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Use of 9-Anthrylcarbinol Derivatives as Chiral Auxiliaries. II. Asymmetric 1,3-Dipolar Cycloaddition

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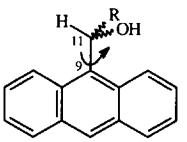
Abstract : The 1,3-dipolar cycloaddition of acrylates derived from 9-anthrylcarbinol to a cyclic nitrone is studied. The composition of the reaction product depends on the steric hindrance of the substituent. A complete study of the diastereoisomers was performed by NMR and we were thus able to determine the absolute configuration of the major adducts.

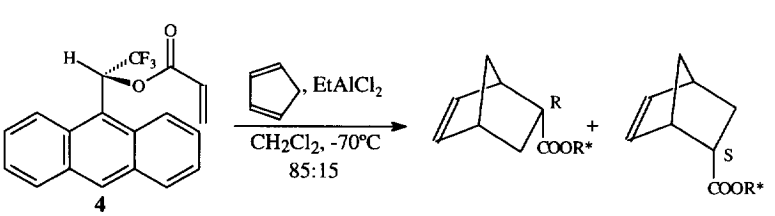
Introduction

Among the arylcarbinols, the most widely used is Pirkle's alcohol, 2,2,2-trifluoro-1-(9-anthryl)ethanol **1**. Its applications include optically active NMR reagents and chiral stationary phases in chromatography.[1] Besides Pirkle's alcohol, among others, anthrylcarbinol derivatives **2** and **3** have also been synthesised.[2] These three compounds **1-3** present a restricted rotation around the C_9-C_{11} bond, which was measured in our laboratory using NMR techniques such as NOE enhancement and relaxation time measurements.



1 R = CF_3
2 R = *t*-Bu
3 R = Me

In a previous paper,[3] we reported the results obtained for the asymmetric Diels-Alder reaction of cyclopentadiene with acrylates derived from the 9-anthrylcarbinols **1-3**, as chiral auxiliaries. The aim of that work was to demonstrate that there was a correlation between the rotational barrier of C_9-C_{11} bond and the stereoselection of the Diels-Alder reaction. Unfortunately, such a correlation could not be shown because the best result was obtained with the acrylate derived from Pirkle's alcohol **4**, which possesses an intermediate value for the free energy of activation for the rotation of this bond (respectively for **1-3**: 14.5, 21.7 and 11.0 kcal/mol). Nevertheless we obtained an interesting diastereoselectivity in *endo*-adducts of 85/15 without any trace of *exo*-products in a quantitative yield (scheme 1).



4

Scheme 1

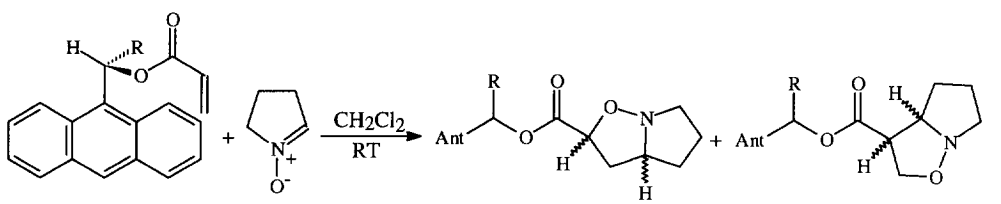
In addition, the steric effects of the substituents are not decisive because quite similar results were obtained with the *t*-butyl and methyl derivatives **5** and **6**. As usually observed for this reaction,[4] the stereoelectronic effects are more important than the steric hindrance.

In connection with this study, we now describe the results obtained for the 1,3-dipolar cycloaddition of the same substrates with a cyclic nitrone. The acrylates **4-6** were reacted with 1-pyrroline-1-oxide, **7**. This dipole is one of the most used with synthetic purposes, since the adducts incorporate the pyrrolidine moiety, which is widespread in nature.[5]

Results and discussion

The reactions were carried out in dichloromethane at room temperature using 1.1 equivalents of nitrone **7**. The composition of the cycloaddition products was determined by integration of ^{1}H-NMR signals corresponding to the proton at the α-position of the carbonyl group or the one at the ring junction.

