Pergamon

Tetrahedron Letters 41 (2000) 8425–8429

TETRAHEDRON LETTERS

Stereoselective construction of quaternary carbon centers by three component coupling reactions

Arun K. Ghosh,* Reiko Kawahama and Donald Wink

Department of Chemistry, University of Illinois at Chicago, 845 W. Taylor Street, Chicago, IL 60607, USA

Received 12 July 2000; revised 13 September 2000; accepted 14 September 2000

Abstract

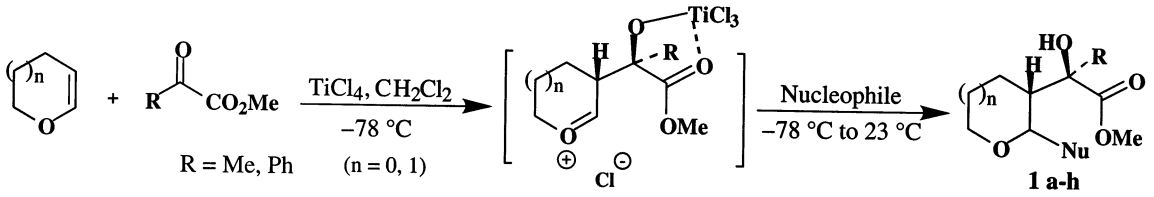
$TiCl_4$ promoted coupling reactions of pyruvates with vinyl ethers such as 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran constructed quaternary carbon centers stereoselectively.

Development of new carbon–carbon bond forming reactions is of particular interest in organic synthesis, especially in the context of creating new quaternary chiral centers involving a stereoselective reaction.[1] Recently, we reported the $TiCl_4$ promoted synthesis of a variety of 2,3-disubstituted tetrahydrofurans and tetrahydropyrans by a novel three component coupling reaction.[2] The reaction involved the treatment of ethyl glyoxylate and 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran with $TiCl_4$, followed by exposure of the resulting oxonium ion to appropriate nucleophiles. The overall process is quite efficient and created up to three contiguous chiral centers in the condensation product. To further develop the synthetic utility of this reaction, we have now investigated coupling reactions of pyruvates with a view to stereoselectively synthesizing functionalized tetrahydrofuran and tetrahydropyran derivatives with quaternary carbon centers. Synthetic access to these structural features is thus far limited.[3] Such structural features are of particular interest to us for probing an enzyme active site with a designed ligand.[4] Herein we report a highly stereoselective protocol for constructing quaternary carbon centers using three component coupling reaction of pyruvates, vinyl ethers and appropriate nucleophiles.

As outlined in Scheme 1, reaction of methyl pyruvate (R = Me) and 3,4-dihydro-2*H*-pyran with $TiCl_4$ in dry CH_2Cl_2 at −78°C for 1 h provided the oxonium ion, which upon treatment with triethylsilane at −78–23°C for 1 h afforded the α-hydroxy ester **1a** as a single diastereomer in 82% yield. As can be seen in Table 1, in the case of methyl benzoylformate, the corresponding coupling product **1b** was obtained in 77% yield, again as a single diastereomer. The relative

* Corresponding author. E-mail: arunghos@uic.edu

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01602-6



Scheme 1.

stereochemistry of these coupling products **1a** and **1b** was determined by X-ray crystallography. The coupling reactions of dihydrofuran with both pyruvates (R = Me) and (R = Ph) using Et_3SiH as a nucleophile provided the corresponding hydroxy esters **1c** and **1d** in 83 and 53% yields, respectively (entries 3 and 4). These products were also obtained as single isomers. The observed stereochemistry can be rationalized based upon stereochemical models **A** and **B**. In these models, we postulate that one of the electron pairs of the methoxy oxygen is donated to the oxonium ion from the axial side (anomeric side) for stabilization of the transition state (Fig. 1). Transition state model **B** (*exo*) is favored over model **A** (*endo*) because of the absence of the developing non-bonded interaction between the C4-hydrogens and the chelated titanium metal.

