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Cyclization of Arylacetoacetates to Indene and Dihydronaphthalene Derivatives in Strong Acids. Evidence for Involvement of Further Protonation of O,O-Diprotonated β-Ketoester, Leading to Enhancement of Cyclization

Hiroaki Kurouchi, Hiromichi Sugimoto, Yuko Otani, and Tomohiko Ohwada*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

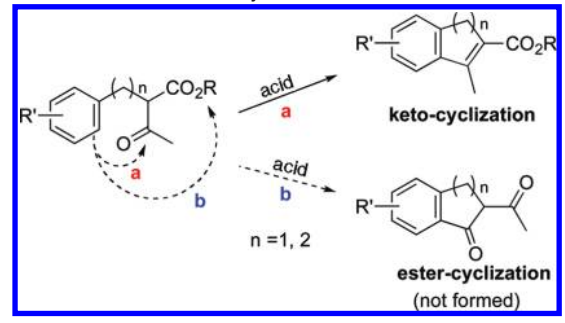
Received October 14, 2009; E-mail: ohwada@mol.f.u-tokyo.ac.jp

Abstract: The chemical features, such as substrate stability, product distribution, and substrate generality, and the reaction mechanism of Brønsted superacid-catalyzed cyclization reactions of aromatic ring-containing acetoacetates (β-ketoesters) were examined in detail. While two types of carbonyl cyclization are possible, i.e., keto cyclization and ester cyclization, the former was found to take place exclusively. The reaction constitutes an efficient method to synthesize indene and 3,4-dihydronapthalene derivatives. Acid−base titration monitored with ^{13}C NMR spectroscopy showed that the acetoacetates are fully O^1,O^3-diprotonated at $H_0 = -11$. While the five-membered ring cyclization of the arylacetoacetates proceeded slowly at $H_0 = -11$, a linear increase in the rate of the cyclization was found with increasing acidity in the high acidity region of $H_0 = -11.8$ to -13.3. Therefore, the O^1,O^3-diprotonated acetoacetates exhibited some cyclizing reactivity, but they are *not* the reactive intermediates responsible for the acceleration of the cyclization in the high acidity region. The reactive cationic species might be formed by further protonation (or protosolvation) of the O^1,O^3-diprotonated acetoacetates; i.e., they may be tricationic species. Thermochemical data on the acid-catalyzed cyclization of the arylacetoacetates showed that the activation energy is decreased significantly as compared with that of the related acid-catalyzed cyclization reaction of a compound bearing a single functional group, such as a ketone. These findings indicate that intervention of the trication contributes to the activation of the cyclization of arylacetoacetates in strong acid, and the electron-withdrawing nature of the O-protonated ester functionality significantly increases the electrophilicity of the ketone moiety.

Introduction

Since sulfuric acid-catalyzed cyclization of 2-aceto-4-phenylbutyrate (β-phenethylacetoacetates) to afford six-membered 3,4-dihydronapthalene derivatives was reported in 1925 (Scheme 1, $n = 2$),[1,2] there have been several studies of related reactions, such as the transformation of 2-aceto-3-arylpropionates to five-membered indene derivatives (Scheme 1, $n = 1$),[3] which was recently applied to the synthesis of bioactive indenone derivatives.[4] However, especially in the case of the five-membered ring cyclization to afford indene derivatives, the previous studies have been limited to substrates containing aromatic rings bearing a strong electron-donating group, such as a hydroxyl or an alkyloxy group.[3]

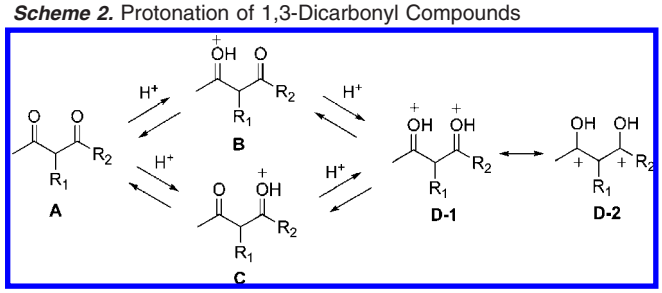
Scheme 1. Chemoselective Cyclization



On the other hand, in the six-membered ring cyclization to afford 3,4-dihydronapthalene derivatives, a halogen substituent on the aromatic ring was reported to allow the cyclization.[2d] Although the previous studies have uncovered the substituent effects at least in part, the scope of these cyclization reactions is still unknown and the mechanisms are poorly understood. Mechanistically, either keto cyclization (a) or ester cyclization (b) appears to be possible (Scheme 1), but in fact, the keto cyclization exclusively takes place. The acetoacetate functionality (generally β-ketoester) (**A**, Scheme 2) is expected to undergo

(1) Auwers, K. v.; Möller, K. *J. Prakt. Chem. (Leipzig)* **1925**, *104*, 124–152.
(2) (a) Bardhan, J. C.; Adhya, R. N.; Bhattacharyya, K. C. *J. Chem. Soc.* **1956**, 1346–1349. (b) Nasipuri, D. *J. Chem. Soc.* **1958**, 2618–2621. (c) Nasipuri, D.; Roy, D. N. *J. Chem. Soc.* **1961**, 3361–3366. (d) Griffin, R. W.; Gass, J. D.; Berwich, M. A.; Shulman, R. S. *J. Org. Chem.* **1964**, *29*, 2109–2116. (e) Wenkert, E.; Greenfield, S. A. *Chem. Ind. (London)* **1967**, 1252.
(3) (a) Koo, J. *J. Am. Chem. Soc.* **1953**, *75*, 1891–1895. (b) Koo, J. *Organic Syntheses*; John Wiley & Sons: New York, 1973; Collect. Vol. V, pp 550−551. (c) Guy, A.; Guetté, J.-P. *Synthesis* **1980**, 222–223. (d) Ghoshal, P. N.; Pathak, B. *J. Indian Chem. Soc.* **1976**, *53*, 1126–1130.
(4) Ahn, J. H.; Shin, M. S.; Jung, S. H.; Kang, S. K.; Kim, K. R.; Rhee, S. D.; Jung, W. H.; Yang, S. D.; Kim, S. J.; Woo, J. R.; Lee, J. H.; Cheon, H. G.; Kim, S. S. *J. Med. Chem.* **2006**, *49*, 4781–4784.

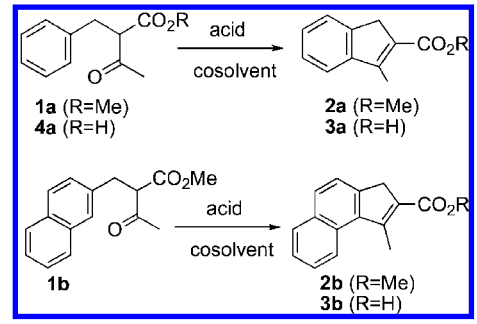
Scheme 2. Protonation of 1,3-Dicarbonyl Compounds



multiple protonations in strong Brønsted acids. Indeed, protonations of 1,3-dicarbonyl compounds, such as 1,3-diketones, β-ketoesters, and β-ketoacids, in superacids have been intensively studied by Brouwer,[5] Olah,[6] Larsen,[7] and others.[8] A number of reports have noted that 1,3-dicarbonyl compounds can be diprotonated: O^1,O^3-diprotonated dicarbonyl species (**D**) have been obtained from β-ketoesters (R_2 = OR),[5–7] as well as β-ketoacids (R_2 = OH)[6] and β-ketoamides (R_2 = NRR′),[9] in superacid solutions. The two important resonance structures for the dication are the bisoxonium structure (**D-1**) and the biscarbenium structure (**D-2**).

