Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Aza-[1,2]-Wittig rearrangements of *N*-benzyl glycine methyl esters. A new approach to the synthesis of *N*-aryl phenylalanine derivatives

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ARTICLE INFO

Article history:
Received 3 December 2014
Revised 5 January 2015
Accepted 6 January 2015
Available online xxxx

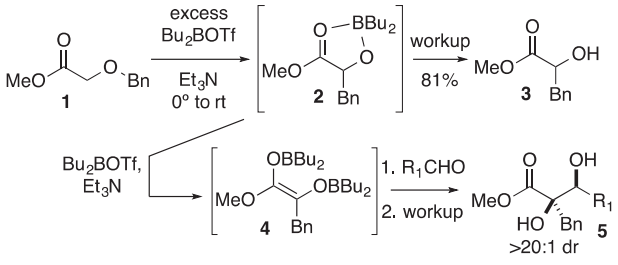
Keywords:
Boron
Wittig rearrangement
Enolate
Heterocycle

ABSTRACT

Treatment of *N*-(arylmethyl)-*N*-aryl glycine methyl ester derivatives with Bu_2BOTf and $^iPr_2NEt$ effects an aza-[1,2]-Wittig rearrangement that provides *N*-aryl phenylalanine methyl esters in good yields. Analogous substrates bearing *N*-carbonyl groups are converted to 1,4,2-oxazaborole derivatives under similar conditions.

In recent years, our group has reported the successful pairing of enolate [1,2]-Wittig rearrangements with aldol reactions, which afford substituted α,β-dihydroxy esters in good yields and high diastereoselectivity (Scheme 1).[1] Asymmetric variants of these reactions using 2-phenylcyclohexanol as a chiral auxiliary provide the diol products in up to 95% ee[2] and analogous tandem Wittig rearrangement/Mannich reactions provide access to the corresponding amino alcohols.[3] Given the synthetic utility of these reactions, we sought to further expand the scope of enolate Wittig rearrangements and we hypothesized that a tertiary amine could undergo the corresponding enolate aza-[1,2]-Wittig rearrangement under similar conditions. The rearrangement itself would yield substituted phenylalanine derivatives and if coupled with a subsequent aldol reaction this sequence could produce biologically interesting β-hydroxy-α-amino acid derivatives.

However, although [1,2]- and [2,3]-Wittig rearrangements of α-alkoxy carbanions have been well documented over the past 70 years,[4,5] the corresponding aza-Wittig rearrangements have been less explored.[6] Moreover, although aza-[2,3]-Wittig rearrangements are not uncommon,[6] aza-[1,2]-Wittig rearrangements have rarely been observed.[7] In most instances these have been reported as side reactions in aza-[2,3]-Wittig rearrangements;[7b,c] the migration of benzyl groups in synthetically useful yields (>60%) has only been reported on a single occasion.[8] Herein we describe the first



Scheme 1. Tandem Wittig rearrangement/aldol reaction.

examples of aza-[1,2]-Wittig rearrangements of *O*-methyl-*N*-benzyl glycine derivatives (via their corresponding boron enolates), which afford substituted phenylalanine methyl ester products.

Given the paucity of examples of successful aza-[1,2]-Wittig rearrangements, our initial studies were focused solely on the rearrangement (rather than the tandem rearrangement/aldol sequence). We first elected to examine the rearrangement of *N*-benzyl-*N*-boc-glycine methyl ester, as prior studies on aza-[2,3]-Wittig rearrangements have shown that electron-withdrawing *N*-substituents improved reactivity. However, as illustrated in Eq. 1, when **6a** was subjected to the reaction conditions we have previously employed in [1,2]-Wittig rearrangements of **1**, no rearrangement occurred. Instead, 1,4,2-oxazaborole derivative **8a** was formed.[9]

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http://dx.doi.org/10.1016/j.tetlet.2015.01.037
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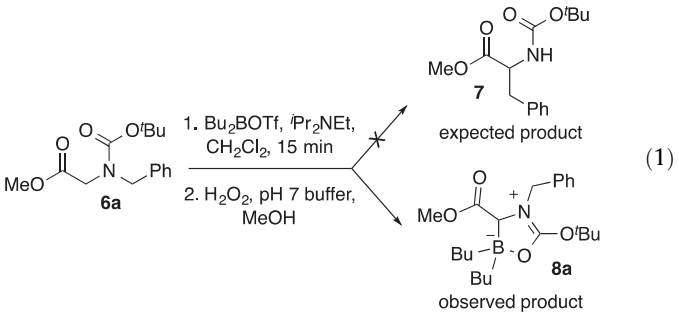


