Synthesis of Aminooxadiazoles And 2,5-diaryl-1,3,4- Oxadiazoles

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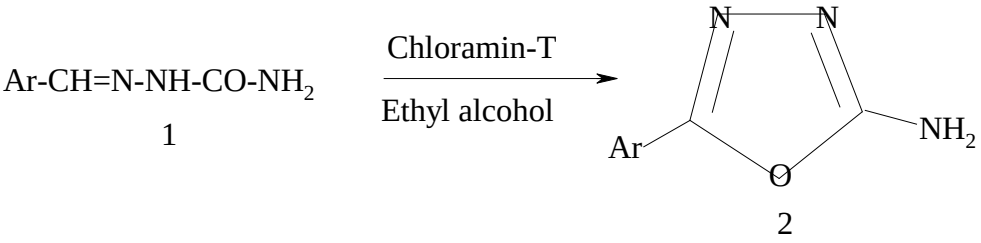
INTRODUCTION

Substituted oxadiazoles have been reported to act as fluorescent whiteners, as herbicides, as funcigides, as hypnitics and sedatives[1]. These compounds also showed analgesic anti-inflammatory, anti-convulsive, diuretic and anti-mitotic activity[2] . Aminooxadiazoles are useful photographic sensitizers and act as muscle relaxants. The usual synthesis of oxadiazoles involves the oxidative cyclisation of hydrazone or semicarbazone[3] with bromine in glacial acetic acid or iodine in aqueous sodium carbonate. Though there are methods for their synthesis, the yields are low (50-70%)[4] or side reactions may predominate[5] . Thus new procedures for the synthesis of aminooxadiazoles remain a topic of interest[6].

Many methods have been reported for the preparation of 2,5-diaryl-1,3,4-oxadiazoles. We developed a simple procedure for the preparation of 2,5-diaryl-1,3,4-oxadiazoles in our laboratory. The synthesis of 2,5-diaryl-1,3,4-oxadiazoles (II a-e) starting from acyl hydrazones (I a-e) using chloramin-T (CAT) as an oxidant. The starting acyl hydrazones were prepared by condensation of aryl aldehyde with acyl hydrazine.

METHODS AND REAGENTS

The procedure for the synthesis of aminooxadiazoles by refluxing an equimolar mixture of semicarbazones with chloramin-T trihydrate in ethanol for 3 hours. In general, aminooxadiazoles were obtained in 80-85% yield. Structural proof for the aminooxadiazoles were provided by mass, H^1 and C^{13} NMR techniques.



a. Ar = Ph b. Ar = 4-Meo-C_6H_4
c. Ar = 3,4-$(MeO)_2$-C_6H_3 d. Ar = 2,4,6-$(MeO)_3$-C_6H_2

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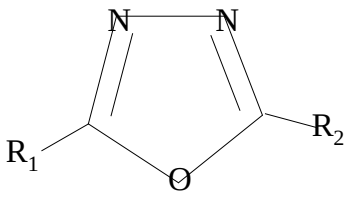
Preparation of aminooxadiazoles

The mixture of semicarbazone (1b) (2 g) and CAT.$3H_2O$ (3g), in ethanol was refluxed with stirringfor 3 hours. The sodium chloride formed in the reaction was filtered off and washed with ethanolthe combined filtrate and washings were evaporated in vacuum and the residue was extracted with 10% HCl and washed thoroughly with dichloromethane. The aqueous layer on neutralization with 10% NaOH (15 mL) gave 2b as a white solid which is washed and dried. Recrysatllisation from ethanol gave 1.67 g of aminooxadiazole.

NMR spectra were recorded on a Bruker MHz spectrometer in $CDCl_3$ solution. H^1 NMR spectra were measured at 300 MHz, TMS was used as an internal standard and chemical shifts areexpressed in ppm (δ scale). C^{13} NMR spectra were measured at 75 MHz and the values are in ppm down field from TMS. Mass spectra were obtained on a Finnigan mass spectrometer. Chromatographic separations were carried out on silica gel column using chloroform/acetone (7:1) as eluent.

The procedure described here is very simple and rapid. The typical reaction equimolar quantities of acyl hydrazone and chloramin-T trihydrate in alcohol was refluxed for 2-3 hours. On work up with the reaction mixture yielded 80-85% of 1,3,4-oxadiazoles (II a-e).

