Vicarious nucleophilic substitution of pyridazinium *N*-dicyanomethylides

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Pyridazines have been allowed to react with tetracyanoethylene oxide to give pyridazinium *N*-dicyanomethylides, which are subjected to vicarious nucleophilic substitution to afford the corresponding 4-substituted derivatives in moderate to good yields. The dicyanomethylene group is readily eliminated by a radical reaction, and 4-substituted pyridazines are obtained.

Introduction

Reactions of pyridazines with nucleophiles have been widely investigated.[1] Although they are electron deficient and susceptible to attack by nucleophiles, in the absence of a suitable leaving group this is usually unfavored due to loss of aromaticity. In particular, there have been few reports concerning reaction of parent pyridazine with nucleophiles.[2]

Makosza reported that 3-chloro- and 3,6-dichloro-pyridazines underwent vicarious nucleophilic substitution[3] (VNS) with the carbanion of chloromethyl *p*-tolyl sulfone to form 4-substituted pyridazines.[4] Parent pyridazine or those which have an electron-donating group, however, were revealed to be resistant to VNS. Thus, an electron-withdrawing substituent seems to be necessary for the progress of VNS toward pyridazines.

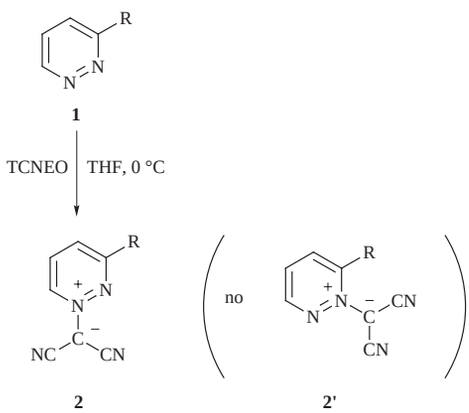
We have recently found that pyridinium and 1,2,3-triazinium dicyanomethylides are good substrates for VNS to give γ-adducts, although parent pyridine and 1,2,3-triazine are inert under the same conditions.[5] In the reaction, the dicyanomethylene group was supposed to function as an electron-withdrawing and regio-directing group. These results prompted us to apply this reaction system to pyridazines, in particular the ones that have a substituent at their 3-positions, and our reaction system was revealed to be useful for a regiospecific introduction of substituents. This paper describes detailed results of the reaction, and the elucidation of the origin of the selectivity using molecular orbital calculations.[6]

Results and discussion

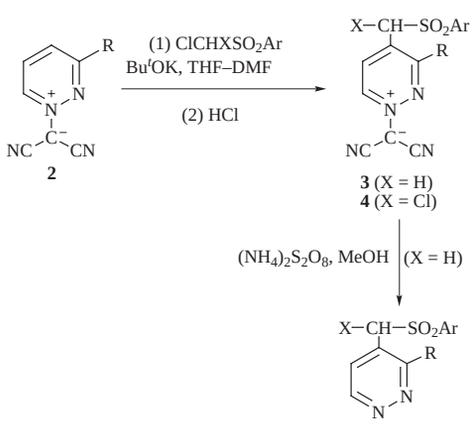
Pyridazines **1** were allowed to react with tetracyanoethylene oxide (TCNEO)[7] to give pyridazinium *N*-dicyanomethylides **2** in good yields (Scheme 1, Table 1). In the cases of 3-substituted pyridazines, exclusive formation of 1-dicyanomethylene derivatives was observed, since the introduction of a dicyanomethylene moiety sustained the steric hindrance of the α-position.[8]

Pyridazinium dicyanomethylides **2** thus obtained were allowed to react under VNS conditions[9] to afford their C-4-substituted derivatives **3** (Scheme 2). Formation of the corresponding C-6 adducts was never observed in the reaction system. Compounds **3** were readily transformed into the corresponding pyridazines **5** by treatment with ammonium persulfate in methanol.[10] As a result, these three steps enabled the selective introduction of a nucleophilic substituent to the C-4 position of pyridazines in the presence of an electron-donating substituent on their C-3 positions, which are the most unreactive positions with respect to both viewpoints of electron deficiency and steric hindrance.

Besides main products **3**, compounds **4** were formed unexpectedly, especially in high yields in the case of the parent pyridazine (Table 1, entry 1). Although the product distribution was altered by the reaction conditions, the best total yield was obtained when the yield of compound **4** was high (Table 2, entry 5).



Scheme 1



Scheme 2

These products seem to have no relation to VNS, because the vicarious leaving chlorine still remains in the compound. The presence of an aryl methyl sulfone, however, was observed in the reaction mixture, and the aryl chloromethyl sulfone was revealed to disproportionate to aryl methyl sulfone and aryl dichloromethyl sulfone **7** under basic conditions (Scheme 3). Compound **7** is supposed to be the more reactive VNS nucleophile,[11] but to be sterically more hindered than monochloride **6**.

