REGIOSELECTIVE SYNTHESIS OF NOVEL 1,4 DISUBSTITUTED BIS 1,2,3 TRIAZOLES : CLICK CHEMISTRY APPROACH

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ABSTRACT:
Regioselective synthesis of a series of new 1,4-disubstituted bis 1,2,3-triazoles 3a-j from 2,4-bis-propargyloxy acetophenones and organic azides are reported. Optimal experimental conditions were established for these triazoles catalysed by copper (II) sulfate pentahydrate in presence of sodium ascorbate by the conventional click chemistry. The compounds are characterized by the IR, \textsuperscript{1}H NMR, MS.

KEYWORDS: 1,2,3-Triazoles, Regioselective synthesis, propargyloxy acetophenones, organic azides, click chemistry

INTRODUCTION:
1,2,3-Triazole compounds have received much attention due to their wide range of applications in organic and medicinal chemistry.1,2,3-Triazoles have been used in pharmaceuticals, agrochemicals, dyes and photographic materials\textsuperscript{1}. There are numerous examples in the literature of the biological activity of triazole compounds as anti-HIV agents\textsuperscript{2} or antibiotic agents\textsuperscript{3} and as selective $\beta_3$ adrenergic agonist receptors\textsuperscript{4}. Several methods have been described for the synthesis of 1,2,3-triazoles, but commonly they are available from the thermally induced Huisgen cycloaddition reaction between azides and alkynes\textsuperscript{5}. This cycloaddition reaction usually affords mixtures of 1,4- and 1,5-disubstituted 1,2,3-triazoles\textsuperscript{6}. K.B.Sharpless and M.Meldal improved the regioselectivity of the reaction by Cu(I) catalyzed ligation (Click Chemistry) of organic azides and terminal alkynes\textsuperscript{7,8}. Exclusive 1,4-regioselectivity, mild reaction conditions, effective catalytic system wide substrate scope and high yields are the main advantages of Sharpless click chemistry. In view of wide range of applications of 1,2,3-triazoles we synthesized novel bis-1,2,3-triazole derivatives. Literature survey reveals that bis triazoles are not much explored.

EXPERIMENTAL SECTION

Instrumentation:
All melting points were measured on a Polmon digital melting point apparatus (Model No MP-96) and were uncorrected. IR spectra were recorded in KBr on Schimadzu-435 spectrophotometer. The \textsuperscript{1}H NMR spectra were recorded at 200 MHz on Varian Gemini Unity
Spectrometer using CDCl$_3$ and DMSO-d$_6$ solvent with TMS as internal standard (chemical shifts in $\delta$ ppm). The mass spectra were recorded on Perkin-Elmer Hitachi RDO-62 instrument.

**General procedure for the synthesis of 2,4 bis propargyloxy acetophenones(2a-b):**

Resacetophenones 1a-b (6g, 10 mmol) dissolved in acetone (40ml), propargylbromide (18.8g, 40mmol) was added and stirred at room temperature for 12 hrs. Acetone decanted and evaporated and then diluted with 200ml of ice cold water and extracted twice with ethyl acetate (2x100ml). The combined organic layer was washed with 200ml of water, 200ml of brine and finally dried over solid sodium sulphate, filtered and concentrated under reduced pressure to get the crude material containing compounds 2a-b as pale pink solid. The solid, which separated on column chromatography (60-120# silica gel) gave compounds 2a-b in pure form. Recrystallization from pet.ether gives as white needles (yield 68%). The products were characterized from their analytical and spectral data.

$1$-[2,4-bis(prop-2-yn-1-yloxy)phenyl]ethanone(2a): IR (KBr, $\nu_{\text{max}}$ cm$^{-1}$): 2160 & 2150 (C≡C), 1685 (CO). $^1$H NMR (200MHz, CDCl$_3$, $\delta$, ppm): 2.77 (d, 1H, $J=2.4$ Hz, C≡CVH), 2.80 (d, 1H, $J=2.4$ Hz, C≡CVH), 4.79 (d, 2H, $J=2.4$ Hz, OCH$_2$), 4.81 (d, 2H, $J=2.4$ Hz, OCH$_2$), 7.00 (d, 1H, $J=8.0$ Hz, aromatic), 7.50 (s, 1H, aromatic), 7.90 (d, 1H, $J=8.0$ Hz, aromatic). MS: m/z 228$[M]^+$.