Structures of the products were proved by IR, PMR and C^{13} NMR and mass spectral analysis. IR spectrum of IIa shown the absence of amide carbonyl frequency in the region 1800-1650 cm-1 and the N—H frequency in the region 3400- 3200 cm-1 and showed a new peak at 1645 cm-1 due to C=N frequency. 2,5-diaryl-1,3,4-oxadiazoles gave significantly stable moleucalr ion peak with relative abundance ranging from 50-60%. The possible common fragmentation pattern involves either fission of oxadiazole ring or formation of ions involving some rearrangement with removal of nitrogen molecule. The base peak was observed at m/z 57, which arises due to the loss of N_2, CO and hydrogen radical.



a. $R_1 = R_2 = C_6H_5$ b. $R_1 = C_6H_5$ $R_2 = C_6H_4(OMe)(4)$

c. $R_1 = C_6H_5$ $R_2 = C_6H_2(OMe)_3(3,4,5)$

d. $R_1 = C_6H_4\text{-}NO_2$ $R_2 = C_6H_2(OMe)_3(3,4,5)$

e. $R_1 = C_6H_4\text{-}NO_2$ $R_2 = C_6H_5$

RESULTS AND DISCUSSION:

The yield, melting point and elemental analysis of aminooxadiazoles are reported in the table-1.

Table-1

Product	Yield (%)	M.P (^{0}C)	Elemental analysis (found)		
			C	H	N
2a	82	238-240	59.6 (59.5)	4.4 (4.3)	26.1 (26.0)
2b	85	242-246	56.5 (56.4)	4.7 (4.6)	21.9 (21.8)
2c	82	213-215	54.3 (54.2)	4.9 (4.8)	19.0 (18.8)
2d	80	197-200	52.6 (52.5)	5.1 (5.0)	16.7 (16.5)

Table-2. Spectral data of aminooxadiazoles.

Product	H^1 NMR ($CDCl_3$) ppm (δ)	C^{13} NMR ($CDCl_3$) ppm (δ)	Mass spectra m/z (relative intensity)
2a	3.34 (bS, 2H, NH_2) 7.52 (m, 2H, ArH) 7.80 (m, 3H, ArH)	124.3 (s, C1) 124.92 (d, C-2, 6) 129.08 (d, C-3, 4) 157.24 (s, C-5) 163.75 (s, C-2)	162 (M+1, 100) 161 , M^+, 81)
2b	3.36 (bS, 2H, NH_2) 3.82 (s, 3H, OMe) 7.15 (d, 2H,3,5-H) 7.72 (d, 2H, 2, 4 –H)	55.31 (q, OMe) 114.61 (d, C-3, 5) 116.95 (s, C-1) 126.94 (d, C-2, 6) 157.29 (s, C-5) 160.79 (s, C-4) 163.47 (s, C-2)	192 (M+1, 100) 191 , M^+, 12)
2c	3.33 (bS, 2H, NH_2) 3.823(s, 6H, OMe) 7.12 (m, 2H,ArH) 7.31 (m, 1H, Ar –H)		222 (M+1, 100) 221, M^+, 9)
2d	3.36 (bS, 2H, NH_2) 3.38 (s, 3H, OMe) 4.02 (s, 6H, OMe) 7.02 (s, 2H, Ar –H)		252 (M+1, 100) 251, M^+, 10)

Melting points were taken in open capillary tubes. The compounds were checked for their purity by TLC using silica gel. Spectra were recorded using Nujol mull on a Perkin Elmer spectrophotometer. NMR spectra were recorded on a Bruker 300 MHz spectrophotometer in $CDCl_3$ solvent. The H^1 NMR spectra were measured at 300 MHz. TMS was used as an internal standard. The chemical shifts are expressed in δ scale. The C^{13} NMR spectra were recorded at 75MHz and the values are downfield from TMS. Mass spectra were obtained on a Fennigen 4021 mass spectrophotometer. Chromatographic separation were carried out on silica gel (70-230 mesh) column using chloroformacetone (7:1) as a eluant.