Table 1 Isolated yields of compounds **2**, **3** (**3′**), **4** (**4′**) and **5**

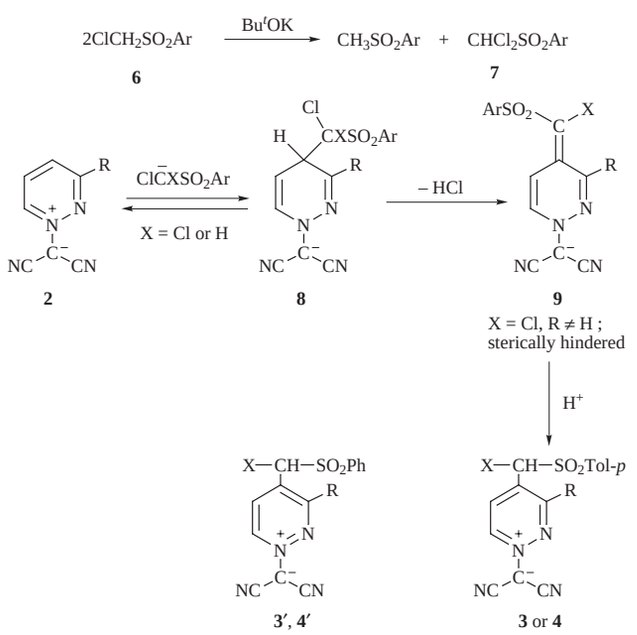
Entry	Compound	R	Yield of **2** (%)	Yield of **3** (**3′**) (%)		Yield of **4** (**4′**) (%)		Yield of **5** (%)[a]
				3 Ar = *p*-Tol	**3′** Ar = Ph	**4** Ar = *p*-Tol	**4′** Ar = Ph	
1	**a**	H	87	14	23	70	68	99
2	**b**	Me	78	71	59	trace	10	88
3	**c**	OMe	94	72	53	7	21	70
4	**d**	OEt	94	75		0		quant.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

[a] The yields were calculated using compounds **3** as the starting materials.

Table 2 Reaction of parent pyridazinium dicyanomethylide **2a** with chloromethyl phenyl sulfone under various conditions

Entry	Amount of $ClCH_2SO_2Ph$	Base (equiv.)	Solvent	Yield of **4a′** (%)	Yield of **3a′** (%)
1	1 equiv.	*t*-BuOK (2.0)	DMSO	0	0
2	2 equiv.	*t*-BuOK (2.0)	THF–DMSO	20	0
3	2 equiv.	NaH (2.0)	THF–DMSO	0	12
4	2 equiv.	*t*-BuOK (2.0)	THF–DMF	47	12
5	5 equiv.	*t*-BuOK (3.0)	THF–DMF	68	23
6	5 equiv.	*t*-BuOK (5.0)	THF–DMF	38	27
7	5 equiv.	NaOMe (3.0)	THF–DMF	0	14
8	5 equiv.	*t*-BuOK (3.0)	DMF	18	7

Thus, reaction with dichloride **7** prevailed in the case of the less hindered parent pyridazinium dicyanomethylide, but other 3-substituted derivatives suffered steric repulsion between the substituent and chlorine in the vicinity (Scheme 3, intermediate **9**). The obtained compound **4a′** was transformed into compound **3a′** by reduction with Sn–HCl in 60% yield.



Scheme 3

Although the mechanism concerning elimination of dicyanomethylene has yet to be rationalized, we supposed that the hydroxymethyl radical attacked the dicyanomethylene carbon to form a radical, which abstracted hydrogen from the solvent, and this was followed by 1,4-elimination to give compounds **5**.[5] Since the arylsulfonylmethyl group thus introduced is a highly useful substituent which forms a stable carbanion on its methylene moiety, and is readily transformed into other groups,[12] the products **5** are thought to be important precursors for other 4-substituted pyridazines.

In order to clarify the reason for the high regiospecificity, molecular orbital calculations were carried out using the PM3 procedure[13] with the standard parameters, as implemented in the MOPAC program,[14] and the results are summarized in Fig. 1.

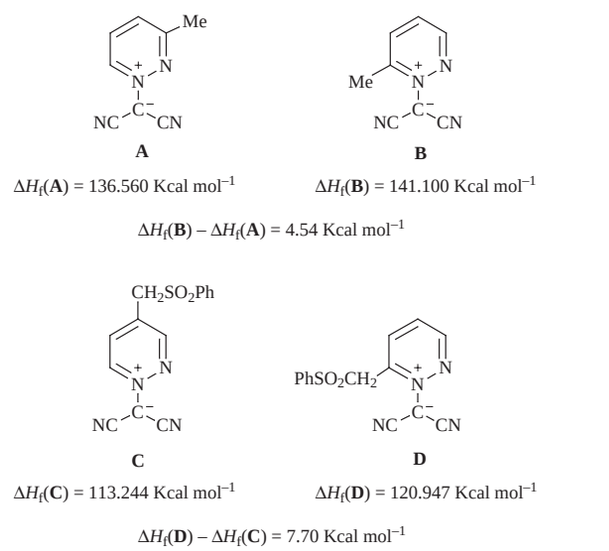
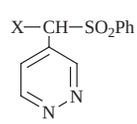


