Regio- and diastereoselective synthesis of (3,4,8,9)-dibenzo-2,7-dioxa-5,10-diaza[4.4.4] propellanes from 4-substituted 1,2-cyclohexanediones and *o*-aminophenols, a computational approach to regioselectivity prediction

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Abstract—The regio- and diastereoselective condensation reactions between 4-Me and 4-*t*-Bu substituted 1,2-cyclohexanediones and substituted *o*-aminophenols yielding the [4.4.4] propellane derivatives have been studied. The possibility of using semi-empirical PM3 calculations for rationalization and prediction of the regioisomer formation has been studied.
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1,2-Diketones have served as valuable precursors for the synthesis of various *N*,*O*-heterocycles due to their high reactivity towards a variety of 4-aminoalcohols.[1] Depending on the ratios of the reagents used and the structures of *N*,*O*-binucleophiles, the condensation reactions led, on one hand, to monocyclic oxazines or oxazolidines, and on the other hand to bicyclic oxazino–oxazines or bisoxazolidine derivatives with high regioselectivity in both mono and bicyclic systems.[1–5]

Apart from acyclic α-diketones, cyclic 1,2-cyclohexanedione has aroused an interest as it can be used to prepare tricyclic bisoxazolines[6] and tricyclic oxazino–oxazine derivatives, belonging to the family of propellanes.[2,7] Moreover, 1,2-cyclohexanedione, having an active α-position with respect to the keto group as a result of keto-enol tautomerism,[8,9] enabled the synthesis of a rare heterocyclic system with substituents at the three neighbouring carbon atoms of the cyclohexane ring.[10]

The above mentioned *N*,*O*-heterocycles are important compounds from a practical point of view. Some of the substituted derivatives of benzoxazine exhibit biological activity.[11] Benzoxazino–benzoxazine derivatives, obtained in the reaction with glyoxal and *o*-aminophenols, have attracted interest as promising optically non-linear materials.[12] The recently obtained optically active bisoxazolidine, prepared from 1,2-cyclohexanedione and *cis*-(1*R*,2*S*)-aminoindan-2-ol, was used as a catalyst for the enantioselective alkynylation of aldehydes.[7]

We have previously reported a synthetic and structural study of propellanes derived from 1,2-cyclohexanedione and *o*-aminophenols while searching for new and efficient materials for nonlinear optics.[13] As a continuation, we investigated the desymmetrization of propellanes by introduction of substituents to the cyclohexane ring and tried to discover the reason for the regioselectivity observed.

In the present Letter we demonstrate that the condensation reaction between 4-substituted 1,2-cyclohexanediones and substituted *o*-aminophenols yields, in a regioselective manner, dibenzodioxadiaza [4.4.4] propellanes as single diastereoisomers (Scheme 1, compound **3**; Table 1). In order to rationalize and/or to predict the observed regioselectivity, semi-empirical PM3 calculations have to be applied. For this study 4-Me (**1a**) and 4-*t*-Bu (**1b**) substituted 1,2-cyclohexanedione and H, NO₂ or Cl substituted *o*-aminophenols **2**
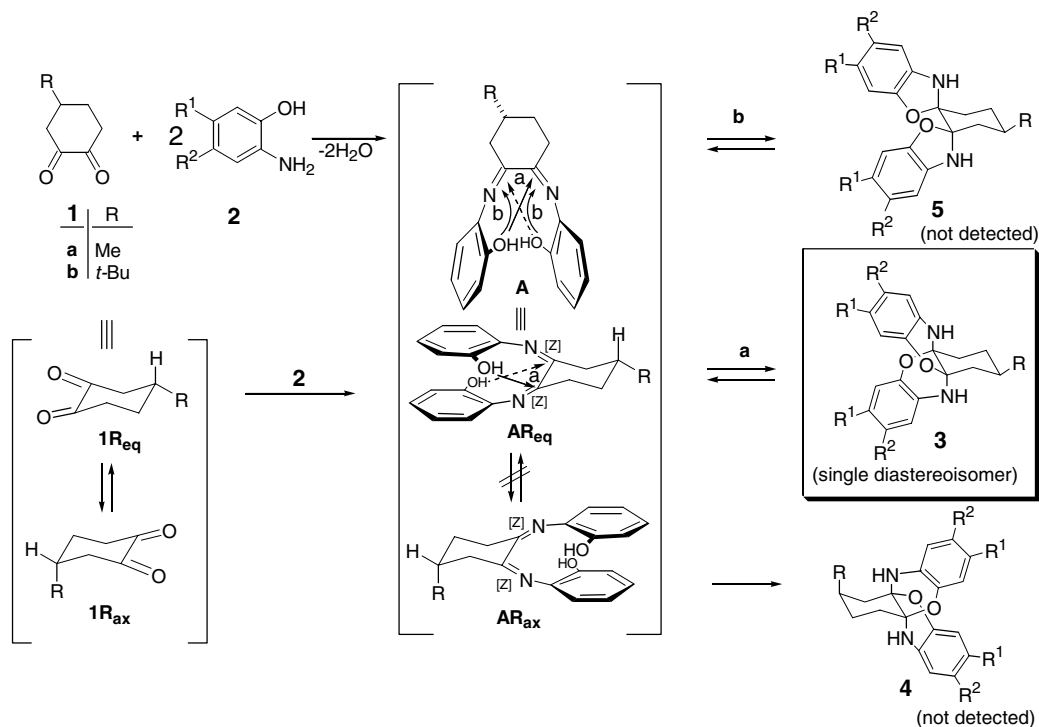
Scheme 1.

