First sequential Mukaiyama–Michael reaction/crossed-Claisen condensation using two molar ketene silyl acetals and one molar α,β-unsaturated esters promoted by a NaOH catalyst†

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The NaOH-catalyzed first sequential Mukaiyama–Michael reaction/crossed-Claisen condensation is developed using two molar ketene silyl acetals and one molar α,β-unsaturated esters in either a stepwise or one-pot manner.

The Michael reaction and Claisen condensation reaction are well-recognized fundamental C–C bond forming protocols in organic syntheses. For the Michael reaction, there are a number of reported methods using α,β-unsaturated ketones, aldehydes, and sometimes esters as the acceptor.[1] The Mukaiyama–Michael (M–M) reaction using silyl enolates is a superb variant because of its mild reaction conditions and conjugate addition regioselectivity.[2] The M–M-reaction, however, lacks substrate-generality for intrinsically less reactive α,β-unsaturated ester acceptors.[3,4] Three crossed-Claisen condensations using silyl enolates with carboxylic acid equivalents (esters and acid chlorides) were exploited, wherein less accessible α,α-dialkylated β-ketoesters were readily prepared.[5]

This background led us to investigate an efficient M–M reaction of ketene silyl acetals (KSAs) **1-A** with α,β-unsaturated esters to give 1,5-diesters **2**, followed by crossed-Claisen condensation of KSAs **1-B** with **2** (Scheme 1). Here, we disclose a mild but powerful LiOH (*or* NaOH)-catalyzed method between KSAs **1-A** and a wide range of α,β-unsaturated esters to afford the corresponding 1,5-diesters **2** and subsequent regioselective NaOH-catalyzed crossed-Claisen condensation, which could be performed in a stepwise or one-pot manner to produce less accessible and uniquely functionalized 1,3,7-tricarbonyl compounds **3**. This is the first report of a sequential (tandem) M–M reaction/crossed-Claisen condensation.

For the M–M reaction step, an initial attempt was guided using KSA **1a** ($R^2 = R^3 = \mathrm{Me}$) as **1-A** and methyl crotonate ($R^1 = \mathrm{Me}$) in DMF at 0–5 °C. Among the readily available inorganic base catalysts, LiOH and NaOH produced the best results; Li_2CO_3 (18%), K_2CO_3 (42%), KOH (70%), NaOH (71%, 81% at rt), and LiOH (93%, 80% at rt).[6]

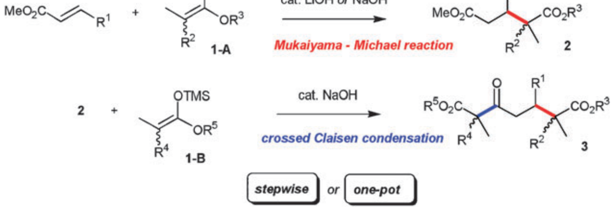
Table 1 lists the successful results of the LiOH (*or* NaOH)-promoted reaction of KSAs **1a** and **1b** ($R^2 = \mathrm{Et}$) with various α,β-unsaturated esters.‡ The salient features are as follows. (i) Due to the high reactivity of the present system, good to excellent yield was obtained in all examples examined despite the simple and mild reaction conditions. (ii) Aliphatic, aromatic, and a 2-furyl α,β-unsaturated esters were applicable as the acceptor. (iii) Terminal double bond, THPO-, and even free HO- groups in R^1 were compatible (entries 4–8).

