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Synthesis of 2-Alkyl(aryl)-3-methylthio-6-methyl-6-arylpyrano-[4, 3-c] pyrazol-4(2H)-ones

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Abstract: The synthesis of 2-alkyl(aryl)-3-methylthiopyrano[4,3-c]pyrazol-4(2H)-ones *via* 5, 6-dihydro-2H-pyran-2, 4-dione-3-dithioacetals with (un)substituted hydrazines is described and the mechanism of the formation of title compounds is discussed. Their structures were confirmed by ^{1}HNMR spectra and elemental analysis.

Keywords: Dithioacetal, hydrazine, mechanism.

Being a structural subunit in numerous natural bioactive products, β-keto-δ-valerolactones exhibits a broad range of biological activity[1]. In addition, it also is a useful intermediate in the synthesis of a variety of important heterocyclic molecules which exhibit antimicrobial, antifungal, antiviral and inhibit phytotoxic activities[2-3]. Recently, it is reported that β-keto-δ-valerolactones derivatives have shown to be potent HIV proteases inhibitors[4-5].

As a part of our program aimed at developing new pesticides, we have interested in synthesizing nitrogen heterocyclic compounds such as isothiazoles and pyrazoles because nitrogen heterocycles play an important role among a wide variety of heterocycles that have been used for developing useful herbicides[6]. Recently, we reported that 5, 6-dihydro-2H-pyran-2, 4-dione derivatives showed potential fungicidal and herbicidal activities[7-8]. We proposed that if β-keto-δ-valerolactones were combined with pyrazole, the new product would possess even better bioactivity. Hence, we designed and synthesized novel substituted pyrano[4, 3-c]pyrazol-4(2H)-ones. 3-[(Bis-methylthio)methylene]-2H-pyran-2, 4-diones were reacted with substituted hydrazines under mild reaction conditions and the title compounds **3** were obtained with high yields. At the same time, the mechanism of the reaction was also discussed.

In a general procedure, the slurry of β-keto-δ-valerolactones and anhydrous potassium carbonate in DMF was agitated for 0.5 h at room temperature, carbon disulfide and methyl iodide were added dropwise and agitated continuously for 4 hours. The suspension was poured into ice-cooled water and extracted with dichloromethane. The solvent was evaporated under vacuum and 3-[(bis-methylthio)methylene]-2H- pyran-2,

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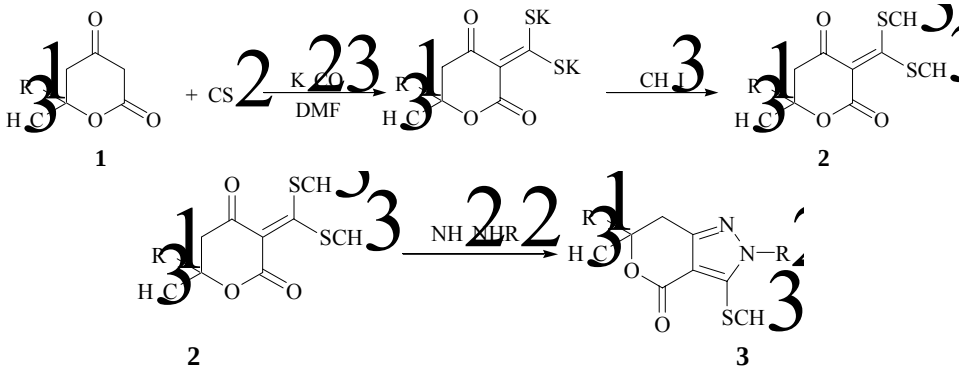
Scheme 1

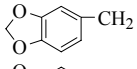
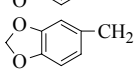
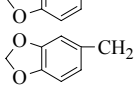


4-diones **2** was obtained, which was purified with silicon gel column or recrystalization. Substituted hydrazine was added dropwise to the solution of 3-[(bis-methylthio)methylene]-2H-pyran-2, 4-diones in ethanol. After the addition, the mixture was stirred for 1 h at room temperature and the crude product **3** was obtained, which was purified with silicon gel column or recrystallization (**Table 1**).

