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SYNTHESIS AND ANTIOXIDANT ACTIVITY OF INDOLIZINE DERIVATIVES

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ABSTRACT

A novel indolizine derivatives were synthesized by using indolizine 1- carboxylate and substituted 1,3,4-thiadiazoles. Indolizine 1-carboxylate were synthesized by using methyl acrylate and pyridinium halide in presence of manganese dioxide, triethylamine and toluene as a solvent. Substituted thiadiazole were prepared by reacting thiosemicarbazide with substituted carboxylic acid. Synthesized derivatives were screened for scavenging activity against 1,1 (DPPH). The results have showed that compound (4a) exhibited reasonable antioxidant activity. The structure of all the synthesized compounds were established by IR, NMR and Mass spectral data.

KEYWORDS: Indolizine, thiadiazole, 1, 3 cycloaddition, antioxidant.

INTRODUCTION

Functionalized indolizine have attracted considerable attention due to their wide applications in biological activities.[1,4] It has shown various biological activities such as anticancer,[5] anti-inflammatory,[6] antiviral,[7] CNS depressant,[8] and possessing antioxidant effects.[9] Several approaches were notable for the synthesis of indolizine such as the method using 1,3-dipolar cycloaddition of pyridinium *N*-methylides with electron-deficient alkenes attracted our attention due to its flexibility and convenience to form the indolizine. On the other hand Compounds containing 1,3,4-thiadiazole scaffold have a broad biological activity spectrum including antimicrobial, antituberculosis, anti-inflammatory, carbonic anhydrase inhibitors, anticonvulsants, antihypertensive, antioxidant, anticancer and antifungal properties.[10,11] The ability of 1,3,4-thiadiazole heterocyclic compounds to undergo various chemical reactions has made them important for molecule planning because of their privileged structure, which has enormous biological potential. Two examples of compounds containing the 1,3,4-thiadiazole unit currently used in clinical medicine are: acetazolamide and methazolamide as carbonic anhydrase inhibitors. The synthesis of novel 1,3,4-thiadiazole derivatives, and investigation of their chemical properties and biological behavior has accelerated in the last two decades. In recent years, the number of scientific studies with these compounds has increased considerably.

As part of our research project we investigated the reaction of Indolizine 1- carboxylate with with a substituted thiadiazole to form the derivatives and found that might have some biological properties. The structures of the synthesized compounds were characterized by IR, ^{1}H NMR and Mass spectral data.

MATERIALS AND METHODS

All reagents and solvents were purchased from Spectrochem. Solvents were re-distilled before use. Characterization of synthesized derivatives including intermediates, were done by FTIR (Bruker spectrophotometer) and, NMR (Bruker-400 spectrometer). Chemical shifts were measured in δ ppm using TMS as internal standard. Mass spectra were recorded on Agilent LC-MS spectrometer. TLC were performed on pre-coated silica gel plates (Merck 60 F_{254}) to check the progress of reaction as well as purity of the synthesized molecules. Melting point was checked by open capillary tube method and reported uncorrected.

General procedure for the synthesis of *N*-(carboxymethyl) pyridinium halides (1a)

To the solution of pyridine (100 mmol) in ethyl acetate (60 mL) appropriate haloacetic acid (100 mmol) was added and the reaction mixture was refluxed for 3 h with constant stirring to get *N*-(carboxymethyl-pyridinium) halides with 80-85% yield.

N-carboxymethyl-pyridiniumchloride (1a): mp: 150-154°C. IR (cm^{-1}): 3392 (-OH str.), 2968 (C-H, str.), 1729 (C=O, str.).

