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NEW APPLICATION OF SWERN OXIDATION: PREPARATION OF 2-PYRAZOLINES WITH ''ACTIVATED'' DMSO

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Abstract
1,3-Dipolar cycloaddition of 2-diazopropane **2** to conjugateddi-substituted alkenes**1** is taking place regiospecifically to give five membered heterocyclic ring **3**. The oxidation of 2-pyrazolines **3a,b** with dimethylsulfoxide and oxalyl chloride under Swern conditions led to a pyrazolenines **5a,b**.

Keywords: 1,3-Dipolar cycloaddition, Diazopropane, Pyrazolines, Regioselectivity, Swern oxidation.

1. Introduction

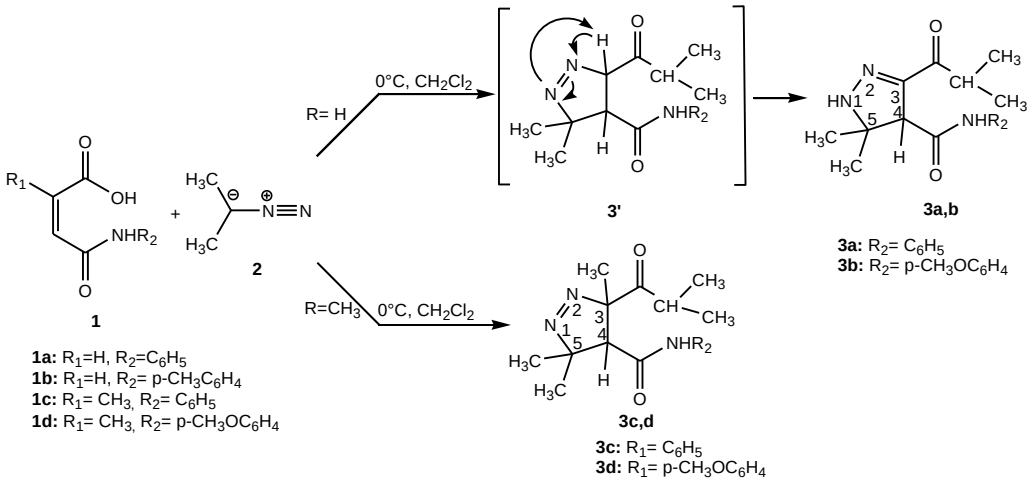
For ten years, the development of new heterocyclic synthesis methods for the research of biologically active molecules has created a growing need for more complex and varied compounds. In this context, heterocyclic chemistry has emerged as a solution for quickly reaching a large number of potentially active products. The cycloaddition reactions of the diazoalkanes with various dipolarophiles have therefore established themselves as an appropriate tool for meeting these requirements.
Considerable attention has been focused on pyrazoline derivatives due to their interesting biological activities [I].

They have several prominent effects such antidepressant activity during screening against monoamine oxidases [II], as antagonists [III], antiviral activity against the West Nile virus [IV], and multidrug resistance modulators in tumor cells [V]. Pyrazoles are very powerful reagents for the preparation of nitrogen containing substance [VI]. Among the other methods used in the synthesis of pyrazolines is the 1,3-dipolar cycloaddition of nitrilimines [VII-XI]. The oxidation of pyrazoline derivatives is, in fact, the pyrazolenines which applies to many synthetic strategies. A large number of methods are found in the literature for achieving this basic setup. Many reagents are available for the preparation of pyrazolines, the nature of the product depending on the choice

of oxidation reagent. Various ways have been made previously in the oxidation of pyrazoline derivatives with a variety of reagents. for example we quote, Zirconium nitrate [XII], Palladium on carbon [XIII], Manganese dioxide [XIV] for the preparation of pyrazolenines. The reaction of dimethyl sulfoxide with an electrophilic species to lead activated dimethyl sulfoxide has been extensivelydemoralized for the oxidation of pyrazoline derivatives [XV].
Nevertheless, numerous of these procedures are dependent upon specific downsides, for example, low yields, long reaction times, and toxicity because of the presence of certain components typified in the reagents used. So still there is requiring for improvement of new catalysts which overcome all these downsides.

