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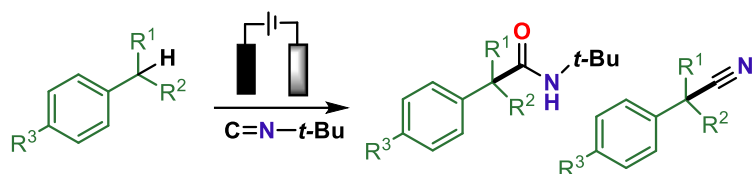
Electrochemical Benzylic C-H Functionalization with Isocyanides

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Supporting Information Placeholder



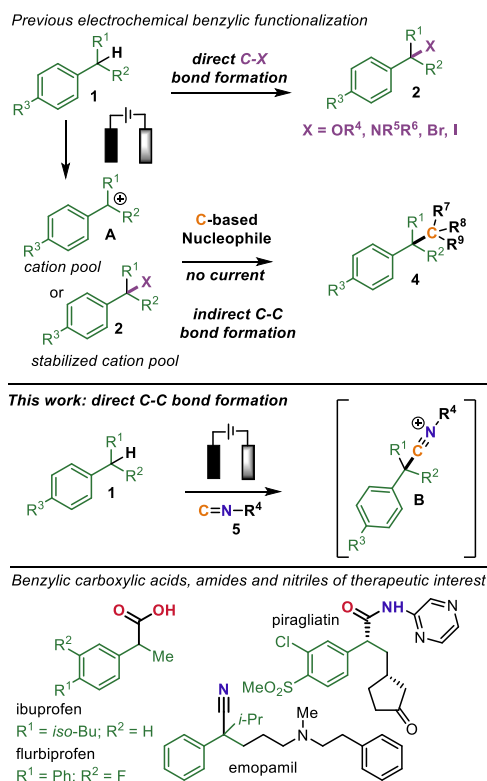
ABSTRACT: We report the challenging direct carbamoylation or cyanation of benzylic C(sp³)-H bonds with an isocyanide via an electrochemical process giving rise to structures which are encountered in several biologically relevant compounds and drugs. This transformation proceeds in mild conditions without the need of any external oxidant and avoids the necessity to start from a prefunctionalized benzylic substrate or the deployment of the cation pool method. Anodic oxidation of the benzylic position and subsequent addition of the isocyanide leads to the formation of a C-C bond and to a nitrilium cation which hydrolysis yields alpha-aryl acetamide derivatives, while elimination of a *t*-butyl cation delivers alpha-aryl acetonitrile derivatives.

The functionalization of benzylic C(sp³)-H bonds, via either metal-catalyzed C-H activation or benzylic oxidation, represents a formidable way to convert feedstock raw materials such as alkyl benzenes into fine chemicals.¹ In this field, photoredox catalysis and electrochemistry have emerged as proficient strategies, with which the use of stoichiometric quantities of strong oxidants and the generation of a substantial amounts of waste can be avoided.² Notably, organic electrochemistry has been employed for the formation of valuable C-N,³ C-O⁴ or C-halogen⁵ bonds at benzylic positions (**1** to **2**, Scheme 1).² Nonetheless, the formation of a C-C bond by anodic oxidation stands challenging, and mainly relies on the use of activated substrates such as tetrahydroisoquinolines, xanthenes or *para*-substituted phenols.⁶ Indeed, inactivated substrates entail them to be used in large excess, which severely impacts the synthetic potential of such benzylic functionalization processes. To overcome some of these difficulties, Yoshida deployed the cation pool method to indirectly construct C-C bonds in electrochemical conditions.⁷ This concept involved an anodic oxidation to generate a carbocation which is then trapped by a C-nucleophile in the absence of current. It could be applied to activated benzylic substrates (**1** to **4** via **A**, Scheme 1) such as diarylmethane precursors^{7d-g} or to the presence of an excess of a temporary stabilizing agent in the case of the stabilized cation pool approach (**1** to **4** via **2**, Scheme 1).^{7a-c} Nevertheless, the development of new electrochemical methods which could permit the direct benzylic functionalization of alkyl arenes with C-based nucleophiles is highly desirable.

