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Hetero-Diels–Alder reaction of photochemically generated α-hydroxy-*o*-quinodimethanes with trifluoromethyl ketones

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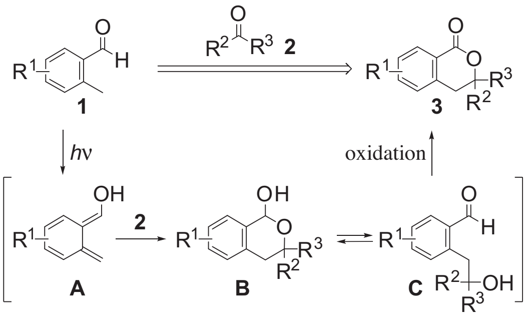
ABSTRACT

Hetero-Diels–Alder reaction of α-hydroxy-*o*-quinodimethanes photochemically generated from *o*-tolualdehydes with trifluoromethyl ketones gave a mixture of hemiacetals and hydroxyaldehydes in fairly good yields. Their subsequent oxidation with PCC provided 1-isochromanones as formal oxidative [4+2] cycloaddition products. In contrast, similar reaction of aromatic ketones such as *o*-methylbenzophenone, 1-indanone, and α-tetralone gave exclusively the corresponding ketones having (trifluoromethyl)methylol groups at the *o*-position.

o-Quinodimethanes (oQDMs) have been well known as reactive dienes in Diels–Alder reaction, and they are generated by various methods such as thermolysis of benzocyclobutenes and benzo-fused heterocyclic compounds, and 1,4-elimination of α,α'-substituted *o*-xylenes.[1] Photochemical generation of α-hydroxy-*o*-quinodimethanes (HoQDMs) from *o*-tolualdehydes is also a convenient and attractive approach to elaborate benzocyclohexane derivatives via Diels–Alder reaction.[2] On the other hand, hetero-Diels–Alder reaction of oQDMs with ketones and imines to yield isochromans and tetrahydroisoquinolines has been little explored, wherein most of the reaction used benzocyclobutene precursors having 1-silyloxy and 1-alkoxy substituents.[3,4] The similar reaction of HoQDM would be more difficult than that of oQDM, because by-products derived from HoQDM and *o*-tolualdehyde precursors could be formed. In fact, only one example has been reported, but the products were isolated as a mixture.[5]

With these results in mind, we designed oxidative hetero-Diels–Alder reaction of *o*-tolualdehydes **1** with ketones **2** to yield 1-isochromanones **3** (Scheme 1). Generation of HoQDM **A** by irradiation of **1** and its trapping with **2** would yield an equilibrium mixture of hemiacetal **B** and hydroxyaldehyde **C**. If the mixture could be efficiently oxidized to **3**,[6] the overall transformation could be regarded as a formal oxidative [4+2] cycloaddition. Herein we would like to report these results.



Scheme 1. Oxidative hetero-Diels–Alder reaction of *o*-tolualdehydes.

After screening of various trapping reagents for HoQDM, it was found that trifluoromethyl ketones acted as good dienophiles.[7] Thus, when a solution of mesitaldehyde (**1a**) and phenyl trifluoromethyl ketone (**2a**) (1.1 equiv) in MeCN was irradiated by Hg lamp for 3 h, an inseparable mixture of hemiacetal **B** and hydroxyaldehyde **C** was obtained, which was subsequently treated with PCC in DCM in the presence of molecular sieves to give only 1-isochromanone **3a** in 75% yield. The results using various *o*-tolualdehyde derivatives **1** and trifluoromethyl ketones **2** are summarized in Table 1.[8] The reactions of 2,4-dimethylbenzaldehyde (**1b**) and *o*-tolualdehyde (**1c**) with the ketone **2a** gave the 1-isochromanones **3b** and **3c** in 57% and 68% yields, respectively, (entries 2 and 3). Similarly the expected product **3d** was obtained from 4-fluoro-2-methylbenzaldehyde (**1d**) (entry 4). *o*-Benzyl- and *o*-heptylbenzaldehyde

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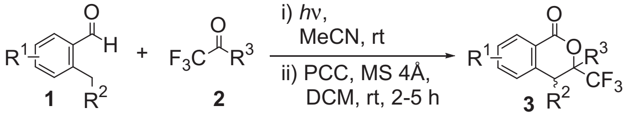
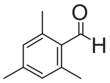
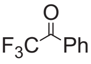
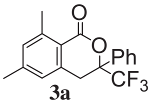
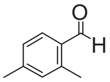
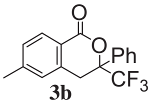
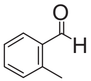
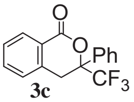
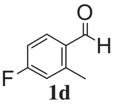
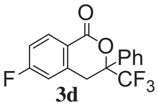
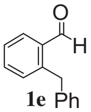
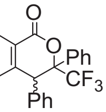
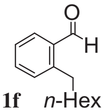
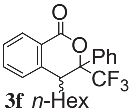
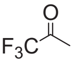
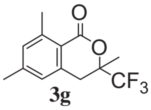
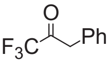
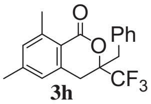
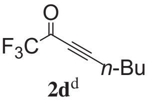
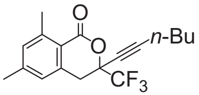
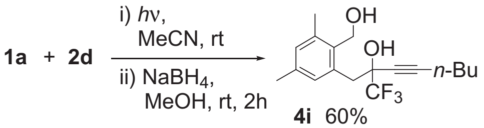
Table 1
Photochemical synthesis of 1-isochromanones by hetero-Diels–Alder reaction followed by PCC oxidation[a]