The former structure is called a distonic (i.e., distant) dication, and the latter is called a gitonic (i.e., close) dication, according to Olah.[10] Both dicationic resonance structures (**D-1** and **D-2**) of O^1,O^3-diprotonated dicarbonyl compounds bear cationic centers that are unconjugated and separated at least by one carbon atom. Thus, these cationic centers are assumed to interact with each other through an inductive effect. Diprotonated ethyl acetoacetate (**D**, R_1 = H, R_2 = OEt) was observed by low-temperature NMR under stable ionic conditions (in $HF-SbF_5$[5] and FSO_3H-SbF_5[6]). These dications (**D**) have been proposed to act as superelectrophiles in some Friedel–Crafts-type reactions.[9,11] In this paper we will disclose the reaction features, substrate generality, and reaction mechanism of the acid-catalyzed cylization reaction of arylacetoacetates **1** to afford indenes and 3,4-dihydronapththalene derivatives in Brønsted superacids. This is the first time that these variations of product distribution, or even the basic reaction features, have been reported. While related O^1,O^3-diprotonated arylacetoacetates (**D**, $R_1 = -(CH_2)_nAr$, R_2 = OMe) show some cyclizing reactivity, the present study provides evidence supporting *the involvement of further protonation (or protosolvation) of O^1,O^3-diprotonated arylacetoacetates* in the high acidity region, generating highly activated tricationic electrophiles. These highly reactive tricationic species enhance the keto cyclization reaction in strong acid.[12]

Scheme 3



Results and Discussion

Chemical Features of the Cyclization Reactions. Reaction Conditions. We optimized the reaction conditions (acid, amount of acid, cosolvent, reaction temperature, reaction time, etc.) by using the parent unsubstituted substrate methyl 2-aceto-3-phenylpropionate (**1a**) as a prototype (Scheme 3 and Table 1). Sulfuric acid, which has frequently been employed,[1,2] was found to promote the five-membered ring cyclization reaction of **1a** to afford indenes, i.e., a mixture of 2-(methoxycarbonyl)-3-methylindene (**2a**) and 3-methylindene-2-carboxylic acid (**3a**) (Table 1 and Scheme 3). However, the yield of the cyclized products was only moderate (49% yield) (Table 1, entry 1). Therefore, we studied the cyclization of **1a** catalyzed by trifluoromethanesulfonic acid (TFSA): In the presence of TFSA, **1a** underwent the cyclization reaction to give a mixture of indenes, **2a** and **3a**, in high yield (Table 1, entries 2–5).

In the presence of various amounts of TFSA (10–50 equiv), the reactions of **1a** were consistently efficient and clean (entries 2–5). In the case of 5 equiv of TFSA, the reaction of **1a** was rather slow (entry 6). On the other hand, in the case of **1b** (entries 11–13), which contains an electron-rich aromatic system, naphthalene, and 5 equiv of TFSA, rather than 10 equiv, together with the use of dichloromethane (DCM) as a cosolvent (entries 11–12) was most efficient (minimizing the formation of some undefined subsidiary reaction products). When 50 equiv of TFSA was used, the combined yield of **2b** and **3b** significantly decreased (entry 13). Therefore, for synthetic practicality, we chose to use 5 or 10 equiv of TFSA together with DCM as a cosolvent, throughout our study of the substrate generality of the reaction.

Reaction Features. As shown in Table 1 and Scheme 3, the acid-catalyzed cyclization reaction of **1a/b** afforded a mixture of ester (**2a/b**) and carboxylic acid (**3a/b**) products. The formation of **3** was rather unexpected, because previous studies have indicated that esters are generally stable in TFSA (this is also the case for the ester products **2q–2s** in Table 2).[13,14] We speculated that indenecarboxylic acid **3a** was formed by aqueous quenching of the acylium ion **5a**, which would be formed in the acid medium through acid-catalyzed ester cleavage of the

(5) Brouwer, D. M. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 225–237.
(6) Olah, G. A.; Ku, A. T.; Sommer, J. *J. Org. Chem.* **1970**, *35*, 2159–2164.
(7) Larsen, J. W.; Bouis, P. *J. Am. Chem. Soc.* **1975**, *97*, 6094–6102.
(8) Bruck, D.; Dagan, A.; Rabinovitz, M. *Tetrahedron Lett.* **1978**, *19*, 1791–1794.
(9) (a) Klumpp, D. A.; Rendy, R.; Zhang, Y.; Gomez, A.; McElrea, A. *Org. Lett.* **2004**, *6*, 1789–1792. (b) Kumar, K.; Sai, S.; Gilbert, T. M.; Klumpp, D. A. *J. Org. Chem.* **2007**, *72*, 9761–9764.
(10) Review:Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767–788.
(11) (a) Olah, G. A.; Klumpp, D. A. *Superelectrophiles and Their Chemistry*; John Wiley & Sons: New York, 2008. (b) Olah, G. A.; Klumpp, D. A. *Acc. Chem. Res.* **2004**, *37*, 211–220. (c) Lammertsma, K.; Schleyer, P. v. R.; Schwarz, H. *Angew. Chem., Int. Ed. Engl.* **1989**, *101*, 1313–35.
(12) Mayr, H.; Ofial, A. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1844–1854.
(13) With poly(phosphoric acid) (PPA) catalyst, the ester functionality remained in the indene products from the reaction of arylacetoacetates (see ref 3).
(14) Nakamura, S.; Sugimoto, H.; Ohwada, T. *J. Org. Chem.* **2008**, *73*, 4219–4224.

Table 1. Reaction and Workup Conditions

entry	substrate	acid//workup	cosolvent[a]	temp (°C)	time (h)	yield (%) (**2**:**3**)[b]
1	**1a**	H_2SO_4 (20 equiv)	none	20	5	49 (12:88)
2	**1a**	TFSA (50 equiv)	none	0	5	97 (38:62)
3	**1a**	TFSA (20 equiv)	none	0	5	90 (69:31)
4	**1a**	TFSA (10 equiv)	DCM	0	20	76 (62:38)[c]
5	**1a**	TFSA (10 equiv)	DCM	19	10	87 (67:33)
6	**1a**	TFSA (5 equiv)	DCM	0	30	24 (63:37)[d]
7	**1a**	TFSA (20 equiv) + CF_3CO_2Na (2 equiv)[e]	none	0−24	7.5	92 (11:89)
8	**1a**	TFSA (10 equiv)//TFA (12 equiv)[f]	DCM	25//25	15//8	85 (0:100)
9	**1a**	TFSA (10 equiv)//(TMS)CHN_2 [g]	DCM	25	15	87 (100:0)
10	**1a**	TFSA (50 equiv)//Na_2CO_3/MeOH [h]	none	0//15	5//22	91 (86:7)
11	**1b**	TFSA (10 equiv)	DCM	0	1.5	83 (77:23)
12	**1b**	TFSA (5 equiv)	DCM	0	2.0	93 (74:26)
13	**1b**	TFSA (50 equiv)	none	0	0.5	44 (40:60)
14	**4a**	TFSA (10 equiv)	DCM	0−25	7	70 (0:100)

[a] DCM = dichloromethane. Typical reaction procedure: To a solution of **1** (1 mmol) in 5 mL of DCM was added a specified amount of the acid at 0 °C. After the specified reaction time at the specified temperature, water was added to the reaction mixture. The whole was extracted with DCM, and the crude products were purified by column chromatography (silica gel). [b] Combined yield of the product ester **2** (R = Me) and carboxylic acid **3** (R = H) based on the isolation yield. The ratio of the ester **2** and the carboxylic acid **3** is shown in parentheses. [c] Recovery 22%. [d] Recovery 73%. [e] Sodium trifluoroacetate (2 equiv) was added to the TFSA solution in the initial stage. [f] After the completion of the cyclization reaction in TFSA, TFA (12 equiv) was added to the TFSA solution. The mixture was stirred at 25 °C for 8 h. [g] The crude product was esterified with TMS-diazomethane (1 equiv) in 3 mL of DCM, followed by isolation with column chromatography. [h] After the completion of the cyclization reaction in TFSA (0 °C, 5 h), the whole was added to a mixture of Na_2CO_3 (50 equiv) and 20 mL of dry methanol, cooled at −78 °C. The whole was stirred at 15 °C for 22 h.

