Transition metal-free steric controlled one - pot synthesis of highly substituted N-amino 1, 2, 3-triazole derivatives via diazo transfer reaction from β-keto esters

Rajendran Nagarajan, Jayadevan Jayashankaran, Lourdusamy Emmanuvel

PII: S0040-4039(16)30495-6
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.04.112
Reference: TETL 47612

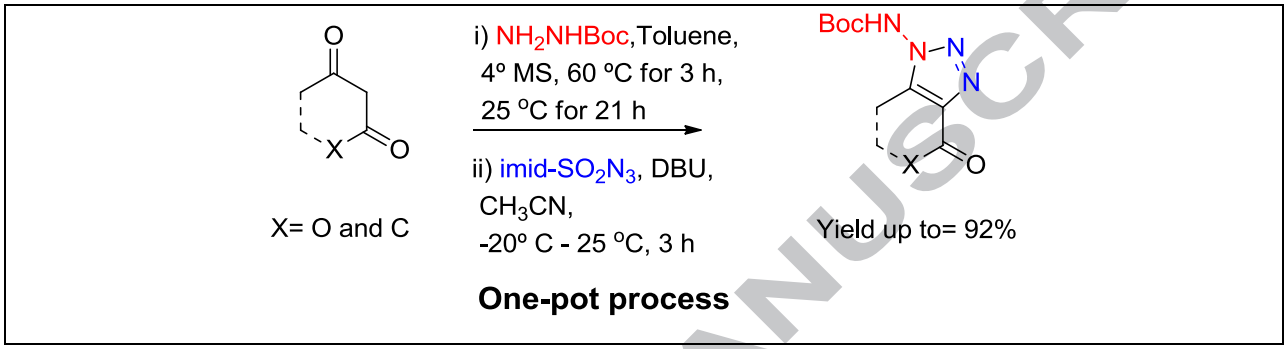
To appear in: *Tetrahedron Letters*

Received Date: 19 February 2016
Revised Date: 28 April 2016
Accepted Date: 29 April 2016

Please cite this article as: Nagarajan, R., Jayashankaran, J., Emmanuvel, L., Transition metal-free steric controlled one - pot synthesis of highly substituted N-amino 1, 2, 3-triazole derivatives via diazo transfer reaction from β-keto esters, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.04.112

Transition metal-free steric controlled one - pot synthesis of highly substituted N-amino 1, 2, 3-triazole derivatives via diazo transfer reaction from β-keto esters

Graphical Abstract:



An efficient, simple protocol for the one- pot synthesis of N-amino 1, 2, 3 – triazole from β-keto esters has been described. This method involves diazo transfer reaction into *in situ* generated hydrazones using imidazole sulfonyl azide as the nitrogen source. This protocol does not involve any transition metal and can be regarded as general method for the synthesis of N-amino 1, 2, 3 – triazole from hydrazones.

Transition metal free steric controlled one - pot synthesis of highly substituted N- amino 1, 2, 3-triazole derivatives via diazo transfer reaction from β-keto esters

Rajendran Nagarajan[a], Jayadevan Jayashankaran[b], Lourdusamy Emmanuvel[a]*

[a] *School of Science and Humanities, Department of Chemistry, Karunya University, Karunya Nagar, Coimbatore, 641114, India*

E-mail:emmanuvel@karunya.edu

Fax: 0422-2615615 *Ph:* +919042678370

[b] *Syngene International Ltd, Biocon Park , Plot 2&3, Bommasandra Industrial Estate - Phase-IV, Bommasandra-Jigani Link Road, Bangalore 560 099, India*

Keywords: N-amino 1, 2, 3-triazole, diazo transfer, metal free reaction, one-pot synthesis.

