One-pot Synthesis of Furo[3,2-*c*]oxepin-4-one Derivatives by the CAN-mediated Reaction of *tert*-Butyl 2-(2-Hydroxytetrahydrofuran-2-yl)acetates with Alkenes

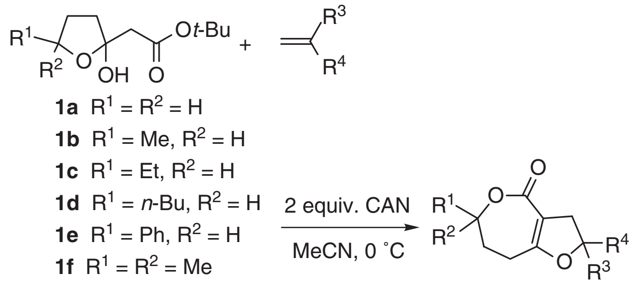
Kazuhiro Kobayashi,* Hironobu Umakoshi, Kazutaka Hayashi, Osamu Morikawa, and Hisatoshi Konishi
Department of Materials Science, Faculty of Engineering, Tottori University, Koyama-minami, Tottori 680-8552

(Received September 16, 2004; CL-041089)

The reaction of *tert*-butyl 2-(2-hydroxytetrahydrofuran-2-yl)acetates with alkenes in the presence of 2 equivalents of cerium(IV) ammonium nitrate (CAN) is presented. 2,3,7,8-Tetrahydrofuro[3,2-*c*]oxepin-4(6*H*)-ones were formed in moderate to fair yields via 3+2-type dihydrofuran formation, followed by lactonization.

In our ongoing efforts[1] on the development of dihydrofuran-fused polycyclic compounds utilizing the CAN-mediated 3+2-type cycloaddition of 1,3-dicarbonyls and related compounds with alkenes,[2] we wished to investigate the possibility of preparing 2,3,7,8-tetrahydrofuro[3,2-*c*]oxepin-4(6*H*)-ones **2** in one-pot from *tert*-butyl 2-(2-hydroxytetrahydrofuran-2-yl)acetates **1**, which are known to be equilibrated with the corresponding 6-hydroxy-3-oxoalkanoates **3** in solution,[3] and alkenes. In this paper, we wish to report our findings regarding the application of the CAN-mediated dihydrofuran formation, which offer a simple and general method for preparing furooxepinone derivatives **2**. Although this class of compounds is potentially interesting from a biological point of view, there have been a few reports on their synthesis, and the methods are quite limited and are of low generality.[4]

The starting materials, *tert*-butyl 2-(2-hydroxytetrahydrofuran-2-yl)acetates **1**, were conveniently synthesized in good yields by reacting *tert*-butyl acetate lithium enolate with γ-lactones, as reported by one of the present authors.[1] The reactions between **1** and alkenes in the presence of two equivalents of CAN were conducted in acetonitrile at 0 °C to afford 2,3,7,8-tetahydrofuro[3,2-*c*]oxepin-4(6*H*)-ones **2** as shown in Scheme 1. Initially, **1a** was allowed to react with α-methylstyrene derivatives. The reactions were complete within 3 h and the desired furo[3,2-*c*]oxepin-4-ones **2a**–**2c** were isolated in fair yields by preparative TLC on silica gel after usual workup. It was found that 1,1-diphenylethene was sufficiently reactive to afford the desired product **2d** in the best yield. In order to investigate the limitation of applicability of alkenes, styrene and 2-ethyl-1-butene were reacted with **1a**. The former gave the desired product **2e** in rather diminished yield, and the latter gave the desired product **2f** in further lower yield. Attempts to apply the same procedure to the 2-(2-hydroxytetrahydrofuran-2-yl)acetates carrying a substituent at the 5-position of the tetrahydrofuran ring **1b**–**1e** were made. In the event, the reactions of these starting materials with 1,1-diphenylethene resulted in the formation of the corresponding desired products **2g**–**2j** in the yields nearly equal to that of **2d**. It was possible to form the desired product **2k** by treating 2-(2-hydroxytetrahydrofuran-2-yl)acetates carrying two methyl groups at the 5-position of the tetrahydrofuran ring **1f** with 1,1-diphenylethene. However, the isolated yield was somewhat inferior to those of **2d** and **2g**–**2j**. The increasing steric bulk is probably responsible for the decrease of the yield.



