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Research Article

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Efficient click synthesis of substituted para acetamido benzene sulfonyl-1, 2, 3 –triazoles using PABSA and various terminal alkynes through cycloaddition

Jagadeesh Kumar Ega[1] and Ravinder Vadde[2*]

[1]*Department of Chemistry, Christu Jyothi Institute of Technology &Science, Jangaon, Warangal, TS, India*
[2]*Department of Chemistry, Kakatiya University, Warangal, Telangana State, India*

ABSTRACT

A two component reaction is used to prepare a series of disubstituted para-acetamidobenzenesulfonyl-1, 2, 3–triazoles from para acetamido benzene sulfonyl azides (PABSA) and terminal alkynes, also it reacts with o-propargylated terminal alkynes. This procedure eliminates the need to handle organic azides, as they are generated in situ, making this already powerful click process even more eco-friendly and safe through 1,3-dipolarcycloaddiation.

Keywords: Triazole, PABSA, Terminal alkyne's, Cycloaddition

INTRODUCTION

The pharmacologically active nitrogenous compounds, particularly 1, 2, 3-triazoles and their derivatives attracted considerable attention for the past few decades due to their chemotherapeutical value and parcel of the biomolecular diversity.[1-7] Many 1,2,3-triazoles, including bis-triazoles, are found to be potent antimicrobial, analgesic, anti-inflammatory, local anesthetic, anti-convulsant, anti-neoplastic, anti-malarial and antiviral agents.[8-10] Some of them exhibited anti-proliferative, anticancer activity, and several are used as DNA cleaving agents and potassium channel activators.

The 'click chemistry' approach method has been used for the regioselective synthesis of 1, 2, 3-triazoles, which involves the copper (I)-catalyzed cycloaddition reaction between azides and terminal alkynes (CuAAC) with mild reaction condition and very high yields.

The bioorthogonality of azide and alkynes[11] has allowed the use of their [3 + 2] 1, 3-dipolar cycloaddition to give triazoles.

EXPERIMENTAL SECTION

The homogeneity of the compounds was using percolated TLC plates (Merk, 60F-254) and spots work visualized in iodine vapor. The ^{1}H NMR spectra were recorded on a Bruker Avance IINMR 400 MHz instrument using $CDCl_3$ /DMSO as solvent and TMS as internal standard, chemical shifts are expressed as δ values (ppm). Mass spectra on Finnegan MAT – 1020, automated GC-MS and VG Auto Spec-M instruments. Elemental analysis was performed on a Carlo Elabs 1108 analyzer.

General procedure for the synthesis of compounds (3a-f)

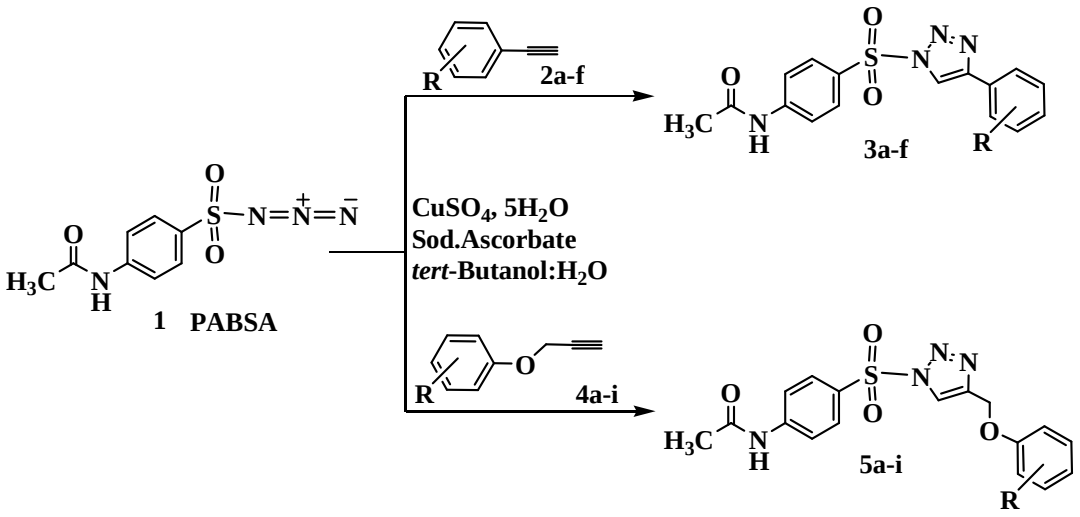
Terminal alkynes **2a-f** (0.040g, 0.22 mmol) was stirred in 5 ml of tertiary butanol and water (1:1 mixture). Copper sulphate (0.066 mmol) and sodium ascorbate (0.28 mmol) were charged into the reaction mixture. After 15 minutes, *p*-acetamido benzene sulphonyl azide (0.096g, 0.22 mmol) was added to the above mixture and the reaction mass was allowed to stirr for 20 min. The mixture was diluted with water extracted with DCM (2 x 20 ml). The combined organic layers were dried over anhydrous sodium sulphate and evaporated under reduced pressure to afford crude products, which were recrystallized (EtOAc/hexane) to afford pure compound**s (3a-f)** in quantitative yields. (Table – 1)