As observed in earlier studies,[6] the reaction of acrylates with cyclic nitrones leads to the formation of all possible regio- and stereoisomers. In our case, for each substrate we obtained a complex mixture of adducts, between six and eight depending on the substituent R. Nevertheless, it was possible to isolate a sample enriched in each major adduct by careful chromatographical separation. In all cases, the regioselectivity favours the formation of adducts **8**, **10** and **12** (scheme 2 and table 1). In NMR, the two regioisomers can be distinguished by the chemical shift of the proton at the α-position of the oxygen included in the isoxazolidine ring. In the isomers **8, 10** and **12**, this proton shows a chemical shift of about 4.6 ppm; the corresponding protons in the adducts **9**, **11** and **13** are about 0.5 ppm upfield shifted.



4 R = CF_3
5 R = *t*-Bu
6 R = Me

7

8 R = CF_3
10 R = *t*-Bu
12 R = Me

9 R = CF_3
11 R = *t*-Bu
13 R = Me

Scheme 2

Entry	Dipolarophile	Time (d)	Yield[a]	regioisomers	ratio
1	**5**	1	56%	**8**:**9**	59:41
2	**6**	3	59%	**10**:**11**	88:12
3	**7**	5	66%	**12**:**13**	79:21

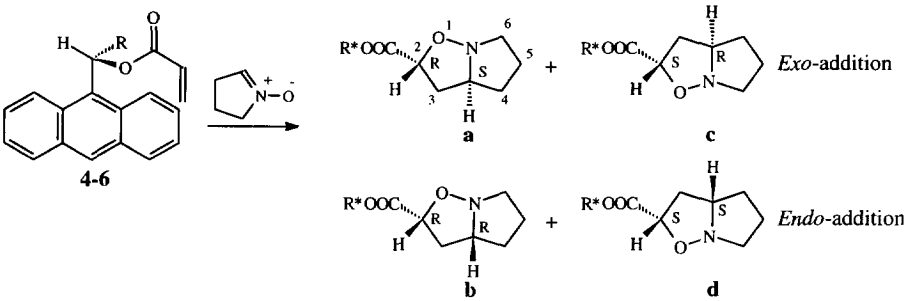
Table 1 : 1,3-dipolar cycloaddition of acrylate **5-7** to nitrone **4**.
[a] Yield based on dipolarophile.

All the substrates led to the four possible diastereoisomers of **8**, **10** and **12** (**a-d**). In the case of **4** and **6**, the composition of the mixture was quite similar, there were two major isomers with a proportion of 34:15:34:17 (**8a**:**8b**:**8c**:**8d**) and 41:7:38:14 (**12a**:**12b**:**12c**:**12d**), respectively. In the case of the *tert*-butyl derivative **5**, one diastereoisomer was largely predominant with a proportion of 70:11:15:4 (**10a**:**10b**:**10c**:**10d**) (scheme 3).

NMR experiments (GOESY sequence)[7] performed on the minor products (**8b, 8d, 10b, 10d, 12b** and **12d**) exhibit a slight NOE (0.6%) between the H_2 and the H_{3a} protons. This means that the latter are in a *cis*-configuration. So, we could conclude that the two minor adducts derive from an *endo*-addition.

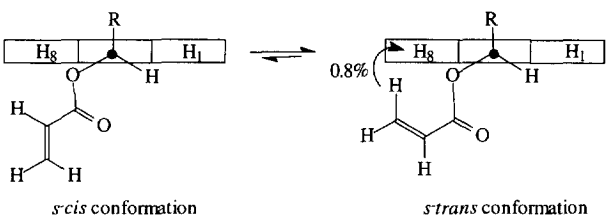
In contrast, the major cycloadducts (**8a, 8c, 10a, 10c, 12a** and **12c**) do not exhibit any NOE between the H_2 and H_{3a} protons, confirming its *trans* geometry. The two major adducts result from an *exo*-addition of the nitrone to the acrylate. Moreover, there is another slight NOE (0.6%) between H_2 and one of the H_4. The geometry of *endo* compounds does not permit this NOE. In addition, in the case of **5**, the two H_3 protons of the

major adduct **10a** undergo the influence of anisotropy due to the anthryl group. They present a shift of 0.1-0.15 ppm to the high field. This effect is not posssible in **10c** because these protons are far away of the π-system. *Endo* transitions states are disfavoured by steric interactions of substituents on the dipolarophile with methylene groups of the nitrone.



