INTERMOLECULAR CYCLOADDITION OF NITRILE IMINES AND NITRILE OXIDES TO 1,3-DIARYL PROP-2-EN-1-ONES

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Abstract: The reaction of nitrile imines and oxides generated *in situ* from the arylhydrazones 2 and araldoximes 5 in the presence of chloramine-T with α,β-unsaturated ketones 1 results tetrasubstituted pyrazolines 3 and trisubstituted isoxazolines 6. The latter on aromatization with chloranil furnished pyrazoles 4 and isoxazoles 7. All the new products have been characterized by elemental analyses, IR and ^{1}H NMR spectral data.

Introduction

The 1,3-dipolar cycloaddition is one of the most important and versatile methods for the construction of manifold five membered heterocycles. Among the 1,3-dipoles known nitrile imines and nitrile oxides have received extensive study and synthetic use as reactive intermediates leading to the formation of heterocyclic compounds (1-3). The generation of nitrile oxides involves oxidative dehydrogenation of aldoximes, dehydration of primary nitro compounds with an aryl isocyanate (4-6) or by reacting aldoximes with N-bromosuccinimide followed by treatment with sodium methoxide or triethylamine (7,8). Similarly nitrile imines can be generated from alkyl/aryl α-halohydrazones (9) and α-nitrohydrazones (10) by treating with a base. These nitrile oxides and nitrile imines are usually unstable and dimerize readily (11). However, alkyl substituted compounds are more prone to dimerization than the more bulky aryl derivatives. Hence, *in situ* generation of these dipoles which adds to dipolarophiles is the most effective method for the synthesis of 2-isoxazolines (5,6,11-14) and 2-pyrazolines (14) in high yield. This may be viewed as a C-C bond forming process where N and O/N groups are present simultaneously in 1,3-position of the acylic system.

Results & Discussion

The successful use of N-chloro-N-sodio-p-toluenesulfonamide (chloramine-T, CAT) for the generation of nitrile imines and nitrile oxides from arylhydrazones and araldoximes prompted us to plan for the syntheses of a new class of tetrasubstituted 2-pyrazolines, 1,3,5-triaryl-4-aroyl-4,5-dihydro-2-pyrazolines 3 and trisubstituted 2-isoxazolines, 3,5-diaryl-4-aroyl-4,5-dihydro-2-isoxazolines 6. This cycloaddition reaction is carried out by heating an equimolecular mixture of an arylhydrazone, 1,3-diaryl prop-2-en-1-one and CAT in ethanol under reflux temperature for 4 hrs (Scheme & Tables 1&2). Earlier, di and trisubstituted pyrazolines and disubstituted isoxazolines were reported either by the reaction of α,β-unsaturated ketones with hydrazine and its derivatives or diazomethane or hydroxylamine (15-18), respectively. However, tetrasubstituted pyrazolines was recently reported by the addition of *in situ* generated nitrile imines from arylhydrazones to activated olefins (19). In this reaction the expected product, 3-alkyl/aryl-4-benzoyl-5-phenyl-2-pyrazoline could not be obtained instead 3-alkyl/aryl-4-phenyl-5-benzoyl-2-pyrazoline was reported. Contrary to this, in the present investigation the former was obtained in high yield in the presence of CAT instead of triethylamine. Furthermore, the trisubstituted 2-isoxazolines which are not hitherto reported are also accomplished in our endeavour by similar process with araldoximes. Moreover, the 2-pyrazolines and 2-isoxazolines can be easily aromatized by autoxidation or thermal dehydrogenation or by treatment with tetrachloro-1,4-benzoquinone (chloranil) and perchloric acid (19). Indeed, the 1,3,5-triaryl-4-aroyl pyrazoles 4 and 3,5-diaryl-4-aroyl isoxazoles 7 are obtained by treatment of 3 and 4 with chloranil in xylene at reflux temperature.

The structures of 3, 4, 6 and 7 are assigned on the basis of their elemental analyses and spectral data. The IR spectra (cm^{-1}) of these compounds exhibited bands in the region 1430-1460 and 1650-1690 for C=N and C=O, respectively. The PMR spectra (δ, ppm) of 3 and 4 shows two doublets in the regions 4.50-4.65 and 5.45-5.58 for H-C_5 and H-C_4, respectively. The coupling constants (J=6.0-6.5 Hz) of the pyrazoline and isoxazoline protons indicates that they possess *trans* geometry. The PMR spectra of 4 and 7 does not indicate the presence of methine protons at C-4 and C-5 which confirms that dehydrogenation has taken place.

