Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 3167–3169

TETRAHEDRON
LETTERS

New transformations of 2-nitro-2,3-dihydrofurans to multi-functionalized dihydrofurans

Jih Ru Hwu,* Thota Sambaiah and Subhasish K. Chakraborty

Organosilicon and Synthesis Laboratory, Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan 30013, ROC

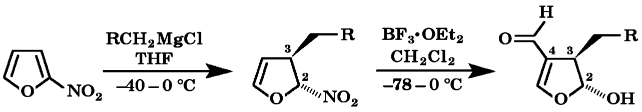
Received 5 December 2002; revised 12 February 2003; accepted 20 February 2003

Abstract—A new type of transformation of 2-nitro-3-substituted-dihydrofurans to 4-formyl-2-hydroxy-3-substituted-2,3-dihydrofurans was accomplished in 63–84% yields by use of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78 to 0°C. © 2003 Elsevier Science Ltd. All rights reserved.

Multi-substituted dihydrofurans are valuable intermediates in the syntheses of natural products[1–7] and pharmaceuticals.[8–11] Considerable attention has been focused on the development of efficient and regioselective methods for their preparation.[12] Nevertheless, to the best of our knowledge, there is limited literature information hitherto on the synthesis of dihydrofurans bearing a C-4 formyl and a C-2 hydroxyl groups with various substituents at the C-3 position. On the other hand, nitro compounds are readily available and play a vital role in organic synthesis.[13–15] Herein we report a highly diastereoselective method for the synthesis of such functionalized dihydrofurans from 2-nitrofuran.

By treating 2-nitrofuran (**1**) with a Grignard reagent in THF at −40–0°C for 1.0 h, we obtained the corresponding adducts (i.e., **2a**–**f**) in 58–68% yields after purification with chromatography (Scheme 1). Among various Lewis acids including $AlCl_3$, $BF_3{\cdot}OEt_2$, $SnCl_4$, and $TiCl_4$, we found that $BF_3{\cdot}OEt_2$ functioned more efficiently than others for the conversion of nitro compound **2a** to 4-formyl-2-hydroxy-2,3-dihydrofuran **3a**. Thus **2a** was allowed to react with 2.0 equiv. of $BF_3{\cdot}OEt_2$ in dichloromethane at −78 to 0°C within 30 min. The resultant was purified by chromatography with silica gel to give a pure colorless oil with exact mass 204.0775 in 82% yield. The structure of this new compound **3a** was assigned on the basis of the following spectroscopic data.

Compound **3a** exhibited a characteristic singlet at 9.94 ppm in its ^1H NMR spectrum, a peak at 185.52 ppm in its ^{13}C NMR spectrum, as well as one strong and one medium peaks at 1695 and 1571 cm^{-1}, respectively, in its IR spectrum. These data clearly indicate the presence of an α,β-unsaturated aldehydic group. Furthermore, we observed a doublet CH proton at 5.71 ppm with $^3J = 1.5$ Hz, a CH carbon at 104.51 ppm, and an IR peak at 3380 cm^{-1}. Accordingly, we assigned the CH moiety attached to a hydroxyl group and an oxygen atom (i.e. the C-2 carbon). In addition, the product showed two doublets of doublet for the prochiral CH_2Ph protons at 2.54 ppm ($^2J = 14.4$ and $^3J = 11.0$ Hz) and 3.19 ppm ($^2J = 14.4$ and $^3J = 4.3$ Hz), respectively, the O=C–C=CH–O proton at 4.53–5.34 ppm,[16] and two sp^2 carbons at 136.67 and 161.79 ppm.



1 2 3

	R =	% yield of 2	% yield of 3	trans/cis
a:	Ph	68	82	9 : 1
b:	*o*-MeC_6H_5	65	80	12 : 1
c:	*p*-BrC_6H_5	60	84	7.3 : 1
d:	1-Naphthyl	62	78	16 : 1
e:	*i*-Pr	58	78	trans only
f:	CH_2Ph	64	74	trans only

Scheme 1. Conditions and yields for the conversions of 2-nitrofuran (**1**) to 4-formyl-2-hydroxy-3-substituted-2,3-dihydrofurans **3** via 2-nitro-2,3-dihydrofurans **2**.

