# Exploiting the Reactivity of Isocyanide: Coupling Reaction between Isocyanide and Toluene Derivatives Using the Isocyano Group as an N1 Synthon

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**S** *Supporting Information*

**ABSTRACT:** An unusual oxidative coupling reaction of isocyanide and toluene derivatives using tetrabutylammonium iodide (TBAI) as a catalyst is disclosed. The experimental results and mechanistic study show that the isocyano group acts formally as an N1 synthon during the transformation, thus expanding the reactivity profile of isocyanide.
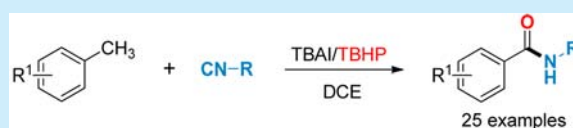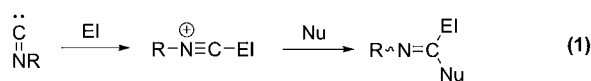
Ever since the Passerini and Ugi reactions were reported, isocyanides have found wide application in a variety of carbon–carbon and carbon–heteroatom bond-forming reactions.[1] From a mechanistic standpoint, the divalent carbon atom of isocyanides has pronounced nucleophilicity, which makes them particularly important reaction partners in multicomponent reactions (IMCRs).[2,3] In particular, the classical carbene-like reactivity of isocyanide has also been well-exemplified by many Lewis acid-catalyzed isocyanide insertion reactions (Scheme 1, eq 1).[4,5] Recently, transition-metal-catalyzed isocyanide insertion reactions (also known as imidoylative reactions) have emerged as a powerful tool in organic synthesis,[6,7] in which the reactivity of isocyanide as a carbon monoxide equivalent has been fully demonstrated. A careful literature survey revealed that most of the reported achievements

in isocyanide chemistry have been devoted to developing the use of isocyanides as carbenes, making them highly valuable and versatile C1 building blocks.[8,9] However, to our knowledge, examples aimed at exploring other novel reactivity profiles of the isocyano group are still rare. Zhu and co-workers have disclosed a multicatalytic reaction of isocyanides and propargylamines to afford imidazole derivatives (Scheme 1, eq 2).[10] In this case, the isocyano group serves as a polarized triple bond rather than a carbene, thereby greatly expanding the reactivity mode of isocyanide. Similar reactivity was also exhibited in the silver-catalyzed synthesis of imidazole from simple alkyne and isocyanide.[11] Xu and co-workers recently reported a very interesting cross-cycloaddition of two different isocyanides to synthesize pyrrolo[3,4-*b*]indoles (Scheme 1, eq 3).[12] According to their experimental outcomes and DFT calculations, the unusual heterodimerization of two isocyanides was believed to be the key step of the whole transformation. Additionally, another interesting reactivity of isocyanide allowed the isocyano group to be used as a cyano source when sterically hindered *tert*-butyl isocyanide was used as a reaction partner.[13] Although much progress has been made in the past decades, exploiting new reactivity patterns of the isocyano group continues to be a challenging goal for organic chemists.
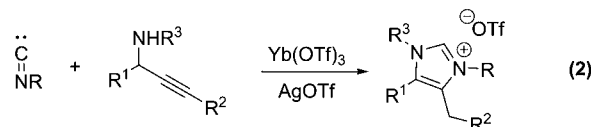
In the past years, we have been particularly interested in isocyanide chemistry and have focused our attention on the development of isocyanide-based novel transformations.[14] Thus, a series of novel strategies have been developed for the construction of structurally unusual drug-like heterocycles using isocyanides as versatile building blocks. Most recently, we also reported that selective double isocyanide insertion reactions could furnish indole-fused polycyclic skeletons in an efficient manner.[14a] On the other hand, toluene and its derivatives have been recognized as simple and valuable starting

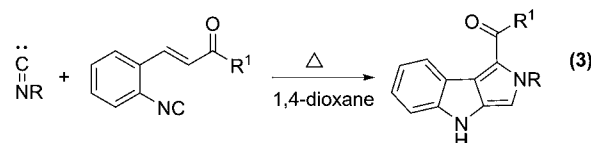**Scheme 1. Versatile Reactivity Profiles of the Isocyano Group**

materials in organic synthesis because of their easy availability and versatile reactivity.[15] It is therefore not surprising that many new reactions have been reported using arylmethanes as significant reaction components.[16] As a continuation of our previous research,[14,17] herein we report the coupling reaction of toluene derivatives and isocyanides using the isocyano group as an N1 synthon. To the best of our knowledge, no such examples have been reported previously.