Experimental

Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked by chromatography over silica gel thin layers (silica gel-G, hexane:ethyl acetate 3:1). IR spectra were run as KBr pellets using a Perkin-Elmer 993 Infrared Spectrometer (ν_{max} in cm^{-1}) and ^1H NMR spectra were recorded in $CDCl_3$ using 90 MHz Perkin-Elmer instrument with TMS as an internal standard (chemical shifts in δ, ppm). Microanalytical data were obtained from Central Electrochemical Research Institution, Karaikudi, India. The araldoximes and arylhydrazones are prepared from araldehydes following the standard procedures.

Preparation of 1,3,5-triaryl-4-aroyl-4,5-dihydro-2-pyrazolines 3:

A mixture of 1,3-diaryl-prop-2-en-1-one (0.002 mole), in ethanol was added to a mixture of arylhydrazone (0.003 mole) and chloramine-T (0.0037 mole) in ethanol is refluxed for 3 hrs. Salts are filtered off, the filtrate is concentrated and the residue is extracted into ether (30 mL). The ethereal layer is washed with 1N sodium hydroxide (2x15 mL), brine solution (2x20 mL) and dried. Concentration of the solvent furnished crude product, which is purified by column chromatography (petroleum ether : ethyl acetate, 8:2) to get a pale yellow solid 3.

Preparation of 3,5-diaryl-4-aroyl-4,5-dihydro-2-isoxazolines 6:

A mixture of 1,3-diaryl prop-2-ene-1-one (0.002 mole) araldoxime (0.0026 mole) and chloramine-T (0.0037 mole) in ethanol (20 mL) is heated to reflux for 3 hrs. The salt formed in the reaction is filtered off and washed with ethanol. The filtrate and washings are concentrated under reduced pressure and the residue is extracted with dichloromethane (20 mL), washed with water (10 mL) and with 1N sodium hydroxide (2x10 mL) and dried. The solvent is evaporated and the remaining yellow solid is recrystallized from chloroform : petroleum ether (2:3) to get 6.

Dehydrogenation of pyrazolines and isoxazolines:

A solution of appropriate 3 or 6 (0.005 mole) and chloranil (0.0052 mole) in xylene (15 mL) is refluxed for 24-32 hrs. It is washed with 5% sodium hydroxide solution. The organic layer is repeatedly washed with water, dried and distilled under reduced pressure. The solid left is purified by recrystallization from alcohol or glacial acetic acid to furnish 4 or 7.

Acknowledgement:

One of the authors (RPS) is grateful to CSIR, New Delhi for the award of Senior Research Fellowship.

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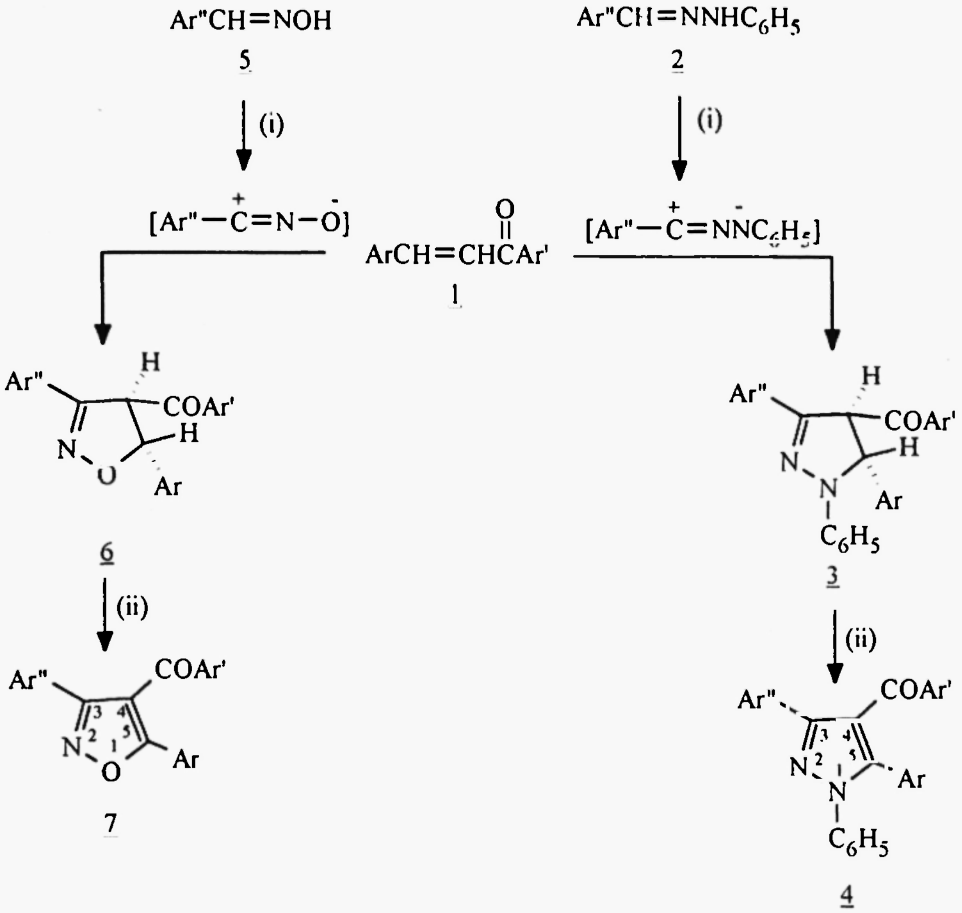

