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General and Chemoselective Bisphosphonylation of Secondary and Tertiary Amides

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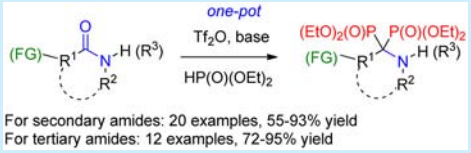
Supporting Information

ABSTRACT: With Tf_2O as the activation reagent, a mild and general method has been developed for the bisphosphonylation of both secondary and tertiary amides. The protocol is highly efficient and chemoselective, and it tolerates a number of sensitive functional groups such as cyano, ester, and aldehyde groups.



α-Amino bisphosphonates are an important class of biologically active compounds that possess inhibitory activity on a variety of biosynthesis pathway enzymes such as farnesyl pyrophosphate synthase (FPPS),[1] squalene synthetase,[2] and 1-deoxyxylulose-5-phosphate reductoisomerase[3] and display antiparasitic,[4] antibacterial,[5] and herbicidal[6] activities. Several α-amino bisphosphonate-based pharmaceuticals are currently in clinical use to treat a variety of bone resorption diseases such as osteoporosis, hypercalcemia, and Paget's disease.[7] Some of them are also of interest in the context of cancer immunotherapy[8] and radiodiagonosis.[9] Representative α-amino bisphosphonates of biological importance are shown in Figure 1. In addition, α-amino bisphosphonates can serve as synthetic precursors of α-amino vinylphosphonates, which are both important pharmacophores and building blocks for the synthesis of biologically active compounds.[10]

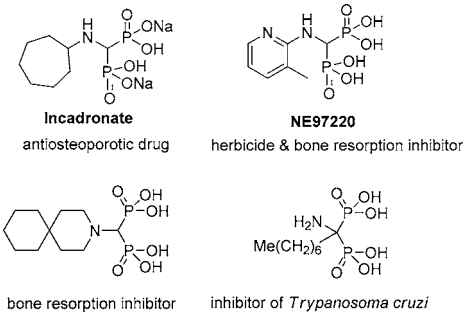


Figure 1. Representative α-amino bisphosphonates of medicinal relevance.

As a result of the exceptionally interesting biological properties of α-amino bisphosphonates, several approaches have been developed for the synthesis of these compounds,[11] which include bisphosphonylation of amides,[12−14] nitriles,[15] and α,β-unsaturated imines,[16] condensation of amines with triethyl orthoformate and phosphites,[17] and Beckman rearrangement of oximes in the presence of phosphorus nucleophiles.[18] Among them, PCl_3/H_3PO_4-,[12] $POCl_3$-,[13] and triphosgene-mediated[14] bisphosphonylations of amides are the most straightforward approaches. Another advantage of this kind of methods resides in the use of highly stable and easily available amides as the starting materials. However, using classical amide activating reagents, these methods have some drawbacks, such as being restricted to alkanecarboxylic amides, the need to perform the reaction at high temperature, and low to moderate yields. In addition, the issue of chemoselectivity has not been addressed. As the substituents on the *N*-atom and the side chains attached to the α carbon have a significant influence on the biological activities,[7d,19] the purposeful synthesis of functionalized α-amino bisphosphonate derivatives is of paramount importance in the search for compounds with a desirable biomedical profile. The development of an efficient and general method for the bisphosphonylation of amides is thus highly desirable.

In recent years, chemoselective addition of nucleophiles to the inert amide carbonyls has attracted much attention.[20] The direct and highly chemoselective nucleophilic addition to active *N*-alkoxyamides[21] and reductive functionalization of amides by Schwartz's reagent[22,23] have been extensively investigated by Sato and Chida, Vincent and Kouklovsky, and Ganem, respectively. In this context, Zhao has developed the first general method for the reductive phosphonylation of amides by using Schwartz's reagent.[23] However, the method cannot be used for the synthesis of α-amino bisphosphonates. On the other hand, trifluoromethanesulfonic anhydride (Tf_2O)[24,25] has proven to be an advantageous reagent for the in situ activation of amides to facilitate the nucleophilic addition of various *N*-, *O*-, *S*-, *H*-, and *C*-nucleophiles. However, to the best our knowledge, the bisphosphonylation of amides using Tf_2O has never been reported.

