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Raney Ni Catalyzed Azide-Alkyne Cycloaddition Reaction

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Abstract:

Raney Ni efficiently catalyzes acetylene azide cycloaddtion reactions to form 1,2,3-triazoles. Unlike $CuSO_4$ / sodium ascorbate reagent system, there is no need for a reducing agent under Raney Ni catalysis. Terminal acetylene selectivity, 1,4-regioselectivity and mild reaction conditions are prominent features of the method. Mechanistic probing revealed that the reaction does not go through nickel acetylides.

1. Introduction

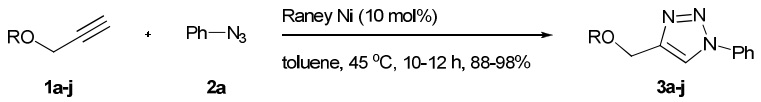
The Huisgen's 1,3-dipolar cycloaddition of azides to alkynes for the synthesis of 1,2,3-triazoles is one of the most prominent name reactions.[1] The reaction has become most applied for covalently linking two divergent molecular entities: one with a terminal acetylene group and other with an azide,[2] owing to independent discoveries by Sharpless and Meldal that copper(I)[3] catalysts efficiently promote azide alkyne cyloaddition (AAC) in high yield as well as in regio- (1,4- over 1,5-) and chemo- (terminal alkyne vs internal alkyne reactivity) selective manner. The copper(I) mediated azide acetylene cycloaddition (CuAAC) reactions have become premier examples for a click reaction as they provide near quantitative yield of the regiochemically pure 1,4-disubstituted 1,2,3-triazoles, tolerate a wide variety of functional groups and can be conducted under mild reaction conditions including in aqueous medium. The CuAAC reaction found applications[4] in diversified fields such as medicinal,[5]

polymer,[6] materials[7] and bioorganic[8] etc. Instead of employing Cu(I) complexes or its salts, which are relatively unstable or difficult to prepare, the CuAAC reactions are generally conducted with a catalytic amount of $CuSO_4$ and sodium ascorbate where sodium ascorbate serves as the reducing agent for *in situ* generation of Cu(I) species. According to well-accepted mechanism Cu(I) species gets intimately involved in every stage of the reaction and helps to bring azide and acetylene units in close proximity for cycloaddition to take place. Although the click reactions with $CuSO_4$ and sodium ascorbate have become hugely popular, still, the need for a reducing agent is one of the disadvantages of the method. Alternatively, some catalysts derived from Ag,[9] Au,[10] Al,[11] Ru,[12] and Ir[13] complexes which work without additional reducing agent have been employed to promote AAC, but the catalysts are difficult to make or expensive and most of the times reactions are cumbersome to conduct. Thus, there is a need to discover an alternative catalyst, which is inexpensive, readily available, reusable and does not require an additional reducing agent.

2. Results and discussion

In a quest to discover such a catalyst, we screened several bench top stable and inexpensive salts like $Ni(OAc)_2$, $NiCl_2$, $NiCO_3$, $NiSO_4$, $BiCl_3$, $BiNO_3$, As_2O_3 and Sb_2O_3 in catalytic amounts (10 mol%) for cycloaddition of phenyl propargyl ether **1a** to phenyl azide **2a** to provide triazole **3a** (Scheme 1). None of these catalysts worked independent of a reducing agent. The nickel salts like $Ni(OAc)_2$, $NiCl_2$, $NiCO_3$ and $NiSO_4$, catalysed the AAC reaction and provided triazole **3a** in moderate yield (< 70%) in presence of 20 mol% of the reducing agents like hydrazine, glucose, lactose or particularly sodium ascorbate. Outcome of the reaction indicated that reactive Ni(0) species could be the catalyst in the reaction. Therefore, in sequel, we employed Raney Ni as the catalyst and discovered that it catalyses the AAC efficiently (Scheme 1). Notably, there was no need for a reducing agent like sodium ascorbate when Raney Ni was employed. Raney Ni is a classical reagent used extensively as

a catalyst for hydrogenation of carbon-carbon and carbon-hetero atom double or triple bonds.[14] It is also used as a reagent for desulfurization. Thus, in continuation of our studies on the Huisgen reaction,[15] herein we report scope and limitations as well as some evidence for mechanism of the Raney Ni mediated AAC for a facile synthesis of several 1,2,3-traizoles.



1a-j **2a** **3a-j**

1a = R = Ph, **3a**: R = Ph (98%); **1b** = R = 4-t-Bu-C_6H_4, **3b**: R = 4-t-Bu-C_6H_4 (93%); **1c** =R = thymyl, **3c**: R = thymyl (91%); **1d** = R = eugenyl, **3d**: R = eugenyl (93%); **1e** =R = n-C_6H_{13}, **3e**: R = n-C_6H_{13} (89%); **1f** =R = $C_2H_5CCCH_2$, **3f**: R = $C_2H_5CCCH_2$(89%); **1g**: R = $C_6H_5CH_2$, **3g**: R = $C_6H_5CH_2$ (97%); **1h** = R = C_6H_{11} **3h**: R = C_6H_{11} (88%); **1i** = R = menthyl, **3i**: R = menthyl (93%); **1j** = R = cholesteryl,. **3j**: R = cholesteryl (89%).

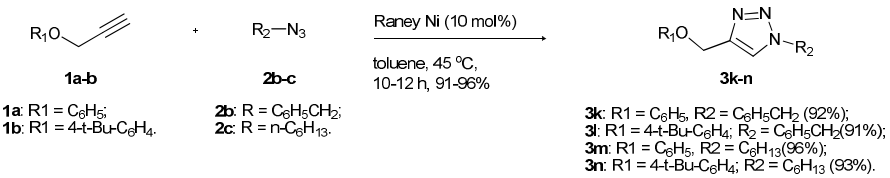
Scheme 1. Raney Ni catalyzed cycloadditions of phenyl azide **2a** with various propargyl ethers **1a-j**.

