Letter

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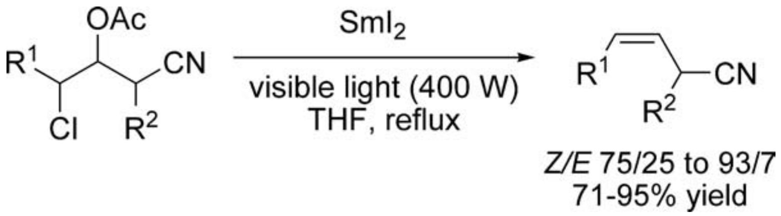

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General, Stereoselective Synthesis of (*Z*)-β,γ-Unsaturated Nitriles Promoted by Samarium Diiodide

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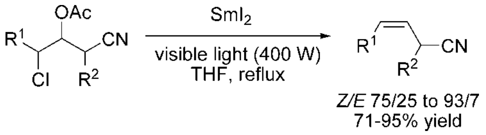
ABSTRACT



A method to obtain (*Z*)-β,γ-unsaturated nitriles in high or good yields and with moderate or high stereoselectivity is described. The products were achieved through the photoinduced metalation of 3-acetoxy-4-chloronitriles with SmI_2. The starting compounds were readily prepared, and a mechanism is proposed to explain this stereoselective β-elimination reaction.

Nitriles are important compounds in organic synthesis since they have been widely employed for the introduction of a variety of functional groups.[1] It has been shown that β,γ-unsaturated nitriles are useful substrates,[2] and several methods have been reported regarding their synthesis. In particular, the synthesis of (*E*)-β,γ-unsaturated nitriles is generally achieved from the cyanation process of different starting materials such as allylic alcohols,[3] halides,[3b] acetates,[4] carbonates,[4] ethers,[2a,b] phosphates,[2c] carbonyl compounds,[5] or the hydrocyanation of butadiene.[6] Other methods employ isomerization processes,[7] a carbenoid insertion into alkenylzirconocenes,[8] Ru-catalyzed cross-metathesis reactions,[9] or classical methods such as the Wittig reaction.[10] However, most of these methods require toxic reagents[2−6] or expensive catalysts.[9] Other methods are limited by their poor generality,[2a,3a,7,8] low yields,[2a,7,8,10] or the low stereoselectivity during the generation of the C=C bond.[4b,8−10] Finally, in other cases, the utilization of unsaturated compounds (with the appropriate relative configuration) as starting materials constitutes a drawback.[2−7] Taking into account that, in general, *Z*-unsaturated compounds are more difficult to access than the corresponding *E*-isomers, it was

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not surprising to find in the literature only one example described. In this case, the (*Z*)-β,γ-unsaturated nitrile was prepared from (*Z*)-1-iodohex-2-ene, and to the best of our knowledge, no general method for the preparation of (*Z*)-β,γ-unsaturated nitriles through an elimination reaction has been reported to date. Therefore, an efficient method to synthesize (*Z*)-β,γ-unsaturated nitriles with high stereoselectivity, in which nontoxic starting materials are employed, would be desirable.

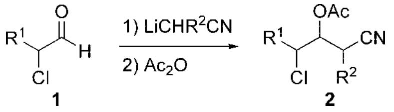
Samarium diiodide has been widely employed to promote β-elimination reactions with high or total stereoselectivity.[11] In this field, we have previously reported the SmI_2-promoted stereoselective synthesis of (*E*)-α,β-unsaturated esters,[12] amides,[13] or ketones,[14] (*Z*)-vinyl halides,[15] and (*Z*)-vinyl and allylsilanes.[16] In all these cases, the 1,2-elimination reaction was initiated by the metalation of an activated C−halogen bond.

