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Synthesis of Acetamides from Aryl Amines and Acetonitrile by Diazotization under Metal-Free Conditions

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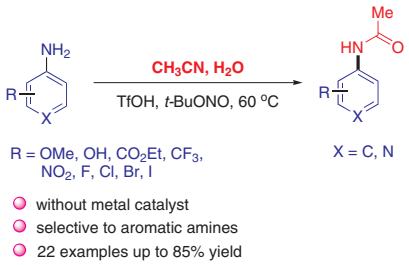

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Abstract An efficient and metal-free coupling reaction has been developed that affords acetamides from the corresponding aryl amines and acetonitrile. This method tolerates a wide range of functional groups and is selective toward aryl amines. Preliminary mechanistic studies were conducted.

Key words aryl amines, amidation, acetonitrile, diazotization, acetamides, coupling reaction

The amide bond is one of the most important and abundant structural motifs found in natural products, peptides, and pharmaceuticals.[1] For instance, oseltamivir,[2] lidocaine,[3] and paracetamol,[4] which are widely used as an antiviral agent, a local anesthetic, and an antipyretic analgesic, respectively, all contain an amide group (Figure 1). In view of the significant pharmacological value of amides, various approaches focusing on their synthesis have been developed.[5] Conventional methods for the construction of the amide bond involve the use of carboxylic acids or their derivatives, such as acid anhydrides, acyl chlorides, or esters.[5c] Although these methods are efficient, they have some limitations. For instance, coupling reagents are always needed to activate carboxylic acids, leading to the production of stoichiometric amounts of waste products.[5d] Furthermore, acetic anhydride and acyl chlorides are hygroscopic and react readily with water to produce acids as byproducts, making isolation procedures more cumbersome.[6] Therefore, it is still desirable to develop new approaches for the synthesis of amides.

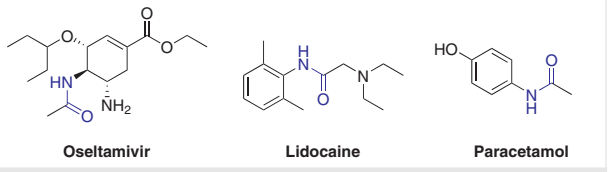

Figure 1 Examples of drugs bearing an amide groups

Nitriles are recognized as important synthons that can be converted into various functional groups, such as carboxylic acids, amines, amides, or aldehydes.[7] An effective method for the synthesis of amides is the coupling of nitriles with amines in the presence of a ruthenium catalyst, as first developed by Murahashi et al.[8] Subsequently, Pt[9] and Fe[10] were found to be effective catalysts for this coupling reaction. In 2013, Zhou and co-workers reported a copper-catalyzed version of the coupling reaction that can be performed in water.[11] However, these methods have several disadvantages, such as the use of metals and extra ligands and the need for high reaction temperatures. A reaction for the synthesis of amides that proceeds under mild conditions in the absence of a metal catalyst would be preferable.

In 2016, Pahari and co-workers reported a trimethylsilyl iodide-catalyzed N-acetylation of aromatic amines by acetonitrile under microwave conditions at 110 °C (Scheme 1a).[12] Dai and co-workers developed a sulfonated graphene oxide (SRGO) catalyst for the N-acetylation of amines with acetonitrile under sonication (Scheme 1b).[13] In these two reported reactions, acetonitrile was considered to act as the acylating reagent. Here, we report a TfOH-promoted coupling reaction between an aromatic amine and acetonitrile in the presence of *t*-BuONO, which proceeds through diazotization and in which acetonitrile acts as the source of an acetylamino group (Scheme 1c).