The cycloaddition of phenyl propargyl ether **1a** to phenyl azide **2a** to give cycloadduct **3a** under 10 mol% of Raney Ni catalysis was selected to optimize the reaction conditions (Scheme 1, Figure 1). Of different solvents like H_2O (15 h, 70%), *t*-BuOH/H_2O (1:2; 15 h, 82%), MeOH (16 h, 90%), DMF (16 h, 90%), dioxane (16 h, 87%) and toluene (10 h, 98%) tried, the reaction worked best in toluene. Stirring the heterogeneous reaction mixture at 45 ^oC for 12 h led to complete reaction in 98% yield as evidenced by the absence of phenyl propargyl ether **1a** in TLC. A study to determine optimal temperature for the reaction revealed that 45 ^oC is ideal for high yield and exclusive regioselectivity (1,4-susbitution over 1,5-substitution) of the product. Although at higher temperatures still, both the rate of the reaction and yield of the triazole were higher (99%), the regio-chemical purity of the product was lower. For example, at 100 ^oC the reaction took 1 h for completion but the product has 2:1 mixture of 1,4- and 1,5-regioisomers. At room temperature (30 ^oC) the reaction took longer time for completion (24 h, 80%). The fact that Raney Ni is practically

immiscible with toluene was used for the recovery of the product and to recycle the catalyst. After each reaction, the reaction mixture was centrifuged in a laboratory centrifuge at 2100 rpm for 1 min. Supernatant solution was separated and the settled Raney Ni cake was reused. The catalytic activity remained excellent for two runs (94%–98%). On further use, the yield started to decrease (84% in the third run) with a concurrent increase in the time required to complete the reaction. Concentration of copper impurities in the Raney Ni sample was analyzed using ICP-MS to evaluate if such copper impurities are responsible for AAC reaction. Using ICP-MS analysis technique one can identify copper, for that matter, most of the metal impurities present even below ppb levels.[16] The analysis clearly showed that the Raney Ni sample we were employing does not have copper impurities up to ppb level. This result made us conclude that Ni is responsible for the AAC reaction.

Building on the results from development of optimal conditions for the NiAAC reaction of phenyl propargyl ether **1a** to phenyl azide **2a** to give the regiochemically selective triazole **3a**, we wanted to probe the effect of different substitution on propargyl ethers and azides. Nine propargyl ethers, namely, 4-*t*-butylphenyl propargyl ether **1b**, thymol propargyl ether **1c**, eugenol propargyl ether **1d**, *n*-hexyl propargyl ether **1e**, 1-(prop-2-ynyloxy)pent-2-yl propargyl ether **1f**, benzyl propargyl ether **1g**, cyclohexyl propargyl ether **1h**, menthyl propargyl ether **1i**, cholesteryl propargyl ether **1j** were reacted with phenyl azide **2a** to realize exclusive formation of regiochemically pure triazoles **3b-j**, in excellent yield. The propargyl ethers were selected for their structural diversity of being derived from an alcohol group present on aromatic, benzylic, aliphatic or natural product scaffolds. Significantly, the NiAAC was not affected in terms of yield or regioselectivity by subtle changes in steric and electronic environment in the aryl ring of the propargyl ethers. Among all the products listed in Scheme 1, **3f** is interesting as it proved that similar to CuAAC reactions, the NiAAC takes place on terminal alkyne rather than internal alkyne.

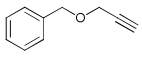
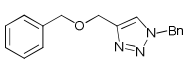
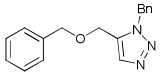
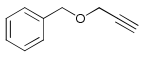
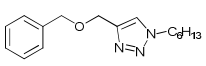
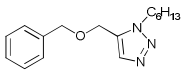
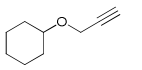
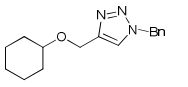
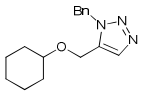
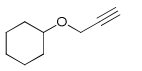
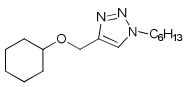
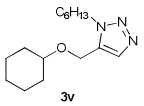
Next, it was our endeavour to evaluate the efficiency of Raney Ni catalyst in the regioselectivity in the cycloaddition of benzyl and hexyl azides to aryl propargyl ethers. Accordingly two aryl propargyl ethers, namely phenyl propargyl ether **1a** and 4-*t*-butylphenyl propargyl ether **1b** were subjected to Raney Ni catalyzed AAC with benzyl azide **2b**, and hexyl azide **2c** in combinatorial fashion to realize four 1,4-disubstituted triazoles **3k**-**n** in near quantitative yield with exclusive regiochemistry (Scheme 2).



Scheme 2. Raney Ni mediated combinatorial cycloaddition of two aryl propargyl ethers to benzyl and *n*-hexyl azides.

The NiAAC reaction of benzyl **1c** and cyclohexyl **1d** propargyl ethers to benzyl **2b** and *n*-hexyl **2c** azides was conducted in combinatorial fashion to evaluate efficiency of the catalyst for promoting the reaction of alkyl propargyl ethers and alkyl azides (Table 1). Raney Ni aided the cycloaddition of benzyl **2b** and *n*-hexyl **2c** azides to propargylic ethers **1c-d** efficiently in providing cycloadducts **3o-v** in excellent yield. But, the regiochemistry, unfortunately, was scrambled to some extent with the formation of major 1,4-regio isomers **3o-r** and along with the corresponding minor 1,5-regioisomers **3s-v** (Table 1). Ratios of the regio-isomers were calculated on the basis of integration of relevant signals in the mixture ^{1}H NMR and ^{13}C NMR spectra. The results indicate that two transition states that lead to 1,4- or 1,5-disubstituted traizoles may not have much difference in free energy and thus both orientations as shown in proposed mechanism are possible (Scheme 4).

