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Synthesis of oxygen-containing heterocyclic compounds based on the intramolecular O–H insertion and Wolff rearrangement of α-diazocarbonyl compounds

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Abstract—The addition products of Ti(IV)-enolate derived from β-keto α-diazo carbonyl compound to ketones or α,β-unsaturated compounds were subjected to $Rh_2(OAc)_4$-catalyzed and photo-induced diazo decomposition. The $Rh_2(OAc)_4$-catalyzed reaction afforded intramolecular O–H insertion products, while the photo-induced reaction gave Wolff rearrangement/intramolecular nucleophilic addition products. The transformations represent new approaches to tetrahydrofuran and γ-butyrolactone derivatives.

Oxygen-containing heterocycles, especially tetrahydrofuran and γ-butyrolactone derivatives, are important synthetic targets due to their occurrence in numerous natural products, their wide range of biological activities, and their utility as versatile intermediates in organic synthesis. In addition to the traditional methods, many new synthetic methodologies have been developed in recent years for this important class of heterocyclic compounds.[1] In particular, transition metal catalyzed transformations have been successful and offer great potential. For example, platinum-catalyzed intramolecular hydroalkoxylation of γ-hydroxy olefins led to the formation of tetrahydrofuran derivatives.[2] Palladium-catalyzed cyclization of allylic 2-alkynoates has been utilized to build γ-butyrolactone derivatives.[3] In this paper, we report a new approach to both tetrahydrofuran and γ-butyrolactone derivatives based on the reaction of α-diazocarbonyl compounds.

We have recently studied the nucleophilic addition of Ti(IV) enolate **2**, derived from β-keto α-diazo carbonyl compound **1**, to various electrophiles (Scheme 1).[4] Although the efficient addition of Ti(IV) enolate **2** to aldehydes has already been reported by Calter and coworkers,[55] carbonyl compounds, a series of δ-hydroxy β-keto α-diazoesters have been prepared—product structures are summarized in Scheme 1.

Since the addition products **3a–j** bear two reactive functional groups (hydroxy and diazo) in appropriate positions, they are expected to undergo some useful intramolecular transformations upon diazo decomposition. First, we investigated the diazo decomposition of the addition products in the presence of rhodium (II) acetate, with the expectation that Rh(II)-carbene intramolecular O–H insertion should occur to afford tetrahydrofuran derivative.[5,6] The reaction only took 10 min to complete after the addition of the diazo compounds to the refluxing toluene in the presence of a catalytic amount of $Rh_2(OAc)_4$. ^1H NMR spectra of the crude products showed that only intramolecular O–H insertion products were formed in all cases (Table 1).[7]

Next, photo-induced reaction of the diazo compounds **3a–j** was examined, with the expectation that Wolff rearrangement should occur to generate the ketene

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Keywords: Diazo compounds; Rh(II) carbene; Wolff rearrangement; Tetrahydrofuran derivative; γ-butyrolactone derivative.

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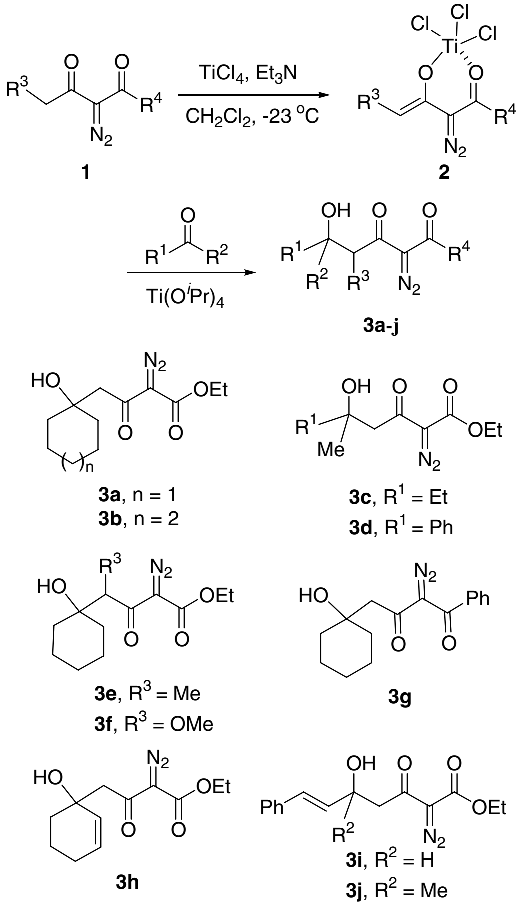
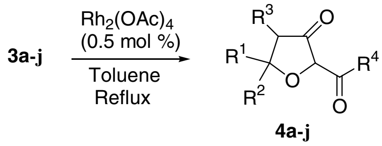


Scheme 1.

Table 1. $Rh_2(OAc)_4$-catalyzed intramolecular O–H insertion[7]



Entry	3a–j	Product 4a–j	Yield (%)[a]	dr[b]
1	**3a**	**4a**	91	—
2	**3b**	**4b**	97	—
3	**3c**	**4c**	95	46:54
4	**3d**	**4d**	95	50:50
5	**3e**	**4e**	97	56:44
6	**3f**	**4f**	99	61:39
7	**3g**	**4g**	93	—
8	**3h**	**4h**	98	49:51
9	**3i**	**4i**	99	44:56
10	**3j**	**4j**	98	43:57

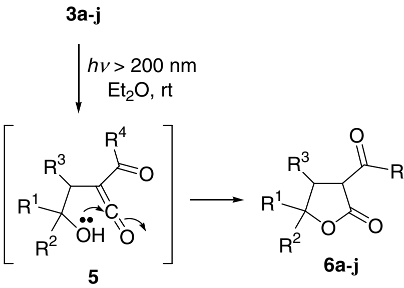
[a] Refer to the yields of crude products.

