Three-step α-Acylation of (*E*)-Cinnamate Esters with Inversion of Stereochemistry through Formation and Cleavage of Carbon–Pentamethylcyclopentadienyl Bonds

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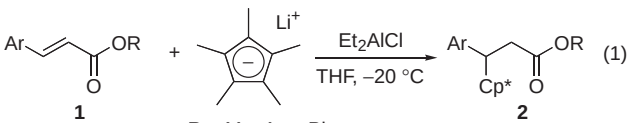
The reaction of cinnamate esters with lithium pentamethylcyclopentadienide in the presence of chlorodiethylaluminum provides the corresponding 1,4-adducts in high yield. The adducts undergo α-acylation reaction upon treatment with lithium diisopropylamide and acid chlorides. Removal of the pentamethylcyclopentadienyl group by the action of base affords α-acylcinnamate esters, in which the aryl and alkoxycarbonyl groups are in cis relationship.

One can accomplish transformation of 2-alkenoate ester into 2-acylalkenoate ester by the following two methods. One is the Morita–Baylis–Hillman reaction followed by oxidation of the resulting alcohol.[1] The other is a sequence of hydrogenation of 2-alkenoate ester, base-mediated α-acylation with acid chloride, and oxidation such as selenoxide elimination.[2] Here, we report an alternative method. Conjugate addition of pentamethylcyclopentadienide ($Me_5C_5^-$, Cp^{*-}) to (*E*)-cinnamate esters yielded the corresponding adducts. The adducts sequentially underwent α-acylation and elimination of pentamethylcyclopentadiene (Cp*H) to yield (*Z*)-α-acylcinnamate esters. The overall transformation thus proceeded with inversion of configuration. The elimination step includes carbon–carbon bond cleavage of the Cp*–C bonds, which we have been focusing on.[3]

Treatment of methyl cinnamate (**1a**) with lithium pentamethylcyclopentadienide (LiCp*) in the presence of chlorodiethylaluminum in THF at −20 °C provided the corresponding 1,4-adduct **2a** in 98% yield (Eq 1).[4] Both electron-donating and -withdrawing groups on the phenyl ring of **1** did not retard the addition reactions. Unfortunately, the addition reactions to methyl crotonate and butyl acrylate provided complex mixtures arising from oligomerizations of the unsaturated esters. The addition of lithium cyclopentadienide (LiC_5H_5), instead of LiCp*, yielded a complex mixture under the otherwise identical reaction conditions. In the absence of chlorodiethylaluminum, the reaction did not proceed smoothly, and a half of **1** was recovered.

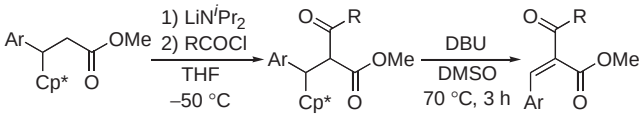


a: R = Me, Ar = Ph 98%
b: R = Me, Ar = *p*-Br-C_6H_4 85%
c: R = Me, Ar = *p*-MeO-C_6H_4 81%
d: R = Et, Ar = *p*-NC-C_6H_4 95%

The adducts **2** were acylated with acid chlorides after deprotonation by lithium diisopropylamide (Table 1, first step).[5] The acylation provided products **3** as a single diastereomer whereas **3d** and **3g** were obtained as mixtures of two diastereomers in ratios of 94:6 (Entries 4 and 7). The relative stereochemistry of the diastereomers could not be determined. The acylation reactions were performed at −50 °C, since higher temperatures induced the formation of **1** through liberation of Cp^{*-} from the corresponding lithium enolate of **2**. The acylation of **2** proceeded not only with aromatic acid chlorides but also with cyclohexanecarbonyl chloride (Entry 3). Attempted acylations with pivaloyl chloride and with propanoyl chloride both resulted in the recovery of most of **2a**. The unsuccessful acylations are attributed to the steric reason of pivaloyl chloride and to the facile deprotonation reaction of propanoyl chloride with the enolate of **2a**. Acylation with electron-rich *p*-methoxybenzoyl chloride also resulted in failure.

Treatment of **3** with 1,8-diazabicyclo[5.4.0]undecene (DBU) in dimethyl sulfoxide (DMSO) at 70 °C gave rise to the formation of the conjugated cinnamate skeleton, furnishing α-acylcinnamate esters **4** in good yields (Table 1, second step).[6] It is worth noting that the aryl and methoxycarbonyl groups are on the same side of the double bond[7] except for **4c** and **4e**. The (*Z*) stereoselectivity of the reactions is quite similar to that of the Knoevenagel reaction.[7] The stereochemistry of **4** would thus be controlled at the elimination step. It is also probable that isomerization of the disfavored (*E*)-form into the thermodynamically stable (*Z*)-form occurred, which was indeed observed in the synthesis of **4e** (Entry 5). The substituent at the ortho position of

Table 1. Transformation of the Cp* adducts **2** to 2-acylcinnamates **4**



Entry	Ar	R	3/%	4/%
1	Ph (**2a**)	Ph	85, **3a**	93, **4a**
2	Ph (**2a**)	*m*-MeO-C_6H_4	83, **3b**	81, **4b**
3	Ph (**2a**)	*c*-C_6H_{11}	82, **3c**	69, **4c**[a]
4	Ph (**2a**)	*p*-Me-C_6H_4	83, **3d**[b]	70, **4d**
5	Ph (**2a**)	*o*-Cl-C_6H_4	83, **3e**	38, **4e**[c]
6	Ph (**2a**)	*m*-Cl-C_6H_4	82, **3f**	78, **4f**
7	*p*-Br-C_6H_4 (**2b**)	Ph	85, **3g**[b]	70, **4g**

[a]A 1:1 mixture of (*E*) and (*Z*) isomers. [b]A 94:6 mixture of diastereomers. [c]Initially a 45:55 mixture of (*E*) and (*Z*) isomers was obtained soon after aqueous workup. The isomeric mixture was quantitatively converted to the pure (*Z*) isomer (>95:5) upon standing the mixture overnight.

the acyl moiety interfered with the removal of the Cp* group (Entry 5). A catalytic amount of DBU also induced the elimination reaction, albeit the efficiency was unsatisfactory. Treatment of **3a** with 0.30 equiv of DBU in DMSO at 70 °C for 6 h furnished **4a** in 68% yield.