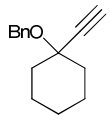
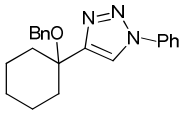
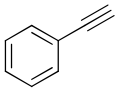
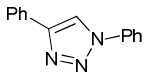
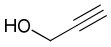
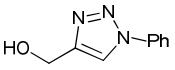
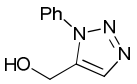
Table 1. The 1,4 and 1,5-isomers formed in the combinatorial NiAAC reaction of benzyl and cyclohexyl propargyl ethers to benzyl and *n*-hexyl azides.

S.No	alkyne	azide	1,4 and 1,5 isomers	1,4 and 1,5 isomers ratio	% yield
1	 **1c**	$C_6H_5CH_2N_3$ **2b**	 **3o**  **3s**	1:07	93
2	 **1c**	$n\text{-}C_6H_{13}N_3$ **2c**	 **3p**  **3t**	1:02	93
3	 **1d**	$C_6H_5CH_2N_3$ **2b**	 **3q**  **3u**	1:1	91
4	 **1d**	$n\text{-}C_6H_{13}N_3$ **2c**	 **3r**  **3v**	1:05	89

Finally, we conducted NiAAC of phenyl azide **2a** with three alkynes namely (((1-ethynylcyclohexyl)oxy)methyl)benzene **1e**, phenyl acetylene **1f** and popargyl alcohol **1g** to evaluate versatility of NiAAC reaction. The NiAAC reaction of propagyl ether **1e**, where C(1) carbon is disubstituted, provided the cycloadduct 4-(1-(benzyloxy)cyclohexyl)-1-phenyl-1*H*-1,2,3-triazole **3w** exclusively, indicating that the reaction is not effected by steric hindrance close to the reaction site. The NiAAC reaction of phenyl acetylene **1f** with phenyl azide provided regiochemically pure 1,4-diphenyl-1*H*-1,2,3-triazole[17] **3x** indicating that NiAAC reaction can be extended to aryl acetylenes. The NiAAC reaction of propargyl alcohol **1g** and phenyl azide, however, provided the 1,4- and 1,5-regioisomeric triazolyl methanols **3y** and **3z** in the ratio of about 3:2. The AAC reaction of propargyl alcohol **1g** and phenyl azide **2a** without any catalyst also provided the 1,4- and 1,5-regioisomeric adducts **3y-z** in 3:2 ratio but the reaction required heating by microwaves to 140 ^{o}C in polyethylene glycol-200 for 2 min. The CuAAC reaction of propargyl alcohol with phenyl azide, on the other hand, provided 1,4-regioisomer **3y** exclusively.[18] The results indicate that AAC under

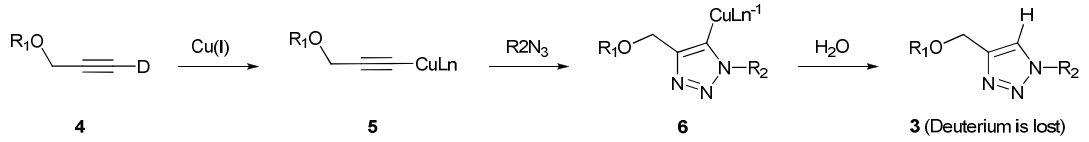
Ni catalysis takes place at much lower temperature (45 ^{o}C vs 140 ^{o}C) and since NiAAC reaction provided both the regioisomers it could go through a mechanistic pathway different from CuAAC.

Table 2. The NiAAC reaction of phenyl azide with different alkynes.

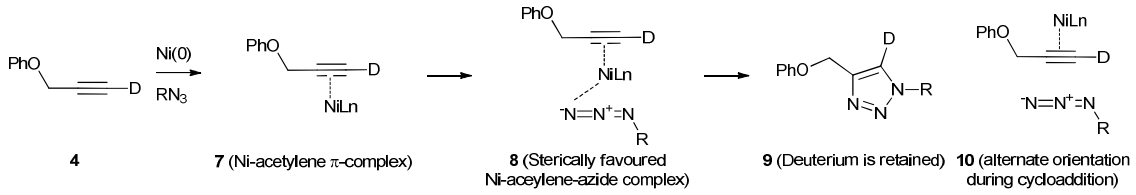
S.No	alkyne	NiAAC products	1,4 and 1,5 isomers ratio	% yield
1	 **1e**	 **3w**	100:0	90
2	 **1f**	 **3x**	100:0	89
3	 **1g**	 **3y**  **3z**	64:36	93