1, 2, 3-triazoles and their derivatives have recently received a considerable interest in organic synthesis and drug discovery.[1] They find applications in various fields such as optical brighteners,[2] dyes,[3] active pharmaceutical ingredients,[4] agrochemicals,[5] etc. Several 1, 2, 3-triazole derivatives have been found to possess biological activities such as anti-HIV, anti-microbial, anti-allergic, anti-fungal, anti-convulsant, etc.[6] Recently, N-amino 1,2,3-triazole derived ionic liquids had been studied for their use as high energy material.[7] After the discovery of regio selective 1,3 dipolar cycloaddition (Huigen's cycloaddition) of organic azide with alkynes or their precursors in the presence of catalyst to get 1,2,3-triazole,[8] one of the most studied click reactions, a large number of triazoles had been synthesized and screened for their potential applications. In spite of this click reaction being considered as a versatile method to obtain 1-alkyl or aryl 1, 2, 3-triazoles, this method cannot be employed to obtain N-amino 1, 2, 3-triazoles. And also, the reaction of azides with internal alkynes is less explored and results in

two regio isomers.[9] This poor regioselectivity limits the application of Huisgen's reaction to apply for the synthesis of 4, 5-disubstituted 1,2,3-triazoles.[9]

N-amino 1,2,3-triazoles, a relatively less explored class of triazoles mainly due to lack of practical method to access them, may be of greater interest as the functionalization would be easier and the extra N-H group would be expected to form hydrogen bonding with biological systems. As far our knowledge, direct introduction of nitrogen atom to the 1-position of 1, 2, 3-triazole (N-N bond formation) has not been reported till date. The most convenient method for the synthesis of N-amino 1, 2, 3-triazole involves MnO_2 mediated oxidation of glyoxal derived dihydrazones (**Fig.1**).[10] However, this method is not convincing for substituted triazole derivatives as the product selectivity is poor in non-symmetrical 1,2-dicarbonyl compounds, which limits the substrate scope of this method.[11] Another approach that involves spontaneous 1,5 electro cyclization of α-diazo hydrazones of α-diazo semicarbazones prepared via condensation of diazo compounds with hydrazines or semicarbazides respectively have also been reported.[12,15] Hence, the search for a simple practical method to obtain 1, 2, 3-triazole with nitrogen heteroatom at 1-position would be appreciated. In this communication we report the synthesis of highly substituted N-amino 1, 2, 3-triazole derivatives *via* diazo transfer reaction to β-keto ester derived hydrazones in one pot process.

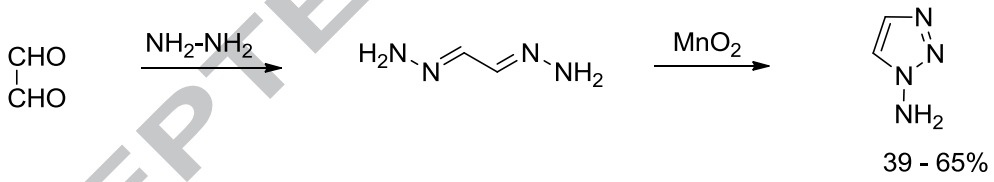
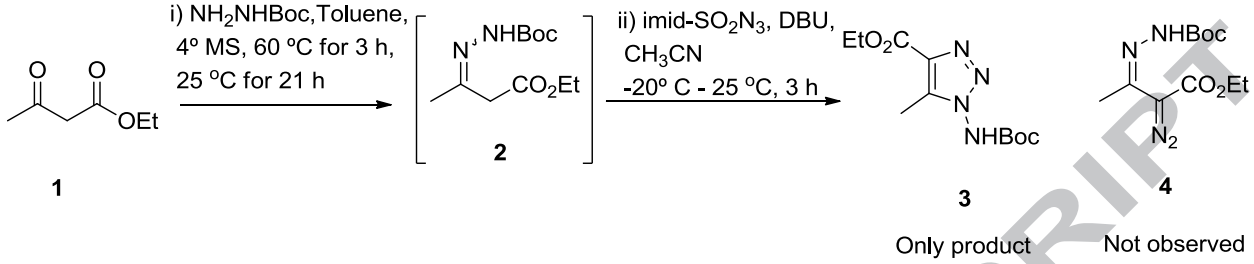


