A NOVEL APPROACH FOR SYNTHESIS OF SUBSTITUTED TETRAZOLES

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A series of novel 5-phenyl-1-acyl 1,2,3,4-tetrazoles (3–10) have been synthesized via condensation of 5-phenyl-1,2,3,4-tetrazoles (2) with various acylating reagents. 5-phenyl-1,2,3,4-tetrazoles was synthesized by the cycloaddition of Benzonitrile (1) with sodium azide and ammonium chloride in presence of Dimethylformamide as solvent. All synthesized compounds which were characterized to be new substituted Tetrazoles. Their structures were determined by 1H NMR, IR, mass spectra and elemental analyses.

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1. Introduction

5-Substituted 1,2,3,4-tetrazoles are reported to possess antibacterial, antifungal, antiviral, analgesic, anti-inflammatory, antiulcer and antihypertensive activities. The tetrazole function is metabolically stable; this feature and a close similarity between the acidic character of the tetrazole group and carboxylic acid group have inspired medicinal chemists to synthesize substituted tetrazoles as potential medicinal agents. Tetrazoles with phenyl ring attached to fifth position and various acyl substitutions at first position are not reported in the literature. Based on these findings, some new novel 5-phenyl-(acyl)-1,2,3,4-tetrazoles were synthesized.

2. Chemistry

Compounds were prepared as shown in Fig. 1. The 1,5-disubstituted tetrazoles can be synthesized by number of methods, viz. reaction of hydrazoic acid or its salts with imidoyl chloride or imino ethers or diazo coupling of heterocyclic hydrazines or hydrocyanic acid. Most of these methods have limited use in preparative organic chemistry because the use of hydrazoic acid presents considerable experimental difficulties due to its toxicity and tendency to explode. However, the simple route reported by Finnegan et al. [14] was adopted for the preparation of 5-phenyl-1-(acyl)-1,2,3,4-tetrazoles. This route replaces the toxic hydrazoic acid by inorganic azide to afford the titled compounds in good yield (59–88%). Compound 1 was cyclized using sodium azide and ammonium chloride to yield compound 2. The substituted tetrazoles were synthesized from 2 by acylation reaction (Figure 1).
3. Experimental

Melting points were determined by Veego melting point apparatus and are not corrected. Infrared spectra were obtained on a Shimadzu FTIR spectrophotometer using potassium bromide discs. Nuclear magnetic resonance spectra were recorded on Brucker 400 MHz spectrophotometer. Chemical shifts are reported in parts per million (δ) units relative to internal standard tetramethylsilane. Elemental analysis were performed and the analyses indicted by the symbols of the elements were within ±0.4% of theoretical values.

Synthesis of 5-phenyl-1,2,3,4-tetrazole(1)

The method described by Finnegam et al. [14] was followed to synthesize the tetrazole. A mixture of compound 1 (3.3 g, 10 mmol), sodium azide (0.65 g, 10 mmol) dimethylformamide (10 ml) and ammonium chloride (5.3 g, 10 mmol) was heated in a oil bath for 7 h at 125 °C. The solvent was removed under reduced pressure. The residue was dissolved in 100 ml of water and carefully acidified with concentrated hydrochloric acid to pH 2. The solution was cooled to 5 °C in ice bath. Compound 2 recrystallized from aqueous methanol.
5-phenyl-1-(benzoyl)-1,2,3,4-tetrazole (2)
Compound 1 was treated with an equimolar amount of Benzoyl chloride in 10 ml of 10% w/v sodium bicarbonate solution. The mixture was shaken vigorously in a stoppered test tube. When the odour of benzoyl chloride has disappeared, the contents were acidified with dilute hydrochloric acid to Congo red. Cooled in ice cold water and filtered.
The dried compound was recrystallized from aqueous ethanol, and was obtained in 55% yield as a white solid; m.p. 107–108 °C. IR: 1455 (C–H), 1285 (N=N=N–), 1108 and 1138 (tetrazole ring) cm–1. 1H-NMR (CDCl3) δ 2.8 (2H, t, J = 7.1 Hz, CH2), 4.3 (2H, t, J = 7.1 Hz, CH2), 6.8–8.1 (13H, m, Ar–H). Anal. Calcd. for C14H10N4O: C, 67.19; H, 4.09; N, 22.39; O, 6.39.

