ORGANIC LETTERS

2008
Vol. 10, No. 12
2569−2572

Rate-Accelerating Effect by the Neighboring-Group Participation of Protecting Groups in the Dehydrative Cyclization of 1,3,5-Triketones

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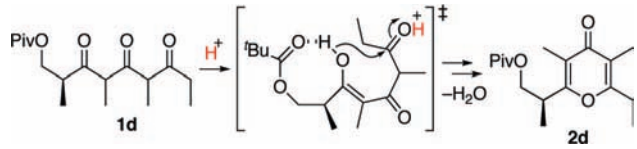
Received April 15, 2008

ABSTRACT



Neighboring-group participation of an acyl protecting group efficiently promotes the Brønsted acid-catalyzed dehydrative cyclization of 1,3,5-triketones to γ-pyrones, whereas a bulky silyloxy group in the β-position retards the cyclization. This reaction provides an efficient synthetic route for a common intermediate for the synthesis of γ-pyrone-containing bioactive natural products.

Polypropionate-derived γ-pyrones are very important heterocycles that have attracted considerable interest from chemists due to their unique structure and remarkable biological activities.[1] The biosynthesis of naturally occurring γ-pyrones appears to involve the dehydrative cyclization of 1,3,5-triketones. Although several methods have been reported for the cyclization of 1,3,5-triketones to γ-pyrones using stoichiometric dehydrating reagents,[2,3] few successful catalytic methods have been reported.

Recently, we reported that bulky diarylammonium pentafluorobenzenesulfonates effectively promoted the dehydrative cyclization of 1,3,5-triketones under reaction conditions without the removal of generated water. The dehydrative cyclization of 4,6-dimethylnonan-3,5,7-trione (**1a**) and 4,6,9-trimethyldecan-3,5,7-trione was effectively promoted by *N*-(2,6-diphenylphenyl)-*N*-mesitylammonium pentafluorobenzenesulfonate (**3**) to give the corresponding γ-pyrones in good yield.[4−6] However, the reactivity of **1c** was very low, and the corresponding γ-pyrone **2c** was obtained in only 53% yield (Scheme 1). γ-Pyrone **2c** is one of the most important common intermediates for the synthesis of many γ-pyrone-containing bioactive compounds,[7] and the development of an efficient method for the synthesis of **2c** is needed.

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(1) Davies-Coleman, M. T.; Garson, M. J. *Nat. Prod. Rep.* **1998**, *15*, 477.

(2) (a) Arimoto, H.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 5491. (b) Arimoto, H.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 5619.

(3) For a review of the synthesis of γ-pyrone-containing marine natural products, see: Yamamura, S.; Nishiyama, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2025.

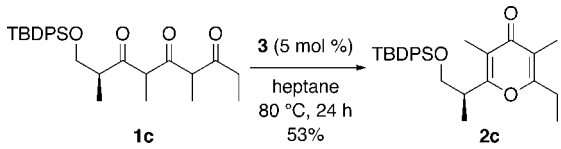
(4) Sakakura, A.; Watanabe, H.; Nakagawa, S.; Ishihara, K. *Chem. Asian J.* **2007**, *2*, 477.

(5) For ester condensation catalyzed by bulky diarylammonium pentafluorobenzenesulfonates, see: (a) Ishihara, K.; Nakagawa, S.; Sakakura, A. *J. Am. Chem. Soc.* **2005**, *127*, 4168. (b) Sakakura, A.; Nakagawa, S.; Ishihara, K. *Tetrahedron* **2006**, *62*, 422. (c) Sakakura, A.; Nakagawa, S.; Ishihara, K. *Nat. Protoc.* **2007**, *2*, 1746.

(6) For other catalytic dehydrative cyclizations of 1,3,5-triketones, see: TsOH (ca. 60% yield): (a) Asami, T.; Yoshida, S.; Takahashi, N. *Agric. Biol. Chem.* **1986**, *50*, 4695% methanolic H_2SO_4 (50% yield): (b) Harris, T. M.; Murphy, G. P.; Poje, A. J. *J. Am. Chem. Soc.* **1976**, *98*, 77330.5 M HCl (50% yield): (c) Dorman, L. C. *J. Org. Chem.* **1967**, *32*, 4105concd H_2SO_4 (59−91% yield): (d) Light, R. J.; Hauser, C. R. *J. Org. Chem.* **1960**, *25*, 53845% HBr or polyphosphoric acid (no data on yields): (e) O'Sullivan, W. I.; Hauser, C. R. *J. Org. Chem.* **1960**, *25*, 1110.

