

β -Oxopropyl Formate As a Formylating Agent of Sterols

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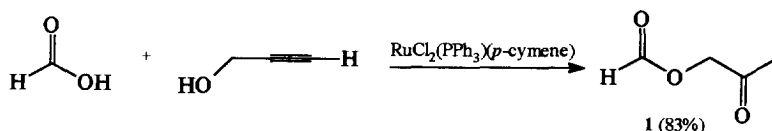
Abstract: Propargylic alcohol reacts with formic acid in the presence of mononuclear catalysts of ruthenium to selectively afford β -oxopropyl formate which has been shown as an excellent mild formylating agent of sterols when the reaction is catalyzed by 1,5-diazabicyclo[4.3.0]non-5-ene (DBN).

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Two initial reports [1,2] described the synthesis of β -oxopropyl esters by the catalytic addition of carboxylic acids, involving α -amino acids to propargylic alcohol and its 1,1-dimethyl derivatives. Complexes of type $\text{RuCl}_2(\text{PR}_3)(\text{arene})$ which were shown to be efficient catalyst precursors for the regioselective synthesis of enol esters [1-6], also catalyze the synthesis of β -oxopropyl esters in milder conditions, via a transesterification, however, it seems that the synthesis of β -oxopropyl formate has not been addressed. We now report that β -oxopropyl formate obtained by the catalytic addition of formic acid to propargylic alcohol is an excellent formylating agent of sterols in the presence of a catalytic amount of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN).

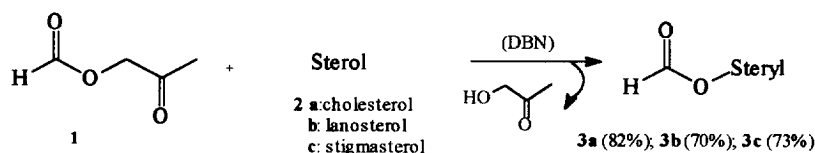
1- Catalytic synthesis of β -oxopropyl formate

Until now, the synthesis of β -oxopropyl formate has not been described; we have prepared it according to the published method for the synthesis of β -oxopropyl esters. Thus, the reaction of 10 mmol of propargylic alcohol and 10 mmol of formic acid in toluene at 60 °C for 6 h in the presence of 1 mol % of complex $\text{RuCl}_2(\text{PPh}_3)(p\text{-cymene})$ gave β -oxopropyl formate in 83% yield [7].



2- β -oxopropyl formate as a formylating agent

The good reactivity of enol formates towards amines and alcohols, under mild conditions [5,6], prompted us to study the behaviour of β -oxopropyl formate as an acylation reagent for the formation of C-N and C-O bonds. We report here that β -oxopropyl formate is an excellent formylating agent of primary amines and alcohols, under very mild conditions, while the formylation of secondary amines and alcohols requires the use of KCN [5,6] as catalyst. Nevertheless, the formylation of sterols in the presence of catalytic amounts of KCN gave rise to the corresponding formates in only 20-30 % yields, even at 70 °C. We tried several classical catalysts of acylation reactions but no significant formate was observed. Fortunately, the use of 1,5-diazabicyclo[4.3.0]non-5-ene allows the unprecedented access to the steryl formates **3** in good yields, with elimination of a hydroxyketone as the only by-product easy to remove.



Thus, when 10 mmol of the sterol, 10 mmol of β -oxopropyl formate and 1 mmol of DBN were heated at 50-70 °C, for 3 hours in 10 ml of THF, the steryl formates **3** were isolated in 70-82% yields [8].

These results show that β -oxopropyl formate, prepared in one step from formic acid and propargylic alcohol under ruthenium catalysis, is an excellent formylating agent of sterols, in the presence of a catalytic amount of DBN.

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7. *β -oxopropyl formate (1)*. 83%, colourless liquid; IR 1728 (CO) cm^{-1} . $^1\text{H NMR } \delta$ (CDCl_3 , 300.133 MHz): 8.12 (s, 1 H, HCO); 4.72 (s, 2 H, CH_2); 2.15 (s, 3 H, CH_3). MS (m/z) 102 (M^+).
8. *Cholesteryl formate (3a)*. 82%, white crystals m.p. 139-142 °C. IR 1727 (CO); 2936 (CH) cm^{-1} . $^1\text{H NMR } \delta$ (CDCl_3 , 300.133 MHz): 7.99 (s, 1 H, CHO); 5.36 (d, 1 H, $^3J_{\text{HH}} = 3.9$ Hz, CH-6); 4.70 (m, 1 H, CH-3); 2.33 (d, 2 H, $^3J_{\text{HH}} = 7.7$ Hz); 1.98 (m, 2 H); 1.87 (m, 4 H); 1.59÷1.03 (m, 20 H). 1.00 (s, 3 H, Me-19); 0.89 (d, 3 H, $^3J_{\text{HH}} = 6.4$ Hz, Me-21); 0.84 (d, 6 H, $^3J_{\text{HH}} = 6.4$ Hz, Me-26 and Me-27); 0.65 (s, 3 H, Me-18). MS (m/z) 386 ($\text{M}-\text{CO}^+$).
Lanosteryl formate (3b). 70%, white crystals m.p. 128-131 °C. IR 1729 (CO); 2930 (CH) cm^{-1} . $^1\text{H NMR } \delta$ (CDCl_3 , 300.133 MHz): 8.04 (s, 1 H, CHO); 5.02 (t, 1 H, $J = 6.9$ Hz, CH-24); 4.54 (m, 1 H, CH-3); 1.95 (m, 4 H); 1.90÷0.93 (m, 19 H); 1.6 (s, 3 H, Me-29); 1.53 (s, 3 H, Me-27); 1.18 (s, 3 H, Me-19); 0.92 (d, 3 H, $^3J_{\text{HH}} = 4.9$ Hz, Me-21); 0.83 (s, 3 H, Me-29); 0.80 (s, 3 H, Me-30); 0.73 (s, 3 H, Me-28); 0.62 (s, 3 H, Me-18). MS (m/z) 454 (M^+).
Stigmasteryl formate (3c). 72%, white crystals m.p. 166-169 °C. IR 1710 (CO); 2920 (CH) cm^{-1} . $^1\text{H NMR } \delta$ (CDCl_3 , 300.133 MHz): 8.02 (s, 1 H, CHO); 5.28 (d, 1 H, $J = 4.7$ Hz, CH-6); 5.08 (dd, 1 H, $J = 15.1$ and 8.5 Hz, CH-23); 4.94 (dd, 1 H, $J = 15.1$ and 8.5 Hz, CH-22); 4.72 (m, 1 H, CH-3); 2.42 ÷ 0.85 (m, 25 H); 1.00 (d, 6 H, $^3J_{\text{HH}} = 6.2$ Hz, Me-26 and Me-27); 0.83 (d, 3 H, $^3J_{\text{HH}} = 6.4$ Hz, Me-21); 0.82 (s, 3 H, Me-19); 0.79 (t, 3 H, $^3J_{\text{HH}} = 7.3$ Hz, Me-29); 0.69 (s, 3 H, Me-18). MS (m/z) 412 ($\text{M}-\text{CO}^+$).