Scheme 3

NMR experiments (GOESY) performed on the acrylate exhibit a NOE between the H_8 proton of the anthryl group and one of the methylene protons of the double bond. This means that the *s-trans* conformation is favoured.



Scheme 4

Molecular Mechanics (MM3) calculations carried out for each conformation of the acrylates **5** confirmed that the one with the lowest energy is the *s-trans* (Scheme 4). The difference of energy is about 5.5 kJ/mol.

The major isomer **10a** comes from an *exo*-addition to the s-*trans* conformation of the acrylate **5**. The presence of the *t*-butyl substituent shields the addition of the nitrone to this face of the acrylate, directing the nitrone to the opposite face.

Unlike the Diels-Alder reaction, and as previously observed, the selectivity of the 1,3-dipolar cycloaddition is governed by steric factors, and the best result is obtained with the acrylate **5**, which possesses the bulkiest substituent.

Experimental :

Procedure for 1,3-dipolar cycloadditions : 1-pyrroline-1-oxide **7** (0.112 g, 1.3 mmol) was added at room temperature to a solution of the (R)-acrylate **5** (0.38 g, 1.2 mmol) in chloroform (10 ml). The mixture was stirred until complete consumption of the acrylate and after evaporation of the chloroform, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate 6/4) to give 0.176 g (36%) of the major adduct **10a**, 0.028 g (6%) of **10c**, 0.035 g (7%) of a mixture of two regioisomers of **11** with a proportion of 70/30, and 0.048 g (10%) of a mixture of **10b** and **10d** in a proportion of 80/20. All the ^1H and ^{13}C spectra were characterized by COSY HH, HMQC, HMBC and GOESY sequences.