$1$-[5-chloro-2,4-bis(prop-2-yn-1-yloxy)phenyl]ethanone (2b): IR (KBr, $\nu_{\text{max}}$ cm$^{-1}$): 2165 & 2152 (C≡C), 1690 (CO). $^1$H NMR (200MHz, CDCl$_3$, $\delta$, ppm): 2.6 (s, 3H, COCH$_3$), 2.78 (d, 1H, $J=2.4$ Hz, C≡CVH), 2.81 (d, 1H, $J=2.4$ Hz, C≡CVH), 4.80 (d, 2H, $J=2.4$ Hz, OCH$_2$), 4.82 (d, 2H, $J=2.4$ Hz, OCH$_2$), 8.00 (s, 1H, aromatic), 7.5 (s, 1H, aromatic). MS: m/z 262$[M]^+$.

**General procedure for the Synthesis of 1,4 disubstituted bis 1,2,3 triazoles (3a-j):**

Compounds 2a-b (10 mmol) and alkyl azides (2.66 mL, 20 mmol) were suspended in a 1:1 mixture of water and t-buty alcohol (40 mL). Sodium ascorbate (600 $\mu$L of freshly prepared 1M solution in water) was added, followed by copper (II) sulfate pentahydrate (0.06 mmol, in 200 $\mu$L of water). The heterogeneous mixture was stirred vigorously overnight and TLC analysis indicated complete consumption of the reactants. The reaction mixture was diluted with water (100 mL), cooled in ice, and the solid was collected by filtration. After washing the precipitate with cold water (2 x 25 mL), it was dried under vacuum to afford (3a-j).

$1$-(2,4-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethanone (3a): m.p. 130-132°C, IR (KBr, $\nu_{\text{max}}$ cm$^{-1}$): 1685 (CO). $^1$H NMR (200MHz, DMSO-d$_6$, $\delta$, ppm): 2.30 (s, 3H, COCH$_3$), 5.10 (s, 2H, benzyl), 5.20 (s, 2H, benzyl), 5.30 (s, 2H, OCH$_2$), 5.70 (s, 2H, OCH$_2$), 6.80-7.30(m, 11H, aromatic), 7.40 (d, $J=8.0$ Hz, aromatic), 7.70 (s, 1H, triazole), 7.80 (d, $J=8.0$ Hz, aromatic), 7.85 (s, 1H, triazole). MS: m/z 494$[M]^+$. Analysis: calculated for C$_{28}$H$_{26}$N$_6$O$_3$: C, 67.94 ; H, 5.25; N, 16.98. Found: C, 67.78; H, 5.18; N, 16.82.

$1$-(2,4-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-5-chlorophenyl)ethanone(3b): m.p. 139-142°C, IR (KBr, $\nu_{\text{max}}$ cm$^{-1}$): 1690 (CO). $^1$H NMR (200MHz, DMSO-d$_6$, $\delta$, ppm): 2.50 (s, 3H, COCH$_3$), 5.25 (s, 2H, benzyl), 5.35 (s, 2H, benzyl), 5.35 (s, 2H, OCH$_2$), 5.70 (s, 2H, OCH$_2$), 7.40 (m, 10H, aromatic), 7.50 (s, 1H, aromatic), 7.80 (s, 1H, aromatic), 7.90-8.00 (2s, 2H, triazole protons). MS: m/z 528$[M]^+$, 530$[M+2]$. Analysis: calculated for C$_{28}$H$_{25}$ClN$_6$O$_3$: C, 63.52 ; H, 4.72; N, 15.86. Found: C, 63.34; H, 4.56; N, 15.60.
1-(2,4-bis((1-butyl-1H-1,2,3-triazol-4-yl) methoxy)phenyl)ethanone (3c): m.p. 128-131°C, IR (KBr, vmax cm\(^{-1}\)): 1685 (CO). \(^1\)H NMR (200MHz, DMSO-d\(_6\), δ, ppm): 0.95 (2t, merged, 6H), 1.50 (m, 4H, (CH\(_2\)_2), 1.80(m, 4H, (CH\(_2\)_2)), 2.30 (s, 3H, COCH\(_3\)), 4.20 (2t, 4H, -N(CH\(_2\)_2)), 6.80 (d, 1H, J=8.3 Hz, aromatic), 7.00 (s, 1H, aromatic), 7.80 (d, 1H, J=8.3Hz, aromatic), 8.10-8.15 (2s, 2H, triazole). MS: m/z 426[M]\(^+\). Analysis: calculated for C\(_{22}\)H\(_{30}\)N\(_6\)O\(_3\): C, 61.89 ; H, 7.03; N, 19.69. Found: C, 61.63; H, 6.72; N, 19.47.

