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Selective cleaving the N—P bond of difluoromethylene phosphabetaines for effective synthesis of β-ketoamides

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ABSTRACT

An unprecedent transition-metal-free protocol for the synthesis of β-ketoamides from β-ketoesters is described. This method involves selective cleaving N—P bond of an unusual aminating reagent, [tris (dimethylamino)phosphonio]difluoroacetate (ADFA), which is well known as the difluoromethylene ylide precursor. The process is notable for its operational simplicity and good functional group tolerance.

Introduction

The β-ketoamides and their derivatives represent important class of units in modern organic synthesis and medicinal chemistry [1]. They are also very important and useful building blocks for the synthesis of various heterocycles including lactams [2], furans [3], pyrans [4], isoquinolines [5], oxocyclohexenones [6], spiroindolines [7], tetrahydropyridines [8], bridged heterocycles [9] and spiroaminals [10]. Furthermore, they can be conveniently converted into β-hydroxyamides [11] and γ-ketoamides [12]. Consequently, a variety of methods have been developed for the synthesis of β-ketoamides. The traditional methods include aminolysis of β-ketoesters [13], α-acylation of amides [14], addition of enolates to isocyanates [15], Wolff Rearrangement of cyclic 2-diazo-1,3-diketones [16] and oxidation β-hydroxy amide [17]. However, most of these approaches often suffer from narrow substrate scope and/or harsh reaction conditions. Recently, the transition-metal-catalyzed methods have been developed for the preparation of β-ketoamides. In 2014, Skrydstrup and Lindhardt reported a mild and effective synthetic route via Pd-catalyzed carbonylative α-arylation of acetoacetamides and subsequent deacetylation [18]. The ruthenium-catalyzed hydration of β-ketonitriles was developed by Crochet and Cadierno for the preparation of β-ketoamides [19]. However, the use of precious transition metals made these processes less applicable to large-scale synthesis. From this point of view, it is deeply worthy to explore broadly applicable methods for the synthesis of β-ketoamides.

In 2013, Xiao and co-workers reported the preparation of [tris (dimethylamino)phosphonio]difluoroacetate (ADFA) as a difluoromethylene phosphonium ylide precursor [20]. The general application of ADFA is to react with ketones for the preparation of *gem*-difluoroalkenes (Scheme 1, left) [21]. Herein, we demonstrate an unusual application of ADFA as a novel aminating reagent in the amination of β -ketoesters to β -ketoamides (Scheme 1, right).

Result and discussion

Recently, we reported an unprecedent reaction of indoline-2,3-diones and (triphenylphosphonio)difluoroacetate (PDFA) [20,22] to afford novel 3-fluoroalkenyl-3-trifluoromethyl-2-oxindoles in moderate to excellent yields [23]. To extend the scope of this unique reaction, we examined the reaction of β-ketoester **1a** with PDFA (Table 1, entry 1). However, no reaction was detected. To our surprise, treatment of **1a** with more nucleophilic ADFA in NMP gave tautomeric mixture of β-ketoamide **4a** and enol forms **4a′** in 49% total yield (entry 2). No *gem*-difluoroalkene **3a** was observed in this reaction. In continuation of our research interest in the

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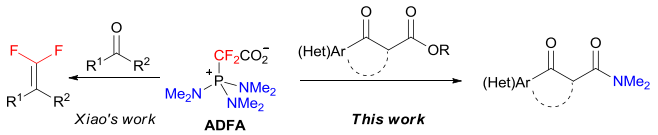
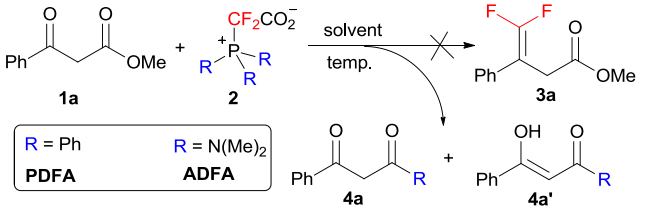


Scheme 1. Applications of ADFA.

