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REVIEW

1st Heterocyclic Update

Synthetic and biological studies of pyrazolines and related heterocyclic compounds

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Pyrazole;
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Abstract This review provides a comprehensive survey relating to the synthesis and biological applications of pyrazolines and related heterocycles in the last five years (2007–2011). These compounds are usually prepared from the cyclization of chalcones with hydrazine and its derivatives under the alcoholic conditions. The major incentive behind the synthesis of these compounds was the immense biological activities associated to these heterocyclic derivatives. The aim of this review is to find out different methods for the synthesis of pyrazoline derivatives.

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1. Introduction

The development of a clean procedure for the preparation of heterocyclic compounds is a major challenge in modern heterocyclic chemistry in view of the environmental, practical and economic issues. Pyrazolines are an important class of heterocyclic compounds containing two nitrogen atoms in the five membered ring. The substituted 2-pyrazolines have found application as activators for polymerization (Bauer and Piatert, 1981), dyes for wool, nylon (Evans and Waters,

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1978), as electro photographic conductors (Murayama and Mater, 1981) and as wavelength shifters in liquid and polymer scintillation (Poduzhailo et al., 1979). Pyrazoline derivatives are the electron rich nitrogen heterocycles which play an important role in the diverse biological activities. These heterocyclic compounds widely occur in nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cell. Considerable attention has been focused on the pyrazolines and substituted pyrazolines due to their interesting biological activities. These compounds have been found to possess anti-fungal (Korgaokar et al., 1996), anti-depressant, anticonvulsant (Palaska et al., 2001; Rajendra et al., 2005; Ozdemir et al., 2007; Ruhogluo et al., 2005), anti-inflammatory (Udupi et al., 1998), anti-bacterial (Nauduri and Reddy, 1998) and anti-tumor (Taylor and Patel, 1992) properties. The pyrazole moiety is found in blockbuster drugs such as celecobix (Penning et al., 1997), sildenafil (Terrett et al., 1996) and rimonabant (Seltzmann et al., 1995). Recently a very important review has been published upon the studies of pyrazoline compounds (Kumar et al., 2009).

2. Discussion

1,3,5-Triaryl-2-pyrazolines **3** (Li et al., 2007) have been prepared through the reaction of chalcones and phenyl hydrazine hydrochloride (Scheme 1) in the presence of sodium acetate-acetic acid aqueous solution under ultrasound irradiation.

3,4,5-Metalated pyrazoles **6** and **7** were synthesized (Gonzalez-Nogal et al., 2007) by 1,3-dipolar cycloadditions of silyl, disilyl, and silylstannylacetylenes with N-phenylsydnone or trimethylsilyldiazomethane (Scheme 2).

The heterocyclics 5-(-4-(Substituted)phenyl)-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolyl-2-toluidinomethane thione **12** and 5-(substituted) phenyl-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolyl-2-methoxyanilino methane thione **13** were obtained (Ali et al., 2007) by the reaction between hydrazine hydrate and chalcones **10** followed by condensation with the appropriate aryl isothiocyanate (Scheme 3).

Synthesis of 5-substituted-3-dimethoxyphosphono-pyrazoles **16** and **17** and 2-pyrazolines **20** and **21** has been accomplished (Conti et al., 2007) through 1,3-dipolar cycloaddition of a suitable nitrile imine to monosubstituted alkynes **15** and alkenes **19** as shown in Scheme 4.

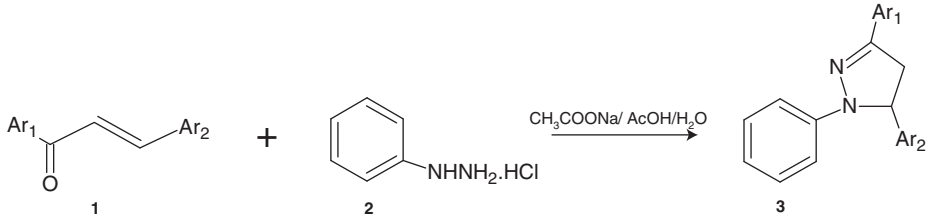
An interesting method ha been reported by Alexander V. Shevtson et al. (2007) for the synthesis of 1-mono- and 1,2-diacylpyrazolidines **23** as well as 1-arylsulfonyl-2-pyrazolines **24** which is described in Scheme 5.

The compounds 1-(2,4-dinitrophenyl)-3-(3-nitrophenyl)-5-(4-substituted phenyl)-2-pyrazolin-4-ones **30** have been prepared by the oxidation of 1-(2,4-dinitrophenyl)-3-(3-nitrophenyl)-5-(4-substitutedphenyl)-4-bromo-2-pyrazolines **29** with dimethylsulfoxide (Mishra et al., 2007). The later has been released via the reactions sequence which is depicted in Scheme 6.

An efficient method (Joshi et al., 2008) has been reported regarding the synthesis of 5-substituted-2-thiol-1,3,4-oxadiazoles **32** according to the protocol as shown in Scheme 7.

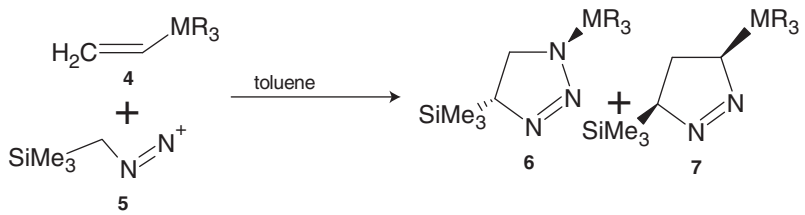
Braulio Insuasty et al. Insuasty et al. (2008) have synthesized new bis-3,5-diphenylpyrazolines **36** from the cyclization of bischalcones **35** with hydrazine hydrate in acetic acid medium. The later was prepared by the Claisen–Schmidt reaction of bis-acetophenone **35** with suitable aromatic aldehydes (Scheme 8).

Some biologically significant bis-heterocycles (Jayashankra and Lokanatha, 2008) bearing pyrazoline moieties **40** have been synthesized starting from pyrazolyl aldehyde **37** through the reaction sequence as described in Scheme 9.



a) $Ar_1=C_6H_5$, Ar_2=4-$CH_3OC_6H_4$ b) $Ar_1=C_6H_5$, 4-$CH_3C_6H_4$ c) $Ar_1=C_6H_5$, $Ar_2=C_6H_5$ d) $Ar_1=C_6H_5$, Ar_2=4-ClC_6H_4, e) $Ar_1=C_6H_5$, Ar_2=3-ClC_6H_4, f) $Ar_1=C_6H_5$, Ar_2=2-ClC_6H_4, g) $Ar_1=C_6H_5$, Ar_2=3-BrC_6H_4, h) $Ar_1=C_6H_5$, Ar_2=4-$O_2NC_6H_4$, i) Ar_1=4-ClC_6H_4, $Ar_2=C_6H_5$, j)Ar_1=3-$O_2NC_6H_4$, $Ar_2=C_6H_5$,

Scheme 1



6a; $MR_3 = SiMe_3$; 6b; MR_3= $SiMe_2Ph$; 6c; MR_3= $SiPh_2Bu^t$; 6d; MR_3= $SnBu_3$

Scheme 2