

Radical Cyclization of *N*-Acylcyanamides: Total Synthesis of Luotonin A**

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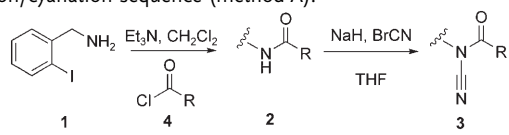
In memory of Marcial Moreno-Mañas

Heterocyclic compounds are of particular interest in medicinal science. This has accelerated the quest for new methods in heterocyclic chemistry. A particular class of alkaloids that incorporate the pyrroloquinazoline chromophore have been isolated from natural sources^[1] and display a wide range of biological activities.^[2] Among them, luotonin A is a human DNA topoisomerase I poison, which has been isolated from *Peganum nigellastrum*, a Chinese medicinal plant.^[3] Ma et al. have examined the biological activity of luotonin A and its analogues,^[4] and Jahng et al. have described structure–activity studies on this class of compounds.^[5] Luotonin A is cytotoxic toward the murine leukemia P388 cell line^[3] by stabilizing the topoisomerase I/DNA complex.^[6] This has established luotonin A as an attractive pyrroloquinazoline target for total synthesis. It appeared to us that we could build the pyrroloquinazoline moiety from *N*-acylcyanamide radical precursors.

Our interest in radical cyclization cascades,^[7,8] especially in the field of heterocyclic synthesis^[9,10,11] prompted us to examine an unprecedented strategy introducing *N*-acylcyanamides as novel radical acceptors. Indeed, to the best of our knowledge, no radical reaction involving these moieties has appeared in the literature. Synthesizing the *N*-acylcyanamides substrates was challenging: the preparation of *N*-acetyl- and *N*-benzoylcyanamides and some of their derivatives has been reported, but those molecules often show a lack of stability.^[12–15] As *N*-acylcyanamides display properties in other fields, for instance, as prodrugs of cyanamide,^[13] enzymatic inhibitors^[16] and heteroanalogues of ethylenes,^[17] there is also an interest in their practical synthesis. We report herein the preparation of stable *N*-acyl-*N*-(2-iodobenzyl)cyanamides and their use as radical partners in cyclization cascade processes, which led to the total synthesis of luotonin A.

N-acyl-*N*-(2-iodobenzyl)-cyanamides **3** were obtained by two different synthetic methods. Acylation of 2-iodobenzylamine (**1**) gave 2-iodobenzylamides **2a–k**, which reacted with cyanogen bromide under basic conditions to yield *N*-acylcyanamides **3a–k** in generally good yields (method A, Table 1). The electrophilic character of the cyanogen bromide reagent limits this acylation/cyanation sequence when nucle-

Table 1: Preparation of *N*-acyl-*N*-(2-iodobenzyl)cyanamides **3a–k** by an acylation/cyanation sequence (method A).



R	Amide 2	Yield [%]	<i>N</i> -acylcyanamide 3	Yield [%]
C ₆ H ₅	2a	86	3a	73
<i>p</i> -NO ₂ -C ₆ H ₅	2b	44	3b	68
<i>p</i> -CF ₃ -C ₆ H ₅	2c	60	3c	58
<i>p</i> -CN-C ₆ H ₅	2d	73	3d	33
<i>p</i> -CO ₂ Me-C ₆ H ₅	2e	90	3e	86
<i>p</i> -Br-C ₆ H ₅	2f	78	3f	47
<i>p</i> -OMe-C ₆ H ₅	2g	57	3g	28
<i>p</i> -C ₅ H ₅ N	2h	73	3h	61
<i>m</i> -C ₅ H ₅ N	2i	56	3i	49
	2j	> 98 ^[6]	3j	17
	2k	> 98 ^[6]	3k	20

ophiles are present in the molecule. For example, *N*-acylcyanamides **3g** and **3j,k** were obtained in lower yields, probably because of the possible reaction of cyanogen bromide with the electron-rich unsaturated compounds **2g** and **2j,k**.^[18] Sensitive substrates were obtained by installing these unsaturated bonds in the last step.

When the steps were reversed, 2-iodobenzylamine (**1**) provided the desired substrates in much better yields through a cyanation/acylation pathway (method B, Table 2).^[19] The vinylic precursors **3j–l** were obtained in good yields, and so were *N*-acylcyanamides **3m,n**, in which the amide function is in conjugation with furyl (73 %) and thienyl substituents (74 %).

We wanted to probe whether the aryl radical obtained from **3a–m** could be trapped by the triple bond of the cyanamide in a 5-*exo*-dig cyclization process, and whether the resulting radical could be captured by an unsaturated bond

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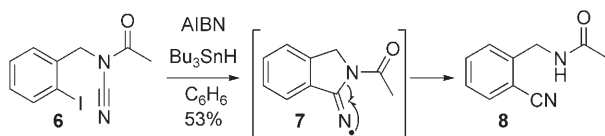
Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

Table 2: Preparation of *N*-acyl-*N*-(2-iodobenzyl)cyanamides **3a–n** by a cyanation/acylation sequence (method B).

R	Product	Yield [%]	R	Product	Yield [%]
	3a	74		3l	54
	3j	70		3m	73
	3k	67		3n	74

conjugated to the amide function. Iminyl radical chemistry has been thoroughly studied in the last decade^[20] and was recently applied to the synthesis of heteroarenes,^[21] notably by means of radical cascade cyclizations.^[22] Nevertheless, *N*-acylcyanamides differ from both nitriles and ynamides^[10] in that they have an additional nitrogen atom. Original reactivities and access to polynitrogenated alkaloid structures might be anticipated.