Fig. 1 Calculated heats of formation of the isolated intermediates (**A** and **C**) and corresponding regioisomers (**B** and **D**)



10 X = Cl
11 X = H

First, calculations were performed with respect to the heats of formation (ΔH_f) of fully geometry-optimized 3-methylpyridazinium 1-dicyanomethylide (**A**) and 2-dicyanomethylide (**B**). In these cases, dicyanomethylene moieties are revealed to be coplanar with the pyridazine ring,† and the 2-dicyanomethylide is less stable than the 1-dicyanomethylide by 4.5 kcal mol^{-1} (1 cal = 4.185 J). Thus, the selectivity of the first step was

† Even when the geometry optimization was begun using an initial structure that has a perpendicular dicyanomethylene group with respect to the pyridazine ring, an optimized geometry was coplanar.

thought to be derived from the stability of the products.‡ Next, the stability of the products was estimated by using 4-(phenylsulfonylmethyl)pyridazinium 1-dicyanomethylide (**C**) and the corresponding 6-substituted derivative (**D**). The results show that 4-substituted derivative (**C**) is more stable by 7.7 kcal mol^{-1} than is isomer **D**. Even in the case of sterically hindered **D**, the dicyanomethylene group was shown to stay almost coplanar to the pyridazine ring.§ Although the N–C bond between the pyridazine ring and the dicyanomethylene group is denoted as a single bond, the barrier to rotation is calculated as 20.8 kcal mol^{-1}, and the structure of the transition state has a dihedral angle of 89.5° between the two planes. Thus, the high regioselectivity of the first and second steps might be attributed to the (co)planar nature of the dicyanomethylene group toward the pyridazine ring.

Conclusions

In summary, we have developed a new method that introduces a *nucleophilic* substituent to the C-4 position (*electron-richest* site among the three carbons) of 3-substituted pyridazines by three steps, in which the first and second ones are regiospecific. The origin of this selectivity might be to do with the coplanarity of the dicyanomethylene moiety with the azaaromatic ring, and this character is thought to be of use for other nucleophilic reactions. Applications are now under investigation.

Experimental

All mps were taken on a Büchi 535 and/or a Yanaco micro melting point apparatus and are uncorrected. NMR spectra were measured with a JEOL GX400 or an LA500 spectrometer using tetramethylsilane as internal standard. *J*-Values are given in Hz.

Reaction of pyridazines with tetracyanoethylene oxide

To a THF solution of pyridazine (5 mmol) at 0 °C was added TCNEO (5 mmol) and the mixture was stirred at 0 °C for 2–5 h. Then the solvent was evaporated off to leave a residue, which was chromatographed on silica gel (CH_2Cl_2–AcOEt) to give compounds **2**. The spectral data of compounds **2a** and **2c** have already been reported.[8a]

3-Methylpyridazinium 1-dicyanomethylide 2b. *Yellow flakes* from MeOH (78%); mp 230–231 °C (decomp.) (Found: C, 61.02; H, 3.52; N, 35.68. $C_8H_6N_4$ requires C, 60.75; H, 3.82; N, 35.42%); δ_H(400 MHz; [$^2H_6$]DMSO) 2.55 (3 H, s), 7.38 (1 H, d, *J* 8.1), 7.95 (1 H, dd, *J* 8.1 and 6.2) and 8.68 (1 H, d, *J* 6.2); δ_C(100 MHz; [$^2H_6$]DMSO) 21.48, 65.97, 116.07, 122.77, 128.04, 133.98 and 161.72.

3-Ethoxypyridazinium 1-dicyanomethylide 2d. *Yellow flakes* from EtOH (94%); mp 201 °C (Found: C, 57.43; H, 4.25; N, 29.67. $C_9H_8N_4O$ requires C, 57.44; H, 4.28; N, 29.77%); δ_H(400 MHz; [$^2H_6$]DMSO) 1.40 (3 H, t, *J* 7.0), 4.40 (2 H, q, *J* 7.0), 7.05 (1 H, d, *J* 8.8), 7.91 (1 H, dd, *J* 8.8 and 6.6) and 8.53 (1 H, d, *J* 6.6); δ_C(100 MHz; [$^2H_6$]DMSO) 13.84, 64.59, 65.62, 113.29, 116.22, 125.45, 135.92 and 164.43.

