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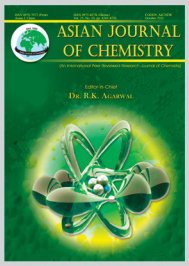

Cyclization of the Semicarbazones to 1,3,4-Oxadiazole Derivatives Using Ceric Ammonium Nitrate as Oxidant

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Cyclization of the semicarbazones to 1,3,4-oxadiazole using ceric ammonium nitrate as oxidant was studied. 2-Imino-1,3,4-oxadiazolines can be produced from semicarbazones, which undergo thermolysis to amides. Benzoic acid benzylidene hydrazide can also be cyclized to 2-methoxy-2-phenyl-1,3,4-oxadiazole in the presence of ceric ammonium nitrate and methanol.

Key Words: 1,3,4-Oxadiazoles, Ceric ammonium nitrate, Semicarbazones, 2-Methoxy-2-phenyl-1,3,4-oxadiazole.

INTRODUCTION

1,3,4-Oxadiazoles have attracted significant interest due to their applications in medicinal and pesticide chemistry[1,2] in polymer and material science[3]. They are stable compound, which can be synthesized from cyclization of acylhydrazones with BF_3-OEt_2,[4] triflic acid[5], silica sulfuric acid[6], alum[7], trichloroisocyanuric acid[8]. One-pot synthesis of these compounds has been reported using hydrazine and carboxylic acids[9], acylation of tetrazoles[10] and the condensation of acyl hydrazides in the presence of ceric ammonium nitrate[11]. 2-Imino-1,3,4-oxadiazolines were prepared from oxidative cyclization of 4-substituted semicarbazone by $Pb(OAc)_4$[12], MnO_2[13], $PhI(OAc)_2$[14] as oxidative agent.

In this paper, the oxidation of semicarbazones and benzoylhydrazones to 2-imino-1,3,4-oxadiazolines and 2-methoxy-2-phenyl-1,3,4-oxadiazoles is reported using ceric ammonium nitrate, which is an inexpensive and easily available oxidant.

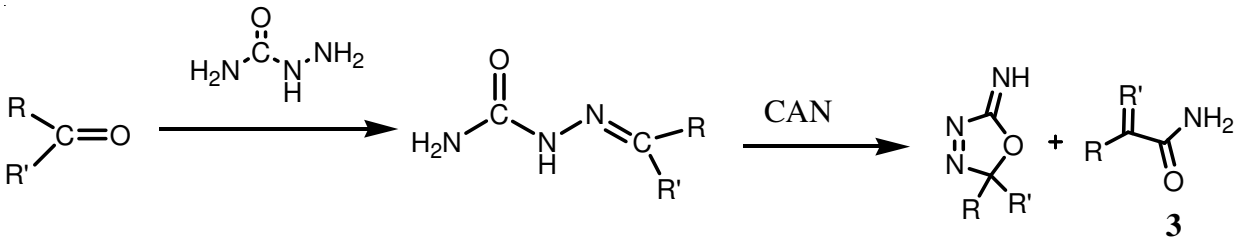
EXPERIMENTAL

General method for the synthesis of 2a-2e: Semicarbazide hydrochloride (1 g, 9 mmol) and sodium acetate (1.5 g, 18 mmol) was dissolved in water (10 mL) in a round bottom flask, followed by adding aldehyde or ketone (1 g). When there was cloudy solution ethanol was added to get a clear solution. The mixture was stirred for 0.5 h, filtered and dried in vacuum to get the pure product.

Cyclization of semicarbazones of 2a-2e: Semicarbazones (0.75 mmol) and ceric ammonium nitrate (1 mmol) placed in a mortar and ground by hand with the pestle for 20 min at room temperature. The mixture was shaked with water (5 mL) and dichloromethane (5 mL). The aqueous phase was separated from the organic phase and washed with dichloromethane (3 × 4 mL). The combined organic phase was dried over Na_2SO_4, filtered and evaporated in vacuum to get the crude product which was purified by flash column chromatography using ethyl acetate/petroleum ether (1:4) as eluent.

Synthesis of benzoic acid benzylidene-hydrazide (4): Benzhydrazide (0.24 mol) and benzaldehyde (0.24 mol) were dissolved in ethanol (60 mL) and stirred for 0.5 h. The precipitate was filtered off and shacked by petroleum ether (10 mL) and filtered. The solvent was evaporated in vacuum to yield the pure product (90 %), FT-IR: 1600 (C=N), 1649 (C=O) and 3220 cm^{-1} (N-H); ^1H NMR ($CDCl_3$) 7.3-7.9 (m, 10H, Ar), 8.44 (s 1H, HC=N), 11.3 (s, 1H, NH; Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49 Found: C,73.19; H, 5.24; N, 11.69.

