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Unprecedented Aromatic Homolytic Substitutions and Cyclization of Amide–Iminyl Radicals: Experimental and Theoretical Study

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Abstract: Amide–iminyl radicals are versatile and efficient intermediates in cascade radical cyclizations of *N*-acylcyanamides. They are easily trapped by alkenes or (hetero-)aromatic rings and cyclize into a series of new heterocyclic compounds which bear a pyrroloquinazoline moiety. As an illustration of the synthetic importance of these compounds, the total synthesis of the natural antitumor compound luotonin A was achieved through a tin-free radical cascade cyclization process. Not only do amide–iminyl radicals lead to new tetracyclic heterocycles but these nitrogen-centered radical species also react in aromatic homolytic substitutions. Indeed, the amide–iminyl radical moiety unprecedentedly displaces methyl, methoxy, and fluorine radicals from an aromatic carbon atom. This seminal reaction in the field of radical chemistry has been developed experimentally and its mechanism has additionally been investigated by a theoretical study.

Keywords: density functional calculations · heterocycles · homolytic substitution · radicals · reaction mechanisms

Introduction

Being deeply involved in the development of radical reactions from the angle of both mechanistic studies and synthetic processes, we examined *N*-acylcyanamides as new substrates for the two types of approach.[1] Our interest in radical cyclization cascades[2] and in the discovery of new radical reaction partners[3] had previously led us to first study radical cyclizations of ynamides.[4] Our recent successful results in this area and the now well-established role of radical chemistry in the field of heterocyclic synthesis[5,6] prompted us to study *N*-acylcyanamides[1] radical transformations.

The reactivity of nitriles under radical conditions has been thoroughly explored[7] and an interesting evaluation has been reported in the context of radical cyclizations of diverse organic structures.[5d,8] However, the first radical use of suitably designed *N*-acylcyanamides was only recently reported by us.[1] Iminyl radical chemistry has been well reported in the last decade[9] and was recently applied to the synthesis of heteroarenes,[10] notably through radical cascade cyclizations.[5d,11] Nevertheless, *N*-acylcyanamides differ from both nitriles[12,13] and ynamides[4] in that they have an additional nitrogen atom. Thus, original reactivities and access to polynitrogenated alkaloid structures might be anticipated.

Increasing interest in new synthetic routes to recently isolated quinazoline alkaloids[14] on one hand and the growing abundance of radical cyclizations of five- and six-membered heterocyclic rings[15] on the other hand speak for the seminal aspect of this chemistry.

A particular class of alkaloid that incorporates the pyrroloquinazoline chromophore has been isolated from natural sources[16] and presents a wide range of biological activities.[17] Among these compounds, luotonin A is a human DNA topoisomerase I poison, which has been isolated from *Peganum nigellastrum*, a Chinese medicinal plant.[18] Ma et al. have examined the biological activity of luotonin A and its analogues,[19] while Jahng and co-workers have reported structure–activity studies on this class of compounds.[20] Luotonin A exhibits cytotoxicity toward the murine leukemia P388 cell line[18] by stabilizing the topoisomerase I/DNA complex.[21] This has established luotonin A as an attractive pyrroloquinazoline target for total synthesis, which we achieved by a tin-free radical cascade cyclization

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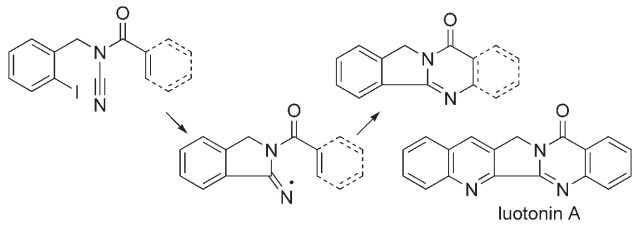
(Scheme 1). Other groups have previously achieved the total synthesis of luotonin A.[22,23,14] Some of these synthetic approaches have been based on a radical cyclization key

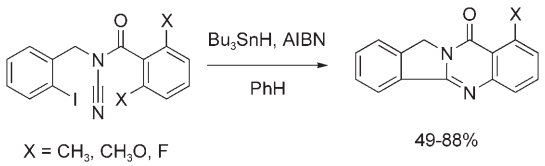


Scheme 1. Radical cyclization cascade of *N*-acylcyanamides.

step.[1,5,11b,24] For instance, Curran and co-workers synthesized luotonin A and a small library of AB-ring-substituted analogues by using a bimolecular radical cascade employing arylisonitrile and propargyl quinazolones.[24] However, none of these works have yet circumvented the use of tin derivatives in the radical process. Therefore, our access to luotonin A through a tin-free radical key step is particularly attractive.

In the general scheme of radical cascade cyclization of *N*-acylcyanamides, an amide–iminyl radical is formed as an intermediate and trapped by an unsaturated moiety, which can be an aromatic ring. In that case, with a rearomatization process being expected in the last step, it appeared to us that trapping by a conveniently substituted aromatic ring could give us insights into the reaction mechanism.

Indeed, intramolecular homolytic aromatic substitution on arenes (or heteroarenes) is involved in a growing number of tin-mediated radical cyclizations.[5h,25] Extrusion of radicals in *ipso*-substitution mechanisms[26] or in rearomatization processes, as achieved in Studer's group,[27–30] have been described recently. We were able to perform homolytic substitution on a substituted aromatic carbon atom during the last step of the radical cascade. Methyl, methoxy, and fluorine radical species were consequently extruded, as proved either by their trapping or by product structure analysis (Scheme 2).

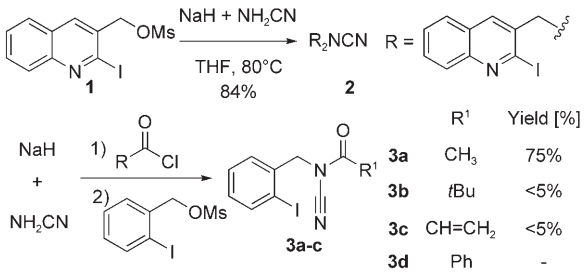


Scheme 2. Radical extrusion from *N*-acylcyanamides **3h**, **3p**, and **3q**. AIBN: azobisisobutyronitrile.

These results drove us to investigate the mechanism of the radical cyclization process by a DFT calculation study, which brings completion to the experimental work.

Results and Discussion

Preparation of the cyclization precursors: Preparing the *N*-acylcyanamide substrates was challenging. The preparation of *N*-acetylcyanamides, *N*-benzoylcyanamides, and some of their derivatives has been reported, but these molecules often show a lack of stability.[31–34] *N*-acylcyanamides display properties in different fields, for instance, as prodrugs of cyanamide,[32] enzymatic inhibitors,[35] or heteroanalogues of ethylenes,[36] so there was also interest in finding a practical way of preparing them. Although *N*-acylcyanamides and their parent compound, cyanamide, have been reported mainly as unstable compounds, the synthesis of a few of the *N*,*N*-diacyl and *N*,*N*-dialkyl analogues has been described under the experimental conditions that we decided to follow first.[33–34,37] Therefore, our preliminary preparation installed the cyanamide moiety by nucleophilic displacement of the mesylate group of quinoline derivative **1** with the cyanamide salt (Scheme 3).[37] As the major product present in the

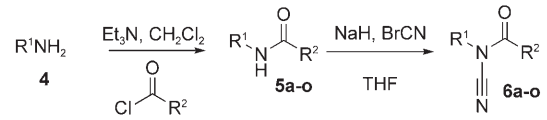


Scheme 3. Preparation of *N*-acyl-*N*-(2-iodobenzyl)cyanamides **3a–c** from the cyanamide sodium salt.

crude material seemed to be the dialkylated cyanamide **2** and in order to prevent the dialkylation process, we treated the cyanamide sodium salt in a one-pot procedure successively with a carboxylic acid chloride[32] and with 2-iodobenzylmesylate. This latter procedure failed to produce the desired *N*-acyl-*N*-(2-iodobenzyl)cyanamides **3**, except with the acetic acid chloride which gave compound **3a** (Scheme 3).

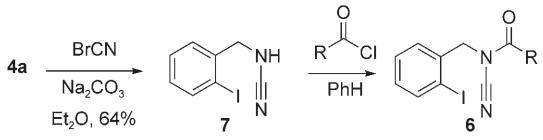
Finally, *N*-acyl-*N*-(2-iodobenzyl)cyanamides **6** were obtained by following two different cyanation/acylation sequences. The cyanation step was performed by addition of cyanogen bromide either on the amide (second step in method A, Table 1) or directly on the amine (first step in method B, Table 2) under basic conditions.[33] In method A, optimization of the reaction conditions was performed on *N*-benzoyl-*N*-(2-iodobenzyl)amide (**5a**) and was achieved by adding three equivalents of BrCN at room temperature after deprotonation by sodium hydride, a process that gives 73% of the *N*-benzoyl-*N*-(2-iodobenzyl)cyanamide (**6a**). A lower temperature or the use of two or four equivalents of BrCN resulted in the formation of *N*-benzoyl-*N*-(2-iodobenzyl)cyanamide (**6a**) in a lower yield. Acylation of 2-iodobenzylamine (**4a**), aniline (**4m**), *p*-trifluoromethylaniline (**4n**), and (2-iodoquinolin-3-yl)methylamine (**4o**) gave *N*-benzyl- or *N*-arylamides **5a–o** in good to excellent yields. Cyanation

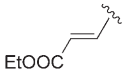
Table 1. Synthesis of *N*-acylcyanamides **6a–o** by an acylation/cyanation sequence (method A).



	R^2	Yield of **5** [%]	Yield of **6** [%]
	type I *N*-acylcyanamides (R^1: 2-iodobenzyl)		
a	C_6H_5	86	73
b	*p*-$NO_2C_6H_4$	44	68
c	*p*-$CF_3C_6H_4$	60	58
d	*p*-CNC_6H_4	73	33
e	*p*-$CO_2MeC_6H_4$	90	86
f	*p*-BrC_6H_4	78	47
g	*p*-$OMeC_6H_4$	57	28
h	*o*,*o*′-$(CH_3)_2C_6H_3$	79	61
i	*p*-C_5H_4N	73	61
j	*m*-C_5H_4N	56	49
	type II *N*-acylcyanamides (R^1: 2-iodobenzyl)		
k		>98[21]	17
l		>98[21]	20
	"reversed" type I *N*-acylcyanamides (R^1: $C_6H_5CH_2$)		
m		100	74
	"reversed" type I *N*-acylcyanamides (R^1: *p*-$CF_3C_6H_5CH_2$)		
n		64	37
	luotonin A precursor (R^1: (2-iodoquinolin-3-yl)methyl)		
o	C_6H_5	47	41

Table 2. Synthesis of *N*-acylcyanamides by a cyanation/acylation sequence (method B).