In connection with our efforts to develop new synthetic methods based on the activation of amides with Tf_2O, our group has recently developed a variety of C−C bond formation

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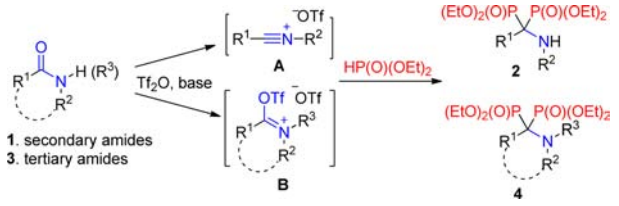
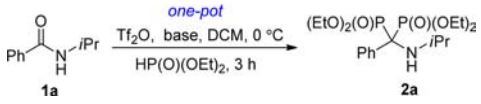
methods starting from tertiary[26] and secondary amides.[27] As an extension of this methodology, herein we report an efficient and general method for the synthesis of α-amino bisphosphonates from secondary and tertiary amides (Scheme 1).

Scheme 1. Bisphosphonylation of Amides by Tf_2O Activation



The bisphosphonylation of secondary amides was investigated at first. *N*-Isopropylbenzamide **1a** was chosen as the model substrate. Initial screening of various base additives showed that the incorporation of sterically hindered, weakly nucleophilic bases, such as 2,6-lutidine, 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), 2-chloropyridine, and 2-fluoropyridine, was crucial to achieve an appreciable level of efficiency (Table 1). Among the base additives screened, 2,6-lutidine was the optimal choice for its high efficiency and low price. Further optimization on the amount of 2,6-lutidine and diethyl phosphite showed that treatment of amide **1a** with 3.0 equiv of diethyl phosphite in the presence of 1.2 equiv of 2,6-lutidine and 1.2 equiv of Tf_2O produced α-amino bisphosphonate **2a** in an optimal isolated yield of 93%.

Table 1. Reaction Optimization for the Bisphosphonylation of Secondary Amides[a]

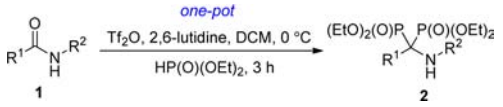


entry	base	base (equiv)	$HP(O)(OEt)_2$ (equiv)	yield[b] (%)
1	none		3.0	40
2	Et_3N	1.2	3.0	55
3	*i*-Pr_2NEt	1.2	3.0	73
4	pyridine	1.2	3.0	87
5	2,6-lutidine	1.2	3.0	98 (93[c])
6	DTBMP	1.2	3.0	96
7	2-chloropyridine	1.2	3.0	90
8	2-fluoropyridine	1.2	3.0	91
9	2,6-lutidine	1.5	3.0	99
10	2,6-lutidine	2.0	3.0	72
11	2,6-lutidine	1.2	2.0	65
12	2,6-lutidine	1.2	2.5	91
13	2,6-lutidine	1.2	4.0	97

[a]Reaction conditions: Tf_2O (1.2 equiv), base, DCM (0.2 M), 0 °C, 30 min then $HP(O)(OEt)_2$, rt, 3 h. [b]Determined by ^{31}P NMR. [c]Isolated yield.

Under the optimized conditions, a wide array of secondary aroyl amides could be converted into the corresponding α-amino bisphosphonates in good to modest yields (entries 1−18, Table 2). In general, benzamide derivatives bearing electron-withdrawing groups on the phenyl ring (entries 2−9) show higher reactivities than those having electron-donating groups (entries 10 and 11). The reaction is widely functional group tolerant and highly chemoselective. Not only halogen, nitro, and cyano