General procedure for synthesis of Substituted Indolizine (2a)

A suspension of *N*-(carboxymethyl)-pyridinium halide (**1a** 10 mmol), methyl acrylate (50 mmol), triethylamine (1.5 mL), MnO_2 (80 mmol) in toluene (80 mL) was stirred at 90° C for 3 h. Completion of reaction was

monitored by TLC. Cooled the reaction mixture at room temperature, filtered and washed the residue with acetone. Combined the filtrates and removed the solvent under reduced pressure. Residue obtained so, was purified by column chromatography using petroleum ether and ethyl acetate as eluent (9:1) to afford product in 60-70 % yield.

Methyl indolizine-1-carboxylate (2a): brown solid, mp: 135°C.IR (cm^{-1}): 2996(CH, str), 1352 (CN, str),1723 (C=O), ^{1}H NMR (400 MHZ, $CDCl_3$): δ = 8.14 (d, 1H), 7.63 (d, 1H), 7.22 (d, 1H), 7.07 (m, 2H), 6.73(m, 1H), 3.73(s, 3H). MS: (m/z) 175 (M).

General procedure for the synthesis of 1, 3, 4 Thiadiazole

Well stirred mixture of appropriate carboxylic acid (0.1 M) and thiosemicarbazide (0.15 M) was added in-part to concentrated sulphuric acid (31.5 mL) at 0-5º C with stirring. Heating was continued for 8 h at 70-80° C. After cooling, reaction mixture was poured into cold water and made basic with concentrated aqueous ammonia. Precipitate of respective 2-amino-5-aralkyl 1, 3,4-thiadiazole obtained so was filtered, washed with water and recrystallized from DMF-ethanol mixture (7:3).

5-Phenyl-1,3,4- thiadiazol-2 amine-2-amine (2a): white solid, mp: 136° C.IR (cm^{-1}): 2974(CH, str), 3310 (NH_2,str), ^{1}H NMR (400 MHZ, $CDCl_3$): δ = 7.14 (d, 1H), 7.31 (d, 1H), 6.89 (d, 1H), 6.07 (m, 2H), 3.98(s, 2H). MS: (m/z) 177 (M).

5- Benzyl-1,3,4-thiadiazol-2- amine (2b): yellowsolid, mp:96° C.IR (cm^{-1}): 2984(CH, str), 3012 (CH_2,str),3290 (NH_2,str), ^{1}H NMR (400 MHZ, $CDCl_3$): δ = 7.11 (d, 1H), 7.21 (d, 1H), 6.80 (d, 1H), 6.90 (m, 2H), 6.81(s,NH_2 ,2H), 3.81 (s,CH_2,2H). MS: (m/z) 191 (M).

5-(4-chlorobenzyl)-1,3,4-thiadiazol-2-amine (2c): yellowsolid, mp:129° C.IR (cm^{-1}): 2980 (CH, str), 3101 (CH_2,str),3296 (NH_2,str), ^{1}H NMR (400 MHZ, $CDCl_3$): δ = 7.61 (d, 1H), 7.26 (d, 1H), 6.89 (d, 1H), 6.95 (m, 1H), 6.88(s,NH_2 ,2H), 3.88 (s,CH_2,2H). MS: (m/z) 225 (M).

General procedure for the synthesis of 3-formylindolizine-1-carboxylate

To 1 ml of DMF stirred for 30 min at temp 0-5° C then added $POCl_3$ and maintain the temp. 0-5° C. Then added indolizine-1-carboxylate (4.2 mmol) and stirred for 6 h. Neutralize with Na_2CO_3 and filter the ppt and dried, then recrystallized from ethanol.

3-formylindolizine-1-carboxylate (3a): brownish solid, mp: 205° C. IR (cm^{-1}): 2980(CH, str), 3101 (CH, str),1796 (C=O, str), ^{1}H NMR (400 MHZ, $CDCl_3$): δ = 7.62 (d, 1H), 7.27 (d, 1H), 6.89 (d, 1H), 6.95 (m, 2H), 9.88(s, CHO,1H), 3.87 (s,CH_3,3H). MS: (m/z) 203 (M).

