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SPIRO HETEROCYCLES: SYNTHESIS AND APPLICATION OF SPIRO PYRAZOL-3-ONE DERIVATIVES

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Abstract – Spiro compounds play an important role in organic chemistry, not only as key structural units in many natural products and pharmaceuticals but also as useful building blocks in synthetic chemistry. This review deals with the synthesis and application of spiro heterocycles, especially spiro pyrazol-3-ones (SPOs). SPOs represent a common scaffold present in a wide range of biological active compounds, such as antibacterial, analgesic, phosphodiesterase, inotropic, acetyl-CoA carboxylase, PPARα, RaIA, and antitumor activities, among others. The structural features of SPOs provide them with increased reactivity, and SPOs undergo a series of interesting reactions under appropriate conditions, giving efficient methods for the construction of many useful organic compounds. The exploration of SPOs novel reaction has attracted much attention of organic chemists. Generally, SPOs reaction types include nucleophilic addition, ring-opening, and ring transformation reactions. The present review summarizes the advances on SPOs during the period of 2008 to 2021 in our laboratory.

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1. INTRODUCTION

Heterocyclic compounds have received considerable attention because of their important biological properties and their role as pharmacophores.[1,2] There are vast numbers of pharmacologically active heterocyclic compounds many of which are in regular clinical use. Among them, pyrazole and its derivatives are known to exhibit a wide spectrum of biological activities such as antipyretic, anti-inflammatory, antiviral, antibacterial, hypoglycemic, antihypertensive, and antitumor activities.[3-8] Therefore, there have been many attempts to develop alternative methods for the synthesis of pyrazole derivatives.[9-14]

Spiro compounds, especially nitrogen-containing spiro heterocycles, served as an important structural unit in many bioactive natural products, pharmaceuticals, and agricultural chemicals.[15-24] Among them, spiro heterocycles containing pyrazol-3-one unit also have biological activities, such as antibacterial (**A**),[25] analgesic (**B**),[26] phosphodiesterase (**C** and **D**),[27,28] inotropic (**E**),[29] acetyl-CoA carboxylase (**F**),[30] PPARα (**G**),[31] RaIA (**H**),[32] and antitumor (**I**)[33] activities (Figure 1). Hence, their synthesis continues to attract attention and provides an interesting challenge.

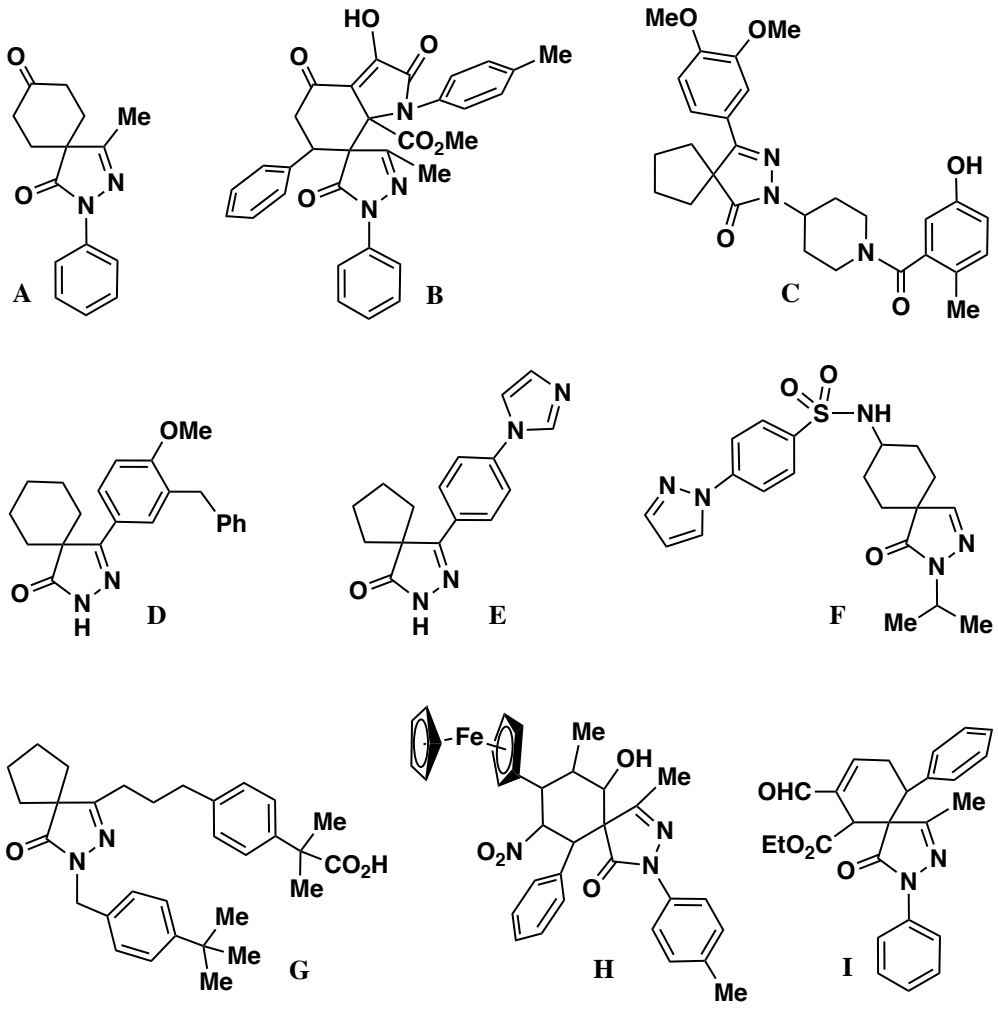


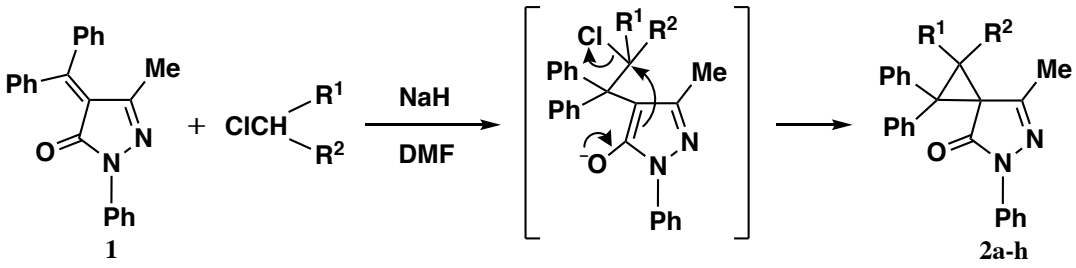
Figure 1. Structures of drugs and bioactive compounds containing SPO unit

This review deals with the synthesis and application of spiro heterocycles, especially spiro pyrazol-3-ones (SPOs). The structural features of SPOs provide them with increased reactivity, and SPOs undergo a series of interesting reactions under appropriate conditions, giving efficient methods for the construction of many useful organic compounds. The exploration of SPOs novel reaction has attracted much attention of organic chemists. Generally, SPOs reaction types include nucleophilic addition, ring-opening, and ring transformation reactions. So far, we have reported some exciting synthetic strategies for the synthesis of this exclusive class of spiro compounds. The main purpose of this review is to present useful data of the literature on the synthesis and application of SPOs for medicinal chemists. The present review summarizes the advances on SPOs during the period of 2008 to 2021 in our laboratory.

2. SYNTHESIS AND APPLICATION OF SPOS CONTAINING CYCLOPROPANE MOIETY

A series of new SPOs **2a-h**[34] were synthesized by the reaction of 4-arylidene-pyrazol-3-one **1**[35,36] with secondary and tertiary carbanions derived from a methylene and methine group bearing a leaving group and electron-withdrawing group, such as methyl chloroacetate, ethyl chloroacetate, isopropyl chloroacetate, *tert*-butyl chloroacetate, chloroacetonitrile, 2-chloro-*N,N*-diethylacetamide, methyl 2-chloropropionate, and 2-chloropropionitrile, in the presence of NaH in DMF at 0-5 ˚C for 2 h or rt for 6 h in 33-88% yields (Table 1).

Table 1. Synthesis of SPOs **2a-h**



Entry	R^1	R^2	Product	Yield (%)
1	H	CO_2Me	**2a**	63[a]
2	H	CO_2Et	**2b**	60[a]
3	H	$CO_2{}^iPr$	**2c**	65[a]
4	H	$CO_2{}^tBu$	**2d**	81[a]
5	H	CN	**2e**	33[a]
6	H	$CONEt_2$	**2f**	59[a]
7	Me	CO_2Me	**2g**	57[b]
8	Me	CN	**2h**	88[b]

[a] 0-5 ˚C for 2 h. [b] rt for 6 h.

Eight of the newly synthesized SPOs **2a-h** were tested for their antifungal activity against *Candida albicans* and *Saccharomyces cerevisiae*. *In vitro* susceptibility tests were performed to evaluate minimum inhibitory concentrations (MICs) using the method described in the guidelines of NCCLS Document M27-A2.[37] Miconazole and Itraconazole were used as standard drugs for comparison of the antifungal activity. The results obtained are summarized in Table 2. All SPOs **2a-h** were active against *Candida albicans* with MIC ≥ 25 and *Saccharomyces cerevisiae* with MIC ≥ 50 μg /mL.

Table 2. *In vitro* antifungal activity of SPOs **2a-h** against *C. albicans* and *S. cerevisiae*

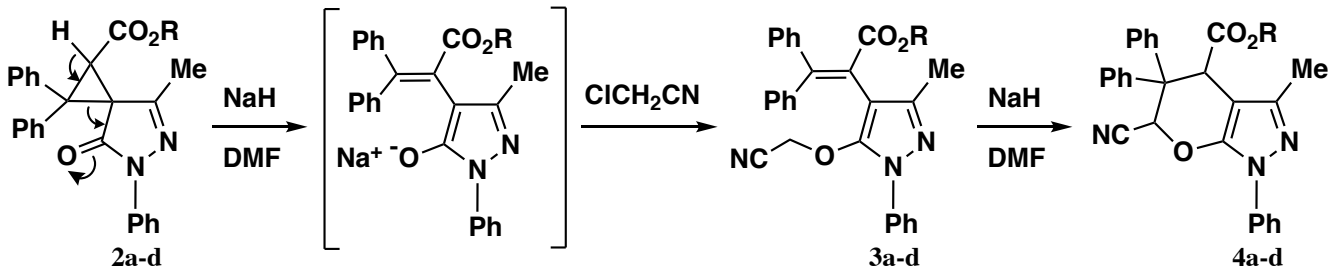
Entry	Compound	MIC (μg/mL)	
		C. albicans[a]	*S. cerevisiae*[b]
1	**2a**	25[c]	50[d]
2	**2b**	25[c]	50[d]
3	**2c**	25[c]	50[d]
4	**2d**	25[c]	50[d]
5	**2e**	25[c]	50[d]
6	**2f**	25[c]	50[d]
7	**2g**	25[c]	50[d]
8	**2h**	25[c]	50[d]
9	Miconazole	2[e]	0.5[f]
10	Itraconazole	2[e]	4[g]
11	DMSO	> 12.5%	> 6.25%
12	EtOH	> 12.5%	> 6.25%

[a] RPMI1640 medium, 37 ˚C. [b] YM medium, 25 ˚C. [c] containing 0.2% DMSO. [d] containing 0.39% DMSO. [e] containing 0.015% DMSO. [f] containing 0.04% DMSO. [g] containing 0.03% DMSO.

