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Selective \([3 + 2]\) Huisgen Cycloaddition. Synthesis of Trans-Disubstituted Triazolodiazepines from Aza-Baylis–Hillman Adducts

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The 1,3-dipolar cycloaddition of linear azido alkyne derived from protected β-amino esters proceeds via diastereomeric differentiation to provide trans-disubstituted triazolodiazepines in good yields.

Introduction

The aza-Baylis–Hillman reaction\(^1\)\(^–\)\(^3\) is a powerful method for the preparation of densely functionalized small molecules which has attracted the attention of organic chemists. We have recently reported a three-component aza-Baylis–Hillman reaction involving a sulfonamide, an aldehyde, and an acrylate for the preparation of highly functionalized 2-(trimethylsilyl)-ethanesulfonyl (or SES)-protected\(^4\)\(^,\)\(^5\) β,β-unsubstituted β-amino esters which can be used in further transformations.\(^6\)\(^,\)\(^7\)

In an ongoing project dealing with the use of these α,β-unsubstituted β-amino esters as building blocks for the synthesis of various heterocyclic structures, we reported the preparation of pyrroles,\(^6\) pyrrolines,\(^8\) pyrrolidines,\(^8\) and benzazepines.\(^9\)\(^,\)\(^10\) We describe herein the synthesis of triazolodiazepines from these β-amino esters involving an intramolecular \([3 + 2]\) Huisgen cycloaddition\(^1\) as a key step.

Triazoles are important molecules due to their unique chemical properties. They possess a wide range of applications in organic, organometallic, medicinal, and material chemistry. Although no product containing the 1,2,3-triazole moiety has been found in nature, this scaffold constitutes an interesting class of pharmacophores since it shows a remarkable resistance to metabolic transformations such as oxidation, reduction, basic or acidic hydrolysis. The 1,2,3-triazole unit is present in various compounds exhibiting interesting antibacterial,\(^12\) anti-HIV,\(^13\) and antiallergic\(^14\) activities. As examples, cefmatilen\(^15\) exhibit antibacterial activities and tazobactam\(^16\) is a β-lactamase inhibitor.
tor. Triazolobenzodiazepines$^{17}$ have high affinity for the benzodiazepine receptors (Figure 1).

**Results and Discussion**

As described in the retrosynthetic scheme (Scheme 1), the triazolobenzodiazepines can be obtained by an intramolecular 1,3-dipolar cycloaddition of a linear precursor possessing an azide function and a triple bond. This precursor can be obtained by sequential Michael addition of HN$_3$ on the azido function and then the propargyl moiety. Introduction of the azido group on the $\alpha$-$\beta$-unsaturated $\beta$-amino esters and alkylation with propargyl bromide.

Starting from the SES-protected amino ester, we had the choice to perform first either the Michael addition of HN$_3$ or the alkylation reaction. A substituted SES-sulfonamide, which would be obtained after alkylation by propargyl bromide, owns a leaving group character similar to that of acetate$^{18}$ and is not suitable for a 1,4-addition (it would provide mainly an elimina-

![Reaction Scheme](image)

**SCHEME 1. Retrosynthetic Analysis**

![Chemical Structures](image)

**FIGURE 1.** Biologically active 1,2,3-triazole containing compounds.

<table>
<thead>
<tr>
<th>TABLE 1. Yields and Stereoselectivities of Isolated Compounds 2, 3, 5, and 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>substituent</td>
</tr>
<tr>
<td>a</td>
</tr>
<tr>
<td>b</td>
</tr>
<tr>
<td>c</td>
</tr>
<tr>
<td>d</td>
</tr>
<tr>
<td>e</td>
</tr>
<tr>
<td>f</td>
</tr>
</tbody>
</table>

$^*$Determined by $^1$H NMR. $^b$Yield in two steps: alkylation and 1,3-dipolar cycloaddition.

Consequently, we have chosen to introduce first the azide function and then the propargyl moiety. Introduction of the azido group on the $\alpha$-$\beta$-unsaturated $\beta$-amino ester was realized according to the procedure described by Miller$^{19}$ to avoid the use of a toxic and explosive HN$_3$ solution. This procedure is well-adapted for the 1,4-addition of N$_3$ to unsaturated ketones, but an intramolecular amine-mediated activation is necessary in the case of $\alpha$-$\beta$-unsaturated esters. Furthermore, to our knowledge no example of the azide addition on a 1,1-disubstituted acrylate has been described. Thus, treatment of the $\alpha$-$\beta$-unsaturated $\beta$-amino esters 1a with an excess of TMSN$_3$ in the presence of acetic acid and triethylamine at 40 °C for 24 h allowed a complete conversion and the azido-$\beta$-amino esters 2 were obtained in high yields as a mixture of anti and syn diastereoisomers, which could not be separated by column chromatography. X-ray analysis of the cyclic compound 5a obtained after the cycloaddition step confirmed that the anti isomer was the major one (Scheme 2, Table 1).

