

Review

Alfons L. Baumstark*, Pedro C. Vasquez and Davita McTush-Camp

Synthesis and chemistry of structurally unique hexasubstituted pyrazolines

Abstract: A review focused on our contributions to the synthesis and chemistry of hexasubstituted pyrazolines is presented. The development of a synthetic route to pentasubstituted 2*H*-pyrazoles **1** provides the key starting materials that are used in the synthesis of several unique series of highly substituted pyrazolines **2–6**. Thermolysis of pyrazolines **2–4** allows the facile synthesis of hexasubstituted cyclopropanes. Autoxidation of pentasubstituted 2*H*-pyrazoles **1** in acetone produces a series of hydroperoxy substituted pyrazolines **5** which are effective oxygen-atom transfer reagents. The thermal decomposition of **5** produces β -keto radicals, the transformation of which in the presence of oxygen provides a good route for the synthesis of 3-hydroxy-1,2-dioxolanes. The reaction of tosyl chloride with a pentasubstituted 2*H*-pyrazole yields a chloro-substituted pyrazoline **6** rather than the expected *N*-tosyl product. Thermolysis of **6** yields products, the structure of which is consistent with the formation of an unstable intermediate chloro-substituted cyclopropane.

Keywords: α -azohydroperoxides; cyclopropanes; 3-hydroxy-1,2-dioxolanes; 2*H*-pyrazoles; pyrazolines.

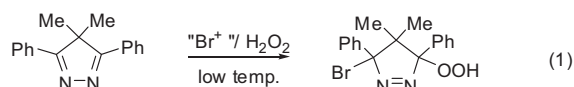
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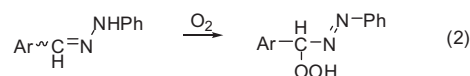
Introduction

Our interest in pyrazoline synthesis was based on our need to develop a general route for the synthesis of 3-hydroperoxy pyrazolines, also known as cyclic α -azohydroperoxides. Our oxygen-atom transfer studies on both cyclic [1–4] and acyclic α -azohydroperoxides [5–8] had shown that the only, known cyclic compound (3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3*H*-pyrazole) at the

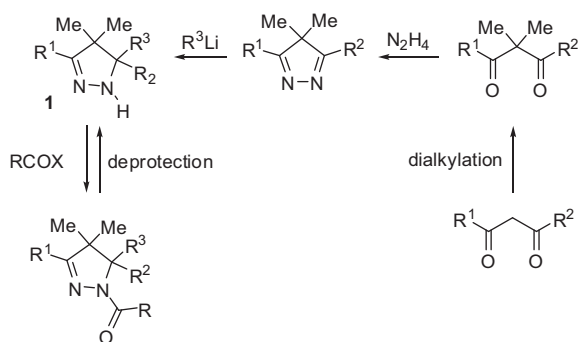
time to be of greater reactivity than the acyclic compounds [9, 10]. Unfortunately, the synthesis of this particular cyclic 3-hydroperoxy pyrazoline was highly specialized (Equation 1) [11] to the point that the approach has yet to be applied successfully to even a closely related analog.



By contrast, the less reactive acyclic α -azohydroperoxides were readily accessible in good yield by autoxidation of phenylhydrazones in aprotic media (Equation 2) [5–8]. Furthermore, the autoxidation approach proved to be relatively insensitive to hydrazone structure, allowing the synthesis of a wide variety of acyclic compounds.



We wished to develop an autoxidation approach as a general route for the synthesis of new cyclic 3-hydroperoxy pyrazolines. Interestingly, at that time, useful autoxidation reactions for cyclic hydrazones (2*H*-pyrazoles) were essentially unexplored. There was ample information on routes to 2*H*-pyrazoles with either one or no R groups on position 4 [12, 13]. However, there was essentially no information on 4,4-disubstituted 2*H*-pyrazoles (cyclic hydrazones) needed to develop an autoxidation route to 3-hydroperoxy pyrazolines. We developed a method [14, 15] for the synthesis of pentasubstituted 2*H*-pyrazoles, **1**, starting from 1,3-diketones (Scheme 1) that provided the key starting materials for the new methodology. We noted that in most aprotic media, autoxidation of 2*H*-pyrazoles **1** and subsequent degradation was very rapid, an observation which may explain the apparent lack of literature on these types of compounds. For ease of handling and storage, the 2*H*-pyrazoles **1** could be protected by *N*-benzoylation [15]. However, the protecting group proved somewhat difficult to be removed to regenerate **1** but the removal could be achieved by reaction with potassium *t*-butoxide in toluene in the presence of a phase transfer catalyst [15]. The synthetic route is essentially dependent

