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A one-pot synthesis of 3-methyl-5-aryl-4*H*-pyrrolo[2,3-*d*]-isoxazoles

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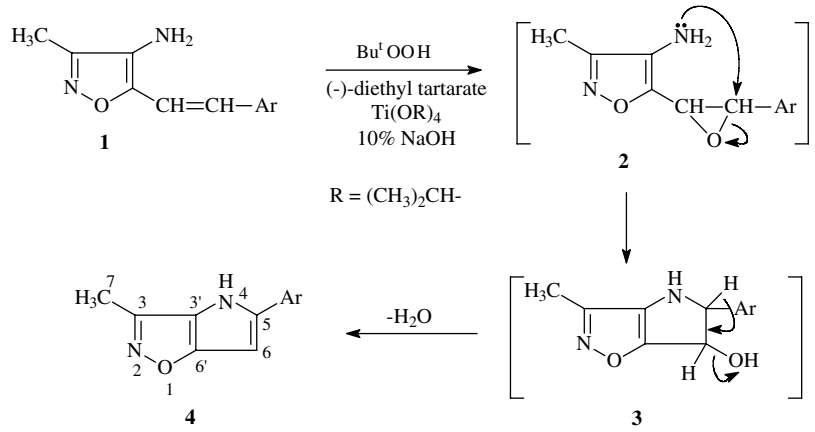
Abstract—Sharpless epoxidation of 4-amino-3-methyl-5-styrylisoxazoles **1** resulted in the formation of 3-methyl-5-aryl-4*H*-pyrrolo[2,3-*d*]-isoxazoles **4** in a one-step reaction. The reaction initially involves epoxide formation, followed by ring-opening and cyclization. Finally dehydration leads to the title compounds. The pyrrolo[2,3-*d*]-isoxazoles **4** were also synthesized via an alternative procedure.

We have investigated several approaches for the preparation of pyrrolo[2,3-*d*]-isoxazoles. One method for the pyrrole ring formation is the deoxygenative cyclization of nitrostyryl compounds using triethyl phosphite (TEP).[1,2] As the reaction requires heating of the starting material in TEP at high temperature under an N_2 atmosphere, the reaction results in the cleavage of the isoxazole ring in our case as the isoxazole ring is unstable at high temperature.[3] To overcome this problem, we utilized another method developed by Carothi and co-workers,[4] which involves the reductive cyclization of a nitrostyryl compound using $SnCl_2$–DMF. However, we could not achieve the synthesis of the target compounds using this procedure even though the reaction was carried out in the presence of $SnCl_2$ in different solvents using a variety of reaction conditions. Thus, we decided to construct the pyrrolo[2,3-*d*]-isoxazoles by utilizing an amino styryl compound rather than nitrostyryl compounds. To our surprise, we were able to prepare the title compounds in a one-pot synthesis via a Sharpless epoxidation. As a continuation of our work on isoxazoles,[5–8] we herein report this novel one-pot synthesis of pyrrolo[2,3-*d*]-isoxazoles.



Scheme 1.

Keywords: Sharpless epoxidation; Epoxide ring-opening; Cyclization; Dehydration; One-pot synthesis.
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The reaction of 4-amino-3-methyl-5-styryl isoxazole **1** with *tert*-butyl hydroperoxide was carried out in the presence of (−)-diethyl tartarate and titanium tetraisopropoxide at −25 °C for 24 h followed by treatment with 10% NaOH solution at −10 °C for 1 h. The product obtained after purification by column chromatography was identified as 3-methyl-5-aryl-4*H*-pyrrolo[2,3-*d*]-isoxazole **4**[9] (Scheme 1).

The reaction may initially involve the formation of an epoxide by a Sharpless epoxidation, which is subsequently ring-opened by an attack of the amino functional group to give the cyclized intermediate **3**. This could undergo dehydration by the action of base to give the product **4**.

Table 1. Synthesis of 3-methyl-5-aryl-4*H*-pyrrolo[2,3-*d*]-isoxazoles via Sharpless epoxidation

Entry[a]	Ar	Time (h)	Yield (%)	Mp (°C)
4a	C_6H_5	24	96	156–158
4b	4-$CH_3C_6H_4$	20	92	143–149
4c	4-$OCH_3C_6H_4$	18	95	128–131
4d	4-ClC_6H_4	21	90	163–168
4e	2-ClC_6H_4	20	93	159–166
4f	2,4-$Cl_2C_6H_3$	16	94	171–175
4g	4-$NO_2C_6H_4$	17	97	183–185
4h	2-$NO_2C_6H_4$	15	95	192–194
4i	3,4-(–O–CH_2–O)–C_6H_3	20	96	178–181
4j	2-$CH_3C_6H_4$	22	94	167–170
4k	4-$N(CH_3)_2C_6H_4$	21	95	180–184
4l	2,6-$Cl_2C_6H_3$	23	97	196–199

[a] All the compounds gave satisfactory C, H and N analyses.