Fig. 1: Synthesis of N-amino 1, 2, 3- triazole

Recently, we found that diazo transfer reaction in oxime ethers results in N-alkoxy 1, 2, 3-triazoles as the minor product and the corresponding diazo compound in major quantity.[13] We envisaged that introduction of a bulkier group on nitrogen atom of imine may control the product selectivity and result in N-hetro atom substituted 1,2,3-triazole exclusively or as major product. Accordingly, when the hydrazone **2** derived from ethyl acetoacetate (**1)** by reacting with NH_2NH-Boc, was treated with imidazole sulfonyl azide in the presence of DBU in CH_3CN: Toluene (1:1) gave the corresponding N-amino 1, 2, 3- triazole derivative **3** as the only product

in 72% yield after column purification (**Scheme 1**). Unlike our earlier observation, α-diazo hydrazone **4** was not observed.

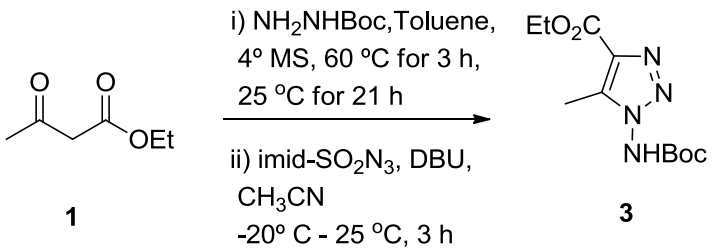


Scheme-1: Synthesis of N-amino 1,2,3-triazole

In order to optimize the reaction condition, we carried out the reaction with several sulfonyl azides and bases in different solvent system and the results are tabulated (**Table-1**). Hydrazone was prepared by reacting ethyl acetoacetate with NH_2NHBoc in toluene and found to be unstable and got converted back to β-keto ester when toluene was removed under rotary evaporator. To overcome this problem, 4^o molecular sieves was added and the reaction mixture was directly taken to the next step without workup.

Among the sulfonyl azides, both 4-toluene sulfonyl azide and imidazole sulfonyl azide gave comparable yields (Entry1 and 5; Table-1). Yet, we prefered imidazole sulfonyl azide as diazo transfer reagent since the by-product is water soluble. Equal volume of toluene and CH_3CN was found to be the best reaction medium. When toluene was employed as the only solvent the yield was poor (Entry 8). Removal of toluene under reduced pressure partially hydrolyzed the C=N bond and resulted in considerable amount of ethyl 2-diazo acetoacetate upon diazo transfer reaction (Entry 7; Table-1). Among the bases screened for the diazo transfer reaction, DBU was found to give better yield than Et_3N and N,N-diisopropylethylamine.

Table-1: Screening of sulfonyl azides, bases and solvent for diazo transfer reaction[a]

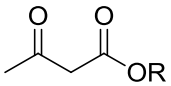
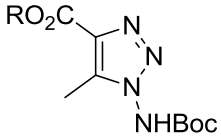