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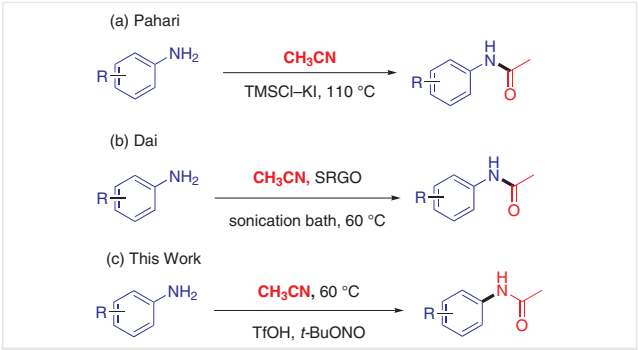
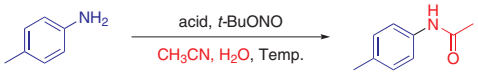


Scheme 1 Various strategies for the synthesis of amides

For our initial investigations, we chose *p*-toluidine as a model substrate and acetonitrile as both the reagent and solvent. A mixture of *p*-toluidine and *t*-BuONO in acetonitrile was stirred under a variety of acidic conditions, and the results are summarized in Table 1. Investigations of various acids suggested that TfOH gave the best yield (Table 1, entries 1–5). To our surprise, adding H_2O (5.0 equiv) to the reaction mixture was beneficial for the yield (entry 6), but increasing its amount had the opposite effect (entries 12–15). Screening of the reaction temperature showed that the product could be obtained in 71% yield when the reaction was performed at 60 °C (entry 8). Next, the optimal stoichiometry of TfOH and *t*-BuONO to *p*-toluidine was examined, and the highest yield was obtained when the ratio of both was increased to 1.5:1 (entry 10). Reducing the reaction time to 12 hours afforded the product in 62% yield (entry 16). Control experiments demonstrated that the acid and *t*-BuONO were both essential for the reaction, as the use of a catalytic amount of TfOH or the omission of either TfOH or *t*-BuONO led to dramatic decreases in the yield (entries 17–19).

Having established the optimal reaction conditions, we next explored the substrate scope of the amine with CH_3CN (Scheme 2). In general, various aryl amines bearing elec-

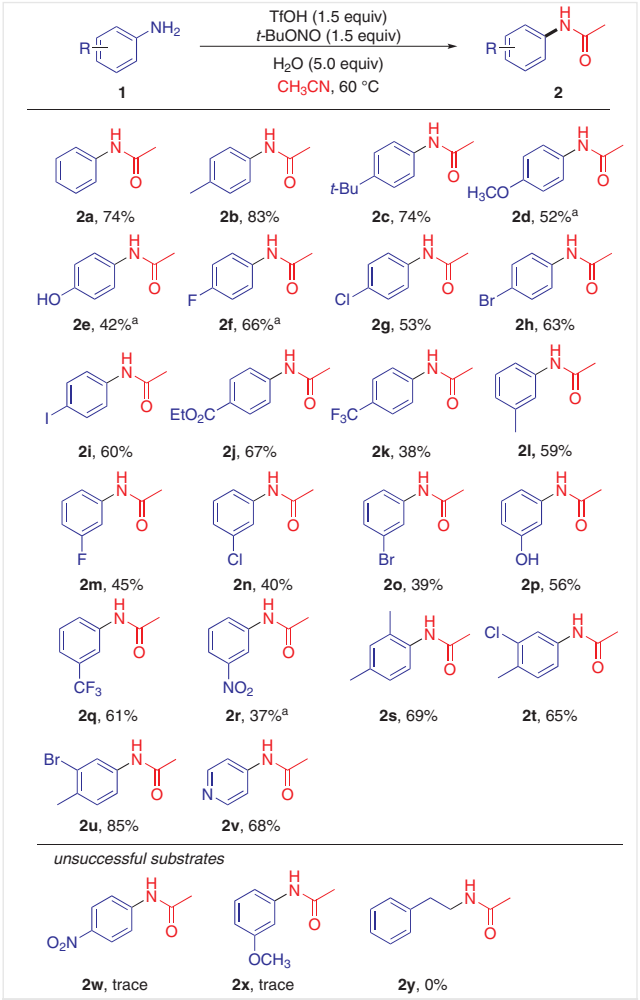
Table 1 Optimization of the Reaction Conditions[a]



