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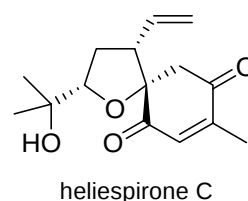
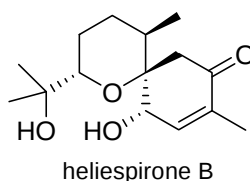
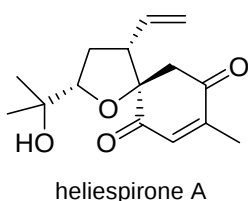
STEREOSELECTIVE SYNTHESIS OF 5-SUBSTITUTED 2-ALLYL-3-OXOTETRAHYDROFURAN-2-CARBOXYLATES USING RHODIUM(II)-CATALYZED OXONIUM YLIDE FORMATION-[2,3] SHIFT

Takayuki Yakura,^{1*} Katsuaki Matsui,^{1,2} Kazumasa Matsuzaka,¹ and
 Masayuki Yamashita²

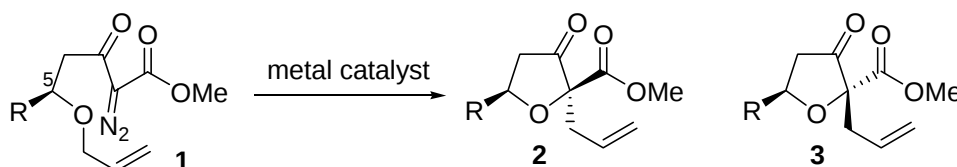
¹Graduate School of Medicine and Pharmaceutical Sciences, University of
 Toyama, Sugitani, Toyama 930-0194, Japan ²Kyoto Pharmaceutical University,
 Misasagi, Yamashina, Kyoto 607-8412, Japan
 E-mail: yakura@pha.u-toyama.ac.jp

Abstract – Reaction of 5-allyloxy-2-diazo-3-ketoesters **1** with catalytic amount
 of dirhodium(II) tetraacetate in dichloromethane proceeded in high yields with
 excellent stereoselectivities to give methyl 5-substituted 2-allyl-3-oxotetrahydro-
 furan-2-carboxylates **2**, which are suitable intermediates for synthesis of
 heliespirones and their derivatives.

Heliespirones A,^{1,2} B,^{2,3} and C² were isolated from leaves of *Helianthus annuus* L. in 1998 and 2006 as
 members of a new family of bioactive sesquiterpenes, potential allelopathic agents. These compounds
 display unusual previously unknown spirosesquiterpene skeletons. Heliespirones A and C have a
 2,2,3,5-tetrasubstituted tetrahydrofuran framework; heliespirone B has a 2,2,3,6-tetrasubstituted
 tetrahydropyran framework. Stereoselective construction of substituted tetrahydrofurans and pyrans is an
 important subject for synthesis of these attractive sesquiterpenes and their analogues. Herein, we describe
 the synthesis of 5-substituted 2-allyl-3-oxotetrahydrofuran-2-carboxylates **2**, which might become
 suitable intermediates for the synthesis of heliespirones, in high yields with excellent stereoselectivities
 by rhodium(II)-catalyzed oxonium ylide formation-[2,3] shift of α -diazo- β -ketoesters **1**.

