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Chemoselective reactions of *N*1-methyl-2-hydroxy-3-methylamino-3-phenylpropanamide with electrophiles. Synthesis of chiral hexahydro-4-pyrimidinones and oxazolidines

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Abstract—The reactivity of (2*S*,3*S*)-*N*1-methyl-2-hydroxy-3-methylamino-3-phenylpropanamide **1**, containing three nucleophilic centres has been studied against dihaloalkanes and aldehydes. Hexahydro-4-pyrimidinones or oxazolidines were obtained chemoselectively. Experimental results were explained by 'ab initio' calculations.

1. Introduction

Reactions of nitrogen and/or oxygen dinucleophiles with dihalomethanes or aldehydes leading to cyclic compounds have been extensively reported.[1] Although amino and hydroxy groups are the most frequent nucleophiles, carboxamides also participate in this type of reactions. In this context, we can mention the reaction of prolinamide with dichloromethane[2a] or the reaction of 2-piperidinecarboxamide with glutaraldehyde[2b] to produce five membered ring aminals and also the reaction of asparagine with pivaldehyde[3] affording a pyrimidinone which has been used as a reagent and as a chiral auxiliary in asymmetric synthesis.[4] There are a few examples of reactions of compounds with three nucleophilic groups in vicinal positions with the mentioned electrophiles and the regioselectivity observed in the formation of the corresponding cyclic compounds in these cases is highly emphasized.[5]

In a previous paper, we presented the regioselective results concerning the synthesis of chiral 4-substituted 3-methyltetrahydro-1,3-oxazin-5-ols, with excellent yields, by reaction of 3-methylamino-1,2-diols with dichloromethane.[6] In this work, in continuation of our interest in the synthesis of polyfunctionalized molecules,[7] we report the remarkable chemoselective results observed in the reaction of *N*1-methyl-2-hydroxy-3-methylamino-3-phenylpropanamide **1**, containing three nucleophilic centres with dihaloalkanes and aldehydes.

2. Results and discussion

The aminohydroxypropanamide **1**, was prepared by oxidation of 3-phenyloxiran-2-ylmethanol[8] further esterified[9] and finally reacted with aqueous methylamine.

There are different possibilities of reaction of compound **1**, containing three nucleophilic centres in 1,2,3 positions with C-1 electrophiles, and in principle, complex mixtures could be expected in these reactions. However, when the amide **1** reacted with dichloromethane, dibromomethane, or paraformaldehyde, the hexahydro-4-pyrimidinone **2a** was the only product that could be isolated from the crude reaction mixture. On the other hand, the reaction with 2,2-dimethoxypropane afforded the oxazolidine **3b** and in the same way as the reaction with acetaldehyde or benzaldehyde the oxazolidines **3c** and **e** were obtained (Scheme 1). The reaction with the aldehydes exhibits a high degree of stereocontrol[10] and just in the case of the reaction with acetaldehyde minor amounts (<5%) of the diastereoisomer **3d** were observed in the ^{1}H NMR spectrum. In the reaction with benzaldehyde, the diastereoisomer **3f** was not detected.

No traces of the corresponding six membered ring cyclization products were detected in the reaction with 2,2-dimethoxypropane or aldehydes.

The structure of the hexahydro-4-pyrimidinone **2a**

Keywords: pyrimidinones; oxazolidines; dichloromethane; aminodiols; regioselectivity.

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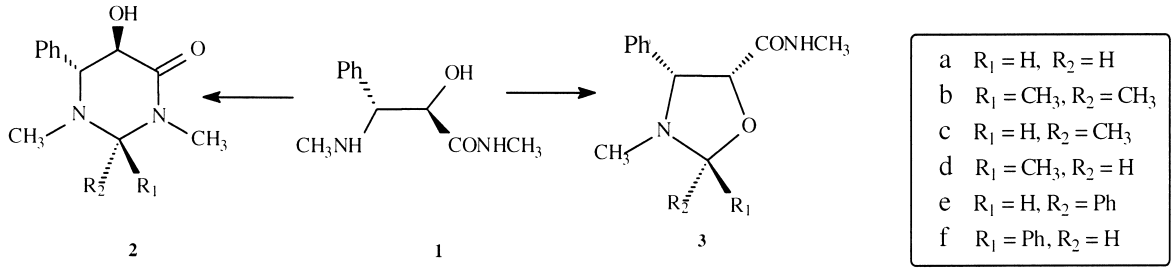

Scheme 1.