One of the principal and initial intermediates in the Sharpless–Meldal version of the CuAAC reaction is the copper acetylide **5** generated by oxidative insertion of Cu(I) into CH bond of a terminal alkyne **4** (Scheme 3). This step appears to be crucial to the cycloaddition of azides to the acetylenic triple bond. In the next step copper gets involved in bringing together copper acetylide and the azide through π-complexation with alkyne and coordination to the terminal nitrogen of the azide. The cycloaddition leads to organocopper intermediate **6**, which gets hydrolysed to provide **3** on addition of water. However, in confined places like in zeolites, there may not be copper acetylide formation and the cylcoaddition could go through metallocycle.[19] The Ni(0) catalyzed AAC reaction could also work in a similar fashion, initiated by Ni acetylide formation. Or, Ni(0) could play a role in bringing the reactants together though π-complexation and coordination. To probe the mechanism of the NiAAC reaction, experiments with deuterated phenyl propargyl ether ((((3-deuteroprop-2-yn-1-

yl)oxy)methyl)benzene)[20] **4** with phenyl azide **2a** were performed. The deuterium present on terminal acetylenic carbon gets lost, if the reaction goes through Ni acetylide formation. On the other hand, if the Ni(0) plays the role of a coordinating species deuterium is retained. In the Ni(0) catalyzed AAC reaction, we observed almost 100% retention of deuterium in the product **8** (Scheme 4). This result indicates that unlike that of CuAAC, in the first step, Ni(0) does not insert into CH of alkyne to form Ni acetylide. Mechanistically, the reaction could go through complexation of the acetylene on Raney Ni surface to form π-complex **7** (Scheme 5) followed by cycloaddition of the azides to form adduct **9** via complex **8** where both acetylene and azide components are held by Ni. On the other hand, the Ni complex with acetylene moiety could undergo cycloaddition with azide moiety in the orientation as shown in **10**. Steric and electronic characteristics of the azide and to some extent those of propargyl ether make the transition states **8** or **10** energetically more favourable to provide 1,4-adduct in preference to 1,5-adduct.



Scheme 3. Accepted mechanism for the CuAAC.[21]



Scheme 4. Proposed mechanism for the NiAAC.

3. Conclusion

In conclusion, we have demonstrated that Raney Ni is an alternative catalyst to copper(II) sulphate and sodium ascorbate recipe for effecting AAC reaction. Notably,

additional reducing agent is not required when Raney Ni is used. Moreover, the recovery of the products by the present method is greatly facilitated, because simple centrifugation and solvent evaporation provide pure 1,4-disubstituted 1,2,3-triazoles. In most of the cases, exclusive 1,4-disubstitution in triazole products is observed. Mechanistic probing indicated that Raney Ni plays the role of coordinating species in bringing together azide and alkyne.

4. Experimental section

4.1 General

Analytical thin-layer chromatography (TLC) was performed on silica gel coated on glass plates (0.25 mm, silica gel G, LOBA Chemicals, UV silica gel GF 254). TLC spots were visualized under UV light and iodine. Column chromatography was carried out using silica gel 100-200 mesh (LOBA Chemicals) using a hexanes-ethyl acetate eluent mixture. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$+ CCl_4 (1:1) and chemical shifts values (δ) are relative to the residual solvent peak (δ 7.26 for ^{1}H, δ 77.16 for ^{13}C) where possible or alternatively to TMS (δ 0.00) as internal standard. Coupling constants (*J*) are given in Hz and multiplicities are designated as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet). NMR spectra were recorded for all the samples to determine the number of hydrogen atoms present on each carbon. Although spectral data was obtained for all the compounds prepared in the present study, spectral data of only unknown compounds are provided here. Melting points were determined using open-ended capillary tubes on VEEGO VMP-DS instrument and are uncorrected. The propargyl ethers were prepared according to the literature procedure from the corresponding alcohol or phenols.[22] Phenyl, benzyl and hexyl azides[23] were prepared by following the literature procedures. **3a**,[24] **3k**,[25] **3m**,[26] **3l**,[27] **3x**,[17] **3y**,[18] **3c**, **3d**, **3i** and **3j**[15] are known compounds. Spectral data of the unknown compounds excepting **3a** is given here. Where mixture of regioisomers were obtained, spectral data of the 1,4-regioisomer culled from the mixture

NMR spectral data was given. Approximately 10 mol% of Raney Ni present as a suspension in dry EtOH was transferred into dry nitrogen flushed RB flask. Excess EtOH was removed under reduced pressure using Schlenk line. The amount of reactants was calculated on the basis of the accurate weight of Raney Ni taken in the RB flask. The reactants were dissolved in dry toluene before transferring into the RB. Contents of the RB with constant stirring were heated to 45 ^{o}C in a preheated oil-bath. We evaluated if any Raeny Ni catalyst leached by taking the NiAAC of phenyl acetylene and phenyl azide as standard and found that less than 0.4% of the catalyst reduced weight in each of the three consecutive runs (see supplementary information for details). Although we cannot rule out absence of leaching, we attribute decrease in weight of Raney Ni to experimental error.

4.2. ICP-MS analysis of Raney Ni for detection of trace amounts of copper

Five samples each having 10 mL of 460 ppb Raney Ni digested in aq 2 N HNO_3 (milli-Q water of specific resistance less than 15 mΩ) and spiked with 0, 1, 2, 3, 4 mL of 24.4 ppb Cu containing $CuSO_4.5H_2O$ solution, were prepared and analyzed in ICP-MS (Thermo Scientific, X SERIES 2) for determination of Cu content at ppb levels in blank by calibration method[28] (Figure 1). The data points which fit into linear scale (three) were taken into consideration while drawing Figure 1.

