Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: R. Mancuso, C. S. Pomelli, F. Malafronte, A. Maner, N. Marino, C. Chiappe and B. Gabriele, *Org. Biomol. Chem.*, 2017, DOI: 10.1039/C7OB00962C.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C7OB00962C

Journal Name

ARTICLE

Divergent syntheses of iodinated isobenzofuranones and isochromenones by iodolactonization of 2-alkynylbenzoic acids in ionic liquids

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

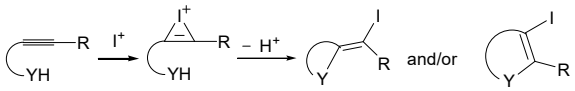
www.rsc.org/

Raffaella Mancuso,[a,*] Christian C. Pomelli,[b] Francesco Malafronte,[a] Asif Maner,[a] Nadia Marino,[c] Cinzia Chiappe,[b] and Bartolo Gabriele[a,*]

The regiochemical outcome of the iodolactonization of 2-alkynylbenzoic acids, carried out at 100 °C in ionic liquids (ILs) as unconventional solvents and with molecular iodine as the iodine source, in the absence of external bases, was found to be strongly dependent on the nature of the IL medium. In particular, while the use of *N*-ethyl-*N*-methylmorpholinium dicyanamide ($Mor_{1,2}N(CN)_2$) promoted the stereoselective formation of (*E*)-3-(iodomethylene)isobenzofuran-1(3*H*)-ones, through an *anti*-5-*exo-dig* cyclization route, the use of 1-ethyl-3-methylimidazolium ethyl sulfate ($EmimEtSO_4$) tended to favor the 6-*endo*-dig cyclization mode, with preferential or selective formation of 4-iodo-1*H*-isochromen-1-ones. In any case, the IL solvent could be easily recycled after extraction of the product from the reaction mixture with diethyl ether. DFT calculations have been carried out to clarify the role exerted by IL nature in favoring either the *anti*-5-*exo-dig* cyclization route or the 6-*endo-dig* mode. In the case of iodocyclization 2-ethynylbenzoic acid, only the 5-*exo-dig* mode was observed in both $EmimEtSO_4$ and $Mor_{1,2}N(CN)_2$ solvents. The structures of two representative products have been confirmed by X-ray diffraction analysis.

Introduction

The iodocyclization of acetylenic substrates bearing a suitably placed nucleophilic group is an excellent method for the direct synthesis of iodine-containing carbo- and heterocycles.[1,2] The importance of this process is further demonstrated by the possibility to functionalize the iodocyclized product through cross-coupling techniques.[3] Iodocyclizations are usually carried out in a classical organic solvent, such as methylene chloride or MeCN, in the presence of a base necessary to trap the acid generated during the process, which occurs through the formation of a iodirenium intermediate followed by *exo* or *endo* intramolecular nucleophilic attack (Scheme 1).[1,2]



(YH = nucleophilic group; I^+ = electrophilic iodine species)

Scheme 1. Iodocyclization of alkynes bearing a suitably placed nucleophilic group, leading to iodine-containing hetero- or carbocycles (both the *exo* and the *endo* possible cyclization modes are shown).[1,2]

In spite of their availability, the iodolactonization of 2-alkynylbenzoic acids **1** has been scantily studied in the literature. The formation of 3-(2-hydroxy-1-iodo-2-methylpropylidene)isobenzofuran-1(3*H*)-one (*E*/*Z* mixture) was briefly mentioned to occur by treatment of 2-(3-hydroxy-3-methylbut-1-ynyl)benzoic acid with ICl.[4] More recently, the reaction between 2-(2-phenylethynyl)benzoic acid or 4-methoxy-2-[2-(4-methoxyphenyl)ethynyl]benzoic acid with I_2 under basic conditions was reported to afford a mixture of the corresponding (*E*)-3-(iodomethylene)isobenzofuran-1(3*H*)-ones (from *anti* 5-*exo* cyclization) and 4-iodo-1*H*-isochromen-1-ones (from 6-*endo* cyclization), the latter being formed preferentially.[5]

In this work, we report a general and regiodivergent method for the iodolactonization of 2-alkynylbenzoic acids, carried out in ionic liquids (ILs) as unconventional and recyclable solvents,[6,7] using I_2 as the iodine source and in the absence of added bases. Density functional calculations have been carried out in order to elucidate the specific role of the IL ions on the reaction course, and, in particular, on the regiochemical output of the process.

Results and discussion

Iodolactonization of 2-alkynylbenzoic acids in ionic liquids

Our initial experiments were carried out using 2-(3,3-dimethylbut-1-ynyl)benzoic acid **1a**. The reaction of **1a** with I_2 (1.1 equiv), carried out at 100 °C for 3 h in 3-butyl-1-methylimidazolium tetrafluoroborate ($BmimBF_4$) as the solvent,

[a] Laboratory of Industrial and Synthetic Organic Chemistry (LISOC), Department of Chemistry and Chemical Technologies, University of Calabria, Via Pietro Bucci 12/C, 87036 Arcavacata di Rende (CS), Italy.
[b] Department of Pharmacy, University of Pisa, Via Bonanno 33, 56126 Pisa, Italy.
[c] Department of Chemical Sciences, University of Padova, Via Marzolo 1, 35131 Padova, Italy.

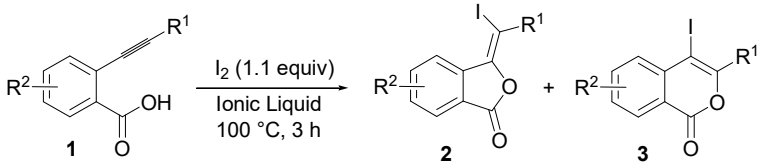
† Electronic Supplementary Information (ESI) available: Preparation of substrates and characterization data, X-ray data for compounds **2a** and **3d**, table of absolute energies (Hartrees) of the optimized structures, geometries of the molecular structures studied in the paper, and copies of ^1H NMR and ^{13}C NMR spectra for all products. See DOI: 10.1039/x0xx00000x

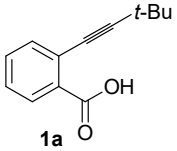
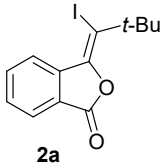
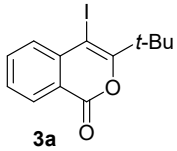
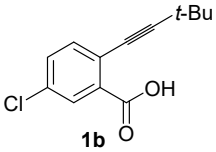
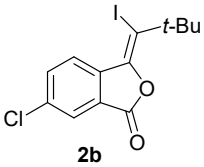
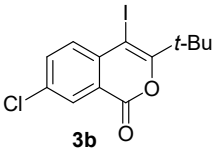
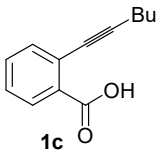
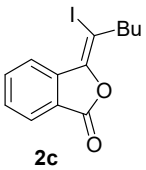
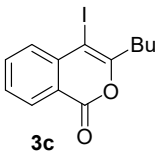
View Article Online
DOI: 10.1039/C7OB00962C

Journal Name

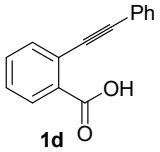
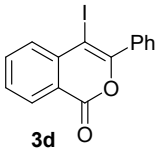
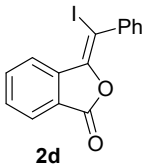
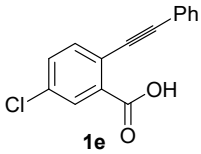
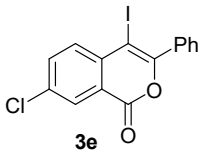
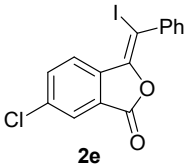
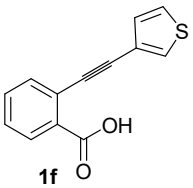
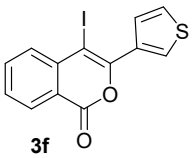
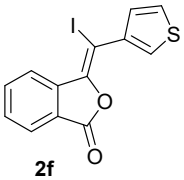
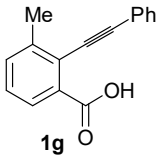
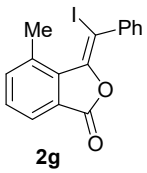
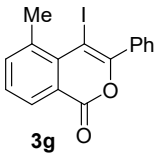
ARTICLE

Table 1. Divergent syntheses of (*E*)-3-(iodoalkylidene)isobenzofuran-1(3*H*)-ones **2** and 4-iodo-1*H*-isochromen-1-ones **3** by base-free iodolactonization of 2-alkynylbenzoic Acids **1** in $Mor_{1,2}N(CN)_2$ and $EmimEtSO_4$, respectively.[a]