Some heterocyclic compounds containing condensed pyrazoles such as pyrano[2,3-*c*]pyrazoles possess a wide spectrum of pharmacological action, including analgesic, anti-inflammatory, vasodilating, and antihypertensive activities.[38-40] Hence, the preparation and biological properties of new substituted pyrano[2,3-*c*]pyrazoles are interest.[41-50]

To check something about reactivity of SPOs **2**, we examined a ring transformation of SPOs **2a-d** into pyrano[2,3-*c*]pyrazoles.[51] SPOs **2a-d** were reacted with chloroacetonitrile in the presence of NaH[52] in DMF at 60 ˚C for 1 h to give the corresponding *O*-cyanomethylated pyrazoles **3a-d** (Table 3, entries 1-4). Treatment of **3a-d** with NaH in DMF at rt for 48 h caused an intramolecular cyclization to afford the corresponding pyrano[2,3-*c*]pyrazoles **4a-d** (Table 3, entries 5-8). On the basis of these results, we have tried to directly construct pyrano[2,3-*c*]pyrazoles **4a-d** starting from SPOs **2a-d** in a one-pot process. Thus, after a mixture of SPOs **2a-d** and NaH in DMF was stirred at rt for 1 h, the reaction mixture was treated with chloroacetonitrile at 60 ˚C for 1 h and then with NaH at rt for 48 h. Subsequently, the corresponding pyrano[2,3-*c*]pyrazoles **4a-d** were obtained in 28, 47, 44, and 59% yields, respectively.

Table 3. Synthesis of **3a-d** and **4a-d**



2a-d 3a-d 4a-d

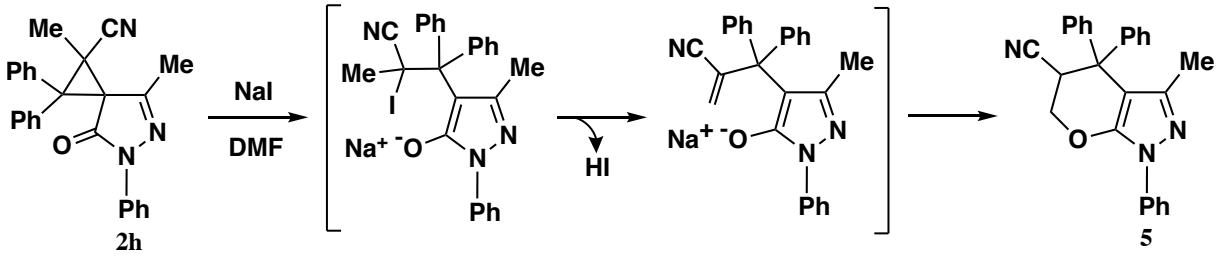
Entry	Substrate	R	Product	Yield (%)
1	**2a**	Me	**3a**	67[a]
2	**2b**	Et	**3b**	58[a]
3	**2c**	^{i}Pr	**3c**	76[a]
4	**2d**	^{t}Bu	**3d**	85[a]

[a] 60 ˚C for 1 h.

Entry	Substrate	R	Product	Yield (%)
5	**3a**	Me	**4a**	35[b]
6	**3b**	Et	**4b**	61[b]
7	**3c**	^{i}Pr	**4c**	56[b]
8	**3d**	^{t}Bu	**4d**	58[b]

[b] rt for 48 h.

Furthermore, thermal treatment of SPO **2h** with NaI in DMF at 140 ˚C for 1 h caused a ring opening/recyclization sequence, giving the pyrano[2,3-*c*]pyrazole **5**[53] as the only isolated product in 78% yield (Scheme 1).



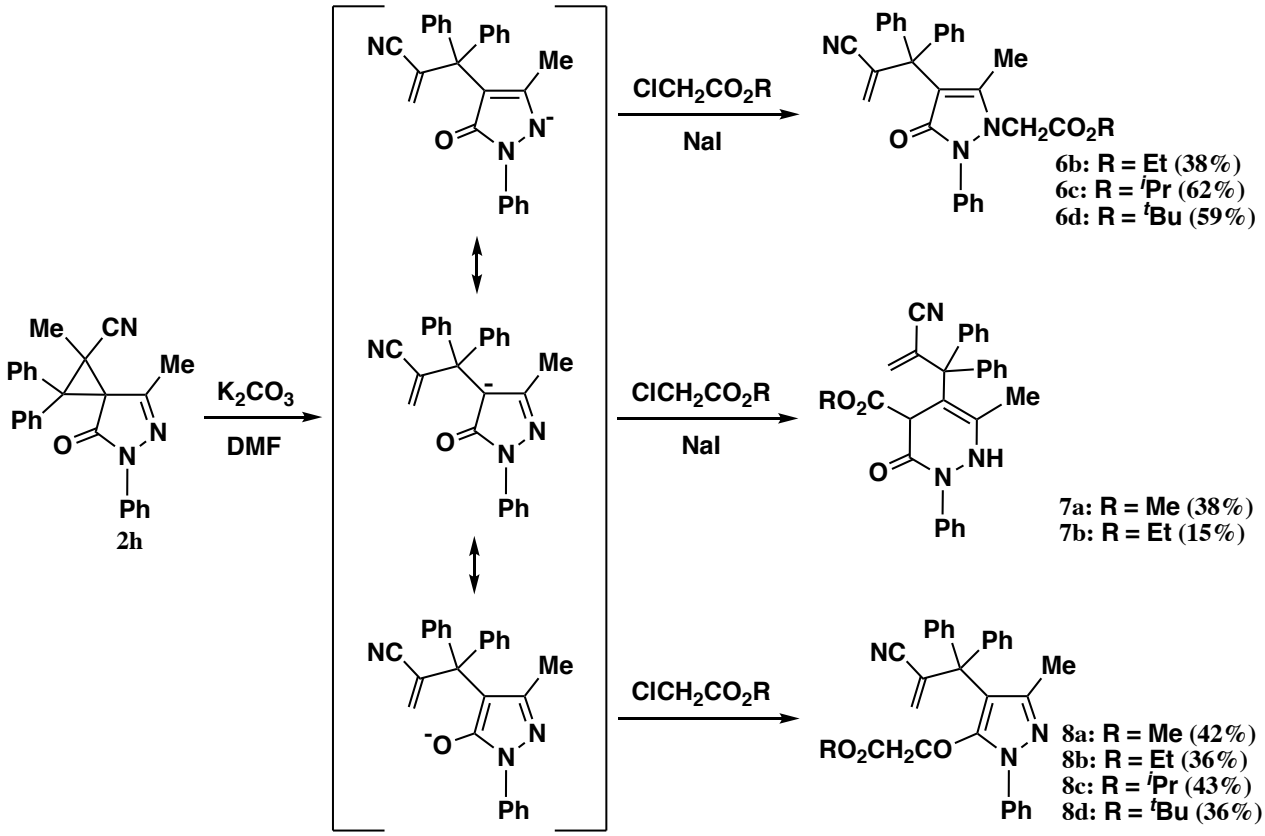
2h 5

Scheme 1. Ring transformation of **2h** into **5**

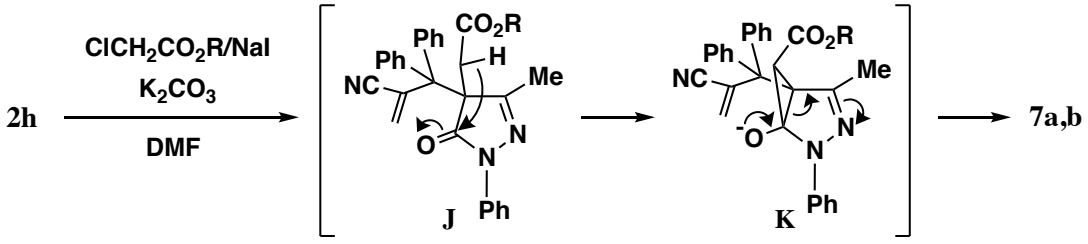
Generally, the utility of cyclopropane derivatives in organic synthesis has been recognized for their ready accessibility originating from the inherent ring strain that can lead to a variety of ring-opening reactions under the influence of a wide range of chemicals, for example, electrophiles, nucleophiles, and radicals.[54-58]

The pyridazine nucleus and derived 3-oxo-derivatives, pyridazin-3-ones, are versatile pharmacophores in many biologically active molecules of contemporary interest.[59-62] For example, these molecules have been previously reported to be platelet aggregation inhibitor, α-adrenoceptor antagonists, and antisecretory/antiulcer agents.[63-65] On the other hand, pyrazole motif makes up the core structure of numerous biologically active compounds, including blockbuster drugs such as Celebrex[66] and Viagra,[67] that find a wide range of applications in pharmaceutical.[1,68,69]

In this context, we tried the divergent synthesis of *N*-substituted dihydropyrazoles, dihydropyridazinones, and *O*-substituted pyrazoles starting from SPO **2h** (Scheme 2).[53] Thus, thermal treatment of **2h** with α-chloro esters, such as methyl chloroacetate, ethyl chloroacetate, isopropyl chloroacetate, and *tert*-butyl chloroacetate, in K_2CO_3/NaI system in DMF at 120 ˚C for 1 h caused a ring opening and subsequent *N*- or *C*-attack nucleophilic substitution to give the corresponding *N*-substituted dihydropyrazoles **6b-d** and dihydropyridazinones **7a,b**. On the other hand, in the absence of NaI under this reaction conditions, *O*-substituted pyrazoles **8a-d** were obtained *via* an *O*-attack nucleophilic substitution.