5-phenyl-1-(p-chlorobenzoyl)-1,2,3,4-tetrazole (3)
Compound 3 was prepared using the same procedure as for 2, and was obtained in 68% yield as a light yellow solid: m.p. 160–162 °C. IR: 1455 (C–H), 1285 (N=N=N–), 1108 and 1138 (tetrazole ring) cm–1. 1H-NMR (CDCl3) δ 2.8 (2H, t, J = 7.1 Hz, CH2), 4.3 (2H, t, J = 7.1 Hz, CH2), 6.8–8.1 (12H, m, Ar–H). Anal. Calcd. for C14H9ClN4O: C, 59.06; H, 3.19; N, 19.68; Found: C, 59.01; H, 3.11; N, 19.54.

5-phenyl-1-(o-nitrobenzoyl)-1,2,3,4-tetrazole (4)
Compound 4 was prepared using the same procedure as for 2, and was obtained in 75% yield as a white solid: m.p. 109–110 °C. IR: 3084 (C–H), 1735 (C=O), 1596 and 1570, 1541 (N=O), 1455 (C–H), 1348 and 1208 (N=O), 1108 and 1138 (tetrazole ring) cm–1. 1H-NMR (CDCl3) δ 2.8 (2H, t, J = 7.1 Hz, CH2), 4.3 (2H, t, J = 7.1 Hz, CH2), 6.7–9 (12H, m, Ar–H). Anal. Calcd. for C14H9N5O3: C, 56.95; H, 3.07; N, 23.72; Found: C, 56.82; H, 3.01; N, 23.33.

5-phenyl-1-(p-nitrobenzoyl)-1,2,3,4-tetrazole (5)
Compound 5 was prepared using the same procedure as for 2, and was obtained in 65% yield as a white solid: m.p. >210 °C. IR: 1458 (C–H), 1320 (C–N), 1285 (N=N=N–), 1108 and 1138 (tetrazole ring) cm–1. 1H-NMR (DMSO-d6) δ 2.8 (2H, t, J = 7.1 Hz, CH2), 3.63 (2H, s, NH2), 4.3 (2H, t, J = 7.1 Hz, CH2), 6.6–7.8 (12H, m, Ar–H). Anal. Calcd. for C14H11N5O: C, 63.39; H, 4.18; N, 26.40; Found: C, 63.30; H, 4.11; N, 26.28.

5-phenyl-1-(p-hydroxybenzoyl)-1,2,3,4-tetrazole (6)
Compound 6 was prepared using the same procedure as for 2, and was obtained in 62% yield as a light brown solid: m.p. 208–210 °C. IR: 1458 (C–H), 1283 (N=N=N–), 1108 and 1138 (tetrazole ring), 885 (O–H) cm–1. 1H-NMR (DMSO-d6) δ 2.5 (3H, s, CH3), 2.8 (2H, t, J = 7.1 Hz, CH2), 3.63 (2H, s, NH2), 4.3 (2H, t, J = 7.1 Hz, CH2), 5 (1H, s, OH), 6.85–7.37 (12H, m, Ar–H). Anal. Calcd. for C14H10N4O2: C, 63.15; H, 3.79; N, 21.01; Found: C, 63.02; H, 3.66; N, 22.93.

5-phenyl-1-(p-aminobenzoyl)-1,2,3,4-tetrazole (7)
Compound 7 was prepared using the same procedure as for 2, and was obtained in 61% yield as a dark brown solid: m.p. >210 °C. IR: 1458 (C–H), 1320 (C–N), 1108 and 1138 (tetrazole ring) cm–1. 1H-NMR (DMSO-d6) δ 2.8 (2H, t, J = 7.1 Hz, CH2), 4.3 (2H, t, J = 7.1 Hz, CH2), 5 (1H, s, OH), 6.85–7.37 (12H, m, Ar–H). Anal. Calcd. for C14H11N5O: C, 63.39; H, 4.18; N, 26.40; Found: C, 63.30; H, 4.11; N, 26.28.