Preparation of 2, 5-diphenyl oxadiazole (IIa): A mixture of aryl hydrazone Ia (0.5g, 2.5mmol) and CAT.$3H_2O$ (0.7g, 2.5mmol) in alcohol were heated at reflux with stirring for 3 hours. NaCl formed in the reaction was filtered off and washed with alcohol. The combined filtrate and washing were evaporated in vaccum and the residue was extracted with ether and ether extract washed with 10% NaOH (3 x 20 ml), water and finally with brine solution. The ethereal solution after drying over anhydrous Na_2SO_4 was evaporated in vacuum. The resultant residue dissolved in chloroform (2 ml) was poured into pet ether and the precipitate thus formed was collected and dried.

Recrystallisation from alcohol gave oxadiazole IIa as a white crystalline solid. Spectral and analytical data of 2,5-diaryl-1,3,4-oxadiazoles (IIa-e). The data obtained for five different compounds are shown in the table.

Table-3: Yield and Physical data of 2,5-diaryl oxadiazoles (IIa-e)

Product	Yield	M P (°C)	Elemental analysis		
			C	H	N
IIa	85	122	75.4	4.6	10.7
IIb	82	120	71.3	4.5	9.3
IIc	90	181	65.2	5.2	8.9
IId	85	203	57.2	4.1	11.8
IIe	80	179	75.6	4.5	10.8

H^1 and C^{13} NMR spectra were recorded in $CDCl_3$

a. H^1 NMR- δ 7.52 (m,6H ArH), δ 8.13 (bs,4H ArH), C^{13} NMR δ 124.03 (s), δ 126.95 (d), δ 129.08 (d), δ 131.7 (d), δ 164.63 (s), Mass spectrum M/z 222 (M^+, 52), 194 (7), 165 (100), 119 (15), 103 (12), 77 (20).
b. H^1 NMR- δ 3.89 (s,3H OMe), δ 7.03 (d,2H ArH), δ 7.53 (m, 3H, ArH) δ 8.08 (d, 2H, ArH), δ 8.12 (bs, 2H, ArH). C^{13} NMR δ 55.47 (q), δ 114.54 (d), δ 116.55 (s), δ 124.18 (s), δ 124.83 (d), δ 124.83 (d), δ128.7 (d), 129.7 (d), 131.47 (b), 162.27 (s), 164.13 (s) Mass spectrum M/z 252 (M^+ , 50), 224 (8), 195 (100), 149 (5), 133 (5), 119 (11), 103 (6), 77 (15).

c. H^1 NMR- δ 3.94 (s,3H OMe), δ 3.93 (s,6H OMe), δ 7.35 (s, 2H, ArH) δ 7.54 (m, 3H, ArH), δ 8.14 (bs, 2H, ArH). C^{13} NMR δ 56.46 (q), δ 61.01 (q), δ 104.38 (d), δ 119.02 (s), δ 123.95 (s), δ 126.9 (d), δ129.03 (d), 131.67 (d), 141.34 (s), 153.7 (s), 164.49 (s) Mass spectrum M/z 312 (M^+, 56), 284 (4), 255 (100), 209 (12), 193 (6), 119 (10), 103 (6), 77 (14).

d. H^1 NMR- δ 3.95 (s,6H OMe), δ 3.99 (s,6H OMe), δ 7.38 (s, 2H, ArH) δ 8.34 (d, 2H, ArH), δ 8.41 (d, 2H, ArH). C^{13} NMR δ 56.57 (q), δ 61.1 (q), δ 104.71 (d), δ 118.34 (s), δ 124.44 (d), δ 127.84(d), δ129.47 (s), 141.99 (s), 149.64 (s), 153.92 (s), 162.84 (s), 165.58 (s). Mass spectrum M/z 357 (M^+, 58), 329 (6), 300 (100), 209 (15), 193 (11), 148 (14).

e. H^1 NMR- δ 7.3 (s,2H ArH), δ 7.52 (d,3H ArH), δ 8.35 (d, 2H, ArH) δ 8.43 (d, 2H, ArH). C^{13} NMR δ 56.57 (q), δ 61.1 (q), δ 104.71 (d), δ 118.34 (s), δ 124.44 (d), δ 127.84(d), δ129.47 (s), 141.99 (s), 149.64 (s), 153.92 (s), 162.84 (s), 165.58 (s). Mass spectrum M/z 267 (M^+, 48), 239 (100), 148 (5), 144 (6), 119 (15), 103 (8).

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