Scheme 2. Divergent synthesis of **6b-d**, **7a,b**, and **8a-d** starting from SPO **2h**



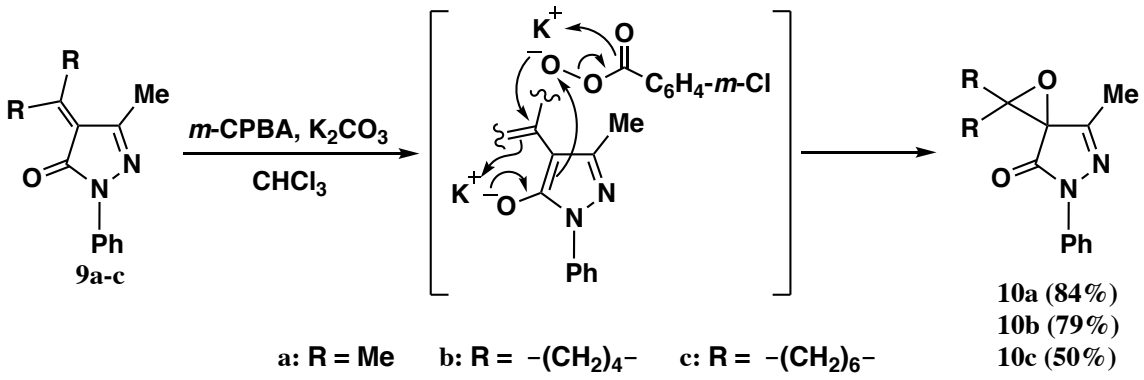
Scheme 3. A plausible mechanism for the formation of **7a,b**

The formation of **7a,b** could be explained by possible mechanism presented in Scheme 3. Thus, it is proposed that a ring-opening reaction of **2h** probably causes in the presence of K_2CO_3 to give the *C*-anions, which undergo *C*-attack nucleophilic substitution to afford *C*-adducts **J**. An intramolecular nucleophilic addition of activated methylene group of *C*-adducts **J** to carbonyl group could occur readily and then the fused pyrazoles **K** would be produced. Subsequently, dihydropyridazinones **7a,b** could be formed *via* a ring expansion of the fused pyrazoles **K**.

3. SYNTHESIS AND APPLICATION OF SPOS CONTAINING OXIRANE MOIETY

Epoxides, especially spiro epoxide-heterocycles, are versatile building blocks for the synthesis of many bioactive natural products. They are an ideal source for diversity because they can be opened with nucleophiles. They are well-known carbon electrophiles and their ability to undergo regioselective ring-opening reactions contributes to their synthetic value.[70-74] In this context, we have developed a diversity-oriented approach to pyrazole-4,5-diols, 4-hydroxy-pyrazol-3-ones, and phenylhydrazones from key intermediate SPO **10a**.[75]

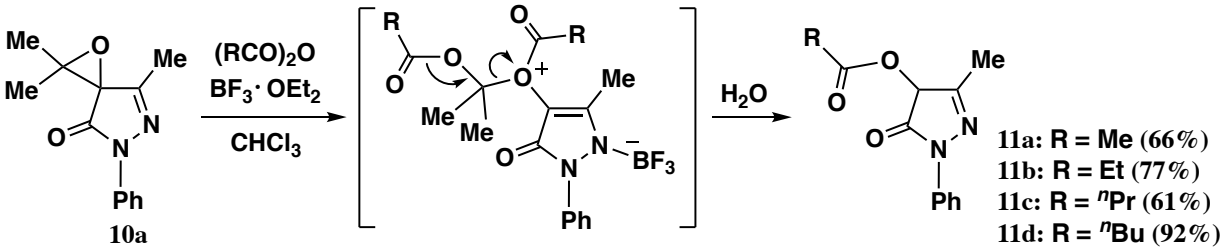
An initial attempt to react 4-alkylidene-pyrazol-3-ones **9a-c**[76-79] with *m*-chloroperbenzoic acid (*m*-CPBA) using the method of DeRuiter and co-workers[80] failed and the expected SPOs **10a-c** were observed as trace level. The reaction was not clean. To achieve an efficient synthesis of SPOs **10a-c**, we examined the epoxidation of **9a-c**. Consequently, the reaction of **9a-c** with *m*-CPBA in the presence of K_2CO_3 in $CHCl_3$ at 0-5 ˚C for 1 h led to the corresponding SPOs **10a-c** (Scheme 4). In this case, it seems that the substrates **9a-c** were activated by deprotonation of alkylidene proton in the presence of K_2CO_3 and then the epoxidation could be promoted by using activated intermediates.



Scheme 4. Synthesis of SPOs **10a-c**

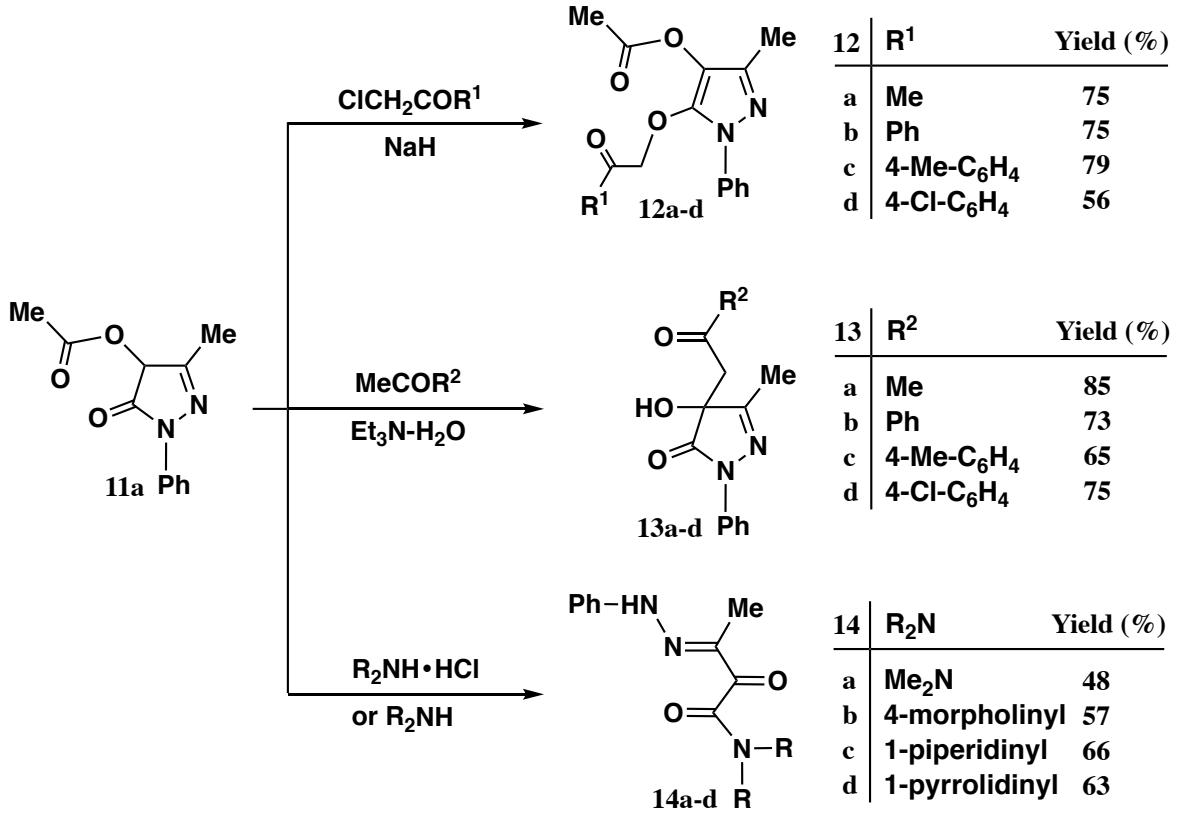
With the aim of extending the ring-opening reaction of SPOs **10a-c**, we next tried the reaction of **10a** with acid anhydride in the presence of Lewis acid as an acid catalyst. Thus, treatment of **10a** with acid anhydride such as acetic, propionic, butyric, and pentanoic anhydride in the presence of $BF_3 \bullet OEt_2$ in

$CHCl_3$ at rt for 12 h led to the corresponding 4-acyloxy-pyrazol-3-ones **11a-d** (Scheme 5). The effect of Lewis acid was observed with $BF_3 \cdot OEt_2$ giving the highest yield of **11a**, while other Lewis acids such as $ZnCl_2$ and $TiCl_4$ gave none of **11a**.



Scheme 5. Ring opening of **10a** with acid anhydride in the presence of $BF_3 \cdot OEt_2$

With these results in hand, we investigated a divergent method for the synthesis of pyrazole derivatives from 4-acetyloxy-pyrazol-3-one **11a** in detail (Scheme 6). Thus, when a mixture of **11a** and α-chloroketones, such as chloroacetone, phenacyl chloride, 4-methylphenacyl chloride, and 4-chlorophenacyl chloride, in the presence of NaH in DMF was stirred at rt for 12 h, the corresponding pyrazole-4,5-diols **12a-d** were obtained with 56-79% isolated yields.



12	R^1	Yield (%)
a	Me	75
b	Ph	75
c	4-Me-C_6H_4	79
d	4-Cl-C_6H_4	56

13	R^2	Yield (%)
a	Me	85
b	Ph	73
c	4-Me-C_6H_4	65
d	4-Cl-C_6H_4	75

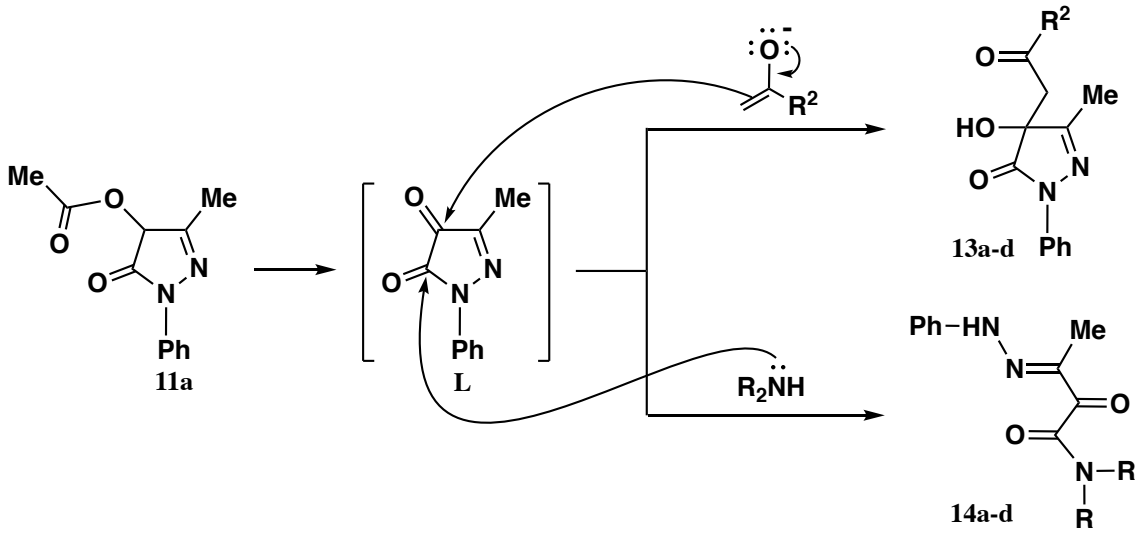
14	R_2N	Yield (%)
a	Me_2N	48
b	4-morpholinyl	57
c	1-piperidinyl	66
d	1-pyrrolidinyl	63

Scheme 6. Divergent synthesis of **12a-d**, **13a-d**, and **14a-d** starting from **11a**

On the other hand, the reaction of **11a** with ketones, such as acetone, acetophenone, 4'-methylacetophenone, and 4'-chloroacetophenone, in the presence of Et_3N and H_2O using air as the oxidant at rt for 12 h led to the corresponding 4-hydroxy-pyrazol-3-ones **13a-d** in 65-85% isolated yields. To simplify the reaction, the ketones were used to serve as the reagent and solvent. Additive effects were observed with H_2O giving the highest yield of **13a**. It makes us believe that this reaction can only be promoted by using Et_3N/H_2O system.

