Preparation of β-Amido Ketones and Aldehydes via Amidoalkylation of Enamines, Enol Silyl Ethers, and Vinyl Ethers

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Novel syntheses of β-amidoalkyl ketones and aldehydes via amidoalkylations of enamines, silyl enol ethers, and vinyl ethers with *N*-(1-benzotriazol-1-ylalkyl)amides are described.

Introduction

β-Amido ketones and β-amido aldehydes are important as building blocks and intermediates in synthesis: for example, they are important precursors of 3-amino alcohols, which are common units in both natural and synthetic biologically active compounds.[1] β-Amido aldehydes are a protected form of β-amino aldehydes, key intermediates in the synthesis, e.g., of aminocyclitols.[2]

β-Amido aldehydes of type $RCH_2CH(NHCOR')CHRCHO$ can be prepared by condensation of primary amides with aliphatic aldehydes (2 equiv) in the presence of trifluoromethanesulfonic acid.[3] A diastereoselective synthesis of β-amido aldehydes has been achieved by rearrangement of *O*-vinyl-*N*,*O*-acetals.[4]

Many approaches to β-amido ketones have been reported. These can be classified according to the bond formed (Figure 1), and include preparations by formation of the A bond by acylation of β-amino ketones,[5] of the B bond by Michael addition to an α,β-unsaturated ketone,[6a−c] or of the D bond by photolysis of phthalimides.[7] However, most β-amido ketones are prepared by forming the C bond: (i) Iqbal et al. report a cobalt-catalyzed synthesis of β-amido ketones from enolates and α-acetoxyamides;[8a,b] (ii) under Lewis acid catalysis, 4-acetoxyazetidin-2-one reacts with various silyl enol ethers to give β-amido ketones in good to excellent yields;[9] (iii) in the presence of 2.1 equiv of various metallic oxidants, 2-pivaloyl-1-tributylstannyl-1,2,3,4-tetrahydroisoquinoline converts diverse silyl enol ethers into β-amido ketones.[10]

Amidoalkylations, which have been used widely in organic synthesis,[11a,b] have provided many β-amidocarbonyl compounds.[12a−e] Our previous work has demonstrated *N*-(1-benzotriazol-1-ylalkyl)amides to be versatile reagents for the amidoalkylation[13] of malonates and acetoacetates,[14] reactive aromatics,[15] cyanide anion,[16] mercaptans,[17] alcohols,[18] ammonia,[19] ethyl diphenylphosphinite anion,[20] primary and secondary amines,[21] and triallylstannanes[22a,b] giving in each case the expected products. We have previously reported one example that used an *N*-(benzotriazol-1-ylmethyl)benzamide to react with isopropenyl acetate to afford a β-amido ketone in relatively poor yield.[23] We now report applications of *N*-(benzotriazol-1-ylalkyl)amides for the synthesis of β-amido ketones and aldehydes via the amidoalkylation of enamines, enol silyl ethers, and vinyl ethers.

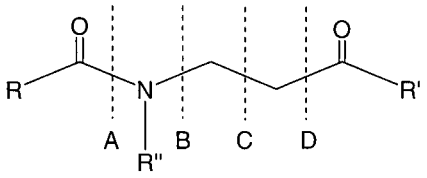

Figure 1.

Results and Discussion

The amidoalkylation reagents *N*-(1-benzotriazol-1-ylalkyl)amides **1a**−**j** and **2**−**5**, derived from primary or

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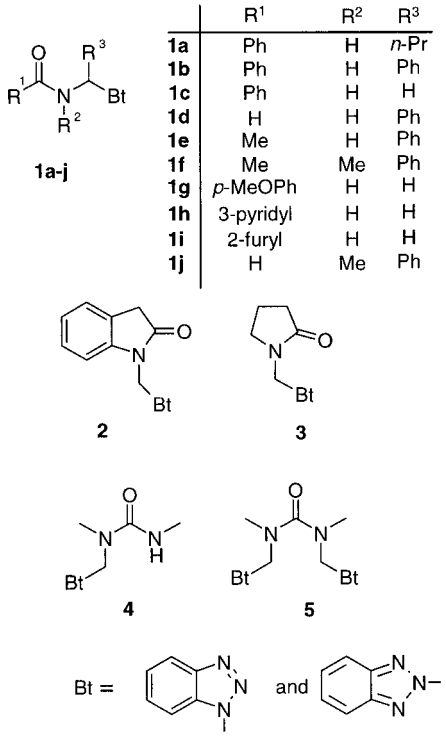
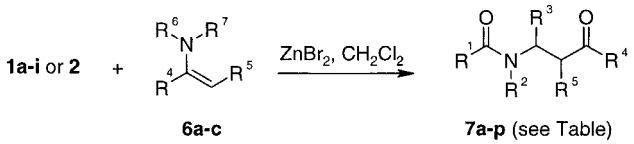
Scheme 1