We initially investigated the coupling reaction with model substrates toluene (**1a**) and *tert*-butyl isocyanide (**2a**) using TBHP as the oxidant. During our early runs, no reaction occurred upon treatment of the mixture in DCE solution with a catalytic amount of CuI or $I_2$ (Table 1, entries 1 and 2).

**Table 1. Optimization of the Reaction Conditions**[a]



| entry | catalyst | solvent | oxidant | yield (%)[b] |
|---|---|---|---|---|
| 1 | CuI | DCE | TBHP | 0 |
| 2 | $I_2$ | DCE | TBHP | 0 |
| 3 | $CuBr_2$ | DCE | TBHP | 40 |
| 4 | $CuCl_2$ | DCE | TBHP | 30 |
| 5 | $Cu(OAc)_2$ | DCE | TBHP | <5 |
| 6 | TBAI | DCE | TBHP | 72 |
| 7 | TBAI | MeCN | TBHP | 45 |
| 8 | TBAI | EtOAc | TBHP | <10 |
| 9 | TBAI | PhCl | TBHP | <5 |
| 10 | TBAI | DMSO | TBHP | 35 |
| 11 | TBAI | THF | TBHP | 20 |
| 12 | TBAI | $PhCF_3$ | TBHP | 57 |
| 13 | TBAI | DCE | $H_2O_2$ | 0 |
| 14 | TBAI | DCE | $K_2S_2O_8$ | 0 |
| 15 | TBAI | DCE | DTBP | 0 |
| 16 | – | | TBHP | 0 |

[a]Unless otherwise noted, all reactions were carried out with **1a** (1.5 mmol), **2a** (0.5 mmol), catalyst (20 mol %), oxidant (6.0 equiv), and solvent (3 mL) at 80 °C in a sealed tube. [b]Yields of products after silica gel chromatography.

Pleasingly, employing $CuBr_2$ as catalyst essentially gave rise to compound **3a** in 40% yield (entry 3). The $^{13}C$ NMR spectrum of compound **3a** clearly showed that only one carbonyl carbon was present, which indicated that one carbon was missing during the reaction. Encouraged by this unusual result, we briefly screened the reaction parameters, including the catalyst, the solvent, and the oxidant, to optimize the reaction performance. Of the catalysts examined, TBHP showed the best catalytic activity toward the formation of **3a** (entry 6), whereas the use of $CuCl_2$ and $Cu(OAc)_2$ only led to decreased yields (entries 4 and 5). The following experimental results showed that the solvent also had a significant impact on this reaction. Lower yields were observed when reactions were performed in other solvents such as $CH_3CN$, EtOAc, chlorobenzene, and THF (entries 7–11). In addition, benzotrifluoride as an eco-friendly solvent was also proven to be compatible (entry 12). Notably, the replacement of TBHP with other oxidants, including $H_2O_2$, $K_2S_2O_8$, and DTBP, failed to generate **3a** (entries 13–15).

After the optimal conditions were established, we focused our attention on investigating the scope and limitations of the present coupling reaction. As shown in Scheme 2, toluene

**Scheme 2. Scope of the Reaction with Respect to the Arylmethane Substrate 1**[a,b]
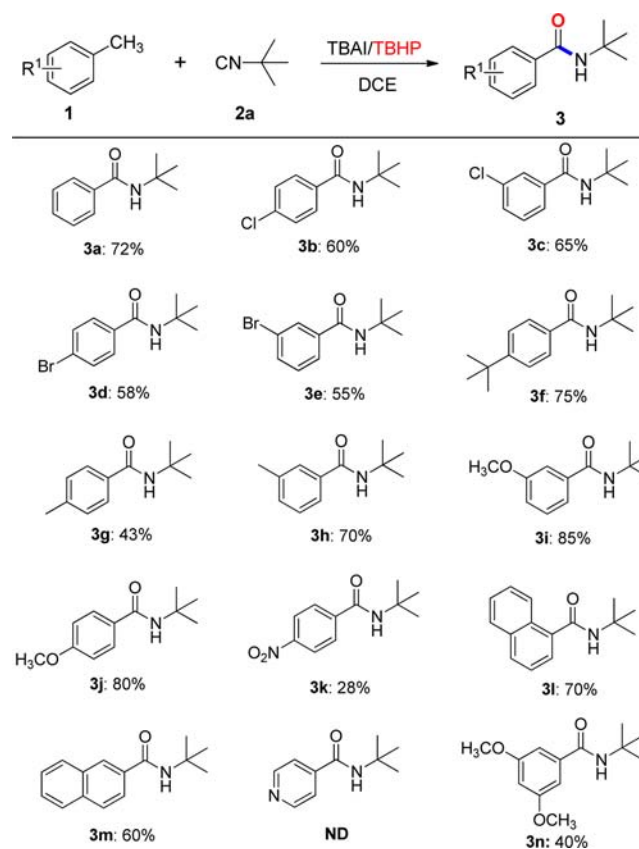