Under standard radical conditions, simple *N*-acetylcyanamide **6** was transformed into 2-cyanobenzylacetamide (**8**) (53% yield, Scheme 1). Radical **7** is formed after an initial 5-



Scheme 1. 5-*exo*-dig cyclization of substrate **6**.

exo-dig cyclization and undergoes N–C bond cleavage prior to reduction. This transfer has been observed with nitriles.^[23] This preliminary result made us confident that *N*-acylcyanamides **3a–m** could be designed precursors for domino processes. Indeed, they generally reacted smoothly, giving rise to new pyrroloquinazoline heterocycles in 56–99% yield (Table 3). Only *N*-(2-iodobenzyl)-*N*-(4-nitrobenzoyl)cyanamide (**3b**) and furanoyl cyanamide **3m** did not react under radical conditions. The nitro group in **3b** was reduced by tributyltin hydride and degraded upon further exposure to the radical conditions.

N-(2-iodobenzyl)-*N*-(cyclohexanoyl)cyanamide **3k** cyclized in good (71%) yield (1.56:1 mixture of the two diastereomers of tetracyclic compound **9k**). The minor diastereomer crystallized out. X-ray diffraction analysis showed that the minor product has a *trans* ring junction, indicating that the major diastereomer is the *cis* one (entry 8, Table 3).

The intermediate radical resulting from the attack of the aromatic radical on the cyanamide triple bond could react further following two pathways: 1) 6-*endo*-trig addition onto

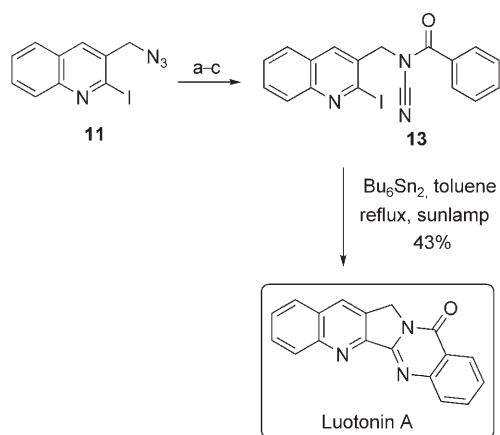
Table 3: Radical cyclization cascade of *N*-acyl-*N*-(2-iodobenzyl)cyanamides **3** to give heterocyclic compounds **9** and **10**.

Entry	R, Precursor	Product	Yield [%]		
1		3a → 9a	71		
2		3c → 9c	72		
3		3d → 9d	99		
4		3e → 9e	74		
5		3h → 9h	56		
6		3i → 9i / 10	79 9i/10 2.2:1		
7		3j → 9j	66		
8		3k → 9k	71 <i>cis/trans</i> 1.56:1		
9		3n → 9n	57		

the unsaturated moiety and subsequent aromatization (or reduction in the case of vinylic derivatives); 2) [1,5] *ipso* substitution followed by rearrangement, thus providing cyclization compounds **9**.^[24] Our preliminary studies in this direction remain inconclusive. Further investigations are beyond the scope of this report and will be the subject of future reports.

We then decided to use this new access to pyrroloquinazolines as the key step for the total synthesis of luotonin A.^[25,2d] A few strategies reported so far involve radical cyclization. For example, Bowman et al. used an intramolecular cascade radical cyclization involving 4-oxo-3,4-dihydroquinazoline-2-carbonitrile in the step leading to the luotonin framework.^[26,9a] Curran et al. synthesized luotonin A and a small library of AB-ring-substituted analogues using a bimolecular radical cascade employing arylisonitrile and propargylquinazolones.^[27]

We considered creating the pyrroloquinazoline skeleton of luotonin A by cyclization of *N*-acylcyanamide **13** (Scheme 2). Azide **11** was prepared from commercially available quinoline chlorocarbaldehyde in four steps (56% overall yield).^[28] Staudinger reduction of the azide delivered



Scheme 2. Total synthesis of luotonin A. Reaction conditions: a) PPh_3 , THF, H_2O ; b) benzoyl chloride, Et_3N , CH_2Cl_2 , 47% (two steps); c) NaH, BrCN, THF, 41%.

an amine, which was benzoylated to give amide **12** in 47% yield (two steps). Cyanation of amide **12** using method A yielded *N*-acylcyanamide **13** in 41% yield.^[29] Under radical conditions with tributyltin hydride, reaction of **13** did not afford the cyclization compound. The reaction proceeded with low conversion that turned into degradation if the precursor was maintained under the same reaction conditions. Gratifyingly atom-transfer conditions using hexabutylditin in refluxing toluene under irradiation for 6 h successfully yielded luotonin A in 43% yield.

In conclusion, *N*-(2-iodobenzyl)-*N*-acylcyanamides are a new and quite effective source of amide-iminyl radicals. This opens 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 this way, which was illustrated by a rapid total synthesis of the naturally occurring alkaloid luotonin A. Work aiming at the elucidation of the mechanism, as well as extending the scope of reactions of *N*-acylcyanamides is in progress and will be reported in due course.

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- [28] See the Supporting Information for complete procedure.
- [29] Method A is fully described in the Supporting Information.