Pergamon

Tetrahedron Letters, Vol. 38, No. 22, pp. 3837-3840, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00766-1

Aldol-Cyclization Reaction Sequence for the Synthesis of Tetrahydrofurans

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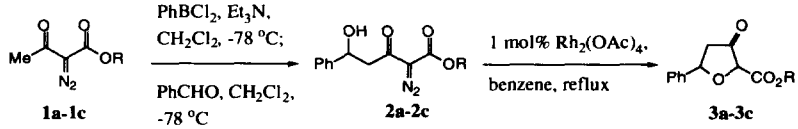
Abstract: The aldol reactions of α-diazo-β-ketoesters with a variety of aldehydes produced adducts which underwent Rh(II)-catalyzed O-H insertion reaction to yield highly substituted tetrahydrofurans. Alkylation and decarboxylation of these tetrahydrofurans formed a wide variety of tetrahydrofuran structures. © 1997 Elsevier Science Ltd.

We have developed a two-step reaction sequence that yields highly substituted tetrahydrofurans (Scheme 1). The reaction sequence consists of an aldol reaction of an α-diazo-β-ketoester followed by a Rh(II)-catalyzed O-H insertion. Both of these steps are precedented; Taber and co-workers recently reported an aldol reaction of an α-diazoketone,[1] and Rapoport *et al.* demonstrated that α-diazo-β-ketoesters undergo efficient intramolecular O-H insertions in 1985.[2] However, our combining these two reactions into an efficient synthesis demonstrates a novel route to tetrahydrofurans. The present work also owes much to the pyrrolidine synthesis developed by Reider and co-workers, which involves a Mannich reaction/N-H insertion sequence.[3]

Scheme 1



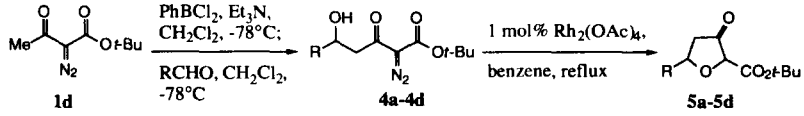
1a-1c **2a-2c** **3a-3c**

	R	% Yield 2a-2c	% Yield 3a-3c
a	Me	68	86
b	Et	80	92
c	Bn	64	91

The sensitivity of the diazo functionality of **1a-1c**[4] to strong acids and bases limited the potential conditions for the enolization and aldol reaction of these compounds. Eventually we found that enolization with a combination of a moderate Lewis acid, $PhBCl_2$, and triethylamine, followed by aldol reaction and quenching at -78°C, gave the optimal yields of **2a-2c**.[5] Warming of the unquenched aldolate to 0°C resulted in complete decomposition of the diazo moiety. Aldol adducts **2a-2c** all cyclized in excellent yields under standard conditions to produce tetrahydrofurans **3a-3c**, each as an approximately 1:1 mixture of diastereomers.[2] These tetrahydrofurans were unstable to both acid and base, so chromatographic purification was not possible.[6] However, they were sufficiently pure for subsequent reactions.

In order to produce fully characterizable derivatives from this reaction sequence, we examined the decarboxylation of **3a-3c**. However, all our attempts at carrying out these reactions met with failure, including the application of both Krapcho's and Taber's reaction conditions.[7,8] The failure of these methods, which involved basic conditions, led us to consider an ester protecting group that we could remove under acid conditions. Therefore, we explored the reactions of *t*-butyl ester **1d** (Scheme 2). The aldol reactions of this compound and the cyclizations of the resulting aldols proceeded as described above for **1a-1c**. In the case of **4b**, it is interesting to note that the desired O-H insertion occurs with complete selectivity over C-H insertion into the *i*-Pr methine, even though both processes would involve a favored five-membered transition state.[9]

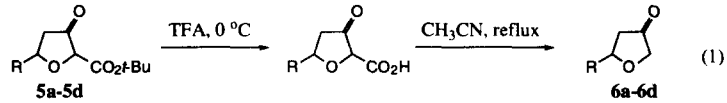
Scheme 2



1d **4a-4d** **5a-5d**

	R	% Yield 4a-4d	% Yield 5a-5d
a	Phenyl	63	93
b	*i*-Pr	72	92
c	*t*-Bu	70	92
d	Pentyl	69	93

