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(*Z*)-3-*p*-Tolylsulfinylacrylonitriles as Chiral Dipolarophiles: Reactions with Diazoalkanes

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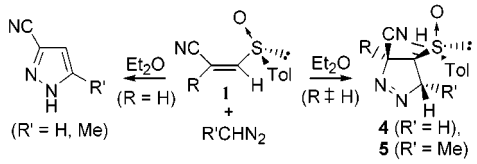
ABSTRACT



The dipolarophilic reactivity of enantiopure (*Z*)-3-*p*-tolylsulfinylacrylonitriles (1) has been evaluated with diazoalkanes. 3-Cyanopyrazoles are obtained when R = H, but with R = alkyl (Bn, *n*-Bu, and *t*-Bu) only one cycloadduct (4 or 5) is formed in high yield under mild conditions, therefore evidencing a complete control of the regioselectivity and the *endo*/*exo* and π-facial selectivities. These reactions are a new straightforward entry to the synthesis of pyrazolines and related structures and reveal the excellent dipolarophilic features of (*Z*)-sulfinylacrylonitriles.

In the course of our studies on the behavior of differently substituted vinyl sulfoxides in asymmetric cycloaddition reactions, searching for the ideal sulfinyl dienophile, we recently reported the results obtained from Diels−Alder reactions of optically pure (*Z*)-sulfinylacrylonitriles with a range of dienes, such as cyclopentadiene,[1] and less reactive dienes such as furan and acyclic dienes.[2] The main feature of these reactions is their complete π-facial selectivity, and in the case of the (*Z*)-3-*p*-tolylsulfinylacrylonitrile, both the reactivity and the *endo*-selectivity are also remarkable, which determines that this compound can be considered as one of the best monosubstituted vinyl sulfoxides reported thus far. On the other hand, its 2-alkyl-substituted derivatives exhibit a poor *endo*-selectivity and a clearly lower reactivity, which makes their reactions with cyclopentadiene the only ones to take place. These results prompted us to study the dipolarophilic behavior of optically pure sulfinylacrylonitriles.

In contrast to the wide scope of uses of chiral vinyl sulfoxides in asymmetric Diels−Alder reactions,[3] their use in dipolar reactions is much less extended,[3a,4] maybe due to the easy desulfinylation of the resulting cycloadducts. Since this problem was minimized with dipolarophiles lacking a hydrogen atom at a *cis*-arrangement with respect to the sulfinyl group, the structure of the easily obtained (*Z*)-3-*p*-tolylsulfinylacrylonitriles suggested their potential efficiency as chiral dipolarophiles. Taking into account that the sulfinyl group was shown to be very efficient in increasing the reactivity of some dipolarophilic moieties with diazoalkanes,[5] we decided to begin our study with these 1,3-dipoles, to

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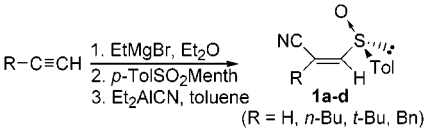
achieve a new entry to enantiomerically pure Δ^1-cyanopyrazolines, whose structures are much less frequently reported in the literature[6] than those of their corresponding Δ^2-analogues.[7] The asymmetric synthesis of pyrazolines has been studied mainly from cyclic[5,8] and much less from acyclic alkenes.[4b,8c,9]

The synthesis of the starting (*Z*)-3-sulfinylacrylonitriles **1** [Scheme 1: R = H (**1a**), *n*-Bu (**1b**), *t*-Bu (**1c**), and Bn (**1d**)]

Scheme 1

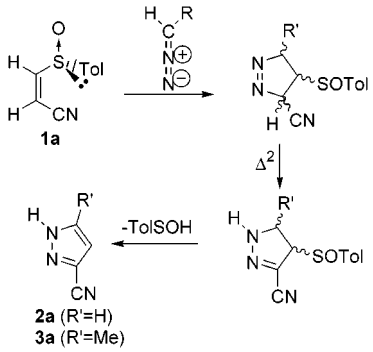


can be performed easily in just two steps from terminal alkynes according to a previously reported method[1] involving sulfinylation with optically pure menthylsulfinate followed by a completely stereoselective conjugated addition of Et_2AlCN to the resulting alkynyl sulfoxides.

