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INTERMOLECULAR HETEROAROMATIC NUCLEOPHILIC SUBSTITUTION REACTION VIA THE SULPHUR YLIDE REARRANGEMENT: C-ATTACK VS. O-ATTACK

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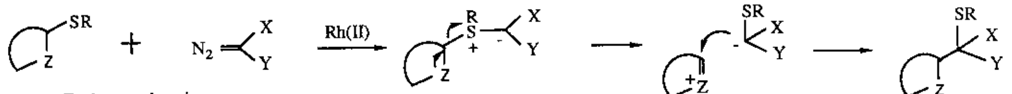
Abstract —— Intermolecular aromatic nucleophilic substitution reaction of the heterocyclic sulphide derivatives with α-diazo esters in the presence of rhodium (II) acetate was investigated to give the oxygen-introduced products *via* the sulphur ylide rearrangement.

Versatile methodology for nucleophilic substitutions at aromatic carbon atoms[1] has been well-developed and many such reactions have been found to be used widely in organic syntheses.

Recently, we have developed a novel carbon-carbon bond forming reaction at the α-position to nitrogen[2] or oxygen,[3] and at a benzylic position[4] by employing inter- or intramolecular carbenoid displacement reaction which involved a sulphur ylide rearrangement as a key step. It has been established that these reactions proceeded through an elimination-addition process of the ylides as shown in Scheme I.

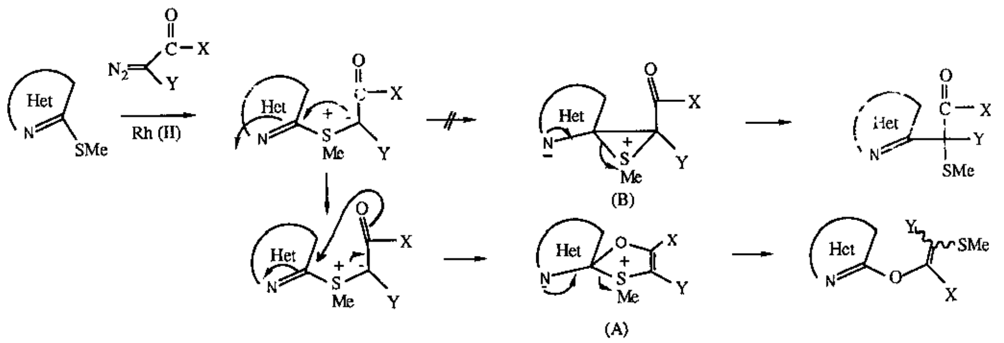
As an extention of our work on carbenoid displacement reaction, we have been interested in the application of the above method to heteroaromatic nucleophilic substitution, where the sp^2 carbon was present on the sulphide group instead of the sp^3 carbon bearing electron donating groups. Therefore it would be reasonable to consider its reaction mechanism to be an addition-elimination process (Scheme II), in which O-attack or C-attack might be competitive in the first addition step.

The sulphur ylides,[5] the key intermediates in this reaction, were easily prepared by treatment of the corresponding heteroaromatic sulphides with dimethyl diazomalonate or methyl α-diazoacetoacetate in the presence of a catalytic amount of rhodium(II) acetate in appropriate solvent, and their rearrangement was conducted at higher temperature. The structures of the rearrangement products were deduced on the basis of their spectroscopic data to be O-introduced products instead of C-introduced products, although the similar reaction[6] of thiophene with diazomalonate furnished the C-introduced compound. This observation suggested that the intramolecular addition process of the sulphur ylide rearrangement prefer to adopt a five-membered transition state (A) rather than a three-membered intermediate (B)(Scheme II). The reaction of **4** with the vinyl diazo compound[7] **30** also afforded the corresponding O-attacked product, although this high reactivity of ester carbonyl function seemed to be unusual (Scheme III). The results summarised in Table indicated that 1) this reaction proceeded through an addition-elimination process as expected with an intramolecular O-attack predominantly in the first addition step, 2) the reaction condition required was neutral and the activated sulphides (entry 2,3,5,8,10,12,13 and 14) brought about the substitution reaction under relatively mild reaction conditions, where the ylide intermediates could not be isolated, 3) the reaction with acetoacetate derivatives proceeded faster than that with malonates, and 4) the reaction-site can be restricted by preferential participation of the rhodium-carbenoid with sulphur atom, and the carbon-oxygen bond can be formed only at a position previously occupied by the sulphide group.

