

A study of influence of temperature and *N,N*-acyl protected keto ylides structure on their predominant transformations

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Abstract The effect of temperature and keto ylides structure on preference of their intramolecular cyclization leading to N-containing heterocyclic compounds or linear products formation has been investigated at the B3LYP/6-31G(d,p) level of theory. It has been determined that the thermodynamic advantage of the cyclization reactions of ylides increases with temperature, while Gibbs free energies of linear products formation reactions depend insignificantly on temperature. The Wittig and the Corey–Chaykovsky reactions are least probable in the case of the sulfonium and ammonium ylides considered. However, for phosphonium ylides the Wittig reaction must be considerably preferable in comparison with other routes, while behavior of the arsonium ylides is predicted to be more complex. Research of S-ylides transformations shows that formation of methylthio-substituted heterocycles with five-, six- or seven-membered rings is possible from a thermodynamic standpoint, while conversion of the corresponding ylide to a four-membered heterocycle is disadvantageous. Presence of a methyl substituent and its position in the ylide carbon chain depends ambiguously on the behavior of sulfur keto ylides.

Keywords *N,N*-acyl protected keto ylides · Intramolecular cyclization · Effect of structure · Thermal dependencies of Gibbs free energy of reactions · DFT calculation

1 Introduction

The interaction of ylides with carbonyl compounds is often used in organic chemical synthesis [1–6]. Oxiranes are formed by the Corey–Chaykovsky reaction in case of sulfur ylides [7–11] (Fig. 1). The Wittig reaction is most characteristic for phosphonium ylides [12–16] and is rare for sulfur ylides [17–20]. However, preferable reaction pathways for arsenic [21–24] and nitrogen [25–29] ylides depend on reagent structure.

In case of *N*-phthalyl protected sulfur keto ylides **1–4**, an unusual intramolecular cyclization resulting in methylthio-substituted derivatives **5–8** was discovered, while corresponding oxirane formation was not observed (Fig. 2) [30]. It has been found that yield of the products rises with increased temperature and reaches a maximum of 85% in the course of refluxing sulfur ylides in toluene (383 K) with an equimolecular amount of benzoic acid.

Further, it has been found that *N*-phthalyl protected ylides **9–11** [31] do not lead to heterocycles **12–14** under the conditions mentioned above, but are transformed into the corresponding linear sulfides **15–17** and benzoates **18–20** in equal ratio (Fig. 3).

It has been demonstrated [32] that β -alkyl substituted ylides **21** and **22** are more reactive than the unsubstituted analogue **23**. Cyclization via the Wittig reaction of the *N*-phthalyl protected phosphonium ylides (Fig. 4) occurs within 12 h, leading to formation of pyrrolo[2,1- α]isoin-dole-2,5-diones **24–26** with yield up to 60% without a catalyst.

Nevertheless, factors preventing the intramolecular cyclization of some sulfur ylides and disadvantage of the Corey–Chaykovsky and Wittig reactions, which are most characteristic for them, remain unknown. Moreover, no

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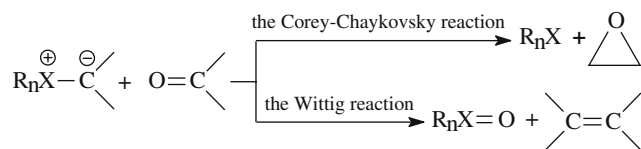


Fig. 1 Characteristic transformation routes of ylides with carbonyl compounds

one has investigated the systematic influence of carbon-chain structure and nature of heteroatom-stabilizing carbanion on the formation of cyclic products. Thereupon, the effect of keto ylide structure on its behavior has been investigated by quantum chemical methods.

2 Calculation methods

It has been demonstrated previously [33,34] that behavior and structure of *N,N*-acyl protected sulfur keto ylides are well reproduced at the B3LYP/6-31G(d,p) level of theory, which has been applied in the present work. The most stable conformers (not shown here) of the reaction participants considered were used during the calculation of Gibbs free energies of reaction.

Vibrational frequencies were calculated for all optimized structures to confirm that they were true minima (i.e. had no imaginary frequencies). The entropy and the zero-point energy were computed with scale factors of 1.0015 and 0.9806, respectively [35]. Calculations were performed using the PC GAMESS version [36] of the GAMESS (US) QC package [37].

3 Results and discussion

Preferable reaction pathways were determined under thermodynamic control, which should be predominant in the reactions studied [33,34,38–43].

