Pergamon

Tetrahedron Letters 42 (2001) 1819–1822

TETRAHEDRON
LETTERS

Stereoselective synthesis of tetrahydrofurans: reactions of protected β-hydroxy ketones with benzyl diazoacetate

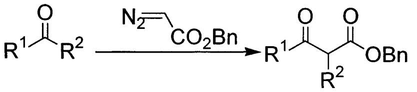
Steven R. Angle* and Keith Chann

Department of Chemistry, University of California-Riverside, Riverside, CA 92521-0403, USA

Received 28 September 2000; accepted 21 December 2000

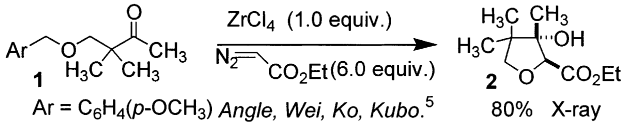
Abstract—The stereoselective synthesis of 2,3,3,4-tetrasubstituted tetrahydrofurans from the Lewis acid catalyzed reaction of protected β-hydroxy ketones with benzyl diazoacetate is described. The reaction can be used to set three contiguous stereocenters including one that is a tertiary alcohol. © 2001 Elsevier Science Ltd. All rights reserved.

There are many tetrahydrofuran containing natural products, some of which possess biological activity and are of potential therapeutic interest.[1] As a result, the stereoselective construction of tetrahydrofurans has been the subject of extensive investigation.[2] We have recently described the stereoselective synthesis of trisubstituted tetrahydrofurans from aldehydes and diazo esters.[3] In order to show the generality and scope of this methodology, we sought to expand the reaction to ketones. The reaction of diazoesters with ketones in the presence of Lewis acids normally results in homologation and/or ring expansion.[4] In these cases, the reaction involves a nucleophilic attack of the diazo compound followed by an alkyl migration to form β-dicarbonyl products (Eq. (1)). Our methodology involves reaction of a diazoester with a ketone possessing a nucleophilic β-oxygen, which provides an alternative to the alkyl shift pathway and leads to annulation products.



(1)

Our previous work on this methodology was limited to a single example in which protected β-benzyloxy ketone **1** was reacted with ethyl diazoacetate (6.0 equiv.) in the presence of $ZrCl_4$ (−78°C, 14 h) to afford tetrahydrofuran **2** in 80% yield.[5] (Eq. (2)). The stereochemistry of this THF product **2** was determined by X-ray crystallographic analysis.



(2)

We describe here our subsequent work with ketones focused on developing general annulation conditions for this reaction. In Table 1, entries 1–3 show the results of this study with a commercially available β-hydroxy ketone protected as the triethylsilyl ether, **3**. Reaction of ketone **3** under the optimized conditions (entry 3) afforded **4** in 62% yield as a 5:1 ratio of diastereomers.[6] Attempts to reduce the amount of Lewis acid to less than stoichiometric (0.2 equiv.) were unsuccessful, yielding only starting material even after 4 days at room temperature.

In general, the choice of ether protecting group for the β-hydroxyl did not seem to have a dramatic effect on the reaction. For example, triethylsilyl ether **5a** and (trimethylsilyl)ethyl ether **5b** afforded THF **6** in essentially identical yields and diastereoselectivity (entries 4 and 5). The same is true for triethylsilyl ether **7a** and *t*-butyldimethylsilyl ether **7c** (entries 7 and 9). The exception is α-phenyl ketone **7b**, with a (trimethylsilyl)ethyl ether, which failed to afford any THF product (entry 8). We attribute this result to two different effects which, when taken together, lead to decomposition of the starting ketone via a retro-Michael reaction: (1) the hydrogen α to the ketone is further activated by the presence of the phenyl group; and (2) the unhindered (trimethylsilyl)ethyl ether protecting group which leaves the ether oxygen accessible to complexation with the Lewis acid.

Keywords: tetrahydrofuran; stereoselective synthesis; ketone; diazoester.

* Corresponding author.

