Synthesis of 3-Acetoxyacetanilide Derivatives by means of Semmler–Wolff-type Aromatization Reaction of Cyclohexane-1,3-dione Monooximes

Teruhiko Ishikawa,*[1,2] Masaki Arai,[1] Hironori Nishiuchi,[2] Hiroshi Ishiguro,[2] and Seiki Saito*[1]
[1]*Department of Medical and Bioengineering Science, Graduate School of Natural Science and Technology, Okayama University, Tsushima, Okayama 700-8530*
[2]*Graduate School of Education, Okayama University, Tsushima, Okayama 700-8530*

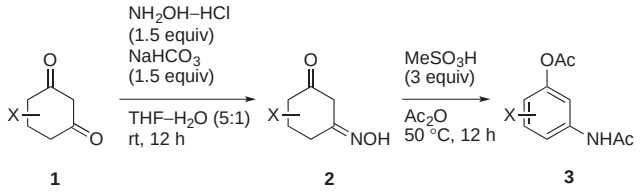
(Received July 22, 2008; CL-080710; E-mail: teruhiko@cc.okayama-u.ac.jp)

A novel method for synthesizing 3-acetoxyaniline derivatives from substituted cyclohexane-1,3-diones is described. This synthetic process includes regioselective formation of cyclohexane-1,3-dione monooximes **2** and their Semmler–Wolff-type aromatization under very simple reaction conditions.

Aniline derivatives are very significant synthetic intermediates for pharmaceuticals and agrochemicals, and development of new methods for aniline synthesis is still important in organic synthesis, particularly in industrial disciplines because of their broad applicability. In general, substituted anilines have been synthesized by the reduction of nitroarenes given through the nitration of aromatic rings.[1] Although this method has been used most commonly, there emerge some problems when applied to selective organic synthesis: the regioselectivity of nitration of substituted benzenes is not so high, and the desired introduction of a nitro group is sometimes deteriorated owing to unwanted orientation dictated by the nature of ring substituents.[1] The Friedel–Crafts acylation or alkylation of simple anilines is also a method for synthesizing substituted anilines, which, however, often suffers from disadvantage that Lewis acid catalysts are deactivated by their coordination to an amino group.[1]

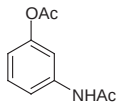
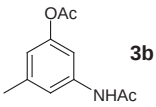
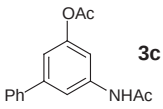
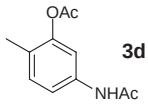
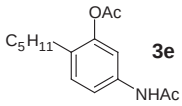
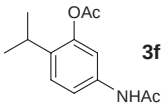
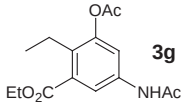
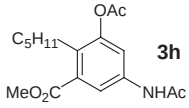
The Semmler–Wolff aromatization reaction (SWAR)[2,3] has also been known for anilines synthesis, which involves the isomerization reaction of α,β-unsaturated cyclohexanone oximes to aromatic amines under acidic conditions. This method was previously improved by Kita et al.,[3b,3c] and partially utilized as a key step in natural product synthesis.[4] However, SWAR has not been established as a versatile and standard method for aniline synthesis because of small availability of substituted cyclohexenones and their oxime derivatives.

During the course of our studies on the synthetic potential of cyclohexane-1,3-diones,[5] we have discovered a novel method for synthesizing aniline derivatives via direct aromatization of cyclohexane-1,3-dione oximes, which is outlined in Scheme 1, in which extremely simple reagents and conditions are used. For instance, cyclohexane-1,3-diones **1** are commercially available or easily synthesized by the chemoselective Michael–Claisen cascade reaction of simple ketones and α,β-unsaturated esters.[5a] The diones can be converted to mono-oximes **2** in a conventional way (NH_2OH–HCl, $NaHCO_3$/THF, rt). Treating