Table 1.

Entry	3	R	R^1	R^2	Yield[a,b] (%)
1	a	Me	H	H	47
2	b	Me	H	NO_2	66
3	c	Me	Cl	H	62
4	d	Me	NO_2	H	0
5	e	t-Bu	H	H	50
6	f	t-Bu	H	NO_2	82
7	g	t-Bu	Cl	H	62
8	h	t-Bu	NO_2	H	0
9	i	t-Bu	H	Cl	86

[a] Single diastereoisomer; selectivity estimated by ^{1}H NMR spectroscopy of the crude reaction mixture.

[b] Isolated yields.

were selected (Scheme 1). The reactions between **1** and **2** (1:2 ratio) were conducted simply by refluxing in ethanol for a few hours. Products **3** were obtained in good to moderate yields depending on *o*-aminophenol employed (Table 1).

Contrary to an earlier report,[13] 5-nitro-2-aminophenol was not reactive. All the products obtained were formed as single diastereoisomers regardless of the size of the substituent on the cyclohexanedione ring.

^{1}H NMR spectra of crude reaction mixtures revealed a single product formation thus indicating the complete regio- and diastereoselectivity of the reaction. The configuration of the products was determined by X-ray analysis of **3f** (Fig. 1).[14] The configurations of the remaining products were determined by comparing their ^{1}H and ^{13}C NMR spectra with those recorded for **3f**.[15] Conformational analysis facilitated by resolution
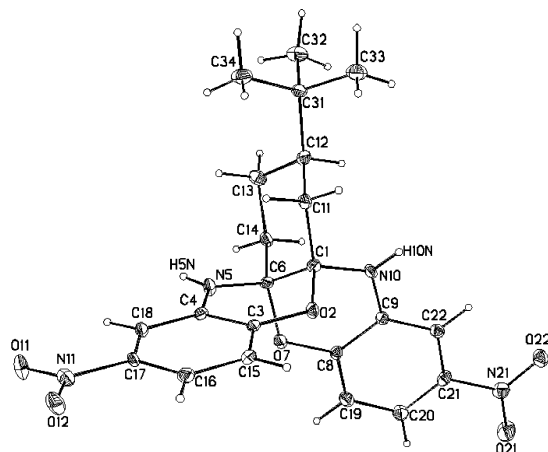

Figure 1. The X-ray structure of propellane **3f**.

enhancement caused by Gaussian to Lorentzian apodization of ^{1}H NMR spectra and by using 2D spectra (^{1}H, ^{1}H COSY; ^{13}C, ^{1}H HETCOR) indicated that the product existed in the same conformation in solution and in the crystal state (i.e., an *N,N*-diaxially and *O,O*-diequatorially substituted cyclohexane ring).

As far as the regioselectivity and diastereoselectivity are concerned, *Z,Z*-bisimine could be considered as an intermediate product (Scheme 1, **A**).[1] Stepwise attack of both oxygen atoms at the C=N groups could take place in a 6-*exo-trig* fashion yielding propellanes **3** (Scheme 1, pathway a) or in a 5-*exo-trig* manner yielding bisoxazolidines **5** (Scheme 1, pathway b). It is important to note that in the intermediate bisimine, the imine groups are out of plane (PM3 calculations,[16] the

N=C—C=N angle is 68.6°). Such an orientation results in the attack of the oxygen atoms from the quasi-equatorial side of the ring and in positioning of the nitrogen atoms in the axial position in the products. The complete diastereoselectivity of the reactions can also be explained by *Z,Z*-bisimine formation, in which the energetically favoured conformer with an equatorially oriented substituent (Scheme 1, **AR$_{eq}$**) does not undergo inversion to the conformer with an axially oriented substituent (Scheme 1, **AR$_{ax}$**) due to the high barrier to inversion.