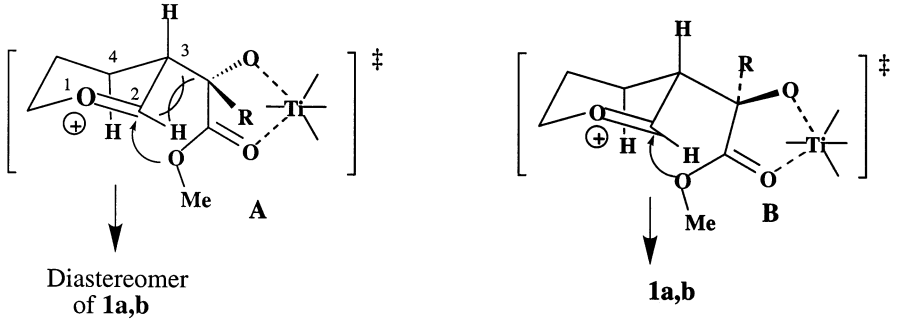
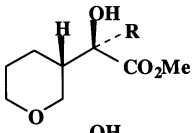
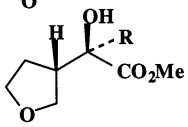
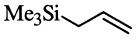
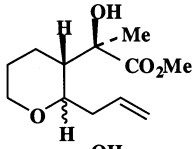
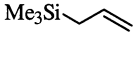
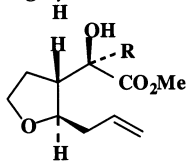
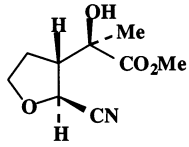
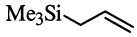
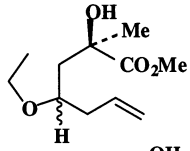
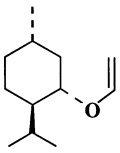
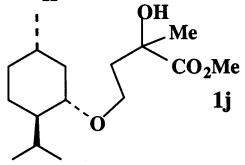


Figure 1.

When the presumed oxonium ion derived from the reaction of methyl pyruvate (R = Me) and 3,4-dihydro-2*H*-pyran was reacted with allyltrimethylsilane as a nucleophile, the reaction proceeded smoothly (−78–23°C for 1 h). However, **1e** was obtained as a 1:1 mixture of diastereomers which were separable by silica gel chromatography (entry 5). The reaction of allyltrimethylsilane with the oxonium ion derived from 2,3-dihydrofuran and pyruvates, however, proceeded with a high degree of selectivity. The reaction of methyl pyruvate and dihydrofuran provided the allylated product **1f** in 74% isolated yield as a 6.6:1 mixture of diastereomers. The reaction with methyl benzoylformate proceeded with even higher stereoselectivity (entry 7). Allyltributylstannane instead of allyltrimethylsilane under similar reaction conditions provided **1g** with reduced selectivity (10:1) and in lower isolated yield (35%). Both pure diastereomers **1f** and **1g** were separable by flash column chromatography (entry 6, 7). The relative stereochemistry of the major isomer **1g** was determined by X-ray crystallography. The stereochemistry of the quaternary carbon center of **1g** is the same as the tetrahydropyran derivatives **1a** and **1b**. Furthermore, the stereochemistry of the C-2 and C-3 substituents on the tetrahydrofuran ring is *trans*, as shown in Fig. 2.[5]

Table 1
$TiCl_4$ promoted coupling reactions of pyruvates with various vinyl ethers[a]

Entry	Vinyl ether	R	Nucleophile	Products[b]			Yield[c]	Ratio[d]
1		Me	Et_3SiH		**1a**	R = Me	82%	>99 : 1
2		Ph	Et_3SiH		**1b**	R = Ph	77%	>99 : 1
3		Me	Et_3SiH		**1c**	R = Me	83%	>99 : 1
4		Ph	Et_3SiH		**1d**	R = Ph	53%[e]	>99 : 1
5		Me	Me_3Si 		**1e**		95%	1 : 1
6		Me	Me_3Si 		**1f**	R = Me	74%	6.6 : 1
7		Ph	Me_3Si		**1g**	R = Ph	58%[f]	15 : 1
8		Me	Me_3SiCN		**1h**		60%	>20 : 1
9		Me	Me_3Si 		**1i**		50%	1.6 : 1
10		Me	Et_3SiH		**1j**		65%	1 : 1

[a]All reactions were carried out by the same procedure described in the text. [b]Major isomer is illustrated. [c]Isolated yield. [d]Determined by ^1H NMR. [e]Methyl α-hydroxy phenyl acetate was obtained in 26%. [f]Methyl 2-hydroxy-2-phenyl-4-pentenoate was obtained in 34%.

