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Tricarbonylchromium Complexation as Stereoselective Tool in Nitrile Oxide Cycloadditions to Styrenes.

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Key Words: Tricarbonylchromium Arenes, Stereoselective Cycloaddition, Nitrile Oxide, 4,5-Dihydroisoxazoles.

Abstract: *The cycloaddition of 3,5-dichloro-2,4,6-trimethylbenzonitriloxide to chiral tricarbonylchromium complexed styrenes proceeds with high stereoselectivity, thus offering a new synthetic route to optically active 3,5-disubstituted 4,5-dihydroisoxazoles.*

The nitrile oxide cycloadditions to alkenes represent the most common entry to 4,5-dihydroisoxazoles[1], a class of heterocyclic compounds which are the object of great attention as precursors of 1,3-difunctional open-chain molecules[2,3]. A major advantage of this approach comes from the stereoconservation property of the cycloaddition, so that the relative stereochemistry of the cycloadduct reflects inequivocally the configuration of the starting alkene[4]. However the control of the absolute stereochemistry of the target product is a challenging goal which still constitutes an open problem[5]. In order to promote discrimination between the two π faces of the alkene, a number of chiral auxiliaries have been tested, e.g. menthyl and bornyl esters[6,7], Oppolzer's sultam[8], Evan's imide and related moieties[9-12], tricarbonyliron coordination[13]. Menthyl and bornyl-type acrilates[6] as well as Evan's imide[9,11], which give excellent results in Diels-Alder cycloadditions, are less effective in nitrile oxide cycloadditions, even in the presence of Lewis acids which coordinate preferably the oxygen of the dipole. Chiral crotonic esters[7,10] show good diastereoselectivity, accompanied however by rather low regioselectivity. Up to date, the best results have been obtained with Oppolzer's sultam[8] and similar acrilamides[9,11,12]. Moreover a valuable goal has been achieved by using chiral iron-complexed trienes[13b].

On continuing a line of research dealing with stereoselective reactions of tricarbonylchromium complexed arenes [14,15], we were interested in studying the reactivity of chiral complexed alkenes in 1,3 dipolar cycloaddition reactions. The only report in this field describes the stereoselective reaction between tricarbonylchromium complexed nitrones and electron rich olefines[16].

We first focussed our attention on the dipolarophilic behaviour of the chiral complexed styrenes **2a-c** toward 3,5-dichloro-2,4,6-trimethylbenzonitriloxide **3** (Scheme 1).

Scheme 1

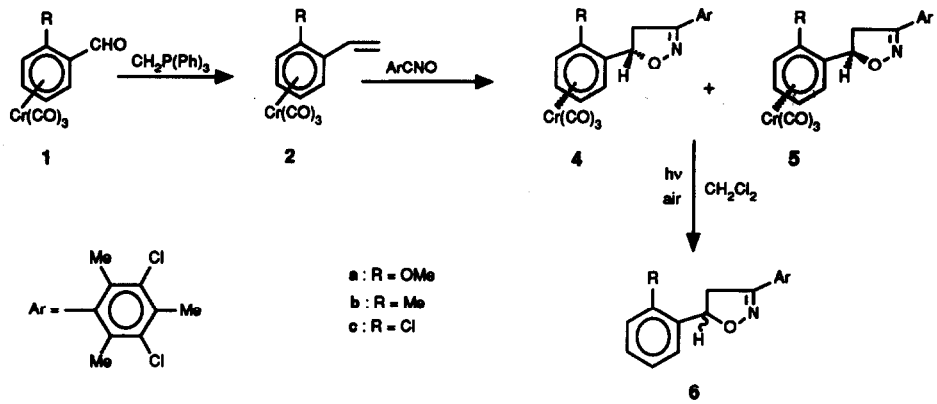


TABLE 1

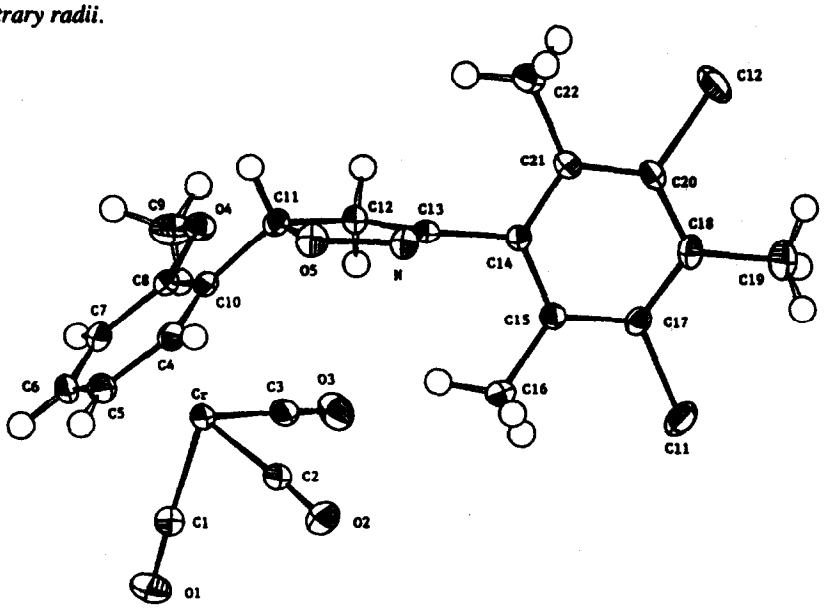
Subst.	Time h	4/5 [a] ratio	Overall yield	Isolation yield of 4
2a	24	80/20	68	51
2b	30	≥ 98/2	70	70
2c	24	96/4	65	56