1-(2,4-bis((1-butyl-1H-1,2,3-triazol-4-yl) methoxy)-5-chlorophenyl)ethanone(3d): m.p. 135-137°C, IR (KBr, vmax cm\(^{-1}\)): 1685 (CO). \(^1\)H NMR (200MHz, DMSO-d\(_6\), δ, ppm): 0.98 (2t, merged, 6H), 1.60 (m, 4H, (CH\(_2\)_2)), 1.90(m, 4H, (CH\(_2\)_2)), 2.40 (s, 3H, COCH\(_3\)), 4.25 (2t, 4H, -N(CH\(_2\)_2)), 7.00 (s, 1H, aromatic), 7.80 (s, 1H, aromatic), 8.10-8.15 (2s, 2H, triazole). MS: m/z 460[M]\(^+\), 462[M+2]. Analysis: calculated for C\(_{27}\)H\(_{32}\)ClN\(_6\)O\(_3\): C, 57.27 ; H, 6.29; N, 18.22. Found: C, 57.05; H, 6.12; N, 18.10.

2',4',6'-4(4-acetyl-1,3-phenylene)bis(oxy)bis(methylene)bis(1H-1,2,3-triazole-4,1-diyl))bis(1-morpholinoethanone) (3e): m.p. 124-126°C, IR (KBr, vmax cm\(^{-1}\)): 1675 (NC=O), 1685 (COCH\(_3\)). \(^1\)H NMR (200MHz, DMSO-d\(_6\), δ, ppm): 2.30 (s, 3H, COCH\(_3\)), 2.92-3.00 (2t, 4H, J=5.4 Hz, (COCH\(_2\)_2)), 3.38-3.40 (m, 8H, (CH\(_2\)_2)), 3.35 (m, 8H, (CH\(_2\)_2)), 4.55-4.60 (2t, 4H, J=5.4 Hz, (N-CH\(_2\)_2)), 5.00 (s, 2H, OCH\(_2\)), 5.30 (s, 2H, OCH\(_2\)), 7.00 (d, 1H, J= 8.0Hz, aromatic), 7.70 (d, 1H, J = 8.0Hz, aromatic), 7.40 (s, 1H, aromatic), 7.80-8.20 (2s, 2H, triazole). MS: m/z 568[M]\(^+\), 604[M+2]. Analysis: calculated for C\(_{56}\)H\(_{54}\)N\(_{13}\)O\(_{13}\): C, 54.88 ; H, 5.62; N, 19.70. Found: C, 54.63; H, 5.48; N, 19.64.

