Synthetic Methods

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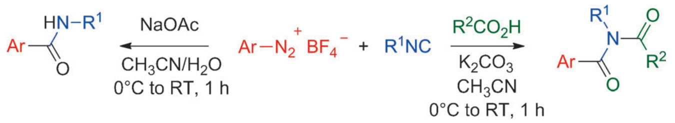

**Mumm's the word**: The title reaction can be performed by the addition of isocyanides to benzenediazonium salts in the presence of sodium or potassium carboxylates. The reaction involves nitrilium intermediates which may be trapped by water or carboxylic acids to form amides and imides, respectively, after Mumm rearrangement.

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# Three-Component Metal-Free Arylation of Isocyanides**

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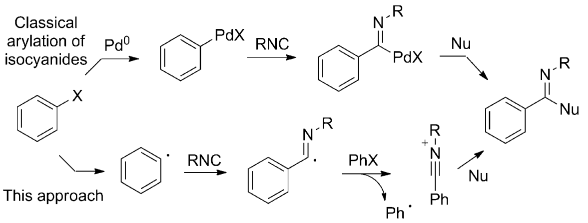
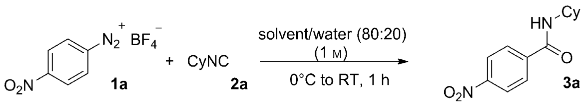
Though the efficiency of isocyanides as strong ligands for transition metals was recognized very early,[1] the disclosure of metal-catalyzed arylation of isocyanides has only been explored quite recently.[2] In most of these studies, the formation of a metal/aryl complex starting from aryl iodide or bromide is followed by isocyanide insertion and trapping of the metal/imidoyl complex with various nucleophiles (Scheme 1). These three-component couplings are mostly described with palladium and suffer from the highly coordinating nature of isocyanides, which often limits the efficiency of bulky isocyanides. To circumvent these difficulties the choice of a metal with moderate affinity for isocyanides or the development of metal-free arylation would be highly desirable. It is in this context that we herein present new three-component couplings involving isocyanides and aryl diazonium salts.



***Scheme 1.*** Three-component arylation of isocyanides.

Considering the known reactivity of radicals with isocyanides,[3] we envisioned that the choice of aryl radical additions might bring an answer to the limitations of the transition-metal triggered couplings. The addition of aryl radicals to isocyanides is a fast process with rate constants estimated at over $10^7\,\mathrm{L\,mol^{-1}}$ at 0 °C.[3d–e] To form structures close to the ones obtained under transition-metal catalysis (Scheme 1), one has to address the fate of the resulting imidoyl radicals, which, if not reduced by hydride donors, are usually engaged in further intramolecular cyclizations[3b,c,g] or fragmentations towards nitriles.[3d,f,g] As these radicals are rather electron rich,[4] more general three-component couplings could be achieved through oxidative pathways leading to nitrilium intermediates and subsequent addition of various nucleophiles (Scheme 1). Because of their ease of reduction and wide availibility from anilines, diazonium salts are often selected as starting materials whenever aryl radicals are expected as reactive intermediates. The conversion of diazonium salts into aryl radicals is a well-studied proccess[5] and triggered by various electron-rich organic species or metal salts, and involved in several classical transformations such as the Sandmeyer reaction[6] or the Meerwein arylation.[7]

To prove the concept, water was selected as a nucleophile towards the isocyanide/diazonium couple. When *para*-nitrophenyldiazonium tetrafluoroborate was added to a solution of cyclohexyl isocyanide in a water/acetonitrile mixture, we observed a slow reaction leading to the expected amide in 10 % yield after one hour (Scheme 2). Diazonium salts are known to generate aryl radicals more efficiently in the presence of nucleophilic weak bases such as tertiary amines,[8] pyridine,[9] or sodium acetate.[10] In addition, the reaction should progress with evolution of tetrafluoroboric acid, a sufficiently strong acid to trigger the hydrolysis of the acid sensitive isocyanide. This analysis was confirmed by the much higher yields obtained when the following trials were performed with added bases.



| Base (equiv) | Solvent | Yield [%] |
|---|---|---|
| – | $CH_3CN$ | 10 |
| pyridine (0.3) | $CH_3CN$ | 21 |
| pyridine (1.5) | $CH_3CN$ | 46 |
| – | pyridine | 28 |
| NaOAc (1.5) | $CH_3CN$ | 52 |
| $NEt_3$ (1.5) | $CH_3CN$ | 15 |
| NaOAc (1.5) | $H_2O$ | 45 |
| NaOAc (1.5) | Acetone | 50 |
| NaOAc (1.5) | MeOH | 52 |