General procedure for the synthesis of derivatives

To 1 mmol of formyl indolizine-1-carboxylate and 1.2 mmol of substituted thiadiazole, 20 ml of ethanol and to the solution add few drops of acetic acid refluxed for 4-5 hrs. Completion of the reaction is monitored by TLC and poured into ice cold water ppt formed filtered and dried. Recrystallization done from Ethanol-chloroform mixture.

Methyl 3-(5-phenyl-1,3, 4-thiadiazol-2-yl)imino) methyl) indolizine-1-carboxylate(4a): light brownish solid, mp: 290° C. IR (cm^{-1}): 3122(CH, str), 2912 (CH, ar),1611 (C=N, str),1229(CN, str) ^{1}H NMR (400 MHZ, DMSO): δ = 9.30 (d, 1H), 9.19 (d, 2H), 8.74 (s, 1H), 8.55 (m, 2H), 8.08 (s, 1H), 7.57 (m, 4H), 3.75 (s, 3H) MS: (m/z) 362 (M).

Methyl 3-(5-Benzyl-1,3,4-thiadiazol-2-yl)imino) methyl) indolizine-1-carboxylate(4b): brownish solid, mp: 278° C. IR (cm^{-1}): 3115(CH, str), 2961 (CH, ar),1615 (C=N, str),1239(CN, str) ^{1}H NMR (400 MHZ, DMSO): δ = 9.20 (d, 1H), 9.16 (d, 2H), 8.70 (s, 1H), 8.53 (m, 2H), 8.18 (s, 1H), 7.59 (m, 4H), 3.85 (s, 3H), 3.79(s, 2H) MS: (m/z) 376 (M).

Methyl 3 -(5-(4-chlorobenzyl)-1,3,4-thiadiazol-2yl) imino)methyl)indolizine-1-carboxylate (4c): yellow solid, mp:280° C. IR (cm-1): 3118(CH, str), 2951 (CH, ar),1619(C=N), str),1249(CN, str) ^{1}H NMR (400 MHZ, DMSO): δ = 9.21 (d, 1H), 9.17 (d, 2H), 8.71 (s, 1H), 8.43 (m, 2H), 8.16 (s, 1H), 7.51 (m, 3H), 3.89 (s, 3H), 3.69(s, 2H) MS: (m/z) 410 (M).

RESULTS AND DISCUSSION

The indolizine 1- carboxylate derivatives were synthesized in the present study. The compound 1a was synthesized from pyridine with chloroacetic acid to pyridinium halide this on treating with electron deficient alkene using toluene as solvent in presence of triethylamine provided methiindolizine-1-carboxylate (2a). The 1,3 dipolar cycloaddition with methyl acrylate in presence of manganese dioxide promoted the preparation of 1- substituted indolizine with improved yields. The structure of the prepared compound (2a) were analyzed on the basis of their various spectral data (IR, ^{1}H NMR and ESI-MS).The IR spectra of compound (1a) showed carbonyl absorption at 1723 Aromatic C-H stretching absorptions at 2996 and CN stretching absorptions at 1352 cm^{-1} respectively. The proton spectra of substituted indolizine exhibited the doublets at δ 8.1-7.63 and a multiplet at δ 6.73, protons belonging to (OCH_3) generated singlet at 3.73. IR spectra of (3a) formyl indolizine -1-carboxylate reveal the presence of C=O group at 1796. IR spectra of substituted thiadiazole (2a-c) showed the NH_2 absorption at 3310 cm^{-1}, CH aromatic 2974cm^{-1}. In ^{1}H NMR spectra of compounds NH_2 resonating at δ 6.9 and aromatic protons resonate at δ 7.14-6.07 and the protons belonging to CH_2 shown the δ 3.81-3.78. The derivatives (4a-c) proton signals resonating at 8.70 (singlet) corresponds to imine proton indicating the absence of C=O group appeared at δ 9.88 spectrum supports the synthesis by absence of peak at

9.88 which corresponds to CHO functional group indicating that CHO group was involved in the reaction. It was converted to imine by formation of new peak at 8.70 which confirms the formation of derivatives and structure of compounds was confirmed by its molecular weight m/z 362 (4a) which was found in agreement with the desired structure. Similarly structures of remaining compounds has been confirmed.