The direct introduction of a carbonyl group at a benzylic position is a valuable method to form alpha-aryl carbonyl moieties which are encountered in numerous biological active compounds such as the anti-inflammatory drugs ibuprofen, flurbiprofen, ketoprofen and naproxen or the glucokinase activator

piragliatin.⁸ Related benzylic cyanation is relevant to alpha-aryl acetonitriles of biological interest such as emopamil, a calcium channel blocker or levocabastine, an antihistaminic (Scheme 1 and see SI).⁹

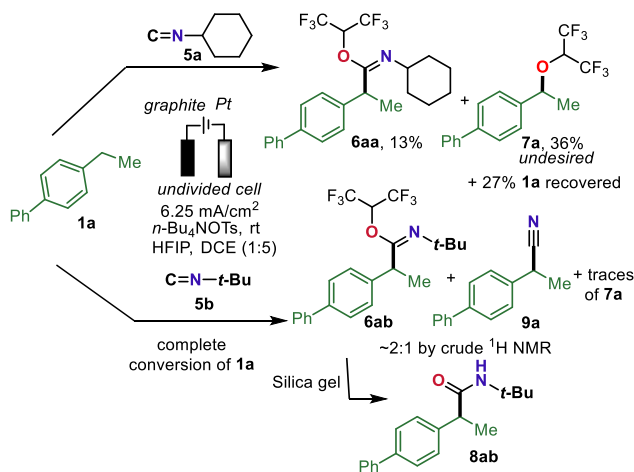
Scheme 1. Electrochemical benzylic functionalization



In line with our interest in the electrochemical functionalization of aromatic compounds,¹⁰ we aimed to develop electrochemical benzylic carbonylation or cyanation through the addition of suitable nucleophilic carbonyl or cyanide surrogates onto the benzylic carbocation generated via anodic oxidation.¹¹ To address this challenge, isocyanides **5** appeared to us to be reagents of choice since they should be capable to intercept an electron-deficient benzylic position of **1** leading to the generation of a transient nitrilium **B** (Scheme 1). Indeed, isocyanides are versatile compounds that are widely used in multicomponent reactions (IMCRs) such as the Ugi or Passerini reactions involving their additions to aldehydes or imines.¹² To the best of our knowledge, the addition of isocyanides to benzylic position were only reported for particularly activated bisbenzylic substrates or α -arylamines with benzoyl peroxide and a copper catalyst.¹³ However, the deployment of isocyanides in electrochemical set-up are scarce. In this context, we recently demonstrated that isocyanides are compatible with electrochemical conditions for oxidative Ugi-type processes through the oxidation of an amine or alcohol with an electrocatalyst.¹⁴ More recently, isocyanides were also employed for the electrochemical synthesis of carbodiimides, carbonimidothioates, S-thiocarbamates or ketoamides.¹⁵

To test, the feasibility of this approach, we selected ethyl biphenyl **1a** as substrate. Inspired by the electrochemical amination of Xu, we performed the reaction in presence of HFIP which is key to perform the benzylic oxidation (Scheme 2).^{3e} With cyclohexyl isocyanide **5a**, we were able to observe the formation in low yield of hexafluoro-*iso*-propyl imidate **6aa** which resulted from the desired addition of the isocyanide to the benzylic position accompanied with the reaction with HFIP. The competitive formation of ether **7a** via addition of HFIP to the oxidized benzylic position was observed. To strongly diminish this undesired reaction, the use of the more nucleophilic *t*-butyl isocyanide **5b**¹⁶ was necessary to obtain a complete consumption of **1a**. The crude ¹H NMR showed that *N-t*-butyl imidate **6ab** was the main product accompanied by nitrile **9a** which also results from the addition of **5b** to **1a**.¹⁷ However **6ab** is partly hydrolyzed into desired amide **8ab** upon purification on silica gel. Therefore, we decided to perform an acidic treatment at the end of the electrolysis to completely convert imidate **6ab** into amide **8ab**.

