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A NOVEL SYNTHETIC PROTOCOL FOR THE BIS-TRIAZOLONES DERIVATIVES THROUGH CORRESPONDING N^1-ETHOXYCARBONYL-N^1-TOSYLHYDRAZONATES

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ABSTRACT

A simple method has been developed for the synthesis of bis-triazolones **2a-n** starting from N^1-ethoxycarbonyl-N^1-tosylhydrazonates **1** and aliphatic diamine. It affords a number of bis-triazolones **2a-n** in reasonable yields. The structures of all new compounds were elucidated using infrared, ^1H and ^{13}C NMR studies as well as elemental analysis. Some of these reactions provide successful means to produce biologically important structures.

Keywords

N^1-ethoxycarbonyl-N^1-tosylhydrazonates; Bis-Triazolones; Infrared spectroscopy; Nuclear magnetic resonance.

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INTRODUCTION

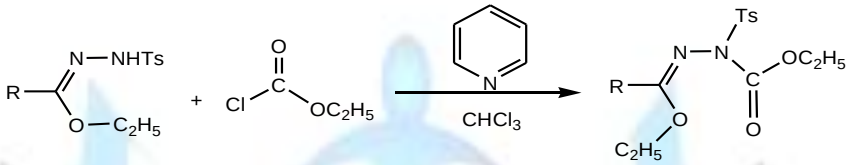
The synthesis of bis-heterocyclic compounds has received considerable attention as it demonstrates a broad spectrum of biological activities such as anticancer, antibacterial, anti-tumor, and anti-mycobacterial activities [1-10]. Among these compounds, we can mention the bis-triazoles derivatives [11-15].

Various methods of the synthesis of 1,2,4- triazolones have been described in the literature [16-18]. Recently, the synthesis of Bis-triazolones, yielded by the reaction of bis-amidrazones with ethyl chloroformate has been illustrated [19].

The present paper proposes a novel method for obtaining Bis-triazolones **2**, as a result of the reaction of N^1-ethoxycarbonyl-N^1-tosylhydrazonates **1** with diamine derivatives.

RESULTS AND DISCUSSION

The N^1-ethoxycarbonyl-N^1-tosylhydrazonates **1a-b,** used in this study, were prepared by the addition of N^1-tosylhydrazonates to the ethyl chloroformate using a previously reported method [20].



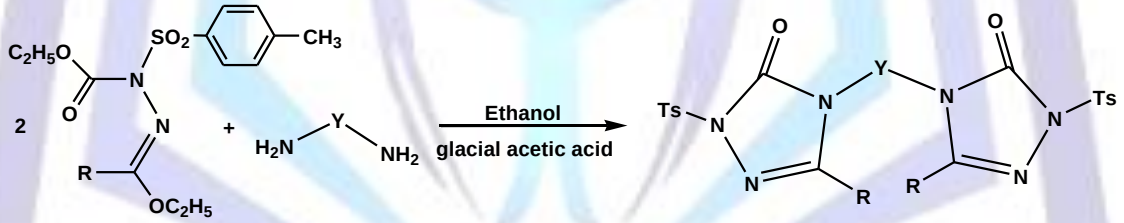
1a-b

1a: R= CH_3; **1b**:R= C_2H_5

Scheme 1: Synthetic route to N^1-ethoxycarbonyl N^1- tosylhydrazonate **1a-b**

These compounds have two electrophilic centers at positions 1, 4 that are very reactive compared with compounds containing a nucleophilic center (e.g., diamines).

In fact, the condensation of two equiv. of N^1-ethoxycarbonyl-N^1-tosylhydrazonates **1a-b** in ethanol with one equiv. of diamine derivatives, in the presence of a catalytic amount of glacial acetic acid produced, with a good yield, a cyclized product. The latter is identified as 1,Y-bis-(5-alkyl-2-tosyl-1,2,4-triazol-3-one-4-yl) alkane **2** (Scheme 2).



