Brønsted Acid Catalyzed Amination of 1,3-Dicarbonyl Compounds by Iminoiodanes

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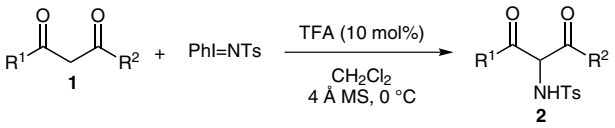
Abstract: A synthetic method to aminate 1,3-dicarbonyl compounds with PhI=NTs using Brønsted acid catalysis is described herein. The method was shown to be applicable to β-keto esters and phosphonates as well as 1,3-diones, providing the corresponding α,α-acyl amino acid derivatives in moderate to excellent yields.

Key words: α,α-acyl amino acid derivatives, iminoiodanes, amination, Brønsted acid catalysis, 1,3-dicarbonyl compounds

Compounds containing unnatural α-amino acids, those outside the set of 20 used by Nature, represent important targets in medicinal chemistry because of their potential to exhibit new modes of bioactivity.[1,2] Not surprisingly, the field has witnessed a number of elegant synthetic methods to prepare derivatives of the biomolecule in an efficient and convenient manner. Recently, we reported one of such approach to ketone-substituted α-amino acid derivatives that relied on $Cu(OTf)_2$-catalyzed amination of a 1,3-dicarbonyl compound by $PhI{=}NSO_2Ar$ (Ar = 4-MeC_6H_4, 4-$O_2NC_6H_4$).[2c,3–5] At about the same time, Zhang and co-workers showed that the analogous reactions of β-keto amides, esters, phosphonates, and 1,3-diones with $TsNH_2$ and PhI=O mediated by $Zn(ClO)_4{\cdot}6H_2O$ could be achieved in good to excellent yields.[2f] In view of these works, we queried whether a Brønsted acid catalyzed version of this functional-group transformation could be realized.[6] In doing so, we disclose herein the details of this study involving TFA-mediated amination of β-keto esters and phosphonates and 1,3-diones by PhI=NTs (Scheme 1). This process provides a convenient and operationally straightforward route to the corresponding α,α-acyl amino acid derivatives in moderate to excellent yields.



Scheme 1 Brønsted acid catalyzed amination of 1,3-dicarbonyl compounds by PhI=NTs

With ethyl benzoylacetate (**1a**) as the model substrate, we began to establish a variety of reactions conditions (Table 1). This initial study showed that treating the β-keto ester with two equivalents of PhI=NTs and 20 mol% of TFA in the presence of 240 mg of 4 Å molecular sieves (MS) in dichloromethane at room temperature for 15 minutes gave the corresponding α-aminated product **2a** in 85% yield (Table 1, entry 1). Subsequent investigations revealed that slightly lower yields of 75–79% could be obtained on either decreasing the catalyst loading from 20 mol% to 10 mol% or the amount of iminoiodane from two equivalents to 1.5 or 1.2 equivalents (Table 1, entries 2–5). Lower product yields (61–72%) were also afforded when the reaction was repeated with 5 mol% of TFA and/or at 0 °C (Table 1, entries 6, 7, and 9). On the other hand, the analogous reactions with 10 mol% of the Brønsted acid at 0 °C for 90 minutes gave **2a** in 86% yield (Table 1 entry 8). In our hands, amination of **1a** by PhI=NTs under these latter reaction conditions in other solvents was found to be less effective (Table 1, entries 10–12). Lower product yields of 11–68% were furnished when THF, MeCN, or toluene in place of dichloromethane was used as the reaction medium. Likewise, reactions with HCl, H_2SO_4, H_3PO_4, and AcOH as the catalyst gave lower yields of 51–78% even on prolonging reaction times to 18 hours at room temperature (Table 1, entries 13–16). On the basis of these results, amination of **1a** by PhI=NTs (1.2 equiv) in the presence of 10 mol% of TFA and 4 Å MS (240 mg) in dichloromethane at 0 °C for 90 minutes was deemed to provide the optimal reaction conditions.[7,8]