Table 2. Bisphosphonylation of Secondary Amides[a]



entry	R^1	R^2	product	yield[b] (%)
1	Ph	*i*-Pr	**2a**	93
2	*p*-ClC_6H_4	*i*-Pr	**2b**	88
3	*m*-BrC_6H_4	*i*-Pr	**2c**	83
4	*p*-$CF_3C_6H_4$	*i*-Pr	**2d**	82
5	*p*-NCC_6H_4	*i*-Pr	**2e**	76
6	*p*-$NO_2C_6H_4$	*i*-Pr	**2f**	76
7	*p*-$MeO_2CC_6H_4$	*i*-Pr	**2g**	82
8	*p*-$HC(O)C_6H_4$	*i*-Pr	**2h**	64
9	*p*-$Et_2NC(O)C_6H_4$	*i*-Pr	**2i**	62
10[c]	*p*-$MeOC_6H_4$	*i*-Pr	**2j**	72
11[c]	3,4,5-$(MeO)_3C_6H_2$	*i*-Pr	**2k**	79
12	*o*-MeC_6H_4	*i*-Pr	**2l**	*d*
13	1-naphthyl	*i*-Pr	**2m**	*d*
14[c]	2-thienyl	*i*-Pr	**2n**	80
15	Ph	*c*-pentyl	**2o**	83
16	Ph	Bn	**2p**	76
17	Ph	CH_2CH_2Cl	**2q**	80
18	Ph	$CH_2CH_2CO_2Me$	**2r**	85
19	*n*-$C_{10}H_{21}$	*i*-Pr	**2s**	57
20	*n*-$C_{10}H_{21}$	*c*-hexyl	**2t**	71
21	$MeO_2C(CH_2)_3$	*n*-butyl	**2u**	63
22	Me	*n*-butyl	**2v**	55
23	Me	Ph	**2w**	*d*
24	Me	2,6-$Me_2C_6H_3$	**2x**	*d*

[a]Reaction conditions: Tf_2O (1.2 equiv), 2,6-lutidine (1.2 equiv), DCM (0.2 M), 0 °C, 30 min then $HP(O)(OEt)_2$ (3.0 equiv), rt, 3 h. [b]Isolated yield. [c]9.0 equiv of $HP(O)(OEt)_2$ was used. [d]No desired product was detected.

groups but also ester and aldehyde groups, which are sensitive and labile under Tf_2O activation, are largely compatible with the current process to furnish the desired α-amino bisphosphonates in good yields (entries 2−3 and 5−8). Significantly, the reactions took place chemoselectively even in the presence of a tertiary amide group (entry 9) to give the corresponding α-amino bisphosphonate **2i**. The bisphosphonylation of sterically hindered 2-methylbenzamide **1l** and 1-naphthamide **1m** failed to give the desired product (entries 12 and 13). Thiophene-2-carboxamide **1n** could also react chemoselectively to produce the corresponding α-amino bisphosphonate **2n** in 80% (entry 14). In addition, the *N*-substituents on the secondary aroyl amides could vary from isopropyl to other alkyl substituents and some functional groups such as halogen and ester groups are tolerated (entries 15−18).

The reaction also proceeded smoothly with alkanamides (entries 19−22). High chemoselectivity was observed when the reaction was carried out with ester functionalized amides **1u**, producing the corresponding α-amino bisphosphonate **2u** in an isolated yield of 63%. The *N*-substituents can be primary or secondary alkyl groups, and they do not have much influence on the reactivity. However, introduction of an *N*-aryl group to a secondary amide completely abolished product formation (entries 23 and 24).

Interestingly, when the reaction was performed with 4-bromo-*N*-isopropylbutanamide **1y**, the tandem bisphosphonylation and

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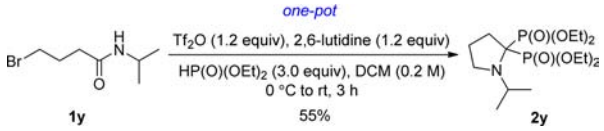
cyclization occurred to afford the cyclic α-amino bisphosphonate **2y** (Scheme 2).

