Preparation of Pyrazolo[5,1-*c*][1,4]benzoxazines by Intramolecular [3⁺ + 2] Cycloaddition Reaction of Hydrazonium Chlorides with Alkenes

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Pyrazolo[5,1-*c*][1,4]benzoxazines were prepared by the reaction of 2-(allyloxy)phenylhydrazine with arylaldehydes in the presence of hydrochloric acid. The formation of the fused heterocycles can be explained by intramolecular 1,3-dipolar cycloaddition reaction of cationic dipole, *i.e.*., hydrazonium chlorides.

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Introduction.

We reported the syntheses of several fused heterocycles by intramolecular [3⁺ + 2] 1,3-dipolar cycloaddition reactions of hydrazonium salts with dipolarophile, in which the dipolarophile was connected by an appropriate linkage to the carbon atom of the hydrazonium group (see Equation 1) [1]. We have now examined the possibility of the reaction for the substrates in which dipolarophile is connected by an appropriate linkage to the terminal nitrogen atom of hydrazonium group (see Equation 2). We will report here the results in detail.

(Eq. 1)

(Eq. 2)

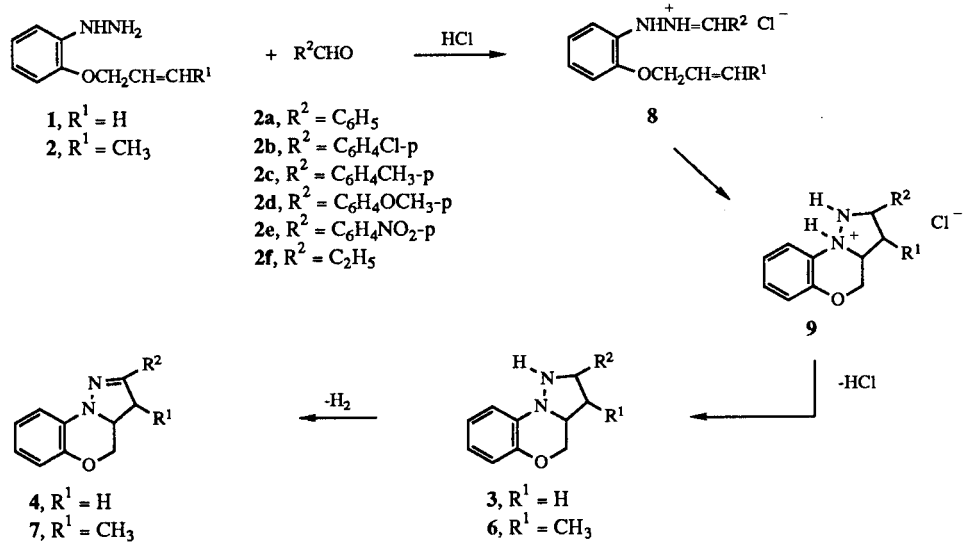
Results and Discussion.

An ethanol solution of an equimolar mixture of [2-(allyloxy)phenyl]hydrazine **1**, arylaldehyde **2a-e**, and concentrated hydrochloric acid was heated to reflux for 4 hours and, then, the mixture was treated with triethylamine to give 2-aryl-1,2,3,3a-tetrahydro-4*H*-pyrazolo[5,1-*c*][1,4]-benzoxazines **3a,b** and/or 2-aryl-3,3a-dihydro-4*H*-pyrazolo-[5,1-*c*][1,4]benzoxazines **4a-e** in yields shown in Table 1.

Table 1
Yields of the Cycloadducts **3**, **4**, and **7**

Substrates	Product (Yield, %)
1 + **2a**	**3a** (6%), **4a** (74%)
1 + **2b**	**3b** (6%), **4b** (72%)
1 + **2c**	**4c** (68%)
1 + **2d**	**4d** (73%)
1 + **2e**	**4e** (28%)
1 + **2f**	**4f** (11%)
5 + **2a**	**7a** (17%)
5 + **2b**	**7b** (10%)
5 + **2c**	**7c** (13%)
5 + **2d**	**7d** (18%)

Scheme 1



The structure of **4a** (aryl = C_6H_5) was established by the agreement of the physical properties with those of an authentic specimen [2]. The structure of **3a** (aryl = C_6H_5) was confirmed by the evidence that **3a** undergoes an oxidation easily to give **4a** in high yield by heating it in bromobenzene for several hours under atmosphere.

