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Copper-Catalyzed Selective Arylation of Nitriles with Cyclic Diaryl Iodonium Salts: Direct Access to Structurally Diversified Diarylmethane Amides with Potential Neuroprotective and Anticancer Activities

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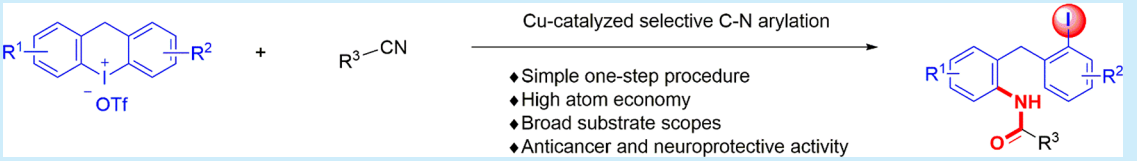


ABSTRACT: A novel, simple, and high-yielding approach for the preparation of diarylmethane amide derivatives has been developed by reacting cyclic diaryl iodonium salts with nitriles using CuCl as a catalyst. The procedure is efficient with high atom economy and a wide substrate range. Importantly, selective arylation of nitriles was obtained without affecting the phenyl amino/hydroxyl groups. Furthermore, two of the diarylmethane amides (**3k**, **3s**) displayed excellent neuroprotective and anticancer activities.

Functionalized amides, especially the diarylmethane amides, are common backbone structures found in many therapeutic agents,[1] functionalized materials,[2] and naturally occurring bioactive molecules[3] (Figure 1). They have found a wide variety of applications in organic synthesis, for example, as directing groups for chelation-assisted activation of C−H bonds[4] or as chiral catalysts for asymmetric synthesis.[5] Construction of amide C−N bonds by metal catalysis has attracted special attention from organic/medicinal chemists, and various methodologies for synthesizing diarylmethane amides have been developed.[6] The conventional approach for the synthesis of diarylmethane amides is by coupling a benzylaniline with an acyl chloride using basic reaction conditions.[7] However, benzylanilines, especially substituted benzylanilines, as starting materials are not easily available. Furthermore, the condensation reactions are generally expensive and wasteful procedures due to a reliance on the preactivation of the carboxylic acids to acyl chlorides or anhydrides with various coupling reagents.

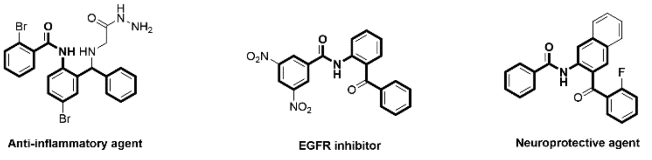
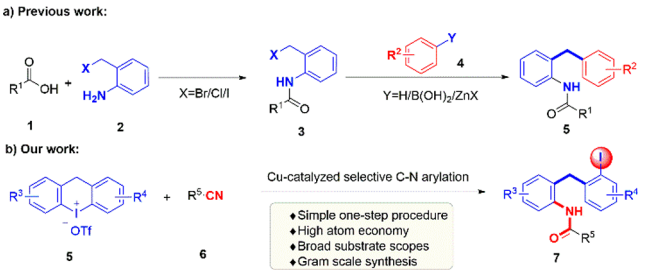


Figure 1. Representative molecules containing diarylmethane amides.[8]

Diarylmethane amides can also be accessed via a two-step route, as shown in Scheme 1a: the condensation between carboxylic acid **1** and substituted aniline **2** produces the monoarylated amide **3**, which can be reacted with an aryl coupling partner **4** (arylboronic acids, substituted benzenes, or arylzinc reagents) to generate the desired diarylmethane amide **5**[9] (Scheme 1a). Although the method is efficient to prepare various diarylmethane amides, there are several disadvantages such as harsh reaction conditions, multistep synthesis, or unavailability of the starting materials, which hindered the application of this method to a broader range of substrates. Therefore, efficient methodologies with high functional group