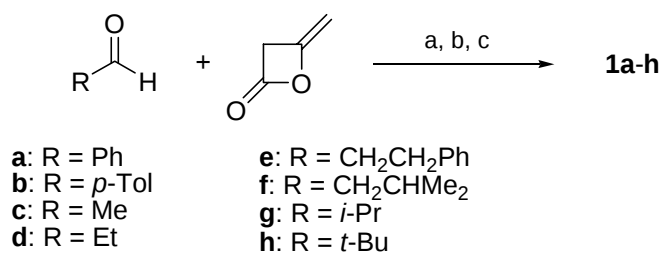


Metal-catalyzed carbenoid reactions⁴ have become a powerful tool for synthesis of functionalized cyclic compounds including oxacycles. However, it is sometimes difficult to control their chemoselectivity because of the high reactivity of the metal carbenoid intermediates, which can react with heteroatoms, inactivated C–H bonds, C–C multiple bonds, *etc.* Moreover, the bulkiness of metal carbenoid influences its chemoselectivity.^{5,6} Formation of cyclic allylic oxonium ylide by intramolecular reaction of diazocarbonyl compound containing suitably positioned allylic etheral oxygen atom and its subsequent [2,3] shift offer an effective approach to the stereoselective construction of substituted cyclic ethers. In contrast to the metal-catalyzed oxonium ylide formation-rearrangement reactions of diazoketones,^{7,8} those of α -diazo- β -ketoester have been little investigated.⁹ Although the Pirrung group^{9a} and West group^{9e} reported, respectively, oxonium ylide formation-[2,3] shift of simple α -diazo- β -ketoester, methyl 5-allyloxy-2-diazo-3-ketopentanoate, using dirhodium(II) tetraacetate and copper(II) hexafluoroacetylacetonate [Cu(hfacac)₂] to give 2-allyl-3-oxotetrahydrofuran-2-carboxylate in high yield (R=H, Scheme 1), no information related to chemoselectivity and diastereoselectivity of similar reactions of substituted α -diazo- β -ketoesters (1, R $\neq$ H) to 2,2,5-trisubstituted 3-oxotetrahydrofurans (2 or 3, R $\neq$ H), which are expected to provide a feasible method for synthesis of the 2,2,3,5-tetrasubstituted tetrahydrofuran framework of heliespiroes A and C, as outlined in Scheme 1.



Scheme 1

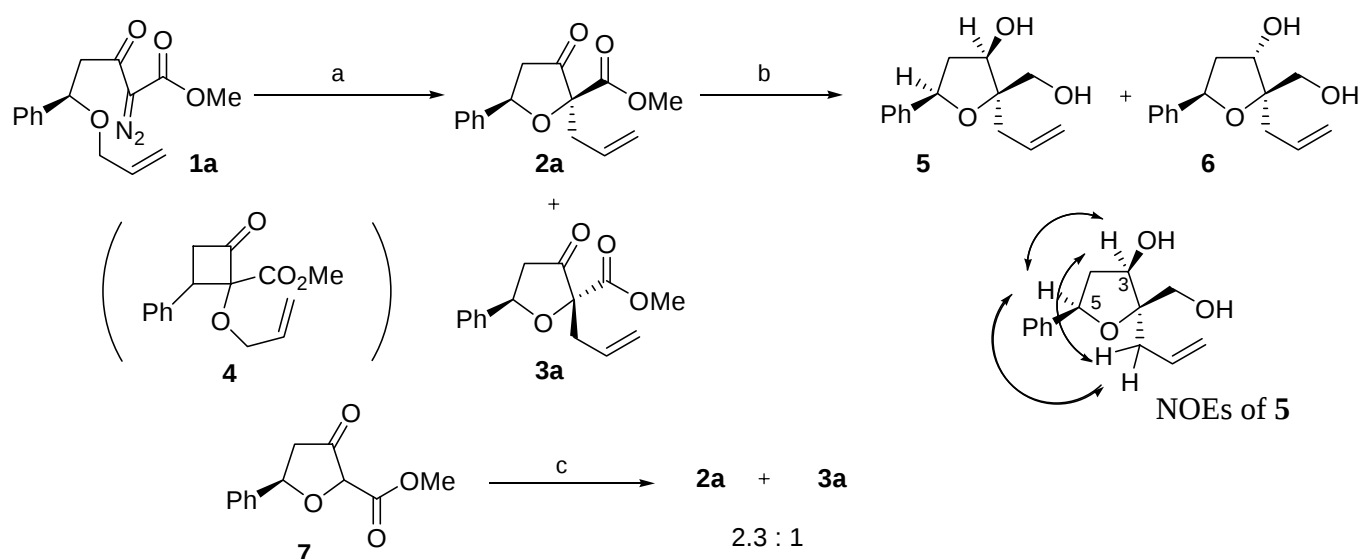
Starting 5-allyloxy-2-diazo-3-ketoesters **1** were prepared from the corresponding aldehyde in three steps: reaction with diketene in the presence of titanium tetrachloride then treatment with methanol,^{5,10} followed by allylation, subsequent diazotransfer reaction with *p*-toluenesulfonyl azide (Scheme 2).



Scheme 2. Reagents and conditions: a) TiCl₄, CH₂Cl₂, -78 °C, then MeOH, -20 °C to rt; b) Cl₃CC(=NH)OCH₂CH=CH₂, TfOH, CH₂Cl₂, rt; c) TsN₃, Et₃N, MeCN, rt