conjugate ester **2a** or its protonated form (**2a-H**) (Scheme 4).[15] To clarify the features of this reaction, the acid solution of **1a** in TFSA (10 equiv) was monitored in situ by ^{1}H NMR spectroscopy at −16 °C (Figure 1).[16] The integral of the ^{1}H NMR signal was normalized in terms of the initial concentration of **1a**.[17] In TFSA solution, protonated **1a** was observed at the initial stage of the cyclization reaction (Figure 1).[17] As the cyclization reaction proceeded (i.e., as **1a** decreased), **2a-H** (protonated **2a**) appeared. Compound **5a** was detected following the accumulation of **2a**, but it was not present in the initial stage of the cyclization reaction (the structure of ion **5a** was experimentally confirmed; see Supporting Information Figure S1).[18] Finally, most of **1a** was consumed, leaving **2a-H** and **5a** in the solution. Cyclized product **2a-H** gave neutral **2a**, and the ion **5a** gave carboxylic acid **3a** in the aqueous workup process.[16]

Because we obtained a mixture of indene ester and indenecarboxylic acid in the reaction of **1a**, it may be reasonable to use benzylacetoacetic acid (**4a**) (Scheme 3), instead of **1a**, as a starting material. However, **4a** was too unstable to be stored under conventional conditions: it undergoes spontaneous decarboxylation at room temperature to give the ketone 4-phenylbutan-2-one (**6a**) (e.g., neat **4a** under an argon atmosphere at rt was completely decarboxylated to **6a** within 30 h). Thus, **4a** is of limited practical value as a starting material of the relevant cyclization reaction (Scheme 3), although when it was used immediately after synthesis, it underwent cyclization to afford only **3a** in 70% yield in TFSA (Table 1, entry 14). In this context, the use of the acetoacetates **1** as the starting material, even though they produce a mixture of the ester **2** and the carboxylic acid **3**, seems the best practical option.

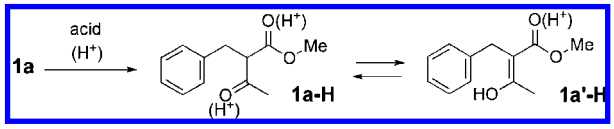
Isolation. When the crude mixture of products (the ester **2a** and acid **3a**), obtained after completion of the cyclization reaction of **1a** in TFSA, was subjected to esterification with TMS-diazomethane, only the indene methyl ester **2a** was obtained in 87% yield (Table 1, entry 9). When the cyclization reaction of **1a** in TFSA (50 equiv) at 0 °C was quenched with cold MeOH/Na_2CO_3, the ester product **2a** was much favored over the acid product **3a** (Table 1, entry 10). Furthermore, when the cyclization reaction of **1a** was accomplished in TFSA containing sodium trifluoroacetate (2 equiv) at 24 °C for 7.5 h, where the acidity of the acid medium was lower, a more biased reaction occurred in favor of the indenecarboxylic acid **3a** (**2a**:**3a** = 11:89, Table 1, entry 7). Instead of the salt, addition of TFA to the acid reaction mixture, obtained after completion of the cyclization of **1a** in TFSA, resulted in complete conversion of the cyclized products to the carboxylic acid **3a** (85% yield) after 8 h at 25 °C (Table 1, entry 8). In a weaker acid, ester cleavage of **2a** was enhanced to afford **3a** (see Scheme 4). These results are consistent with the present and previous observations that the formation of **3** was favored (**3a** in Table 1, entry 1) or exclusive (in the literature[1,2]) in sulfuric acid ($H_0 \approx -10$), a weaker acid than TFSA.

Substrate Generality. We studied the substrate generality of the cyclization reaction of arylacetoacetates (Table 2). Ethyl esters, such as **1c**, showed reactivity similar to that of methyl ester **1a**. In the case of the five-membered ring cyclization to afford indene derivatives, the compounds bearing alkyl (**1e**−**1h**) and phenyl (**1i**) substituents on the benzene ring underwent efficient cyclization reaction in a similar manner to that of the naphthalene substrate **1b**, affording the cyclized products

(15) Olah, G. A.; Hartz, N.; Rasul, G.; Burrichter, A.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1995**, *117*, 6421–6427.

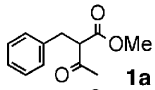
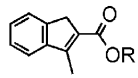
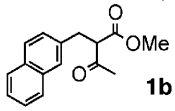
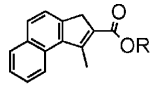
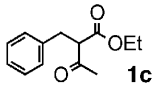
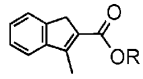
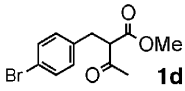
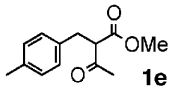
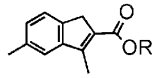
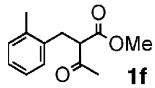
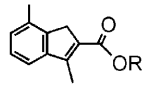
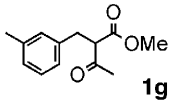
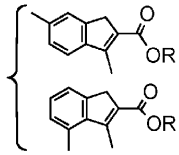
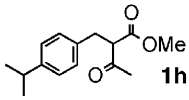
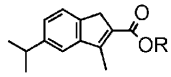
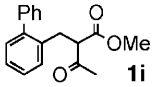
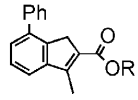
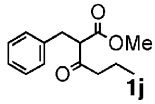
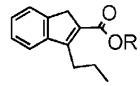
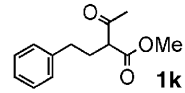
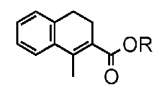
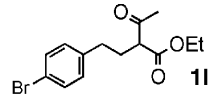
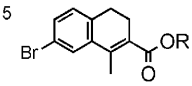
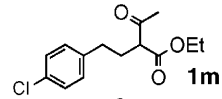
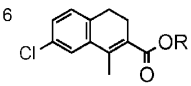
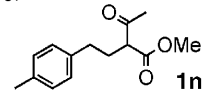
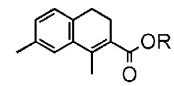
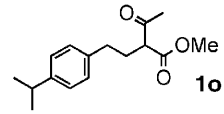
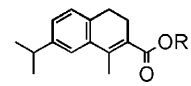
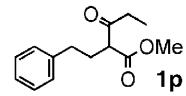
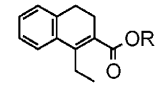
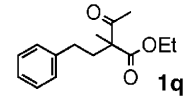
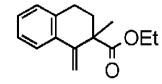
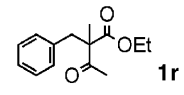
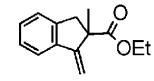
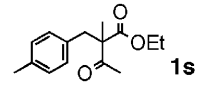
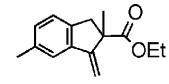
(16) This experiment used an amount of TFSA similar to that in the cases of entries 3−6 in Table 1. The ratios of **2a-H** and **5a** (they correspond to **2a** and **3a** after aqueous workup) in Figure 1 are consistent with those of **2a** and **3a** observed in entries 3−6 in Table 1.

(17) In TFSA, **1a** formed protonated keto (**1a-H**) and enol (**1a′-H**) forms. Similar enol formation in the acid was also observed in the case of **1d** (see Scheme 5). In Figure 1, we show the summation of **1a-H** and **1a′-H** as the amount of **1a** for the sake of simplicity.