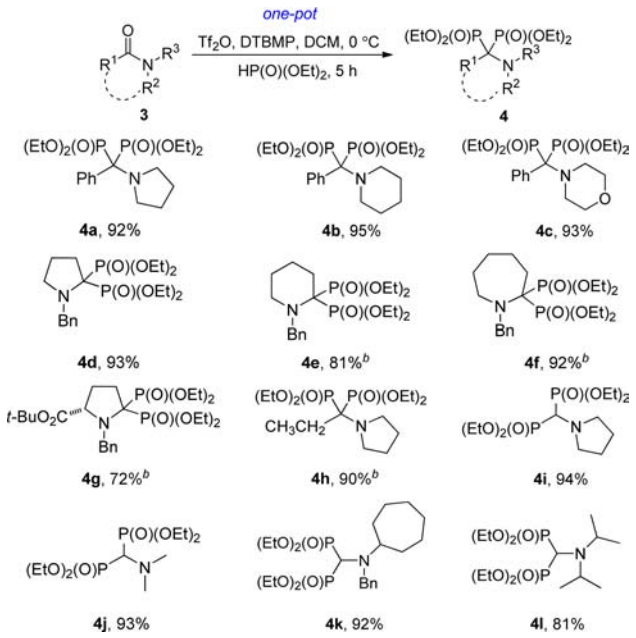
Scheme 2. Tandem Bisphosphonylation-Cyclization of *N*-Isopropyl-4-bromobutanamide



Having established an efficient method for the bisphosphonylation of secondary amides, the application of this method to tertiary amides was envisaged. Using *N*-benzoylpyrrolidine **3a** as the model substrate, the effects of base additives were screened (see the Supporting Information for details). Among them, DTBMP was shown to give the best results. In the event, treatment of tertiary amide **3a** with 1.2 equiv of Tf_2O, 4.0 equiv of DTBMP, and 3.0 equiv of diethyl phosphite, the corresponding α-amino bisphosphonate **4a** was obtained in an isolated yield of 92%. The expensive DTBMP could be recovered from the reaction mixture by column chromatography in high yield and reused in the subsequent bisphosphonylation without any influence on the outcome of the reaction.

With the optimal reaction conditions defined, the scope of the reaction was then explored by varying both the acyl group and *N*-substituents of the tertiary amides. As can be seen from Scheme 3, both aroyl and alkanoyl amides could be converted to the corresponding α-amino bisphosphonates in good to high yields. Additionally, the reactions could also be extended to lactams. Noteworthy is that *tert*-butyl (*S*)-*N*-benzylpyroglutamate **3g** also underwent chemoselective transformation to give α-amino bisphosphonate **4g** in 72% yield.

Scheme 3. Bisphosphonylation of Tertiary Amides/Lactams[a]



[a]Reaction conditions: Tf_2O (1.2 equiv), DTBMP (4.0 equiv), DCM (0.2 M), −78 °C, 30 min then $HP(O)(OEt)_2$ (3.0 equiv), rt, 5 h. Isolated yield. [b]5.0 equiv of $HP(O)(OEt)_2$ was used.

Furthermore, the bisphosphonylation reactions also proceeded smoothly with tertiary formamides. The *N*-substituents of formamides could vary from alkyl to benzyl and cyclic substituents. Even the highly sterically hindered *N*,*N*-diisopropyl fomamide[12f] reacted smoothly to give the desired α-amino bisphosphonate **4l** in an isolated yield of 81%. The bisphosphonylation of *N*-benzyl-*N*-*c*-heptylformamide gave α-amino bisphosphonate **4k** in 92% yield, which after debenzylation, hydrolysis, and neutralization would produce disodium cycloheptylaminomethylene bisphosphonate, a representative of the latest generation of antiosteoporotic drug commercialized as incadronate.[7c,28]

In summary, we report the first bisphosphonylation of amides using Tf_2O as the activation reagent. Under mild conditions, both secondary and tertiary amides could be converted into α-amino bisphosphonates in good to excellent yields. Compared with previously reported methods, this protocol is highly efficient and chemoselective and tolerant of a number of functional groups such as cyano, ester, and aldehyde groups.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Dr. Yu-Fen Zhao.

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