Rhenium- and manganese-catalyzed insertion of acetylenes into β-keto esters: synthesis of 2-pyranones†

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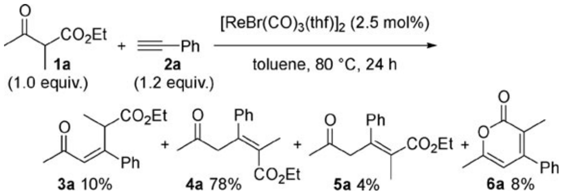
Rhenium- and manganese-catalyzed reactions between β-keto esters and acetylenes, followed by treatment with tetrabutylammonium fluoride, gave 2-pyranone derivatives regioselectively.

2-Pyranone derivatives are important because they serve as structural units of natural products[1] and building blocks of organic molecules.[2] There have been many reports on the synthesis of 2-pyranones.[3] To construct 2-pyranone frameworks regioselectively, we have employed a new synthetic route *via* C–C single bond cleavage (Fig. 1). The reaction proceeds *via* the insertion of an acetylene into a carbon–carbon single bond of a β-keto ester and intramolecular cyclization with the elimination of an alcohol.

By the reaction of β-keto ester **1a** with phenylacetylene (**2a**) in the presence of a rhenium complex, $[ReBr(CO)_3(thf)]_2$, as a catalyst, the insertion of the acetylene into a carbon–carbon single bond of the β-keto ester proceeded, and δ-keto esters **3a**, **4a** and **5a**, which are olefinic isomers, were obtained in 10, 78, and 4% yields, respectively (eqn (1)).[4–6] Interestingly, 2-pyranone **6a** was formed in 8% yield as a side product (eqn (1)).



(1)

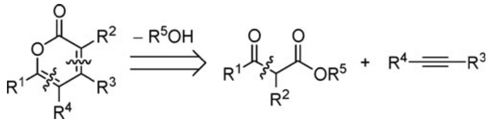
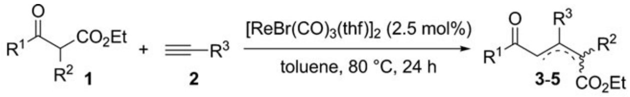


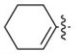
Fig. 1 Retrosynthetic strategy for 2-pyranones.

The reaction forming 2-pyranone **6a** consists of two main parts: (a) the insertion of phenylacetylene (**2a**) into a carbon–carbon single bond of β-keto ester **1a** (carbon chain extension reaction) and (b) the cyclization of the formed δ-keto esters **3a–5a** to give 2-pyranone **6a**. As a preliminary investigation, we examined the first step (Table 1). The reaction of a β-keto ester having a phenethyl group at the active methylene moiety, **1b**, with **2a** in the presence of a rhenium catalyst and molecular sieves (MS) 4A gave a mixture of δ-keto esters in 88% yield (**3b** : **4b** : **5b** = 14 : 84 : 2) (Table 1, entry 1).[7] A β-keto ester without any substituents at the active methylene moiety, **1c**, provided the corresponding δ-keto esters **3c–5c** in moderate yields (Table 1, entry 2). By using β-keto ester **1d**, the yield of the δ-keto esters decreased (Table 1, entry 3). Arylacetylenes having an electron-donating or -withdrawing groups at the *para*-position of the phenyl group, **2b**, **2c** and **2d**, gave δ-keto esters **3–5** in good to excellent yields (Table 1, entries 4–6). By using 1-bromo-4-ethynylbenzene (**2e**), the corresponding δ-keto esters **3h–5h** were obtained without losing the bromo group (Table 1, entry 7). 1-Cyclohexenylacetylene (**2f**) also afforded a mixture of δ-keto esters **3i–5i** in excellent yield (Table 1, entry 8). Acetylenes bearing a primary alkyl group, **2g** and **2h**, provided the corresponding keto esters in moderate to good yields (Table 1, entries 9 and 10).[8] The reaction did not proceed with internal acetylenes at 80 °C. However, when the reactions of internal acetylenes were carried out at 135 °C, they proceeded but did not stop at the formation of δ-keto esters **3–5** (low yields); 2-pyranone **6** was obtained as a major product, as described in Table 2.