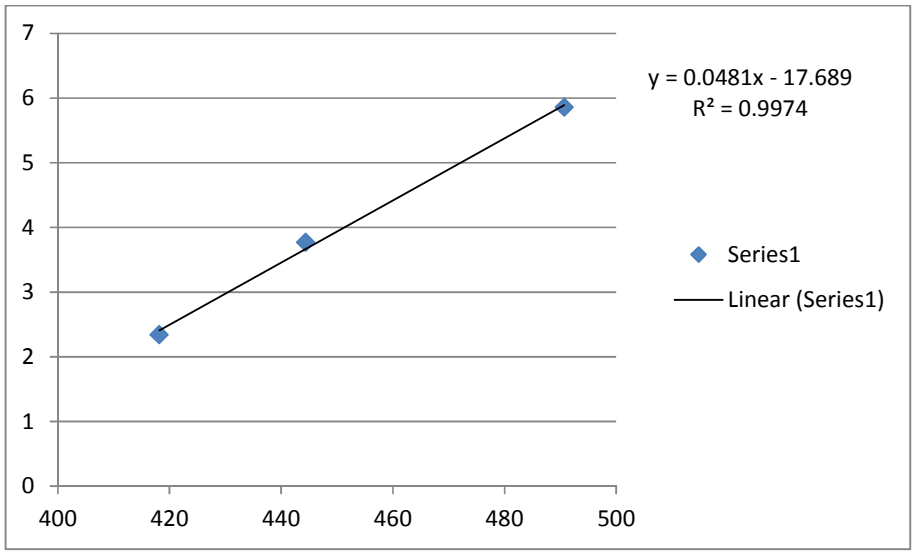


Figure 1. The calculated concentrations (Y-axis) were plotted against the obtained counts (X-axis) and linear regression considering minimum 3 points. Intercept value -17.689 ppb indicates that Cu is not present in Raney Ni.

The analysis did not indicate presence of even ppt amounts of copper in the Raney Ni sample used in the NiAAC reactions.

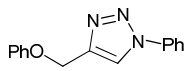
4.3. Preparation of Raney Ni

Approximately 10 mol% of Raney Ni present as a suspension in absolute EtOH was transferred into dry nitrogen flushed RB flask. Excess EtOH was removed under reduced pressure using Schlenk line. The amount of reactants was calculated on the basis of the accurate weight of Raney Ni taken in the RB flask. To Raney Ni (42 mg, 0.7 mmol) the azide (7.0 mmol) and then the propargyl ether (7.0 mmol) dissolved in dry toluene (10 mL each) were added. The reaction mixture was placed in a preheated oil bath maintained at 45 ºC and stirred for 14 h by which time reaction was complete (TLC). Contents of the flask was transferred into centrifuge tubes and centrifuged for 2 min at 2100 rpm. Supernatant clear solution was withdrawn followed by washing of the catalyst twice with 10 mL dry toluene. Removal of toluene from pooled solutions resulted in triazoles **3** in over 90% yield which

was sufficiently pure for spectral characterization. Column chromatography was performed when necessary.

4.4. General procedure for the Raney Ni catalyzed [3+2] cycloaddition of azides and terminal alkynes:

4.4.1. Synthesis of 1-phenyl-4-(phenoxymethyl)-1*H*-1,2,3-triazole 3a:



3a

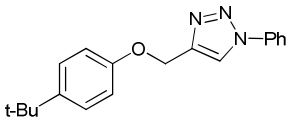
To Raney Ni (42 mg, 0.7 mmol) taken under a blanket of dry nitrogen, phenyl azide (1.0 g, 7.0 mmol) and then phenyl propargyl ether (1.0 g, 7.0 mmol) dissolved in dry toluene (10 mL each) were added. The reaction mixture was placed in a preheated oil bath maintained at 45 ºC. The reaction mixture was stirred for 14 h by which time reaction was complete (TLC). Contents of the flask was transferred into a centrifuge tube and centrifuged for 2 min at 2100 rpm. Supernatant clear solution was withdrawn followed by washing of the catalyst twice with 10 mL dry toluene. Removal of toluene from pooled solutions resulted is **3a** in 98% yield (186 mg) as a colorless viscous liquid, which was sufficiently pure for spectral and analytical characterization. IR (KBr) 3112, 3059, 3032, 1741, 1455, 1357, 1246, 1080, 752 cm^{-1}; ^{1}H NMR ($CDCl_3 + CCl_4$ (1:1), 400 MHz) δ 8.05 (s, 1H), 7.75-7.72 (m, 2H), 7.55-7.44 (m, 3H), 7.33-7.29 (m, 2H), 7.04-6.97 (m, 3H), 5.31 (s, 2H) ppm; ^{13}C NMR ($CDCl_3 + CCl_4$ (1:1), 100 MHz) δ 158.3, 129.9, 129.7, 129.0, 121.5, 120.7, 114.9, 62.1 ppm.

4.4.2. Experiments with deuterium labeled phenyl propargyl ether 4

To elucidate if the NiAAC reaction goes through Ni acetylide intermediate, deuteriated phenyl propargyl ether **1** was employed and it was prepared according to the procedure described by Bew and co-workers.[18] The NMR spectral data showed that **1** was 90% enriched with deuterium as indicated by its ^{1}H NMR spectrum. The NiAAC reaction with **1** (50 mg,

0.4 mmol, 1equiv) and phenyl azide **2a** (54 mg, 0.45 mmol, 1.1 equiv) under our optimised conditions provided traizole **8** (R = Ph) with complete retention of deuterium.

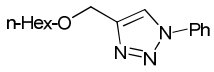
4.4.3. 4-((4-*tert*-Butylphenoxy) methyl)-1-phenyl-1*H*-1,2,3-triazole 3b:



3b

Yield 93% (151 mg), white solid, mp. 68 ºC; IR (KBr): 3156, 3043, 2966, 2869, 1606, 1512, 1244, 1048, 858, 711, 548 cm^{-1}; ^{1}H NMR ($CDCl_3 + CCl_4$ (1:1), 400 MHz) δ 8.02 (s, 1H), 7.76-7.74 (m, 2H), 7.54-7.49 (m, 2H), 7.44-7.40 (m, 1H), 7.30-7.28 (m, 2H), 6.93-6.91 (m, 2H), 5.28 (s, 2H), 1.31 (s, 9H) ppm; ^{13}C NMR ($CDCl_3 + CCl_4$ (1:1), 100 MHz) δ155.8, 145.3, 143.7, 137.0, 129.5, 128.5, 126.2, 120.4, 120.2, 114.1, 62.0, 34.0, 31.5 ppm; HRMS m/z (ESI-MS): calcd. for $C_{19}H_{21}N_3ONa$ (M + Na) 330.1582, found 330.1580.