(iv) The yield and reactivity using aromatic α,β-unsaturated esters were somewhat higher than those using aliphatic esters (entries 9–18). (v) Diastereoselectivity of the products **2** derived from **1b** was *ca.* 1 : 1. Thus, substrate-generality of the present simple LiOH (*or* NaOH)-catalyzed method is equal or better than that of the hitherto reported methods.[3,4]

We next investigated a stepwise M–M reaction/crossed-Claisen condensation between KSAs **1-B** and the M–M adducts **2**. The reported method of NaOH-catalyzed crossed-Claisen condensation of KSAs with methyl esters[5a,d] was applied for this objective.[6] The crossed-Claisen condensation of KSAs **1a–1d** as **1-B** with **2** proceeded smoothly to give the desired 1,3,7-tricarbonyl products **3** in good to excellent yield. Table 2 lists the successful results.‡ It is noteworthy that the present condensation occurred at the less stereocongested methyl ester side with complete regioselectivity, which is consistent with a characteristic feature that Claisen condensation that it is strongly affected by a steric environment.

Based on these successful results, we envisioned a one-pot sequential (tandem) M–M reaction/crossed-Claisen condensation promoted by a NaOH catalyst. Table 3 lists the successful results using 2 molar amounts of the *same two* KSA **1a** (**1-A** and **1-B**) with α,β-unsaturated esters.‡ To our delight, all five examples examined produced good to excellent yields. In the present sequential (tandem) version, the M–M reaction step predominates over the crossed-Claisen condensation step; when using **1a** and methyl crotonate under controlled conditions (0 C, for 3 h), intermediary M–M adduct **2a** was isolated in *ca.* 50% yield with tandem adduct **3a** in 45% yield.

Encouraged by our results, we next focused our attention on a more challenging one-pot sequential (tandem) reaction using *different two* KASs, that is, **1-A** (the M–M reaction nucleophile) and **1-B** (the crossed-Claisen nucleophile) (Table 4)‡.



Scheme 1 Sequential Mukaiyama–Michael reaction/crossed-Claisen condensation.

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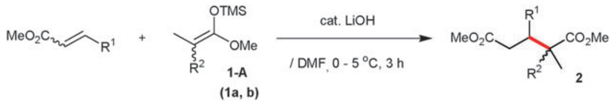
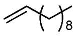
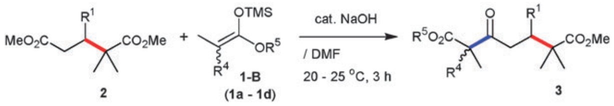
Table 1 LiOH (*or* NaOH)-catalyzed Mukaiyama–Michael reaction of KSAs **1-A** with α,β-unsaturated esters[a]



Entry	R^1	KSA (R^2)	Product	Yield/%
1	Me	**1a** (Me)	**2a**	77
2		**1b** (Et)	**2b**	68
3	*n*-Pr	**1a**	**2c**	77
4		**1b**	**2d**	75
5		**1a**	**2e**	70
6		**1b**	**2f**	69
7	THPO$(CH_2)_4$	**1a**	**2g**	74
8	HO$(CH_2)_4$	**1a**	**2h**	56[b]
9	Ph	**1a**	**2i**	93[c] (70)[d] 70[e] (81)[e]
10		**1b**	**2j**	98[c]
11	(4-MeO)C_6H_4	**1a**	**2k**	96[c]
12		**1b**	**2l**	81[c]
13	(4-Cl)C_6H_4	**1a**	**2m**	86[c]
14		**1b**	**2n**	83[c]
15	[3,4-$(MeO)_2$]C_6H_3	**1a**	**2o**	81[c]
16		**1b**	**2p**	92[c]
17	2-Furyl	**1a**	**2q**	79
18		**1b**	**2r**	81

[a] α,β-Unsaturated ester : **1** : LiOH = 1.0 : 1.5 : 0.3. [b] 2.4 equiv. of **1a** was used to give its TMS ether. [c] 1.2 equiv. of **1** was used. [d] Carried out at rt for 3 h. [e] NaOH catalyst was used instead LiOH at rt for 3 h.

