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Rhodium-Catalyzed Synthesis of 3-Hydroxy-β-lactams via Oxonium Ylide Generation: Three-Component Reaction between Azetidine-2, 3-diones, Ethyl Diazoacetate, and Alcohols

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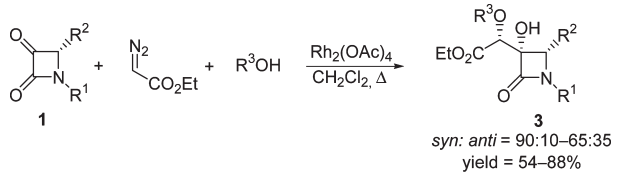
Received September 11, 2009



3-Substituted-3-hydroxy-β-lactams, with two new adjacent stereogenic centers, have been prepared in a single step by a rhodium-catalyzed, three-component reaction between azetidine-2,3-diones, ethyl diazoacetate, and alcohols. Good to moderate stereoselectivity was obtained depending on the alcohol used. The stereochemistry of the new centers has been undoubtedly assigned by single crystal X-ray diffraction.

The 3-substituted-3-hydroxy-β-lactam skeleton represents an efficient carboxylate mimic,[1] showing a promising activity in acyl CoA-cholesterol acyltransferase inhibition assays,[2] and is present in several pharmacologically active monobactams such as sulfacezin and related products[3] and in enzyme inhibitors such as tabtoxin and its analogues.[4] In addition, these compounds are precursors of therapeutically important compounds.[5]

On the other hand, the chemistry of diazo compounds is a prolific area and a wide variety of literature has been reported.[6] In this context, the chemistry of carbonyl, phosphorus, sulfur, and ammonium ylides has been widely employed in organic synthesis.[7]

Multicomponent reactions (MCR) are a straightforward synthetic tool to obtain structural complexity from three or more reactants in a single reaction process, with greater efficiency and atom economy.[8] Recently, Hu has described a novel reaction involving the Rh(II)-catalyzed aldol-type three-component reaction of methyl phenyldiazoacetate with an alcohol and an aldehyde(imine) providing a synthetic route to access highly substituted hydroxy(amino) acid skeletons with several quaternary centers in a single step (Scheme 1).[9] Of particular interest was the reaction with isatins as the carbonyl component.[9d]

Continuing with our work on the asymmetric synthesis of nitrogenated compounds of biological interest,[10] in this contribution we report the synthesis of 3-substituted-3-hydroxy-β-lactams with two new adjacent stereogenic centers in a single step via an efficient and stereoselective trapping of oxonium ylide with azetidine-2,3-diones.

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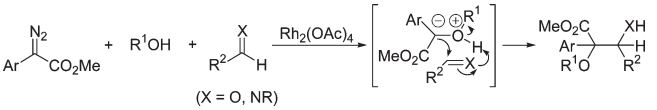
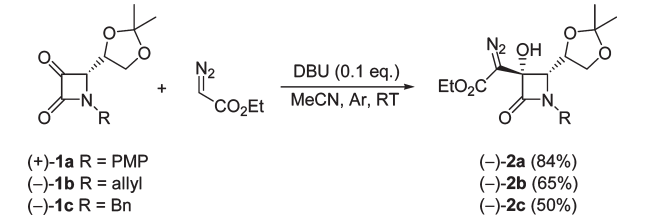
DOI: 10.1021/jo9019013 Published on Web 10/15/2009