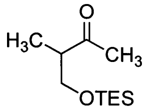
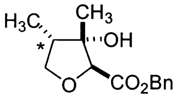
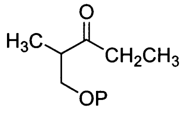
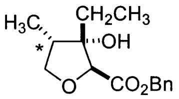
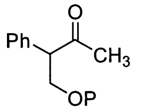
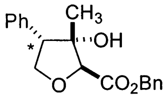
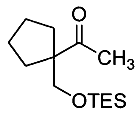
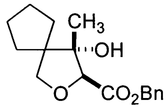
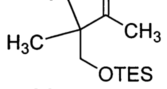
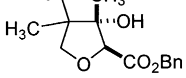
0040-4039/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(00)02352-2

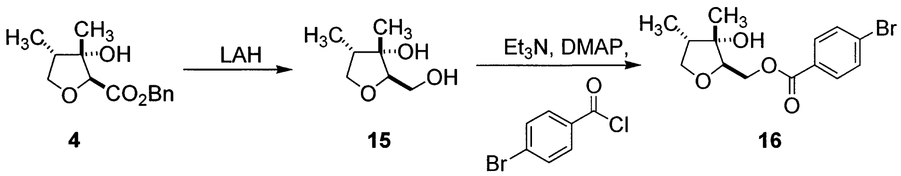
In the case of ketone **11**, increasing the amount of benzyl diazoacetate from 2 to 4 equiv. led to a higher yield (entries 11 and 12) of THF **12**. The steric hindrance of the α-substituent may be the mitigating factor in this case. In support of this notion, ketone **9** required only 2.0 equiv. of benzyl diazoacetate to achieve a 68% yield of THF **10** (entry 10), while ketone **11**, which is similarly substituted but more hindered, required 4.0 equiv. to afford a 52% yield of tetrahydrofuran **12** (entries 11 and 12).

Substitution in the α position of the ketones seemed to play a role in the stereoselectivity of the reactions as well. The single α-methyl substituent in ketone **3** (entry 3) resulted in the formation of two diastereomeric THFs (1.3:1), while the slightly bulkier α-phenyl ketone **7a** afforded only one diastereomer (entry 7). Also, the change from a methyl ketone **3** to an ethyl ketone **5a** led to a decrease in the diastereoselectivity (entries 3 and 4) which showed that substitution at both α positions of the ketone had an affect on the stereoselectivity of the reaction.

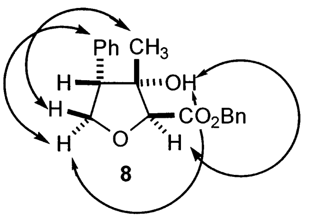
The stereochemistry of **8** was tentatively assigned by a NOESY NMR experiment (Fig. 1). The *trans*-orientation of the hydroxyl and ester groups is consistent with the stereochemistry of THF **2**, which was confirmed by X-ray crystallographic analysis. The *cis*-relationship between the hydroxyl group and the phenyl substituent is also consistent with the stereochemistry seen in the aldehyde cases.[3b]

Table 1. Synthesis of tetrahydrofurans from protected β-hydroxy ketones

Entry	Substrate	Diazoester	Product[7,8]	Yield (diast. ratio)[6]
				
1	**3**	6.0 equiv.	**4**	50%
2	**3**	4.5	**4**	65%
3	**3**	2.0	**4**	62% (* 5:1)
				
4	**5a** P=TES	2.0	**6**	59% (* 1.3:1)
5	**5b** P=CH$_2$CH$_2$TMS	2.0	**6**	58% (* 1.3:1)
				
6	**7a** P=TES	2.0	**8**	44% (* >20:1)
7	**7a** P=TES	6.0	**8**	68% (* >20:1)
8	**7b** P=CH$_2$CH$_2$TMS	6.0	**8**	0%
9	**7c** P=TBS	6.0	**8**	66% (* >20:1)
				
10	**9**	2.0	**10**	68%
				
11	**11**	2.0	**12**	39%
12	**11**	4.0	**12**	52%



Scheme 1. Preparation of the THF derivative for X-ray analysis.



(Arrows indicate NOEs)

Figure 1. NOE enhancements in NOESY experiments.

