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Synthesis of Densely Functionalised 5-Halogen-1,3-oxazin-2-ones by Halogen-Mediated Regioselective Cyclisation of *N*-Cbz-Protected Propargylic Amines: A Combined Experimental and Theoretical Study**

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Abstract: A very efficient synthesis of 5-halogen-1,3-oxazin-2-ones has been accomplished by the halocyclisation reaction of chiral nonracemic *N*-carbobenzyloxy (*N*-Cbz)-protected propargylic amines by using I_2, Br_2 and Cl_2 as electrophile sources. The nature of the halogen influences the reaction time and yield. However, in all cases the reaction is totally regioselective taking place through a 6-*endo-dig* process regardless of the nature of the halogen and of the substituents in the starting material. To rationalise the experimental results, theoretical studies at the B3LYP/6-311G* level have been performed.

Keywords: density functional calculations · halocyclisation · oxazinones · propargylic amines · reaction mechanisms · regioselectivity

Introduction

The electrophilic cyclisation of functionalised alkynes possessing a nucleophilic group in close proximity to the triple bond constitutes an important strategy in the construction of a wide variety of heterocycles and carbocycles.[1] Typically, the activation of the carbon–carbon triple bond is based on the formation of a cationic metal complex (in transition-metal-catalysed reactions)[2] or an incipient halonium ion (in halogen-mediated reactions).[3] This second activation method leads to the synthesis of halogen-containing heterocycle or carbocycle derivatives, which are versatile precursors in many synthetic processes. With regard to the internal nucleophile, a wide range of nucleophilic groups, such as alcohols,[4] ethers,[5] thioethers,[6] selenoethers,[7] amines,[8] imines,[9] oximes,[10] azides,[11] aldehydes and ketones,[12] carboxylic acids and their derivatives,[13] 1,3-dicarbonyl compounds[14] and aromatic rings,[15] has been investigated. However, the use of functionalised alkynes possessing a carbamate derivative as the internal nucleophilic group remains relatively unexplored.[2a,16]

Very recently, we have reported a convenient method for the synthesis of chiral nonracemic *N*-benzyloxycarbonyl (*N*-Cbz)-protected propargylic amines by the addition of terminal alkynes to imines generated in situ from α-amido sulfones in the presence of diethylzinc and 1,1′-binaphthol (BINOL)-type ligands as catalysts.[17] On the basis of early reported results in the synthesis of halo derivatives of heterocycles by halocyclisation of conveniently functionalised alkynes we envisioned that the *N*-Cbz-protected propargylic amines must be suitable substrates to investigate a novel route for preparing densely-functionalised 1,3-oxazin-2-ones or oxazolidin-2-ones (cyclic carbamates) through an *O*-halocyclisation process. Carbamates represent an important class of compounds with interesting properties and have found wide utility in several areas, such as pharmaceuticals[18] or agrochemicals.[19] Cyclic carbamates are less known, although they have been used as chiral auxiliaries[20] and, besides, present interesting biological activity.[21] There is a variety of methods[22] for the synthesis of this kind of compounds, however, the development of practical and efficient methods for the preparation of these cyclic carbamates, especially those densely functionalised, is of great interest.

When a substrate of the *N*-Cbz-protected propargylic amine-type **1** is subjected to an *O*-cyclisation process, two reaction modes are possible: the 6-*endo-dig* mode that should yield the 1,3-oxazin-2-ones **2** and the 5-*exo-dig* mode that should yield the oxazolidin-2-ones **3**. Therefore, the highly effective control of the regioselectivity of the *O*-halocyclisation mode is essential for the selective preparation of compounds **2** or **3** (Scheme 1). A metal-catalysed cyclisation of *N*-butyloxycarbonyl (Boc)-protected propargylic amines has been previously described by Carretero et al.,[2a] which

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[**] Cbz = carbobenzyloxy.

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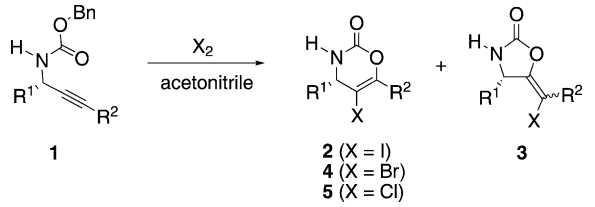


Scheme 1. Halocyclisation of *N*-Cbz-protected propargylic amines (Bn = benzyl).

took place according to an intramolecular 5-*exo-dig* process to afford the five-membered ring products **3**. Also, a metal-catalysed 5-*exo-dig* cyclisation of propargylic ureas to provide cyclic five-membered carbamimidates has been recently described by Toste and Campbell.[2b] In this paper we report for the first time a halogen-mediated regioselective cyclisation of *N*-Cbz-protected propargylic amines to provide the six-membered isomers, 1,3-oxazin-2-ones **2**, through a 6-*endo-dig* route with a regioselectivity that contrasts with the previously reported in metal-catalysed cyclisation reactions of propargylic amine derivatives.[2a,b] Additionally, the mechanism of this reaction has been theoretically investigated.