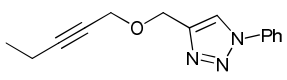
4.4.4. 4-(Hexyloxymethyl)-1-phenyl-1*H*-1,2,3-triazole 3e:



3e

Yield 89 % (164 mg),viscous liquid, IR (KBr) 3079, 3016, 2924, 2853, 1593, 1509, 1491, 1453, 693 cm^{-1}; ^{1}H NMR ($CDCl_3 + CCl_4$ (1:1), 400 MHz) δ 7.75 (s, 1H), 7.66-7.63 (m, 2H), 7.53-7.50 (m, 3H), 4.48 (s, 2H), 3.44 (t, *J* = 4.0 Hz, 2H), 1.58-1.54 (m, 2H), 1.31-1.27 (m, 6H), 0.88 (t, *J* = 4.0 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3 + CCl_4$ (1:1), 100 MHz) δ136.6, 135.0, 133.9, 129.5, 124.7, 70.9, 60.8, 31.8, 29.7, 26.0, 22.8, 14.2 ppm; HRMS m/z (ESI-MS): (M + H) calcd. for $C_{15}H_{22}N_3O$ 260.1763, found 260.1763.

4.4.5. 4-((Pent-2-yn-1-yloxy)methyl)-1-phenyl-1*H*-1,2,3-triazole 3f:

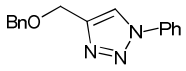


3f

Yield 89% (175 mg), viscous liquid, IR (KBr) 3081, 3052, 3016, 2921, 2851, 1598, 1509, 1493, 1451, 1432, 696 cm^{-1}; ^{1}H NMR ($CDCl_3 + CCl_4$ (1:1), 400 MHz) δ 7.98 (s, 1H), 7.72 (d,

J = 8.3 Hz, 2H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 6.9 Hz, 1H), 4.78 (s, 2H), 4.23 (s, 2H), 2.25-2.23 (m, 2H), 1.15 (t, *J* = 8.0 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$ + CCl_4 (1:1), 100 MHz) δ 145.7, 137.2, 129.8, 128.8, 120.8, 120.6, 89.1, 74.9, 63.0, 58.4, 13.9, 12.6 ppm; HRMS m/z (ESI-MS): calcd. for $C_{14}H_{15}N_3ONa$ (M + Na) 264.1113, found 264.1113.

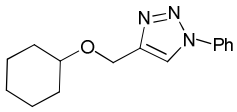
4.4.6. 4-(Benzyloxymethyl)-1-phenyl-1*H*-1,2,3-triazole 3g:



3g

Yield 97% (176 mg), viscous liquid, IR (KBr) 3103, 2956, 2923, 2863, 1504, 1285, 1098, 1061, 768, 692, 587 cm^{-1}; ^{1}H NMR ($CDCl_3$ + CCl_4 (1:1), 400 MHz) δ 7.96 (s, 1H), 7.74-7.71 (m, 2H), 7.52-7.43 (m, 2H), 7.43-7.27 (m, 6H), 4.75 (s, 2H), 4.64 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$ + CCl_4 (1:1), 100 MHz) δ146.0, 137.7, 137.1, 129.6, 128.5, 128.4, 127.8, 127.7, 120.4, 120.3, 72.6, 63.6 ppm; ; HRMS m/z (ESI-MS): 288.1113 calcd. for $C_{16}H_{15}N_3ONa$ (M + Na) 288.1112.

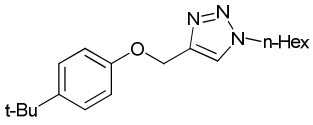
4.4.7. 4-(Cyclohexyloxymethyl)-1-phenyl-1*H*-1,2,3-triazole 3h:



3h

Yield 88% (163 mg), viscous liquid, IR (KBr) 3032, 2932, 2856, 1605, 1496, 1453, 1363, 1082, 722 cm^{-1}; ^{1}H NMR ($CDCl_3$ + CCl_4 (1:1), 400 MHz) δ 7.80 (s, 1H), 7.66-7.64 (m, 2H), 7.55-7.50 (m, 3H), 4.53 (s, 2H), 3.34-3.29 (m, 1H), 1.84-1.69 (m, 6H), 1.53-1.51 (m, 1H), 1.31-1.20 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$ + CCl_4 (1:1), 100 MHz) δ 147.2, 137.4, 129.8, 128.7, 120.6, 120.3, 77.6, 61.7, 32.4, 26.0, 24.2 ppm; HRMS m/z (ESI-MS): calcd. for $C_{15}H_{20}N_3O$ (M + H) 258.1606, found 258.1602.