2. Results and discussion

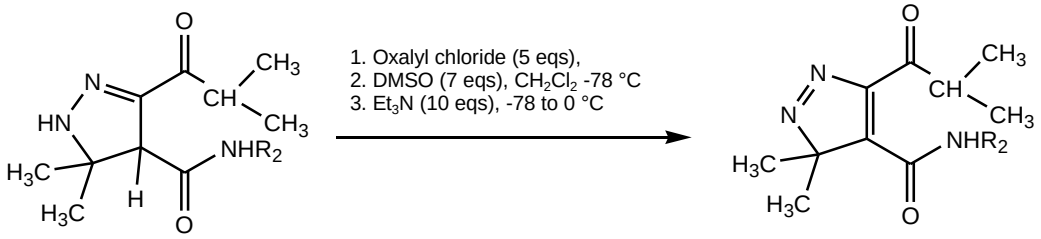
The addition of diazopropane **2** to di-substituted alkenes **1a-d**, led to the exclusive formation of compounds pyrazolines **3a-d** (Scheme 1). Remember, however, that obtaining 2-pyrazolines **3** as products of this addition results from the prototropic isomerization of the corresponding 1-pyrazolines **3'** which are very unstable [XVI].
Fast atom bombardment mass spectrometry and microanalysis showed that 2-pyrazolines **3** were the consequence of the reaction of two equivalents of dipole. For this situation, alkylation of the carboxylic acids was completed utilizing diazopropane (Scheme 1) [XVII].



Scheme 1: Synthesis of pyrazoline derivatives 3a-d

We now have to establish the addition manner of diazopropane **2** with alkenes **1**. Unambiguous proofs for the obtained pyrazoline regiochemistry arised from their NMR spectral data. However, regiochemical assignments of all adduct were deduced from their ^{1}H-NMR spectra. In particular, the chemical shifts of C-3 in pyrazolines **3** are in excellent agreement with those usually obtained when this quaternary carbon is attached to nitrogen atom [XVIII].

As shown in Scheme 2, the Swern oxidation of pyrazoline derivatives **3a,b** with dimethylsulfoxide gave good yields of pyrazolenine derivatives **4a,b** [XV].



3a,b **4a,b**

3a: R_2= C_6H_5
3b: R_2= p-$CH_3OC_6H_4$

Scheme 2 :Swern oxydation of pyrazolines 3a,b

3. Conclusion

In conclusion, we have described the preparation of new pyrazoline derivatives with total regioselectivity. The Swern oxidation, regarding the employ of extremely easy and economical reagents, allow the one-pot conversion of pyrazolines to a pyrazolenines into synthetically valuable.

4. Experimental procedure

4.1. General Methods

All separation was performed by chromatography column used silica gel 60 (230–400 mesh). The IR spectral frequencies are given in cm^{-1}. NMR spectra were determined in deuterium chloroform solutions at 300 and 75.5 MHz for proton and carbon thirteen NMR, respectively; chemical shifts have been reported in ppm and *J* values are given in hertz.

4.2. 1,3-dipolar cycloaddition of 2-diazopropane 2with di-substituted alkenes 1

To a solution of 1 mmol of alkenes **1a-c** in 50 mL of anhydrous dichloromethane, cooled to –40 °C was added a solution of 2-diazopropane 2.6 M freshly prepared and stored at - 60 °C in diethyl ether. After adding four fractions, the red color of DAP persists and a thin layer chromatography of the reaction crude indicates the appearance of a new product. The solvent was removed and the crude product was purified by chromatography (SiO_2; ethyl acetate/petroleum ether, 7:3) to afford compounds **3a-d**.