	R	Yield of **6** [%]
	type I *N*-acylcyanamides	
a	C_6H_5	74
g	*p*-$MeOC_6H_4$	93
p	*o*,*o*′-$(MeO)_2C_6H_3$	36
q	*o*,*o*′-$F_2C_6H_3$	83
t		73
u		74
	type II *N*-acylcyanamides	
k		70
l		67
r		74
s		54

of the latter amides under basic conditions yielded *N*-acylcyanamides **6a–o** in generally satisfactory yields, except for compounds **5g**, **5k**, and **5l** which present a nucleophilic acyl moiety (method A, Table 1). The possible addition of cyanogen bromide on the electron-rich unsaturated compounds **5g**, **5k**, and **5l** may decrease the yield of the cyanamides in these cases.[38]

To avoid this difficulty, we considered reversing the steps in the cyanation/acylation pathway (method B, Table 2).[39] In method B, the cyanation of 2-iodobenzylamine (**4a**) was performed by following a literature procedure that describes the efficient cyanation of benzylamine.[40] Although one might suggest that the strong conjugation of the nitrogen doublet in *N*-(2-iodobenzyl)cyanamide (**7**) could slow down the acylation reaction in the second step, previous works made us believe it could occur.[41] Indeed, not only were cyanamides **6g**, **6k**, and **6l** obtained in much improved yields by this method but it also afforded new structures such as *N*-disubstituted benzoylcyanamides **6p** and **6q** (36 and 84%), *N*-furanoyl- and *N*-thiophenoylcyanamides **6t** and **6u** (73 and 74%), and *N*-vinylcyanamides **6r** and **6s** (74 and 54%).

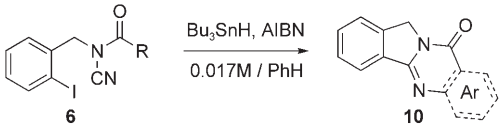
Finally, the preparation methods A and B have provided us with over 20 *N*-acylcyanamides, which we could discriminate by the acyl moiety being either "aromatic" or "vinylic", respectively, for type I (**6a–j**, **6m–q**, **6t**, **6u**) and type II (**6k**, **6l**, **6r**, **6s**) radical precursors. In the following sections, we describe separately the study of the radical reactivity in terms of experimental results, mechanistic elucidation, and DFT calculations for each type of *N*-acylcyanamide.

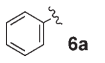
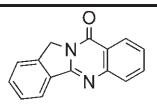
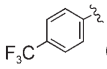
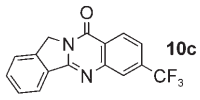
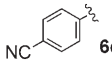
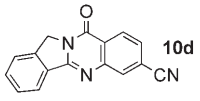
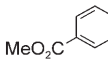
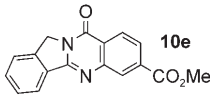
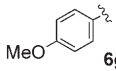
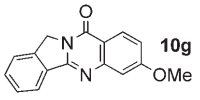
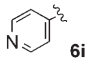
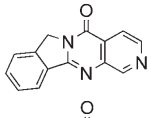
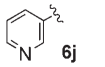
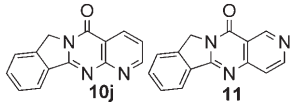
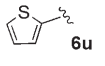
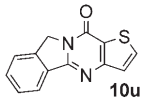
Radical cyclization cascades of type I *N*-acylcyanamides:

Reactivity: *N*-Acylcyanamides **6a–u** could be used as designed precursors for domino processes, which proceeded smoothly and selectively to close two rings in 57–99% yield. Only compounds **6b** and **6t** did not undergo the cyclization with success. The nitro group in *N*-(2-iodobenzyl)-*N*-(4-nitrobenzoyl)cyanamide (**6b**) was reduced by tributyltin hydride and the reduced product did not cyclize, whereas *N*-furanoylcyanamide **6t** did not react under the radical conditions.

N-Benzoyl-*N*-(2-iodobenzyl)cyanamide (**6a**) cyclized into the pyrroloquinazoline **10a** with a yield of 71%. Table 3 reports a wide series of cyclizations of type I cyanamides deriving from the parent compound **10a**; these compounds feature an "arenoyl" moiety substituted by electron-withdrawing/donating groups or presenting a heteroatom. The *p*-trifluoromethyl, *p*-cyano, *p*-carbomethoxy, and *p*-methoxy

Table 3. Cyclization of type I *N*-acylcyanamides **6** into heterotetracyclic compounds **10**.

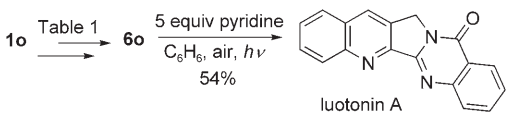


Entry	R	Product	Yield [%]
1	 **6a**	 **10a**	71
2	 **6c**	 **10c**	72
3	 **6d**	 **10d**	99
4	 **6e**	 **10e**	74
5	 **6g**	 **10g**	93
6	 **6i**	 **10i**	56
7	 **6j**	 **10j** **11**	79 (**10j**/**11** 2.2:1)
8	 **6u**	 **10u**	57

derivatives **10c–e** and **10g** were obtained in good to excellent yields of 72, 99, 74, and 93%, respectively, thereby demonstrating that the reaction occurs efficiently both with electron-withdrawing and electron-donating substituents on the aromatic radical acceptor.

Compound **10u** interestingly presents the thienopyrimidinone core which has been characterized in potent and selective melanin-concentrating hormone receptor antagonists.[42] Entries 5 and 6 of Table 3 expand the cyclization scope to *N*-pyridynoylcyanamides giving pyridinopyrimidinones. The regioselectivity of the transformation of compound **6j** in particular triggered our mechanistic investigation.

Total synthesis of luotonin A: We reported the closure of the pyrroloquinazoline skeleton of luotonin A by cyclization of *N*-acylcyanamide **6o** (Scheme 4).[1] Atom-transfer conditions



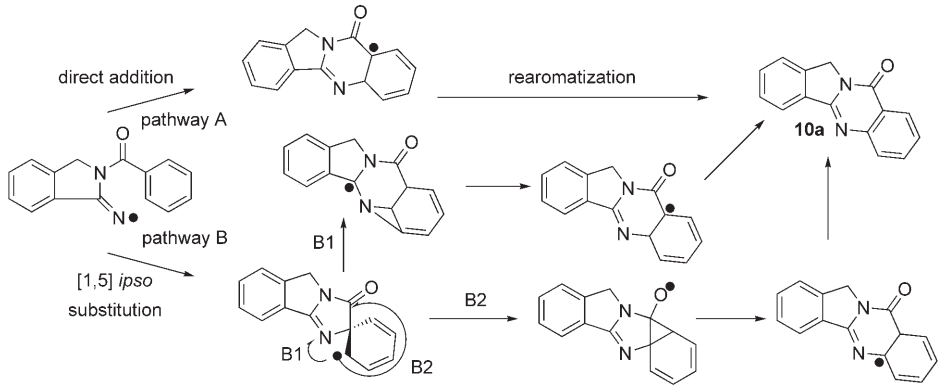
Scheme 4. Tin-free cyclization key step in the total synthesis of luotonin A.

with hexabutylditin in refluxing toluene under irradiation for 6 h successfully yielded luotonin A in 43% yield, thereby proving our radical cascade synthetic strategy towards luotonin A.[1]

As the cleavage of the Sn–Sn bond requires intense UV irradiation,[43] we did not expect that the daylight provided by our lamp could efficiently break it. Instead, it probably abstracts the iodide radical and creates the aryl radical, as demonstrated by the yield of 15% of luotonin A (65% of **6o** is recovered) obtained upon irradiation of cyanamide **6o** for nine hours in refluxing toluene. Irradiation of the cyanamide is indeed sufficient to start the radical cyclization cascade of **6o**, but free iodide radicals are not trapped in this tin-free process and could be responsible for the observed degradation through the formation of hydrogen iodide. To avoid this acidic side product, pyridine has proved to be efficient in radical additions of aryl iodides to arenes.[44] Besides this, other examples of the use of a nitrogen base under radical conditions have been reported. For instance, Cossy et al. reported that triethylamine allowed the formation of the unsaturated radical moiety upon irradiation of unsaturated halides.[45] The last step in the formation of luotonin A implies a rearomatization process which we thought might be induced by dioxygen, as previously described.[44] Taking into account the precedent studies, we tried different sets of experimental conditions. In these different assays, benzene proved to be a better solvent than toluene (24% instead of 15% yield). Addition of one equivalent of pyridine in the presence of air in toluene increased the yield to 38%. Finally, the best conditions were the irradiation of cyanamide **6o** in refluxing benzene with five equivalents of pyridine in the presence of air, conditions which successfully yielded 54% of luotonin A in a tin-free cyclization process (Scheme 4).

Mechanistic study: The mechanism of the radical cascade begins with the abstraction of the iodide radical and the formation of the aryl radical, which is then trapped by the cyanamide triple bond. The subsequently formed amide–iminyl radical cyclizes on an aryl substituent either by direct addition to form the hexadienyl radical which undergoes

rearomatization (pathway A, Scheme 5) or by a [1,5] *ipso* substitution (pathway B, Scheme 5) which gives a spirocyclohexadienyl radical species. The latter possibility ends either by attack of the arene radical on the nitrogen atom (pathway B1, Scheme 5) or on the carbonyl function (pathway B2, Scheme 5).



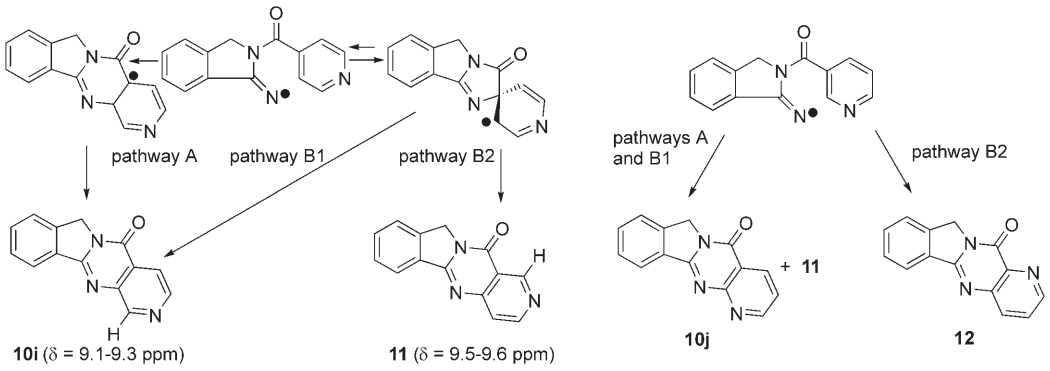
Scheme 5. Two mechanistic pathways for the addition of the amide–iminyl radical on an arene.

