ISSN No:-2456-2165

Synthesis of novel 1H-1,2,3-triazol-1-yl-N-phenylacetamide Derivatives using Click Chemistry Via (CuAAC) Approach.

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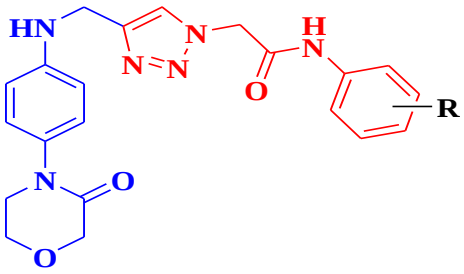
Abstract:- A series of seventeen novel analogues of 1H-1,2,3-triazol-1-yl-N-phenylacetamide derivatives were synthesized. The target compound 2-(4-(((4-oxomorpholino)phenyl)amino)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide have been synthesized by 4-(4-(prop-2-ynylamino)phenyl)morpholin-3-one and 2-azido-N-phenylacetamide addition of catalytic amount of sodium ascorbate and copper sulphate pentahydrate. The structures of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, Mass, ^{1}H NMR spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate and NMR analysis technique.

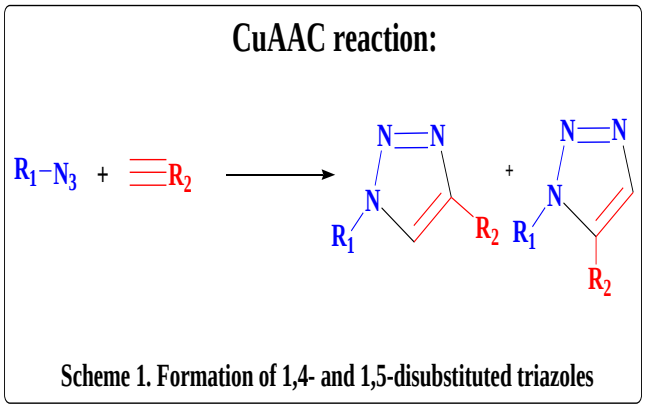


Keyword:- *2-(4-(((4-oxomorpholino)phenyl)amino)methyl)-1H-1,2,3-triazol-1- yl)-N-phenylacetamide, 4-(4-(prop-2-ynylamino)phenyl)morpholin-3-one, 2-azido-N-phenylacetamide, (CuAAC) Approach.*

I. INTRODUCTION

The word "Click Chemistry" was bring in by K. B. Sharpless in 2001 to illustrate reactions which are high percentage yielding, broad spectrum, impurity formed which are eliminated without use of chromatography, are stereospecific reactions, easy to operate and can be performed in benign or simply recoverable solvents. This idea was emerged to pharmaceutical, agrochemical and other industries for the synthesis of huge number of compounds used for screening in research work. These specifications are accomplished by some sorts of reactions which are thermodynamically controlled yields single product such as cycloaddition reactions, formation of heterocycles, addition reactions to olefin and alkyne bonds and oxidative formation of epoxides reactions.

1,3-dipole Azides, nitriloxides or diazoalkanes are 1,3-dipole which reacts with a alkenes, alkynes or carbonyl (dipolarophile) in a concerted means to yield a five-membered heterocycle. The significant reaction of click chemistry is the formation of 1,2,3-triazole from alkyne and azide by cycloaddition reaction. Reaction has low region-specificity as a result yields 1,4- and 1,5-substituted triazoles mixture and due to low tendency of alkynes as 1,3-dipolar acceptors requires high temperature for the reaction. (Scheme 1).