(R_1=R_2=H) was elucidated by spectroscopy. The stereochemistry was confirmed by X-ray analysis (Fig. 1).

The structures of compounds **3** were elucidated by ^{1}H and ^{13}C NMR spectroscopy. NOE experiments carried out with compound **3b** (R_1=CH_3, R_2=CH_3) and **3c** (R_1=H, R_2=CH_3) confirmed the *cis* disposition of hydrogens at C4 and C5 in **3b** and C2, C4 and C5 in **3c**. The *N*-methyl group that appears in ^{1}H NMR as a doublet in compounds **3** because of the restricted rotation of the amide, was a singlet in the cyclic hexahydro-4-pyrimidinone **2a**.

The chemoselectivity observed in the reaction of the amide **1** with different C-1 electrophiles could be the result of thermodynamic control in these reactions. We have carried out an 'ab initio' theoretical study of the thermodynamic stability of compounds **2a**–**d** and **3a**–**d**.

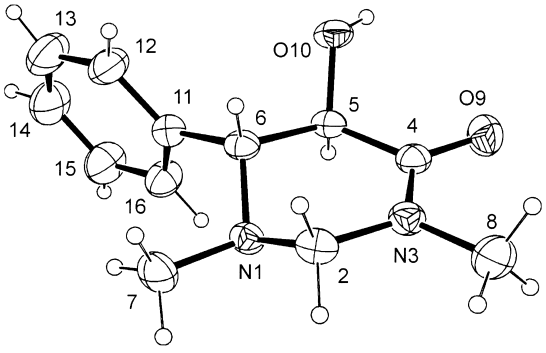

Figure 1. A view of the compound **2a** showing the labelling scheme. Labels for carbon atoms only include the number used in the X-ray crystal analysis. Displacement ellipsoids are drawn at 50% probability level.

All calculations were carried out with the Gaussian 98 suite of programs.[11] The HF/3-21G set parameters were used for initial energy calculation for all possible conformations and then, optimisation of geometries and energies were performed at DFT level using B3LYP/6-31G*.

The hexahydro-4-pyrimidinones **2a**–**d**, can adopt the boat conformations B1 and B2 and chair conformations C1 and C2 (Fig. 2), and the oxazolidines **3a**–**d** present two envelope conformations, E1 with N-atom towards β-face, and E2 with N-atom towards α-face (Fig. 3). The $CONHCH_3$ group in both conformers presents a hydrogen bond between the NH and the oxygen atom of the oxazolidine. The *N*-Me group in hexahydro-4-pyrimidinones **2** and oxazolidines **3** can be up and down and duplicates the number of possibilities.

The results of this thermodynamic study are shown as relative energies for each group of compounds. In Table 1, we can find the relative energies of the different conformations of compounds **2a** and **3a** that could be obtained in the reaction of amide **1**, with dichloromethane, dibromomethane or paraformaldehyde. In the same table, we present the relative energies of compounds **2b** and **3b** that could be obtained by the reaction with dimethoxypropane. In the reaction of amide **1** with acetaldehyde, in addition to regioisomers there is the possibility of diastereoisomers. The relative energies for all the possible conformers of compounds **2c**,**d**, **3c** and **d** are also presented in the same table.