Pathways A and B give different products when the aromatic ring is substituted or includes an heteroatom. Although iminyl radicals have already been reported to undergo a [1,5] *ipso* substitution on an aryl moiety under flash vacuum pyrolysis,[46] several pieces of evidence led us to decide for the direct addition/rearomatization pathway (A). Indeed, the quantitative transformation of the *p*-cyanobenzoylcyanamide **6d** into the sole tetracyclic regioisomer **10d** (entry 3, Table 3) indicates that pathways A and/or B1 have been followed. The pyridine derivatives **6i** and **6j** are good probes for this mechanistic determination (Scheme 6). The *para*-carboxylpyridinylcyanamide **3i** would give compound **10i** through pathways A/B1 whilst compound **11** would be obtained through pathway B2. Experimentally, we isolate only one tetracyclic product the ^{1}H NMR spectroscopic analysis of which shows a proton singlet at $\delta = 9.23$ ppm, which fits with the structure of compound **10i**, whilst the corresponding singlet in compound **11** is expected at a lower field (around $\delta = 9.5$–9.6 ppm).

Besides this, pathway B2 would transform compound **6j** into one sole regioisomer, **12** (Scheme 6), which presents no singlet signal for the pyridinyl protons. After cyclization of compound **6j**, we isolated two different regioisomers, **10j** and **11**; the latter presents a singlet NMR signal ($\delta =$ 9.6 ppm) for one of the protons linked to the pyridine moiety (as proposed in pathway B2 for **6i** of Scheme 6). This is exactly what we can predict if compound **6j** should react along pathways A/B1.

We can definitely abandon the [1,5] *ipso* substitution/C–CO bond cleavage hypothesis (pathway B2). We could not experimentally discriminate between pathways A and B1, which should give the same product, and we decided to address this question through a DFT study of the two pathways.

The different mechanistic processes occurring during the radical cyclization will be discussed from a DFT point of view on the basis of the results shown in Figure 1 for the compound with a phenyl substituent. The starting point of the energetic profile is the reagent called **1H**, an amide–iminyl radical species generated by the first step of the radical cascade. The radical is mainly localized on the nitrogen atom of the iminyl moiety (0.97 of spin density, UB3LYP/BS1). From **1H**, there are two options, as explained in Scheme 5: either direct addition on the *ortho* carbon atom of the phenyl ring (**TS12H**) or an attack on the *ipso* carbon atom (**TS13H**). According to DFT calculations, the *ortho* process is easier than the *ipso* process. At the BS2//BS1 level of calculations, the difference between them is 5.8 kcal mol^{-1}. Nevertheless, we will continue to evaluate the feasibility of the *ipso* process by looking at the subsequent steps, as the ratio between the *ortho* and *ipso* processes could be expected to vary depending on the substituents on the phenyl ring. From **3H**, there are two mechanistic possibilities to create finally **2H**. The first one is to generate an aziridine by creating a bond between the nitrogen and the



Scheme 6. Mechanistic fate of the pyridine derivatives **6i** and **6j**.

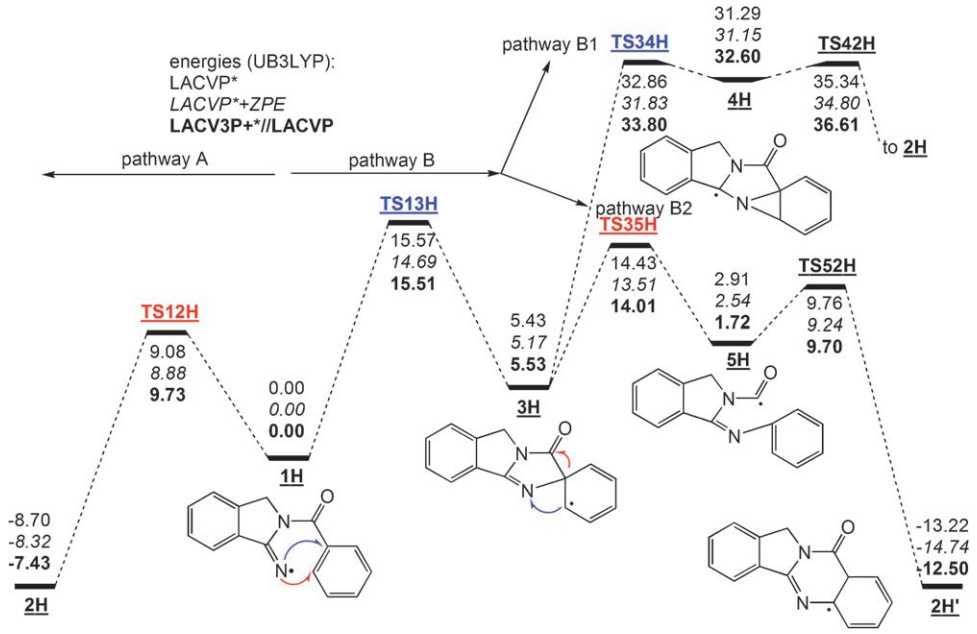
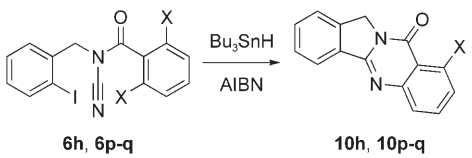


Figure 1. Energetic profile summarizing the different processes occurring during the cyclization of the substrate with a phenyl substituent. Geometries are optimized at the UB3LYP/BS1 level. The red and blue single-headed arrows show the two possible attacks in each case and not the complete electronic reorganization for clarity.

ortho carbon atoms, leading to **4H**. In a second step, the bond between the nitrogen atom and the *ipso* carbon atom is broken, which gives **2H** directly. One can see from Figure 1 that this process is very high in energy, as the intermediate **4H** is metastable (27.1 kcal mol^{-1} above **3H** at the BS2//BS1 level). The other mechanistic possibility is to generate an intermediate acyl radical (**5H**) by breaking the bond between the *ipso* carbon atom and the carbonyl carbon atom. In fact, this mechanism was found while searching for a pathway leading to the intermediate of mechanism B2 (see Scheme 6). This cyclopropane with a radical centered on the oxygen atom cannot be found and instead intermediate **5H** is calculated. This acyl radical is subsequently rearranged to form **2H′** by creation of a C–C bond with a carbon atom in the *ortho* position with respect to the imine group. This process is clearly far easier than the aziridine process as the highest barrier is only 14.01 kcal mol^{-1} (BS2//BS1 level). From all of these computational data, we can establish that pathway A is clearly favored in the case of aromatic substitution and the formation of an aziridine as an intermediate (through pathway B1) is a very unlikely process.

We could still improve our experimental knowledge concerning the 6-*endo*-*trig* step by studying the fate of the amide–iminyl radical upon trapping by a carbon atom in a substituted aromatic ring. Therefore, we prepared *N*-(2,6-disubstituted-benzoyl)-*N*-(2-iodobenzyl)cyanamides **6h**, **6p**, and **6q** (Table 1 and 2) and submitted them to the usual radical cyclization conditions. The dimethyl derivative **6h** was transformed into the tetracyclic pyrroloquinazoline **10h** (Scheme 7) in 88% yield by extrusion of a methyl radical which we were fortunate enough to trap by addition of benzylidenemalononitrile. The dimethoxy derivative **6p** cyclizes into compound **10p**, containing only one methoxy group (49%; Scheme 7). The loss of one methoxy radical is proved by the structure of the product but this easily reduced radical species could not be trapped by either phenylvinylether (up to ten equivalents) or benzylidenemalononitrile. To avoid reduction of the extruded methoxy radical species, atom-transfer conditions (30% of **10p**) have been tested in the presence of a radical acceptor but no trapping was ever observed. The cyclization of the difluoro-substituted cyanamide **6q** differs from the two former examples by giving two monofluorinated regioisomers **10q** and **13**, respectively, in 73 and 15% yield (Scheme 7). Extrusion of heteroatomic radicals has been previously reported[27–30] and so has homolytic substitution on arenes;[5h,25] nevertheless, homolytic substitution of a substituted arene by an iminyl radical followed by extrusion of the substituent as a carbon- or fluorine-centered radical species is a new and promising feature in the field of radical reactions. It appears appropriate and logical to propose a similar mechanism for the formation of **10h**, **10p**, and **10q** by homolytic substitution of methyl, methoxy, and fluorine radicals by the amide–iminyl radical. However, the formation of **13** requires further elucidation through modeling and calculations.

If substituents are introduced on the phenyl ring of the substrate that traps the final radical, one can observe some modifications in the energetic profile. These are summarized in Figure 2. First of all, the *ipso* substitution is now more favorable than the *ortho* substitution. The difference is small for the dimethyl substitution (0.82 kcal mol^{-1} at the BS2//



X	Product	Yield [%]
CH_3	**10h**	88
OCH_3	**10p**	49
F	**10q**	73[a]

Scheme 7. Extrusion of methyl, methoxy, and fluorine radical species. [a] The minor regioisomer **13**, bearing a fluorine atom at the β-position with respect to the nitrogen atom, is obtained in a yield of 15%.

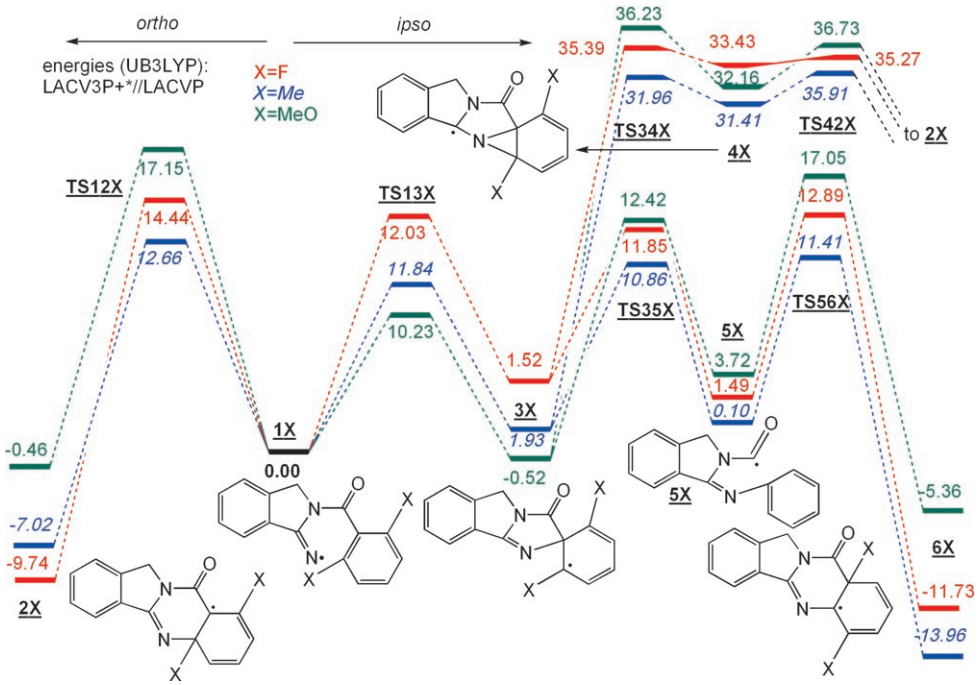


Figure 2. Energetic profile summarizing the different processes occurring during the cyclization of the substrate with a di-*ortho*-substituted (F, Me, OMe) phenyl group. Geometries are optimized at the UB3LYP/B1 level.