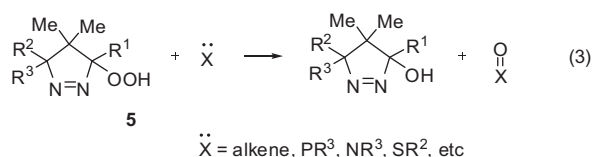


Scheme 1 Synthetic approach to pentasubstituted 2*H*-pyrazoles **1**.

on the addition of aryl or alkyl lithium reagents to cyclic azines derived from hydrazine addition to 1,3-dicarbonyl compounds. Along the way, good methodology for dialkylation of 1,3-diketones was also developed [16]. In this review, we will focus on the synthesis and subsequent chemistry of several series of hexasubstituted pyrazolines made accessible by development of the methodology [14, 15] for the synthesis of pentasubstituted 2*H*-pyrazoles **1**.

Synthesis of hexasubstituted pyrazolines

The methodology shown in Scheme 1 provides the key starting materials for the synthesis of several unique series of hexasubstituted pyrazolines. Pentasubstituted 2*H*-pyrazoles **1** undergo reaction with lead tetraacetate [17, 18] or iodobenzene diacetate [19] to generate acetoxy containing hexasubstituted pyrazolines **2** in high yield. In a similar way, alkoxy-substituted pyrazolines **3** can be synthesized by carrying out the lead tetraacetate reaction in ROH as solvent [17]. The reaction of **1** with TsF generates the stable *N*-Ts species [20], which undergoes reaction with RLi to generate hexaalkyl/phenyl-substituted pyrazolines **4** [21]. Pyrazolines **2–4** are stable compounds generated in good to excellent yield. Autooxidation of **1** in acetone yields new cyclic α -azohydroperoxides **5** (3-hydroperoxy-pyrazolines) in good to excellent yield [14]. Compounds **5** are excellent oxygen-atom transfer reagents (Equation 3) toward alkenes and heteroatoms [22] producing the oxidized substrate and α -azohydroxides (3-hydroxypyrazolines).



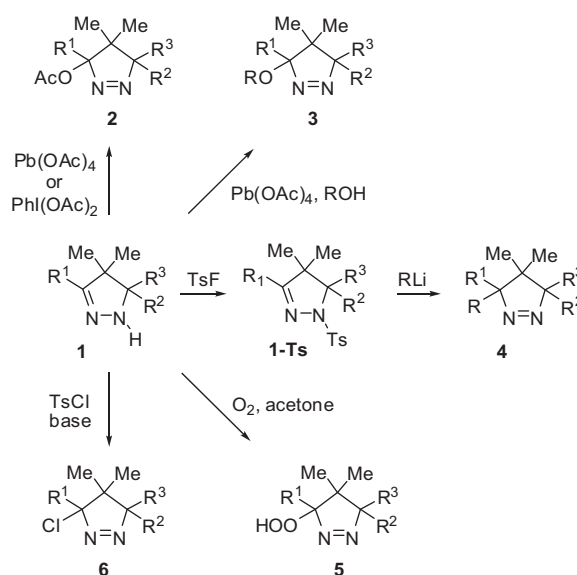
Interestingly, under basic conditions, 3,4,4-trimethyl-3,4-dihydro-3,5-diphenyl-2*H*-pyrazole undergoes an unexpected reaction with TsCl to yield a chloro-substituted pyrazoline **6** in good yield [23, 24]. The general structures for the series of hexasubstituted pyrazolines **2–6** synthesized by reactions with **1** are summarized in Scheme 2. Table 1 contains information in all the specific pyrazolines synthesized to date with the exclusion of the 3-hydroxypyrazolines as they have only been investigated as part of the structure proof for series **5**.

Thermolysis of pyrazolines 2–6

Thermolysis of pyrazolines is a classic method for the synthesis of cyclopropanes by extrusion of N_2 gas [26, 27]. As expected, pyrazolines **2–6** undergo smooth thermal decomposition with evolution of nitrogen gas; however, in some cases non-cyclopropane products are observed. Hydroperoxy-pyrazolines **5** undergo thermolysis slowly at ambient temperatures, whereas series **2–4** and **6** generally require relatively high temperatures (150–200°C). The results are summarized in Scheme 3.

