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First highly regio- and diastereoselective synthesis of Δ^2–pyrazolines by [3+2] cycloaddition of chiral non-racemic Fischer carbene complexes with nitrilimines

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Abstract

[3+2] Cycloaddition of Fischer carbene complexes with nitrilimines is described for the first time. The "one-pot" conversion of Fischer carbenes into enantiomerically pure Δ^2-pyrazolines with high regio- and diastereoselectivity is presented as an expeditious route to these compounds.

Keywords: cycloadditions, carbenes, nitrilimines, pyrazolines

The use of Fischer carbene complexes in organic synthesis has undergone rapid development in the last decades [1]. In this way, α,β-unsaturated derivatives have been widely employed as synthons in cycloaddition reactions [2,3]. However, these substrates have been scarcely used in [3+2] cycloadditions with 1,3-dipoles. Thus, (alkoxy)alkynyl carbenes were converted into pyrazoles and dihydroisoxazoles by reaction with diazomethane derivatives [4,5] and nitrones [6] respectively and have also been shown to react with masked 1,3-dipoles [7]. On the other hand, only one case of reaction of alkenyl Fischer carbene complexes with 1,3-dipoles had been published [8] until we reported the first 1,3-dipolar cycloaddition of enantiopure (alkenyl)alkoxy carbene complexes with diazomethane derivatives [9].

1,3-Dipolar cycloadditions using nitrilimines is a very well known process [10]. These synthons [11] are often generated *in situ* from hydrazonoyl chlorides and trapped with dipolarophiles to give the corresponding Δ^2-pyrazolines as a mixture of regioisomers [12]. Δ^2-Pyrazolines are of interest due to their biological activity (*e.g.*, as anti-inflammatory agents [13, 14]) and physical applications (*e.g.*, as optical brighteners [15, 16]), hence procedures to prepare these systems in a regio- and diastereoselective way are of great value. In this context, we present here our preliminary results in the reaction of Fischer carbene complexes with nitrilimines.

The first experiments were carried out with (±)-menthol derived alkenyl carbenes **1** which by treatment with *in situ* generated nitrilimines led to Δ^2-pyrazolines **2** in moderate yields (Scheme 1, Table 1). Compounds **2** were found to be fairly unstable, which prompted us to promote their *in situ* oxidation to the corresponding esters in moderate to good yields, by

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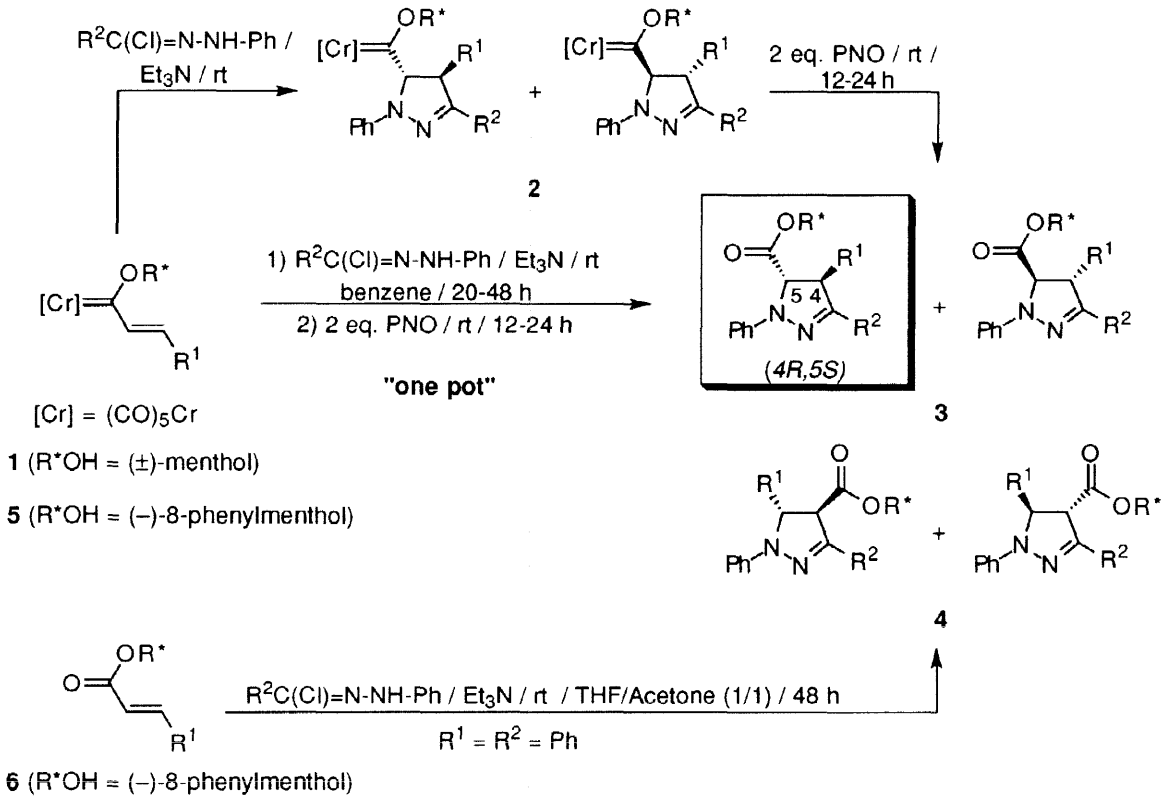
using pyridine *N*-oxide (PNO). Only one regioisomer **3** (R*OH = (±)-menthol), out of two possible **3** and **4**, was detected. Regioisomer **3** is obtained as a mixture of two diastereomers (ratio ≤ 2:1) with *trans* relative stereochemistry.