Results and Discussion

The required starting materials, that is, the *N*-Cbz-protected propargylic amines **1**, are readily prepared by the addition of terminal alkynes to imines generated in situ from α-amido sulfones in the presence of diethylzinc and BINOL-type ligands as catalysts, following our previously reported method.[17] In order to determine the general conditions for the halocyclisation reaction of *N*-Cbz-protected propargylic amines **1**, *N*-Cbz-1,3-diphenylprop-2-yn-1-amine (**1a**) was submitted to iodocyclisation conditions in the presence of iodine/$NaHCO_3$ in dichloromethane at room temperature, such as it has been described for the iodocyclisation of several functionalised alkynes. Under these conditions we obtained the corresponding iodinated 1,3-oxazin-2-one (**2a**) with an endocyclic double bond as the only isolated product (67% yield). After a brief optimisation process, including the solvent, the temperature, the base and the stoichiometry, we observed that the best result in product **2a** was obtained with iodine (2 equiv) in acetonitrile at 0°C and the absence of $NaHCO_3$ (82% yield). These optimised reaction conditions allowed us to synthesise a wide range of 4,6-disubstituted 3,4-dihydro-5-iodo-1,3-oxazin-2-ones **2** through a 6-*endo-dig* *O*-cyclisation process in good to excellent yields. So the optimised conditions were used for the iodocyclisation of several *N*-Cbz-protected propargylic amines **1** derived from the addition of phenylacetylene to *N*-Cbz-protected imines of substituted benzaldehydes (Table 1, entries 1–4) in good to excellent results. Both electron-donating (Me) and electron-withdrawing (Cl) substituents in *ortho* and *para* positions of the aromatic ring were well tolerated, with yields ranging from 76 to 94%. On the other hand, the iodocyclisation of *N*-Cbz-protected propargylic amines **1** derived from

Table 1. Electrophilic cyclisation of *N*-Cbz-protected propargylic amines to 5-halogen-1,3-oxazin-2-ones.[a]

Entry	**1**	R^1	R^2	X_2	Time [h]	Product	Yield [%][b]
1	**1a**	Ph	Ph	I_2	18	**2a**	82
2	**1b**	4-ClC_6H_4	Ph	I_2	30	**2b**	76
3	**1c**	4-MeC_6H_4	Ph	I_2	24	**2c**	94
4	**1d**	2-MeC_6H_4	Ph	I_2	24	**2d**	94
5	**1e**	cyclohexyl	Ph	I_2	4	**2e**	94
6	**1f**	*n*Bu	Ph	I_2	4	**2f**	45
7	**1g**	$PhCH_2CH_2$	Ph	I_2	20	**2g**	70
8	**1h**	Ph	4-FC_6H_4	I_2	18	**2h**	98
9	**1i**	Ph	4-$MeOC_6H_4$	I_2	2	**2i**	91
10	**1j**	Ph	2-$MeOC_6H_4$	I_2	1	**2j**	93
11	**1k**	Ph	3,5-$(MeO)_2C_6H_3$	I_2	52	**2k**	97
12	**1l**	Ph	2-thienyl	I_2	1	**2l**	98
13	**1m**	Ph	$C_6H_5CH_2CH_2$	I_2	30	**2m**	97
14	**1n**	Ph	*t*Bu	I_2	24	**2n**	65
15	**1a**	Ph	Ph	Br_2	0.5	**4a**	93
16	**1b**	4-ClC_6H_4	Ph	Br_2	0.3	**4b**	82
17	**1d**	2-MeC_6H_4	Ph	Br_2	0.5	**4d**	79
18	**1e**	cyclohexyl	Ph	Br_2	1	**4e**	91
19	**1h**	Ph	4-FC_6H_4	Br_2	0.5	**4h**	80
20	**1o**	Ph	4-ClC_6H_4	Br_2	0.5	**4o**	86
21	**1m**	Ph	$PhCH_2CH_2$	Br_2	1	**4m**	80
22	**1a**	Ph	Ph	Cl_2	0.15	**5a**	62
23	**1c**	4-MeC_6H_4	Ph	Cl_2	0.15	**5c**	50
24	**1e**	$PhCH_2CH_2$	Ph	Cl_2	0.15	**5e**	61
25	**1i**	Ph	4-$MeOC_6H_4$	Cl_2	0.15	**5i**	59

[a] All iodocyclisation reactions were run with 0.1 mmol of the starting material and 2.0 equivalents of iodine in 2.5 mL of acetonitrile at 0°C. All bromocyclisation reactions were run with 0.1 mmol of the starting material and 1.2 equivalents of bromine in 12.5 mL of acetonitrile at 0°C. All chlorocyclisation reactions were run with 0.1 mmol of the starting material and 1.2 equivalents of chlorine in 12.5 mL of acetonitrile at −20°C. [b] Yield of the isolated product.

alkyl-substituted imines gave the corresponding products in variable yields (Table 1, entries 5–7). Whereas the cyclohexyl-substituted starting material **1e** afforded the iodocyclisation product with an excellent yield, the *n*-butyl-substituted and the 2-phenylethyl-substituted starting materials **1f** and **1g** gave moderate yields. Then we examined the reactivity of various *N*-Cbz-protected propargylic amines **1** bearing different aromatic, heteroaromatic and aliphatic groups attached to the alkyne moiety affording the corresponding products **2** in excellent yield in most cases (Table 1, entries 8–14).

The structures of products **2** were established on the basis of NMR spectroscopic analysis. In particular, the four carbon atoms in the 6-membered-ring-containing cyclic carbamate gave characteristic signals. So, the carbonyl group corresponds to the signal at $\delta = 149$–150 ppm (when R^1 is aromatic) and $\delta = 151$–152 ppm (when R^1 is aliphatic), the quaternary olefinic =C–O carbon atom gives a signal at $\delta =$ 148–150 ppm, the signal of the quaternary olefinic I–C= carbon atom appears at high field at $\delta = 69$–72 ppm and the benzylic CH group appears at $\delta = 60$–65 ppm. Moreover, the structural and configurational assignments of **2j** and **2l** were confirmed by means of X-ray diffraction analysis (Figure 1).[23,24] In all cases, the 6-*endo-dig* *O*-cyclisation led to 3,4-dihydro-5-iodo-1,3-oxazin-2-ones **2**. Determination of

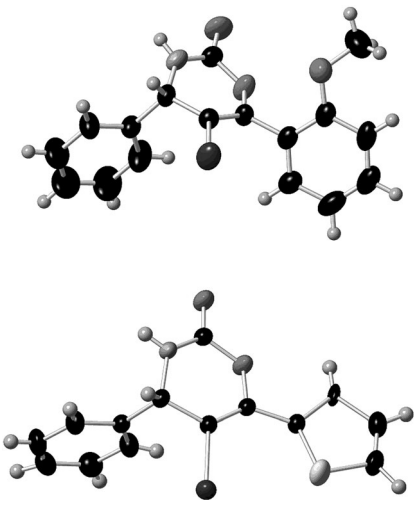


Figure 1. ORTEP plots for the X-ray structures of compounds **2j** (top) and **2l** (bottom). The thermal ellipsoids are drawn at the 50% probability level.

