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Ag-catalysed double-benzylic isocyanation affording bisisonitriles and their utility as molecular linkers

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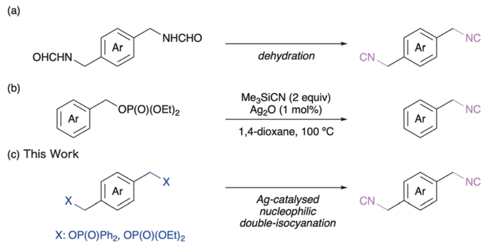
We describe a Ag-catalysed nucleophilic double isocyanation at benzylic positions forming bisisonitriles. In the presence of a catalytic amount of Ag_2O, bisdiphenylphosphinates or bisdiethylphosphates derived from the corresponding arenedimethanols successfully reacted with trimethylsilyl cyanide as a source of the isocyano group. A wide variety of bisisocyano-methyl arenes were obtained in moderate-to-high yields. The obtained bisisonitriles served as valuable molecular linkers using a Sc-catalysed multi-component reaction to afford light-emitting bis-3-amino-imidazo[1,2-*a*]pyridines.

Introduction

Isonitriles (R–NC) are versatile building blocks in organic synthesis.[1,2] The *C*-termini of isonitriles can uniquely accept both nucleophiles and electrophiles at the same time, making them useful in various multicomponent reactions (the Ugi reaction, the Passerini reaction, *etc.*) and heterocyclizations. Numerous bond-forming reactions are available to connect molecular components using isonitrile as a substrate ‘linker’ under mild reaction conditions. Building on this versatility, bisisonitriles (CN–R–NC), which contain two isonitrile groups, serve as valuable tethering reagents or artificial building units for macrocyclic compounds and functionalized polymers. For example, Wessjohann and coworkers reported multicomponent macrocyclization using a bisisonitrile *via* a Ugi reaction to form unnatural cyclic peptides.[3] Some biologically active dicarboxylic acids were also incorporated by connecting them with bisisonitriles.[4] Rivera, Dömling, and coworkers successfully applied a bisisonitrile as a stapling reagent to the peptide side chain.[5] In this case, the linear peptide was converted into a component of the macrocyclic compound in a one-shot reaction. Hu, Tang, and coworkers developed a facile methodology for preparation of polythiourea using bisisonitriles, diamines, and elemental sulfur.[6] The polymer exhibits high efficiency for Hg^{2+} ion-selective capture.

Despite the broad applicability of bisisonitriles, their synthesis remains limited to the traditional strategy.[7] Namely, dehydration of the corresponding *N*,*N*′-bisformamide is the only choice for production of bisisonitriles (Scheme 1a). However, the dehydration conditions are somewhat harsh and are problematic in terms of the tolerance of functional groups. In addition, *N*,*N*′-bisformamides are usually less soluble in organic solvents. As a result of these limitations, only a small number of bisisonitriles have been prepared to date. Nucleophilic isocyanation is another straightforward method furnishing isonitriles.[8] Cyanide is one of the most typical ambident nucleophiles, and its *C*- and *N*-termini are both available as reactive sites. However, a free cyanide usually reacts at the more nucleophilic *C*-terminus to form the more stable nitrile. Use of appropriate cyanide reagents under devised reaction conditions is required to obtain isonitriles selectively. Catalytic isocyanation has recently garnered interest from the viewpoint of efficiency and mechanistic novelty.[9–11] In the presence of an appropriate transition metal catalyst, cyanide reagent functions as a source of the isocyano group. Gassman, Utimoto, Shenvi, and Miura individually developed elegant methods for the catalytic nucleophilic isocyanation.[12–14]



Scheme 1 Preparation of bisisonitriles through traditional dehydration and catalytic nucleophilic isocyanation.

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However, these procedures have never been applied generally to benzylic compounds. We previously succeeded in Ag-catalysed benzylic isocyanation using the corresponding diethyl phosphate as an electrophile (Scheme 1b).[10] The silyl cyanoargentate complex, $(Me_3Si)[Ag(CN)_2]$, generated *in situ* from Ag_2O and Me_3SiCN (excess) acts as an effective catalytic active species: the trimethylsilyl group activates the leaving group to form the benzylic cation, followed by the substitution with $[Ag(CN)_2]^-$ as a *C*-protected cyanide source.