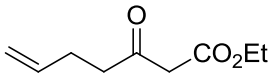
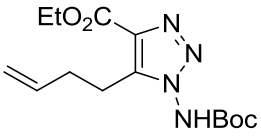
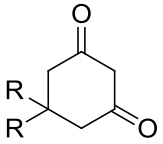
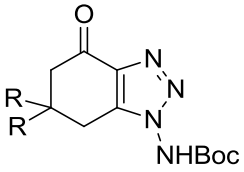
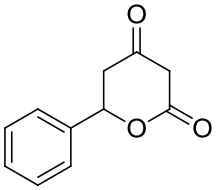
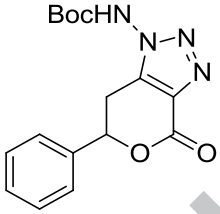
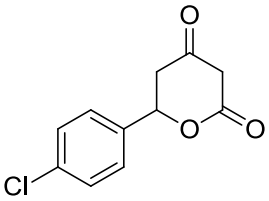
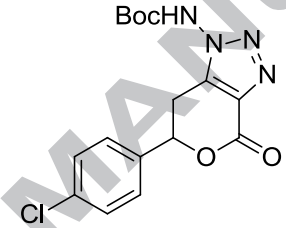
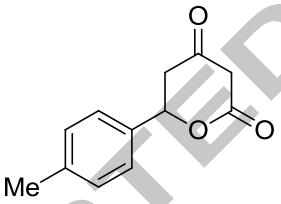
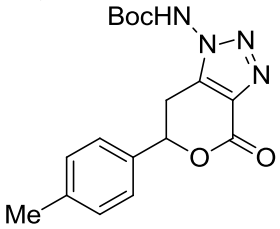
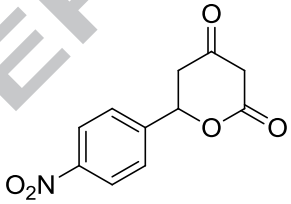
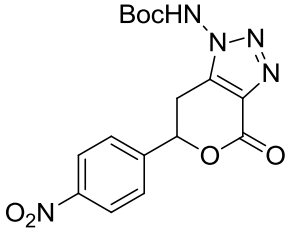
Entry	Sulfonyl azide	Base	Solvent	Yield(%)[b]
1	TsN_3	Et_3N	CH_3CN: Toluene	63
2	MsN_3	Et_3N	$CHCl_3$: Toluene	42[c]
3	4-$NO_2PhSO_2N_3$	Et_3N	CH_3CN: Toluene	40
4	Imid-SO_2N_3	Et_3N	CH_3CN: Toluene	58
5	Imid-SO_2N_3	DBU	CH_3CN: Toluene	72
6	Imid-SO_2N_3	DIPEA	CH_3CN: Toluene	32
7	Imid-SO_2N_3	DBU	CH_3CN	25(21)[d]
8	Imid-SO_2N_3	DBU	Toluene	19

[a]Reaction condition: i) NH_2NHBoc (3 mmol), substrate (3 mmol), 4^o MS (1 g), Toluene (10 ml), 60 ^{o}C for 3 h then 25 ^{o}C for 21 h. ii) sulfonyl azide (3.6 mmol), base (3.6 mmol), solvent (20 ml). [b]Yield refers to isolated yield by column chromatography. [c]Freshly prepared from MsCl was used. [d]Yield of the ethyl 2-diazo acetoacetate.

In order to study the substrate scope of this method, [14] several β-keto esters were subjected to this reaction and the results are given in table 2. From the table, we can find that β-keto esters gave the desired product in good yields irrespective of the ester groups (Entry a-c; table 2). It is surprising to observe that conformationally locked cyclic β-keto lactones gave better yields (Entry g-j; Table- 2) than non-cyclic β-keto esters. β-keto lactones were found to be stable under the reaction condition and the ring opening was not observed. Not only β-keto esters, but also cyclic 1, 3-diones (Entry e and f; Table-2) underwent this transformation in good yield. However, non-cyclic 1, 3 dione such as acetyl acetone failed to give the desired product.

Table-2: Synthesis of N- amino 1, 2, 3-triazole *via* diazo transfer reaction[a]