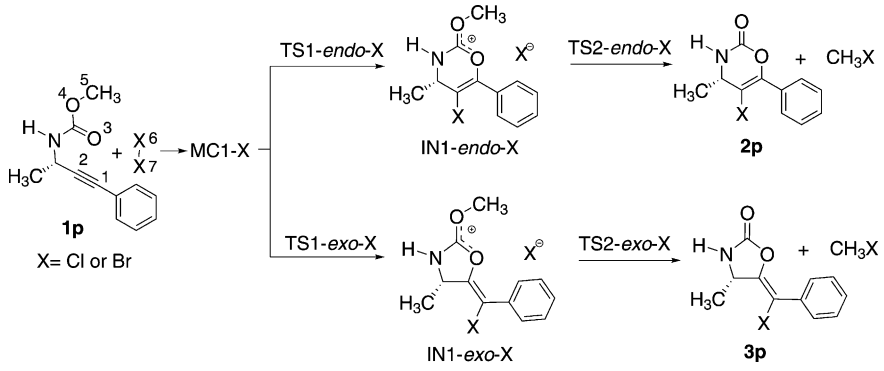
the enantiomeric excesses (*ee*) by chiral HPLC of the products showed no epimerisation at the stereogenic centre regardless of the reaction time.

When we applied the optimised conditions for the iodocyclisation to the reaction between *N*-Cbz-1,3-diphenylprop-2-yn-1-amine (**1a**) and bromine in acetonitrile at 0°C a shorter reaction time was required but, besides 3,4-dihydro-5-bromo-1,3-oxazin-2-one (**4a**) corresponding to the cyclisation process, a second product was observed, probably resulting from a simple addition of Br_2 to the triple bond. To our delight, in the presence of only 1.2 equivalents of bromine (instead of 2.0 equiv) and by using a more diluted reaction mixture (1:5) this secondary addition reaction was completely avoided and the bromocyclisation product **4a** was obtained with good yield (93%) (Table 1, entry 15). The reaction scope was then explored under the new optimised conditions for the bromocyclisation. The reaction has proven to be a general route to a variety of 3,4-dihydro-5-bromo-1,3-oxazin-2-ones **4** (Table 1, entries 16–21). The structural characterisation of products **4** was carried out by spectroscopic methods. As for the iodinated products, the four carbon atoms in the brominated 6-membered-ring-containing cyclic carbamate gave characteristic signals. So, the carbonyl group corresponds to the signal at $\delta = 149$–151 ppm, the quaternary olefinic =C–O carbon atom gives a signal at $\delta = 145$–148 ppm, the quaternary olefinic Br–C= carbon atom appears at $\delta = 97$–99 ppm and the benzylic CH group appears at $\delta = 58$–63 ppm.

Finally, the chlorocyclisation reaction of several *N*-Cbz-protected propargylic amines (Table 1, entries 22–25) was carried out in the same way as the bromocyclisation reaction with chlorine in acetonitrile at −20°C. A very short reaction time (0.15 h) was required, and the chlorocyclisation products **5** were obtained with moderate yields (50–60%). As for the iodinated and brominated analogues, the four carbon atoms in the chlorinated 6-membered-ring-containing cyclic carbamate gave characteristic signals. So, the carbonyl group corresponds to the signal at $\delta = 149$–151 ppm, the quaternary olefinic =C–O carbon atom gives a signal at $\delta = 144$–146 ppm, the quaternary olefinic Cl–C= carbon atom appears at $\delta = 107$–109 ppm and the benzylic CH group appears at $\delta = 56$–61 ppm.

The 3,4-dihydro-5-halogen-1,3-oxazin-2-ones **2**, **4** and **5** prepared by this method offer a great potential as precursors for compounds of increasing molecular complexity, particularly when one considers the different ways to transform the resulting halogen functionalities through palladium- and copper-catalysed reactions.[25]

In order to understand the mechanism of the regioselective halogen-mediated cyclisation of protected propargylic amines **1** to yield the corresponding 6-membered 1,3-oxazin-2-ones **2** a computational study by using density functional theory (DFT) methods at the B3LYP/6-311G* level (see computational methods in the Experimental Section) was carried out (Scheme 2). In the theoretical study, the R^1 group and the benzyl group present in the *N*-Cbz-protected propargylic amines **1a**–**1o** were modelled by methyl groups. Starting from the protected propargylic amine **1p** a study of the potential energy surface for the title reactions indicates that these halogen-mediated cyclisation reactions take place through a two-step mechanism. In the first step, the halogen molecule X_2 electrophilically attacks on the C1 or C2 carbon atom of the triple bond of these propargylic amines to yield the cationic intermediates IN1-*endo*-X or IN1-*exo*-X through TS1-*endo*-X or TS1-*exo*-X. In the second step, the methyl group present in the carboxylate substituent is eliminated in these cationic intermediates assisted by the halide ion X^- yielding the final 1,3-oxazin-2-one **2p** or the oxazolidin-2-one **3p** (Scheme 2). For the reaction in the



Scheme 2. Possible reaction routes for the regioselective halogen-mediated cyclisation of protected propargylic amines that were studied by DFT methods.

presence of bromine (Br_2) the two regioisomeric channels were studied, whereas for the reaction in the presence of chlorine (Cl_2) only the most favourable channel yielding the 6-membered 1,3-oxazin-2-one **2p** was considered. Relative energies in the gas phase as well as in acetonitrile are given in Table 2. Total energies are given in Table S1 in the Supporting Information. Because some species involved in the reactions are charged, the energy discussion will be done by using the relative energies in acetonitrile.