First we tested the reaction of phenyl substituted α -diazo- β -ketoester **1a** lacking C–H bonds at the C-6 position that can react with generated metal carbenoid (Scheme 3). Reaction of **1a** with 3 mol% of Rh₂(OAc)₄ in dichloromethane^{9e} at rt for 30 min proceeded stereoselectively to give separable

tetrahydrofurans **2a** and **3a** in 94% yield and with a high level of diastereocontrol (**2a:3a**=91:9) (Table 1, entry 1). Another possible product **4** via Stevens [1,2] shift was not detected. A similar reaction of **1a** with Cu(hfacac)₂ in CH₂Cl₂^{9e} required higher temperature (reflux) and longer time (4 days) to afford a mixture of **2a** and **3a** in 94% yield with a slightly lower diastereoselectivity (79:21) (Table 1, entry 2). The *trans* relation between the phenyl group at C-5 position and migrated allyl group at C-2 position of **2a** was determined after the reduction with diisobutylaluminum hydride (DIBAL-H) to diols **5** and **6**.¹¹ In the NOESY spectrum of **5**, positive NOEs were observed among H-3 proton and H-5 proton, and allylic methylene protons at C-2 position. As an alternative stereoselective synthesis of **2a**, we attempted allylation of 5-phenyl-3-oxotetrahydrofuran-2-carboxylate **7**.¹² The unstable **7** was treated with allyl bromide in the presence of potassium carbonate as a base in acetonitrile^{12a} to give **2a** as a major product. This procedure, however, was unsuitable for synthesis of **2a** because of low yield (39% for a mixture of **2a** and **3a**) and low stereoselectivity (2.3:1).



Scheme 3. Reagents and conditions: a) see Table 1; b) DIBAL-H, CH₂Cl₂, -80-0 °C, 2 h (50% for **5**, 39% for **6**); c) K₂CO₃, allyl bromide, MeCN, rt, 4 h (39%)

Because Rh₂(OAc)₄ showed better results than copper catalyst did, we next investigated reactions using other solvents (Table 1, entries 3 and 4) and other rhodium(II) catalysts (Table 1, entries 5–9). Unfortunately, better results than that of entry 1 were not obtained. Interestingly, rhodium catalysts having bulky ligands such as pivaloate and triphenylacetate decreased the stereoselectivities (entries 8 and 9).

Reactions of several α -diazo- β -ketoesters **1b–1h** with 3 mol% of Rh₂(OAc)₄ in CH₂Cl₂ were investigated as standard conditions.¹³ Table 2 presents the results. All reactions were completed within 30 min. Reaction of **1b** (R = *p*-Tol) produced almost identical results as that of **1a** (Entry 1). Alkyl substituted derivatives **1c–1g**, which have reactive C–H bonds at the C-6 position, reacted chemoselectively at the ether oxygen to give the corresponding tetrahydrofurans in high yields with excellent

diastereoselectivities (Entries 2–6). Reaction of **1h** having bulky *tert*-butyl group at the C-5 position decreased the chemical yield because of steric hindrance around the ethereal oxygen atom (Entry 7). The yield was increased when **1h** reacted with Rh₂(OCOC₇H₁₅)₄ in stead of Rh₂(OAc)₄ (Entry 8).

Table 1. Metal-catalyzed reaction of **1a**

Entry	Catalyst (mol%)	Solvent	Temperature	Time	Yield (%)	2a:3a ^a
1	Rh ₂ (OAc) ₄ (3)	CH ₂ Cl ₂	rt	30 min	94	91: 9
2	Cu(hfacac) ₂ (10)	CH ₂ Cl ₂	reflux	4 d	94	79:21
3	Rh ₂ (OAc) ₄ (3)	benzene	rt	4 h	94	90:10
4	Rh ₂ (OAc) ₄ (3)	THF	rt	4 h	no reaction	
5	Rh ₂ (OCOCF ₃) ₄ (3)	CH ₂ Cl ₂	rt	30 min	94	86:14
6	Rh ₂ (OCOC ₇ H ₁₅) ₄ (3)	CH ₂ Cl ₂	rt	5 min	97	89:11
7	Rh ₂ (OCOC ₇ H ₁₅) ₄ (3)	CH ₂ Cl ₂	0 °C	90 min	94	89:11
8	Rh ₂ (OCOCMe ₃) ₄ (3)	CH ₂ Cl ₂	rt	5 min	94	83:17
9	Rh ₂ (OCOCPh ₃) ₄ (3)	CH ₂ Cl ₂	rt	5 min	92	54:46

a) Determined by ¹H-NMR.