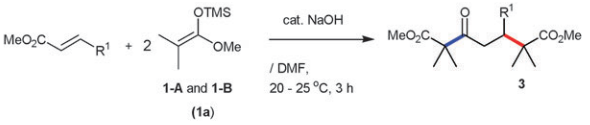
Table 2 NaOH-catalyzed crossed-Claisen condensation of KSAs **1-B** with Mukaiyama–Michael adducts **2**[a]



Entry	R^1	**2**	**1-B** (R^4, R^5)	Product	Yield/%
1	Me	**2a**	**1a** (Me, Me)	**3a**	74
2			**1b** (Et, Me)	**3b**	84
3			**1c** (Me, ^{t}Bu)	**3c**	64
4			**1d** (OTBS, Me)	**3d**	92
5	Ph	**2i**	**1a**	**3e**	96
6			**1b**	**3f**	88
7			**1c**	**3g**	86
8	(4-MeO)C_6H_4	**2k**	**1a**	**3h**	81
9	(4-Cl)C_6H_4	**2m**	**1a**	**3i**	72
10	[3,4-$(MeO)_2$]C_6H_3	**2o**	**1a**	**3j**	98
11			**1b**	**3k**	84
12			**1c**	**3l**	80

[a] **2** : **1** : NaOH = 1.0 : 2.4 : 0.3.

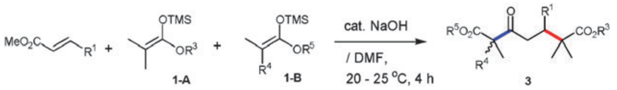
Table 3 NaOH-catalyzed one-pot sequential (tandem) Mukaiyama–Michael/crossed-Claisen condensation of the same two KSAs **1a** (**1-A**, **1-B**) with α,β-unsaturated esters[a]



Entry	R^1	Product	Yield/%
1	Me	**3a**	57
2	Ph	**3e**	85
3	(4-MeO)C_6H_4	**3h**	80
4	(4-Cl)C_6H_4	**3i**	80
5	[3,4-$(MeO)_2$]C_6H_3	**3j**	48

[a] α,β-Unsaturated ester : **1a** : NaOH = 1.0 : 3.3 : 0.3.

Table 4 NaOH-catalyzed one-pot sequential (tandem) Mukaiyama–Michael/crossed Claisen condensation of different two KSAs **1-A** and **1-B** with α,β-unsaturated esters[a]



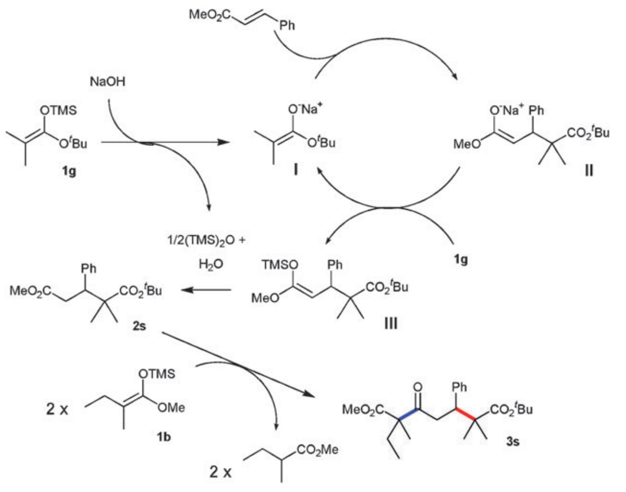
Entry	R^1	**1-A** (R^3)	**1-B** (R^4, R^5)	Product	Yield/%
1	Ph	**1a** (Me)	**1e** (Me, Et)	**3m**	60
2		**1a**	**1f** (Me, ^{i}Pr)	**3n**	60
3		**1a**	**1g** (Me, ^{t}Bu)	**3o**	48
4		**1a**	**1b** (Et, Me)	**3p**	65
5		**1e** (Et)	**1a** (Me, Me)	**3q**	70
6		**1f** (^{i}Pr)	**1a**	**3r**	69
7		**1g** (^{t}Bu)	**1a**	**3s**	59
8	(4-MeO)C_6H_4	**1e**	**1a**	**3t**	70
9		**1f**	**1a**	**3u**	52
10		**1g**	**1a**	**3v**	52
11		**1a**	**1b**	**3w**	53
12	(4-Cl)C_6H_4	**1e**	**1a**	**3x**	69
13		**1f**	**1a**	**3y**	53
14		**1g**	**1a**	**3z**	55
15	Me	**1e**	**1a**	**3α**	46
16		**1g**	**1a**	**3β**	35