1b 2b

Entry	Acid (equiv)	Temp (°C)	H_2O (equiv)	Yield[b] (%)
1	$TsOH·H_2O$ (1.2)	r.t.	–	50
2	CH_3SO_3H (1.2)	r.t.	–	53
3	TfOH (1.2)	r.t.	–	55
4	F_3CCO_2H (1.2)	r.t.	–	37
5	AcOH (1.2)	r.t.	–	5
6	TfOH (1.2)	r.t.	5	60
7	TfOH (1.2)	50	5	63
8	TfOH (1.2)	60	5	71
9	TfOH (1.2)	70	5	51
10[c]	TfOH (1.5)	60	5	83
11[c]	TfOH (1.5)	60	2	69
12[c]	TfOH (1.5)	60	10	55
13[c]	TfOH (1.5)	60	20	37
14[c,d]	TfOH (1.5)	60	–	21
15[c,e]	TfOH (1.5)	60	–	48
16[f]	TfOH (1.5)	60	5	62
17	TfOH (0.2)	60	5	39
18	–	60	5	24
19[g]	TfOH (1.5)	60	5	trace

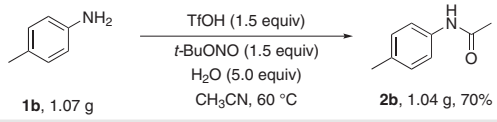
[a] Reaction conditions: **1b** (0.5 mmol), *t*-BuONO (1.2 equiv), acid, MeCN (3.0 mL), H_2O, air atmosphere, 24 h.
[b] Isolated yield.
[c] *t*-BuONO (1.5 equiv).
[d] CH_3CN (1.5 mL) + H_2O (1.5 mL).
[e] CH_3CN (2.0 mL) + H_2O (1.0 mL).
[f] 12 h.
[g] Without *t*-BuONO.



Scheme 2 Scope of amines. *Reagents and conditions*: **1** (1.0 mmol, 1.0 equiv), *t*-BuONO (1.5 mmol, 1.5 equiv), TfOH (1.5 mmol, 1.5 equiv), H_2O (5.0 equiv), CH_3CN (5.0 mL), 60 °C, 24 h, in air. [a] At 120 °C.

tron-withdrawing or electron-donating functional groups were successfully converted into the corresponding amides in yields ranging from 37 to 85%. Various substituents such as fluoro (**2f** and **2m**), chloro (**2g**, **2n**, and **2t**), bromo (**2h**, **2o**, and **2u**), iodo (**2i**), ethoxycarbonyl (**2j**), hydroxy (**2e** and **2p**), or trifluoromethyl (**2k** and **2q**) were well tolerated under the standard conditions. However, a higher temperature was needed for substrates bearing 4-methoxy (**2d**), 4-hydroxy (**2e**), 4-fluoro (**2f**), or 3-nitro groups (**2r**). Notably, 4-aminopyridine (**2v**) was also a suitable substrate for the reaction, affording the corresponding product in 68% yield. Unfortunately, this method was not compatible with alkyl amines (**2y**), and only trace amounts of products were detected for substrates containing 4-nitro (**2w**) or 3-methoxy (**2x**) groups.

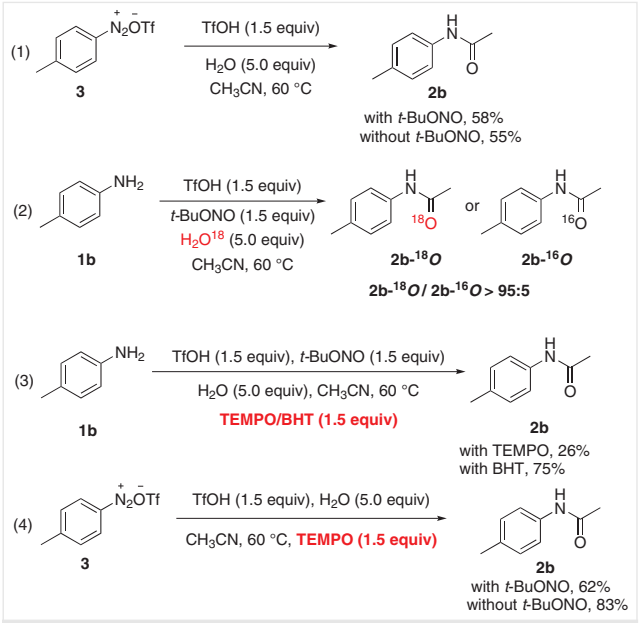
To demonstrate the scalability of this method, we carried out a gram-scale reaction under the standard conditions. To our delight, this reaction of **1b** with *t*-BuONO in the presence of TfOH in CH_3CN at 60 °C provided amide **2b** in 70% yield (Scheme 3).