a) By the NMR spectrum of the crude product mixture

Compounds **2a-c** were prepared by Wittig condensation between complexed benzaldehydes **1a-c** and methyltriphenylphosphonium iodide[17], and reacted with equimolar amount (0.4 mmol.) of **3** in dioxane solution (3 ml) at room temperature. After a standard work-up of the reaction mixture the complexed diastereoisomeric cycloadducts **4** and **5** were recovered as yellow solids by preparative thin-layer chromatography. Table 1 collects raction times, diastereoisomeric ratios, and product yields .

The stereochemistry of the major cycloadduct deriving from **2a** was established by X-ray diffraction analysis, which revealed the 1*R**,5'*S** configuration (see Fig.1)[18]. By analogy, the same stereochemistry can be reasonably assumed for the preferred cycloadducts obtained from **2b** and **2c**.

Fig. 1. *ORTEP drawing of compound 4a with 30% probability level ellipsoids. Hydrogen atoms were given arbitrary radii.*



Removal of the tricarbonyl chromium fragment was achieved by exposure of a solution of compounds **4** (and **5**) in CH_2Cl_2 to the sunlight for 1-2 hrs. and led to the unknown 4,5 dihydroisoxazoles **6a-c** in good yields. For the sake of comparison, compounds **6a-c** were also synthesised by reacting the nitrile oxide **3** with the proper uncomplexed *ortho*-substituted styrenes (80-85% yields).

The above results demonstrate that the cycloaddition of **3** to the chiral dipolarophiles **2a-c** proceeds with full regioselectivity (as expected for terminal alkenes[19]) and with high diastereoselectivity.

The synthetic potentiality of the latter feature was exploited on doing the same experiments with enantiomerically pure 1*R*-**2a** (α_D= -561°, C= 0,2 $CHCl_3$) and 1*R*-**2b** (α_D= -717°, C= 0,21 $CHCl_3$)[20]. Direct decomplexation of the reaction mixtures afforded optically active 4,5 dihydroisoxazoles **6a** and **6b** in 63% and 98% e.e. respectively. Enantiomeric purity was determined by H^1NMR using $Eu(tfc)_3$ (in $CDCl_3$ solution) as chiral shift reagent. It's worthy of note that we were able to isolate by preparative chromatography the pure complexed diastereoisomers **4a** (α_D= + 127°, C= 0.18 $CHCl_3$) and **4b** (α_D= -314°, C= 0.19 $CHCl_3$).Their subsequent decomplexation gave optically pure dihydroisoxazoles *S*-**6a** (α_D= + 281°, C=0.71 $CHCl_3$,) and *S*-**6b** (α_D= +132, C=0.74 $CHCl_3$).

The preferred formation of the cycloadducts **4** implies that: *i*) the nitrile oxide attacks the π face opposite to the tricarbonylchromium tripod and *ii*) the reactive rotamer of the dipolarophile is that having "transoid" disposition . Such a conformation, which is the more stable one in the case of *ortho* substituted styrenes[21], minimizes the steric repulsion between the reactants.

In the case of **2a**, the angular geometry of the methoxy group permits a larger degree of freedom and therefore reduces the discrimination betweeen the two rotamers, so accounting for the lower level of diastereoselectivity.

In conclusion, our approach to optically active 4,5-dihydroisoxazoles may have immediate preparative value. To wide it, further work will involve different nitrile oxides and dipolarophiles.

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18 Crystal data for **4a**: $C_{22}H_{19}Cl_2CrNO_5$, M = 500.3, monoclinic, space group $P2_1/n$; *a*= 14.798(5), *b*= 7.973(4), *c*= 19,345(6)Å, β=104.37(3)°,*U*= 2211(3)Å^3, F(000)= 1024, Z= 4, D_c= 1.503 g cm^{-3}, Mo-Kα radiation, λ= 0.71073 Å, μ(Mo-Kα)= 7.8 cm^{-1}. Intensity were measured on a CAD4 diffractometer at room temperature; data were corrected for Lorentz-polarization, absorbtion and decay effects. 2152 reflections with I 2.5σ(I) were used in the structure refinement. The final R value was 0.043 (R_w= 0.046).

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