Guanidines

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Radical Synthesis of Guanidines from *N*-Acyl Cyanamides**

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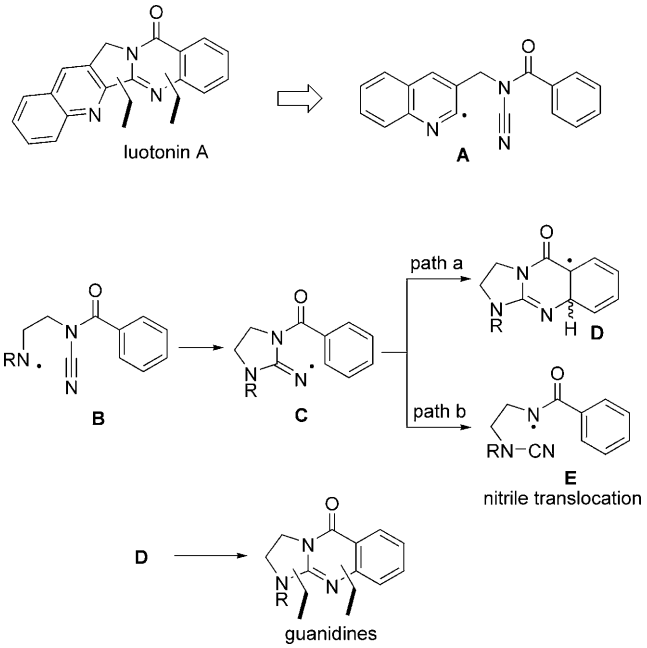
Guanidines—especially those embedded into polyclic frameworks—are an important structural unit of valuable synthetic intermediates and/or natural products.[1] Therefore guanidines are appealing targets for total synthesis,[2] bio-inspired molecular recognition,[3] organocatalysis,[4] and coordination chemistry.[5] The development of innovative, efficient, and flexible methods to access these compounds thus remains an important goal.[6]

Radical cascade cyclization reactions have become an important tool used to construct polycyclic structures, in particular nitrogen-containing heterocycles.[7] Our research group has introduced *N*-acyl cyanamides as novel radical partners for the preparation of quinazolinone systems such as luotonin A, through a radical domino sequence.[8]

Our approach to luotonin A included a retrosynthetic disconnection featuring the cyclization of a 2-quinolyl radical to an acylcyanamide **A** (Scheme 1). We reasoned that switching the initial carbon radical to a nitrogen-centered one (as in **B**) would provide an entry to cyclic guanidines after aromatic substitution of iminyl radical **C**, via tricyclic radical **D** (path a). To the best of our knowledge, a radical synthesis of guanidines is unprecedented in the literature. Iminyl radical **C** could also lead to a competing and unproductive β-elimination of an amidyl radical and deliver **E**, where the cyano group of the starting cyanamide has translocated to form a nitrogen-centered radical (path b). Nonetheless, our previous results with carbon-centered radicals made us confident that this would, at worst, be a minor path.

Spagnolo and co-workers have shown that the stannylaminyl radicals obtained from reactions of tin radicals with alkyl azides add efficiently to the electrophilic cyano group.[9] We thus decided to follow the same strategy, even though the reactivity of cyanamides may differ from that of nitriles because of the added nitrogen substituent. Substrate **1a** was selected to validate our approach and was assembled in a very modular fashion from the corresponding amine, cyanogen bromide, and benzoyl chloride.



Scheme 1. Access to luotonin A and proposed route to guanidine derivatives.

We initially used the reaction conditions developed in our previous work; Bu_3SnH (2 equiv) and AIBN (1.5 equiv) were slowly added (0.2 mol h^{-1}) to **1a** in benzene at reflux.[8] Gratifyingly, the desired tricyclic guanidine **2a** was isolated, but in a modest 41% yield (Table 1, entry 1).

