LETTERS

One-Step Transformation of Trichloroacetamide into Isonitrile

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Supporting Information

ABSTRACT: A one-step transformation of trichloroacetamide, a protective group for the amine function, into isonitrile was successfully developed. The substrate scope and functional group tolerance of this procedure are also described.



sonitrile^{1,2} is a unique functional group possessing dual nucleophilic and electrophilic character that has been used as an important reactant in multicomponent condensations such as Passerini and Ugi reactions³ for the syntheses of a variety of functionalized peptides and synthetic intermediates. For some years now, two classical methods have generally been used to prepare isonitrile compounds: (i) carbylamine reaction between a primary amine and dichlorocarbene⁴ and (ii) dehydration of N-substituted formamide utilizing a toxic phosgene or Vilsmeier reagent.⁵ To date, biomimetic synthesis using Ritter reactions has also been reported as an alternative strategy for the preparation of tertiary-type isonitrile compounds.⁶ Recently, Shenvi and co-workers reported a chemoselective and stereoselective synthesis of tertiary alkyl isonitrile facilitated by a Lewis acid catalyzed solvolysis of the tertiary alcohol derivative through attack of the contact ion pair.⁷

In the course of our synthetic studies on tetrodotoxin and its analogues,^{8a} we have developed several unique and useful reactions involving the trichloroacetamide (N-trichloroacetyl group),^{8b} such as site-selective hydroxylation using neighboring-group participation,⁹ guanidine synthesis,¹⁰ a one-pot transformation into carbamates,¹¹ and mild chemoselective deprotection to amines.¹² These established methods associated with trichloroacetamide have played important roles in the syntheses of tetrodotoxins, a densely functionalized class of natural products.^{9a-d,13-18} Recently, we incidentally encountered a new reaction that allowed us to transform trichloroacetamide into isonitrile when we attempted the synthesis of allylic alcohol 2 from epoxytrichloroacetamide 1^{19} by use of the neighboring trichloroacetamide. The epoxytrichloroacetamide 1 was treated with an excess amount of LDA in THF to give an unexpected isonitrile 3 as a sole product (Scheme 1). Since this transformation of trichloroacetamide has never been reported before, we embarked on a detailed investigation of the reaction conditions, substrate scope, and functional group tolerance of the new procedure.

We first examined several conventional bases utilizing a tertiary-type allylic trichloroacetamide 4 as a substrate, which was prepared from the Overman rearrangement of farnesol in two steps.²⁰ When 4 was treated with LDA at -78 °C, followed by gradually increasing the reaction temperature to 0 °C, the isonitrile 5 was obtained in moderate yield (Table 1, entry 1).

Scheme 1. Discovery of an Unexpected Transformation of Trichloroacetamide 1 into Isonitrile 3



Treatment of the trichloroacetamide 4 with LHMDS did not give the expected isonitrile 5, but rather the starting material 4 was recovered quantitatively, even when an excess amount of the base was employed (entry 2). Extensive experimentation led us to find that 3.5 equiv of *n*-BuLi in THF at -78 °C were the optimal conditions for this transformation, giving the desired isonitrile 5 in 82% yield as a single product (entry 3). Reaction with 1.0 equiv of n-BuLi in THF at -78 °C gave dichloroacetamide 6 as a major side product along with the isonitrile 5, and a significant amount of starting material was recovered (entry 4). This result indicates that a carbanion of dichloroacetamide 6 would be generated as one of the initial intermediates from trichloroacetamide 4. Thus, the isolated dichloroacetamide 6 was subjected to the optimized conditions to give the desired isonitrile 5 in 85% yield as a sole product, whereas no intermediates were observed by TLC monitoring. We therefore established the efficient conditions for the transformation of trichloroacetamide into isonitrile.