[a] α,β-Unsaturated ester: KSA **1-A** : KSA **1-B** : NaOH = 1.0 : 1.2 : 2.0 : 0.4.

Gratifyingly, under carefully optimized conditions (molar ratio, temperature, and period), various reactions proceeded in reasonable yield with excellent regioselectivity to produce highly multi-functionalized 1,3,7-tricarbonyl compounds **3m–3z**, **3α**, and **3β**.[7] The salient features of the reaction are as follows. (i) The success is ascribed to the smooth and a high yielding M–M reaction, followed by a highly regiocontrolled crossed-Claisen condensation. (ii) Reactions using methyl cinnamates (R^1 = aromatic) produced better yield (entries 1–14) than those using methyl crotonate (R^1 = Me). (iii) The variation between Me or Et and ^{i}Pr or ^{t}Bu ester moieties affords differentiation for further synthetic functionalization.

Scheme 2 illustrates a plausible mechanism for the present one-pot reaction exemplified by Table 4, entry 7. Initially, the NaOH catalyst reacts with KSA **1g** to form Na-enolate **I** with the release of 1/2$(TMS)_2O$ and H_2O. **I** couples with methyl cinnamate to give Na-enolate adduct intermediate **II**, which in turn captures a TMS group from **1a** to give intermediary TMS enolate **III** by reforming **I**. **III** is protonated by *in situ*-generated H_2O to form **2s**. Finally, consistent with a reported speculation,[5a,d] **2s** condenses with 2 equiv. of **1b** to produce 1,3,7-dicarbonyl compound **3s**.

In conclusion, we developed a sequential Mukaiyama–Michael reaction and regioselective crossed-Claisen condensation to yield unique 1,3,7-tricarbonyl structural scaffolds. The present method provides a new useful avenue for organic synthesis.



Scheme 2 Plausible mechanism.

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Notes and references

‡ *A typical procedure* of Table 1, entry 1: Methyl crotonate (methyl but-2-enoate) (100 mg, 1.0 mmol) and methoxy-2-methyl-1-(trimethylsiloxy)propene **1a** (261 mg, 1.5 mmol) were successively added to a stirred suspension of LiOH (8 mg, 0.3 mmol) in DMF (commercially technical grade; 1.0 mL) at 0–5 °C under an Ar atmosphere, followed by being stirred at the same temperature for 3 h. Water was added to the reaction mixture, which was extracted with ether. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane : ether = 5 : 1) to give the desired product **2a** (156 mg, 77%).

A typical procedure of Table 2, entry 1: **1a** (209 mg, 1.20 mmol) was added to a stirred solution of **2a** (101 mg, 0.5 mmol) and NaOH (crushed powder, prepared under dry atmosphere; 2 mg, 0.05 mmol) in DMF (0.2 mL) at 20–25 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 3 h. A similar work-up gave the crude product, which was purified by silica-gel column chromatography (hexane : Et_2O = 6 : 1) to give the desired product **3a** (100 mg, 74%).

A typical procedure of Table 3, entry 2: **1a** (288 mg, 1.65 mmol) was added to a stirred solution of methyl cinnamate (81 mg, 0.5 mmol), NaOH (crushed powder, prepared under dry atmosphere; 8 mg, 0.2 mmol) in DMF (0.1 mL) at 20–25 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1.5 h. 1M-HCl–MeOH was added to the reaction mixture to deprotect the TMS group and the mixture was stirred at the same temperature for 0.5 h. A similar work-up gave the crude product, which was purified by silica-gel column chromatography (hexane : Et_2O = 4 : 1) to give the desired product **3e** (142 mg, 85%).

