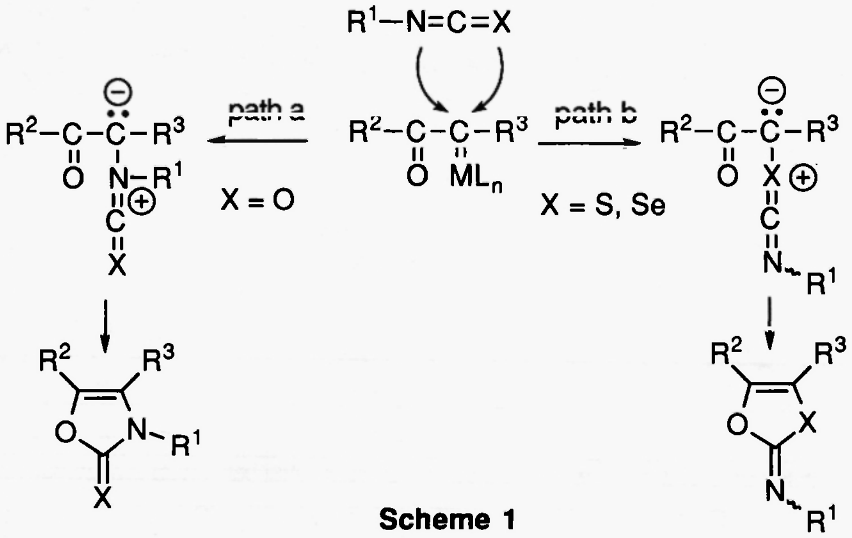
REGIO-SELECTIVITY AND RELATIVE REACTIVITY OF YLIDE FORMATION IN THE REACTION OF KETOCARBENOID WITH HETERO-CUMULENES

Toshikazu Ibata,* Motomu Himori, Kazuaki Fukushima,
Hiroyuki Suga, and Hirofumi Nakano

Department of Chemistry, Faculty of Science, Osaka University,
Toyonaka, Osaka 560, Japan

Abstract: The regiochemistry of the reaction of ketocarbenoid with phenyl isocyanate, phenyl isothiocyanate, and phenyl isoselenocyanate was studied and relative reactivity of these heteromultiple compounds was determined by competitive reactions. The order of the reactivity and the regio-selectivity in the reactions are explained by molecular orbital calculation.

Recently, a transition metal catalyzed reaction of diazo compounds with substrates having hetero atom has been accepted as a versatile method for ylide formation (1). Especially, the reaction of ketocarbenoid with hetero-multiple bond such as nitrile or carbon disulfide is the subject of much interest due to its potential role as a synthetic method for five-membered heterocycles such as oxazoles (2) and oxathiol-2-thione (3) through thermally allowed 6π-electron cyclization of acyl-substituted nitrile ylide and thiocarbonyl ylide intermediates, respectively.



