1,3-Dipolar Cycloaddition of Dipolar Reagents to Bifunctional Olefins in the Presence of Chloramine-T (CAT)

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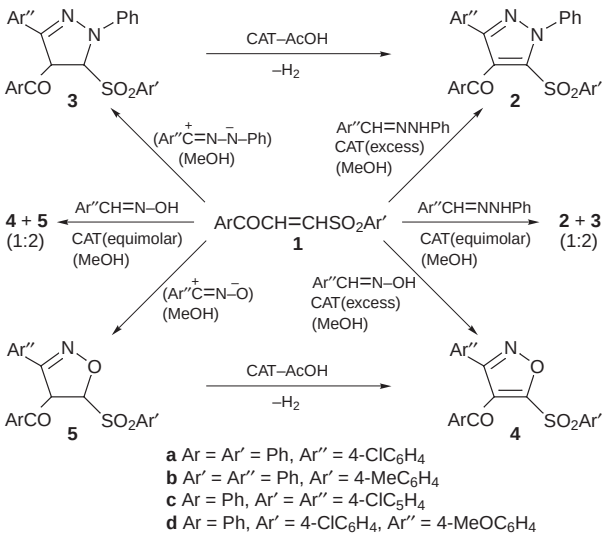
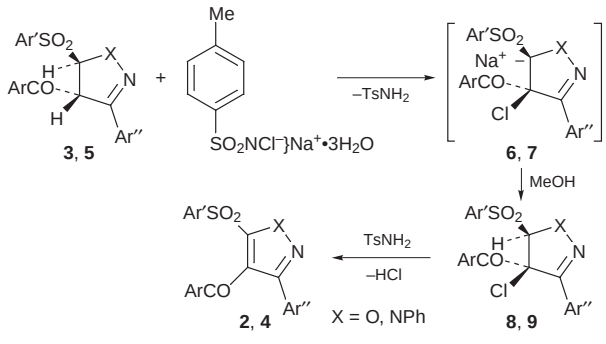
2-Pyrazolines and 2-isoxazolines are prepared by the reaction of araldehyde hydrazones and araldoximes with bifunctional olefins in the presence of chloramine-T, which also functions as a reagent for aromatization of the former.

1,3-Dipolar cycloaddition is amongst the most important and versatile methods for the construction of five-membered heterocycles. Within this class, the reaction of nitrile imines and nitrile oxides with olefins is of synthetic interest since the resulting pyrazolines and isoxazolines are versatile intermediates for the synthesis of bifunctional compounds.[1] Dipolar reagents can be generated by the dehydrogenation of araldehyde hydrazones and araldoximes with lead tetraacetate,[2] mercuric acetate,[3] 1-chlorobenzotriazole,[4] chloramine-T (CAT),[5] *etc*. We recently reported the synthesis of tetrasubstituted 2-pyrazolines and trisubstituted 2-isoxazolines by the cycloaddition of nitrile imines and nitrile oxides to α,β-unsaturated ketones and sulfones in the presence of CAT.[6,7] In continuation of our study, we examined the reaction of araldehyde hydrazones and araldoximes with bifunctional olefinic systems activated by both carbonyl and sulfonyl groups, 1-aroyl-2-arylsulfonylethenes, **1**[8] in the presence of CAT.



Scheme 1

The reaction of **1** with araldehyde hydrazones in the presence of CAT in equimolar proportions in refluxing methanol (Scheme 1) gave a mixture of products in 1:2 ratio which were separated by silica gel chromatography. They were identified as 1,3-diaryl-4-aroyl-5-arylsulfonyl-2-pyrazoles **2** (minor) and 1,3-diaryl-4-aroyl-5-aryl-sulfonyl-2-pyrazolines **3** (major) by their ^{1}H NMR spectra. Compounds **2** exhibited only a multiplet at δ_H 6.95–8.00 for the aromatic protons while compounds **3** showed two doublets at δ_H 5.85 (4-H, $J = 6.9$ Hz) and 6.40 (5-H, $J = 6.9$ Hz) in addition to the multiplet for the aromatic protons at δ_H 6.98–7.95. Likewise, when cycloaddition was carried out between araldoximes and **1** in the presence of CAT in equimolar ratio again products in a 1:2 ratio were obtained which were identified by ^{1}H NMR spectroscopy as 3-aryl-4-aroyl-5-arylsulfonyl-2-isoxazoles **4** (minor) and 3-aryl-4-aroyl-5-arylsulfonyl-2-isoxazolines **5** (major) which were separated by column chromatography. Compounds **4** exhibited only a multiplet in the region δ_H 6.97–8.10 whereas compounds **5** showed two doublets at δ_H 5.95 (4-H, $J = 5.95$ Hz) and at 6.45 (5-H, $J = 5.95$ Hz) and a multiplet at δ_H 7.00–8.00. In the above reactions the nitrile imines and nitrile oxides were generated *in situ*. In order to ascertain the role of CAT in these cycloaddition reactions, the reaction of **1** was carried out by the direct addition of nitrile imines and nitrile oxides in equimolar ratio. The latter were separated from the respective araldehyde hydrazones and araldoximes in the presence of CAT. Interestingly, **3** and **5** alone were obtained. This indicates that the excess CAT present in the reaction mixture during *in situ* generation of dipolar reagents might be primarily responsible for dehydrogenation of **3** and **5** to **2** and **4**, respectively. In order to ascertain this, attempts were made to dehydrogenate **3** and **5** with CAT in acetic acid at reflux and, as expected, the products obtained in this reaction were identified as **2** and **4**. When the reaction of **1** with araldehyde hydrazones and araldoximes was repeated with an excess of CAT, **2** and **4** alone resulted. The authenticity of **2** and **4** obtained by different routes was confirmed by ^{1}H NMR spectral data. These results indicate that the excess CAT present during *in situ* generation of dipolar reagents was responsible for the formation of **2** and **4** in minor amounts by dehydrogenation of **3** and **5**, respectively. The aromatization mechanism is summarized in Scheme 2. Compounds **3**/**5** formed in the