Entry	Substrate	Product (**3**)	Yield (%)[b]
a b c			R= Et; 68 R=Bn; 72 R=Me; 65

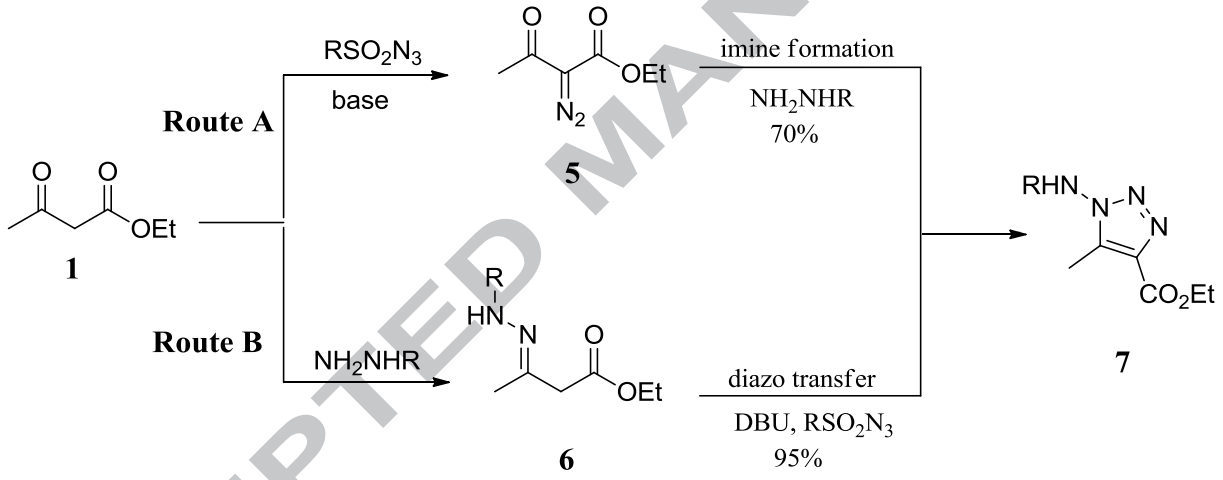
d			77
e f			R=H; 76 R= Me; 72
g			86
h			88
i			92
j			83

[a] Reaction condition: i) β Keto ester (3 mmol), NH_2NHBoc (3 mmol), Toluene (9 ml), 4^{o} MS, 60 ^{o}C, 3 h then rt for 21 h; ii) imidazole sulfonyl azide (3.3 mmol) Toluene:CH_3CN (1:1), DBU (3.3 mmol) 2 h; [b]isolated yield from column chromatography.

Cunha, A.C et.[15] al have followed a different approach to synthesize N aryl-amino-1, 2, 3-triazole derivatives **7** that involves hydrazone formation between aryl hydrazine and ethyl 2-diazo acetoacetate (**5**) and its 1,5-electro cyclization (**Route A, Scheme-2**). However, in the case

of NH_2NHBoc, contrary to many aryl hydrazines,[14] this route did not lead to Boc protected N-amino 1,2,3-triazole **7** even after reacting and diazo compound **5** in MeOH for 24 h. Moreover the yield of triazoles **7** decreased when electron deficient aryl hydrazine[15] was employed and completely failed to give triazole with 2, 4-dinitro phenyl hydrazine.

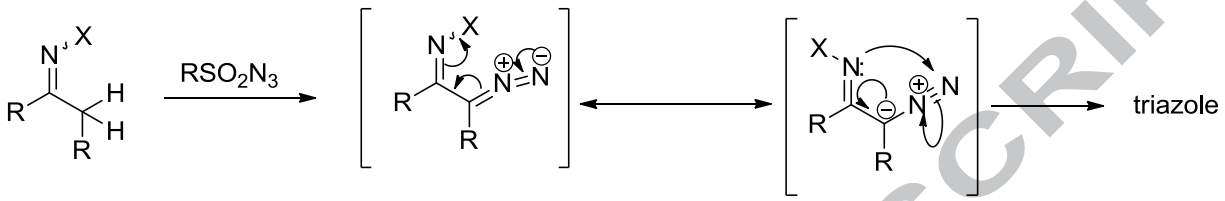
On the other hand, we were able to extend our present protocol for the synthesis of N-aryl amino 1, 2, 3-triazole derivatives more conveniently with improved yields. Accordingly, the hydrazone **6** was prepared from ethyl acetoacetate (**1**) and aryl hydrazine in quantitative yields and subjected to diazo transfer reaction using imidazole sulfonyl azide and DBU in acetonitrile to get **7** in excellent yields (**Route B; Scheme-2**). However, this route cannot be used with phenyl hydrazine as the condensation with ethyl acetoacetate does lead to a subsequent cyclization to give 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one.