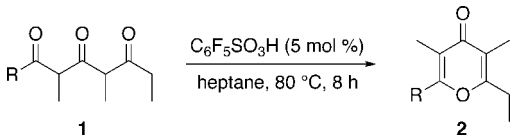
10.1021/ol800860p CCC: $40.75
Published on Web 05/27/2008

Scheme 1. Dehydrative Cyclization of 1,3,5-Triketone **1c** Catalyzed by *N*-(2,6-Diphenylphenyl)-*N*-mesitylammonium Pentafluorobenzenesulfonate (**3**)

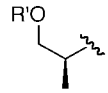
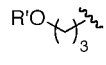
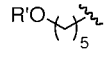


We first examined the reactivities of various 1,3,5-triketones **1**[8] for dehydrative cyclization catalyzed by pentafluorobenzenesulfonic acid ($C_6F_5SO_3H$, 5 mol %) in heptane under heating conditions without the removal of water (Table 1). 1,3,5-Triketone **1c** was much less reactive than **1a** (entries 1 and 4). When the reaction was conducted with **3** (5 mol %) instead of $C_6F_5SO_3H$, the reactivity of **1c** was slightly improved, but the yield of **2c** was still insufficient (53%, entry 5). One of the reasons for the low reactivity of **1c** may be the steric hindrance due to a methyl group at its 2-position. In fact, 2,4,6-trimethylnonan-3,5,6-trione (**1b**) was slightly less reactive than **1a** (entries 1 and 2). However, low reactivity of **1c** can mainly be attributed to the TBDPS group, since **1c** was much less reactive than **1b** (entry 2 vs entry 4). As in the case of **1c**, 1,3,5-triketones **1g** and **1j**, which have a TBDPS group, were much less reactive than **1a** and **1b**, despite the fact that **1g** and **1j** did not have an additional methyl group at the α-position of the carbonyl group (entries 10 and 13). The TBDPS group is conventionally used to protect a hydroxyl group in 1,3,5-triketones but is not suitable for the present catalytic dehydrative cyclization.

Table 1. Dehydrative Cyclization of 1,3,5-Triketones **1** to γ-Pyrones **2**[a]



1 **2**

entry	triketone **1** R	triketone **1** R'	yield (%) of **2**[b]	solubility of **2**[c]
1	Et (**1a**)	—	74	Y
2	*i*-Pr (**1b**)	—	68	Y
3[d]		—	65	Y
4		TBDPS (**1c**)	36	Y
5[e]		TBDPS (**1c**)	53	Y
6		Piv (**1d**)	82 [95][f]	Y
7[g]		Piv (**1d**)	50	Y
8		*p*-MeOC$_6$H$_4$CO (**1e**)	91	N
9		Bn (**1f**)	75	N
10		TBDPS (**1g**)	29	Y
11		Piv (**1h**)	80	Y
12		*p*-MeOC$_6$H$_4$CO (**1i**)	96	N
13		TBDPS (**1j**)	37	Y
14		Piv (**1k**)	76	Y
15		*p*-MeOC$_6$H$_4$CO (**1l**)	96	N

[a] Reactions of **1** (0.1 mmol) were carried out with $C_6F_5SO_3H$ (5 mol %) in heptane (2 mL) at 80 °C for 8 h without the removal of water. [b] Isolated yield. [c] Y, soluble in the reaction mixture; N, insoluble in the reaction mixture. [d] The reaction was conducted with methyl pivalate (1 equiv). [e] The reaction was conducted with **3** (5 mol %) instead of $C_6F_5SO_3H$. [f] The reaction was conducted for 24 h. [g] The reaction was carried out in toluene.

