Multicomponent reactions involving tricyclooxonium ylide intermediate: diastereoselective synthesis of mono- and bisalkoxyoctahydro-1,4-benzodioxocin-6(5*H*)-one frameworks†

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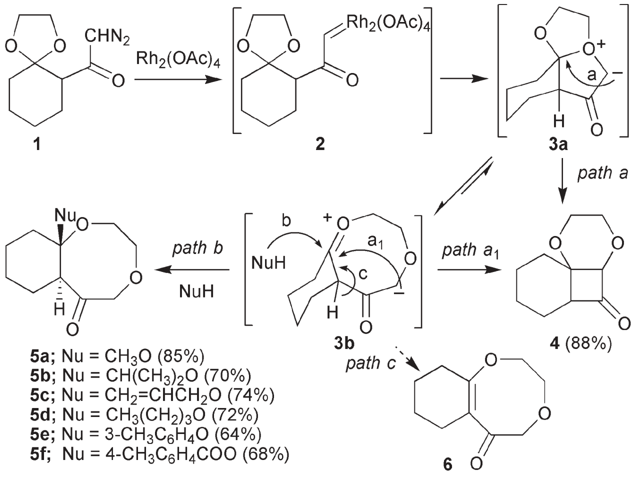
A highly diastereoselective tandem ring-enlargement and aldol condensation process involving multicomponent reactions of ethereal tricyclooxonium ylide intermediate with alcohols, mono- or dialdehydes in the presence of titanium(IV) isopropoxide is described to furnish alkoxyoctahydro-1,4-benzodioxocin-6(5*H*)-one ring systems.

The rhodium(II)-catalyzed reaction of α-diazocarbonyl compounds involves attractive transformations in organic synthesis.[1] In particular, transition metal catalyst derived carbenes or carbenoids react with heteroatoms to form onium ylides. Sulfur, phosphorus and nitrogen ylides have been utilized for synthesis because of the relatively long lifetime of onium ylides.[2] Carbenes or carbenoids react with ethereal oxygen to form oxonium ylides,[3] which have been subsequently utilized in syntheses based on their rearrangement[3,4] or with the help of nucleophiles[5] as well as Lewis acids.[6] However, the use of oxonium ylides for synthesis has been limited, probably due to their short lifetime,[7] in comparison with the widely acknowledged utility of carbonyl ylides.[2,8] Further, the reactions of ethereal oxonium ylides are known to furnish a mixture of isomers.[4–6] The ambiphilic character of oxonium ylides should be properly controlled by imparting a relatively long lifetime. In continuation of our work[9] on the chemistry of carbonyl ylides, herein we report the multicomponent reactions involving rhodium(II)-generated tricyclooxonium ylides with various alcohols, mono- or dialdehydes in the presence of titanium isopropoxide furnishing the mono- and bisalkoxyoctahydro-1,4-benzodioxocin-6(5*H*)-one frameworks with high stereoselectivity.

To investigate the multicomponent reactions of the tricyclooxonium ylide intermediate, initially, treatment of diazocarbonyl-substituted dioxaspiro compound **1** with rhodium(II) acetate catalyst afforded the cyclobutane fused tricyclic compound **4** *via* Stevens rearrangement (Scheme 1, path a). Reaction of diazocarbonyl compound **1** was performed in the presence of rhodium(II) acetate catalyst and methanol in dichloromethane to afford the ring-enlarged dioxocinone compound **5a** in 85% yield (Scheme 1, path b). Product **5a** was obtained as a single diastereoisomer and the structure characterized by spectral data. We also observed the similar ring-enlarged compound **5b** when isopropanol was used as a nucleophile. Similar reaction of diazocarbonyl compound **1** was also carried out in the presence of other nucleophiles such as allyl alcohol, butanol, *m*-cresol to afford the respective ring-enlarged dioxocinone products **5c–e**. Notably, reaction of **1** was also performed with 4-methylbenzoic acid to furnish the carboxylate substituted dioxocinone **5f**. These experiments indicate that the distinct formation of bicyclic dioxocinone compounds with *trans*-fusion **5** occurs as a single diastereoisomer in the presence of nucleophiles (alcohol/carboxylic acid), otherwise resulting only in the rearrangement product **4**. The tricyclooxonium ylide intermediate **3a** and its ring-opened bicyclic zwitterion **3b** are stabilized by charge delocalization between two oxygen atoms. Selective nucleophilic attack on **3b** furnished the *trans*-geometry in **5**. The possible product **6** *via* intramolecular H-migration[5] of **3** was not observed (path c).



