ORGANIC LETTERS

2009
Vol. 11, No. 21
5018−5021

Gold(III) Chloride Catalyzed Synthesis of 1-Cyanoisoindoles

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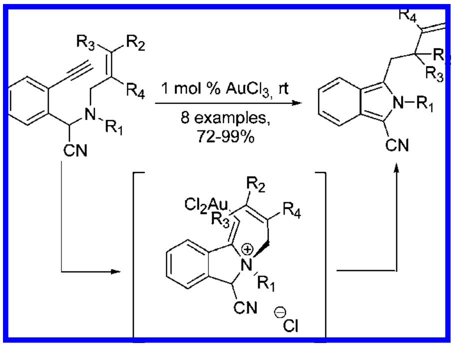
Received September 1, 2009

ABSTRACT

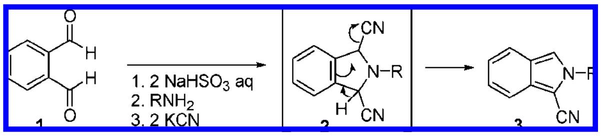


A two-step synthesis of 1-cyanoisoindoles starting from ethynylbenzaldehyde is presented. The key step is a mild, high-yielding, gold-catalyzed rearrangement of N-allylic aminonitriles.

Recently, N-aromatic 1-cyanoisoindoles have been widely used for their fluorescent properties. They have been used to lower the detection limits by a factor 10 during the Edman degradation of proteins[1] and for the nonradioactive ligand binding study of histamine H_2 and H_3 receptors.[2] Furthermore they provide an easy entry to many potent antitumor agents.[3]

Their nonaromatic substituted counterparts, however, have been scarcely studied, despite their high potential as pharmaceutical building blocks.[4] This is mainly due to the lack of convenient methods of synthesis. In fact, only one truly convergent synthesis of these compounds has been reported, by a double cyanide addition to a bis-imine followed by aromatization (Scheme 1).[5] This method, however, involves the loss of 1 equiv of the highly toxic HCN and does not allow for substitutions at the 3-position.

Scheme 1. Literature Synthesis of 1-Cyanoisoindoles



In this paper, we present a convenient two-step entry to 1-cyanoisoindoles avoiding both of these disadvantages. The synthesis is initiated by a lithium perchlorate catalyzed three-component reaction of 2-ethynylbenzaldehyde **4**, trimethyl-

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(1) Wainaina, M.; Shibata, T.; Smanmoo, C.; Kabashima, T.; Kai, M. *Anal. Biochem.* **2008**, *374*, 423.

(2) Amon, M.; Ligneau, X.; Camelin, J.; Berrebi-Bertrand, I.; Schwartz, J.; Stark, H. *Chem. Med. Chem.* **2007**, *2*, 708.

(3) (a) Diana, P.; Martorana, A.; Barraja, P.; Lauria, A.; Montalbano, A.; Almerico, A.; Dattolo, G.; Cirrincione, G. *Bioorg. Med. Chem.* **2007**, *15*, 343. (b) Diana, P.; Martorana, A.; Barraja, P.; Montalbano, A.; Dattolo, G.; Cirrincione, G.; Dall'Acqua, F.; Salvador, A.; Vedaldi, D.; Basso, G.; Viola, G. *J. Med. Chem.* **2008**, *51*, 2387. (c) Girolamo, C.; Diana, P. Eur. Patent C07D487/04, 2008.

(4) (a) Jaunin, R. U.S. Patent 4077978, 1976. (b) Barraja, P.; Spanò, V.; Patrizia, D.; Carbone, A.; Cirrincione, G.; Vedaldi, D.; Salvador, A.; Viola, G.; Dall'Acqua, F. *Bioorg. Med. Chem. Lett.* **2009**, *16* (6), 1711.

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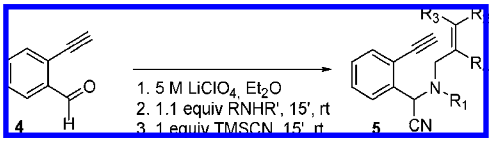
10.1021/ol902031f CCC: $40.75

silylcyanide, and an allylic secondary amine yielding aminonitriles **5** (Table 1).[6] Complete conversion could be obtained in almost all cases after 30 min at room temperature. Chromatography was performed to obtain the pure compounds **5**, resulting in yields ranging from 72% to 91%. The use of a strongly hindered *tert*-butylamine caused a significant drop in conversion, which could not be improved by increasing reaction temperature or time.