The theoretical study has shown that hexahydro-4-pyrimidinones **2** present greater stability than oxazolidines **3** just in case of **2a** where R_1=R_2=H. For example, at DFT level, the more stable conformation of **2a** (C2D) is 1.64 kcal/mol

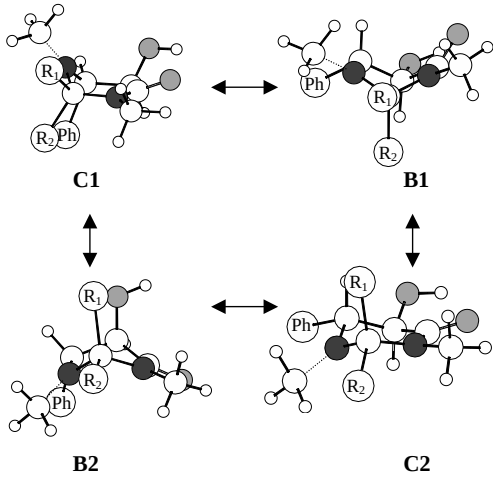

Figure 2. Different conformations for compounds **2**.

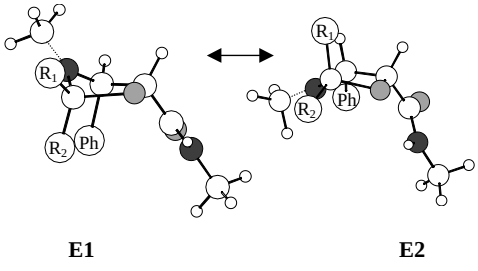

Figure 3. Different conformations for compounds **3**.

Table 1. 3-21G ($\Delta E_{3\text{-}21G}$) and B3LYP/6-31G* (ΔE_{B3LYP}) relative energies (kcal/mol) (relative to the most stable conformation of each group of compounds) of the different conformations for compounds **2a/3a** (upper left), **2b/3b** (upper right) and **2c/3c/2d/3d** (down)

	Conformation[a]	$\Delta E_{3\text{-}21G}$	ΔE_{B3LYP}		Conformation[a]	$\Delta E_{3\text{-}21G}$	ΔE_{B3LYP}
2a	C1A	6.45	3.25	**2b**	C1A	B1A[c]	
	C2A	4.22	0.12		C2A	13.13	10.87
	B1A	0.00	0.14		B1A	9.11	9.92
	B2A	7.33	5.25		B2A	15.46	C2A[b]
	C1D	9.34	4.43		C1D	19.74	16.19
	C2D	1.79	0.00		C2D	8.56	8.74
	B1D	C2D[b]			B1D	B1A[b]	
	B2D	10.55	C2D[b]		B2D	C2D[b]	
3a	E1A	1.77	1.64	**3b**	E1A	E2A[b]	
	E2A	E1A[b]			E2A	0.00	0.00
	E1D	2.51	2.29		E1D	1.55	2.89
	E2D	9.80	5.19		E2D	E2A[b]	
2c	C1A	B1A[b]		**2d**	C1A	10.19	9.24
	C2A	B1A[b]			C2A	7.61	6.02
	B1A	2.95	5.11		B1A	3.20	5.95
	B2A	11.73	11.79		B2A	9.32	C2A[b]
	C1D	15.26	12.28		C1D	13.83	11.07
	C2D	5.00	5.44		C2D	3.47	4.35
	B1D	B1A[b]			B1D	B1A[b]	
	B2D	B1A[b]			B2D	C2D[b]	
3c	E1A	E2A[b]		**3d**	E1A	4.58	5.00
	E2A	0.00	0.00		E2A	1.52	2.85
	E1D	3.08	5.09		E1D	0.10	2.02
	E2D	E2A[b]			E2D	E2A[b]	

[a] The final A or D letter for different conformations of compounds **2** and **3** indicates the position of the methyl group on the nitrogen atom. A (above or β), D (down or α).
[b] Conformation obtained by evolution of the original conformation.

more stable than the more stable conformation of **3a** (E1A) (Table 1, upper left). In all other cases with substituents at C-2, the oxazolidines **3b**,**c** are much more stable than the corresponding hexahydro-4-pyrimidinones. For example, conformation E2A for **3b** is more stable than any conformation of **2b** (Table 1, upper right) and conformation E2A for **3c** is more stable than any conformation of **2c**,**d**, and **3d** (Table 1, down).

It is worth noting that the predicted conformation C2 (C2A and C2D have similar energies) for **2a** according DFT calculations is the same as that found in the X-ray spectrum of this compound. It is also important to stand out that oxazolidine **3c**, with hydrogens at C-2, C-4 and C-5 in *cis* position is more stable than its diastereoisomer **3d**.