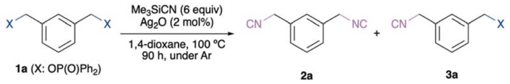
We here describe catalytic double isocyanation affording bisisonitriles (Scheme 1c). Benzene dimethanol-type substrate was converted into the corresponding bisisonitrile selectively. Some of these bisisonitriles have only rarely been synthesized. No possible benzylic nitrile isomers were observed through the reaction because of the predominant *N*-terminus bond formation of this method. We also attempted the transformation of the series of bisisonitriles into the highly functionalized fluorescent compounds with a 3-amino-imidazo[1,2-*a*]pyridine structure.

Results and discussion

Our investigation began with the optimization of the reaction conditions in the double isocyanation. Diphenylphosphinate of 1,3-benzenedimethanol **1a** was selected as the model substrate (Table 1). In the presence of Ag_2O (2 mol%) and Me_3SiCN (6 equiv.), **1a** was fully consumed after 90 h in 1,4-dioxane at 100 °C (entry 1). The target double-isocyanation product **2a** was obtained in 75% yield. The compound was sufficiently stable on silica gel to be isolated in 64% yield. Mono-isocyanated product **3a** was also obtained in 4% yield, because the second isocyanation was relatively slow. No **2a** was obtained in the absence of Ag_2O (entry 2). When 1 mol% of the catalyst was used, the yield of **2a** decreased to 65% (entry 3). AgTFA (4 mol%) and $Pd(OAc)_2$ (4 mol%)[9,11] were also employable as catalysts, although the yields were not comparable (entries 4, 5). Four equivalents of Me_3SiCN were not sufficient for the reaction (entry 6). Temperature control was found to be important for the reaction. At 120 °C, the yield of the product was slightly low (entry 7). On the other hand, the content of mono-isonitrile **3a** was clearly increased when the reaction was carried out at 80 °C (entry 8). We then screened solvents to identify the suitable one for the reaction. When 1,2-dimethoxyethane (1,2-DME) was used in place of 1,4-dioxane, **1a** was almost completely decomposed (entry 9). A moderate yield of **2a** with a non-negligible amount of **3a** was obtained in toluene and 1,2-dichloroethane (entries 10, 11). When a diethyl phosphate derivative of **1a** was applied to the standard conditions (entry 1), a relatively large amount of monoisonitrile remained, probably due to the slow reaction (entry 12), although diethyl phosphate was a useful substrate for mono-benzylic isocyanation (Scheme 1b).[10]

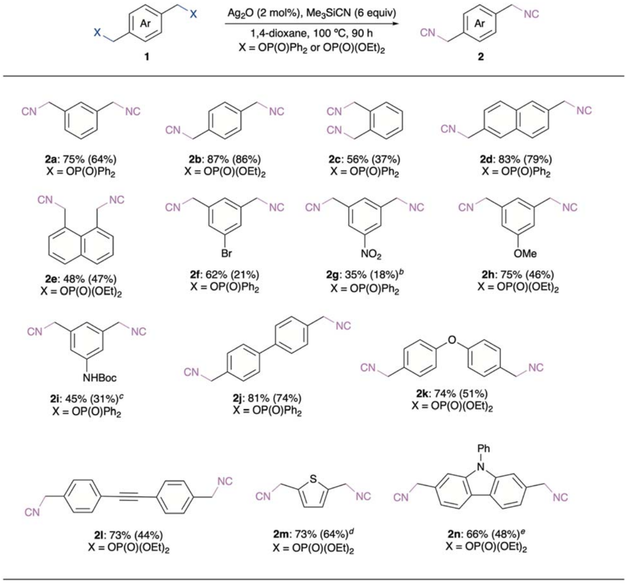
With the optimized reaction conditions in hand, we then investigated the substrate scope (Scheme 2). Not only the 1,3-dimethanol derived bisisonitrile **2a**, but also the 1,4- and 1,2-disubstituted compounds, **2b** and **2c**, were obtained in moderate-to-high yield. The 2,6-naphthyl moiety was also suitable for the reaction (**2d**). In contrast, 1,8-naphthylbisisonitrile **2e** was obtained in 48% yield, possibly because of the steric hindrance. Introduction of functionalities on the aryl rings influenced stability of the products: The ^1H NMR yields of electron-deficient 5-bromo-1,3-bisisocyanomethylbenzene **2f** and the electron-abundant 5-methoxy product **2h** were high, but the yields were drastically decreased through the isolation procedure with silica-gel column chromatography. Substitution of strongly electron-withdrawing nitro group at the C5 position (**1g**) decelerated the reaction rate. The reaction using 10 equivalents of Me_3SiCN with 10 mol% of Ag_2O afforded **2g** in 35%

Table 1 Optimization of reaction conditions[a]



