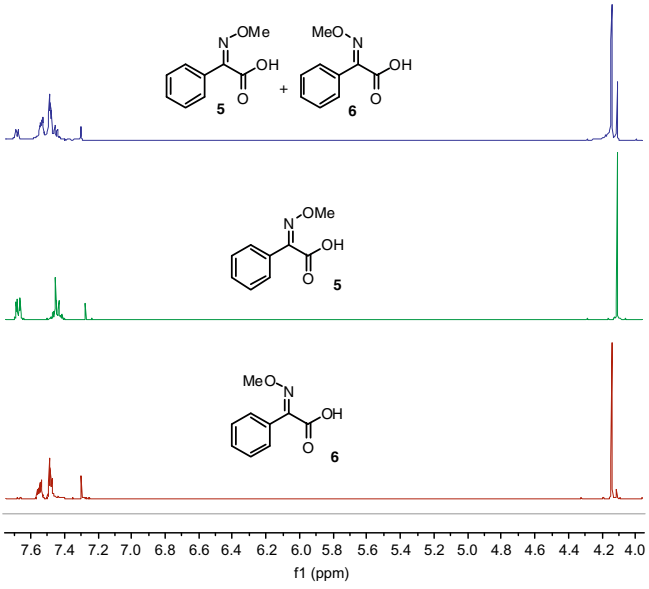


Figure 2. ^{1}H NMR spectra of **6** (bottom), **5** (middle), and the equilibrium mixture of **5** and **6** (top).

In our current studies, ketoester **3** was used for the sizable preparation of both oxime isomers **1** and **2**. Certainly, the *E* isomer **2** can be made directly from ketoacid **4** in three steps: oximation, isomerization, and methylation.

The oxime geometry of compounds **1**, **2**, and **5** was assigned by comparing ^{1}H NMR data with those reported in the literature.[1,3] With compound **5** assigned as *Z* configuration, compound **6** must have *E* configuration. In addition, we obtained ^{15}N chemical shifts of the four oximes from ^{1}H–^{15}N correlation spectra as shown in Table 1. These stereochemical assignments are consistent with the general observation that the *Z* oximes exhibit more downfield

Table 1
^{15}N chemical shifts of oximes[a]

Compd	Observed δ_N (ppm)	Configuration assignment	X-ray confirmation
1	401.2	*Z*	Yes
2	371.0	*E*	No
5	402.8	*Z*	Yes
6	376.4	*E*	Yes

[a] The ^{15}N chemical shift was referenced to NH_3 (liquid) at −380.2 ppm.

nitrogen chemical shifts than their corresponding *Z* oximes.[5] Finally, we obtained X-ray crystal structures of **1**, **5**, and **6**, thus confirming our stereochemical assignments.

The dominance of **6** over **5** in the equilibrium is not well understood. The hydrogen bonding hypothesis would favor the *Z* isomer **5**, while the argument based on the steric repulsion between methoxy and carboxylic acid or phenyl does not seem to be obvious (Fig. 3). Other factors such as dipole–dipole interaction may play important roles.

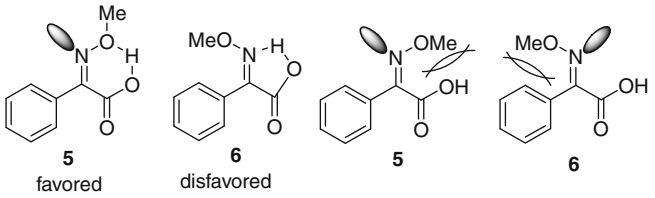


Figure 3.

To better understand the oxime isomerization of **5** and **6**, we carried out preliminary computational studies. Since thermodynamic equilibration was observed for the oxime acids **5** and **6**, we sought to determine whether their quantum mechanical (QM) ground state energies agreed with the observed ratios. Calculations were performed by first taking the OPLS2005[6] molecular mechanics force-field minima in vacuum for each,[7] then subjecting them to density functional theory geometry optimizations using the 6-31G* basis set.[8] The conformational minima identified through this procedure agreed with the expected internally hydrogen bonded conformations. Single-point ground state energies were then calculated at the RIMP2 level of theory with Dunning's aug-cc-pvtz[9] basis set in both vacuum and water dielectric ($\varepsilon = 78$) environments. All QM calculations were carried out using the QCHEM package.[10] The resulting calculated energies (Table 2) correctly identified oxime **6** as the preferred isomer over **5** but over-estimated the energy difference, predicting a 1:91 ratio of **5** to **6** (cf. observed ratio: 1:3.5). The discrepancy is likely due to neglect of other minor conformational populations as well as microscopic solvent effects.

Since both oximes **1** and **2** do not isomerize under standard conditions, we hypothesized that the intermediate **10** (Fig. 4) (which would lead to **1** and **2** in the oximation of keto ester **3**) exhibits conformational preferences that kinetically dictate the final oxime isomer ratio. In our computational studies, the dihedral angle of interest was defined by the phenyl ring, the tetrahedral carbon, the oxime nitrogen, and the methoxy group. Calculations of the force-field (OPLS2005[6]) dihedral potential profile with several simplified implicit solvent models (Generalized Born[11] and simple dielectrics) all consistently yielded a global torsional minimum near 300° (data not shown). Since the *E* and *Z* oxime isomers have torsion angles 0° and 180°, respectively, these simplified models predicted that the system would favor the *E* isomer **2**, which is closer to the torsional minimum. However, this does not agree with experimental observations, suggesting the need for a more accurate solvent description and proper ensemble averaging of conformational populations. We therefore performed molecular dynamics simulations of intermediate **10** in a periodic 38 × 38 × 38 Å box of explicit methanol solvent. Simulations were carried out using the AMBER GAFF force-field[12] at 300 K in the NPT ensemble. Simulation temperatures were periodically ramped up to 600 K and annealed back down to 300 K in the NVT ensemble to allow for escape from potentially stable intramolecular hydrogen bonds and other conformational wells. Torsional data were collected only during the 300 K NPT intervals, and ten separate 200 ps data collection intervals were used (total of 2 ns of production simulation time). The resulting torsion angle distribution shown in Table 3 predicted that the *Z* oxime **1** is preferred over the *E* oxime **2** by an approximately 3.5 to 1 ratio which is in excellent agreement with the observed ratio (3:1).