SCHEME 1. Trapping of Oxonium Ylides with Aldehydes and Imines



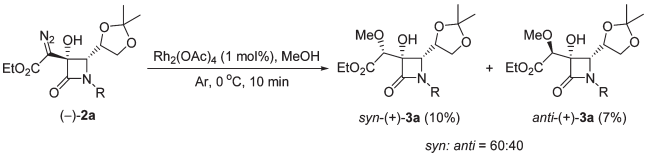
The starting materials, azetidine-2,3-diones **1a**−**c**, have been efficiently prepared in optically pure form from aromatic or aliphatic (*R*)-2,3-*O*-isopropylideneglyceraldehyde-derived imines by Staudinger reaction with acetoxyacetyl chloride in the presence of Et_3N, followed by sequential transesterification and Swern oxidation, as we have previously reported.[11] Racemic azetidine-2,3-dione **1d** has been prepared from a tolyl-derived imine following our previous procedure.[12] First, the nucleophilic addition of azetidine-2,3-diones **1** with ethyl diazoacetate in the presence of catalytic amounts of DBU affording the corresponding addition products **2** in moderate to good yields has been investigated (Scheme 2). Incorporation of the diazo functionality to 3-hydroxy-β-lactams **2** was confirmed by IR spectroscopy (2100−2110 cm^{-1}). Interestingly, under basic conditions, no epimerization of the starting ketones was observed.

SCHEME 2. Nucleophilic Addition of Ethyl Diazoacetate to Azetidine-2,3-diones 1 (PMP = 4-$MeOC_6H_4$)



The initial aim was to explore the reactivity of diazo-β-lactams **2** in the presence of alcohols and catalytic amounts of $Rh_2(OAc)_4$ in order to obtain the corresponding insertion products. Thus, treatment of diazo-β-lactam (−)-**2a** in methanol with a catalytic amount of $Rh_2(OAc)_4$ at 0 °C gave **3a** as a mixture of *syn*/*anti* isomers in a 60:40 ratio in very low yield (Scheme 3).

SCHEME 3. Insertion Reaction of Diazo-β-lactam 2a with MeOH Catalyzed by $Rh_2(OAc)_4$



Due to the unsuccessful result obtained under the above sequential conditions, we decided to test the reaction of azetidine-2,3-diones **1** under the three-component conditions.[9] For our first experiment we chose azetidine-2,3-dione (+)-**1a** as a model system for the study of the three-component reaction with methanol. Thus, reaction of azetidine-2,3-dione **1a** in the presence of 1 equiv of ethyl diazoacetate and 1 equiv of methanol under rhodium catalysis (1 mol %) cleanly afforded 3-substituted-3-hydroxy-β-lactam **3a** with good diastereoselectivity (*syn*:*anti*, 90:10) in high yield (88%). Fortunately, both isomers were separated by flash chromatography. When azetidine-2,3-diones (−)-**1b** and (±)-**1d** were used instead of the α-keto β-lactam (+)-**1a**, the reactions proceeded in a similar manner, giving the corresponding polysubstituted-β-lactams **3** with a slight reduction in yield and selectivity (entries 2 and 3, Table 1). Comparable yields and selectivities were obtained when other primary alcohols were tested, as allyl alcohol (see entry 4, Table 1); however, β-lactam **3d** was obtained as an inseparable mixture of *syn*:*anti* diastereomers (85:15). Replacing $Rh_2(OAc)_4$ by affordable $Cu(acac)_2$ did not improve the reactivity of the azetidine-2,3-diones **1**. In fact, lower yield and selectivity were observed along with longer reaction times (see entry 5, Table 1). Interestingly, reaction of azetidine-2,3-diones (+)-**1a** and (±)-**1d** with a more hindered alcohol (*i*-PrOH) in the conditions described above gave the corresponding alcohols **3e** and **3f** in similar reaction times with a slight decrease of the diastereoselectivity (see entries 6 and 7, Table 1). However, when the three-component reaction of azetidine-2,3-diones **1** was carried out with *tert*-butanol, addition of a second batch of ethyl diazoacetate and *tert*-butanol was necessary to obtain full conversion with a slight decrease of the diastereomeric excess in alcohols **3** (see entries 8 and 9, Table 1). A dramatic reduction of the selectivity (57:43−56:44) was observed when the reaction was carried out in ketones **1** with water (see entries 10, 11, and 12, Table 1). Probably, the high reactivity of the oxonium ylide generated is responsible for the low diastereoselectivity observed in these experiments.