Similar reaction was also carried out using [2-(butenoxy)phenyl]hydrazine **5** as a substrate, and 3-methyl derivative of **4**, *i.e.* **7**, was obtained in poorer yields (see Table 1).

Formation of these cycloadducts, **3**, **4**, and **7**, can be explained by the following consecutive reactions (see Scheme 1); (i) the formation of hydrazonium chlorides **8** by the acid-catalyzed reaction of hydrazines, **1** and **5**, with arylaldehyde **2**, (ii) intramolecular [3^+ + 2] cycloaddition of the hydrazonium group to alkenyl group giving hydrochlorides of **3** and **6**, (iii) dehydrochlorination of the initial cycloadducts by triethylamine giving free bases, **3** and **6**, and (iv) dehydrogenation of **3** and **6** giving **4** and **7**, respectively. This final oxidation reaction of pyrazolidines to pyrazolines is well-known to occur under the conditions used here [3].

2-Ethyl-3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine **4f**, the 2-ethyl derivative of **4a**, was also prepared using propionaldehyde instead of arylaldehyde **2a-e** though the yield is poor.

The low yield of the cycloadduct **4f** may be ascribed to the inaccessibility of dipole-LUMO/dipolarphile-HOMO interaction by raising the LUMO energy level of the dipole that effected by substitution of aryl group with alkyl group. The steric hindrance between R^1 and R^2 groups produced in cycloaddition reaction may be presumed to be a factor for the poor yields of cycloadducts **7a-d**.

Several studies on the preparation of **4** (R^2 = C_6H_5 [2] or COOEt [4]) by intramolecular 1,3-dipolar cycloaddition reactions have been reported so far, and somewhat troublesome methods for preparation of dipole, nitrilimines, had been used. Our method described here consists of the use of the dipole that can be prepared easily.

EXPERIMENTAL

All melting and boiling points are uncorrected. The ^{1}H nmr spectra were measured on a Varian T-60A instrument using tetramethylsilane as an internal standard: chemical shifts are given in δ units and coupling constants (J) are in herz: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were measured on a Hitachi M-80 mass spectrometer.

Preparation of [2-(Alkenyloxy)phenyl]hydrazine (1) and [2-(2-Butenoxy)phenyl]hydrazine (5).

These compounds were prepared from 2-nitrophenol by the following series of reactions: *O*-alkenylation of 2-nitrophenol, reduction of nitro group to amino group, diazotization of the amino group, and the following reduction of the diazonium salts giving hydrazines. These reaction were carried out in a similar manner as described in literatures [4,5]. Yields, boiling and melting points, nmr and mass spectral data, and analytical data of newly prepared compounds are shown below.

2-Butenyl 2-Nitrophenyl Ether.

This compound was obtained as yellow oil in 100% yield, bp 120° (0.4 mm Hg); ^{1}H nmr (deuteriochloroform): δ 1.75 (d, 3 H, J = 5 Hz), 4.5-4.8 (m, 2 H), 5.37-6.30 (m, 2 H), 6.8-8.0 (m, 4 H).

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.10; H, 5.66; N, 7.20.

2-(2-Butenoxy)aniline.

This compound was obtained as yellow oil in 70% yield, bp 132° (7 mm Hg); ^{1}H nmr (deuteriochloroform): δ 1.75 (d, 3 H, J = 5 Hz), 3.77 (br, 2 H), 4.37-4.60 (m, 2 H), 5.4-6.2 (m, 2 H), 6.74 (s, 4 H).

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.62; H, 8.01; N, 8.64.

[2-(Allyloxy)phenyl]hydrazine (1).

This compound was obtained as reddish crystals (petroleum ether) in 58% yield, mp 48-50°; ^{1}H nmr (deuteriochloroform): δ 3.55 (br, 3 H), 4.4-4.6 (m, 2 H), 5.10-5.55 (m, 2 H), 5.70-6.45 (m, 1 H), 6.65-7.05 (m, 4 H) ppm.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 66.02; H, 7.45; N, 17.11.