[b] Product ratio was determined by ^1H NMR (300 MHz).

intermediate **5**, which may be followed by a intramolecular nucleophilic attack by the hydroxy group.[8,9] The reaction was carried out in the anhydrous ether solution under UV irradiation (150 W high-pressure Hg lamp, $\lambda > 200$ nm) at room temperature. The starting diazo compound was completely consumed after 14–17 h, and separation with silica gel chromatography afforded the major product in moderate yield for each case. ^1H and ^{13}C NMR spectra indicated that the major product was the expected γ-butyrolactone derivative **6a–j** (Table 2).[10] As showed by the data collected in Table 2, the yields were generally moderate. Products **6c–d** were isolated each as a isomeric mixture with ratio near 1:1, while **6e** was obtained as a single diastereomer (Table 2, entries 3–5). For the diazo compounds **3h–j**, the irradiation was carried out with a 500 W high-pressure Hg lamp (Table 2, entries 8–10). The reaction time was significantly shortened, while the yield was comparable.

When diazo compound **3f** was irradiated under the same condition, the expected **6f** was not isolated. Instead, α,β-unsaturated product **7** was isolated in moderate yield. The product **7** was obviously formed through the elimination of MeOH from **6f**. This result may be due to the instability of **6f** which eliminates methanol quickly to give the more stable product **7** after **6f** was first formed in the reaction (Scheme 2).

Table 2. Photo-induced diazo decomposition of **3a–j**[a,10]



Entry	3a–j	Reaction time (h)	Product 6a–j	Yield (%)[b]	dr[c]
1	**3a**	14	**6a**	69	—
2	**3b**	16	**6b**	78	—
3	**3c**	17	**6c**	67	50:50
4	**3d**	14.5	**6d**	58	47:53
5	**3e**	14	**6e**	71	100:0
6	**3f**	17	**7**[d]	54	—
7	**3g**[e,f]	6	**6g**	33	—
8	**3h**[f]	5	**6h**	67	50:50
9	**3i**[f]	5	**6i**	77	65:35
10	**3j**[f]	5	**6j**	57	56:44

[a] The reaction mixture in a quartz tube was irradiated with a 150 W high-pressure Hg lamp if not specially noted.

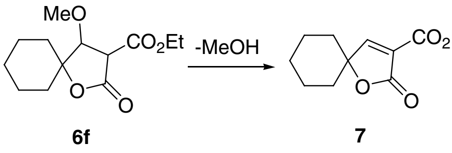
[b] Refer to the yields after separation with silica gel column.

[c] Determined by ^1H NMR (300 MHz) of the crude product.

[d] The product was **7**, as shown in Scheme 2.

[e] The reaction gave a complex mixture when irradiated with 150 W high-pressure Hg lamp.

[f] Irradiation was carried out in a Pyrex tube with a 500 W high-pressure Hg lamp.



Scheme 2.

It was also noticed that photo-induced decomposition of **3g** resulted in a complex mixture when irradiated with 150 W high-pressure Hg lamp for long time. When irradiated with 500 W high-pressure Hg lamp, γ-butyrolactone **6g** was isolated in 33% yield (Table 2, entry 7). Considering the mechanism of this rearrangement reaction, it could be expected that both alkyl and phenyl group could transfer to form ketene intermediates **9** and **10** (Scheme 3). The phenyl shift has been known to have higher 1,2-shift preference in Wolff rearrangement.[8b] Consequently, 1,2-phenyl shift may predominate in this case, thus giving **9** as the main Wolff rearrangement product. The intramolecular nucleophilic addition may not be efficient for ketene **9**, because of the steric bulkiness of the phenyl group as well as the unfavorable 1,6 addition. Side reactions may occur from **9**. As a result, the reaction gave a complex mixture or low yield of γ-butyrolactone **6g**.

Finally, when substrate **3i** and **3j** were irradiated, in addition to **6i** and **6j**, **11** and **12** were separated as minor products (Scheme 4). The double bond cis/trans isomerization occurred under the photochemical conditions.

In summary, we have developed a concise and efficient protocol to synthesize tetrahydrofuran derivatives via intramolecular O–H insertion, and γ-butyrolactone derivatives via Wolff rearrangement from simple sub-

10. *General procedure for photo-induced Wolff rearrangement.* A quartz tube or a Pyrex tube was charged with a solution of **3a**–**j** (0.30 mmol) in dry ethyl ether (6 mL) under nitrogen atmosphere. The resulting solution was irradiated with a high-pressure mercury lamp (150 W or 500 W) at room temperature until complete disappearance of the diazo substrate. The reaction mixture was then concentrated under vacuum, and the residue was purified by silica gel column chromatography (petroleum ether–EtOAc, 5:1) to afford the γ-butyrolactone derivatives **6a**–**j**. **6a**: 69%; colorless oil; IR (neat) 2937, 2862, 1772, 1734 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.33 (t, $J = 7.2$ Hz, 3H), 1.37–1.88 (m, 10H), 2.31 (dd, $J = 13.2$, 9.9 Hz, 1H), 2.42 (dd, $J = 13.2$, 9.6 Hz, 1H), 3.70 (dd, $J = 9.9$, 9.6 Hz, 1H), 4.26 (q, $J = 7.2$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 13.8, 22.3, 24.5, 36.4, 36.5, 37.2, 46.7, 61.9, 85.3, 167.9, 171.1; EI-MS (*m*/*z*, relative intensity): 226 (M$^+$, 6), 208 (8), 183 (32), 153 (63), 137 (84), 98 (100), 55 (85). HRMS calcd for $C_{12}H_{18}O_4$ 226.1205; found: 226.1201.