---

* Corresponding author. Tel.: +886-3-572-5813; fax: +886-3-572-1594; e-mail: jrhwu@mx.nthu.edu.tw

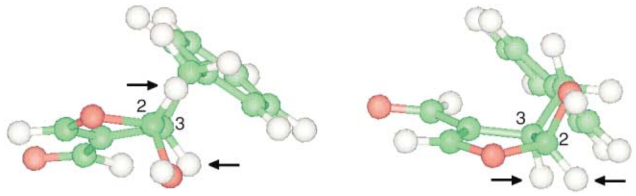
doi:10.1016/S0040-4039(03)00463-5

To determine the relative stereoconfiguration for the C-2 and the C-3 centers of 4-formyl-2-hydroxy-3-substituted-2,3-dihydrofurans, we performed the CVFF calculations to obtain their molecular geometry (e.g. see Scheme 2). The H–C_2–C_3–H dihedral angle was 108° for the thermodynamically most stable conformational isomer of *trans*-**3a**, of which the total energy was 52.8237 kcal/mol. The ^3J value was calculated as 1.49 Hz by use of the Karplus equation.[17] By the same computational methods, this dihedral angle was determined as 22° for the corresponding *cis* isomer. The ^3J value therein was calculated as 8.9 Hz. Our experimental results showed that the allylic proton at C-3 exhibited a doublet of doublet of doublet with $^3J = 11.0$, 4.3, and 1.5 Hz at 3.60 ppm. The value of 1.5 Hz consists well with $^3J_{\text{calcd}}$ 1.49 Hz associated with the *trans* isomer.

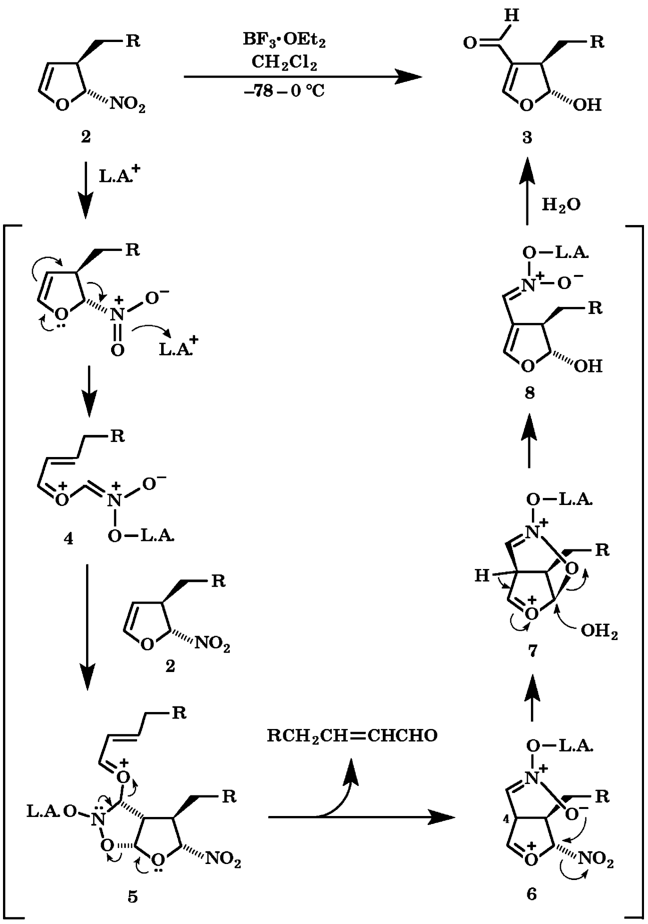
By following the same synthetic strategy, we converted **2b**–**f** to **3b**–**f** in 74–84% yields, respectively. The structures of these new compounds were fully determined by ^{1}H, ^{13}C NMR, and IR spectroscopic methods. These compounds include a phenyl moiety attached with an electron-donating (i.e. *o*-Me) or -withdrawing group (i.e. *p*-Br), a naphthyl moiety, an alkyl (i.e. *i*-Pr) and an aralkyl (i.e. benzyl) moieties for the R in **3**. For the reactions producing **3a**–**d**, we also detected a trace amount of the corresponding *cis* isomers. Their structures were determined by ^{1}H NMR techniques. The ratios of *trans*/*cis* ranged from 7.3:1 to 16:1 (see Scheme 1). Products **3e** and **3f** with a *trans* configuration, however, were generated as the exclusive products.

The current results are in marked contrast to those in previously reported reactions where only nitro substrates with an organosilylmethyl group at the C-3 position of **2** give products **3**.[18] In those reactions, γ-silyl groups therein can easily depart from nitro compounds under acidic conditions.[19] In the present work, the limitation of the reaction is improved; the substrates bearing an aryl or alkyl substituents at the same position can be successfully converted to **3** as well. Nevertheless, the present reactions required harsher conditions, including a higher temperature (0°C versus −40°C)[18] and longer time (30 min versus 15 min).