Table 2. Relative energies in acetonitrile (in [kcal mol^{-1}], relative to **1p** or **1q** plus the halogen X_2) of the stationary points involved in the halogen-mediated cyclisation reactions of protected propargylic amines **1p** and **1q**.

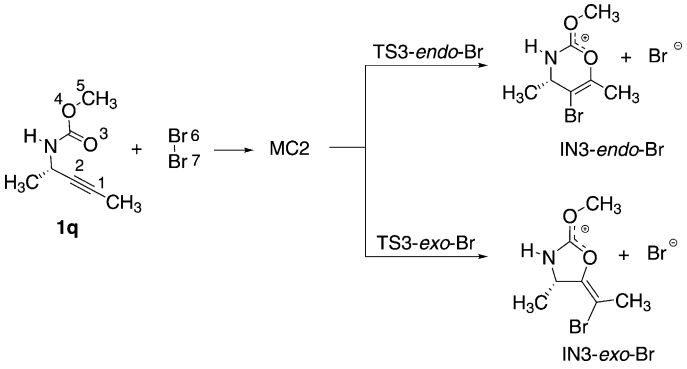
Bromination of **1p**		Chlorination of **1p**		Bromination of **1q**	
MC1-Br	−1.0	MC1-Cl	−1.2	CM2-Br	−4.1
TS1-*endo*-Br	0.5	TS1-*endo*-Cl	−12.8	TS3-*endo*-Br	2.0
TS1-*exo*-Br	8.4			TS3-*exo*-Br	3.3
IN1-*endo*-Br	−20.0	IN1-*endo*-Cl	−41.3	IN3-*endo*-Br	−27.5
IN1-*exo*-Br	−19.4			IN3-*exo*-Br	−25.4
TS2-*endo*-Br	−7.3	TS2-*endo*-Cl	−29.1		
TS2-*exo*-Br	−8.5				
2p+MeBr	−28.6	**2p**+ MeCl	−51.4		
3p+MeBr	−31.8				

In an earlier step of the reaction, the halogens X_2 form a weak molecular complex (MC) with the π system of the triple bond of propargylic amine **1p**. These MCs are located at −1.0 (MC1-Br) and −1.2 kcal mol^{-1} (MC1-Cl) for Br_2 and Cl_2, respectively, below the separated reagents. For the reaction in presence of bromine, the activation energies associated with the electrophilic attack of Br_2 on the C2 and C1 carbon atoms of the propargylic amine **1p** are 0.5 (TS1-*endo*-Br) and 8.4 kcal mol^{-1} (TS1-*exo*-Br); formation of the corresponding cationic intermediates are exothermic by −20.0 (IN1-*endo*-Br) and −19.4 kcal mol^{-1} (IN1-*exo*-Br). Elimination of the methyl group from these cationic intermediates takes place through a bimolecular nucleophilic substitution of the methyl group assisted by the bromide ion Br^- generated in the first step of the reaction. From the corresponding intermediates, the activation energies associated with the extrusion of the methyl group are: 12.7 (TS2-*endo*-Br) and 10.9 kcal mol^{-1} (TS2-*exo*-Br). Formation of **2p** and **3p** plus MeBr is exothermic by −28.6 and −31.8 kcal mol^{-1}, respectively.

From these energy results some relevant conclusions can be drawn: 1) the electrophilic attack of bromine on the triple bond of the propargylic amine **1p** is completely regioselective, TS1-*endo*-Br being 7.9 kcal mol^{-1} lower in energy than TS1-*exo*-Br, 2) the high exothermic character of the first step makes this step irreversible, 3) the activation energy associated with the second step is higher than that associated with the first step, thus, the elimination of the methyl substituent is the rate-determining step (RDS) of the reaction. Consequently, although the electrophilic attack of bromine to the propargylic amine **1p** is the regioselectivity-determining step, the methyl elimination is the RDS of the reaction.

For the reaction in presence of chlorine, TS1-*endo*-Cl associated with the electrophilic attack of Cl_2 on the C2 carbon atom of the propargylic amine **1p** is located −12.8 kcal mol^{-1} below the separated reagents; formation of the 1,3-oxazin-2-one intermediate IN1-*endo*-Cl is strongly exothermic by −41.3 kcal mol^{-1}. The activation energy associated with the elimination of the methyl group in intermediate IN1-*endo*-Cl through TS2-*endo*-Cl is 12.2 kcal mol^{-1}, the overall process is exothermic by −51.4 kcal mol^{-1}. The fact that TS1-*endo*-Cl is located below the separated reagents is a consequence of the strong solvation of the chloride ion Cl^-, which develops along the electrophilic attack. Note that in the gas phase TS1-*endo*-Cl is located 9.5 kcal mol^{-1} above the reagents. A comparison of the relative energies of the transition states (TSs) associated with the electrophilic attack of halogens Br_2 or Cl_2 on the propargylic amine **1p** in the gas phase and in acetonitrile indicates that the addition of Cl_2 to these propargylic amines is favoured over the addition of Br_2.