Replacement of benzene by toluene or *t*BuOH reduced the yields (Table 1, entries 2 and 3). Slow addition of Bu_3SnH from a syringe pump was required and resulted in the yields increasing from 20% (addition of Bu_3SnH in one batch; Table 1, entry 4), to 41% (0.2 mmol h^{-1}; Table 1, entry 1), and then to 76% (0.06 mmol h^{-1}; Table 1, entry 5). Lowering the amount of tin was not helpful (43% yield with 1.2 equiv of Bu_3SnH; Table 1, entry 6). Switching to $[(CH_3)_3Si]_3SiH$ or running the reaction at room temperature with initiation by light led to a near complete shutdown of the reaction (Table 1, entries 7 and 8). Therefore, the best yield was obtained by slowly adding Bu_3SnH (0.06 mol h^{-1}, 2 equiv) and AIBN (1.5 equiv) to a solution of ω-azido *N*-acyl cyanamide in benzene at reflux (Table 1, entry 5).

With these optimized reaction conditions in hand, we next examined the scope for the radical synthesis of guanidine

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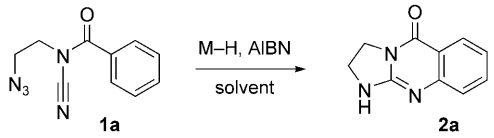
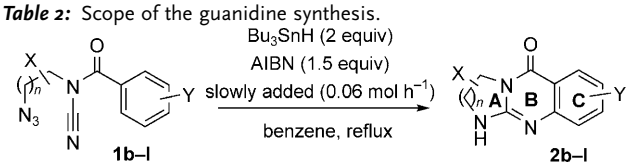
Table 1: Optimization of the guanidine radical synthesis.



Entry	Hydride (equiv)	ν_{add} [mmol h^{-1}]	Solvent, T[a]	Yield [%][b]
1	Bu_3SnH (2)	0.2	benzene, Δ	41
2	Bu_3SnH (2)	0.2	toluene, Δ	30
3	Bu_3SnH (2)	0.2	*t*BuOH, Δ	31
4	Bu_3SnH (2)	one batch	benzene, Δ	20
5	**Bu_3SnH (2)**	**0.06**	**benzene, Δ**	**76**
6	Bu_3SnH (1.2)	0.06	benzene, Δ	43
7	$[(CH_3)_3Si]_3SiH$ (2)	0.06	benzene, Δ	<10
8	Bu_3SnH (2)	0.06	benzene, RT[c]	<10

[a] Reaction heated to reflux unless otherwise noted. [a] Yield of isolated product. [b] Reaction was initiated by irradiation. AIBN = 2,2′-azobisisobutyronitrile.

Table 2: Scope of the guanidine synthesis.



Entry	Substrate	Guanidine	Yield [%][a]
1	**1b**	**2b**	76
2	**1c**	**2c**	75
3	**1d**	**2d**	77
4	**1e**	**2e**	59
5	**1f**	**2f**	24
6	**1g**	**2g**	82
7	**1h**	**2h**	82
8	**1i**	**2i**	81
9	**1j**	**2j**	71
10	**1k**	**2k**	49
11	**1l**	**2l**	69

[a] Yield of isolated product.

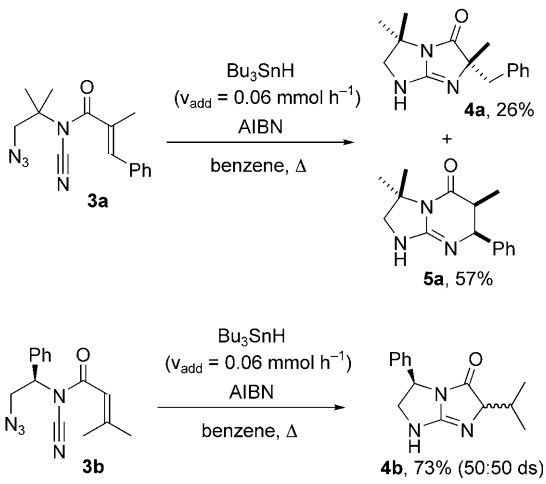
(Table 2). The substitution on the azide side of the molecule was examined first. The 5,6,6-tricyclic guanidine derivatives were obtained in good yields (Table 2, entries 1–3). The yields decreased gradually when the size of ring A was increased from five- to six- and to seven-membered rings (76% for **2a**, Table 1, entry 5; 59% for **2e**, and 24% for **2f**, Table 2, entries 4, and 5, respectively). In this latter case, as the uncyclized amino cyanamide was observed in the crude reaction mixture. Therefore access to 7,6,6-tricyclic guanidines may be affected by a competitive 1,5-hydrogen transfer.