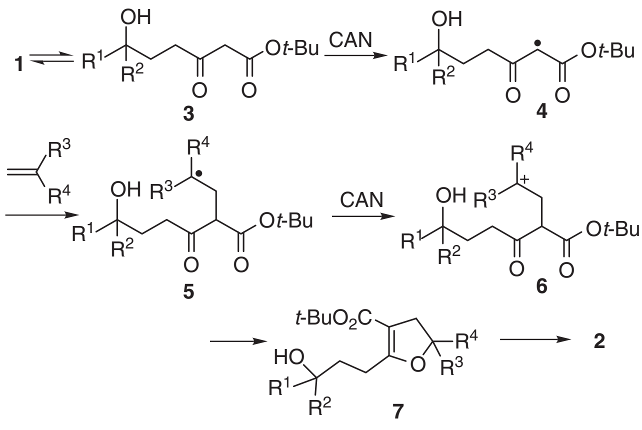
1a $R^1 = R^2 = H$
1b $R^1 = Me, R^2 = H$
1c $R^1 = Et, R^2 = H$
1d $R^1 = n\text{-}Bu, R^2 = H$
1e $R^1 = Ph, R^2 = H$
1f $R^1 = R^2 = Me$

2a $R^1 = R^2 = H, R^3 = Ph, R^4 = Me$ 46%
2b $R^1 = R^2 = H, R^3 = 4\text{-}FC_6H_4, R^4 = Me$ 42%
2c $R^1 = R^2 = H, R^3 = 4\text{-}ClC_6H_4, R^4 = Me$ 44%
2d $R^1 = R^2 = H, R^3 = R^4 = Ph$ 56%
2e $R^1 = R^2 = R^3 = H, R^4 = Ph$ 28%
2f $R^1 = R^2 = H, R^3 = R^4 = Et$ 22%
2g $R^1 = Me, R^2 = H, R^3 = R^4 = Ph$ 55%
2h $R^1 = Et, R^2 = H, R^3 = R^4 = Ph$ 54%
2i $R^1 = n\text{-}Bu, R^2 = H, R^3 = R^4 = Ph$ 52%
2j $R^1 = Ph, R^2 = H, R^3 = R^4 = Ph$ 52%
2k $R^1 = R^2 = Me, R^3 = R^4 = Ph$ 41%

Scheme 1.

The preparation of 2-methyl-2-phenyl-2,3,7,8-tetrahydrofuro[3,2-*c*]oxepin-4(6*H*)-one (**2a**) is representative. To a stirred solution of **1a** (0.24 g, 1.2 mmol) and α-methylstyrene (0.43 g, 3.6 mmol) in acetonitrile (15 mL) at 0 °C was added CAN (1.3 g, 2.4 mmol) portionwise. After 3 h stirring saturated aqueous NH_4Cl (15 mL) was added. The resulting mixture was stirred for an additional 30 min and extracted with Et_2O three times (15 mL each). The combined extracts with washed with aqueous $NaHCO_3$ and then brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified using preparative TLC on silica gel (3:1 hexane–EtOAc) to give **2a** (0.13 g, 46%).[5]