In the rationalization of the regioselectivity it was taken into account that both products **3** and **5**, as cyclic bis *O,N*-ketals, could exist in equilibrium due to their reversible character. Thus, the formation of single regioisomers indicates a thermodynamically controlled process and allows application of calculations in order
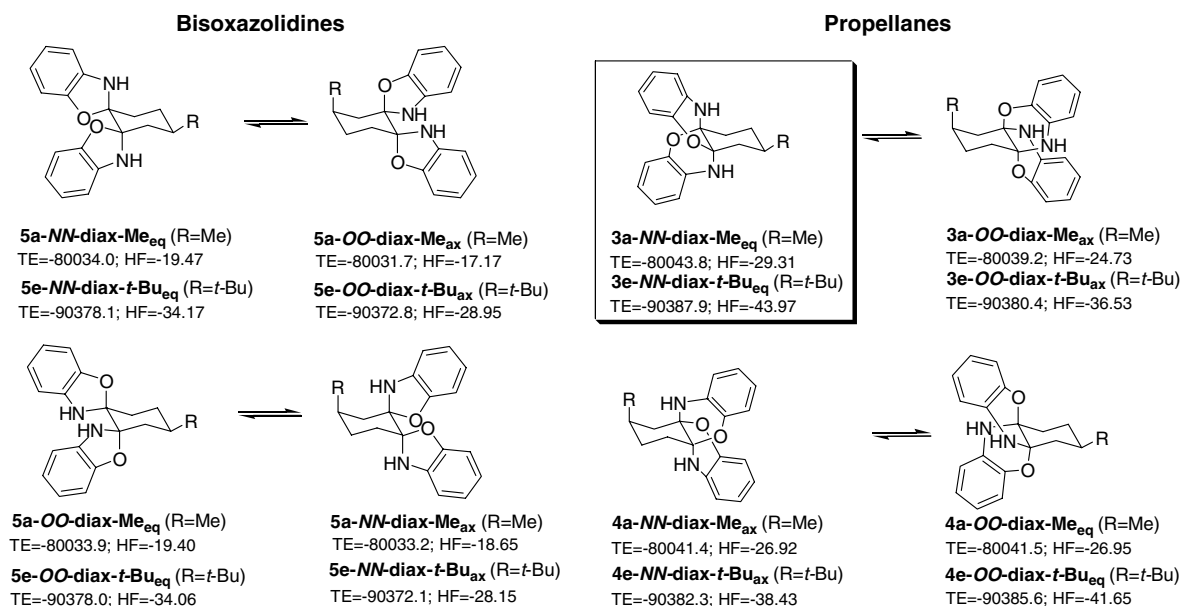
Scheme 2. Calculated (PM3) total energies (TE [kcal/mol]) and heat of formation (HF [kcal/mol]) of the obtained propellanes (framed), and their hypothetical diastereoisomers and conformers together with isomeric bisoxazolidines.

Table 2. Calculated energies (PM3 method) of both possible regioisomers from the condensation reaction of aminoalcohols with 1,2-cyclohexanedione found in the literature

	N,O-Binucleophile used	Calculated energy[a] of the obtained product (Baldwin classification)	Calculated energy[a] of the hypothetical regioisomer (Baldwin classification)	Ref.
1		Propellane (**o1**) TE = −76594.9; HF = −23.51; (6-*exo-trig*)	Bisoxazolidine (**h1**) TE = −76586.6; HF = −15.18; (5-*exo-trig*)	2
2		Propellane (**o2**) TE = −80923.8; HF = −109.41; (6-*exo-trig*)	Bisoxazolidine (**h2**) TE = −80910.9; HF = −96.61; (5-*exo-trig*)	6
3		Bisoxazolidine (**o3**) TE = −95849.5; HF = −33.71; (5-*exo-trig*)	Propellane (**h3**) TE = −95842.9; HF = −27.09; (6-*exo-trig*)	7
4		Bisoxazolidine (**o4**) TE = −83480.2; HF = −22.56; (6-*exo-trig*)	Propellane (**h4**) TE = −83470.4; HF = −12.73; (7-*exo-trig*)	17

o—refers to the obtained product, **h**—refers to the hypothetical product.
All the obtained products (second column) are distinguished by lower energy.
[a] TE = total energy [kcal/mol]; HF = heat of formation [kcal/mol].

to identify the most energetically stable product. In a tentative approach, the total energy as well as the heat of formation were calculated by the semi-empirical PM3 method for both possible regioisomers (bisoxazoline **5**, and propellanes **3** and **4**, Scheme 2), their ring-inverted conformers and additionally for both possible diastereoisomers, revealed that propellanes **3** and **4** are more stable than bisoxazolidines **5** (Scheme 2). These results also indicate that among propellanes **3** the *N,N*-diaxial substituted isomers are more stable than their *O,O*-diaxially substituted conformers. These results are in agreement with the configuration and conformation determined by X-ray and NMR methods.

