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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 3807–3809

Stereoselective alkenylation of a 1,3-disubstituted pyrazol-5-one through ring transformation of 2*H*-pyran-2-ones☆

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Received 31 January 2005; revised 24 March 2005; accepted 30 March 2005
Available online 16 April 2005

Abstract—A one-pot stereoselective alkenylation of 1-(3-chlorophenyl)-3-methyl-1,4-dihydro-5-pyrazolone **2** by 2*H*-pyran-2-ones **1** to give (*E*,*E*)-5-aryl-5-[1-(3-chlorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4- ylidene]-3-methylsulfanyl-pent-3-en-carbonitrile/methyl carboxylate **3** has been delineated through ring transformation in moderate yields.

Pyrazoles are key structures in numerous compounds of therapeutic importance.[1] Compounds containing this ring system are known to display diverse pharmacological activities such as antibacterial,[2] antifungal,[2] anti-inflammatory,[3] analgesic,[3] and antipyretic.[3] 3-Alkyl-4-arylmethylpyrazol-5-ones **I** are reported to exhibit potent antihyperglycemic[4] activity, while 1-phenyl-3-tetrafluoroethylpyrazol-5-one **II** is an anxiolytic.[5] Thus, the biological activities of pyrazol-5-ones depend on the nature of the substituents (Fig. 1).

The therapeutic importance of this class of compounds inspired us to develop an innovative approach to synthesize **III** directly from 5-pyrazolones in order to explore their pharmacological activities. Previously, 4-substituted pyrazoles were produced either by the condensation–cyclization of methyl arylacetoacetates and arylhydrazine[4] or by reduction of 4-arylidene/alkenylidene derivatives derived from the condensation of a 5-pyrazolone with an aromatic or aliphatic aldehyde. Our approach to introduce a substituent at position 4 in 5-pyrazolone **2** is entirely different and involves a base-catalyzed ring transformation of 2*H*-pyran-2-ones **1**.

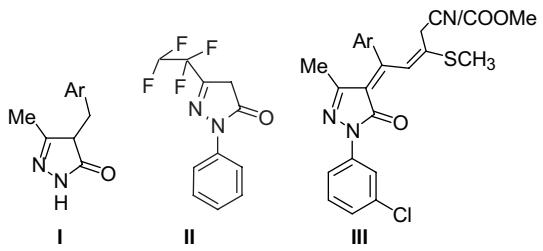

Figure 1.

Here, we report the construction of pyrazoles **3** through ring transformation of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitrile/methyl carboxylate[6] **1** with 1-(3-chlorophenyl)-3-methyl-1,4-dihydro-5-pyrazolone **2**. Thus, stirring an equimolar mixture of **1**, **2** and powdered KOH in dry DMF for 24 h at ambient temperature led to the chromatographically pure single geometrical *E*-isomer **3** in moderate yield.[7]

The topography of the precursor 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitrile/methyl carboxylate is such that it may be viewed as a cyclic ketene hemithioacetal, of which position 6 is highly prone to nucleophilic attack due to extended conjugation and the presence of electron withdrawing substitutents CN or $COOCH_3$ at position 3 of the pyran ring.

The greater electrophilicity of position 6 compared to 4 makes position 6 of the pyran ring more vulnerable to nucleophilic attack. Thus, the carbanion generated at position 4 of 1,4-dihydro-5-pyrazolone **2** attacks at position 6 of the pyran ring with ring-opening and

Keywords: Ring transformation; Stereoselective; Pyrazol-5-one; 2*H*-pyran-2-one.
☆CDRI Communication No. 6660.
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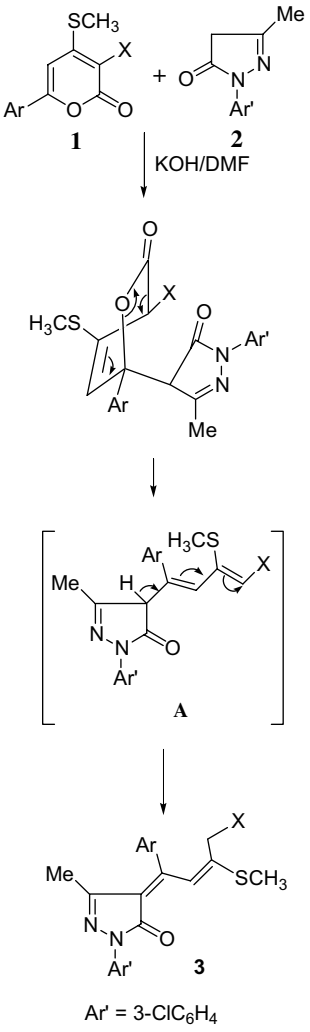
doi:10.1016/j.tetlet.2005.03.207



3	Ar	X	Yield (%)
a	C_6H_5	$COOCH_3$	55
b	4-ClC_6H_4	$COOCH_3$	60
c	4-BrC_6H_4	$COOCH_3$	58
d	3,4-$Cl_2C_6H_3$	$COOCH_3$	63
e	2-furyl	$COOCH_3$	65
f	2-thienyl	$COOCH_3$	62
g	C_6H_5	CN	60
h	4-BrC_6H_4	CN	52
i	4-$CH_3OC_6H_4$	CN	57
j	4-ClC_6H_4	CN	56

Scheme 1. Proposed mechanism for the formation of **3**.

decarboxylation as depicted in Scheme 1. The initially formed ring transformed intermediate **A** tautomerizes to **3** to attain a more stable configuration with extended conjugation. Non-covalent interactions also play an important role in the stereoselectivity.

