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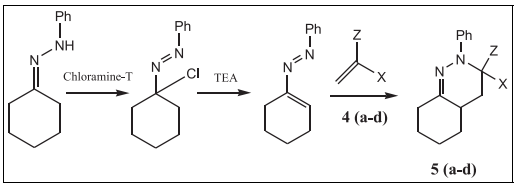

Cyclic ketohydrazones containing α-methylene group are oxidized by chloramine-T followed by treatment with triethylamine leads to the formation of azoalkenes via azochloride, which are trapped by olefinic compounds to produce fused ring pyridazine derivatives in good yield.

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INTRODUCTION

In our previous report [1], we described the generation of azoalkenes from ketohydrazones containing α-methylene group and their application to the synthesis of pyridazine derivatives. Azoalkenes proved to be of great value and importance due to their synthetic applications as building blocks or key intermediates in organic synthesis [2,3]. Azoalkenes are usually very reactive species and normally observed only in solution [2]. The synthetic applications of azoalkenes have been reviewed recently [4–6]. Azoalkenes act as 4π-elecron component in [4 + 2] cycloaddition reaction. In continuation to our work herein, we report the generation of azoalkenes from cyclic ketohydrazones containing α-methylene group and its application to the synthesis of fused ring pyridazine derivatives, which are of great practical value in clinical use as therapeutic agents [7–10].

In our laboratory, we have used chloramine-T for the generation of α-nitroso olefins [11], azoalkenes [1], nitrile oxides [12], nitrile imines [13] etc., which are the intermediates for the synthesis of biologically active six-membered and five-membered heterocycles. During the course of these studies, we have observed that treatment of cyclohexanone oxime with chloramine-T produced a blue color suggestive of formation of 1-chloro-1-nitroso cyclohexane. This prompted us to treat the corresponding hydrazones of cyclic ketones bearing reactive methylene groups with chloramine-T aiming to get azochloride similar to that of nitrosochloride. Interestingly, we are able to isolate azochlorides. With this success, we now report the use of chloramine-T as a new efficient reagent for the conversion of cyclic ketohydrazones bearing reactive methylene group into azochloride, which are suitable for *in situ* generation of azoalkenes during [4 + 2] cycloaddition to olefins. Typically, the cycloaddition is carried out by refluxing an equimolecular mixture of a ketohydrazone, chloramine-T trihydrate in ethanol followed by addition of triethylamine at RT and an alkene in ethanol at reflux temperature. In general, pyridazine derivatives are thus obtained in good yield (Scheme 1).

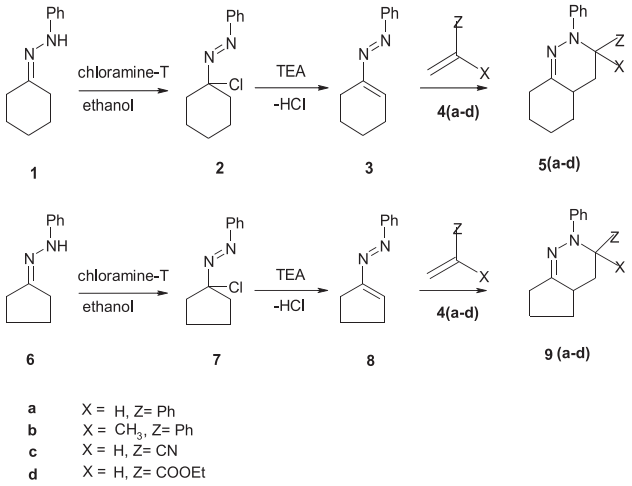
RESULTS AND DISCUSSION

The reaction with chloramine-T proceeds with cyclic ketohydrazones bearing α-hydrogen followed by cycloaddition with styrene, α-methyl-styrene, acrylonitrile, and ethyl acrylate.