When β-keto ester **7** was exposed to the reaction conditions shown in eqn (2), intramolecular insertion of the acetylene moiety into a carbon–carbon bond proceeded, and cyclohexene **8** and methylenecyclohexane **9** were obtained in 66 and 16% yields, respectively (eqn (2)).[9–11] The yield and selectivity

Table 1 Reactions between β-keto esters **1** and acetylenes **2**



	β-Keto ester			Acetylene^a		Yield (%)^b		
Entry		R^1	R^2		R^3		**3** + **4** + **5**	[**3** : **4** : **5**]
1^c	**1b**	Me	$Ph(CH_2)_2$	**2a**	Ph	**3b-5b**	88 (91)	[14 : 84 : 2]
2^c	**1c**	Me	H	**2a**	Ph	**3c-5c**	72 (75)	[33 : 67 : <1]
3^d	**1d**	Ph	Me	**2a**	Ph	**3d-5d**	51 (54)	[15 : 78 : 7]
4	**1a**	Me	Me	**2b**	$4\text{-}(MeO)(C_6H_4)$	**3e-5e**	88 (90)	[17 : 80 : 3]
5	**1a**	Me	Me	**2c**	$4\text{-}Me(C_6H_4)$	**3f-5f**	85 (88)	[10 : 89 : 1]
6^e	**1a**	Me	Me	**2d**	$4\text{-}CF_3(C_6H_4)$	**3g-5g**	90 (93)	[9 : 86 : 5]
7^e	**1a**	Me	Me	**2e**	$4\text{-}Br(C_6H_4)$	**3h-5h**	87 (90)	[8 : 86 : 6]
8	**1a**	Me	Me	**2f**		**3i-5i**	92 (94)	[27 : 67 : 6]
9^f	**1a**	Me	Me	**2g**	$^nC_{10}H_{21}$	**3j-5j**	86 (89)	[35 : 51 : 14]
10^g	**1a**	Me	Me	**2h**	$Ph(CH_2)_2$	**3k-5k**	73 (76)	[29 : 53 : 18]

^{a} **2a** (1.2 equiv). ^{b} Isolated yield. The yield in parentheses and the ratio [**3** : **4** : **5**] were determined by ^1H NMR. ^{c} MS 4A (100 wt% Re cat.), 100 °C. ^{d} MS 4A (200 wt% Re cat.), 100 °C. ^{e} MS 4A (100 wt% Re cat.). ^{f} $2,6\text{-}^iPr_2C_6H_3NC$ (5.0 mol%), MS 4A (200 wt% Re cat.). ^{g} MS 4A (200 wt% Re cat.).

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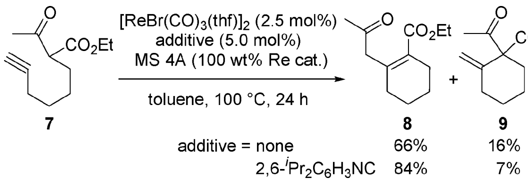
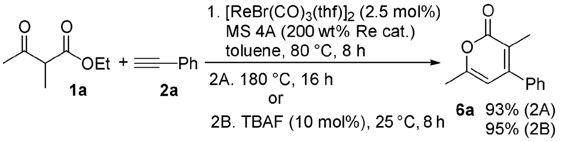
were increased by adding 2,6-diisopropylphenylisocyanide,[12] and cyclohexene **8** was obtained in 84% yield.



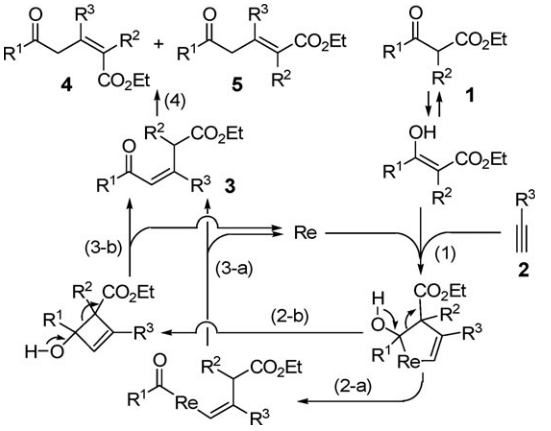
(2)

The proposed mechanism for the formation of δ-keto esters is as follows (Scheme 1): (1) the formation of a rhenacyclopentene intermediate by the reaction of a rhenium catalyst, β-keto ester and terminal acetylene.[13] After the formation of the intermediate, there are two possible pathways; the difference is the timing of the reductive elimination. Path A: (2-a) ring opening by a retro-aldol reaction, (3-a) reductive elimination and (4) isomerization of the olefin moiety.[14] Path B: (2-b) reductive elimination, (3-b) ring opening by a retro-aldol reaction and (4) isomerization of the olefin moiety.[13,14]

Next, we investigated the reaction conditions to improve the yield of 2-pyranone **6a**. In the case of using the rhenium complex $[ReBr(CO)_3(thf)]_2$ as the catalyst, a high temperature (180 °C) was found to be unavoidable (eqn (3), 2A).