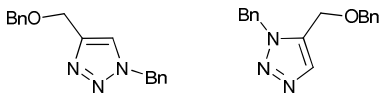
4.4.8. 4-((4-*tert*-Butylphenoxy)methyl)-1-hexyl-1*H*-1,2,3-triazole 3n:



3n

Yield 93% (155 mg), white solid, mp.69 ºC; IR (KBr): 3155, 2963, 1604, 1510, 1463, 1243, 1045, 822, 710, 547 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4 (1:1), 400 MHz) δ 7.52 (s, 1H), 7.23 (dd, *J* =8.4 Hz, 2H), 6.85 (dd, *J* = 8.6, 1.4 Hz, 2H), 5.12 (d, *J* = 2.5 Hz, 2H), 4.28-4.24 (m, 2H), 1.84 (t, *J* = 5.6 Hz, 2H), 1.26 (s, 9H), 1.25 (s, 6H), 0.84 (t, *J* = 1.6 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$ + CCl_4 (1:1), 100 MHz) δ 156.0, 144.2, 143.6, 126.2, 122.3, 114.2, 62.1, 50.2, 34.1, 31.2, 31.1, 30.2, 26.1, 22.4, 13.9 ppm; HRMS m/z (ESI-MS): calcd. For $C_{19}H_{29}N_3ONa$ (M + Na) 338.2208, found 338.2196.

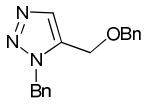
4.4.9. 1-benzyl-4-(benzyloxymethyl)-1*H*-1,2,3-triazole, 5-(benzyloxymethyl)-1-bromo-1*H*-1,2,3-triazole (1:1) 3o, 3s:



3o **3s**

The regioisomers **3o** and **3s** were obtained in 1:0.7 ratio. Overall yield 93% (177 mg), viscous liquid, IR (KBr) 3139, 3066, 2930, 2860, 1597, 1494, 1240, 755 cm^{-1}; NMR spectral data of the 1,5-regio isomer was culled from the mixture NMR spectra by locating the signals meant for 1,4- regioisomer.[29]

4.4.9.1. 1-Benzyl-5-(benzyloxymethyl)-1*H*-1,2,3-triazole 3s:

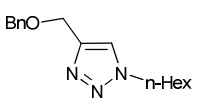


3s

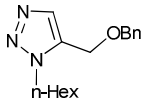
Yield 89%, viscous liquid, IR (KBr) 3139, 3066, 2930, 2860, 1597, 1494, 1240, 755 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4 (1:1), 400 MHz) 7.32 (s, 1H), 7.28-7.07 (m, 10 H), 5.42 (s, 2H), 4.56 (s, 2H), 4.30 (s, 2H), ^{13}C NMR 137.9, 133.0, 134.8, 133.0, 129.0, 128.7, 28.50, 128.35, 128.30,

128.1, 127.7, 72.4, 59.8, 52.4 ppm; HRMS m/z (ESI-MS): calcd. for $C_{17}H_{18}N_3O$ (M + H) 280.1450, found 280.1452.

4.4.10. 4-(Benzyloxymethyl)-1-hexyl-1*H*-1,2,3-triazole, 5-(benzyloxymethyl)-1-hexyl-1*H*-1,2,3-triazole 3p, 3t:



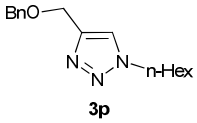
3p



3t

The regioisomers **3p** and **3t** were obtained in 1:0.2 ratio. Overall yield 93% (173 mg), viscous liquid, IR (KBr) 3032, 3061, 2958, 2926, 2856, 1597, 1489, 1243, 755 cm^{-1}; NMR spectral data of the 1,5-regio isomer was identified from the mixture NMR by deducting the spectrum meant for 1,4-regio-isomer. The 1,4-regioisomer **3p** was prepared by Cu(I) mediated cycloaddtion of benzyl propargyl ether and *n*-hexylazide by following the general procedure described by us previously.[15]

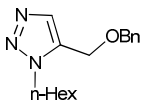
4.4.10.1. 4-(Benzyloxymethyl)-1-hexyl-1*H*-1,2,3-triazole 3p



3p

Yield 98%, viscous liquid, IR (KBr) 3137, 3065, 2926, 2858, 1649, 1496, 1240, 736 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4 (1:1), 400 MHz) 7.48 (s, 1H), 7.28-7.25 (m, 5H), 4.60 (s, 2H), 4.52 (s, 2H), 4.26-4.22 (t, J = 7.2 Hz, 2H), 1.82-1.79 (m, 2H), 1.27-1.22 (m, 6H), 0.85-0.82 (m, 3H) ppm; ^{13}C NMR 144.8, 137.7, 128.3, 128.1, 122.1, 72.1, 63.4, 49.9, 31.0, 30.9, 25.9, 22.2, 13.7 ppm.

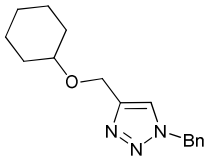
4.4.10. 2. 5-(Benzyloxymethyl)-1-hexyl-1*H*-1,2,3-triazole 3t:



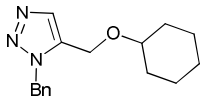
3t

Yield 89%, viscous liquid, IR (KBr) 3081, 3052, 3016, 2921, 2851, 1598, 1509, 1493, 1451, 1432, 696 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4 (1:1), 400 MHz) δ 7.48 (s, 1H), 7.27-7.25 (m, 5H), 4.60 (d, , *J* = 0.4 Hz, 2H), 4.52 (s, 2H), 1.82-1.79 (m, 2H), 1.25-1.22 (m, 7H) ppm; ^{13}C NMR ($CDCl_3$ + CCl_4(1:1), 100 MHz) δ 144.7, 137.7, 128.3, 127.8, 127.7, 122.1, 72.1, 63.4, 49.9, 30.99, 30.93, 30.02, 25.9, 22.2, 13.7 ppm; HRMS m/z (ESI-MS): calcd. for $C_{16}H_{23}N_3ONa$ (M + Na) 296.1738, found 296.1723.