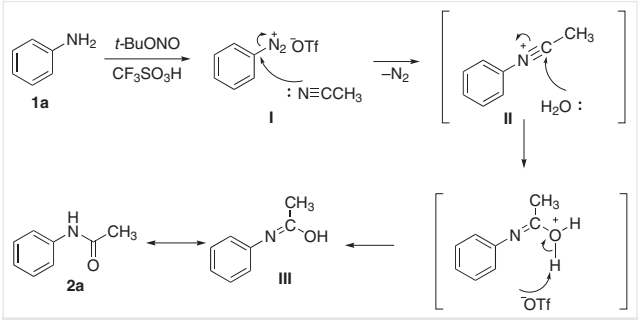
Scheme 3 Gram-scale synthesis of amide **2b**

To elucidate the mechanism of this reaction, some preliminary experiments were performed (Scheme 4). When the arenediazonium triflate **3** was synthesized and exposed to the standard reaction conditions, the amide product **2b** was obtained in 58% yield. Furthermore, this reaction also proceeded in the absence of *t*-BuONO, suggesting that the arenediazonium salt might be an intermediate in the original transformation (Scheme 4, eq. 1). An isotope-labeling experiment indicated that the oxygen atom of the amide might originate from H_2O (Scheme 4, eq. 2). We then conducted two radical-trapping experiments. When 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) was added, product **2b** was obtained in 26% yield, whereas butylated hydroxytoluene (BHT) had little effect on the transformation (Scheme 4, eq. 3). In addition, the arenediazonium triflate **3** could be successfully converted into the product **2b** in the presence of TEMPO (Scheme 4, eq. 4).

Based on the above mechanistic studies and previous reports,[14] a proposed mechanism is outlined in Scheme 5. Aniline is initially converted into the arenediazonium triflate **I** in the presence of *t*-BuONO and TfOH.[15] Subsequently, this arenediazonium triflate is trapped by CH_3CN with release of nitrogen gas and the generation of cation **II**. Finally, cation **II** is attacked by H_2O to deliver the enol **III**, which isomerizes into product **2a**. However, an alternative radical mechanism for the reaction cannot be excluded.[14b]



Scheme 4 Preliminary mechanistic studies



Scheme 5 Proposed mechanism

In conclusion, we have developed a TfOH-promoted method for the preparation of acetamides from aryl amines and CH_3CN under metal-free conditions.[16] This method tolerates a wide range of functional groups and is selective toward aryl amines. Preliminary mechanistic studies indicated that an arenediazonium salt is generated in the reaction process.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690237.

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(16) **Acetamides 2a–v; General Procedure**
To a stirred solution of the appropriate arylamine (1.0 mmol) in CH_3CN (5.0 mL) were added *t*-BuONO (1.5 mmol, 1.5 equiv), TfOH (1.5 mmol, 1.5 equiv), and H_2O (5.0 mmol, 5.0 equiv). The mixture was stirred under air at 60 °C for 24 h until the reaction was complete. The resulting mixture was purified by flash chromatography (silica gel, PE–EtOAc).
***N*-(4-Tolyl)acetamide (2b)**
White solid; yield: 83%; 123.8 mg; mp 150–151 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (br s, 1 H), 7.37 (d, *J* = 8.1 Hz, 2 H), 7.10 (d, *J* = 8.1 Hz, 2 H), 2.30 (s, 3 H), 2.14 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.5, 135.4, 134.1, 129.6, 120.2, 24.6, 21.0. MS (ESI): *m/z* = 150 $[M + H]^+$