3-Phenylpyridazinium 1-dicyanomethylide 2e. *Yellow needles* from EtOH (97%); mp 210–213 °C (Found: C, 70.93; H, 3.52; N, 25.39. $C_{13}H_8N_4$ requires C, 70.89; H, 3.66; N, 25.44%); δ_H(400 MHz; [$^2H_6$]DMSO) 7.57–7.61 (3 H, m), 8.01–8.12 (4 H, m) and 8.77 (1 H, d, *J* 6.2); δ_C(100 MHz; [$^2H_6$]DMSO) 66.53, 116.11, 119.44, 127.01, 129.14, 129.31, 131.78, 132.59, 134.79 and 158.34.

3-Piperidinopyridazinium 1-dicyanomethylide 2f. *Yellow needles* from EtOH (91%); mp 176–177 °C (Found: C, 63.68; H, 5.77; N, 30.90. $C_{12}H_{13}N_5$ requires C, 63.42; H, 5.77; N, 30.82%); δ_H(400 MHz; [$^2H_6$]DMSO) 1.57 (4 H, br), 1.64 (2 H, br), 3.59 (4 H, br), 7.18 (1 H, d, *J* 9.2), 7.65 (1 H, dd, *J* 9.2 and 5.9) and 8.15 (1 H, d, *J* 5.9); δ_C(100 MHz; [$^2H_6$]DMSO) 23.67, 24.80, 45.16, 64.43, 109.90, 117.05, 121.02, 133.29 and 157.83.

Vicarious nucleophilic substitution of pyridazinium dicyanomethylides with aryl chloromethyl sulfone

Potassium *tert*-butoxide (374 mg, 3 mmol) was suspended in THF (3 ml), the mixture was cooled to 0 °C, then aryl chloromethyl sulfone (5 mmol) was added dropwise under vigorous stirring. The mixture was stirred for 15 min at 0 °C, then a DMF solution (2 ml) of pyridazinium dicyanomethylide (1 mmol) was introduced to the mixture. The reaction was allowed to continue for another 10 min at 0 °C, then the mixture was quenched with 1 M HCl (5 ml). The mixture was extracted with AcOEt, and the organic layer was dried over $MgSO_4$, then evaporated. The residue was chromatographed on alumina or silica gel to separate products **3** and **4**. The products were obtained as yellow solids, and were purified by recrystallization.

4-(*p*-Tolylsulfonylmethyl)pyridazinium 1-dicyanomethylide 3a. *Yellow needles* from AcOEt (14%); mp 258 °C (decomp.) (Found: C, 57.77; H, 3.76; N, 17.92. $C_{15}H_{12}N_4O_2S$ requires C, 57.68; H, 3.87; N, 17.94%); δ_H(400 MHz; [$^2H_6$]DMSO) 2.44 (3 H, s), 4.85 (2 H, s), 7.45 (2 H, d, *J* 8.1), 7.67 (2 H, d, *J* 8.1), 7.77 (1 H, dd, *J* 6.6 and 2.6), 8.63 (1 H, s) and 8.76 (1 H, d, *J* 6.6); δ_C(100 MHz; [$^2H_6$]DMSO) 21.35, 56.78, 67.05, 115.98, 123.91, 128.50, 130.03, 130.16, 134.94, 135.56, 145.37 and 152.94.

4-(Phenylsulfonylmethyl)pyridazinium 1-dicyanomethylide 3a′. *Yellow flakes* from CH_3CN (23%); mp 236–237 °C (decomp.) (Found: C, 56.36; H, 3.29; N, 18.70. $C_{14}H_{10}N_4O_2S$ requires C, 56.36; H, 3.38; N, 18.79%); δ_H(400 MHz; [$^2H_6$]DMSO) 4.90 (2 H, s), 7.64–7.81 (6 H, m), 8.62 (1 H, s) and 8.76 (1 H, d, *J* 6.6); δ_C(100 MHz; [$^2H_6$]DMSO) 56.50, 66.86, 115.73, 123.50, 128.25, 129.53, 129.80, 134.54, 135.34, 137.53 and 152.71.

4-[Chloro(*p*-tolylsulfonyl)methyl]pyridazinium 1-dicyanomethylide 4a. *Orange prisms* from MeOH (70%); mp 200–201 °C (decomp.) (Found: C, 51.83; H, 3.10; N, 16.06. $C_{15}H_{11}ClN_4O_2S$ requires C, 51.95; H, 3.20; N, 16.16%); δ_H(400 MHz; [$^2H_6$]DMSO) 2.47 (3 H, s), 6.95 (1 H, s), 7.52 (2 H, d, *J* 8.1), 7.76 (2 H, d, *J* 8.1), 7.91 (1 H, dd, *J* 7.0 and 2.6), 8.75 (1 H, d, *J* 7.0) and 8.78 (1 H, br s); δ_C(100 MHz; [$^2H_6$]DMSO) 21.24, 68.43, 69.69, 115.09, 123.39, 129.27, 129.93, 130.13, 130.75, 133.60, 146.63 and 150.85.

