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Multigram scale synthesis of a useful aza-Diels–Alder adduct in a one-step procedure

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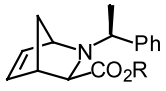
Abstract—The aza-Diels–Alder reaction between a chiral imine (derived from methyl glyoxylate and (*S*)-(−)-1-phenylethylamine) and cyclopentadiene, in the presence of trifluoroacetic acid and boron trifluoride diethyl etherate have been performed in a one-step procedure. Without isolation of intermediates, 111.5 g of the major *exo*-isomer was isolated in a total yield of 56% using a protocol where extensive chromatography was not required.

1. Introduction

The hetero Diels–Alder adduct **1** (Fig. 1) has proved its versatility and importance as synthetic intermediate for a number of ligands which in turn have found use in a variety of catalytic asymmetric processes. Derivatives of **1** have been used with excellent results, both by our group[1,2] and others[3] in as varied applications as, for example, the rearrangement of epoxides, the transfer hydrogenation of prochiral ketones and addition of diethylzinc to aldehydes.

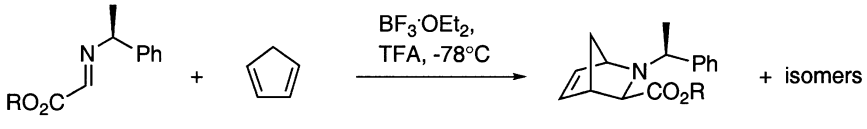


1

Figure 1.

The synthesis of **1** was published in 1990–91 by the groups of Stella,[4] Bailey[5] and Waldmann.[6] A chiral imine, derived from the condensation of 1-phenylethylamine with an alkyl glyoxylate was utilized in the aza-Diels–Alder reaction with cyclopentadiene catalyzed by TFA and $BF_3{\cdot}OEt_2$ which furnished the azabicyclo[2.2.1]heptene derivative **1** (Scheme 1).

The reaction is highly *exo*-selective, the *exo*:*endo* selectivity reported varied from 86:14 to 98:2 and the diastereomeric excess of the two *exo*-isomers have been reported in a range from 80 to 98%.[4–6] Analogues of **1**, synthesized with other chiral auxiliaries[7] or using chiral catalysts[8] have also been reported in the literature. The attractive feature of the protocol outlined in Scheme 1 lies in the use of inexpensive starting materials in combination with the high selectivity observed when utilizing 1-phenylethylamine as a chiral auxiliary.



1a R = Me
1b R = Et

Scheme 1. Synthesis of aza-Diels–Alder adduct **1**.

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Earlier, an extensive amount of work was needed in order to separate the major *exo*-isomer **1** in the reaction from its diastereomers by flash chromatography. This was also the case in our laboratory until we found that the methyl ester of **1** could be easily recrystallized from pentane to afford diastereomerically pure **1a** in high yields. We also found that there was no need to purify the glyoxylate derived by cleavage of dimethyl L-tartrate nor the imine used in the reaction.

Thus, we report herein an expedient synthesis of **1a**, starting from dimethyl L-tartrate, (*S*)-(−)-1-phenylethylamine and cyclopentadiene in a one step procedure yielding 111.5 g of the single major *exo*-isomer without the need for time consuming chromatographic purification.

2. Results and discussion

The synthesis of **1a** started with oxidative cleavage of 69 g of dimethyl L-tartrate with periodic acid yielding the product, methyl glyoxylate as a mixture of mono- and trimers in 1 h. This mixture was used immediately for condensation with (*S*)-(−)-1-phenylethylamine after filtration and changing the solvent to CH_2Cl_2. Imine formation was complete within an hour with the aid of molecular sieves, which also removed the water produced in the previous reaction from the cleavage of dimethyl L-tartrate. Upon complete imine formation, the temperature was changed from 4 to −75°C and TFA, $BF_3{\cdot}OEt_2$ and cyclopentadiene were subsequently added to the mixture. For the Diels–Alder reaction, efficient stirring was necessary otherwise the reaction tended to freeze upon addition of the cyclopentadiene. To avoid freezing, we used a mechanical stirrer instead of a magnetic stirring bar and the reaction proceeded smoothly without problems. After quenching the acids using aqueous Na_2CO_3, the crude products were filtered through a 5 cm pad of silica in order to separate the Diels–Alder adducts from polymeric materials. Recrystallization of the product mixture from *n*-pentane then afforded a total of 111.5 g of the desired *exo*-isomer corresponding to an overall yield of 56%.

3. Conclusion

A multigram scale synthesis of the very useful aza-Diels–Alder adduct **1a** has been performed. In this new protocol no purification of the intermediates, methyl glyoxylate and the imine used for the Diels–Alder reaction, is necessary. In addition, chromatographic purification of the reaction mixture in order to isolate the major *exo*-isomer is not needed. Simple filtration followed by efficient recrystallization yielded the desired compound on a large scale and in good yield.

4. Experimental

4.1. Synthesis of (1*R*,3*R*,4*S*)-2-[(1*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylic acid methyl ester 1a

In a 2 L round-bottomed flask equipped with a magnetic stirrer, dimethyl L-tartrate (69.1 g, 0.388 mol) was dissolved in diethyl ether (1 L) and cooled to 0°C with an ice-water bath. To this mixture, *ortho*-periodic acid (88.4 g, 0.388 mol) was added over a period of 30 min. The ice bath was then removed and the mixture was allowed to reach ambient temperature and stirred for 30 min. The inorganic salts were then filtered off, washed with diethyl ether into a 2 L two-necked round-bottomed flask and the solvent was evaporated. The two-necked flask was then equipped with a mechanical stirrer, the methyl glyoxylate was dissolved in dichloromethane (1.2 L), molecular sieves (410 g, 4 Å) were added under a N_2 atmosphere and the mixture was then cooled to approx. 4°C using cold water. (*S*)-(−)-1-Phenylethylamine (100 mL, 0.776 mol) was then added to the cold mixture and stirred for 1 h. The water bath was replaced with a dry ice/acetone bath with an external cooler and the reaction was cooled to approx. −75 to −78°C. With 10 min intervals trifluoroacetic acid (60.0 mL, 0.783 mol), boron trifluoride diethyl etherate (100 mL, 0.783 mol) and cyclopentadiene (78.0 mL, 0.931 mol) were added to the flask. The reaction was then stirred for 20 h at −75 to −78°C before the cooling was removed. When the reaction had reached room temperature it was quenched with Na_2CO_3 (aq. satd) and stirred for 3 h. The quenched mixture was filtered through a pad of Celite and extracted with dichloromethane (3×300 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give crude product (191 g). The crude was dissolved in dichloromethane (600 mL) together with silica gel and the solvent was evaporated. The crude products on the silica were filtered through a 5 cm pad of silica in a large Büchner funnel (pentane/ethyl acetate, 90:10). The combined filtrate was evaporated to give 168 g crude product that was dissolved in refluxing pentane (250 mL) and allowed to crystallize at −26°C (in a freezer) to give the desired diastereomerically pure **1a** as white crystals (95 g, 0.369 mol). The mother liquid was evaporated and the remaining yellow oil was recrystallized again according to the same procedure from pentane (80 mL) to give an additional crop of **1a** (16.5 g, 0.064 mol). Combining the products resulted in a total yield of 111.5 g (0.433 mol, 56%) of pure **1a**. All physical and spectroscopic data for the product were in complete agreement with those published.[2d,4b]

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