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A new method for the generation of azoalkenes from ketohydrazones and its application to the synthesis of tetrahydropyridazine derivatives

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Abstract—The reaction of ketohydrazones containing an α-methylene group with chloramine-T followed by treatment with triethylamine leads to the formation of azoalkenes via an α-chloroazo-compound, which can react intermolecularly and in situ with olefinic compounds to produce tetrahydropyridazine derivatives in good yield.

Cycloaddition reactions in which an azo group participates as the 2π-electron component have been known for several years.[1] Azoalkenes can also act as the 4π-electron component in [4+2]cycloaddition reactions. [4+2]Cycloaddition reactions of azoalkenes with olefinic compounds are of synthetic interest since tetrahydropyridazine derivatives formed are important in the synthesis of an antihypertensive agent,[2] vasodilators,[3] glycosidase inhibitors,[4] etc. The generation of azoalkenes can be difficult. They are unstable and normally are only observed in solution, their presence sometimes being detectable by blue coloration.[5] The usual method of generating azoalkenes is via elimination of a hydrogen halide from the hydrazones of α-monohaloketones.[6] However, azoalkenes are highly reactive and unstable, hence they are usually only generated in situ. The yield of the cycloaddition products is often low and side reactions can predominate, hence an improved procedure for the generation of azoalkenes is of interest.

We have used chloramine-T extensively for the preparation of biologically active heterocycles via [3+2]cycloaddition reactions of 1,3-dipolar species such as nitrile oxides and nitrile imines with olefinic compounds. We have successfully isolated the reactive intermediate nitrile oxides during the oxidation of aldoximes with chloramine-T. During the course of these studies, it was observed that treatment of cyclohexanone oxime with chloramine-T produced a blue colour suggestive of the formation of 1-chloro-1-nitroso cyclohexane.[7] This observation prompted us to treat the hydrazones of several ketones bearing reactive methylene groups with chloramine-T to generate the corresponding α-chloroazo-compound. Interestingly, we were able to isolate the α-chloroazo-compounds. We now report the use of chloramine-T as a new and efficient reagent for the conversion of ketohydrazones bearing a reactive methylene group into α-chloroazo-compounds, which are suitable for the in situ generation of azoalkenes for [4+2]cycloadditions to olefins. Typically, the cycloaddition is carried out by refluxing an equimolecular mixture of the ketohydrazone and chloramine-T trihydrate in ethanol followed by the addition of triethylamine and the alkene in ethanol at rt. In general, tetrahydropyridazine derivatives were obtained in good yields (Scheme 1).

The reaction with chloramine-T proceeds with aromatic as well as aliphatic ketohydrazones bearing an α-hydrogen [e.g., **1a**–**e**] followed by the cycloaddition with styrene, acrylonitrile and 1-methyl styrene.

^{1}H NMR, ^{13}C NMR, MS studies and elemental analyses confirmed the structures of the pyridazine derivatives. As expected, the cycloadditions were regioselective. ^{1}H NMR indicated the presence of a single isomer in all cases. All the ^{1}H NMR spectra of the cycloadducts **5**,

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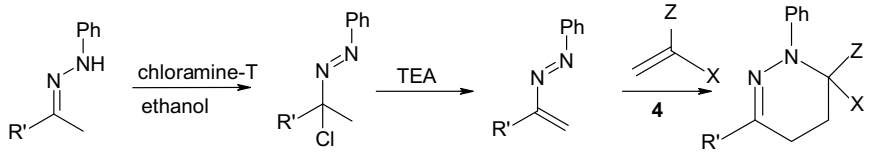

1 2 3 5

1	R'	4	X	Z
a	Ph	a	H	Ph
b	*p*-ClC_6H_4-	b	H	CN
c	*p*-$NO_2C_6H_4$-	c	Me	Ph
d	Ethyl			
e	Furyl			

Scheme 1.

when X = H, showed signals due to H-6 as a doublet of doublets in the region δ 3.5–4.5 while in cycloadduct **5c** (X = CH_3) there was no signal in this region and the H-4 protons appeared as a triplet in the region δ 1.2–1.7. The H-5 protons appeared as multiplets in the region δ 1.7–2.3.

