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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.

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 Atorvastain,[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-workers[13] reported a convenient approach to the preparation of imides that involves the reaction of ynamides with HOAc/Acetone/H_2O at 100 °C (Scheme 1, a). Using Sn-W mixed oxide, Mizuno and co-workers[14] 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/CH_3CN/H_2O 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 CH_3CN (76%), THF (65%). The addition of 3.0 equiv TFA produced the highest yield of **2a** (Table 1, entries

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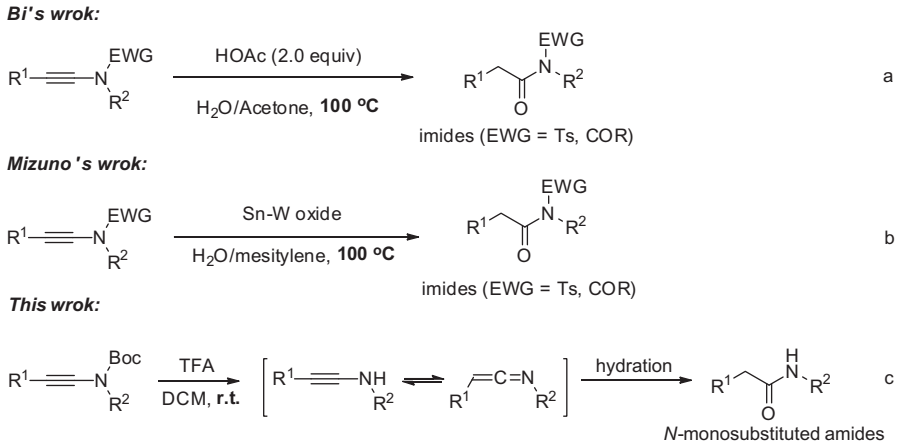
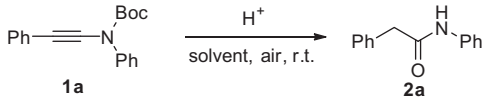


Scheme 1. TFA-mediated hydration of ynamides.

Table 1
Optimization of reaction conditions[a]



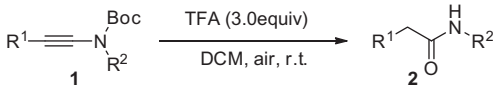
Entry	Solvent	H^+ (equiv)	Time (h)	Isolated yield (%)
1	CH_3CN	TFA (1.0)	12	76
2	THF	TFA (1.0)	12	65
3	DCM	TFA (1.0)	12	80
4	DCM	TFA (2.0)	5	81
5	**DCM**	TFA (**3.0**)	**3**	**85**
6	DCM	TFA (6.0)	3	86
7	DCM	CH_3COOH (3.0)	24	0
8[b]	DCM	HCl (3.0)	24	0

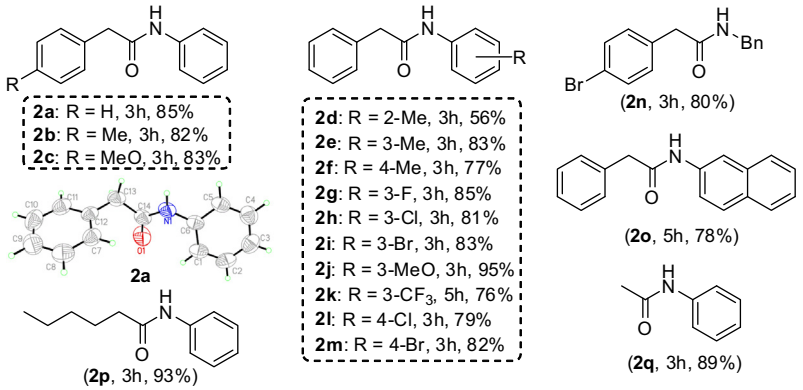
[a] *Reaction conditions*: **1a** (0.3 mmol), TFA or other acids, H_2O (5.0 equiv) and solvent (2.0 mL) at rt under air atmosphere.
[b] 5.0 wt% (m/v) of HCl in H_2O was used, and unidentified mixture was given.

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

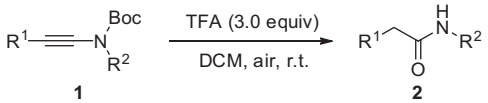
Table 2
TFA-mediated hydration of ynamides[a]

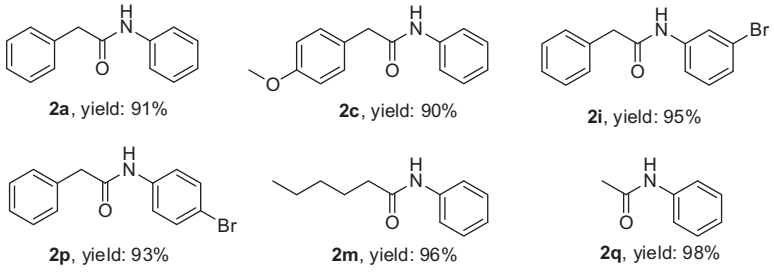




[a] *Reaction conditions*: **1** (0.3 mmol), TFA (3.0 equiv), H_2O (5.0 equiv) and DCM (2.0 mL) at rt under air atmosphere.

