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Regioselective Nucleophilic Addition to Carbonyl Ylide Intermediates: A Novel Diastereoselective Synthesis of Cycloalkyl Fused Furan-3-ones

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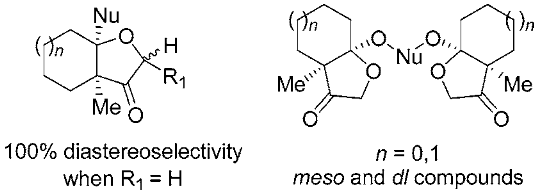
ABSTRACT



A range of *cis*-fused hexahydro-1-benzofuran-3(2*H*)-one or tetrahydro-2*H*-cyclopenta[*b*]furan-3(3a*H*)-one ring systems was synthesized by the rhodium(II) acetate catalyzed reaction of α-diazo carbonyl compounds in the presence of various oxygen, nitrogen, and sulfur nucleophiles. A double-nucleophilic addition was possible by using an excess of α-diazo ketone. These reactions proceeded with complete diastereoselectivity, and the stereochemistry was confirmed by the single-crystal X-ray analysis. This process discloses the first example of tandem cyclization–nucleophilic addition reaction.

The synthesis of bicyclic compounds, particularly of tetrahydrofuran derivatives from a simple synthon with high degree of chemo-, regio-, and stereoselectivity, has been a major challenge to organic chemists. Several natural products contain fused furan bicyclic ring systems (Figure 1, e.g., apotrichothecene,[1a] (+)-kuhistaferone,[1b] and avermectin[1c]) and bear a bridgehead substituent with *cis*-stereochemistry. Thus, the development of novel, concise methods for the *cis*-fused furan ring systems are strongly required. During the course of our investigation[2] aimed at developing new stereoselective strategies based on the metal-catalyzed reactions of diazo carbonyl compounds, we visualized synthesizing the *cis*-fused bicyclic ring systems. The metal-catalyzed reactions of diazo carbonyl compounds[3] provide metallocarbenoid intermediates, which undergo subsequent processes such as ylide generation, cyclopropanation, or insertion in a tandem manner.[4] The generation of carbonyl ylide intermedi-

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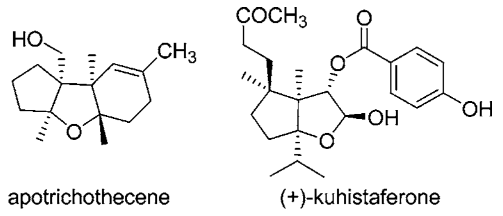
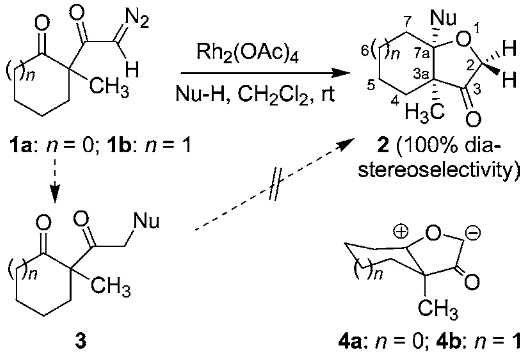


Figure 1. *Cis*-fused furan ring systems in natural products.

ates from diazo carbonyl compounds and their successive reaction with C=C or C=O bonds has been well described in the literature.[5] Participation of metal-derived onium ylides in ionic trapping processes as the nucleophilic partner[6] and the interception of oxonium ylides,[7a,b] isomünchnones[7c] in the presence of protic nucleophiles are reported. To the best of our knowledge, there is no literature dealing with the reaction of transition-metal-generated transient carbonyl ylides and nucleophiles. This is because of the competitive reaction of electrophilic metallocarbene intermediate in the presence of a nucleophile, which always affords the insertion product.[3b,8] Interestingly, we report herein the first examples of the reaction of carbonyl ylide intermediates with various nucleophiles to afford the cycloalkyl fused furanone ring systems diastereoselectively.