When titanium(IV) isopropoxide was used instead alcohols,[13] the corresponding 3-hydroxy-β-lactams **3** were obtained, with a notable change in the selectivity being the *anti*-isomer as the major product of the reaction (see entries 13 and 14, Table 1).

The stereoselectivity at the new stereogenic center C3 is believed to be controlled by the bulky substituent at C4; one face of the carbonyl group is blocked and thus the oxonium ylide preferentially approaches the less hindered face.[10c] The stereochemical outcome of the overall addition reaction of oxonium ylides to azetidine-2,3-diones can be rationalized by the five-membered cyclic transition states **TS1** and **TS2** (Scheme 4). Thus, interaction of the ethoxycarbonyl group of the oxonium ylide with H4 of the β-lactam would determine the reaction to take place mainly through **TS1**, affording the *syn*-isomer. However, the opposite selectivity observed in the reaction with titanium(IV) isopropoxide would be explained via transition states **TS3** and **TS4**. In this case, chelation of the titanium atom to both carbonyl functionalities of azetidine-2,3-dione and the ester group via **TS4** would explain the preferential formation of the *anti*-isomer.

Configurational assignment for adducts *syn*- and *anti*-**3** was achieved by derivatization to the corresponding acetonides **4** (Scheme 5). Treatment of enantiomerically pure *syn*-**3i**, *anti*-**3i**, *syn*-**3j**, and *anti*-**3j** in the presence of 2,2-dimethoxypropane and catalytic amounts of pyridinium *p*-toluenesulfonate at reflux temperature provided the expected acetonides *syn*- and *anti*-**4** in

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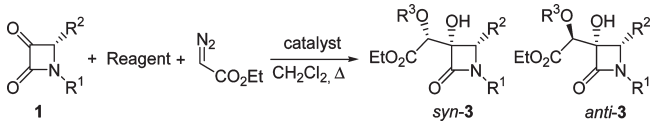
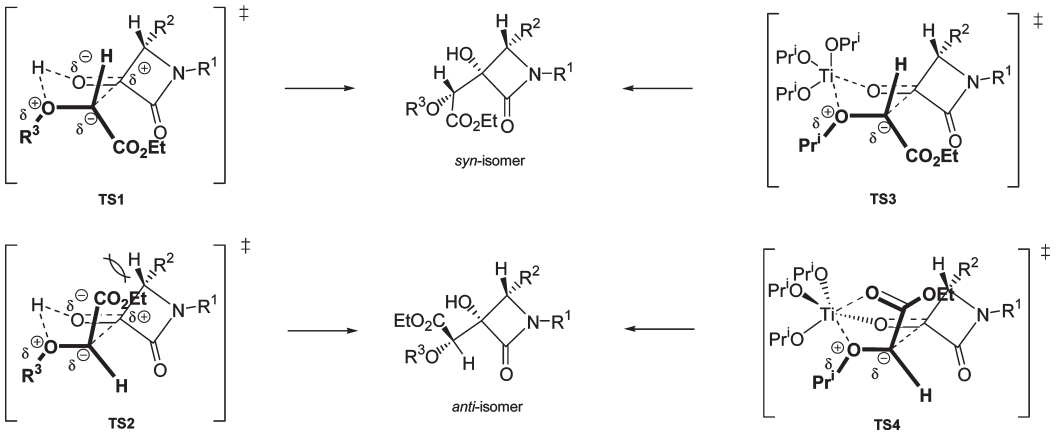
TABLE 1. Rh(II)-Catalyzed Three-Component Reaction of Azetidine-2,3-diones 1a−d, Ethyl Diazoacetate, and Alcohols