Table 1
Reaction condition optimization.[a]



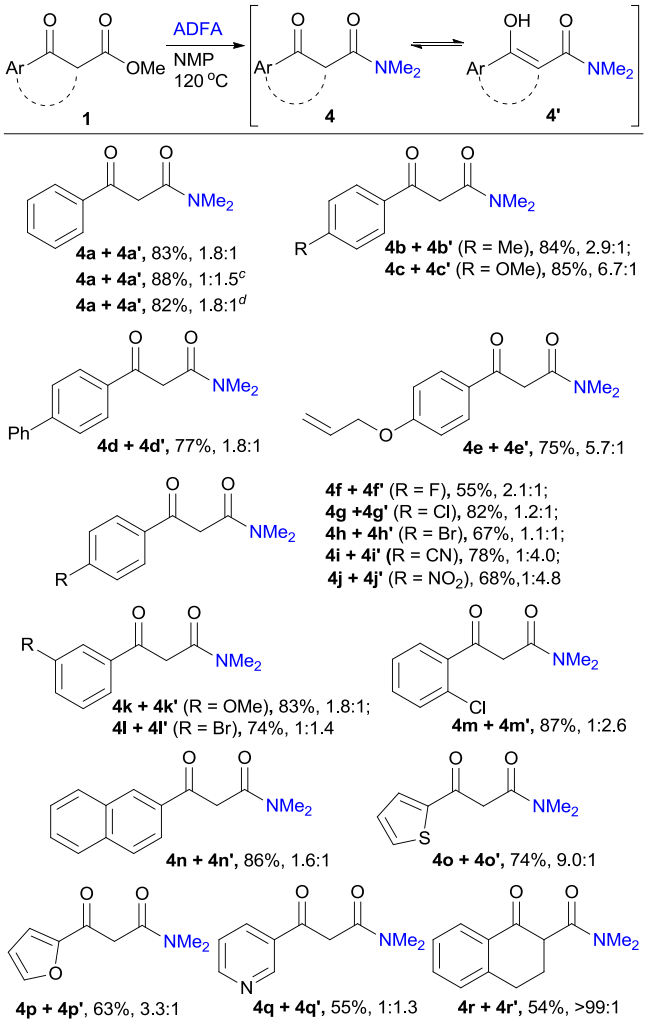
Entry	2	Solvent	Temperature (°C)	4 Yield (%)[b]
1	**PDFA**	NMP	120	ND
2	**ADFA**	NMP	120	49
3	**ADFA**	DMF	120	32
4	**ADFA**	DMA	120	20
5	**ADFA**	1,4-dioxane	120	27
6	**ADFA**	toluene	120	trace
7	**ADFA**	NMP	140	34
8	**ADFA**	NMP	130	47
9	**ADFA**	NMP	110	41
10[c]	**ADFA**	NMP	120	21
11[d]	**ADFA**	NMP	120	68
12[e]	**ADFA**	NMP	120	83
13[f]	**ADFA**	NMP	120	73

[a] Reaction conditions: **1a** (0.5 mmol), difluoromethylene phosphabetaine (1.0 mmol), solvent (1.0 mL), temperature, under N_2, 12 h.
[b] Isolated yields.
[c] ADFA (1.5 mmol).
[d] NMP (2.5 mL).
[e] NMP (5.0 mL). [f]NMP (7.5 mL).