We next examined the scope and limitations of the newly developed conditions for various substrates including tertiary-, secondary-, and primary-type trichloroacetamide. The results

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Table 1. Optimization for Transformation ofTrichloroacetamide 4 into Isonitrile 5



are summarized in Table 2. The transformation of tertiary-type allylic trichloroacetamides 7^{21} and 8^{22} proceeded smoothly under the optimized conditions to give the allylic isonitriles 16 and 17 in 85% and 61% yield, respectively (entries 1 and 2). The sterically hindered tertiary-type alkyl trichloroacetamides, such as 9^{23} and 10,²⁴ could also be transformed into the corresponding isonitriles 18 and 19 in good yields (entries 3 and 4). Unfortunately, the same conditions were not applicable for secondary- and primary-type allylic trichloroacetamides; exposure of the secondary-type allylic trichloroacetamides $(11, 20, 12^{20})$ and the primary-type allylic trichloroacetamide 14^{24} to the optimized conditions did not give the corresponding desired isonitriles but rather complex mixtures of products (entries 5, 6, and 8). On the other hand, the reaction of secondary- and primary-type alkyl trichloroacetamides 13^{24} and 15^{25} under the same conditions provided the isonitriles 22 and 24 in 49% and 52% yields, respectively (entries 7 and 9).²⁶ Although the reason for the failure of this transformation for secondary- and primary-type allylic trichloroacetamides was not clarified, the markedly contrasting results might be attributable to the removal of acidic protons from the allylic methylene and methine moieties adjacent to the trichloroacetamides or to the instability of the generated allylic isonitriles under the basic conditions.

The successful transformation of trichloroacetamides described above indicated that acetonide and alkene (vinyl and trisubstituted alkene) were compatible with the conditions employed. Further functional group tolerance and utility of this transformation were investigated using various other functionalized substrates as shown in Table 3. The tertiary-type allylic trichloroacetamides 1^{19} and 25^{9d} bearing an epoxide were transformed into epoxy isonitriles 28 and 29 in 75% and 74% yield, respectively. The conventional protective groups such as benzyl ether (25) and TBS and TBDPS silyl ethers ($26,^{27} 27^{15}$) were also tolerated, giving the corresponding isonitriles in good yields without any problems.

One of the possible reaction mechanisms for the formation of isonitrile is proposed in Scheme 2.²⁸ At first, the halogen–lithium exchange reaction of trichloroacetamide A with *n*-BuLi proceeds to give a carbanion intermediate B, which undergoes an intramolecular proton abstraction from the amide group. Then, the resulting enolate C is cyclized to an imino oxirane





Isolated yield.

D,²⁹ which finally yields the observed isonitrile **E** by fragmentation.^{5,29d,30} Another possibility that the isonitrile **E** would be obtained via an imidoyl chloride adduct **G** is not excluded; the imino oxirane **D** would give the zwitterionic intermediate **F** by epoxide opening. Then, elimination of the chloride moiety followed by attack of the resulting chloride ion to a nitrilium intermediate affords the imidoyl chloride **G**. Finally, nucleophilic addition of the remaining *n*-BuLi and α -





^{*a*}Isolated yield. ^{*b*}4.0 equiv of *n*-BuLi was used. ^{*c*}6.0 equiv of *n*-BuLi was used. ^{*d*}4.5 equiv of *n*-BuLi was used.

Scheme 2. Proposed Mechanism for the Formation of Isonitrile from Trichloroacetamide



elimination would provide the isonitrile E. The other reaction pathway of the direct proton abstraction from trichloroacetamide A may also proceed to give the equilibrium intermediate C', which is transformed into the isonitrile E via an intermediate D' in a similar manner.

In summary, we have developed a novel one-step transformation of trichloroacetamide into an isonitrile under mild conditions by utilizing *n*-BuLi. Unfortunately, as the conditions were not applicable for secondary- and primary-type allylic trichloroacetamides, tertiary-type trichloroacetamides and secondary-/primary-type alkyl trichloroacetamides could be successfully converted into isonitriles. We also demonstrated that the conditions were generally applicable to substrates containing a wide range of functional groups, such as alkene, epoxide, acetonide, TBS, TBDPS, and Bn. The present studies should increase the utility of trichloroacetamides and provide a new entry for the syntheses of isonitrile-containing natural products.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.6b03583.

Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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