To assess the generality of the present procedure, we next turned our attention to the amination of a variety of 1,3-dicarbonyl compounds, and the results are summarized in Scheme 2. These experiments revealed reactions of β-keto esters containing an electron-donating (**1b–e**) or electron-withdrawing (**1f–i**) phenyl group with PhI=NTs proceed well to afford the corresponding α,α-acyl amino acid derivatives **2b–i** in 53–86% yield. Likewise, β-keto esters in which the phenyl group was replaced with a furan moiety (**1j**) or alkyl substituent (**1l**,**m**) were well tolerated, giving **2j**,**l**,**m** in 47–73% yield. The only exception was the reaction of **1k** with PhI=NTs providing **2k** in a lower yield of 27%. Changing the β-keto ester to its phosphonate analogue **1n** was also found to give the corresponding α-aminated product **2n** in 53% yield on treatment with 10 mol% of TFA and 1.2 equivalents of PhI=NTs under standard reaction conditions. Similarly, the reaction condi-

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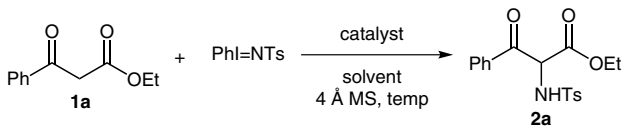
tions could be extended to the 1,3-diones **1q**–**s** to give the corresponding 2-amino-1,3-dione products in 57–63% yield. However, replacing the alkyl substituents in the 1,3-dione substrate with presumably more bulky *tert*-butyl groups, as in **1t**, was found to result in recovery of the substrate in near quantitative yield. Additionally, the analogous reactions with the alkyl malonates **1o** and **1p** were found, in both instances, to lead to the recovery of the 1,3-dicarbonyl compound in near quantitative yield based on TLC analysis and ^{1}H NMR measurements of the respective crude mixtures. As shown in Scheme 3, the amination of 1,3-cyclohexadione (**1u**) was also investigated but was found to afford the iodonium ylide **3u** in 83% yield.

A tentative mechanism for the present Brønsted acid catalyzed amination reaction is illustrated in Scheme 4. Under the acidic conditions, this could involve enolization of **1** to its enolate **1′** that subsequently adds to PhI=NTs to give the putative iodine(III) species **A** (path a in Scheme 4).[2f] Reductive elimination of the hypervalent iodine(III) moiety in this key intermediate would result in the release of PhI and deliver the product **2**. The role of the Brønsted acid catalyst in facilitating the enolization of the 1,3-dicarbonyl compound would be consistent with the recovery of the substrate in reactions with less acidic dialkyl malonates.[9]

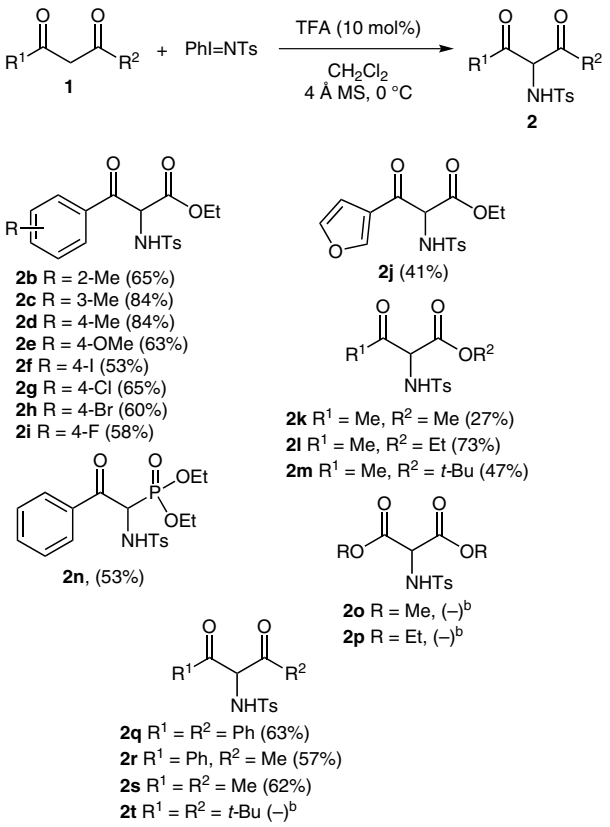
The formation of iodonium ylide **3u** could be due to preferential α-H elimination in intermediate **A** (path b in Scheme 4). This could be due to the more stable nature of the species provided by secondary bonding interactions between the carbonyl oxygen atoms and the iodine(III) center on generating the cyclic form of the hypervalent iodine product.[10] The side product additionally argues in favor of species **A** being the actual intermediate that undergoes reductive elimination to afford the product. Added to this, competition experiments on the amination of β-keto esters **1d**,**e**,**g**–**i** revealed $\log(K_x/K_H)$ values of 0.02 (**1d**), 0.09 (**1e**), –0.09 (**1g**), –0.07 (**1h**), and –0.06 (**1i**). This suggests that 1,3-dicarbonyl compounds substituted with an electron-donating group are more reactive than **1a**, whereas those with an electron-withdrawing substituent retard the reaction. Fitting (by least-squares method) the $\log(K_X/K_H)$ data to the σ_p scale gave rise to