***Scheme 2.*** Amide formation from diazonium salts.

Sodium acetate was selected because of the lower reproducibility when using pyridine. Finally, lower concentrations (0.25 M and 0.5 M) gave much lower yields in

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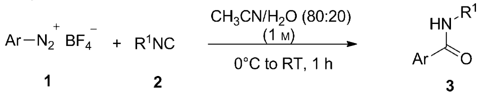
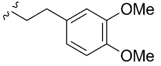
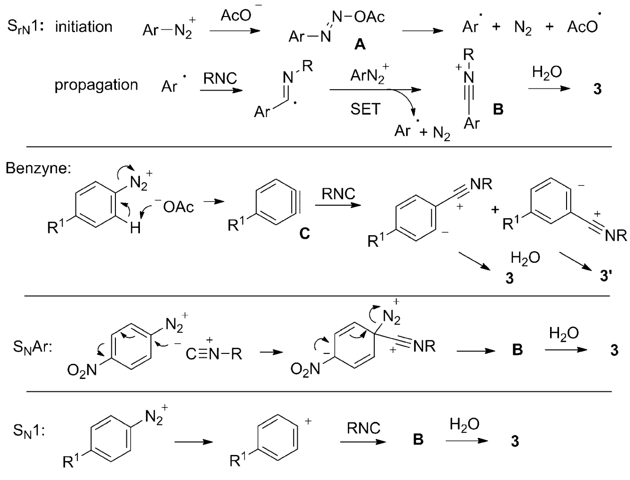
***Table 1:*** Scope of the amide formation.



| Entry | Ar | $R^1$ | 3 | Yield [%] |
|---|---|---|---|---|
| 1 | 4-$ClC_6H_4$ | Cy | **3b** | 50 |
| 2 | 4-$MeOC_6H_4$ | Cy | **3c** | 55 |
| 3 | 4-$NO_2C_6H_4$ | *t*Bu | **3d** | 35 |
| 4 | 4-$MeOC_6H_4$ | *t*Bu | **3e** | 43 |
| 5 | 4-$NO_2C_6H_4$ | $CH_2C_6H_4$-4-OMe | **3f** | 55 |
| 6 | 4-$NO_2C_6H_4$ | $CH_2C_6H_4$-4-Cl | **3g** | 42 |
| 7 | 4-$NO_2C_6H_4$ |  OMe OMe | **3h** | 60 |
| 8 | 4-$ClC_6H_4$ |  | **3i** | 52 |
| 9 | 4-$NO_2C_6H_4$ | $CH_2CO_2Et$ | **3j** | 76 |
| 10 | 4-$MeOC_6H_4$ | $CH_2CO_2Et$ | **3k** | 67 |
| 11 | 2-$CF_3C_6H_4$ | *t*Bu | **3l** | 33 |

acetonitrile as classically observed in many isocyanide-based multicomponent reactions. Different diazonium salts and isocyanides were then treated under these reaction conditions to give amides in overall moderate yields (Table 1).

The formation of amides with isocyanides prone to easy fragmentation towards nitriles under radical conditions was rather unexpected (Table 1, entries 3–6 and 11) and raised questions about the radical nature of the reaction. Indeed several different mechanisms may be proposed for the process. Beside the Meerwein-type radical chain reaction initiated by the decomposition of the acetoxyazo intermediate **A** (Scheme 3), a nonradical pathway involving the benzyne intermediate **C** could also lead to the final amides **3** (Scheme 3). The latter mechanism is supported by the known formation of benzamides under addition of isocyanides to benzyne[11] (obtained through nitrosation of anthranilic acid) together with few reports on the generation of benzyne under treatment of simple diazonium salts with sodium acetate.[12] However, the formation of benzyne intermediates is usually associated with regioselectivity issues because of the potential attack of nucleophiles to either side of the benzyne moiety. In all our trials, the isolation of a single regiomer possessing the same substitution pattern as the starting diazonium salt rejects benzyne as a possible intermediate. For instance, no trace of a 3-substituted amide has been isolated in the case of 2-trifluoromethyl benzenediazonium tetrafluoroborate, in opposition to what would be expected for a benzyne-type reaction path (Table 1, entry 11).



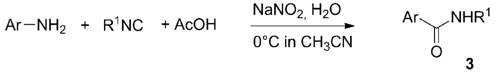
***Scheme 3.*** Possible mechanisms for the arylation of isocyanides.