4-[Chloro(phenylsulfonyl)methyl]pyridazinium 1-dicyanomethylide 4a′. *Yellow powder* from MeOH (68%); mp 206–207 °C (decomp.) (Found: C, 50.53; H, 2.64; N, 16.74. $C_{14}H_9ClN_4O_2S$ requires C, 50.53; H, 2.73; N, 16.84%); δ_H(400 MHz; [$^2H_6$]DMSO) 6.89 (1 H, s), 7.61–7.71 (2 H, m), 7.82–8.04 (4 H, m), 8.76 (1 H, d, *J* 7.0) and 8.79 (1 H, s); δ_C(100 MHz; [$^2H_6$]DMSO) 67.60, 68.04, 112.85, 121.30, 126.52, 127.81, 128.34, 132.30, 132.56, 133.76 and 149.62.

3-Methyl-4-(*p*-tolylsulfonylmethyl)pyridazinium 1-dicyanomethylide 3b. *Yellow prisms* from CH_3CN (71%); mp 236–237 °C (decomp.) (Found: C, 58.83; H, 4.23; N, 17.07; S, 9.53. $C_{16}H_{14}N_4O_2S$ requires C, 58.88; H, 4.32; N, 17.17; S, 9.82%); δ_H(400 MHz; [$^2H_6$]DMSO) 2.29 (3 H, s), 2.44 (3 H, s), 4.90 (2 H, s), 7.46 (2 H, d, *J* 8.4), 7.67 (1 H, d, *J* 6.6), 7.70 (2 H, d, *J* 8.4) and 8.70 (1 H, d, *J* 6.6); δ_C(100 MHz; [$^2H_6$]DMSO) 19.43, 21.11, 56.27, 66.28, 115.95, 123.22, 128.22, 128.37, 130.00, 135.11, 136.02, 145.30 and 161.58.

3-Methyl-4-(phenylsulfonylmethyl)pyridazinium 1-dicyanomethylide 3b′. *Yellow needles* from CH_3CN (59%); mp 232–

‡ When 3-methylpyridazine was oxidized with MCPBA, a 2:1 mixture of 1-oxide and 2-oxide was obtained. The calculated heats of formation are 43.281 kcal mol^{-1} (1-oxide) and 43.930 kcal mol^{-1} (2-oxide), respectively, thus the stability of the products seems to control the product distribution dominantly. This is probably because the two transition states would have similar structures.

§ In the calculated structure **D**, the dihedral angle between the pyridazine ring and the dicyanomethylene group is 10°, while that in structure **C** is 0.1°.

233 °C (decomp.) (Found: C, 57.53; H, 3.78; N, 17.68; S, 10.09. $C_{15}H_{12}N_4O_2S$ requires C, 57.68; H, 3.87; N, 17.94; S, 10.26%); δ_H(400 MHz; [$^2H_6$]DMSO) 2.30 (3 H, s), 4.92 (2 H, s), 7.65–7.69 (3 H, m), 7.79–7.85 (3 H, m) and 8.70 (1 H, d, *J* 6.6); δ_C(100 MHz; [$^2H_6$]DMSO) 19.42, 56.17, 66.34, 115.91, 123.02, 128.19, 128.34, 129.60, 134.61, 136.05, 137.91 and 161.60.

4-[Chloro(phenylsulfonyl)methyl]-3-methylpyridazinium 1-dicyanomethylide 4b′. *Orange prisms* from MeOH (10%); mp 253 °C (decomp.) (Found: C, 51.62; H, 3.06; N, 15.94. $C_{15}H_{11}ClN_4O_2S$ requires C, 51.95; H, 3.20; N, 16.16%); δ_H(400 MHz; [$^2H_6$]DMSO) 2.42 (3 H, s), 7.05 (1 H, s), 7.70–7.74 (2 H, m), 7.87–7.92 (4 H, m) and 8.68 (1 H, d, *J* 7.0); δ_C(100 MHz; [$^2H_6$]DMSO) 19.81, 68.18, 68.93, 115.25, 123.11, 128.09, 129.78, 130.27, 134.11, 134.18, 135.81 and 160.35.

3-Methoxy-4-(*p*-tolylsulfonylmethyl)pyridazinium 1-dicyanomethylide 3c. *Yellow prisms* from MeOH (72%); mp 226–229 °C (decomp.) (Found: C, 56.23; H, 4.04; N, 16.32; S, 8.90. $C_{16}H_{14}N_4O_3S$ requires C, 56.13; H, 4.12; N, 16.36; S, 9.36%); δ_H(400 MHz; [$^2H_6$]DMSO) 2.48 (3 H, s), 3.76 (3 H, s), 4.30 (2 H, s), 7.37 (2 H, d, *J* 8.4), 7.56 (1 H, d, *J* 6.2), 7.65 (2 H, d, *J* 8.4) and 8.17 (1 H, d, *J* 6.2); δ_C(100 MHz; [$^2H_6$]DMSO) 21.27, 54.15, 55.69, 66.71, 114.36, 115.94, 125.35, 128.49, 129.90, 135.55, 137.26, 145.23 and 162.68.