	Yield (%) of **7**	
$RNHNH_2$	Route **A**	Route **B**
(**7 a**) R = Ph	70%	- [16]
(**7 b**) R = 2,4-$(NO_2)_2$Ph	No reaction	90
(**3 a**) R = Boc	No reaction	68

Scheme-2: Synthetic approaches to N aryl-amino-1, 2, 3-triazole

Mechanistically, it is very clear that the diazo compound **6** formed in the reaction was unstable and underwent spontaneous 1, 5-electro cyclization[17] triggered by the lone pair of electron on imine nitrogen (**Fig-2**). Resonance effect of diazo group destroys the stereo chemistry of the hydrozones and result in triazole as the only product.



6

Fig 2: Plausible Mechanism

In conclusion we have developed a simple method for the synthesis of N-amino 1, 2, 3-triazole derivatives *via* steric controlled diazo transfer reaction. These derivatives can readily be functionalized and can be screened for their biological activities. This method is free from transition metal and can be referred as general procedure for the synthesis of N-amino-1, 2, 3-triazole from hydrazones.

Acknowledgments:

The authors thank DST/SERB, New Delhi, India, for Fast Track financial support to carry out this research work. The authors also thank Dr. J. Daphy Louis Lovenia, Director, School of Science and Humanities and Dr. K. Parameswari, Head of the Department, Department of Chemistry for their constant support and encouragement.

References and notes:

1 (a) Benjamin, S.; Ulrich, S. S. *Chem. Soc. Rev.* **2014**, *43*, 2522. (b) Benson, F. R.; Savell, W. L. *Chem. Review.* **1950**, *46*, 1. (c) Antonino, L.; Riccardo, D.; Francesco, M.; Alessio, T.; Annamaria, M.; Giampaolo, B.; Anna, M. A. *Eur. J. Org. Chem.* **2014**, *16*, 3289. (d) Marcus, B.; Ian, R. B. *Beilstein. J. Org. Chem.* **2015**, *11*, 1194. (e) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249. (f) Finn, M. G.; Fokin. V. V. *Chem.Rev*. **2010**, *39*,

1231. (g) Hawker, C. J.; Wooley, K. L. *Science*, **2005**, *309*, 1200. (h) Donnelly, K. F.; Petronilho, A.; Albrecht, M. *Chem. Commun*. **2013**, *49*, 1145. (i) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev*. **2013**, *113*, 3084.

2 (a) Dougherty, E. M.; Guthrie, K. P.; Shapiro, M. *Biological Control.* **1996**, *7*, 71. (b) Daniel, L.; Florian, G.; Brigitte, H.; Berthold, S.; Christian, H.; Georg, A.; Reider.; Johannes, F. *Cryst. Growth Des*. **2014**, *14*, 1018. (c) Nicholas, W. S.; Annabel, A.; Christopher, M. B.; Sergei, V. D. *Bio-chem. Biophys. Res. Commun.* **2010**, *391*, 1455.

3 (a) Byungkwon, J.; Sung, Y. K.; Jung, Y. D. *Dyes. Pigm.* **2012**, *94*, 217. (b) Julian, J. L.; Plainfield.; Robert, S. L.; Bound, B.; Harold, M. F.; Somerville, N . J. *U.S. Patent.* **1958**, 2,865,916. (c) Lanter, J. *J. Soc. Dyers Colourists*. **1966**, *82*, 125.

4 (a) Nadeem, S.; Waquar, A.; Shamsher, A. M.; Ruhi, A.; Sanjay.; Jainb, B. A.; Jawaid, A. *Int. J. Phrm. Sci. Rev.Res.* **2011**, *8*, 161. (b) Simon, C.; Pranatharthi, H. C. *J. Antimicrob. Chemother*. **2010**, *65*, 410.