^{1}H-NMR, ^{13}C-NMR, MS studies, and elemental analysis provided the structure proof of the pyridazine derivatives. As expected, the cycloaddition was regioselective. ^{1}H-NMR spectra of **5** (when X═H) showed the signals due to –CH (C_3-carbon) as a doublet of doublet in the region δ 3.6–4.4 ppm and –CH2 (C_4-carbon) as a triplet in the region δ 1.70–1.90 ppm, while **5** (when X = CH_3) shows no signal in the said region, a new signal at δ 1.69 indicates the presence of methyl group and –CH2 (C_4-carbon) appears as doublet in the region δ 1.70–1.90 ppm.

In ^{13}C-NMR spectra, all pyridazines gave consistent signals for the newly formed ring carbons. For example, in **5** (when X═H), the signals due to –CH (C_3-carbon) appears in the region δ 54−67 ppm, while **5** (when X═CH_3) appears in the region δ 62−69 ppm and a new signal in the region δ 23−26 ppm due to methyl group. In **5c**, the signal at δ 119 ppm indicates the presence of CN group. The relatively stable molecular ion peaks were observed in mass spectra, which support the structure of the products. The formation of the products was further supported by correct elemental analyses. Azoalkenes are potentially very versatile components in cycloadditions and represent a useful starting point for exploring the preparation of new heterocyclic systems.

Scheme 1



EXPERIMENTAL

^{1}H-NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer (MIT, India) using $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C-NMR spectra were measured on Bruker Avance (100 MHz) instrument. The chemical shifts are expressed in δ and following abbreviations were used. s = singlet, d = doublet, t = triplet, and m = multiplet. Mass spectra were obtained on a Finnigan 4021 mass spectrometer at an ionizing energy of 35 eV. Elemental analyses were obtained on a Vario-EL instrument. TLC was done with pre-coated silica gel G plates using chloroform-acetone (9:1) as eluent.

Typical procedure for the preparation of 2,3-diphenyl-2,3-,4,4a,5,6,7,8-octahydrocinnoline (5a). A mixture of **1** (1.0 g, 5.3 mmol) and chloramine-T trihydrate (1.52 g, 5.40 mmol) in ethanol (10 mL) were refluxed for 2 h. The mixture was cooled to room temperature, triethylamine (2 mL) was added and stirred at room temperature for 30 min. A solution of **4a** (0.56 g, 5.38 mmol) in ethanol (5 mL) was then added and the mixture was refluxed for 3 h. It was then concentrated under reduced pressure, and the residue was extracted with CH_2Cl_2 (25 mL). This extract was then washed with water (15 mL), with 1N aq. NaOH (2 × 15 mL) and dried (Na_2SO_4). The solvent was evaporated, and the remaining residue was purified by column chromatography (chloroform/ethyl acetate, 7:3) to give **5a** as yellow oil to yield 1.06 g (69%); ^{1}H-NMR $CDCl_3$: δ 1.26–1.36 (m, 8H, CH_2), 1.61–163 (m, 1H, CH_2), 1.92 (t, 2H, CH_2), 3.95 (dd, 1H, J = 9.8 and 2.9 Hz, CH), 6.6–6.7 (m, 3H, ArH), 7.10–7.25 (m, 7H, ArH); ^{13}C-NMR $CDCl_3$: δ 27.1, 29.7, 30.8, 31.2, 31.9, 38.4, 66.3, 113.3, 118.2, 126.2, 128.6, 129.2, 130.8, 139.0, 144.4, 158.3; MS (relative abundance) *m/z*: 290 (M^+, 15%), 213, 195, 104, 95, 91, 77 (100%). Anal. Calcd for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64; N, 9.65%. Found: C, 82.77; H, 7.70; N, 9.53%.