The theoretical study agrees with our experimental results and supports the idea that the reaction of compound **1** with dichloromethane or dibromomethane or paraformaldehyde to give hexahydro-4-pyrimidinone **2a** and the reaction with 2,2-dimethoxypropane, acetaldehyde or benzaldehyde to give oxazolidines **3b**,**c**,**e** takes place under thermodynamic control.

3. Conclusions

In summary, a new highly chemoselective transformation has been developed for the preparation of chiral hexahydro-4-pyrimidinones **2**, and oxazolidines **3**, useful as chiral templates in asymmetric synthesis. The experimental results are explained by ab initio calculations.

4. Experimental

4.1. General

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. CH_2Cl_2 was distilled from calcium hydride under argon. Analytical thin layer chromatography was performed on Merck precated silica gel (60 F_{254}) plates and flash column chromatography was accomplished on Merck Kieselgel 60 (230–240 mesh). Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were measured for $CDCl_3$ solutions at 250, 300 and 62.9, 75.4 MHz, respectively, using a Bruker AC-250, Bruker AC-300 spectrometer and chemical shifts are recorded relative to Me_4Si. High-resolution mass spectral data were obtained on a VG Autospec, TRIO 1000 (Fisons) instrument. The ionisation mode used in mass spectra was electron impact (EI), or chemical ionisation (CI) at 70 eV.

4.2. Computing methods

Theoretical HF/3-21G and B3LYP/6-31G* ab initio calculations were performed on a Cray-Silicon Graphics Origin 2000 with 64 processors of the Servicio de Informática de la Universitat de València. All calculations were carried out with the Gaussian 98 suite of programs.[11] The HF/3-21G level gives reasonable results with just a short time of calculation, nevertheless the more time-consuming B3LYP/6-31G* level gives better results.

Therefore, an extensive characterisation for all possible

conformations was initially carried out at the HF/3-21G level and then, optimisation of geometries and energies were performed at DFT level using B3LYP/6-31G*.

4.2.1. (2*S*,3*S*)-*N*1-Methyl-2-hydroxy-3-methylamino-3-phenylpropanamide (1). A mixture of (2*S*,3*R*)-2,3-epoxy-3-phenylpropionate methyl ester[9] (1 g, 5.2 mmol), methanol (10 mL) and aqueous methylamine 40% (2.5 mL), was heated in the pressure reactor at 100°C for 3 h. After cooling to room temperature, the crude was concentrated in vacuo to give a white solid which was recrystallised from hexane–dichloromethane to give **1** (95%). Mp 149–150°C. ^{1}H NMR spectrum of (2*S*,3*S*)-*N*1-methyl-2-hydroxy-3-methylamino-3-phenylpropanamide **1** with Mosher acid[12] indicated that we had a pure enantiomer (≥95%). $[\alpha]_D^{20}=-114$ (*c* 0.033, $CHCl_3$). ν_{max} (KBr) 3365, 3034, 1659. ^{1}H NMR (250 MHz): δ=2.21 (s, 3H), 2.45 (d, *J*=4.9 Hz, 3H), 3.90 (d, *J*=4 Hz, 1H), 4.31 (bs, 1H), 4.38 (d, *J*=4.0 Hz, 1H), 6.73 (d, *J*=4.9 Hz, 1H), 7.23 (s, 5H). ^{13}C NMR (62.9 MHz): δ=25.31 (q), 33.40 (q), 65.93 (d), 72.76 (d), 127.71 (d), 128.01 (d), 128.12 (d), 136.98 (s), 172.64 (s). HRMS (EI): (MH^+), found: 209.1281. $C_{11}H_{17}N_2O_2$ requires 209.1290.

4.2.2. (5*S*,6*S*)-6-Phenyl-5-hydroxy-1,3-dimethylhexahydro-4-pyrimidinone (2a). *Procedure a*. A solution of (2*S*,3*S*) *N*1-methyl-2-hydroxy-3-methylamino-3-phenylpropanamide **1** (0.42 g, 2 mmol) in dichloromethane (20 mL) was heated in a pressure reactor at 100°C for 3 days.