Therefore, we examined protecting groups for the hydroxyl group in 1,3,5-triketone to improve their reactivities. Surprisingly, we found that 1,3,5-triketone **1d**, the hydroxyl group of which is protected by a pivaloyl group, showed high reactivity (82% yield, entry 6). When the reaction was conducted for 24 h, γ-pyrone **2d** was obtained in 95% yield. Since **1d** was more reactive than **1a** and **1b**, the pivaloyl group may effectively promote the acid-catalyzed dehydrative cyclization of 1,3,5-triketones. This rate-accelerating effect of a pivaloyl group can be attributed to intramolecular neighboring-group participation, since the reaction of **1b** in the presence of methyl pivalate (1 equiv) gave the same result (65% yield, entry 3) as that of **1b** in the absence of the additive (entry 2). When the reaction of **1d** was conducted in toluene, the product **2d** was obtained in low yield (50%, entry 7). This lower reactivity in toluene of **1d** may be attributed to the stronger solvatation, which resulted in inhibition of the neighboring-group participation. 1,3,5-Triketones **1h** and **1k** were also much more reactive than **1g** and **1j** (entries 10, 11, 13, and 14). The pivaloyl group of **2d** can be removed in 93% yield using $LiAlH_4$ (2.0 equiv) without a loss of optical purity.

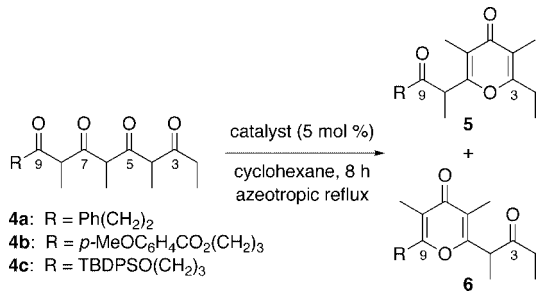
Further investigation of the protecting group for the hydroxyl group revealed that 1,3,5-triketone **1e**, which has a *p*-methoxybenzoyloxy group, was more reactive than **1d** (Table 1, entry 8). This rate-accelerating effect may be attributed to the insolubility of the corresponding γ-pyrone **2e** under the reaction conditions, in addition to the neighboring-group participation of the *p*-methoxybenzoyloxy group. It is conceivable that the catalyst preferentially activated **1e** and efficiently promoted the reaction because **2e** was insoluble. In fact, benzyl-protected 1,3,5-triketone **1f**, which gave insoluble γ-pyrone **2f**, was slightly more reactive than **1b** (entry 9), despite the fact that 1,3,5-triketone **1f** did not have an acyloxy group. 1,3,5-Triketones **1i** and **1l** also gave insoluble γ-pyrones **2i** and **2l**, and were more reactive than **1h** and **1k** (entries 11, 12, 14, and 15).

We next investigated the dehydrative cyclization of 1,3,5,7-tetraketones **4** (Table 2). In principle, the reaction of **4** would produce γ-pyrones **5** and **6**. When the reaction of 1,3,5,7-tetraketone **4a** was conducted with $C_6F_5SO_3H$ (5 mol %) in heptane under heating conditions (80 °C) without the removal of water, a 1:1 mixture of **5a** and **6a** was obtained in 39% yield, along with some byproducts (entry

(7) (a) Arimoto, H.; Cheng, J.-F.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1993**, *34*, 5781. (b) Paterson, I.; Franklin, A. S. *Tetrahedron Lett.* **1994**, *35*, 6925. (c) Arimoto, H.; Yokoyama, R.; Okumura, Y. *Tetrahedron Lett.* **1996**, *37*, 4749. (d) Arimoto, H.; Yokoyama, R.; Nakamura, K.; Okumura, Y.; Uemura, D. *Tetrahedron* **1996**, *52*, 13901. (e) Paterson, I.; Chen, D. Y.-K.; Aceña, J. L.; Franklin, A. S. *Org. Lett.* **2000**, *2*, 1513. (f) Paterson, I.; Chen, D. Y.-K.; Franklin, A. S. *Org. Lett.* **2002**, *4*, 391.

(8) For the synthesis of 1,3,5-triketones **1**, see Supporting Information.