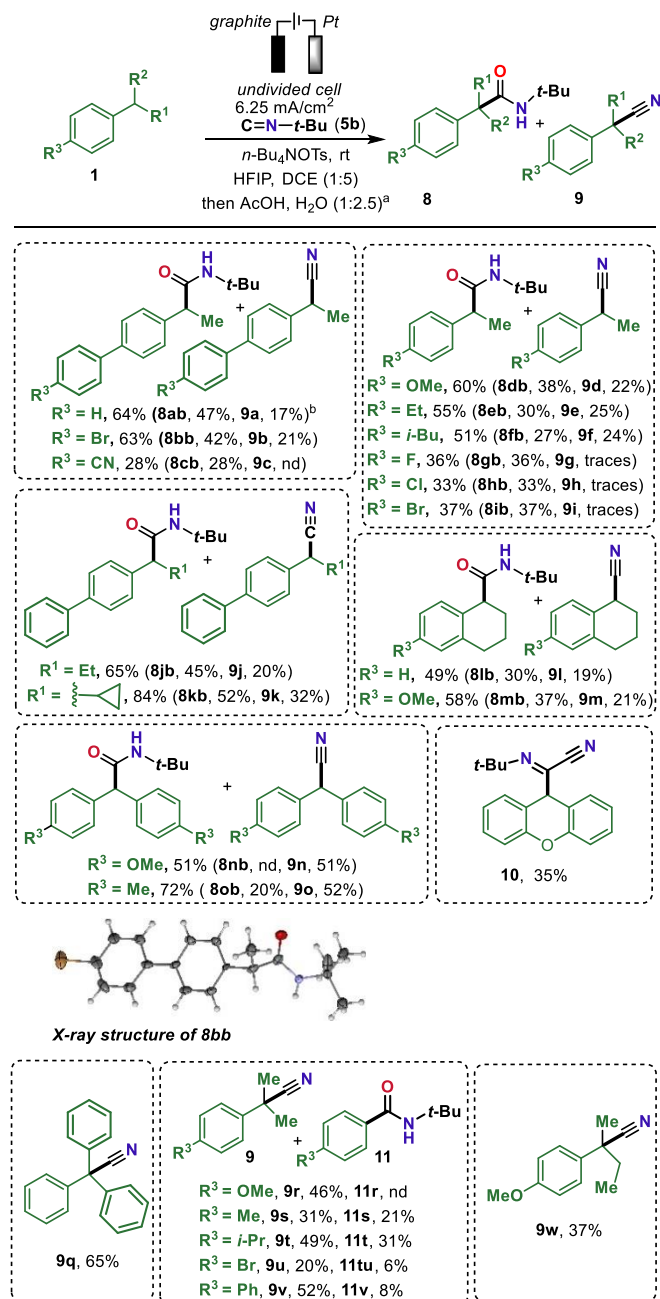
Scheme 2. Effect of the isocyanide on the electrochemical benzylic carbamoylation/cyanation with isocyanides.



Upon evaluation of the parameters of the reaction we found out that the nature of the anion of the tetrabutyl ammonium electrolyte proved to be important since the tosylate salt ensured a better conversion of **1a** than the nitrate salt and a better selectivity of the addition to **1a** of the isocyanide over HFIP than the tetrafluoroborate or hexafluorophosphate salts. The use of both HFIP and dichloroethane is key to promote the C-C bond formation with an optimal ratio of 1:5 since performing the reaction in pure dichloroethane or pure HFIP lead to the formation of complex mixtures (see SI). Eventually, electrolysis in an undivided cell at a constant current of 6.25 mA/cm² with a graphite anode and a platinum-plated cathode in a 5:1 mixture of dichloroethane and HFIP with tetrabutyl ammonium tosylate as electrolyte at room temperature followed by hydrolysis with acetic acid and water at room temperature to generate **8ab** from **6ab** appeared to be the optimal conditions. Overall, benzylic amide **8ab** was produced with 47% along with 17% of nitrile **9a** which represent a 64% yield of addition of the isocyanide onto the benzylic position (Scheme 3). Minor amounts of unreacted **1a** and hexafluoro-*iso*-propyl ether **7a** were detected. Despite our efforts, we were not able to improve further the selectivity of the amide over the nitrile.