(3)

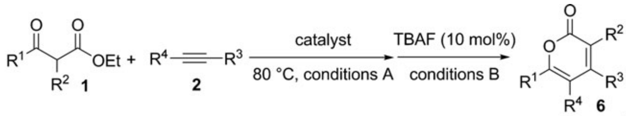


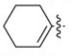
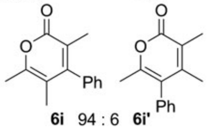
Scheme 1 Proposed mechanism for the formation of δ-keto esters.

The temperature could be lowered substantially when tetrabutylammonium fluoride (TBAF) was added to the reaction mixture. For example, the treatment of β-keto ester **1a** with **2a** in the presence of a catalytic amount of the rhenium complex $[ReBr(CO)_3(thf)]_2$ and MS at 80 °C for 8 h, followed by the addition of a catalytic amount of TBAF and stirring the mixture at 25 °C for 8 h, gave 2-pyranone **6a** in 95% yield (eqn (3), 2B; Table 2, entry 1).[15–18] In this reaction, TBAF has an important role in promoting the formation of 2-pyranone **6a** at 25 °C.[19] Arylacetylenes with electron-donating or -withdrawing groups at the *para*-position, **2b** and **2d**, provided 2-pyranones **6b** and **6c** in almost quantitative yields (Table 2, entries 2 and 3). Enyne **2f** produced the corresponding 2-pyranone **6d** in 92% yield (Table 2, entry 4). By using alkyl acetylene **2g**, 2-pyranone **6e** was formed in 83% yield (Table 2, entry 5). By the reaction of **1b** with **2a**, 2-pyranone **6f** was afforded in good yield (Table 2, entry 6). Next, internal acetylenes were investigated (Table 2, entries 7–10). The insertion of internal acetylenes into a carbon–carbon bond of β-keto esters was found to occur, and four substituted 2-pyranones were obtained in moderate to quantitative yields. The reaction of **1a** with diphenyl acetylene (**2i**) at 150 °C for 24 h gave 2-pyranone **6g** quantitatively (Table 2, entry 7). β-Keto ester **1b** also provided 2-pyranone **6h** in 82% yield (Table 2, entry 8). 1-Phenyl-1-propyne (**2j**) and 6-dodecyne (**2k**) afforded 2-pyranones **6i** + **6i′** and **6j** in 94 and 79% yields, respectively (Table 2, entries 9 and 10). A β-keto ester with no substituent at the active methylene position, **1c**, also produced 2-pyranone **6k** in excellent yield (Table 2, entry 11).

Because transition metals of the first row are abundant and cheap compared to those of the second and third rows of the periodic table, it is important to be able to replace rhenium (third row) catalysts with manganese (first row) catalysts. We noticed that the manganese complex $MnBr(CO)_5$ was also effective for the transformation in some cases, and in contast to the rhenium catalyst, the reaction did not stop at the insertion of the acetylene, even at 80 °C, producing pyranone **6a** in 82% yield (eqn (4)). The results with $MnBr(CO)_5$ are also shown in Table 2. In the case of aryl or conjugated acetylenes, the corresponding 2-pyranones were obtained in moderate to excellent yields (Table 2, entries 1–4 and 6); however, the yields dropped substantially in the case of an alkyl acetylene (Table 2, entry 5). Furthermore, in contrast to the rhenium

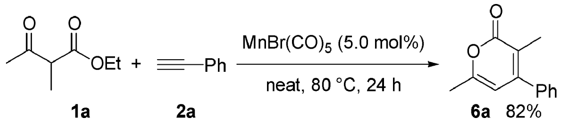
Table 2 Synthesis of 2-pyranones **6** from β-keto esters **1** and acetylenes **2**



