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Note

Synthesis of pyrazolines promoted by Amberlyst-15 catalyst

B Shivarama Holla[1*], M Mahalinga[1,2], Boja Poojary[1], Mithun Ashok[1] & P M Akberali[2]

[1]Department of Chemistry, Mangalore University, Mangalagangothri-574199, India

[2]Strides Arcolab Limited, 120 A & B, Industrial Area, Baikampady, New Mangalore, India

E-mail: hollabs@rediffmail.com

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The condensation of a series of aromatic ketones with aromatic aldehydes under aldol conditions affords 1-aryl-3-(substituted-phenyl/phenyl furanyl/thienyl)-2-propen-1-ones **1**. The resulting propenones undergo facile and clean cyclization with hydrazine and substituted hydrazine derivatives to yield 3-aryl-5-(substitutedphenyl/phenylfuranyl/thienyl)-2-pyrazolines **2**. This reaction is carried out in the presence of Amberlyst–15 catalyst to afford the above pyrazolines **2** in considerably good yield. All the synthesized compounds have been characterized by spectral studies.

Keywords: Pyrazolines, propenones, cyclization, Amberlyst–15 catalyst,

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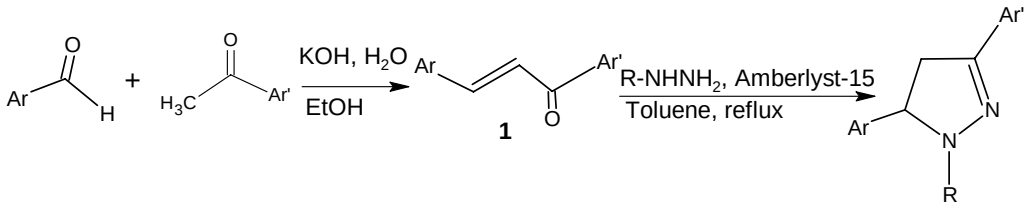
Pyrazoline systems are known to be biologically active and are important constituents of many pharmaceutical and agrochemical products. 1,3,5-Trisubstituted pyrazolines represent a very important class of biologically active agents and the focus of a significant amount of research interest. In particular, pyrazoline derivatives have found use as antitumor, antibacterial, antifungal, antiviral, antiparasitic, antitubercular and insecticidal agents[1-10].

The most common synthetic approach to pyrazoline synthesis involves cyclization of propenones with hydrazines in the presence of acetic acid as cyclizing agent[11]. A variety of reaction conditions influence the cyclization reaction. Herein is reported a relatively simple and useful method for the synthesis of pyrazolines in good yield using Amberlyst-15[12,13] catalyst in toluene medium. The obvious advantage of solid catalysts in organic reactions prompted the use of the macro reticular sulphonic acid cation exchange resin, Amberlyst-15. It was found that Amberlyst-15 efficiently catalyses the cyclization reaction with improved yield and better positional selectivity. The treatment of propenones with hydrazines in anhydrous toluene in the presence of Amberlyst-15 catalyst under reflux afforded pyrazolines in good yield.

The advantage with Amberlyst-15 is that it is cheap, non-toxic, stable and easy to handle. The catalyst can be recycled after washing with toluene followed by drying. The recovered resin catalyst can be reused at least four to five times. Another advantage of this process is that toluene can be easily recovered by distillation and there is no effluent generation. Therefore, the method is eco-friendly. However, the longer duration of reaction is a limitation from which this method suffers as compared to other reported methods.