Table 1 Optimization of the Reaction Conditions[a]

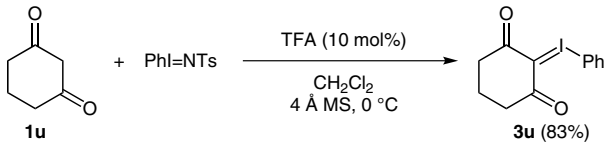


Entry	Catalyst	Catalyst loading (mol%)	PhI=NTs loading (equiv)	Solvent	Temp (°C)	Time (min)	Yield (%)[b]
1	TFA	20	2	CH_2Cl_2	r.t.	15	85
2	TFA	20	1.5	CH_2Cl_2	r.t.	10	77
3	TFA	10	1.5	CH_2Cl_2	r.t.	10	79
4	TFA	20	1.2	CH_2Cl_2	r.t.	15	79
5	TFA	10	1.2	CH_2Cl_2	r.t.	10	75
6	TFA	5	1.2	CH_2Cl_2	r.t.	15	61
7	TFA	20	1.2	CH_2Cl_2	0	90	62
8	TFA	10	1.2	CH_2Cl_2	0	90	86
9	TFA	5	1.2	CH_2Cl_2	0	90	72
10	TFA	10	1.2	MeCN	0	90	68
11	TFA	10	1.2	PhMe	0	90	51[c]
12	TFA	10	1.2	THF	0	90	11[c]
13	HCl	20	2	CH_2Cl_2	r.t.	1080	52
14	H_2SO_4	20	2	CH_2Cl_2	r.t.	1080	78
15	H_3PO_4	20	2	CH_2Cl_2	r.t.	1080	66
16	AcOH	20	2	CH_2Cl_2	r.t.	1080	51

[a] Unless otherwise stated, all reactions were performed in the presence of the given catalyst and 4 Å MS (240 mg) in given solvent (2 mL) at given temperature and time with 0.5 mmol of **1a**.
[b] Isolated yield.
[c] Product yield was determined by ^{1}H NMR analysis of the crude mixture with CH_2Br_2 as the internal standard.



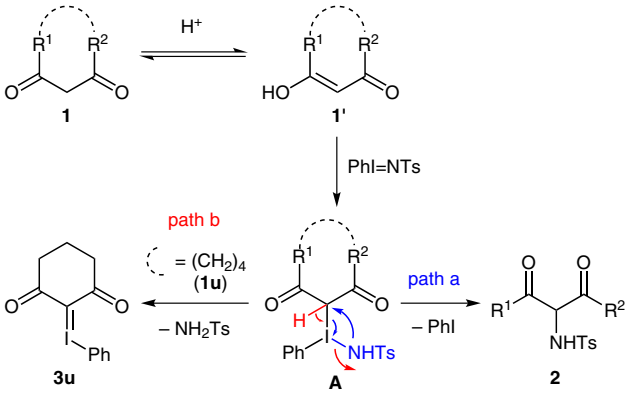
Scheme 2 TFA-mediated amination of **1b–t** by PhI=NTs. Refer to the Supporting Information for the reaction times. Values in parentheses denote isolated product yields. For compounds **2o**,**p**,**t**: no reaction based on TLC and ^{1}H NMR analysis of the crude mixture.



Scheme 3 Formation of iodonium ylide **3u**

moderate linearity (R^2 = 0.947) with a ρ value of –0.306 (Figure 1).[11] The small and negative ρ value indicates minimal positive-charge development on the aromatic ring of the intermediate **A** and implies that its formation could be the rate-limiting step.[12]

In summary, we have developed a Brønsted acid catalyzed method to access unnatural α,α-acyl amino acid derivatives from 1,3-dicarbonyl compounds and PhI=NTs. Our studies show the reaction to be applicable to β-keto esters and phosphonates as well as 1,3-diones and compliment earlier works that make use of Cu(II)[2c] and Zn(II)[2f] catalysis. Further exploration on the synthetic utility of the present transformation is currently underway and will be reported in due course.