Scheme 1

Table 1

One-pot synthesis of Δ^2-pyrazolines **3** (R*OH = (±)-menthol)[a]

Entry	R^1	R^2	**2**	Solvent	Time (h)[b]	Yield (%)[c]	**3**	Yield (%)[c]
1	Ph	Ph	**a**	THF/Acetone: 1/1	14	67	**a**	80
2	2-Furyl	Ph	**b**	THF/Acetone: 1/1	84	80	**b**	99
3	*p*-Anisyl	Ph	-	PhH	60	-	**c**	82
4	Ph	*p*-Anisyl	-	PhH	2	-	**d**	80
5	2-Furyl	*p*-Anisyl	-	PhH	16	-	**e**	87[d]
6	*p*-Anisyl	*p*-Anisyl	-	PhH	20	-	**f**	82
7	Ph	CO_2Et	**g**	THF/Acetone: 1/1	84	30	**g**	40
8	Ph	CO_2Et	-	PhH	84	-	**g**	55
9	Ph	CO_2Et	-	Hexane	120	-	**g**	46
10	Ph	CO_2Et	-	$CHCl_3$	96	-	**g**	42

[a] All products showed satisfactory NMR and MS data.
[b] Cycloaddition reaction times monitored by TLC.
[c] Isolated yields.
[d] Regioselectivity 85/15.

As shown in Table 1 (entries 7-10), the influence of solvent polarity in the reaction rate is negligible; this would support a concerted mechanism in the cycloaddition process. The presence of an electron–releasing group in the carbene (entry 1 *vs* 2 and 3) or an electron–withdrawing group in the nitrilimine (entry 1 *vs* 7) decreases the reaction rate while an electron–releasing group in the dipole (entry 1 *vs* 4) accelerates the process. The Frontier Molecular Orbital theory would explain these observations taking into account that the expected reactivity pattern between Fischer carbenes and nitrilimines should be HOMO(dipole)-LUMO(dipolarophile) due to the strong electron–withdrawing ability of the metal pentacarbonyl group in **1** [17].

In order to improve the diastereoselectivity of the cycloaddition process, (–)-8-phenylmenthol derived carbenes **5** were used in view of the excellent results obtained in related reactions of Fischer carbene complexes [9,18,19] The reaction of carbenes **5** with nitrilimines followed by one-pot oxidation with PNO affords Δ^2-pyrazolines **3** (R*OH = (–)-8-phenylmenthol) in moderate yields (Scheme 1, Table 2).