[a]Reaction conditions: **1** (1.5 mmol), **2a** (0.5 mmol), TBAI (20 mol %), TBHP (6.0 equiv), and DCE (3 mL) at 80 °C in a sealed tube. [b]Yields of products after silica gel chromatography are shown.

derivatives **1** having different electron-withdrawing and electron-donating substituents on the aromatic ring were first employed to react with **2a** under the standard conditions (**3a–j**). The experimental outcome revealed that a wide range of substituents in arylmethanes **1**, including halide, alkyl, methoxy, and nitro groups at the *ortho*, *meta*, and *para* positions of the aromatic ring, were well-tolerated, affording the desired compounds **3**. Representative results are summarized in Scheme 2, and all new compounds were characterized by $^1H$ and $^{13}C$ NMR spectroscopy and HRMS (see the Supporting Information for details). Remarkably, *p*- and *m*-xylene were proven to be good reaction components, affording the corresponding products **3g** and **3h**. It is also worth noting that the methoxy group seemed to favor the formation of **3** (**3i** and **3j**), whereas the presence of a nitro group in substrate **1** dramatically decreased the yield (**3k**). After a broad scope of simple benzene-based substrates **1** were examined, reactions with arylmethanes **1** containing naphthyl and pyridyl groups were conducted. The naphthyl groups were proven to be compatible in the present reaction (**3l** and **3m**), but no reaction took place when a pyridyl group was present in substrate **1**.

To further explore the utility of the present reaction, the substituents of isocyanides **2** were then varied. As shown in Scheme 3, a series of aliphatic and aromatic isocyanides **2** were subjected to the optimal conditions. Gratifyingly, almost all of the reactions proceeded smoothly to produce the products **4a–g**. Unfortunately, no reaction occurred when sterically hindered

## Scheme 3. Scope of the Reaction with Respect to the Isocyanide Substrate 2[a,b]
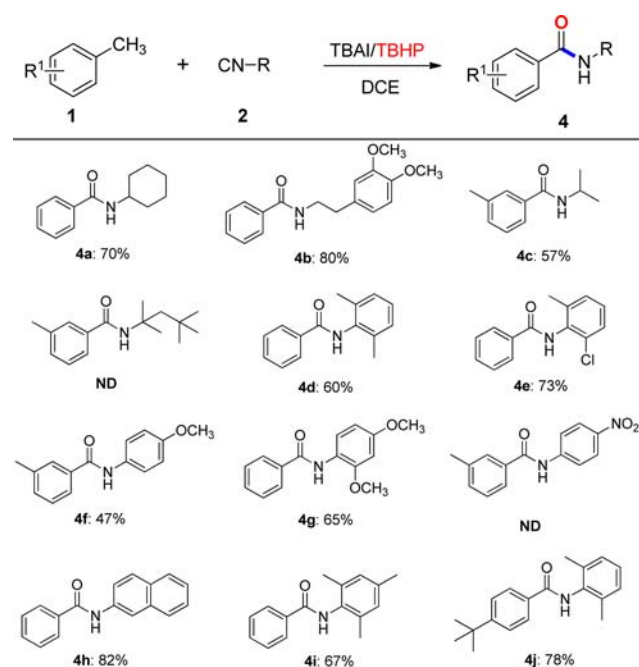


[a]Reaction conditions: **1** (1.5 mmol), **2** (0.5 mmol), TBAI (20 mol %), TBHP (6.0 equiv), and DCE (3 mL) at 80 °C in a sealed tube. [b]Yields of product after silica gel chromatography are shown.

1,1,3,3-tetramethylbutyl isocyanide and less reactive 4-nitrophenyl isocyanide were used. Subsequent experiments showed that 2-naphthyl isocyanide (**2k**) worked well to furnish the corresponding product **4h** with good performance. Furthermore, the methyl groups in 2,6-dimethylphenyl isocyanide and 2,4,6-trimethylphenyl isocyanide remained intact during the oxidative coupling (**4i** and **4j**), thus significantly featuring the chemical selectivity and substrate scope.