The introduction of substituents in the *para* position of the aromatic group did not affect the radical cascade. Substrates **1g** (electron-withdrawing group) and **1h** (electron-donating group) behaved similarly, and delivered the desired adducts in 82% yield (Table 2, entries 6 and 7). Naphthyl and pyridyl derivatives **1i** and **1j** delivered **2i** and **2j**, respectively, in good yields (Table 2, entries 8 and 9). On the other hand, a thiophene substituent proved more fragile, and **2k** was isolated in the somewhat diminished yield of 49% (Table 2, entry 10). Finally, cyanamide **1l** led to desmethyl adduct **2l** via a final radical aromatization through extrusion of a methyl radical.[8b]

In all the cases where the final rearomatization proceeded by hydrogen abstraction, the process is formally a radical C–H activation.[10] The reaction is thus complementary to metal-mediated approaches, in particular the rhodium-catalyzed C–H insertion of guanidines developed by Du Bois and co-workers.[2c,e] Also, we never observed any sign of the cyano-translocated products.

Replacement of the final aryl acceptor with an olefin delivered new insights into the cascade process (Scheme 2). Azide **3a**, which features an α-methyl cinnamyl substituent, provided two bicyclic guanidines; one with a 5,5 framework (**4a**, 26%), and another with a 5,6 framework (**5a**, 57%).[11] These compounds arose from a final 5-*exo*-*trig* cyclization (**4a**), or a 6-*endo*-*trig* cyclization and subsequent diastereoselective hydrogen transfer (**5a**). The single diastereomer of guanidine **5a** was determined to be *cis* by examination of its coupling constants (see the Supporting Information for details). Introduction of an additional substituent on the β carbon atom (as in **3b**) blocked the 6-*endo*-*trig* process—no diastereoselectivity was observed in that case.

In conclusion, bi- and tricyclic guanidines were efficiently prepared for the first time via a radical domino process involving cyanamides as relay partners. The adducts obtained are a new class of molecules, whose architecture should prove attractive to the chemical community at large.



Scheme 2. Extension to *N*-enoyl cyanamides ds = diastereoselectivity.

Experimental Section

Bu_3SnH (0.4 mmol, 2 equiv, 108 μL) and AIBN (0.24 mmol, 1.2 equiv, 39 mg) in benzene (3 mL) were added over 6.5 h (0.06 mmol h^{-1} relative to Bu_3SnH) to a degassed solution of **1b** (0.20 mmol, 58 mg) and AIBN (0.06 mmol, 0.3 equiv, 10 mg) in benzene (9 mL) at reflux. The resulting solution was heated at reflux for an additional hour, cooled to RT and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: pentane/EtOAc/EtOH = 5:5:1) to afford the desired guanidine **2b** (40 mg, 76%) as a white solid. m.p. = 237–239 °C; IR (neat): $\tilde{\nu}$ = 1681, 1650, 1608, 758, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.98–4.14 (m, 1H, NCH*H*), 4.66 (dd, *J* = 11.8, 9.4 Hz, 1H, NC*H*H), 5.17 (t, *J* = 8.3 Hz, 1H, PhC*H*), 6.86 (d, *J* = 8.2 Hz, 1H, arom), 7.15 (t, *J* = 7.5 Hz, 1H, arom), 7.34–7.50 (m, 6H, arom), 7.57 (bs, 1H, NH), 8.11 ppm (d, *J* = 8.0 Hz, 1H, arom); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.2 (NCH_2), 56.3 (Ph*CH*), 118.1 (C, arom), 123.1 (CH, arom), 124.2 (CH, arom), 126.5 (CH, arom), 126.8 (CH, arom), 129.1 (CH, arom), 129.5 (CH, arom), 134.5 (CH, arom), 140.2 (C, arom), 150.3 (C, arom), 154.3 (NC=N), 161.0 ppm (C=O); HRMS: *m/z* calcd for $C_{16}H_{14}N_3O$ ($[M+H]^+$): 264.1131; found: 264.1130.

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