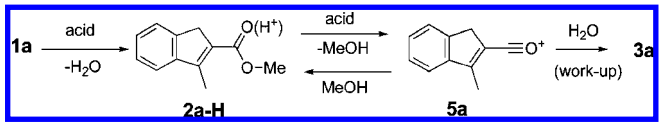
(18) Methyl cinnamate afforded cinnamic acid (9% yield) in TFSA (10 equiv) with DCM as a cosolvent at 25 °C for 15 h, followed by aqueous workup (86% recovery, based on ^{1}H NMR integration). Similarly, in TFSA (50 equiv), methyl cinnamate afforded the carboxylic acid in 31% yield (recovery 54%, isolation yield) after 40 h. The saturated methyl ester **16a** did not yield the corresponding carboxylic acid in TFSA at−6 °C.

Table 2. Substrate Generality of the Cyclization Reaction of **1a**−**1s**

entry	substrate **1**	temp. (°C)	time (hr)	product	yield [a] (ester **2**: acid **3**)
a	 **1a**	20	10		87% (67 : 33) 97% [b] (38 : 62)
b	 **1b**	0	2		93% [c] (74 : 26)
c	 **1c**	20	7		81% [d] (56 : 44) 94% [b,d] (35 : 65)
d	 **1d**	-15 ~ -10	1	—	86 % (recovery)
e	 **1e**	20	5		89% (39 : 61)
f	 **1f**	0	1		91% (72 : 28)
9	 **1g**	0	1		57% [e] (75 : 25) (**g-1**) 32% [e] (67 : 33) (**g-2**)
h	 **1h**	0	7		88% (72 : 28)
i	 **1i**	0	38		[c,f] 84% (67 : 33)
j	 **1j**	0 to 20	24		82% (30 : 70)
k	 **1k**	0	1		87% (48 : 52) 93% [g] (15 : 78)
l	 **1l**	20	15		80% (63 : 37)
m	 **1m**	20	16		82% (48 : 52)
n	 **1n**	0	0.3		75% (49 : 51)
o	 **1o**	0	1		87% (50 : 50)
p	 **1p**	0	1		92% (38 : 62)
q	 **1q**	0	1		80% (**2q**)
r	 **1r**	20	16		42% (**2r**)
s	 **1s**	20	13		34% (**2s**)

[a] Isolation yield. Reaction conditions: **1** (1 mmol), TFSA (10 equiv), and DCM (5 mL). The ratio of the ester **2** (R = Me or Et) and the carboxylic acid **3** (R = H) is shown in parentheses. [b] TFSA (50 equiv), 0 °C, 5 h (without DCM). [c] A 5 equiv amount of TFSA was used. [d] The carboxylic acid product **3c** is the same as **3a**. [e] The ratios of the products were determined by the integration of ^{1}H NMR signals after column chromatography. [f] When 10 equiv of TFSA was used, the product ester **2i** (55%) and carboxylic acid **3i** (20%) were obtained after 3 h at 22 °C. [g] TFSA (50%)−TFA (50%) (10 equiv), DCM, 0 °C, 1 h.

Scheme 4



(84−91% yield, Table 2). On the other hand, a bromo substituent on the benzene ring (**1d**) hampered the cyclization under typical reaction conditions. As for six-membered ring cyclization, methyl 2-aceto-4-phenylbutyrate (**1k**) underwent the cyclization reaction in TFSA to afford 1-methyl-2-carbomethoxy-3,4-dihydronaphthalene (**2k**) and 1-methyl-3,4-dihydronaphthalene-2-carboxylic acid (**3k**) in high yield (87% combined yield). In the case of the six-membered ring cyclization, the substrates bearing halogen substituents (**1l** and **1m**) also underwent efficient cyclization reaction (80% and 82% yield, respectively) in a manner similar to that of substrates bearing an alkyl substituent (**1n** and **1o**). The results for **1l** and **1m** are consistent with those of a previous study using sulfuric acid.[2d] Therefore, the six-membered ring cyclization proceeds more readily than the five-membered ring cyclization under similar conditions. This is probably because a 6-exo-trigonal cyclization transition state is more favorable than a 5-exo-trigonal one, having less conformational strain.[14,19]

The effects of variation of the acyl group of **1** on the reaction were also studied: **1j** (*n*-propyl group) and **1p** (ethyl group) underwent the cyclization reaction efficiently to afford the corresponding cyclized products (**2j/3j** and **2p/3p**) in high yields. However, an isopropyl substituent in the acetyl moiety of **1k** resulted in the formation of a complex mixture (data not shown).

Furthermore, the arylacetoacetates **1q**, **1r**, and **1s** (Table 2), in which the α-proton was replaced with a methyl group, afforded the keto-cyclized products in TFSA: the reaction of

(19) (a) Nakamura, E.; Sakata, G.; Kubota, K. *Tetrahedron Lett.* **1998**, *39*, 2157–2158. (b) Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476–482.

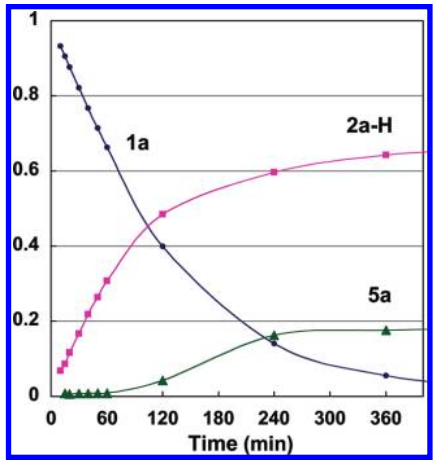


Figure 1. ^{1}H NMR-monitored reaction profile of cyclization of **1a** in TFSA (at −16 °C).

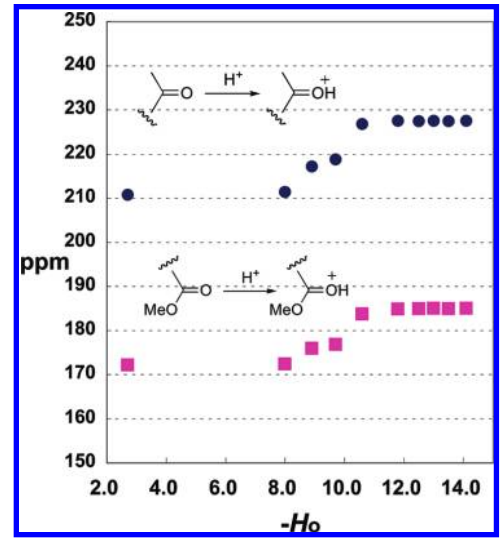


Figure 2. Acid titration curves of **1d** (at −15 °C).

1q afforded the ester **2q** (as a single product) in 80% yield in TFSA, the yield being comparable to that of the reaction of nonmethylated **1k**. In the five-membered ring cyclization, the yields of the cyclized products **2r** and **2s** were lower, but similar keto cyclization proceeded. These facts exclude the possibility that an enolizable α-proton is a prerequisite for the reaction and the resultant enol forms of the acetoacetate **1** participated in the cyclization reaction (vide post; see also ref 22).

Acidity Dependence of the Cyclization. The reaction showed apparent acidity dependence (Table 3). As the acidity of the acid medium increased,[20] the indene cyclization of **1a** started, and the yield of the cyclized products (combined yield of ester **2a** and acid **3a**) increased. We studied the acidity dependence of the reaction of **1a** in the absence (Table 3) and in the presence of DCM as a cosolvent (Supporting Information Table S1).[21] The cyclization reaction of **1a** proceeded, but only slightly (6% yield of **3a**), in a weaker acid, e.g., at $H_0 = -9.7$, at 0 °C for 5 h (Table 3, entry 3), and a large amount of the starting **1a** was recovered (recovery 83%). At −11.8 (H_0) (entry 4), the yield of the cyclized products was increased (35%). As judged from the yield of the cyclized products (under the present reaction conditions: 0 °C, 5 h), the cyclization of **1a** to afford indenes **2a** and **3a** was complete in the acidity range of −13 to −14.1 (H_0). The kinetics of **1a** were studied in the acidity range of −11 to −13 (vide post).