1a-b **2a-n**

2a: R=CH_3, Y=$(CH_2)_3$;**2b**:R= C_2H_5, Y= $(CH_2)_3$
2c:R= CH_3, Y= $(CH_2)_4$; **2d**: R= C_2H_5, Y= $(CH_2)_4$
2e:R= CH_3, Y= $(CH_2)_6$; **2f:**R= C_2H_5, Y= $(CH_2)_6$
2g:R= CH_3, Y= $(CH_2)_8$; **2h**:R= C_2H_5, Y= $(CH_2)_8$
2i:R= CH_3, Y= $(CH_2)_{10}$; **2j**:R= C_2H_5, Y= $(CH_2)_{10}$
2k:R= CH_3, Y= $(CH_2)_{12}$; **2l**:R= C_2H_5, Y= $(CH_2)_{12}$
2m:R= CH_3, Y= (C_6H_{10}) ; **2n**:R= C_2H_5, Y= (C_6H_{10})

Scheme 2: Synthetic route to bis-triazolones **2 a-n**

The structural assignments of the new compounds were based on their elemental analysis and spectral (IR, ^1H NMR and ^{13}C NMR) data. The characterisation data of all new compounds is presented in the experimental section. The IR spectra of compounds **2** shows absorption bands in the range of 1590-1610 cm^{-1}, which are attributed to the C=N group. However, carbonyl stretching vibration bands are found to appear at around 1735cm^{-1}. The NMR spectrum of **2** essentially shows the absence of the signal of ethoxy group of the parent N^1-ethoxycarbonyl-N^1-tosylhydrazonates **1**. It also illustrates the presence of the characteristic resonance signals of protons introduced by the diamine derivatives. The ^{13}C NMR signal for the C=O group is observed at around 151 ppm, whereas the signal of the C=N group is noted at values in the range of 147-150 ppm. Moreover, the elemental analyses are consistent with the proposed formula.

Some of these compounds have already been synthesized from the condensation of bis-amidrazones with ethyl chloroformate as described above[19]. Given the substantially reduced number of bis-amidrazones, the synthesis presented in this paper is found to be advantageous following a more general and lower-cost approach. Furthermore, the proposed method is also proven to have better yields than the others.

CONCLUSION

The present research study reports the success of a novel strategy in the synthesis and characterization of new 1,Y-bis(5-alkyl-2-tosyl-1,2,4-triazol-3-one-4-yl) alkane derivatives in good yields.

EXPERIMENTAL

The melting points were determined by Electrothermal 9100 apparatus. The infrared spectra were determined on a Perkin Elmer Spectrum Version 10.00.00 with a precision of 2 cm^{-1} covering field 400-4000 cm^{-1}. NMR spectra were recorded in $CDCl_3$ or in DMSO-d6 on a Bruker Avance spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C). ^1H and ^{13}C chemical shifts are given on the δ scale (ppm) and referenced to internal T.M.S. The multiplicities of the signals are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quadruplet, m: multiplet, br: broad and coupling constants are expressed in Hz. The elemental analyses were performed on a Thermo Finnigan EA 1112 apparatus, both at the Service Commun d'Analyses, University of Lorraine, Nancy.

GENERAL EXPERIMENTAL PROCEDURE

A mixture of compound 1 (0.01 mol), diamino-alkane (represented in the scheme 1) (0.005 mol) and 4–5 drops of glacial acetic acid in ethanol was heated to reflux for 8 h. The resulting solution was cooled to room temperature and the precipitated solid was filtered and washed with cold ethanol, then dried to get pure product.