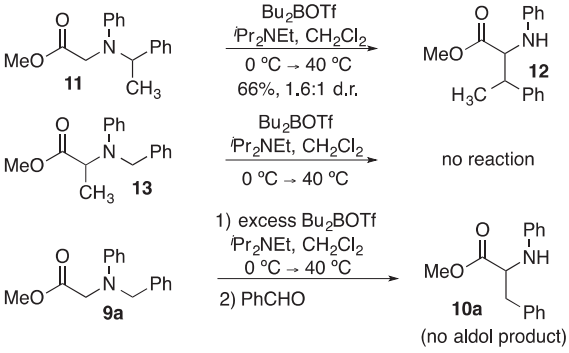
(1)

A brief survey of the reactivity of other glycine methyl ester derivatives bearing *N*-pivaloyl or *N*-acetyl groups gave similar results (Table 1), as did the use of 9-BBNOTf in place of Bu_2BOTf (Table 1, entry 4). The structure of **8d** was confirmed via X-ray crystallography, which clearly revealed the presence of a boron–oxygen bond. Unfortunately, efforts to force these compounds to undergo the desired rearrangement by increasing temperature and reaction time were unsuccessful. Moreover these compounds were also unreactive towards acids, bases and oxidants such as alkaline hydrogen peroxide.

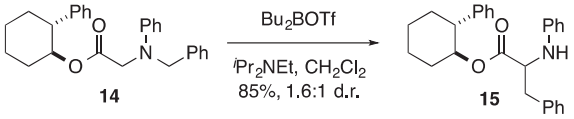
Given the lack of rearrangement of substrates **6**, we elected to modify the glycine *N*-substituent in hopes that changing the steric or electronic properties of the nitrogen atom would facilitate the desired transformation. Efforts to effect rearrangements of *N*-benzyl glycine methyl esters bearing *N*-alkyl, *N*-phosphoryl and *N*-tosyl groups were also unsuccessful. However, we were gratified to find that a substrate bearing an *N*-phenyl group did undergo [1,2] rearrangement. Further experimentation revealed that by extending reaction time and increasing temperature, the desired amine could be isolated in 65% yield (Table 2, entry 1).[10]

With the optimized reaction conditions in hand, additional substrates were examined in order to determine the scope of the transformation. The requisite substrates were prepared in three steps from substituted anilines and benzaldehyde derivatives via imine formation, reduction and *N*-alkylation with α-bromo methyl acetate. As shown in Table 2, substitution on both the *N*-aryl group and benzyl group was tolerated. Additionally, substrates bearing heteroaromatic groups underwent the [1,2] rearrangement in good yields (Table 2, entries 7–9).[11] However, the rearrangement of **9d**, which contains an *N*-*p*-trifluoromethylphenyl group proceeded in poor yield due to a combination of slow reaction rate and product decomposition as a result of the extended reaction time.

To further explore reaction scope and elements of stereocontrol we prepared substrates **13** and **11**, which bear a methyl group adjacent to the ester or at the benzylic position, respectively. Substitution at the benzylic position was tolerated as the rearrangement of **11**–**12** proceeded in good yield. However, the diastereoselectivity of this reaction was low (Eq. 2). Efforts to improve the diastereoselectivity through use of 9-BBN-OTF in place of Bu_2BOTf were unsuccessful; a similar mixture of diastereomers was obtained under these conditions. Substrate **13** proved to be unreactive under our standard conditions (Eq. 3), which may be due to difficulty in generating the requisite boron enolate from the more sterically encumbered substrate. This hypothesis is consistent with our observation that treatment of **9a** with excess Bu_2BOTf/$^iPr_2NEt$ followed by addition of an aldehyde to the reaction mixture (Eq. 4) did not afford an aldol product as was previously observed in reactions of **1** (Scheme 1).

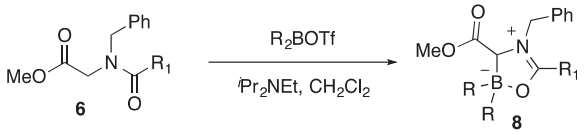


Finally, we have conducted preliminary studies on asymmetric aza-[1,2]-Wittig rearrangements. We previously have illustrated that 2-phenylcyclohexanol provides good results in asymmetric Wittig rearrangement/aldol reactions of glycolate esters. As such, substrate **14** bearing this chiral auxiliary was synthesized and subjected to the standard reaction conditions. Unfortunately, although the yield of this transformation was good, the diastereoselectivity was modest (Eq. 5). Nonetheless, this experiment indicates the possibility of achieving asymmetric induction, although further optimization is clearly needed.