Scheme 2

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first step react with another molecule of CAT, resulting in the formation of short-lived intermediates **6**/**7**, which abstract a proton from the solvent to afford **8**/**9** which upon dehydrohalogenation under mildly basic conditions lead to **2**/**4**.

These results are rather surprising as the analogous reaction of α,β-unsaturated ketones and sulfones with araldehyde hydrazones and araldoximes in the presence of CAT gave only 2-pyrazolines and 2-isoxazolines, respectively. In fact, dehydrogenation of the latter has been carried out with chloranil to obtain pyrazoles and isoxazoles.[6,7] In the present investigation, however, the olefinic protons in **1** flanked between the CO and SO_2 groups become more acidic and consequently CAT, which is also a strong oxidant, dehydrogenates **3** and **5**. Thus, in the presence of an excess of oxidant, the intermediate pyrazolines **3** and isoxazolines **5** react further to afford the corresponding pyrazoles **2** and isoxazoles **4**. This sequence exemplifies a method for synthesis of the aromatic heterocycles, comprising *in situ* generation of dipolar reagents, followed successively by 1,3-dipolar cycloaddition and aromatization.

Experimental

All melting points were uncorrected. The purity of the compounds was checked by thin layer chromatography over silica gel [Silica gel-G, hexane–ethyl acetate (3 : 1)], IR spectra were run as KBr pellets using Perkin-Elmer 993 infrared spectrometer and ^{1}H NMR spectra were recorded in $CDCl_3$–DMSO using a 200 MHz Perkin-Elmer Instrument. Microanalytical data were obtained from Dr Reddy's Research Foundation, Hyderabad, India. The araldoximes and araldehyde phenylhydrazones were prepared from araldehydes following standard procedures.[9]

General Procedure for the Synthesis of 1,3-*Diaryl*-4-*aroyl*-5-*arylsulfonyl*-2-*pyrazoles* **2**.—1-Aroyl-2-arylsulfonyl ethene **1** (0.6 mmol) in methanol was added to a mixture of araldehyde phenylhydrazone (0.6 mmol) and chloramine-T (1.2 mmol) in methanol (20 ml) at room temp. and the mixture refluxed for 3 h. Salts were filtered off, the filtrate was concentrated and the residue extracted with diethyl ether (30 ml). The ethereal layer was washed with 1 M NaOH (2 × 15 ml), brine (2 × 20 ml) and dried over anhydrous Na_2SO_4. Concentration of the solvent gave the crude product, which was purified by column chromatography [(hexane–ethyl acetate (4 : 1)] to give **2**,

2a: yield 63%, mp 169–170 °C (Found: C, 67.41; H, 3.92; N, 5.71. Calc. for $C_{28}H_{19}ClN_2O_3S$: C, 67.39; H, 3.83; N, 5.61%). ν_{max}/cm^{-1} 1310, 1146 (SO_2); 1445 (C=N); 1655 (C=C); 1699 (C=O). δ_H ($CDCl_3$–DMSO) 6.98–7.85 (m, 19H, aromatic H).

When the same reaction was carried out with an equimolar ratio of chloramine-T, a mixture of products, 1,3-diaryl-4-aroyl-5-arylsulfonyl-2-pyrazoles **2** and 1,3-diaryl-4-aroyl-5-arylsulfonyl-2-pyrazolines **3** were obtained in 1 : 2 ratio. These compounds have same physical and spectral characteristics as above and below.