Thermolysis of pyrazolines **2–4** yields the corresponding hexasubstituted cyclopropanes **7** and **8** in excellent yield [17–20]. Table 2 contains data for the hexasubstituted cyclopropanes synthesized to date by this approach.

Thermolysis of **6** yields products consistent with the initial formation of an unstable chlorocyclopropane intermediate **10** [23, 24]. Compound **10** has been postulated



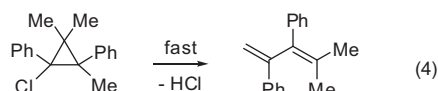
Scheme 2 Summary of reactions of pentasubstituted 2*H*-pyrazoles to yield hexasubstituted pyrazolines **2–6**.

Table 1 Summary of data for 3*Z*-3*R*¹-4,4-dimethyl-5*R*²-6*R*³ pyrazolines, 2–6.

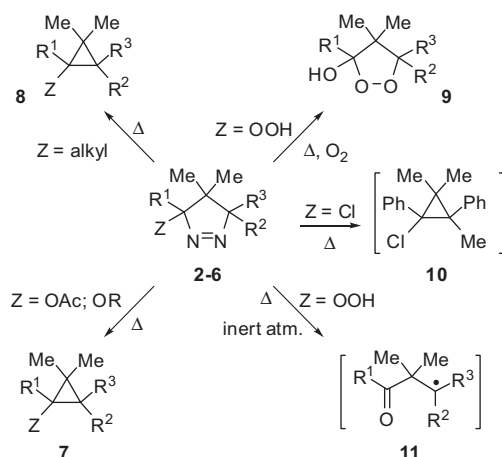
Compound number	Z	R ¹	R ²	R ³	Yield, % ^a	m.p., °C	Ref.
2a	AcO	Ph	Ph	Ph	83	168–169	[17]
2b	AcO	Ph	Ph	Me	81	182–183	[17]
2c	AcO	Ph	Ph	vinyl	42	135–137	[19]
2d	AcO	Ph	Me	vinyl	30	82–84	[19]
3a	MeO	Ph	Ph	Ph	76	132–133	[17]
3b	MeO	Ph	Ph	Me	73	98–100	[17]
3c	MeO	Ph	Me	Me	72	93–96	[17]
3d	EtO	Ph	Ph	Ph	79	124–125	[17]
4a	Me	Ph	Me	Me	87	Liq.	[21]
4b	Me	Ph	Ph	Me	59	144–145	[21]
4c	Me	Ph	Ph	Ph	55	117–118	[21]
5a	HOO	Ph	Ph	Me	~80	^b	[14]
5b	HOO	<i>p</i> -anisyl	<i>p</i> -anisyl	Me	~80	^b	[14]
5c	HOO	Ph	Ph	Ph	~80	^b	[27]
5d	HOO	Ph	Me	Me	^c	^b	[27]
5e	HOO	Me	Me	Ph	^c	^b	[27]
6	Cl	Ph	Ph	Me	92	123.5–124.5	[23]

^aIsolated yield; ^bdue to the potential explosive nature of the hydroperoxy compounds, structure was elucidated after reduction to the 3-hydroxypyrazolines; ^cstable at -20°C.

to undergo a series of rearrangements to yield initially a diene (Equation 4), which undergoes a slow acid-catalyzed rearrangement to 1,1,3-trimethyl-1-phenylindene.



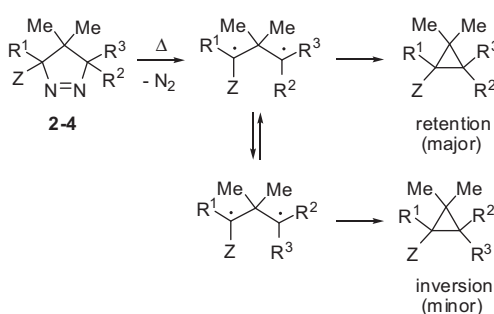
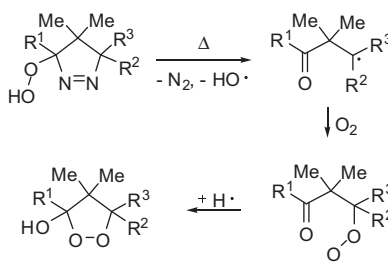
Mechanistically, the results for thermolysis of pyrazoline 2–4 and 6 are consistent with the classic diradical process

**Scheme 3** Overview of the primary products 7–9 or intermediates 10, 11 generated by N₂ loss during the thermolysis of pyrazolines, 2–6.**Table 2** Hexasubstituted cyclopropanes 7, 8 synthesized by thermolysis of pyrazolines, 2–4.