Table 2. Rh(II)-catalyzed reactions of 5-allyloxy-2-diazo-3-ketoesters **1**^a

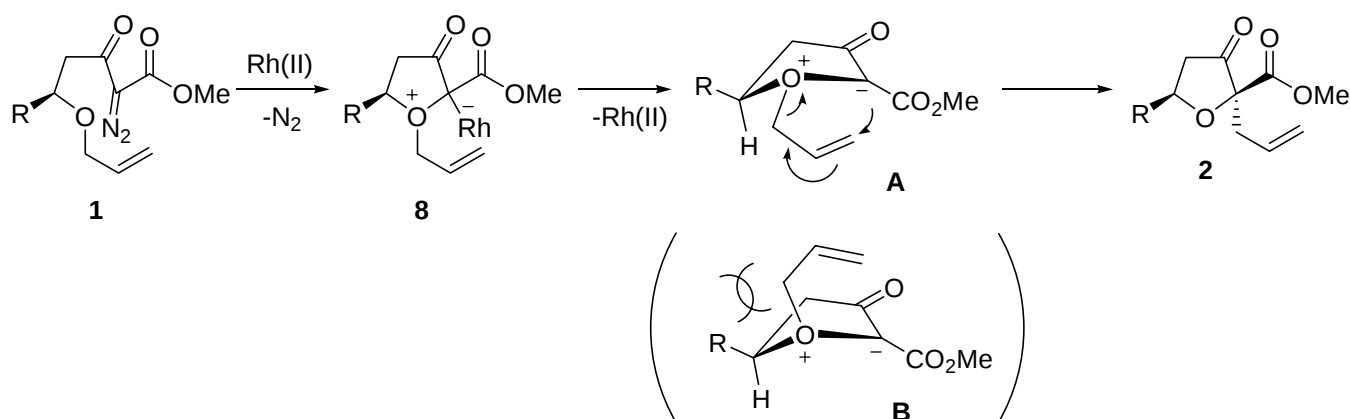
Entry	1	Yield (%)	2:3 ^b
1	b	94	88:12
2	c	80	96: 4
3	d	86	>99: 1
4	e	93	>99: 1
5	f	86	>99: 1
6	g	89	>99: 1
7	h	58	>99: 1
8 ^c	h	65	>99: 1

a) Reactions were carried out with 3 mol% of Rh₂(OAc)₄ in CH₂Cl₂ at rt for 30 min.

b) Determined by ¹H-NMR.

c) Rh₂(OCOC₇H₁₅)₄ (3 mol%) was used.

A possible rationalization of the observed stereoselectivity in rhodium(II)-catalyzed reaction of **1** is based on the consideration of the conformations of oxonium ylides **A** and **B**,^{7k,7m,8} generated through rhodium-bound ylide **8**^{7e} (Scheme 4).¹⁴ In conformer **A**, both the allyl group and the substituent at C-5 position can be accommodated in pseudoequatorial positions. In contrast, in conformer **B**, severe steric repulsion between these two groups becomes evident. We assumed, therefore, that the oxonium ylide formation-[2,3] shift would proceed via the sterically favored conformer **A** to form tetrahydrofuran **2**.



Scheme 4

In conclusion, rhodium(II)-catalyzed reaction of 5-allyloxy-2-diazo-3-ketoesters **1** gave methyl 5-substituted 2-allyl-3-oxotetrahydrofuran-2-carboxylates **2** in high yields with excellent stereoselectivities. Synthetic studies on the heliespirones using this methodology are now in progress.

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11. Treatment of **5** with 2,2-dimethoxypropane in the presence of camphorsulfonic acid (CSA) gave the corresponding acetonide within 10 min, although a similar reaction of **6** did not proceed after 24 h.
- The diagram shows two chemical structures, **5** and **6**, which are substituted tetrahydrofuran derivatives. Structure **5** has a phenyl group at C2, a hydroxyl group at C3, and a 2-hydroxyethyl group at C4. Structure **6** is similar but has a different substitution pattern. Above the reaction arrow is 2,2-dimethoxypropane (MeO-C(OMe)-CH₃). Below the arrow are the reagents CSA and rt, and the time 10 min. The product of the reaction of **5** is an acetonide where the hydroxyl group at C3 and the hydroxyl group of the 2-hydroxyethyl group at C4 are protected as a five-membered cyclic acetal. Structure **6** is shown to the right of the reaction arrow with a crossed-out arrow pointing to it, indicating no reaction.
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13. Typical reaction procedure: A solution of **1** (0.2 mmol) and Rh₂(OAc)₄ (0.006 mmol) in CH₂Cl₂ (20 mL) was stirred at rt. After **1** was consumed completely, as indicated by TLC, the mixture was concentrated and purified using column chromatography on silica gel to give pure **2**. All new compounds gave satisfactory spectroscopic data.
14. Alternatively, the reaction may proceed through stepwise allyl-transfer to rhodium metal followed by reductive elimination, in analogy to that proposed in the case of [1,2] shift of benzyl group by Dhavale group¹⁵.
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