The reactions of **1a** with diazomethane and diazoethane take place instantaneously, even at −10 °C, yielding the corresponding cyanopyrazoles **2a**[10,11] and **3a**.[11]

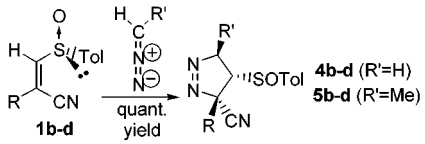
This reaction results from the easy desulfinylation of the obtained cycloadducts into the aromatic compounds, once the Δ^2 rearrangement of the initially formed pyrazolines,[7] favored by the conjugation of the C=N bond with the cyano group, has taken place (Scheme 2).

Scheme 2



The reactions of **1b**−**d** with diazomethane take place under very mild conditions (T < 0 °C) and moderated reaction times (<90 min).[12] Only one cycloadduct (**4b**−**d**) was detected in the NMR spectra of the crude reactions, and it was isolated in almost quantitative yields (Table 1). Reactions

Table 1



substrate	R	R′	*T* (°C)	time	product[a]
1b	*n*-Bu	H	−10	1.5 h	**4b**
1c	*t*-Bu	H	0	1.5 h	**4c**
1d	Bn	H	−10	45 min	**4d**
1b	*n*-Bu	Me	−10	2 min	**5b**
1c	*t*-Bu	Me	0	5 min	**5c**
1d	Bn	Me	−10	10 min	**5d**

[a] Isolated yield >93%.

with diazoethane were even faster, yielding the pyrazolines **5b**−**d** in less than 10 min under the same reaction conditions, also in quantitative yields (Table 1). Since compounds **4** and **5** bear a cyano group on a quaternary carbon (R = alkyl), thus preventing the formation of a conjugated double bond by $\Delta^1 \rightarrow D^2$ pyrazoline rearrangement, desulfinylation is not so favored (the formation of the aromatic heterocycle is not possible), making them stable enough to be isolated and purified.

Since the reactivity of diazoalkanes with acrylonitriles[13] is lower than that of compound **1a** (see above), we must conclude that the sulfinyl group increases the dipolarophilic reactivity with these 1,3-dipoles. The same conclusion had also been reached from the results obtained for 3-*p*-tolylsulfinyl-5-alkoxyfuranones with diazoalkanes.[5] Otherwise, the reactivity of compounds **1** as dipolarophiles is clearly higher than their dienophilic reactivity. **1b** and **1d** react with cyclopentadiene[1] after 1 day at room temperature in the presence of 2 equiv of $ZnBr_2$, whereas they do not

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(12) **General procedure:** To a solution of (*Z*)-3-*p*-tolylsulfinylacrylonitrile (**1**) (1 mmol) in anhydrous Et_2O (substrates **1a**−**c**) or MeOH (substrate **1d**) (2 mL), cooled at the indicated temperature (see Table 1), was added a 0.95 M solution of diazoalkane in Et_2O (10 equiv). The resulting mixture was stirred under the conditions shown in Table 1 and evaporated.

(13) In our hands, reaction of acrylonitrile with diazomethane was complete in ca. 15 min at −5 °C.

react either with furan or acyclic dienes, even at high pressures.[2] **1c** does not react with any dienes.

The most outstanding result concerning these 1,3-dipolar cycloadditions is the complete control of the stereoselectivity. Only one adduct is isolated in practically quantitative yield, even in the case of reactions with diazoethane, where four adducts could have been formed. This result indicates that the sulfinyl group is able to control the π-facial diastereoselectivity at both the starting sulfinylacrylonitrile and the dipole.

The cis relationship between the R and methyl groups in cycloadducts derived from diazoethane was established from the ^{1}H NMR parameters (values of NOE's) observed for **5b** (see Figure 1).[14]

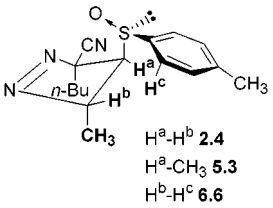


Figure 1. NOE values for **5b**.