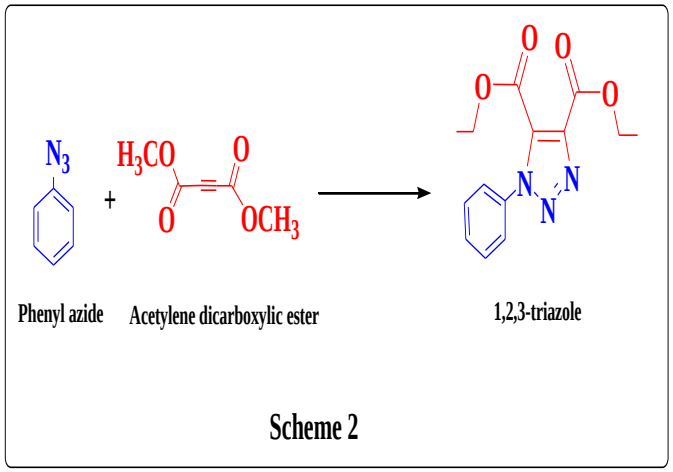


Scheme 1. Formation of 1,4- and 1,5-disubstituted triazoles

The thermal Huisgen1,3-dipolar cycloaddition reaction of alkynes and azides accomplished by higher temperature yields two regioisomers by using aassymetric alkynes. Hence cycloaddition reaction of 1,3-dipolar is not proper click reaction. The reaction was modified by employing copper catalyst has altered pathway of mechanism as well as

reaction carried out in aqueous media and at room temperature. Furthermore, mixture of regioisomers were produced in classic Huisgen 1,3-dipolar cycloaddition reaction while only one regioisomer 1,4-disubstituted synthesised in copper catalysed modified reaction. Later on opposite regioisoemr of 1,5-disubstituted 1,2,3-triazoles synthesized by using ruthenium catalyst. Such catalysed reaction fullfills all requirement of click chemistry and hence focused on click reaction of alkyne-azide cycloaddition.

Initially A. Micheall synthesized 1,2,3-triazole from acetylene dicarboxylic ester and phenyl azide in 1893 (Scheme 2) later by F. Holder and K. Raschig.



Scheme 2

II. MATERIALS AND EXPERIMENTAL METHODS

All reaserch reactions were carried out by Sigma–Aldrich chemicals. The progress of reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel GF254 plates from E-Merck Co. and compounds visualized by exposure to UV light. Melting points opf synthesized compounds were determined in open capillaries and are uncorrected. The IR spectra of compounds were recorded on SHIMADZU-FTIR-8400 spectrophotometer using KBr pellet method and ^{1}H NMR spectra of synthesized compounds were recorded on Bruker 300-MHz NMR spectrometer in DMSO-d6 solvent with Tetramethylsilane as internal standard. Mass spectra were recorded on JOEL SX 102/DA-600-Mass spectrometer.

EXPERIMENTAL:

General synthesis of INT-A (2-chloro-N-phenylacetamide)

To a solution of different substituted amine(1 equi) in acetone, chloroacetyl chloride (1 equi) was added dropwise and the resulting mixture was stirred for 2-3 hr at room temperature. Reaction mixture was then dumped into crushed ice and solid intermediate product fall out. It was separated and filtered and washed with water. Dry it and used in next step for reaction without further any purification.

General synthesis of INT-B (2-azido-N-phenylacetamide)

To a solution of INT-A(0.1 mmol.) in dimethylformamide(DMF), sodium azide(NaN3) was added (0.3 mmol) in round bottom flask. The resulting reaction mixture was stirred at room temperature for 24 hr. After completion of the reaction which was monitered by TLC. Reaction mixture was poured into crushed ice. Filter the separated product and dry it.

General synthesis of INT-C (4-(4-(prop-2-ynylamino)phenyl)morpholin-3-one)

In RBF, Take Amine (50mmol) in acetone(150ml) and added anhydrous potassium carbonate (100mmol) with stirring. After 5 minute propagyl bromide(55 mmol) was added slowly. As the addition was completed then reflux the reaction mass for 12 hrs. with continuous stirring. The progress of reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured into the crushed ice. Filter the separated product and wash with water to afford final compound.

General synthesis of Final Compound (2-(4-(((4-oxomorpholino)phenyl)amino)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide)

In a RBF containing DMF:H_2O:n-Butanol (1:1:1), INT-C(1 eqi), and INT-B(1eqi) was added at room temperature and followed by addition of catalytic amount of sodium Ascorbate and coppersulphate pentahydrate. Stir the resulting reaction mixture for RT for 24hrs. After the completion of the reaction, mixture was poured into the crushed ice and filter the separated product and wash with dilute ammonia and filter the product again.

