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The *syn*-selective conjugate addition of amines to enoates derived from D-mannitol

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ABSTRACT

The *syn*-selective conjugate addition of neat amines to enoates *Z*-**1** and *E*-**1**, prepared from D-(+)-mannitol, is reported. The reactions with benzyl and allylamine **2a**,**d** at −50 °C or **2e** at −25 °C in the absence of a solvent led to *syn*-adducts in moderate to good chemical yields and good *syn*/*anti* ratios, and were accelerated in the presence of DBU. Enoate *Z*-**1** was more reactive than *E*-**1**, leading to products with better *syn*-selectivity. The *syn*-selectivity slightly decreased for reactions at rt. The reaction of both enoates with primary amines **2c**,**d** (Ph changed by 2- and 3-pyridyl) only occurred at rt, leading to adducts in good chemical yields and with moderate to good *syn*-selectivities. Secondary acyclic amine **2f** showed very low reactivity (rt, DBU, several hours) and led to the adduct in moderate chemical yields and with low *syn*-stereoselectivity while higher reactivity and moderated yields and *syn*-selectivities were observed for cyclic secondary amines **2g**–**i**.

1. Introduction

The conjugate addition is one of the most useful reactions in organic synthesis, and allows the formation of carbon–carbon and carbon–heteroatom bonds.[1] The reaction of ammonia with crotonic acid, reported by Fisher and Scheibler in 1911,[1,2] was the first published aza-conjugate addition and nowadays a great set of nitrogen-centered nucleophiles and acceptors are available to accomplish these reactions, thus increasing its synthetic importance.[1] Acrylic acid, acrolein and acrylonitrile, produced industrially in large scale, are toxic reagents and alkylate DNA in vitro at the amino group in guanosine.[3] This aza-conjugate addition is probably the origin of the carcinogenicity as well as the mutagenicity presented by these compounds.[4] However, alkylation of the biomolecules through aza-conjugate addition is also the mechanism of action of some anticancer drugs.[5]

Several Michael acceptors can be easily prepared from the chiral pool and undergo stereoselective conjugate additions with a variety of nucleophiles, to prepare enantiomerically enriched products.[6] Enoates *E*-**1** and *Z*-**1**, easily obtained from D-mannitol[7] (Fig. 1), are among the most studied chiral acceptors.[8] The *syn*-selective conjugate addition of neat **2a** to enoates *E*-**1** and *Z*-**1** was first reported by Yamada et al. (Fig. 1).[9] The resulting adduct *syn*-**3a** was used to prepare enantiomerically enriched β-lactam **4**, an intermediate for the synthesis of antibiotics.[9] This adduct was also used by us to prepare substituted pyrrolidines **5** and D-aminoacids **6** with an affinity for the allosteric site of the NMDA sub-type of glutamate receptor.[10]

Popov et al. reported that in low polar media, kinetic data suggest the participation of a second molecule of amine in the

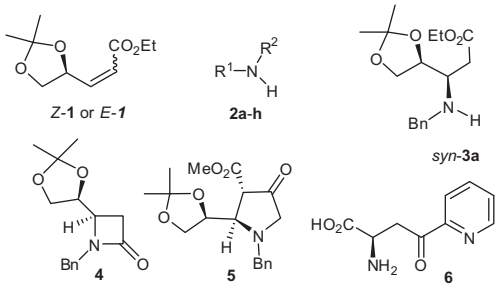

Figure 1. Adduct *syn*-**3b** as precursor of bioactive compounds.

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determining step.[11] This proposal is in agreement with results reported on the DBU and DABCO-catalyzed aza-conjugate addition of to activated olefins.[12]

As part of a program aimed at the synthesis of D-amino acids with an affinity for glutamate receptors, we herein report our results on the *syn*-selective conjugate addition of neat primary and secondary amines **2a–i** to enoates *E*-**1** and *Z*-**1**, in the absence of a solvent and in the presence or absence of DBU.

2. Results and discussion

Although aza-conjugate additions are sometimes called thermal additions and generally require the use of rt or heating to occur,[1d] in the absence of a solvent, the reaction of primary amines **2a–e** with enoates *E*-**1** and *Z*-**1** took place smoothly at low temperature.[9] After 8 h of reaction of *Z*-**1** with **2a** at −50 °C in the absence of a solvent, *syn*-**3a** was formed in 73% yield (Table 1, entry 1). In the presence of 20 mol % of DBU, the reaction was accelerated and the same yield was obtained in only 4 h (entry 2). A *syn*-**3a**:*anti*-**3a** ratio of approximately 90:10 was observed in both reactions.

Table 1
Product distribution for the reactions of Scheme 1, involving primary amines **2a–e**

Entry	1	2	*T* (°C)	*t* (h)	**3** (%)[a]	**3** (*syn*:*anti*)[c]
1	*Z*	**a**	−50	8	73	**a** (88:12)
2[b]	*Z*	**a**	−50	4	77	**a** (91:9)
3	*E*	**a**	−50	12	75	**a** (82:18)
4[b]	*E*	**a**	−50	8	74	**a** (83:17)
5[b]	*Z*	**a**	rt	1	94	**a** (85:15)
6[b]	*E*	**a**	rt	2.5	99	**a** (79:21)
7[b]	*Z*	**b**	rt	0.3	93	**b** (83:17)
8[b]	*E*	**b**	rt	0.5	97	**b** (73:27)
9[b]	*Z*	**c**	rt	0.3	90	**d** (78:22)
10[b]	*E*	**c**	rt	30	83	**d** (74:26)
11	*Z*	**d**	−50	8	85	**d** (90:10)
12[b]	*Z*	**d**	−50	2	85	**d** (91:9)
13	*E*	**d**	−50	8	80	**d** (85:15)
14[b]	*E*	**d**	−50	4	89	**d** (85:15)
15	*Z*	**d**	rt	12	95	**d** (80:20)
16[b]	*Z*	**d**	rt	12	96	**d** (84:16)
17	*E*	**d**	rt	12	76	**d** (74:26)
18[b]	*E*	**d**	rt	12	75	**d** (80:20)
19	*Z*	**e**	−25	2	78	**e** (79:21)
20[b]	*Z*	**e**	−25	1	83	**e** (85:15)
21	*E*	**e**	−25	3	70	**e** (79:21)
22[b]	*E*	**e**	−25	1.5	65	**e** (78:22)