Scheme 1. Current Methods for the Preparation of Diarylmethane Amides



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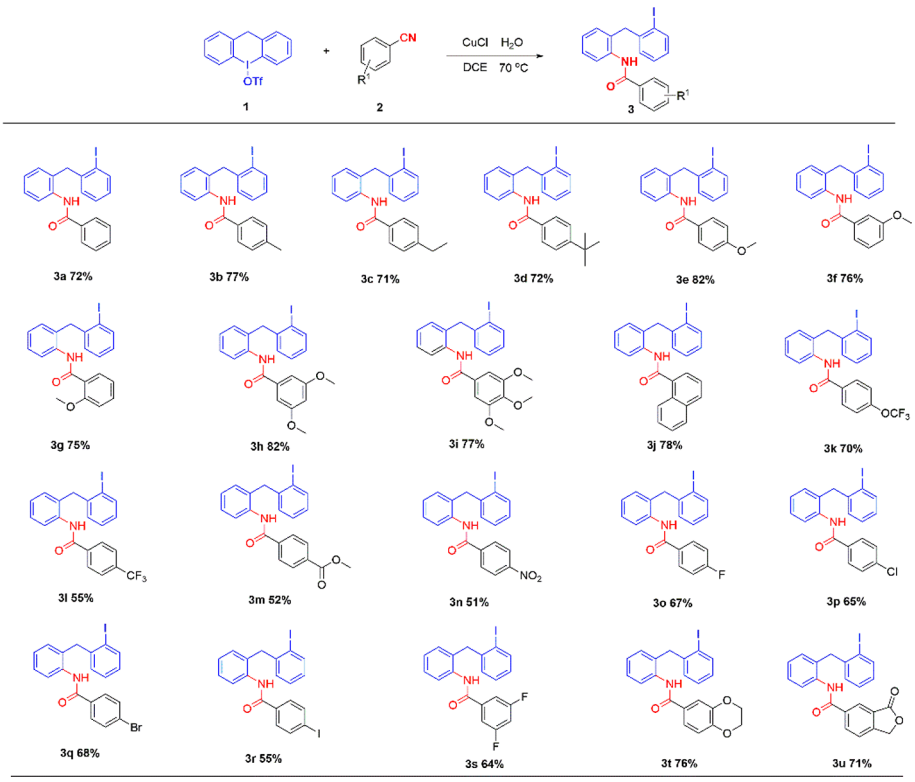

Figure 2. Arylation of aryl nitriles.

tolerance to obtain structurally diverse diarylmethane amides are still preferable. Recently, hypervalent diaryliodoniums have gained significant interest for use as replacements to aryl iodides owing to their excellent reactivity and environmentally friendly nature.[10] Particularly, Gaunt and co-workers have performed pioneering work on the catalytic activation of acyclic aryliodonium salts with Cu^{I} catalysts to generate highly electrophilic aryl−Cu^{III} intermediates, which are able to react with various electron-rich systems.[11] However, the arylation of nucleophiles by acyclic diaryliodoniums produced an iodoarene in addition to the expected products, and the iodoarene was unavoidably wasted. Compared to acyclic aryliodonium salts, especially from medicinal chemistry standpoint, the use of cyclic iodoniums is superior because the iodoarene could be retained, which provides an opportunity for further functionalization.[12]

It is believed that nitriles are fairly inert and do not readily take part in reactions, particularly arylation reactions.[12e,13] Thus, it would be of great significance if nitriles can be utilized for arylation. Continuing with our curiosity about diaryliodoniums,[14] we anticipated that diarylmethane amides could be obtained if nitriles were applied as an arylation acceptor. In this article, we describe an efficient approach to quickly prepare diarylmethane amides **7** from six-membered cyclic diaryliodoniums **5** and commercial nitrile analogue **6** through copper-catalyzed reaction (Scheme 1b).