In conclusion, we have developed a three-step α-acylation of (*E*)-cinnamate ester with inversion of configuration. The transformation takes advantage of the facile Cp*–carbon bond cleavage.

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References and Notes

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4 Procedure for nucleophilic addition of Cp*Li to α,β-unsaturated ester: A solution of *n*-BuLi in hexane (1.67 M, 12.0 mL, 20 mmol) was added to a solution of 1,2,3,4,5-pentamethyl-1,3-cyclopentadiene (3.3 mL, 21 mmol) in THF (100 mL) at −20 °C. The mixture was stirred for 30 min at the same temperature to provide a white suspension of lithium pentamethylcyclopentadienide. Chlorodiethylaluminum (2.5 mL, 21 mmol) was added to the resulting mixture, and the reaction mixture was stirred for 30 min at −20 °C. After an addition of **1a** (1.62 g, 10 mmol) in THF (10 mL), the mixture was stirred for an additional 1 h at −20 °C. The reaction was quenched with water, and the mixture was extracted with ethyl acetate. The combined organic parts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude oil. The oil was purified by chromatography on silica gel (hexane/ethyl acetate = 30:1) to afford **2a** (2.92 g, 9.8 mmol, 98%). Methyl 3-(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)-3-phenylpropanoate (**2a**): IR (nujol) 1743 cm^{-1}; ^{1}H NMR (C_6D_6) δ 0.92 (s, 3H), 1.55 (s, 6H), 1.64 (brs, 3H), 1.82 (s, 3H), 2.44 (dd, J = 2.1, 9.6 Hz, 1H), 2.75 (dd, J = 6.9, 9.6 Hz, 1H), 3.15 (s, 3H), 5.54 (dd, J = 2.1, 6.9 Hz, 1H), 7.01–7.11 (m, 5H); ^{13}C NMR (C_6D_6) δ 10.89, 11.04, 11.07, 11.88, 20.30, 34.79, 46.66, 50.94, 58.88, 126.72, 127.55 (×2), 128.29, 129.52 (×2), 131.48, 135.72, 140.31, 140.71, 172.87. Found: C, 80.50; H, 8.78%. Calcd for $C_{20}H_{26}O_2$: C, 80.80; H, 8.97%. mp 47–49 °C.

5 General procedure for acylation of 1,4-adduct: A solution of *n*-BuLi in hexane (1.55 M, 0.71 mL, 1.1 mmol) was added to a solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (10 mL) at 0 °C. The mixture was stirred for 30 min at the same temperature. The reaction mixture was cooled to −50 °C. Ester **2a** (298 mg, 1.0 mmol) in THF (1 mL) was added to the resulting mixture, and the reaction mixture was stirred for 5 h. Benzoyl chloride (0.14 mL, 1.2 mmol) was added to the reaction mixture, and the mixture was stirred for 2 h at −50 °C. After being stirred for 2 h, the reaction was quenched with water. The mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried, and concentrated. The oil obtained was chromatographed on silica gel (hexane/ethyl acetate = 10:1) to afford **3a** (342 mg, 0.85 mmol, 85% yield). Methyl 2-benzoyl-3-(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)-3-phenylpropanoate (**3a**): IR (nujol) 1736, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.79 (s, 3H), 1.62 (s, 3H), 1.66 (s, 3H), 1.81 (s, 3H), 2.02 (s, 3H), 3.62 (s, 3H), 3.98 (d, J = 6.9 Hz, 1H), 5.11 (d, J = 6.9 Hz, 1H), 6.94–7.02 (m, 5H), 7.34–7.38 (m, 2H), 7.46–7.50 (m, 1H), 7.76–7.80 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 10.85, 11.21, 11.76, 12.18, 21.00, 49.65, 52.32, 55.52, 58.46, 125.96, 126.97 (×2), 128.10 (×2), 128.23 (×2), 129.11 (×2), 132.78, 135.73, 135.82, 137.12, 138.92, 139.48, 139.93, 168.23, 193.98. Found: C, 80.30; H, 7.50%. Calcd for $C_{27}H_{30}O_3$: C, 80.56; H, 7.51%. mp 135–136 °C.

6 Typical procedure for elimination of Cp*H: DBU (0.050 mL, 0.36 mmol) was added to a solution of **3a** (121 mg, 0.30 mmol) in DMSO (6.0 mL). The reaction mixture was warmed to 70 °C and the mixture was stirred for 3 h. The reaction was quenched with water, and the mixture was extracted with ethyl acetate. The combined organic parts were washed with brine, dried, and concentrated. Chromatographic purification on silica gel (hexane/ethyl acetate = 5:1) afforded **4a** (62.4 mg, 0.28 mmol, 93%). The NMR spectra of **4a** were identical to those reported in Ref. 7.

7 The stereochemistry of **4a** was confirmed according to the literature: R. Tanikaga, N. Konya, K. Hamamura, A. Kaji, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3211.

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