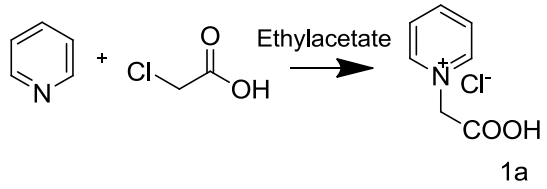
Antioxidant activity

The synthesized derivatives were screened for their antioxidant evaluation. 1 mL DPPH solution (0.1 mM) was added to 3 mL test/reference compounds (5, 10, 20, µg/mL). The reaction mixture was shaken vigorously and kept in dark for 30 minutes. Absorbance was measured at 517 nm using UV-visible spectrophotometer (Shimadzu-Uv1800). The % scavenging activity was calculated and results were summarized in table.

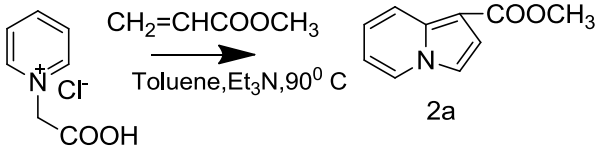
$$\% \text{ Inhibition} = \frac{(A_0 - A_1 X 100)}{A_0}$$

Where, %SA=Percentage scavenging activity, A_0=Absorbance of control, A_1=Absorbance of Sample.

Conc. (µg\ml)	4a	4b	4c	Ascorbic acid
5	28.3	32.3	33.3	26.9
10	31.2	37.6	39.3	35.1
20	38.9	43.2	44.5	40.2

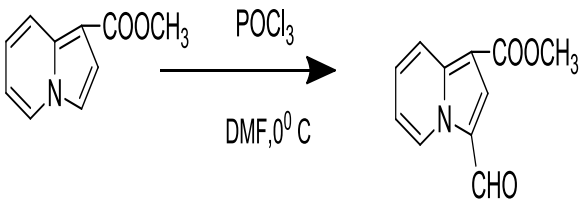


1a



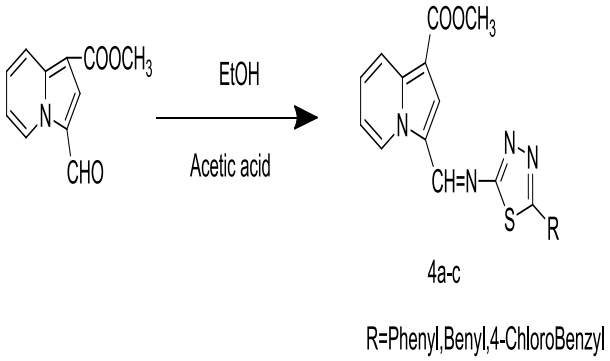
2a

Scheme I: Synthesis of Indolizine 1- carboxylate



3a

Scheme II: Synthesis of 3-formylindolizine-1-carboxylate



4a-c

R=Phenyl,Benyl,4-ChloroBenzyl

Scheme III: Synthesis of derivatives

CONCLUSION

In this study, we have synthesized indolizine-1-carboxylate by using electron deficient alkenes to form indolizine in good yields. Substituted 1,3,4 thiadiazole synthesized by using substituted carboxylic acid and thiosemicarbazide. Derivatives (4a-c) of Indolizine prepared by reacting 3- formyl indolizine-1-carboxylate with substituted thiadiazole. The purity and confirmation were established by physical, analytical and spectral data. The compounds were investigated for their antioxidant screening activity. The compound 4a could prove itself as potential antioxidant as compared to other indolizine derivatives.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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