Compound number	Z	R ¹	R ²	R ³	Yield, % ^a	m.p., °C	Ref.
7a	OAc	Ph	Me	Me	82	^b	[17]
7b	OAc	Ph	Ph	Me	84	^b	[17]
7c	OMe	Ph	Ph	Me	85	^b	[17]
7d	OAc	Ph	Ph	Ph	83	126–127	[17]
7e	OMe	Ph	Ph	Ph	82	176–177	[17]
7f	OEt	Ph	Ph	Ph	88	128–130	[17]
7g	OAc	Ph	Ph	vinyl	47 ^c	57–59	[19]
8a	Me	Ph	Me	Me	93	^b	[21]
8b	Me	Ph	Ph	Ph	91	^b	[21]
8c	Me	Ph	Ph	Me	84	79–81	[21]

^aIsolated yield; ^bcolorless viscous oil; ^cafter Kugelrohr distillation; only observable product.

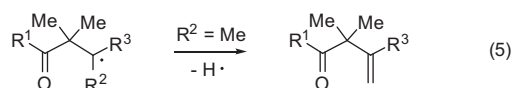
of cyclopropane formation (Scheme 4). The initial step upon heating the pyrazolines to 150–200°C either neat or in solution involves loss of N₂ to generate a singlet diradical, the closure of which, in general, yields a cyclopropane with retention of configuration. In several cases dependent on the lifetime of the singlet diradical, some rotation has been observed to occur before closure yielding minor products with inverted configuration. As expected in these examples, retention of configuration is strongly favored;

**Scheme 4** Mechanism of cyclopropane formation in the thermolysis of pyrazolines 2–4.**Scheme 5** Mechanism of thermolysis of 3-hydroperoxy pyrazoline 5 in the presence of O₂; 3-hydroxy-1,2-dioxolane formation.

at most, approximately 5% of products with inversion of configuration have been noted.

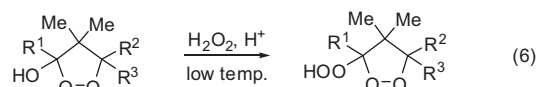
The thermal decomposition of pyrazoline **5**, due to the presence of the hydroperoxy group, is an interesting route to generate β -keto radicals **11** [22, 25, 28] by loss of N_2 and hydroxyl radicals. In the presence of O_2 , trapping of the β -keto radical and subsequent hydrogen atom abstraction provides a new synthetic route to the synthesis of 3-hydroxy-1,2-dioxolanes **9** [28] (Scheme 5) in reasonable yield.

Thermolysis of **5** under inert atmosphere leads, in most cases, to complex mixtures of products that appear to arise from H -abstraction, β scission, intramolecular ring closure, and rearrangements, all consistent with the formation of the β -keto radical **11** (Scheme 3) [25]. When either R^2 or R^3 are methyl groups, the process yields a useful route to β,γ -unsaturated ketones (Equation 5) in reasonable yield.



Given that the sequence starts with a 1,3-diketone (Scheme 1), the formation of a β,γ -unsaturated ketone is the equivalent of a formal Wittig reaction.

The synthesis of 3-hydroxy-1,2-dioxolanes (Scheme 5) provides the gateway into a variety of new dioxolane derivatives and reactions [29–34]. From our point of view, the most interesting transformation is the synthesis of new oxygen atom transfer reagents, 3-hydroperoxy-1,2-dioxolanes, by the reaction of hydrogen peroxide with 3-hydroxy-1,2-dioxolanes (Equation 6) [33, 34].



Summary

Development of a pathway for the synthesis of penta-substituted 2*H*-pyrazoles has opened the door to new applications and approaches in pyrazoline chemistry and related fields. For example, the synthesis of structurally interesting hexasubstituted pyrazolines has led to specific advancements in synthesis of highly substituted cyclopropanes and synthesis of novel oxygen-atom transfer reagents, cyclic α -azohydroperoxides (3-hydroperoxy-pyrazoline) and 3-hydroperoxy-1,2-dioxolanes. Furthermore, the thermolytic reactions of the various, unique pyrazolines and their derivatives have produced mechanistic insights and yielded new routes to selected compounds including hexasubstituted cyclopropanes and 3-hydroxy-1,2-dioxolanes.

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