The stereochimical outcome of this reaction was governed by the reprotonation of the enolate intermediate formed after the 1,4-addition (Scheme 2). According to the studies of Perlmuter et al. on 1,4-addition of amines to 2-hydroxyalkylpropenoates,$^{20}$ the two possible conformers A and B of the enolate resulting from the addition of HN$_3$ are depicted in Scheme 3. Since the bulky SES-NH group does not accommodate easily an interaction with the azidomethylene moiety, conformer A is preferred, leading to the formation of the azidomethylene product. Consequently, we have chosen to introduce first the azide function and then the propargyl moiety. Introduction of the azido group on the $\alpha$-$\beta$-unsaturated $\beta$-amino ester was realized according to the procedure described by Miller$^{19}$ to avoid the use of a toxic and explosive HN$_3$ solution. This procedure is well-adapted for the 1,4-addition of N$_3$ to unsaturated ketones, but an intramolecular amine-mediated activation is necessary in the case of $\alpha$-$\beta$-unsaturated esters. Furthermore, to our knowledge no example of the azide addition on a 1,1-disubstituted acrylate has been described. Thus, treatment of the $\alpha$-$\beta$-unsaturated $\beta$-amino esters 1a with an excess of TMSN$_3$ in the presence of acetic acid and triethylamine at 40 °C for 24 h allowed a complete conversion and the azido-$\beta$-amino esters 2 were obtained in high yields as a mixture of anti and syn diastereoisomers, which could not be separated by column chromatography. X-ray analysis of the cyclic compound 5a obtained after the cycloaddition step confirmed that the anti isomer was the major one (Scheme 2, Table 1).

The next step was the alkylation of the azido-$\beta$-amino ester 2a by propargyl bromide (Table 2). Under classical alkylation conditions using K$_2$CO$_3$ in DMF for 6 h (entry 1),$^b$ we observed

![Reaction Scheme](image)

**SCHEME 2. Conjugate Addition of HN$_3$**


(18) Declerck, V.; Martine, J.; Lamaty, F. Unpublished results.


the formation of compound 4a resulting from elimination of HN3. The use of a crown ether to accelerate the alkylation decreased the elimination (entry 2). Changing K2CO3 for the more basic Cs2CO3 decreased the elimination to 9% and the reaction time to 30 min (entry 3). Addition of NaI slowed down the reaction, but the elimination was decreased (entry 4). Finally, heating the linear precursor 3a in toluene for 12 h allowed the preparation of the bicyclic triazole 5a, which was easily separated from the elimination compound 4a by silica gel chromatography and obtained in a 45% yield. The prolonged reaction time resulted in the degradation of the product. We speculated on the use of the microwave heating to reduce reaction time and probably diminish the degradation. Heating compound 3a in toluene at 100 °C under microwave irradiation for 30 min did not yield a complete conversion but showed that the linear precursor anti-3a cyclized more rapidly than the syn isomer. By carefully monitoring by 1H NMR the reaction under classical heating conditions, we found that after 4 h in toluene at 80 °C, only the anti diastereoisomer had fully cyclized while the syn one did not react. The reaction gave a mixture of bicyclic triazole trans-5a, linear precursor syn-3a, and elimination compound 4a (present in the starting material). The triazolodiazepine trans-5a was obtained in 77% yield after purification by chromatography on silica gel (Scheme 4). An NOE NMR experiment performed on 5a did not show any effect between the phenyl group protons and those of the ester group, which implies a trans relationship between these substituents. Furthermore, X-ray analysis of 5a showed that the two substituents are in a trans configuration, thus confirming the formation of the anti diastereoisomer during the addition of HN3. Similar results were obtained with the other substrates which allowed the preparation of bicyclic triazoles in good yields with a selectivity higher than 98% for the trans isomer (Table 1).

The difference of reactivity between anti-3a and syn-3a could be explained by unfavorable interactions between substituents. Newman projections showed that the conformer presenting weaker interactions possess the alkyne and azido substituents in close proximity in the diastereoisomer syn-3a (Scheme 5). Diastereomeric differentiation of the two linear diastereomers provided only trans-5a as a cyclic product.