Alternative known fragmentations of diazonium salts through $S_NAr$ or $S_N1$ paths[5] (Scheme 3c,d) may also be discarded because of the close behavior of both electron-rich (Table 1, entries 2,4, and 10) and electron-poor (Table 1, entries 3, 5–7, and 9) benzenediazonium salts. In addition, the triggering effect of added acetate is more in favor of a radical pathway. Single-electron transfer (SET) between radical intermediates and diazonium salts has been classically observed in Meerwein arylation of electron-rich alkenes[13] or in the reduction of diazonium salts by THF when used as solvent.[14] In our case the electron-rich nature of the imidoyl radical probably favors the electron transfer with the starting diazonium salt over competing fragmentation to nitriles.

In terms of synthetic efficiency, the required preparation of diazonium tetrafluoroborate may be considered as a limitation of the synthetic interest of this new arylation process. Very few diazonium salts are commercially available and when a large amount of dry salts are required, even though tetrafluoroborates are considered rather safe, explosion hazards must always be considered. To lower such risks, their in situ preparation from anilines with addition of nucleophiles in an additional step offers a good alternative.[15] In our case, as a result of their moderate nucleophilicity, the presence of isocyanides in the medium may not disturb the nitrosation process of anilines. This was indeed the case as shown by the successful preparation of the amides **3a–f** and **3m** under addition of a solution of sodium nitrite in water to a solution of aniline, acetic acid, and isocyanide in acetonitrile at 0 °C (Table 2). Most impressive is the resulting increase in yields, thus converting this new reaction into an efficient formal homologation of anilines into amides.

Even if this amide formation is formally a new three-component coupling of isocyanides,[16] water as the third component does not allow much diversity. The integration of

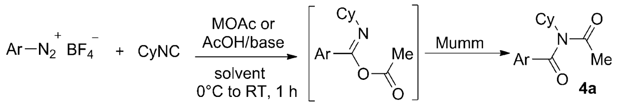
***Table 2:*** Direct arylation of isocyanides with anilines.



| Entry | Ar | $R^1$ | 3 | Yield [%] |
|---|---|---|---|---|
| 1 | 4-$NO_2C_6H_4$ | Cy | **3a** | 92 |
| 2 | 4-$ClC_6H_4$ | Cy | **3b** | 60 |
| 3 | 4-$MeOC_6H_4$ | Cy | **3c** | 61 |
| 4 | 4-$NO_2C_6H_4$ | *t*Bu | **3d** | 85 |
| 5 | 4-$MeOC_6H_4$ | *t*Bu | **3e** | 59 |
| 6 | 4-$NO_2C_6H_4$ | $CH_2C_6H_4$-4-OMe | **3f** | 63 |
| 7 | 4-$ClC_6H_4$ | *t*Bu | **3m** | 71 |

Reaction conditions: acetic acid (1.5 mmol) and isocyanide (1 mmol) were added successively to aniline (1 mmol) in 7.5 mL of $CH_3CN$. The mixture was cooled to 0 °C before the addition of of sodium nitrite (1.5 mmol) in water (2.5 mL).

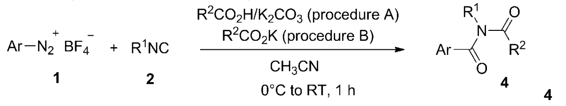
more complex nucleophiles would be highly desirable. Sodium acetate is used to trigger aryl radical formation and to buffer the reactive medium, therefore we surmised that sodium acetate could also act as a nucleophile for nitrilium intermediates in the absence of water. To our delight, when *para*-nitrobenzenediazonium tetrafluoroborate was added portionwise to a mixture of sodium acetate and cyclohexyl isocyanide in acetonitrile, the new imide **4a** was isolated instead of the former amide **3a** (Scheme 4). The outcome of this modified process may be easily explained by a final Mumm rearrangement[17] of an intermediate imidoyl acetate. Various acetate or acetic acid/base combinations were tested in acetonitrile showing the higher efficiency of the potassium salt added as such, or obtained in situ with addition of $K_2CO_3$. As observed for amides, acetonitrile remains the best solvent for this reaction (Scheme 4).



| in $CH_3CN$ | Yield [%] | with NaOAc (1.5 equiv) | Yield [%] |
|---|---|---|---|
| NaOAc (1.5 equiv) | 58 | acetone | 50 |
| **KOAc (1.5 equiv)** | **63** | MeOH | 48 |
| AcOH/lutidine (1.5 equiv) | 25 | $CH_2Cl_2$ | 44 |
| AcOH/DIPEA (1.5 equiv) | 30 | THF | 30 |
| **AcOH/$K_2CO_3$ (1.5 equiv)** | **59** | toluene | 14 |
| AcOH/$Cs_2CO_3$ (1.5 equiv) | 46 | | |