	R^1	R^2	R^3
1a	Ph	H	*n*-Pr
1b	Ph	H	Ph
1c	Ph	H	H
1d	H	H	Ph
1e	Me	H	Ph
1f	Me	Me	Ph
1g	*p*-MeOPh	H	H
1h	3-pyridyl	H	H
1i	2-furyl	H	H
1j	H	Me	Ph

Scheme 2



6a: R^4, R^5 = -$(CH_2)_4$-, R^6, R^7 = -$(CH_2)_2O(CH_2)_2$-
6b: R^4 = CH_3CH_2, R^5 = CH_3, R^6,R^7 = -$(CH_2)_2O(CH_2)_2$-
6c: R^4 = Ph, R^5 = CH_3, R^6 = R^7 = CH_3CH_2

secondary amides and aliphatic or aromatic aldehydes, were prepared following literature procedures (Scheme 1).[23,24a,b] Among them, **1g**,**i** are new compounds. Their structures were confirmed by ^{1}H and ^{13}C NMR spectra and by elemental analyses.

It was previously reported that benzotriazole adducts are readily assisted by Lewis acids to form the benzotriazole anion and the corresponding carbocations which then react with nucleophiles.[15] Accordingly, compounds **1a**−**i** or **2** reacted smoothly with enamines **6** on refluxing in CH_2Cl_2 in the presence of zinc bromide (Scheme 2). Enamines **6** from cyclic **6a**, acyclic **6b** and aryl ketone **6c** could all be used as nucleophiles. The desired products **7a**−**p** were obtained in 50−90% yields (Table 1). Structures **7a**−**p** were confirmed by their ^{1}H and ^{13}C NMR spectra and by elemental analyses or high-resolution MS data. The amide and ketonic carbonyl groups showed the expected chemical shifts in the ^{13}C NMR spectra.

Following these successful results, we extended our nucleophiles to enol silyl ethers under similar reaction conditions. Using compound **1f** as starting material to react with 1-(trimethylsiloxy)cyclopent-1-ene (**8a**) under the same reaction conditions, we obtained product **7q** in 50% yield. Compound **1e** also was used as starting material to react with 1-(trimethylsiloxy)cyclohex-1-ene (**8b**) to give product **7e**, but the yield was slightly lower compared with the yield using enamine **6a** as nucleophile (see Table 1) (Scheme 3).

Ethyl vinyl ether (**9**) reacted as a nucleophile with compounds **1a** or **1e** in this reaction sequence to afford β-amido aldehydes **10a** and **10b**, respectively, in reasonable yields. (Scheme 4).

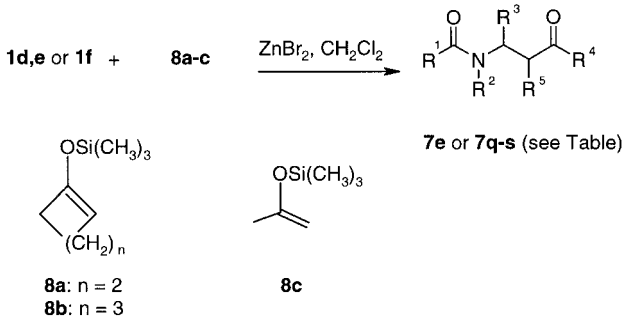
As expected, two diastereoisomers were found for product **7** when $R^3 \neq$ H: their GC/MS spectra clearly showed two peaks possessing the same molecular weight. Only one peak was found for **7f** in the GC/MS spectrum, which could indicate only one isomer was formed or that the two diastereoisomers overlapped in the GC/MS spectrum. Although the reaction appears to proceed smoothly with a variety of starting materials, derived both from primary and from secondary amides, some failures were noted. Thus, when compounds **1j** or **3**−**5** were treated with enamines **6** in the presence of zinc bromide, complex mixtures and no desired products were obtained.