3-Methyl-2,3-diphenyl-2,3,4,4a,5,6,7,8-octahydrocinnoline (5b). This compound was obtained from **1** (1.0 g, 5.3 mmol), **4b** (0.64 g, 5.42 mmol), chloramine-T trihydrate (1.52 g, 5.40 mmol), and triethylamine as a pale yellow oil to yield 1.14 g (71%); ^{1}H-NMR $CDCl_3$: δ 1.29–1.41 (m, 8H, CH_2), 1.59–164 (m, 1H, CH_2), 1.71 (s, 3H, CH_3), 1.92 (d, 2H, CH_2), 6.65–6.74 (m, 3H, ArH), 7.10–7.25 (m, 7H, ArH); ^{13}C-NMR $CDCl_3$: δ 23.8, 27.5, 28.2, 30.7, 31.1, 32.0, 41.2, 67.5, 112.7, 117.6, 126.1, 128.6, 128.9, 130.6, 139.0, 144.6, 158.6; MS (relative abundance) *m/z*: 304 (M^+, 12%), 227, 209, 118, 95, 91, 77 (100%). Anal. Calcd for $C_{21}H_{24}N_2$: C, 82.85; H, 7.95; N, 9.20%. Found: C, 82.80; H, 8.04; N, 9.16%.

2-Phenyl-2,3,4,4a,5,6,7,8-octahydrocinnoline-3-carbonitrile (5c). This compound was obtained from **1**(1.0 g, 5.3 mmol), **4c** (0.30 g, 5.66 mmol), chloramine-T trihydrate (1.52 g, 5.40 mmol) and triethylamine as a pale yellow oil to yield 0.91 g (72%); ^{1}H-NMR $CDCl_3$: δ 1.30–1.40 (m, 8H, CH_2), 1.60–164 (m, 1H, CH_2), 1.92 (t, 2H, CH_2), 4.22 (dd, 1H, J = 9.8 and 2.9 Hz, CH), 6.63–6.75 (m, 3H, ArH), 7.10 (t, 2H, ArH); ^{13}C-NMR $CDCl_3$: δ 27.4, 28.9, 30.6, 30.9, 31.3, 33.4, 56.5, 113.0, 116.5, 119.9, 143.4, 157.2; MS (relative abundance) *m/z*: 239 (M^+ 20%), 212, 144, 95 (100%), 91, 77, 53. Anal. Calcd for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56%. Found: C, 75.35; H, 7.14; N, 17.51%.

2-Phenyl-2,3,4,4a,5,6,7,8-octahydrocinnoline-3-carboxylic acid ethyl ester (5d). This compound was obtained from **1** (1.0 g, 5.3 mmol), **4d** (0.54 g, 5.40 mmol), chloramine-T trihydrate (1.52 g, 5.40 mmol), and triethylamine as a pale yellow oil to yield 1.08 g (71%); ^{1}H-NMR $CDCl_3$: δ 1.28 (t, 3H, CH_3), 1.33–1.44 (m, 8H, CH_2), 1.58–162 (m, 1H, CH_2), 1.93 (t, 2H, CH_2), 4.21 (dd, 1H, J = 9.7 and 2.8 Hz, CH), 4.65 (q, 2H, CH_2), 6.68–6.76 (m, 3H, ArH), 7.09 (t, 2H, ArH); ^{13}C-NMR $CDCl_3$: δ 12.9, 27.4, 29.7, 30.5, 31.0, 31.3, 61.2, 68.3, 113.3, 116.4, 130.2, 144.4, 157.2, 176.3; MS (relative abundance) *m/z*: 286 (M^+), 241 (100%), 213, 191, 146, 95, 91, 77. Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78%. Found: C, 71.37; H, 7.70; N, 9.70%.

2,3-Diphenyl-3,4,4a,5,6,7-hexahydro-2H-cyclopenta[c] pyridazine (9a). This compound was obtained from **6** (1.0 g, 5.74 mmol), **4a** (0.60 g, 5.76 mmol), chloramine-T trihydrate (1.64 g, 5.83 mmol), and triethylamine as a pale yellow oil to yield 1.10 g (70%); ^{1}H-NMR $CDCl_3$: δ 1.30–1.40 (m, 6H, CH_2), 1.60–164 (m, 1H, CH_2), 1.92 (t, 2H, CH_2), 4.12 (dd, 1H, J = 9.8 and 2.9 Hz, CH), 6.60–6.72 (m, 3H, ArH), 7.02 (t, 2H, ArH), 7.15–7.25 (m, 5H, ArH); ^{13}C-NMR $CDCl_3$: δ 27.0, 32.9, 33.7, 36.9, 37.2, 66.5, 113.6, 117.0, 125.2, 128.6, 128.9, 130.7, 140.8, 144.4, 157.1; MS (relative abundance) *m/z*: 276 (M^+, 14%), 199, 195, 91, 81, 77 (100%). Anal. Calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14%. Found: C, 82.62; H, 7.20; N, 10.18%.

