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Sequential 1,4-Addition and Ireland−Claisen Rearrangement Promoted by a Manganese−$PbCl_2$−Me_3SiCl System[1]

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Carbon−carbon bond formation from radicals provides an attractive alternative to methods based on anions, with carbon radicals having different selectivity from the corresponding anionic reagents. As a result, this approach is being increasingly employed in organic synthesis.[2]

Ketene silyl acetals of allylic esters are the precursors of the Ireland−Claisen rearrangement[3] and are usually prepared by deprotonation and trapping with Me_3SiCl. A 1,4-addition to allylic acrylates and silylation can also be used;[4,5] however, since the acrylates have four potential electrophilic sites that can result in 1,2-addition (a), 1,4-addition (b), S_N2 (c), and S_N2' (d) positions (Figure 1), it is necessary to control the regiochemistry. Alkyllithium and magnesium reagents selectively add to the carbonyl carbon in a 1,2-fashion, while dialkylcopper lithium reagents react exclusively at the S_N2' position.[4] Here, the 1,4-selectivity of alkyl radicals derived by reduction with activated manganese[6] was utilized in the preparation of ketene silyl acetals. It was found that the successive Ireland−Claisen rearrangement from the intermediate silyl acetals proceeded smoothly at ambient temperature.

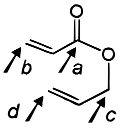
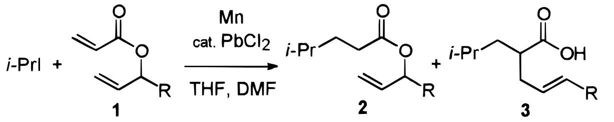


Figure 1. Potential electrophilic sites of allyl acrylate.

Table 1. Effects of Additives on 1,4-Addition and Sequential Rearrangement[a]



run	Me_3SiCl (equiv)	additive (equiv)	*T* (°C)	time (h)	yield of **2**[b] (%)	yield of **3**[b] (%)
1	0.1		90	3	47	0
2	1.0		25	0.5	48	43
3	3.0		25	0.5	43	31
4	3.0	DMAP, 3.0	25	0.5	14	81
5	3.0	NMI, 3.0	25	0.5	7	92

[a] Reaction was conducted on a 1.0 mmol scale. Three mol of isopropyl iodide, 6.0 mol of manganese, and 0.06 mol of $PbCl_2$ were used per mol of acrylate **1**. R = *n*-C_5H_{11}. [b] Isolated yields.

Treatment of acrylate **1** with isopropyl iodide and manganese[7] activated by a catalytic amount of $PbCl_2$[8] and Me_3SiCl[9] in a mixed solvent of DMF and THF at 90 °C for 3 h afforded 1,4-adduct **2** in 47% yield (Table 1, run 1).[10] When an equimolar amount of Me_3SiCl was used with the substrate, the adduct **2** and rearranged product **3** were produced in 48% and 43% yields, respectively, at 25 °C for 30 min (Table 1, run 2). This result suggests that the rearrangement does not proceed from a manganese enolate anion[11] but, rather, occurs after trapping to its silyl acetal. It is known that 4-(dimethylamino)pyridine (DMAP) and *N*-methylimidazole (NMI) accelerate the silylation step,[12] and thus, when added, the sequential Claisen rearrangement proceeded smoothly, and the acid **3** was obtained in excellent yields (Table 1, runs 4 and 5). The double bond produced was proven to have *E* geometry as expected from the Ireland−Claisen rearrangement.[13]

Primary, secondary, and tertiary alkyl iodides can be used for the sequential 1,4-addition and Ireland−Claisen rearrangement, the results of which are shown in Table 2.[17] Because the reduction of a primary iodide proceeds slower than that of a secondary iodide, in this case, the reaction was conducted with 5 mol % of $PbCl_2$ and heated at 40 °C (Table 2, run 7). Although 1,4-addition occurred smoothly with *tert*-butyl iodide in almost quantitative yield, the successive rearrangement proceeded slowly,

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(1) Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

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(13) Authentic samples of γ,δ-unsaturated esters with *E* geometry were prepared by the following route: (1) Inanaga's Claisen rearrangement;[5] (2) esterification; (3) 1,4-addition. For comparison of the geometry of the double bond, (*Z*)-methyl esters were prepared: (1) dihydroxylation of (*E*)-methyl esters, OsO_4, NMO/acetone, H_2O, 25 °C, 5 h, 84−75%;[14] (2) $NaIO_4$, SiO_2, CH_2Cl_2, 25 °C, 15 h, 69−55%;[15] $Ph_3P(CH_2)_5CH_3^+Br^-$, $NaN(SiMe_3)_2$, −78 to +25 °C, 70−35%.[16] In the case of the Wittig olefination with benzylidenetripenylphosphorane (for Table 2, run 3), a mixture of olefins (*Z*/*E* = 26/74) was obtained.

