

Free radical-promoted conjugate addition of activated bromo compounds using titanocene(III) chloride as the radical initiator

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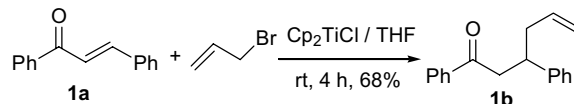
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Abstract—Free radical-promoted conjugate addition of activated bromo compounds to α,β -unsaturated ketones and reactive α,β -unsaturated esters has been described using titanocene(III) chloride (Cp_2TiCl) as the radical initiator. Cp_2TiCl was prepared in situ from commercially available Cp_2TiCl_2 and activated zinc dust in THF.

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Carbon–carbon bond formation through conjugate addition to α,β -unsaturated carbonyl compounds is a powerful synthetic tool in organic chemistry.¹ Typically, an ionic species or an organocopper reagent is used as the nucleophile for this purpose. Only recently have conjugate addition reactions of free radicals to α,β -unsaturated carbonyl compounds, including carbohydrate derivatives, been successfully studied mainly using tin hydrides as the radical initiator.² Some other reagents have also been reported in the literature for conjugate additions.³ However, the radical initiator titanocene(III) species, Cp_2TiCl , has not been explored in detail for conjugate addition of nucleophiles to α,β -unsaturated carbonyl compounds. To our knowledge, only one report on the titanium(III)-promoted C-glycosidation of α,β -unsaturated carbonyl compounds with glycosyl halides has appeared very recently.⁴ In continuation of our studies⁵ towards radical-promoted carbon–carbon bond formation using Cp_2TiCl as the radical initiator, we recently reported an excellent method for the allylation of aldehydes.⁶ We wish to report here a mild and efficient method for the titanium(III)-induced conjugate addition of activated bromo compounds to α,β -unsaturated ketones and reactive α,β -unsaturated esters. The radical initiator Cp_2TiCl was generated⁷ in situ from commercially available Cp_2TiCl_2 and activated zinc dust



Scheme 1.

in THF. In a preliminary experiment, treatment of the enone **1a** with allyl bromide in the presence of Cp_2TiCl in THF at room temperature under argon for 4 h afforded⁸ the 1,4-addition product **1b** in 68% yield (Scheme 1).

Thus, a series of α,β -unsaturated ketones and reactive α,β -unsaturated esters were treated with various activated bromo compounds in the presence of Cp_2TiCl and the results are summarized in Table 1.

Three types of bromo compounds, for example, allyl bromide, propargyl bromide and benzyl bromide were chosen for the conjugate addition. Cyclic ketone **9a**, acyclic ketone **10a** and β -aryl substituted ketones **1a–8a** underwent smooth conjugate addition. While reactive esters **11a** and **12a** took part in the reaction satisfactorily, less reactive esters such as methyl cinnamate remained unchanged under the reaction conditions even after prolonged stirring. It is noteworthy that the results of the conjugate addition of benzyl bromide only to compounds **9a–12a** are shown in Table 1. Conjugate addition of the other bromo compounds (allyl bromide and propargyl bromide) to

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Table 1. 1,4-Conjugate addition of activated bromo compounds to α,β -unsaturated ketones and reactive esters

Entry	Enone	RBr	Time (h)	Product ^a	Yield (%) ^b
1			5		65
2		PhCH ₂ Br	4.5		69
3		PhCH ₂ Br	4.5		67
4			5		66
5		PhCH ₂ Br	6		66
6			4.5		72
7		PhCH ₂ Br	5.5		69
8		PhCH ₂ Br	4.5		71
9		PhCH ₂ Br	4		78
10		PhCH ₂ Br	5		73
11		PhCH ₂ Br	6		70

^a Products were characterized by IR, NMR and HRMS.^b Yield refers to pure isolated product.

9a–12a have also been attempted, however, due to their high volatility, the products could not be isolated after usual work-up.

In conclusion, a free radical-promoted mild and efficient method for conjugate addition of activated bromo compounds to α,β -unsaturated ketones and reactive α,β -

unsaturated esters in good yields using titanocene(III) chloride has been developed.

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- Typical procedure: A solution of titanocene dichloride (249 mg, 1 mmol) in dry THF (10 mL) was stirred with activated zinc dust (196 mg, 3 mmol) (activated zinc dust was prepared by washing 20 g of commercially available zinc dust with 60 mL of 4 N HCl followed by thorough washing with water until the washings became neutral and finally washed with dry acetone and then dried in vacuo) for 1 h under argon. The resulting green solution was added slowly to a stirred solution of the enone **1a** (104 mg, 0.5 mmol) and allyl bromide (60 mg, 0.5 mmol) in dry THF (5 mL) at room temperature over 1.5 h. The reaction mixture was then stirred for an additional 2.5 h and finally decomposed with 10% aqueous H₂SO₄ solution (5 mL). Most of the solvent was removed under reduced pressure and the residue obtained was extracted with diethyl ether (4 × 25 mL). The ether layer was successively washed with water (2 × 10 mL), brine (2 × 10 mL) and finally dried (Na₂SO₄). After removal of the solvent, the crude residue obtained was purified by column chromatography over silica gel (5% ethyl acetate in petroleum ether) to afford **1b** (85 mg, 68%) as a crystalline solid mp 50–51 °C. IR (neat): 2927, 1678, 1639, 1595, 1494, 1448, 1352, 1261, 1215 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.38 (dd, *J* = 7.2, 6.9 Hz, 2H), 3.21 (d, *J* = 6.6 Hz, 2H), 3.35–3.45 (m, 1H), 4.88 (d, *J* = 9.9 Hz, 1H), 4.92 (d, *J* = 16.5 Hz, 1H), 5.54–5.68 (m, 1H), 7.07–7.23 (m, 5H), 7.34 (dd, *J* = 8.1, 7.5 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 40.5, 40.6, 44.4, 116.6, 126.2, 127.4, 128.3, 128.4, 128.8, 132.8, 136.1, 137.0, 144.2, 198.8. HRMS (ESI) calcd for C₁₈H₁₉O (M⁺+H): 251.1436; found 251.1430.