Finally, the role of the phenyl substituent attached to the alkyne moiety was analysed by studying the two regioisomeric channels associated with the addition of bromine on the C1 and C2 carbon atoms of the methyl-substituted propargylic amine **1q** (see Scheme 3). The activation energies



Scheme 3. Two regioisomeric channels associated with the addition of bromine to the propargylic amine **1q**.

associated with the formation of intermediates IN3-*endo*-Br and IN3-*exo*-Br through TS3-*endo*-Br and TS3-*exo*-Br are 2.0 and 3.3 kcal mol^{-1}, respectively, the formation of these intermediates is exothermic by −27.5 and −25.4 kcal mol^{-1}, respectively (see Table 2). Consequently, the cyclisation reaction with the methyl-substituted propargylic amine **1q** should be slightly slower, and should present a low regioselectivity. Note that the reaction with the phenyl-substituted propargylic amine **1p** is completely regioselective. Thus, the phenyl substituent induces a total regioselectivity in these halogen-mediated cyclisation reactions of protected propargylic amines as a consequence of the stabilisation of the incipient carbocationic C1 centre generated along the electrophilic attack on the conjugated C2 carbon atom.

The geometries of the TSs involved in the regioisomeric channels associated with the bromine-mediated cyclisation of the phenyl-substituted propargylic amine **1p** are given in Figure 2, whereas those associated with the reaction mediated by chlorine are given in Figure S1 in the Supporting Information. At the TSs associated with the first step of the bromine-mediated cyclisation process the lengths of the Br6–C2(1) and the O3–C1(2) forming bond are 2.180 and 2.867 Å at TS1-*endo*-Br and 2.247 and 2.193 Å at TS1-*exo*-Br, respectively. For the corresponding intermediates IN1-*endo*-Br and IN1-*exo*-Br the lengths of the Br6–C2(1) and the O3–C1(2) bond are 1.910 and 1.440 as well as 1.933 and 1.437 Å, respectively. These geometrical parameters indicate that at the most favourable TS1-*endo*-Br, the Br6–C2 bond formation is very advanced, whereas the O3–C1 bond formation is rather delayed. At the most unfavourable TS1-*exo*-Br, the O3–C2 bond formation is more advanced than the O3–C1 bond formation at TS1-*endo*-Br, showing a more synchronous bond-formation process. Note that in the gas phase the lengths of the Br6–C2(1) and the O3–C1(2) forming bond are 2.156 and 1.806 Å at TS1-*endo*-Br and 2.214 and 1.760 Å at TS1-*exo*-Br, respectively, indicating that both bond-formation processes are coupled. Consequently, polar solvent effects change the mechanism of the first step of the most favourable reactive channel from a synchronous Br6–C2 and O3–C1 bond formation in the gas phase to a highly asynchronous process in acetonitrile. This behaviour is illustrated by the analysis of the atomic movements at the unique imaginary frequency associated with each TS; at TS1-*endo*-Br in the gas phase, the unique imaginary frequency $\tilde{\nu} = -221.78\ cm^{-1}$ is associated with the movement of the Br6, C2, O3 and C1 atoms along the Br6–C2 and O3–C1 bond formation, whereas at TS1-*endo*-Br in acetonitrile, the unique imaginary frequency $\tilde{\nu} = -28.85\ cm^{-1}$ is mainly associated with the rotation of the N–C bond favouring the approach of the O3 and C1 atoms. This change of the mechanism can be understood as a strong stabilisation of both the bromine anion and the incipient benzyl carbocationic C1 centre at TS1-*endo*-Br in the polar solvent acetonitrile. At the most favourable TS1-*endo*-Cl associated with the first step of the chlorine-promoted cyclisation process, the lengths of the forming bonds are 1.771 (Cl6–C2) and 2.752 Å (O3–C1) Å (see Figure S1 in the Supporting Information). At TS1-*endo*-Cl, the Cl6–C2 bond formation is more advanced than the Br6–C2 bond formation at TS1-*endo*-Br.

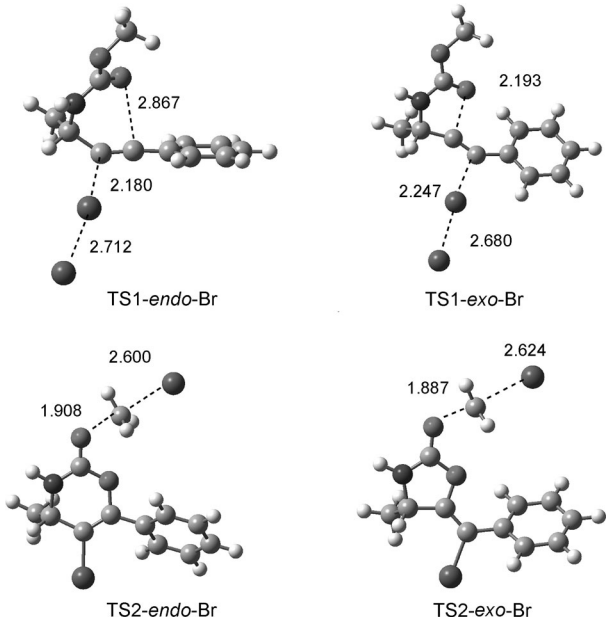


Figure 2. Geometry of the TSs involved in the regioisomeric channels associated with the bromine-mediated cyclisation of the protected propargylic amine **1p**. The lengths of the forming and breaking bonds are given in Ångstrom.

At the TSs associated with the elimination of the methyl group in IN1-*endo*-Br and IN1-*endo*-Br, the lengths of the O4–C5 breaking bond and the C5–Br7 forming bond are 1.908 and 2.600 Å, respectively, at TS2-*endo*-Br, and 1.887 and 2.624 Å, respectively, at TS2-*exo*-Br. In these asynchronous TSs, the O4–C5 breaking bonds are more advanced than the C5–Br7 forming bond. Similar O4–C5 breaking-bond and C5–Cl7 forming-bond processes are found at TS2-*endo*-Cl (see Figure S1 in the Supporting Information).