Furthermore, we found the reaction condition under which phenylhydrazone derivatives **14a-d** could be isolated. Indeed, thermal treatment of **11a** with secondary amines, such as dimethylamine hydrochloride, morpholine, piperidine, and pyrrolidine, using air as the oxidant for 1-2 h gave the corresponding phenylhydrazones **14a-d** with 48-66% isolated yields. In this reaction, secondary amines were used to serve as the reagent and solvent to simplify the reaction.

A plausible mechanism for the formation of **13a-d** and **14a-d** is shown in Scheme 7. These reactions are assumed to proceed through the formation of the non-isolable intermediate pyrazole-4,5-dione **L**. In all cases of synthesis of compounds **13** and **14**, **L** was not observed at all, and this could be explained by the instability structure of **L** under these reaction conditions. Thus, a deacetylation and subsequent aerobic oxidation[81-83] of 4-acetyloxy-pyrazol-3-one **11a** easily occurs and then **L** would be produced. The reaction of **L** with ketones probably causes aldol-type addition of activated methyl group of ketones to C-4 position of **L**, giving the 4-hydroxy-pyrazol-3-ones **13a-d**. On the other hand, thermal treatment of **L** with secondary amines would cause nucleophilic addition of secondary amines to C-5 position of **L** and subsequent ring opening to afford the phenylhydrazones **14a-d**.



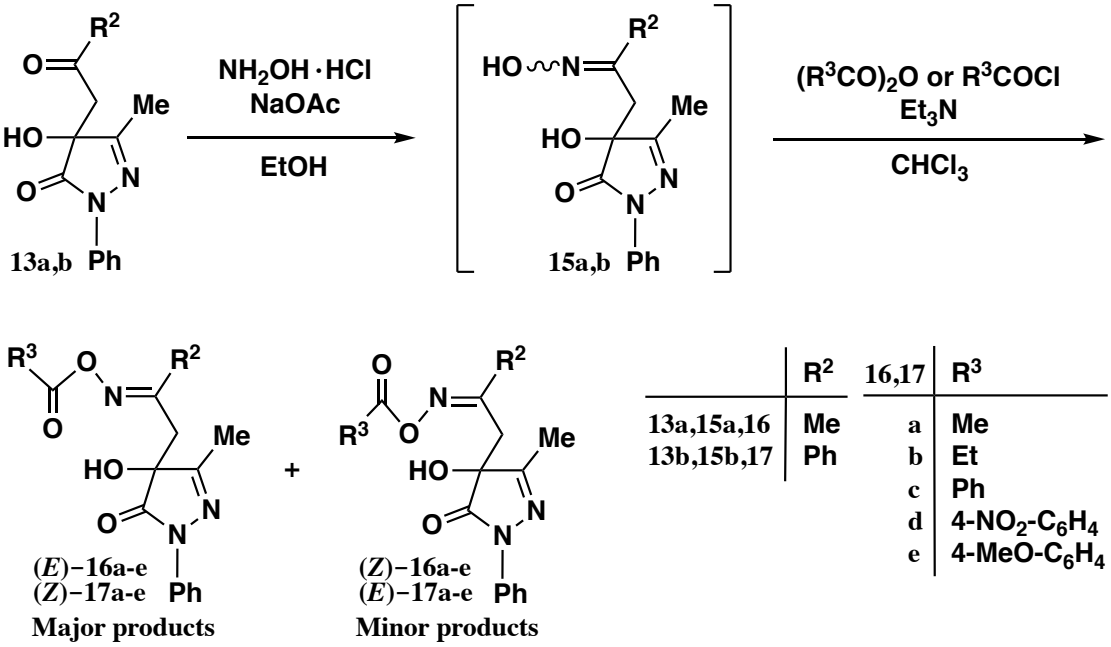
Scheme 7. A plausible mechanism for the formation of **13a-d** and **14a-d**

Oxime esters are a small, but valuable intermediates for the synthesis of heterocyclic compounds.[84] They are also an important class of biologically useful compounds for the synthesis of fragrances[85] and therapeutic studies,[86] and useful building blocks in peptide synthesis.[87] In addition, oxime esters are selective covalent inhibitors of serine hydrolase retinoblastoma-binding protein 9 (RBBP9)[88] and cleave DNA under photolytic conditions.[89] Hence, their synthesis continues to attract attention and provides an interesting challenge.[90-92]

Owing to the importance of oxime esters, we tried to extend our previous studies to synthesize the functionalized pyrazol-3-ones **16a-e** and **17a-e** containing oxime ester from **13a,b**, which might have useful biological and therapeutic activities, especially *in vitro* their DNA cleavage activities.[93] The cleaving agents of nucleic acid have attracted extensive attention due to their potential applications in the fields of molecular biological technology and drug development.[94,95] DNA is an important cellular receptor and many chemicals exert their antitumor effects through binding to DNA thereby changing the replication of DNA and inhibiting the growth of tumor cells.[96,97] Then discussing the mechanism of compounds cleaving and/or binding to DNA possesses significant meanings. For these reasons, we have been interested in the preparation of functionalized pyrazol-3-ones containing oxime ester to evaluate their DNA cleavage activity.

In the first step, we examined the conversion of compounds **13a,b** into the oxime derivatives **15a,b** (Scheme 8). In this reaction, the base NaOAc was investigated because of its ease of handling. Indeed, when **13a,b** were treated with $NH_2OH{\cdot}HCl$ in the presence of NaOAc in refluxing EtOH for 1 h, the expected pyrazol-3-one oxime derivatives **15a,b** were produced in good yields as crude products.

On the basis of this result, in the next step, we have tried to directly construct pyrazol-3-one oxime esters **16a-e** and **17a-e** starting from **13a,b** and acid anhydride or chloride in a one-step process, without isolation of the intermediate oxime derivatives **15a,b**. The results are summarized in Table 4. Thus, when a mixture of **13a,b** and $NH_2OH{\cdot}HCl$ in the presence of NaOAc in refluxing EtOH for 1 h and then the reaction mixture was treated with acid anhydride or chloride in the presence of Et_3N in refluxing $CHCl_3$ for 1 h, the desired pyrazol-3-ones (*E*)-**16a-e** and (*Z*)-**17a-e** containing oxime ester were obtained together with *(Z)*-**16a-e** and (*E*)-**17a-e** as minor products.



Scheme 8. Synthesis of **16a-e** and **17a-e** starting from **13a,b**

Table 4. Synthesis of pyrazol-3-ones **16a-e** and **17a-e** containing oxime ester

Entry	Substrate	R^2	R^3	Product	Yield (%)	Ratio of *E/Z*
1	**13a**	Me	Me	**16a**	72	7/1[a]
2	**13a**	Me	Et	**16b**	80	9/1[a]
3	**13a**	Me	Ph	**16c**	45	5.4/1.0[b]
4	**13a**	Me	4-NO_2-C_6H_4	**16d**	62	6.8/1.0[b]
5	**13a**	Me	4-MeO-C_6H_4	**16e**	47	1/0[b]
6	**13b**	Ph	Me	**17a**	60	1.0/2.3[b]
7	**13b**	Ph	Et	**17b**	67	1.0/4.2[b]
8	**13b**	Ph	Ph	**17c**	69	1.0/1.5[b]
9	**13b**	Ph	4-NO_2-C_6H_4	**17d**	65	1.0/2.8[b]
10	**13b**	Ph	4-MeO-C_6H_4	**17e**	62	0.9/1.0[b]

[a] The ratio of *E* and *Z* was determined based on the ^{1}H NMR data.
[b] The ratio of *E* and *Z* was determined based on the isolated yield.

Finally, we have tested *in vitro* DNA cleavage activity of the synthesized compounds **10a**, **11a**, **13a,b**, (*E*)-**16c-e**, and (*Z*)-**17a-e**. The values obtained for activity were based on the remaining amounts of covalently closed circular duplex DNA, namely ccc-DNA, of plasmid pBR322.[98-101] The data of DNA cleavage activity is summarized in Table 5. Indeed, in the absence of Cu^{2+}, all the tested compounds showed no DNA cleavage activity. These activities of compounds **10a**, **13a**, and (*Z*)-**17a**, however, were

obviously accelerated by the addition of 1 mM Cu^{2+} (entries 3, 4, and 9). Furthermore, it was found that compounds (*E*)-**16c-e** and (*Z*)-**17b-e** have moderate activity with Cu^{2+} (entries 6-8 and 10-13).