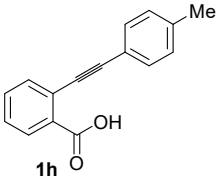
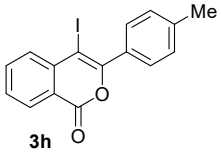
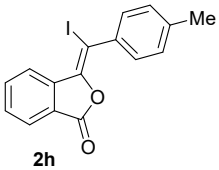
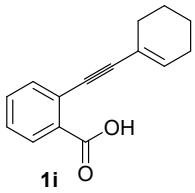
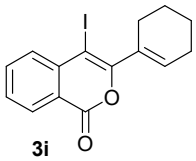
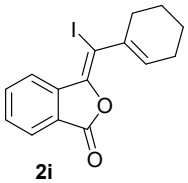
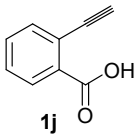
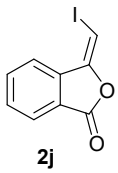


Entry	1	IL	2	3	2 / 3 molar ratio[b]	Total Yield[c] (%)
1	 **1a**	$BmimBF_4$	 **2a**	 **3a**	5.70	49[d]
2	**1a**	BmimOAc				NR[e]
3	**1a**	$EmimEtSO_4$	**2a**	**3a**	0.71	95
4	**1a**	$BmimN(CN)_2$	**2a**		**2a** only	77
5	**1a**	$Mor_{1,2}N(CN)_2$	**2a**		**2a** only	85 (84-83-85-83-82-83)
6	 **1b**	$EmimEtSO_4$	 **2b**	 **3b**	0.45	83
7	**1b**	$Mor_{1,2}N(CN)_2$	**2b**		**2b** only	85 (84-85-83-85-83)
8	 **1c**	$EmimEtSO_4$	 **2c**	 **3c**	0.57	72
9	**1c**	$Mor_{1,2}N(CN)_2$	**2c**	**3c**	2.13	74

View Article Online
DOI: 10.1039/C7OB00962C

10	 **1d**	$EmimEtSO_4$		 **3d**	**3d** only	80 (79-78-80-80-79-79)
11	**1d**	$Mor_{1,2}N(CN)_2$	 **2d**		**2d** only	73 (72-73-72-72-71-72)
12	 **1e**	$EmimEtSO_4$		 **3e**	**3e** only	88 (87-88-86-87-88)
13	**1e**	$Mor_{1,2}N(CN)_2$	 **2e**		**2e** only	72 (72-71-72-72-71)
14	 **1f**	$EmimEtSO_4$		 **3f**	**3f** only	91 (89-90-91-89-90)
15	**1f**	$Mor_{1,2}N(CN)_2$	 **2f**		**2f** only	75 (72-74-74-75-74)
16	 **1g**	$EmimEtSO_4$	 **2g**	 **3g**	0.78	87 31% (**2g**) 56%(**3g**)
17	**1g**	$Mor_{1,2}N(CN)_2$	**2g**		**2g** only	75 (73-74-75-73-75)

View Article Online
DOI: 10.1039/C7OB00962C

18	 **1h**	$EmimEtSO_4$		 **3h**	**3h** only	94 (90-93-90-91-90-90)
19	**1h**	$Mor_{1,2}N(CN)_2$	 **2h**	**3h**	2.32	73
20	 **1i**	$EmimEtSO_4$		 **3i**	**3i** only	80 (77-79-80-78-78)
21	**1i**	$Mor_{1,2}N(CN)_2$	 **2i**	**3i**	1.63	71 60% (**2i**) 11% (**3i**)
22	 **1j**	$EmimEtSO_4$	 **2j**		**2j** only	83 (82-82-81-83-82)
23	**1j**	$Mor_{1,2}N(CN)_2$	**2j**		**2j** only	76 (75-76-74-76-75)

[a] Unless otherwise noted, all reactions were carried out at 100 °C under nitrogen for 3 h with a substrate concentration of 0.2 mmol of **1** per mL of ionic liquid, in the presence of 1.1 equiv of I_2. [b] Determined by GLC [c] Isolated yield based on starting **1**. In parentheses are given the yields obtained in the recycling experiments (see text for details). [d] Substrate conversion was 67% (determined by GLC). [e] Partial substrate degradation occurred (substrate conversion was 38%, by GLC).

led to the formation of a mixture of (*E*)-3-(1-iodo-2,2-dimethylpropylidene)isobenzofuran-1(3*H*)-one **2a** and 3-*tert*-butyl-4-iodo-1*H*-isochromen-1-one **3a** (5.7:1 molar ratio) in 49% total isolated yield at 67% substrate conversion (Table 1, entry 1). With the aim of improving this initial result both in terms of yield and regioselectivity, we then changed the nature of the IL medium; the results obtained are shown in Table 1, entries 2-5. Only partial substrate degradation was obtained using 3-butyl-1-methylimidazolium acetate (BmimOAc, Table 1, entry 2). On the other hand, an inversion of the regioselectivity of the process in favor of **3a** (**3a**/**2a** molar ratio = 1.4, total yield = 95%) was observed in 1-ethyl-3-methylimidazolium ethyl sulfate ($EmimEtSO_4$, Table 1, entry 3). Very interestingly, the process turned out to be completely regioselective toward the formation of the 5-membered product **2a** (whose structure was confirmed by X-ray diffraction analysis, see the Supporting Information for details) when using as solvent 3-butyl-1-methylimidazolium dicyanamide ($BmimN(CN)_2$; 77% yield, Table 1, entry 4) or *N*-ethyl-*N*-methylmorpholinium dicyanamide ($Mor_{1,2}N(CN)_2$; 85% yield, Table 1, entry 5). Similar results were obtained with 5-chloro-2-(3,3-dimethylbut-1-ynyl)benzoic acid **1b**: in $EmimEtSO_4$, the reaction was more selective toward the formation of 3-*tert*-butyl-7-chloro-4-iodo-1*H*-isochromen-1-one **3b** (**3b**/**2b** molar ratio = 2.2, total yield = 83%; Table 1, entry 6), while only (*E*)-6-chloro-3-(1-iodo-2,2-dimethylpropylidene)isobenzofuran-1(3*H*)-one **2b** was obtained in $Mor_{1,2}N(CN)_2$ (85 % yield; Table 1, entry 7).

View Article Online
DOI: 10.1039/C7OB00962C

Encouraged by these initial results, we then studied the reactivity of other differently substituted substrates in the most performing ILs found for the iodocyclization of **1a** and **1b** ($EmimEtSO_4$ and $Mor_{1,2}N(CN)_2$). The reactions of 2-(hex-1-ynyl)benzoic acid **1c**, bearing a linear rather than a branched alkyl group on the triple bond, turned out to be less selective when compared to the analogous reactions of **1a** and **1b**, and mixtures of the corresponding isobenzofuranone **2c** and isochromenone **3c** were consistently obtained. However, in agreement with the trend already observed in the case of **1a** and **1b**, the 6-membered product **3c** turned out to be the major isomer in $EmimEtSO_4$ (Table 1, entry 8), while the 5-membered product **2c** predominated in $Mor_{1,2}N(CN)_2$ (Table 1, entry 9).

On the other hand, the divergent selective formation of either the isochromenone or the isobenzofuranone product in the two ILs was observed with 2-(2-phenylethynyl)benzoic acid **1d** (Table 1, entries 10 and 11) and 5-chloro-2-(2-phenylethynyl)benzoic acid **1e** (Table 1, entries 12 and 13), bearing a phenyl group on the triple bond, as well as with 2-[2-(thiophen-3-yl)ethynyl]benzoic acid **1f**, bearing a 3-thienyl substituent on the triple bond (Table 1, entries 14 and 15). The structure of 4-iodo-3-phenyl-1*H*-isochromen-1-one **3d** was confirmed by X-ray diffraction analysis (see the Supporting Information for details). With an *o*-methyl-substituted substrate, such as **1g**, a selective reaction toward the formation of the corresponding isobenzofuranone **2g** was obtained in $Mor_{1,2}N(CN)_2$ (Table 1, entry 17), while isochromenones **3h** and **3i** were selectively formed in $EmimEtSO_4$ from 2-(2-*p*-tolylethynyl)benzoic acid **1h** and 2-(2-cyclohexenylethynyl)benzoic acid **1i**, respectively (Table 1, entries 18 and 20, respectively). Finally, in the case of 2-ethynylbenzoic acid **1j**, bearing a terminal triple bond, only the 5-membered product, (*E*)-3-(iodomethylene)isobenzofuran-1(3*H*)-one **2j**, was produced in both $EmimEtSO_4$ and $Mor_{1,2}N(CN)_2$ media (Table 1, entries 22 and 23, respectively).