Spectral Data of New Compounds

***1,3-bis(5-methyl-3-tosyl-1,3,4-triazol-2-onyl)propane* (2a).** yield (67%), mpq 130–132 ºC; IR spectrum (v/cm^{-1}): 1711 (C=O), 1602 (C=N); ^1H NMR spectrum ($CDCl_3$): δ (ppm): 1.99 (m, 2H), 2.19 (s, 6H), 2.44 (s, 6H), 3.54 (t, J= 6.9 Hz, 4H), 7.34-7.97 (2AB(Ts), J=7.8 Hz, 8Harom); ^{13}C NMR spectrum ($CDCl_3$): δ (ppm): (150.7, 2C=O), (146.1, 2C=N), (21.2, $2CH_3$(Ts)), (11.4, $2CH_3$), (38.7, $2CH_2$-N), (26.9, CH_2), Carom 127.6-145.5; Anal. Calcd. for $C_{23}H_{26}N_6O_6S_2$: C, 50.54; H, 4.79; N, 15.37. Found: C, 50.90; H, 5.00; N, 15.60.

***1,3-bis(5-ethyl-3-tosyl-1,3,4-triazol-2-onyl)propane* (2b).** yield (57%), mp 136–138 ºC; IR spectrum (v/cm^{-1}): 1709 (C=O), 1597 (C=N); ^1H NMR spectrum ($CDCl_3$): δ (ppm): 0.83 (t, J= 7.5Hz, 3H), 1.53 (m, 2H), 1.98 (q, J= 7.5Hz, 4H), 2.28 (s, 6H), 3.21 (t, J= 6.9 Hz, 4H), 7.39-7.65 (2AB(Ts), J=8.1 Hz, 8Harom); ^{13}C NMR spectrum ($CDCl_3$): δ (ppm): (151.4, 2C=O), (145.4, 2C=N), (21.4, $2CH_3$(Ts)), (9.0, $2CH_3$), (13.8, $2CH_2$), (38.3, $2CH_2$-N), (26.2, CH_2), Carom 127.6-139.0; Anal. Calcd. for $C_{25}H_{30}N_6O_6S_2$: C, 52.25; H, 5.26; N, 14.62. Found: C, 52.50; H, 5.50; N, 14.85.

***1,4-bis(5-methyl-3-tosyl-1,3,4-triazol-2-onyl)butane* (2c).** yield (55%), mp 260–262 ºC; IR spectrum, v, cm^{-1}: 1716 (C=O), 1593 (C=N); ^1H NMR spectrum (DMSO-d6): δ (ppm): 1.44 (m, 4H), 2.16 (s, 6H), 2.41 (s, 6H), 3.47 (m, 4H), 7.45-7.83 (2AB(Ts), J= 8.1Hz, 8Harom);^{13}C NMR spectrum (DMSO-d6): δ (ppm): (151.1, 2C=O), (148.4, 2C=N), (21.0, $2CH_3$(Ts)), (11.5, $2CH_3$), (41.5, $2CH_2$-N), (24.7, $2CH_2$), Carom 127.3-145.7; Anal. Calcd. for $C_{24}H_{28}N_6O_6S_2$: C, 51.42; H, 5.03; N, 14.99. Found: C, 51.75; H, 5.35; N, 15.30.

***1,4-bis(5-ethyl-3-tosyl-1,3,4-triazol-2-onyl)butane* (2d).** yield (64%), mp 226-228ºC; IR spectrum (v/cm^{-1}): 1735 (C=O), 1591 (C=N); ^1H NMR spectrum (DMSO-d6): δ (ppm): 1.12 (t, J= 7.5Hz, 3H), 1.43 (m, 4H), 2.40 (s, 6H), 2.51 (q, J= 7.5Hz, 2H), 3.45 (m, 4H), 7.44-7.84 (2AB(Ts), J= 7.8Hz, 8Harom);^{13}C NMR spectrum (DMSO-d6): δ (ppm): (152.0, 2C=O), (151.3, 2C=N), (9.0, $2CH_3$), (18.5, $2CH_2$), (21.0, $2CH_3$(Ts)), (24.8, $2CH_2$), (38.9, $2CH_2$-N), Carom 127.3-145.7; Anal. Calcd. for $C_{26}H_{32}N_6O_6S_2$: C, 53.05; H, 5.48; N, 14.28. Found: C, 53.05; H, 5.62; N, 13.99.

