ABSTRACT: Isonitriles are frequently employed as both substrates for organic transformations and ligands for organometallic chemistry. However, despite the wide application of the isonitriles, their synthesis generally depends on the traditional dehydration of N-formamide. "Nucleophilic isocyanation" using cyanide as an N-nucleophile is another straightforward strategy affording the corresponding isonitriles. This method has been available since the 19th century but is still an immature procedure and is therefore more rarely used. In this review, we summarize the concepts and recent progress in nucleophilic isocyanation, including the relatively rare examples of catalytic isocyanation.

1. INTRODUCTION
Isonitrile (A: \( R^-\text{NC} \)) is a regioisomer of the corresponding nitrile (\( R^-\text{CN} \)) (Figure 1). The structure of C–NC is almost linear. The bond length of the isocyano group (–NC) is slightly longer than that of the cyano group (–CN) because of a postulating contribution of resonance structure B. For example, the NC bond length of methyl isonitrile (MeNC) is reported to be 116.7 pm, while the CN bond length of acetonitrile (MeCN) is 115.8 pm. Isonitriles are well-known surrogates of carbon monoxide in organometallic chemistry, whose C termini show carbene-like reactivity (structure B in Figure 1). These compounds are also regarded as unique and important building blocks in organic transformations because they can react with both nucleophiles and electrophiles at their C sites. A number of researchers have focused on the attractive characteristics of isonitriles, and the applications of these compounds have been notably expanded. For example, organometallic complexes coordinated by isonitriles have been prepared to investigate their specific chemical properties. The isonitriles in these complexes are convertible to many other organic ligands. In addition, organic synthesis reactions using isonitriles, such as specific heterocyclizations and multicomponent condensations, have enabled the construction of highly functionalized compounds (right part of Figure 1). However, in contrast to the versatility of isonitriles, methods for synthesizing these compounds are quite limited. Indeed, most isonitriles are prepared according to a single protocol: dehydration of the corresponding formamides.

An alternative, traditional protocol affording isonitriles is nucleophilic isocyanation using cyanide as an N-nucleophile. In 1888, Schneidewind published the pioneering study on this strategy using benzyl iodide and AgCN to afford benzylic isonitrile (Scheme 1). Cyanide is one of the most typical ambident nucleophiles, and its C- and N-termini are both reactive. In general, however, the C-terminus preferentially reacts with several electrophiles to form the corresponding nitriles. In this mini-review, we will discuss several efficient strategies for obtaining the less-accessible isonitriles by nucleophilic substitution or addition of cyanide reagents. The nucleophilic reactions have traditionally utilized stoichiometrically activated cyanide reagents or less-reactive cyanide sources with stoichiometric activators. Recently, however, some efficient
nucleophilic isocyanations with catalytic amounts of activators have been reported.

2. CONCEPT OF CHEMOSELECTIVITY FOR NUCLEOPHILIC CYANATION AND ISOCYANATION

Kornblum and co-workers proposed a chemoselectivity preference for the nucleophilic substitutions using ambivalent reagents (Kornblum’s rule): The “harder” terminus tends to react through the SN1 pathway, while the “softer” terminus reacts in an SN2 fashion. According to this rule, isocyanation proceeds through an SN1-type mechanism, since the N-terminus of cyanide is harder than the C-terminus. However, there are some exceptions to explain the selectivity of cyanide: (1) Methylation using very hard reagents trimethyloxonium tetrafluoroborate and methyl triflate with tetrabutylammonium cyanide exclusively gave acetonitrile, a C-terminus-substituted product (Scheme 2).8 (2) When erythro-2-bromo-3-(methyl-thio)butane was applied as an electrophile, the erythro isomers of nitrile and isonitrile, 4 and 5, were selectively obtained by using NaCN and AgCN as nucleophiles, respectively, although both reactions occurred through the same trans-thiiranium intermediate, 6 (Scheme 3).9 These substitution reactions using the threo isomer of 3 afforded the corresponding threo products.