Table 2
One-pot synthesis of Δ^2-pyrazolines **3** (R*OH = (–)-8-phenylmenthol)[a]

Entry	R^1	R^2	**3**/**4**[b]	Yield (%)[c]	dr[b]
1	Ph	Ph	**a** (>95/5)	55	92/8[d]
2[e]	Ph	Ph	**a** (38/62)	quantitative	12/26:44/18[d,f]
3[g]	2-Furyl	Ph	**b** (>95/5)	35	>95/5
4	Ph	*p*-Anisyl	**c** (>95/5)	40	>95/5
5	2-Furyl	*p*-Anisyl	**d** (>95/5)	73	>95/5
6	*p*-Anisyl	*p*-Anisyl	**e** (>95/5)	69	>95/5

[a] All products showed satisfactory NMR and HRMS data.

[b] Regio- and diastereomeric ratio determined by ^{1}H NMR (300 MHz) of the crude mixture.

[c] Isolated yields.

[d] Diastereomers not isolated.

[e] Reaction performed starting from cinnamate **6**.

[f] Values on the left refer to **3** and those on the right refer to **4**.

[g] Reaction carried out at 40 °C.

Only regioisomer **3** (R*OH = (–)-8-phenylmenthol) was obtained (**3**/**4** > 95/5) as a sole diastereomer (dr > 95/5) in almost all the cases. The absolute stereochemistry of these compounds was proposed to be *4R,5S* based on the model that assumes that, in the most stable conformation of **5**, the phenyl group on the chiral auxiliary shields the double bond frontface inducing the dipole to attack selectively from the (*Si*,*Si*)-backface (Fig. 1), as it has been demonstrated by X-ray analysis for prior addition reactions of these carbenes [18,19].

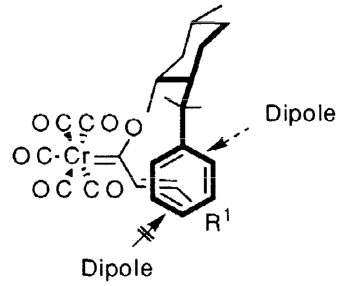


Figure 1

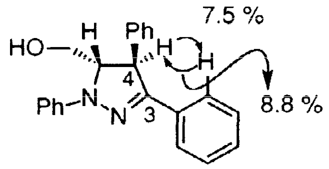


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Figure 2

Compound **3a** was also prepared from cinnamate **6** (R^1 = Ph). In this case, both regioisomers **3a** and **4a** were obtained in quantitative yield as a mixture of diastereomers (Scheme 1, Table 2, entry 2). Comparing both synthesis of **3a**, from carbene **5** and from cinnamate **6**, the advantages of Fischer carbene complexes **5** in the preparation of Δ^2-pyrazolines **3** are obvious (Table 2, entry 1 *vs* 2). The role of the metal pentacarbonyl moiety was, once more, crucial for the regio- [5] and diastereoselectivity [9] of the [3+2] cycloaddition process.

In order to confirm the regiochemistry of the cycloaddition, Δ^2-pyrazoline **3a** (R*OH = (–)-8-phenylmenthol), obtained from **5** (R^1 = Ph), and diphenylnitrilimine (R^2 = Ph) was converted into its alcohol derivative **7** (Fig. 2) by reduction with lithium aluminum hydride. The structure of **7** was unequivocally ascertained with the help of ^1H–^{13}C correlations and upon irradiation of the hydrogen on C4 or the *ortho*-hydrogen atoms of the phenyl group at C3, reciprocal NOE enhancements were observed (Fig. 2).

In conclusion, the [3+2] cycloaddition of enantiomerically pure Fischer carbene complexes and nitrilimines described here must be considered as a convenient synthesis of Δ^2-pyrazolines in a highly regio- and diastereoselective manner. Further experiments to explore the synthetic potential of **3** continue in our laboratory and will be reported in due course.

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