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$TiCl_4$ promoted three component coupling reaction: an efficient method for the substituted tetrahydropyrilidene acetates

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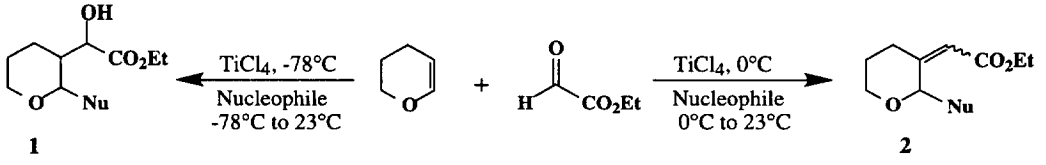
Abstract

The syntheses of substituted tetrahydropyrilidene acetates were accomplished by $TiCl_4$ promoted carbon–carbon bond forming reaction of ethyl glyoxylate, 3,4-dihydro-2*H*-pyran and an appropriate carbon, oxygen or sulfur nucleophile. The reaction constitutes an efficient three component coupling process and the olefinic coupling product is dependent upon reaction temperature. © 1999 Elsevier Science Ltd. All rights reserved.

The development of synthetic methods for functionalized tetrahydropyrans is of considerable importance in synthesis.[1] While methods for the synthesis of 2,6-disubstituted tetrahydropyrans have been reported, synthesis of 2,3-disubstituted tetrahydropyrans has received much less attention.[2] We recently reported the synthesis of a variety of 2,3-disubstituted tetrahydrofurans and pyrans by a three component coupling process.[3] As illustrated in Scheme 1, the reaction of ethyl glyoxylate and dihydropyran in the presence of $TiCl_4$ at −78°C generated oxonium ion intermediates which, upon reaction with a nucleophilic trapping agent such as allyltrimethylsilane, provided 2-substituted 3-(β-carboethoxy-α-hydroxymethyl)tetrahydropyrans (**1**) in excellent yields. Interestingly, when the coupling reaction was carried out at 0°C, the corresponding elimination product, ethyl α-(tetrahydro-3-pyrilidene)acetate **2a** was formed as the major product. Herein we report a $TiCl_4$ promoted three component coupling reaction as a useful entry to the synthesis of 2-substituted α-(tetrahydro-3-pyrilidene)acetates. This is of particular interest, as there have been only a few reports of substituted α-(tetrahydro-3-pyrilidene)acetates in the literature.[4]



1 **2**

Scheme 1.

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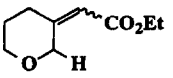
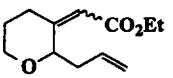
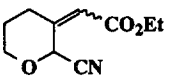
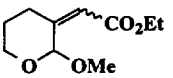
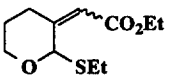
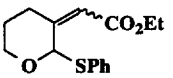
As described, ethyl glyoxylate and dihydropyran in CH_2Cl_2 were reacted with $TiCl_4$ (1 M in CH_2Cl_2) at −78°C for 1 h and the resulting mixture was treated with triethylsilane at −78° to 23°C for 1 h to provide 3-(β-carboethoxy-α-hydroxymethyl)tetrahydropyran **1a** (Nu=H) in 95% yield. When the above coupling reaction was carried out at 0°C, the major product ethyl α-(tetrahydro-3-pyrilidene)acetate **2a** (Nu=H), was isolated in 77% yield and the addition product **1a** was obtained in only 10% yield. Further optimization of the reaction conditions resulted in the formation of product ethyl α-(tetrahydro-3-pyrilidene)acetate **2a** exclusively. Thus, in a mixture of ethyl glyoxylate (1 equiv.) and dihydropyran (1.5 equiv.) in CH_2Cl_2 at −78°C, $TiCl_4$ (1 M in CH_2Cl_2, 1 equiv.) was added, and the resulting yellow solution was stirred for 1 h at −78°C and then the cooling bath was removed and the mixture was stirred at 23°C for 1 h. After this period, the resulting orange suspension was cooled to 0°C and triethylsilane (3 equiv.) was added and stirring of the resulting reaction mixture continued at 0°C to 23°C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. Standard workup and chromatography over silica gel afforded ethyl α-(tetrahydro-3-pyrilidene)acetate **2a** in 95% yield. The ratio of geometric isomers (*E*:*Z*) was determined as 1:2 by ^1H NMR (400 MHz), and its geometry was determined by ^1H NMR NOE experiments. As depicted in Table 1, the reaction of the resulting oxonium ion with carbon nucleophiles provided excellent yield of the corresponding coupling product compared to oxygen and sulfur nucleophiles. When allyltrimethylsilane was used as a nucleophile, the reaction provided ethyl (*E*) and (*Z*)-(2-allyl-tetrahydro-3-pyrilidene)acetate **2b** in 83% yield as the sole products.[5] Similarly, use of TMSCN as a nucleophile, resulted in the cyanide **2c** as a 7:1 mixture of isomers (*E*:*Z*) in 84% isolated yield. When the oxonium ion was quenched with methanol, a mixture of methyl glycosides **2d** was obtained in 44% yield. The instability of the acetal group under acidic reaction conditions may account for the low yield of methyl glycosides compared to **2a–c**. Indeed, addition of diisopropylethylamine (2 equiv.) followed by methanol to the resulting oxonium ion at 0°C followed by warming up to 23°C, provided a mixture of methyl glycosides **2d** in 74% yield. Trapping of the oxonium ion with sulfur nucleophiles also provided the corresponding sulfides, however isolated yields were modest. Reaction of the oxonium ion with trimethylsilylazide under similar conditions afforded the corresponding azides (3:2, *E*:*Z* mixture) in 32% yield.