3-Methoxy-4-(phenylsulfonylmethyl)pyridazinium 1-dicyanomethylide 3c′. *Yellow needles* from MeOH (53%); mp 220–222 °C (decomp.) (Found: C, 55.07; H, 3.59; N, 16.97; S, 9.68. $C_{15}H_{12}N_4O_3S$ requires C, 54.87; H, 3.68; N, 17.06; S, 9.76%); δ_H(400 MHz; [$^2H_6$]DMSO) 3.55 (3 H, s), 4.73 (2 H, s), 7.64–7.66 (2 H, m), 7.76–7.82 (4 H, m) and 8.69 (1 H, d, *J* 6.2); δ_C(100 MHz; [$^2H_6$]DMSO) 54.09, 55.70, 66.71, 114.23, 115.95, 125.40, 128.44, 129.51, 134.56, 137.28, 138.38 and 162.65.

4-[Chloro(*p*-tolylsulfonyl)methyl]-3-methoxypyridazinium 1-dicyanomethylide 4c. *Orange prisms* from MeOH (7%); mp 229 °C (decomp.) (Found: C, 51.21; H, 3.47; N, 14.82. $C_{16}H_{13}ClN_4O_3S$ requires C, 51.00; H, 3.48; N, 14.87%); δ_H(400 MHz; [$^2H_6$]DMSO) 2.46 (3 H, s), 3.71 (3 H, s), 6.66 (1 H, s), 7.48 (2 H, d, *J* 8.1), 7.73 (2 H, d, *J* 8.1), 7.89 (1 H, d, *J* 6.6) and 8.55 (1 H, d, *J* 6.6); δ_C(100 MHz; [$^2H_6$]DMSO) 21.36, 56.06, 66.89, 68.25, 114.35, 115.11, 124.90, 130.03, 130.10, 131.52, 135.45, 146.61 and 161.30.

4-[Chloro(phenylsulfonyl)methyl]-3-methoxypyridazinium 1-dicyanomethylide 4c′. *Yellow prisms* from MeOH (21%); mp 193–194 °C (decomp.) (Found: C, 49.64; H, 2.95; N, 15.32. $C_{15}H_{11}ClN_4O_3S$ requires C, 49.66; H, 3.06; N, 15.44%); δ_H(400 MHz; [$^2H_6$]DMSO) 3.66 (3 H, s), 6.78 (1 H, s), 7.67–7.71 (2 H, m), 7.84–7.92 (4 H, m) and 8.55 (1 H, d, *J* 6.6); δ_C(100 MHz; [$^2H_6$]DMSO) 55.92, 66.76, 68.05, 114.13, 115.06, 124.94, 129.49, 129.92, 134.32, 135.36, 135.51 and 161.09.

3-Ethoxy-4-(*p*-tolylsulfonylmethyl)pyridazinium 1-dicyanomethylide 3d. *Yellow prisms* from AcOEt (75%); mp 184–186 °C (Found: C, 57.35; H, 4.46; N, 15.70; S, 8.80. $C_{17}H_{16}N_4O_3S$ requires C, 57.29; H, 4.52; N, 15.72; S, 9.00%); δ_H(400 MHz; [$^2H_6$]DMSO) 1.06 (3 H, t, *J* 7.0), 2.42 (3 H, s), 3.97 (2 H, q, *J* 7.0), 4.67 (2 H, s), 7.43 (2 H, d, *J* 8.4), 7.61 (2 H, d, *J* 8.4), 7.82 (1 H, d, *J* 6.2) and 8.59 (1 H, d, *J* 6.2); δ_C(100 MHz; [$^2H_6$]DMSO) 13.48, 21.25, 54.12, 65.03, 66.61, 114.44, 116.09, 125.40, 128.50, 129.99, 135.68, 137.32, 145.28 and 162.21.

3-Phenyl-4-(*p*-tolylsulfonylmethyl)pyridazinium 1-dicyanomethylide 3e. *Yellow needles* from MeOH (20%); mp 209 °C (decomp.) (Found: C, 65.02; H, 4.10; N, 14.46. $C_{21}H_{16}N_4O_2S$ requires C, 64.93; H, 4.15; N, 14.42%); δ_H(400 MHz; [$^2H_6$]DMSO) 2.42 (3 H, s), 4.77 (2 H, s), 7.17 (2 H, d, *J* 8.4), 7.28 (2 H, d, *J* 7.6), 7.36 (2 H, d, *J* 8.4), 7.42 (2 H, t, *J* 7.6), 7.50 (1 H, t, *J* 7.6), 8.06 (1 H, d, *J* 6.7) and 8.87 (1 H, d, *J* 6.7); δ_C(100 MHz; [$^2H_6$]DMSO) 21.28, 56.27, 67.44, 115.79, 121.86, 128.07, 128.67, 128.76, 128.79, 130.15, 130.21, 132.58, 134.98, 137.00, 145.38 and 161.39.