The geometry of the TSs involved in the first step of the regioisomeric channel associated with the bromine-mediated cyclisation of the protected methyl-substituted propargylic amine **1q** are given in Figure 3. At the TSs, the lengths of the Br6–C2(1) and O3–C1(2) forming bonds are 2.204 and 2.453 Å, respectively, at TS3-*endo*-Br, and 2.208 and 2.251 Å, respectively, at TS3-*exo*-Br. At the most favourable TS3-*endo*-Br, the Br6–C2 bond length indicates that the Br6–C2 bond formation at this TS is more advanced than that at TS1-*endo*-Br, 2.867 Å. This behaviour accounts for the role of the phenyl substituent in TS1-*endo*-Br, stabilising the incipient carbocationic C1 centre along the electrophilic attack of bromine on the C1 carbon atom.

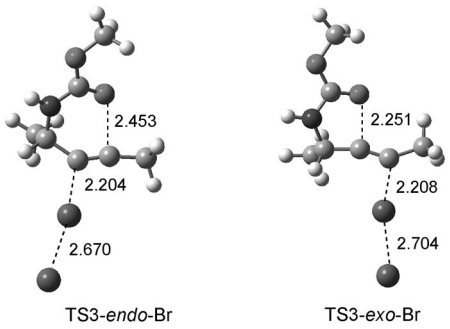


Figure 3. Geometry of the TSs involved in the first step of the regioisomeric channels associated with the bromine-mediated cyclisation of the protected propargylic amine **1q**. The lengths of the forming and breaking bonds are given in Ångstrom.

Finally, an analysis of the reactivity of the protected propargylic amines **1p** and **1q** was performed by using the reac-

tivity indices defined within the conceptual DFT method.[26] The global and local reactivity indices, named global electrophilicity ω, global nucleophilicity N, nucleophilic Parr functions P_k^- and the local nucleophilicity indices N_k of the propargylic amines **1p** and **1q** are given in Figure 4.

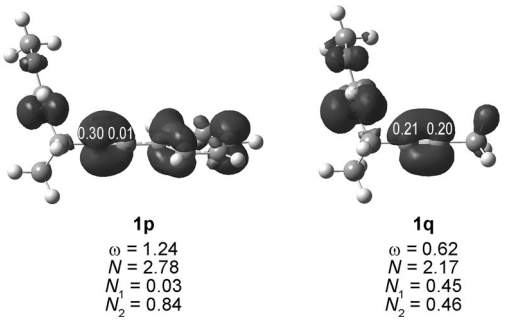


Figure 4. Maps of the atomic spin density of the cation radicals of the propargylic amines **1p** and **1q** and the nucleophilic Parr functions P_k^- at the C1 and C2 carbon atoms, and global electrophilicity ω, global nucleophilicity N, and local nucleophilicity indices N_k, in [eV], of compounds **1p** and **1q**.

The propargylic amines **1p** and **1q** have low electrophilicity values, 1.24 (**1p**) and 0.62 eV (**1q**), being classified as moderate and marginal electrophiles,[27] respectively. On the other hand, the corresponding nucleophilicity N indices, 2.78 (**1p**) and 2.17 eV (**1q**), indicate that they will behave as moderate nucleophiles.[28] The higher nucleophilic character of the phenyl-substituted propargylic amine **1p** compared to the methyl-substituted propargylic amine **1q** accounts for the lower activation energy found for the bromine-mediated addition to compound **1p** than to compound **1q**.

Building upon recent studies devoted to the bonding changes in polar reactions,[29] Domingo and Pérez have proposed two new electrophilic, P_k^+, and nucleophilic, P_k^-, Parr functions, based on the analysis of the atomic spin density (ASD) at the corresponding anion and cation radicals, to study the regio- and chemoselectivity in polar reactions.[30] Analysis of the nucleophilic Parr functions P_k^- in the propargylic amines **1p** and **1q** indicates that the phenyl-substituted propargylic amine **1p** presents a strong nucleophilic activation of the C1 carbon atom, 0.30, when compared to the C1 carbon atom, 0.01, whereas the methyl-substituted propargylic amine **1q** shows a similar nucleophilic activation at the two acetylenic C1 and C2 carbon atoms (see Figure 4). As a consequence, analysis of the local nucleophilicity indices of the phenyl-substituted propargylic amine **1p** indicates that the C2 carbon atom is the most nucleophilic centre of this molecule, $N_2 = 0.84$ eV, whereas the corresponding values for methyl-substituted propargylic amine **1p** show that the C2 carbon atom, $N_2 = 0.46$ eV is slightly more nucleophilically activated than the C1 carbon atom, $N_2 = 0.45$ eV. This local analysis is in complete agreement with the entire regioselectivity found in the bromine-mediated cyclisation of the phenyl-substituted propargylic amines **1p**. A lower regioselectivity should be observed in the reaction of compound **1q**.[31]

Conclusion

In summary, a very efficient synthesis of 5-halogen-1,3-oxazin-2-ones has been developed involving a halogen-mediated regioselective cyclisation of chiral nonracemic *N*-Cbz-protected propargylic amines. A wide variety of substrates undergoes this cyclisation process in good to excellent yields. The halogens I_2, Br_2 and Cl_2 have been utilised as electrophiles and the results obtained demonstrate the importance of the nature of the halogen on the reaction time and yield, but not on the regioselectivity. This synthetic approach allows a simultaneous construction of the 1,3-oxazin-2-one system and the installation of a halogen functionality at the 5-position of the heterocyclic ring and it constitutes a useful complement to the literature-known protocols for preparing cyclic carbamates. In addition DFT calculations were performed to obtain an insight into various aspects of the reactivity of protected propargylic amines under halocyclisation reaction conditions.