For the most selective reactions, we also assessed the possibility to recycle the IL medium, by extracting the product from the reaction mixture with diethyl ether and adding fresh substrate and iodine to the ionic liquid residue. As can be seen from the results reported in Table 1, entries 5, 7, 10-15, 17, 18, 20, 22, and 23, the solvent could be successfully recycled for several additional runs in all cases.

DFT calculations

In order to rationalize the effect exerted by the nature of the IL on the regioselectivity of the process, we have performed a DFT study. The products of the reaction presented in this paper depend strongly on the ionic liquid used as solvent. Thus, initially we have defined the model system to study that contains one or more explicit ions in order to take into account of the above mentioned specific effects. The scheme that we have adopted is the supermolecular one. This scheme has been proved to be very effective in the description of organic reactivity in ionic liquids[8] and we have assumed successfully this scheme in a previous paper on a similar reaction[6a]. In this case, the model system consisted on the iodonium complex of the substrate complemented by two ionic liquid anions: one near the iodonium center acting as counterion and the other, near the proton of a thiolic moiety, acting as proton acceptor. In the present investigation, we can consider a very similar model system where the second anion is localized near the carboxylic proton. However, since this study involves two different ionic liquids that differ both in anion and in cation (while in the previous paper the systems considered share the cation) we decided to include also a cation, localized near the second anion. Thus the resulting system does not present a neat charge. The model system is shown in Figure 1.

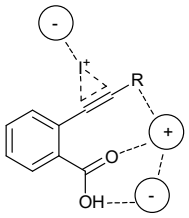


Figure 1. Model system as defined in the text. The ions are represented generically by charged spheres. The spatial arrangement leads the cation present in the model system to interact simultaneously with an anion, the carboxylic group and the sidechain R.

The two anions involved in the above defined model system play a role on two different subreactions, that take place synchronously in different portions of the space. The first subreaction is the iodirenium opening. The nature of the anion should be able to modulate the reactivity and the symmetry/asymmetry of the iodirenium ring. Since there is no sterical hindering on this side of the encounter complex and the subsystem iodirenium-anion is uncharged, there is no necessity to include a cation here. In the second subreaction the anion, acting as a proton acceptor triggers the polarity inversion of the carboxylic group. The cation here has been included to neutralize the anion charge and furthermore it gives a more realistic picture of eventually sterical hindering phenomena that probably depend also on the nature of the R group on the triple bond. We will analyze the effect of the IL ions on these two different subreaction.

The supermolecular system, shown in Figure 1, has been used as starting point of the reaction. It is an encounter complex (ec): a system where all actors are in place, practically immediately before the reaction takes place. This kind of structures is fully reasonable in an organized solvent matrix like ionic liquids. Furthermore, encounter complexes have already been used for similar reactions.[11] The same model system after the reaction will be called product complex (pc). For every choice of anion/cation and sidechain R we will have two different product complexes: the one where a five-membered ring has been closed (pc5) and the other one where a six membered ring is obtained (pc6). Therefore, the two complexes correspond to the two different possible reaction products. While the encounter complex is shared there are, obviously, two different product complexes. Any ec will be connected to pc5 and pc6 by two reaction paths. The geometry and energetic profile of these two paths will rationalize and elucidate the

View Article Online
DOI: 10.1039/C7OB00962C

Journal Name

ARTICLE

Table 2. Energetic and geometric quantities obtained by the DFT calculations. Geometrical parameters are related to the encounter complexes (ec). For definition of ΔG_f, ΔG_b and ΔG_r, see Figure 2. For definition of θ, see Figure 3.

Solvent	R	path	ΔG_f	ΔG_b	ΔG_r	$r_{C5\text{-}I}$	$r_{C6\text{-}I}$	$r_{A\text{-}I}$	θ
			(KJ/mol)				(Å)		(°)
$Mor_{1,2}N(CN)_2$	Ph	5	23.98	88.74	-64.76	3.02	2.83	2.19	26.8
		6	37.38	118.62	-87.01				
	H	5	22.34	87.84	-110.12	3.09	2.82	2.19	30.2
		6	46.61	106.43	-148.63				
	C_4H_3S	5	26.32	100.26	-73.93	2.79	3.16	2.20	25.8
		6	40.34	121.1	-80.76				
	$C(CH_3)_3$	5	36.55	81.10	-44.55	2.97	2.86	2.21	38.9
		6	54.06	116.55	-62.49				
$EmimEtSO_4$	Ph	5	-	-	-72.63	2.89	2.65	2.19	6.3
		6	-	-	-116.79				
	H	5	-	-	-99.06	2.98	2.47	2.21	9.3
		6	-	-	-109.98				
	C_4H_3S	5	-	-	-63.70	2.96	2.46	2.25	9.8
		6	-	-	-72.08				
	$C(CH_3)_3$	5	18.19	49.70	-31.51	2.78	2.62	2.20	23.5
		6	28.67	73.03	-44.43				

experimental evidences presented in this paper. A Nudged Elastic Band (NEB) method has been used. The details are reported in the experimental part. We have studied the two possible paths for the two ionic liquids considered in this paper with selected sidechains: two aromatic sidechains (phenyl and 3-thienyl), hydrogen and *tert*-butyl. These choices will permit us to evaluate the effects of conjugation and of sterical hindering on this reaction along with the solvent specific effect.

Some selected energetic and geometric quantities are reported in Table 2. We found two very different behaviors. In the cases in which the solvent is $Mor_{1,2}N(CN)_2$, we have a reaction with barrier (Figure 2a): between ec and pc5/pc6 there is an energetic barrier summoned by a transition state structure. For all the four investigated sidechains, the barrier that leads to pc6 is higher than the one leading to pc5, while the product stability is inverted: the six-membered isomers are thermodynamically more stable than the five-membered one.

View Article Online
DOI: 10.1039/C7OB00962C

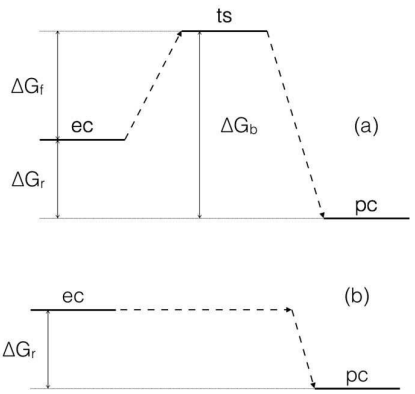


Figure 2. The reaction paths investigated show two different behaviors: (a) reaction with barrier. (b) barrierless reaction. The energetic quantities here defined are reported in Table 2.

Since in these cases the barrier height determines the reaction path that is effectively followed, there is a full concordance with experimental evidences. When the solvent is $EmimEtSO_4$ the behavior is very different. Except the case with R = *tert*-butyl, having a behavior similar to the cases in which the solvent is $Mor_{1,2}N(CN)_2$, the reaction paths are barrierless (Figure 2b) or present very small barriers easily overwhelmed by zero-point energy. From the thermodynamical point of view, also in this case, the six-membered isomers are more thermodynamically stable than the five-membered one.

An exhaustive analysis of the various geometrical and electronic structures and related parameters of the encounter complexes leads to the following results:

1. The anion that acts as counteranion of the iodirenium species strongly affects the nature of this intermediate. When the anion is $[N(CN)_2]^-$ the two distances between the iodine atoms and the two sp carbon atoms (reported in Table 2) are larger, the complex is more symmetric and the trigonalization of the two sp carbon atoms is less pronounced than when the anion is $[EtSO_4]^-$, with the sole remarkableexception is represented by $R=C(CH_3)_3$, where the steric hindering of *tert*-butyl force the iodine atom far from the triple bond. Speaking in reaction terms: the complex formation is more advanced when the sulfate based anion is involved (in absence of sterical hindering). A more activated triple bond corresponds to a lower or even to a no barrier and a lower selectivity.
2. On the other side of the activated triple bond there is a relevant sterical effect exerted by the IL cation, which interacts both with the anion and with the carboxyl/carboxylate group. Furthermore, the steric interactions with the R sidechain are also significant.

In the case of $EmimEtSO_4$ with $R=C_6H_5$, H, C_4H_3S, the R group is nearly collinear with the two sp carbon atoms. The torsion between the two groups is lower than 10° (the structure with R=H is reported in Figure 3, along with the definition of the torsion angle. Related values are reported in Table 2). In this condition, the positions and orientations of all atoms participating to the reaction are favorable to a six ring closure that corresponds also to the energetically more stable product.