2',4',6'-4(4-acetyl-6-chloro-1,3-phenylene)bis(oxy)bis(methylene)bis(1H-1,2,3-triazole-4,1-diyl))bis(1-morpholinoethanone)(3f): m.p. 130-131°C, IR (KBr, vmax cm\(^{-1}\)): 1670(NC=O), 1685 (COCH\(_3\)). \(^1\)H NMR (200MHz, DMSO-d\(_6\), δ, ppm): 2.40 (s, 3H, COCH\(_3\)), 2.95- 3.00 (2t, 4H, J=5.4 Hz, (COCH\(_2\)_2)), 3.40-3.43 (m, 8H, (CH\(_2\)_2)), 3.55 (m, 8H, (CH\(_2\)_2)), 4.58- 4.62 (2t, 4H, J=5.4 Hz, (N-CH\(_2\)_2)), 5.20 (s, 2H, OCH\(_2\)), 5.40 (s, 2H, OCH\(_2\)), 7.40 (s, 1H, aromatic), 7.80 (s, 1H, aromatic), MS: m/z 602[M]\(^+\), 604 [M+2]. Analysis: calculated for C\(_{56}\)H\(_{54}\)ClN\(_{13}\)O\(_{13}\): C, 51.73 ; H, 5.14; N, 18.57. Found: C, 51.49; H, 4.93; N, 18.36.

3,3'-(4,4'-4-acetyl-1,3-phenylene bis (oxy) bis (methylene) bis (1H-1,2,3-triazole-4,1-diyl)) bis (1-morpholinoopropan-1-one)(3g): m.p. 127-130°C, IR (KBr, vmax cm\(^{-1}\)): 1680(NC=O), 1690 (COCH\(_3\)). \(^1\)H NMR (200MHz, DMSO-d\(_6\), δ, ppm): 2.60 (s, 3H, COCH\(_3\)), 3.0-3.3 (2t, 4H, J=5.1Hz, (COCH\(_2\)_2)), 3.32-3.53 (m, 8H, (CH\(_2\)_2)), 3.65-3.67 (m, 8H, J=4.2 Hz, -(CH\(_2\)_4)), 4.58-4.60(2t, 4H, J=5.1Hz, (NCH\(_2\)_2)), 5.10 (s, 2H, OCH\(_2\)), 5.18 (s, 2H, OCH\(_2\)), 7.30 (s, 1H, aromatic), 7.50 (d, 1H, J= 8.0 Hz, aromatic), 7.80 (d, 1H, J=8.0 Hz, aromatic), 8.00-8.20 (2s, 2H, triazole). MS: m/z 630[M]\(^+\). Analysis: calculated for C\(_{28}\)H\(_{35}\)ClN\(_8\)O\(_7\): C, 53.24 ; H, 5.54; N, 17.74. Found: C, 53.09; H, 5.30; N, 17.58.

3,3'-(4,4'-4-acetyl-6-chloro-1,3-phenylene bis (oxy) bis (methylene) bis (1H-1,2,3-triazole-4,1-diyl)) bis(1-morpholinopropan-1-one)(3h): m.p. 135-137°C, IR (KBr, vmax cm\(^{-1}\)) 1682 (NC=O), 1690 (CO). \(^1\)H NMR (200MHz, DMSO-d\(_6\), δ, ppm): 2.70 (s, 3H, COCH\(_3\)), 3.0-3.33(2t, 4H, J=5.1Hz, (COCH\(_2\)_2)), 3.40-3.53 (m, 8H, N(CH\(_2\)_2)), 3.67-3.70 (m, 8H, -(OCH\(_2\)_4)), 5.15 (s, 2H, OCH\(_2\)), 5.20 (s, 2H, OCH\(_2\)), 5.60 (s, 2H, N-CH\(_2\)), 7.40 (s, 1H, aromatic), 7.90 (s, 1H, aromatic),
8.20-8.40 (2s, 2H, triazole). MS: m/z 596[M]+, 598 [M+2]. Analysis: calculated for C_{28}H_{36}N_{8}O_{7}: C, 56.31; H, 6.03; N, 18.77. Found: C, 56.15; H, 5.89; N, 18.62.