entry	substrate	R^1	R^2	R^3	reagent	catalyst[i]	t (h)[d]	product	*syn*/*anti*	yield (%)
1	(+)-**1a**	PMP[a]	Diox[b]	Me	MeOH	$Rh_2(OAc)_4$	7	**3a**	90:10[e]	80:8[g]
2	(−)-**1b**	Allyl	Diox[b]	Me	MeOH	$Rh_2(OAc)_4$	28	**3b**	86:14[f]	46:8 [g]
3	(±)-**1d**	PMP[a]	4-MeC_6H_4	Me	MeOH	$Rh_2(OAc)_4$	24	**3c**	85:15[e]	60:11 [g]
4	(+)-**1a**	PMP[a]	Diox[b]	2-propenyl	Allyl alcohol	$Rh_2(OAc)_4$	21	**3d**	85:15[f]	67 [h]
5	(+)-**1a**	PMP[a]	Diox[b]	Me	MeOH	$Cu(acac)_2$[c]	48	**3a**	67:33[e]	49:23 [g]
6	(+)-**1a**	PMP[a]	Diox[b]	*i*-Pr	*i*-PrOH	$Rh_2(OAc)_4$	7	**3e**	75:25[e]	62:14
7	(±)-**1d**	PMP[a]	4-MeC_6H_4	*i*-Pr	*i*-PrOH	$Rh_2(OAc)_4$	24	**3f**	81: 19[e]	68:16
8	(+)-**1a**	PMP[a]	Diox[b]	*t*-Bu	*t*-BuOH	$Rh_2(OAc)_4$	46	**3g**	75:25[e]	60 [h]
9	(±)-**1d**	PMP[a]	4-MeC_6H_4	*t*-Bu	*t*-BuOH	$Rh_2(OAc)_4$	44	**3h**	65:35[e]	43:23 [g]
10	(+)-**1a**	PMP[a]	Diox[b]	H	H_2O	$Rh_2(OAc)_4$	4	**3i**	56: 44[f]	37:29 [g]
11	(±)-**1d**	PMP[a]	4-MeC_6H_4	H	H_2O	$Rh_2(OAc)_4$	7	**3j**	56:44[f]	37:29 [g]
12	(−)-**1c**	Bn	Diox[b]	H	H_2O	$Rh_2(OAc)_4$	7	**3k**	57:43[f]	40:30 [g]
13	(+)-**1a**	PMP[a]	Diox[b]	*i*-Pr	Ti(*i*-PrO)$_4$	$Rh_2(OAc)_4$	2.5	**3e**	37:63[e]	23:47 [g]
14	(±)-**1d**	PMP[a]	4-MeC_6H_4	*i*-Pr	Ti(*i*-PrO)$_4$	$Rh_2(OAc)_4$	6	**3f**	40:60[e]	26:54 [g]

[a]PMP = 4-$MeOC_6H_4$. [b]Diox = 2,2-dimethyl-1,3-dioxolan-4-yl. [c]acac = acetylacetonate. [d]Reaction progress was followed by TLC. [e]The ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [f]The ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures after purification. [g]Yield of pure, isolated isomers with correct analytical and spectral data. [h]Yield of pure, isolated mixture of isomers. [i]$Rh_2(OAc)_4$ (1 mol %); $Cu(acac)_2$ (10 mol %).

SCHEME 4. Rationalization of the Selectivity Observed in the Three-Component Reaction of Azetidine-2,3-diones 1 via TS1−TS4



excellent yields. The structures and configurations of compounds **2**−**4** were established by one- and two-dimensional NMR techniques. The configuration at C3′ for isomers *syn*- and *anti*-**4a** was deduced by comparison of NOE experiments.[14] This structural and configurational assignment was confirmed by X-ray diffraction analysis of compounds *syn*-(±)-**3f**[15] (Figure S1 in the SI) and *syn*-(−)-**3k** (Figure S3 in the SI).[16]

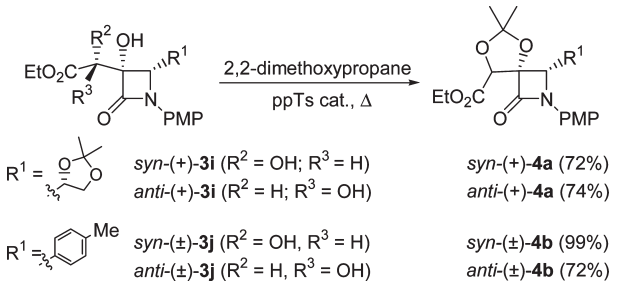
In conclusion, we have presented a new synthesis of densely functionalized enantiopure 3-substituted-3-hydroxy-β-lactams via a three-component reaction between azetidine-2,3-diones,