Experimental Section

General methods: Reactions were carried out under a nitrogen atmosphere in round bottom flasks oven-dried overnight at 120 °C. Commercial reagents were used as purchased. The *N*-Cbz-protected propargylic amines **1** were prepared from the corresponding α-amido sulfone and alkyne as described in the literature.[17] Solvents were dried when necessary: Dichloromethane was distilled from CaH_2. Reactions were monitored by TLC analysis by using Merck silica gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040–0.063 mm. Melting points were determined in a Buchi M-560 apparatus. ^{1}H NMR spectroscopy was run at 300 MHz for ^{1}H and at 75.5 MHz for ^{13}C NMR in a Bruker Avance 300 DPX spectrometer. ^{1}H NMR spectra and ^{13}C NMR spectra were internally referenced to $CDCl_3$ signal ($\delta = 7.26$ and 77.0 ppm, respectively). Chemical shifts are reported in [ppm]. The carbon-atom type was determined by DEPT experiments. High-resolution mass spectra were recorded on a Waters Q-TOF premier spectrometer (ESI). Specific optical rotations were measured by using sodium light (D-line, $\lambda = 589$ nm). Chiral HPLC analyses were performed in an Agilent 1100 Series chromatograph equipped with a UV diode-array detector by using chiral stationary columns from Daicel.

Typical procedure for the iodocyclisation of the *N*-Cbz-protected propargylic amines 1: A solution of iodine (0.2 mmol) in acetonitrile (1.0 mL) was added to a solution of the *N*-Cbz-protected propargylic amine **1** (0.1 mmol) in acetonitrile (1.5 mL) at 0 °C. The solution was stirred until the reaction was complete (TLC). The reaction mixture was quenched with a saturated aqueous solution of sodium bisulfate (1.0 mL), extracted with CH_2Cl_2 (3×15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **2**.[32]

(*S*)-5-Iodo-4,6-diphenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (2a): M.p. 65–68 °C; $[\alpha]_D^{20} = +64.7$ ($c = 1.00$ in $CHCl_3$, 87% *ee*); the enantiomeric excess (87%) was determined by chiral HPLC (Chiralcel OD-H), hexane/*i*PrOH 90:10, 1 mL min^{-1}, major enantiomer: $t_r = 13.9$ min, minor enantiomer: $t_r = 23.1$ min; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.65$–7.61 (m, 2H), 7.42–7.39 (m, 8H), 6.49 (br s, 1H), 5.19 ppm (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 149.8$ (C), 148.9 (C), 140.2 (C), 133.6 (C), 130.0 (CH), 129.4 (CH), 129.2 (CH), 129.1 (CH), 128.0 (CH), 127.5 (CH), 71.4 (C), 64.9 ppm (CH); HRMS (ESI): *m/z* calcd for $C_{16}H_{13}NO_2I$: 377.9986 $[M+H]^+$; found: 377.9984.

Typical procedure for the bromocyclisation of the *N*-Cbz-protected propargylic amines 1: Bromine (0.12 mmol) was added to a solution of the *N*-Cbz-protected propargylic amine **1** (0.1 mmol) in acetonitrile (12.5 mL) at 0 °C. The solution was stirred until the reaction was complete (TLC). The reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **4**.

(*S*)-5-Bromo-4,6-diphenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (4a): M.p. 52–54 °C; $[\alpha]_D^{20} = +62.7$ ($c = 1.00$ in $CHCl_3$, 87 % *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.72$–7.69 (m, 2H), 7.43–7.41 (m, 8H), 6.12 (br s, 1H), 5.19 ppm (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 149.3$ (C), 146.2 (C), 139.6 (C), 131.6 (C), 130.1 (CH), 129.3 (CH), 129.2 (CH), 128.9 (CH), 128.1 (CH), 127.4 (CH), 98.3 (C), 62.3 ppm (CH); HRMS (ESI): *m/z* (%) calcd for $C_{16}H_{13}BrNO_2$: 330.0130/332.0109 $[M+H]^+$; found: 330.0110/332.0090 (100/96.5).

General procedure for the chlorocyclisation of the *N*-Cbz-protected propargylic amines 1: A solution of chlorine[33] (0.19 M, 0.12 mmol) in acetonitrile was added to a solution of the *N*-Cbz-protected propargylic amine **1** (0.1 mmol) in acetonitrile (12.5 mL) at −20 °C. The solution was stirred until the reaction was complete (TLC). The reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **5**.

(*S*)-5-Chloro-4,6-diphenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (5a): Viscous oil; $[\alpha]_D^{20} = +45.3$ ($c = 0.83$ in $CHCl_3$, 87 % *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.76$–7.73 (m, 2H), 7.44–7.40 (m, 8H), 5.98 (br s, 1H), 5.12 ppm (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 149.0$ (C), 144.9 (C), 139.2 (C), 130.5 (C), 130.0 (CH), 129.4 (CH), 129.2 (CH), 128.6 (CH), 128.1 (CH), 127.3 (CH), 108.9 (C), 60.4 ppm (CH); HRMS (ESI) *m/z* calcd for $C_{16}H_{13}ClNO_2$: 286.0629 $[M+H]^+$; found: 286.0632.