BS1 level) but more important for the difluoro substitution (2.41 kcal mol^{-1} at the BS2//BS1 level), and the greatest difference is obtained for the dimethoxy compound (6.94 kcal mol^{-1} at the BS2//BS1 level). The minor product observed experimentally for the difluoro-substituted substrate can thus be explained by the *ipso* mechanism followed by the rearrangement called pathway B2 in Scheme 6.

The low yield obtained experimentally in the case of the dimethoxy substrate can also be attributed to this pathway. As there is a high transition state for the last step (**TS56OMe**), the radical intermediate **5OMe** may decompose and therefore no other product can be observed. For the dimethyl substrate, the difference between the *ortho* and *ipso* processes is too small to make conclusions on the basis of the DFT calculations. Experiments show us that the *ortho* process is more favored.

One of the striking features of this radical reaction is the fact that for the dimethylphenyl-substituted reagent, a methyl radical is spontaneously eliminated during the propagation steps. It is shown in Figure 3 that this process can occur after the formation of **2Me**, through a transition state (**TsdMe**) which is only 14.62 kcal mol^{-1} (BS2//BS1 level) above **2Me**. The cost of breaking a C–C bond in the α position with respect to a radical is therefore minimal compared to the common value of a C–C bond. This radical departure was also found experimentally in the case of dimethoxyphenyl substrate. DFT calculations show that the process is even easier in that case (barrier of 6.91 kcal mol^{-1} at the BS2//BS1 level) and more exothermic.

In the case of type I *N*-acylcyanamides **6n** and **6m**, the amide–iminyl intermediate radical is expected to be trapped by the aromatic part of a benzyl moiety (Scheme 8), where-

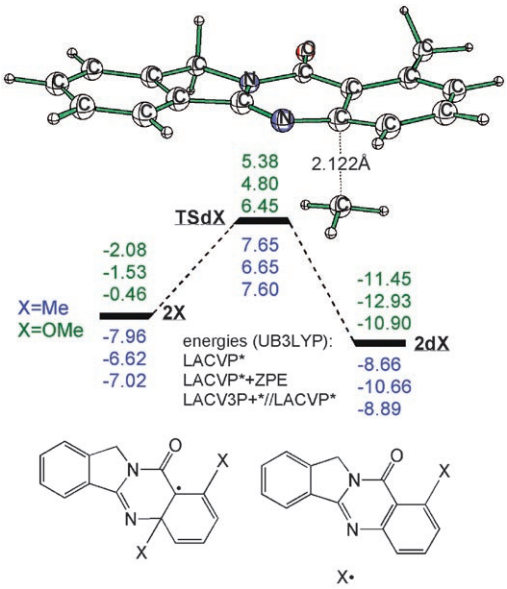
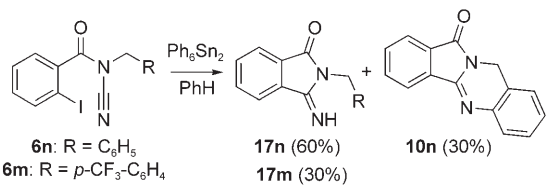


Figure 3. Methyl departure and rearomatization of **2Me**. Geometries are optimized at the UB3LYP/BS1 level. The structure of the transition state for the departure of the methyl radical (**TSdMe**) is also shown.

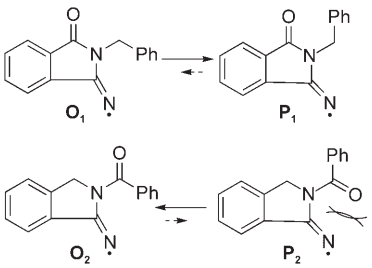


Scheme 8. 5-*exo-dig* cyclization of "reversed" type I *N*-acylcyanamides **6n** and **6m**.

as in the precedent examples (type I compounds **6a**, **6c–e**, **6g**, **6i**, **6j**, and **6u**; displayed in Table 3) the radical trap is a benzoyl entity.

Under slow-addition radical conditions, *N*-acylcyanamide **6n** is transformed into the 5-*exo-dig*/reduction imine product **14n** in 86% yield when Bu_3SnH is the mediator. To avoid as much as possible the reduction of the amide–iminyl radical into the imine **14n**, atom-transfer[47] conditions with Bu_6Sn_2 were tried in toluene and in the less reductive benzene to yield, respectively, 70 and 90% of **14n** together with less than 10% of the initial material **6n**. As we targeted the best nonreductive experimental conditions we could achieve, we tried to cyclize compound **6n** with Ph_6Sn_2 in refluxing benzene (Scheme 8). Satisfactorily, only these conditions afforded the tetracyclic product **10n**, in 30% yield. Having avoided the reduction of the amide–iminyl radical as much as possible, the second step was to take into account the structure of the aromatic acceptor. As the type I cyanamides depicted in Table 3 have an electron-poor benzoyl moiety, our next assays consisted of modifying the structure of the aromatic acceptor by linking to it the trifluoromethyl electron-withdrawing group, as in **6m** (Scheme 8). In that case, the best set of experimental conditions is also Ph_6Sn_2 in benzene but only trace amounts of **10m** are isolated.

Compound **10n** is stable on silica gel and under the Ph_6Sn_2/refluxing benzene conditions; therefore, it neither degrades into the imine during the purification steps nor during the reaction. However, it undergoes partial conversion into imine **14n** when resubmitted to the Bu_3SnH/AIBN medium, so the hypothesis of a transformation of **10n** into **14n** could not be discarded. The difference in reactivity between the two "reversed" compounds **6n** and **6m** and the other type I *N*-acylcyanamides may find its origin in different structural features. The structure of the amide–iminyl radical formed from compound **6n** allows two different rotamers $\mathbf{O_1}$ and $\mathbf{P_1}$, with $\mathbf{P_1}$ being favored (Scheme 9). In



Scheme 9. The importance of the amide position for the mechanism.

compound **6a**, the amide–iminyl radical can probably not face the carbonyl–oxygen free doublet without a strong repulsion, thereby implying that rotamer $\mathbf{O_2}$ is favored in this case. Moreover, the equilibrium between the amide–iminyl radical and the final radical is easily displaced towards the latter species if the last oxidation step has a driving force.[48]

DFT calculations helped us to rationalize the reactivity of the "reversed" type I *N*-acylcyanamides **6n** and **6m**. To understand the difference in reactivity between the two carbonyl systems, DFT calculations were done on the two types of system. In Figure 4, some data are shown that were extracted from these calculations. We compared the same transition state of cyclization (*ortho* attack). In the case of the normal type I compound, the barrier is found to be 8.88 kcal mol^{-1} (UB3LYP/BS1 level, ZPC included). For the reversed type, the barrier is now 14.80 kcal mol^{-1}. In that case, one expects some noticeable differences between these two different structures. When the carbonyl group is near to the reactive center (type I), the process should be more ionic than when the carbonyl group is not directly related to the cyclization (reversed type I). In fact, according to the DFT calculations, the Mulliken atomic charges are rather similar for the two cases at the transition state, which means that the reaction is mainly radical. This is moreover confirmed by the HOMO and LUMO for the two systems, which show no (or small) weight on the carbonyl groups.

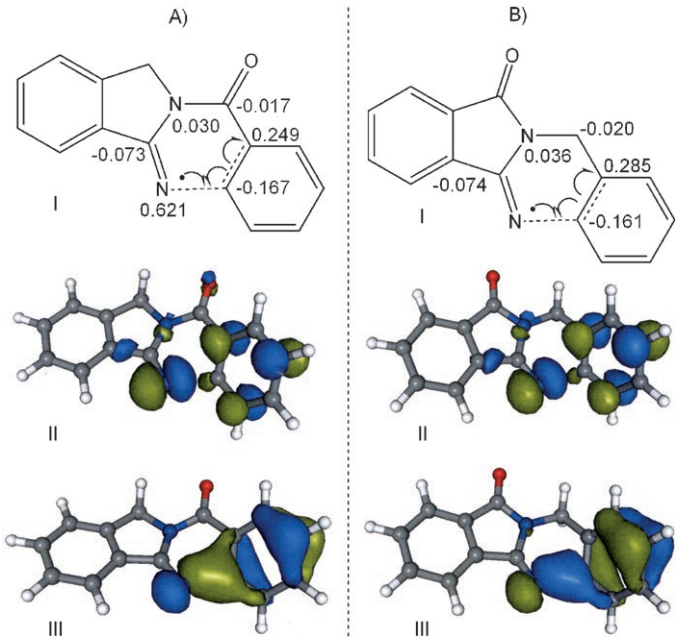


Figure 4. A) The Mulliken atomic charges obtained at the UB3LYP/BS1 level (I) transition state of *ortho* cyclization, II) LUMO of the transition state at *ortho* cyclization, and III) HOMO of the transition state at *ortho* cyclization) for the "right" carbonyl system. B) The same information for the "left" carbonyl system.

The lack of reactivity of the reversed-type system can be mainly attributed to conformational differences between the two types of system (see Figure 5). Analysis of data extracted from relaxed scans clearly shows that, when the phenyl group is attached to the carbonyl group, minima on the potential energy surface are well suited for an *ortho* attack. However, in the reversed system, the best conformation for such an attack is, in fact, a transition state corresponding to the benzyl rotation (around 10–12 kcal mol^{-1} above).

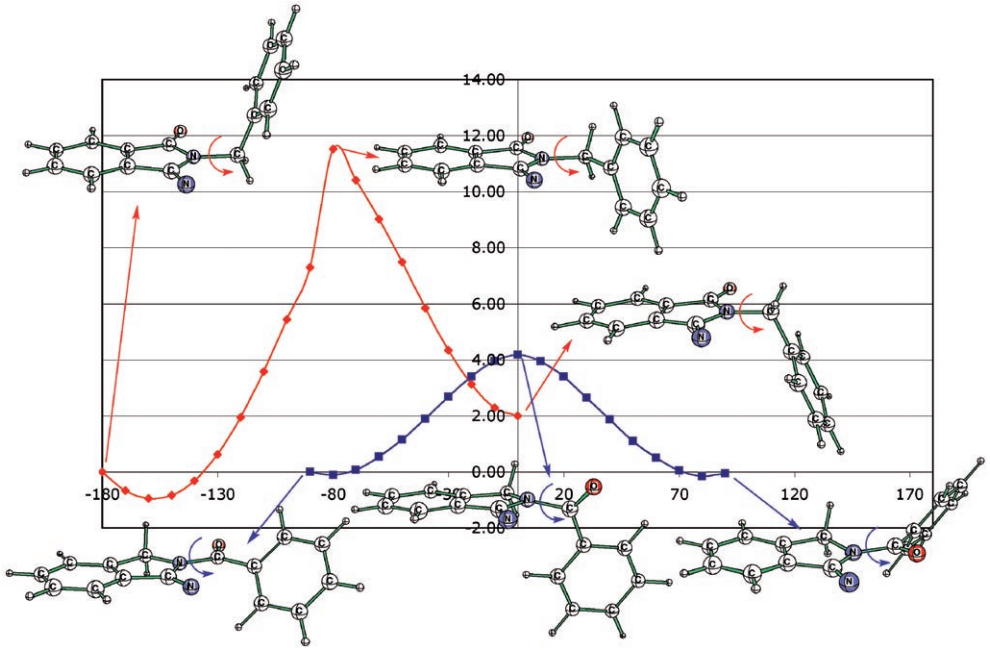


Figure 5. Conformational analysis through relaxed scans on the dihedral angles implied in the cyclization process. Calculations were done at the UB3LYP/BS1 level. Only the region of the scan in which the phenyl ring is closed to the radical is computed.