Table 2. Dehydrative Cyclization of 1,3,5,7-Tetraketones **4** to γ-Pyrones **5** and **6**[a]



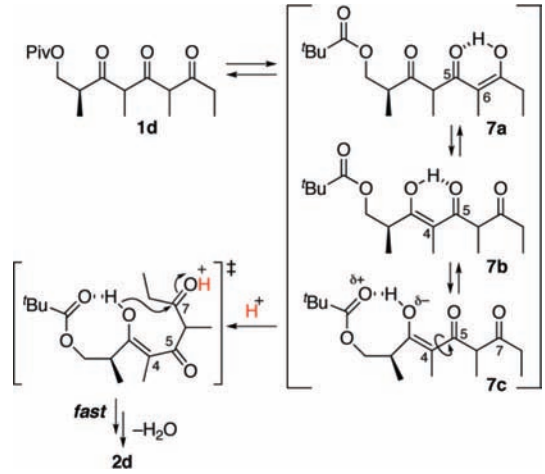
entry	tetraketone **4**	catalyst	yield of **5** and **6** (%)[b]	**5**/**6**[b]
1[c]	**4a**	$C_6F_5SO_3H$	39	1:1
2	**4a**	$C_6F_5SO_3H$	68	1:1
3	**4b**	$C_6F_5SO_3H$	83	2:1
4	**4b**	Tf_2NH	78	3:1
5	**4c**	$C_6F_5SO_3H$	71	1:1

[a] Reaction of **4** (0.1 mmol) was carried out with $C_6F_5SO_3H$ (5 mol %) in cyclohexane (2 mL) under azeotropic reflux conditions for 8 h. [b] Determined by ^1H NMR analysis. [c] The reaction was conducted in heptane (2 mL) at 80 °C without the removal of water.

1). The generation of byproducts can be attributed to decomposition by water. In fact, the reaction of **4a** in cyclohexane (bp = 80.7 °C) under azeotropic reflux conditions increased the yield of **5a** and **6a** (68%), while the ratio of **5a** and **6a** did not change (entry 2). As in the case of 1,3,5,7-tetraketone **4b** bearing a *p*-methoxybenzoyloxy group, the reactivity increased and the corresponding γ-pyrones **5b** and **6b** were obtained in 83% yield under azeotropic reflux conditions (entry 3). Interestingly, the reaction of **4b** gave a 2:1 mixture of **5b** and **6b**. This preferential production of **5b** might be attributed to the intramolecular participation of the *p*-methoxybenzoyl group. In contrast, 1,3,5,7-tetraketone **4c**, bearing a TBDPS group, showed reactivity similar to **4a**, and gave a 1:1 mixture of **5c** and **6c** (entry 5). To improve the selectivity of **5b**, we examined several acid catalysts. We were pleased to find that the use of bulky Brønsted acid catalysts such as trifluoromethanesulfonimide (Tf_2NH) gave a better result (**5b**/**6b** = 3:1, entry 4).

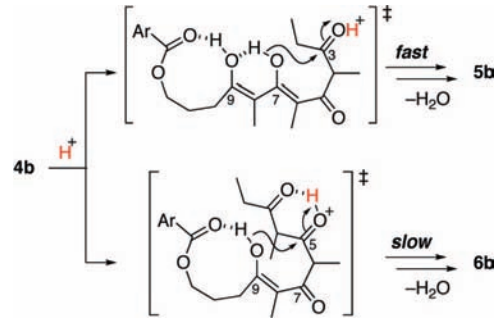
On the basis of the results described above, we propose a mechanism for rate acceleration by the intramolecular pivaloyl group and for rate deceleration by the TBDPS group, as shown in Scheme 2. 1,3,5-Triketone **1d** is thought to be in equilibrium with enol **7c**, as well as **7a** and **7b**. Intramolecular hydrogen bondings restrict the free rotation of the C5−C6 bond of **7a** and the C4−C5 bond of **7b**. In contrast, intramolecular participation of the pivaloyl group in **7c** resulted in free rotation of the C4−C5 bond, which helped **7c** to adopt a conformation suitable for cyclization. Furthermore, this intramolecular participation increased the nucleophilicity of the enol oxygen. After protonation at the C-7 carbonyl oxygen of **7c**, cyclization proceeded rapidly with the assistance of intramolecular abstraction of the enol proton by the pivaloyl group.[9]

Scheme 2. Proposed Mechanism for the Dehydrative Cyclization of **1d** with the Aid of Neighboring-Group Participation



The preferential formation of **5b** in the dehydrative cyclization of 1,3,5,7-tetraketone **4b** could also be explained by the neighboring-group participation of the *p*-methoxybenzoyl group (Scheme 3). The *p*-methoxybenzoyl group was