As far as we know, this is the first report on the preparation of diarylmethane amides by arylation of nitriles with cyclic diaryl iodonium salts which, with the rigid geometry of the tricoordinate iodine complex, are generally less reactive than the more flexible cyclic/acyclic counterparts for reductive eliminations.[15] Several of the newly synthesized diarylmethane amides displayed excellent neuroprotective effects against glutamate-induced HT-22 cell death and potent anticancer activity as well. In addition, with the valuable iodo-functionalizable handles, these amides can be further converted into diverse bioactive compounds.

In light of the above considerations, we began with the optimization of the reaction conditions as detailed in Supporting Information (Table S1). After optimization, we established the best reaction conditions as follows: six-membered cyclic diaryliodonium salts (1.0 mmol), nitriles (1.2 mmol), CuCl (0.1 mmol), DCE (10.0 mL), H_2O (1.15 mmol) at 70 °C for 17 h with N_2.

Using the optimized reaction conditions, we tested the scope of the new procedure at first with a range of nitriles. As shown in Figure 2, the yields ranged from good to excellent for different aryl nitriles. The aryl nitriles with electron-donating groups (EDGs, **3b**−**3k**) or electron-withdrawing groups (EWDs, **3l**−**3n**) were well-tolerated and produced the desired products smoothly. In particular, substrates with a methoxy group at different positions of the phenyl ring gave similar yields (82% for **3e** vs 75% for **3g**), suggesting that the efficiency of reaction was not drastically influenced by substitution positions. It is worth noting that aryl nitriles bearing strong EDGs (e.g., methoxy) on the phenyl ring were favorable for this reaction; however, a further increase in the number of EDGs did not alter the results (**3e**, **3f**, **3g** vs **3h**, **3i**). Aryl nitriles with biologically relevant functionalities, such as 4-trifluoromethoxy and 4-trifluoromethyl groups, were tolerated well to provide the expected amides **3k** and **3l** in modest to good yields (55−70%). Interestingly, aryl nitriles with an ester or nitro substituent were effective in this system to generate the expected products (**3m**, **3n**) in moderate yields (51 and 52%). Gratifyingly, the aryl nitriles with various halogen substitutions (e.g., Cl, Br, F, and I) on the phenyl ring were applicable under optimized conditions to produce the products (**3o**−**3s**) in modest to good yields (55−68%), and these halogenated products offer further functionalization potential. In addition, the benzodioxine carbonitrile and

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piperonylonitrile were also compatible in this reaction (**3t**, **3u**), and the dioxane and lactone moieties in **3t** and **3u** are common structural features found in many biologically important compounds.[16] Moreover, these iodo-bearing amides can be easily derivatized and modified into structurally diversified molecules with potential biological activities.

Next, the reaction scope was tested with heterocyclic and alkyl nitriles as substrates (Figure 3). To our satisfaction, the

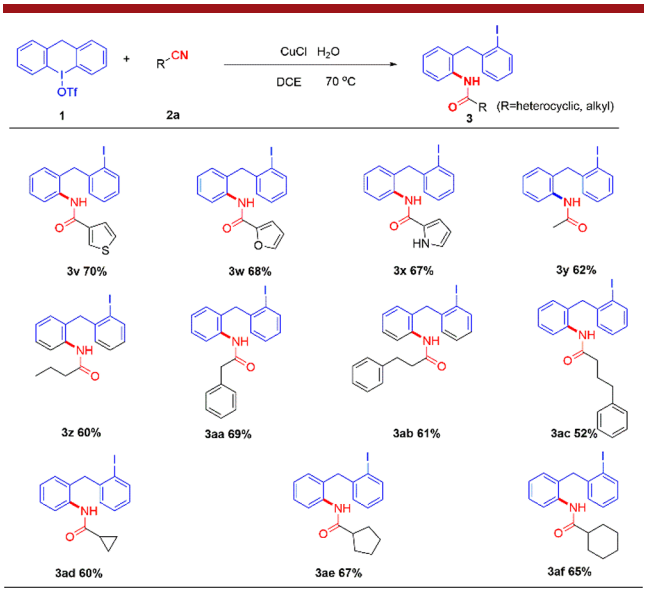

Figure 3. Arylation of heterocyclic and alkyl nitriles.