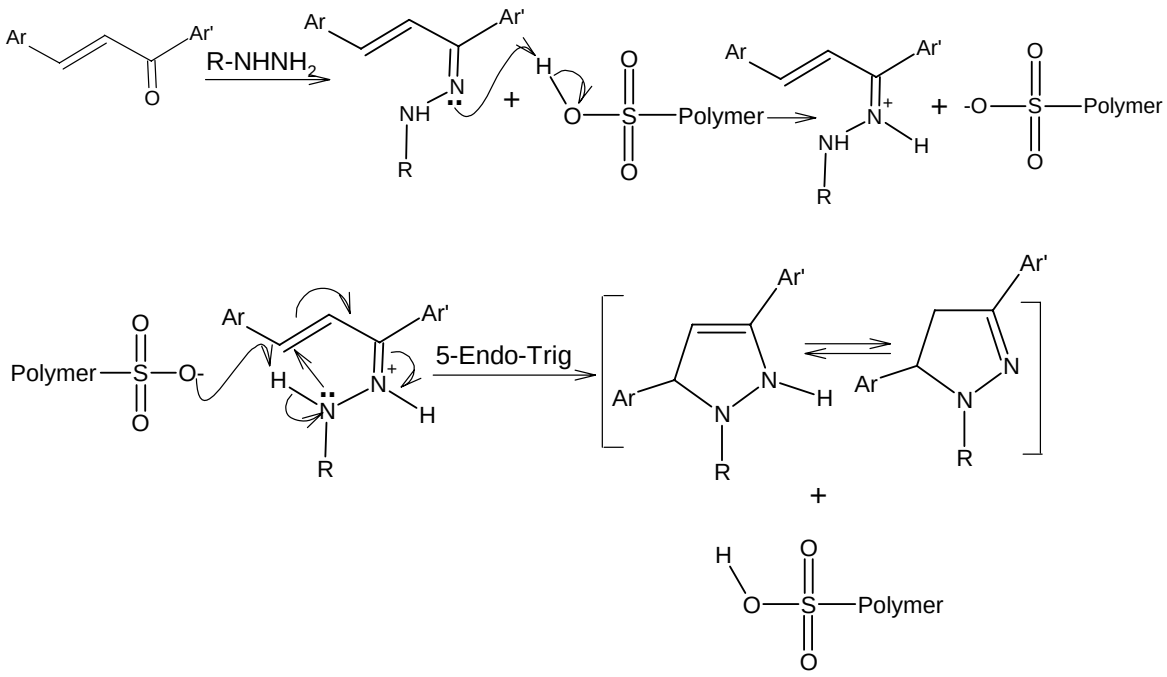
The newly synthesized 1-aryl-3-(substitutedphenyl/phenylfuranyl/thienyl)-2-propen-1-ones **1a-e** were characterized on the basis of IR, ^{1}H NMR and mass spectral data. All the compounds showed a characteristic IR absorption band in the region 1660-1700 cm^{-1} indicating the presence of a conjugated carbonyl group (C=O). Their ^{1}H NMR spectra clearly suggest that the vinylic protons are considerably shifted downfield to the extent that they appear in the aromatic region (δ 6.5- 8.5). As a result, these protons can hardly be distinguished from those of the aromatic rings.

The propenones **1a-e** were then reacted with hydrazines to give 3-aryl-5-(substitutedphenyl/phenylfuranyl/thienyl)-2-pyrazolines (**Scheme I**). This reaction probably takes place *via* an appropriate α,β-unsaturated hydrazone intermediate followed by the attack of NH on the carbon-carbon double bond of the propenone moiety to give a pyrazoline ring. The mechanism for the reaction using macro reticular sulfonic acid cation exchange resin might involve an initial protonation of the NH group followed by the intramolecular cyclization. The ^{1}H NMR spectrum of compound **2a-j** indicated that the -CH_2 protons of the pyrazoline ring resonated as a pair of doublet of doublets due to geminal and vicinal coupling. The -CH proton appeared as a doublet of doublet due to vicinal coupling with the two magnetically non-equivalent protons of the methylene group at position 4 of the pyrazoline ring.



Scheme I

Mechanism



Experimental Section

The melting points were determined by open capillary method and are uncorrected. The IR spectra were recorded in KBr discs on a Shimadzu FT-IR 157 spectrophotometer. ^{1}H NMR spectra was recorded on a Bruker WH-200(270 MHz) spectrometer using TMS as an internal standard. The mass spectra were recorded on a JEOL JMS D-300 spectrometer operating at 70 eV. The homogeneity of the compounds was checked by thin layer chromatography (TLC) on silica gel plates using a mixture of hexane: ethyl acetate (4:1) as eluting solvent. Iodine vapour was used as a visualizing agent.

General procedure for the synthesis of 1-aryl-3-(substituted phenyl/phenylfuranyl/thienyl)-2-propen-1-ones 1a-e. Suitably substituted acetophenones (10 mmoles) were dissolved in ethanol. To this was added sodium hydroxide solution (5 mL, 30%) and various aromatic aldehydes (10 mmoles) with continuous stirring. The resulting clear solution was left for 4 hr at rt with stirring and then allowed to stand overnight. The solid which separated out was filtered, dried and purified by recrystallization from ethanol. The characterization data for these compounds are given in **Table I**.

1a: IR (KBr): 3030 (Ar-H), 2914.2 (C-H), 1649 (C=O), 957 cm^{-1} (C-F); ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3H, SCH_3), 6.99-6.96 (d, 2H, *p*-methylthiolphenyl, *J*=8.84 Hz), 7.11-7.06 (d, 2H, *p*-methylthiophenyl, *J*=8.6 Hz), 7.44-7.40 and 7.77-7.73 (2d, 2H, CH=CH, *J*=16 Hz), 7.61-7.60 (t, 2H, *p*-fluorophenyl, *J*=5.4 Hz), 8.04-8.01(d, 2H, *p*-fluorophenyl, *J*=8.8 Hz); MS: m/z (%), 272 (100, M^+), 225 (35), 178 (90), 152 (20), 102 (20), 69 (38), 55 (25).