3-Methyl-2,3-Diphenyl-3,4,4a,5,6,7-hexahydro-2H-cyclopenta [c]pyridazine (9b). This compound was obtained from **6** (1.0 g, 5.74 mmol), **4b** (0.69 g, 5.84 mmol), chloramine-T trihydrate (1.64 g, 5.83 mmol), and triethylamine as a pale yellow oil to yield 1.21 g (73%); ^{1}H-NMR $CDCl_3$: δ 1.32–1.41 (m, 6H, CH_2), 1.58 (s, 3H, CH_3), 1.62–166 (m, 1H, CH_2), 1.92 (d, 2H, CH_2), 6.65–6.75 (m, 3H, ArH), 7.05 (t, 2H, ArH), 7.10–7.20 (m, 5H, ArH),; ^{13}C-NMR $CDCl_3$: δ 24.8, 27.3, 33.7, 34.6, 35.3, 39.9, 65.5, 113.3, 117.4, 125.9, 128.7, 128.9, 130.7, 140.5, 144.8, 157.4; MS (relative abundance) *m/z*: 290 (M^+, 14%), 213, 209, 118, 91, 81, 77 (100%). Anal. Calcd for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64; N, 9.65%. Found: C, 82.79; H, 7.60; N, 9.61%.

2-Phenyl-3,4,4a,5,6,7-hexahydro-2H-cyclopenta[c]pyridazine-3-carbonitrile (9c). This compound was obtained from **6** (1.0 g, 5.74 mmol), **4c** (0.32 g, 6.0 mmol), chloramine-T trihydrate (1.64 g, 5.83 mmol), and triethylamine as a pale yellow oil to yield 0.93 g (72%); ^{1}H-NMR $CDCl_3$: δ 1.34–1.43 (m, 6H, CH_2), 1.60–164 (m, 1H, CH_2), 1.94 (t, 2H, CH_2), 4.59 (dd, 1H, J = 9.9 and 2.9 Hz, CH), 6.72–6.83 (m, 3H, ArH), 7.12 (t, 2H, ArH); ^{13}C-NMR $CDCl_3$: δ 27.8, 30.1, 32.6, 33.4, 36.6, 55.5, 113.1, 116.8, 119.3, 144.2, 157.5; MS (relative abundance) *m/z*: 225 (M^+,10%), 224, 198, 144, 91, 81 (100%), 77. Anal. Calcd for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65%. Found: C, 74.70; H, 6.70; N, 18.60%.

2-Phenyl-3,4,4a,5,6,7-hexahydro-2H-cyclopenta[c]pyridazine-3-carboxylic acid ethyl ester (9d). This compound was obtained

from **6** (1.0 g, 5.74 mmol), **4d** (0.58 g, 5.80 mmol), chloramine-T trihydrate (1.64 g, (5.83 mmol), and triethylamine as a pale yellow oil to yield 1.25 g (72%); ^{1}H-NMR $CDCl_3$: δ 1.25 (t, 3H, CH_3), 1.35–1.44 (m, 6H, CH_2), 1.55–168 (m, 1H, CH_2), 1.90 (t, 2H, CH_2), 4.24 (dd, 1H, J = 9.9 and 2.9 Hz, CH), 4.69 (q, 2H, CH_2), 6.70–6.79 (m, 3H, ArH), 7.10 (t, 2H, ArH); ^{13}C-NMR $CDCl_3$: δ 13.2, 27.3, 30.6, 33.6, 33.9, 35.5, 61.1, 68.9, 113.0, 116.6, 130.3, 144.8, 158.2, 176.8; MS (relative abundance) *m/z*: 272 (M^+,10%), 227, 199, 191, 146, 91, 81 (100%), 77. Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29%. Found: C, 70.64; H, 7.36; N, 10.25%.

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