heterocyclic nitriles (3-cyanothiophene, 2-furonitrile, and pyrrolenitrile) delivered the desired amide products in good yields (70, 68, and 67% for **3v**, **3w**, and **3x**, respectively), as shown in Figure 3. However, the reaction did not occur for cyanopyridine derivatives to provide the desired product, probably owing to the electron deficiency (data not shown). Pleasingly, the alkyl nitriles (e.g., acetonitrile, butyronitrile) and phenyl-containing nitriles (2-phenylacetonitrile, 3-phenylpropionitrile, 4-phenylbutyronitrile) were all able to give the corresponding amides (**3y**−**3ac**) in modest to good yields (52−69%). The results also revealed that this reaction is negatively impacted by the length of the alkyl chain between the phenyl ring and cyanide group of the nitrile compound; as the chain length increases, the yield decreases (**3aa** vs **3ab**, **3ac**). Importantly, we also found that the alicyclic nitrile species were equally effective as the cyclic counterparts in providing the desired amide products (**3ad**−**3af**) in good yields (60−67%). Taken together, these results suggest that the reaction has a broad substrate scope and is efficient in the preparation of various diarylmethane amides with decent yields.

To further explore the reaction scope, a series of cyclic diphenyleneiodoniums with various substituents on the phenyl rings were prepared and reacted with 4-methylbenzonitrile (*p*-tolunitrile) under the optimized reaction conditions (Figure 4). First, we examined the symmetric cyclic diaryliodoniums, both the fluorine (**4a**) and chlorine (**4b**,**c**) are compatible in the reaction with good yields (66−70%). Next, the unsymmetrical cyclic diaryliodonium salts were tested, and it was found that the cyclic diaryliodoniums with strong electron-withdrawing substituents were able to give a single product (**4d**,**e**) in a modest yield (52%). When the substituent was introduced at the ortho position to the iodine of the diaryliodoniums, single

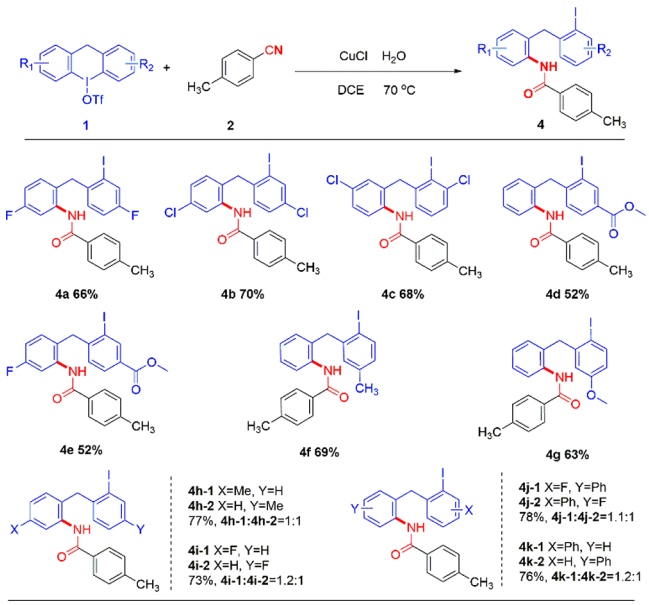

Figure 4. Examination of the substrate scope with six-membered cyclic diaryliodoniums.

products (**4f**,**g**) were formed, suggesting that this reaction is sensitive to the steric hindrance on cyclic diaryliodonium salts. However, the iodoniums with non-electron-withdrawing substituents yielded a mixture of products (**4h-1**/**4h-2** and **4i-1**/**4i-2**) with ratios of around 1:1 and 1.2:1, respectively. Additionally, other non-electron-withdrawing moieties such as the phenyl and fluorine groups were tolerated well under the optimized conditions to give a mixture of products with ratios of 1.1:1 and 1.2:1 for **4j-1**/**4j-2** and **4k-1**/**4k-2**, respectively. Collectively, the above results demonstrated the generality of this reaction.