General Procedure for the Synthesis of 1,3-*Diaryl*-4-*aroyl*-5-*arylsulfonyl*-2-*pyrazolines* **3**.—A solution of araldehyde phenylhydrazone (0.6 mmol) in methanol (15 ml) was heated to 30–40 °C, chloramine-T (0.6 mmol) was then added and the contents were heated to reflux. The solvent was then removed *in vacuo*. The residue obtained was extracted with ether, washed with 1 M NaOH, brine solution and dried (anhydrous Na_2SO_4). Removal of the solvent under reduced pressure yielded the nitrile imine. This (0.6 mmol) was added to **1** (0.6 mmol) in methanol (30 ml) and refluxed for 3 h. Then the reaction mixture was concentrated and the residue extracted with ether. The ethereal layer was washed, dried and then the solvent removed *in vacuo*. The crude product was obtained, purified by column chromatography [ethyl acetate–hexane (2 : 3)] as eluent, to afford **3**.

3a: yield 73%, mp 199–200 °C (Found: C, 67.01; H, 4.25; N, 5.65. Calc. for $C_{28}H_{21}ClN_2O_3S$: C, 67.11; H, 4.22; N, 5.61%). ν_{max}/cm^{-1} 1335, 1157 (SO_2); 1447 (C=N); 1686 (C=O). δ_H ($CDCl_3$–DMSO) 5.84 (d, 1H, 4-H, J = 6.9 Hz); 6.43 (d, 1H, 5-H, J = 6.9 Hz); 7.20–8.20 (m, 19H, aromatic H).

General Procedure for the Synthesis of 3-*Aryl*-4-*aroyl*-5-*arylsulfonyl*-2-*isoxazoles* **4**.—A mixture of 1-aroyl-2-arylsulfonylethene (0.6 mmol), araldoxime (0.6 mmol) and chloramine-T (1.2 mmol) in methanol (25 ml) was heated to reflux with stirring for 3 h. Further work-up of the reaction mixture was similar to that of **2**.

4a: yield 62%, mp 170–171 °C (Found: C, 62.35; H, 3.39; N, 3.32. Calc. for $C_{22}H_{14}ClNO_4S$: C, 62.33; H, 3.33; N, 3.30%). ν_{max}/cm^{-1} 1363, 1169 (SO_2); 1485 (C=N); 1654 (C=C); 1697 (C=O). δ_H ($CDCl_3$–DMSO) 6.97–8.10 (m, 14H, aromatic H).

When the same reaction was carried out with equimolar ratio of chloramine-T, a mixture of products, 3-aryl-4-aroyl-5-arylsulfonyl-2-isoxazoles **4** and 3-aryl-4-aroyl-5-arylsulfonyl-2-isoxazolines **5** were obtained in 1 : 2 ratio. These compounds have the same physical and spectral characteristics as those mentioned above and below.

General Procedure for the Synthesis of 3-*Aryl*-4-*aroyl*-5-*arylsulfonyl*-2-*isoxazolines* **5**.—A solution of araldoxime (0.6 mmol) in methanol (15 ml) was heated to 30–40 °C. Chloramine-T (0.6 mmol) was then added and the contents were heated to reflux. Then the solvent was removed *in vacuo*. The residue obtained was extracted with CH_2Cl_2 (30 ml), washed with 1 M NaOH and brine, and dried. Removal of the solvent under reduced pressure yielded the nitrile oxide. This (0.6 mmol) was added to **1** (0.6 mmol) in ethanol and refluxed for 3 h. After work-up, the reaction mixture was treated as for in **3** to give **5**.

5a: yield 76%, mp 195–196 °C (Found: C, 62.16; H, 3.76; N, 3.26. Calc. for $C_{22}H_{16}ClNO_4S$: C, 62.04; H, 3.78; N, 3.28%). ν_{max}/cm^{-1} 1312, 1133 (SO_2); 1448 (C=N); 1688 (C=O). δ_H ($CDCl_3$–DMSO) 5.97 (d, 1H, 4-H, J = 5.9 Hz); 6.45 (d, 1H, 5-H, J = 5.9 Hz); 7.21–8.20 (m, 14H, aromatic H).

Aromatization of Pyrazolines **3** *and Isoxazolines* **5**.—A mixture of **3**/**5** (0.4 mmol) and chloramine-T (0.4 mmol) in acetic acid (20 ml) was refluxed for 2 h. The reaction mixture was concentrated, extracted with CH_2Cl_2 (30 ml), washed with 1 M NaOH and water, and dried (anhydrous Na_2SO_4). Evaporation of the solvent gave the product which was filtered through a column of silica gel to afford pure **2**/**4**. The physical and spectral parameters of these compounds were the same as above.

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