General procedure for the synthesis of compounds (5a-i)

o-propargylated terminal alkynes **4a-i** (0.0584g, 0.22 mmol) was stirred in 5 ml of tertiary butanol and water (1:1 mixture). Copper sulphate (0.066 mmol) and sodium ascorbate (0.28 mmol) were charged into the reaction mixture. After 15 minutes, *p*-acetamido benzene sulphonyl azide (0.096g, 0.22 mmol) was added to the above mixture and the reaction mass was allowed to stirr for 35-40 min. The mixture was diluted with water extracted with DCM (2 x 20 ml). The combined organic layers were dried over anhydrous sodium sulphate and evaporated under reduced pressure to afford crude products, which were recrystallised (EtOAc/hexane) to afford pure compounds **(5a-i)** in quantitative yields. (Table – 1)

Materials and Methods

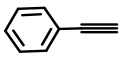
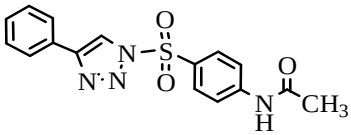
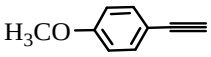
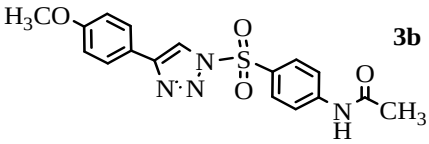
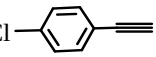
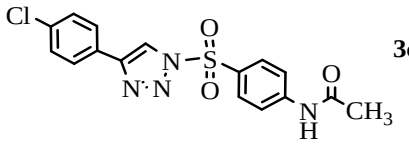
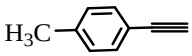
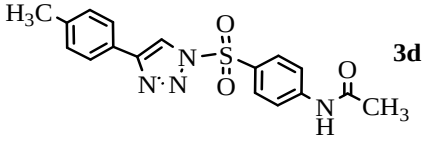
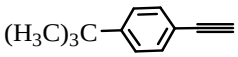
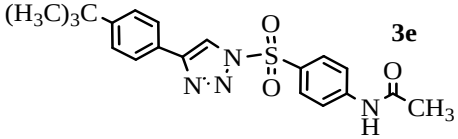
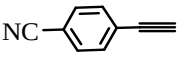
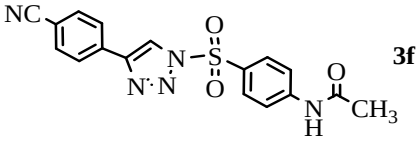
We describe a facile route for the synthesis of substituted 1,2,3-triazoles by readily available materials *via* catalytic azide-alkyne 1,3-dipolar cycloaddition. The compounds **(3a-f** & **5a-i)** were prepared by reacting terminal alkynes, o-propaglated alkynes (**2a-f & 4a-i**) with the respective *para*-acetamidobenzenesulphonyl azide (**1**) **(**Scheme - 1**).**

