

Highly regio-, chemo- and diastereoselective synthesis of oxa-bridged spirocycles: A novel observation of reverse selectivity†

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Received (in Cambridge, UK) 6th April 2005, Accepted 27th May 2005

First published as an Advance Article on the web 21st June 2005

DOI: 10.1039/b504692k

The reverse regio- and diastereoselectivities are observed between the reactions involving 5- and 6-membered-ring cyclic carbonyl ylide dipoles with α -methylene ketones. A mild catalytic route to synthesize spirocyclic systems with high regio-, chemo- and diastereoselectivities is described.

Tandem reactions offer many advantages compared to stepwise processes.¹ In particular, tandem cyclization–cycloaddition methodology based on diazo carbonyl compounds has been developed as an important approach² to various natural products such as illudin³ (sesquiterpenes), phorbol esters⁴ (diterpenes), vindoline⁵ (alkaloids) and brevicomin⁶ (pheromones). This process conceptually involves the 1,3-dipolar cycloaddition reaction of carbonyl ylide dipoles with π -bonds of olefin or carbonyl groups and presents an attractive strategy for tetrahydrofuran and dioxabridged ring systems.² The reaction of carbonyl ylides with the substrates having both olefin and carbonyl groups was studied^{7,8} to provide cycloadducts without any regio- or stereoselectivity. Furthermore, spirocyclic skeletons widely occur in a large number of natural products⁹ including the oxa-bridged spirocyclic skeletons,¹⁰ e.g. oxachamigrene **1** and 5-acetoxyoachamigrene **2** (Fig. 1). Among many approaches to construct spirocycles, [3 + 2]-cycloaddition is one of the most efficient methods. The common difficulty lies in the selective formation of spirocycles and the control of their stereochemistry.¹¹ It is still a challenge for synthetic chemists to develop a simple method to construct stereoselective spirocarbocycles. In continuation of our interest on the reactions of diazo carbonyl compounds,¹² we herein delineate a mild catalytic method to synthesize oxa-bridged spirocarbocyclic compounds with high regio-, chemo- and diastereoselectivities.



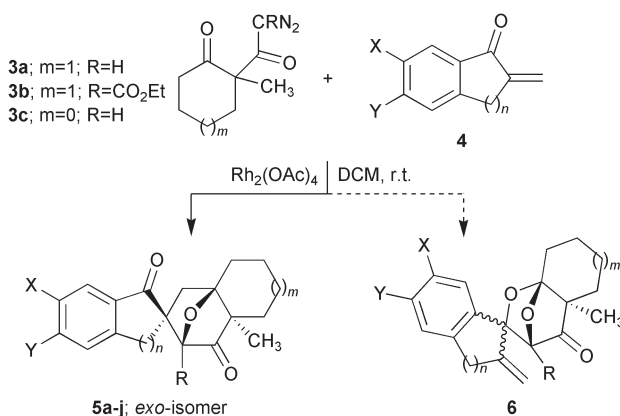
Fig. 1 Naturally existing molecules.

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† Electronic supplementary information (ESI) available: experimental procedures, spectral data for all new compounds and X-ray structural data of compounds **5a**, **8a** and **10a**. See <http://dx.doi.org/10.1039/b504692k>

To develop the stereoselective reaction of cyclic carbonyl ylide dipoles, we planned to study the reaction of various α -diazo ketones **3,7,9** (that are capable of generating five- or six-membered-ring carbonyl ylide intermediates) with α -methylene ketones **4** having both olefin and carbonyl functionalities. To initiate our studies, the reaction of α -diazo ketone **3a** and α -methylene tetralone **4** was carried out in the presence of a catalytic amount of rhodium(II) acetate under an inert atmosphere. The reaction mixture was stirred at room temperature and following column chromatographic purification of the reaction mixture afforded the product **5a** in 89% yield (Scheme 1) as a single isomer. The ¹H-NMR spectrum of compound **5a** exhibited a characteristic singlet resonance for the bridgehead proton (when R = H). Further, ¹³C NMR and DEPT-135 spectral analyses of product **5a** showed peaks for one CH₃ carbon, seven CH₂ carbons, five CH carbons and seven quaternary carbons including two carbonyl groups at δ 196.8 and 216. The product **5a** was characterized as oxa-bridged spirocarbocyclic ring system based on its interrelated spectral data. The stereochemistry and diastereoselectivity of five-membered-ring carbonyl ylide with α -methylene ketone were unequivocally corroborated based on the single crystal X-ray analysis¹³ (Fig. 2) of the cycloadduct **5a** as *exo*-isomer. In principle, the reaction of α -diazo ketone **3a** and **4** has the possibility to produce¹⁴ eight and/or four isomeric products with C=C and C=O functional groups, respectively. We did not observe any products produced by the possible 1,3-dipolar cycloaddition reaction^{6,8,15} of carbonyl ylides with the carbonyl group of α -methylene ketones **4**. In contrast, the similar reaction of α -diazo ketone **3** with C=O group of arylidene tetralones afforded⁸ the cycloadduct of type **6** without diastereoselectivity. Interestingly, our experiment revealed that the carbonyl ylide intermediate