	β-Keto ester[a]			Acetylene[a]				Yield (%)[b]	
Entry		R^1	R^2		R^3	R^4		$[ReBr(CO)_3(thf)]_2$ (2.5 mol%) MS 4A (200 wt% Re cat.)[c]	$MnBr(CO)_5$ (5.0 mol%)[d]
1	**1a**	Me	Me	**2a**	Ph	H	**6a**	95 (98)	96 (>99)
2	**1a**	Me	Me	**2b**	4-(MeO)(C_6H_4)	H	**6b**	93 (96)	97 (>99)
3	**1a**	Me	Me	**2d**	4-CF_3(C_6H_4)	H	**6c**	93 (98)	75 (79)[k]
4	**1a**	Me	Me	**2f**		H	**6d**	92 (94)[e]	98 (>99)[k]
5	**1a**	Me	Me	**2g**	$^nC_{10}H_{21}$	H	**6e**	83 (86)[f]	13 (14)
6	**1b**	Ph	Me	**2a**	Ph	H	**6f**	82 (84)[g]	68 (69)
7	**1a**	Ph	Me	**2i**	Ph	Ph	**6g**	98 (>99)[h]	0 (0)
8	**1b**	Ph	Me	**2i**	Ph	Ph	**6h**	82 (85)[i]	0 (0)
9	**1a**	Ph	Me	**2j**	Ph	Me	**6i** + **6i'**	94 (97)[i]	0 (0)
								 **6i** 94 : 6 **6i'**	
10	**1a**	Ph	Me	**2k**	$^nC_5H_{11}$	$^nC_5H_{11}$	**6j**	79 (81)[j]	0 (0)
11	**1c**	Me	H	**2i**	Ph	Ph	**6k**	93 (97)[i]	0 (0)

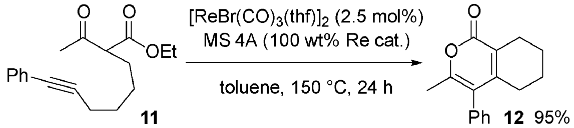
[a] **1** (1.0 equiv); **2** (1.2 equiv). [b] Isolated yield. Yield determined by ^1H NMR is reported in parentheses. [c] Conditions A: toluene, 8 h; conditions B: 25 °C, 8 h. [d] Conditions A: neat, 24 h; conditions B: 50 °C, 2 h. [e] After TBAF was added, the reaction mixture was stirred for 12 h. [f] After TBAF was added, the reaction mixture was stirred for 24 h. [g] 135 °C, 48 h. TBAF was not added. [h] 150 °C. TBAF was not added. [i] 180 °C, 24 h. TBAF was not added. [j] 180 °C, 48 h. TBAF was not added. [k] TBAF (20 mol%).

catalyst, internal acetylenes did not give 2-pyranones (Table 2, entries 7–11).



(4)

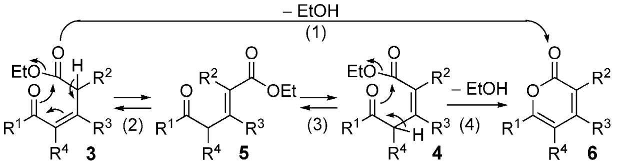
By the treatment of a β-keto ester with an acetylene moiety, **11**, with the rhenium catalyst $[ReBr(CO)_3(thf)]_2$ and MS, bicyclic 2-pyranone **12** was produced in 95% yield (eqn (5)).



(5)

2-Pyranone **6** could be formed by the cyclization of δ-keto ester **3** *via* the elimination of ethanol (Scheme 2). Another possible mechanism is an equilibrium between δ-keto esters **3**, **4** and **5**, and intramolecular cyclization from **4**.

In summary, we have succeeded in the rhenium-catalyzed regioselective insertion of terminal and internal acetylenes into a carbon–carbon single bond of β-keto esters. As a result, δ-keto esters were obtained. At higher temperatures, the δ-keto esters were cyclized to 2-pyranone derivatives *via* the elimination of ethanol. In addition, by using a manganese catalyst, 2-pyranone derivatives could be obtained under milder conditions. In both the rhenium- and manganese-catalyzed transformations, the addition of a catalytic amount of TBAF was effective at promoting the formation of a 2-pyranone framework. We hope that these highly atom-economical transformations will become a powerful tool in synthetic organic chemistry.



Scheme 2 Proposed mechanism for the formation of 2-pyranones.

Notes and references

1 A. Ichihara, K. Murakami and S. Sakamura, *Tetrahedron*, 1987, **43**, 5245; X. Shi, W. S. Leal, Z. Liu, E. Schrader and J. Meinwald, *Tetrahedron Lett.*, 1995, **36**, 71; Y. Kamano, T. Nogawa, A. Yamashita, M. Hayashi, M. Inoue, P. Drasar and G. R. Pettite, *J. Nat. Prod.*, 2002, **65**, 1001.

2 N. T. Tam and C.-G. Cho, *Org. Lett.*, 2008, **10**, 601.

3 J. Fried and R. C. Elderfield, *J. Org. Chem.*, 1941, **6**, 566; J. D. Bu'Lock and H. G. Smith, *J. Chem. Soc.*, 1960, 502; R. C. Larock, M. J. Doty and X. Han, *J. Org. Chem.*, 1999, **64**, 8770.