Reaction of dihydrofuran and methyl pyruvate derived oxonium ion with trimethylsilyl cyanide also provided the corresponding cyanide **1h** with excellent selectivity (>20:1, entry 8).[6] To examine acyclic stereoselection, the reaction of methyl pyruvate and ethyl vinyl ether was carried out with allyltrimethylsilane. However, the corresponding coupling product **1i** was obtained as a 1.6:1 mixture of diastereomers (entry 9). Similarly, the reaction of optically active menthyl vinyl ether, methyl pyruvate and triethylsilane provided the coupling products **1j** as a 1:1 mixture of diastereomers which were separated by silica gel chromatography (entry 10).[7]

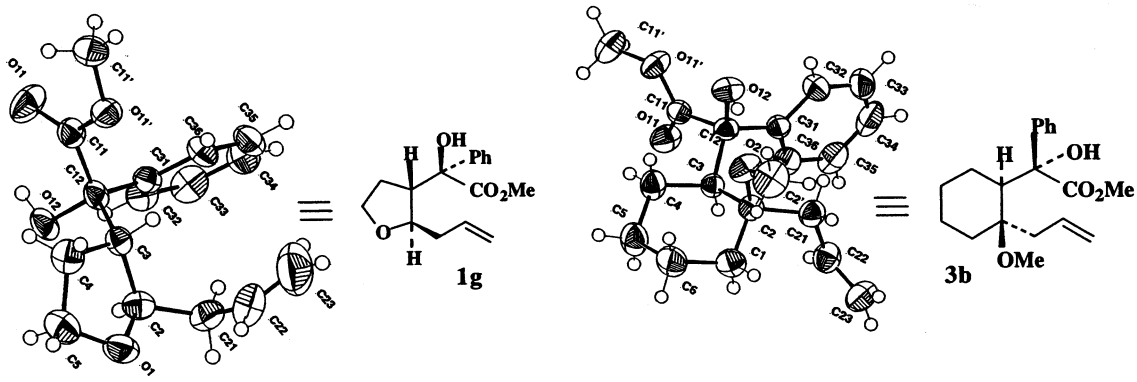
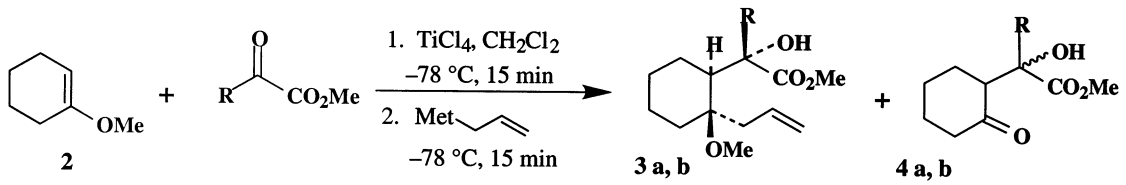


Figure 2. ORTEP drawing of X-ray crystal structures of **1g** and **3b**

We have also investigated stereoselection with 1-methoxycyclohexene **2**. As shown in Scheme 2, when the reaction was carried out with methyl pyruvate and allyltrimethylsilane at −78°C for 15 min, the coupling product **3a** was obtained as a single diastereomer in 63% isolated yield.[8] A mixture of cyclic ketones **4a** (20%, ratio 5.4:1) also resulted from the aldol reaction of the resulting Ti-enolate.[9] The use of allyltributyltin instead of allyltrimethylsilane improved the reaction yield (**3a** and diastereomer, 67%), however, selectivity was reduced (ratio 4.6:1) significantly. Ketone **4a** was isolated in 13% yield (ratio 1.7:1). The corresponding reaction with methyl benzoylformate and allyltributyltin furnished diastereomerically pure **3b** in 53% isolated yield (**3b** and diastereomer, 61%) along with methyl ketone **4b** (21%). The relative stereochemistry of **3b** was determined by X-ray crystallography (Fig. 2).[5]



R = Me, Met = Me_3Si	**3a**	63% (>99 : 1)	**4a**	20% (5.4 : 1)
R = Me, Met = Bu_3Sn	**3a**	67% (4.6 : 1)	**4a**	13% (1.7 : 1)
R = Ph, Met = Bu_3Sn	**3b**	61% (6.6 : 1)	**4b**	21% (1.7 : 1)

Scheme 2.