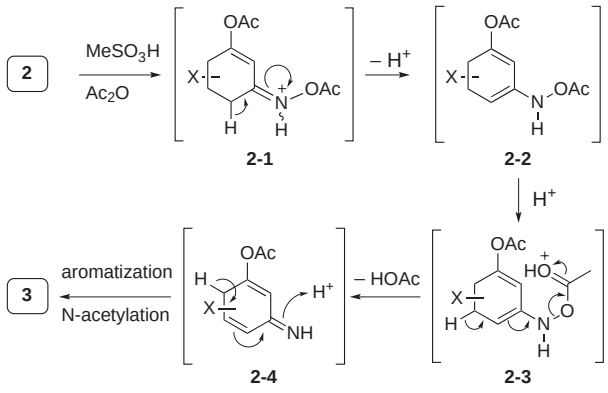
Scheme 1. Synthesis of 3-acetoxyacetanilides from cyclohexane-1,3-dione via its monooxime.

Table 1. Results for 3-acetoxyacetanilide synthesis from cyclohexane-1,3-diones[a]

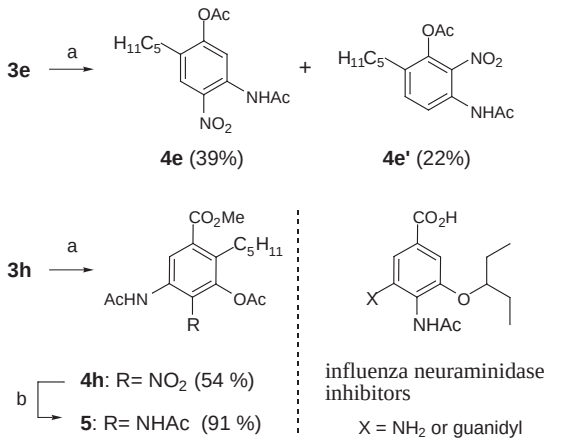
Entry	X of dione **1**	Yield of oxime **2**/%[b]	Product		Yield of **3**/%[b,c]
1	H	72		**3a**	48
2	5-Me	75		**3b**	50
3	5-Ph	78		**3c**	65
4	4-Me	70		**3d**	50
5	4-pentyl	74		**3e**	65
6	4-*i*-Pr	72		**3f**	51
7	4-Et 5-CO_2Et	73		**3g**	31
8	4-pentyl 5-CO_2Me	71		**3h**	71

[a]Conditions: NH_2OH–HCl (1.5 equiv), $NaHCO_3$ (1.5 equiv), THF–H_2O (5:1), rt, 12 h for **1** → **2**; $MeSO_3H$ (3 equiv), Ac_2O, 50 °C, 12 h for **2** → **3**. [b]For product isolated by SiO_2 column chromatography. [c]Yield for **2** → **3**.

Copyright © 2008 The Chemical Society of Japan



Scheme 2. Plausible reaction mechanism.



Scheme 3. Nitrations of acetoxyacetanilide **3**: (a) NH_4NO_3, $(CF_3CO)_2O/CHCl_3$; (b) Zn–6 M HCl/THF then Ac_2O and $NaHCO_3$.

thus-obtained oximes **2** with acetylating reagent such as acetic anhydride in the presence of methanesulfonic acid (3.0 equiv) led to 3-acetoxyacetanilides **3** in an acceptable yield and purity. Successful results for the synthesis of **3** from **1** are summarized in Table 1.

The regioselective formation of monooxime from dissymmetrical diones was effected under the given reaction conditions to afford the one of sterically less congested carbonyl group (Entries 4–8). Subsequent SWAR-type reactions smoothly proceeded to obtain substituted 3-acetoxyacetanilides **3** in an acceptable yield.[6] Only two steps were required for the conversion of **1** to **3**. For every entry, seven-membered lactam expected via possible Beckmann rearrangement was not detected at all. While previous SWAR of cyclohexenone oximes generally required high temperature (over 100 °C) in the presence of excessive strong acid such as hydrogen chloride, concd hydrochloric acid, polyphosphoric acid (PPA), concd sulfuric acid, and so forth,[2] the present aromatization reaction proceeds under much milder conditions (50 °C) by using acetic anhydride and methanesulfonic acid. In addition, the present synthesis of 3-acetoxyacetanilides should be highly profitable to organic synthesis because meta-oriented introduction of a nitro group to phenols or a hydroxy group to anilines are well known to be energetically highly unfavorable reaction pathway.