III. REACTION SCHEME

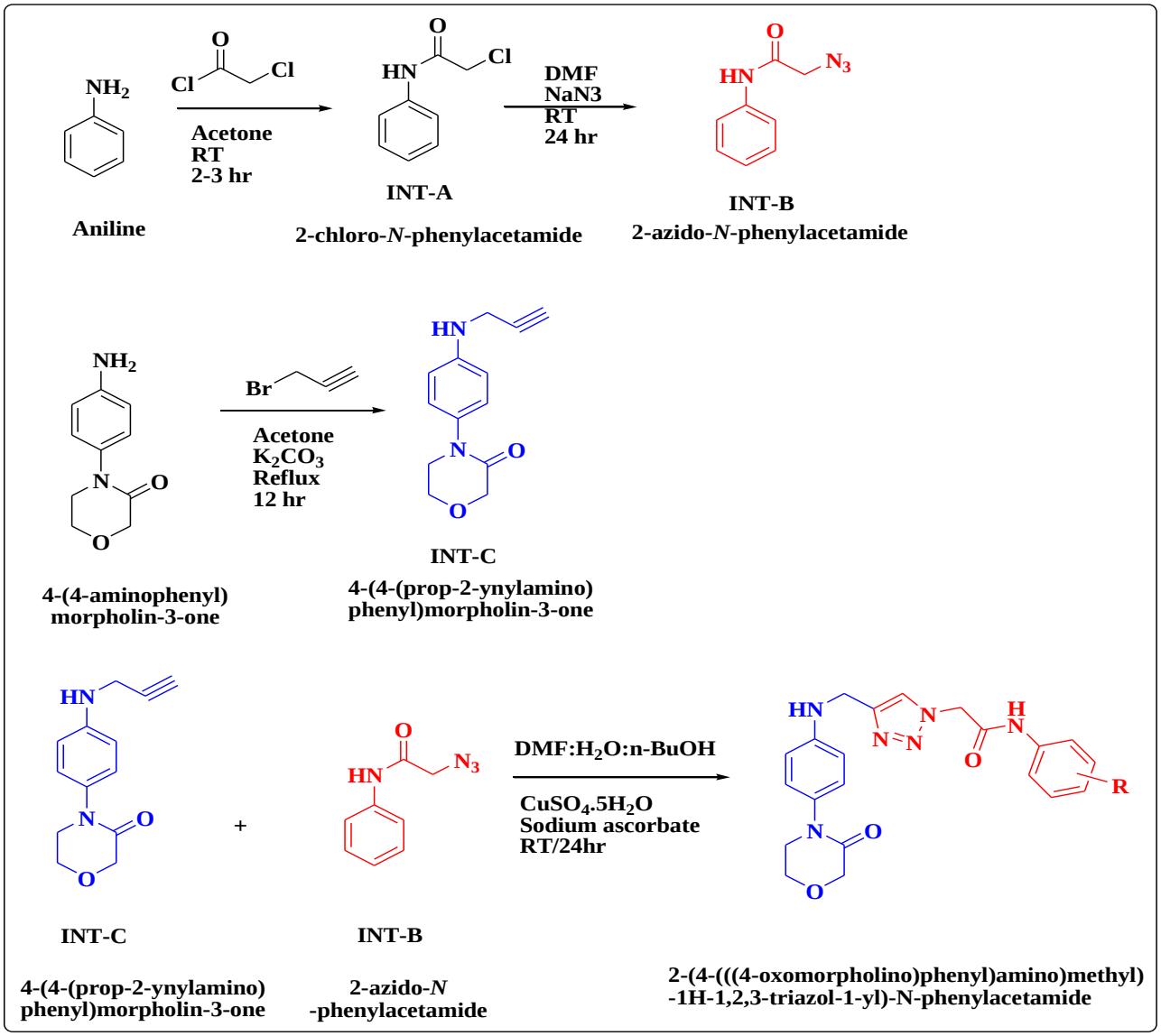


Table-1 Physical constant of synthesized library

Code	M.F.	R	M.W.	M.P. ^{0}C	% Yield
RRK-301	$C_{21}H_{22}N_6O_3$	H	406	186-188	72
RRK-302	$C_{21}H_{21}BrN_6O_3$	4-Br	485	182-184	75
RRK-303	$C_{21}H_{21}ClN_6O_3$	4-Cl	440	188-190	69
RRK-304	$C_{22}H_{24}N_6O_4$	4-OCH_3	436	186-188	82
RRK-305	$C_{22}H_{24}N_6O_3$	4-CH_3	420	190-192	80
RRK-306	$C_{21}H_{22}N_6O_4$	4-OH	422	184-186	72
RRK-307	$C_{21}H_{21}FN_6O_3$	4-F	424	192-194	68
RRK-308	$C_{21}H_{21}BrN_6O_3$	2-Br	485	184-186	83
RRK-309	$C_{21}H_{21}ClN_6O_3$	2-Cl	440	188-190	74
RRK-310	$C_{21}H_{21}FN_6O_3$	2-F	424	186-188	75
RRK-311	$C_{22}H_{24}N_6O_4$	2-OCH_3	436	190-192	68
RRK-312	$C_{22}H_{24}N_6O_3$	2-CH_3	420	186-188	78
RRK-313	$C_{21}H_{22}N_6O_4$	3-OH	422	192-194	81
RRK-314	$C_{21}H_{21}ClN_6O_3$	3-Cl	440	188-190	70
RRK-315	$C_{22}H_{24}N_6O_3$	3-CH_3	420	186-188	88
RRK-316	$C_{22}H_{26}N_6O_3$	2,4-dimethyl	434	192-194	81
RRK-317	$C_{21}H_{20}Cl_2N_6O_3$	2,4-dichloro	475	190-192	71

IV. SPECTRAL DATA OF SYNTHESIZES COMPOUND

