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Asymmetric Synthesis of 3-Alkoxycarbonyl-2-amino-5-cyano-4,6-diphenyl-4*H*-pyrans

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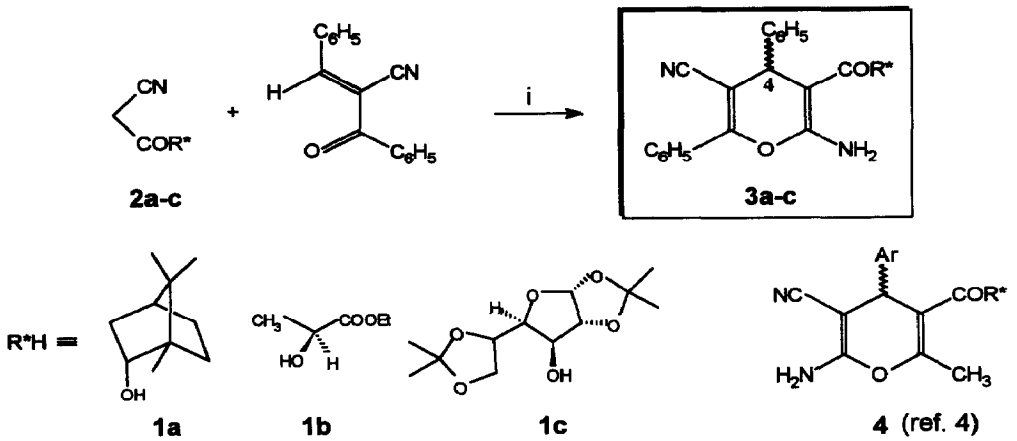
Abstract: The asymmetric Michael addition of cyanoacetates **2a-c** to α-benzoylcinnamonitrile has been studied. The resulting 2-amino-4*H*-pyrans **3a-c** have been obtained in good diastereomeric excesses and, after recrystallization, major isomers **3a** and **3b** have been isolated in diastereomerically pure form. The absolute configuration at C-4 has been assigned as *S* by X-Ray analysis.

In previous reports from our group we have addressed for the first time the asymmetric synthesis of multiply functionalized 2-amino-4*H*-pyrans.[1] We have studied the Michael addition[2] of malononitrile to enantiomerically pure α-acylacrylates (chiral substrate control)[3] and the 1,4-conjugate addition of homochiral ß-ketoesters to arylidenemalononitriles (chiral auxiliary control).[4]

In this communication we describe the preparation of some 3-alkoxycarbonyl-2-amino-5-cyano-4,6-diphenyl-4*H*-pyrans **3**, in enantiomerically pure form, by means of Michael addition of chiral cyanoacetates **2** to α-benzoylcinnamonitrile.[5]

Using the readily available chiral auxiliaries **1a-c** [(1*S*)-endo-(-)-borneol, ethyl (*S*)-(-)-lactate, 1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranose], cyanoacetates **2a-c**[6] have been synthesized from cyanoacetic acid following standard methodology.[7] Under the usual conditions[8] (piperidine, toluene, r.t.) substrates **2a-c** were submitted to reaction with α-benzoylcinnamonitrile (Scheme 1). As shown in the Table, 2-amino-4*H*-pyrans **3a-c** have been obtained in good diastereomeric excesses (40-60%), higher than the diastereomeric excess observed (20%) in the preparation of 5-alkoxycarbonyl-6-alkyl-2-amino-4-aryl-3-cyano-4*H*-pyrans **4**[4] with the same chiral alcohols **1a-c**. These values have been determined in the ^{1}H NMR spectra ($CDCl_3$ as solvent) of the purified compounds, by integrating the observed signals for H-4 [δ: 4.59 (**3a**) and 4.64 (**3b**) for the major isomer; δ: 4.58 (**3a**) and 4.59 (**3b**) for the minor one)]. In the case of compound **3c**, H-4 (in

both isomers) and H-2' (in the major isomer) appear at the same δ value. When the ^{1}H NMR spectrum of **3c** was repeated in CD_3COCD_3 the signals for H-2' and H-4 were clearly separated. Then, we could observe that H-4 in the minor isomer was more deshielded (4.56 ppm) than in the major one (4.54 ppm). In the ^{1}H NMR spectra of compounds **3a,b** using CD_3COCD_3 as solvent, we could detect that, also in these cases, the relative δ values for H-4 were reversed. Then, we can conclude without any doubt, that in compounds **3** the major isomer has always the same absolute configuration at C-4 (*S*, see below).



Reagents. i: toluene, piperidine, r.t.

Scheme 1

Table. 2-Amino-4*H*-pyrans **3a-c**.