The situation is different for $Mor_{1,2}N(CN)_2$: in fact, in the presence of this IL there is a relevant torsion between the two groups. The torsion angle values for this set of reactions are between 23° and 38°. The reason of this torsion is the steric hindering: morpholinium cation is bigger than imidazolium (this latter presents a smaller ring and is nearly flat). Furthermore, the presence of three terminal oxygen atoms on the ethylsulfate anion allows a more flexible organization of the cation around the anion than in the case of $[N(CN)_2]^-$ (for a more detailed description, see Figure 3 caption). In the presence of the *tert*-butyl group, even the smaller and more tunable ion pair ($Emim^+$ $EtSO_4^-$) is not able to compensate the sterical hindering of the sidechain that is forced between the cation and the iodine atom. The reaction proceeds with a moderate selectivity and, in agreement with the experimental data, the barrier values are very low. This is not unexpected: the supermolecular systems that we compare are very similar. Differences in bonds and geometry are small and limited to few atoms. Within this degree of similarity, there is no possibility of computational artifacts. On the other hand, in $Mor_{12}N(CN)_2$ the reduced reactivity caused by the less pronounced trigonalization of the triple bond (less iodirenium character) and by the steric hindering lead to a higher selectivity.

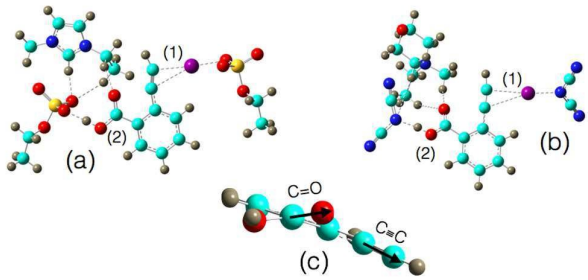


Figure 3. The two encounter complexes with R=H. We decided to report these structures since the reduced dimension of the sidechain leads to clearer pictures. (a) $EmimEtSO_4$ case. (b) $Mor_{12}N(CN)_2$ case. (c) The torsion angle is defined by the four atoms reported or, alternatively by the two bond axes. (1). Different symmetry of the iodirenium group and the different degree of trigonalization of the two sp carbon atoms in the two cases. (2) In the left (a) case the carboxyl group is coplanar with iodirenium while in the right (b) is bent.

Experimental

General methods

Solvent and chemicals were reagent grade and were used without further purification. All reactions were analyzed by TLC on silica gel 60 F254 and by GLC (Shimadzu GC-2010) using capillary columns with polymethylsilicone + 5% phenylsilicone (HP-5) as the stationary phase. Column chromatography was

View Article Online
DOI: 10.1039/C7OB00962C

performed on silica gel 60 (Merck, 70-230 mesh). Evaporation refers to the removal of solvent under reduced pressure. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ with Me_4Si as internal standard with a Bruker DPX Avance 300 spectrometer, operating at 300 MHz and 75 MHz, respectively. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. IR spectra were taken with a JASCO FTIR 4200 spectrometer. Mass spectra were obtained using a GC-MS apparatus at 70 eV ionization voltage (Shimadzu QP-2010) and by electrospray ionization mass spectrometry (ESI-MS). ESI-MS spectra were obtained on an Agilent 6540 UHD accurate-mass Q-TOF spectrometer equipped with a Dual AJS ESI source working in positive mode. The experimental conditions were as follows: N_2 was employed as desolvation gas at 300°C and a flow rate of 8 L/min. The nebulizer was set to 45psig. The Sheat gas temperature was set at 400°C and a flow of 12 L/min. A potential of 3.5 kV was used on the capillary for positive ion mode. The fragmentor was set to 175 V. MS spectra were recorded in the 150–1000 m/z range. Microanalyses were carried out in our analytical laboratory with a Thermo-Fischer Elemental Analyzer Flash 2000.

Computational details

All the calculation has been performed using the Terachem Package, version 1.5k[12] on a Linux workstation equipped with four NVIDA GTX Titan GPUs. The level of calculation was B3LYP/6-311++G(d,p). Nudged elastic band (NEB) algorithm with six sample points and a climbing image has been used to investigate the reaction path between optimized encounter and product complexes[13]. Default optimization and convergence parameters has been used. Grimme D3 dispersion correction[14] has been used. Optimized geometries and absolute energies are reported in the Supporting Information.

Preparation of ionic liquids

3-Butyl-1-methylimidazolium acetate (BmimOAc) was prepared by dropwise addition of a stoichiometric amount of acetic acid to a methanolic solution of 3-buthyl-1-methylimidazolium methylcarbonate (Proionic). Ionic liquids 3-butyl-1-methylimidazolium tetrafluoroborate ($BmimBF_4$), 1-ethyl-3-methylimidazolium ethyl sulfate ($EmimEtSO_4$), 3-butyl-1-methylimidazolium dicyanamide ($BmimN(CN)_2$), and *N*-ethyl-*N*-methylmorpholinium dicyanamide ($Mor_{1,2}N(CN)_2$) were prepared according to literature procedures: structure and purity of all ILs were confirmed by ^{1}H and ^{13}C NMR spectroscopy.[15]

General procedure for the iodolactonization of 2-alkynylbenzoic acids in ionic liquids (Table 1). In a Schlenk flask containing the ionic liquid was added, under nitrogen, the pure substrate (for **1a**, **1b**, and **1d-j**) or a solution of the substrate in Et_2O (2 mL; for **1c**) (0.40 mmol; **1a**, 81.0 mg; **1b**, 95.0 mg; **1c**, 81.0 mg; **1d**, 89.0 mg; **1e**, 103.0 mg; **1f**, 91.0 mg; **1g**, 94.3 mg; **1h**, 94.3 mg; **1i**, 90.5 mg; **1j**, 59.0 mg). In the case of **1c**, the excess Et_2O was then eliminated under vacuum for 10 min. To the solution of the substrate in the IL, was added, under nitrogen, I_2 (112.0 mg, 0.44 mmol), and the resulting mixture was heated with stirring at 100 °C (oil bath) for 3 h. After cooling, the product was extracted with diethyl ether (2 mL, followed by 6 × 5 mL), and the IL residue, after elimination of the traces of Et_2O under vacuum, was used as such for the next recycle (see below). The collected ethereal phases were concentrated. After evaporation of the solvent, products were purified by column chromatography on silica gel using 95:5 hexane–AcOEt as the eluent.

Recycling procedure. To the residue obtained as described above, was added the fresh substrate **1** (0.40 mmol) and I_2 (111.7 mg, 0.44 mmol) in Et_2O (3 mL), and then the same procedure described above was followed.

*(E)-3-(1-Iodo-2,2-dimethylpropylidene)-3H-isobenzofuran-1-one (**2a**).* Yield: 112 mg, starting from 81 mg of **1a** (85%; Table 1, entry 5). White solid, mp = 109-110 °C. IR (KBr): ν = 1768 (s), 1469 (m), 1251 (w), 1224 (w), 1105 (m), 1003 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.1 (d, J = 8.2, 1 H), 7.92 (d, J = 7.7, 1 H), 7.73 (td, J = 7.4, 1.2, 1 H), 7.58 (td, J = 7.4, 0.4, 1 H), 1.51 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 143.8, 140.2, 133.8, 130.1, 126.3, 126.0, 125.7, 102.5, 41.0, 32.6; GC-MS: *m/z* =328 (M^+) (39), 313 (7), 272 (54), 201 (100), 186 (98), 171 (8), 159 (25), 145 (16), 129 (22), 115 (27); anal. calcd for $C_{13}H_3IO_2$ (328.15): C, 47.58; H, 3.99; I, 38.67; found C, 47.55; H, 4.01; I, 38.69.

*Mixture of (E)-3-(1-Iodo-2,2-dimethylpropylidene)-3H-isobenzofuran-1-one (**2a**) + 3-tert-Butyl-4-iodo-1-isochromen-1-one (**3a**)* Total yield: 125 mg, starting from 81 mg of **1a** (95%; **3a** / **2a** = 1.41, determined by GLC; Table 1, entry 3). White solid. IR (KBr): ν = 1771 (s), 1733 (s), 1471 (w), 1371 (w), 1251 (w), 1106 (m), 1002 (m), 962 (w), 762 (s), 688 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.01 (d, J = 8.2, 1 H, **2a**), 8.21 (d, J = 7.6, 1 H, **3a**), 8.02-7.87 [m, 1 H (**2a**) + 1 H (**3a**)], 7.82-7.68 [m, 1 H (**2a**) + 1 H (**3a**)], 7.63-7.46 [m, 1 H (**2a**) + 1 H (**3a**)], 1.62 (s, 9 H, **3a**), 1.50 (s, 9 H, **2a**); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0 (**2a**), 162.4 (**3a**), 161.1 (**3a**), 143.8 (**2a**), 140.2 (**2a**), 139.5 (**3a**), 135.2 (**3a**), 133.8 (**2a**), 131.3 (**3a**), 130.1 (**2a**), 129.4 (**3a**), 128.7 (**3a**), 126.3 (**2a**), 126.0 (**2a**), 125.7 (**2a**), 120.5 (**3a**), 102.5 (**2a**), 73.3 (**3a**), 41.0 (**2a**), 39.4 (**3a**), 32.6 (**2a**), 29.5 (**3a**); GC-MS: **2a**: *m/z* = 328 (M^+) (27), 272 (49), 201 (100), 186 (94), 159 (27), 145 (18), 129 (24), 115 (32); **3a**: *m/z* = 328 (M^+) (51), 243 (10), 201 (11), 186 (18), 159 (100), 158 (41), 129 (10), 115 (11); anal. calcd for $C_{13}H_3IO_2$ (328.15): C, 47.58; H, 3.99; I, 38.67; found C, 47.57; H, 4.00; I, 38.65.