Entry	Aldehyde **1**	Ketone **2**	Time[b] (h)	Product **3**	Yield[c] (%) (dr)
1	 **1a**	 **2a**	3	 **3a**	75
2	 **1b**	**2a**	6	 **3b**	57
3	 **1c**	**2a**	12	 **3c**	68
4	 **1d**	**2a**	4	 **3d**	54
5	 **1e**	**2a**	17	 **3e**	44 (63/37)
6	 **1f**	**2a**	6	 **3f**	61 (53/47)
7	**1a**	 **2b**[d]	24	 **3g**	30
8	**1a**	 **2c**[d]	8	 **3h**	39
9	**1a**	 **2d**[d]	9	 **3i**	36

[a] Reaction conditions: (i) **2** (1.1 equiv), anhydrous MeCN (0.1 M), high-pressure Hg lamp (100 w); (ii) PCC (1.1 equiv), DCM (0.3 M).
[b] Irradiation time.
[c] Isolated yield.
[d] 2 Equiv of **2b**–**2d** were used.

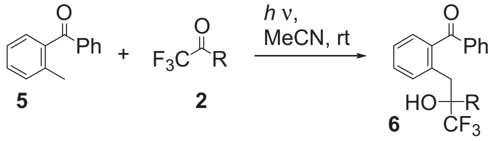
(**1e**) and (**1f**) participated the reaction to yield **3e** and **3f** in 44% and 61% yields with diastereomer ratios of 63/37 and 53/47, respectively, (entries 5 and 6). Trifluoromethyl ketones other than **2a** could be used in this transformation. Thus, the reaction of mesitaldehyde (**1a**) with 1,1,1-trifluoroacetone (**2b**) and benzyl trifluoromethyl ketone (**2c**) gave the corresponding products **3g** and **3h** in 30% and 39% yields, respectively, (entries 7 and 8). 3-Hexynyl-1-isochromanone **3i** was also prepared in 36% yield from **1a** and 1-trifluoroacetyl-1-hexyne (**2d**) by the standard procedure (entry 9). However, when the reaction mixture formed by irradiation of **1a** with **2d** was reduced with NaBH$_4$, diol **4i** was obtained in 60% yield (Eq. 1). Thus, low yield of **3i** may be caused by the oxidation step to yield unidentified by-products.



(1)

Next, hetero-Diels–Alder reaction of 2-methylbenzophenone (**5**) with trifluoromethyl ketones **2** was investigated (Table 2).[8] In contrast with the reaction of *o*-tolualdehydes **1**, irradiation of **5** together with phenyl trifluoromethyl ketone (**2a**) gave directly *o*-(hydroxyethyl)benzophenone **6a** in 65% yield, wherein a corresponding ketal was not detected (entry 1). Similar results were obtained using various trapping reagents **2**. The difference between **1** and **5** would be attributed to the equilibrium of the

Table 2
Photochemical reaction of *o*-methylbenzophenone (**5**) with trifluoromethyl ketones **2**[a]



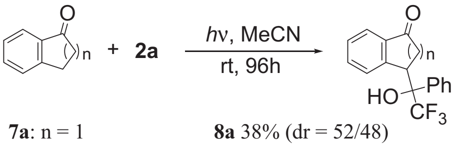
5 **2** **6**

Entry	Ketone		Time (h)	Product 6	Yield[b] (%)
	2	**R**			
1	2a[c]	Ph	11	6a	65
2	2b	Me	21	6b	53
3	2c	CH$_2$Ph	8	6c	61
4	2d	≡–*n*-Bu	14	6d	74
5	2e	≡–Ph	48	6e	73
6	2f	CF$_3$	48	6f	46

[a] Reaction conditions: **2** (2.0 equiv), anhydrous MeCN (0.1 M).
[b] Isolated yield.
[c] 1.5 Equiv of **2a** were used.

hetero-Diels–Alder products, that is, ketals could shift to hydroxyketones exclusively. Moreover, the products **6** may be converted to the other HoQDM by further irradiation, because they have carbonyl and *o*-methylene groups. However, no photoreaction of the isolated **6a** was observed in the presence of the representative trapping reagents such as *N*-phenylmaleimide and dimethyl acetylenedicarboxylate.[1]

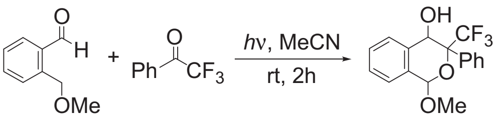
The photoreaction of *o*-methylacetophenone with **2a** was found to take place by GC monitoring, but isolation of the expected products failed because of many by-products. Surprisingly, 1-indanone (**7a**) and α-tetralone (**7b**) gave the hydroxyketones **8a** and **8b** in 38% and 32% yields with diastereomer ratios of 52/48 and 50/50, respectively, (Eq. 2). Although the yield and stereoselectivity were low, the results would demonstrate unprecedented generation of the HoQDM from benzocycloalkan-1-ones.