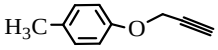
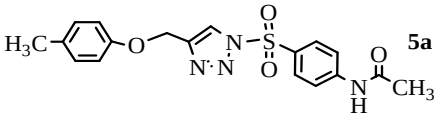
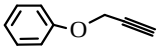
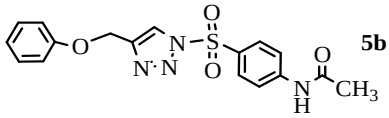
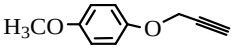
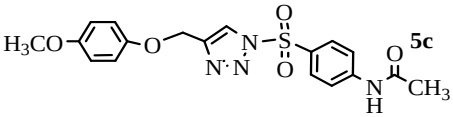
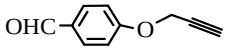
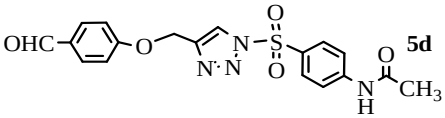
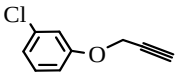
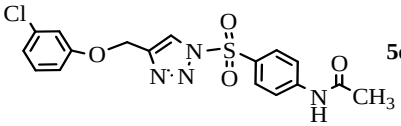
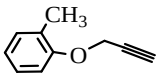
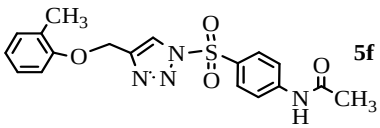
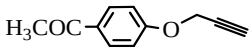
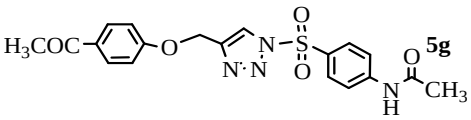
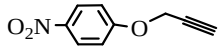
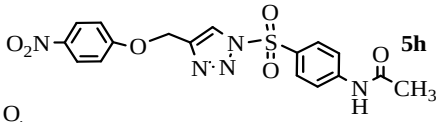
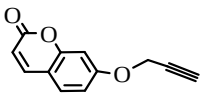
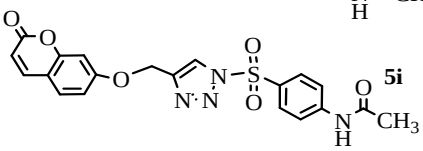


SCHEME – 1

Reaction of para acetamido benzene sulfonyl azides **(1)** with terminal alkynes **(2a-f)** and o-propargylated terminal alkynes **(4a-i).**

Table-1 Cu-catalyzed cycloaddition of terminal alkynes (2a-f) and o-propargylated terminal alkynes (4a-i) with azide (1)

Compd	Terminal alkyne	Product		Reaction time (min.)	Yield(%)
2a			**3a**	25	87
2b			**3b**	15	92
2c			**3c**	20	90
2d			**3d**	20	92
2e			**3e**	20	88
2f			**3f**	20	82

4a		 **5a**	40	92
4b		 **5b**	40	90
4c		 **5c**	25	95
4d		 **5d**	30	88
4e		 **5e**	35	90
4f		 **5f**	20	90
4g		 **5g**	20	85
4h		 **5h**	20	82
4i		 **5i**	20	92

All products were characterized by NMR and mass spectral analysis, GC yield based on azide after 20 minutes.

Spectral and Analytical data of compounds (3a–f) and (5a–i)

3a

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.12 (s, 3H), 6.82-7.14 (m, 5H, Ar-H), 7.82 (d, 2H, *J* = 7.2 Hz, Ar-H), 8.02 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.25 (s, 1H), 8.42 (s, 1H).
MS (EI, 70 eV): *m*/*z* (%) = 365 $[M + Na]^+$.
[Found C, 56.09, H, 4.10, N, 16.32 $C_{16}H_{14}N_4O_3S$ requires C, 56.13, H, 4.12, N, 16.36 %]