Table 1. Step 1: Precursor Synthesis

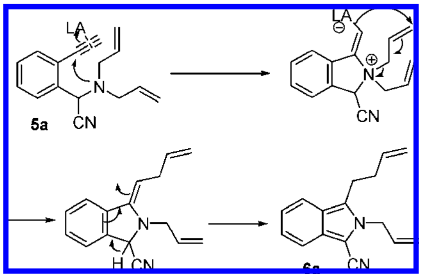


	R_1	R_2	R_3	R_4	yield (%)^{a,b}
a	allyl	H	H	H	91
b	benzyl	H	H	H	77
c	benzyl	methyl	methyl	H	72
d	*o*-Br-benzyl	H	H	H	77
e	propyl	phenyl	H	H	72
f	*tert*-butyl	phenyl	H	H	9^c
g	propyl	phenyl	H	Cl	73
h	*p*-MeO-benzyl	isopropyl	H	H	76

^{a} Isolated yields. ^{b} Chromatography performed. ^{c} 25% conversion.

These aminonitriles were subsequently converted into the desired 1-cyanoisoindoles by a 5-*exo-dig* cyclization followed by a [1,3]-alkyl migration and 1,5-prototropic aromatization (Scheme 2).

Scheme 2. Step 2: Rearrangement

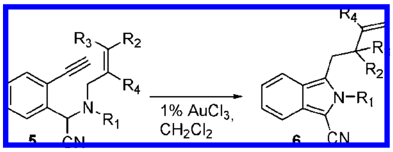


In analogy with our recently reported synthesis of 1-phosphonoisoindoles, this conversion was first attempted by means of microwave irradiation.[7] However, even after prolonged heating (2 h at 165 °C), no conversion could be detected. To facilitate the conversion of the aminonitriles into the desired isoindoles, an activation of the triple bond by Lewis acids was needed. The use of 10 mol % silver triflate was unsuccesful. $LiClO_4$ (10%) delivered the isoindole **6a** in a yield of 46% after 60 min at 165 °C. Unfortunately, this result was not reproducible.

In a next attempt, we were pleased to find that upon addition of 5 mol % $AuCl_3$, which is well-known for its use in alkyne hydroamination,[8] no microwave irradiation was needed to obtain complete conversion within 5 min. The same result was observed using 1 mol % $AuCl_3$.

Using these optimized conditions, the scope of the reaction was examined (Table 2). Upon addition of the gold catalyst, the progress of the reactions was followed by TLC. When no more starting material could be detected, the catalyst was removed by filtration over a small plug of silica, and the solvent was evaporated, yielding the pure 1-cyanoisoindoles. Only in the case where R_4 was a chloride substituent was further chromatography needed.

Table 2. Reaction Scope



	R_1	R_2	R_3	R_4	yield (%)^a	conditions
a	allyl	H	H	H	98	5 min, rt
b	benzyl	H	H	H	95	1 h 40 min, rt
c	benzyl	methyl	methyl	H	72	22 h, rt
d	*o*-Br-benzyl	H	H	H	95	1 h, rt
e	propyl	phenyl	H	H	98	2 h 30 min, rt
f	*tert*-butyl	phenyl	H	H	99	0 h 10 min, rt
g	propyl	phenyl	H	Cl	76^b	8 h 30 min, rt
h	*p*-MeO-benzyl	isopropyl	H	H	85	0 h 45 min, Δ

^{a} Isolated yields. ^{b} Chromatography performed.

As shown, all reactions provided the desired isoindoles in high yields, which dropped only slightly for substrates that need prolonged stirring (**6c**) or heating (**6h**) to reach full conversion. Comparing all derivatives, it is clear that reaction times are increased by steric factors related to the migrating group (compare **6b** and **6c**) and decreased by the sterical demand of the second N-substituent (compare **6e** and **6f**).

On the basis of these observations, it was assumed that a distinction could be made between the two possible migrating groups in **5i** (Scheme 3). However, upon treatment of this compound with the catalyst, there was no differentiation between both groups, and after 25 min a 50:50 mixture of compounds **6i** and **6j** was formed. This unexpectedly fast conversion led us to believe that the exothermic character of the fast allyl migration (formation of **6j**) caused a heating of the reaction mixture that allowed migration of the

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(7) Dieltiens, N.; Stevens, C. V. *Org. Lett.* **2007**, *9*, 465.