Table 1. The Preparation of β-Amido Ketones 7a−s and Aldehydes 10a,b

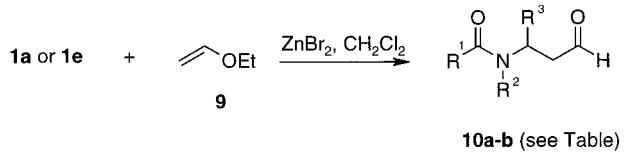
sm[a]	nucleophile	product	R^1	R^2	R^3	R^4	R^5	yield (%)
1a	**6a**	**7a**	Ph	H	*n*-Pr	−$(CH_2)_4$−		50
1b	**6a**	**7b**	Ph	H	Ph	−$(CH_2)_4$−		62
1c	**6a**	**7c**	Ph	H	H	−$(CH_2)_4$−		90
1d	**6a**	**7d**	H	H	Ph	−$(CH_2)_4$−		70
1e	**6a** (**8b**)	**7e**	Me	H	Ph	−$(CH_2)_4$−		75 (52)
1f	**6a**	**7f**	Me	Me	Ph	−$(CH_2)_4$−		70
1g	**6a**	**7g**	*p*-MeOPh	H	H	−$(CH_2)_4$−		61
1h	**6a**	**7h**	3-pyridyl	H	H	−$(CH_2)_4$−		55
1i	**6a**	**7i**	2-furyl	H	H	−$(CH_2)_4$−		30
2	**6a**	**7j**	−$PhCH_2$−		H	−$(CH_2)_4$−		60
1a	**6b**	**7k**	Ph	H	*n*-Pr	Et	Me	50
1b	**6b**	**7l**	Ph	H	Ph	Et	Me	72
1c	**6b**	**7m**	Ph	H	H	Et	Me	85
1g	**6b**	**7n**	*p*-MeOPh	H	H	Et	Me	60
1c	**6c**	**7o**	Ph	H	H	Ph	Me	66
1e	**6c**	**7p**	Me	H	Ph	Ph	Me	34
1f	**8a**	**7q**	Me	Me	Ph	−$(CH_2)_3$−		50
1d	**8c**	**7r**	H	H	Ph	Me	H	65
1e	**8c**	**7s**	Me	H	Ph	Me	H	40
1a	**9**	**10a**	Ph	H	*n*-Pr	H	H	40
1e	**9**	**10b**	Me	H	Ph	H	H	40

[a] sm = starting material.

Scheme 3



Scheme 4



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Conclusions

In conclusion, the versatile amidoalkylation reagents *N*-(1-benzotriazol-1-ylalkyl)amides react with enamines, enol silyl ethers, and vinyl ethers to afford *β*-amido ketones and aldehydes in good yields. Unlike many amidoalkylation reagents, which are difficult to prepare, unstable, and/or need severe reaction conditions, our stable and easily prepared starting materials are available from a wide range of aldehydes and amides and react in relatively mild conditions with good yields. The byproduct benzotriazole formed during the reaction was easily removed by washing the reaction mixture with dilute alkali, making the whole procedure very simple.

Experimental Section

General Comments. Melting points were determined on a hot stage apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ with TMS and $CDCl_3$, respectively, as the internal reference. Column chromatography was carried out on MCB silica gel (230−400 mesh). Methylene chloride (CH_2Cl_2) was distilled from phosphorus pentoxide. Compounds **1a**−**j** and **2**−**5** were prepared by literature methods.[23,24a,b]

General Procedure for the Synthesis of *β*-Amido Ketones and Aldehydes 7a−s and 10a,b. Zinc bromide (1.1 g, 5 mmol) was added to a solution of **1a**−**i** or **2** (5 mmol) in methylene chloride (15 mL), and the mixture was refluxed with stirring under argon during 2 h. Enamine **6a**−**c**, enol silyl ether **8a**−**c**, or ethyl vinyl ether (**9**) (10 mmol) was added in one portion, and the mixture was refluxed during 20 h. The reaction mixture was cooled and subsequently washed with saturated aqueous solutions of ammonium chloride (15 mL), sodium carbonate (15 mL), and sodium chloride. The organic phase was dried over anhydrous sodium sulfate. After removal of solvent, the residue was subjected to column chromatography to produce **7a**−**s** and **10a,b**.

Supporting Information Available: Characterization data for compounds **1g**,**i**, **7a**−**s**, and **10a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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