Fig. 2 New transformation of *N*-phthalyl protected sulfur keto ylides

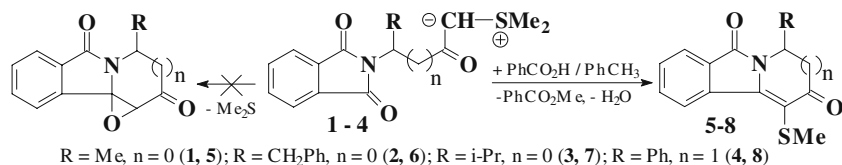
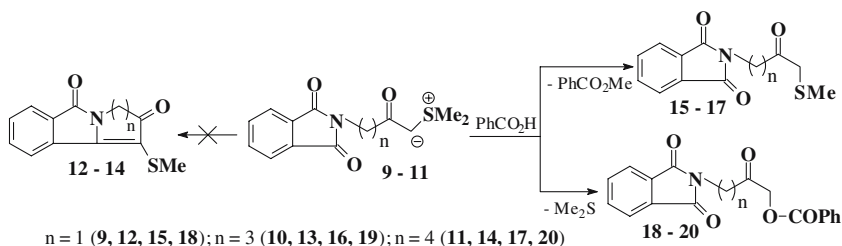


Fig. 3 Competitive reactions of *N*-phthalyl protected sulfur keto ylides transformations



It has been determined [34] that the Gibbs free energy of reactions of sulfur keto ylides depends insignificantly on the structure of the *N,N*-acyl group and ylides substituted by phthalimidic or maleimidic fragments behave similarly. However, the effect of temperature and nature of substituent R at the β -position of an ylide such as **1** on the cyclization reaction performance is significant.

In this regard, relative preference of *N*-maleyl protected ylide transformations via Schemes IA–IE has been studied by calculation of dependencies of Gibbs free energies of reactions on temperature and reactant structure.

The thermal dependencies obtained at the B3LYP/6-31G(d,p) level of theory have been studied in order to investigate influence of heteroatom nature on prevailing reaction route of ylides **27–30** (Fig. 5).

It is shown (Table 1) that for ylides **27–30** an increase in temperature from 298 to 473 K leads to increased cyclization reactions preference (~ 25 kJ/mol), while formation of linear products **37–41** depends slightly on temperature. Moreover, the presence of a methyl substituent at the β -position leads to increased thermodynamic preference of the intramolecular cyclization.

Results of calculations show that the values of electronic energies and enthalpies of the reactions are close. The entropy contribution to the Gibbs free energy of linear products formation reactions in case of ylides **27–30a,b** is insignificant and reaches 3–9 kJ/mol at 298 K. However, the magnitude of the entropy contribution at the same temperature equals 38–52 kJ/mol for the cyclization reactions.

Obviously, thermal dependence of free energy of reactions via Schemes IA–IC is driven by entropy, which can be explained by increased molecule number due to the cyclization. Therefore, it is necessary to consider Gibbs free energy in order to find favorable reaction routes amongst those considered.

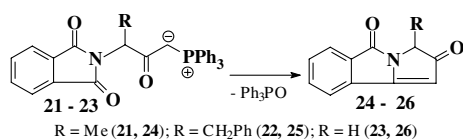


Fig. 4 Transformations of *N*-phthalyl protected triphenylphosphonium keto ylides by the Wittig reaction

It has been found that transformations of sulfonium **27** and ammonium **29** ylides resulting in heterocycles **35** and **36** by the Wittig and the Corey–Chaykovsky

Fig. 5 Transformations of *N*-maleyl protected keto ylides **27–30a,b**

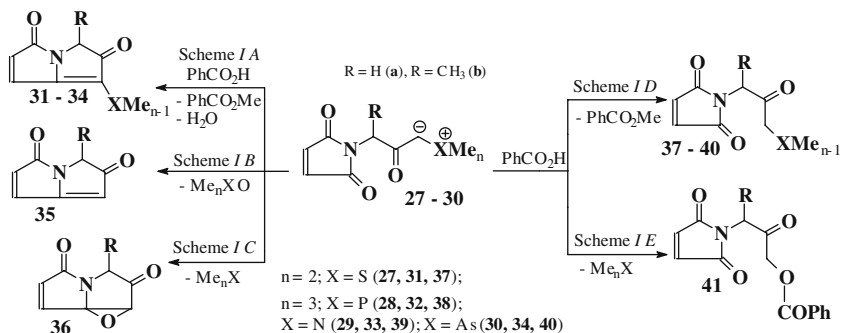


Table 1 Enthalpies, electronic energies and thermal dependencies of Gibbs free energy of reactions (in kJ/mol) of keto ylides **27–30a,b** obtained at the B3LYP/6-31G(d,p) level