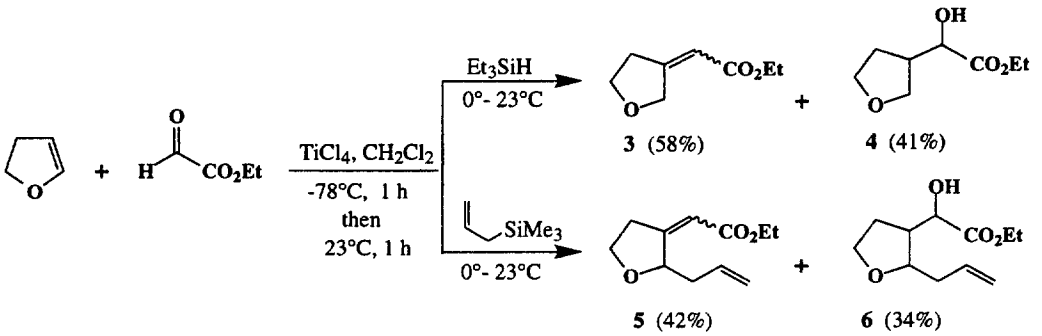
While various (tetrahydro-3-pyrilidene)acetates can be formed exclusively from dihydropyran, corresponding substituted (tetrahydro-3-furylidene)acetates from dihydrofuran could not be obtained as the sole product. As shown in Scheme 2, generation of oxonium ion from dihydrofuran and subsequent reaction with triethylsilane afforded a 1:1 mixture (*E*:*Z*) of (tetrahydro-3-furylidene)acetates **3** (58%) along with 3-(β-carboethoxy-α-hydroxymethyl)tetrahydrofurans **4** (41%, 1:1 mixture). Similarly, reaction with allyltrimethylsilane provided substituted (tetrahydro-3-furylidene)acetates **5** (42%, 1:1 mixture) and a mixture of hydroxy esters **6** (34%) respectively. Attempted optimization of the elimination products under longer reaction time (3–5 h), or higher reaction temperature (30°C) did not improve the overall yields.

Interestingly, attempted elimination of the hydroxy group from **1a** with *p*-toluenesulfonic acid or camphorsulfonic acid in refluxing benzene did not provide **2a**, the starting material was recovered unchanged. Similarly, reaction of the mesylate of **1a** with Et_3N or DBU in refluxing benzene for several hours, did not provide any elimination product. Furthermore, exposure of **1a** to an excess of $TiCl_4$ in CH_2Cl_2 at −78°C to 23°C did not result in any elimination product **2a**. Again, the hydroxy ester **1a** was recovered quantitatively. Taken together, it is presumed that the elimination had occurred on the titanium complex **A** (Fig. 1), resulting in a new oxonium ion intermediate **B**, which subsequently reacted with nucleophiles to give unsaturated esters **2**.[6] Indeed, the initial titanium complex **A** generated at −78°C was a clear yellow solution. However, as the reaction temperature was raised to 23°C, elimination presumably

Table 1
Synthesis of substituted tetrahydropyrilidene acetates[a]

Entry	Nucleophile	Product		Yield (%)[b]	Ratio (E : Z)[c]
1	Et_3SiH		**2a**	95	1 : 2
2	Me_3Si 		**2b**	83	1 : 2
3	Me_3SiCN		**2c**	84	7 : 1
4	MeOH		**2d**	74[d]	3 : 2
5	EtSH		**2e**	46[d]	3 : 2
6	PhSH		**2f**	35[d]	3 : 2

[a] All reactions were carried out as described in the text. [b] Isolated yield. [c] Determined by ^1H NMR. [d] With addition of 2 equiv of iPr_2NEt.



Scheme 2.

proceeded with the formation of titanium dioxide and the solution containing **B** became a suspension. Further studies concerning the mechanism of this reaction are currently ongoing.