2-(4-(((4-oxomorpholino)phenyl)amino)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide (RRK-301)
Off white solid, Rf Value 0.33(Methylene dichloride 9:Methanol 1), IR(KBr pallet) in CM^{-}3788, 3586, 3372, 3056, 2868, 2346, 1666, 1536, 1317, 1115, 987, 835, 665. ^{1}H NMR(DMSO, 400.1 MHz) in δ PPM: 8.00(Singlet, 1H of -NH), 7.56-7.58(Doublet, 1H -CH), 7.02-7.34(Multiplet, 15H aromatic), 6.64-6.66(Doublet, 1H -CH), 6.23(Singlet, 1H -CH_2), 5.29(Singlet, 1H -CH_2), 4.33(Singlet, 1H -CH_2), 4.13(Singlet, 1H of -NH), 3.58-3.93(Multiplet, 15H aromatic), Analytical calculated for Molecular formula $C_{21}H_{22}N_6O_3$ is C; 62.06%, H; 5.46%, N; 20.68%, found C; 60.68%, H; 5.18%, N; 19.26%.

N-(4-bromophenyl)-2-(4-(((3-oxomorpholino)phenyl)amino)methyl)-1H-1,2,3-triazol-1-yl)acetamide (RRK-302)
Off white solid, Rf Value 0.30(Methylene dichloride 9:Methanol 1), Analytical calculated for Molecular formula $C_{21}H_{21}BrN_6O_3$ is C; 51.97%, H; 4.36%, Br; 16.46% N; 17.32%, found C; 52.12%, H; 4.05%, Br; 15.96%, N; 18.65%.