In the ^{13}C NMR spectra, all the pyridazines gave consistent signals for the newly formed ring carbons. For example, the signals due to C-6 appeared in cycloadduct **5** (when X = H) as a doublet in the region δ 65–75 while in cycloadduct **5c** (X = CH_3), C-6 appeared as a singlet in the region δ 65–75; C-5 and C-4 appeared as triplets in the region δ 25–35 and δ 20–30, respectively. The formation of the product was further supported by mass spectra and correct elemental analyses.

Typical procedure: 1,3,6-Triphenyl-1,4,5,6-tetrahydropyridazine (**5a**): A mixture of acetophenone phenylhydrazone (**1a**, 0.50 g, 2.38 mmol) and chloramine-T trihydrate (0.68 g, 2.41 mmol) in ethanol (20 mL) was refluxed for 2 h. The mixture was cooled to rt, triethylamine (1 mL) was added and the mixture was stirred for 15 min. A solution of styrene (**4a**, 0.25 g, 2.40 mmol) in ethanol (5 mL) was then added and the mixture was stirred at rt for 2 h. It was then concentrated under reduced pressure and the residue was extracted with diethyl ether (25 mL). The extract was washed with water (15 mL) and 1 N aq NaOH (2×5 mL), then dried (Na_2SO_4). The solvent was evaporated and the remaining yellow oil was stirred in *n*-hexane. The resulting solid was filtered and recrystallized from ethanol:*n*-hexane (1:1) to gave **5a** as a pale yellow crystalline solid (0.55 g, 74%), mp 116–118 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.26–1.29 (t, 2H, J = 6.9 Hz, CH_2), 1.74–1.77 (m, 2H, CH_2), 3.81–3.87 (dd, 1H, J = 9.2, 2.1 Hz, CH), 6.60–6.68 (m, 3H, ArH), 7.10–7.19 (m, 7H, ArH), 7.35–7.45 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1 (t), 29.4 (t), 71.10 (d), 110.6 (d), 118.9 (d), 124.2 (d), 128.1 (d), 128.8 (d), 129.2 (d), 129.5 (d), 131.1 (d), 132.3 (s), 138.0 (s), 143.5 (s) 156.1 (s). MS *m/z*: 313 (MH^+), 312 (M^+), 208, 181, 104, 103, 102, 77 (100%). Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58, H, 6.45, N, 8.97. Found: C, 84.62, H, 6.44, N, 8.94. The same procedure was used in all cases (Table 1).

Table 1.

Entry	Keto-hydrazone + alkene	Product	Mp/bp (°C)	Yield (%)
1	**1a+4a**	**5a**	116–118	74
2	**1a+4b**	**5b**	96–98	78
3	**1a+4c**	**5c**	109–111	65
4	**1b+4a**	**5d**	Thick oil	70
5	**1b+4b**	**5e**	Thick oil	80
6	**1b+4c**	**5f**	Thick oil	62
7	**1c+4a**	**5g**	142–143	72
8	**1c+4b**	**5h**	Thick oil	75
9	**1c+4c**	**5i**	134–136	68
10	**1d+4a**	**5j**	Thick oil	69
11	**1d+4b**	**5k**	Thick oil	76
12	**1d+4c**	**5l**	Thick oil	65
13	**1e+4a**	**5m**	122–124	70
14	**1e+4b**	**5n**	Thick oil	74
15	**1e+4c**	**5o**	105–106	65

In summary, we have demonstrated that tetrahydropyridazines can be synthesized by the reaction of ketohydrazones bearing an α-methylene group with alkenes in the presence of chloramine-T and triethylamine in typically 62–80% yields.

References and notes

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