With the eventual primary goal to synthesize *cis*-fused furan ring systems, we examined the rhodium(II)-catalyzed reactions of diazo carbonyl compounds. Initially, the moist dichloromethane solution of α-diazo ketone **1b** was stirred in the presence of rhodium(II) acetate catalyst to afford the product **2a** (entry 1, Table 1) in 90% yield and characterized as 7a-hydroxy-3a-methylhexahydro-1-benzofuran-3(2*H*)-one. The *cis*-stereochemistry was confirmed by the single-crystal X-ray crystallographic analysis,[9] and the above reaction was completely diastereoselective. The formation of product **2a** indicates that the successful generation of five-membered-ring carbonyl ylide intermediate **4a** and followed by the diastereoselective addition of water. Notably, the well-known competitive O−H insertion product **3a** under similar experimental conditions is not observed at all (Scheme 1).

Scheme 1. Diasteroselective Reaction of Carbonyl Ylides with Oxygen, Nitrogen, and Sulfur Nucleophiles



This interesting result encouraged us to investigate this reaction with various oxygen nucleophiles. To evaluate this strategy, the reaction was performed in the presence of several aliphatic and aromatic alcohols. The rhodium(II) acetate catalyzed reaction of an equimolar amount of α-diazo ketone with primary alcohols under inert atmosphere provided the corresponding substituted fused furanone ring systems **2** (entries 2−5, Table 1). The secondary alcohols smoothly underwent nucleophilic addition reaction (entries 6−7) with the carbonyl ylide intermediate **4**. The reaction with aromatic alcohols furnished the corresponding aryloxy-substituted bicyclic systems (entries 8−10). Further, the reaction was carried out with mercaptoethanol (entry 11) to furnish the product **2k** with chemoselectivity. Though the sulfur atom is more nucleophilic than an oxygen atom, the reaction afforded the product **2k** derived from oxygen nucleophile.

Table 1. Synthesis of Compounds **2** via Scheme 1

entry	*n*	nucleophiles	Nu−	prdt	yield[a] (%)
1	1	water	HO−	**2a**	90
2	1	methanol	CH_3O-	**2b**	86
3	1	benzyl alcohol	BnO−	**2c**	72
4	1	1,2-ethanediol	$HOCH_2CH_2O-$	**2d**	88
5	1	1,4-butanediol	$HOCH_2CH_2$-CH_2CH_2O-	**2e**	80
6	1	2-propanol	$CH(CH_3)_2O-$	**2f**	78
7	1	cyclohexanol	$C_6H_{11}O-$	**2g**	56
8	0	4-bromophenol	4-BrC_6H_4O-	**2h**	92
9	1	hydroquinone	4-OHC_6H_5O-	**2i**	88
10	1	resorcinol	3-OHC_6H_5O-	**2j**	86
11	1	2-mercaptoethanol	$HSCH_2CH_2O$-	**2k**	76
12	0	4-nitroaniline	4-$NO_2C_6H_4NH-$	**2l**	90
13	0	2-chloroaniline	2-ClC_6H_4NH-	**2m**	95
14	1	2-chloroaniline	2-ClC_6H_4NH-	**2n**	92
15	1	4-aminophenol	4-OHC_6H_4NH-	**2o**	88
16	1	*p*-thiocresol	4-$CH_3C_6H_4S-$	**2p**	78
17	0	*p*-thiocresol	4-$CH_3C_6H_4S-$	**2q**	80

[a] Isolated yields.

We were further interested to study the selectivity with nitrogen and sulfur nucleophiles. Toward this, we have

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(9) For details see the Supporting Information.

carried out the representative rhodium(II) acetate catalyzed reaction of an equimolar amount of α-diazo ketone **1a** and 4-nitroaniline under inert atmosphere to afford the product **2l** (Table 1) and characterized as 3a-methyl-6a-(4-nitrophenylamino)tetrahydrocyclopenta[*b*] furan-3-one. The *cis*-stereochemistry was undoubtedly confirmed by the X-ray crystallographic analysis[10] (Figure 2). This reaction was generalized using 2-chloroaniline under similar experimental conditions to afford the respective anilino-substituted furan-3-one ring systems **2m,n** (Table 1). Importantly, the rhodium(II) catalyzed reaction of **1b** in the presence of 4-aminophenol occurred chemoselectively with NH rather than OH group to furnish the product **2o**.