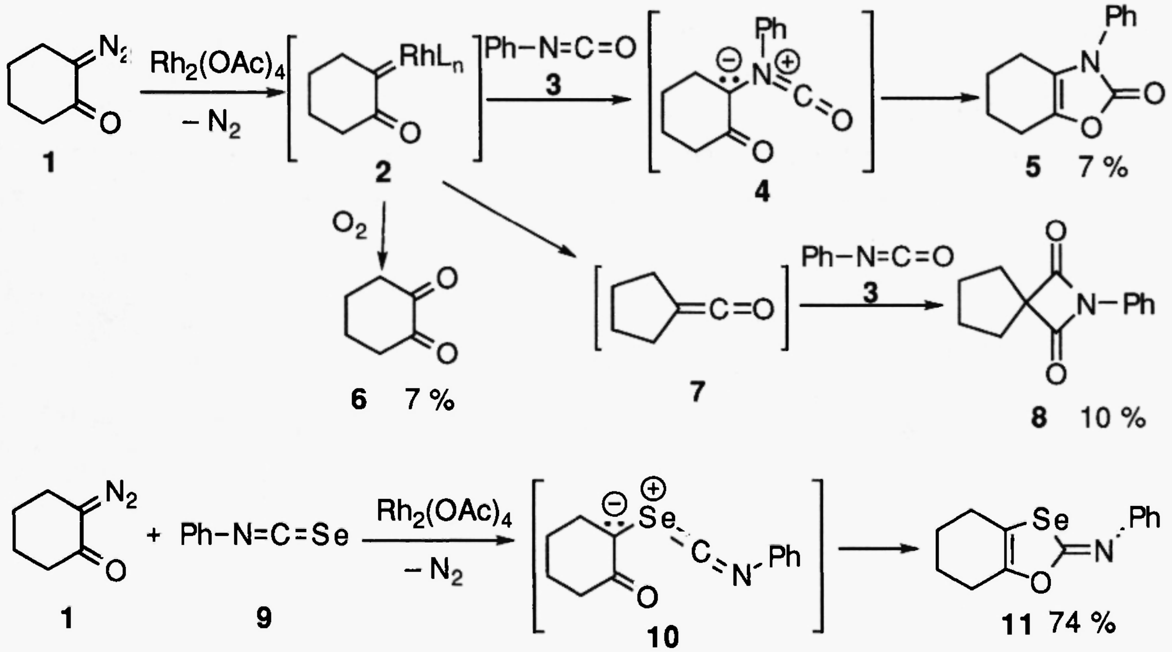
Scheme 1

When unsymmetrical hetero-cumulenes such as isocyanate, isothiocyanate, and isoselenocyanate are employed in the reaction with ketocarbenoid, the formation of two isomeric heterocycles can be expected through azomethine ylide or carbonyl ylide, thiocarbonyl ylide, and selenocarbonyl ylide *via* path a and path b, respectively (Scheme 1). For example, Ibata and Nakano reported that the reaction of isothiocyanate with α-diazoketones in the presence of $Rh_2(OAc)_4$-catalyst gave 2-iminooxathioles exclusively through thiocarbonyl ylide intermediate (Scheme 1, path b; X =

S) (4).

Although the selectivity for the formation of heterocycles depends on the reactivity of the two hetero-atoms of cumulenes toward ketocarbenoid, no experimental result has been shown yet. In this paper, we wish to report the reactions of hetero-cumulenes with ketocarbenoid, and discuss their reactivity in detail.

The $Rh_2(OAc)_4$-catalyzed decomposition of 2-diazocyclohexanone 1 in the presence of 10 molar amounts of phenyl isocyanate 3 in dichloromethane at room temperature gave oxazolone 5 in 7 % yield together with 1,2-cyclohexanedione (6: 7 %) and spiro malonimide (8: 10 %). The formation of 5 was explained by 1,5-cyclization of azomethine ylide intermediate 4 generated by the nucleophilic attack of nirogen atom of isocyanate on carbon atom of ketocarbenoid 2 through path a in Scheme 1. On the other hand, the reaction of 1 with phenyl isoselenocyanate 9 (5) resulted in the formation of 2-imino-1,3-oxaselenole 11 in 74 % yield, which is explained by 1,5-cyclization of selenocarbonyl ylide intermediate 10. These results indicate that the reaction site of isothiocyanate and isoselenocyanate is terminal hetero-atom (S or Se) in contrast to the case of isocyanate that reacts at nitrogen atom. Other combination of reactions of α-diazoketones such as diazoacetophenones and diazodimedone with isocyanates, isothiocyanates, and isoselenocyanates showed the same tendency of reactivity (6).

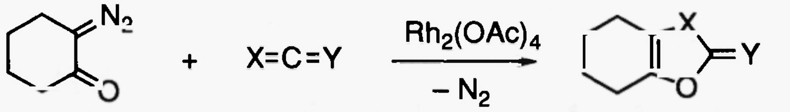


For elucidation of this regio-selectivity, semiempirical molecular orbital calculations were carried out (Table 1) (7). The ylide formation is considered to be initiated by the nucleophilic attack of PhNCX on the vacant *p*-orbital of carbene center of ketocarbenoid 2. Thus the effective interaction will be expected between HOMO of PhNCX and LUMO of ketocarbenoid. From this viewpoint, the hetero-atom of each PhNCX with larger coefficient is concluded to attack carbene center selectively. Table 1 indicates that the largest coefficient is on a nitrogen terminal in phenyl isocyanate, and is on a sulfur or selenium terminal in phenyl isothiocyanate or isoselenocyanate. According to the hard-soft principle, the lone pair electrons on sulfur or selenium atom are expected to have more contribution to the π-system of PhNCX than those on oxygen. These computational results can rationalize the experimental outcome very well.

Table 1. Orbital Coefficients and Energy Level of HOMO of PhNCX.

X	Coefficients			Energy Level / eV
	N	C	X	
O	– 0.466	– 0.222	0.312	– 9.17
S	– 0.485	– 0.123	0.678	– 8.85
Se	– 0.428	– 0.026	0.826	– 8.68

In order to estimate the relative reactivity of these three hetero-cumulenes comparing with that of carbon disulfide toward ketocarbenoid, competitive reactions of seven combinations of these hetero-cumulenes with α-diazocyclohexanone 1 were carried out using each 10 molar amounts of hetero-cumulene in CH_2Cl_2 at room temperature in the presence of $Rh_2(OAc)_4$ (Table 2) (8).



