Synthesis of 4-(substituted benzyl)-1H,3H-benzo[f]1,3,5-triazepin-2-ones

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This paper presents the synthesis of 4-(substituted benzyl)-1H,3H-benzo[f]1,3,5-triazepin-2-ones 3 from o-phenylenediamines 1 and 4-(arylmethylene)-6-phenyl-3H-1,3,5-oxadiazin-2-ones 2.

Keywords: Azlactones, oxadiazin-2-ones, triazepin-2-one, tautomeric form, disproportionation

Benzotriazepines comprise an interesting class of heteroaromatic compounds because of their significant biological and pharmaceutical properties such as antibacterial, antiviral, psychotropic and antimalarial properties. Azlactones are well known compounds that possess multi functional reactive sites. Previously the use of azlactones for the synthesis of different condensed nitrogen heterocycles has been described.

Results and Discussion

The reaction of o-phenylenediamine 1 (R=H) with 4-(4-methoxyphenyl methylene)-6-phenyl-3H-1,3,5-oxadiazin-2-one 2a in 2:1 molar ratio in acetic acid at 90°C affords a single insoluble product from acetic acid as evidenced by TLC (single spot on ethylacetate-benzene 1:1). The isolated product has been identified as 4-(4-methoxybenzyl)-1H,3H-benzo[f]1,3,5-triazepin-2-one 3a and obtained in good yield. The spectral data and elemental analysis was in complete agreement with the assigned structure [m.p. 185°C; MS: m/z 280 (M-1); IR (KBr): 3449 (NH), 3250 (NH), 1705 cm⁻¹ (CO); ¹H NMR (DMSO-d₆): δ 3.7 (s, 3H, OCH₃), 6.2 (s, 1H, NH), 6.7-8.2 (m, 10H), 9.4 (s, 1H, NH)].

The acetic acid filtrate from the reaction mixture on dilution with water followed by neutralization and usual work-up gave another crystalline compound. It is characterized as 2-phenylbenzimidazole 4 (R=H) on the basis of its spectral data followed by comparison with authentic sample; m.p. 289°C (lit. m.p. 290°C).

The formation of compounds 3 can be explained according to the following mechanism. The reaction proceeds by the nucleophilic attack of the amino group of o-phenylenediamine 1 on C-2 of compound 2 leading to intermediate A which readily cyclises to intermediate B. The intermediate B undergoes disproportionation into 2-phenylbenzimidazoles 4 and intermediate C. The open chain intermediate C in its tautomeric form, D, reacts readily with second mole of o-phenylenediamine 1, to give cyclic intermediate E, which by the elimination of ammonia yielded compound 3. Four other 1,3,5-oxadiazin-2-ones 2 reacted with o-phenylenediamines 1 (R=H, NO₂) in a similar manner and yielded the corresponding 4-(substituted benzyl)1H,3H-benzo[f]1,3,5-triazepin-2-ones 3 (Scheme 1).

The 4-(arylmethylene)-6-phenyl-3H-1,3,5-oxadiazin-2-ones 2 were prepared from the corresponding azlactones by a known method.

Experimental Section

Melting points were obtained in sulphuric acid bath and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 1650 spectrophotometer. ¹H NMR spectra were recorded on a Bruker DRX-200 spectrometer with TMS as an internal standard (chemical shifts in δ, ppm) and mass spectra on MS PE SCIEX API 3000 instrument. Elemental analysis was carried out on a Yanaco CHN MT-3 apparatus.

General procedure for the synthesis of 4-(substituted benzyl)-1H,3H-benzo[f]1,3,5-triazepin-2-ones 3. A solution of o-phenylenediamine 1 (0.02 mole) and the appropriate 1,3,5 oxadiazin-2-ones 2 (0.01mole) in acetic acid (15mL) was refluxed for 1 hr and concentrated to half the volume. The reaction mixture was cooled, and the separated solid was filtered and purified by recrystallization with methanol-dichloromethane.

4-(4-Methoxybenzyl)-1H,3H-benzo[f]1,3,5-triazepin-2-one 3a. Yield 54%, m.p.185-87°C; IR (KBr): 3449 (NH), 3250 (NH), 1705 cm⁻¹ (CO); ¹H NMR (DMSO-d₆): δ 3.7 (s, 3H, OCH₃), 6.2 (s, 1H, NH), 6.7-8.2 (10H, Ar-H & CH₂-Ar), 9.4 (s, 1H, NH); MS:
m/z 280 (M-1). Anal. Calcd for C_{18}H_{15}N_{3}O_{2}: C, 68.32; H, 5.33; N, 14.94. Found: C, 68.10; H, 5.13; N, 14.63%.

4-Benzyl-1H,3H-benzo[1,3,5-triazepin-2-one 3b. Yield 63%, m.p. 159-62°C; IR (KBr): 3402 (NH), 3240 (NH), 1703 cm^{-1} (CO); $^1$H NMR (DMSO-$d_6$): δ 6 (s, 1H, NH), 6.9-8.1 (11H, Ar-H & CH$_2$-Ar), 9.3 (s, 1H, NH); MS: m/z 250 (M-1). Anal. Calcd for C$_{15}$H$_{13}$N$_3$O: C, 71.71; H, 5.18; N, 16.73. Found: C, 71.40; H, 5.13; N, 16.63%.

4-(3-Nitrobenzyl)-1H,3H-benzo[1,3,5-triazepin-2-one 3c. Yield 60%, m.p. 215-18°C; IR (KBr): 3400 (NH), 3245 (NH), 1710 cm$^{-1}$ (CO); $^1$H NMR (DMSO-$d_6$): δ 6.1 (s, 1H, NH), 6.7-8.1 (10H, Ar-H & CH$_2$-Ar), 9.2 (s, 1H, NH); MS: m/z 295 (M-1). Anal. Calcd for C$_{15}$H$_{12}$N$_4$O$_3$: C, 60.81; H, 4.05; N, 18.92. Found: C, 61.10; H, 4.13; N, 18.63%.

4-(4-Chlorobenzyl)-1H,3H-benzo[1,3,5-triazepin-2-one 3d. Yield 60%, m.p. 173-76°C; IR (KBr): 3390 (NH), 3250 (NH), 1700 cm$^{-1}$ (CO); $^1$H NMR (DMSO-$d_6$): δ 6.1 (s, 1H, NH), 6.7-8.1 (10H, Ar-H & CH$_2$-Ar), 9.1 (s, 1H, NH); MS: m/z 285 (M-1). Anal. Calcd for C$_{15}$H$_{12}$ClN$_3$O: C, 63.04; H, 4.20; N, 14.71. Found: C, 63.15; H, 4.16; N, 14.40%.

4-(4-Methoxybenzyl)-7-nitro-1H,3H-benzo[1,3,5-triazepin-2-one 3e. Yield 55%, m.p. 186°C; IR
(KBr): 3350 (NH), 3190 (NH), 1653 cm$^{-1}$ (CO); $^1$H
NMR (DMSO-$d_6$): $\delta$ 3.8 (s, 3H, OCH$_3$) 6.2 (s, 1H, NH), 6.7-8.2 (9H, Ar-H & CH$_2$-Ar), 9.2 (s, 1H, NH);
MS: $m/z$ 325 (M-1). Anal. Calcd for C$_{16}$H$_{14}$N$_4$O$_4$: C, 58.89; H, 4.29; N, 17.17. Found: C, 58.40; H, 4.13; N, 17.63%.

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