However, samarium diiodide has been scarcely utilized to promote elimination reactions through the metalation of nonactivated C−Cl bonds due to the lack of reactivity of these bonds. Several methods have been described to overcome this drawback, the photoinduced metalation of nonactivated C−Hal bonds being the most effective. Thus, some synthetic applications based on the photoinduced metalation of nonactivated C−Hal bonds with SmI_2 have been reported.[17] In this field, we have recently reported the photoinduced SmI_2-promoted metalation of nonactivated C−Cl bonds of *O*-acetyl chlorohydrins toward the synthesis of nonfunctionalized alkenes with total or high (*Z*)-selectivity.[18]

In this paper, we wish to report a new and easy route to (*Z*)-β,γ-unsaturated nitriles by treatment of 3-acetoxy-4-chloronitriles, with SmI_2 in the presence of visible light (400 W). A mechanism to explain the *Z*-stereoselectivity of this process is also proposed.

The starting materials **2** were readily prepared in good overall yields (63−85%) after the successive treatment of α-chloroaldehydes **1**[19] with the lithium enolate of the corresponding nitrile and acetic anhydride. The structure of the starting compounds **2** could be readily modified by using the appropriate (linear, branched, or unsaturated) aldehyde or/and nitrile (Scheme 1).

Scheme 1. Synthesis of Starting Materials **2**



Initially, the β-elimination reaction of compounds **2** was carried out on 3-acetoxy-4-chlorodecanenitrile **2a** ($R^1 = n\text{-}C_6H_{13}$; $R^2 = H$) at room temperature and in the absence of visible light. No reaction took place, and the starting material was recovered unchanged (Table 1).

Table 1. Synthesis of **2a** under Various Reaction Conditions

entry	400 W lamp	temp	time (h)	*Z*/*E*[a]	yield (%)[b]
1	no	rt	10	-	-
2	no	reflux	10	80/20	22
3	yes	rt	6.5	78/22	85
4	yes	reflux	6.5	80/20	87

[a] *Z*/*E* ratio was determined by GC-MS and/or 300 MHz ^1H NMR analysis of the crude product **3a**. [b] Isolated yield after column chromatography based on compound **2a**.

After testing the reaction conditions shown in Table 1, the best results were obtained by treatment of 3-acetoxy-4-chlorodecanenitrile **2a** (0.4 mmol, 1 equiv) with SmI_2[20] (3.0 equiv) at reflux, in the presence of visible light (400 W lamp). β,γ-Unsaturated nitrile **3a** was then obtained with good (*Z*)-stereoselectivity and high yield (Table 1, entry 4).

To study the generality of this method, the β-elimination reaction was performed on various 3-acetoxy-4-chloronitriles **2**. As shown in Table 2, the reaction seems to be general, and linear or branched aliphatic or unsaturated nitriles could be efficiently obtained with good *Z*-stereoselectivity and high yield.

When compounds **2g** and **2l** (derived from 2-chlorophenylacetaldehyde) were utilized as starting materials, a change of the stereoselectivity was observed, affording the corresponding (*E*)-β,γ-unsaturated nitriles **3g** and **3l** with good stereoselectivity (Table 2, entries 7 and 12). An explanation of the different *E*- or *Z*-stereoselectivity observed on products **3** depending on the aldehyde used will be discussed below.

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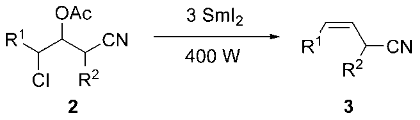
Table 2. Synthesis of (*Z*)-β,γ-Unsaturated Nitriles **3**



entry	**3**	R^1	R^2	*Z*/*E*[a]	yield (%)[b]
1	**3a**	n-C_6H_{13}	H	81/19	87
2	**3b**	n-$C_{10}H_{21}$	H	84/16	85
3	**3c**	$CH_2{=}CH(CH_2)_7$	H	75/25	80
4	**3d**	(Z)-$EtCH{=}CH(CH_2)_4$	H	80/20	77
5	**3e**	$PhCH_2$	H	75/25	92
6	**3f**	PhCH(Me)	H	75/25	71
7	**3g**	Ph	H	15/85	95
8	**3h**	n-C_6H_{13}	Me	87/13[c]	84
9	**3i**	$CH_2{=}CH(CH_2)_7$	Me	85/15[c]	81
10	**3j**	$PhCH_2$	Me	93/7	76
11	**3k**	n-$C_{10}H_{21}$	n-Pr	93/7[c]	74
12	**3l**	Ph	n-Pr	10/90[c]	86