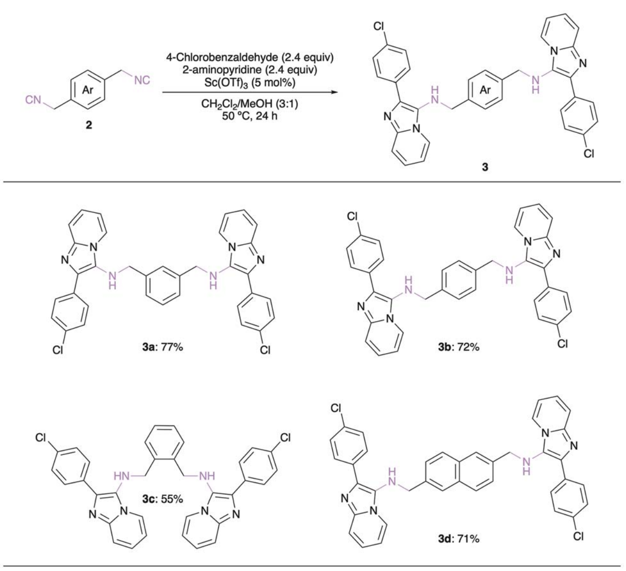
Entry	Deviation from the standard conditions	Conversion[b] (%)	Yield[b,c] (%)	
			2a	**3a**
1	None	>99	75(64)	4
2	No catalyst was used	46	0	0
3	Catalyst: Ag_2O (1 mol%)	96	65	4
4	Catalyst: AgTFA (4 mol%)	>99	70	3
5	Catalyst: $Pd(OAc)_2$ (4 mol%)	>99	60	0
6	Me_3SiCN (4 equiv.)	98	64	5
7	Reaction at 120 °C	>99	60	5
8	Reaction at 80 °C	>99	53	18
9	Solvent: 1,2-DME	>99	5	3
10	Solvent: Toluene	99	44	17
11	Solvent: 1,2-DCE	97	45	13
12	X: $OP(O)(OEt)_2$	>99	55	14

[a] Reactions were conducted using **1a** (0.5 mmol) and Me_3SiCN (3.0 mmol) in 1,4-dioxane (2.0 mL) with Ag_2O (2 mol%) at 100 °C for 90 h. [b] Determined by ^1H NMR analysis using pyrazine as an internal standard. [c] The isolated yield is shown in parenthesis.

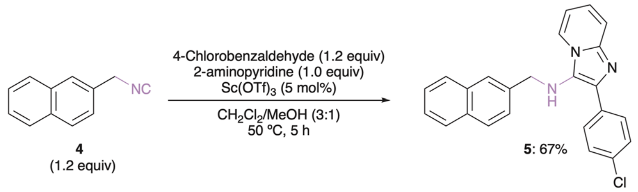


Scheme 2 Scope and limitations for Ag-catalysed double isocyanation.[a] [a] ^{1}H NMR yield is described. The isolated yield is shown in parenthesis. [b] 10 mol% of Ag_2O and 10 equiv. of Me_3SiCN were used for 72 h. [c] The reaction time was 45 h. [d] The reaction time was 2 h. [e] The reaction time was 1 h.

yield. *N*-Boc aniline function was left intact throughout the reaction (**2i**). These bisisonitriles are hardly synthesized by the traditional dehydration procedure. Bisisonitriles with linked aryl core structures, namely, biphenyl (**2j**), diphenylether (**2k**), and diphenylacetylene (**2l**), were also synthesized by this reaction. A heteroaryl-containing compound, 2,5-bisisocyanomethylthiophene **2m**, was obtained in 73% yield. Notably, the reaction completed in 2 h. The more electron-abundant *N*-phenylcarbazolyl compound **1n** was converted to the bisisonitrile **2n** (64%) in only 1 h. The selection of the leaving group was significant for synthesis of the desired bisisonitriles **2** in high yield. Diphenylphosphinate was the first choice due to the eminent reactivity. However, in some cases, the solubility of bisdiphenylphosphinate in less polar 1,4-dioxane was insufficient for this reaction. The use of bisdiethyl phosphate showing better solubility resulted in a higher yield of **2.**



Scheme 3 Formation of bis-3-amino-imidazo[1,2-*a*]pyridines from bisisonitriles.



Scheme 4 Multi-component cyclization using 2-naphthylmethylisonitrile **4** affording 3-amino-imidazo[1,2-*a*]pyiridine **5**.