To gain further insight into the aforementioned coupling reaction, three mechanistic experiments were conducted. First, the radical scavenger TEMPO was added to the preformed solution of **1a** and **2a** under the optimal conditions and was found to completely inhibit the present reaction (Scheme 4, eq 4). To our delight, two significant radical intermediates were also captured.[18] To find out the real reaction intermediate, the reaction of benzaldehyde (**5**) with **2a** was also carried out. In this case, **3a** was isolated in 82% yield under the optimal conditions, indicated that **5** is a possible reaction intermediate (Scheme 4, eq

## Scheme 4. Preliminary Mechanistic Studies
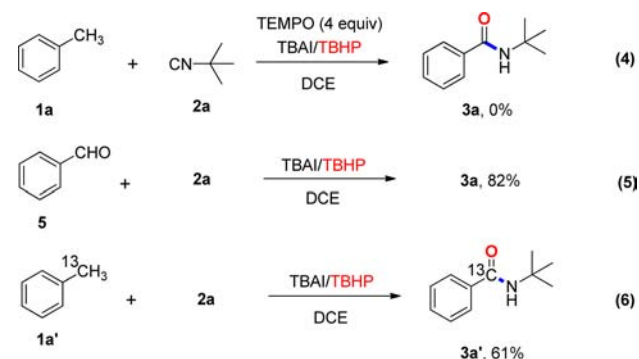


5). Finally, an isotope-labeling experiment was also performed. The reaction of toluene-[methyl-$^{13}C_1$] (**1a′**) and **2a** proceeded readily to give the amide-[carbonyl-$^{13}C_1$] product **3a′** (Scheme 4, eq 6), which clearly indicated that the carbon of the isocyano group was eliminated during the reaction.

The mechanism of this unusual oxidative coupling reaction has not been unequivocally established, but one reasonable mechanistic process is proposed to explain the formation of product **3**. As shown in Scheme 5, the beginning of this reaction

## Scheme 5. Proposed Mechanism
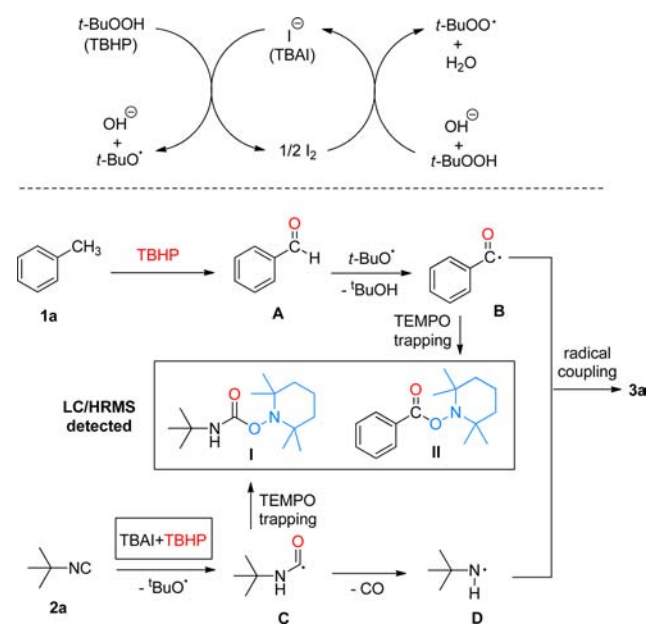


involves the formation of *tert*-butoxyl and/or *tert*-butylhydroperoxide radicals from the catalytic cycle of TBAI and TBHP.[19] Subsequently, toluene **1** is oxidized to benzoyl radical **B**[20] via intermediate benzaldehyde **A**. This step can also explain the formation of benzil as a byproduct. On the other hand, the reaction between isocyanide and TBHP in the presence of TBAI leads to the formation of reactive formamido radical **C**, which is believed to be the key step. The resultant intermediate **C** then eliminates carbon monoxide to generate radical **D**.[21] Finally, radical coupling of the two radicals **B** and **D** essentially yields the product **3**.

In conclusion, we have developed a novel and interesting coupling reaction between arylmethanes and isocyanides. In this reaction, the reactivity of the isocyano group as an N1 synthon other than a carbene is unprecedented, offering a new opportunity to enrich isocyanide chemistry. A broad range of toluene derivatives and isocyanides readily participated in this coupling reaction. As a result, the present reaction has potential to be further applied in organic synthesis.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01928.

> Experimental procedures, full characterization of all compounds, spectral data, and $^1H$ and $^{13}C$ NMR spectra for all products (PDF)

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**Author Contributions**

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**Notes**

The authors declare no competing financial interest.

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