Scheme 2. Selective Formation of Acetonitrile with Very Hard Methylation Reagents

| Reagent | Reaction Conditions | Product | Yield |
|---------|---------------------|---------|-------|
| Bu$_3$O(BF$_4$) | nBu$_2$N(CN) (3 equiv) | MeCN | 95% 1H NMR yield |
| MeOTf | nBu$_2$N(CN) (3 equiv) | MeCN | quant. |

Today, Kornblum’s rule is regarded as an outdated principle for explaining the selectivity of ambient cyanide. Mayr and co-workers carefully analyzed the preference of the reaction site (C or N) selectivity based on the reported observations and some experimental data by themselves and consequently proposed the following revised hypotheses. (a) A free cyanide preferentially reacts at the C-terminus regardless of whether the reaction proceeds through the SN1 or SN2 pathway. (b) Isocyanation with free cyanide occurs only in the case in which C-addition reaches the diffusion limit, affording a mixture of nitrile and isonitrile. (c) When the C-terminus is blocked by another group, such as Me$_3$Si$^+$ or Ag$,^+$ the N-terminus exclusively reacts to afford the corresponding isonitriles.8

3. ISOCYANATION WITH A STOICHIOMETRIC ACTIVATOR

As mentioned above, the combination of alkyl halides, especially alkyl iodides, and AgCN (a C-terminus-blocked cyanide) is the most typical approach affording the alkylisonitriles.8 Tu and co-workers applied the procedure to the isocyanation of an in-situ-generated allylic iodide during the final step in the synthesis of 7-epi-14-isocyano-isodauc-5-ene, which is the epimer of the natural product isolated from marine sponge Acantkella acuta (Scheme 4).10

Scheme 4. Allylic Isocyanation Using AgCN in the Synthesis of an Isocyano Sesquiterpene

Benzoyl iodide 9 was rapidly consumed (within 10 min) with an excess amount of AgCN to afford N-benzoylisonitrile 10, which was regarded as an electrophilic carbene surrogate, in 73% yield.11 This compound reacted with both electron-rich and -poor alkynes, giving complex molecules of completely different types from each other (Scheme 5).

Some alkyl bromides are also applicable to the transformation using stoichiometric silver reagents. For the synthesis of 1-isocyano sugars, as reported by Descotes and co-workers, the combination of 1-bromosugar and AgCN is effective.12 Kitano and co-workers discovered an efficient method that furnished benzylic isonitriles using primary benzylic bromides and trimethylsilyle cyanide (TMSCN) in the presence of AgClO$_4$ as a stoichiometric activator (Scheme 6).13 In this reaction, they proposed that highly reactive benzylic perchlorate was generated

Scheme 6. Stoichiometric Isocyanation of Primary Benzylic Bromide

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in situ, and the following substitution by TMSCN as a C-blocked cyanide formed the isonitrile.

Songstad and co-workers focused on easily isolable onium dicyanoargentates \( [\text{Q}^+\text{[Ag(CN)]}_2^-] \) as nucleophiles.\(^{14,15}\) High nucleophilicity was expected due to their anionic character. In fact, benzhydryl bromide 15 was transformed to isonitrile 16 in 88% yield by using (Ph\(_4\)As)\[Ag(CN)\(_2\)] in acetonitrile (Scheme 7).\(^{14}\) (Me\(_4\)N)\[Ag(CN)\(_2\)] reacted even with an alkyl chloride, although the reaction rate was slow. Then they proposed the rate dependency upon the alkyl groups of halides and the leaving groups for this isocyanation as follows: tert-RX > sec-RX > primary-RX and RI > RBr > RCl.\(^{15}\)

The modified procedure was reported by El Kaim, Grimaud, and co-workers.\(^{16}\) In the presence of 20 mol % Et\(_3\)NBnCl (TEBAC), benzylic isonitriles were obtained through the reaction of benzylic bromides and in-situ-prepared KAg(CN)\(_2\) from KCN and AgCN (Scheme 8).\(^{16a}\) The yield of the product obviously decreased without using phase-transfer catalyst TEBAC. This method was applied to a one-pot sequential transformation affording oxazoles or Ugi-type adducts, without the isolation of the stinking isonitriles.

As Songstad reported,\(^{15}\) isocyanation of tertiary alkyl halides including chlorides through the formation of stable tertiary alkyl cations is relatively easy. Sasaki and co-workers reported that adamantyl isonitrile 18 was furnished by the reaction of adamantyl chloride 17 and TMSCN with the stoichiometric activation of TiCl\(_4\) (Scheme 9).\(^{17}\) A modified method was employed as the key step in the total synthesis of 7,10-diisocyanoadociane reported by Corey and co-workers (Scheme 10).\(^{18}\) In this case, readily prepared trifluoracetate was used as a leaving group instead of halide. In the presence of excess amounts of TMSCN and TiCl\(_4\), double isocyanation product 20 as a mixture of four diastereomers was obtained in 70% yield from 19. The diastereomeric ratio of the diaxial/axial—equatorial and equatorial—axial/di-equatorial isomers was 30:55:15.