In summary, we have described the $TiCl_4$ promoted coupling reaction of 3,4-dihydro-2*H*-pyran and ethyl glyoxylate as an efficient synthetic method for not only 2-substituted 3-(β-carboethoxy-α-hydroxy)tetrahydropyrans (**1**), but also for 2-substituted (tetrahydro-3-pyrilidene)acetates (**2**). Application of this chemistry in the synthesis of bioactive compounds is currently under investigation. The following example is representative of this procedure.

Preparation of ethyl (tetrahydropyrilidene)acetate **2b**: to a mixture of ethyl glyoxylate (204 mg, 2 mmol) and 3,4-dihydro-2*H*-pyran (252 mg, 3 mmol) in dry CH_2Cl_2 (5 mL) was added a solution of $TiCl_4$

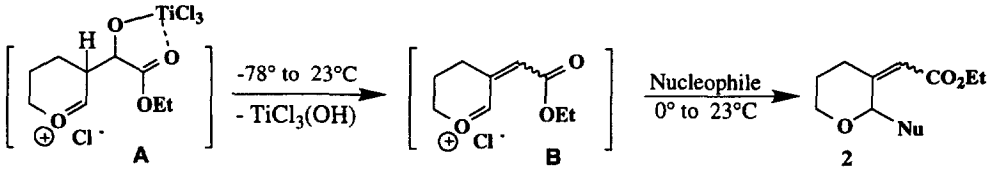


Figure 1.

(1 M in CH_2Cl_2, 2 mL, 2 mmol) at –78°C, and the resulting yellow solution was stirred at –78°C for 1 h. After this period, the cooling bath was removed and the mixture was stirred for an additional hour at 23°C. The resulting suspension was then cooled to 0°C, allyltrimethylsilane (0.95 mL, 6.0 mmol) was added and the mixture was stirred at 0°C to 23°C for 1 h. The reaction was quenched with aqueous $NaHCO_3$ solution. The mixture was extracted with EtOAc (50 mL), washed with brine, dried over Na_2SO_4 and evaporated. Flash chromatography (2.5% EtOAc/hexane) of the residue afforded the tetrahydropyrilidene derivatives **2b** (348 mg) as a 1:2 mixture (*E*:*Z*) in 83% yield: *E*-isomer: R_f=0.33 (10% EtOAc in hexane); IR (neat) 1717, 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, *J*=7.1 Hz), 1.70–1.85 (2H, m), 2.37–2.53 (2H, m), 2.72 (1H, m), 3.25 (1H, dt, *J*=14.2 and 5.8 Hz), 3.62 (1H, ddd, *J*=11.5, 8.2, and 4.2 Hz), 3.91 (1H, dd, *J*=7.8 and 5.8 Hz), 3.94 (1H, dt, *J*=11.5 and 4.6 Hz), 4.13 (2H, q, *J*=7.1 Hz), 5.07 (1H, m), 5.10 (1H, m), 5.66 (1H, d, *J*=0.6 Hz), 5.81 (1H, ddt, *J*=17.1, 10.2, and 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 25.6, 27.4, 36.0, 59.8, 65.6, 79.0, 113.8, 117.1, 134.3, 157.9, 166.4; *Z*-isomer: R_f=0.32 (10% EtOAc in hexane); IR (neat) 1712, 1649 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t, *J*=7.1 Hz), 1.79 (1H, m), 1.88 (1H, m), 2.25 (1H, br dd, *J*=14.0 and 4.9 Hz), 2.38 (1H, m), 2.53 (1H, br ddd, *J*=14.0, 12.5, and 6.7 Hz), 2.62 (1H, m), 3.57 (1H, ddd, *J*=11.7, 5.8, and 0.9 Hz), 3.83 (1H, ddd, *J*=11.7, 9.1, and 4.7 Hz), 4.13 (2H, q, *J*=7.1 Hz), 5.08 (1H, m), 5.13 (1H, m), 5.43 (1H, dd, *J*=9.3 and 4.6 Hz), 5.64 (1H, br s), 5.90 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 26.6, 29.7, 35.8, 59.9, 60.7, 74.1, 114.9, 116.9, 134.6, 160.0, 165.5.

Acknowledgements

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4. For syntheses of (tetrahydro-2-pyrilidene) and (tetrahydro-2-furylidene) acetates, see: (a) Takahashi, A.; Kirio, Y.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1989**, *111*, 643; (b) Sauve, G.; Deslongchamps, P. *Syn. Commun.* **1985**, *15*, 201; (c) Casty, G. L.; Stryker, J. M. *Organometallics* **1997**, *16*, 3083 and references cited therein.
5. All new compounds gave satisfactory spectroscopic and analytical results.
6. The intermediate **B** can be formed by loss of the substituted ring proton of **A**, followed by elimination of the resulting neutral dihydropyran under the action of the released protic acid.