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Powerful Claisen condensation and Claisen–aldol tandem reaction of α,α-dialkylated esters promoted by $ZrCl_4$–$^iPr_2NEt$

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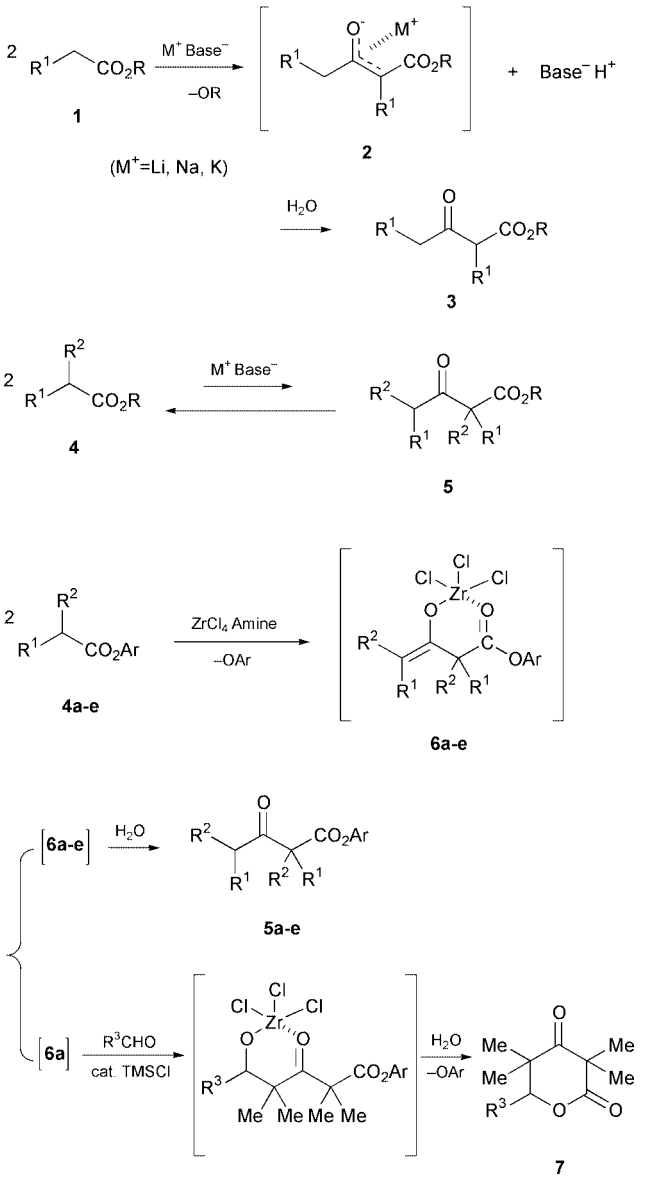
Powerful Claisen ester condensations of α,α-dialkylated esters mediated by $ZrCl_4$–$^iPr_2NEt$ were performed to give the corresponding thermodynamically unfavorable α,α-dialkylated β-ketoesters, and Claisen–aldol tandem reactions between an intermediary Zr-enolate of a α,α-dialkylated β-ketoester and aldehydes also proceeded.

The Claisen ester condensation is recognized as a fundamental and useful C–C bond-forming reaction.[1] Traditional Claisen condensations using alkali-metal basic reagents such as NaOR, NaH, LDA and LiHMDS are widely applied to α-monoalkylated esters **1** giving the corresponding dimeric β-ketoesters **3** (Scheme 1). However, α,α-dialkylated esters **4** could not undergo this type of the condensation, because **4** lacks the ability to force the formation of a stable enolate.[1,2] Actually, the reversible equilibrium barely shifts from **4** to the unfavorable production of the β-ketoesters **5**. Thermodynamics dictate that the starting α,α-dialkylated esters **4** are more stable than the desired β-ketoesters **5**, namely, the retro-Claisen condensation of esters **5** should predominate.[1,2] Although two methods for the Claisen condensation of alkyl 2-methylpropanoate using strong bases ($Ph_3C^-\cdot Na^+$ or KH)[3,4] have been reported, the yields were moderate to low (~35%).† In addition, these methods describe the sole example of the condensation of alkyl 2-methylpropanoate.