Table 1—Characterization data of propenones **1a-e**

Compd	Ar	Ar [1]	Mol. formula	Yield (%)	m.p. °C
1a	4-fluorophenyl	4-methylthiophenyl	$C_{16}H_{13}FOS$	80	112
1b	4-fluorophenyl	4-methoxyphenyl	$C_{16}H_{13}FO_2$	83	104
1c	3-methyl thienyl	2,4-dichloro-3-fluorophenyl	$C_{14}H_9FCl_2OS$	82	132
1d	4-chlorophenyl furanyl	4-methylthiophenyl	$C_{20}H_{15}ClO_2S$	83	195
1e	2,4,5-trichlorophenyl furanyl	4-methylthiophenyl	$C_{20}H_{13}Cl_3O_2S$	80	188

Table II—Characterization data of pyrazolines **2a-j**

Compd	Ar	Ar[1]	R	Mol. formula	Yield (%)	m.p. °C
2a	4-fluorophenyl	4-methylthiophenyl	H	$C_{16}H_{15}FN_2S$	56	152-53
2b	4-fluorophenyl	4-methylthiophenyl	Ph	$C_{22}H_{19}FN_2S$	65	141-42
2c	4-fluorophenyl	4-methoxyphenyl	H	$C_{16}H_{15}FN_2O$	58	144-45
2d	4-fluorophenyl	4-methoxyphenyl	Ph	$C_{22}H_{19}FN_2O$	65	139-40
2e	3-methylthienyl	2,4-dichloro-3-fluorophenyl	H	$C_{14}H_{11}FCl_2N_2S$	58	155-56
2f	3-methylthienyl	2,4-dichloro-3-fluorophenyl	Ph	$C_{20}H_{15}FCl_2N_2S$	65	140-41
2g	4-chlorophenyl-furanyl	4-methylthiophenyl	H	$C_{20}H_{17}ClN_2OS$	56	176-77
2h	4-chlorophenyl-furanyl	4-methylthiophenyl	Ph	$C_{26}H_{21}ClN_2OS$	65	169-70
2i	2,4,5-trichloro- phenylfuranyl	4-methylthiophenyl	H	$C_{20}H_{15}Cl_3N_2OS$	56	180-81
2j	2,4,5-trichloro-phenyl furanyl	4-methylthiophenyl	Ph	$C_{26}H_{19}Cl_3N_2OS$	63	178-79

1d: IR (KBr): 3029 (Ar-H), 2915 (C-H), 1665 (C=O), 1025 (C-F), 820 cm^{-1} (C-Cl); ^{1}H NMR (DMSO-d_6): δ 2.55 (s, 3H, SCH_3), 6.77-6.76 (d, 1H, furanyl, *J*=3.5 Hz), 6.81-6.79 (d, 1H, furanyl, *J*=3.5 Hz), 7.33-7.31 (d, 2H, *p*-methylthiophenyl, *J*=8.4 Hz), 7.42-7.39 (2H, *p*-methylthiophenyl, *J*=8.5 Hz), 7.63-7.46 (2d, 2H, CH=CH, *J*=15.3 Hz), 7.71-7.69 (d, 2H, *p*-chlorophenyl, *J*=8.5 Hz), 8.00-7.98 (d, 2H, *p*-chlorophenyl, *J*=8.3 Hz); MS: m/z (%), 354 (100, M^+), 307 (22), 243 (20), 215 (20), 151 (30), 139 (50), 111 (12), 79 (20), 57 (10).

1e: IR (KBr): 3032 (Ar-H), 2930 (C-H), 1680 (C=O), 1025 (C-F) cm^{-1}, 822 (C-Cl), 815 (C-Cl), 820 cm^{-1}(C-Cl); ^{1}H NMR (DMSO-d_6): δ 2.55 (s, 3H, SCH_3), 6.84-6.62 (d, 1H, furanyl, *J*= 3.6 Hz), 7.27-7.26 (d, 2H, furanyl, *J*=3.6 Hz), 7.27 (s, 1H, 2,4,5-trichlorophenyl), 7.34-7.32(d, 2 H, *p*-methylthiophenyl, *J*=8.4 Hz), 7.63-7.48 (2d, 2H, CH=CH, *J*=15.3 Hz), 8.00-7.93(d, 2H, *p*-methylthiophenyl, *J*=8.5 Hz), 8.03(s, 1H, 2,4,5-trichlorophenyl).