[a] Yields after chromatography in silica gel.
[b] 20 mol % of DBU was added.
[c] *syn*/*anti* ratio measured by ^{1}H NMR.

Enoate *E*-**1** was less reactive towards **2a** and only after 12 h was completely consumed in the absence of DBU (entry 3). In this case, the reaction rate increased in the presence of 20 mol % of DBU, with total consumption of *E*-**1** in 8 h (entry 4). At rt a slight decrease in the *syn*-selectivity was observed from both enoates (entries 5 and 6).

Amines **2b**,**c** bearing a pyridine ring in their structures, were less reactive than **2a** towards both enoates (entries 7–10), and the reaction required the present of DBU at room temperature, leading to adducts with lower stereoselectivities. For the addition of allylamine **2d**, the reactivity, chemical yield and stereoselectivity are quite similar to those observed for benzylamine, (entries 11–18).

All experiments with amine **2e** (entries 19–22) were carried out at −25 °C because below this temperature, the reaction mixture froze. As in other experiments, reactions were faster in the presence of DBU, but the stereoselectivities were very similar starting from *Z*- or *E*-enoates.

The reactions between *E*-**1** or *Z*-**1** with secondary amine **2f** were very slow and only occurred at rt in the presence of DBU leading to **3f** in moderate yields and stereoselectivities (Table 2, entries 1 and 2). However, cyclic secondary amine **2g**, in which the *N* atom is less sterically hindered, was very nucleophilic and reacted with enoates *Z*-**1** and *E*-**1** in only 0.5 h of reaction at −50 °C, leading to adduct *syn*-**3g** in good yield and with moderate stereoselectivity (entries 3–6). The same trend was observed in the reaction of these enoates with **2h**, leading very quickly to adduct **3h** but with moderate *syn*-selectivity, in the presence or absence of DBU (entries 7–10). Finally, in the reactions with **2i**, the adduct *syn*-**3i** was obtained with good stereoselectivity and moderate chemical (entry 11 and 12). In these cases, the reaction rate was independent of the presence of DBU.

Table 2
Product distribution for the reactions of Scheme 1, involving secondary amines **2f–i**

Entry	1	2	*T* (°C)	*t* (h)	**3** (%)[a]	**3** (*syn*:*anti*)[a]
1	*Z*	**f**	rt	360	42	**f** (70:30)
2[b]	*E*	**f**	rt	360	41	**f** (60:40)
3	*Z*	**g**	−50	0.5	89	**g** (73:27)
4[b]	*Z*	**g**	−50	0.5	89	**g** (73:27)
5	*E*	**g**	−50	0.5	80	**g** (73:27)
6[b]	*E*	**g**	−50	0.5	78	**g** (73:27)
7	*Z*	**h**	−25	1	35	**h** (61:39)
8[b]	*Z*	**h**	−25	0.5	35	**h** (78:22)
9	*E*	**h**	−25	1.5	54	**h** (61:39)
10[b]	*E*	**h**	−25	1.5	62	**h** (69:31)
11[b]	*Z*	**i**	−25	3	40	**i** (79:21)
12[b]	*E*	**i**	−25	45	47	**i** (76:24)

[a] Yields after purification by chromatography in silica gel, *syn*/*anti* ratio measured by ^{1}H NMR and ^{13}C NMR.
[b] 20 mol % of DBU was added.

The stereochemistry at Cβ in adduct *syn*-**3d** was determined by chemical correlation. Since the configuration at Cβ in *syn*-**3a** was previously established by Yamada et al.,[9] this compound was transformed into *syn*-**3j** by N-alkylation with allyl bromide (Scheme 2). The same product was also obtained by *N*-benzylation of *syn*-**3d** with benzyl bromide (same $\alpha_{[D]}$ values). The stereochemistry of other *syn*-adducts was suggested based on the comparison of ^{1}H NMR chemical shifts for Hα, Hβ and ^{13}C NMR chemical shifts for C=O (Table 3).

As shown in Table 2, in the ^{1}H NMR spectra, except for *syn*-**3f**, Hα are more shielded in the *syn*-isomers, while Hβ are more shielded in *anti*-isomers. In all cases, ^{13}C NMR chemical shifts for C=O are more shielded for *syn*-isomers.[10]

3. Conclusion

The scope of the conjugate addition of amines to enoates derived from D-mannitol was studied. In the absence of a solvent, the reaction rate, chemical yields and *syn*-stereoselectivities observed depended on the structure of the primary amines. Cyclic secondary amines were also very reactive, but the adducts formed with lower *syn*-stereoselectivity.

4. Experimental

4.1. General

The ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Gemini-200 (400 MHz and 500 MHz). Coupling constants (*J*) are in Hertz (Hz). Chemical shifts are reported in ppm downfield to