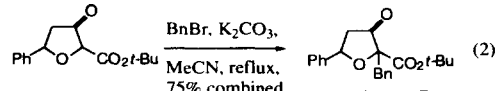
Gratifyingly, we found that we could indeed cleave the *t*-butyl ester from compounds **5a-5d** with neat TFA at 0°C to afford the corresponding β-keto acids in practically quantitative yields (eq 1).[10] Heating of the acids in refluxing acetonitrile provided fully characterizable, decarboxylated tetrahydrofurans **6a-6d** in moderate yields. Attempted decarboxylations in benzene, chloroform or TFA resulted in significant decomposition. Furthermore, failure to remove all the TFA from the β-keto acids prior to the decarboxylation reaction in acetonitrile resulted in formation of numerous decomposition products.



5a-5d **6a-6d** (1)

	R	% Yield 6a-6d
a	Phenyl	65
b	*i*-Pr	65
c	*t*-Bu	50
d	Pentyl	70

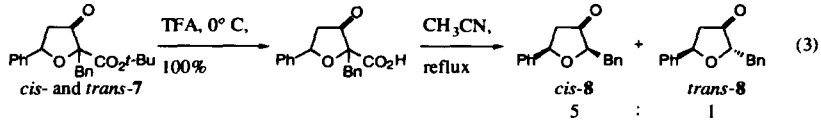
We also studied the alkylation of compound **5a**. Treatment of this compound with benzyl bromide and K_2CO_3 in acetonitrile gave the alkylated compound as a 4:1 mixture of diastereomers (eq 2).[11,12] This ratio was independent of the solvent and the base used for the alkylation.



5a *cis*- and *trans*-**7** (2)

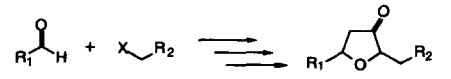
4:1 mixture of diastereomers

Decarboxylation of the mixture of *cis*- and *trans*-**7** under the conditions described above led to a 5:1 mixture of *cis*- and *trans*-**8** (eq. 3).[13] Control experiments in which the diastereomers of **7** were seperately hydrolyzed and decarboxylated revealed that both diastereomers of **7** went to the same diastereomeric mixture of *cis*- and *trans*-**8**. While this stereochemical divergence is consistent with the intermediacy of an enol containing only one stereocenter, NMR experiments indicated the presence of an intermediate that was *not* the enol. We are currently attempting to identify this intermediate.



(3)

In summary, we have developed a reaction sequence that allows the rapid assembly of the tetrahydrofuran moiety present in many biologically active natural products. In particular, the overall conversion of **1d** to **8** allows one to couple an aldehyde and an alkyl halide with the concommitant formation of a tetrahydrofuran ring (eq 4). We are currently using the methods reported here to synthesize nucleoside analogs and polyether ionophores.



(4)

Representative Procedure for Aldol Reaction: To a solution of 0.400 g (2.17 mmol) of **1d** in 50 mL of CH_2Cl_2 at -78°C was added 0.61 mL (0.44 g, 4.4 mmol) of Et_3N, followed by 0.34 mL (0.42 g, 2.64 mmol) of $PhBCl_2$. After 3 h, 0.34 mL (0.35 g, 3.3 mmol) of benzaldehyde was added. After an additional 2 h, the reaction was quenched by addition of 30 mL of a 1:1 mixture of MeOH:pH 7 buffer, the reaction mixture was warmed to 0 °C and7 mL of a 1:1 solution of MeOH:H_2O_2 was added. After stirring for 0.5 h at 0 °C, the mixture was separated and the aqueous layer was washed with CH_2Cl_2 (2 X 5 mL). The combined organic extracts were consecutively washed with sat. $NaHCO_3$ solution and 1M NaOH solution. The combined aqueous layers were washed with CH_2Cl_2 (1 X 5 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The crude reaction mixture was chromatographed (silica gel, hexanes/EtOAc 20:1) to obtain **4a** (0.4020 g, 63%) as a pale yellow solid: mp 68-70 °C (hexanes/dichloromethane); IR (neat) 3500, 2970, 2135, 1715, 1135, 1050, 745, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.20-7.40 (m, 5 H), 5.18 (m, 1 H), 3.47 (m, 1 H), 3.24 (d, J = 6.3 Hz, 1 H), 1.49 (s, 9 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 192.80, 160.28, 142.75, 128.46, 127.58, 125.75, 83.59, 70.24, 52.97, 48.56, 28.24; Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 62.06 ; H, 6.25 ; N, 9.65. Found: C, 62.13 ; H, 6.23 ; N, 9.53.