N-(4-chlorophenyl)-2-(4-(((3-oxomorpholino)phenyl)amino)methyl)-1H-1,2,3-triazol-1-yl)acetamide (RRK-303)
Off white solid, Rf Value 0.32(Methylene dichloride 9:Methanol 1), IR(KBr pallet) in CM^{-}3896, 3561, 3389, 3210, 2921, 2599, 2373, 2112, 1630, 1417, 1293, 1058, 960, 749, 650. ^{1}H NMR(DMSO, 400.1 MHz) in δ PPM: 7.99(Singlet, 1H of -NH), 7.58-7.60(Doublet, 1H -CH), 7.01-7.39(Multiplet, 15H aromatic), 6.63-6.65(Doublet, 1H -CH), 6.23(Singlet, 1H -CH_2), 5.29(Singlet, 1H -CH_2), 4.33(Singlet, 1H -CH_2), 4.13(Singlet, 1H of -NH), 3.32-3.91(Multiplet, 15H aromatic), Analytical calculated for Molecular formula $C_{21}H_{21}ClN_6O_3$ is C; 57.21%, H; 4.80%, Cl; 8.04% N; 19.06%, found C; 58.09%, H; 4.65%, Cl; 9.24%, N; 20.75%.

N-(4-methoxyphenyl)-2-(4-(((3-oxomorpholino)phenyl)amino)methyl)-1H-1,2,3-triazol-1-yl)acetamide (RRK-304)
Off white solid, Rf Value 0.34(Methylene dichloride 9:Methanol 1), Analytical calculated for Molecular formula $C_{22}H_{24}N_6O_4$ is C; 60.54%, H; 5.54%, N; 19.25% found C; 59.15%, H; 6.07%, N; 18.11%.

N-(4-p-tolyl-2-(4-(((3-oxomorpholino)phenyl)amino)methyl)-1H-1,2,3-triazol-1-yl)acetamide (RRK-305)
Off white solid, Rf Value 0.31(Methylene dichloride 9:Methanol 1), Analytical calculated for Molecular formula $C_{22}H_{24}N_6O_3$ is C; 62.84%, H; 5.75%, N; 19.99% found C; 63.19%, H; 4.62%, N; 21.10%.

N-(4-hydroxyphenyl)-2-(4-(((3-oxomorpholino)phenyl)amino)methyl)-1H-1,2,3-triazol-1-yl)acetamide (RRK-306)
Off white solid, Rf Value 0.34(Methylene dichloride 9:Methanol 1), Analytical calculated for Molecular formula $C_{21}H_{22}N_6O_4$ is C; 59.71%, H; 5.25%, N; 19.89% found C; 58.31%, H; 6.35%, N; 18.80%.

N-(4-fluorophenyl)-2-(4-(((3-oxomorpholino)phenyl)amino)methyl)-1H-1,2,3-triazol-1-yl)acetamide (RRK-307)
Off white solid, Rf Value 0.34(Methylene dichloride 9:Methanol 1), Analytical calculated for Molecular formula $C_{21}H_{21}FN_6O_3$ is C; 59.43%, H; 4.99%, F; 4.48%, N; 19.80% found C; 59.89%, H; 4.24%, F; 3.65%, N; 20.14%.

V. RESULTS AND DISCUSSION

We have described the simple and economical route for the synthesis of triazole derivatives in excellent yield. In a RBF containing DMF:H2O:n-Butanol (1:1:1), INT-C and INT-B was added at room temperature. Then addition of catalytic amount of sodium ascorbate and copper sulphate pentahydrate. Then starring the resulting solution for room temperature for 24 hrs. After the completion of the reaction, reaction mass was poured into the crushed ice. Then filter the separated product and diluted with ammonia and again filtered the product. All the compounds were synthesized in good to high yield. We have confirmed the structure confirmation on the basis of spectroscopic techniques.

VI. CONCLUSION

In summary, the advantages of this current developed method over other prevailing methods are reduced milder conditions, higher yields, low costs and environmental safety. A series of substituted 1H-1,2,3-triazol-1-yl)-N-phenylacetamide have designed and synthesized in good to excellent yield. Suitable reaction condition for the synthesis of targeted compounds was studied. All the compounds are well characterized by various analytical techniques.

ACKNOWLEDGEMENTS

We are very much thankful to Department of Chemistry of Maharshi Dayanand Science College, Porbandar affiliated to Saurashtra University Rajkot for providing laboratory facilities.

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