A Regiospecific Reaction of Pyridazines with Vicarious Nucleophilic Substitution *via* Their Dicyanomethylide Derivatives

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The phenyl(or *p*-tolyl)sulfonylmethyl group is introduced with complete regiospecificity to the C-4 position of 3-substituted pyridazines using vicarious nucleophilic substitution of pyridazinium dicyanomethylides.

Vicarious nucleophilic substitution (VNS) of hydrogen[1] has been a useful method for the introduction of substituents to electron deficient aromatic compounds. In general, a nitro substituent on the aromatic ring is necessary for the reaction, and few electron-deficient heteroaromatics were shown to be reactive under VNS conditions without a nitro group.[2] Recently, Makozsa *et al.* reported that 3-chloro- and 3,6-dichloropyridazines underwent VNS with the carbanion of chloromethyl *p*-tolyl sulfone to form 4-substituted pyridazines.[3] Parent pyridazine or those which have electron-donating groups, however, were revealed to be reluctant to VNS.

We have recently found that pyridinium and 1,2,3-triazinium dicyanomethylides were good substrates for the VNS reaction to give γ-adducts.[4] These results prompted us to apply this reaction to pyridazines, in particular the ones that have an electron-donating substituent at their 3-positions. Although these compounds were thought to be challenging substrates due to their low reactivity and multi-reactive sites, our reaction system proved to be useful for the regiospecific introduction of substituents. Here we describe these results.

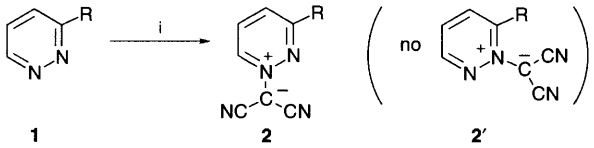
In order to increase the electron deficiency of the ring system of pyridazines **1**, their dicyanomethylide derivatives **2** were synthesised. Compound **2** was prepared by reacting **1** with tetracyanoethylene oxide (TCNEO).[5] The results are shown in Table 1. The 1,3-isomer **2** was exclusively formed since the introduction of the dicyanomethylene moiety sterically hindered the α-position due to its planar nature.[6]

The pyridazinium dicyanomethylides **2** thus obtained were allowed to react under VNS conditions[7] to afford their C-4 substituted derivatives **3**. The reaction was entirely regiospecific because of the planar conformation of the dicyanomethylene group, which might cause the steric hindrance at C-6 position.† Compounds **3** were readily transformed to the corresponding pyridazines **4** by treatment with ammonium persulfate in methanol.[8] Therefore, these three steps enabled the selective introduction of the nucleophilic substituent to the C-4 position of the pyridazines in the presence of an electron-donating substituent on their C-3 positions.

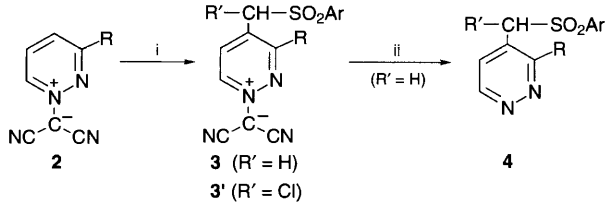
The unanticipated compounds **3′** were formed in almost all cases, and in high yields in the case of the parent pyridazine (Table 1, entry 1). These products seem to have no relation to the VNS reaction, because the vicarious leaving group still remains in the compound. The presence of aryl methyl sulfone, however, was observed in the reaction mixture, and chloromethyl aryl sulfone was revealed to disproportionate to methyl aryl sulfone and dichloromethyl aryl sulfone **6** under basic conditions (Scheme 3).‡

Compound **6** is supposed to be a more reactive VNS nucleophile,[9] but is sterically more hindered than compound **5**. Thus, reaction with compound **6** prevailed with less hindered parent pyridazinium dicyanomethylide. The obtained compound **3′** was reduced to **3** by reduction with Sn–HCl in 50–60% yield.

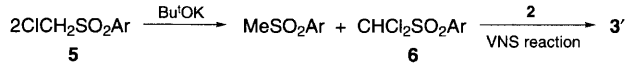
Since the arylsulfonylmethyl group thus introduced is a very useful substituent which forms a stable carbanion on its methylene moiety and can be readily transformed to other groups,[10] the products **4** are thought to be important precursors for other 4-substituted pyridazines.



Scheme 1 *Reagents and conditions*: i, tetracyanoethylene oxide, tetrahydrofuran, 0 °C, 2–5 h



Scheme 2 *Reagents and conditions*: i, chloromethyl aryl sulfone (5 equiv.), Bu^{t}OK (3 equiv.), THF, 0 °C, 15 min, then **2** (1 equiv.), DMF, 0 °C, 10 min, 1 mol dm^{-3} HCl; ii, $(NH_4)_2S_2O_8$ (2 equiv.), MeOH, reflux, 1 h



Scheme 3

Table 1 Isolated yields of compounds **2**, **3** (**3′**) and **4**

Entry	R	Yield of **2** (%)	Yield of **3** (%)		Yield of **3′** (%)		Yield of **4** (%)[a]
			Ar=Ph	Ar=*p*-Tol	Ar=Ph	Ar=*p*-Tol	
1	H	87	23	14	68	70	99
2	Me	78	59	71	10	trace	88
3	OMe	94	53	72	21	7	70
4	OEt	94	—	75	—	0	quant.
5	Ph	97	—	20	—	0	91
6	—N⬡	91	—	60	—	trace	85

[a] The yields were obtained using **3** (Ar=*p*-Tol) as the starting material.

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Footnotes

† In the previous paper,[4c] we proposed that the γ-selectivity is derived from the stability of the intermediate of the VNS reaction. Professor Makosza suggested that the anionic part of dicyanomethylide might inhibit the approach of the carbanion at the α-position by electrostatic repulsion to form the γ-adducts. This idea is also reasonable, and the mechanistic problem has not yet been clarified.

‡ When chloromethyl phenyl sulfone was dissolved in THF and Bu^{t}OK was added to the solution, two new spots emerged on TLC plates. These spots corresponded to those of methyl aryl sulfone and dichloromethyl aryl sulfone.

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