Table 5. DNA cleavage by **10a**, **11a**, **13a,b**, (*E*)-**16c-e**, and (*Z*)-**17a-e**

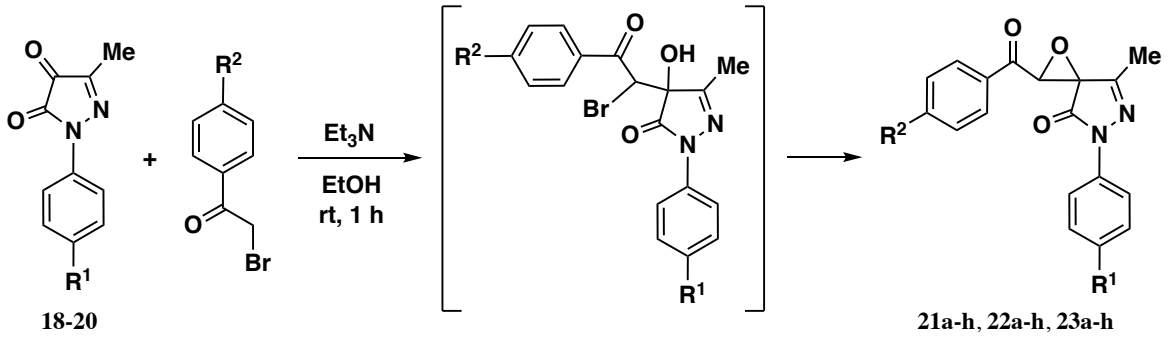
Entry	Compound	DNA type	Relative amounts of DNA (%)	
			Without Cu^{2+} [a]	With Cu^{2+} [b]
1	Control[c]	ccc- oc-	100 0	100 0
2	**10a**[d]	ccc- oc-	100 0	28 72
3	**11a**[d]	ccc- oc-	100 0	100 0
4	**13a**[d]	ccc- oc-	100 0	24 76
5	**13b**[d]	ccc- oc-	100 0	80 20
6	**(*E*)-16c**[d]	ccc- oc-	100 0	89 11
7	**(*E*)-16d**[d]	ccc- oc-	100 0	87 13
8	**(*E*)-16e**[d]	ccc- oc-	100 0	91 9
9	**(*Z*)-17a**[d]	ccc- oc-	100 0	61 39
10	**(*Z*)-17b**[d]	ccc- oc-	100 0	84 16
11	**(*Z*)-17c**[d]	ccc- oc-	100 0	88 12
12	**(*Z*)-17d**[d]	ccc- oc-	100 0	88 12
13	**(*Z*)-17e**[d]	ccc- oc-	100 0	88 12

[a] Incubation for 3 h. [b] Incubation for 3 h. [c] Amount: 0 mM. [d] Amount: 10 mM.
As activity was accelerated upon addition of Cu^{2+}, the quantity of compounds and the incubation time were minimized until differences in activity could be observed.

A series of new SPOs **21-23** containing oxirane moiety were synthesized by the reaction of pyrazole-4,5-diones **18-20** with phenacyl bromides through the Darzens-type reaction.[102] Furthermore, we have demonstrated the ring transformation of SPOs **21-23** with pyrrolidine, giving pyridazinone derivatives **24-26**. Pyridazinones are one of the most important subtypes of pyridazine heterocyclic family highly attractive in modern drug discovery and agrochemicals, such as Azelastine,[103] Lynparza,[104] Emorfazone,[105] Diclomezine,[106] and Flufenpyr.[107]

The convenient substrates, three types of pyrazole-4,5-diones **18-20**,[108,109] were reacted with phenacyl bromides in the presence of Et_3N in EtOH at rt for 1 h to give the corresponding SPOs **21-23** containing oxirane moiety in moderate to good yields (Table 6).

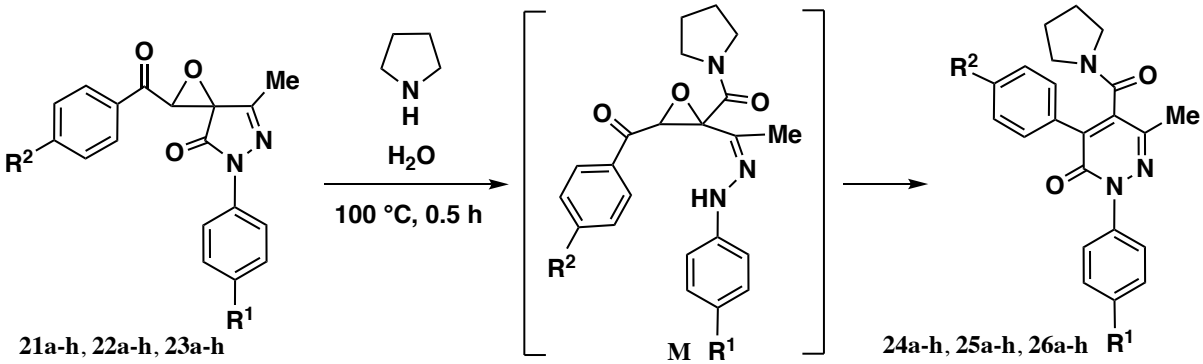
Table 6. Substrate scope of the synthesis for SPOs **21-23**



Entry	Substrate	R^1	R^2	Product	Yield (%)[a]
1	**18**	H	H	**21a**	81
2	**18**	H	F	**21b**	84
3	**18**	H	Cl	**21c**	89
4	**18**	H	Br	**21d**	91
5	**18**	H	Me	**21e**	77
6	**18**	H	OMe	**21f**	56
7	**18**	H	CF_3	**21g**	79[b]
8	**18**	H	NO_2	**21h**	90
9	**19**	Me	H	**22a**	88
10	**19**	Me	F	**22b**	83
11	**19**	Me	Cl	**22c**	84
12	**19**	Me	Br	**22d**	87
13	**19**	Me	Me	**22e**	70
14	**19**	Me	OMe	**22f**	53
15	**19**	Me	CF_3	**22g**	85[b]
16	**19**	Me	NO_2	**22h**	92
17	**20**	Cl	H	**23a**	89
18	**20**	Cl	F	**23b**	90
19	**20**	Cl	Cl	**23c**	90
20	**20**	Cl	Br	**23d**	89
21	**20**	Cl	Me	**23e**	94
22	**20**	Cl	OMe	**23f**	88
23	**20**	Cl	CF_3	**23g**	81[b]
24	**20**	Cl	NO_2	**23h**	92

[a] Isolated yield. [b] Reaction for 0.5 h.

Table 7. Ring transformation of SPOs **21-23** into pyridazinones **24-26**



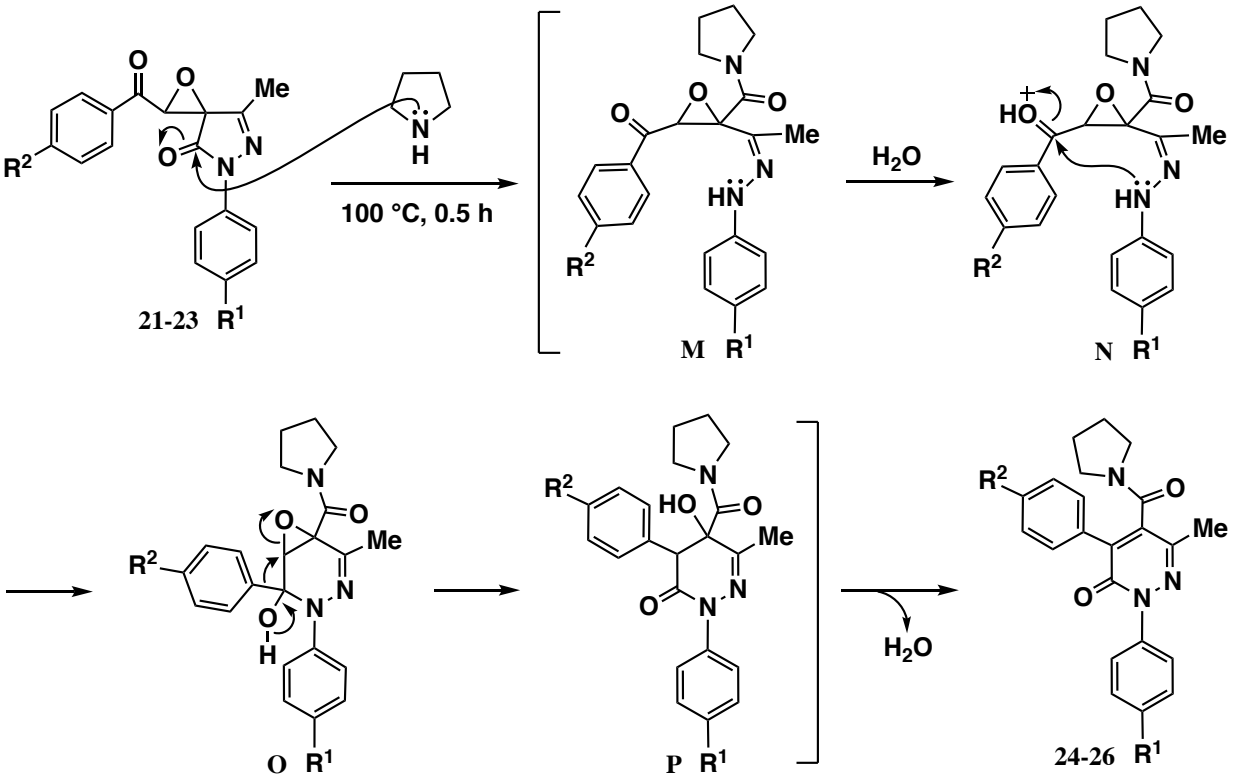
Entry	Substrate	R^1	R^2	Product	Yield (%)[a]
1	**21a**	H	H	**24a**	66
2	**21b**	H	F	**24b**	ND[b]
3	**21c**	H	Cl	**24c**	58
4	**21d**	H	Br	**24d**	49
5	**21e**	H	Me	**24e**	57
6	**21f**	H	OMe	**24f**	62
7	**21g**	H	CF_3	**24g**	39
8	**21h**	H	NO_2	**24h**	ND[b]
9	**22a**	Me	H	**25a**	53
10	**22b**	Me	F	**25b**	ND[b]
11	**22c**	Me	Cl	**25c**	46
12	**22d**	Me	Br	**25d**	36
13	**22e**	Me	Me	**25e**	47
14	**22f**	Me	OMe	**25f**	46
15	**22g**	Me	CF_3	**25g**	24
16	**22h**	Me	NO_2	**25h**	ND[b]
17	**23a**	Cl	H	**26a**	77
18	**23b**	Cl	F	**26b**	ND[b]
19	**23c**	Cl	Cl	**26c**	75
20	**23d**	Cl	Br	**26d**	80
21	**23e**	Cl	Me	**26e**	60
22	**23f**	Cl	OMe	**26f**	77
23	**23g**	Cl	CF_3	**26g**	55
24	**23h**	Cl	NO_2	**26h**	ND[b]

[a] Isolated yield. [b] Not detected.

To expand the scope application of reactions of SPOs **21-23**, we next examined the ring transformation of SPOs **21-23** in detail. Interestingly, we found the reaction condition under which pyridazinone derivatives **24-26** could be isolated (Table 7). Thus, thermal treatment of SPOs **21-23** with pyrrolidine in the presence

of H_2O for 0.5 h caused a ring transformation easily to afford the corresponding pyridazinones **24-26**. In the case of **21b**,**h**, **22b**,**h**, and **23b**,**h** as the substrates, the expected products **24b**,**h**, **25b**,**h**, and **26b**,**h** were not detected at all and the reaction was not clean (entries 2, 8, 10, 16, 18, and 24). It is assumed that an intramolecular nucleophilic addition of secondary amino group of the ring-opening intermediate **M** to carbonyl group may be less likely to occur due to the influence of fluorine, nitro, or trifluoromethyl substituent as electron withdrawing substituent.