Scheme 1

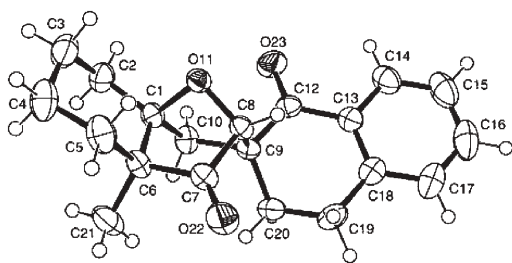


Fig. 2 ORTEP view of the compound **5a**.

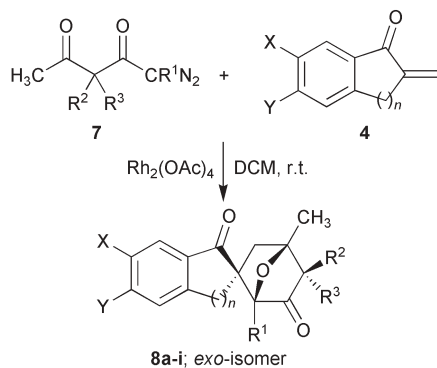
generated from α -diazo ketone **3a** cycloadds regio- and diastereoselectively with the C=C group of α -methylene ketone **4**. The above reaction was intended to generalize with substituted α -diazo ketones, α -methylene tetralone and indanone systems **4**. The tandem cyclization–cycloaddition reaction of α -diazo ketones **3b,c** and α -methylene ketones **4** was performed to furnish spirocycles **5b–j** (Scheme 1) in very good yields with high regio-, chemo- and diastereoselectivities (Table 1).

These results encouraged us to further study of the reaction of other five-membered-ring carbonyl ylides generated from acyclic and cyclopropane substituted α -diazo ketones **7**. Treatment of substituted α -diazo ketones **7** with α -methylene ketones **4** in the presence of rhodium(II) acetate catalyst afforded the oxa-bridged spirocarbocyclic ring systems **8a–i** (Scheme 2) and the results are summarized in Table 2. The spectral data and the representative single crystal X-ray analysis¹⁶ of the cycloadduct **8a** confirmed the *exo*-selectivity and this observation is in line with the above studies. It is worth mentioning that the reaction of cyclopropane

Table 1 Synthesis of oxa-bridged spirocycles **5a–j** using five-membered-ring carbonyl ylides

Entry	<i>m</i>	<i>n</i>	R	X	Y	Yield (%) ^a
a	1	2	H	H	H	89
b	1	1	H	NHCOCH ₃	H	66
c	0	2	H	H	H	60
d	0	2	H	H	OCH ₃	51
e	1	1	H	H	H	94
f	1	2	CO ₂ Et	H	H	93
g	1	2	H	H	OCH ₃	95
h	1	2	CO ₂ Et	H	OCH ₃	90
i	1	2	H	Br	H	63
j	1	2	H	NHCOCH ₃	H	64

^a Yields are unoptimized and refer to isolated pure compounds **5**.