Plausible route from **1** to **3** can be described by modifying previous SWAR mechanism as shown in Scheme 2.[3d] Both enol and oxime functions of **2** could be acetylated under the employed reaction conditions to afford 3-acetoxycyclohexanone oxime acetate such as **2-1**, which could lead to enamine intermediate **2-2**. On protonation of *N*-acetoxy group (**2-3**), an acetic acid unit would depart via 1,4-elimination to end up with the formation of iminodiene **2-4**.[5b] The final aromatization process from **2-4** may be triggered by N-protonation and thus-generated amino group would be acetylated by acetic anhydride to afford the acetoanilide **3** although direct acetylation of imine cannot be ruled out.

In Scheme 3 is outlined the further aromatic ring functionalizations of 3-acetoxyacetanilide such as **3e** or **3h** obtained by the present method. For example, nitration of **3e** with ammonium nitrate in the presence of trifluoroacetic anhydride afforded the separable mixture of **4e** and **4e′** in moderate yield. On the other hand, highly regioselective nitration of aromatic ring for **3h** was effected to obtain **4h** in moderate yield (54%), which was converted to **5** sequentially through reduction followed by acetylation because of the structure similarity of **5** to anilines derivatives of biological interest such as a potent influenza neuraminidase inhibitor and its analogue.[7]

In conclusion, we have developed the novel chemical process for converting cyclohexan-1,3-dione-based mono-oximes **2** to 3-acetoxyaniline derivatives **3** by the Semmler–Wolff-type aromatization protocol operated under mild conditions.[9] Since we can easily prepare diverse cyclohexane-1,3-diones relying on Michael–Claisen cascade reactions,[5] the present synthesis would become highly attractive in diversity-oriented organic synthesis.[8]

References and Notes

1 For example, see: J. March, in *Advanced Organic Chemistry*, 3rd ed., Wiley-Interscience Publication, **1985**, Chap. 11.
2 a) F. W. Semmler, *Ber.* **1892**, *25*, 3352. b) L. Wolff, *Ann.* **1902**, *322*, 351.
3 a) M. I. El-Sheikh, J. M. Cook, *J. Org. Chem.* **1980**, *45*, 2585. b) Y. Tamura, Y. Yoshimoto, K. Sakai, Y. Kita, *Synthesis* **1980**, 483. c) Y. Tamura, Y. Yoshimoto, K. Sakai, J. Haruta, Y. Kita, *Synthesis* **1980**, 887. d) L. Bauer, R. E. Hewitson, *J. Org. Chem.* **1962**, *27*, 3982.
4 For example, see: a) J. P. Davidson, E. J. Corey, *J. Am. Chem. Soc.* **2003**, *125*, 13486. b) J. Haseltine, M. Visnick, A. B. Smith, III, *J. Org. Chem.* **1988**, *53*, 6160.
5 a) T. Ishikawa, R. Kadoya, M. Arai, H. Takahashi, Y. Kaisi, T. Mizuta, K. Yoshikai, S. Saito, *J. Org. Chem.* **2001**, *66*, 8000. b) T. Ishikawa, T. Miyahara, M. Asakura, S. Higuchi, Y. Miyauchi, S. Saito, *Org. Lett.* **2005**, *7*, 1211.
6 Only a trace amount of **3** was detected for the reactions of monooximes prepared from 2-methylcyclohexane-1,3-dione and 4,6-dimethylcyclohexane-1,3-dione under the reaction conditions.
7 V. R. Atigadda, W. J. Brouillette, F. Duarte, Y. S. Babu, S. Bantia, P. Chand, N. Chu, J. A. Montgomery, D. A. Walsh, E. Sudbeck, J. Finley, G. M. Air, M. Luo, G. W. Laver, *Bioorg. Med. Chem.* **1999**, *7*, 2487.
8 S. L. Schreiber, *Science* **2000**, *287*, 1964.
9 Supporting Information is also available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

Published on the web (Advance View) September 13, 2008; doi:10.1246/cl.2008.1066