The mechanism for this new transformation is shown in Scheme 3, which involves the extrusion of an aryl or alkyl crotonaldehyde, not crotonaldehyde itself from γ-silyl nitro substrates. For example, in the conversion of **2d**→**3d**, naphthyl aldehyde $C_{10}H_7CH_2CH{=}CHCHO$ was detected by GC–mass spectrometer as a by-product.



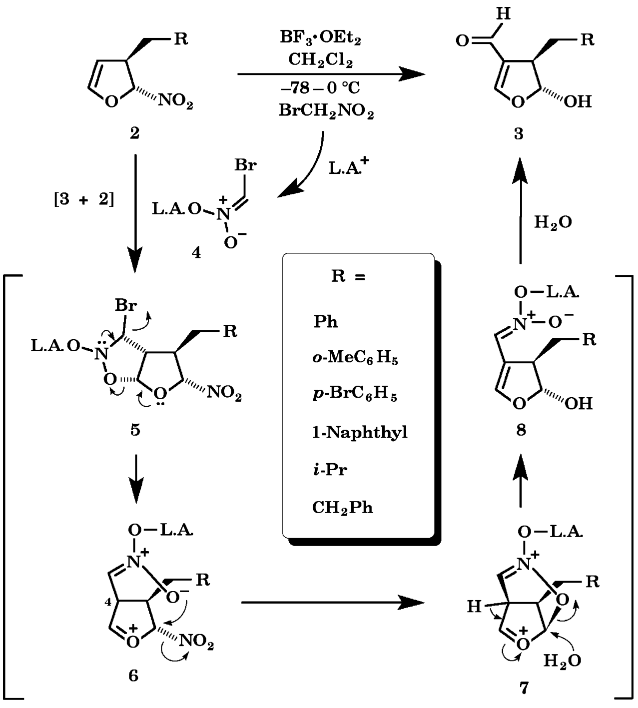
Scheme 2. The thermodynamically most stable conformational isomers, obtained by the CVFF calculations, for *trans*-**3a** (left) with dihedral angle $\phi = 108°$ for the H–C_2–C_3–H and the corresponding *cis* isomer (right) with $\phi = 22°$.



Scheme 3. A proposed mechanism for the conversion of 2-nitro-2,3-dihydrofurans **2** to 4-formyl-2-hydroxy-3-substituted-2,3-dihydrofurans **3** upon Lewis acid treatment.

In Scheme 3, the substrates **2** served as a dipole at the nitro group and as a dipolarphile at the olefinic part of the dihydrofuran ring. Therefore, in one reaction, two molar amounts of the starting material **2** would be required to produce one molar amount of **3**, in which the formyl carbon came from the second molecule of 2-nitro-2,3-dihydrofurans. To circumvent this disadvantage, we considered an intriguing way by applying a commercially available reagent bromonitromethane as the 'formyl group supplier'. Accordingly, the transformation of 2-nitrodihydrofurans **2** to 4-formyl-2-hydroxy-2,3-dihydrofurans **3** could be accomplished with the aid of bromonitromethane as shown in Scheme 4. In this new transformation, bromonitromethane would be a 1,3-dipole bearing a good leaving group. Its participation in the reaction media should allow us to save the second equivalent of 2-nitro-2,3-dihydrofurans **2**.

To support this hypothesis, we treated **2a**–**f** with 1.0 equiv. of commercially available $BrCH_2NO_2$ in the presence of 1.0 equiv. of $BF_3{\cdot}OEt_2$[20] in dichloro-



Scheme 4. A proposed mechanism for the conversion of 2-nitro-2,3-dihydrofurans **2** to 4-formyl-2-hydroxy-3-substituted-2,3-dihydrofurans **3** upon Lewis acid treatment.

methane at −78 to 0°C for 60 min. The desired products **3a**–**f** were produced in 72, 70, 73, 63, and 68% yields, respectively, after purification with column chromatography packed with silica gel. In these reactions, we obtained **3** in the *trans* form only.

A plausible, but not exclusive, mechanism shown in Scheme 4 could account for the unprecedented transformation of **2** to **3**. It involves sequential [3+2] cycloaddition between dihydrofurans **2** and the nitronate **4**,[21,22] fragmentation of heterobicycles **5**, intramolecular cyclization of **6**,[13c] ring opening of bridged intermediates **7**, and the Nef reaction of nitronates **8**. The C_4 carbon of the intermediates **6** is allylic to the nitronate and the oxonium functionalities; as a result, it is epimerizable.