***Scheme 4.*** Three-component imide formation. Ar = 4-$NO_2C_6H_4$. DIPEA = diisopropylethylamine.

***Table 3:*** Scope of the three-component imide formation.



| Entry | Ar | $R^1$ | $R^2$ | 4 | Yield [%][a] |
|---|---|---|---|---|---|
| 1 | 4-$MeOC_6H_4$ | Cy | Me | **4b** | 31 (35) |
| 2 | 4-$ClC_6H_4$ | $CH_2C_6H_4$-4-Cl | Me | **4c** | 39 (45) |
| 3 | 2-$CF_3C_6H_4$ | Cy | Me | **4d** | 45 (54) |
| 4 | 2-$CF_3C_6H_4$ | CH(*i*Pr)$CO_2$Me | Me | **4e** | 53 (62) |
| 5 | 2-$CF_3C_6H_4$ | CH(Me)$CO_2$Me | Ph | **4f** | 60 (57) |
| 6 | 4-$NO_2C_6H_4$ | Cy | Ph | **4g** | 40 (48) |
| 7 | 2-$CF_3C_6H_4$ | *t*Bu | Ph | **4h** | 76 (78) |
| 8 | 4-$ClC_6H_4$ | *t*Bu | $CH_2C_6H_4$-4-F | **4i** | 51 |
| 9 | 4-$ClC_6H_4$ | *t*Bu | Ph | **4j** | 47 (57)[b] |
| 10 | 4-$ClC_6H_4$ | *t*Bu | *i*Pr | **4k** | 54 |
| 11 | 4-$NO_2C_6H_4$ | $CH_2C_6H_4$-4-Cl | *t*Bu | **3g** | 54[c] |

[a] Yield determined for the reaction using procedure A. The value within parentheses is that determined for the reaction using procedure B. [b] Yield is 12% with $PhCO_2Na$ and no imide formation with $PhCO_2Li$ and $PhCO_2Ag$. [c] Amide was obtained instead of the expected imide.

The combination of acetic acid and potassium carbonate appears slightly less satisfying than the direct use of potassium acetate. However, it represents an interesting procedure for the extension of this reaction to more complex carboxylic acids, thus avoiding the tedious preparation of dry potassium carboxylates. To test the scope of this new three-component coupling, a set of isocyanides, diazonium salts, and carboxylic acids were added together in acetonitrile with potassium carbonate (Table 3). For acetic and benzoic acid, this procedure could be compared with the direct addition of the potassium carboxylate, which proved to be more efficient in most cases. The better behavior of the potassium salts over sodium salts was confirmed in the coupling of benzoic acid with *tert*-butyl-isocyanide and 4-chlorophenyldiazonium tetrafluoroborate (Table 2, entry 9). In the latter case, the lithium or silver salt did not give any imide.

Compared to the previous amide formation, the behavior of the 4-methoxybenzenediazonium salt turned out to be much less efficient, thus giving imide in low yields (Table 3, entry 1) whereas the 2-trifluoromethylphenyl diazonium salt behaved surprisingly well in the coupling (Table 3, entries 3–5 and 7). These differences could be analyzed considering the Mumm rearrangement in the last step of the process. Indeed, these rearrangements normally proceed through four-membered transition states with concerted C−O breaking and C−N bond formation.[18] The choice of an electron-rich aryl group is expected to decrease the stability of the intermediate imidate, thus promoting the formation of a nitrilium/carboxylate ion pair which may further evolve by different pathways (fragmentation, hydrolysis, etc.). The high yielding formation of the 2-substituted imide (Table 3, entries 3–5 and 7) additionally rejects the mechanistic path involving benzyne intermediates. In the case of pivalic acid (Table 3, entry 11), the expected imide was not formed. The steric hinderance of the *tert*-butyl group probably prevents the intermediate pivaloyl imidate from undergoing the Mumm rearrangement. The conversion of the latter into the amide **3g** may be explained by an intermolecular attack of a pivalate on the imidate with evolution of pivalic anhydride.

In conclusion, we have developed a new arylation of isocyanides with diazonium salts. The reaction features a new mode of coupling for isocyanides with aryl nitrilium species as key intermediates. The initially disclosed amide formation could be easily extended to highly diverse three-component imide formation from carboxylic acids, isocyanides, and diazonium salts. Though the formation of imides in isocyanide-based multicomponent reactions was disclosed very early by Ugi, they still remain rather uncommon scaffolds.[19] Additional work is in progress to extend these first successful trappings to the use of other nucleophiles with or without added metal catalyst as described in the Sandmeyer reactions.

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**Keywords:** arylation · isocyanides · reaction mechanisms · rearrangement · synthetic methods

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