A typical procedure of Table 4, entry 1: **1a** (105 mg, 0.6 mmol) was added to a stirred solution of methyl cinnamate (81 mg, 0.5 mmol), NaOH (crushed powder, prepared under dry atmosphere; 8 mg, 0.2 mmol) in DMF (0.1 mL) at 20–25 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1.5 h. Next, **1e** (188 mg, 1.0 mmol) was added to the mixture, which was stirred at the same temperature for 2 h. 1M-HCl–MeOH was added to the reaction mixture to deprotect the TMS group and the mixture was stirred at the same temperature for 0.5 h. A similar work-up gave the crude product, which was purified by silica-gel column chromatography (hexane : Et_2O = 4 : 1) to give the desired product **3m** (105 mg, 60%).

1 For examples, (*a*) E. D. Bergmann, D. Ginsburg and R. Rappo, in *Org. React.*, Wiley, New York, 1959, vol. 10, p. 179; (*b*) M. B. Smith and J. March, in *March's Advanced Organic Chemistry*, Wiley, New York, 6th edn, 2007, p. 1110; (*c*) L. Kürti and B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier, Burlington, 2005, p. 286.

2 (*a*) K. Narasaka, K. Soai, Y. Aikawa and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 779; Original $TiCl_4$–promoted method. (*b*) T. Nakagawa, H. Fujisawa, Y. Nagata and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 236; Recent base-catalyzed method. Other references cited therein.

3 (*a*) V. M. Swamy and A. Sarkar, *Tetrahedron Lett.*, 1998, **39**, 1261; (*b*) F.-Y. Zhang and E. J. Corey, *Org. Lett.*, 2001, **3**, 639; (*c*) J. Boyer, R. J. P. Corriu, R. Perz and Reya, *Tetrahedron*, 1983, **39**, 117; (*d*) P. G. Klimko and D. A. Singleton, *J. Org. Chem.*, 1992, **57**, 1733; (*e*) M. O. Ratnikov, V. V. Tumanov and W. A. Smit, *Angew. Chem., Int. Ed.*, 2008, **47**, 9739.

4 Contrary to general belief, a literature survey indicates that the M–M reaction using α,β-unsaturated esters has not been fully investigated with regard to substrate-generality, compared with α,β-unsaturated ketones or aldehydes. A notable method involves *ca.* 10 examples using a clay montmorillonite catalyst: M. Kawai, M. Onaka and Y. Izumi, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 2157.

5 (*a*) A. Iida, K. Takai, T. Okabayashi, T. Misaki and Y. Tanabe, *Chem. Commun.*, 2005, 3171; (*b*) A. Iida, S. Nakazawa, T. Okabayashi, A. Horii, T. Misaki and Y. Tanabe, *Org. Lett.*, 2006, **8**, 5215; (*c*) A. Iida, J. Osada, R. Nagase, T. Misaki and Y. Tanabe, *Org. Lett.*, 2007, **9**, 1859; (*d*) K. Takai, Y. Nawate, T. Okabayashi, H. Nakatsuji, A. Iida and Y. Tanabe, *Tetrahedron*, 2009, **65**, 5596.

6 LiOH is more reactive than NaOH for the M–M step. Use of powdered LiOH is convenient and robust enough under bench-top handling due to its less-hygroscopic property. The next crossed Claisen condensation step, however, failed to proceed using a LiOH catalyst. NaOH was therefore employed to link M–M reaction and crossed-Claisen condensation.

7 A related double nucleophilic reactions are reviewed by Shimizu's group; M. Shimizu, I. Hachiya and I. Mizota, *Chem. Commun.*, 2009, 874.