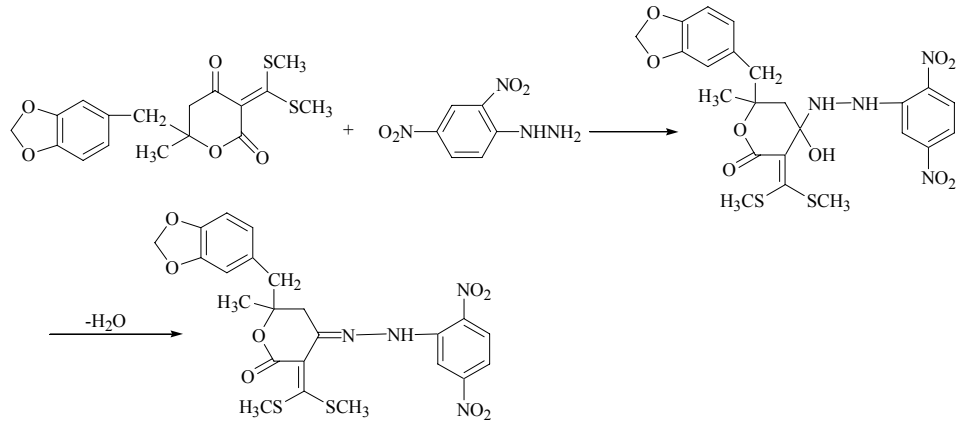
Generally, the reactions proceeded quickly with excellent yields. However, if the applied substituted hydrazine possesses spatial hindrance in some extent, longer reaction time was necessary. For example, when the coupling reaction of substituted **2** with phenylhydrazine was carried out at room temperature, three hours were needed.

Interestingly, although the reaction of substituted 3-[(bis-methylthio)methylene]-6-methyl-6-piperonyl-2H-pyran-2, 4-dione with 2, 4-dinitrophenylhydrazine was failed to gain the title compound, we successfully separated an oil substance. ^{1}HNMR spectra and MS spectrum of the compound showed that it is an uncyclized product **4**. Therefore, the possible mechanisms of the formation **3** and **4** were proposed in **Scheme 2**. The results showed that the carbon atom at 4 position is much more electrophilic than the carbon atom of the chain at α position.

Table 1 Physical data of title compounds **3a-h** and elemental analysis

Compound **3**	R_1	R_2	Yield (%)	mp (°C)	Elemental analysis % (calcd., %) C	H	N
a	H	CH_3	98	102-103	50.90(50.94)	5.72(5.66)	13.20(13.20)
b	H	Ph	94	167-169	61.20(61.30)	5.12(5.11)	10.18(10.22)
c	$PhCH_2$	H	68	145-146	62.55(62.50)	5.54(5.56)	10.00(9.72)
d	$PhCH_2$	CH_3	63	oil	63.60(63.58)	6.02(5.96)	9.20(9.27)
e	$PhCH_2$	Ph	73	140-141	69.08(69.23)	5.54(5.49)	7.69(7.69)
f		H	88	165-166	57.90(57.83)	5.06(4.82)	8.32(8.43)
g		CH_3	80	140~141	58.79(58.96)	5.19(5.20)	7.90(8.09)
h		Ph	85	169~170	64.75(64.70)	4.93(4.90)	6.82(6.86)

Scheme 2



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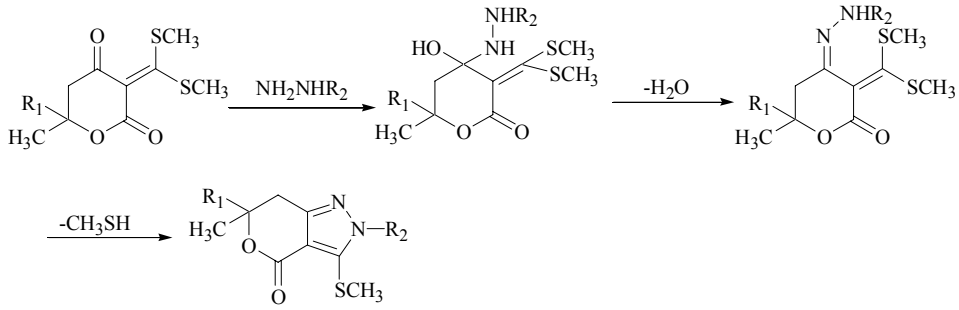

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Acknowledgments

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References

1. P. W. Brian, P. J. Curtis *et al*., *Nature*, **1949**, *164*, 534.
2. R. Ficher, A. Krebs *et al*., EP patent 588137.
3. K. Nakamura, M. Shibata *et al*., JP patent 25279.
4. S. Thaisrivongs, C. P. Yang *et al*.,WO patent 11361.
5. E. L.Ellsworch, E. Lunney *et al*., WO patent 14001.
6. H. S. Chen, Z. M. Li *et al*. *J. Agric*., *Food Chem.*, **2000**, *48*, 5312.
7. Y. M. Wang, Z. M. Li *et al*., *Chem. J. Chinese Univ.*, **1999**, *20* (5), 1559.
8. Y. M. Wang, Z. M. Li *et al*., *J. Applied Chem.*, **2001**,*12* (6),475.

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