[a] *Z*/*E* ratio was determined by GC-MS and/or 300 MHz ^1H NMR analysis of the crude products **3**. [b] Isolated yield after column chromatography based on compound **2**. [c] The major diastereoisomer was obtained pure after flash chromatography.

When compounds **2**, in which the chlorine atom is attached to a tertiary carbon atom, were used, the corresponding nitriles were obtained as a 1/1 *Z*/*E* mixture.

Starting from nitriles **2** in which ($R^2 \neq H$), β,γ-unsaturated nitriles were obtained with higher stereoselectivity (Table 1, entries 8−11).

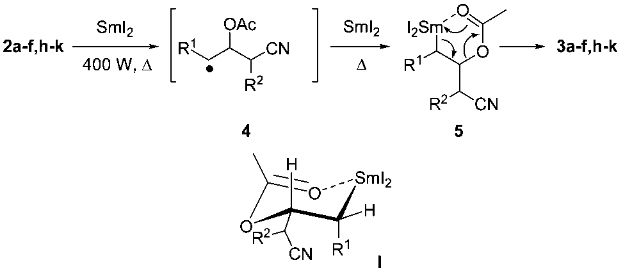
The *Z*/*E* ratio was determined on the crude reaction products by GC-MS and/or ^1H NMR (300 MHz) spectroscopy. Unsaturated nitriles **2h**, **i**, **k**, and **l** could be purified by flash chromatography and were isolated as a pure diastereoisomer (Table 2).

The (*Z*)-stereochemistry of the C−C double bond in β,γ-unsaturated nitriles **3a**−**f** and **3h**−**k** was assigned on the basis of the value of the ^1H NMR coupling constants between the olefinic protons.[21] In the particular case of (*E*)-β,γ-unsaturated nitriles **3g** and **3l**, the stereochemistry was assigned by the value of the ^1H NMR coupling constant between the olefinic protons (15.9 and 15.8 Hz, respectively) and comparison with the NMR data previously reported in the literature for compound **3g**.[9]

It is noteworthy that in all cases the starting materials were used as a nearly equimolecular mixture of two (**2a**−**g**) or four (**2h**−**l**) diastereoisomers.

The synthesis of compounds **3** takes place by an initial reaction of the C−Cl bond in compounds **2**, with 1 equiv of SmI_2 mediated by irradiation with visible light (400 W lamp), to generate a radical **4** (Scheme 2). Reduction of **4** with a second equivalent of SmI_2 would afford the organosamarium species **5** which, after 1,2-elimination, yields alkenes **3**.[22]

Scheme 2. Mechanistic Proposal for the Conversion of **2a**−**f** and **2h**−**k** into **3a**−**f** and **3h**−**k**



We could surmise that the stereochemistry of this β-elimination reaction is governed by the chelation of the oxophilic samarium(III) center[23] to the carbonyl oxygen atom of the acetoxy group to generate species **5**. Thus, the elimination reaction could take place through transition state **I**, depicted in Scheme 2.[15,16b,8] It is noteworthy that the acetyl group plays two key roles: on one hand, it facilitates the elimination reaction (acetoxy group is a better leaving group than OH), and on the other hand, the coordination with the Sm^{III} center controls the stereochemical course of the elimination reaction. Thus, the elimination reaction (under the same reaction conditions) from nonacetylated compounds **2** afforded a complex mixture of unidentified products.