In order to check the reliability of the applied methodology and its possible extension to regioselectivity prediction of reactions with other *N,O*-binucleophiles, the energies of products described in the literature and their hypothetically formed regioisomers were calculated. The results, shown in Table 2 and in the Supplementary data, fully support this approach. The most noteworthy result is the agreement between the calculated energies of both potential products with the results of the regioselective formation of bisoxazoline **o3**, in the reaction of 1,2-cyclohexadione with *cis*-(1*R*,2*S*)-aminoindan-2-ol (Table 2, entry 3) as the calculated energy of **o3** is lower with respect to **h3**. It should be emphasized that this reaction takes place according to the 5-*exo-trig* process, while in the typical reactions with the other 1,2-aminoalcohols leading to the formation of propellanes, the 6-*exo-trig* process dominates (Table 2, entries 1 and 2).

In summary, we have demonstrated that the synthesis of dibenzodioxadiaza [4.4.4] propellanes from *o*-aminophenols and substituted 1,2-cyclohexanedione occurred in a regio- and diastereoselective manner, and was independent of the size of the substituents on 1,2-cyclohexanediones. The formation of *Z,Z*-bisimine seems to play a crucial role in this reaction. PM3 calculations provide a successful identification of which of the two possible products (bisoxazolidine or propellane) is formed in a thermodynamically controlled reaction. The computational approach proposed and verified by the agreement between the calculated energies and the earlier described regioselectivity serves as a promising tool for the regioselectivity predictions. A study on the use of new *N,O*-binucleophiles in the reaction and on the possibility of regioselectivity prediction by other computational methods (e.g., DFT) is underway.

Acknowledgement

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.008.

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14. Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 637874.
15. Selected spectroscopic data: **3f** (1*RS*,6*RS*,12*RS*)-12-*t*-Butyl-(3,4,8,9)-dibenzo-2,7-dioxa-5,10-diaza-17,21- dinitro-[4.4.4]propellane. Yellow solid, mp 229–231 °C (decomposition), (ethanol). IR (KBr pellet): $\nu = 3490$ br, 3392, 2960, 2868, 1600, 1528 (br), 1330, 1280, 1256, 1238, 1090, 1028, 960, 940, 868, 832, 744 cm^{-1}. ^{1}H NMR (400.1 MHz, DMSO-d_6): $\delta = 0.85$ (9H, s, 12-C(CH$_3$)$_3$), 1.42 (1H, qd, $J = 12.6$, ca. 3.8 Hz, H-13$_{ax}$), 1.54 (1H, t, $J = 12.4$ Hz, H-11$_{ax}$), 1.65 (1H, tt, $J = 12.4$, ca. 2.5 Hz, H-12$_{ax}$), 1.73 (1H, br d, $J = $ ca 12.5 Hz, H-13$_{eq}$), 1.78 (1H, td, $J = 13.0$, 3.6 Hz, H-14$_{ax}$), 2.00 (1H, br d, $J = $ ca. 13.4 Hz, H-14$_{eq}$), 2.03 (1H, br d, $J = $ ca 12.2 Hz, H-11$_{eq}$), 6.87 and 6.88 (1H, d, $J = 8.8$ Hz and 1H, d, $J = 8.8$ Hz, H-15, H-19), 7.56 and 7.57 (1H, dd, $J = 8.8$, 2.8 Hz and 1H, dd, $J = 8.8$, 2.8 Hz, H-16, H-20), 7.63 and 7.64 (1H, d, $J = 2.8$ Hz and 1H, d, $J = 2.8$ Hz, H-18, H-22), 8.00 (1H, s, NH), 8.06 (1H, s, NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 24.03$ (CH$_2$-13), 27.77 (C(CH$_3$)$_3$), 32.23 (*C*(CH$_3$)$_3$), 32.94 (CH$_2$-14), 34.70 (CH$_2$-11), 44.57 (CH-12), 83.42, 83.95 (C-1, C-6), 109.31, 109.44 (C-18, C-22), 115.68, 115.84 (C-16, C-20), 116.64 (C-15, C-19), 130.19, 130.25 (C-17, C-21), 141.89 (C-4, C-9), 147.44, 147.52 (C-3, C-8). Anal. Calcd for C$_{22}$H$_{24}$N$_4$O$_6$ (440.45): C, 59.99; H, 5.49; N, 12.72. Found: C, 59.96; H, 5.61; N, 12.63.
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