The probable pathway to furooxepinone derivatives **2** is outlined in Scheme 2, and the dihydrofuran formation is essentially parallel to that demonstrated in our earlier reports on the formation of fused furan derivatives.[2] Thus, the abstraction of 2-H of the keto ester **3**, equilibrated with 2-(2-hydroxytetrahydrofuran-2-yl)acetates **1**, with CAN, forming the radical intermediate **4**, is followed by its addition to an alkene to give the second radical intermediate **5**. This is oxidized with the second molecule of CAN to the cationic intermediate **6**, which undergoes an intramolecular cyclization, probably via its enol form, to result in formation of the dihydrofuran derivative **7**. Lactonization of **7** in the acidic media takes place to provide **2**. The lower yields of **2e** and **2f** are thought to be attributable to the low stability of the corresponding intermediates **5** and **6**. The generally modest yields of **2** may be ascribed to the lability of **1** to dehydration under reaction



Scheme 2.

conditions.

In conclusion, we have been able to show that the CAN-mediated reactions of *tert*-butyl 2-(2-hydroxytetrahydrofuran-2-yl)acetates with alkenes provide a general method to prepare 2,3,7,8-tetrahydrofuro[3,2-*c*]oxepin-4(6*H*)-ones. Although the yields of the products are not so high, this method is useful because of its efficiency, the readily availability of the starting materials and the ease of operation. Works on investigating the possibility of preparing dihydrofuran-fused lactones having other ring sizes are currently in progress in our laboratory.

We wish to express our appreciation to Mrs. Miyuki Tanmatsu of this department for her support in determining the MS spectra and performing combustion analyses. This work was partially supported by a Grant-in-Aid for Scientific Research (C) No. 15550092 from Japan Society for the Promotion of Science.

References and Notes

1 K. Kobayashi, M. Mori, T. Uneda, O. Morikawa, and H. Konishi, *Chem. Lett.*, **1996**, 451; K. Kobayashi, T. Uneda, K. Tanaka, M. Mori, H. Tanaka, O. Morikawa, and H. Konishi, *Bull. Chem. Soc. Jpn.*, **71**, 1691 (1998); K. Kobayashi, K. Sakashita, H. Akamatsu, K. Tanaka, M. Uchida, T. Uneda, T. Kitamura, O. Morikawa, and H. Konishi, *Heterocycles*, **51**, 2881 (1999); K. Kobayashi, H. Tanaka, K. Tanaka, K. Yoneda, O. Morikawa, and H. Konishi, *Synth. Commun.*, **30**, 4277 (2000); K. Kobayashi, K. Nagase, O. Morikawa, and H. Konishi, *Heterocycles*, **60**, 939 (2003).

2 Many reagents, including CAN and $Mn(OAc)_3$, have been used as a mediator for the cycloaddition reaction of 1,3-dicarbonyl and related compounds with alkenes forming 1,2-dihydrofuran derivatives. For earlier works: W. J. De Klein, "Organic Syntheses by Oxidation with Metal Compounds," ed. by W. J. Mijs and C. R. H. I. de Jonge, Plenum Press, New York (1986), Chapter 4; For recent reviews: V. Nair, J. Matthew, and J. Prabhakaran, *Chem. Soc. Rev.*, **26**, 127 (1997); J. Iqval and M. Mukhopadhyay, *Synlett*, **1997**, 876; For more recent reports: Y. R. Lee, J. Y. Suk, and B. S. Kim, *Org. Lett.*, **2**, 1387 (2000); Y. R. Lee, B. S. Kim, and H. I. Kweon, *Tetrahedron*, **56**, 3867 (2000); G. Bar, A. F. Parsons, and C. B. Thomas, *Tetrahedron Lett.*, **41**, 7751 (2000); Y. R. Lee, B. S. Kim, and D. H. Kim, *Tetrahedron*, **56**, 8845 (2000); S. Kajiwara, H. Nishino, and K. Kurosawa, *Heterocycles*, **54**, 171 (2001); Y. R. Lee and B. S. Kim, *Synth. Commun.*, **31**, 381 (2001); G. Bar, A. F. Parsons, and C. B. Thomas, *Chem. Commun.*, **2001**, 1350; M. Yilmaz and A. T. Pekel, *Synth. Commun.*, **31**, 2189 (2001); G. Bar, A. F. Parsons, and C. B. Thomas, *Tetrahedron*, **57**, 4719 (2001); V. Nair, P. M. Treesa, D. Maliakal, and N. P. Rath, *Tetrahedron*, **57**, 7705 (2001); S. Muthusamy, C. Gunanathan, and S. A. Babu, *Synlett*, **2002**, 787; Y. R. Lee, B. S. Kim, Y. U. Yung, W. S. Koh, J. S. Cha, and N. W. Kim, *Synth. Commun.*, **32**, 3099 (2002); M. C. S. de-Mattos, S. P. L. de-Souza, and S. M. Elias, *Heterocycl. Commun.*, **9**, 247 (2003); Y. R. Lee, K. Y. Kang, G. J. Lee, and W. K. Lee, *Synthesis*, **2003**, 1977; N. N. Karade, S. G. Shirodkar, M. N. Patil, R. A. Potrekar, and H. N. Karade, *Tetrahedron Lett.*, **44**, 6729 (2003); R. Kumabe and H. Nishino, *Heterocycl. Commun.*, **10**, 135 (2004); V. Jadhav, M. Y. Park, and Y. H. Kim, *Synthesis*, **2004**, 329 and references cited therein.