Scheme 1 Reaction of diazocarbonyl-substituted dioxaspiro compound **1** in the presence of various alcohols or a carboxylic acid.

Next, we were interested to study the ambiphilic character of tricyclooxonium ylide **3** in the presence of a carbonyl compound and a Lewis acid. Thus, Rh(II)-acetate catalysed reaction of α-diazoketone **1**, benzaldehyde and 1.1 equivalent of titanium(IV) isopropoxide in dichloromethane furnished the product **7a** in 79% yield (Scheme 2). Significantly, the dioxocinone **7a** was obtained as a single diastereomer having four stereogenic centers. Similar reaction in the presence of 0.5 equivalent of titanium(IV) isopropoxide yielded major amounts of product **7a** and a minor quantity of **4** (Table 1, Entry b). The above reaction was extended to various substituted aromatic aldehydes. Good yields were

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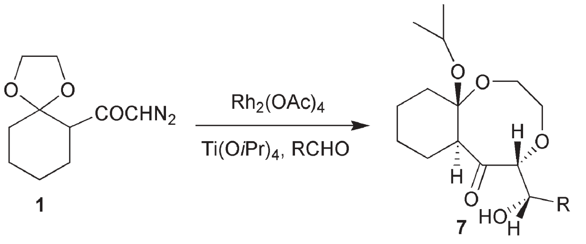
† Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, representative NMR spectra and X-ray structural data of compound **11d**. See DOI: 10.1039/b613008a



Scheme 2

Table 1 Synthesis of isopropoxyoctahydro-1,4-benzodioxocin-6(5*H*)-one systems **7a–g**

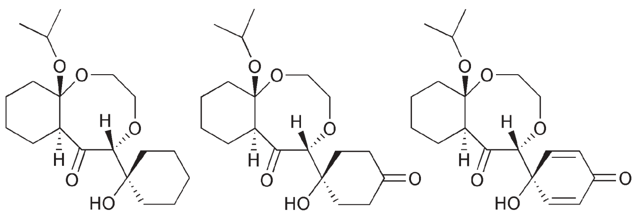
Entry	R	Product	Yield (%)[a]
a	C_6H_5	**7a**	79
b	C_6H_5	**7a**	42[b]
c	$4\text{-}HOC_6H_4$	**7b**	87
d	$4\text{-}CH_3OC_6H_4$	**7c**	90
e	$4\text{-}CHOC_6H_4$	**7d**	78[c]
f	$3\text{-}CHOC_6H_4$	**7e**	72[c]
g	$4\text{-}BrC_6H_4$	**7f**	82

[a] Yields are unoptimized and refer to isolated pure compounds **7**. All the above reactions were carried out at rt with the slow addition of **1** for 2 h into the reaction mixture containing 1.1 equiv. Ti(O*i*Pr)$_4$ and the appropriate aldehyde. [b] The compound **4** (20%) was isolated in addition to **7a** when 0.5 equiv. Ti(O*i*Pr)$_4$ were used. [c] No observation of product **12a** or **12b** based on crude NMR data.

observed from aromatic aldehydes bearing electron-donating (OH, OMe) or electron-withdrawing (CHO, Br) groups affording products **7b–f** in a diastereoselective manner *via* ring-enlargement and aldol condensation process of oxonium ylide intermediate **3**.

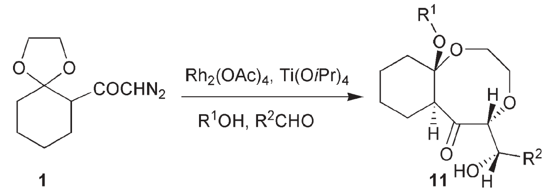
Subsequently, we studied the reactions involving ethereal tricyclooxonium ylide intermediate **3** with keto-group in the presence of titanium(IV) isopropoxide. Thus, the reaction of **1** with cyclohexanone was carried out to afford the isopropoxide induced ring-enlargement followed by aldol condensation product **8** in 82% yield (Fig. 1). The structure of the product **8** was confirmed by spectral analysis as a single diastereomer having three stereogenic centers. Similar reaction with 1,4-cyclohexanedione or benzoquinone was also furnished the respective products **9, 10**. Interestingly, the above reactions with aromatic aldehydes as well as symmetrical ketones provided the products **7–10** with complete diastereoselectivity.