Scheme 2

Table 2 Synthesis of oxa-bridged spirocycles **8a–i** using five-membered-ring carbonyl ylides

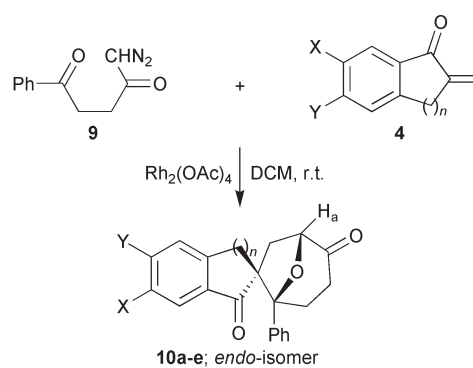
Entry	<i>n</i>	R ¹	R ²	R ³	X	Y	Yield (%) ^a
a	1	H	CH ₃	CH ₃	H	H	92
b	1	H	CH ₃	CH ₃	NHCOCH ₃	H	78
c	2	H	CH ₃	CH ₃	H	H	81
d	2	CO ₂ Et	CH ₃	CH ₃	H	H	75
e	2	H	CH ₃	CH ₃	H	OCH ₃	75
f	2	CO ₂ Et	CH ₃	CH ₃	H	OCH ₃	87
g	1	H	–CH ₂ –CH ₂ –	H	H	H	90
h	2	H	–CH ₂ –CH ₂ –	H	H	H	78
i	2	H	–CH ₂ –CH ₂ –	H	H	OCH ₃	67

^a Yields are unoptimized and refer to isolated pure compounds **8**.

substituted α -diazo ketones **7** afforded the dispiro-oxa-bridged systems **8g–i**.

Subsequent to this investigation, we were interested in investigating the reactions of six-membered-ring carbonyl ylides with α -methylene ketones. The rhodium(II) acetate catalyzed reaction of α -diazo ketone **9** and α -methylene ketone **4** in dichloromethane afforded the product **10a** in 76% yield (Scheme 3). The FT-IR spectrum of compound **10a** exhibited two strong bands at 1738 and 1698 cm^{–1} indicating the presence of carbonyl groups. The bridgehead proton H_a of compound **10a** in the ¹H-NMR spectrum appeared as a characteristic doubled doublet at 4.48 ppm, which clearly indicated the reverse regioselectivity of six-membered-ring carbonyl ylide dipole towards α -methylene ketone. In the ¹³C-NMR spectrum of compound **10a**, the signals due to two carbonyl groups appeared at 207.6 and 206.7 ppm. The structure was assigned as a spiro oxa-bridged tetrahydropyranone ring system based on the spectral data. The *endo*-stereochemistry was unequivocally established by the X-ray analysis¹⁷ (Fig. 3) of the product **10a**, which has two asymmetric units present in a unit cell. The reactions of other α -methylene ketones **4** with α -diazo ketone **9** were also performed to afford the products **10b–e** (Table 3) that are characterised as *endo*-isomers based on their interrelated spectral data. The spectroscopic and X-ray data confirmed the reverse regio- and diastereoselectivity for the reactions involving six-membered-ring carbonyl ylide intermediates.

The above results show that the carbonyl ylide intermediates underwent cycloaddition only to the C=C group despite the presence of the C=O group of α -methylene ketones. Importantly, the regio- and diastereoselectivities reversed between the 1,3-dipolar cycloaddition reactions pertaining to five- and six-membered-ring



Scheme 3

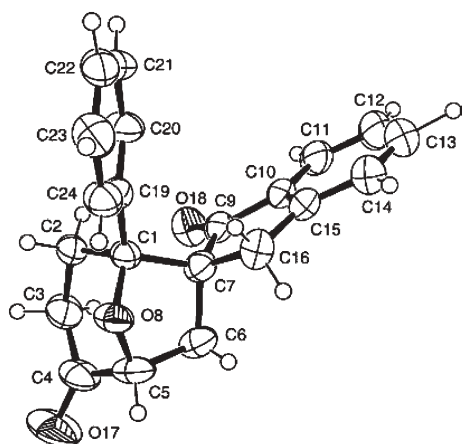


Fig. 3 ORTEP view of the compound **10a**. There are two molecules in the asymmetric unit and only one is shown.

Table 3 Synthesis of oxa-bridged spirocycles **10a–e** using six-membered-ring carbonyl ylides

Entry	<i>n</i>	X	Y	Yield (%) ^a
a	1	H	H	76
b	1	Br	H	90
c	1	NHCOCH ₃	H	82
d	2	NHCOCH ₃	H	55
e	2	H	OMe	30

^a Yields are unoptimized and refer to isolated pure compounds **10**.