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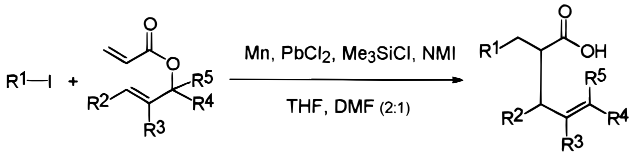
Table 2. Sequential 1,4-Addition and Ireland-Claisen Rearreangement[a]

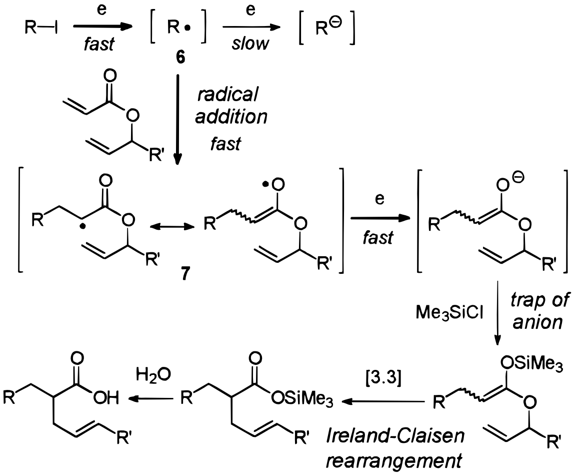


run	R^1	R^2	R^3	R^4	R^5	T (°C)	time (h)	yield[b] (%)	E/Z[c]
1	*i*-Pr	H	H	*n*-C_5H_{11}	H	25	0.5	92	>99/<1
2		H	H	c-C_6H_{11}	H	25	0.5	95	>99/<1
3		H	H	Ph	H	25	0.5	75	98/2
4		H	H	−$(CH_2)_5$−		25	0.5	88	
5		Me	H	H	H	40	2	83[d]	
6		H	Me	H	H	40	3	75[e]	
7	*n*-Pr	H	H	*n*-C_5H_{11}	H	40	2	88[f]	>99/<1
8	*t*-Bu	H	H	*n*-C_5H_{11}	H	25	0.5	52[g]	>99/<1

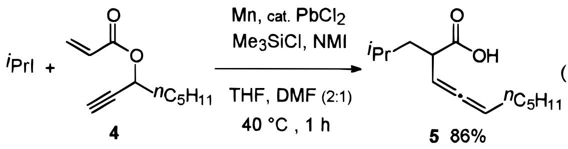
[a] Reaction was conducted on a 1.0 mmol scale. See typical procedure. [b] Isolated yields. [c] Determined by ^{1}H NMR and/or ^{13}C NMR analysis of the corresponding methyl ester. [d] *Anti*/*syn* = 48/52. [e] 1,4-Adduct was obtained in 20% yield. [f] 5 mol % of $PbCl_2$ was used. [g] 1,4-Adduct was produced in 42% yield. When the mixture was treated at 40 °C for 3 h, the rearranged carboxylic acid was produced in 53% yield along with the 1,4-adduct in 39% yield.

probably due to steric hindrance around the newly formed carbon−carbon bond (Table 2, run 8). Heating the mixture at 40 °C, however, did not improve the yield of rearranged carboxylic acid. In contrast to the reported Ireland−Claisen rearrangement,[3b] a substituent at R^2 did not accelerate the rearrangement. For example, the reaction at 25 °C for 1 h produced the rearranged carboxylic acid and 1,4-adduct in 30% and 47% yield, respectively, while the reaction at 40 °C for 3 h produced the acid in 83% yield (Table 2, run 5). The product in run 5 was obtained as an *anti*/*syn* mixture of diastereomers in a 48/52 ratio.[3b] The low diastereoselectivity stems from the fact that both *E* and *Z* ketene silyl acetals are produced in an almost 1/1 ratio under the conditions.[18]

Scheme 1



Treatment of propargylic acrylate **4** with isopropyl iodide and the manganese system at 40 °C for 1 h produced the corresponding allenic carboxylic acid **5** in 86% yield as a 1/1 mixture of diastereomers (eq 1).



(1)

A plausible mechanism for this sequential reaction is shown in Scheme 1. The reduction of an iodoalkane with the manganese−$PbCl_2$−Me_3SiCl system produces the corresponding alkyl radical **6**, which has a sufficient lifetime for intermolecular addition to an acrylate, even under the reduction conditions. In contrast, reduction of the adduct radical **7** takes place smoothly to give an ester enolate that is trapped with Me_3SiCl. The Ireland−Claisen rearrangement and hydrolysis affords an (*E*)-γ,δ-unsaturated acid. This sequential reaction is made possible by the moderate manganese reducing system discriminating between the two radicals **6** and **7**.[6]

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Supporting Information Available: Characterization data for all new compounds (4 pages).

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(17) **Typical Procedure for 3.** Me_3SiCl (0.38 mL, 3.0 mmol) and *N*-methylimidazole (NMI, 0.25 g, 3.0 mmol) were added at 25 °C to a mixture of manganese powder (0.33 g, 6.0 mmol) and $PbCl_2$ (17 mg, 0.060 mmol) in THF (4 mL) under an argon atmosphere, and the mixture was stirred at 25 °C for 30 min. To the mixture was added a solution of an allylic acrylate **1** (0.18 g, 1.0 mmol) in DMF (1 mL) at 25 °C. A solution of isopropyl iodide (0.51 g, 3.0 mmol) in DMF (1 mL) was then added to the mixture at 25 °C, producing an exothermic reaction (ca. 35 °C). After the resulting mixture was stirred at 25 °C for 30 min, saturated NH_4Cl solution (10 mL) was added, and the mixture was filtered with Celite and washed well with ether (3 × 10 mL). Organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel (hexane−ethyl acetate, 30:1) gave the γ,δ-unsaturated acid **3** (0.21 g, 0.92 mmol) in 92% yield.

(18) Trapping of the enolate derived from 2-phenylpropyl acrylate and isopropyl iodide with manganese, $PbCl_2$, and Me_3SiCl produced *E* and *Z* ketene silyl acetals in a 44/56 ratio.