In conclusion, we have developed a new aza-[1,2]-Wittig rearrangement of *N*-aryl-*N*-benzyl glycine methyl esters. These transformations constitute rare examples of benzyl group migration in aza-Wittig rearrangements and provide a concise four-step

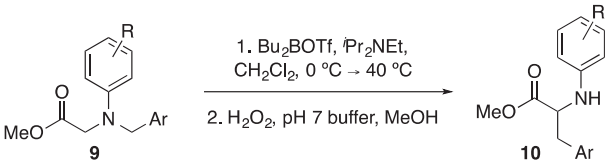
Table 1
Formation of 1,4,2-Oxazaborole derivatives[a]



Entry	R_1	R_2BOTf	Yield[b]
1	O^{t}Bu (**6a**)	Bu_2BOTf	40% (**8a**)
2	^{t}Bu (**6b**)	Bu_2BOTf	87% (**8b**)
3	CH_3 (**6c**)	Bu_2BOTf	48% (**8c**)
4	^{t}Bu (**6b**)	9-BBNOTf	90% (**8d**)

[a] Conditions: (i) 1.0 equiv of **6**, 3.2 equiv of R_2BOTf, 4.0 equiv of $^iPr_2NEt$, CH_2Cl_2, 0.25 M, 15 min, 0 °C to rt. (ii) H_2O_2, pH 7 buffer, MeOH, 1 h, 0 °C to rt.
[b] Isolated yield, average of two or more experiments.

Table 2
Aza-[1,2]-Wittig rearrangement[a]



Entry	R	Ar	Yield[b]
1	H (**9a**)	Ph	64% (**10a**)
2	*p*-Br (**9b**)	Ph	54% (**10b**)
3	*p*-OMe (**9c**)	Ph	65% (**10c**)
4	*p*-CF_3 (**9d**)	Ph	24% (**10d**)
5	H (**9e**)	*p*-BrPh	67% (**10e**)
6	H (**9f**)	*o*-BrPh	53% (**10f**)
7	H (**9g**)	2-Furyl	68% (**10g**)
8	H (**9h**)	2-Thiophenyl	66% (**10h**)
9	H (**9i**)	*N*-Ts-2-pyrrolyl	54% (**10i**)

[a] Conditions: (i) 1.0 equiv of **9**, 3.2 equiv of Bu_2BOTf, 4.0 equiv of $^iPr_2NEt$, CH_2Cl_2, 0.25 M, 0–40 °C. (ii) H_2O_2, pH 7 buffer, MeOH.
[b] Isolated yield, average of two or more experiments.

approach to the construction of substituted *N*-arylphenylalanine derivatives. In contrast to prior examples of aza-[1,2-]-Wittig rearrangements, these reactions do not require the use of the strong reducing agents or strong bases and proceed under relatively mild conditions. Future studies will be directed towards improvements and new synthetic applications of this method.

Acknowledgment

The authors thank the NSF (CHE 1111218) for financial support of this work.

Supplementary data

Supplementary data associated with this article (experimental procedures, characterization data and ^{1}H and ^{13}C NMR spectra for all new compounds, and crystallographic structural data for compound **8d**), in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.037.

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10. When a single equivalent of dibutylboron triflate was used the rearrangement reaction proceeded to 74% conversion (26% unreacted starting material) as judged by ^{1}H NMR analysis. This experiment suggests that the reaction proceeds through a boron enolate that contains a single equivalent of an organoboron species, rather than an intermediate that bears two dialkylboron units (one bound to oxygen and one bound to nitrogen). We have elected to classify this as a Wittig-type rearrangement as it does not appear that an ammonium ion resulting from protonation of the amino group (as in a Stevens-type rearrangement) is required. However, there likely is a Lewis acid/base chelate interaction between the O-BR_2 group and the amino group, so in this case there may not be a clean division between classification as a Wittig rearrangement versus a Stevens rearrangement.
11. We were unable to examine the reactivity of the corresponding NH or *N*-alkylpyrrole derivatives as these compounds were unstable and rapidly decomposed upon isolation.