3b

^{1}H NMR(400 MHz,$CDCl_3$,25 °C):δ=2.12 (s, 3H),3.45 (s, 3H),6.65 (d, 2H, *J* = 7.8 Hz, Ar-H),7.73 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.82 (d, 2H, *J* = 7.2 Hz, Ar-H), 8.02 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.25 (s, 1H), 8.42 (s, 1H).
MS (EI, 70 eV): *m*/*z* (%) = 395 $[M + Na]^+$.
[Found C, 54.80, H, 4.32, N, 14.94 $C_{17}H_{16}N_4O_4S$ requires C, 54.83, H, 4.33, N, 15.04 %]

3c

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.12 (s, 3H), 6.68 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.70 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.82 (d, 2H, *J* = 7.2 Hz, Ar-H), 8.02 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.25 (s, 1H), 8.42 (s, 1H).
MS (EI, 70 eV): *m*/*z* (%) = 399 $[M + Na]^+$.
[Found C, 49.88, H, 3.46, N, 14.85 $C_{16}H_{13}ClN_4O_3S$ requires C, 51.00, H, 3.48, N ,14.87 %]

3d

^{1}H NMR(400 MHz, $CDCl_3$, 25 °C): δ = 2.10 (s, 3H), 2.12 (s, 3H),6.62 (d, 2H, *J* = 7.8 Hz, Ar-H),7.72 (d, 2H, *J* = 8.6 Hz, Ar-H),7.82(d, 2H, *J* = 7.2 Hz, Ar-H), 8.02 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.25 (s, 1H),8.42 (s, 1H).
MS (EI, 70 eV): *m*/*z* (%) = 379 $[M + Na]^+$.
[Found C, 57.28, H, 4.50, N, 15.70 $C_{17}H_{16}N_4O_3S$ requires C, 57.29, H, 4.52, N, 15.72%]

3e

^{1}H NMR(400 MHz, $CDCl_3$, 25 °C): δ = 0.94 (s, 9H), 2.12 (s, 3H), 6.81 (d, 2H, *J* = 7.8 Hz, Ar-H),7.76 (d, 2H, *J* = 8.6 Hz, Ar-H),7.82 (d, 2H, *J* = 7.2 Hz, Ar-H),8.02 (d, 2H, *J* = 8.1 Hz, Ar-H),8.25 (s, 1H),8.42 (s, 1H).
MS (EI, 70 eV): *m*/*z* (%) = 421 $[M + Na]^+$.
[Found C, 60.26, H, 5.52, N, 14.02 $C_{20}H_{22}N_4O_3S$ requires C, 60.28, H, 5.56, N, 14.06 %]

3f

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.12 (s, 3H), 6.85 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.82 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.94 (d, 2H, *J* = 8.6 Hz, Ar-H), 8.02 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.25 (s, 1H), 8.42 (s, 1H).
MS (EI, 70 eV): *m*/*z* (%) = 390 $[M + Na]^+$.
[Found C, 55.56, H, 3.55, N, 19.04 $C_{17}H_{13}N_5O_3S$ requires C, 55.58, H, 3.57, N, 19.06 %]

5a

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.10 (s, 3H), 2.12 (s, 3H), 5.32 (s, 2H), 6.80 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.45 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.82 (d, 2H, *J* = 7.2 Hz, Ar-H), 8.02 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.25 (s, 1H), 8.42 (s, 1H).
MS (EI, 70 eV): *m*/*z* (%) = 409 $[M + Na]^+$.
[Found C, 55.92, H, 4.65, N, 14.48 $C_{18}H_{18}N_4O_4S$ requires C, 55.95, H, 4.70, N, 14.50 %]

5b

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.12 (s, 3H), 5.32 (s, 2H), 6.42-7.26 (m, 5H, Ar-H), 7.82 (d, 2H, *J* = 7.2 Hz, Ar-H), 8.02 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.25 (s, 1H), 8.42 (s, 1H).
MS (EI, 70 eV): *m*/*z* (%) = 395 $[M + Na]^+$.
[Found C, 54.80, H, 4.32, N, 14.94 $C_{17}H_{16}N_4O_4S$ requires C, 54.83, H, 4.33, N, 15.04 %]

