Isonitrile–nitrile rearrangement promoted by samarium(ii) iodide

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A samarium(II) iodide-promoted rearrangement of isonitriles to nitriles, which requires an α-alkoxycarbonyl group at the carbon atom bearing the isonitrile group, occurs under very mild conditions and contrasts with the thermal version of the rearrangement, which usually requires high temperature.

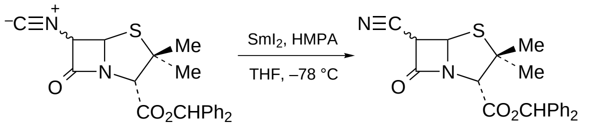
The isonitrile–nitrile rearrangement, which has been known for about ninety years, proceeds thermally with retention of stereochemistry at the migrating carbon [eqn. (1)].[1–3] This

$$\mathrm{R{-}NC} \longrightarrow \mathrm{R{-}CN} \qquad (1)$$

implies that the bond-forming and -breaking steps occur simultaneously and that there is little development of charge in the transition state. This rearrangement occurs at high temperature (250–280 °C) and is believed to take place *via* a radical intermediate. When the migrating carbon atom contains delocalizing groups such as alkoxycarbonyl or phenyl, then rearrangement also takes place but with low retention of configuration.[4] This reaction has also been the focus of theoretical investigation.[5]

Samarium(ii) iodide is a useful tool for synthetic organic chemists since it is known for promoting various organic transformations.[6] Among the useful reactions of this reagent, reductive cleavage of α-heteroatom-substituted carbonyl substrates, involving deoxygenation of the functionality containing heteroatoms such as oxygen, sulfur and halogen, has been one of the most utilized.[7] However, in the case of functional groups containing a nitrogen atom, reductive cleavage has rarely been studied despite the importance of the transformation. The first systematic study of the reductive cleavage of aziridines adjacent to a carbonyl group has recently been reported.[8]

During the course of investigations on reactions promoted by samarium(ii) iodide we had an opportunity to study the reaction of penicillanate **1** in the presence of this powerful single electron-transferring agent [eqn. (2)].



(2)

1 **2**

We anticipated a reduced product. However, to our surprise, a nitrile **2** was obtained in 70% yield (contained 5% of the reduced product). The diastereoisomers of **1** were separated,† and each was treated under the same reaction conditions. Both diastereoisomers (α-NC and β-NC) provided approximately the same ratio of **2** (α-CN : β-CN = 1 : 1.5), which indicated that the stereoselection induced by the migrating NC group and/or the β-lactam nucleus is low.

In order to investigate the generality and limitations of this isonitrile–nitrile rearrangement, various carboxylic acid derivatives with an α-isonitrile group were prepared. Synthesis of the substrates was easily achieved in a straightforward manner starting from the corresponding α-amino acids.‡

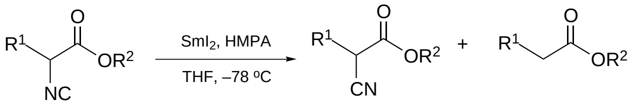
The results of the isonitrile–nitrile rearrangement promoted by samarium(ii) iodide are summarized in Table 1. The rearrangement proceeds under very mild conditions in contrast to the thermal version, in which a temperature of up to 300 °C is required. The samarium(ii) iodide-promoted isonitrile–nitrile rearrangement tolerates various types of functionality as shown in Table 1. Yields are variable, and usually formation of the corresponding reduced products **5** is also observed.

Decyanation of α-cyanocarboxylic esters promoted by samarium(ii) iodide was reported by us.[9] Conversion of nitriles **4** to the reduced products **5** is precluded since this process in the presence of samarium(ii) iodide requires higher temperature (room temperature). Therefore, the reduced products **5** are believed to be formed directly from the isonitrile substrate and not *via* the rearranged compounds, nitriles **4**. Under our conditions (SmI_2, THF–HMPA, −78 °C) the rearranged products **4** are usually formed predominantly. The substrate **3d**, having an isocyano group at the benzylic position, produced only the corresponding reduced product **5d**. Importantly, the isonitrile substrate has to be activated by an alkoxycarbonyl group for successful rearrangement. In the case of **3e** only the isonitrile group attached to the carbon α to the carbonyl group was isomerized, as expected.