Recently, Ti–Claisen condensations were demonstrated[5–9] and proved to be more reactive and practical between α-monoalkylated esters than the representative method using NaH or LDA.‡ However, this method is unfortunately limited to the case of α-monoalkylated esters **1**. Here we introduce the powerful Claisen ester condensation of α,α-dialkylated esters **4** promoted by the $ZrCl_4$–$^iPr_2NEt$ reagent and its extension to the Claisen–aldol tandem reaction.

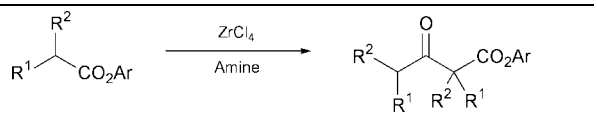
First, the Claisen condensation of α,α-dialkylated esters is described. Although ethyl 2-methylpropanoate was inert (no reaction) to $ZrCl_4$–amine (Et_3N, Bu_3N, or $^iPr_2NEt$) reagent, successful results were obtained using a slightly more acidic substrate, phenyl 2-methylpropanoate (**4a**). Treatment of **4a** with $ZrCl_4$–$^iPr_2NEt$ afforded the desired phenyl 2,2,4-trimethyl-3-oxopentanoate (**5a**) in 72% yields under optimized conditions.§ Table 1 summarizes the results of the Zr–Claisen condensation of α,α-dialkylated esters **4a**–**e**. Replacement of phenyl ester **4b** for 4-chlorophenyl analog **4e** increased the yield. On the other hand, $TiCl_4$–Bu_3N agent (with or without cat. TMSCl *or* cat. TMSOTf) failed to drive the reaction (no reaction).

Phenyl esters are readily prepared by several methods and, in addition, are smoothly hydrolyzed under milder conditions compared with alkyl esters.[10] A little higher acidity of phenyl esters than that of alkyl esters is suggested by the following two experiments: (a) ^1H NMR chemical shifts of α-hydrogen of **4a**



Scheme 1

Table 1 Claisen condensations of α,α-dialkylated esters promoted by $ZrCl_4$–amine[a]



4	R^1	R^2	Ar	Amine	Yield (%)
4a	Me	Me	Ph	Et_3N	6
4a	Me	Me	Ph	Bu_3N	19
4a	Me	Me	Ph	TMEDA	Trace
4a	Me	Me	Ph	$^iPr_2NEt$	72
4b	Me	Et	Ph	$^iPr_2NEt$	44
4c	Me	Et	2-Cl-Ph	$^iPr_2NEt$	29
4d	Me	Et	2-MeO-Ph	$^iPr_2NEt$	22
4e	Me	Et	4-Cl-Ph	$^iPr_2NEt$	55

[a] In CH_2Cl_2 at −15 to −20 °C for 3 h. Molar ratio; **4**–$ZrCl_4$–amine = 1.0:2.0:3.0.

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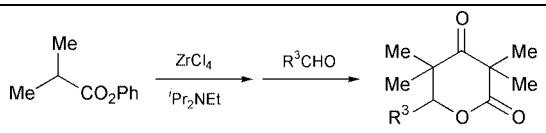
Table 2 Claisen–aldol tandem reactions of phenyl 2-methylpropanoate (**4a**) with aldehydes promoted by ZrCl–$^{i}Pr_2NEt$–(catalytic TMSCl)[a]



4a **7**

R^3	Product	Yield	R^3	Product	Yield[b] (%)
Ph	**7a**	71	PhCH=CH	**7e**	57
4-Cl-Ph	**7b**	59	2-Naphthyl	**7f**	43 (54)
4-NO_2-Ph	**7c**	61	*n*-Pr	**7g**	54 (74)
4-MeO-Ph	**7d**	57	^{i}Pr	**7h**	31 (61)

[a] In CH_2Cl_2 at −15 to −20 °C for 3 h. Molar ratio; **4a**–$ZrCl_4$–amine–aldehyde = 1.0:2.0:3.0:1.0. [b] Parentheses indicate the yields using catalytic TMSCl (0.05 equiv.).

and ethyl 2-methylpropanoate were located at 2.80 and 2.53 ppm, respectively; and (b) when equimolar mixtures of **4a** and ethyl 2-methylpropanoate in THF were treated with 1 equiv. of LDA at 0–5 °C for 1 h, followed by quenching with D_2O, the ratio of α-deuterated esters was *ca*. 9:1 by the ^{1}H NMR measurement.