Furthermore, in the case of the cyclization to dihydronaphthalene, the cyclization of **1k** is also promoted as the acidity of the medium is increased (Table 3, entries 7−12). In the case of the reaction of **1k**, the cosolvent DCM was used. The reaction of **1k** started even at $H_0 = -7.8$ (6% yield of the cyclized products) (entry 8), and a 58% yield of the cyclized products (10% yield of ester **2k** and 48% yield of the acid **3k**) was obtained at $H_0 = -9.7$ (entry 9), together with recovery of the acetoacetate **1k** (38%). The cyclization of **1k** to afford dihydronaphthalenes **2k** and **3k** was complete at acidity between $H_0 = -11.8$ and $H_0 = -14.1$ under the present reaction conditions (0 °C, 1 h). The cyclization of **1k** to afford **2k/3k** was too rapid to allow precise study of the kinetics.

Acid−Base Titration of Arylacetoacetates. We carried out titration of arylacetoacetate with the present acid system, TFSA−TFA, at various levels of acidity. Methyl 2-aceto-3-(*p*-bromophenyl)propionate (**1d**) was used as a base substrate because of its inertness to cyclization (see Table 2). In the ^{1}H and ^{13}C NMR spectra obtained at −15 °C (in the absence of DCM), we could detect the carbonyl form and the enol form of **1d** (Scheme 5).[17,22] For the carbonyl form, by plotting the ^{13}C chemical shift variation of the carbonyl carbon atoms of the acetyl and carbomethoxy groups of **1d** against the acidity of the acid medium, we obtained two acid−base titration curves (Figure 2 and Supporting Information Table S2).[23] Because the O-monoprotonated species **7d** and **7d′** are in equilibrium (Scheme 5),[5–8] it is difficult to determine the pK_{BH}^+ values of the acetoacetate **1d** as a ketone base or an ester base. However, the pK_{BH}^+ values for the acetyl group and the methoxycarbonyl group of related compounds bearing a single carbonyl group (i.e., ketone (**6a**) and ester (**16a**), respectively; see Figure 4 and Supporting Information Figure S5) are similar in magnitude,[24] so we can estimate the pK_{BH}^+ values of the acetoacetate **1d** to be $H_0 = -9.0$ (for the acetyl group, **1d** → **7d′**) and $H_0 = -9.2$

(20) Saito, S.; Saito, S.; Ohwada, T.; Shudo, K. *Chem. Pharm. Bull.* **1991**, *39*, 2718–2720.

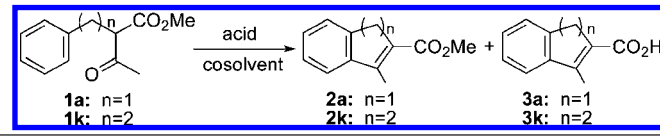
(21) The trends of the acidity dependence in the presence of DCM were consistent with those in the absence of DCM (see Table 3 and Table S1 in the Supporting Information).

(22) The enol structures of **1d** started to appear in the ^{1}H NMR spectra in the acid region stronger than $H_0 = -8$ (Scheme 5 and Table S2 in the Supporting Information). As shown in Figure S3 (Supporting Information), the ^{13}C NMR chemical shifts of the two carbonyl groups were almost constant in the range of acidity from $H_0 = -8$ to $H_0 = -14$. The reported pK_{BH}^+ values of the carbonyl oxygen atoms of conjugate ketones (e.g., benzalacetophenone, −4.3 to −5.7) and conjugate esters (e.g., *trans*-cinnamic acid, −6.2) (see ref 25a and (a) Högfeldt, E.; Bigeleisen, J. *J. Am. Chem. Soc.* **1960**, *82*, 15–20. (b) Noyce, D. S.; King, P. A.; Kirby, F. B.; Reed, W. L. *J. Am. Chem. Soc.* **1962**, *84*, 1632−1635) are estimated to be as large as −6. Furthermore, in the enol forms of the arylacetoacetate **9d** or **9d′** (Scheme 5), the olefin was substituted with an electron-donating hydroxyl group. Thus, the carbonyl oxygen atoms of **9d** and **9d′** were more basic than those of typical compounds. Therefore, in the acid range of $H_0 = -8$ to −14, practically complete O-protonation of the enol carbonyl group occurred, resulting in the generation of the monocation **10d** (Scheme 5), which is resonance-stabilized. α-Methylated acetoacetates **1q**, **1r**, and **1s** afforded the cyclized product in the acid (Table 2), though enolization is impossible. Therefore, we concluded that the enol form or its O-protonated form (such as **10d**) of the acetoacetates **1** is in equilibrium with the (O-protonated) keto form (Scheme 5).

(23) Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Superacids*; John Wiley & Sons: New York, 1985.

(24) The pK_{BH}^+ values of the ketone **6a** and ester **16a** were estimated to be −8.5 and −8.5, respectively, in an acid−base titration experiment (see Figure 4 and Supporting Information Figure S5).

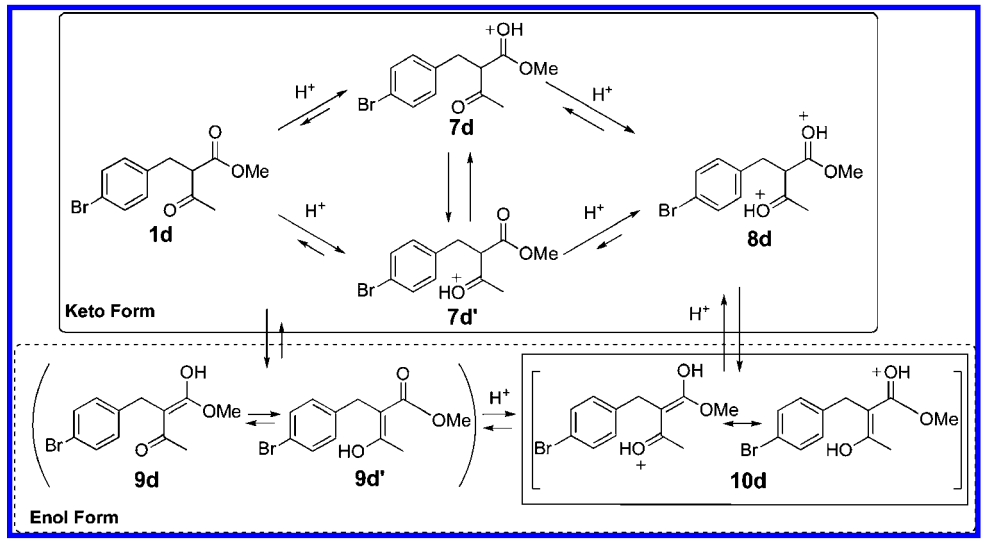
Table 3. Acidity Dependence of Cyclization Reactions[a]



entry	substrate	acid system	acidity ($-H_0$)	yield of **2** (%)	yield of **3** (%)	yield of **2** + **3** (%)	recovery of **1** (%)
1	**1a**[b]	100% TFA	2.7	0 (**2a**)	0 (**3a**)	0	97
2	**1a**[b]	1% TFSA−99% TFA	7.8	0 (**2a**)	0 (**3a**)	0	97
3	**1a**[b]	10% TFSA−90% TFA	9.7	0 (**2a**)	6 (**3a**)	6	83
4	**1a**[b]	50% TFSA−50% TFA	11.8	5 (**2a**)	30 (**3a**)	35	55
5	**1a**[a]	90% TFSA−10% TFA	13.0	25 (**2a**)	71 (**3a**)	96	0
6	**1a**[b]	100% TFSA	14.1	37 (**2a**)	60 (**3a**)	97	0
7	**1k**[c]	100% TFA	2.7	0 (**2k**)	0 (**3k**)	0	94
8	**1k**[c]	1% TFSA−99% TFA	7.8	3 (**2k**)	3 (**3k**)	6	89
9	**1k**[c]	10% TFSA−90% TFA	9.7	10 (**2k**)	48 (**3k**)	58	38
10	**1k**[c]	50% TFSA−50% TFA	11.8	15 (**2k**)	78 (**3k**)	93	0
11	**1k**[c]	90% TFSA−10% TFA	13.0	29 (**2k**)	60 (**3k**)	89	0
12	**1k**[c]	100% TFSA	14.1	30 (**2k**)	59 (**3k**)	89	0

[a] Isolation yield. [b] Reaction conditions: **1** (1 mmol), acid (50 equiv), 0 °C, 5 h (without DCM). [c] Reaction conditions: **1k** (1 mmol), acid (10 equiv), DCM, 0 °C, 1 h.