(2)

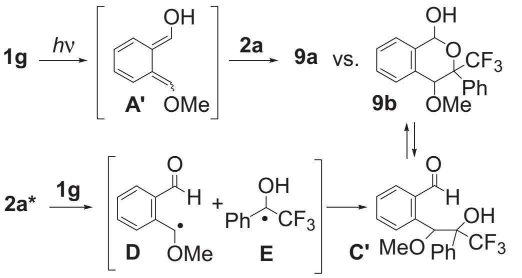
7a: n = 1 **8a** 38% (dr = 52/48)
7b: n = 2 **8b** 32% (dr = 50/50)

When *o*-(methoxymethyl)benzaldehyde (**1g**) was irradiated together with **2a** under standard conditions, 4-isochromanol **9a** was directly formed in 55% yield as a mixture of two diastereomers (60/40) (Eq. 3).[9] However, hemiacetal **9b**, regioisomer of **9a**, and hydroxyaldehyde **C'** were not obtained. Regioselectivity in the hetero-Diels–Alder reaction of HoQDM **A'** generated from **1g** was reversed probably by the methoxy substituent (Scheme 2). More importantly, formation of **9a** would rule out an alternative reaction process, which includes hydrogen abstraction from **1g** by photoexcited ketone **2a***[10]and subsequent coupling of the resulting two radicals **D** and **E**, because this process should provide **9b** via **C'**, instead of **9a**.



1g **2a** **9a** 55% (60/40)

(3)



Scheme 2. Reaction process by hetero-Diels–Alder reaction versus radial coupling.

In summary, formal oxidative [4+2] cycloaddition of *o*-tolualdehydes with trifluoromethyl ketones to yield 1-isochromanones has been achieved through hetero-Diels–Alder reaction of the photochemically generated α-hydroxy-*o*-quinodimethanes and subsequent oxidation with PCC. On the other hand, *o*-methylbenzophenone and benzocycloalkan-1-ones reacted with the trapping reagents under irradiation to yield *o*-substituted ketones exclusively.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.082.

References and notes

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4. Palladium-catalyzed generation of an equivalent to oQDM and its reaction with ketones and imines have been recently reported; see: (a) Ueno, S.; Ohtsubo, M.; Kuwano, R. *Org. Lett.* **2010**, *12*, 4332–4334; (b) Ueno, S.; Ohtsubo, M.; Kuwano, R. *J. Am. Chem. Soc.* **2009**, *131*, 12904–12905.
5. Griesbeck, A. G.; Stadtmüller, S. *Chem. Ber.* **1993**, *126*, 2149–2150.
6. DDQ oxidation of trimethylsilylhemiacetal to ester has been known; see: Ref. 3b.
7. Irradiation of mesitaldehyde (**1a**) in the presence of other ketones such as acetophenone, phenyl trichloromethyl ketone, phenylglyoxal, and ethyl benzoylformate resulted in the quantitative recovery of the both starting materials or decomposition of the trapping reagents.
8. General procedure for the reaction listed in Tables 1 and 2. A pyrex test tube containing *o*-tolualdehydes **1** (1.0 mmol), trifluoromethyl ketones **2** (1.1 mmol), and CH$_3$CN (10 mL) was purged with nitrogen and irradiated at room temperature by high-pressure Hg lamp (100 W) with monitoring by GC and TLC. After the reaction being completed, the solvent was evaporated to leave a solid or viscous oil. Then, this mixture and pyridinium chlorochromate (237 mg, 1.1 mmol) were dissolved in dichloromethane (3 mL). After addition of molecular sieves 4 Å (100 mg), the mixture was stirred for 2–5 h at room temperature. The reaction mixture was passed through celite, evaporated in vacuo, and chromatographed on silica gel using hexane-EtOAc (10/1) eluent to give the 1-isochromanones **3**. The reactions of **5** and **7** were carried out similarly, but the products **6** and **8** were isolated without the oxidation.
9. Although stereochemistry of **9a** could not be determined, its regiochemistry was distinguishable from that of **9b**, because **9a** was recovered unchanged on treatment with NaBH$_4$.
10. Kamijo, S.; Hoshikawa, T.; Inoue, M. *Tetrahedron Lett.* **2011**, *52*, 2885–2888.