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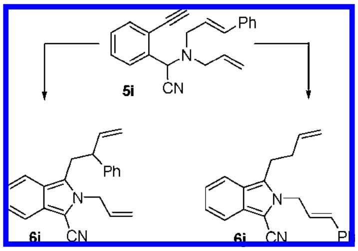
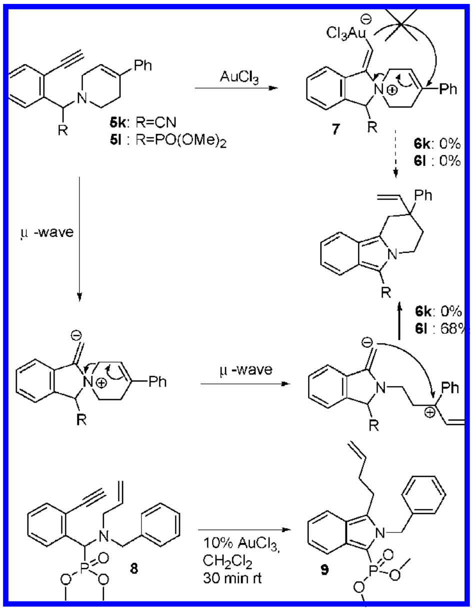
Scheme 3. Kinetic Selectivity



cinnamyl group and thus precluded any kinetic selectivity. Upon cooling the reaction mixture to 0 °C, it was indeed seen that selectivity rose slightly to 55% in favor of **6j**.[9] Further reduction of the reaction temperature increased the selectivity to a maximum of 63% at −78 °C. Although the selectivity is quite poor, this example shows that a differentiation can be made between two migrating groups with different sterical demand.

With regard to the mechanism, there are clear indications that the gold catalyst induces a concerted mechanism rather than a stepwise one, as is the case upon microwave irradiation.[10] Upon treatment of compound **5k** with the gold catalyst, no ring-closed product **6k** could be detected, even after prolonged heating with 10% catalyst (Scheme 4).

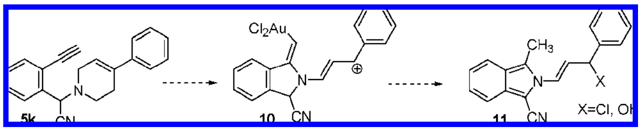
Scheme 4. Mechanistic Indications



This lack of reactivity was traced back to originate solely from the specific amine used. Indeed, no conversion of aminophosphonate **5l** into 1-phosphonoisoindole **6l** was observed even after prolonged stirring in the presence of 10 mol % $AuCl_3$ at room temperature. This is in sharp contrast with the fast and quantitative conversion of aminophosphonate **8** under the same conditions.

This reactivity profile is consistent with a stepwise mechanism under thermal conditions and a concerted mechanism under gold-catalyzed conditions. The conversion of the gold-stabilized E-carbanion by a nucleophilic attack onto the allyl group is most likely inhibited by the configuration of intermediate **7**. The alkene is unable to fold back toward the gold complex, and no conversion is observed. Thermal fragmentation by microwave irradiation relieves this rigidity and allows further conversion in the case of **5k**. The formation of a similar allylic carbocation **10** under gold catalysis, as is the case in the work reported by Toste and co-workers,[11] was excluded by treatment of **5i** with 1 equiv of gold(III)chloride followed by aqueous quench (Scheme 5). After this workup the starting material was recovered quantitatively, and not a single trace of **11** was detected.

Scheme 5. Cation Trapping



On the basis of these observations, **12** is proposed as a likely intermediate for the gold-catalyzed conversion of N-allylic aminonitriles (Figure 1). The gold catalyst completes its coordination sphere by complexation of the alkene, and in this way it aligns the nucleophilic and electrophilic moieties for further conversion. Indeed, a very similar conformation was recently reported by Malacria as a low energy intermediate in the cycloisomerisation of allenynes.[12]

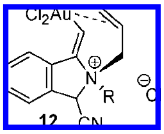


Figure 1. Suggested transition state.

To provide further proof of the intermediacy of **12**, the addition of nucleophiles (e.g., methanol) to the reaction medium was evaluated. Unfortunately, the intermediate could not be trapped, and no change in both reaction speed or outcome was observed.

In summary, a convenient approach toward 3-substituted 1-cyanoindoles has been presented by a very mild gold-

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[9] Temperature control was shown to be complete by a similar experiment where the substrate was slowly dripped into a cooled solution of catalyst. The observed selectivity remained the same.

[10] For a detailed discussion of the microwave induced reaction, see ref 7.

[11] (a) Uemura, M.; Watson, I.; Katsukawa, M.; Toste, D *J. Am. Chem. Soc*. **2009**, *131*, 3464. (b) Mauleón, P.; Krinsky, J.; Toste, D. *J. Am. Chem. Soc*. **2009**, *131*, 4513.

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catalyzed rearrangement involving a 5-*exo*-*dig* cyclization followed by [1,3]-alkyl shift and 1,5-prototropic aromatization.

Acknowledgment. Financial support for this research from the Fund for Scientific Research Flanders (FWO vlaanderen) is gratefully aknowledged.

Supporting Information Available: Experimental procedures, spectroscopic data and copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902031F