[2-(2-Butenoxy)phenyl]hydrazine (5).

This compound was obtained as reddish crystals (petroleum ether) in 64% yield, mp 27-29°; ^{1}H nmr (deuteriochloroform): δ 1.70 (d, 3 H, J = 5 Hz), 3.8 (br, 3 H), 4.3-4.6 (m, 2 H), 5.37-6.20 (m, 2 H), 6.63-7.03 (m, 4 H) ppm.

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.35; H, 7.92; N, 15.71.

Reaction of [2-(Alkenyloxy)phenyl]hydrazines 1 and 5 with Aldehydes 2a-f in the Presence of Concentrated Hydrochloric Acid.

General Procedure.

An equimolar mixture (6.1 mmoles) of **1** or **5**, aldehyde **2a-f**, and concentrated hydrochloric acid (0.64 g) in ethanol (50 ml) was heated to reflux for 4 hours with stirring. Triethylamine (1.0 ml) was added to the reaction mixture and further refluxed it for 1 hour with stirring. After evaporation of the solvent by rotary evaporator, the residue was dissolved in chloroform and washed with water several times. The chloroform layer was dried over anhydrous sodium sulfate and evaporated to give oily residue. The oily residue was chromatographed on silica gel with chloroform to give 2-substituted 1,2,3,3a-tetrahydro-4*H*-pyrazolo[5,1-*c*][1,4]-benzoxazines **3** and/or the dehydrogenated compounds **4** and **7** in yields shown in Table 1. The melting points, ^{1}H nmr (in deuteriochloroform) and mass spectral data of these cycloadducts are shown below.

2-Phenyl-3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (4a).

This compound was obtained as colorless crystals (ethanol), mp 151-152°; ^{1}H nmr: δ 2.87 (dd, 1 H, J = 5.0, 17.5 Hz), 3.37 (t, 1 H, J = 12 Hz), 3.37 (dd, 1 H, J = 10.0, 17.5 Hz), 3.90-4.45 (m, 2 H), 6.8-7.8 (m, 9 H) ppm; ms: (m/e) 250.1098 (M^+) [Calcd: 250.1103].

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.58; H, 5.78; N, 10.96.

2-(4-Chlorophenyl)-3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (**4b**).

This compound was obtained as pale yellow oil; ^{1}H nmr: δ 2.87 (dd, 1 H, J = 5.5, 17.5 Hz), 3.42 (t, 1 H, J = 11.5 Hz), 3.40 (dd, 1 H, J = 10.0, 17.5 Hz), 4.17 (dd, 1 H, J = 3.0, 11.5 Hz), 3.85-4.47 (m, 1 H), 6.8-7.8 (m, 8 H) ppm; ms: (m/e) Calcd. for $C_{16}H_{13}N_2OCl$ (M^+): 284.0715. Found: 250.1098.

2-(*p*-Tolyl)-3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (**4c**).

This compound was obtained as colorless crystals (ethanol), mp 121-123°; ^{1}H nmr: δ 2.35 (s, 3 H), 2.86 (dd, 1 H, J = 5, 18 Hz), 3.37 (t, 1 H, J = 11.5 Hz), 3.37 (dd, 1 H, J = 10, 18 Hz), 4.12 (dd, 1 H, J = 3.0, 11.5 Hz), 3.83-4.47 (m, 1 H), 6.8-7.8 (m, 8 H) ppm; ms: (m/e) Calcd. for $C_{17}H_{16}N_2O$ (M^+): 264.1259. Found: 264.1260.

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.28; H, 6.04; N, 10.67.

2-(4-Methoxyphenyl)-3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (**4d**).

This compound was obtained as colorless crystals (ethanol), mp 130-132°; ^{1}H nmr: δ 2.85 (dd, 1 H, J = 5.0, 17.5 Hz), 3.35 (t, 1 H, J = 11.5 Hz), 3.35 (dd, 1 H, J = 10.5, 17.5 Hz), 3.78 (s, 3 H), 4.12 (dd, 1 H, J = 3.0, 11.5 Hz), 3.9-4.45 (m, 1 H), 6.7-7.2 (m, 5 H), 7.5-7.8 (m, 3 H) ppm; ms: (m/e) Calcd. for $C_{17}H_{16}N_2O_2$ (M^+): 280.1210. Found: 280.1202.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.88; H, 5.65; N, 10.03.