The last step consisted of the cleavage of the SES group to obtain the free amine. The use of CsF at 80 °C in DMF or n-Bu4NF,4 usually employed to deprotect the SES group, yielded only degradation products. We turned our attention to anhydrous HF, a nonbasic fluoride source which has proved to be a very efficient reagent for the deprotection of the SES group in other cyclic β-amino esters.8,10 Deprotection of the SES group by anhydrous HF followed by neutralization of the hydrofluoride

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**Table 2.** Optimization of Alkylation of 2a with Propargyl Bromide

<table>
<thead>
<tr>
<th>entry</th>
<th>RBr (equiv)</th>
<th>base (equiv)</th>
<th>additive (equiv)</th>
<th>time (h)</th>
<th>2a</th>
<th>3a</th>
<th>4a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>K2CO3 (10)</td>
<td></td>
<td>6</td>
<td>0</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>K2CO3 (10)</td>
<td>18-C-6 (1)</td>
<td>4</td>
<td>0</td>
<td>82</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>Cs2CO3 (10)</td>
<td>0.5</td>
<td>1</td>
<td>0</td>
<td>91</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>Cs2CO3 (10)</td>
<td>0.5 NaI (8)</td>
<td>0.5</td>
<td>13</td>
<td>83</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>Cs2CO3 (10)</td>
<td>NaI (16)</td>
<td>1</td>
<td>0</td>
<td>96</td>
<td>4</td>
</tr>
</tbody>
</table>

* Determined by 1H NMR.

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**Scheme 3.** Transition Structure Analysis of the Addition of HN3 on β-Amno Esters 1

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**Scheme 4.** 1,3-Dipolar Cycloaddition of Compound 3a

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Scheme 5. Conformational Analysis of Compound 3a

Experimental Section

General Procedure for HN\textsubscript{3} Addition on β-Amino Esters 1. To a solution of β-amino ester 2 (0.4 mmol, 1 equiv) in toluene were added azidotrimethylsilane (1.06 mL, 8 mmol, 20 equiv), acetic acid (137 μL, 2.44 mmol, 6 equiv), and triethylamine (45 μL, 0.32 mmol, 0.8 equiv). The solution was heated for 24 h at 40°C, and the solvent was evaporated. Silica gel chromatography (Et\textsubscript{2}O/cyclohexane) yielded the corresponding azido-β-amino ester 3a as a mixture of anti and syn diastereomers.

Methyl 6-Phenyl-5,6,7,8-tetrahydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepine-7-carboxylate (trans-5a). Selectivity of the intermediate 2a. A solution of crude azido-β-amino ester 3a in 10 mL of toluene was heated at 80°C for 4 h. The solvent was evaporated. Silica gel chromatography (AcOEt/CH\textsubscript{2}Cl\textsubscript{2}) yielded the trans-5a.

General Procedure for Alkylation of Azido-β-amino Esters 2 and 1,3-Dipolar Cycloaddition of the Intermediate 3. A mixture of azido-β-amino ester 2 (0.35 mmol, 1 equiv), Cs\textsubscript{2}CO\textsubscript{3} (1.14 g, 3.5 mmol, 10 equiv), and NaI (839 mg, 5.6 mmol, 5.6 equiv) in 9.8 mL of DMF was added propargyl bromide (210 μL, 2.8 mmol, 8 equiv). The mixture was stirred at room temperature for 1 h and then filtered through Celite. The residue was diluted in AcOEt, washed successively with water and brine, dried over MgSO\textsubscript{4}, and evaporated to give the alkylated azido-β-amino ester 3 as a mixture of anti and syn diastereoisomers and enyme 4.

To a solution of methyl 6-phenyl-5,6,7,8-tetrahydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepine-7-carboxylate (trans-5a), selective Huisgen cycloaddition was reported the first example of selective Huisgen cycloaddition, with HF.

In conclusion, we have described an efficient synthesis of new bicyclic triazoles by sequential azidation/alkylation/1,3-dipolar cycloaddition/deprotection starting from SES-protected azal-Baylis–Hillman β-amino esters. To our knowledge, we have reported the first example of selective Huisgen cycloaddition, starting from a mixture of diastereoisomers. The bicyclic triazoles are obtained in their trans form in good yields and very high diastereomeric ratios.

Acknowledgment. We thank the MENRT and the CNRS for financial support.