***1,6-bis(5-methyl-2-tosyl-1,2,4-triazol-3-one-4-yl)hexane* (2e).** yield (80%), mp 190-192 °C; IR spectrum (v/cm^{-1}): 1722 (C=O), 1601 (C=N); ^1H NMR spectrum ($CDCl_3$): δ (ppm): 1.24 (m, 4H), 1.54 (m, 4H), 2.18 (s, 6H), 2.40 (s, 6H), 3.45 (t, J=6.9 Hz, 4H), 7.31-7.93 (2AB(Ts), J= 7.8Hz, 8Harom); ^{13}C NMR spectrum ($CDCl_3$): δ (ppm): (151.3, 2C=O), (147.1, 2C=N), (21.8, $2CH_3$(Ts)), (12.2, $2CH_3$), (41.6, $2CH_2$-N), (28.4, $2CH_2$), (25.8, $2CH_2$), Carom 128.2-145.9; Anal. Calcd. for $C_{26}H_{32}N_6O_6S_2$: C, 53.05; H, 5.48; N, 14.28. Found: C, 53.05; H, 5.62; N, 13.99.

***1,6-bis (5-ethyl-2-tosyl-1,2,4-triazol-3-one-4-yl)hexane* (2f).** yield (75%), mp 194-196 °C; IR spectrum (v/cm^{-1}): 1735 (C=O), 1594 (C=N); ^1H NMR spectrum ($CDCl_3$): δ (ppm): 1.20 (m, 10H), 1.49 (m, 4H), 2.35 (s, 6H), 2.42 (q, J=7.2 Hz, 4H), 3.39 (t, J=7.2 Hz, 4H), 7.27- 7.89 (2AB(Ts), J= 8.1 Hz, 8Harom); ^{13}C NMR spectrum ($CDCl_3$): δ (ppm): (152.0, 2C=O), (151.3, 2C=N), (22.2, $2CH_3$(Ts)), (19.9, $2CH_2$-CH_3), (10.2, $2CH_3$-CH_2), (41.8, $2CH_2$-N), (28.8, $2CH_2$), (26.2, $2CH_2$), Carom 128.5-146.2; Anal. Calcd. for $C_{28}H_{36}N_6O_6S_2$: C, 54.53; H, 5.88; N, 13.63. Found: C, 54.49; H, 5.81, N, 13.42.

***1,8-bis (5-methyl-2-tosyl-1,2,4-triazol-3-one-4-yl)octane* (2g).** yield (85%), mp 162-164 °C; IR spectrum (v/cm^{-1}): 1732 (C=O), 1593 (C=N); ^{1}H NMR spectrum ($CDCl_3$): δ (ppm):1.00 (m, 4H), 1.38 (m, 4H), 2.11 (s, 6H), 2.31 (s, 6H), 2.43 (m, 4H), 3.39 (t, J=6.8Hz, 4H), 7.39-7.74 (2AB(Ts), J= 7.9 Hz, 8Harom); ^{13}C NMR spectrum ($CDCl_3$): δ (ppm): (151.5, 2C=O), (149.1, 2C=N), (21.5, $2CH_3$(Ts)), (12.0, $2CH_3$), (41.5, $2CH_2$-N), (28.6, $2CH_2$), (28.0, $2CH_2$), (26.0, $2CH_2$), Carom 127.8-146.2; Anal. Calcd for $C_{28}H_{36}N_6O_6S_2$: C, 54.53; H, 5.88; N, 13.63. Found: C, 54.50; H, 5.82; N, 13.59.