Representative Procedure for Insertion and Decarboxylation: To a suspension of 0.005 (0.003 mmol) of $Rh_2(OAc)_4$ in 1.5 mL benzene at 80 °C was added dropwise 0.0871 g (0.30 mmol) **4a** in 3 mL CH_2Cl_2. After the addition, the heterogeneous reaction mixture was refluxed for 15 min and then allowed to cool to room temperature and filtered through celite. The solvent was removed *in vacuo* to obtain **5a** as a 1:1 mixture of diastereomers (0.074 g, 93%) as a colorless oil.

To the unpurified sample of **5a** from the previous reaction was added 1 mL TFA at 0 °C. After 3h at 0°C, the solvent was removed on the rotary evaporator and residual TFA was removed at room temperature at a pressure of 0.5 torr. The unpurified acid was then dissolved in 5 mL acetonitrile and the reaction mixture was refluxed for 8 h. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. Chromatography (silca gel, EtOAc/hexanes 1:20) provided **6a** as a pale yellow oil (0.033 g, 65%): IR (neat) 3030, 1757, 1500, 1454, 1154, 910, 735, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.30-7.50 (m, 5 H), 5.30 (dd, J = 9.5 , 6.3 Hz, 1 H), 4.35 (d, J = 6.9 Hz, 1 H), 4.20 (d, J = 6.9 Hz, 1 H), 2.83 (dd, J = 17.8, 6.3 Hz, 1 H), 2.50 (dd, J = 17.8, 9.5 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 214.26, 139.96, 128.74, 128.33, 125.88, 79.36, 71.74, 44.72; Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06 ; H, 6.21. Found: C, 74.10; H, 6.20.

Acknowledgement: We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society and to the Virginia Tech Chemistry Department for financial support of this project.

References

1. Taber, D. F.; Herr, R. J.; Gleave, D. M. *J. Org. Chem.* **1997**, *62*, 194-198.
2. Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223.
3. Reider, P. J.; Rayford, R.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *38*, 379-382.
4. Koskinen, A. M. P.; Munoz, *J. Chem. Soc., Chem. Commun.* **1990**, 652-653.
5. Hamana, H.; Saskura, K.; Sugawasa, T. *Chem. Lett.* **1984**, 1729-1732.
6. We obtained satisfactory spectral data (^1H and ^{13}C NMR, IR) and elemental analyses for **2a-2c**, **4a-4d**, **6a-6d**, *cis*- and *trans*-**7**, and *cis*- and *trans*-**7**. We were only able to obtain ^1H NMR spectra for compounds **3a-3c** and **5a-5f**.
7. Taber, D. A.; Amedio Jr., J. C.; Gulino, F. *J. Org. Chem.* **1989**, *54*, 3474-3475.
8. (a) Krapcho, A. P. *Synthesis* **1982**, 893-914. (b) Krapcho, A. P. *Synthesis* **1982**, 805-822.
9. Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808.
10. Bryan, D. B.; Hall, R. F.; Holden, K. G.; Huffman, W. F.; Gleason, J. G. *J. Am. Chem. Soc.* **1977**, *99*, 2353-2355.
11. Johnson, A. W.; Markham, E.; Price, R. *Organic Synthesis* **1973**, *Coll. V5*, 785-786.
12. Mazur, Y.; Sondheimer, F. *J. Am. Chem. Soc.* **1958**, *80*, 5220-5229.
13. The stereochemistry of the major diastereomer of **7** was assigned as *cis* on the basis of a 3% NOE observed between the two protons flanking the tetrahydrofuran oxygen.

(*Received in USA* 24 *March* 1997; *revised* 15 *April* 1997; *accepted* 17 *April* 1997)