*(E)-6-Chloro-3-(1-iodo-2,2-dimethylpropylidene)-3H-isobenzofuran-1-one (**2b**).* Yield: 124 mg, starting from 95 mg of **1b** (85%; Table 1, entry 7). White solid, mp = 66-68 °C. IR (KBr): ν = 1772 (s), 1598 (w), 1460 (m), 1253 (m), 1223 (m), 1119 (m), 1013 (m), 891 (w), 840 (w), 680 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.96 (d, J = 8.6, 1 H), 7.88 (dd, J = 2.1, 0.6, 1 H), 7.68 (dd, J = 8.6, 2.1, 1 H), 1.50 (s, 9 H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9, 142.8, 138.0, 136.3, 134.0, 127.3, 126.8, 125.3, 103.8, 40.8, 32.4; GC-MS: *m/z* = 364 [(M+2)$^+$] (19), 362 (M^+) (56), 347 (10), 306 (29), 235 (100), 220 (98), 193 (23), 149 (12), 128 (21), 110 (22); anal. calcd for $C_{13}H_{12}ClIO_2$ (362.59): C, 43.06; H, 3.34; Cl, 9.78; I, 35.00; found C, 43.09; H, 3.31; Cl, 9.79; I, 35.02.

*Mixture of (E)-6-Chloro-3-(1-iodo-2,2-dimethylpropylidene)-3H-isobenzofuran-1-one (**2b**) + 3-tert-Butyl-7-chloro-4-iodo-1-*

View Article Online
DOI: 10.1039/C7OB00962C

*isochromen-1-one (**3b**).* Total yield: 120 mg, starting from 95 mg of **1b** (83%; **3b** / **2b** = 2.22, determined by GLC; Table 1, entry 6). White solid. IR (KBr): ν = 1780 (s), 1721, 1462 (m), 1322 (w), 1101 (m), 1009 (m), 965 (m), 828 (m), 776 (w), 681 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.96 (d, J = 8.6, 1 H, **2b**), 8.20 (d, J = 2.4, 1 H, **3b**), 7.92 (distorted d, J = 8.8, 1 H, **3b**), 7.87 (d, J = 2.1, 1 H, **2b**), 7.68 (dd, J = 8.8, 2.4, 1 H, **3b**), 7.61 (dd, J = 8.6, 2.1, 1 H, **2b**), 1.61 (s, 9 H, **3b**), 1.49 (s, 9 H, **2b**); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9 (**2b**), 162.2 (**3b**), 160.4 (**3b**), 142.8 (**2b**), 138.0 (**2b**), 137.6 (**3b**), 136.3 (**2b**), 135.4 (**3b**), 134.8 (**3b**), 134.0 (**2b**), 132.9 (**3b**), 128.4 (**3b**), 127.3 (**2b**), 126.8 (**2b**), 124.9 (**2b**), 120.8 (**3b**), 103.8 (**2b**), 72.6 (**3b**), 40.8 (**2b**), 39.2 (**3b**), 32.4 (**2b**), 29.0 (**3b**); GC-MS: **2b**: *m/z* = 364 [$(M+2)^+$] (19), 362 (M^+) (57), 347 (10), 306 (28), 235 (100), 220 (99), 193 (23), 149 (12), 128 (21), 110 (22); **3b**: *m/z* = 364 [$(M+2)^+$] (35), 362 (M^+) (100), 347 (15), 319 (4), 277 (9), 249 (10), 235 (22), 220 (29), 193 (95), 157 (13), 122 (29); anal. calcd for $C_{13}H_{12}ClIO_2$ (362.59): C, 43.06; H, 3.34; Cl, 9.78; I, 35.00; found C, 43.05; H, 3.33; Cl, 9.80; I, 35.04.

*Mixture of (E)-3-(1-Iodopentylidene)-3H-isobenzofuran-1-one (**2c**) + 3-Butyl-4-iodo-1-isochromen-1-one (**3c**).* Total yield: 97 mg, starting from 81 mg of **1c** (74%; **2c** / **3c** = 2.13, determined by GLC; Table 1, entry 9). Yellow oil. IR (film): ν = 2957 (m), 2929 (m), 2871 (m), 1781 (s), 1738 (s), 1611 (m), 1472 (m), 1316 (w), 1053 (m), 1031 (m), 996 (m), 763 (m), 687 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.86 (dd, J = 8.1, 0.8, 1 H, **2c**), 8.25-8.18 (m, 1 H, **3c**), 7.96-7.89 (m, 1 H, **2c**), 7.81-7.70 (m, 1 H, **2c** + 2 H, **3c**), 7.58 (td, J = 8.1, 0.8, 1 H, **2c**), 7.54-7.46 (m, 1 H, **3c**), 3.10 (t, J = 7.4, 2 H, **2c**), 2.93 (t, J = 7.8, 2 H, **3c**), 1.80-1.69 (m, 2 H, **3c**), 1.69-1.55 (m, 2 H, **2c**), 1.47-1.33 [m, 2 H (**2c**) + 2 H (**3c**)], 1.01-0.89 [m, 3 H (**2c**) + 3 H (**3c**)]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6 (**2c**), 161.9 (**3c**), 158.1 (**3c**), 144.1 (**2c**), 138.3 (**2c**), 138.0 (**2c**), 135.5 (**3c**), 134.1 (**3c**), 130.4 (**3c**), 130.2 (**2c**), 129.6 (**3c**), 128.5 (**3c**), 126.3 (**2c**), 125.7 (**2c**), 124.1 (**2c**), 119.9 (**3c**), 88.2 (**2c**), 76.1 (**3c**), 39.7 (**2c**), 37.1 (**3c**), 31.4 (**2c**), 29.3 (**3c**), 22.2 (**3c**), 21.7 (**2c**), 13.9 (**2c**), 13.8 (**3c**); GC-MS: **2c**: *m/z* =328 (M^+) (22), 285 (19), 272 (21), 257 (10), 201 (11), 183 (6), 159 (100), 147 (14), 130 (24), 115 (8), 102 (16), 76 (14); **3c**: *m/z* = 328 (M^+) (52), 285 (9), 272 (7), 257 (10), 201 (5), 183 (7), 159 (100), 147 (8), 131 (45), 115 (9), 102 (14); anal. calcd for $C_{13}H_3IO_2$ (328.15): C, 47.58; H, 3.99; I, 38.67; found C,47.60; H, 3.98; I, 38.65. The spectroscopic data for **3c** agreed with those reported.[16]

*(E)-3-(Iodophenylmethylene)-3H-isobenzofuran-1-one (**2d**).* Yield: 102 mg, starting from 89 mg of **1d** (73%; Table 1, entry 11). White solid, mp = 164-165 °C. IR (KBr): ν = 1783 (s), 1640 (m), 1468 (m), 1253 (m), 1095 (m), 1002 (s), 768 (m), 686 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.92 (d, J = 8.1, 1 H), 7.95 (d, J = 7.7, 1 H), 7.86-7.75 (m, 1 H), 7.68-7.51 (m, 3 H), 7.44-7.28 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 140.5, 138.8, 134.1, 131.6, 130.8, 130.2, 129.0, 128.2, 126.6, 125.9, 125.1, 79.9; GC-MS: *m/z* = 348 (M^+) (18), 221 (100), 193 (30), 165 (62), 139 (7), 110 (11); anal. calcd for $C_{15}H_9IO_2$ (348.14): C, 51.57; H, 2.61; I, 36.45; found C, 51.55; H, 2.64; I, 36.46.