5c

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.12 (s, 3H), 3.45 (s, 3H), 5.34 (s, 2H), 6.65 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.78 (d, 2H, *J* = 8.2 Hz, Ar-H), 7.82 (d, 2H, *J* = 7.2 Hz, Ar-H), 8.02 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.25 (s, 1H), 8.42 (s, 1H).
MS (EI, 70 eV): *m*/*z* (%) = 425 $[M + Na]^+$.
[Found C, 53.70, H, 4.48, N, 13.90 $C_{18}H_{18}N_4O_5S$ requires C, 53.72, H, 4.51, N, 13.92 %]

5d
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.12 (s, 3H), 5.34 (s, 2H), 6.65 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.78 (d, 2H, *J* = 8.2 Hz, Ar-H), 7.82 (d, 2H, *J* = 7.2 Hz, Ar-H), 8.02 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.25 (s, 1H), 8.42 (s, 1H), 9.58 (s, 1H).
MS (EI, 70 eV): *m*/*z* (%) = 423 $[M + Na]^+$.
[Found C, 53.96, H, 4.00, N, 13.96 $C_{18}H_{16}N_4O_5S$ requires C, 53.99, H, 4.03, N, 13.99 %]

5e
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.12 (s, 3H), 5.32 (s, 2H), 6.40-7.58 (m, 4H, Ar-H), 7.82 (d, 2H, *J* = 7.2 Hz, Ar-H), 8.02 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.25 (s, 1H), 8.42 (s, 1H).
MS (EI, 70 eV): *m*/*z* (%) = 429 $[M + Na]^+$.
[Found C, 50.18, H, 3.70, N, 13.75 $C_{17}H_{15}ClN_4O_4S$ requires C, 50.19, H, 3.72, N, 13.77 %]

5f
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.06 (s, 3H), 2.12 (s, 3H), 5.32 (s, 2H), 6.80 (m, 4H, Ar-H), 7.82 (d, 2H, *J* = 7.2 Hz, Ar-H), 8.02 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.25 (s, 1H), 8.42 (s, 1H).
MS (EI, 70 eV): *m*/*z* (%) = 409 $[M + Na]^+$.
[Found C, 55.92, H, 4.68, N, 14.48 $C_{18}H_{18}N_4O_4S$ requires C, 55.95, H, 4.70, N, 14.50 %]

5g
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.08 (s, 3H), 2.12 (s, 3H), 5.32 (s, 2H), 6.80 (d, 2H, *J* = 6.5 Hz, Ar-H), 7.45 (d, 2H, *J* = 8.2 Hz, Ar-H), 7.82 (d, 2H, *J* = 7.2 Hz, Ar-H), 8.02 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.25 (s, 1H), 8.42 (s, 1H).
MS (EI, 70 eV): *m*/*z* (%) = 437 $[M + Na]^+$.
[Found C, 55.04, H, 4.35, N, 13.50 $C_{19}H_{18}N_4O_5S$ requires C, 55.06, H, 4.38, N, 13.52 %]

5h
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.12 (s, 3H), 5.34 (s, 2H), 6.94 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.82 (d, 2H, *J* = 7.2 Hz, Ar-H), 8.02 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.10 (d, 2H, *J* = 8.2 Hz, Ar-H), 8.25 (s, 1H), 8.42 (s, 1H).
MS (EI, 70 eV): *m*/*z* (%) = 440 $[M + Na]^+$.
[Found C, 48.90, H, 3.60, N, 16.75 $C_{17}H_{15}N_5O_6S$ requires C, 48.92, H, 3.62, N, 16.78 %]

5i
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.12 (s, 3H), 5.32 (s, 2H), 6.65-7.82 (m, 5H, Ar-H), 7.82 (d, 2H, *J* = 6.8 Hz, Ar-H), 8.02 (d, 2H, *J* = 7.4 Hz, Ar-H), 8.25 (s, 1H), 8.42 (s, 1H).
MS (EI, 70 eV): *m*/*z* (%) = 463 $[M + Na]^+$.
[Found C, 54.52, H, 3.64, N, 12.70 $C_{20}H_{16}N_4O_6S$ requires C, 54.54, H, 3.66, N, 12.72 %]

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