5 (a) Varsha, P. S.; Indu, S. S.; Kaushik, B.; Pallavi, N. W.; Sanjay, D. S. *J. Agric. Food. Chem*. **2015**, *63*, 10736. (b) Wechsler, K.; Rombourg, M.; Bindler, F.; Exinger, A.; Breuzin, C. *Intern. J. Enb. imn. Anal. Che.* **1996**, *65,* 277; (c) *Euro. Food. Saft. Auth. J.* **2009**, *7*, 1167.

6 (a) Derek, R. B.; Caroline, J. M. R.; Harry, S.; Barbara A, S. *J. Med. Chem.* **1984**, *27*, 223. (b) Pankaja, K.; Kadaba. *J. Med. Chem.* **1988**, *31***,** 196. (c) Sandip, G. A.; Suleman, R. M.; Vandana, S. P.; *Chem. Asian. J*. **2011**, *6*, 2696. (d) Alessandro, K. J.; Vitor, F. F.; Thiago, M. L. S.; Gabrielle, G.; Souza, F.; Viviane, M.; Juliana, L. A.; Maria C. B. V. S.; Anna, C. C. *Bioorg. Med. Chem.* **2011**, *19*, 1860.

7 (a) Ghule, V. D. *Comp. Theor. Chem.* **2012**, *992*, 92. (b) Ghule, V. D. *J. Phys. Chem. A.* **2012**, *116*, 9391. (c) Koguchi, S.; Izawa, K. *ACS Comb. Sci.* **2014**, *16*, 381. (d) Zhang, Y.; Parrish, D. A.; Shreeve, J, M. *J. Mater. Chem. A*, **2013**, *1*, 585.

8 (a) Huisgen, R. In *1, 3-Dipolar Cycloaddition Chemistry* In Padwa, A., Ed.; Wiley: New York, 1984; pp 1–176. Chapter 1; (b) Amblard, F.; Cho, J, H.; Schinazi, R. F. *Chem. Rev.* **2009,** *109*, 4207. (c) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.*, **2007**, *36*, 1249. (d) Wu, L. -Y.; Xie, Y. -X.; Chen, Z. -S.; Niu, Y. -N.; Liang, Y. -M. *Synlett.* **2009**, *9*, 1453. (e) Smith, C. D.; Greaney, M. F. *Org. Lett*, **2013**, *15*, 4826. (f) Luvino, D.; Amalric, C.;

Smietana, M.; Vasseur, J, -J. *Synlett*. **2007**, *19*, 3037. (g) Belskaya, N.; Subbotina, J.; Lesogorova, S. *Top. Heterocycl. Chem.* **2015**, *40*, 51.

9 (a) Vsevolod, V. R.; Luke, G. G.; Valery, V. F.; Sharpless, K. B. *Angew. Chem. Int. Ed*. **2002**, *41*, 2596. (b) Brant, C. B.; Sridhar, N.; Lars, K. R.; Li, Z.; Haitao, Z.; Zhenyang, L.; Guochen, J.; Valery V. F. *J. Am. Chem. Soc.* **2008**, *130*, 8923. (c) Masoud, F.; Mojtaba, A.; Alireza, P. A. *Cat. Comm.* **2016**, *76*, 72.

10 (a) Qiu, H. L.; Yu, C. Li.; Ya, Y. L.; Zhu, W.; Wei, L.; Cai, Q.; Si, P. P. *J. Mater. Chem*., **2012**, *22*, 666. (b) Greg, K.; Greg, D.; Kerri, T.; Leslie, H.; Tommy, H. *J. Heterocyclic Chem*. **2005**, *42*, 19. (c) Alexandrou, N. E.; Adamopoulos, S. *Synthesis*., **1976**, *7*, 482. (d) Bargamov, G. G.; Bargamova, M. D. *J. Fluorine Chem*., **1996**, *79*, 45.

11 (a) Stephanidou, J. S.; Varella, E.; Micromastoras, E. D.; Alexandrou, N. E. *J. Hetrocyclic Chem*., **1979**, *16*, 1373. (b) Benedetti, F.; Bozzini, S.; Forchiassin, M.; Nardin, G.; Pitacco, G.; Russo, C.; Valetin, E. *J. Heterocyclic Chem*. **1989**, *26*, 301.