*4-Iodo-3-phenylisochromen-1-one (**3d**).* Yield: 112 mg, starting from 89 mg of **1d** (80%; Table 1, entry 10). White solid, mp = 135-136 °C, lit.,[32] 136 °C. IR (KBr): ν = 1739 (s), 1624 (m), 1473 (m), 1444 (w), 1306 (w), 1231 (m), 1072 (s), 1054 (m), 1027 (m), 1017 (m), 949 (m), 768 (s), 748 (m), 700 (s), 687 (s), 641 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.29 (dd, J = 7.8, 0.2, 1 H), 7.88 (distorted dd, J = 8.1, 0.2, 1 H), 7.81 (distorted td, J = 7.7, 1.4, 1 H), 7.73-7.66 (m, 2 H), 7.61-7.53 (m, 1 H), 7.51-7.44 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5, 154.8, 138.1, 135.7, 135.2, 131.5, 130.2, 130.0, 129.7, 129.2, 128.1, 120.2, 76.5; GC-MS: *m/z* =348 (M^+) (100), 320 (41), 221 (10), 193 (44), 165 (46), 139 (6), 105 (49), 77 (37); anal. calcd for $C_{15}H_9IO_2$ (348.14): C, 51.57; H, 2.61; I, 36.45; found C, 51.56; H, 2.59; I, 36.48. The spectroscopic data agreed with those reported.[16]

*(E)-6-Chloro-3-(iodophenylmethylene)-3H-isobenzofuran-1-one (**2e**).* Yield: 110 mg, starting from 103 mg of **1e** (72%; Table 1, entry 13). White solid, mp = 165-166 °C. IR (KBr): ν = 1778 (s), 1462 (m), 1242 (m), 1176 (w), 1106 (w), 1008 (m), 904 (w), 862 (w), 783 (m), 692 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.88 (d, J = 8.5, 1 H), 7.92 (distorted d, J = 2.9, 1 H), 7.76 (dd, J = 8.5, 1.9, 1 H), 7.59-7.51 (m, 2 H), 7.44-7.28 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.0. 143.7, 139.7, 137.1, 136.7, 134.4, 130.0, 129.2, 128.2, 127.7, 126.0, 125.6, 81.4; GC-MS: *m/z* =384 [$(M+2)^+$] (8), 382 (M^+) (27), 257 (33), 256 (18), 255 (100), 229 (10), 227 (29), 176 (8), 163 (31), 127 (14); anal. calcd for $C_{15}H_8ClI$ (382.58): C, 47.09; H, 2.11; Cl, 9.27; I, 33.17; found C, 47.11; H, 2.09; Cl, 9.25; I, 33.14.

*7-Chloro-4-iodo-3-phenylisochromen-1-one (**3e**).* Yield: 135 mg, starting from 103 mg of **1e** (88%; Table 1, entry 12). White solid, mp = 197-199 °C. IR (KBr): ν = 1734 (s), 1589 (m), 1467 (m), 1311 (w), 1217 (m), 1083 (m), 949 (m), 836 (w), 765 (w), 693 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, J = 1.5, 1 H), 7.84 (distorted d, J = 8.6, 1 H), 7.76-7.63 (m, 3 H), 7.50-7.42 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4, 155.0, 136.8, 135.8, 135.3, 134.9, 133.3, 130.4, 129.9, 128.9, 128.1, 121.2, 75.1; GC-MS: *m/z* = 384 [$(M+2)^+$] (33), 382 [M^+] (100), 354 (45), 255 (10), 227 (34), 199 (36), 163 (26), 105 (52), 77 (42); anal. calcd for $C_{15}H_8ClIO_2$ (382.58): C, 47.09; H, 2.11; Cl, 9.27; I, 33.17; found C, 47.11; H, 2.08; Cl, 9.30; I, 33.16. The spectroscopic data agreed with those reported.[16]

*(E)-3-(Iodothiophen-3-yl-methylene)-3H-isobenzofuran-1-one (**2f**).* Yield: 106 mg, starting from 91 mg of **1f** (75%; Table 1, entry 15). White solid, mp = 111-112 °C. IR (KBr): ν = 1778 (s), 1469 (w), 1248 (m), 1096 (m), 1006 (s), 954 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.90 (d, J = 8.2, 1 H), 7.94 (d, J = 7.6, 1 H), 7.84-7.75 (m, 2 H), 7.66-7.55 (m, 2 H), 7.36 (dd, J = 5.1, 3.1, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 143.6, 139.5, 138.8, 135.7, 134.2, 131.7, 130.6, 130.2, 129.2, 125.9, 125.0, 75.1; GC-MS: *m/z* = 354 (M^+) (29), 227 (100), 199 (55), 171 (35), 127 (14); anal. calcd for $C_{13}H_7ClO_2S$ (354.16): C, 44.09; H, 1.99; I, 35.83; S, 9.05; found C, 44.12; H, 1.97; I, 35.84; S, 9.08.

*4-Iodo-3-thiophen-3-ylisochromen-1-one (**3f**).* Yield: 129 mg, starting from 91 mg of **1f** (91%; Table 1, entry 14). White solid, mp = 73-75 °C. IR (KBr): ν = 1728 (s), 1611 (m), 1469 (w), 1324 (w), 1236 (m), 1072 (m), 1021 (m), 968 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.26 (dd, J = 8.0, 0.7, 1 H), 8.04-7.99 (m, 1 H), 7.86 (distorted d, J = 8.2, 1 H), 7.82-7.74 (m, 1 H), 7.63 (dd, J = 5.1, 1.2, 1 H), 7.54 (td, J = 7.5, 1.1, 1 H), 7.39 (dd, J = 5.1, 3.0, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.3, 150.3, 138.3, 135.7, 135.2, 131.6, 129.7, 129.5, 129.1, 128.6, 125.1, 120.2, 75.6; GC-MS: *m/z* = 354 (100), 326 (66), 227 (13), 199 (79), 171 (52), 127

View Article Online
DOI: 10.1039/C7OB00962C

(17), 111 (41); anal. calcd for $C_{13}H_7ClO_2S$ (354.16): C, 44.09; H, 1.99; I, 35.83; S, 9.05; found C, 44.05; H, 1.96; I, 35.85; S, 9.07.

*(E)-3-(Iodophenylmethylene)-4-methyl-3H-isobenzofuran-1-one (**2g**).* Yield: 109 mg, starting from 94.5 mg of **1g** (75%; Table 1, entry 17). White solid, mp = 65-66 °C. IR (KBr): *v* = 1768 (s), 1484 (w), 1442 (w), 1266 (m), 1120 (m), 1068 (m), 990 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* = 7.80-7.74 (m, 1 H), 7.59-7.47 (m, 4 H), 7.41-7.33 (m, 2 H), 7.33-7.25 (m, 1 H), 3.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 165.4, 148.6, 142.0, 138.3, 137.4, 134.2, 130.9, 130.2, 128.8, 128.0, 127.4, 123.4, 81.1, 27.8; GC-MS: *m/z* = 362 (M^+) (11), 235 (100), 207 (19), 179 (24), 152 (6), 117 (8), 89 (29); anal. calcd for $C_{16}H_{11}IO_2$ (362.16): C, 53.06; H, 3.06; I, 35.04; found C, 53.08; H, 3.03; I, 35.02.

*4-Iodo-5-methyl-3-phenylisochromen-1-one (**3g**).* Total yield: 80.5 mg, starting from 94.3 mg of **1g** (56%; Table 1, entry 16). White solid, mp = 95-97 °C. IR (KBr):1736 (s), 1587 (m), 1492 (m), 1383 (w), 1308 (w), 1221 (w), 1084 (m), 1029 (w), 957 (w), 760 (m), 696 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* = 8.30 (d, J= 7.4, 1 H), 7.70-7.59 (m, 3 H), 7.49-7.42 (m, 4 H), 2.98 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* =162.0, 155.8, 139.4, 136.8, 136.1, 131.6, 130.1, 128.9, 128.5, 128.3, 128.2, 122.3, 77.2, 25.3; GC-MS: *m/z* = 362 (M^+) (86), 334 (15), 235 (14), 207 (24), 179 (22), 152 (7), 117 (6), 105 (100), 102 (9), 89 (8); anal. calcd for $C_{16}H_{11}IO_2$ (362.16): C, 53.06; H, 3.06; I, 35.04; found C, 53.05; H, 3.08; I, 35.01. The spectroscopic data for **3g** agreed with those reported.[16]