The absolute configuration of the cycloadduct **4b** was unequivocally determined by X-ray crystallography. To get good crystals, the N−N double bond in compound **4b** was reduced by treatment with Al(Hg) in THF−H_2O (9:1) to afford compound **6b** in 90% yield, whose X-ray structure is represented in Figure 2.[15]

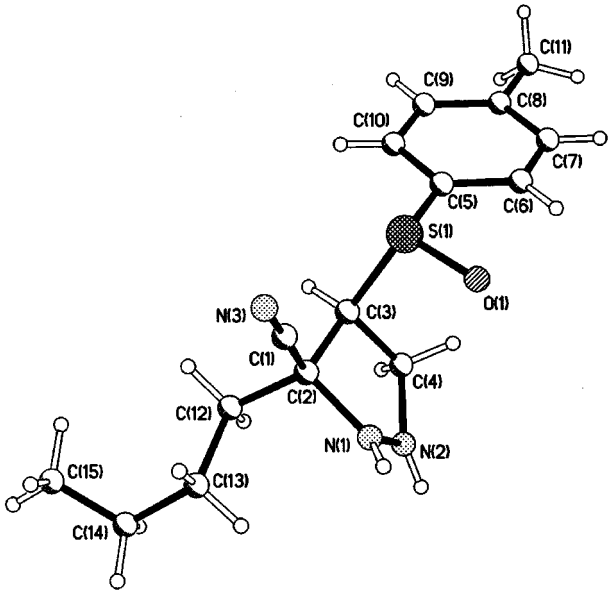
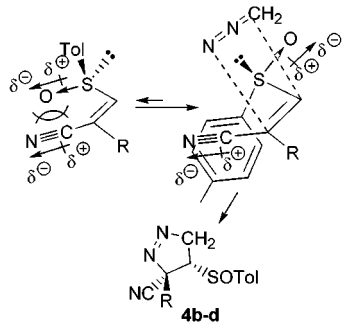


Figure 2. X-ray structure of compound **6b**.

The stereochemical result of these reactions can be rationalized as follows. The dipolar repulsion between the S−O and C−N bonds, which unstabilizes the conformation with the sulfinyl oxygen in an s-cis arrangement, must be strong enough to shift the conformational equilibrium around the C−S bond completely toward the s-trans rotamer. A more detailed discussion of the conformational preference of compounds **1** can be found in ref 1.

As shown in Scheme 3, the *p*-tolyl group sterically hinders

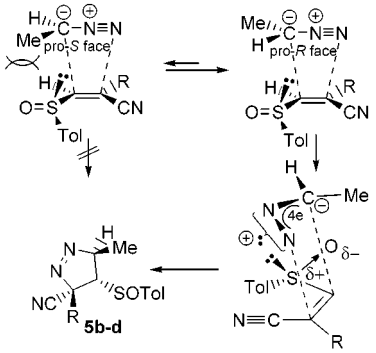
Scheme 3. Stereochemical Course of the Reactions of **1b−d** with Diazomethane



the dipole approach to the lower face of the favored s-trans conformation, thus determining exclusive attack to the less hindered upper face of the dipolarophile, which is the one supporting the lone electron pair. This assumption, which is able to explain the configuration at C-3 and C-4 of the adducts **4** and **5**, was also used to explain the behavior of compound **1a** as dienophile.[1, 2]

To explain the control of the π-facial selectivity on the dipole fragment, we assume that the interaction of Me and SOTol groups, which unstabilizes the approach of the dipolarophiles (from the less hindered face in their most stable s-trans conformation) to the pro-*S* face of the dipole (Scheme 4), must be strong enough to justify the exclusive evolution of the reagents through the most stable *endo*-like

Scheme 4. Stereochemical Course of the Reactions of **1b−d** with Diazoethane



TS resulting from the approach of the dipolarophile to the pro-*R* face of the diazoethane, where such an interaction is absent.

In conclusion, we have shown that 2-alkyl-substituted (*Z*)-3-*p*-tolylsulfinylacrylonitriles exhibit very good properties as chiral dipolarophiles in their reaction with diazoalkanes. Their reactivity is very high and they are able to control the stereoselectivity of both the dipole and the dipolarophile fragments. These reactions are one of the most straightforward and efficient entries to the asymmetric synthesis of enantiomerically pure Δ^1-pyrazolines.

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Supporting Information Available: Experimental section containing characterization of compounds **4**, **5**, and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016481O

(14) Double Pulsed Field Gradient Echo-DPFGS (Bruker DRX-500).

(15) The authors have deposited atomic coordinates for **6b** with the Cambridge Crystallographic Data Centre (deposition number CCDC 167473). The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.