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3: X=PhN, Y=O
9: X=Se, Y=PhN
12: X=S, Y=PhN
14: X=S, Y=S

5: X=PhN, Y=O
11: X=Se, Y=PhN
13: X=S, Y=PhN
15: X=S, Y=S

Table 2. Competitive Reactions of Hetero-cumulenes with **1**

Run	Hetero-cumulenes	Adducts (Yields / %)	Relative Rate
1	**3** and **12**	**13** (67)	**3** : **12** = 0 : 1
2	**3** and **9**	**11** (76)	**3** : **9** = 0 : 1
3	**9** and **12**	**11** (60), **13** (33)	**9** : **12** = 1.8 : 1
4	**9** and **14**	**11** (61)	**9** : **14** = 1 : 0
5	**12** and **14**	**13** (56), **15** (6)	**12** : **14** = 9.3 : 1
6	**3** and **14**	**15** (26)	**3** : **14** = 0 : 1
7*	**3** and **14**	**5** (10), **15** (61)	**3** : **14** = 0.16 : 1

* 100 molar amounts of **3** and **14** were used without CH_2Cl_2.

The reactivity of phenyl isothiocyanate 12 and phenyl isoselenocyanate 9 is shown to be much larger than that of phenyl isocyanate 3, because the competitive reactions of (3 and 12) and (3 and 9) did not give oxazolone 5 at all (Runs 1 and 2). The ratio of reactivities between 9 and 12 is evaluated 1.8 by the competitive reaction that gave oxaselenole 11 in 60 % and oxathiole 13 in 33 % yields (Run 3).

Although the competitive reaction of phenyl isoselenocyanate 9 and carbon disulfide 14 did not give the corresponding adduct derived from 14 (Run 4), the competition between 12 and 14 gave 2-iminooxathiole 13 in 56 % yield together with small amount of oxathiole-2-thione 15 (6 % yield) (Run 5). The competitive reaction of 3 and 14 under similar reaction conditions gave only 15 in low yield (26 %) (Run 6). To have a precise relative reactivity of 3 and 14 toward ketocarbenoid, the competitive reaction was studied using each 100 molar amounts of 3 and 14 without solvent and obtained both **6** and **15** in 10 % and 61 % yields, respectively (Run 7). From these results the relative reactivity among phenyl isocyanate, phenyl isothiocyanate, phenyl isoselenocyanate, and carbon disulfide was determined as 1 : 57 : 102 : 6.

The order of the reactivity of PhNCX (X = Se > S > O) is also rationalized in terms of the HOMO (PhNCX) — LUMO (ketocarbenoid) interaction in transition state. In other word, the largest stabilizing interaction is expected in the reaction of PhNCSe having highest HOMO level (HOMO = –8.68 eV) and *vice versa* (Table 1). The least reactivity of phenyl isocyanate resulted in the formation of cyclohexanedione **6** through the reaction of ketocarbenoid with oxygen and spiro imide **8** through the Wolff rearrangement.

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References and notes

(1) A. Padwa and S. F. Hornbuckle, *Chem. Rev.*, 91, 263 (1991).

(2) T. Ibata and K. Fukushima, *Chem. Lett.*, 2197 (1992).

(3) a) T. Ibata and H. Nakano, *Chem. Express*, 4, 93 (1989); b) T. Ibata and H. Nakano, *Bull. Chem. Soc. Jpn.*, **63**, 3096 (1990).

(4) T. Ibata and H. Nakano, *Bull. Chem. Soc. Jpn.*, 65, 3088 (1992).

(5) Phenyl isoselenocyanate was prepared by the reaction of phenyl isocyanate with bis(dimethylaluminum)-selenide which was generated *in situ* from bis(tributyltin)-selenide and trimethylaluminum according to the method shown by a private communication of Profs. Segi and Nakajima.

(6) Unpublished results of our group.

(7) Molecular orbital calculations were carried out using PM3 hamiltonian in MOPAC 94 program in CAChe system.

(8) General procedure for the competitive reactions: a solution of 1 mmol of α-diazocyclohexanone **1** in 5 ml of CH_2Cl_2 was added dropwise into a solution of each 10 mmol of two hetero-cumulenes and 0.01 mmol of $Rh_2(OAc)_4$ (except for the reaction of phenyl isoselenocyanate **9** that required 0.05 mmol of $Rh_2(OAc)_4$ for complete decomposition of **1**) in 5 ml of CH_2Cl_2 for 2 hours at room temperature. After stirring for 15 minutes, the solvent was removed under reduced pressure. Then the residual oil was separated by medium pressure column chromatography eluted with hexane-ethyl acetate to obtain the corresponding 1:1-adducts of ketocarbenoid with hetero-cumulenes.

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