development of new applications of fluoroalkylphosphoniums [23,24], we decided to further explore the amination reaction with ADFA. We continued to optimize the reaction conditions started with the screening of other solvents including DMF, DMA, 1,4-dioxane, and toluene (entries 3–6), but none of them gave better results. Further screening of reaction temperature showed that 120 °C was optimal (entries 2, 7–9). Given the unsatisfactory reaction yield, three equivalents of ADFA was also used in this reaction system (entries 10). To our surprise, this reaction gave out β-ketoamide **4a** and enol forms **4a′** in lower yields than the one obtained with two equivalent ADFA (entries 10 *vs.* 2). We therefore speculated that the concentration of ADFA could play important roles in determining the yield of the product. To our delight, the yield of **4a** and **4a′** was sharply improved when the reaction concentration was decreased (entries 11–13). Finally, the optimal reaction conditions were defined as 1 equiv of **1a** (0.1 mol/ L) and 2 equiv of ADFA(0.2 mol/ L) in NMP (5 mL) at 120 °C (entry 12).

With the optimized reaction conditions in hand, the substrate scope of this reaction was surveyed. As shown in Table 2, this reaction is compatible with a wide range of electron-donating (Me, OMe, and phenyl; **1b**-**1d**) and electron-withdrawing (F, Cl, Br, CN, and NO_2; **1f**-**1j**) groups on benzene ring of β -ketoesters. In general, the substitution of electron-donating groups is favored for this reaction. Moreover, allyl functional group that is commonly employed in cross coupling reactions was also tolerated giving the corresponding **4e** and **4e′** in moderate yields, thus providing opportunities for additional transformations. The substituent on

Table 2
Amination of β -ketoesters with ADFA.[a,b]

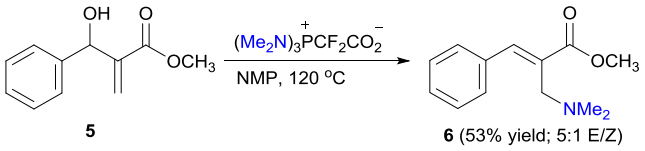


[a]Reaction conditions: **1** (0.5 mmol), ADFA (1.0 mmol), NMP (5.0 mL), 120 °C, under N_2, 12 h, all reaction yields are isolated yields.
[b]Keto/enol ratios are determined by ^{1}H NMR spectroscopy in $CDCl_3$.
[c]Ethyl 3-oxo-3-phenylpropanoate (**1 s**) as the substrate.
[d]**1a** (8.0 mmol), ADFA (16.0 mmol), NMP (80.0 mL).

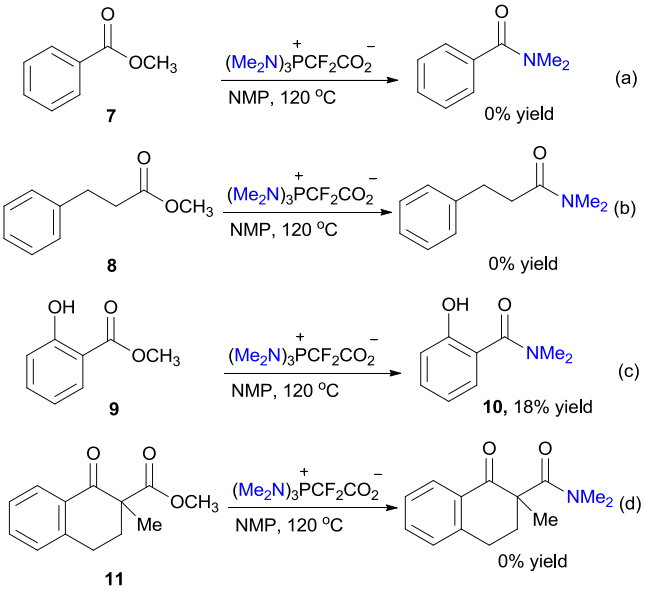
the *para*, *meta* or *ortho* position of aromatic ring had no obvious effect on the reaction yield (**1c** *vs.* **1k**; **1h** *vs.* **1l**; **1g** *vs.* **1m**). Furthermore, this procedure was also applicable to polycyclic (**1n**), heterocyclic aromatic-substituted (**1o**-**1q**), and even α-alkyl substituted (**1r**) β-ketoesters, albeit the yield was slightly reduced. Lastly, ethyl 3-oxo-3-phenylpropanoate (**1s**) was also investigated under standard conditions. The corresponding tautomeric mixture **4a** and **4a′** were obtained in 88% yields. It was noteworthy that this reaction can also be used to gram scale synthesis β-ketoamides without significant reduction in yield and the structure of product **4** was confirmed by X-ray crystallographic analysis of compound **4a′** (see the Supporting information).