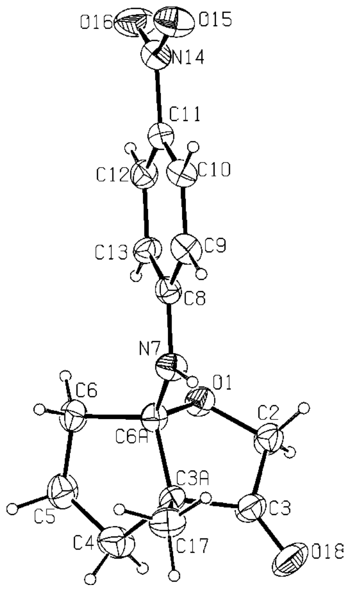

Figure 2. ORTEP representation of the crystal structure of **2l**.

We then examined the reactions in the presence of sulfur nucleophiles. Thus, the reaction in the presence of 4-thiocresol furnished the bicyclic ring systems having bridgehead thioether linkage **2p**,**q** (Table 1). The two protons present at C_2-position of compounds **2a**−**q** appeared as two AB doublets indicating their distereotopic nature. All these reactions provided the cyclohexane or cyclopentane fused furan-3-ones **2** with complete diasteroselectivity in very good yield.

We next examined these reactions having ester substitution at diazo functionality carbon. Thereby, one expects to bring three stereocenters in the bicyclic derivatives **2** based on the above findings. Thus, the reaction of the corresponding ester substituted α-diazo ketone with *p*-thiocresol in the presence of rhodium(II) acetate catalyst afforded the furan-3-one derivative **5a** in good yield (Figure 3, Table 2) with better diastereoselectivity. This reaction was generalized with sulfur, oxygen or nitrogen nucleophiles to afford the products **5b**−**g**. The major diastereomer of the product **5g** was successfully separated by the crystallization technique. The stereochemistry of C_2−H in **5g** was confirmed as syn to bridgehead methyl group by the X-ray crystallographic analysis,[9] and the same stereochemistry is tentatively assigned to other major diastereomers of **5a**−**f**.

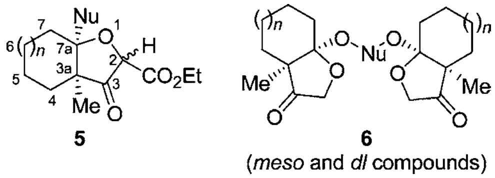

Figure 3. Diasteroselective reaction of carbonyl ylides with mono- and dinucleophiles.

Table 2. Diastereoselective Synthesis of Compounds **5** and **6**

entry	*n*	nucleophiles used	Nu−	prdt	yield[a] (%)
1	1	*p*-thiocresol	4-$CH_3C_6H_4S$−	**5a**[b]	82 (98:2)
2	0	*p*-thiocresol	4-$CH_3C_6H_4S$−	**5b**[b]	84 (85:15)
3	1	benzyl alcohol	$C_6H_5CH_2O$−	**5c**[b]	90 (75:25)
4	0	ethanol	C_2H_5O−	**5d**[b]	82 (75:25)
5	1	ethanol	C_2H_5O−	**5e**[b]	87 (77:23)
6	0	2-chloroaniline	2-ClC_6H_4NH−	**5f**[b]	91 (75:25)
7	1	4-nitroaniline	4-$NO_2C_6H_4NH$−	**5 g**[b,c]	89 (70:30)
8	1	1,2-ethanediol	-CH_2CH_2O−	**6a**[d]	48
9	1	hydroquinone	−1,4-C_6H_4O−	**6b**[d]	72
10	1	1,2-benzene-dimethanol	−1,2-$CH_2C_6H_4CH_2O$−	**6c**[d]	70
11	0	1,4-benzene-dimethanol	−1,4-$CH_2C_6H_4CH_2O$−	**6d**[d]	67
12	1	*cis*-2-butene-1,4-diol	−$CH_2CH{=}CHCH_2O$−	**6e**[d]	65

[a] Isolated yields. [b] Inseparable diastereomers and dr based on crude NMR experiments. [c] Major isomer was separated by crystallization. [d] It was not possible to determine whether one or both diastereomers was formed.