Further, we extended the study to include the three-component reactions involving a diazoketone, an alcohol and an aldehyde. Towards this, reaction of diazoketone **1**, an excess amount of methanol and equimolar quantities of titanium(IV) isopropoxide and benzaldehyde in dichloromethane at 10 °C furnished the methoxydioxocinone **11a** in 81% yield (Scheme 3 and Table 2). Interestingly, ^{1}H NMR analysis of the crude reaction mixture indicated that the product was obtained as a single diastereomer.



8 (82%) **9** (76%) **10** (84%)

Fig. 1



Scheme 3

Table 2 Synthesis of alkooxyoctahydro-1,4-benzodioxocin-6(5*H*)-one systems **11a–e**

Entry	R^1	R^2	Yield (%)[a] of **11**
a	CH_3	C_6H_5	81
b	CH_3CH_2	C_6H_5	77
c	$CH_3CH_2CH_2CH_2$	C_6H_5	50[b]
d	CH_3	$4\text{-}CHOC_6H_4$	78[c]
e	CH_3	$3\text{-}CHOC_6H_4$	64[c]

[a] Yields are unoptimized and refer to isolated pure compounds **11**. All the above reactions were carried out at 10 °C with the slow addition of **1** for 3 h into the reaction mixture containing 1.0 equiv. Ti(O*i*Pr)$_4$ and the appropriate aldehyde. [b] Additionally product **7a** (15%) was also isolated. [c] No observation of product **12d** or **12e** based on crude NMR data.

This methodology reveals that the methoxy group exclusively acts as nucleophile and the isopropoxy group from the titanium reagent did not participate as described in Scheme 2. This reaction forms an example of a three-component reaction. A similar reaction was performed in the presence of ethanol or *n*-butanol to furnish the respective alkoxydioxocinones **11b, c**. Reaction with dialdehydes bearing electron-withdrawing substituents in the presence of methanol also furnished the products **11d, e** in good yield. The structure and stereochemistry of **11** were established by solving the single crystal X-ray crystallographic analysis[10] of the representative methoxydioxocinone **11d** (Fig. 2). Notably, the above three-component reactions yielded alkoxydioxocinones **11** having four stereogenic centers with complete diastereoselectivity.

As a preliminary illustration of the utility of the above reactions, it is planned to perform the reaction with symmetrical bis-carbonyl compounds. Thus, the reaction of terephthalaldehyde, two equivalents of α-diazoketone **1** and titanium(IV) isopropoxide in the presence of Rh$_2$(OAc)$_4$ catalyst in dichloromethane afforded the bis-isopropoxydioxocinone **12a** in 82% yield (Scheme 4 and Table 3) as a single isomer. Similar reaction in the presence of isophthalaldehyde yielded bis-dioxocinone **12b**. But the reaction with *p*-benzoquinone resulted a mixture of diastereomers **12c** in the ratio of 2 : 1. The observation of a mixture of diastereomers **12c** is due to the presence of asymmetry on the quinone carbonyl group of **10** after the first ring enlargement–aldol condensation process.

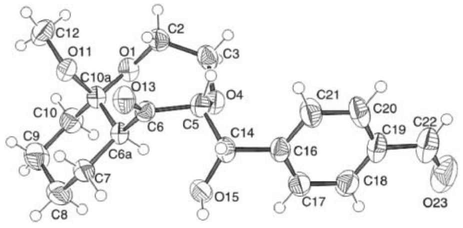
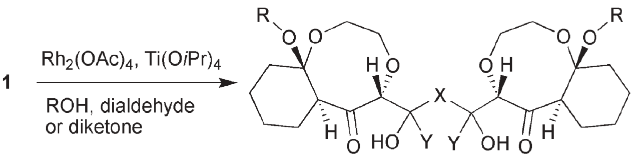


Fig. 2 ORTEP view of the compound **11d**, using 50% probability for the ellipsoids.