*Mixture of 3-(Iodo-p-tolylmethylene)-3H-isobenzofuran-1-one (**2h**) + 4-(Iodo-3-p-tolylisochromen-1-one (**3h**).* Total yield: 106 mg, starting from 94.5 mg of **1h** (73%; **2h** / **3h** = 2.32, determined by GLC; Table 1, entry 19). White solid. IR (KBr): *v* = 1770 (s), 1732 (m), 1603 (m), 1469 (m), 1249 (m), 1095 (m), 1006 (m), 894 (w), 810 (w), 763 (m), 686 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* = 8.91 (d, *J* = 8.1, 1 H, **2h**), 8.28 (d, *J* = 7.8, 1 H, **3h**), 7.94 (distorted d, *J* = 7.6, 1 H, **2h**), 7.90-7.74 [m, 1 H (**2h**) + 2 H (**3h**)], 7.67-7.51 [m, 1 H (**2h**) + 3 H (**3h**)], 7.46 (distorted d, *J* = 8.1, 2 H, **2h**), 7.26 (distorted d, *J* = 8.0, 2 H, **3h**), 7.18 (distorted d, *J* = 8.1, 2 H, **2h**), 2.43 (s, 3 H, **3h**), 2.38 (s, 3 H, **2h**); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 165.5 (**2h**), 161.6 (**3h**), 154.9 (**3h**), 144.1 (**2h**), 140.4 (**3h**), 139.1 (**2h**), 138.5 (**2h**), 138.3 (**3h**), 137.2 (**2h**), 135.6 (**3h**), 134.2 (**2h**), 132.3 (**3h**), 131.5 (**3h**), 130.6 (**3h**), 130.0 (**2h**), 129.9 (**3h**), 129.7 (**2h**), 129.1 (**3h**), 128.8 (**2h** + **3h**), 126.0 (**2h**), 125.8 (**2h**), 124.8 (**2h**), 120.2 (**3h**), 80.9 (**2h**), 76.1 (**3h**), 21.5 (**3h**), 21.3 (**2h**); GC-MS: (**2h**) *m/z* = 362 (M^+) (28), 235 (100), 207 (35), 179 (38), 152 (9), 117 (13); (**3h**) *m/z* = 362 (M^+) (100), 334 (64), 235 (25), 207 (62), 179 (62), 163 (7), 152 (13), 119 (32), 91 (48); anal. calcd for $C_{16}H_{11}IO_2$ (362.16): C, 53.06; H, 3.06; I, 35.04; found C, 53.03; H, 3.08; I, 35.01.

*4-Iodo-3-p-tolylisochromen-1-one (**3h**).* Yield: 136 mg, starting from 94.5 mg of **1h** (94%; Table 1, entry 18). White solid, mp = 166-167 °C, lit.[32] 174 °C IR (KBr): *v* = 1731 (s), 1602 (m), 1509 (w), 1471 (w), 1326 (w), 1227 (w), 1075 (m), 817 (m), 753 (m), 685 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* = 8.27 (d, *J* = 7.8, 1 H), 7.91 (distorted d, *J* = 7.8, 1 H), 7.79 (t, *J* = 7.6, 1 H), 7.59 (distorted d, *J* = 8.0, 2 H), 7.51 (distorted t, *J* = 7.1, 1 H), 7.25 (distorted d, *J* = 8.0, 2 H), 2.42 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 161.3, 155.4, 140.5, 138.6, 135.5, 132.9, 131.5, 130.0, 129.8, 129.0, 128.8, 120.7, 75.7, 21.4; GC-MS: *m/z* = 362 (M^+) (100), 334 (67), 235 (15), 207 (62), 189 (6), 179 (62), 163 (7), 152 (12), 119 (32), 103 (10), 91 (44); anal. calcd for $C_{16}H_{11}IO_2$ (362.16): C, 53.06; H, 3.06; I, 35.04; found C, 53.05; H, 3.03; I, 35.05.

*(E)-3-(Cyclohex-1-enyliodomethyene)-3H-isobenzofuran-1-one (**2i**).* Yield: 84.6 mg, starting from 90.5 mg of **1i** (60%; Table 1, entry 21). Yellow solid, mp = 148-149 °C. IR (KBr): *v* = 1775 (s), 1470 (w), 1340 (m), 1268 (w), 1196 (w), 997 (m), 768 (m), 714 (w), 687 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* = 7.90-7.80 (m, 2 H), 7.63 (td, *J* = 7.6, 1.1, 1 H), 7.53 (td, *J* = 7.6, 0.9, 1 H), 6.13-6.07 (m, 1 H), 2.43-2.25 (m, 2 H), 2.25-2.13 (m, 2 H), 1.91-1.80 (m, 2 H), 1.80-1.69 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 165.9, 146.5, 136.82, 136.78, 134.5, 130.8, 129.9, 126.5, 125.7, 122.8, 86.8, 27.6, 25.8, 22.5, 21.7; GC-MS: *m/z* =352 (M^+) (45), 225 (100), 210 (11), 197 (6), 179 (10), 159 (67), 133 (29), 105 (19); anal. calcd for $C_{15}H_{13}IO_2$ (352.17): C, 51.16; H, 3.72; I, 36.04; found C, 51.18; H, 3.70; I, 36.01.

*3-Cyclohex-1-enyl-4-iodoisochromen-1-one (**3i**).* Yield: 113 mg, starting from 90.5 mg of **1i** (80%; Table 1, entry 20). Yellow solid, mp = 82-83 °C, lit.,[17] 87-89 °C IR (KBr): *v* = 1725 (s), 1603 (m), 1472 (w), 1201 (w), 1067 (m), 1038 (m), 932 (w), 758 (m), 685 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* = 8.23 (d, *J* = 8.1, 1 H), 7.82-7.72 (m, 2 H), 7.55-7.46 (m, 1 H), 6.21-6.10 (m, 1 H), 2.41-2.16 (m, 4 H), 1.86-1.61 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* =161.6, 157.5, 138.6, 135.3, 135.1, 134.3, 131.4, 129.8, 128.7, 120.7, 74.6, 26.6, 25.2, 22.5, 21.7; GC-MS: *m/z* = 352 (M^+) (100), 324 (38), 298 (17), 225 (14), 215 (6), 197 (33), 179 (27), 169 (12), 141 (20), 128 (9), 115 (13), 88 (20), 79 (12); anal. calcd for $C_{15}H_{13}IO_2$ (352.17): C, 51.16; H, 3.72; I, 36.04; found C, 51.15; H, 3.74; I, 36.07. The spectroscopic data agreed with those reported.[18]

*(E)-3-Iodomethylene-3H-isobenzofuran-1-one (**2j**).* Yield: 90 mg, starting from 59 mg of **1j** (83%; Table 1, entry 22). Yellow solid, mp = 82-84 °C, lit.[18] 80-82 °C IR (KBr): *v* = 1771 (s), 1469 (w), 1347 (w), 1268 (m), 1204 (m), 1146 (w), 1097 (w), 1078 (w), 1005 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* = 8.69 (distorted d, *J* = 8.0, 1 H), 7.94 (distorted d, *J* = 7.7, 1 H), 7.79 (td, *J* = 7.4, 1.2, 1 H), 7.66 (distorted td, J = 7.4, 0.6, 1 H), 6.56 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 165.5, 148.9, 137.7, 134.5, 131.2, 126.4, 125.8, 124.2, 57.7; GC-MS: *m/z* = 272 (M^+) (100), 231 (9), 203 (1), 168 (2), 140 (1), 117 (5), 104 (9), 69 (39); anal. calcd for $C_9H_5IO_2$ (272.04): C, 39.74; H, 1.85; I, 46.65; found C, 39.72; H, 1.83; I, 46.68. The spectroscopic data agreed with those reported.[18]

Conclusions

In conclusion, we have found that the iodolactonization of 2-alkynylbenzoic acids **1** can be conveniently performed in ionic liquids as reaction media, in the absence of an external base and with the possibility to recycle several times the IL solvent. We have found that the regiochemical output of the process may be modulated by the nature of the IL employed: in particular, *N*-ethyl-*N*-methylmorpholinium dicyanamide ($Mor_{1,2}N(CN)_2$) promoted the *anti* 5-*exo* cyclization mode, with preferential or sole formation of (*E*)-3-(iodomethylene)isobenzofuran-1(3*H*)-ones **2**, while 1-ethyl-3-methylimidazolium ethyl sulfate ($EmimEtSO_4$) tended to favor the 6-*endo* cyclization mode, with

View Article Online
DOI: 10.1039/C7OB00962C

selective or exclusive formation of 4-iodo-1*H*-isochromen-1-ones **3**. The structures of representative products (isobenzofuranone **2a** and isochromenone **3d**) were confirmed by XRD analysis, and DFT calculations have been performed to clarify the role of the nature of the IL medium on the regioselectivity of the process. The heterocyclic derivatives synthesized in this work belong to particularly important classes of heterocycles, known to possess a wide range of biological activities.[9,10]

Acknowledgements

Thanks are due to Dr. Antonio Palumbo Piccionello (Dipartimento di Scienze e Tecnologie Biologiche, Chimiche e Farmaceutiche, Università di Palermo, Italy) for LC-MS measurements.