12 (a) Sezer, O.; Dabak, K.; Akar, A.; Anac, O. *Helv. Chim. Acta*., **1996**, *79*, 449. (b) Jordao, A. K.; Ferreira, V. F.; Souza, T. M. L.; Faria, G. G. S.; Machado, V.; Abrantes, J. L.; Souza, M. C. B. V.; Cunha, A. C. *Bioorg. Med. Chem*., **2011**, *19*, 1860.

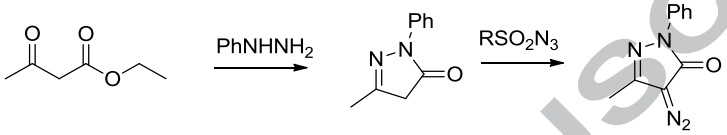
13 (a) Lourdusamy, E.; Yao, L.; Park. C. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 7963. (b) Kuruba, B. K.; Shariff, N.; Vasanthkumar, S.; Emmanuvel, L. *Synth. Commun*., **2015**, *45*, 2454.

14 **General Procedure for the synthesis of N-amino 1, 2, 3 triazole:** A two neck round bottom flask was charged with β-keto ester (3 mmol), NH_2NHBoc (3.3 mmol), toluene (10 ml), 4 ^{o} MS (1g) and was heated at 60 ^{o}C for 3 h then at 25 ^{o}C for 21 h. After confirming the formation of hydrazone by TLC, the reaction mixture was cooled to -20 ^{o}C and a solution of imidazole sulfonyl azide (3.3 mmol) in CH_3CN (10 ml) was added followed by DBU (3.3 mmol). After 2 h the reaction was quenched with water, diluted with ethyl acetate washed with water, brine, dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to get the crude product which was purified by column chromatography (silica gel) using pet.ether/ethyl acetate (90:10) to get pure compound. **Spectral data for tert-butyl (6-(4-nitrophenyl)-4-oxo-6,7-dihydropyrano[3,4-d][1,2,3]triazol-1(4H)-yl)carbamate (3j)**: Yellow solid , 83% (0.933 g); m.p 102 ^{o}C, IR (ν, cm^{-1}): 3250, 2982, 1752, 1606, 1524, 1349, 1276, 1158, 1039. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.56 (s, 1H), 8.30

(d, 2H, *J* = 9 Hz), 7.74 (d, 2 H, *J* = 9 Hz), 5.93 (dd, *J* =12, 4.2 Hz), 3.49 (s, 1H), 3.35 (s, 1H), 1.15 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.03, 152.90, 143.86, 142.35, 132.40, 127.30, 124.12, 84.64, 77.50, 28.03. HR-MS: Calculated=375.3268, found= 375.3259.

15 Jordao, A. K.; Afonso, P. P.; Ferreira, V. F.; Souza, M. C. B. V.; Almeida, M. C. B.; Beltrame, C. O.; Paiva, D. P.; Wardell, S. M. S. V.; Wardell, J. L.; Tiekink, E. R. T.; Clarissa R. Damaso, C. R.; Cunha, A. C. *Eur. J. Med. Chem.* **2009**, *44*, 3777.

16 Hydrazone formation resulted in 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one which can be subjected to diazo transfer reaction



17 (a) Vogel, M.; Lippmann, E. *J. Prakt. Chem*. **1989**, *331*, 75. (b) Raghavendra, M. S.; Lam, Y. *Tetrahedron Lett*. **2004,** *45*, 6129. (c) Jones, G.; Ollivierre, H.; Fuller, L. S.; Young, J. H. *Tetrahedron*, **1991**, *47*, 2851. (d) Augusti, R.; Kascheres, C. *Tetrahedron*, **1994**, *50*, 6723.

Highlights:

1) One pot synthesis of N-amino 1, 2, 3-triazole derivatives.
2) Transition metal free protocol.
3) It involves different approach from usual azide alkyne cyclization.