Scheme	T(K)	Ylide							
		27a	27b	28a	28b	29a	29b	30a	30b
Gibbs free energy of reactions									
IA	298	-96	-105	21	1	-110	-130	-36	-50
	383	-109	-117	10	-12	-123	-144	-46	-61
	423	-114	-123	5	-17	-129	-151	-51	-67
	473	-121	-129	-1	-24	-137	-159	-57	-73
IB	298	5	-5	-92	-111	101	81	-8	-22
	383	-7	-16	-103	-122	89	68	-19	-34
	423	-12	-21	-108	-127	83	62	-24	-40
	473	-19	-28	-114	-134	76	55	-31	-47
IC	298	-3	-11	113	96	7	-12	63	51
	383	-14	-22	103	86	-5	-24	54	40
	423	-19	-27	99	81	-10	-30	49	35
	473	-25	-33	93	75	-16	-37	44	29
ID	298	-119	-114	-1	0	-102	-107	-64	-55
	383	-120	-115	0	1	-103	-109	-63	-53
	423	-120	-115	1	1	-104	-110	-62	-52
	473	-120	-115	2	2	-105	-111	-61	-50
IE	298	-122	-116	-6	-9	-112	-117	-55	-54
	383	-124	-117	-6	-9	-114	-119	-56	-55
	423	-124	-117	-6	-9	-115	-120	-56	-55
	473	-125	-117	-6	-9	-116	-121	-56	-55
Enthalpy of reactions									
IA	298	-52	-61	61	45	-62	-79	5	-6
IB	298	50	41	-49	-65	147	131	36	25
IC	298	41	33	154	139	52	38	105	95
ID	298	-116	-110	-4	0	-96	-99	-66	-57
IE	298	-115	-112	-2	-6	-104	-108	-52	-50
Electronic energies of reactions									
IA	0	-43	-54	68	53	-47	-62	10	0
IB	0	56	46	-46	-61	155	141	40	30
IC	0	46	37	158	144	62	49	108	99
ID	0	-119	-114	-9	-3	-92	-94	-71	-59
IE	0	-115	-113	-3	-6	-99	-102	-53	-51

rearrangements than those in the Wittig reaction, while the Corey–Chaykovsky reaction leads to disadvantageous formation of hindered tricycles. Thermodynamic preference of the cyclization reaction by Scheme IA in comparison with the formation of linear products **37**, **39**, **41a,b** at 383 K (boiling point of toluene) is predicted for both types of ylides indicated except ylide **27a**. Therefore, the intramolecular cyclization of N-ylides by Scheme IA is thermodynamically more favorable in comparison with sulfur ylides.

To judge from the results demonstrated in Table 1, enormous thermodynamic preference of the Wittig reaction by Scheme IB in comparison with other reaction pathways is predicted for phosphonium ylides **28**, which corresponds to known results of experimental [5,13,32,44] and theoretical [45–47] works. Thermodynamic advances of the reaction by Schemes IA, IB, ID and IE are comparable in the case of arsonium ylides **30a,b**, while formation of the corresponding oxiranes **36a,b** via the Corey–Chaykovsky reaction seems to be least probable.

It is known from experimental observations [31] that the structure and carbon-chain length of sulfonium ylides affects their cyclization performance. Therefore, preferable transformations of *N,N*-acyl protected sulfur keto ylides were researched from a thermodynamic standpoint.

Values of Gibbs free energies of reactions of sulfur ylides **27a–b**, **42**, **43a–c**, **49**, and **50a–d** have been obtained (Table 2) in order to compare the possibility of

forming heterocyclic compounds with five- (Fig. 5), four- (Fig. 6), six- (Figs. 7, 8) and seven-membered (Fig. 9) rings. Presence of the alkyl group leads to significantly increased thermodynamic advantage for the five-membered heterocycle formation via sulfur ylides **27a,b**. This is perhaps a result of the phenomenon described earlier that the efficiency of ring closure increases with increased number of substituents in the forming ring [48].