12

Scheme 4

Table 3 Synthesis of bis-alkoxyoctahydro-1,4-benzodioxocin-6(5*H*)-one systems **12a–e**

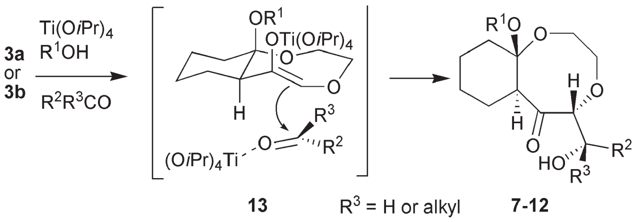
				Yield (%)[a]	
Entry	R	-X-	-Y-	**12**	Other products
a	$CH(CH_3)_2$	-1,4-C_6H_4-	H	82	—
b	$CH(CH_3)_2$	-1,3-C_6H_4-	H	70	**5b** (5)
c	$CH(CH_3)_2$	-1,4-Benzoquinone-		65[b]	**10** (15)
d	CH_3	-1,4-C_6H_4-	H	63	**5a** (trace)
e	CH_3	-1,3-C_6H_4-	H	54	**5a** (6), **5b** (4)

[a] Yields are unoptimized and refer to isolated pure compounds **12** and all the above reactions were carried out at 5 °C with the slow addition of **1** for 5.0 h. [b] **12c** derived as an inseparable diastereomeric mixture in the ratio of 2 : 1.

The three-component reaction is extended further as described in Scheme 3 in the presence of dialdehydes. To this end, reactions of **11d, e** were repeated in the presence of two equivalents of diazoketone **1** as well as titanium(IV) isopropoxide to yield the bis-methoxydioxocinone **12d, e**, respectively as a single isomer. The formation of **12d, e** can be considered as a double three-component reaction (equivalent to a five-component reaction). Furthermore bis-alkoxydioxocinones **12a, b, d, e** were isolated as single isomers, which may exist as a mixture of *meso* and *dl*-mixtures, based on the reaction of dicarbonyl compounds with the opposite or same enantiomers of enolate **13** (Scheme 5), respectively. In turn, this tandem ring enlargement and C–C bond formation process, from simple starting materials, provides up to six new bonds with eight stereocentres and with stereoselectivity in a single synthetic operation.

Mechanistically, the tricyclooxonium ylide **3** as an intermediate is proposed to contribute to the stereoselectivity. The selectivity behavior could tentatively be attributed to the presence of fused tricyclooxonium ylide **3** system with a relatively longer lifetime than previously reported oxonium ylides.[7,8] The diastereoselective products **7–12** were obtained *via* ring-enlargement followed by an aldol condensation process. The alkoxide either from the titanium reagent or the alcohol participates in nucleophilic addition on ylide **3** followed by the formation of titanium enolate **13**, and the titanium reagent also activates the aldehyde towards C–C bond formation[11] (Scheme 5). The diastereoselectivity (Schemes 3, 4) indicates that the multicomponent reaction selectively occurs between bottom face of the titanium enolate **13** and the top face of the titanium activated carbonyl compound.

In conclusion, the Rh(II)-catalyzed multicomponent reactions involving diazocarbonyl-substituted dioxaspiro compound, alcohol and carbonyl compound are described. The mono- as well as bisalkoxyoctahydro-1,4-benzodioxocin-6(5*H*)-one ring systems have been successfully synthesized with complete diastereoselectivity. This method constitutes a distinct example for a three-component reaction in which ethereal tricyclooxonium ylide participates as an intermediate. The potential application and mechanism of this stereoselective methodology involving oxonium ylides are in progress.



Scheme 5 Mechanistic pathway for the formation of dioxocinones.

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10 Crystal data for compound **11d**: Colourless block crystal. $C_{19}H_{24}O_6$, $M = 348.39$, $0.32 \times 0.26 \times 0.22$ mm^3, monoclinic, space group $P21/c$, $a = 9.6678(14)$ Å, $b = 11.1324(17)$ Å, $c = 16.858(3)$ Å, $\beta = 101.138(3)°$, $V = 1780.2(5)$ Å^3, $T = 273(2)$ K, $R_1 = 0.0649$, $wR_2 = 0.1588$ on observed data, $Z = 4$, $D_{calcd} = 1.300$ g cm^{-3}, $F(000) = 744$, absorption coefficient = 0.096 mm^{-1}, $\lambda = 0.71073$ Å, 8627 reflections were collected on a smart apex CCD single crystal X-ray diffractometer, 3111 unique measured reflections, 2016 observed reflections ($I \geqslant 2\sigma(I)$). The largest difference peak and hole = 0.279 and −0.252 e Å^{-3}, respectively. The structure was solved by direct methods and refined by full-matrix least squares on F^3 using SHELXL-97 software. CCDC 619131. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b613008a.

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