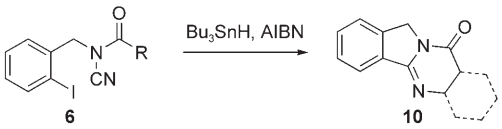
Radical cyclization cascades of type II *N*-acylcyanamides:

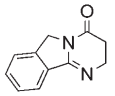
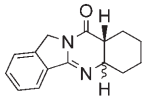
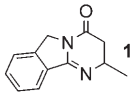
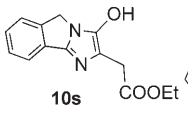
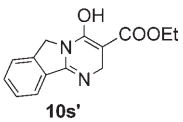
Reactivity: Radical cyclization cascades of type II *N*-acylcyanamides proceeded smoothly with good yields ranging from 66 to 79%. The diastereoselectivity of the formation of the cyclohexyl derivative **10l** (71%) yielded the *cis* derivative as the main isomer and has been confirmed by X-ray analysis of the minor diastereomer, which showed a *trans* stereochemical relationship between the two rings (entry 2, Table 4). A study of this reaction at different temperatures gave a good indication that the *cis*-fused ring was indeed the kinetic product, an experimental result that has been totally confirmed by the calculations.

Entries 3 and 4 of Table 4 report the reactivity of substituted enamides **6r** and **6s**, which are good mechanistic probes for this reaction. The *N*-crotylcyanamide **6r** is transformed into one sole fully characterized compound **10r**, the X-ray analysis of which fully confirmed that the methyl substituent is on the carbon atom at the α-position with respect to the sp^2 nitrogen atom. To enlarge the type of substituents tolerated on the vinyl moiety to electron-withdrawing groups, we decided to prepare *N*-(2-ethylcarboxyvinyl)cyanamide **6s**, which leads chemoselectively to two isomeric esters **10s** and **10s′** in a 1.8:1 ratio (79%). The aromatic hydroxyimidazole substructure of **10s** surely makes it a more stable tautomeric form than the amido ester produced after the 5-*exo*-*trig* cyclization/reduction sequence on **6s**.

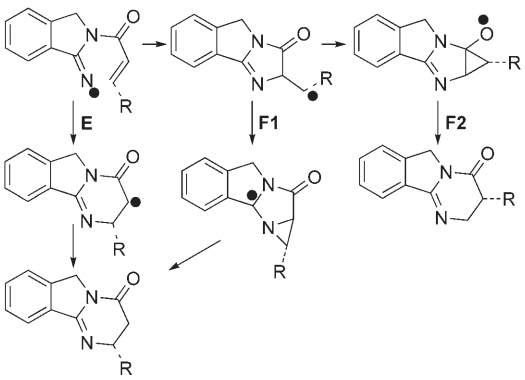
Mechanistic study: These results led us to rationalize the possible mechanistic evolution of the intermediate amide–iminyl radical which can cyclize in a 6-*endo*-*trig* mode along

Table 4. Cyclization of type II *N*-acylcyanamides **6** into polycyclic compounds **10**.



Entry	R	Product	Yield [%]
1	 **6k**	 **10k**	66
2	 **6l**	 **10l**	71 (*cis*/*trans* 2:1)
3	 **6r**	 **10r**	79
4	EtOOC **6s**	 **10s** COOEt  **10s'**	79 (**10s**/**10s′** 1.8:1)

pathway E (Scheme 10). Pathway F implies a 5-*exo-trig* cyclization giving a carbon-centered radical species that can follow two different subpathways, F1 and F2. Pathway F1



Scheme 10. Different pathways for the radical cyclization of type II *N*-acylcyanamides.

starts with the attack on the imine nitrogen atom and goes on with the rearrangement of the intermediary aziridine. The one-carbon ring expansion of pathway F2 has already been described[49] with the formation of an oxygen-centered cyclopropyloxy radical that can rearrange in a transposition previously reported by Dowd, Beckwith and co-workers.[12d,50] In the case of the *N*-crotylcyanamide **6r**, the experimentally obtained product **10r** may have been formed through pathways E and/or F1. The obtention of two regioisomers from the ester derivative **6s** shows that pathway F2 has also been followed in this case. This indicates that the mechanism depends very much on the substitution of the vinyl moiety. These results have been usefully rationalized by calculations.

DFT calculations: In Figure 6 are summarized the main results of the computational study for the type II cyclizations, that is, those with vinylic substrates instead of aromatic substrates. Two vinylic substrates were studied: the simple vinyl (labeled as **V** in Figure 6) and an acrylate (labeled as **A**). One can see from Figure 6 that pathway E is favored for the vinyl substrate. The *exo-trig* cyclization leading to different pathways (F1, F2, F3) through **TS13V** is less favorable. From **3V**, pathway F2, which is a concerted rearrangement, can be eliminated. The cyclopropyl intermediate for this pathway, postulated in Scheme 10, was not found. Instead we found, as with the aromatic case, an acyl radical intermediate (**5V**), which subsequently undergoes an easy 6-*endo-trig* closure (**TS56V**). The process through intermediate **4V** can be excluded as pathway F3 is easier. Therefore, the only mechanistic pathway to obtain **2V** is the direct 6-*endo-trig* cyclization. When the vinyl group is substituted by an ester moiety, it is observed experimentally that two products are formed, corresponding to the direct reduction of **3A** (**10s**) and to **6A** (**10s′**). The **3A** product is obtained through direct 5-*exo-trig* cyclization, which is more favored than the 6-*endo-trig* cyclization. The **6A** product is obtained through pathway F3 (through an acyl radical intermediate), the lowest pathway starting from **3A**.

In the case of a substitution by a cyclohexenyl group, the radical cyclization leads to a mixture of diastereoisomers (see Table 4 and Figure 7). It is shown experimentally that the ratio between the *trans* and *cis* configurations is temper-

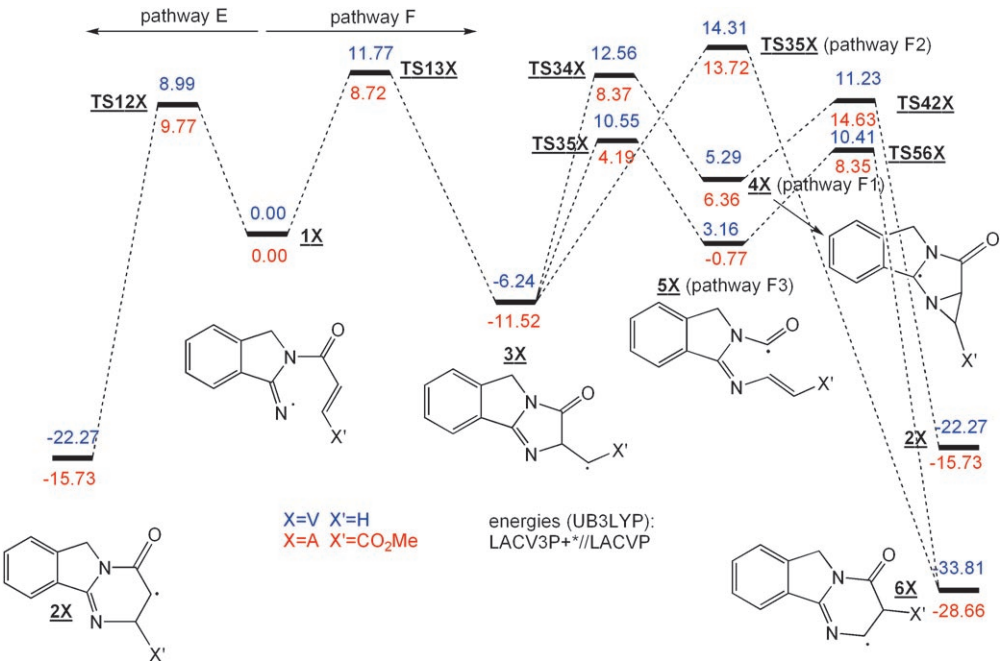


Figure 6. Energetic profile summarizing the different processes occurring during the cyclization of the substrate with a vinyl (X: V) or acrylate (X: A) group. Geometries are optimized at the UB3LYP/BS1 level.

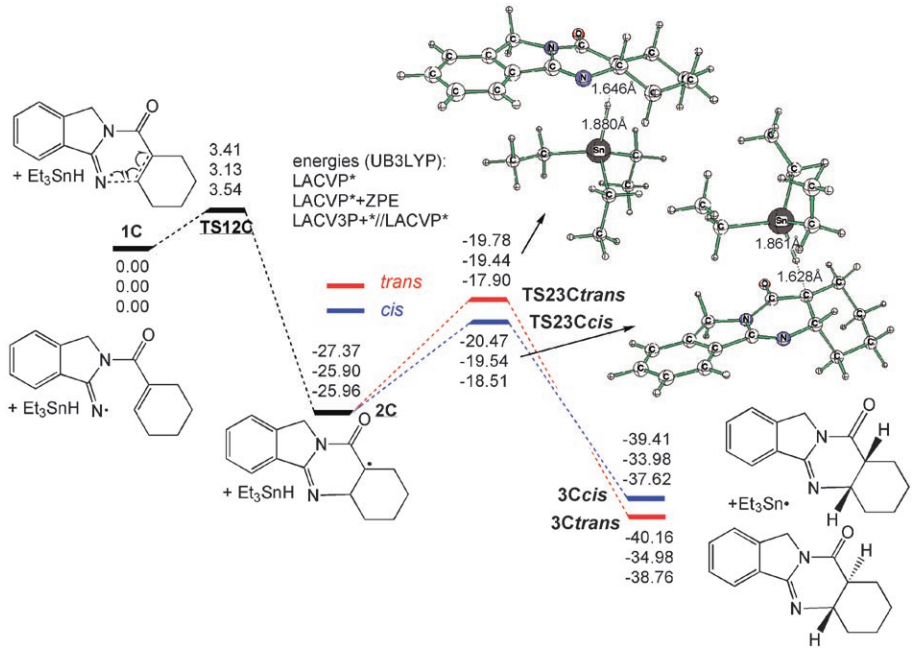


Figure 7. Energetic profile for the radical cyclization with a cyclohexenyl group. The experimental data show the minor stereoisomer is *trans*. Geometries are optimized at the UB3LYP/BS1 level.