Notes and references

1 For recent reviews, see: a) S. Singh and S. S. Chimni, *Synthesis*, 2015, **47**, 1961-1989; b) B. Gabriele, R. Mancuso and R. C. Larock, *Curr. Org. Chem.*, 2014, **18**, 341-358. c) R. Mancuso and B. Gabriele, *Molecules*, 2014, **19**, 15687-15719; d) P. T. Parvaktar, P. S. Parameswaran and S. G. Tilve, *Chem. - Eur. J.*, 2012, **18**, 5460-5489; e) A. Palisse, and S. F.Kirsch, *Org. Biomol. Chem.*, 2012, **10**, 8041-8047; f) A. K. Banerjee, M. S. Laya and E. V. Cabrera, *Curr. Org. Chem.*, 2011, **15**, 1058-1080; g) M. J. Mphahlele, *Molecules*, 2009, **14**, 4814-4837.

2 For very recent examples, see: a) A. Gupta and B. L. Flynn, *J. Org. Chem.*, 2016, **81**, 4012-4019; b) T. Kesharwani, C. T. Kornman, A. L. Tonnaer, and A. D. Royappa, *Tetrahedron Lett.*, 2016, **57**, 411-414; c) T. P. Willumstad, P. D. Boudreau and R. L. Danheiser, *J. Org. Chem.*, 2015, **80**, 11794-11805; d) Y.-L. Li, J. Li, S.-N. Yu, J.-B. Wang, Y.-M. Yu and J. Deng, *Tetrahedron*, 2015, **71**, 8271-8277; e) G. M. Martins, G. Zeni, D. F. Back, T. S. Kaufman and C. C. Silveira, *Adv. Synth. Catal.*, 2015, **357**, 3255-3261; f) D. Yagandhar and A. K. Srivastava, *ACS Comb. Sci.*, 2015, **17**, 474-481; g) R. Volpe, L. Aurelio, M. G. Gillin, E. H. Krenske and B. L. Flynn, *Chem. – Eur. J.*, 2015, **21**, 10191-10199; h) H. Huang, X. Zhu, G. He, Q. Liu, J. Fan and H. Zhu, *Org. Lett.*, 2015, **17**, 2510-2513.

3 For an excellent review, see: A. V. Dubrovskiy, N. A. Markina and R. C. Larock, *Comb. Chem. High Throughput Screen.*, 2012, **15**, 451-472.

4 N. G. Kundu, M. Pal and B. Nandi, *J. Chem. Soc., Perkin Trans. 1*, 1998, 561-568.

5 M. Biagetti, F. Bellina, A. Carpita, P. Stabile and R. Rossi, *Tetrahedron*, 2002, **58**, 5023-5038.

6 The first examples of iodocyclizations carried out in an ionic liquid or a deep eutectic solvent were recently reported by our reserch group, and concerned the synthesis of 3-iodothiophenes by iodocyclization of 1-mercapto-3-yn-2-ols: a) R. Mancuso, C. S. Pomelli, C. Chiappe, R. C. Larock and B. Gabriele, *Org. Biomol. Chem.*, 2014, **12**, 651-659; b) R. Mancuso, A. Maner, L. Cicco, F. M. Perna, V. Capriati and B. Gabriele, *Tetrahedron*, 2016, **72**, 4239-4244.

7 For a very recent review on the use of ionic liquids as novel media for electrophilic/onium ion chemistry and metal-mediated reactions, see: K. K. Laali, *Arkivoc*, 2016, Part 1, 150-171.

8 C.S. Pomelli and C. Chiappe, *Phys. Chem. Chem. Phys.*, 2013, **15**, 412-423.

9 For recent examples of bioactive 3-(alkylidene)isobenzofuran-1(3*H*)-one derivatives, see: a) M. Chen and W. Ko, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 2016, **389**, 159-166; b) W. Gong, Y. Zhou, X. Li, X. Gao, J. Tian, X. Qin and G. Du, *Molecules*, 2016, **21**, art. no. 549, c) W. M. Eldehna, S. M. Abou-Seri, A. M. El Kerdawy, R. R. Ayyad, A. M. Hamdy, H. A. Ghabbour, M. M. Ali and D. A. Abou El Ella, *Eur. J. Med. Chem.*, 2016, **113**, 50-62; d) L. Wang, S. Huang, B. Chen, X.-Y. Zang, D. Su, J. Liang, F. Xu, G.-X. Liu, M.-Y. Shang and S.-Q. Cai, *Planta Med.*, 2016, **82**, 362-370; e) Y. L. Lin, K. F. Chang, X. F. Huang, C. L. Hung, S. C. Chen, W. R. Chao, K. W. Liao and N. M. Tsai, *Int. J. Nanomed.*, 2015, **10**, 6009-6020. f) J. W. Blunt, B. R. Copp, R. A. Keyzers, M. H. G. Munro and M. R. Prinsep, *Nat. Prod. Rep.*, 2014, **31**, 160-258; g) G. Ortar, A. Schiano Moriello, E. Morera, M. Nalli, V. Di Marzo and L. De Petrocellis, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 5614-5618; h) R. Yan, N. L. Ko, B. Ma, Y. K. Tam and G. Lin, *Curr. Drug Metab.*, 2012, **13**, 524-534.

10 For very recent examples of bioactive 1*H*-isochromen-1-one derivatives, see: a) M. Simic, N. Paunovic, I. Boric, J. Randjelovic, S. Vojnovic, J. Nikodinovic-Runic, M. Pekmezovic and V. Savic, *Bioorg. Med. Chem. Lett.,* 2016, **26**, 235-239; b) Z. Zhang, J. Q. Huo, H. J. Dong, J. M. Shi and J. L. Zhang, *Asian J. Org. Chem.*, 2016, **28**, 666-668; c) K. G. Guimares, R. P. De Freitas, A. L. T. G. Ruiz, G. F. Fiorito, J. E. De Carvalho, E. F. F. Da Cunha, T. C. Ramalho and R. B. Alves, *Eur. J. Med. Chem.* **2016**, *111*, 103-116; d) S. Chen, Y. Liu, Z. Liu, R. Cai, Y. Lu, X. Huang and Z. She, *RSC Adv.*, 2016, **6**, 26412-26420; e) M. Zhou, K. Zhou, P. He, K.-M. Wang, R.-Z. Zhu, Y.-D. Wang, W. Dong, G.-P. Li, H.-Y. Yang, Y.-Q. Ye, G. Du, X.-M. Li and Q.-F. Hu, *Planta Med.*, 2016, **82**, 414-417.

11 R. Mancuso, C.S. Pomelli, D. S. Raut, N. Marino, S. V. Giofré, R. Romeo, S. Sartini, C. Chiappe and B. Gabriele, *ChemistrySelect*, 2017, **2**, 894-899.

12 a) Terachem v1.5, Petachem LLC, 2009, 2015; b) I. S. Ufimtsev and T. J. Martinez, *J. Chem. Theory Comput.*, 2009, **5**, 2619 − 2628.

13 J. Kästner, J. M. Carr, T. W. Keal, W. Thiel, A. Wander and P. Sherwood, *J. Phys. Chem. A*, 2009, **113**, 11856 − 11860.

14 L. Goerigk and S. Grimme, *Phys. Chem. Chem. Phys.* 2011, **13**, 6670 − 6688.

15 a) R. Bini, C. Chiappe, V. Llopsis Mestre, C. S. Pomelli and T. Welton, *Org. Biomol. Chem.*, 2008, **6**, 2522-2529; b) J. D. Holbrey, W. M. Reichert, R. P. Swatloski, G. A. Broker, W. R. Pitner, K. R. Seddon and R. D. Rogers, *Green Chem.*, 2002, **4**, 407-413; c) O. Russina, R. Caminiti, A. Triolo, S. Rajamani, B. Melai A. Bertoli and C. Chiappe, *J. Mol. Liq.*, 2013, **187**, 252-259; d) C. Chiappe, A. Sanzone, D. Mendola, F. Castiglione, A. Famulari, G. Raos and A. Mele, *J. Phys. Chem. B*, 2013, **117**, 668-676.

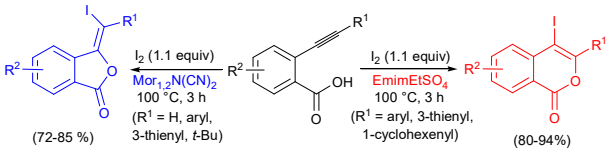
16 M. Peuchmaur, V. Lisowski, C. Gandreuil, L. Maillard, J. Martinez and J.-F. Hernandez, *J. Org. Chem.*, 2009, **74**, 4158-4165.

17 A. Nagarajan, T. R. Balasubramanian and R. Tiruvenkat, *Indian J. Org. Chem. Sect. B*, 1987, **26**, 917-919.

18 T. Yao, and R. C. Larock, *J. Org. Chem.* 2003, **68**, 5936 – 5942.

View Article Online
DOI: 10.1039/C7OB00962C

GRAPHICAL ABSTRACT



2-Alkynylbenzoic acids can by divergently iodocyclized to either isobenzofuranones or isochromenones by changing the nature of the ionic liquid medium.