3 K. Kobayashi, H. Minakawa, H. Sakurai, S. Kujime, and H. Suginome, *J. Chem. Soc., Perkin Trans. 1*, **1993**, 3007.

4 Previous syntheses of furo[3,2-*c*]oxepin-4-one derivatives: D. P. Curran, T. M. Morgan, C. E. Schwartz, B. B. Snider, and M. A. Dombroski, *J. Am. Chem. Soc.*, **113**, 6607 (1991); H. A. Stefani, N. Petragnani, C. J. Valduga, and S. A. Brandt, *Teterahedron Lett.*, **38**, 4977 (1997); A. Lattanzi, P. Iannece, and A. Scettri, *Teterahedron Lett.*, **40**, 3899 (1999).

5 All new products gave satisfactory spectral and analytical data. Physical and spectral data for **2** follow. **2a**: R_f 0.29 (3:1 hexane–EtOAc); IR (neat) 1738, 1674 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.70 (3H, s), 2.10 (2H, quint, $J = 7.3$ Hz), 3.05–3.2 (4H, m), 4.2–4.35 (2H, m), 7.2–7.45 (5H, m); MS m/z 244 (M^+, 28), 124 (100). **2b**: R_f 0.34 (2:1 hexane–EtOAc); IR (neat) 1742, 1674 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.68 (3H, s), 2.11 (2H, quint, $J = 7.3$ Hz), 3.04 (2H, t, $J = 2.3$ Hz), 3.05–3.2 (2H, m), 4.2–4.35 (2H, m), 7.02 (2H, t, $J = 8.9$ Hz), 7.36 (2H, dd, $J = 8.9$ and 5.3 Hz); MS m/z 262 (M^+, 100). **2c**: R_f 0.36 (2:1 hexane–EtOAc); IR (neat) 1741, 1674 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.68 (3H, s), 2.12 (2H, quint, $J = 7.3$ Hz), 3.04 (2H, t, $J = 2.3$ Hz), 3.05–3.2 (2H, m), 4.2–4.35 (2H, m), 7.31 (2H, d, $J = 7.9$ Hz), 7.33 (2H, d, $J = 7.9$ Hz); MS m/z 278 (M^+, 4.9), 124 (100). **2d**: mp 142–143 °C (hexane–CH_2Cl_2); IR (KBr disk) 1734, 1670 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.10 (2H, quint, $J = 7.3$ Hz), 3.05–3.2 (2H, m), 3.58 (2H, t, $J = 2.3$ Hz), 4.27 (2H, t, $J = 7.3$ Hz), 7.2–7.5 (10H, m); MS m/z 306 (M^+, 5.2), 124 (100). **2e**: R_f 0.32 (2:1 hexane–EtOAc); IR (neat) 1742, 1674 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.13 (2H, quint, $J = 7.3$ Hz), 2.75–2.9 (1H, m), 3.1–3.2 (2H, m), 3.25–3.4 (1H, m), 4.30 (2H, t, $J = 7.0$ Hz), 5.48 (1H, dd, $J = 8.4$ and 6.2 Hz), 7.25–7.4 (5H, m); MS m/z 230 (M^+, 100). **2f**: R_f 0.40 (2:1 