Scheme 5



(for the methoxycarbonyl group, **1d** → **7d**). The magnitudes of deshielding shifts in the ^{13}C NMR of the ketone and ester carbonyl carbon atoms of **1d** upon O-protonation are comparable to those observed in reference compounds bearing a single ketone (**6a**, Figure 4) and an ester (**16a**, Figure S5) group, respectively.[25,26]

In the acid region stronger than $H_0 = -11.8$, simultaneous O^1,O^3-diprotonation of the acetoacetate **1d** was practically complete to yield the dication **8d**.[27] A similar acid−base titration curve was obtained in the case of methyl acetoacetate, the simplest model substance (at −20 °C, Supporting Information Figure S2), indicating an insignificant effect of the phenylethyl moiety on the basicity of the acetoacetate. These observations were consistent with previous studies on the formation of O^1,O^3-diprotonated β-ketoesters in superacids.[5–8]

Acidity−Rate Relationship of Cyclization. To further clarify the reaction mechanism, we measured the rate constants of the cyclization reaction of **1a**, **1c**, and **1e** in solutions with defined acidity. The reaction was conducted in NMR tubes at −6 °C, and the concentration of **1a** (or **1c** or **1e**) was followed by means of ^1H NMR spectroscopy in the presence of 50 equiv of acid (without the use of DCM). The results are shown in Table 4.

All the reactions followed good first-order kinetics ($r > 0.99$). The order of the rate constants was **1e** > **1a** ≈ **1c**. At $H_0 = -11.8$, where the O^1,O^3-diprotonation of **1** was complete (see Figure 2), **1a**, **1c**, and **1e** underwent five-membered ring cyclization, but slowly (Table 4). This observation demonstrated that the O^1,O^3-diprotonated acetoacetates **8a**, **8c**, and **8e** show reduced cyclization reactivity (Scheme 6).[28] On the other hand,

(25) (a) Amett, E. M. *Prog. Phys. Org. Chem.* **1963**, *1*, 223–403. (b) Campbell, H. J.; Edward, J. T. *Can. J. Chem.* **1960**, *38*, 2109–2116. (c) Edward, J. T.; Wang, I. C. *Can. J. Chem.* **1962**, *40*, 966–975.

(26) The reported basicity of aliphatic ketones lies at around $H_0 = -7.2$ and that of esters at $H_0 = -6.8$ (see ref 25). Thus, the estimated basicity values of the ketone and ester carbonyl groups of **1d** seem to be rather decreased. This is probably because the two carbonyl groups of the acetoacetate **1d** mutually interact through the insulating carbon atom and attenuate the electron density through their electron-withdrawing inductive effects. This electron-withdrawing effect would be increased upon O-protonation of individual carbonyl oxygen atoms.

(27) The chemical shifts of **1d** observed in CF_3SO_3H−1% (w/w) SbF_5 ($H_0 = -16.8$) indicated the chemical shift data change very little with increasing acidity and the dication formation is practically complete at $H_0 - 11.8$ (Supporting Information Table S2).

(28) The preference of the keto cyclization of **8** is consistent with the lower lying π^* orbital of the ketone moiety as compared with the π^* orbital of the ester moiety (see Figure 6).

Table 4. Rate Constants for Cyclization of **1a**, **1c**, and **1e** at −6 °C[a,b]

1a		1c		1e	
H_0	10^4k (s^{-1})	H_0	10^4k (s^{-1})	H_0	10^4k (s^{-1})
−11.8	0.185	−11.8	0.113	−11.8	0.817
−12.2	0.282	−12.2	0.277	−12.2	1.78
−12.5	0.736	−12.5	0.792	−12.5	4.15
−13.0	3.09	−13.0	2.05	−13.0	14.9
−13.3	3.12	−13.3	3.85	−13.3	27.4
−13.5	3.63	−13.5	3.43		
−14.1	4.38	−14.1	4.82		

[a] Acidity function values; see refs 20 and 28. [b] Errors of rates ±2%.

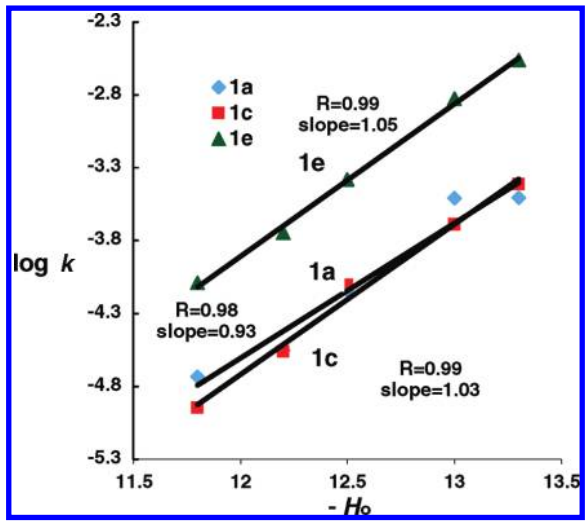
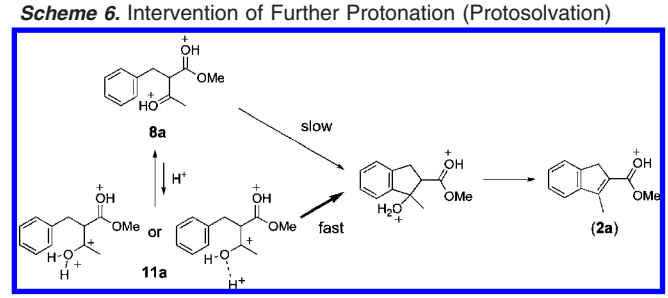


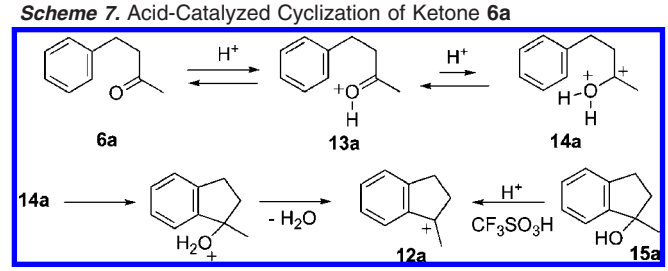
Figure 3. Acidity−rate profiles of the cyclization of arylacetoacetates **1a**, **1c**, and **1e** (−6 °C).

as shown in Figure 3, the reaction rates for **la**, **1c**, and **1e** are proportional to the acidity of the medium. Acceleration of the reaction was significant: the slopes in the acidity−rate profiles were 0.93 for **la**, 1.03 for **lc**, and 1.05 for **1e**, which are close to unity. According to the Zucker−Hammett hypothesis,[29] when a low concentration of cationic species formed by protonation is the reactive species and is involved in the rate-determining step of the reaction, linear dependency of the rate on the acidity should be observed. Several applications of this hypothesis have been reported among reactions involving monocations[30a,b] and superelectrophiles generated by multiprotonation (protosolvation).[30c−h] It has been shown that the substrate **1** is already fully diprotonated at acidity stronger than $H_0 = -11$. Therefore, the diprotonated **1** (i.e., dication **8**) is *not* the reactive intermediate responsible for the linear increase of the rate in this region of high acidity ($H_0 = -11.8$ to -13.3). Thus, further protonation (or protosolvation) of the diprotonated ketoester **8a**, i.e., the