To investigate the regioselectivity of the arylation of nitriles in the presence of the other nucleophiles, 4-aminobenzonitrile (Figure 5, intermediate **5**) and 3-methoxy-4-hydroxybenzoni-

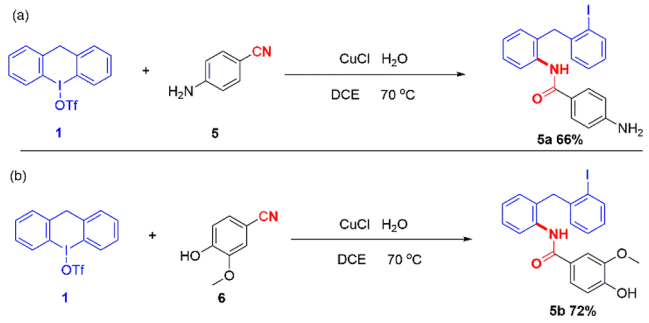

Figure 5. Selective arylation of nitriles with aryliodonium salts.

trile (Figure 5, intermediate **6**) were reacted with the diaryliodonium salt **1**. Pleasingly, the benzonitriles with *para*-amino or *para*-hydroxyl substitutions underwent the reaction smoothly to generate the desired amides **5a** and **5b** in good yields (66 and 72%, respectively). More importantly, the desired diarylmethane amides **5a** and **5b** were selectively obtained without arylation at the phenyl hydroxyl or aniline positions under standard reaction conditions, which is more advantageous compared to the reported condition.[17] A plausible mechanism for the selective arylation is that the Ph−Cu (III) intermediate

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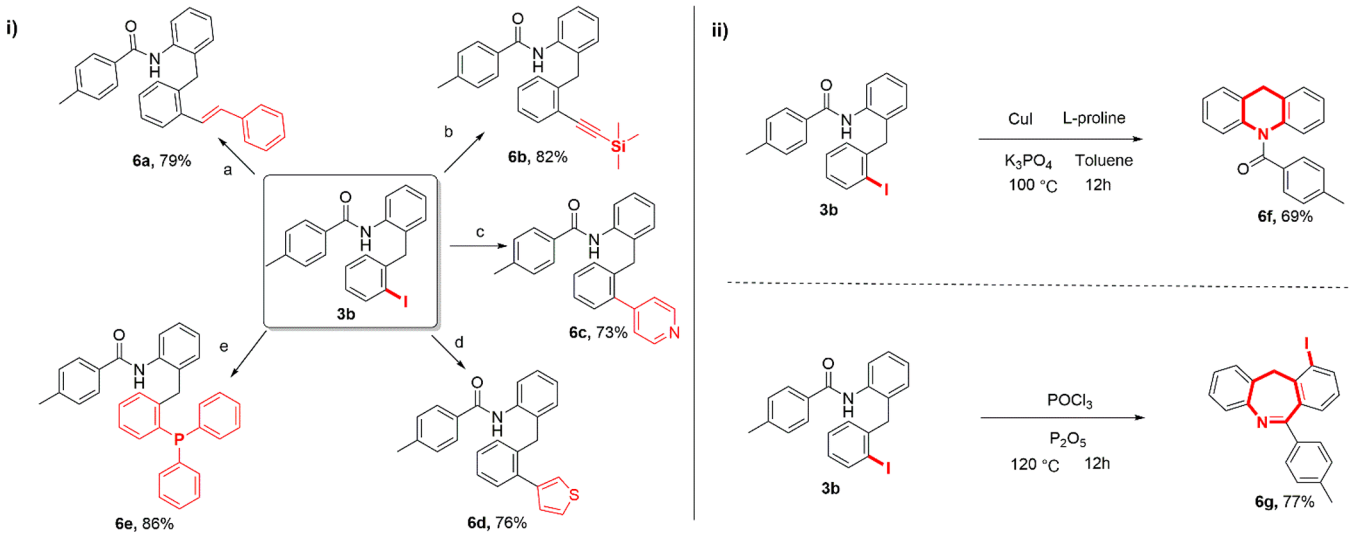