Procedure b. A solution of (2*S*,3*S*) *N*1-methyl-2-hydroxy-3-methylamino-3-phenylpropanamide **1** (0.42 g, 2 mmol) in dibromomethane (30 mL) was heated in a pressure reactor at 50°C for 3 days.

Procedure c. A solution of (2*S*,3*S*) *N*1-methyl-2-hydroxy-3-methylamino-3-phenylpropanamide **1** (0.42 g, 2 mmol) in benzene (30 mL) or methanol (20 mL) and paraformaldehyde (0.08 g) was heated in a pressure reactor at 100°C for 8 h.

The mixtures obtained by the procedures a, b or c were cooled at room temperature. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel eluting with hexane/ethyl acetate mixtures affording **2a**. (a) 67%, (b) 85%, (c) 92%. White solid. Mp 130–131°C. $[\alpha]_D^{20}=+31$ (*c* 0.05, $CHCl_3$). ν_{max} (KBr) 3405, 1654. ^{1}H NMR (250 MHz): δ=2.14 (s, 3H), 3.00 (s, 3H), 3.37 (d, *J*=9.5 Hz, 1H), 3.94 (d, *J*=9.5 Hz, 1H), 4.19 (d, *J*=9.9 Hz, 1H), 4.20 (d, *J*=9.9 Hz, 1H), 7.37 (m, 5H). ^{13}C NMR (62.9 MHz): δ=32.15 (q), 39.36 (q), 69.85 (d), 70.63 (d), 71.65 (t), 128.02 (d), 128.61 (d), 138.69 (s), 170.53 (s). HRMS (EI): (M^+), found: 220.1213. $C_{12}H_{16}N_2O_2$ requires 220.1211.

4.2.3. (4*S*,5*S*)-4-Phenyl-2,2,3-trimethyl-oxazolidin-5-*N*-methylcarboxamide (3b). To a solution of (2*S*,3*S*) *N*1-methyl-2-hydroxy-3-methylamino-3-phenylpropanamide **1** (0.260 g, 1.25 mmol) in acetone (15 mL) was added 2,2-dimethoxypropane (2 mL, 16.3 mmol) and catalytic amount of *p*-toluenesulfonic acid and the mixture was stirred at room temperature for 3 days or a pressure reactor at 100°C for 3 h. After the solution was concentrated in vacuo, dissolved in dichloromethane (10 mL) and washed with 40% aqueous $NaHCO_3$ solution (15 mL), brine (8 mL), dried ($MgSO_4$) and concentrated in vacuo to give **3b** (94%). Partial decomposition of **3b** into the starting material **1** was observed after storing for a few days. White solid. Mp 143–144°C. $[\alpha]_D^{20}=+55$ (*c* 0.07, $CHCl_3$). ν_{max} (CH_2Cl_2): 3360, 1669. ^{1}H NMR (300 MHz): δ=1.16 (s, 3H), 1.44 (s, 3H), 2.05 (s, 3H), 2.44 (d, *J*=5 Hz, 3H), 4.02 (d, *J*=9.0 Hz, 1H), 4.42 (bs, 1H), 4.51 (d, *J*=9.2 Hz, 1H), 7.20 (m, 5H). ^{13}C NMR (75.4 MHz): δ=17.49 (q), 25.13 (q), 26.7 (q), 33.14 (q), 69.36 (d), 79.14 (d), 95.83 (s), 127.75 (d), 128.10 (d), 128.31 (d), 137.26 (s), 169.93 (s). HRMS (CI): (MH^+), found: 249.1597. $C_{14}H_{21}N_2O_2$ requires 249.1603.