3-Piperidino-4-(*p*-tolylsulfonylmethyl)pyridazinium 1-dicyanomethylide 3f. *Yellow flakes* from MeOH (60%); mp 219–221 °C (decomp.) (Found: C, 60.85; H, 5.32; N, 17.64; S, 7.77. $C_{20}H_{21}N_5O_2S$ requires C, 60.74; H, 5.35; N, 17.71; S, 8.11%); δ_H(400 MHz; [$^2H_6$]DMSO) 1.40 (6 H, br), 2.41 (3 H, s), 2.87 (4 H, br), 4.62 (2 H, s), 7.41 (2 H, d, *J* 8.1), 7.57 (2 H, d, *J* 8.1), 7.85 (1 H, d, *J* 6.2) and 8.51 (1 H, d, *J* 6.2); δ_C(100 MHz; [$^2H_6$]DMSO) 21.20, 23.34, 24.66, 50.61, 56.33, 66.09, 116.31, 117.13, 124.82, 128.32, 129.94, 135.71, 137.26, 145.27 and 162.13.

Transformation of chlorides 4′ into 3′

A mixture of compound **4a′** (0.2 mmol), 1 M HCl (2 ml), MeOH (3 ml), and Sn powder (1 mmol) was heated for 1 h under reflux, then diluted with water and neutralized with K_2CO_3. Then CH_2Cl_2 was added and the mixture was filtered. The organic layer was separated from the filtrate, and the residual aqueous layer was extracted with CH_2Cl_2. All the organic layers were combined, dried over $MgSO_4$, and evaporated to leave a residue, which was chromatographed on alumina to give the product **3a′** in 60% yield.

Elimination of dicyanomethylene group

A mixture of a pyridazinium dicyanomethylide (0.5 mmol) and ammonium persulfate (1 mmol) in methanol (2 ml) was heated for 0.5–2 h under reflux. After the mixture had cooled, 10 ml of water was added and the solution was neutralized with K_2CO_3. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$, and then evaporated. The oily residue was chromatographed on alumina to afford the product. In the case of solid products, direct recrystallization was enough for purification of the products.

4-(*p*-Tolylsulfonylmethyl)pyridazine 5a. *Needles* from CH_2Cl_2–hexane (99%); mp 139 °C (Found: C, 58.01; H, 4.70; N, 11.24. $C_{12}H_{12}N_2O_2S$ requires C, 58.05; H, 4.87; N, 11.28%); δ_H(400 MHz; $CDCl_3$) 2.45 (3 H, s), 4.33 (2 H, s), 7.32 (2 H, d, *J* 8.4), 7.46 (1 H, d, *J* 5.5), 7.55 (2 H, d, *J* 8.4), 8.84 (1 H, s) and 9.18 (1 H, d, *J* 5.5); δ_C(100 MHz; $CDCl_3$) 21.70, 59.45, 127.80, 128.44, 128.59, 130.13, 134.04, 145.97, 151.16 and 152.45.

3-Methyl-4-(*p*-tolylsulfonylmethyl)pyridazine 5b. *Flakes* from CH_2Cl_2–hexane (88%); mp 134 °C (Found: C, 59.42; H, 5.35; N, 10.64. $C_{13}H_{14}N_2O_2S$ requires C, 59.52; H, 5.38; N, 10.68%); δ_H(400 MHz; $CDCl_3$) 2.45 (3 H, s), 2.49 (3 H, s), 4.36 (2 H, s), 7.24 (1 H, d, *J* 5.1), 7.32 (2 H, d, *J* 8.4), 7.55 (2 H, d, *J* 8.4) and 9.01 (1 H, d, *J* 5.1); δ_C(100 MHz; $CDCl_3$) 19.87, 21.66, 58.37, 127.49, 128.34, 128.43, 130.12, 134.58, 145.91, 149.64 and 160.01.

3-Methoxy-4-(*p*-tolylsulfonylmethyl)pyridazine 5c. *Needles* from CH_2Cl_2–hexane (70%); mp 164–165 °C (Found: C, 56.05; H, 5.04; N, 9.99. $C_{13}H_{14}N_2O_3S$ requires C, 56.10; H, 5.07; N, 10.06%); δ_H(400 MHz; $CDCl_3$) 2.43 (3 H, s), 3.74 (3 H, s), 4.37 (2 H, s), 7.28 (2 H, d, *J* 8.1), 7.45 (1 H, d, *J* 4.8), 7.52 (2 H, d, *J* 8.1) and 8.85 (1 H, d, *J* 4.8); δ_C(100 MHz; $CDCl_3$) 21.48, 54.65, 54.91, 118.67, 128.42, 129.49, 130.29, 134.87, 145.21, 147.23 and 162.73.