The formation of pyridazinones **24-26** could be explained by a plausible reaction mechanism presented in Scheme 9. SPOs **21-23** would be reacted with pyrrolidine to give the key intermediate hydrazones **M** *via* a nucleophilic addition of the adjacent pyrrolidine nitrogen atom to the pyrazol-3-one carbonyl carbon. An intramolecular cyclization of **N**, which would be produced by a protonation of **M**, easily occurs, leading to intermediates **O**. An aryl migration[110] of **O** possibly proceeds to afford the intermediates **P**, which undergo elimination of H_2O to yield pyridazinone derivatives **24-26**.



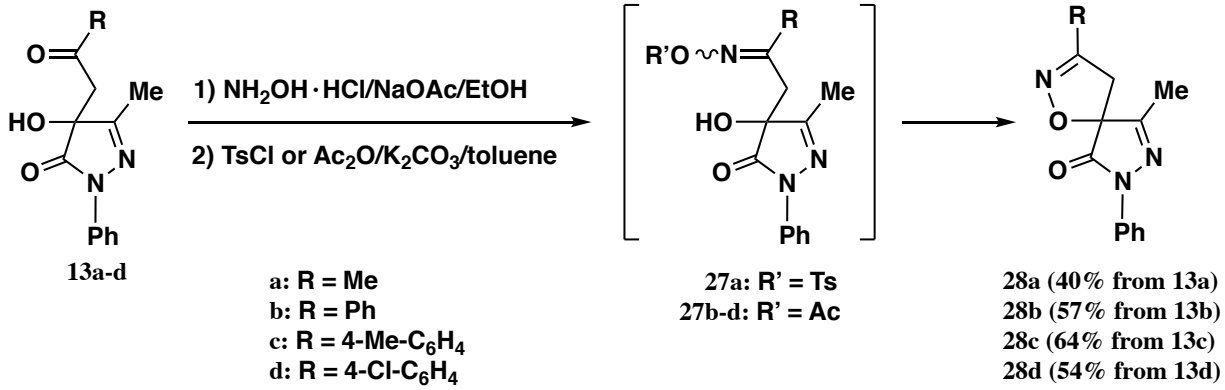
Scheme 9. A plausible mechanism for the formation of **24-26**

4. SYNTHESIS AND APPLICATION OF SPOS CONTAINING ISOXAZOLINE MOIETY

Many papers have accounted in the last decade for the synthesis and occurrence of isoxazoline derivatives in nature and medicinal chemistry.[111,112] Besides its natural occurrence, isoxazoline is also an important skeleton found in many synthetic bioactive compounds. Isoxazoline derivatives have wide-ranging collection of conventional biological activities, for example, antimicrobial, anticancer, anti-inflammatory,

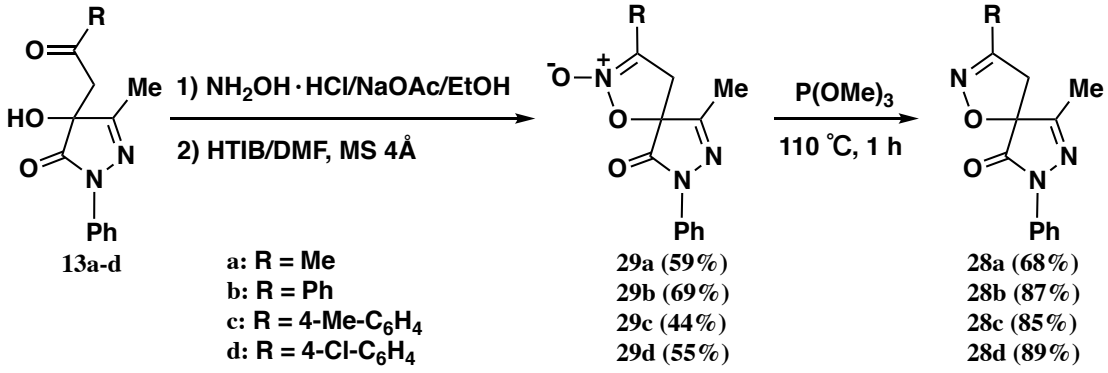
and antiplatelet activities.[113-119] In this context, several synthetic methods used for the formation of isoxazole and its derivatives have recently been reported in the literature.[120-125]

Prompted by these observations, novel SPOs **28** containing isoxazoline moiety were prepared by the K_2CO_3-assisted intramolecular cyclocondensation reaction of β-hydroxy ketoximes, which were prepared from pyrazol-3-ones **13a-d** containing β-hydroxy ketone moiety through an oximation.[126] Thus, treatment of **13a-d** with $NH_2OH·HCl$/NaOAc in refluxing EtOH for 2 h and subsequent TsCl or Ac_2O/ K_2CO_3 combinations in refluxing toluene for 3 h caused an intramolecular S_N2-type reaction of the key intermediate *O*-tosylated or -acetylated oximes **27a-d** *via* an elimination of tosyloxy or acetyloxy group to give the corresponding SPOs **28a-d** with 40-64% isolated yields (Scheme 10).



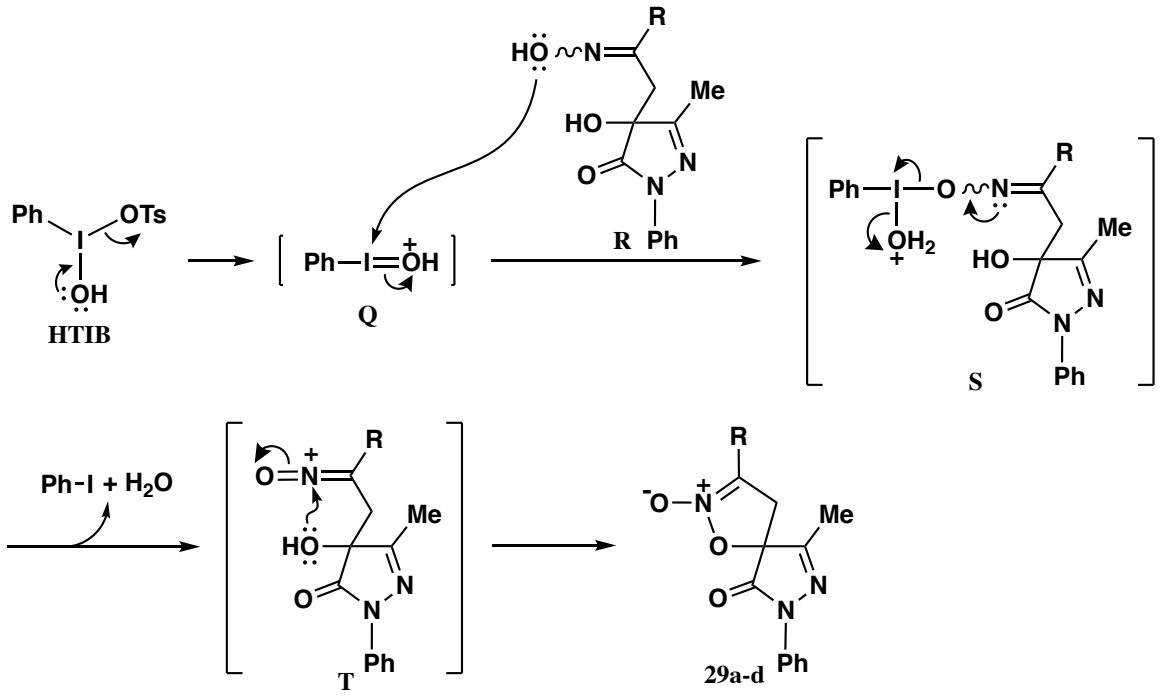
Scheme 10. Synthesis for SPOs **28a-d**

On the other hand, treatment of β-hydroxy ketoximes, which were prepared from **13a-d** and $NH_2OH·HCl$, with [hydroxy(tosyloxy)iodo]benzene (HTIB)[127-130] in the presence of 4Å molecular sieves (MS 4Å) in DMF at rt for 1 h caused an oxidative N-O coupling reaction to provide the corresponding SPOs *N*-oxides **29a-d** with 2 steps 44-69% isolated yields (Scheme 11). Subsequently, thermal treatment of **29a-d** with $P(OMe)_3$ at 110 ˚C for 1 h without solvent caused a deoxygenation to give the corresponding SPOs **28a-d** in 68-89% yields, which were identical with authentic samples prepared according to Scheme 10.



Scheme 11. Synthesis for SPOs **29a-d**

A plausible mechanism for this cascade cyclization was proposed, as shown in Scheme 12. HTIB would undergo a release of tosylate anion to form hydroxyphenyliodonium ion **Q** as an active species in the oxidative N-O coupling reaction. The reaction of **Q** with β-hydroxy ketoximes **R** probably causes a nucleophilic addition of oxime hydroxyl group of **R** to **Q** *via* a proton migration, giving the intermediate nucleophilic adduct **S**, which would undergo an elimination of iodobenzene and H_2O to produce the key intermediate *N*-oxonitrenium ion **T**. The neighboring alcoholic oxygen of **T** would attack the nitrogen center and then the desired isoxazoline *N*-oxides **29a-d** would be formed through a deprotonation.



Scheme 12. A plausible mechanism for the formation of **29a-d**

All the synthesized SPOs **28a-d** and **29a-d** were tested for their DNA cleavage activity *in vitro*. The values obtained for activity were based on the remaining amounts of covalently closed circular duplex DNA, namely ccc-DNA, of plasmid pBR322. The data of DNA cleavage activity is summarized in Table 8. Indeed, in the absence of Cu^{2+}, the tested compounds other than **29a** showed no DNA cleavage activity. These activities of compounds **28a**,**d** and **29b-d**, however, were obviously accelerated by the addition of 1 mM Cu^{2+} (entries 5, and 7-9). Interestingly, it was found that compound **28a** showed high DNA cleavage activity *in vitro* with Cu^{2+} (entry 2).