Compound	Yield[1] (%)	Ratio[1] S:R (d.e.)[2]	$[\alpha]_D^{25}$ (*c*, solvent)	Configuration
3a	80	80:20 (>99)	+107.8 (1.02, CH_2Cl_2)	*S*
3b	70	70:30 (>99)	+96.1 (0.93, CH_2Cl_2)	*S*
3c	60	75:25	-	-

[1] After flash chromatography. [2] After flash chromatography and recrystallization.

We could not separate diastereomers in compounds **3a-c** by flash chromatography.[9] Nevertheless, after recrystallization, major isomers **3a** and **3b** (see Table) were isolated diastereomerically pure. In the case of major isomer **3a**, we have obtained a suitable crystal for X-Ray analysis[10] (Figure 1). This enabled us to assign the absolute configuration at C-4 in this compound as *S* and, by comparison of the chemical shifts for H-4 (see above), the configuration at this stereocenter in the major isomers of the other members of this series.

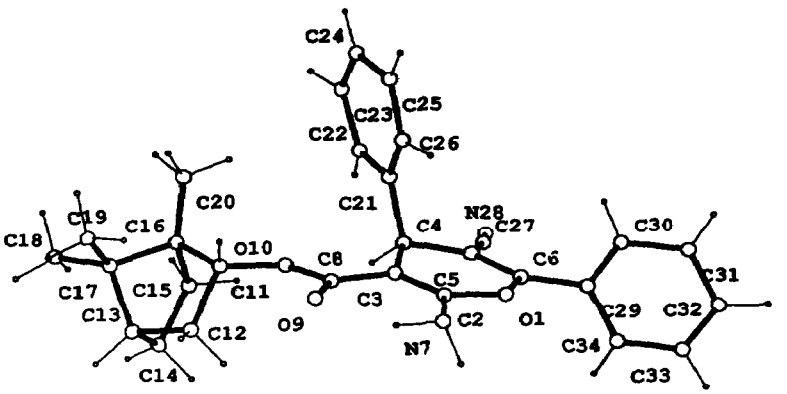
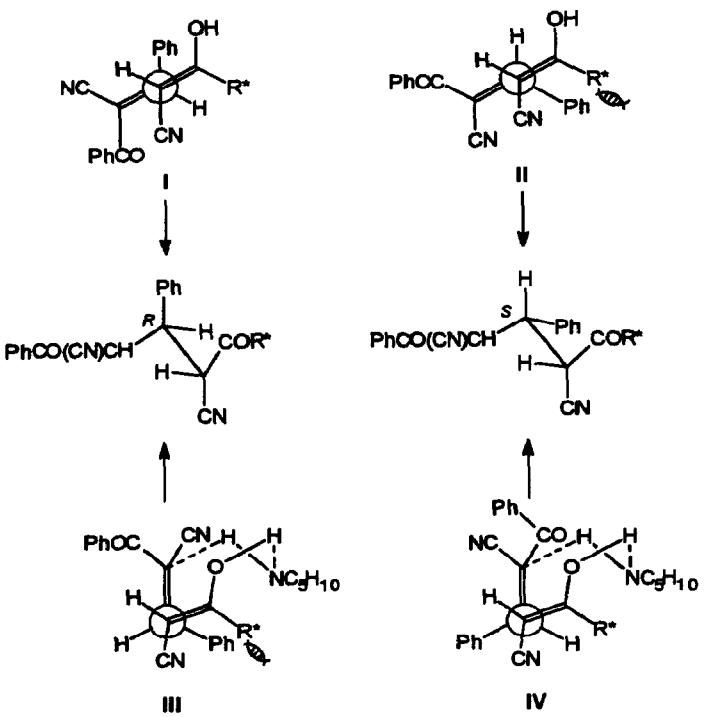


Figure 1. Molecular structure of **3a** (major isomer, C-4 *S*), showing the atomic numbering.



Scheme 2

From the stereochemical point of view, the observed results can be rationalized as follows. Although we have no direct evidence, we have assumed on simple electronic grounds (minimization of the dipole-dipole interaction between the hydroxyl and cyano groups) that the Z isomer is preferred for the cyanoacetates. In an open-chain transition state model[11] (Scheme 2), and by steric interactions, the approach of reagents as shown in **I** should be favoured with respect to **II**, giving major isomers with *R* as absolute configuration at C-4. On the contrary, considering chelated transition states,[12] a favoured transition state **IV**, free of steric interactions between chiral auxiliary and phenyl ring (Scheme 2) should result in the formation of major C-4 *S* isomers, as observed. In this model we have hypothesized the formation of an eight-membered ring,[12] incorporating the catalytic piperidine.

In summary, the results obtained in this study show that the Michael addition of chiral cyanoacetates to highly destabilized acceptors proceeds in good diastereomeric excess and high chemical yield.

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