The stereochemistry of the major diastereomer of THF **4** was preliminarily assigned by NOESY NMR data similar to that shown for THF **8**. Tetrahydrofuran **4** was converted to the crystalline derivative **16**, as shown in Scheme 1, in order to confirm the stereochemical assignment by an X-ray structure.

This methodology provides an efficient and stereoselective way of synthesizing substituted tetrahydrofuran compounds resulting in the setting of three contiguous stereocenters, one of which is a tertiary alcohol.

References

1. (a) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448–3467; (b) Kang, S. H.; Lee, S. B. *Tetrahedron Lett.* **1995**, *36*, 4089–4092 and references cited therein; (c) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, 1995; p. 379.
2. For recent examples and leading references, see: (a) Koert, U. *J. Prakt. Chem.* **2000**, *342*, 325–333; (b) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461–464; (c) Yang, J.; Cohn, S. T.; Romo, D. *Org. Lett.* **2000**, *2*, 763–766.
3. (a) Angle, S. R.; Bernier, D. S.; El-Said, N. A.; Jones, D. E.; Shaw, S. Z. *Tetrahedron Lett.* **1998**, *39*, 3919–3922; (b) Angle, S. R.; Bernier, D. S.; Chann, K.; Jones, D. J.; Kim, M.; Neitzel, M. L.; White, S. L. *Tetrahedron Lett.* **1998**, *39*, 8195–8198.
4. For examples and leading references, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley and Sons: New York, 1998; pp. 534–567; (b) Liu, H. J.; Majumdar, S. P. *Synth. Commun.* **1975**, *5*, 125–130; (c) Mock, W. L.; Hartman, M. E. *J. Org. Chem.* **1977**, *42*, 459–465.
5. Angle, S. R.; Wei, G. P.; Ko, Y. K.; Kubo, K. *J. Am. Chem. Soc.* **1995**, *117*, 8041–8042.
6. Diastereomer ratios were determined by HPLC.
7. Selected spectral data: **THF (4)**: (major diastereomer, $(2R^*,3R^*,4R^*)$) clear oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (m, 5H), 5.23 (ABq, $J=16.1$ Hz, $\Delta\nu=10.7$ Hz, 2H), 4.37 (s, 1H), 4.29 (t, $J=8.2$ Hz, 1H), 3.64 (dd, $J=9.7$, 8.2 Hz, 1H), 2.18 (m, 1H), 1.72 (bs, 1H), 1.17 (s, 3H), 0.97 (d, $J=6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3, 135.2, 128.6, 128.5, 87.4, 80.6, 74.5, 66.7, 41.7, 21.2, 8.7; IR (neat) 3454, 2973, 1743, 1456 cm^{-1}; MS (CI/NH_3) *m*/*z* 267 (52, MNH_4^+), 250 (17), 232 (32), 107 (82); HRMS calcd for $C_{14}H_{22}NO_4$ (MNH_4^+) 268.1538, found 268.1548. **THF (4)**: (minor diastereomer, $(2R^*,3R^*,4S^*)$) clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (m, 5H), 5.24 (s, 2H), 4.32 (s, 1H), 4.17 (t, $J=8.4$ Hz, 1H), 3.60 (t, $J=9.2$ Hz, 1H), 2.42 (m, 1H), 1.93 (bs, 1H), 1.04 (s, 3H), 0.95 (d, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 135.1, 128.6, 128.5, 128.4, 85.5, 79.8, 76.5, 73.6, 66.7, 43.7, 17.8, 10.7; HRMS calcd for $C_{14}H_{22}NO_4$ (MNH_4^+) 268.1550, found 268.1548. **THF (6)**: (major diastereomer, $(2R^*,3R^*,4R^*)$) clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (m, 5H), 5.17 (s, 2H), 4.39 (s, 1H), 4.31 (t, $J=8.2$ Hz, 1H), 3.63 (dd, $J=9.7$, 8.2 Hz, 1H), 