



Metal-free hydration of ynamides: convenient approach to amides



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ABSTRACT

The trifluoroacetic acid (TFA) mediated hydration of ynamides was developed, which is an efficient approach for the synthesis of *N*-monosubstituted amides. This convenient method is effective with a wide range of substrates under room temperature condition, and the products are obtained in high to excellent yields through an easy work-up process.

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Introduction

Amides have been paid much attention in both biological and chemical studies for a long time.¹ On the one hand, benefitting from the special properties (e.g., stability, polarity, conformational diversity, etc.) of the amide moiety, amides and their derivatives are widely applied as biologically active compounds, such as Atorvastatin,² Lisinopril,³ Valsartan,⁴ and Diltiazem.⁵ On the other hand, amides act as especially useful and versatile building blocks for organic synthesis,⁶ especially open a wide access to the synthesis of nitrogen-contained heterocyclic compounds, for examples, the synthesis of benzoxazoles,⁷ quinolinones,⁸ and phenanthridinones.⁹ To date, various methods for the synthesis of amides have been developed, in which amidation of carboxylic acid derivatives is the traditional method for the synthesis of amides. However, the lability of those functional carboxylic acid derivatives often restricts its wide applications.¹⁰ In addition, this procedure produces a stoichiometric amount of waste products and thus innately faces serious environmental problems.¹¹ Therefore, developing alternative, efficient, and convenient methods to synthesize amides at mild reaction conditions is highly attractive.¹²

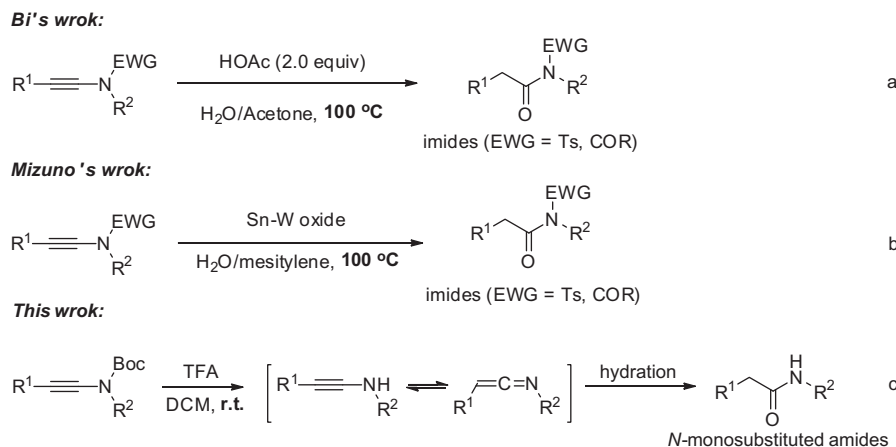
Ynamides have thus emerged as versatile building blocks in organic synthesis, while an impressive number of transformations from ynamides have been reported in recent years. Compared with other methods for synthesis of amides, the hydration of ynamides is a straightforward method to produce amides. However, only two literatures described such a hydration systematically. For instance,

Bi and co-workers¹³ reported a convenient approach to the preparation of imides that involves the reaction of ynamides with HOAc/Acetone/H₂O at 100 °C (Scheme 1, a). Using Sn-W mixed oxide, Mizuno and co-workers¹⁴ have successfully achieved the goal of hydration of ynamides for synthesis imides (Scheme 1, b). Thus, as part of the functionalization of ynamides, as well as a lack of systematic studies on hydration of ynamides, developing efficient and convenient methods to synthesize amides through hydration of ynamides is still of great value. We herein report a convenient and straightforward method based on the TFA-mediated hydration of ynamides for synthesizing *N*-monosubstituted amides (Scheme 1, c). To the best of our knowledge, this is the first example of metal-free hydration of ynamides giving *N*-monosubstituted amides under room temperature.