Kitano and co-workers reported the direct isocyanation of tertiary alcohols. Both ZnBr\(_2\) and AgClO\(_4\) efficiently promoted the reaction using TMSCN as a cyanide source.\(^{19}\) The reaction of 1-adamantanone 21 with AgClO\(_4\) quantitatively afforded the desired product (Scheme 11).\(^{19b}\) The Brønsted acid-assisted one-pot (three steps) formal isocyanation of tertiary alcohols was also reported (Scheme 12).\(^{20}\) This procedure without metallic species was applied to the formation of benzylic isonitriles with medium yield.

Mukaiyama’s oxidation—reduction condensation is a potent strategy for the synthesis of secondary alkyl isonitriles (Scheme 13).\(^{21}\) An alkoxy diphenylphosphine is a suitable electrophile under the oxidative condition when using 2,6-dimethyl-1,4-benzoquinone (DMBQ) and (EtO)\(_2\)P(O)CN as a cyanide source. In the presence of soft metal oxides such as ZnO and CdO, the corresponding isonitriles are obtained preferentially, while the nitriles are obtained without the addition of these metal oxides. Notably, the optically active secondary alkoxy diphenylphosphine is converted to the isonitrile with almost perfect stereoinversion.

The AgClO\(_4\)-promoted isocyanation of alkenes was reported by Kitano and co-workers (Scheme 14).\(^{22}\) This is the only example affording the hydroisocyanation products from alkenes.
through the nucleophilic addition of cyanide. AgClO₄ acts as a π-Lewis acid to activate alkenes, and the isocyanation proceeds on the positive site in accordance with the Markovnikov rule.

4. CATALYTIC NUCLEOPHILIC ISOCYANATION

The first catalytic isocyanation was reported by Gassman and co-workers through the ring-opening reaction of epoxides (Scheme 15). Only 0.5 mol % ZnI₂ was sufficient to promote the reaction between epoxides and TMSCN affording the β-hydroxyisonitrile derivatives. Isocyanation selectively occurred at the most substituted carbon center with stereoinversion. Utimoto and co-workers discovered a similar isocyanation that proceeds with Pd(CN)₂, SnCl₂, or Me₃Ga as a catalyst, while the nitriles were obtained when an aluminum-based catalyst, such as Et₂AlCl or (iPr)₂AlOEt, was employed. Oxetanes were also converted to the corresponding γ-hydroxyisonitriles in the presence of a relatively larger amount of ZnI₂ than in the case of epoxides.

The only example to date of catalytic enantioselective isocyanation was reported by Zhu, Pan, and co-workers. They demonstrated the desymmetrization of meso-epoxides with chiral BINOL−Ga(III) complex as a catalyst (Scheme 16). Although the substrate scope was limited, the chiral β-hydroxyisonitriles were obtained in up to 95% ee after desilylation.

Shenvi and co-workers reported the catalytic conversion of tertiary alkyl trifluoroacetates with TMSCN into the isonitriles catalyzed by Sc(OTf)₃ (Scheme 17). It is well known that the nucleophilic substitution of tertiary alcohol derivatives usually proceeds through an S₈₁-type mechanism; therefore, the chiral information on the substrates is lost through the reaction. However, the titled isocyanation preferentially occurs with stereoinversion because of the formation of a contact ion pair upon substitution. The Sc(OTf)₃-catalyzed isocyanation has been employed as the key step in the total synthesis of isocyanoterpenoids, which have antiplasmodial and antimalarial activities. Some examples are shown in Figure 2.

5. CONCLUSIONS

Herein, we summarized the basic concepts and representative examples of nucleophilic isocyanation, which is a traditional but immature strategy for the synthesis of isonitriles. Nucleophilic isocyanation was first described in the late 19th century, but the advancement and extension of this chemistry are still limited.
This is probably due to the difficulty in the selective formation of isonitrile over the thermodynamically and kinetically favored isomer, nitrile. Moreover, excess amounts of toxic metal cyanides are usually required for this transformation. Currently, the relatively reliable dehydration of formamides is most often chosen for the synthesis of isonitriles. However, this procedure also has unignorable drawbacks, such as the use of excess amounts of harmful dehydration reagents and the inevitable isolation of isonitriles with offensive odors. In contrast, some nucleophilic isocyanations are included in the sequential one-pot process to afford more complex molecules without the isolation of the isonitriles. Recently, several catalytic systems for the nucleophilic isocyanation using less toxic TMSCN have been developed. We believe that these new protocols will solve many of the pending problems and finally open the door to the progression of the chemistry of isonitriles to the next stage.

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