2-(4-Nitrophenyl)-3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (**4e**).

This compound was obtained as yellowish crystals (ethanol), mp 162-163°; ^{1}H nmr: δ 2.95 (dd, 1 H, J = 6, 18 Hz), 3.45 (dd, 1 H, J = 11, 18 Hz), 3.51 (t, 1 H, J = 11.5 Hz), 4.03-4.67 (m, 2 H), 6.85-7.30 (m, 3 H), 7.4-7.8 (m, 1 H), 7.80 (d, 2 H, J = 9 Hz), 8.27 (d, 2 H, J = 9 Hz) ppm; ms: (m/e) Calcd. for $C_{16}H_{13}N_3O_3$: (M^+): 295.0955. Found: 295.0953.

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 64.99; H, 4.42; N, 14.25.

2-Ethyl-3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (**4f**).

This compound was obtained as colorless crystals (ethanol), mp 82-84°; ^{1}H nmr: δ 1.15 (t, 3 H, J = 7 Hz), 2.0-3.1 (m, 4 H), 3.3 (t, 1 H, J = 11.5 Hz), 4.02 (dd, 1 H, J = 3, 11 Hz), 3.7-4.2 (m, 1 H), 6.8-7.6 (m, 4 H) ppm; ms: (m/e) Calcd. for $C_{12}H_{14}N_2O$ (M^+): 202.1105. Found: 202.1105.

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.18; H, 7.05; N, 13.96.

3-Methyl-2-phenyl-3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (**7a**).

This compound was obtained as pale yellow oil; ^{1}H nmr: δ 1.35 (d, 3 H, J = 7 Hz), 3.07-3.90 (m, 3 H), 4.10 (dd, 1 H, J = 2, 9 Hz), 6.75-7.83 (m, 9 H) ppm; ms: (m/e) Calcd. for $C_{17}H_{16}N_2O$ (M^+): 264.1259. Found: 264.1258.

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.33; H, 6.05; N, 10.49.

2-(4-Chlorophenyl)-3-methyl-3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]-benzoxazine (**7b**).

This compound was obtained as colorless crystals (ethanol), mp 109-111°; ^{1}H nmr: δ 1.37 (d, 3 H, J = 7 Hz), 3.07-3.97 (m, 3 H), 4.15 (dd, 1 H, J = 2.5, 9.5 Hz), 6.85-7.85 (m, 8 H) ppm; ms: (m/e) Calcd. for $C_{17}H_{15}N_2OCl$ (M^+): 298.0871. Found: 298.0866.

Anal. Calcd. for $C_{17}H_{15}N_2OCl$: C, 68.34; H, 5.06; N, 9.38. Found: C, 68.20; H, 4.98; N, 9.55.

3-Methyl-2-(*p*-tolyl)-3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (**7c**).

This compound was obtained as colorless crystals (ethanol), mp 122-124°; ^{1}H nmr: δ 1.37 (d, 3 H, J = 7 Hz), 2.35 (s, 3 H), 3.10-3.93 (m, 3 H), 4.12 (dd, 1 H, J = 2.5, 8.5 Hz), 6.85-7.80 (m, 8 H) ppm; ms: (m/e) Calcd. for $C_{18}H_{18}N_2O$ (M^+): 278.1417. Found: 278.1416.

Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.07. Found: C, 77.55; H, 6.63; N, 10.01.

2-(4-Methoxyphenyl)-3-methyl-3,3-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]-benzoxazine (**7d**).

This compound was obtained as yellow crystals (ethanol), mp 146-148°; ^{1}H nmr: δ 1.37 (d, 3 H, J = 7 Hz), 3.08-3.97 (m, 3 H), 3.82 (s, 3 H), 4.08 (dd, 1 H, J = 2.5, 9.0 Hz), 6.75-7.20 (m, 5 H), 7.35-7.93 (m, 3 H) ppm; ms: (m/e) Calcd. for $C_{18}H_{18}N_2O_2$ (M^+): 294.1368. Found: 294.1370.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.44; H, 6.19; N, 9.70.

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