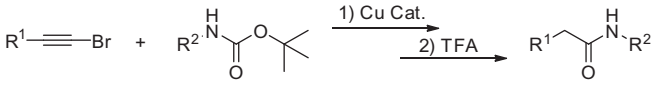
Table 3
Gram-scale experiments[a]

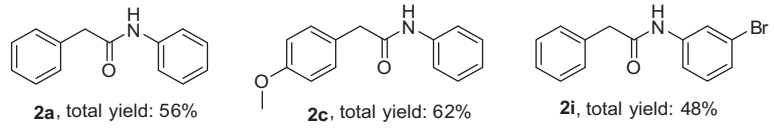




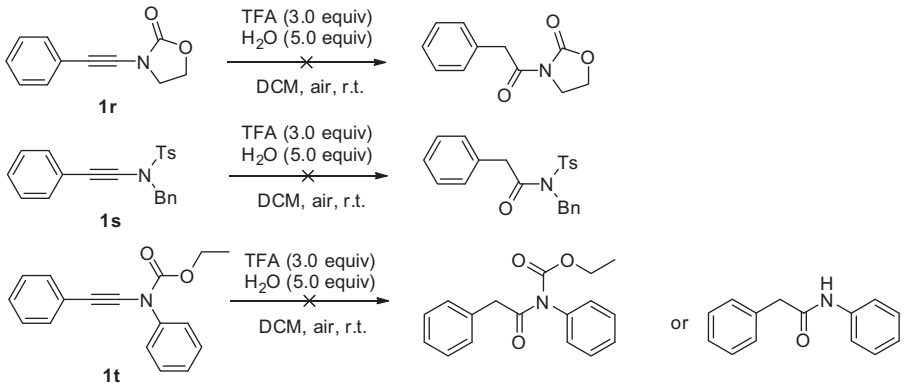
[a] *Reaction conditions:* Ynamides **1** (6.0 mmol), H_2O (5.0 equiv), TFA (1.5 mL), DCM (30 mL), rt, 5 h.

Table 4
One-pot preparation of amides from bromoalkynes[a]





[a] *Reaction conditions*: 1) *tert*-butyloxycarbamates (0.6 mmol), bromoalkynes (0.72 mmol), $CuSO_4{\cdot}5H_2O$ (0.06 mmol), 1,10-Phenanthroline (0.12 mmol), K_3PO_4 (1.2 mmol), and toluene (2 mL), 85 °C, 18 h. 2) TFA (0.2 mL), toluene, rt, 5 h; isolated yield was given.

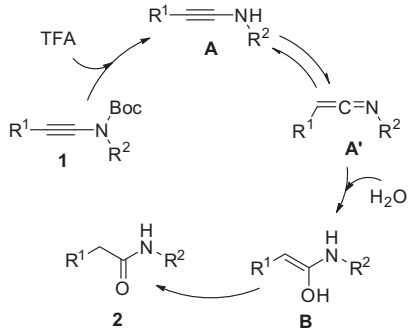


Scheme 2. TFA-mediated hydration of ynamides without Boc group.

conditions (Table 2, **2p**). Finally, terminal ynamide was also tested, that *N*-phenylacetamide was obtained in 89% yield (Table 2, **2q**).

To demonstrate the synthetic potential of this strategy, scale-up experiments were carried out for several substrates. To our delight, the reactions all proceeded well and the corresponding amides could be isolated in excellent yield via simple work-up process (Table 3).[17] For example, an excellent yield (91%) of product **2a** was obtained when **1a** was employed in the gram-scale reaction condition.

Further application of our method was extended in developing a one-pot method for synthesis of amides employing bromoalkynes as starting materials. And the procedure is very simple as follows: $CuSO_4{\cdot}5H_2O$ and K_3PO_4 are filtered off after completion of the cross-coupling of bromoalkynes and *tert*-butyloxycarbamates,



Scheme 3. Plausible reaction mechanism.

and TFA was added to the filtrate. The products were provided in moderate yields after purified by chromatography column (Table 4).

Different ynamides derivatives without the Boc group were also investigated (Scheme 2). Ether 3-(phenylethynyl)-oxazolidin-2-one **1r** or ynesulfonamide **1s** was unable to convert into the corresponding amides. Additionally, hydration of ynamides containing ethyl on the ester moiety (**1t**) also did not take place. These results reveal the important role of Boc group in this hydration system.

By employing our experimental results and literature reports, we have proposed a mechanism for this hydration (Scheme 3). After deprotection of the Boc group under TFA condition, ynamides **1** can afford the intermediate **A**, which are also characterized by keteniminium forms **A′** increasing their electrophilicity and regioselectivity.[18] The addition of H_2O to intermediate **A′** would lead to the formation of enol intermediate **B**.[15] Through a keto/enol tautomerism, intermediate **B** can then form the corresponding amides **2**.

Conclusion

In conclusion, a novel and efficient method has been developed for the construction of *N*-monosubstituted amides through TFA-mediated hydration of ynamides. This protocol takes place at room temperature and utilizes readily available starting materials under metal-free conditions, which provides a convenient and highly attractive route to various amides. Further studies on exploring the reactivity and application of ynamides are underway.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.03.052.

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16. *Crystal date of* **2a**: $C_{14}H_{13}NO$; M = 211.25; Monoclinic'; space group *P*21/*n*; final *R* indices [$I > 2\sigma(I)$]: $R_1 = 0.0379$, $wR_2 = 0.0915$, *R* indices(all data): $R_1 = 0.0536$, $wR_2 = 0.1017$, $a = 5.6832(5)$ Å, $b = 25.278(2)$ Å, $c = 8.0124(7)$ Å; $\beta = 91.916(2)°$, $V = 1150.44(17)$ Å^3; $T = 296$ K; $Z = 4$; reflection measured/independent: 6372/2032 ($R_{int} = 0.022$), number of observations [$I > 2\sigma(I)$]: 1561, parameters: 145. CCDC-1447766 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
17. *General procedure for the preparation of amides:* To a mixture of ynamides (6.0 mmol) and DCM (30 mL) in a reaction vial was added TFA (18.0 mmol). The reaction mixture was stirred at rt for 4 h while being monitored with TLC analysis. Upon completion, the reaction mixture was concentrated in vacuum to give directing products.
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