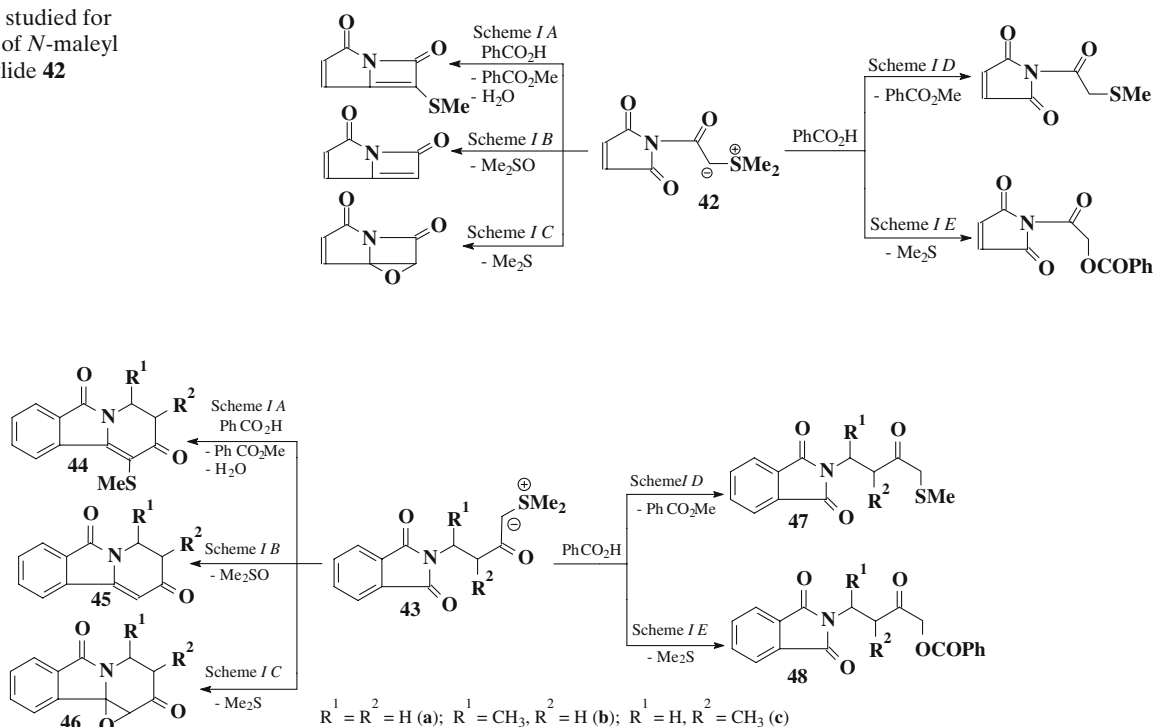
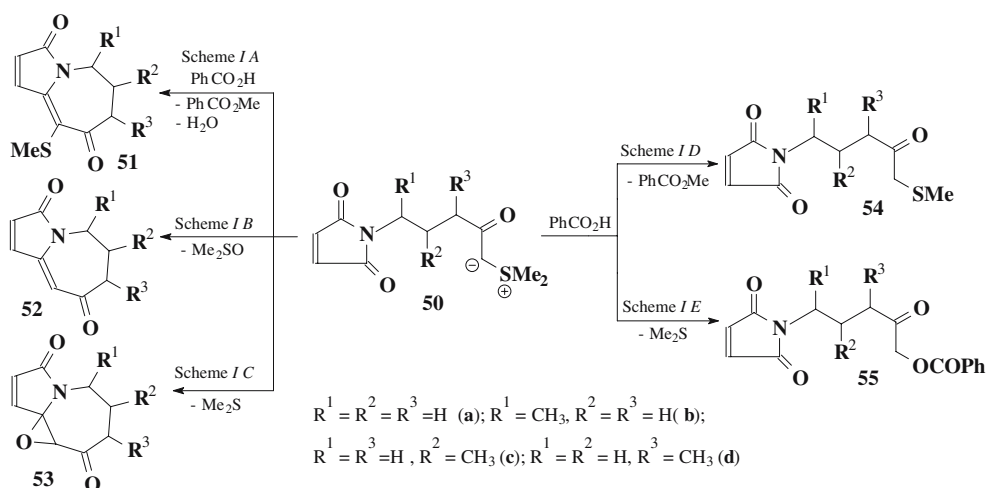
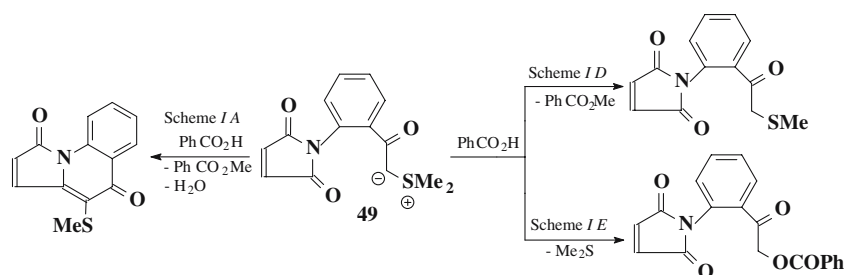
The intramolecular cyclization reactions of ylide **42** resulting in formation of a hetero bicycle with a four-membered ring are least probable among the routes considered. Gibbs free energies of reactions IA–IC have positive values, while the energies of reactions of linear product formation by Schemes ID and IE are similar, equaling -120 kJ/mol.