3-Isobutyryl-3,5,5-trimethyl-4,5-dihydro-3H-pyrazole-4-carboxylic acid phenylamide 3a

Yield = 70%. M.p = 187 ±2 °C [ethanol] (white crystals). IR (KBr) υmax/cm^{-1}: 1520 (C=N), 3300 (NH). ^{1}H NMR (300 MHz, $(CD_3)_2CO$)δ_{ppm} 1.11 (d, 3H, CH_{3isop}), 1.19 (d, 3H, $CH_{3\ isop}$),1.44 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 2.30 (s, 1H, H_4), 5.01 (m, 1H, H_{isop}), 7.05-7.41 (m, 5H, H_{arom}), 7.19 (s, 1H, NHCO), 10.01 (s, 1H, NH).^{13}C NMR (75.5 MHz, $(CD_3)_2CO$) δ_{ppm}: 22.1, 22.3, 22.8, 29.1 (CH_3), 60.4 (C4), 67.0 (C5), 93.4 (Cisop), 119.8-136.8 (C_{arom}), 155.4 (C3), 162.4 (C=O), 167.6 (C=O) Elemental analysis: $C_{17}H_{23}N_3O_2$ requires C, 67.75; H, 7.69; N, 13.94%; foundC, 67.70; H, 7.72; N, 13.90%.

3-Isobutyryl-5,5-dimethyl-4,5-dihydro-1H-pyrazole-4-carboxylic acid (4-methoxy-phenyl)-amide 3b

Yield = 80%. M.p = 135 ±2 °C [ethanol] (white crystals). IR (KBr) υmax/cm^{-1}: 1540 (C=N), 3300 (NH). ^{1}H NMR (300 MHz, $(CD_3)_2CO$)δ_{ppm} 1.13 (d, 3H, CH_{3isop}), 1.20 (d, 3H, $CH_{3\ isop}$), 1.40 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.35 (s, 1H, H_4), 3.79 (s, 3H, OCH_3), 5.10 (m, 1H, H_{isop}), 7.05-7.78 (m, 4H, H_{arom}), 7.32 (s, 1H, NHCO), 10.11 (s, 1H, NH). ^{13}C NMR (75.5 MHz, $(CD_3)_2CO$) δ_{ppm}: 22.1, 22.2, 22.5, 29.0 (CH_3), 55.0 (OCH_3), 60.4 (C4), 66.8 (C5), 93.4 (Cisop), 119.8-163.1 (C_{arom}), 155.4 (C3), 161.4 (C=O), 167.7 (C=O) Elemental analysis: $C_{17}H_{23}N_3O_3$ requires C, 64.33; H, 7.30; N, 13.24%; found C, 64.29; H, 7.32; N, 13.27%.

3-Isobutyryl-3,5,5-trimethyl-4,5-dihydro-3H-pyrazole-4-carboxylic acid phenylamide 3c

Yield = 85%. M.p = 123 ±2 °C [ethanol] (white crystals). IR (KBr) υmax/cm^{-1}: 1630 (N=N); ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ_{ppm}: δ_{ppm}: 1.11 (d, *J* = 6.3 Hz, 3H, $CH_{3\ isop}$), 1.14 (d, *J* = 6.3 Hz, 3H, $CH_{3\ isop}$), 1.44 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 2.34 (s, 1H, H_4), 5.12 (m, *J* = 6.3 Hz, 1H, H_{isop}), 7.01-7.56 (m, 5H, H_{arom}). ^{13}C NMR (75.5 MHz, $(CD_3)_2CO$) δ_{ppm}: 21.8, 22.3, 22.6, 25.9, 29.2 (CH_3), 60.4 (C4), 93.3 (Cisop), 97.7 (C3), 114.5-138.7 (Carom), 167.3 (C=O), 169.5 (C=O). Elemental analysis: $C_{17}H_{23}N_3O_2$ requires C, 67.75; H, 7.69; N, 13.94%; found C, 67.77; H, 7.65; N, 13.90%.