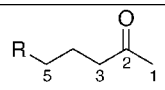
Scheme 3. Proposed Mechanism for the Preferential Production of **5b** in the Dehydrative Cyclization of **4b**



thought to form an intramolecular hydrogen bond with the closest enol proton. The enol oxygen at the C-7 position, which would be activated through intramolecular hydrogen bonding, could rapidly react with the protonated C-3 carbonyl group to give **5b** preferentially. In contrast, cyclization of the enol oxygen at the C-9 position to the C-5 carbonyl group would proceed slowly due to steric hindrance around the C-5 carbonyl group. It is conceivable that Tf_2NH, a bulky Brønsted acid, would increase the preference for the protonation at the terminal C-3 carbonyl group, which improved the ratio of **5b** and **6b**.

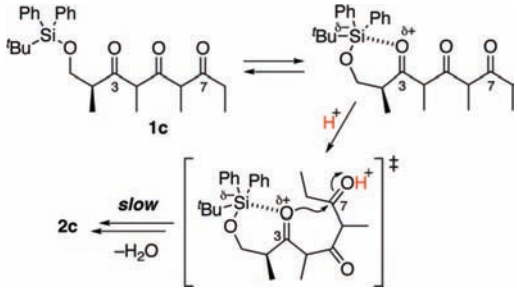
(9) The neighboring-group participation of the acyl protecting groups might explain the rate acceleration for the reaction of 1,3,5-triketones **1d** and **1e**, as we proposed in Scheme 2. However, this neighboring-goup participation is still controversial, especially for the reaction of **1h**, **1i**, **1k**, and **1l**, which might proceed via a 9- or 11-membered cyclic transition state. A detailed mechanistic study on the rate-accelerating effect by the acyl groups is currently underway.

Table 3. ^{13}C NMR Data of 5-Substituted 2-Pentanones **8** and 2-Hexanone (**9**)

entry		^{13}C NMR (ppm) in C_6D_{12}		
		C1	C2	C3
1	R = TBDPSO (**8a**)	29.3	205.6	40.0
2	R = TBSO (**8b**)	29.3	204.0	39.8
3	R = PivO (**8c**)	29.3	203.4	39.9
4	R = Me (**9**)	29.2	203.5	43.4

To explore the effect of TBDPS group on the reactivity of 1,3,5-triketones **1** and 1,3,5,7-tetraketones **5**, we compared the ^{13}C NMR data of 5-substituted 2-pentanones **8** and 2-hexanone (**9**) in C_6D_{12} (Table 3). All compounds we examined showed almost same chemical shifts for C-1 (29.3 ppm) and C-3 (39.9 ppm), except that the C-3 carbon of **9**. However, the chemical shifts for C-2 carbons of **8a** (205.6 ppm) and **8b** (204.0 ppm), which had a silyoxy group, were slightly higher than those (203.4 ppm) of other compounds without a siloxy group. These results imply the existence of intramolecular interaction between a TBDPS group and carbonyl oxygen. In the case of **1c**, the TBDPS group would interact with the C-3 carbonyl oxygen (Scheme 4). This interaction might preclude enol formation at the C-3 carbonyl group and decrease its basicity and nucleophilicity. The low nucleophilicity of the C-3 carbonyl oxygen would decrease the rate of cyclization of **1c**.

Scheme 4. Proposed Mechanism for the Rate-Decelerating Effect of TBDPS Group in **1c**



In conclusion, we found a rate-accelerating effect in the Brønsted acid-catalyzed dehydrative cyclization of 1,3,5-triketones by the neighboring-group participation of acyl protecting groups. This rate-accelerating effect provided **2d** in high yield, which could be easily converted to a common synthetic intermediate for γ-pyrone-containing bioactive natural products. Furthermore, the Tf_2NH-catalyzed dehydrative cyclization of 1,3,5,7-tetraketone **4b** preferentially gave γ-pyrone **5b** with the aid of the acyloxy group.

Acknowledgment. This project was supported by JSPS.KAKENHI (Grant No. 20245022), the Toray Science Foundation, and the G-COE in Chemistry, Nagoya.

Supporting Information Available: Experimental details, spectroscopic data for all new compounds, and ^1H and ^{13}C NMR charts of products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800860P