We then studied the scope of this electrochemical carbamoylation/cyanation of benzylic secondary carbons with *t*-butyl isocyanide (Scheme 3).¹⁸ *para*-Bromo and *para*-cyano derivatives of ethyl biphenyl (**8bb/9b** and **8cb**) were also competent acceptors of the carbon nucleophile. We were able to resolve the structure of amide **8bb** by X-ray analysis of a monocrystal of this compound. Other substituents at the *para* position of ethyl benzene such as a methoxy, ethyl, *iso*-butyl, fluoro, chloro or bromo substituents delivered satisfactorily the C-C bond formation products (**8db-ib/9d-f**).¹⁹ The length of the alkyl chain which contains the benzylic CH₂ to be functionalized was also evaluated with success in the cases of a propyl (**8jb/9j**) instead of an ethyl and also with a methyl cyclopropyl (**8kb/9k**) without opening of the cyclopropyl and as well for tetrahydronaphthalene derivatives (**8lb,mb/9l,m**). In all these cases, the amide is predominant in comparison to the nitrile. In contrast, with more activated benzylic substrates such as biphenylmethane derivatives, the nitrile (**9n,o**) is the major product over the amide (**8nb,ob**). Very interestingly, xanthene resulted in the formation of α -imino-nitrile **10** which resulted in the interception of nitrilium **B** by a second isocyanide. *t*-Butyl isocyanide **5b** could also add to a benzylic tertiary carbon in these electrochemical conditions leading to quaternary center-containing nitriles **9q-w** (Scheme 3). Indeed, highly activated triphenyl methane delivered efficiently triphenyl acetonitrile **9q**. The *iso*-propyl group is also suitable for benzylic C-H cyanation of substrates *para*-substituted with methoxy, methyl, *iso*-propyl, bromide or phenyl groups (**9r-v**). Surprisingly, *ipso*-substitution of the *iso*-propyl group by the isocyanide leading to benzamides **11r-v** was also observed. The *sec*-butyl group could also lead to trisubstituted acetonitrile **9w**.

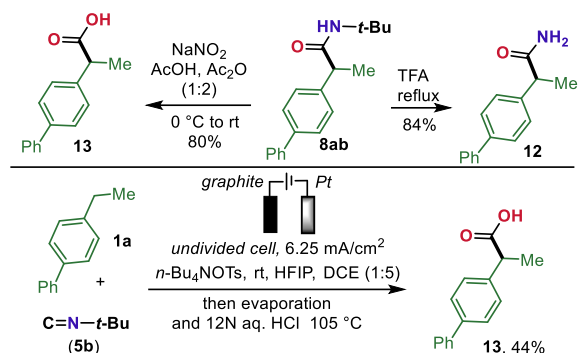
Scheme 3. Scope of the electrochemical carbamoylation/cyanation with isocyanides of benzylic secondary carbons.



a) Undivided cell, graphite-SK50 anode (1.5 cm x 0.8 cm x 0.2 cm submerged), platinum-plated cathode (1.5 cm x 0.8 cm x 0.2 cm submerged), 7.5 mA, **1a** (0.2 mmol), **5b** (0.5 mmol), *n*-Bu₄NOTs (0.2 mmol), 3 mL of DCE/HFIP (5:1), room temperature; argon; b) 61% (**8ab**, 37%+**9a**, 24%) on a 1 mmol scale.

In terms of post-synthetic transformations, the *t*-butyl group of amide **8ab** is easily removed with TFA to deliver primary amide **12** (Scheme 4). The *t*-Bu amide **8ab** could also be hydrolyzed at room temperature to generate the corresponding carboxylic acid **13**. Alternatively, after the electrolysis of **1a** and evaporation of the solvents, the crude mixture of amide **8ab** and nitrile **9a** is directly hydrolyzed into carboxylic acid **13** with aqueous chlorhydric acid.

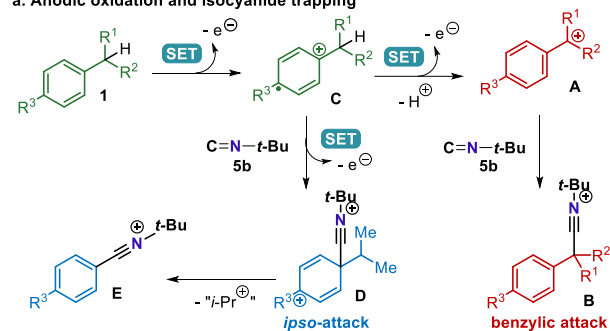
Scheme 4. Synthesis of the corresponding primary amide or carboxylic acid.