2.28 (m, 1H), 1.75 (bs, 1H), 1.62 (dq, $J=22.0$, 7.7 Hz, 1H), 1.27 (dq, $J=22.0$, 7.7 Hz, 1H), 0.96 (d, $J=8.2$ Hz, 3H), 0.95 (t, $J=6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1, 135.0, 128.4, 86.6, 83.0, 74.6, 66.8, 40.4, 27.3, 9.6, 8.1; IR (neat) 3457, 2974, 1743, 1457 cm^{-1}; MS (CI/NH_3) *m*/*z* 282 (MNH_4^+, 53), 264 (20), 108 (73); HRMS calcd for $C_{15}H_{24}NO_4$ (MNH_4^+) 282.1705, found 282.1698. **THF (6)**: (minor diastereomer, $(2R^*,3R^*,4S^*)$) clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (m, 5H), 5.18 (ABq, $J=11.8$ Hz, $\Delta\nu=4.8$ Hz, 2H), 4.33 (s, 1H), 4.28 (dd, $J=8.2$, 6.6 Hz, 1H), 3.84 (dd, $J=8.5$, 3.8 Hz, 1H), 2.23 (dp, $J=7.1$, 3.8 Hz, 1H), 1.90 (bs, 1H), 1.64 (dq, $J=22.0$, 7.3 Hz, 1H), 1.46 (dq, $J=22.0$, 7.3 Hz, 1H), 0.98 (d, $J=7.2$ Hz, 3H), 0.95 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 128.6, 128.5, 128.4, 86.8, 85.1, 75.0, 66.8, 43.9, 25.2, 14.8, 8.1; HRMS calcd for $C_{15}H_{24}NO_4$ (MNH_4^+) 282.1705, found 282.1717. **THF (12)**: white solid: mp 60–62°C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5H), 5.20 (ABq, $J=12.3$ Hz, $\Delta\nu=4.96$ Hz, 2H), 4.45 (s, 1H), 3.76 (s, 2H), 2.15 (bs, 1H), 1.08 (s, 3H), 1.06 (s, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0, 135.0, 128.5, 128.4, 128.3, 85.8, 81.7, 79.7, 66.6, 44.5, 20.8, 20.7, 19.7; IR (neat) 3484, 2969, 1744, 1456 cm^{-1}; MS (EI/) *m*/*z* 264 (2, M^+), 148 (51), 99 (30); HRMS calcd for $C_{15}H_{20}O_4$ (M^+) 264.1356, found 264.1361. **THF (10)**: white solid: mp 55–56°C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5H), 5.23 (s, 2H), 4.39 (s, 1H), 3.83 (s, 2H), 1.98–1.47 (m, 9H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9, 135.2, 128.5, 128.4, 85.3, 80.7, 79.0, 66.6, 56.5, 30.8, 24.7, 24.1, 20.0; IR (neat) 3459, 2954, 1750, 1456 cm^{-1}; MS (CI/NH_3) *m*/*z* 307 (31, MNH_4^+), 272 (100), 198 (22), 182 (36); HRMS calcd for $C_{17}H_{26}NO_4$ (MNH_4^+) 308.1846, found 308.1861. **THF (8)**: white solid: mp 84–86°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41–7.26 (m, 10H), 5.23 (ABq, $J=20.0$ Hz, $\Delta\nu=15.7$ Hz, 2H), 4.57 (s, 1H), 4.48 (t, $J=8.2$ Hz, 1H), 4.35 (dd,

$J = 10.2$, 8.2 Hz, 1H), 3.35 (dd, $J = 10.2$, 8.2 Hz, 1H), 1.47 (bs, 1H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6, 135.5, 134.4, 129.9, 129.1, 129.0, 128.9, 128.2, 87.4, 81.3, 72.6, 67.4, 54.6, 22.8; IR (neat) 3459, 2970, 1743, 1454 cm^{-1}; MS (CI/NH_3) m/z 330 (3, MNH_4^+), 104 (46); HRMS calcd for $C_{19}H_{21}O_4$ (M^+) 313.1430, found 313.1439.

8. **General experimental**: A solution of ketone, benzyl diazoacetate (2–6 equiv., Table 1) and CH_2Cl_2 was added to a suspension of $ZrCl_4$ in CH_2Cl_2 (0.2 M final concentration in ketone) at 0°C under N_2. After 5 h the reaction mixture was poured into satd aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic layers were dried ($MgSO_4$) and concentrated to afford crude product. Silica gel chromatography provided THF products in the yields indicated.