Finally, we extended our study with di-nucleophiles. Hence, an excess amount α-diazo ketone **1a** and 1,2-ethanediol were reacted in the presence of rhodium(II) acetate catalyst to afford the product **6a** with complete diastereoselectivity (Table 2). This reaction was supported with additional examples using various dihydroxy compounds to furnish the corresponding bis-furan-3-one compounds **6b**−**e** (Figure 3, Table 2) having four stereocenters in moderate to good yields. These products might exist as a mixture of *meso* and *dl* compounds; based on the reaction of diol with the opposite or same enantiomers of carbonyl ylides **4**, respectively.

From the above experiments, one can visualize that the potential formation of insertion products **3** via O−H, N−H,

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[10] Crystal data for the compound **2l**: $C_{14}H_{16}N_2O_4$, $M = 276.29$, $0.20 \times 0.12 \times 0.08$ mm^3, monoclinic, space group P with $a = 12.4574(18)$ Å, $b = 7.9073(11)$ Å, $c = 14.806(2)$ Å, $\alpha = 90°$, $\beta = 109.547(3)°$, $\gamma = 90°$, $V = 1374.4(3)$ Å^3, $T = 273(2)$ K, $R_1 = 0.0676$, w$R_2 = 0.1870$ on observed data, $z = 4$, $D_{calcd} = 1.335$ g cm^{-3}, $F(000) = 584$, absorption coefficient $= 0.099$ mm^{-1}, $\lambda = 0.71073$ Å, 5273 reflections were collected on a smart apex CCD single-crystal diffractometer, 1786 observed reflections ($I \geq 2\sigma(I)$). The largest difference peak and hole = 0.205 and −0.213 e Å^{-3}, respectively. The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2 using SHELXL-97 software.

or S−H insertion[3b,8] to the diazo functionality under similar experimental conditions, and no such products were observed/isolated. The possible intramolecular cyclization of the insertion product **3** to **2** (Table 1) is also ruled out based on the reactions with nitrogen and sulfur nucleophiles. This indicates that the formation of ylide intermediate **4** is a more favorable process. The reactive center of the dipole is completely planar and the fused cycloalkane ring adopts envelope (**4a**) or chair (**4b**) like conformation.[9] Mechanistically, the generation of the carbonyl ylide intermediate and followed by the incoming oxygen, nitrogen, sulfur, or dinucleophile adds syn to methyl group of the facially dissymmetric carbonyl ylide intermediates **4** furnishing the products **2**, **5**, and **6** diasteroselectively in a tandem manner.

In summary, the efficient synthesis of 3a-methyltetrahydro-2*H*-cyclopenta[*b*]furan-3(3a*H*)-one or 3a-methylhexahydro-1-benzofuran-3(2*H*)-one ring systems via the generation and regioselective nucleophilic addition to the transient carbonyl ylide 1,3-dipole derived from the easily prepared α-diazo ketones is described with complete diastereoselectivity. This novel process forms as the first example of tandem cyclization-nucleophilic addition reaction. This facile method provides an opportunity to synthesize a range of *cis*-fused bicyclic compounds toward naturally existing compounds. Further investigation into the selectivity and generality of this process toward other bicyclic systems are currently underway.

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Supporting Information Available: Experimental details, characterization data for all new compounds, energy minimized structures of ylides **4**, proposed mechanism, and ORTEP views of compounds **2a**,**5g** and their CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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