10a : ^{1}H-NMR (400 MHz, $CDCl_3$) : 1.05 (s, 9H); 1.54 (ddt, *J* = 12.5, 9.3, 5.3 Hz, 1H); 1.65-1.74 (m, 1H); 1.88 (ddt, *J* = 12.5, 8.2, 6.9 Hz, 1H); 1.93-2.02 (m, 1H); 2.26 (ddd, *J* = 12.5, 8.5, 3.5 Hz, 1H); 2.55 (ddd, *J* = 12.5, 7.7, 5.3 Hz, 1H); 3.01 (dt, *J* = 13.3, 8.2 Hz, 1H); 3.37 (ddd, *J* = 13.3, 7.4, 4.2 Hz, 1H); 3.54 (ddt, *J* = 8.0, 5.7, 3.5 Hz, 1H); 4.69 (dd, *J* = 8.5, 5.3 Hz, 1H); 7.36 (s, 1H); 7.38-7.44 (m, 3H); 7.50 (ddd, *J* = 9.0, 6.6, 1.6 Hz, 1H); 7.93-7.97 (m, 2H); 8.39 (s, 1H); 8.51 (d, *J* = 9.0 Hz, 1H); 8.87-8.89 (m, 1H). ^{13}C-NMR : 24.11; 28.28; 31.09; 38.54, 39.94; 56.79; 65.05; 75.04; 79.84; 124.43; 124.46; 124.61; 124.64; 125.98; 128.67; 129.07; 129.21; 129.23; 130.37; 131.19; 131.49; 131.93; 171.31. **10c** : ^{1}H-NMR : 1.03 (s, 9H); 1.52-1.58 (m, 1H); 1.65-1.76 (m, 1H); 1.89-1.99 (m, 2H); 2.36 (ddd, *J* = 12.2, 8.2, 3.2 Hz, 1H); 2.71 (ddd, *J* = 12.2, 7.7, 5.6 Hz, 1H); 3.01 (dt, *J* = 13.3, 7.5 Hz, 1H); 3.32 (ddd, *J* = 13.3, 7.2, 4.5 Hz, 1H); 3.66 (ddt, *J* = 7.9, 5.6, 3.5 Hz, 1H); 4.64 (dd, *J* = 8.2, 5.6 Hz, 1H); 7.33 (s, 1H); 7.37-7.44 (m, 3H); 7.48-7.54 (m, 1H); 7.92-7.98 (m, 2H); 8.39 (s, 1H); 8.51 (d, *J* = 9.0 Hz, 1H); 8.93 (d, *J* = 8.5 Hz, 1H). ^{13}C-NMR : 24.14; 27.74; 31.11; 38.50; 40.33; 56.76; 65.00; 75.16; 80.05; 124.35; 124.45; 124.57; 124.64; 125.92; 128.78; 128.95; 129.04; 129.24; 130.23; 131.14; 131.44; 131.94; 132.59; 171.29. **11** : (major isomer) ^{1}H-NMR : 0.85 (ddt, *J* = 13.5, 8.0, 6.5 Hz, 1H); 0.89-0.98 (m, 1H); 1.06 (s, 9H); 1.29-1.39 (m, 1H); 1.56-1.64 (m, 1H); 2.95 (dt, *J* = 12.7, 7.4 Hz, 1H); 3.09 (ddd, *J* = 12.7, 7.2, 5.7 Hz, 1H); 3.79 (dt, *J* = 8.2, 8.0, 1H); 3.87 (dt, *J* = 8.2, 8.0, 1H); 4.06 (t, *J* = 8.2 Hz, 1H); 4.13 (t, *J* = 8.2 Hz, 1H); 7.41 (s, 1H); 7.39-7.46 (m, 3H); 7.53 (ddd, *J* = 9.0, 6.4, 1.3 Hz, 1H); 7.93-7.99 (m, 2H); 8.42 (s, 1H); 8.50 (d, *J* = 9.0 Hz, 1H); 8.75-8.80 (m, 1H). ^{13}C-NMR : 24.34; 26.26; 28.40; 38.29; 52.03; 56.63; 66.33; 66.59; 79.78; 124.33; 124.50; 126.24; 128.78; 128.95; 129.03; 129.13; 129.22; 130.30; 131.17; 131.45; 131.85; 131.93; 171.49. (minor isomer)* ^{1}H-NMR ($CDCl_3$) : 1.68-1.75 (m 1H); 1.92-1.97 (m, 1H), 3.10 (dt, *J* = 12.7, 7.4 Hz, 1H); 3.24 (ddd, *J* = 12.7, 7.4, 5.8 Hz, 1H); 3.78 (dt, *J* = 8.0, 7.7, 1H); 4.03 (t, *J* = 8.2 Hz, 1H); 8.41 (s, 1H). **10b** (major adduct) : ^{1}H-NMR : 1.20 (s, 9H); 1.47-1.55 (m, 1H); 1.66 (dtt, *J* = 12.2, 7.4, 4.2 Hz, 1H); 1.79 (ddt, *J* = 12.7; 8.2, 7.4 Hz, 1H); 1.98-2.06 (m, 2H); 2.72 (dt, *J* = 12.5, 8.1 Hz, 1H); 3.00 (ddd, *J* = 13.0, 8.2, 7.4 Hz, 1H); 3.43 (ddd, *J* = 13.0, 7.4, 4.2 Hz, 1H); 3.65 (tt, *J* = 8.1, 5.0 Hz, 1H); 4.65 (t, *J* = 7.7 Hz, 1H); 7.34 (s,, 1H); 7.38-7.45 (m, 3H); 7.52 (ddd, *J* = 9.0, 6.6, 1.6 Hz, 1H); 7.92-7.96 (m, 2H); 8.40 (s, 1H); 8.51 (d, *J* = 9.0 Hz, 1H); 8.82-8.86 (m, 1H). ^{13}C-NMR : 23.66; 28.43; 30.58; 38.73; 40.56; 56.80; 65.99; 77.02; 80.72; 125.15; 125.38; 126.85; 129.15; 129.63; 129.87; 129.95; 130.09; 131.05; 131.92; 132.21; 132.69; 171.49. **10d** (minor adduct)* : ^{1}H-NMR : 1.86 (ddt, *J* = 12.2, 7.7, 4.3 Hz, 1H); 2.16 (ddd, *J* = 12.5, 7.7, 4.8 Hz, 1H); 2.81 (dt, *J* = 12.5, 8.0 Hz, 1H); 2.93 (ddd, *J* = 13.0, 8.7, 7.2 Hz, 1H); 3.39 (ddd, *J* = 13.0, 7.4, 4.0 Hz, 1H); 4.59-4.66 (m, 1H); 8.87-8.91 (m, 1H).

* The low quantity of product and the superposition of some signals with those of the major adduct prevent the attribution of all the protons.

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