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A Novel Nucleophilic Substitution of 3-Halo-6-phenoxypyridazines

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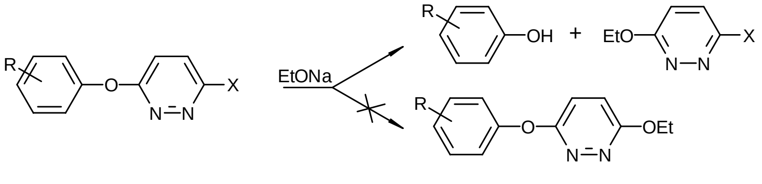
Abstract: A novel nucleophilic substitution of pyridazines is found, in which phenoxy group is dislodged rather than the halogen atom, on treating 3-halo-6-phenoxypyridazines with alkoxy anion. The reactivity of substituents on benzene ring and the halogen atom of pyridazines are studied. Reasonable explanation based on the quantum chemical calculations are given.

Keywords: Nucleophilic substitution; 3-halo-6-phenoxypyridazines; mechanisms.

Pyridazines have been found wide application in chemistry of pharmaceuticals and agrochemicals[1, 2], therefore methods of direct introduction of substituents into pyridazine ring are of great interest[3]. Pyridazine belongs to highly electrophilic heterocycles, it undergoes various nucleophilic substitution with X^-, O^-, S^-, C^- and H^- anions[4].

In general, monosubstitution of 3, 6-dihalopyridazine is quite easy, but the substitution of the second halogen atom is very difficult[5]. When we try to replace the halogen atom of 3-halo-6-phenoxypyridazine with the strong necleophile alkoxy anion, a novel nucleophilic substitution of the pyridazine derivatives is found, in which phenoxy group is replaced rather than the halogen atom. So far, the substitution has not been reported.

Scheme 1



Ethoxy anion reacting with pyridazine I_a~III_b using sodium ethoxide undre reflux for 3h provides 3-halo-6-ethoxypyridazines in 45-98% yields as shown in **Table**. The results show: When X=I, the phenoxy group is easier to be substituted. The reactivity of the pyridazines with substituents on benzene ring is in the order $NO_2 > Cl > Me$. Under mild condition, the reaction time is longer with higher yield.

Table The Results of Pyridazines Reacting with Ethoxide and Their Calculations

No	R	X	Yield/%	σ (C_3)	σ (C_6)	LUMO
I_a	2-Me	I	77.0	-0.280	0.088	-0.66
I_b	2-Me	Cl	45.6	-0.079	0.075	-0.71
I_b^*	2-Me	Cl	70.5	-0.079	0.075	-0.71
II_a	2-Cl	I	97.9	-0.278	0.087	-0.73
Ii_b	2-Cl	Cl	57.0	-0.077	0.073	-0.78
III_a	2-NO_2	I	98.4	-0.273	0.091	-1.13
III_b	2-NO_2	Cl	52.6	-0.072	0.078	-1.14

* Reacted for 90h at r.t.

When a mixture of 1mmol of 3-chloro and 1mmol of 3-iodo-6- (2-methylphenoxy)-pyridazine is heated under reflux for 7.5h with 1mmol of sodium ethoxide, the product mixture has a GC-MS spectrum, which indicates that the ratio of recovered chloro and iodo substrate is about 4 to 1. The ratio of 3-iodo and 3-chloro product is about 2 to 1. The results show that the iodo substrate is more prone to react than the chloro substrate.

In order to explain the experimental results, quantum chemical calculation of 3-halo-6-phenoxypyridazines using the MOPAC program at the SYBYL work-station gives the values of charge and LUMO as shown in the above **Table** .The results show that the nucleophilic substitution should occur on the 6 position of the pyridazines with positive charge. The 3-iodo substrate with lower LUMO energy should be more prone to react, because it may have a more stable transition state.

The research on similar reactions of other heterocycles is in progress.

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