Actually, we intended to carry out the epoxidation first and then the ring-opening reaction under different conditions, followed by dehydration to afford the title compounds. To our surprise, all these steps occurred in one-pot. The structures of the products were confirmed on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectral data, and also by elemental analyses.

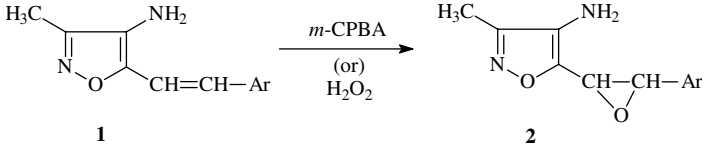
In order to study the scope of this reaction, twelve different substituted aminostyryl isoxazoles were subjected to epoxidation under Sharpless conditions. The desired product was obtained in excellent yield in each case[9] (Table 1).

Finally, the results indicate that our method is compatible with various functional groups and the approach proved to be of general applicability. This synthetic

Table 2. Synthesis of *N*-(3,5-dimethyl-4-isoxazole)benzamides

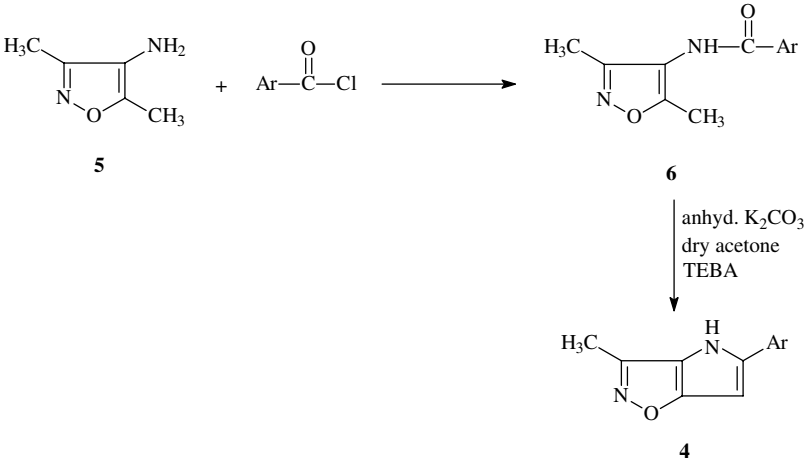
Entry[a]	Ar	Time (h)	Yield (%)	Mp (°C)
6a	C_6H_5	1	93	181–183
6b	4-$CH_3C_6H_4$	2	85	168–170
6c	4-$OCH_3C_6H_4$	2	90	154–157
6d	4-ClC_6H_4	1	88	190–192
6e	2-ClC_6H_4	2	80	185–188
6f	2,4-$Cl_2C_6H_3$	1	87	175–178
6g	4-$NO_2C_6H_4$	1	95	202–204
6h	2-$NO_2C_6H_4$	2	85	210–212
6i	3,4-(O–CH_2–O)C_6H_3	2	81	189–191
6j	2-$CH_3C_6H_4$	2	87	185–187
6k	4-$N(CH_3)_2C_6H_4$	1	92	198–200
6l	2,6-$Cl_2C_6H_3$	1	90	220–222

[a] All the compounds gave satisfactory C, H and N analyses.



1 **2**

Scheme 2.



5 **6** **4**

Scheme 3.

strategy permits the introduction of a diverse array of substituents onto the benzene ring. To the best of our knowledge, this report is the first of its kind to construct a pyrrole ring employing a Sharpless epoxidation process.

When epoxidation of **1** was carried out with *m*-chloroperbenzoic acid or hydrogen peroxide, the reaction resulted only in the formation of epoxide **2**[10] (Scheme 2). Hence, the one-pot synthesis of pyrrolo[2,3-*d*]-isoxazoles **4** could only be achieved under Sharpless epoxidation conditions.

The synthesis of pyrrolo[2,3-*d*]-isoxazoles **4** could also be accomplished by adopting a different methodology. 3,5-Dimethyl-4-aminoisoxazole **5** was benzoylated by treatment with an aromatic acid chloride in dichloromethane[11] (Table 2). The resulting benzamide **6** was subjected to cyclization to give the title compounds **4** by reaction with anhydrous potassium carbonate and dry acetone in the presence of the phase transfer catalyst triethylbenzylammonium chloride (TEBA)[12] (Scheme 3). The products obtained were found to be the same as those prepared via the Sharpless epoxidation process from mps., ^{1}H NMR, ^{13}C NMR and mass spectra.