(i) CAT / C_2H_5OH / Δ (ii) Chloranil / xylene / Δ

a) Ar = Ar′ = Ar″ = C_6H_5
b) Ar = Ar′ = C_6H_5; Ar″ = p-$OCH_3C_6H_4$
c) Ar = Ar′ = C_6H_5; Ar″ = p-ClC_6H_4
d) Ar = Ar″ = C_6H_5, Ar′ = p-$CH_3C_6H_4$
e) Ar = Ar″ = C_6H_5, Ar′ = p-ClC_6H_4
f) Ar = Ar″ = C_6H_5, Ar′ = p-BrC_6H_4
g) Ar = C_6H_5; Ar′ = p-$CH_3C_6H_4$; Ar″=p-ClC_6H_4
h) Ar = p-$OCH_3C_6H_4$; Ar′ = Ar″= C_6H_5
i) Ar = Ar″ = p-$OCH_3C_6H_4$, Ar′ = C_6H_5
j) Ar = p-$OCH_3C_6H_4$; Ar′ = C_6H_5; Ar″ = p-ClC_6H_4
k) Ar = p-$OCH_3C_6H_4$; Ar′ = p-BrC_6H_4; Ar″ = C_6H_5
l) Ar = p-ClC_6H_4, Ar′ = Ar″ = C_6H_5
m) Ar = p-ClC_6H_4; Ar′ = C_6H_5, Ar″ = p-$OCH_3C_6H_4$

SCHEME

Table 1: Physical data of compounds 3 and 4

Compd	Yield (%)	m.p. (°C)	Molecular formula	Found (Calcd) %		
				C	H	N
3a	72	154-155	$C_{28}H_{22}N_2O$	83.55(83.61)	5.47(5.50)	7.12(6.96)
3b	65	163-164	$C_{29}H_{24}N_2O_2$	80.71(80.53)	5.49(5.59)	6.39(6.48)
3c	69	133-134	$C_{28}H_{21}ClN_2O$	76.92(76.97)	4.76(4.84)	6.46(6.41)
3d	72	172-173	$C_{29}H_{24}N_2O$	83.60(83.62)	5.85(5.80)	6.61(6.72)
3e	75	153-154	$C_{28}H_{21}ClN_2O$	76.91(76.97)	4.92(4.84)	6.37(6.41)
3f	82	175-176	$C_{28}H_{21}BrN_2O$	69.82(69.86)	4.36(4.39)	5.88(5.82)
3g	68	190-192	$C_{29}H_{23}ClN_2O$	77.20(77.24)	5.18(5.14)	6.30(6.21)
3h	68	163-164	$C_{29}H_{24}N_2O_2$	80.40(80.53)	5.66(5.59)	6.51(6.48)
3i	70	173-174	$C_{30}H_{26}N_2O_3$	77.77(77.90)	5.72(5.66)	6.18(6.05)
3j	73	178-179	$C_{29}H_{23}ClN_2O_2$	74.45(74.59)	4.91(4.96)	6.06(5.99)
3k	85	183-184	$C_{29}H_{23}BrN_2O_2$	68.00(68.11)	4.58(4.53)	5.51(5.48)
3l	64	130-130.5	$C_{28}H_{21}ClN_2O$	77.07(76.97)	4.76(4.84)	6.30(6.41)
3m	70	125-126.5	$C_{29}H_{23}ClN_2O_2$	74.66(74.59)	5.04(4.96)	6.05(5.99)
4a	69	169-170	$C_{28}H_{20}N_2O$	84.17(83.97)	5.00(5.03)	6.87(6.99)
4b	65	153-154	$C_{29}H_{22}N_2O_2$	81.09(80.90)	5.14(5.15)	6.62(6.50)
4c	68	131-132	$C_{28}H_{19}ClN_2O$	77.10(77.32)	4.51(4.40)	6.26(6.44)
4d	65	165-166	$C_{29}H_{22}N_2O$	83.84(84.03)	5.19(5.34)	6.84(6.75)
4e	70	165-166	$C_{28}H_{19}ClN_2O$	77.45(77.32)	4.34(4.40)	6.32(6.44)
4f	66	183-184	$C_{28}H_{19}BrN_2O$	70.00(70.15)	4.07(3.99)	5.99(5.84)
4g	70	182-183	$C_{29}H_{21}ClN_2O$	77.72(77.58)	4.60(4.71)	6.31(6.23)
4h	65	158-159	$C_{29}H_{22}N_2O_2$	80.77(80.90)	5.30(5.15)	6.47(6.50)
4i	64	169-170	$C_{30}H_{24}N_2O_3$	81.27(81.05)	5.52(5.44)	6.24(6.30)
4j	67	169-170	$C_{29}H_{21}ClN_2O_2$	74.74(74.91)	4.32(4.55)	6.15(6.02)
4k	67	186-187	$C_{29}H_{21}BrN_2O_2$	68.25(68.37)	4.28(4.15)	5.36(5.49)
4l	68	142-143	$C_{28}H_{19}ClN_2O$	77.46(77.32)	4.48(4.40)	6.28(6.44)
4m	67	137-138	$C_{29}H_{21}ClN_2O_2$	74.70(74.91)	4.69(4.55)	5.87(6.02)