All the synthesized compounds were fully characterized by spectroscopic and elemental analyses.[7]

The structure of **3b** was further confirmed through single crystal X-ray diffraction analysis.[8] The ORTEP diagram of the compound is shown in Figure 2.

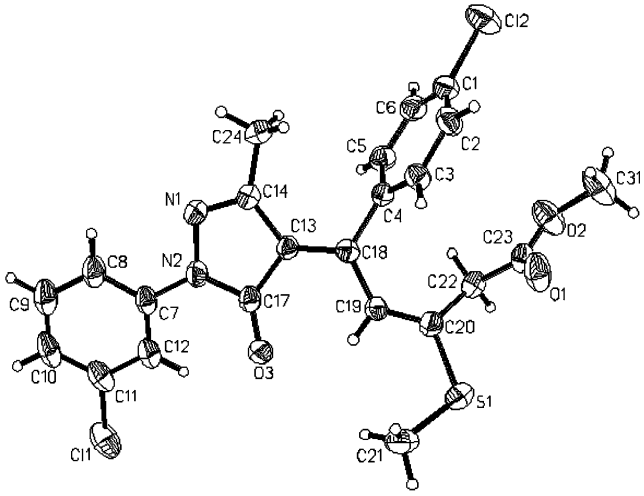


Figure 2. ORTEP diagram of **3b** showing the X-ray molecular structure at the 30% probability level.

The X-ray structure revealed the presence of a network of strong intermolecular H-bonding between atoms C21–H21B···O3 and C9–H9···O1 with interatomic distances 2.776 and 2.891 Å, respectively.

In summary, our methodology opens a new avenue to the synthesis of substituted pyrazol-5-ones, which may be useful precursors for the construction of various heterocycles of therapeutic importance. The methodology is very simple and economical. No catalyst is required in this ring transformation reaction.

Acknowledgements

D.S. and A.S. thank the CSIR, New Delhi, India for Senior Research Fellowships. The authors thank SAIF, CDRI Lucknow for providing spectroscopic and analytical data.

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7. *Typical procedure*. A mixture of 2H-pyran-2-one **1** (1 mmol), 1-(3-chlorophenyl)-3-methyl-1,4-dihydropyrazol-one **2** (1 mmol) and powdered KOH (1.5 mmol) in dry DMF (15 mL) was stirred for 24 h at room temperature. The reaction mixture was poured into ice-water and neutralized with 10% HCl. The separated solid was filtered, washed with water and dried. The crude product was purified on a silica gel column to afford **3** as a single isomer. Compound **3g**: yield 60%, mp 98–100 °C, IR (KBr) $\nu = 2202\ cm^{-1}$ (CN), $1593\ cm^{-1}$ (CO); ^1H NMR (300 MHz, $CDCl_3$): δ 1.57 (s, 3H, CH_3), 2.21 (s, 3H, SCH_3), 4.74 (s, 1H, CH), 4.91 (s, 2H, CH_2), 7.14–7.18 (m, 1H, ArH), 7.27–7.54 (m, 7H, ArH), 7.89–7.93 (m, 1H, ArH); MS (FAB) 408 (M^++1). Anal. Calcd for $C_{22}H_{18}ClN_3OS$: C, 64.78; H, 4.45; N; 10.30. Found: C, 64.65; H, 4.55; N, 10.11.
Compound **3j**: yield 56% mp 118–120 °C, IR (KBr) $\nu = 2203\ cm^{-1}$ (CN), $1593\ cm^{-1}$ (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 1.57 (s, 3H, CH_3), 2.21 (s, 3H, SCH_3), 4.76 (s, 1H, CH), 4.89 (s, 2H, CH_2), 7.15–7.47 (m, 6H, ArH) 7.88–7.92 (m, 1H, ArH), 8.02–8.04 (m, 1H, ArH); MS (FAB) 443 (M^++1). Anal. Calcd for $C_{22}H_{17}Cl_2N_3OS$: C, 59.73; H, 3.87; N; 9.50. Found: C, 59.84; H, 3.66; N, 9.67.
8. Crystal data of **3b**: $C_{23}H_{20}Cl_2N_2O_3S$ M = 475.37, triclinic, space group P-1, $a = 9.188(1)$, $b = 9.254(1)$, $c = 14.500(2)$ Å, $\alpha = 73.41(1)$, $\beta = 75.12(1)$, $\gamma = 80.08(1)$, $V = 1135.4(2)$ Å^3, $T = 293$ K, $Z = 2$, $\mu = 0.41\ mm^{-1}$, $R1 = 0.0492$ for 1864 $F_0 > 4\,sig(F_0)$ and 0.1272 for all 3959 data. CCDC 264229 contains the supplementary crystallographic data. These data can be obtained free of charge from http://www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk]. Programs: XSCANS [Siemens Analytical X-ray Instrument Inc.: Madison, WI, USA 1996], SHELXTL-NT [Bruker AXS Inc.: Madison, WI, USA 1997].