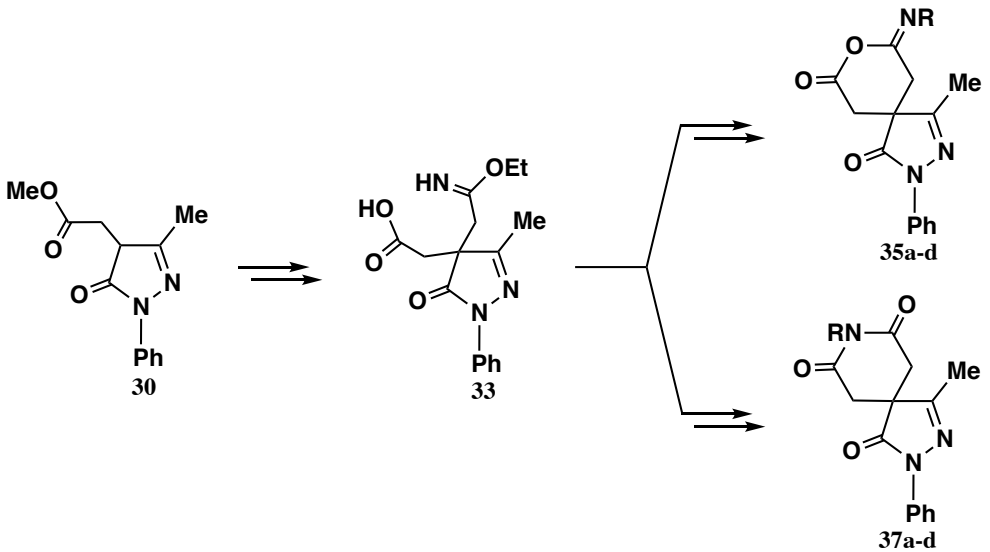
Table 8. DNA cleavage by **28a-d** and **29a-d**[a]

Entry	Compound	DNA type	Relative amounts of DNA (%)	
			Without Cu^{2+} [b]	With Cu^{2+} [c]
1	Control[d]	ccc- oc-	100 0	100 0
2	**28a**[e]	ccc- oc-	100 0	0 100
3	**28b**[e]	ccc- oc-	100 0	100 0
4	**28c**[e]	ccc- oc-	100 0	100 0
5	**28d**[e]	ccc- oc-	100 0	87 13
6	**29a**[e]	ccc- oc-	79 21	77 23
7	**29b**[e]	ccc- oc-	100 0	73 27
8	**29c**[e]	ccc- oc-	100 0	83 17
9	**29d**[e]	ccc- oc-	100 0	86 14

[a] Incubation for 3 h. [b] $CuCl_2$: 0 mM. [c] $CuCl_2$: 1 mM. [d] Amount: 0 mM. [e] Amount: 10 mM.
As activity was accelerated upon addition of Cu^{2+}, the quantity of compounds and the incubation time were minimized until differences in activity could be observed.

5. SYNTHESIS OF SPOS CONTAINING IMINOLACTONE AND/OR CYCLIC IMIDE MOIETY

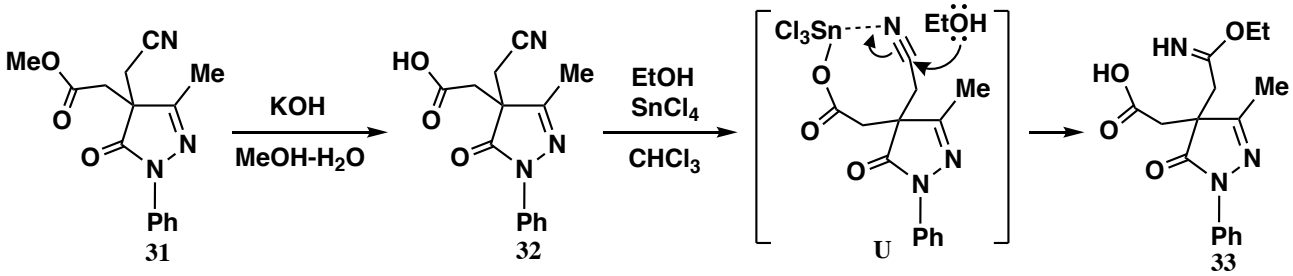
We have developed a divergent synthesis of SPO **35** and **37** containing iminolactone and/or cyclic imide moiety through an intramolecular cyclization of the key intermediate ethyl imidate **33** (Scheme 13).[131]



a: R = CH_2CO_2Me b: R = CH_2CO_2Et c: R = $CH_2CO_2{}^iPr$ d: R = $CH_2CO_2{}^tBu$

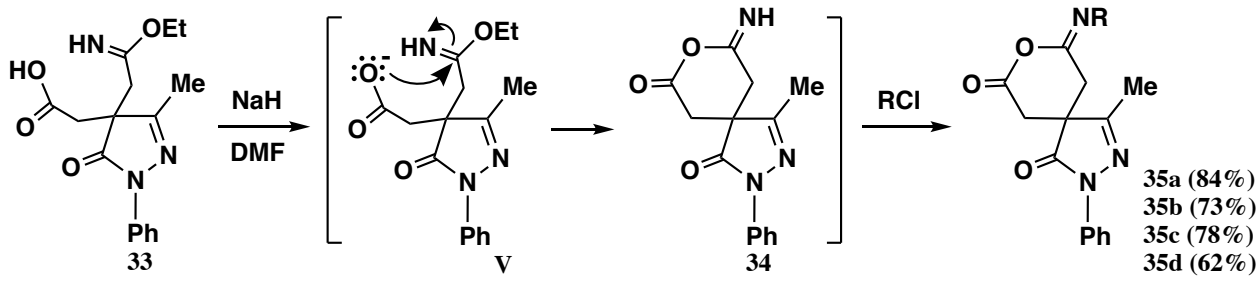
Scheme 13. Divergent synthesis of **35a-d** and **37a-d** starting from **30**

In our initial studies, we carried out the hydrolysis of *C*-cyanomethylated pyrazole-4-acetic acid methyl ester **31**, which was easily prepared by treatment of pyrazole-4-acetic acid methyl ester **30**[132] and iodoacetonitrile. Thus, the treatment of **31** with KOH in aqueous MeOH at rt for 1 h gave the carboxylic acid **32** in 62% isolated yield (Scheme 14). Fortunately, we found the reaction condition under which the ethyl imidate **33** could be isolated. Thus, the reaction of **32** with EtOH in the presence of $SnCl_4$ in boiling $CHCl_3$ for 3 h provided the ethyl imidate **33** in 62% isolated yield most likely *via* the nucleophilic addition of EtOH to CN group of the intermediate Sn(IV) complex **U**, which would be probably formed by the reaction of **32** with $SnCl_4$.



Scheme 14. Synthesis of **33**

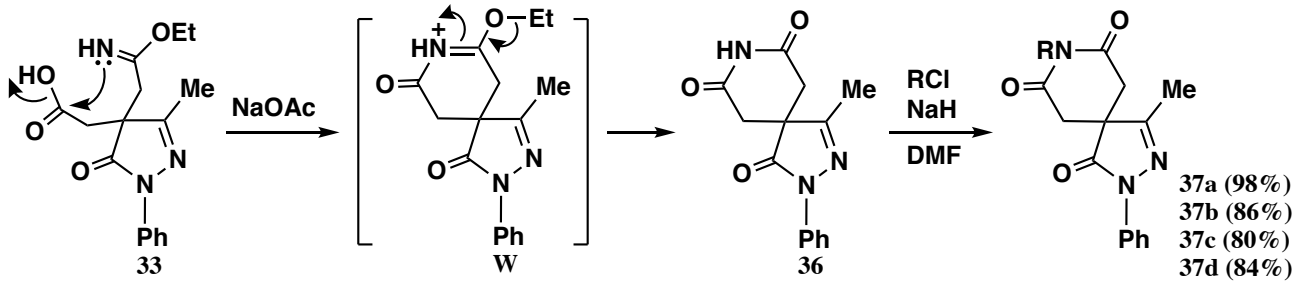
We next investigated a divergent method for the synthesis of SPO from ethyl imidate **33** in detail. Thus, after treating **33** with NaH in DMF at 100 ˚C for 1 h, the desired SPO **34** containing iminolactone moiety was isolated in 73% yield. The formation of the **34** could be explained by the possible mechanism presented in Scheme 15. Thermal treatment of **33** with NaH would cause intramolecular nucleophilic addition of carboxylate anion of **V** to imino carbon, giving the desired SPO **34** with elimination of ethoxide ion. Based on this result, we have tried to directly construct substituted SPOs **35a-d** from **33** and α-chloro esters, such as methyl chloroacetate, ethyl chloroacetate, isopropyl chloroacetate, and *tert*-butyl chloroacetate, in a one-pot process. Thus, when a solution of **33** in the presence of NaH in DMF was stirred at 100 ˚C for 1 h and then the reaction mixture was treated with α-chloro esters at 100 ˚C for 1 h, the desired SPOs **35a-d** were obtained in 62-84% yields.



a: R = CH_2CO_2Me b: R = CH_2CO_2Et c: R = $CH_2CO_2{}^iPr$ d: R = $CH_2CO_2{}^tBu$

Scheme 15. Synthesis of SPOs **35a-d**

On the other hand, we found the reaction condition under which the SPO **36** containing cyclic imide moiety could be isolated. Subsequently, treatment of **33** with NaOAc at 180 ˚C for 1 h without solvent gave **36** in 77% yield (Scheme 16). Interestingly, in this reaction, the SPO **34** was not detected at all. This reaction possibly proceeds through attack of the imino group at the carbonyl of the carboxylic acid with nucleophilic addition followed by ring closure with loss of hydroxide ion to produce the key intermediate **W**, which undergoes elimination of ethyl group to yield **36**. Furthermore, we carried out the reaction of **36** with α-chloro esters to obtain substituted SPOs **37a-d**. Thus, SPO **36** was reacted with α-chloro esters in the presence of NaH in DMF at 120 ˚C for 1 h to provide the desired SPOs **37a-d** with 80-98% isolated yields.