Figure 6. Procedures for the further transformations of product **3b**. [a]Styrene, $Pd(OAc)_2$, Et_3N, PPh_3, DMF, 110 °C; [b]trimethylsilyl acetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, rt; [c]pyridine-4-boronic acid, $PdCl_2(PPh_3)_2$, K_2CO_3, DMF, 90 °C; [d]3-thiopheneboronic acid, $PdCl_2(PPh_3)_2$, K_2CO_3, DMF, 90 °C; [e]$HPPh_2$, $Pd(OAc)_2$, KOAc, DMA, 100 °C.

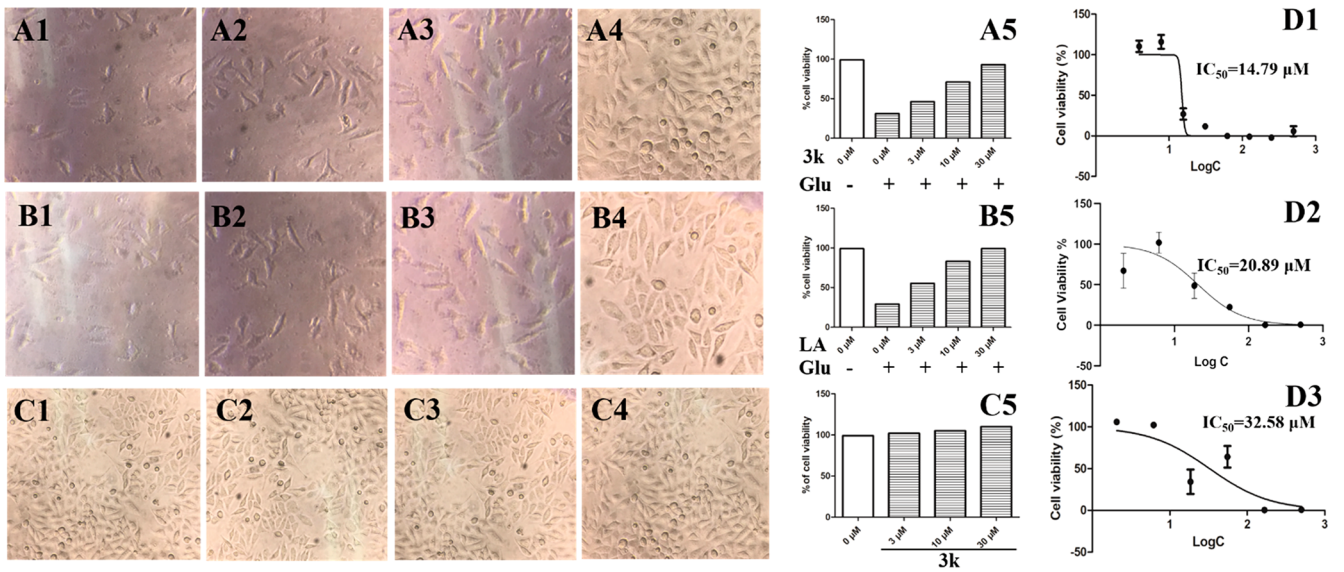

Figure 7. Compound **3k** protected HT-22 cells from Glu-induced neurotoxicity in a dose-dependent manner. (A1−A4) HT-22 cells treated with DMSO and **3k** (3, 10, 30 μM) for 30 min followed by exposure to 2 mM Glu for 24 h. (B1−B4) HT-22 cells pretreated with DMSO or LA (3, 10, 30 μM) for 0.5 h and then exposed to 2 mM Glu for 24 h. (C1−C4) HT-22 cells pretreated with DMSO or **3k** (3, 10, 30 μM). The colored pictures (A1−A4, B1−B4, C1−C4) on the left panel show the morphological changes of HT-22 cells. The bar graphs (A5,B5,C5) show the quantitative effects of **3k** and LA at 3, 10, and 30 μM on HT-22 cell viability with or without exposure to Glu, normalized by control (DMSO). (D1−D3) In vitro antiproliferative activity of compound **3s** against three cancer cell lines: (D1) H1299, (D2) B16, and (D3) MCF-7.

produced during the reaction is more likely to attack the cyano group, as shown in Figure S1 (Supporting Information). In summary, these results indicated that regioselective arylation of benzonitriles can be achieved by reacting the nitriles with cyclic iodonium salts, and various valuable amides with different functionalities could be prepared quickly and efficiently.

To understand the potential utility of these iodo-functionalized handle-bearing diarylmethane amide products, compound **3b** was converted to various functionalized amides by diversity-oriented transformations (Figure 6). First, the functionalization of the iodo-position was carried out to obtain different products (**6a**−**6e**) such as the bidentate phosphino ligand **6e** (Figure 6,i). Next, the amide moiety of **3b** was cyclized to produce the acridine **6f** and azepine-type of cyclic imine **6g** (Figure 6,ii). The detailed description is provided in Supporting Information (Figure S2).