Table 2: Physical data of compounds 6 and 7

Compd	Yield (%)	m.p. (°C)	Molecular formula	Found (Calcd) % C	H	N
6a	68	118-120	$C_{22}H_{17}NO_2$	80.83(80.71)	5.12(5.23)	4.18(4.29)
6b	71	138-140	$C_{23}H_{19}NO_3$	77.15(77.29)	5.25(5.36)	3.88(3.92)
6c	82	125-127	$C_{22}H_{16}ClNO_2$	73.16(70.49)	4.35(4.63)	3.95(3.57)
6d	81	172-174	$C_{23}H_{19}NO_2$	80.85(80.92)	5.72(5.61)	4.25(4.10)
6e	76	126-128	$C_{22}H_{16}ClNO_2$	73.18(73.03)	4.58(4.46)	3.75(3.87)
6f	69	145-147	$C_{22}H_{16}BrNO_2$	65.17(65.04)	3.85(3.97)	3.60(3.45)
6g	75	155-157	$C_{23}H_{18}ClNO_2$	73.65(73.50)	4.91(4.82)	3.83(3.72)
6h	65	130-132	$C_{23}H_{19}NO_3$	77.39(77.29)	5.40(5.36)	3.85(3.92)
6i	67	118-120	$C_{24}H_{21}NO_4$	74.46(74.31)	5.48(5.58)	3.55(3.61)
6j	80	168-170	$C_{23}H_{18}ClNO_3$	70.54(70.49)	4.52(4.63)	3.65(3.57)
6k	76	172-174	$C_{23}H_{18}BrNO_3$	63.45(63.31)	4.25(4.16)	3.31(3.21)
6l	80	127-129	$C_{22}H_{16}ClNO_2$	73.51(73.03)	4.58(4.46)	3.72(3.87)
6m	78	142-144	$C_{23}H_{18}ClNO_3$	70.55(70.49)	4.71(4.63)	3.45(3.57)
7a	65	133-134	$C_{22}H_{15}NO_2$	81.39(81.21)	4.56(4.64)	4.21(4.30)
7b	63	127-128	$C_{23}H_{17}NO_3$	77.88(77.73)	4.91(4.82)	4.00(3.94)
7c	67	131-132	$C_{22}H_{14}ClNO_2$	73.61(73.43)	3.87(3.92)	4.01(3.89)
7d	65	162-163	$C_{23}H_{17}NO_2$	81.57(81.39)	4.94(5.04)	4.00(4.12)
7e	66	142-143	$C_{22}H_{14}ClNO_2$	73.30(73.43)	3.89(3.92)	3.95(3.89)
7f	60	157-158	$C_{22}H_{14}BrNO_2$	65.53(65.36)	3.43(3.49)	3.52(3.46)
7g	64	139-140	$C_{23}H_{16}ClNO_2$	74.05(73.89)	4.42(4.31)	3.81(3.74)
7h	62	125-126	$C_{23}H_{17}NO_3$	77.55(77.73)	4.75(4.82)	3.82(3.94)
7i	63	132-133	$C_{24}H_{19}NO_4$	74.65(74.79)	5.05(4.96)	3.71(3.63)
7j	65	175-176	$C_{23}H_{16}ClNO_3$	70.74(70.86)	4.04(4.13)	3.50(3.59)
7k	64	165-166	$C_{23}H_{16}BrNO_3$	63.72(63.60)	3.77(3.71)	3.20(3.22)
7l	62	140-141	$C_{22}H_{14}ClNO_2$	73.60(73.43)	3.85(3.92)	3.94(3.89)
7m	65	135-136	$C_{23}H_{16}ClNO_3$	71.02(70.86)	4.22(4.13)	3.67(3.59)

Received on February 10, 1998