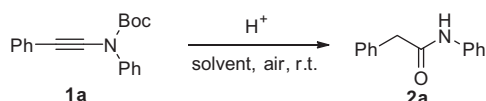
Results and discussions

Recently we have developed the iodine-mediated oxidation of ynamides to synthesize varied α -keto-amides.¹⁵ In the course of our study, we noticed the hydration of ynamide **1a** was transformed into amide **2a** in 76% isolated yield under TFA/CH₃CN/H₂O condition (Table 1, entry 1). Thus, we started this synthesis by conducting the reaction of *tert*-butyl *N*-phenyl- *N*-(phenylethynyl) carbamate (**1a**) as the model case for condition optimization. The use of TFA allowed the direct conversion of benzyl-phenylethynyl-carbamic acid *tert*-butyl ester (**1a**) into the corresponding *N*-monosubstituted phenylacetamides **2a** in the yield of 65–80% under mild condition (Table 1, entries 1–3), and DCM was superior to CH₃CN (76%), THF (65%). The addition of 3.0 equiv TFA produced the highest yield of **2a** (Table 1, entries

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Scheme 1. TFA-mediated hydration of ynamides.

Table 1
Optimization of reaction conditions^a

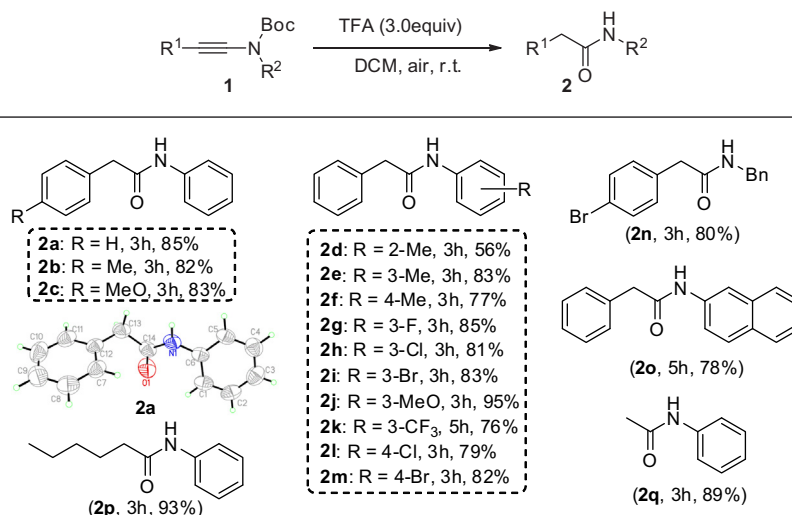
Entry	Solvent	H ⁺ (equiv)	Time (h)	Isolated yield (%)
1	CH ₃ CN	TFA (1.0)	12	76
2	THF	TFA (1.0)	12	65
3	DCM	TFA (1.0)	12	80
4	DCM	TFA (2.0)	5	81
5	DCM	TFA (3.0)	3	85
6	DCM	TFA (6.0)	3	86
7	DCM	CH ₃ COOH (3.0)	24	0
8 ^b	DCM	HCl (3.0)	24	0

^a Reaction conditions: **1a** (0.3 mmol), TFA or other acids, H₂O (5.0 equiv) and solvent (2.0 mL) at rt under air atmosphere.

^b 5.0 wt% (m/v) of HCl in H₂O was used, and unidentified mixture was given.

3–5). Other acids, such as acetic acid, HCl (5.0%), failed to provide the corresponding amides (Table 1, entries 6–7).

With the optimized conditions in hand (Table 1, entry 5), we examined the scope and generality of various ynamides in this transformation. The results are summarized in Table 2. Groups such as methyl, methoxy that are substituted in the aryl ring were tolerated and readily produced high yields of the corresponding phenylacetamides (Table 2, **2b–2c**). The structure of **2a** was further confirmed via single-crystal X-ray diffraction (Table 2).¹⁶ Under the optimized reaction conditions, various substrates bearing *ortho*, *meta*, and *para* substitutions in the *N*-aryl ring were converted (moderate to high yields) into the corresponding *N*-monosubstituted amides (Table 2, **2d–2m**). The yields decreased when having an electron-withdrawing group in the *meta* position of *N*-aryl ring (Table 2, **2k** vs **2j**). Ynamides with different *N*-substituted groups, such as benzyl, 2-naphthyl, were also used to this reaction to produce the corresponding *N*-monosubstituted amides with good yield (Table 2, **2n–2o**). In addition, an excellent yield of alkyl-substituted ynamide **1p** was obtained under the reaction

Table 2
TFA-mediated hydration of ynamides^a

^a Reaction conditions: **1** (0.3 mmol), TFA (3.0 equiv), H₂O (5.0 equiv) and DCM (2.0 mL) at rt under air atmosphere.

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