Gibbs free energies of reactions by Schemes IA–IE of sulfur keto ylides **43a–c** have been studied in order to research the possibility of six-membered ring formation (Fig. 7) and investigate the influence of methyl group presence and its position in the carbon chain on ylides behavior.

Calculations (at 298 K) demonstrate that in the case of ylide **43a** the Wittig (-17 kJ/mol) and the Corey–Chaykovsky (-31 kJ/mol) reactions occurring by Schemes IB and IC, respectively, are least advantageous among those studied. Therefore, these transformation pathways have not been further considered for ylides **43b,c** and **49**. Calculation data show that an increase in temperature and the presence of an alkyl substituent

Table 2 Thermal dependencies of Gibbs free energies of reactions (in kJ/mol) of sulfur keto ylides obtained at the B3LYP/6-31G(d,p) level

Scheme	<i>T</i> (K)	Ylide										
		27a	27b	42	43a	43b	43c	49	50a	50b	50c	50d
IA	298	-96	-105	46	-104	-106	-99	-175	-88	-71	-83	-87
	383	-109	-117	31	-119	-121	-111	-186	-103	-80	-95	-102
	423	-114	-123	24	-126	-128	-117	-191	-110	-84	-100	-109
	473	-121	-129	16	-134	-137	-124	-197	-118	-89	-107	-117
IB	298	5	-5	165	-17	-	-	-	-12	-	-	-
	383	-7	-16	153	-31	-	-	-	-26	-	-	-
	423	-12	-21	148	-38	-	-	-	-33	-	-	-
	473	-19	-28	142	-46	-	-	-	-41	-	-	-
IC	298	-3	-11	111	-31	-	-	-	-42	-	-	-
	383	-14	-22	99	-45	-	-	-	-55	-	-	-
	423	-19	-27	93	-52	-	-	-	-61	-	-	-
	473	-25	-33	87	-60	-	-	-	-69	-	-	-
ID	298	-119	-114	-120	-123	-116	-112	-118	-121	-117	-121	-113
	383	-120	-115	-121	-124	-118	-113	-119	-122	-118	-122	-114
	423	-120	-115	-121	-124	-118	-113	-120	-122	-119	-123	-114
	473	-120	-115	-121	-125	-119	-114	-120	-123	-119	-124	-114
IE	298	-122	-116	-120	-116	-111	-114	-122	-118	-122	-116	-110
	383	-124	-117	-120	-116	-109	-114	-121	-118	-122	-116	-107
	423	-124	-117	-120	-116	-108	-114	-121	-118	-123	-116	-106
	473	-125	-117	-120	-117	-106	-114	-121	-118	-123	-116	-104

Fig. 6 Schemes studied for transformations of *N*-maleyl protected keto ylide **42****Fig. 7** Schemes studied for transformations of *N*-phthalyl protected keto ylides **43a–c****Fig. 8** Schemes studied for transformations of *N*-maleyl protected *o*-phenylidene-substituted keto ylide **49****Fig. 9** Schemes studied for transformations of *N*-maleyl protected keto ylides **50a–d**

are needed in order for the formation of methylthio dihydropyrdoisindoleione **44** to be preferable. Heterocycle formation becomes most advantageous when the methyl group is located at the γ -position, as in ylide **43b**.