In summary, $TiCl_4$ promoted three component coupling reactions of pyruvates, vinyl ethers and carbon nucleophiles provided stereocontrolled access to the synthesis of quaternary carbon centers. The overall protocol is practical and quite efficient. Further studies of these reactions are currently under investigation.

Acknowledgements

Financial support for this work was provided by the National Institutes of Health. The authors thank Professors Martin Newcomb and Vladimir Gevorgyan for helpful discussions.

References

1. (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *37*, 388; (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037 and references cited therein.
2. (a) Ghosh, A. K.; Kawahama, R. *Tetrahedron Lett.* **1999**, *40*, 1083; (b) Ghosh, A. K.; Kawahama, R. *Tetrahedron Lett.* **1999**, *40*, 4751.
3. (a) Westley, J. W. In *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Marcel Dekker: New York, 1982; Vols. I and II; (b) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. In *Comprehensive Heterocyclic Chemistry II*; Pergamon Press: Oxford, 1996; Vol. 2, pp. 386–392 and Vol. 5, pp. 390–396.
4. (a) Ghosh, A. K.; Shin, D.; Downs, D.; Koelsch, G.; Lin, X.; Ermolieff, J.; Tang, J. *J. Am. Chem. Soc.* **2000**, *122*, 3522; (b) Ghosh, A. K.; Kincaid, J. F.; Cho, W.; Walters, D. E.; Krishnan, K.; Hussain, K. A.; Koo, Y.; Cho, H.; Rudall, C.; Holland, L.; Buthod, J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 979.
5. Detailed data can be obtained at the Cambridge Crystallographic Data Center, Cambridge, UK.
6. The reaction with methyl benzoylformate provided the corresponding cyanide in 38% isolated yield as a single diastereomer. The coupling constant $J_{2-3}=5.4$ Hz is consistent with *trans* stereochemistry.
7. Optically active menthyl vinyl ether was prepared from the reaction of menthol and ethyl vinyl ether in the presence of $Hg(OAc)_2$, see: Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1957**, *79*, 2828.
8. All new compounds gave satisfactory spectroscopic and analytical results. Preparation of compound **3a**: To a solution of methyl pyruvate (102 mg, 1.00 mmol) and 1-methoxycyclohexene (168 mg, 1.50 mmol) in dry CH_2Cl_2 (2.5 mL) was added $TiCl_4$ (1.0 M in CH_2Cl_2; 1.0 mL, 1.00 mmol) at −78°C and the resulting orange solution was stirred for 15 min at −78°C. Allyltrimethylsilane (0.32 mL, 2.00 mmol) was added and the mixture was stirred for 15 min at −78°C. The reaction was quenched at −78°C with sat. $NaHCO_3$ (aq.) and warmed to 23°C. The mixture was extracted with EtOAc and the organic layer was dried over Na_2SO_4. Evaporation of the solvents gave a residue which was purified by chromatography (3% EtOAc in hexane) to give the title compound (162 mg, 63%). $R_f=0.48$ (20% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (1H, m), 1.29–1.43 (3H, m), 1.46 (3H, s), 1.54 (1H, m), 1.68–1.75 (2H, m), 1.80–1.90 (2H, m), 2.28 (1H, dd, $J=13.4$ and 9.1 Hz), 2.78 (1H, ddt, 13.4, 5.1 and 1.6 Hz), 3.12 (3H, s), 3.75 (3H, s), 4.05 (1H, br s), 5.04–5.10 (2H, m), 6.06 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 24.7, 25.9, 28.0, 31.7, 41.9, 48.0, 51.0, 52.2, 77.1, 78.0, 117.5, 135.7, 177.8.
9. Ethyl ester of **4a** has been synthesized by the $TiCl_4$ promoted reaction of ethyl pyruvate and trimethylsiloxycyclohexene, see: Banno, K. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2284.