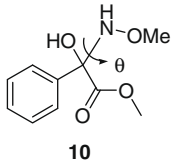


Figure 4.

Table 2

	ΔE vacuum (kcal/mol)	ΔE dielectric ε = 78 (kcal/mol)	Calculated ratio of **5**:**6** 25°C, vacuum
E_5–	E_6 1:90	2.67	2.61

Table 3

Torsion angles	Proportion
$90 < \theta < 270$	0.778
$\theta < 90$ or $\theta > 270$	0.222

In summary, we have developed an efficient synthesis of (*E*)-methyl 2-(methoxyimino)-2-phenylacetate (**2**) using a facile isomerization of the *Z* oxime acid **5**.[13] This methodology should be applicable to other *E* oximes of 2-arylacetates. Our preliminary computational studies suggest that the isomerization of **5** is thermodynamically driven, while direct oximation of ketoester **3** is kinetically controlled. Future efforts will be directed toward delineating the full scope of this isomerization, understanding the isomerization mechanism, and applying this methodology to the synthesis of biologically important compounds.

Acknowledgments

We thank Drs. Lorin Thompson and John Macor for their encouragement and support.

Supplementary data

Supplementary data (X-ray crystal structures of compounds **1**, **5** and **6**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.073.

References and noes

1. Uda, J.; Okamoto, Y.; Iwabuchi, T.; Inoue, T.; Nakano, H.; Ishikawa, T.; Kawasaki, N.; Katoh, M.. PCT Int. Appl., WO 2005068415 A1, 2005.
2. Ziegler, H.; Neff, D.; Stutz, W. PCT Int. Appl., WO 9520569 A1, 1995.
3. Tsukiyama, T.; Sato, K. PCT Int. Appl., WO 2002059078 A1, 2002.
4. Kitamura, M.; Yoshida, M.; Kikuchi, T.; Narasaka, K. *Synthesis* **2003**, *15*, 2415.
5. Berger, S.; Braum, S.; Kalinowski, H. *NMR Spectroscopy of the None-Metallic Elements*; John Wiley & Sons: New York, 1996. P206.
6. Kaminski, G. A.; Friesner, R. A.; Tirado-Rives, J.; Jorgensen, W. J. *J. Phys. Chem. B* **2001**, *105*, 6474.
7. Conformational searches conducted using Monte Carlo Multiple Minima Method with Default Settings in Maestro, Version 8.5, Schrodinger, LLC, New York, NY, 2008.
8. Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta.* **1973**, *28*, 213.
9. Dunning, T. H., Jr.; Hay, P. J. In *Modern Theoretical Chemistry*; Schaefer, E. D., III, Ed.; Plenum: New York, 1976; pp 1–28.
10. Shao, Y.; and 65 co-workers. *Phys. Chem. Chem. Phys.* **2006**, *8*, 3172.
11. Still, W. A.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127–6129; Onufriev, A.; Bashford, D.; Case, D. A. *J. Comput. Chem.* **2002**, *23*, 1297.
12. Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz Jr, K. M.; Ferguson, D. M.; Spellmeyer, D. C.; Fox, T.; Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 5179.
13. All new compounds have spectral and analytical data in agreement with the indicated structures. *Compound* **1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (3H, s), 4.01 (3H, s), and 7.40 (3H, m), and 7.55 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ (attached H's) 164.2 (0), 150.6 (0), 130.5 (1), 130.2 (0), 128.9 (2C, 0), 126.3 (2C, 0), 63.1 (3), 52.5 (3). HRMS calcd m/z for $C_{10}H_{12}NO_3$ 194.0817 $(M+H)^+$, found 194.0811. *Compound* **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (3H, s), 4.05 (3H, s), and 7.40 (5H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ (attached H's) 164.0 (0), 149.2 (0), 129.7 (1), 129.2 (2C, 0), 129.5 (0), 128.1 (2C, 0), 63.8 (3), and 53.1 (3). HRMS calcd m/z for $C_{10}H_{12}NO_3$ 194.0817 $(M+H)^+$, found 194.0810. *Compound* **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (3H, s), 7.43 (3H, m), and 7.65 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ (attached H's) 63.3 (3), 126.5 (2C, 1), 128.8 (2C, 1), 129.8 (0), 130.6 (0), 149.6 (0), and 167.4 (0). HRMS calcd m/z for $C_9H_{10}NO_3$ 180.0660 $(M+H)^+$, found 180.0654. *Compound* **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (3H, s), 7.43 (3H, m), and 7.49 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) (attached H's) δ 64.3 (3), 127.4 (0), 128.0 (2C, 1), 129.6 (2C, 1), 130.3 (1), 147.4 (0), and 162.7 (0). HRMS calcd m/z for $C_9H_{10}NO_3$ 180.0661 $(M+H)^+$, found 180.0654.