(14) Selected NOE enhancements are collected in the Supporting Information. NOE irradiation of H3′ in *syn*-(+)-**4a** resulted in enhancement of the signal corresponding to H4 (3%). Conversely, the same NOE enhancement was observed for H3′ upon irradiation of H4, which is consistent with a syn relative stereochemistry between H4 and H3′ and *R* configuration at C3′. A NOE enhancement of 0.2% for H4 in *anti*-(+)-**4a** on irradiating the signal corresponding to H3′ is in good agreement with an anti relative disposition between H3′ and H4 in *anti*-(+)-**4a** (*S* configuration at the new stereogenic center at C3′).

(15) X-ray data of *syn*-(±)-**3f**: crystallized from *n*-hexane/CH_2Cl_2 at 20 °C; $C_{24}H_{29}NO_6$ (M_r = 427.48); triclinic; space group = $P\bar{1}$; a = 9.2178(10) Å, b = 10.9974(12) Å, c = 12.3831(13) Å; α = 79.964(2)°, β = 71.839(2)°, γ = 89.979(2)°; V = 1172.6(2) Å^3; Z = 2; ρ_{calcd} = 1.211 mg m^{-3}; μ = 0.087 mm^{-1}; F(000) = 456. A transparent crystal of dimensions 0.35 × 0.17 × 0.17 mm^3 was used; 4016 [R(int) = 0.0425] independent reflections were collected. Data were collected [Mo Kα radiation (λ = 0.71073 Å)] over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 20 and 30 s covered 0.3 in γ. The structure was solved by direct methods and Fourier synthesis. It was refined by full-matrix least-squares procedures on F^2 (SHELXL-97). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were refined only in terms of their coordinates. CCDC-739823 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/deposit.

(16) X-ray data of *syn*-(−)-**3k**: crystallized from *n*-hexane/CH_2Cl_2 at 20 °C; $C_{19}H_{25}NO_7$ (M_r = 379.40); orthorhombic; space group = $P2(1)2(1)2(1)/n$; a = 5.5776(7) Å, b = 13.9511(17) Å, c = 25.656(3) Å; α = 90°, β = 90°, γ = 90°; V = 1996.4(4) Å^3; Z = 4; ρ_{calcd} = 1.262 mg m^{-3}; μ = 0.096 mm^{-1}; F(000) = 808. A transparent crystal of dimensions 0.45 × 0.07 × 0.04 mm^3 was used; 3507 [R(int) = 0.1120] independent reflections were collected. Data were collected [Mo Kα radiation (λ = 0.71073 Å)] over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 20 and 30 s covered 0.3 in γ. The structure was solved by direct methods and Fourier synthesis. It was refined by full-matrix least-squares procedures on F^2 (SHELXL-97). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were refined only in terms of their coordinates. CCDC-739824 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/deposit.

SCHEME 5. Synthesis of Acetonides 4



ethyl diazoacetate, and alcohols in the presence of a catalytic amount of $Rh_2(OAc)_4$.

Experimental Section

General. The same experimental techniques were used as previously reported.[10b]

General Procedure for the Synthesis of 3-Hydroxy-3-substituted β-Lactams 5 via Multicomponent Reaction: Method A. To a refluxed solution of azetidine-2,3-dione **1** (1 mmol) in anhydrous dichloromethane (10 mL) were added the corresponding alcohol or water (1.2 mmol), $Rh_2(OAc)_4$ (0.01 mmol), and ethyl diazoacetate (1.2 mmol). After 2 h, a second batch of alcohol or water (1.2 mmol) and ethyl diazoacetate (1.2 mmol) were added. Then, the reaction mixture was heated under reflux until complete disappearance of the starting material (TLC). The reaction mixture was allowed to cool to room temperature and filtered off over a short path of Celite. The solvent was removed under reduced pressure and the residue was purified by flash chromatography.