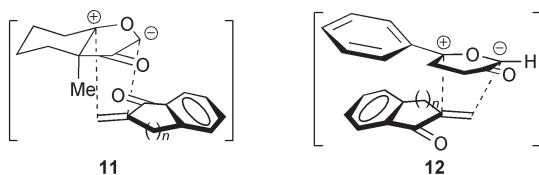


Fig. 4 Possible transition state structures of five- and six-membered-ring carbonyl ylide intermediates toward α -methylene ketones.

carbonyl ylide intermediates. Based on our previous study,¹⁴ the tentative structures of transition states of 5- and 6-membered carbonyl ylides **11,12**, which illustrate the cycloaddition approach towards α -methylene ketone, are shown in Fig. 4. Due to the steric interaction between the bridgehead methyl group and the carbonyl oxygen of dipolarophile possibly favour the transition state **11**. The interaction between the phenyl ring and the aromatic part of dipolarophile perhaps favours the reverse transition state **12**.

In conclusion, an efficient approach to synthesize spirocarbo-cycles with various ring sizes *via* rhodium(II)-catalyzed tandem cyclization-1,3-dipolar cycloaddition reaction was developed that features a rapid construction of the oxa-bridged spiro[*n,m*]alkanes under mild conditions with high regio-, chemo and diastereoselectivities. Importantly, the reverse stereoselectivity was observed between the reactions concerning five- and six-membered-ring carbonyl ylide intermediates. Further, the detailed investigation of this novel selectivity is in progress.

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- Crystal data for compound **5a**: Colourless rectangular crystal. C₂₀H₂₂O₃, *M* = 310.38, 0.35 × 0.30 × 0.25 mm³, monoclinic, space group *P21/c*, *a* = 12.644(7), *b* = 9.115(5), *c* = 14.429(7) Å, β = 106.578(10), *V* = 1593.7(14) Å³, *T* = 293(2) K, *R*₁ = 0.0569, *wR*₂ = 0.1498 on observed data, *Z* = 4, *D*_{calcd} = 1.294 g cm⁻³, *F*(000) = 664, Absorption coefficient = 0.086 mm⁻¹, λ = 0.71073 Å, 3982 reflections were collected, 3082 observed reflections (*I* ≥ 2σ(*I*)). The largest difference peak and hole = 0.229 and -0.358 e Å⁻³, respectively. CCDC 266143. See <http://dx.doi.org/10.1039/b504692k> for crystallographic data in CIF or other electronic format.
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- Crystal data for compound: **8a** Colourless chunky crystal. C₁₇H₁₈O₃, *M* = 270.31, 0.36 × 0.20 × 0.16 mm³, monoclinic, space group *P21/c*, *a* = 11.322(3), *b* = 9.237(2), *c* = 13.982(4) Å, β = 103.010(5)°, *V* = 1424.8(6) Å³, *T* = 273(2) K, *R*₁ = 0.0682, *wR*₂ = 0.1558 on observed data, *Z* = 4, *D*_{calcd} = 1.260 g cm⁻³, *F*(000) = 576, Absorption coefficient = 0.085 mm⁻¹, λ = 0.71073 Å, 7232 reflections were collected, 3124 observed reflections (*I* ≥ 2σ(*I*)). The largest difference peak and hole = 0.309 and -0.191 e Å⁻³, respectively. For ORTEP view of the compound **8a** see the supporting information.
- Crystal data for compound **10a**: Colourless rectangular crystal. C₂₁H₁₈O₃, *M* = 318.35, 0.45 × 0.40 × 0.40 mm³, monoclinic, space group *Cc*, *a* = 6.265(4), *b* = 20.618(13), *c* = 25.042(16) Å, β = 97.062(11), *V* = 3210(4) Å³, *T* = 293(2) K, *R*₁ = 0.0541, *wR*₂ = 0.1266 on observed data, *Z* = 8, *D*_{calcd} = 1.317 g cm⁻³, *F*(000) = 1344, Absorption coefficient = 0.087 mm⁻¹, λ = 0.71073 Å, 5769 reflections were collected on a smart apex ccd single crystal CCD diffractometer, 4770 observed reflections (*I* ≥ 2σ(*I*)). The largest difference peak and hole = 0.192 and -0.184 e Å⁻³, respectively. The structure was solved by direct methods and refined by full-matrix least squares on *F*² using SHELXL-97 software. CCDC 266143, 267635 and 266144 for **5a**, **8a** and **10a**, respectively. See <http://dx.doi.org/10.1039/b504692k> for crystallographic data in CIF or other electronic format.