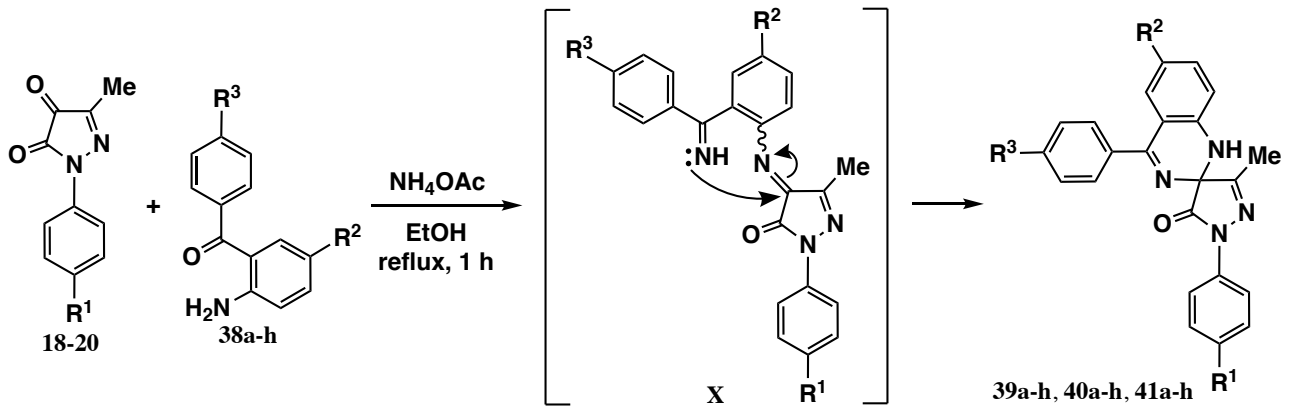
Scheme 16. Synthesis of SPOs **37a-d**

6. SYNTHESIS OF SPOS CONTAINING QUINAZOLINE MOIETY

Quinazoline and its derivatives are an important class of heterocycles found in a wide range of natural products and pharmaceuticals. They exhibit several biological activities including antibacterial, antitumor, anti-inflammatory, antiviral, and anti-oxidant activities.[133-137] Quinazoline scaffold is also the building block for many naturally occurring alkaloids such as *Bacillus cereus*, *Bouchardatia neurococca*, *Dichroa febrifuga*, and *Peganum nigellastrum*.[138-141] Therefore, the development of quinazoline-based drugs has renewed the interest in developing new synthetic strategies for the synthesis of quinazoline derivatives.[142-147] The growing importance of quinazolines in medicine is highlighted by the huge sales of the drugs Erlotinib, which is used in the treatment of several types tumors, and Prazosin, an α-adrenergic blocker. Likewise, Iressa, an epidermal growth factor receptor inhibitor, was recently approved by the U.S. Food and Drug Administration for the treatment of lung cancer.[148-151]

A simple, efficient, and three-component procedure has been developed for the synthesis of a series of SPOs **39-41** containing dihydroquinazoline moiety by the reaction of pyrazole-4,5-diones **18-20**, 2-aminobenzophenones **38**, and NH_4OAc in moderate to good yields (Table 9).[152] This method provides several advantages such as operational simplicity, shorter reaction time, and higher yields.

Table 9. Substrate scope of the three-component reaction for SPOs **39-41**[a]



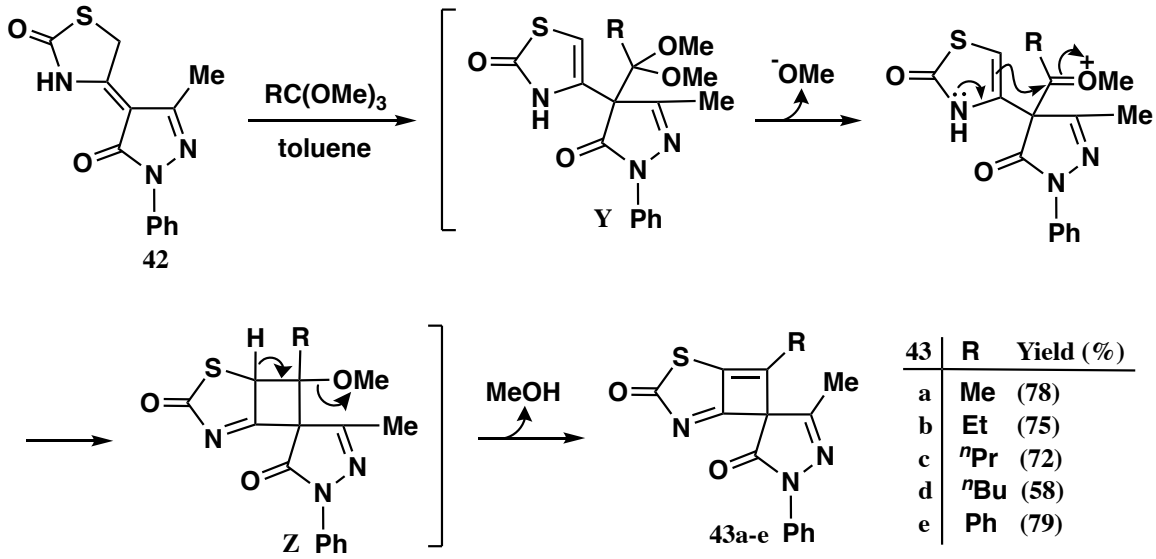
Entry	Substrate	R^1	R^2	R^3	Product	Yield (%)[b]
1	**18**	H	H	H	**39a**	77
2	**18**	H	Cl	H	**39b**	67
3	**18**	H	Br	H	**39c**	62
4	**18**	H	Me	H	**39d**	81
5	**18**	H	H	F	**39e**	78
6	**18**	H	H	Cl	**39f**	76
7	**18**	H	H	Br	**39g**	70
8	**18**	H	H	Me	**39h**	71
9	**19**	Me	H	H	**40a**	76
10	**19**	Me	Cl	H	**40b**	65
11	**19**	Me	Br	H	**40c**	58
12	**19**	Me	Me	H	**40d**	87
13	**19**	Me	H	F	**40e**	77
14	**19**	Me	H	Cl	**40f**	77
15	**19**	Me	H	Br	**40g**	76
16	**19**	Me	H	Me	**40h**	79
17	**20**	Cl	H	H	**41a**	63
18	**20**	Cl	Cl	H	**41b**	48
19	**20**	Cl	Br	H	**41c**	43
20	**20**	Cl	Me	H	**41d**	72
21	**20**	Cl	H	F	**41e**	58
22	**20**	Cl	H	Cl	**41f**	57
23	**20**	Cl	H	Br	**41g**	49
24	**20**	Cl	H	Me	**41h**	62

[a] Reactions were carried out with **18-20** (1 mmol), **38** (1 mmol), and NH_4OAc (4 mmol). [b] Isolated yield.

A plausible reaction mechanism was proposed as shown in Table 9 to explain the formation of SPOs **39-41**. Pyrazole-4,5-diones **18-20** would be reacted with 2-aminobenzophenones **38** and NH_4OAc to give the key intermediate diimines **X** with the expulsion of H_2O and AcOH. The intramolecular cyclization of **X** easily occurs *via* a nucleophilic addition of the adjacent nitrogen atom to the imine carbon and then the corresponding SPOs **39-41** would be produced *via* a proton migration.

7. SYNTHESIS AND APPLICATION OF SPOS CONTAINING CYCLOBUTATHIAZOLE MOIETY

In medicinal chemistry, thiazole and related compounds have been very well known for their therapeutic applications. Thiazole moiety has been found as integral part of the structure of therapeutic agents and is widely used like sulfathiazole as antimicrobial agent, ravuconazole as antifungal agent, ritonavir as antiretroviral agent, and meloxicam as nonsteroidal anti-inflammatory drug.[153] In addition, thiazole derivatives have wide-ranging collection of conventional biological activities, for example, antiallergic, antioxidant, anti-HIV, anticancer, antihypertensive, and antidiabetic activities.[154-159] In this context, several synthetic methods used for the formation of thiazole derivatives have recently been reported in the literature.[160] Based on these properties, it can be reasonably supposed that the development of synthetic strategies for some novel structures incorporating both the pyrazole and thiazole ring systems might provide additional lead molecules for drug discovery. Therefore, the preparation of some bioactive thiazole derivatives containing pyrazole moiety has been reported.[161-164]



Scheme 17. Synthesis of SPOs **43a-e** starting from **42**

We have developed a facile and efficient synthesis of novel SPOs **43** containing cyclobutathiazole moiety (Scheme 17).[165] Thus, thermal treatment of the key substrate pyrazole-thiazolidine derivative **42** as the

building block for bis-heterocycles with orthoesters such as trimethyl orthoacetate, trimethyl orthopropionate, trimethyl orthobutyrate, trimethyl orthovalerate, and trimethyl orthobenzoate in refluxing toluene for 3 h caused an *C*-attack nucleophilic substitution, followed by an intramolecular cyclization/elimination sequence, giving the corresponding SPOs **43** in moderate to good yields. The reaction of **42** with orthoesters is assumed to proceed through the formation of the intermediate acetals **Y**, which undergo an intramolecular cyclization with an elimination of MeOH to result in the formation of **Z**. Furthermore, an elimination of MeOH from **Z** easily occurs and then SPOs **43a-e** would be produced.

To check something about application of SPOs **43**, we have tested *in vitro* DNA cleavage activity of the synthesized compounds **42** and **43a-e**. The data of DNA cleavage activity is summarized in Table 10. Indeed, in the absence of Cu^{2+}, all the tested compounds showed no DNA cleavage activity. These activities of compounds **42** and **43b**, however, were obviously accelerated by the addition of 1 mM Cu^{2+} (entries 2 and 4). Furthermore, it was found that compounds **43c,d** have moderate activity with Cu^{2+} (entries 5 and 6).

Table 10. DNA cleavage by **42** and **43a-e**

Entry	Compound	DNA type	Relative amounts of DNA (%)	
			Without Cu^{2+} [a]	With Cu^{2+} [b]
1	Control[c]	ccc- oc- linear-	100 0 0	100 0 0
2	**42**[d]	ccc- oc- linear-	100 0 0	0 48 52
3	**43a**[d]	ccc- oc- linear-	100 0 0	100 0 0
4	**43b**[d]	ccc- oc- linear-	100 0 0	37 63 0
5	**43c**[d]	ccc- oc- linear-	100 0 0	76 24 0
6	**43d**[d]	ccc- oc- linear-	100 0 0	71 29 0
7	**43e**[d]	ccc- oc- linear-	100 0 0	100 0 0

[a] Incubation for 3 h. [b] Incubation for 1 h. [c] Amount: 0 mM. [d] Amount: 10 mM.
As activity was accelerated upon addition of Cu^{2+}, the quantity of compounds and the incubation time were minimized until differences in activity could be observed.

8. CONCLUSION

The SPOs have proven to be a privileged scaffold in medicinal chemistry and pharmaceutical industry. Recently, the examples describing the synthesis of SPOs have grown exponentially in the scientific community. This review has covered the synthesis and application of SPOs. The functionalized SPOs represent useful synthetic building blocks. The content of the present review was mostly published between 2008 to 2021. The authors regret any omission that may have occurred in this review. Future work would be directed to develop efficient, practical, and scalable synthetic routes to heterocyclic frameworks for biological and preclinical studies. We strongly believe that this area will continue to grow with optimizing known procedures and exploring new useful synthetic methodology.

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