3-Hydroxyazetidine-2-one 3a: Method A. From 50 mg (0.17 mmol) of azetidine-2,3-dione (+)-**1a**, compound **3a** was obtained as a mixture of isomers in a *syn*/*anti* ratio (90:10). After flash chromatography (*n*-hexane/ethyl acetate 3:1) 56 mg (80%) of the less polar compound *syn*-(+)-**3a** and 6 mg (8%) of the more polar compound *anti*-(+)-**3a** were obtained. *syn*-(+)-**3a**: Colorless oil. $[\alpha]_D$ +108.4 (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz) δ 1.34, 1.44, 3.40, 3.79 (s, 3H each), 1.34 (t, 3H, *J* = 7.1 Hz), 3.80 (dd 1H, *J* = 8.6, 7.1 Hz), 4.12 (s, 1H), 4.18 (dd, 1H, *J* = 8.7, 6.6 Hz), 4.31 (m, 2H), 4.42 (q, 1H, *J* = 7.2 Hz), 4.58 (d, 1H, *J* = 6.6 Hz), 4.96 (br s, 1H), 6.85 (AA′XX′, 2H), 7.54 (AA′XX′, 2H). ^{13}C NMR (75 MHz) δ 170.1, 165.9, 156.8, 130.4, 120.4, 114.0, 109.7, 84.3, 79.8, 76.3, 66.4, 62.7, 61.8, 58.8, 55.4, 26.4, 25.3, 14.2. IR ($CHCl_3$, cm^{-1}) ν 3314, 1731. EM-IE (*m*/*z*) 409 ($M^{+\bullet}$, 30), 149 ([PMP − N=C=O]$^{+\bullet}$, 100). HRMS (ESI) for $C_{20}H_{27}NNaO_8$ (M + Na) calcd 432.1634, found 432.1629. *anti*-(+)-**3a**: Colorless oil. $[\alpha]_D$ +81.7 (*c* 0.2, $CHCl_3$). ^{1}H NMR (700 MHz) δ 1.18 (t, 3H, *J* = 7.2 Hz), 1.34, 1.48, 3.55, 3.80 (s, 3H each), 3.76 (dd, 1H, *J* = 8.7, 6.4 Hz), 3.89 (br s, 1H), 4.10 (s, 1H), 4.12−4.23 (m, 3H), 4.30 (d, 1H, *J* = 7.2 Hz), 4.42 (q, 1H, *J* = 6.9 Hz), 6.86 (AA′XX′, 2H), 7.59 (AA′XX′, 2H). ^{13}C NMR (175 MHz) δ 168.9, 164.2, 156.6, 130.7, 119.8, 114.0, 109.9, 84.2, 80.8, 76.6, 66.5, 63.5, 62.2, 59.5, 55.4, 26.5, 25.0, 14.0. IR ($CHCl_3$, cm^{-1}) ν 3350, 1747. HRMS (ESI) for $C_{20}H_{28}NO_8$ (M + H) calcd 410.1815, found 410.1803.

Acknowledgment. We would like to thank the Dirección General de Investigación, Ministerio de Educación y Ciencia (DGI-MEC) (Project CTQ2006-10292), and the Universidad Complutense UCM-BSCH (Grant GR58/08) for financial support. C.A. thanks the MEC for a Ramón y Cajal contract cofinanced by the European Social Fund. R.C. thanks the MEC for a predoctoral grant.

Supporting Information Available: Compound characterization data and experimental procedures for compounds **2a**−**c**, **3b**−**k**, **4a**, and **4b**, as well as X-ray data for compounds *syn*-(±)-**3f** and *syn*-(−)-**3k**. This material is available free of charge via the Internet at http://pubs.acs.org.