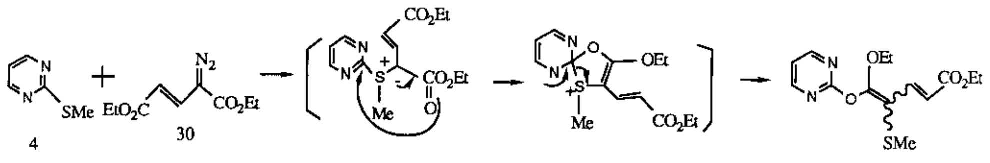


Z=electron donating group

Scheme I

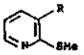
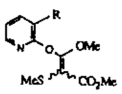
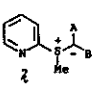
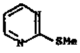
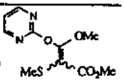
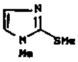
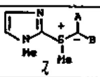
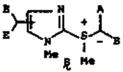
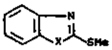
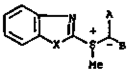
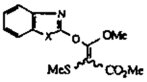
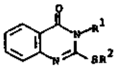
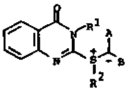
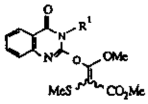
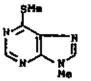
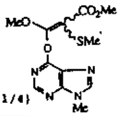
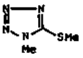
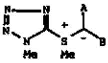
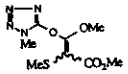
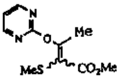


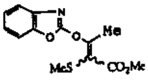
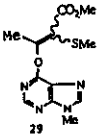
Scheme II



Scheme III

Table $S_{Ar}N$ Reaction by an Intermolecular Carbenoid Displacement Process

Entry	Substrate	$N_2{=}\!<^{A}_{B}$	Time (h)	Yield(%)[a]	Ylide	Rearrangement [Solvent, Temp.(°C), Time(h)]	Yield(%)[a]	Product[b] (ratio of isomer)
		A=B=CO_2Me						
1	1a R = H	2.0	2	99.3	 2	toluene, 200, 16	23.2 (77.3)	3a R = H (1/1)
2	1b R = CO_2Me	1.5	7	——	——	——	6.7 (13.4)	3b R = CO_2Me (2/1)
3	 4	A=B=CO_2Me 1.3	2	——	——	——	66.5 (77.3)	5 (2/1) 
4	 6	A=B=CO_2Me 1.3	7	38.2 for 7	 7	o-dichlorobenzene, 180, 7	35.5	6
				31.7 for 8	 8	xylene, reflux, 7		decomposition
		A=B=CO_2Me						
5	9 X = O	1.3	2.5	——	——	——	64.4 (76.0)	10 X = O (3/2)
6	11 X = NMe	1.5	4	72.8 (99.7)	12 X = NMe	xylene, reflux, 8	64.3 (93.3)	13 X = NMe (2/1)
7	14 X = S	1.3	2.5	93.1	15 X = S	xylene, reflux, 48	21.5 (41.3)[c]	16 X = S (2/1)
		A=B=CO_2Me						
8	17 $R^1 = R^2 = Me$	1.5	2	——	——	——	52.9 (88.2)	18 $R^1 = R^2 = Me$
9	19 $R^1 = H$, $R^2 = Et$	1.5	2	——	——	——	55.0	
				2.0[d]	20 $R^1 = H$, $R^2 = Et$	benzene, reflux, 3	67.1 (88.6)	21 $R^1 = H$, $R^2 = Et$
10	 22	A=B=CO_2Me 2.6	3	——	——	——	26.6 (63.0)	 23 (11/4)
11	 24	A=B=CO_2Me 1.3	2	80.0 (87.0)	 25	xylene, reflux, 4	39.3 (58.7)	 26 (5/4)
12	4	A=Ac, B=CO_2Me 1.3	2	50.0 (87.0)	——	——	——	 27

Entry	Substrate	$N_2{=}\!<^{E}_{E}$ (equiv.) E = CO_2Me	Time (h)	Yield(%)[a]	Ylide	Rearrangement (Solvent, Temp.(°C), Time (h))	Yield(%)[a]	Product[b] (ratio of isomer)
13	9	A=Ac, B=CO_2Me 1.3	2	65.0	————	————	——	 28
14	22	A=Ac, B=CO_2Me 1.3	3	38.3 (80.6)	————	————	——	 29

a) Isolated yield of the product. The yield in the parenthesis was based on the consumed starting material.

b) All the new compounds prepared were fully characterized by spectroscopic data including ^{13}C-nmr and elemental analyses. The ratio of geometrical isomers were determined based on their nmr spectra.

c) The starting material (14) was also obtained by the rearrangement reaction in 21.5 (33.7) % yield.

d) Rearrangement product (21) was obtained in 55.0 % yield by treatment of 19 with dimethyl diazomalonate in refluxing benzene, together with 2 % yield of the ylide (20), whose further rearrangement afforded 21 in 67.1 (88.6) % yield.

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