4.2.4. (2*S*,4*S*,5*S*)-4-Phenyl-2,3-dimethyloxazolidine-5-*N*-methylcarboxamide (3c). The (2*S*,3*S*) *N*1-methyl-2-hydroxy-3-methylamino-3-phenylpropanamide **1** (0.42 g, 2 mmol) was dissolved in methanol (20 mL), and acetaldehyde (2.2 mmol) was added. The mixture was stirred at room temperature for 2 h. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel eluting with hexane/ethyl acetate mixtures affording **3c** (92%). Colourless oil. $[\alpha]_D^{20}=+47$ (*c* 0.051, $CHCl_3$). ν_{max} (film) 3380, 1669. ^{1}H NMR (300 MHz): δ=1.40 (d, *J*=5.1 Hz, 3H), 2.09 (s, 3H), 2.51 (d, *J*=5.1 Hz, 3H), 3.75 (d, *J*=9.1 Hz, 1H), 4.02 (q, *J*=5.1 Hz, 1H), 4.49 (d, *J*=9.1 Hz, 1H), 6.48 (bs, 1H), 7.21 (m, 5H). ^{13}C NMR (75.4 MHz): δ=18.89 (q), 25.31 (q), 35.59 (q), 72.23 (d), 80.16 (d), 93.36 (d), 127.91 (d), 127.96 (d), 128.01 (d), 136.06 (s), 170.00 (s). HRMS (EI): (MH^+), found: 234.1359. $C_{13}H_{18}N_2O_2$ requires 234.1368.

4.2.5. (2*S*,4*S*,5*S*)-2,4-Diphenyl-*N*5,3-dimethyl-1,3-oxazolane-5-carboxamide (3e). The (2*S*,3*S*) *N*1-methyl-2-hydroxy-3-methylamino-3-phenylpropanamide **1** (0.42 g, 2 mmol) was dissolved in methanol (20 mL), and benzaldehyde (2.2 mmol) was added. The mixture was stirred at room temperature for 5 h. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel eluting with hexane/ethyl acetate mixtures affording **3e** (91%). White solid. Mp 156–157°C. $[\alpha]_D^{20}=-69$ (*c* 0.6, $CHCl_3$). ν_{max} (KBr) 3320, 1659. ^{1}H NMR (300 MHz): δ=2.04 (s, 3H), 2.52 (d, *J*=5.1 Hz, 3H), 3.99 (d, *J*=9.2 Hz, 1H), 4.67 (d, *J*=9.2 Hz, 1H), 4.84 (s, 1H), 6.44 (bs, 1H), 7.26 (m, 3H), 7.36 (m, 2H), 7.41 (m, 3H), 7.61 (m, 2H). ^{13}C NMR (75.4 MHz): δ=25.46 (q), 35.51 (q), 71.74 (d), 80.82 (d), 98.13 (d), 128.16 (d), 128.21 (d), 128.95 (d), 129.94 (d), 136.37 (s), 137.22 (s), 169.64 (s). Calcd For $C_{18}H_{20}N_2O_2$: C, 72.95; H 6.80; N 9.45. Found: C, 72.75; H 6.86; N 9.23.

X-Ray crystal data. **2a**, $C_{12}H_{16}N_2O_2$, *M*=220.27, orthorhombic *Pcab*, *a*=10.031(1), *b*=10.764(1), *c*=22.090(1) Å, *U*=2385.1(3) Å^3, D_c=1.23 g cm^{-3}, *Z*=8, Mo Kα (λ=0.7107 Å), μ=0.85 cm^{-1}. Data reduction with XRAY76 System.[13] From the 2335 independent reflections, 1243 were considered observed with the $I>2\sigma(I)$ criterion. The structure was solved by direct methods using the program SIR92.[14] Refinement by least-squares on F^2 with SHELXL97[15] (175 parameters). All non-hydrogen atoms were anisotropically refined. Hydrogen atoms, except those of methyl groups that were placed at calculated positions, were found in Fourier difference maps and their positions were refined. Weighting scheme

$w=1/[\sigma^2(F_o^2)+(0.0854P)^2]$ were $P=(F_o^2+2F_c^2)/3$. Final values: $R1=0.055$, $wR2=0.129$, $S=1.001$ and $\Delta\rho_{max}=0.28$, $\Delta\rho_{min}=-0.21$ e $\AA^{-3}$. Molecular graphics were done with ORTEP3 for Windows.[16]

The crystal structure has been deposited at the Cambridge Crystallographic Data Centre (CCDCC 168109).

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