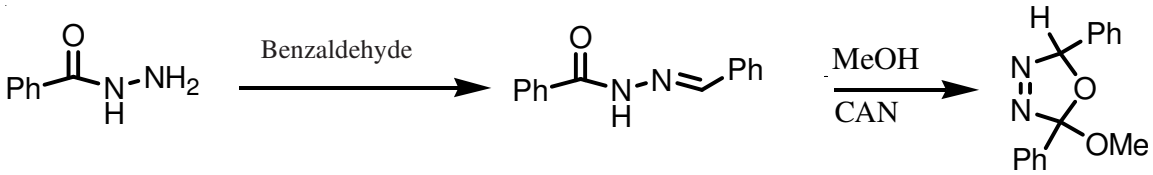
Synthesis of 2-methoxy-2,5-diphenyl-2,5-dihydro-[1,3,4]oxadiazole (5): A solution of ceric ammonium nitrate (9.04 g, 16.5 mmol) in methanol (65 mL) was cooled to -10 ºC, the hydrazone (**4**) (15 mmol) was added and the mixture was stirred for 1 h. Potassium hydroxide (0.22 g, 16 mmol) in methanol (10 mL) was added at -10 ºC and the mixture was stirred over night at room temperature. The solvent was evaporated off, water (8 mL) was added and extracted by dicholomethane (3 × 5 mL) and finally dried over sodium sulphate. The solvent was evaporated off in vacuum to obtain the product as a pale yellow solid. (60 %), FT-IR: 1268 (C-O), 2927 (C-H aliphatic), 3057 cm^{-1} (C-H aromatic) and; ^1H NMR ($CDCl_3$) 7.2-8.3 (m, 10H, Ar), 3.4 (s, 3H, OCH_3), 4.2 (s, 1H, CH); ^{13}C NMR ($CDCl_3$) 39.0 (OCH_3), 67.0 (C-5),126.5 (C-2), 127.7, 128.5, 128.7, 129.1, 129.2, 129.3, 129.9.



1a R = R' = CH_3
1b R = R' = $(CH_2)_5$
1c R = CH_3, R' = C_2H_5
1d R = H, R' = Ph
1e R = R' = Ph

2a R = R' = CH_3
2b R = R' = $(CH_2)_5$
2c R = CH_3, R' = C_2H_5

Scheme-1: Reaction of semicarbazones with CAN



Scheme-II: Reaction of benzoic acid benzylidene hydrazide with ceric ammonium nitrate (CAN)

RESULTS AND DISCUSSION

Semicarbazones **1a-1e** were prepared from semicarbazide and the corresponding aldehyde or ketones by the procedure reported[15]. All semicarbazones are identified by comparison of their physical and spectral data with those of authentic samples[16]. IR spectra of semicarbazones **1a-1e** showed a signal in the region of 1693-1651 (C=O) and 1598-1571 cm^{-1} (C=N) (Table-1). In ^1H NMR spectra singlet for NH and NH_2 appeared around 7.7 and 5.6 ppm which were disappeared on D_2O exchange.

TABLE-1
IR FREQUENCIES (cm^{-1}) OF SEMICARBAZONES (**1a-1e**)

Entry	Semicarbazones	ν(C=O)	ν(C=N)	ν(NH_2)	ν(NH)
1	**1a**	1685	1579	3230, 3201	3462
2	**1b**	1689	1571	3193, 3253	3463
3	**1c**	1693	1581	3190, 3200	3462
4	**1d**	1687	1598	3284, 3168	3456
5	**1e**	1651	1589	3284, 3168	3452

The semicarbazones were subjected to the reaction with ceric ammonium nitrate in solvent free reaction condition (**Scheme-I**). IR, ^1H NMR and ^{13}C NMR confirmed the structure of 1,3,4-oxadiazole **2a-2c** including decomposed derivatives of the amides (**3**). Compound **2a-2c** proved to be very difficult to obtain in pure form either by extraction or chromatography due to thermal decomposition. The decomposition of 1,3,4-oxadiazoles to amides has been reported[13]. **2a-2c** showed absorptions at 1650-1645, 1490-1475, 3163-3134 cm^{-1} due to adsorption of C=N, N=N and N-H groups.

^1H NMR spectra confirms the structure by showing the signals at 1.5-2.7 ppm for R and R` groups for example in **2a** methyls appeared at 1.7 ppm. ^{13}C NMR confirmed the structure of **2a-2c** by showing signals at 22-45 (R), 86(C5), 169 (C=N) and also their decomposition to the amide **3b-3c** by signals at 130-134 ppm (unsaturated carbons of amide). However, under the same reaction conditions the semicarbazones **1d-1e** did not react with ceric ammonium nitrate and the starting materials were recovered unchanged. This was found by comparing IR, ^1H NMR spectra of the resulted compounds with those of the starting materials.

The synthesis of 2-alkoxy-2,5-dihydro-1,3,4-oxadiazoles using lead tetraacetate (LTA) from the appropriate hydrazones in methanol has been reported[17]. To evaluate the efficiency of ceric ammonium nitrate in this reactions benzoic acid benzylidene-hydrazide (**4**) was synthesized from benzhydrazide and benzaldehyde (**Scheme-II**). The absorptions bands at 1600 ν(C=N), 1649 ν(C=O) and 3220 cm^{-1} ν(N-H) in infrared spectrum and in ^1H NMR spectra the peaks at 7.3-7.9 (Ar), 8.44 (HC=N) and 11.3 ppm (NH), which was exchanged with D_2O are the characteristic of the hydrazone (**4**). The reaction of (**4**) in methanol in the presence of ceric ammonium nitrate afforded the oxadiazole (**5**). The absorption at 1268 ν(C-O), 1455 ν(N=N), 3057 cm^{-1} ν(C-H aromatic) in IR spectrum and singlet at 3.4 (OCH_3) and 4.2 ppm (CH) in ^1H NMR and finally, the signals in the region of 126-129 (Ar), 39.0 (OCH_3) and 67.0 (C-5) in ^{13}C NMR confirm the structure of (**5**).

Conclusion

In conclusion, this investigation constitutes a route for the cyclization of semicarbazones to 1,3,4-oxadiazoles using ceric ammonium nitrate under the solvent free reaction condition. These compounds undergo thermolysis to amides. It was also found that benzoic acid benzylidene hydrazide can be cyclized to 2-methoxy-2-phenyl-1,3,4-oxadiazole in the presence of ceric ammonium nitrate and methanol.

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