Scheme 4 Plausible mechanism for amination of 1,3-dicarbonyl compounds with PhI=NTs mediated by TFA

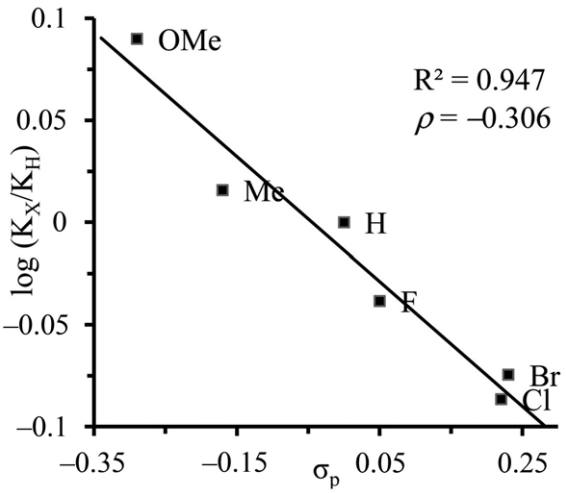


Figure 1 Linear free-energy correlation of $\log(K_X/K_H)$ against σ_p on the Brønsted acid catalyzed amination of 1,3-dicarbonyl compounds **1d**,**e**,**g–i** with PhI=NTs

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(7) **General Procedure**
To a degassed mixture of PhI=NTs (0.6 mmol, 224 mg) and powdered 4 Å MS (240 mg) was added CH_2Cl_2 (1 mL). The reaction was cooled to 0 °C, and a solution of TFA (0.05 mmol, 3.83 μL) in CH_2Cl_2 (1 mL) was added. The 1,3-dicarbonyl compound was added, and the reaction was monitored by TLC analysis. Upon completion, the reaction mixture was filtered, washed with EtOAc (40 mL), concentrated under reduced pressure, and purified by flash chromatography [*n*-hexane–EtOAc (4:1) as eluent] to furnish the title compound.

(8) **Representative Experimental Data**
Ethyl 2-(4-Methylphenylsulfonamido)-3-oxo-3-phenylpropanoate (2a)
Reaction time = 1.5 h; yield 86%; 0.162 g; white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.4 Hz, 2 H), 7.73 (d, *J* = 8.3 Hz, 2 H), 7.62 (t, *J* = 7.4 Hz, 1 H), 7.47 (t, *J* = 7.7 Hz, 2 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 6.00 (d, *J* = 8.9 Hz, 1 H), 5.58 (d, *J* = 8.9 Hz, 1 H), 3.97 (q, *J* = 7.1 Hz, 2 H), 2.38 (s, 3 H), 1.04 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.2, 165.9, 144.1, 144.0, 136.6, 134.7, 129.8, 129.5, 128.9, 127.4, 62.6, 60.9, 21.6, 13.8.
Ethyl 3-(4-Bromophenyl)-2-(4-methylphenylsulfonamido)-3-oxopropanoate (2h)
Reaction time = 1.5 h; yield 60%; 0.114 g; white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.2 Hz, 2 H), 7.72 (d, *J* = 8.3 Hz, 2 H), 7.62 (d, *J* = 8.7 Hz, 2 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 5.96 (d, *J* = 8.7 Hz, 1 H), 5.52 (d, *J* = 8.7 Hz, 1 H), 4.02–3.93 (m, 2 H), 2.39 (s, 3 H), 1.05 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.6, 165.9, 144.2, 136.5, 132.3, 130.9, 130.2, 129.8, 127.4, 62.9, 60.9, 21.6, 13.8.
***N*-(2,4-Dioxopentan-3-yl)-4-methylbenzenesulfonamide (2s)**
Reaction time = 2 h; yield 62%; 0.0840 g; yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 16.3 (s, 1 H), 7.84 (s, 1 H), 7.71 (d, *J* = 8.1 Hz, 2 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 6.16 (s, 1 H), 5.16 (s, 1 H), 2.44 (s, 3 H), 1.87 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.1, 144.3, 136.6, 130.1, 127.4, 110.1, 22.1, 21.6.

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