hexane–EtOAc); IR (neat) 1736, 1676 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.91 (6H, t, $J = 7.3$ Hz), 1.66 (4H, q, $J = 7.3$ Hz), 2.12 (2H, quint, $J = 7.3$ Hz), 2.61 (2H, t, $J = 2.3$ Hz), 3.05–3.15 (2H, m), 4.28 (2H, t, $J = 7.0$ Hz); MS m/z 210 (M^+, 31), 181 (100). **2g**: mp 168–169 °C (hexane–EtOAc); IR (KBr disk) 1738, 1669 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.37 (3H, d, $J = 6.0$ Hz), 1.66 (1H, ddd, $J = 12.5$, 8.9, and 3.6 Hz), 2.15–2.3 (1H, m), 2.9–3.05 (1H, m) 3.25–3.35 (1H, m), 3.57 (2H, t, $J = 2.6$ Hz), 4.5–4.65 (1H, m), 7.2–7.35 (6H, m), 7.4–7.5 (4H, m); MS m/z 320 (M^+, 6.6), 138 (69), 110 (100). **2h**: mp 152–153 °C (hexane–EtOAc); IR (KBr disk) 1736, 1666 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.98 (3H, t, $J = 7.3$ Hz), 1.55–1.8 (3H, m), 2.15–2.25 (1H, m), 2.9–3.0 (1H, m), 3.25–3.4 (1H, m), 3.57 (2H, t, $J = 2.3$ Hz), 4.37 (1H, quint, $J = 6.6$ Hz), 7.2–7.35 (6H, m), 7.4–7.5 (4H, m); MS m/z 334 (M^+, 7.3), 152 (78), 124 (100). **2i**: mp 85–86 °C (hexane–EtOAc); IR (KBr disk) 1744, 1674 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.92 (3H, t, $J = 7.3$ Hz), 1.3–1.45 (4H, m), 1.55–1.75 (3H, m), 2.1–2.3 (1H, m), 2.9–3.0 (1H, m), 3.25–3.4 (1H, m), 3.57 (2H, t, $J = 2.3$ Hz), 4.42 (1H, quint, $J = 7.2$ Hz), 7.2–7.35 (6H, m), 7.4–7.5 (4H, m); MS m/z 362 (M^+, 8.1), 180 (99), 152 (100). **2j**: mp 180–181 °C (hexane–EtOAc); IR (KBr disk) 1732, 1674 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.0 2.15 (1H, m), 2.45–2.6 (1H, m), 2.95–3.15 (1H, m), 3.4–3.55 (1H, m), 3.65 (2H, t, $J = 2.3$ Hz), 5.43 (1H, dd, $J = 8.5$ and 6.3 Hz), 7.2–7.5 (15H, m); MS m/z 382 (M^+, 6.1), 247 (13), 200 (100). **2k**: mp 222–223 °C (hexane–EtOAc); IR (KBr disk) 1736, 1663 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.37 (6H, s), 1.91 (2H, t, $J = 7.9$ Hz), 3.15–3.25 (2H, m), 3.56 (2H, t, $J = 2.3$ Hz), 7.15–7.35 (6H, m), 7.4–7.5 (4H, m); MS m/z 334 (M^+, 6.7), 191 (6.9), 152 (99), 124 (100).

Published on the web (Advance View) November 13, 2004; DOI 10.1246/cl.2004.1588