Computational methods: DFT calculations were carried out by using the B3LYP[34] exchange-correlation functionals, together with the standard 6-311G* basis set.[35] Optimisations were carried out by using the Berny analytical gradient optimisation method.[36] Stationary points were characterised by frequency calculations in order to verify that the TSs have one and only one imaginary frequency. Intrinsic reaction coordinate (IRC)[37] paths were traced in order to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism by using the second-order González–Schlegel integration method.[38] Solvent effects of acetonitrile were taken into account through full optimisations by using the polarisable continuum model (PCM) as developed by Tomasi et al.[39] in the framework of self-consistent reaction field (SCRF).[40] All calculations were carried out with the Gaussian 09 suite of programs.[41]

The global electrophilicity index[42] ω is given by the following simple expression:[42] $\omega = (\mu^2/2\eta)$, in terms of the electronic chemical potential μ[43] and the chemical hardness η.[43] Both quantities may be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L - \varepsilon_H)$, respectively.[43] Recently, we have introduced an empirical (relative) nucleophilicity index[44] *N*, defined as $N = E_{HOMO}(Nu) - E_{HOMO}(TCE)$. The nucleophilicity refers to tetracyanoethylene (TCE), as it presents the lowest HOMO energy in a large series of molecules already investigated in the context of polar cycloadditions. This choice allows us to conveniently handle a nucleophilicity scale of positive values.[44a]

The nucleophilic P_k^- Parr functions[30] were obtained through the analysis of the Mulliken ASD of the radical cation by single-point energy calculations over the optimised neutral geometries by using the unrestricted UB3LYP formalism for radical species. With these values at hand, the local nucleophilicity indices N_k were evaluated by using the following expressions: $N_k = NP_k^-$.[30]

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[23] a) X-ray data for compound **2j**: crystallised from ethyl acetate/*n*-hexane at −20 °C; $C_{17}H_{14}N_1O_3I_1$; $M_r = 407.19$; monoclinic; space group = $P2(1)$; $a = 7.7700(5)$, $b = 6.9880(7)$; $c = 15.5130(12)$ Å.; $\beta = 101.387(4)°$; $V = 825.73(12)$ Å^3; $Z = 2$; $\rho_{calcd} = 1.638$ Mg m^{-3}; $\mu = 1.950$ mm^{-1}; $F(000) = 400$. A colourless crystal of $0.04 \times 0.04 \times 0.08$ mm^3 was used; 3430 [R(int) = 0.0418] independent reflections were collected on a Enraf Nonius CCD diffractomer by using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) operating at 50 kV and 30 mA. The cell parameters were determined and refined by a least-squares fit of all reflections. The first 100 frames were re-collected at the end of the data collection to monitor crystal decay, and no appreciable decay was observed. The structure was solved by direct methods and Fourier synthesis. It was refined by full-matrix least-squares procedures on $F2$ (SHELXL-97[45]). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in calculated positions and refined riding on the respective carbon atoms. Final $R(\omega R)$ values were $R = 0.0304$ and $\omega R = 0.0798$. b) CCDC-941482 (**2j**) and CCDC-941483 (**2l**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[24] X-ray data for compound **2l**: crystallised from ethyl acetate/*n*-hexane at −20 °C; $C_{14}H_{10}N_1O_2S_1I_1$; $M_r = 383.19$; triclinic; space group = $P\bar{1}$; $a = 5.6330(2)$, $b = 10.5035(4)$; $c = 12.6292(6)$ Å.; $\alpha = 112.356(4)$, $\beta = 93.186(4)$, $\gamma = 93.506°$; $V = 687.25(5)$ Å^3; $Z = 2$; $\rho_{calcd} = 1.852$ Mg m^{-3}; $\mu = 2.478$ mm^{-1}; $F(000) = 372$. A colourless crystal of $0.04 \times 0.08 \times 0.10$ mm^3 was used; 4658 [R(int) = 0.0322] independent reflections were collected on a Enraf Nonius CCD diffractomer by using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) operating at 50 kV and 30 mA. The cell parameters were determined and refined by a least-squares fit of all reflections. The first 100 frames were re-collected at the end of the data collection to monitor crystal decay, and no appreciable decay was observed. The structure was solved by direct methods and Fourier synthesis. It was refined by full-matrix least-squares procedures on F^2 (SHELXL-97[45]). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in calculated positions and refined riding on the respective carbon atoms. Final $R(\omega R)$ values were $R = 0.0385$ and $\omega R = 0.0930$.[23b]

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[31] In fact, when *N*-Cbz-1-phenylbut-2-yn-1-amine (**1r**, R^1 = Ph, R^2 = Me) was subjected to the bromocyclisation reaction a 92:8 mixture of the two regioisomeric products (**4r** and **3r**) was obtained (75% yield).

[32] Full spectroscopic and analytical data for compounds, which are not included in the Experimental Section, are described in the Supporting Information.

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Cyclisation Reactions

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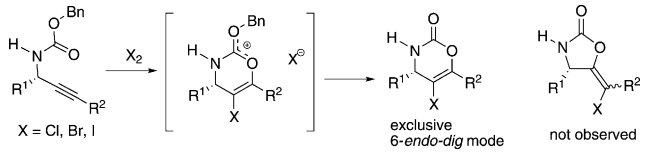
Synthesis of Densely Functionalised 5-Halogen-1,3-oxazin-2-ones by Halogen-Mediated Regioselective Cyclisation of *N*-Cbz-Protected Propargylic Amines: A Combined Experimental and Theoretical Study



Regioselective *O*-halocyclisation: A halocyclisation reaction of chiral non-racemic *N*-carbobenzyloxy (Cbz)-protected propargylic amines by using I_2, Br_2 and Cl_2 as electrophile sources (see scheme, Bn = benzyl) provides a very efficient synthesis of 5-halo-1,3-oxazin-2-ones. The reaction is totally regioselective, taking place through a 6-*endo-dig* process. The experimental results have been rationalised by theoretical studies at the B3LYP/6-311G* level.