From a mechanistic point of view, the direct anodic oxidation of the aromatic moiety of **1** would provide the corresponding radical cation **C**^{•+} which could evolve through various scenarios depending on the substitution pattern of the arene (Scheme 5, a). With a substituent at the *para*-position,¹⁸ radical cation **C** could lose a proton to generate the corresponding benzylic radical (not shown), which in turn is oxidized to the corresponding benzylic carbocation **A**. The latter would then be trapped by *t*-BuNC, and the corresponding nitrilium **B** would either (Scheme 5, c) fragment to form the cyano derivative **9** (via the loss of the *tert*-butyl cation, further evolving to isobutene after proton release),¹⁷ or generate imidate **F** upon capture by the alkoxide of HFIP generated by reduction of proton at the cathode (Scheme 5, b). Amide **8** would finally be generated by hydrolysis.

Scheme 5. Mechanistic proposal.

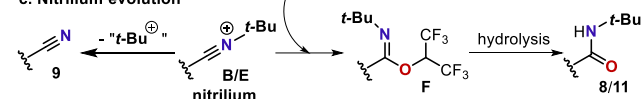
a. Anodic oxidation and isocyanide trapping



b. Cathodic reduction



c. Nitrilium evolution



It could not be excluded that the benzylic radical can add directly to the isocyanide. However, we believe that the formation of benzylic ether in presence of methanol or *t*-butanol (see SI) is diagnostic of the rapid formation of benzylic carbocation **A**. Moreover, in the case of a less nucleophilic isocyanide (i.e. cyclohexylisocyanide **5a**), the benzylic carbocation can competitively be trapped by HFIP to yield **7a** (Scheme 2). Worthy of note, we ruled out that hexafluoro-*iso*-propanol ether **7a** could be a transient intermediate because no amide **8a** nor nitrile **9a** was observed when **7a** was reengaged in the reaction conditions with isonitrile **5b**.

In presence of an *iso*-propyl group, *ipso*-substitution becomes also possible through the addition of the isonitrile to the oxidized aromatic ring of **C**, thus liberating a relatively stable *iso*-

propyl secondary carbocation from **D** and delivering the corresponding imidate **F** after reaction of aromatic nitrilium **E** with HFIP and the benzamide **11** after hydrolysis.

Low yields were obtained in plain dichloroethane and the addition of HFIP, even if nucleophilic enough to trap the nitrilium **B** before fragmentation, proved essential to finely tune and reach the desired reactivity (see SI). While other polar protic co-solvents such as MeOH or *t*-BuOH induced the preferential formation of the corresponding benzyl ethers (see SI), HFIP allows to lower the oxidation potential of ethyl biphenyl **1a** (see SI) and most certainly subtly favours the selective oxidation of the starting material vs oxidation of the product(s) (see SI), as previously proposed by Xu.^{3e} Indeed, the cyclic voltammetry (see SI) proved that the oxidation potential of ethyl biphenyl ($E_{1/2} = +1.61$ V vs Ag|AgCl) is slightly lower than those of the nitrile ($E_{1/2} = +1.71$ V), of the imidate ($E_{1/2} = +1.62$ V) and of the amide ($E_{1/2} = +1.75$ V) – the latter could be in situ formed in small amounts due to traces of water) in a mixture of HFIP and DCE (1:5). We also confirmed that isocyanide **5b** is stable in our electrolytic conditions up to more than 2V (see SI).

In conclusion, we were able to develop a direct electrochemical benzylic carbamoylation or cyanation process via the anodic oxidation of arenes at the benzylic position followed by the addition of isocyanides. It allows to access valuable alpha-aryl acetamide or acetonitrile derivatives without the use of prefunctionalized starting materials. This electrochemical C-C bond formation via an oxidative C(sp³)-H functionalization proceeds in an undivided cell under mild conditions at room temperature without stoichiometric oxidant or transition-metal catalyst and does not need to rely on the cation-pool approach.²⁰

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

optimization studies, experimental procedures, characterization and copies of spectra of compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

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