We then investigated the possibility of using bisisonitrile as a molecular linker. The multicomponent reaction using isonitrile, aldehyde, and 2-aminopyridine is known to afford the corresponding 3-amino-imidazo[1,2-*a*]pyridine, which is used as a chromophore.[15] We attempted to apply the reaction to the bisisonitriles to furnish the dimethylaryl group-tethered fluorescent compounds. 4-Chlorobenzaldehyde and 2-aminopyridine were employed for the model reaction (Scheme 3). Bisisonitriles **2a–2d** were smoothly converted into the bis-3-amino-imidazo[1,2-*a*]pyridines **3a–3d** in the presence of a catalytic amount of $Sc(OTf)_3$.[16] In the case of preparation of **3c**, the yield was moderate, possibly because of the steric hindrance of the *o*-substituted substructure.

We also prepared the 3-amino-imidazo[1,2-*a*]pyridine **5** from 2-naphthylmethylisonitrile **4** under the same conditions in 67% yield, as a reference sample (Scheme 4). All imidazo[1,2-*a*]pyridines **3a–3d** and **5** had fluorescent properties, emitting cyan light under 365 nm UV light irradiation in the solid states (Fig. S1 and S2).

The optical properties of **3a–3d** and **5** in dimethyl sulfoxide (DMSO) were investigated and summarized in Fig. 1, S3 and S4, and Table 2 and S1. Intense absorption bands and cyan fluorescence were observed in these compounds. All compounds exhibited a maximum absorption wavelength (λ_{abs}^{max}) at 343–344 nm and maximum emission wavelength (λ_{em}^{max}) at 488–489 nm (Fig. 1 and Table 2). *N*-Benzyl-linked **3a–3c** exhibited a high photoluminescence quantum yield (Φ_{PL}) of 67–72% with

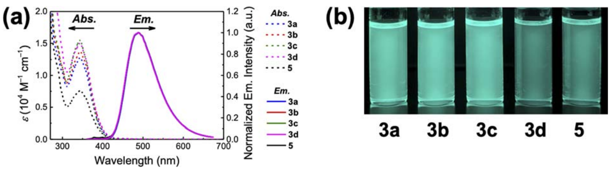


Fig. 1 The optical properties of 3-amino-imidazo[1,2-*a*]pyridines **3** and **5** in DMSO. (a) The absorption and emission spectra. (b) Images of the fluorescence of **3** and **5** under the irradiation of 365 nm UV light irradiation.

Table 2 The optical properties of 3-amino-imidazo[1,2-*a*]pyridines **3** and **5** in DMSO

Compd[a]	λ_{abs}^{max}/nm (ε [$\times 10^4$ M^{-1} cm^{-1}])[b]	λ_{em}^{max}/nm[c]	Φ_{PL}[d]	τ_{av}/ns[e]	Stokes shift (cm^{-1})
3a	343 (1.28)	489	0.72	8.79	8700
3b	344 (1.37)	488	0.72	8.95	8600
3c	343 (1.56)	488	0.67	8.30	8700
3d	344 (1.50)	488	0.25	3.28	8600
5	344 (0.77)	488	0.27	3.79	8600

[a] $c = 10^{-5}$ M. [b] Absorption maxima. ε: molar extinction coefficient. [c] Emission maxima, excited at λ_{abs}^{max}. [d] Absolute photoluminescence quantum yields, excited at λ_{abs}^{max}. [e] Excited at 365 nm in DMSO, emission wavelength at λ_{em}^{max}.

a lifetime (τ) ranging from 8.30 ns to 8.95 ns, demonstrating that there is no dependency of substituent positions of 3-amino-imidazo[1,2-*a*]pyridines on the optical properties (Fig. S3 and S4 and Table 2 and S1). Moreover, *N*–CH$_2$-naphthyl-linked **3d** afforded a Φ_{PL} of 25% (τ = 3.28 ns), corresponding to the reference compound **5** (Φ_{PL} = 27%, τ = 3.79 ns). The stronger fluorescence of **3a–3c** compared to **3d** and **5** was attributed to the weaker charge–transfer interactions from the 3-amino-imidazo[1,2-*a*]pyridine to the benzyl group compared to those to the naphthyl group. All compounds exhibited a large Stokes shift over 8600 cm^{-1} in DMSO. Our work suggests a new direction and the possibility of designing multifunctional chromophores based on bisisonitriles.

Conclusions

In conclusion, we successfully demonstrated a Ag-catalysed double isocyanation at benzylic positions to afford bisisonitriles. A wide variety of aryl core-structures were incorporated into the bisisonitriles, which have rarely been synthesized previously. The corresponding bisdiphenylphosphinates or bisdiethylphosphates were shown to be suitable substrates for the reaction. The selection depended on the substrate solubility in 1,4-dioxane. The obtained bisisonitriles were available as molecular linkers using a Sc(OTf)$_3$-catalysed multi-component reaction. This procedure was applied to the synthesis of several light-emitting molecules.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d5ra04458h.

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