ature dependent. Therefore, the formation of the stereogenic centers is controlled by the kinetics of the reaction. This is further confirmed by DFT calculations. As in the case of vinyl substrates, there is first a [1,6] attack of the amide–iminyl radical on the double bond of the cyclohexenyl group (through **TS12C**, see Figure 7). This costs only 3.54 kcal mol^{-1} at the best level (BS2//BS1 level). From **2C**, there are two ways for the hydrogen donor (Et_3SnH in the DFT models instead of Bu_3SnH experimentally) to perform the reduction: either from the opposite face of the new sp^3 C–H bond created by **TS12C** or from the same face. This gives two transition states of reduction, **TS23C*trans*** and **TS23C*cis***. The *cis* process is clearly favored at the BS1 level (0.69 kcal mol^{-1}) and the BS2//BS1 level (0.61 kcal mol^{-1}). Looking at the *trans* transition state, one can see the radical is making a pocket, inside which Et_3SnH should approach to transfer the hydrogen atom. In the *cis* approach, there is less steric repulsion between the radical and Et_3SnH, with the cyclohexyl moiety being distorted on the opposite face. This is why the kinetic product is mainly obtained during this reaction: the approach of the reductor Bu_3SnH is easier in the *cis* configuration.

Computational Details

All of the structures were calculated by DFT by using the unrestricted hybrid functional UB3LYP[51] and the double-zeta basis set LACVP(d),[52] henceforth termed BS1, which includes an effective core potential for heavier elements like Sn. In geometry optimization procedures, we use the JAGUAR 6.5[53] program and subsequently employ the Gaussian 03[54] software for analytic frequency calculations. Reaction pathways were verified by a scan along a given coordinate, while optimization was free along all other coordinates. Single-point calculations were carried out, on the optimal species, with the larger basis set LACV3P(d,p), henceforth termed BS2, for energy evaluation. These calculations are labeled in the usual way as being performed at the BS2//BS1 level. The data are summarized in the Supporting Information.

Conclusion

N-Acyl-*N*-(2-iodobenzyl)-cyanamides are a new and quite effective source of amide–iminyl radicals. Their reactivity opens up a general access to pyrroloquinazoline-type polycyclic *N*-heterocycles through radical processes. A broad variety of pyrimidones fused with alkyl, aryl, or heteroaryl moieties can be prepared in this way. As an illustration of this transformation, luotonin A, a naturally occurring alkaloid, has been prepared through a tin-free radical key step. Another field of reactivity could be discovered in the case of suitably designed aromatic *N*-acylcyanamides that released methyl, methoxy, and fluorine radicals in an unprecedented homolytic substitution. Theoretical work aimed at the elucidation of the mechanism has been pursued in closed relationship with the experimental study and has corroborated the bench results to provide a complete study of the reactivity of *N*-acylcyanamides.

Experimental Section

General: ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature at 400 MHz on an ARX 400 Bruker spectrometer. Chemical shifts (δ) are reported in ppm referenced to the residual proton resonances of the solvents. Coupling constants are expressed in Hertz. We use the notation (I), (II), (III), and (IV) to characterize primary, secondary, tertiary, and quaternary carbon atoms. IR spectra were recorded with a Bruker Tensor 27 (ATR diamond) spectrometer. Thin-layer chromatography (TLC) was performed on Merck 60F254 silica gel. Merck Geduran SI silica gel (40–63 μm) was used for column chromatography. The melting points reported were measured with an SMP3 Stuart Scientific melting point apparatus and are uncorrected. THF and Et_2O were distilled over sodium/benzophenone and CH_2Cl_2 was distilled from CaH_2. Compounds **3a**, **5a–f**, **5i–l**, **5o**, **6a–f**, **6i–l**, **6o**, **6s–u**, **7**, **9**, **10a**, **10c–e**, **10i–l**, **10u**, and **11** have been previously described.[1]

Preparation of *N*-acyl-*N*-(2-iodobenzyl)cyanamides 3a–c: Sodium hydride (10 mmol) was added to a cold (0 °C) stirred solution of cyanamide (5 mmol) in THF (15 mL). When gas evolution had ceased, acyl chloride was introduced at 0 °C and the mixture was stirred at room temperature

for 48 h. The solution was then treated with 2-iodobenzylmethanesulfonate (5 mmol) and refluxed overnight before a solution of saturated sodium carbonate was added. Extraction with diethyl ether and drying over $MgSO_4$ gave the expected crude compound, which could be purified by chromatography on silica gel.

***N*-Cyano-*N*-(2-iodobenzyl)pivalamide (3b)**: Yield: 5%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.87$ (d, $J = 7.8$ Hz, 1H; H_{arom}), 7.37 (m, 2H; H_{arom}), 7.07 (m, 1H; H_{arom}), 5.18 (s, 2H; ArCH_2), 1.43 ppm (s, 9H; C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 186.4$ (IV), 139.8 (III), 136.9 (IV), 130.6 (III), 130.2 (III), 128.5 (III), 112.2 (IV), 98.2 (IV), 74.9 (II), 41.8 (IV), 27.0 ppm (I, 3C); IR (neat): $\tilde{\nu} = 2976$, 2168, 1601, 1304, 1213 cm^{-1}.

General procedure for the synthesis of amides: *N*,*N*-Dimethylformamide (DMF; 2 drops) and oxalyl chloride (1 mL, 1.5 equiv) were added to a solution of the appropriate acid (5 mmol) in benzene (15 mL). When gas evolution had ceased, the reaction mixture was concentrated under vacuum to afford the crude acyl chloride, which was used without further purification. Et_3N (15 mmol) was added to a solution of the appropriate amine (5 mmol) in CH_2Cl_2 (20 mL). The acyl chloride (5 mmol) in CH_2Cl_2 (20 mL) was added to this mixture. After 30 min, a solution of saturated ammonium chloride was added. Extraction with CH_2Cl_2 and drying over $MgSO_4$ gave crude amides, which could be purified by chromatography on silica gel or used without further purification.

***N*-(2-Iodobenzyl)-2,6-dimethylbenzamide (5h)**: Yield: 79%; white solid; m.p. 124–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.83$ (m, 1H; H_{arom}), 7.52 (m, 1H; H_{arom}), 7.35 (m, 1H; H_{arom}), 7.14 (m, 1H; H_{arom}), 6.99 (m, 3H; H_{arom}), 6.17 (brs, 1H; NH), 4.67 (d, $J = 5.8$ Hz, 2H; ArCH_2), 2.26 ppm (s, 6H; Ar(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.3$ (IV), 140.4 (IV), 139.6 (III), 137.3 (IV), 134.4 (III), 130.5 (IV, 2C), 129.6 (III), 128.9 (III), 128.8 (III), 127.6 (III, 2C), 99.4 (IV), 48.5 (II), 19.3 ppm (I, 2C); IR (neat): $\tilde{\nu} = 3250$, 3058, 1638, 1505 cm^{-1}; elemental analysis: calcd (%) for $C_{16}H_{16}INO$: C 52.62, H 4.42, N 3.84; found: C 52.69, H 4.44, N 3.85.

***N*-Benzyl-2-iodobenzamide (5n)**: Yield: 100%; yellow solid; m.p. 104–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.79$ (d, $J = 8.1$ Hz, 1H; H_{arom}), 7.35–7.24 (m, 7H; H_{arom}), 7.02 (m, 1H; H_{arom}), 6.49 (brs, 1H; NH), 4.52 ppm (d, $J = 5.8$ Hz, 2H; ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 169.3 (IV), 141.9 (IV), 139.8 (III), 137.7 (IV), 131.0 (III), 128.6 (III, 2C), 128.2 (III), 128.1 (III, 3C), 127.5 (III), 92.6 (IV), 44.0 ppm (II); IR (neat): $\tilde{\nu} = 3269$, 1640, 1584, 1518 cm^{-1}; elemental analysis: calcd (%) for $C_{14}H_{12}INO$: C 49.87, H 3.59, N 4.15; found: C 49.68, H 3.51, N 4.07.

2-Iodo-*N*-(4-(trifluoromethyl)benzyl)benzamide (5m): Yield: 64%; white solid; m.p. 163 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.85$ (dd, $J = 8.1$, 1.0 Hz, 1H; H_{arom}), 7.60 (d, $J = 8.1$ Hz, 2H; H_{arom}), 7.52 (d, $J = 8.1$ Hz, 2H; H_{arom}), 7.39 (m, 2H; H_{arom}), 7.10 (m, 1H; H_{arom}), 6.27 (brs, 1H; N*H*), 4.68 ppm (d, $J = 6.0$ Hz, 2H; ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 169.5 (IV), 141.8 (IV), 140.1 (III), 131.5 (III), 128.5 (III), 128.4 (III, 2C), 128.3 (III), 125.8 (III), 125.7 (III), 92.5 (IV), 43.7 ppm (II); IR (neat): $\tilde{\nu} =$ 3261, 1325, 903, 723 cm^{-1}; HRMS (ES+): *m*/*z*: calcd for $C_{15}H_{11}NOF_3NaI$: 427.9735; found: 427.9740; elemental analysis: calcd for $C_{15}H_{11}F_3INO$: C 44.47, H 2.74, N 3.46; found: C 44.37, H 2.69, N 3.42.

General procedure for the preparation of *N*-acylcyanamides:

Method A: Sodium hydride (1.1 equiv) was added to a solution of the amide (1 mmol) in distilled THF (8 mL). After gas evolution, cyanogen bromide (3 equiv) was added and the mixture was stirred at room temperature. After 20 h, the reaction mixture was filtered through a short pad of silica gel and the filtrate was concentrated. The solid obtained was purified on silica gel to give the *N*-acylcyanamide. The remaining starting material was also isolated.

Method B: Sodium carbonate (2 equiv) and *N*-(2-iodobenzyl)amine (1 equiv) in diethyl ether (2.5 mL) were added to a solution of cyanogen bromide (10 mmol, 1 equiv) in diethyl ether (2.5 mL) at −15 to −20 °C. The reaction mixture was stirred for 2 h and then allowed to warm to 0 °C. The mixture was filtered through Celite and concentrated. It was then purified on silica gel (petroleum ether/ethyl acetate 8:2) to afford the cyanamide as a white solid. The *N*-(2-iodobenzyl)cyanamide (258 mg, 1 mmol, 1 equiv) was dissolved in a mixture of water and THF (1:1, 3 mL) and KOH (56 mg, 1 equiv) was added. The mixture was stirred for 30 min and concentrated under reduced pressure. Water was removed by azeotropic evaporation with toluene.