***1,8-bis (5-ethyl-2-tosyl-1,2,4-triazol-3-one-4-yl)octane* (2h).** yield 82%, mp 174-176 °C; IR spectrum (v/cm^{-1}): 1727 (C=O), 1588 (C=N); ^{1}H NMR spectrum ($CDCl_3$): δ (ppm): 1.04-1.15 (m, 14H), 1.49 (m, 4H), 2.38(s, 6H), 2.53(q, J=7.5 Hz, 4H), 3.45(t, J=7.3 Hz, 4H), 7.46-7.82 (2AB(Ts), J= 8.2 Hz, 8Harom);^{13}C NMR spectrum ($CDCl_3$): δ (ppm): (151.6, 2C=O), (151.0, 2C=N), (21.5, CH_3(Ts)), (19.0, $2CH_2$-CH_3), (9.3, $2CH_3$-CH_2), (41.3, $2CH_2$-N), (28.6, $2CH_2$), (28.0, $2CH_2$), (26.0, $2CH_2$), Carom 128.1-146.7; Anal. Calcd for $C_{30}H_{40}N_6O_6S_2$: C, 55.88; H, 6.25; N, 13.03. Found: C, 55.61; H, 6.23; N, 12.92.

1,*10-bis (5-methyl-2-tosyl-1,2,4-triazol-3-one-4-yl)decane* (2i). yield (90%), mp 180-182 °C; IR spectrum (v/cm^{-1}): 1736 (C=O), 1603 (C=N); ^{1}H NMR spectrum ($CDCl_3$): δ (ppm): 1.20-1.28 (m, 12H), 1.54 (m, 4H), 2.18 (s, 6H), 2.40 (s, 6H), 3.45 (t, J=7.2 Hz, 4H), 7.31-7.93 (2AB(Ts), J= 8.4 Hz, 8Harom);^{13}C NMR spectrum ($CDCl_3$): δ (ppm): (151.3, 2C=O), (147.2, 2C=N), (21.8, $2CH_3$(Ts)), (12.2, $2CH_3$), (41.9, $2CH_2$-N), (29.2, $2CH_2$), (28.9, $2CH_2$), (28.6, $2CH_2$), (26.4, $2CH_2$), Carom 128.2-145.9; Anal. Calcd for $C_{30}H_{40}N_6O_6S_2$: C, 55.88; H, 6.25; N, 13.03. Found: C, 55.57; H, 6.19; N, 12.82.

***1,10-bis (5-ethyl-2-tosyl-1,2,4-triazol-3-one-4-yl)decane* (2j).** yield (76%), mp 188-190 °C; IR spectrum (v/cm^{-1}): 1735 (C=O), 1600 (C=N);^{1}H NMR spectrum ($CDCl_3$): δ (ppm): 1.08-1.23 (m, 18H), 1.51 (m, 4H), 2.31-2.48 (m, 10H), 3.41 (t, J=6.5 Hz, 4H), 7.26-7.92 (2AB(Ts), J= 7.3 Hz, 8Harom);^{13}C NMR spectrum ($CDCl_3$): δ (ppm): (151.6, 2C=O), (150.9, 2C=N), (21.8, $2CH_3$(Ts)), (18.2, $2CH_2$-CH_3), (10.9, $2CH_3$-CH_2), (41.9, $2CH_2$-N), (29.2, $2CH_2$), (28.9, $2CH_2$), (28.6, $2CH_2$), (26.4, $2CH_2$), Carom 128.2-145.6; Anal. Calcd for $C_{32}H_{44}N_6O_6S_2$: C, 57.12; H, 6.59; N, 12.49. Found: C, 56.99; H, 6.41; N 12.32.