General procedure for the synthesis of 3-aryl-5-[substitutedphenyl/phenylfuranyl/thienyl]-2-pyrazolines 2a-j. To a solution of the above synthesized propenones **1a-e** (10 mmoles) in anhydrous toluene (15 mL), was added hydrazine hydrate (90%, 5 mL) dropwise. The mixture was stirred for 10 min at rt and then 0.1 g of Amberlyst–15 catalyst was added. It was heated to reflux and maintained for 40-48 hr. The reaction mixture turned deep orange in colour. It was then cooled to rt and the catalyst was recovered by filtration. The filtrate was concentrated under reduced pressure to obtain a residue. It was purified by recrystallization from methanol (*cf*. **Table II**).

2a: IR (KBr): 3380 (N-H), 3031 (Ar-H), 2928 (C-H), 1035 cm^{-1} (C-Cl); ^{1}H NMR (DMSO-d_6): δ 2.51 (s, 3H, SCH_3), 3.13-3.06 (dd, 1H, CH_2, *J*=4.5 Hz), 3.76-3.66 (dd, 1H, CH_2, *J*=11.7 Hz), 5.58-5.52 (dd, 1H, CH, *J*=4.6 Hz), 7.02-7.01 (d, 2H, *p*-methylthiophenyl, *J*=8.4 Hz), 7.20-7.19 (t, 2H, *p*-fluorophenyl, *J*=5.4 Hz), 7.28-7.27 (d, 2H, *p*-methylthiophenyl, *J*=8.5 Hz), 7.65-7.62 (d, 2H, *p*-fluorophenyl, *J*=8.5 Hz); MS: m/z (%), 286 (100, M^+), 269 (10), 245 (10), 225 (20), 165 (20), 149 (25), 109 (30), 77 (30), 55 (15).

2b: IR (KBr): 3035 (Ar-H), 2940 (C-H), 1026 cm^{-1} (C-F); ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3H, SCH_3), 3.11-3.03 (dd, 1H, CH_2, *J*=7.2 Hz), 3.85-3.75 (dd, 1H, CH_2, *J*=12.2 Hz), 5.28-5.21 (dd, 1H, CH, *J*=7.1 Hz), 7.64-6.76 (m, 13H, Ar-H); MS: m/z (%), 362 (20, M^+), 149 (10), 122 (10), 109 (20), 91 (100), 77 (65), 58 (45).

2h: IR (KBr): 3030, 2928 (Ar-H), 816 (C-Cl) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.51 (s, 3H, SCH_3), 3.45-3.37 (dd, 1H, CH_2, *J*=6.5 Hz), 3.78-3.68 (dd, 1H, CH_2, *J*=12.0 Hz), 5.41-5.34 (dd, 1H, CH, *J*=6.8 Hz), 7.68-6.21 (m, 15H, Ar-H).

2i: IR (KBr): 3410 (N-H), 3033 (Ar-H), 2928 (C-H), 822 (C-Cl), 818 (C-Cl), 816 cm^{-1}(C-Cl); ^1H NMR (DMSO-d_6): δ 2.52 (s, 3H, SCH_3), 3.48-3.42 (dd, 1H, CH_2, *J*=4.8 Hz), 3.67-3.60 (dd, 1H, CH_2, *J*=11.6 Hz), 5.75-5.70 (dd, 1H, CH, *J*=4.8 Hz), 6.43-6.42 (d, 1H, furanyl, *J*=3.2 Hz), 7.07-7.06 (d, 1H, furanyl, *J*=3.6 Hz), 7.28-7.26 (d, 2H, *p*-methylthiophenyl, *J*=8.4 Hz), 7.49 (s, 1H, 2,4,5-trichlorophenyl), 7.68-7.66 (d, 2H, *p*-methylthiophenyl, *J*=8.4 Hz), 7.77 (s, 1H, 2,4,5-trichlorophenyl).

2j: IR (KBr): 3030 (Ar-H), 2925 (Ar-H), 822 (C-Cl), 820 (C-Cl), 816 cm^{-1} (C-Cl); ^1H NMR (DMSO-d_6): δ 2.53 (s, 3H, SCH_3), 3.43-3.37 (dd, 1H, CH_2, *J*=6.8 Hz), 3.79-3.71 (dd, 1H, CH_2, *J*=12.0 Hz), 5.43-5.38 (dd, 1H, CH, *J*=6.4 Hz), 7.53-6.85 (m, 11H, Ar-H).

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