The previously prepared potassium salt of the cyanamide was taken up in benzene (1 mL) and the acyl chloride (2 equiv) was added dropwise at 0 °C. After 2 h, the mixture was extracted with dichloromethane and washed with water. The organic phase was dried with magnesium sulfate, filtered, and concentrated under reduced pressure. It was purified on silica gel to afford the acyl cyanamide.

***N*-Cyano-*N*-(2-iodobenzyl)-4-methoxybenzamide (6g)**: Yield: 93% (method B); white paste; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.94$–7.87 (m, 3H; H_{arom}), 7.42 (m, 2H; H_{arom}), 7.09 (t, $J = 6.3$ Hz, 1H; H_{arom}), 6.96 (d, $J = 8.6$ Hz, 2H; H_{arom}), 4.92 (s, 2H; ArCH_2), 3.86 ppm (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 167.6$ (IV), 163.8 (IV), 140.2 (III), 136.1 (IV), 131.4 (III, 2C), 130.9 (III), 130.8 (III), 128.9 (III), 122.6 (IV), 114.0 (III, 2C), 111.1 (IV), 99.4 (IV), 55.7 (II), 55.5 ppm (I); IR (neat): $\tilde{\nu} =$ 2935, 2841, 2231, 1697, 1604 cm^{-1}.

***N*-Cyano-*N*-(2-iodobenzyl)-2,6-dimethylbenzamide (6h)**: Yield: 61% (method A); white paste; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.92$ (dd, $J =$ 7.8, 1.0 Hz, 1H; H_{arom}), 7.49 (dd, $J = 7.6$, 1.5 Hz, 1H; H_{arom}), 7.41 (td, $J =$ 7.6, 1.3 Hz, 1H; H_{arom}), 7.26 (t, $J = 7.6$ Hz, 1H; H_{arom}), 7.10 (m, 3H; H_{arom}), 5.04 (s, 2H; ArCH_2), 2.37 ppm (s, 6H; Ar(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.2$ (IV), 140.3 (III), 135.9 (IV), 134.7 (IV, 2C), 132.7 (IV), 130.9 (III), 130.8 (III), 130.7 (III), 128.9 (III), 127.9 (III, 2C), 109.1 (IV), 99.8 (IV), 54.2 (II), 19.3 ppm (I, 2C); IR (neat): $\tilde{\nu} = 2924$, 2234, 1713 cm^{-1}; HRMS (ES+): *m*/*z*: calcd for $C_{17}H_{15}N_2ONaI$: 413.0127; found: 413.0134; elemental analysis: calcd (%) for $C_{17}H_{15}IN_2O$: C 52.33, H 3.87, N 7.18; found: C 52.22, H 3.95, N 7.15.

***N*-Cyano-*N*-(2-iodobenzyl)-2,6-dimethoxybenzamide (6p)**: Yield: 37% (method B); pale-yellow solid; m.p. 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.89$ (d, $J = 7.8$ Hz, 1H; H_{arom}), 7.50 (d, $J = 7.6$ Hz, 1H; H_{arom}), 7.42–7.35 (m, 2H; H_{arom}), 7.04 (t, $J = 7.6$ Hz, 1H; H_{arom}), 6.59 (d, $J = 8.3$ Hz, 2H; H_{arom}), 4.97 (s, 2H; ArCH_2), 3.87 ppm (s, 6H; Ar-(OCH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.9$ (IV), 157.7 (IV), 139.8 (III), 136.0 (IV), 133.1 (III), 130.1 (III), 128.8 (III), 128.7 (III), 110.7 (IV), 110.1 (IV), 103.9 (III, 2C), 98.5 (IV), 56.1 (I, 2C), 54.3 ppm (II); IR (neat): $\tilde{\nu} = 2939$, 2841, 2236, 1718, 1595, 1475 cm^{-1}; HRMS (ES+): *m*/*z*: calcd for $C_{17}H_{15}N_2O_3NaI$: 445.0025; found: 445.036; elemental analysis: calcd (%) for $C_{17}H_{12}N_2O_3I$: C 48.36, H 3.58, N 6.63; found: C 48.49, H 3.43, N 6.53.

***N*-Cyano-2,6-difluoro-*N*-(2-iodobenzyl)benzamide (6q)**: Yield: 84% (method B); off-white solid; m.p. 100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.92$ (d, $J = 8.1$ Hz, 1H; H_{arom}), 7.52 (m, 1H; H_{arom}), 7.42 (d, $J =$ 4.3 Hz, 2H; H_{arom}), 7.10 (m, 1H; H_{arom}), 7.04 (t, $J = 8.1$ Hz, 2H; H_{arom}), 5.01 ppm (s, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.9$ (IV), 158.4 (IV, 2C, d, $J = 252$ Hz), 140.2 (III), 135.1 (IV), 134.2 (III, t, $J =$ 10 Hz), 130.9 (III), 129.9 (III), 129.0 (III), 112.4 (III, 2C, d, $J = 24$ Hz), 110.6 (IV), 108.7 (IV), 99.1 (IV), 54.9 ppm (II); ^{19}F NMR (400 MHz, $CDCl_3$): $\delta = -110.9$ ppm (m); IR (neat): $\tilde{\nu} = 2240$, 1722, 1625, 1470, 731 cm^{-1}; HRMS (ES+): *m*/*z*: calcd for $C_{15}H_9N_2OF_2NaI$: 420.9625; found: 420.9642; elemental analysis: calcd (%) for $C_{15}H_9IN_2OF_2$: C 45.25, H 2.28, N 7.04; found: C 45.31, H 2.02, N 6.78.

***N*-Benzyl-*N*-cyano-2-iodobenzamide (6n)**: Yield: 74% (method A); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.88$ (dd, $J = 8.1$, 0.5 Hz, 1H, H_{arom}), 7.48 (m, 2H, H_{arom}), 7.46–7.39 (m, 4H, H_{arom}), 7.35 (dd, $J = 7.6$, 1.5 Hz, 1H, H_{arom}), 7.21 (td, $J = 7.8$, 1.8 Hz, 1H, H_{arom}), 4.90 ppm (s, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.6$ (IV), 139.8 (III), 138.1 (IV), 133.2 (IV), 132.6 (III), 129.3 (III), 129.2 (III), 129.1 (III, 3C), 128.3 (III), 127.9 (III), 109.6 (IV), 91.8 (IV), 50.7 ppm (II); IR (neat): $\tilde{\nu} = 2237$, 1716 cm^{-1}; HRMS (ES+): *m*/*z*: calcd for $C_{15}H_{11}N_2ONaI$: 384.9814; found: 384.9824.

***N*-Cyano-2-iodo-*N*-(4-(trifluoromethyl)benzyl)benzamide (6m)**: Yield: 37% (method A); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.89$ (d, $J = 8.1$ Hz, 1H; H_{arom}), 7.69 (d, $J = 8.1$ Hz, 2H; H_{arom}), 7.61 (d, $J = 8.1$ Hz, 2H; H_{arom}), 7.46 (t, $J = 7.6$ Hz, 1H; H_{arom}), 7.36 (d, $J = 7.6$ Hz, 1H; H_{arom}), 7.22 (td, $J = 7.8$, 1.5 Hz, 1H; H_{arom}), 4.95 ppm (s, 2H; ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.5$ (IV), 139.9 (III), 137.8 (IV), 137.1 (IV), 132.8 (III), 131.4 (IV), 129.6 (III, 2C), 128.5 (III), 128.1 (III), 126.2 (III),

126.1 (III), 122.5 (IV), 109.4 (IV), 91.8 (IV), 50.1 ppm (II); IR (neat): $\tilde{\nu}$= 3057, 2237, 1717, 1323 cm^{-1}; elemental analysis: calcd (%) for $C_{16}H_{10}N_2OF_3I$: C 44.67, H 2.34, N 6.51; found: C 44.57, H 2.32, N 6.38.

(*E*)-*N*-Cyano-*N*-(2-iodobenzyl)but-2-enamide (6k): Yield: 74% (method B); white solid; m.p. 62°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.86 (dd, J=7.8, 1.0 Hz, 1H; H_{arom}), 7.35 (td, J=7.6, 1.0 Hz, 1H; H_{arom}), 7.29 (m, 1H; H_{arom}), 7.24 (m, 1H; CH_3–*CH*=CH–C=O), 7.02 (td, J=7.6, 1.5 Hz, 1H; H_{arom}), 6.59 (dd, J=14.9, 1.8 Hz, 1H; CH_3–CH=*CH*–C=O), 4.81 (s, 2H; Ar*CH*$_2$), 1.96 ppm (dd, J=7.1, 1.8 Hz, 3H; *CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.1 (IV), 149.9 (III), 139.9 (III), 135.9 (IV), 130.5 (III), 130.0 (III), 128.8 (III), 119.1 (III), 109.9 (IV), 99.1 (IV), 53.8 (II), 18.5 ppm (I); IR (neat): $\tilde{\nu}$=3058, 2942, 2231, 1704 cm^{-1}; HRMS (ES+): m/z: calcd for $C_{12}H_{11}N_2ONaI$: 348.9814; found: 348.9802.

Typical cyclization procedure: Tributyltin hydride (0.5 mmol, 2 equiv) and AIBN (0.25 mmol, 1 equiv) in benzene (4 mL) were added to a degassed solution of *N*-acylcyanamide (0.25 mmol) in refluxing benzene (11 mL) over 2 h. The reflux was maintained until monitoring of the reaction by TLC showed total consumption of the starting material. Once the mixture was back to room temperature, aqueous NaOH (1 M, 15 mL) was added and the mixture was stirred for 30 min. The organic phase was extracted with ethyl acetate (2×20 mL), dried over $MgSO_4$, and concentrated under vacuum. Purification of the residue by silica-gel flash chromatography afforded the cyclization products.

7-Methoxyisoindolo[1,2-*b*]quinazolin-10(12*H*)one (10g): Yield: 70%; white solid; m.p. 206–208°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.26 (d, J=8.8 Hz, 1H; H_{arom}), 8.15 (d, J=7.3 Hz, 1H; H_{arom}), 7.60 (m, 2H; H_{arom}), 7.58 (m, 1H; H_{arom}), 7.21 (d, J=1.9 Hz, 1H; H_{arom}), 7.05 (dd, J=8.7, 1.9 Hz, 1H; H_{arom}), 5.12 (s, 2H; Ar*CH*$_2$), 3.94 ppm (s, 3H; O*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.7 (IV), 160.4 (IV), 155.8 (IV), 151.9 (IV), 139.9 (IV), 132.8 (IV), 132.4 (III), 128.9 (III), 128.0 (III), 123.7 (III), 123.5 (III), 116.7 (III), 114.3 (IV), 108.1 (III), 55.8 (I), 49.8 ppm (II); IR (neat): $\tilde{\nu}$=2926, 1664, 1608 cm^{-1}; HRMS (ES+): m/z: calcd for $C_{16}H_{12}N_2O_2Na$: 287.0796; found: 287.0806.