Scheme 6. Intervention of Further Protonation (Protosolvation)



Scheme 7. Acid-Catalyzed Cyclization of Ketone **6a**



intervention of the trication **11a**, should be involved (Scheme 6; see also the Supporting Information).[30c,31]

Acceleration of Keto Cylization by the Ester Group. To evaluate the effect of the coexisting ester group of arylacetoacetates **1**, we studied the acid-catalyzed cyclization reaction of a compound bearing a single functional group, such as a ketone, i.e., 4-phenyl-2-butanone (**6a**) (Scheme 7). We first carried out the acid−base titration of **6a** in acids with defined acidity. When the ^{13}C chemical shift variation of the carbonyl carbon atom of **6a** (measured at −6 °C) was plotted against the acidity of the acid medium, we observed a typical acid−base titration curve (Figure 4 and Supporting Information Table S3),[22] and the pK_{BH^+} value of **6a** was estimated to be about −8.5. This value is close to those (around −6.2 to −7.5) reported for aliphatic ketones.[25]

We carried out the cyclization reaction of **6a** in TFSA at 32 °C, but obtained a complex mixture after aqueous workup. This is in sharp contrast to the previous study of the acid-catalyzed cyclization of 1,3-diphenyl-1-propanone, in which 3-phenyl-1*H*-indene was obtained in high yield after aqueous workup.[30c] Unexpectedly, however, when we monitored the acid solution of **6a** in TFSA (at 32 °C), the ion **12a** formed by cyclization was clearly observed (Scheme 7). The ion **12a** was identical, in terms of chemical shifts in the ^1H and ^{13}C NMR spectra, with the ion formed from 1-methyl-2,3-dihydro-1*H*-inden-1-ol (**15a**) in TFSA at −6 °C (Scheme 7 and Supporting Information Figure S4).

We thus studied the acidity−rate profile of the reaction of **6a** to afford the ionized product **12a**. The cyclization reaction did not proceed in acid weaker than $H_0 = -12$. The reaction

(29) Zucker, L.; Hammett, L. P. *J. Am. Chem. Soc.* **1939**, *61*, 2791–2798.
(30) For monocations: (a) Lucchini, V.; Modena, G.; Scorrano, G.; Tonellato, U. *J. Am. Chem. Soc.* **1977**, *99*, 3387–3392. (b) Baigrie, L. M.; Cox, R. A.; Slebocka-Tilk, H.; Tencer, M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 3640–3645. For dications: (c) Satio, S.; Sato, Y.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1994**, *116*, 2312–2317. (d) Sato, Y.; Yato, M.; Ohwada, T.; Saito, S.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 3037–3043. (e) Suzuki, T.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1997**, *119*, 6774–6780. (f) Ohwada, T.; Suzuki, T.; Shudo, K. *J. Am. Chem. Soc.* **1998**, *120*, 4629–4637. (g) Yokoyama, A.; Ohwada, T.; Shudo, K. *J. Org. Chem.* **1999**, *64*, 611–617. (h) Olah, G. A.; Mathew, T.; Marinez, E. R.; Esteves, P. M.; Etzkorn, M.; Rasul, G.; Prakash, G. K. S. *J. Am. Chem. Soc.* **2001**, *125*, 11556–11561.
(31) In the case of six-membered ring cyclization reaction, the O^1,O^3-diprotonated dication **8k** contributed significantly to the cyclization, because the cyclization reaction proceeded at $H_0 = -9.7$ (Table 3, entry 9), where the O^1,O^3-diprotonated dication **8k** would be in equilibrium with monoprotonated cations **7k** and **7k′** (Scheme 5). In the high acidity region (stronger than $H_0 = -11.8$), a similar intervention of the corresponding tricationic species **11k** can also be considered because the basicity of the acetoacetate of **1k** is similar to that of **1a** (see Figure 2). Therefore, in the six-membered ring cyclization reaction, the dication **8k** would participate significantly in the cyclization, while the tricationic species **11k** is postulated to accelerate the cyclization in the strong acid region.
(32) Ammann, C.; Meier, P.; Merbach, A. E. *J. Magn. Reson.* **1982**, *46*, 319–321.

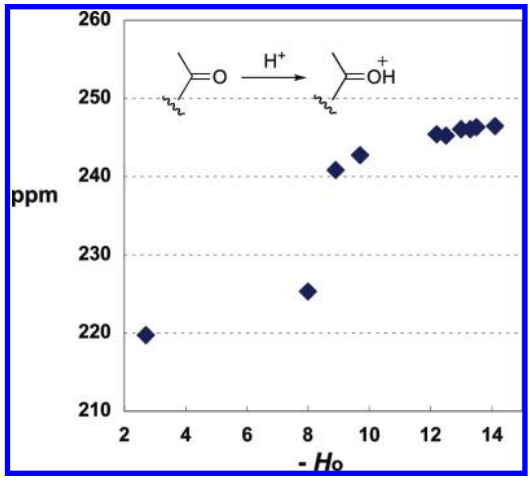


Figure 4. Acid titration curve of ketone **6a** (at −6 °C).

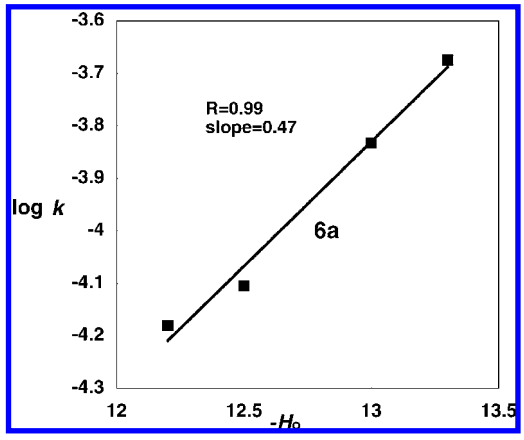


Figure 5. Acidity−rate profiles of the cyclization of ketone **6a** (at 32 °C).

showed good first-order kinetics ($r > 0.99$) in the acidity region of $H_0 = -12.2$ to -13.3 (Table S4, Supporting Information). As shown in Figure 5, the logarithm of the rate constant increased proportionally to the acidity, and the slope was 0.47 ($r > 0.99$). In the acidity region $H_0 = -12.2$ to -13.3, the ketone **6a** is fully monoprotonated to generate **13a** (Figure 4). This result is consistent with the postulation that the reactive species should be a further protonated (or protosolvated) form of **13a**, that is, the O,O-diprotonated ketone **14a**. A similar dication has been proposed in the related acid-catalyzed cyclization reaction of 1,3-diphenyl-1-propanone.[30c] Intervention of this kind of dication was also demonstrated in an acid-catalyzed aldehyde−ketone isomerization reaction.[30h]

The reaction rates of **1a** and **6a** in TFSA were obtained at three different temperatures to calculate the thermochemical parameters for the acid-catalyzed cyclization (Table 5):[31] for **1a**, $E_a = 54.2$ kJ mol^{-1} (13.0 kcal mol^{-1}), $\Delta H^{\ddagger} = 51.9$ kJ mol^{-1} (12.4 kcal mol^{-1}), and $\Delta G^{\ddagger} = 84.2$ kJ mol^{-1} (20.1 kcal mol^{-1}) (0 °C) and, for **6a**, $E_a = 114.0$ kJ mol^{-1} (27.2 kcal mol^{-1}), $\Delta H^{\ddagger} = 97.1$ kJ mol^{-1} (23.2 kcal mol^{-1}), and $\Delta G^{\ddagger} = 96.1$ kJ mol^{-1} (23.0 kcal mol^{-1}) (0 °C). For comparison, thermochemical parameters for acid-catalyzed cyclization of a compound bearing a single ester group, i.e., methyl 3-phenylpropionate (**16a**), in