3-Ethoxy-4-(*p*-tolylsulfonylmethyl)pyridazine 5d. *Needles* from CH_2Cl_2–hexane (quant.); mp 104 °C (Found: C, 57.72; H, 5.53; N, 9.42. $C_{14}H_{16}N_2O_3S$ requires C, 57.51; H, 5.52; N, 9.58%); δ_H(400 MHz; $CDCl_3$) 1.15 (3 H, t, *J* 7.0), 2.41 (3 H, s), 4.18 (2 H, q, *J* 7.0), 4.39 (2 H, s), 7.26 (2 H, d, *J* 8.4), 7.48 (1 H, d, *J* 4.4), 7.50 (2 H, d, *J* 8.4) and 8.83 (1 H, d, *J* 4.4); δ_C(100 MHz; $CDCl_3$) 14.04, 21.54, 54.91, 63.54, 118.60, 128.53, 129.60, 130.31, 135.11, 145.27, 147.04 and 162.65.

3-Phenyl-4-(*p*-tolylsulfonylmethyl)pyridazine 5e. Oil (91%) (Found: 324.0933. Calc. for $C_{18}H_{16}N_2O_2S$: *M*, 324.0927); δ_H(400 MHz; $CDCl_3$) 2.43 (3 H, s), 4.45 (2 H, s), 7.12–7.14 (2 H, m), 7.18 (2 H, d, *J* 8.4), 7.31 (2 H, d, *J* 8.4), 7.34–7.43 (3 H, m), 7.79 (1 H, d, *J* 5.1) and 9.22 (1 H, d, *J* 5.1); δ_C(100 MHz; $CDCl_3$) 21.57, 57.24, 126.94, 128.12, 128.40, 128.69, 129.00, 129.15,

129.98, 134.78, 135.11, 145.49, 149.77 and 162.16. The above mass spectrum was recorded on a JEOL JMS-SX102A instrument.

3-(Piperidino)-4-(*p*-tolylsulfonylmethyl)pyridazine 5f. *Flakes* from CH_2Cl_2–hexane (85%); mp 135 °C (Found: C, 61.89; H, 6.35; N, 12.69. $C_{17}H_{21}N_3O_2S$ requires C, 61.61; H, 6.39; N, 12.68%); δ_H(400 MHz; $CDCl_3$) 1.52 (6 H, br), 2.38 (3 H, s), 2.82 (4 H, br), 4.37 (2 H, s), 7.22 (2 H, d, *J* 7.7), 7.42 (2 H, d, *J* 7.7), 7.65 (1 H, d, *J* 4.8) and 8.89 (1 H, d, *J* 4.8); δ_C(100 MHz; $CDCl_3$) 21.48, 23.82, 25.65, 52.10, 55.79, 123.18, 128.21, 129.44, 129.53, 134.88, 145.18, 147.50 and 164.36.

Although compounds **4** or **4′** are also available for the elimination of the dicyanomethylene group, partial reduction of chlorine occurred to give a mixture of products. In the case of compound **4a′**, the main product **10** was obtained in 72% yield accompanied by dechlorinated product **11** (22%).

4-[Chloro(phenylsulfonyl)methyl]pyridazine 10. *Needles* from CH_2Cl_2–hexane (72%); mp 161 °C (Found: C, 48.94; H, 3.25; N, 10.32. $C_{11}H_9ClN_2O_2S$ requires C, 49.17; H, 3.38; N, 10.42%); δ_H(400 MHz; $CDCl_3$) 5.72 (1 H, s), 7.57–7.62 (3 H, m), 7.75–7.80 (3 H, m), 9.17 (1 H, s) and 9.28 (1 H, d, *J* 5.5); δ_C(100 MHz; $CDCl_3$) 72.20, 126.54, 129.38, 130.30, 130.84, 133.45, 135.52, 150.60 and 151.06.

4-(Phenylsulfonylmethyl)pyridazine 11. *Needles* from CH_2Cl_2–hexane (22%); mp 188 °C (Found: C, 56.22; H, 4.25; N, 11.90. $C_{11}H_{10}N_2O_2S$ requires C, 56.39; H, 4.30; N, 11.96%); δ_H(400 MHz; $CDCl_3$) 4.31 (2 H, s), 7.38–7.40 (1 H, m), 7.52–7.56 (2 H, m), 7.68–7.70 (3 H, m), 8.82 (1 H, s) and 9.18 (1 H, d, *J* 4.0); δ_C(100 MHz; $CDCl_3$) 59.39, 127.80, 128.37, 128.43, 129.53, 134.69, 137.04, 151.16 and 152.42.

Molecular orbital calculations

The calculations were performed using PM3 with the standard parameters, as implemented in the MOPAC program. The initial geometries of calculated compounds were determined using molecular mechanics 2 (MM2).[15] The transition state was located approximately by the reaction-coordinate method,[16] refined by minimizing gradient norm, and then characterized by calculating force matrix.[17]

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