The successful results using the Zr reagent suggest that the strong chelation effect of zirconium toward two carbonyl oxygens and longer bond length between Zr–O than that between Ti–O contribute to drive the reactions, releasing steric constraint around the crowded Zr-intermediate **6**.

Next, the intermediary Zr-enolate **6a** was utilized for further C–C bond formation. Namely, the first Claisen–aldol tandem reaction between 2 equiv. of phenyl 2-methylpropanoate **4a** and several aldehydes successfully proceeded in a one-pot manner through intermediary Zr-enolate **6a**, eventually affording pyran-2,4-diones **7** with a concomitant lactonization.¶ Table 2 summarizes these results. It should be noted that catalytic TMSCl significantly affects the second aldol addition step for some aldehydes.[7]

Thus, we achieved an efficient, powerful and practical Zr–Claisen condensation and the first Claisen–aldol tandem reaction of α,α-dialkylated esters **4**.

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Notes and references

† In the first method,[3] preparation of the $Ph_3C^{-}\cdot Na^{+}$ reagent includes a tedious procedure from a practical and green chemical standpoint: *ca*. 9.3 g of 1% Na(Hg) *vs*. 0.28 g (1 mmol) of Ph_3CCl is used for ethyl 2-methylpropanoate (0.21 g, 1.8 mmol). The second method[4] using KH lacks generality; this reaction failed to proceed in several of our experiments when ethyl 2-methylpropanoate was employed as the substrate.

‡ For an example of the Claisen condensation of methyl dec-9-enoate using NaH by the reported method,[11] the desired β-ketoester was obtained in *ca*. 75% (DME, reflux, 20 h). The Ti–Claisen condensation proceeded with a 93% yield (toluene, 0–5 °C, 1 h).[8] Accordingly, the Ti–Claisen condensation clearly has the advantage of a high yield, mild conditions and a shorter reaction time. Related Dieckmann condensation using $AlCl_3$ is also reported.[12]

§ A typical procedure is as follows. $^{i}Pr_2NEt$ (388 mg, 3.0 mmol) in CH_2Cl_2 (0.5 cm^3) was added to a stirred suspension of $ZrCl_4$ (466 mg, 2.0 mmol) and phenyl 2-methylpropanoate (164 mg, 1.0 mmol) in CH_2Cl_2 (2.5 cm^3) at −15 to −20 °C. After stirring at the same temperature for 3 h, the mixture was quenched with water (5 cm^3) and extracted twice with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (hexane–ether = 30:1) to give phenyl 2,2,4-trimethyl-3-oxopentanoate (84 mg, 72%). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (6H, d, J = 7.2 Hz), 1.53 (6H, s), 3.01–3.11 (1H, m), 7.05–7.09 (2H, m), 7.22–7.26 (2H, m), 7.37–7.41 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.42, 21.85, 36.98, 56.33, 121.11, 126.08, 129.51, 150.51, 172.35, 212.12. IR (film) 2980, 2938, 1763, 1717, 1196, 1121 cm^{-1}.

¶ A typical procedure is as follows. In place of quenching with water, TMSCl (0.006 cm^3, 0.05 mmol) and isobutyraldehyde (72 mg, 1.0 mmol) were successively added to a stirred reaction mixture at 0–5 °C. The mixture was stirred for 2 h, and was then quenched with water (5 cm^3) and extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude crystals were purified by SiO_2-column chromatography (hexane–AcOEt = 20:1 → 10:1) to give 3,3,5,5-tetramethyl-6-(1-methylethyl)pyran-2,4-dione (65 mg, 61%). Colorless crystals; mp 34.0–34.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, d, J = 6.8 Hz), 1.13 (3H, s), 1.14 (3H, d, J = 6.8 Hz), 1.22 (3H, s), 1.43 (3H, s), 1.44 (3H, s), 2.08–2.16 (1H, m), 4.12 (1H, d, J = 3.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.15, 18.21, 20.60, 22.50, 23.88, 25.63, 28.93, 47.59, 50.03, 83.97, 174.79, 211.36. IR (film) 2978, 2942, 1750, 1711, 1290, 1152, 1024 cm^{-1}.

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