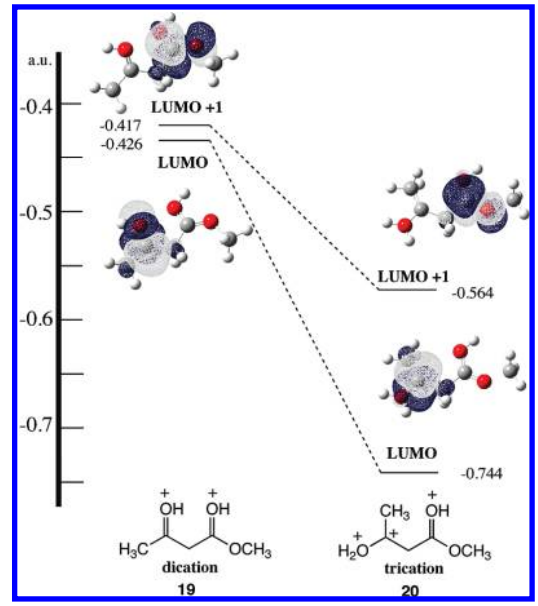
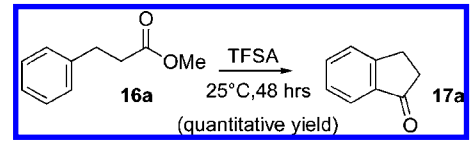


Figure 6. LUMO levels and orbital distributions.

TFSA were also evaluated (see Table 5 and Supporting Information Figure S5).[30d,33] The reaction of **16a** in TFSA (25 °C, 48 h) afforded 1-indanone **17a** in quantitative yield.[14]

The reaction of **16a** also followed good first-order kinetics ($r > 0.99$) (see Table S5, Supporting Information). The obtained thermodynamic parameters of **16a** were as follows: $E_a = 113.0$ kJ mol^{-1} (27.0 kcal mol^{-1}), $\Delta H^{\ddagger} = 110.4$ kJ mol^{-1} (26.4 kcal mol^{-1}), and $\Delta G^{\ddagger} = 95.0$ kJ mol^{-1} (22.7 kcal mol^{-1}) (0 °C) (Table 5).



The ester cyclization (**16a**) has activation energies (E_a and $\Delta H^{\ddagger}$) similar in magnitude to those of the keto cyclization (**6a**). As compared with the keto cyclization of **6a** and ester cyclization of **16a**, the cyclization of **1a** (for the keto cyclization) is energetically much more favorable. Therefore, it is reasonable to assume that the observed acid-catalyzed keto cyclization of **1a** can be attributed to the intervention of the tricationic **11a** (which bears a substructure similar to that of the dication **14a**), and the electron-withdrawing nature of the O-protonated ester functionality present in **11a** significantly enhanced the electrophilicity of the ketone moiety (Schemes 6 and 7).[9,11]

Such activation of the electrophilicity, favoring the cyclization, can be seen in a comparison of the calculated orbital levels and orbital distributions of the LUMO/LUMO + 1 of model cations, O^1,O^3-diprotonated (**19**) and triprotonated (**20**) methyl acetoacetate (energy minima obtained by full geometry optimization with B3LYP/6-311G**)[34] (Figure 6). In the case of O^1,O^3-diprotonated methyl acetoacetate (**19**), the LUMO and LUMO + 1 (natural bond orbital analysis)[35] are assigned to the carbonyl π^* orbitals of the keto and ester moieties, respectively,[28] and they are relatively close in energy. On the other hand, in the case of triprotonated methyl acetoacetate (**20**),

(33) (a) Olah, G. A.; Germain, A.; Lin, H. C.; Forsyth, D. A. *J. Am. Chem. Soc.* **1975**, *97*, 2928–2929. (b) Hwang, J. P.; Prakash, G. K. S.; Olah, G. A. *Tetrahedron* **2000**, *56*, 7199–7203. (c) Hulin, B.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 207–209.

(34) Frisch, M. J.; et al. *Gaussian 03*; Gaussian, Inc.: Pittsburgh, PA, 2003.

(35) (a) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899. (b) NBO version 3.

Table 5. Observed Rate Constants for the Cyclization Reactions in TFSA and Calculated Activation Parameters

temp[a] (°C)	10^4k (s^{-1})	log k	E_a[b] (kJ mol^{-1})	$\Delta H^{\ddagger}$[c] (kJ mol^{-1})	$\Delta G^{\ddagger}$(0 °C)[d] (kJ mol^{-1})	$\Delta S^{\ddagger}$[e] (J K^{-1} mol^{-1})
			1a → 2a/3a			
−15	1.23	−3.91	54.2	51.9	84.2	−118
−3	3.79	−3.42				
9	9.66	−3.01				
			6a → 12a			
20	0.535	−4.27	114.0	97.1	96.1	3.85
33	2.31	−3.64				
45	10.6	−2.97				
			16a → 17a			
20	1.29	−3.89	113.0	110.4	95.0	56.6
33	7.24	−3.14				
45	38.0	−2.42				

[a] The temperature was corrected (see ref 32). Errors ±0.2 °C. [b] Errors ±2.0 kJ mol^{-1}. [c] Errors ±2.0 kJ mol^{-1}. [d] Errors ±3.7 kJ mol^{-1}. [e] Errors ±6.5 eu at 273.15 K (0 °C).

both the LUMO and LUMO + 1 have decreased energy, and the significantly lower lying LUMO indicates activation of **20** as an electrophile. Furthermore, the LUMO is comprised of the keto carbonyl π^* orbital. Thus, these orbital diagrams are consistent with the enhanced cyclization reactivity of the tricationic species (such as **11**).

Conclusion

Herein, we have uncovered the chemical features, such as substrate stability, product distribution control, and substrate generality, and the reaction mechanism of Brønsted superacid-catalyzed cyclization reactions of aromatic ring-containing acetoacetates (arylacetoacetates). While two types of carbonyl cyclization are possible, i.e., keto cyclization and ester cyclization, the former exclusively takes place. The reactions constitute an efficient method to synthesize indene and 3,4-dihydronapthalene derivatives. Acid−base titration using ^{13}C NMR spectra showed that the acetoacetates are fully O^1,O^3-diprotonated at acidity stronger than $H_0 = -11$. While the five-membered ring cyclization of **1** (e.g., **1a**) proceeded slowly at $H_0 = -11$, a linear increase in the rate of the cyclization was found in the acidity region of $H_0 = -11.8$ to -13.3. Therefore, the O^1,O^3-diprotonated acetoacetates (e.g., **8a**) exhibited some cyclizing reactivity, but they are *not* the reactive intermediate responsible for the acceleration of the cyclization in the high acidity region. The reactive cationic species can be deduced to be further protonated (or protosolvated) forms of the O^1,O^3-diprotonated acetoacetates; i.e., the tricationic species **11** intervene. Thermochemical data for the acid-catalyzed cyclization of the arylacetoacetates indicated that the activation energy is decreased significantly as compared with that of the related acid-catalyzed cyclization reaction of a compound bearing a single functional group, such as a ketone and an ester. Therefore, it is reasonable to assume that the intervention of the trication contributes to the activation of the cyclization of the arylacetoacetates in strong acid, and the electron-withdrawing nature of the O-protonated ester functionality embedded in **11** significantly increases the electrophilicity of the ketone moiety. Thus, the present study offers a new concept to explain the activation of electrophilicity of the cations in these, and probably also other, reactions.[11,14]

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Supporting Information Available: Additional tables and figures, Experimental Section, additional computation and experiments, and complete ref 34. This material is available free of charge via the Internet at http://pubs.acs.org.

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