***1,12-bis (5-methyl-2-tosyl-1,2,4-triazol-3-one-4-yl)dodecane* (2k).** yield (87%), mp166-168 °C; IR spectrum (v/cm^{-1}): 1732 (C=O), 1605 (C=N); ^{1}H NMR spectrum ($CDCl_3$): δ (ppm): 1.14 (m, 16H), 1.50 (m, 4H), 2.14 (s, 6H), 2.36 (s, 6H), 3.41 (m, 4H), 7.26-7.90 (2AB(Ts), J= 6.9 Hz, 8Harom);^{13}C NMR spectrum ($CDCl_3$): δ (ppm): (150.8, 2C=O), (146.6, 2C=N), (21.3, $2CH_3$(Ts)), (11.7, $2CH_3$), (41.5, $2CH_2$-N), (28.8, $2CH_2$), (28.5, $2CH_2$), (28.5, $2CH_2$), (28.3, $2CH_2$), (26.0, $2CH_2$), Carom 127.7-145.3; Anal. Calcd for $C_{32}H_{44}N_6O_6S_2$: C, 57.12; H, 6.59; N, 12.49. Found: C, 57.11; H, 6.61; N; 12.58.

***1,12-bis (5-ethyl-2-tosyl-1,2,4-triazol-3-one-4-yl)dodecane* (2l).** yield (47%), mp166-168 °C; IR spectrum (v/cm^{-1}): 1730 (C=O), 1607 (C=N); ^{1}H NMR spectrum ($CDCl_3$): δ (ppm): 0.98 (t, J= 7.5Hz, 3H),1.59 (m, 16H), 2.10 (q, J= 7.5Hz, 2H), 2.37 (s, 6H), 2.80 (m, 4H), 4.66 (m, 4H), 7.31-7.79 (2AB(Ts), J= 8.1 Hz, 8Harom); Anal. Calcd for $C_{32}H_{44}N_6O_6S_2$: C, 57.12; H, 6.59; N, 12.49. Found: C, 57.11; H, 6.61; N; 12.58.

***1,2-bis(5-methyl-3-tosyl-1,3,4-triazol-2-onyl)cyclohexane* (2m).** yield (60%), mp 180-182ºC; IR spectrum (v/cm^{-1}): 1721 (C=O), 1585 (C=N); ^{1}H NMR spectrum ($CDCl_3$): δ (ppm): 1.36 (m, 4H), 1.76 (m, 4H), 2.00 (s, 6H), 2.45 (s, 6H), 4.63 (t, J= 6.3 Hz, 2H), 7.33-7.82 (2AB(Ts), J= 8.1, 8Harom);^{13}C NMR spectrum ($CDCl_3$): δ (ppm): (150.4, 2C=O), (146.9, 2C=N), (11.2, $2CH_3$), (21.7, $2CH_3$(Ts)), (24.4, $2CH_2$), (29.2, $2CH_2$), (53.5, 2CH-N), Carom 127.5-145.6; Anal. Calcd. for $C_{26}H_{30}N_6O_6S_2$: C, 53.23; H, 5.25; N, 14.32. Found: C, 53.05; H, 5.62; N, 13.99.

***1,2-bis(5-éthyl-3-tosyl-1,3,4-triazol-2-onyl)cyclohexane* (2n).** yield (30%), mp 190-192ºC; IR spectrum (v/cm^{-1}): 1718 (C=O), 1595 (C=N); ^{1}H NMR spectrum ($CDCl_3$): δ (ppm): 1.09 (t, J= 7.5Hz, 6H), 1.18 (m, 4H), 1.57 (m, 4H), 1.97 (q, J= 7.5Hz, 2H), 2.23 (s, 6H), 3.97 (t, J= 6.9 Hz, 2H), 7.42-7.67 (2AB(Ts), J= 8.1, 8Harom);^{13}C NMR spectrum ($CDCl_3$): δ (ppm): (151.7, 2C=O), (148.6, 2C=N), (8.9, $2CH_3$), (14.3, $2CH_2$), (21.3, $2CH_3$(Ts)), (29.2, $2CH_2$), (42.4, $2CH_2$), (61.4, 2CH-N), Carom 123.9-143.4; Anal. Calcd. for $C_{28}H_{34}N_6O_6S_2$: C, 54.71; H, 5.57; N, 13.67. Found: C, 54.49; H, 5.81, N, 13.42.

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