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9. 3-Methyl-5-aryl-4*H*-pyrrolo[2,3-*d*]-isoxazole **4**. To a solution of (−)-diethyl tartarate (20 ml) in dichloromethane (50 ml) at −25 °C, titanium tetraisopropoxide (7.5 ml) was added and the contents stirred for 1 h. To this, 3-methyl-4-amino-5-styrylisoxazole (100 mg) and *tert*-butyl hydroperoxide (2.5 ml) were added whilst maintaining the reaction at −25 °C. The reaction mixture was stirred at this temperature for 24 h. It was then filtered and cooled to −10 °C, and L-tartaric acid (1.5 g in 15 ml of H_2O) was added and the reaction stirred for 1 h. The precipitate formed was removed by filtration and the organic layer cooled to −10 °C, and 10% NaOH solution (6 g in 25 ml of H_2O) saturated with NaCl was added and stirring continued for 1 h. The separated organic layer was washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography by elution with ethyl acetate/hexane (1:10). Compound **4a**, mp 156–158 °C; IR cm^{-1}; 3250 (s), 1600, 980, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (s, 3H, CH_3), 7.40–7.62 (m, 5H, Ar–H), 7.76 (s, 1H, C_6–H), 7.85 (s, 1H, NH, D_2O exchangeable). MS (EI): *m*/*z* 198 (M^+). ^{13}C NMR (75 MHz): δ 12.5 (C-7), 100.2 (C-3′), 110.4 (C-6), 128.5 (Ar–C), 129.4 (C-5), 130.2 (Ar–C), 132.8 (Ar–C), 136.3 (Ar–C), 143.2 (C-3), 152.4 (C-6′). Compound **4b**, mp 143–149 °C, IR cm^{-1}; 3300 (s), 1610, 975, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 7.29–7.50 (m, 4H, ArH), 7.81 (s, 1H, C_6–H), 7.93 (s, 1H, NH, D_2O exchangeable); MS (EI): *m*/*z* 212 (M^+). ^{13}C NMR (75 MHz): δ 11.3 (C-7), 21.1 (Ar–CH_3), 100.1 (C-3′), 112.6 (C-6); 127.3 (Ar–C), 128.5 (C-5), 130.0 (Ar–C), 133.1 (Ar–C), 137.8 (Ar–C), 145.5 (C-3), 156.0 (C-6′).
10. 3-Methyl-5-(3-phenyl-oxiranyl)-isoxazol-4-yl amine **2**. A mixture of 4-amino-3-methyl-5-styryl isoxazole (0.1 mol) and *m*-chloroperbenzoic acid (0.1 mol) in dichloromethane (20 ml) was stirred at room temperature for 6 h. The precipitated *m*-chlorobenzoic acid was filtered off and the filtrate washed with 10% aq $NaHCO_3$ solution. Dichloromethane was evaporated to give the crude product, which was purified by column chromatography by elution with benzene. **2** (Ar = Ph), mp 115–118 °C, IR cm^{-1}; 3350 (s), 1120 (s); ^{1}H NMR (300 MHz $CDCl_3$): δ 2.35 (s, 3H, CH_3), 3.82 (br s, 1H, NH), 5.10 (d, 1H, $J = 7$ Hz, –CH), 5.33 (d, 1H, $J = 7$ Hz, CH), 7.20–7.81 (m, 5H, ArH); MS (EI): *m*/*z* 216 (M^+).
11. *N*-(3,5-dimethyl-4-isoxazole) benzamide **6**. 3,5-Dimethyl-4-amino isoxazole (0.1 mol) was dissolved in 20 ml of dichloromethane, and benzoyl chloride (0.1 mol) was added dropwise with stirring and the reaction continued at room temperature for 1 h. The solid obtained on cooling was filtered and recrystallized from ethanol. **6** (Ar = Ph), mp 181–183 °C; IR cm^{-1}, 3525 (s), 1685 (s), ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.22 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 7.62–8.01 (m, 5H, ArH), 9.80 (br s, 1H, NH, D_2O exchangeable); MS (EI): *m*/*z* 216 (M^+).
12. 3-Methyl-5-phenyl-4*H*-pyrrolo[2,3-*d*]-isoxazole **4a**. To a magnetically stirred mixture of benzamide **6**, and anhydrous K_2CO_3 (6 equiv) and dry acetone (20 ml), triethylbenzyl-ammonium chloride (0.05 mol) was added and the reaction mixture was stirred at reflux for 48 h. After completion of the reaction, it was cooled and K_2CO_3 was removed by filtration. The organic layer was distilled under reduced pressure. The residue obtained was dissolved in ethyl acetate and washed with water, brine and dried over $MgSO_4$. The solvent was distilled under vacuum to give a crude product, which was purified by column chromatography by elution with ethyl acetate/hexane (1:10).