In conclusion, new transformations were established for the conversion of 2-nitro-3-substituted-2,3-dihydrofurans to 4-formyl-2-hydroxy-3-substituted-2,3-dihydrofurans. These transformations, requiring only simple manipulation by use of $BF_3\cdot OEt_2$, can be applied to the synthesis of multi-functionalized dihydrofurans from readily available 2-nitrofurans.

Acknowledgements

For financial support, we thank the National Science Council of Republic of China.

References

1. Lee, Y. R.; Kim, N. S.; Kim, B. S. *Tetrahedron Lett.* **1997**, *38*, 5671.
2. Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195.
3. Smith, A. B., III; Sestelo, J. P.; Dormer, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 10755.
4. Crimmins, M. T.; Jung, D. K.; Gray, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 3146.
5. Palmisano, G.; Danieli, B.; Lesma, G.; Passarella, D.; Toma, L. *J. Org. Chem.* **1991**, *56*, 2380.
6. Hudlicky, T.; Barbieri, G. *J. Org. Chem.* **1991**, *56*, 4598 and references cited therein.
7. Vogel, P.; Fattori, D.; Gasparini, F.; Drian, C. L. *Synlett* **1990**, 173.
8. Anies, C.; Pancrazi, A.; Lallemand, J.-Y. *Tetrahedron Lett.* **1995**, *36*, 2075.
9. Anies, C.; Pancrazi, A.; Lallemand, J.-Y. *Tetrahedron Lett.* **1994**, *35*, 7771.
10. Stojanac, N.; Valenta, Z. *Can. J. Chem.* **1991**, *69*, 853.
11. Nagashima, S.; Kanematsu, K. *Tetrahedron: Asymmetry* **1990**, *1*, 743.
12. For recent representative works, see: (a) Davies, H. M. L.; Ahmed, G.; Calvo, R. L.; Churchill, M. R.; Churchill, D. G. *J. Org. Chem.* **1998**, *63*, 2641; (b) Arai, S.; Nakayama, K.; Suzuki, Y.; Hatano, K.-i.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 9739; (c) Lee, Y. R.; Kim, B. S. *Tetrahedron Lett.* **1997**, *38*, 2095; (d) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180; (e) Hojo, M.; Ohkuma, M.; Ishibashi, N.; Hosomi, A. *Tetrahedron Lett.* **1993**, *34*, 5943.
13. For reviews, see: (a) Ono, N. *The Nitro Group in Organic Synthesis*; John Wiley, 2001; (b) Tafesh, A. M.; Weiguny, J. *Chem. Rev.* **1996**, *96*, 2035; (c) Barrett, A. G. M. *Chem. Soc. Rev.* **1991**, *20*, 95; (d) Ono, N. *Nitro Compounds*; Feuer, H.; Nielsen, A. T., Ed.; VCH: New York, 1990; Chapter 1 and references cited therein; (e) Wade, P. A.; Giuliano, R. M. *Nitro Compounds*; Feuer, H.; Nielsen, A. T., Ed.; VCH: New York, 1990; Chapter 2 and references cited therein.
14. Beck, A. K.; Seebach, D. *Chem. Ber.* **1991**, *124*, 2897.
15. Seebach, D.; Missbach, M.; Calderari, G.; Eberle, M. *J. Am. Chem. Soc.* **1990**, *112*, 7625.
16. Kondo, Y.-t.; Ge, S.; Katsumura, S.; Nakatani, K.; Isoe, S. *Tetrahedron* **1993**, *49*, 10555.
17. Richards, S. A. *Laboratory Guide to Proton NMR Spectroscopy*; Blackwell: London, 1988; p. 118.
18. Hwu, J. R.; Sambaiah, T.; Liao, J.-H.; Chen, K.-L.; Wen, Y.-S. *Org. Lett.* **2001**, *3*, 4267.
19. Horng, D.-N.; Chen, K.-L.; Hwu, J. R. *Tetrahedron* **2000**, *56*, 1631.
20. Lanfranchi, M.; Pellinghelli, M. A.; Predieri, G.; Bigi, F.; Maggi, R.; Sartori, G. *J. Chem. Soc., Dalton Trans.* **1993**, 1463.
21. Righi, P.; Marotta, E.; Landuzzi, A.; Rosini, G. *J. Am. Chem. Soc.* **1996**, *118*, 9446.
22. Barco, A.; Benetti, S.; Pollini, G. P.; Spalluto, G.; Zanirato, V. *Tetrahedron Lett.* **1991**, *32*, 2517.