2-Benzyl-3-iminoisoindolin-1-one (14n): Yield: 86%; pale-yellow solid; m.p. 122–123°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.30 (br s, 1H, C=N*H*), 7.86 (m, 1H; H_{arom}), 7.73 (m, 1H; H_{arom}), 7.64 (m, 2H; H_{arom}), 7.42 (d, J=7.1 Hz, 2H; H_{arom}), 7.30 (t, J=7.1 Hz, 2H; H_{arom}), 7.26 (d, J=7.3 Hz, 1H; H_{arom}), 5.02 ppm (s, 2H, Ar*CH*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.9 (IV), 160.3 (IV), 136.8 (IV), 133.2 (III), 132.5 (III), 132.4 (IV), 131.1 (IV), 128.8 (III, 2C), 128.2 (III, 2C), 127.7 (III), 123.6 (III), 121.3 (III), 42.0 ppm (II); IR (neat): $\tilde{\nu}$=3276, 1726, 1649 cm^{-1}; MS: m/z: 237 $[M+H]^+$, 259 $[M+Na]^+$; HRMS (ES+): m/z: calcd for $C_{15}H_{13}N_2O$: 237.1028; found: 237.1017.

3-Imino-2-(4-(trifluoromethyl)benzyl)isoindolin-1-one (14m): Yield: 90%; off-white solid; m.p. 136°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.6 (m, 1H; H_{arom}), 7.25 (m, 4H; H_{arom}), 6.90 (m, 2H; H_{arom}), 6.82 (m, 1H; H_{arom}), 4.75 ppm (s, 2H; Ar*CH*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.2 (IV), 159.7 (IV), 141.5 (IV), 134.9 (IV), 132.6 (III), 132.1 (IV), 132.0 (III), 131.3 (IV), 128.9 (III, 2C), 125.6 (III), 125.5 (III), 123.5 (IV), 123.2 (III), 120.8 (III), 41.3 ppm (II); IR (neat): $\tilde{\nu}$=3281, 2925, 1722, 1653 cm^{-1}; HRMS (ES+): m/z: calcd for $C_{16}H_{12}N_2OF_3$: 305.0902; found: 305.0910; elemental analysis: calcd (%) for $C_{16}H_{11}N_2OF_3$: C 63.16, H 3.64, N 9.21; found: C 62.84, H 3.63, N 9.02.

9-Methylisoindolo[1,2-*b*]quinazolin-10(12*H*)one (10h): Yield: 88%; white solid; m.p. 236–237°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.11 (d, J=7.6 Hz, 1H; H_{arom}), 7.64–7.53 (m, 5H; H_{arom}), 7.19 (d, J=7.3 Hz, 1H; H_{arom}), 5.06 (s, 2H; Ar*CH*$_2$), 2.92 ppm (s, 3H, Ar*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.4 (IV), 154.7 (IV), 151.2 (IV), 141.2 (IV), 139.8 (IV), 133.4 (III), 132.8 (IV), 132.2 (III), 129.2 (III), 128.9 (III), 125.8 (III, IV), 123.5 (III), 49.9 (II), 23.2 ppm (I); IR (neat): $\tilde{\nu}$=2924, 1668, 1629, 1594 cm^{-1}; MS: m/z: 249 $[M+H]^+$.

9-Methoxyisoindolo[1,2-*b*]quinazolin-10(12*H*)one (10p): Yield: 49%; white solid; m.p. 254°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.12 (d, J=7.6 Hz, 1H; H_{arom}), 7.65 (t, J=8.1 Hz, 1H; H_{arom}), 7.59 (m, 2H; H_{arom}), 7.55 (m, 1H; H_{arom}), 7.38 (d, J=8.1 Hz, 1H; H_{arom}), 6.89 (d, J=8.1 Hz, 1H; H_{arom}), 5.09 (s, 2H; Ar*CH*$_2$), 4.0 ppm (s, 3H; ArO*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.5 (IV), 159.2 (IV), 155.4 (IV), 152.4 (IV), 140.1 (IV), 134.6 (III), 132.8 (IV), 132.4 (III), 128.9 (III), 123.6 (III, 2C), 119.8 (III), 110.6 (IV), 107.7 (III), 56.4 (I), 49.9 ppm (II); IR (neat): $\tilde{\nu}$= 2924, 2850, 1677 cm^{-1}; HRMS (ES+): m/z: calcd for $C_{16}H_{12}N_2O_2Na$: 287.0796; found: 287.0785.

9-Fluoroisoindolo[1,2-*b*]quinazolin-10(12*H*)one (10q): Yield: 73%; off-white solid; m.p. 256°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.15 (d, J=7.6 Hz, 1H; H_{arom}), 7.6 (m, 5H; H_{arom}), 7.12 (m, 1H; H_{arom}), 5.15 ppm (s, 2H; Ar*CH*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=163.1 (IV), 159.2 (IV, d, J=243 Hz), 157.9 (IV), 155.9 (IV), 151.9 (IV), 139.9 (IV), 134.7 (III, d, J=10.3 Hz), 132.8 (III), 132.5 (IV), 129.1 (III), 123.8 (III), 123.7 (III), 123.4 (III, d, J=3.4 Hz), 113.1 (III), 50.0 ppm (II); ^{19}F NMR (400 MHz, $CDCl_3$): δ=−110.9 ppm (m); IR (neat): $\tilde{\nu}$=1672, 1609, 730 cm^{-1}; MS: m/z: 253 $[M+H]^+$; HRMS (ES+): m/z: calcd for $C_{15}H_{10}N_2OF$: 253.0777; found: 253.0765.

6-Fluoroisoindolo[1,2-*b*]quinazolin-10(12*H*)one (13): Yield: 15%; off-white solid; m.p. 248°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.25 (d, J=7.6 Hz, 1H; H_{arom}), 8.15 (d, J=7.8 Hz, 1H; H_{arom}), 7.65 (m, 2H; H_{arom}), 7.58 (m, 1H; H_{arom}), 7.52 (m, 1H; H_{arom}), 7.43 (m, 1H; H_{arom}), 5.17 ppm (s, 2H; Ar*CH*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.9 (IV), 159.8 (IV), 157.4 (IV, d, J=253 Hz), 155.6 (IV), 139.8 (III), 139.1 (IV, d, J=12.0 Hz), 132.8 (III), 132.6 (IV), 129.1 (III), 126.4 (III, d, J=7.8 Hz), 124.2 (III), 123.6 (III), 122.7 (IV), 122.2 (III, d, J=4.3 Hz), 119.8 (III, d, J=19.8 Hz), 50.1 ppm (II); ^{19}F NMR (400 MHz, $CDCl_3$): δ=−125.1 ppm (m); IR (neat): $\tilde{\nu}$=2955, 1677, 1625, 1613, 782 cm^{-1}; HRMS (ES+): m/z: calcd for $C_{15}H_9N_2OFNa$: 275.0597; found: 275.0594.

2-Methyl-2,3-dihydropyrimido[2,1-*a*]isoindol-4(6*H*)one (10r): Yield: 79%; pale-yellow crystals; m.p. 149°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.85 (m, 1H; H_{arom}), 7.50 (m, 1H; H_{arom}), 7.41 (m, 2H; H_{arom}), 4.81, 4.73 (AB, d, J=16.7 Hz, 1H each; C*H*$_2$Ar), 3.95 (m, 1H; CH_3–C*H*–CH_2–C=O), 2.61 (dd, J=16.9, 5.8 Hz, 1H; CH_3–CH–CH*H*–C=O), 2.27 (dd, J=16.9, 10.6 Hz, 1H; CH_3–CH–C*H*H–C=O), 1.38 ppm (d, J=6.8 Hz, 3H; *CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.6 (IV), 154.3 (IV), 139.8 (IV, 2C), 132.1 (III), 128.5 (III), 123.4 (III), 123.3 (III), 51.3 (III), 48.3 (II), 36.9 (II), 21.9 ppm (I); IR (neat): $\tilde{\nu}$=2965, 2928, 1696, 1679, 1364 cm^{-1}; HRMS (ES+): m/z: calcd for $C_{12}H_{13}N_2O$: 201.1028; found: 201.1022.

CCDC-648622 contains the supplementary crystallographic data for compound **10r**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Ethyl 2-(3-hydroxy-5*H*-imidazo[2,1-a]isoindol-2-yl)acetate (10s): Yield: 51%; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.75 (d, J=7.6 Hz, 1H; H_{arom}), 7.49 (m, 2H; H_{arom}), 7.34 (t, J=7.6 Hz, 1H; H_{arom}), 4.73 (s, 2H; Ar*CH*$_2$), 3.96–3.84 (m, 3H; O*CH*$_2$CH$_3$, *CH*HC=O), 3.15 (d, J=15.9 Hz, 1H; CH*H*C=O), 1.06 ppm (t, J=7.1 Hz, 3H; *CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=177.9 (IV), 169.5 (IV), 169.0 (IV), 145.9 (IV), 132.8 (III), 128.7 (III), 126.8 (IV), 124.6 (III), 123.9 (III), 80.6 (IV), 60.9 (II), 44.9 (II), 35.6 (II), 14.0 ppm (I); IR (neat): $\tilde{\nu}$=2926, 2854, 1735, 1658 cm^{-1}.

Ethyl 4-hydroxy-2,6-dihydropyrimido[2,1-*a*]isoindole-3-carboxylate (10s′): Yield: 28%; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.99 (d, J=7.6 Hz, 1H; H_{arom}), 7.64 (m, 1H; H_{arom}), 7.52 (m, 2H; H_{arom}), 4.74, 4.65 (AB d, J=16.4 Hz, 1H each; Ar*CH*$_2$), 4.12–4.04 (m, 2H; O*CH*$_2$CH$_3$), 3.12 (s, 2H; *CH*$_2$N=C), 1.15 ppm (t, J=7.1 Hz, 3H; OCH$_2$*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.8 (IV), 168.9 (IV), 145.9 (IV, 2C), 133.9 (III), 129.2 (III), 126.3 (IV), 124.6 (III, 2C), 97.4 (IV), 61.1 (II), 45.2 (II), 42.1 (II), 14 ppm (I); HRMS (ES+): m/z: calcd for $C_{14}H_{15}N_2O_3$: 259.1083; found: 259.1071.

Tin-free radical cyclization of 6o to yield luotonin A: A solution of *N*-acylcyanamide **6o** (100 mg, 0.24 mmol) and pyridine (98 μL, 5 equiv) in benzene (14 mL) was refluxed under air and irradiated with a sun lamp (300 W) until monitoring of the reaction by TLC showed total consumption of the starting material. The reaction mixture was concentrated and purified on silica gel (pentane/ethyl acetate 5:5) to give luotonin A (37 mg, 54%).

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