2,2'-(4,4'-(4-acetyl-1,3-phenylene)bis(oxy)bis(methylene)bis(1H-1,2,3-triazole-4,1-diyl))bis(butane-4,1-diyl))diisoindoline-1,3-dione(3i): m.p. 149-151°C, IR (KBr, vmax cm⁻¹) 1690 (CO), 1730 (CO, pthaloyl). ¹H NMR (200MHz, DMSO-d₆, δ, ppm): 1.80-2.10 (m, 8H, (CH₂)₄), 2.50 (s, 3H, COCH₃), 3.80-3.90 (2t, 4H, -NCH₂, pthaloyl), 4.25-4.27 (2t, 4H, -NCH₂), 5.10-5.20 (2s, 4H, OCH₂), 6.90 (d, 1H, J=8.0 Hz, aromatic), 7.00-7.40 (m, 10H, aromatic), 7.70 (d, 1H, J=8.0 Hz, aromatic). MS: m/z 716[M]+. Analysis: calculated for C_{38}H_{36}N_{8}O_{7}: C, 63.62; H, 5.02; N, 15.62. Found: C, 63.45; H, 4.85; N, 15.48.

2,2'-(4,4'-(4-acetyl-6-chloro-1,3-phenylene)bis(oxy)bis(methylene)bis(1H-1,2,3-triazole-4,1-diyl))bis(butane-4,1-diyl))diisoindoline-1,3-dione(3j): m.p. 154-156°C, IR (KBr, vmax cm⁻¹) 1695 (CO), 1750 (CO, pthaloyl). ¹H NMR (200MHz, DMSO-d₆, δ, ppm): 1.80-2.00 (m, 8H, (CH₂)₄), 2.40 (s, 3H, COCH₃), 3.70-3.80 (2t, 4H, -NCH₂, pthaloyl), 4.20-4.25 (2t, 4H, -NCH₂), 5.00-5.10 (2s, 4H, OCH₂), 7.00-7.40 (m, 10H, aromatic), 7.70 (s, 1H, aromatic), 7.90-8.10 (2s, 2H, triazole). MS: m/z 750[M]+, 752[M+2]. Analysis: calculated for C_{38}H_{35}ClN_{8}O_{7}: C, 60.70; H, 4.65; N, 14.90. Found: C, 60.56; H, 4.54; N, 14.78.

RESULTS AND DISCUSSION:

The aim of the present work was to develop simple and efficient procedure for the synthesis of bis 1,2,3-triazoles. The compounds resacetophenones 1a-b synthesized according to the literature procedure. The key intermediate 2a-b obtained by treating 1a-b with propargyl bromide in acetone-K₂CO₃ medium. The structures of 2a-b are characterized by spectral analysis. Compound 2a in its IR showed peaks at 2160 and 2150 cm⁻¹ (C≡C) and 1685 (CO). In the ¹H NMR of 2a the characteristic protons appeared at δ 2.50 (s, COCH₃), δ 2.70 (d, J=2.4 Hz, C≡CH), δ 2.80 (d, J=2.4 Hz, C≡CH), δ 4.79 (d, J=2.4 Hz, OCH₂), δ 4.81 (d, J=2.4 Hz, OCH₂), δ 7.00 (d, J=8.0 Hz, aromatic), δ 7.50 (s, aromatic), δ 7.90 (d, J=8.0 Hz, aromatic). The azides are prepared by the reaction of alkyl halides with sodium azide in water acetone medium (1:4). The compound 2a on reaction with benzyl azide in presence of CUSO₄.5H₂O and sodium ascorbate in water and t-butanol affords exclusively 1,4-regioisomer 1-(2,4-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethanone 3a, similarly 3b-j are synthesized under similar conditions. The compounds 3a-j characterized by spectral data. In the IR of 3a peak appeared at 1685 cm⁻¹ (CO). In the ¹H NMR the proton of the newly formed triazole rings appeared at δ 7.56 and 7.85 the benzyl protons as singlets at δ 5.20 and δ 5.60 and the OCH₂ protons as singlets at δ 5.30 and δ 5.70. The aromatic protons δ 6.80-7.30 (m, aromatic), δ 7.40 (d, J=8.0 Hz, aromatic), δ 7.80 (d, J=8.0 Hz, aromatic),
CONCLUSION: In conclusion we have developed a facile and convenient regioselective synthesis of a series of new 1,4-disubstituted bis 1,2,3-triazoles from bis propargyloxy acetophenones and organic azides catalysed by copper (II) sulfate pentahydrate in presence of sodium ascorbate by the conventional click chemistry.

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REFERENCE:

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