4 This reaction proceeded using several transition metal complexes. However, the yields of δ-keto esters were low: $Re_2(CO)_{10}$ (1.5 mol%; **3a**: 5%, **4a**: 15%, **5a**: <1%), $ReBr(CO)_5$ (3.0 mol%; **3a**: 15%, **4a**: 72%, **5a**: 3%), $Mn_2(CO)_{10}$ (1.5 mol%; **3a**: 1%, **4a**: 14%, **5a**: <1%), $MnBr(CO)_5$ (3.0 mol%; **3a**: <1%, **4a**: 36%, **5a**: 0%) and $Ru_3(CO)_{12}$ (1.0 mol%; **3a**: <1%, **4a**: 5%, **5a**: <1%).

5 This reaction did not proceed using $RhCl(PPh_3)_3$, $Ir_4(CO)_{12}$, $Pd(OAc)_2/PPh_3$ (1 : 2), $Ni(cod)_2/PPh_3$ (1 : 2), $AuCl_3$ or $PtCl_2$.

6 **3a–5a** could not be separated by column chromatography on silica gel.

7 The yields of δ-keto esters **3–5** decreased without MS. It is still unclear why MS accelerate the reaction.

8 3,3-Dimethyl-1-butyne, ethynyltrimethylsilane and ethyl propiolate did not give δ-keto esters under the same reaction conditions.

9 In this reaction, methylenecyclohexane **9** was formed: Y. Kuninobu, A. Kawata and K. Takai, *Org. Lett.*, 2005, **7**, 4823. See also: M. Nakamura, K. Endo and E. Nakamura, *J. Am. Chem. Soc.*, 2003, **125**, 13002; J. J. Kennedy-Smith, S. T. Staben and F. D. Toste, *J. Am. Chem. Soc.*, 2004, **126**, 4526; S. T. Staben, J. J. Kennedy-Smith and F. D. Toste, *Angew. Chem., Int. Ed.*, 2004, **43**, 5350; Q. Gao, B.-F. Zheng, J.-H. Li and D. Yang, *Org. Lett.*, 2005, **7**, 2185.

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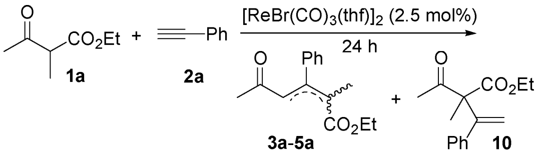

The substrates/catalyst combination in this reaction is almost the same as that for the insertion of terminal acetylenes into a C–H bond of the active methylene moieties of β-keto esters, leading to **10** (see ref. 9). The selectivities of **3a–5a** over **10** increased when the reactions were conducted in toluene, at low concentrations, at higher temperature and by the addition of THF or isocyanide.

11 Only a cyclopentane derivative was formed in 93% yield using methyl 2-acetylhept-6-ynoate.

12 M. Suginome and Y. Ito, *Top. Organomet. Chem.*, 1999, **3**, 131.

13 Y. Kuninobu, A. Kawata and K. Takai, *J. Am. Chem. Soc.*, 2006, **128**, 11368.

14 As the reaction time increased, the yield of δ-keto ester **3** decreased and the yield of δ-keto ester **4** increased. This result shows that isomerization of **3** proceeded and that **4** was formed under the reaction conditions.

15 When the reaction was conducted at 180 °C for 24 h, the polymerization of **2a** took place.

16 The structure of **6f** was determined by comparison with reported ^{1}H and ^{13}C NMR data. See: L. S. Liebeskind and J. Wang, *Tetrahedron*, 1993, **49**, 5461.

17 The addition of MS is important to promote the reaction efficiently. In the absence of MS, **6a** was obtained in 78% yield.

18 The reaction required the addition of the rhenium or manganese catalyst. When a mixture of **1a**, **2a**, and a catalytic amount of the rhenium complex and TBAF in toluene, was heated at 80 °C for 8 h, dimerization of phenylacetylene, leading to (*E*)-1,4-diphenylbut-1-en-3-yne, proceeded in 92% yield. On the other hand, the manganese complex $MnBr(CO)_5$ did not promote any reactions, and **1a** and **2a** were recovered.

19 The formation of 2-pyranones **6** were also promoted by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Therefore, we think that the role of TBAF is asa base. Other fluoride sources, such as KF, CsF and AgF, were not as effective as TBAF.