In the proposed transition state **I**, the CHR^2CN group adopts an equatorial orientation to avoid 1,3-diaxial interactions with the samarium coordination sphere. R^1 adopts an axial orientation since no 1,3-diaxial interactions are present and would avoid interactions with the samarium coordination sphere. A β-elimination reaction from **I** as that shown in **5** affords (*Z*)-β,γ-unsaturated nitriles **3**.

The higher stereoselectivities observed from chloronitriles **2** in which $R^2 \neq H$ could be explained by taking into account that when the size of R^2 (H, Me, and *n*-Pr) is increased the equatorial orientation of the CHR^2CN group is even more favored than the axial orientation.

This model also explains the absence of selectivity observed from compounds **2**, in which the chlorine atom is attached to a tertiary carbon atom. In this case, the alkyl group would occupy the equatorial orientation that, in the case of compounds **2a**−**f**, **h**−**k**, is occupied by the hydrogen atom bonded to C-4 atom. Thus, since the steric hindrance of the alkyl group is higher than that shown by an H atom, this alkyl group competes with R^1 to occupy the axial

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(21) The coupling constants between the olefinic protons of compounds **3a**−**f** and **3h**−**k** ranging between $J = 10.2$ and 10.8 Hz were in accordance with the average literature values: Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compound*; John Wiley and Sons: New York, 1991; Chapter 4, Appendix F, p 221.

(22) The treatment of a mixture of diastereoisomers of the starting compounds **2** with SmI_2 could allow to the corresponding organosamarium intermediate, as a mixture of diastereoisomers. The diastereoisomer with the adequate stereochemistry to generate the proposed cyclic transition state **I** could eliminate affording the corresponding unsaturated nitrile **3**. The other diastereoisomer, in which the coordination of the samarium with the oxygen carbonyl group would not be favored, could experiment an isomerization affording the other diastereoisomer, which could afford **3** through the transition state **I**. This elimination mechanism has been used to explain an important number of 1,2-elimination reactions promoted by SmI_2 (see refs 12−16).

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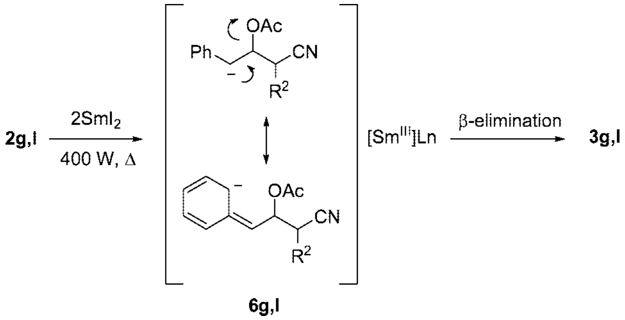
orientation, and the elimination process takes place without stereoselectivity.

The *E*-selectivity observed in the reaction of aromatic chlorohydrins **2g** and **2l**, which is in opposition to the *Z*-selectivity shown by the other compounds, could be explained by taking into account the fact that the metalation with 2 equiv of SmI_2 affords a benzylic anion **6g**,**l** which is stabilized by the phenyl group. This delocalization by resonance would impede the elimination taking place via the cyclic transition state. Thus, the 1,2-elimination reaction occurs from the anion **6g**,**l** affording the thermodynamically favored *E*-alkene (Scheme 3). This result is in accordance with other previously described β-elimination processes promoted by samarium diiodide in which a benzylic radical or anion is generated.[16b,18,24]

Scheme 3. Mechanistic Proposal for the Conversion of **2g**,**l** into **3g**,**l**



In conclusion, we have described a β-elimination reaction promoted by samarium diiodide utilized in the stereoselective synthesis of (*Z*)-β,γ-unsaturated nitriles. This process has been carried out by the photoinduced metalation of nonactivated C−Cl bonds on readily available 3-acetoxy-4-chloronitriles.

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Supporting Information Available: General procedures for the synthesis of compounds **2** and **3** and copies of ^{1}H and ^{13}C NMR spectra for compounds **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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