Experimental findings show that introducing an aromatic ring into the sulfur ylide chain leads to a considerable increase in its reactivity. For example, the phthalimide-substituted analogue of ylide **49** undergoes intramolecular cyclization via Scheme IA with 68% yield at room temperature [2]. Behavior of this ylide type (Fig. 8) has been studied by means of quantum chemical methods in order to explain such a phenomenon.

It has been found that, even at 298 K, the intramolecular cyclization of keto ylide **49** is notably more advantageous (-175 kJ/mol) than reactions by Schemes ID (-118 kJ/mol) or IE (-122 kJ/mol). This may be explained by formation of the large united π -system of the N-containing tricycle.

Experimental observations have shown that [2] attempts at the cyclization of keto ylide **10** were unsuccessful. In order to research the possibility of seven-membered ring formation via cyclization of sulfur ylides **50a–d** (Fig. 9), Gibbs free energies of reactions IA–IE have been calculated. The effect of a methyl substituent in the carbon chain and its position on ylide behavior have been investigated.

Results show that for sulfonium ylide **50a** the Wittig (-12 kJ/mol) and the Corey–Chaykovsky (-42 kJ/mol) reactions occurring by Schemes IB and IC, respectively, are least probable in comparison with the formation of methylthio dihydropyrroloazepinedione **51a** or acyclic products **54a** and **55a** (Fig. 9). However, the Corey–Chaykovsky reaction becomes preferable to the Wittig reaction. Therefore, Schemes IB and IC have not been studied further for ylides **50b–d**.

It was discovered that the presence and location of an alkyl substituent in the carbon chain of ylides affects the Gibbs free energy of reaction by Scheme IA. The formation of the corresponding methylthio pyrroloazepinediones **51** seems to be preferable for sulfur ylide **50d** with a methyl substituent at the β -position (-87 kJ/mol at 298 K) and for unsubstituted keto ylide **50a** (-88 kJ/mol). Reaction via Scheme IA becomes least thermodynamically advantageous for ylide **50b** with a methyl substituent at the δ -position (-71 kJ/mol at 298 K), while Gibbs free energy of said reaction equals -83 kJ/mol for sulfonium keto ylide **50c**. However, preference of the IA reaction over corresponding formation of linear products **54** and **55** is not expected for ylides **50a–d** at 383 K. According to calculation data obtained, formation of the pyrroloazepinedione derivatives will not take place

under standard conditions, which corresponds well with experimental findings [31].

4 Conclusions

Several conclusions can be drawn from the computational study presented in this article.

Gibbs free energies of cyclization reactions for all *N,N*-acyl protected ylides studied become more negative with temperature increase, while free energies of linear products formation generally depend insignificantly on temperature. The thermal dependence is explained by different values of entropy contribution to the free energies due to molecule number increase in the course of cyclization.

The preferable theme of intramolecular cyclization of sulfonium and ammonium ylides is methylthio or methylamino substituted pyrrolisindione formation, while conversions of this type of ylides by the Wittig and the Corey–Chaykovsky reactions are the least probable among those considered. The Wittig reaction becomes most advantageous in case of the phosphonium ylides studied from the thermodynamic standpoint, which corresponds with experimental observations. This may be explained by the trend of P-ylides to be involved in the Wittig reaction in comparison with N- and S-ylides. However, Gibbs free energies of the arsonium ylide reactions studied are comparable, excepting the Corey–Chaykovsky reaction. Indeed, it has been experimentally found that As-ylide application leads to the Wittig reaction or oxirane formation, depending on reagent structure.

It is demonstrated that for the sulfur keto ylides studied, formation of the corresponding methylthio substituted heterocycles with five- or six-membered rings is possible under the standard conditions indicated (383 K), while ylide conversion to a heterocycle possessing four- or seven-membered rings is disadvantageous from the thermodynamic standpoint. This corresponds with the general preference of the cyclization reaction depending on the ring size formed: $5 \sim 6 > 7 > 4$ [38].

Thermodynamic preference of ylide intramolecular cyclization depends ambiguously on the methyl group position in the ylide carbon chain. Presence of an alkyl group leads to significantly increased thermodynamic advantage in case of five-membered heterocycle formation, which corresponds with known data. However, introduction of a phenyl ring in the ylide carbon chain leads to notably increased preference of methylthio pyrdoisindoleione formation, possibly due to resonance

stabilization caused by the conjugation of the aromatic rings.

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