Besides β-ketoesters, other compounds could also be aminated by ADFA. For example, the Morita–Baylis–Hillman adduct **5** reacted with ADFA in NMP to give an allylic amine **6** in 53% yield and a moderate stereoselectivity (Scheme 2) [25].

To gain insight into the reaction mechanism, the following experiments were performed. Firstly, methyl benzoate **7** and methyl 3-phenyl propanoate **8** were examined to react with ADFA, and the amination reaction did not happen (Scheme 3a and 3b).



Scheme 2. Amination of Morita–Baylis–Hillman adduct **5**.



Scheme 3. Mechanism experiments.

This result demonstrated that the carbonyl of β-ketoester played an important role in this reaction. In contrast, treatment of methyl 2-hydroxybenzoate **9** with ADFA gave the corresponding amide **10**, albeit in low yield (Scheme 3c). Furthermore, when α-dialkyl substituted β-ketoester **11** was subjected to the standard conditions, the corresponding amide was not obtained (Scheme 3d). These results confirmed that enolization of β-ketoester was the key step for this reaction. Lastly, we also used GC–MS to identify the reaction solution and no dimethyl amine can be observed from the spectra. Base on this, we believe dimethyl amine generated from decomposition of ADFA should be not involving in this reaction system.

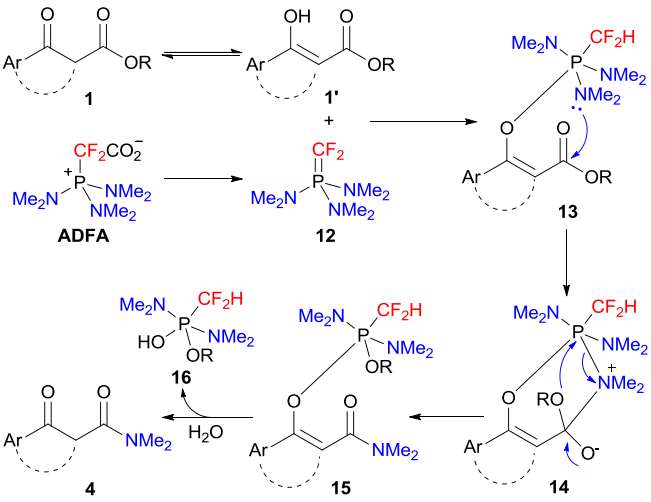


Fig. 1. Proposed reaction mechanism.

On the basis of the above results, we proposed a plausible mechanism (Fig. 1). The ADFA underwent decarboxylation process under the mild heating to generate transient difluoromethylene phosphonium ylide **12** [20]. Then, ylide **12** was trapped by enol **1′** to form a five-coordinate phosphorus intermediate **13**. Subsequently, an intramolecular nucleophilic substitution [26] happened via a selective cleavage of the N—P bond of ADFA to give intermediate **15**. Finally, protonation of **15** furnished the desired product β-ketoamide **4**.

Conclusion

In summary, we have developed an efficient method for the preparation β-ketoamides from β-ketoesters via a selective cleavage of the N—P bond of difluoromethylene phosphabetaines. Compared with other methods, this current one has some advantages, such as wide substrate scope, operational simplicity, transition-metal-free, and no need to add base. Thus, the difluoromethylene phosphabetaines might be expected to become a unique and efficient aminating reagent for the formation of C—N bond. Further exploration of this protocol and development of other reagents will be carried on in our group.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.06.036.

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