3-Isobutyryl-3,5,5-trimethyl-4,5-dihydro-3H-pyrazole-4-carboxylic acid (4-methoxy-phenyl)-amide 3d

Yield = 85%. M.p = 119 ±2 °C [ethanol] (white crystals). IR (KBr) υmax/cm^{-1}: 1633 (N=N);^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ_{ppm}: 1.12 (d,*J* = 6.3 Hz, 3H, $CH_{3\ isop}$), 1.13 (d, *J* = 6.3 Hz, 3H, $CH_{3\ isop}$), 1.43 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 2.32 (s, 1H, H_4), 3.73 (s, 3H, OCH_3), 5.02 (m,*J* = 6.3 Hz, 1H, H_{isop}), 6.75 and 7.30 (d, *J* = 8.7 Hz, 4H, H_{arom}).^{13}C NMR (75.5 MHz, $(CD_3)_2CO$) δ_{ppm}: 21.9, 22.0, 22.6, 25.8, 29.1 (CH_3), 55.4 (OCH_3), 60.5 (C4), 93.0 (Cisop), 97.4 (C3), 114.5-157.1 (Carom), 167.1 (C=O), 170.0 (C=O). Elemental analysis: $C_{18}H_{25}N_3O_3$ requires C, 65.23; H, 7.60; N, 12.68%; found C, 65.19; H, 7.63; N, 12.65%.

4.3. Dehydrogenation of 2-Pyrazolines

To a solution of five equivalents oxalyl chloride in 10 mL of dry dichloromethane, at -78 °C under anitrogen atmosphere, was includedseven equivalents dimethylsulfoxide. The mixture was stirred for 20 min, until effervescence ceased. To this solution, 1 mmole of 2-pyrazolines **3a,b** dissolved in 5 mL of dry dichoromethane was added dropwise, and the mixture was stirred for 15 min at -78 °C. 10 equivalents of triethylamine was then added and the mixture was left to warm to 0 °C for 20 min, while stirred.The mixture was diluted with 20 mL ofethyl diethyl and washed with saturated aqueous NH_4Cl (3×20 mL). The organic layer was dried with $MgSO_4$ and evaporated, and the residue was purified by chromatography (SiO2; ethyl acetate/petroleum ether, 1:4) to afford compounds **4a,b**.

5-Isobutyryl-3,3-dimethyl-3H-pyrazole-4-carboxylic acid phenylamide 4a

Yield = 65%. M.p = 111±2 °C [ethanol] (white crystals). IR (KBr) υmax/cm^{-1}: 1630 (N=N), 3200 (NH). ^{1}H NMR (300 MHz, $CDCl_3$)δ_{ppm} 1.26 (d, *J* = 6.3 Hz, 6H, CH_{3isop}), 1.35 (s, 6H, CH_3), 5.47 (m, *J* = 6.3 Hz, 1H, H_{isop}), 7.17-7.74 (m, 5H, H_{arom}), 7.36 (s, 1H, NHCO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_{ppm}: 22.3, 28.1 (CH_3), 53.3 (C5), 93.4 (Cisop), 114.6-138.5 (C_{arom}), 131.2 (C3), 154.1 (C4), 164.7 (C=O), 178.4 (C=O).Elemental analysis: $C_{16}H_{19}N_3O_2$ requires C, 67.35; H, 6.71; N, 14.73%; found C, 67.33; H, 6.69; N, 14.68%.

5-Isobutyryl-3,3-dimethyl-3H-pyrazole-4-carboxylic acid (4-methoxy-phenyl)-amide 4b

Yield = 85%. M.p = 144±2 °C [ethanol] (white crystals). IR (KBr) υmax/cm^{-1}: 1635 (N=N), 3200 (NH). ^{1}H NMR (300 MHz, $CDCl_3$)δ_{ppm} 1.21 (d, *J* = 6.3 Hz, 6H, CH_{3isop}), 1.37 (s, 6H, CH_3), 5.43 (m, *J* = 6.3 Hz, 1H, H_{isop}), 6.78 and 7.54 (d, *J* = 8.7 Hz, 4H, H_{arom}), 7.33 (s, 1H, NHCO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_{ppm}: 22.4, 28.5 (CH_3), 53.1 (C5), 53.1 (C5), 55.4 (OCH_3), 119.6-154.5 (C_{arom}), 131.6 (C3), 151.2 (C4), 164.5 (C=O), 178.1 (C=O). Elemental analysis: $C_{17}H_{21}N_3O_3$ requires C, 64.74; H, 6.71; N, 13.32%; found C, C, 64.70; H, 6.69; N, 13.35%.

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