5-phenyl-1-(p-methylbenzoyl)-1,2,3,4-tetrazole (8)
Compound 8 was prepared using the same procedure as for 2, and was obtained in 64% yield as a light grey solid: m.p. 121–122 °C. IR: 1457 (C–H), 1283 (N=N=N–), 1108 and 1138 (tetrazole ring) cm–1. 1H-NMR (DMSO-d6) δ 2.5 (3H, s, CH3), 2.8 (2H, t, J = 7.1 Hz, CH2), 4.3 (2H, t, J = 7.1 Hz, CH2), 6.8–7.9 (12H, m, Ar–H). Anal. Calcd. for C15H10N4O: C, 68.17; H, 4.58; N, 21.20; Found: C, 68.10; H, 4.51; N, 21.18.
5-phenyl-1-(p-methoxybenzoyl)-1,2,3,4-tetrazole (9)

Compound 9 was prepared using the same procedure as for 2, and was obtained in 68% yield as a light brown solid: m.p. 160-162 °C. IR: 2985 (C–H), 1604 (C=C), 1596 and 1570 (tetrazole ring), 1457 (C–H), 1283 (N–N=N–), 1108 and 1138 (tetrazole ring) cm–1. 1H-NMR (CDCl3) δ 2.8 (2H, t, J = 7.1 Hz, CH2), 3.9 (3H, s, CH3), 4.3(2H, t, J = 7.1 Hz, CH2), 6.4–8.1 (12H, m, Ar–H). Anal. Calcd. for C15H12N4O2: C, 64.28; H, 4.32; N, 19.99. Found: C, 64.25; H, 4.24; N, 19.91.

5-phenyl-1-(phenyl acetyl)-1,2,3,4-tetrazole (10)

Compound 10 was prepared using the same procedure as for 2, and was obtained in 59% yield as a light brown solid: m.p. 127–128 °C. IR: 1583 (C=C), 1457 (C–H), 1283 (N–N=N–), 1108 and 1138 (tetrazole ring) cm–1. 1H-NMR (CDCl3) δ 2.3 (2H, s, CH2), 2.8 (2H, t, J = 7.1 Hz, CH2), 4.3 (2H, t, J = 7.1 Hz, CH2), 6.8–7.3 (13H, m, Ar–H). Anal. Calcd. for C15H12N4O: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.12; H, 4.51; N, 21.12.

4. Results and discussion

Benzonitrile was readily converted to 5-phenyl-1,2,3,4-tetrazole by treating them with sodium azide and ammonium chloride in dimethylformamide. The secondary amino group of tetrazole at position 1 of tetrazole is free and hence 8 different derivatives are synthesized using various acyl chlorides. Infra red spectrum of compound 1 showed a sharp absorption and at 3421 cm–1 which is attributed to secondary amino group group.

The synthesized compounds (2–10) showed absorption bands at 1048, 1120, 1208, 1296 and 1598 cm–1 which are attributed to tetrazole ring. Characteristic absorption bands were observed for carbonyl group, nitro group, hydroxyl group, amino group, methyl group, methoxyl group and aromatic region of the synthesized compounds. 1H-NMR spectra of the synthesized compounds showed two triplets at d 2.8 and d 4.2. A triplet at d 2.8 is due to two protons which are attached to the carbon atom of the nitrile function. The triplet at d 4.2 is due to the two protons attached to the carbon atom of nitride function. 1-H (NH) proton of the tetrazole is undetectable in NMR spectra. Aromatic protons showed multiplets in the range of d 6.8–7.3. The expected signals with appropriate multiplicities for different types of protons were observed for the derivatives.

5. Conclusion

The method described in this paper, allows the preparation of unique substituted Tetrazoles from commercial and available nitriles and easy to prepare from sodium azides and various acylating agents. The important aspects of this protocol, are high yielding, mild reaction conditions, availability of the precursors and purity of the obtained products with no further crystallization.

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References