Generally, 1.2–1.5 equiv. of samarium(ii) iodide are sufficient for the rearrangement. However, in some cases, 2.5 equiv. were employed to complete the reaction. It is also appropriate to note that this process, which provides α-cyanocarboxylates and the corresponding reduced (deaminated) products, can be understood as an efficient method for deamination of α-amino acid derivatives, since the isonitriles prepared were made from the corresponding α-amino acids and at higher temperature α-cyanocarboxylates are known to undergo decyanation in the presence of samarium(ii) iodide.[9]

From the view-point of the synthetic potential of this rearrangement, we investigated the possibility of utilization of the reaction for asymmetric synthesis (Table 2). We prepared

Table 1 Isonitrile–nitrile rearrangement promoted by samarium(ii) iodide



3 **4** **5**

				Product (% yield)	
Isonitrile	R¹	R²	SmI_2 (equiv.)	**4**	**5**
3a	H	PMB[a]	1.2	**4a** (50)	**5a** (11)
3b	$(CH_3)_2CHCH_2$	PMB[a]	1.2	**4b** (50)	**5b** (10)
3c	Bn	Me	1.0	**4c** (57)	**5c** (12)
3d	Ph	Me	2.5	**4d** (0)	**5d** (46)
3e	$CN(CH_2)_4$	PMB[a]	2.5	**4e** (50)	**5e** (20)
3f	$PMBO_2CCH_2$	PMB[a]	1.8	**4f** (40)	**5f** (11)

[a] PMB = *p*-methoxybenzyl.

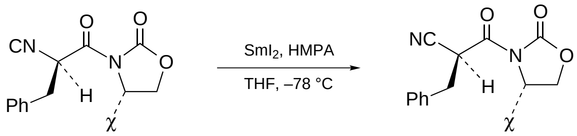
the substrates shown in Table 2 having chiral oxazolidinone auxiliaries.§

The efficiency of the differentiation of the diastereotopic faces by Evans' chiral auxiliaries (**3g** and **3h**) was first tested. Both cases show reasonable diastereoselectivities. Hoping to enhance the effectiveness of shielding to achieve a better de, a recently reported chiral auxilary (χ = $CHPh_2$; **3i** in Table 2) was also introduced.[10] However, in this case, no further increase in de was observed. Although only limited cases were tested, the results from Table 2 indicate that diastereoselectivity might be achieved if an appropriate chiral environment can be maintained. However, the systems considered here are not effective enough to obtain the desired level of diastereoselectivity. The reason could be either that the stereocentres responsible for the stereoselection are located far away from the carbon bearing the isocyano group or that the isocyano and cyano groups are linear, and thus are unable to provide efficient shielding of one diastereotopic face compared with the other.¶

Ito and co-workers have reported their investigation of the reaction of samarium(II) iodide with an isonitrile group.[11] In their cases, samarium(II) iodide promotes α-addition reactions of isonitriles. In our cases it is, however, probably reasonable to conclude that the reaction starts with an electron-transfer to the carbonyl group since no reaction was observed with a substrate without an α-alkoxycarbonyl group. The next step would involve breaking the bond between the migrating carbon atom and the nitrogen atom of the isocyano group, although the exact nature of the intermediate is not clear at the moment. At this stage, when benzylic stabilization is possible, return of the removed isonitrile moiety is not allowed and this results in exclusive formation of the reduced product. Otherwise the removed isonitrile moiety returns, with rearrangement, to the migrating carbon atom or, if this process cannot compete, the carbon atom previously bearing the isocyano group is captured by a hydrogen atom.

In conclusion, the samarium(II) iodide-promoted rearrangement of isonitriles to nitriles has been discovered and investigated. This rearrangement occurs under very mild conditions, in contrast to the thermal version of this rearrangement, which usually requires high temperature. This rearrangement should be included in the list of useful organic transformations promoted by samarium(II) iodide.

Table 2 Rearrangement of substrates with chiral auxiliaries



3 **4**

Isonitrile	χ	SmI_2 (equiv.)	Product (% yield)	De (%)
3g	$CH(CH_3)_2$	1.2	**4g** (60)	65
3h	CH_2Ph	1.2	**4h** (55)	68
3i	$CHPh_2$	1.2	**4i** (48)	68

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Footnotes

† Lichrosorb Si60 Semi-prep column, hexane–ethyl acetate = 3 : 1.

‡ The required isonitrile substrates were prepared by one of the following routes from the corresponding α-amino acids. Method A: i, $SOCl_2$, MeOH; ii, HCO_2H, Ac_2O, pyridine; iii, triphosgene, Et_3N, CH_2Cl_2, −78 °C. Method B: i, HCO_2H, Ac_2O; ii, *p*-Methoxybenzyl chloride, K_2CO_3, DMF; iii, triphosgene, Et_3N, CH_2Cl_2, −78 °C.

§ The purity of the substrates in Table 2 was checked by NMR spectroscopy. The isonitriles **3g**–**i** were all pure single diastereoisomers. For compounds **3g**–**i** the absolute stereochemistry of the carbon atom bearing the isonitrile group is, however, not clear at this point since epimerization could take place during the synthesis from the corresponding amino acids under the reaction conditions described in ref. 10. In all cases in Table 2, formation of the reduced products (corresponding to **5**) was not observed.

¶ The de values could be affected by epimerization during purification.

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