As aforementioned, many diarylmethane amides exhibit important bioactivities (e.g., neuroprotection and antiproliferation). Hence, we examined the neuroprotective and anticancer activities of the newly synthesized compounds. As shown in Figure 7, **3k** produced significant HT-22 neuronal cell protection from glutamate (Glu)-induced damage, and the neuroprotective effect was comparable to that of the positive control (lipoic acid (LA))[18] (Figure 7A1−A5,B1−B5). Specifically, compound **3k** at 10 μM concentration could dramatically enhance HT-22 cell survival following exposure to 2 mM Glu (Figure 7A3). At a higher concentration of 30 μM, **3k** provided almost 100% protection to HT-22 cells from Glu-

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induced cell death (Figure 7A4,A5). Importantly, **3k** did not cause any cytotoxicity to the HT-22 neuronal cells at the three tested concentrations (3, 10, 30 μM) (Figure 7C1−C5). In addition to the neuroprotective effects, we also found that several of the amide compounds exhibited moderate antiproliferative activities against three cancer cell lines (H1299, B16, MCF-7) with IC_{50} values in the micromolar range. Among them, compound **3s** (3,5-difluorobenzoyl) is the best, with IC_{50} values of 14.79, 20.89, and 32.58 μM for H1299, B16, and MCF-7 cells, respectively (Figure 7D1−D3). Further structural optimization and mechanism of action studies for these new molecules are currently in progress.

In summary, we have developed a novel, simple, and practical protocol for the preparation of a broad range of iodo-functionalized diarylmethane amides via copper-catalyzed acylation of cyclic diaryliodoniums with commercial and relatively inert nitrile species. This transformation is efficient with high atom economy and excellent tolerance for a wide variety of functional groups (e.g. halogens, nitro, alkyl, alkoxy groups) on the coupling partners. Notably, selective arylation of nitriles can be obtained without affecting the phenyl amino/hydroxyl groups. Furthermore, the corresponding diarylmethane amides with an iodo-functionalized handle can be readily converted to structurally diverse products with potential biological utility. Moreover, our study also demonstrates that compound **3k** has excellent neuroprotective effects against glutamate-induced HT-22 cell death, whereas compound **3s** exhibits moderate to potent antiproliferative activities against different cancer cell lines. In conclusion, our method provides facile access to a novel molecular scaffold with potential neuroprotective and anticancer activities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01829.

Full experimental procedures and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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