4.4.11. 1-Benzyl-4-(cyclohexyloxymethyl)-1*H*-1,2,3-triazole, 1-benzyl-5-(cyclohexyloxymethyl)-1*H*-1,2,3-triazole 3q, 3u:



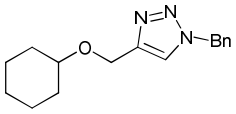
3q



3u

The regioisomers **3q** and **3u** were obtained in 1:1 ratio. Overall yield 91% (178 mg), viscous liquid, IR (KBr) 3031, 2931, 2852, 1497, 1450, 1356, 1082 cm^{-1}; NMR spectral data of the 1,5-regio isomer was identified from the mixture NMR by deducting the spectrum meant for 1,4-regio-isomer. The 1,4-regioisomer **3q** was prepared by Cu(I) mediated cycloaddtion of benzyl propargyl ether and *n*-hexylazide by following the general procedure described by us previously.[15]

4.4.11.1. 1-Benzyl-4-(cyclohexyloxymethyl)-1*H*-1,2,3-triazole 3q

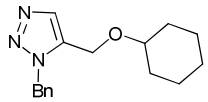


3q

Yield 97%, White solid, mp 91-93 ^oC, IR (KBr) 3140, 2930, 2857, 1454, 1368, 1089, 953, 730 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4 (1:1), 400 MHz) 7.40 (s, 1H), 7.33-7.32 (m, 3H), 7.24-7.23 (m, 2H) 5.47 (s, 2H), 4.60 (s, 2H), 3.35-3.32 (m, 1H), 1.90-1.87 (m, 2H), 1.71-1.69 (m,

2H), 1.51-1.50 (m, 1H), 1.28-1.19 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$ + CCl_4 (1:1), 100 MHz) 146.7, 134.8, 129.2, 128.8, 128.2, 122.1, 61.7, 54.2, 32.3, 25.9, 24.2 ppm.

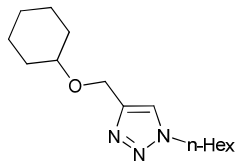
4.4.11.2. 1-Benzyl-5-(cyclohexyloxymethyl)-1*H*-1,2,3-triazole 3u:



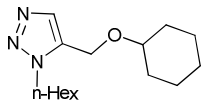
3u

Yield 89%, viscous liquid, IR (KBr) 3031, 2931, 2852, 1497, 1450, 1356, 1082 cm^{-1}; ^{1}H NMR ($CDCl_3$ + CCl_4 (1:1), 400 MHz) δ 7.55 (s, 1H), 7.34-7.28 (m, 5H), 5.59 (s, 2H), 4.60 (s, 2H), 3.21-3.17 (m, 1H), 1.87-1.69 (m, 5H), 1.27-1.20 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$ + CCl_4 (1:1), 100 MHz) δ146.8, 134.8, 134.0, 133.9, 128.2, 127.5, 77.4, 76.8, 57.9, 52.2, 31.9, 25.7, 23.9 ppm; HRMS m/z (ESI-MS): calcd. for $C_{16}H_{21}N_3ONa$ (M + Na) 294.1582, found 294.1584.

4.4.12. 4-(Cyclohexyloxymethyl)-1-hexyl-1*H*-1,2,3-triazole, 5-(cyclohexyloxymethyl)-1-hexyl-1*H*-1,2,3-triazole 3r, 3v:



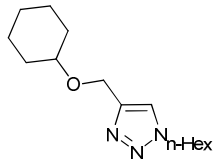
3r



3v

The regioisomers **3r** and **3v** were obtained in 1:0.5 ratio. Overall yield 89% (170 mg), viscous liquid, IR (KBr) 3034, 2987, 2854, 1605, 1496, 1453, 1082, 722 cm^{-1}; NMR spectral data of the 1,5-regio isomer was identified from the mixture NMR by deducting the spectrum meant for 1,4-regio-isomer. The 1,4-regioisomer **3r** was prepared by Cu(I) mediated cycloaddtion of benzyl propargyl ether and *n*-hexylazide by following the general procedure described by us previously.[15]

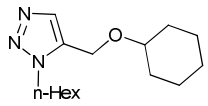
4.4.12.1. 4-(Cyclohexyloxymethyl)-1-hexyl-1*H*-1,2,3-triazole 3r



3r

Yield 98%, viscous liquid, IR (KBr) 3137, 3065, 2926, 2858, 1496, 1458, 1368, 1072, 736 cm^{-1}; ^1H NMR ($CDCl_3 + CCl_4$ (1:1), 400 MHz) 7.42 (s, 1H), 4.52 (s, 2H), 4.22 (t, J = 7.2 Hz, 2H), 3.29 (m, 1H), 1.79 (d, J = 9.2 Hz, 5H), 1.61 (s, 3H), 1.43-1.41 (m, 2H), 1.20-1.15 (m, 5H), 0.77 (s, 3H) ppm; ^{13}C NMR ($CDCl_3 + CCl_4$ (1:1), 100 MHz) 146.0, 121.9, 77.4, 76.8, 69.8, 61.4, 50.1, 35.4, 31.1, 26.0, 23.9, 22.3, 13.8 ppm.

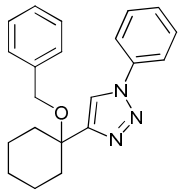
4.4.12.2. 5-(Cyclohexyloxymethyl)-1-hexyl-1*H*-1,2,3-triazole 3v:



3v

Yield 91%, viscous liquid, IR (KBr) 3034, 2987, 2854, 1605, 1496, 1453, 1082, 722 cm^{-1}; ^1H NMR ($CDCl_3 + CCl_4$ (1:1), 400 MHz) δ 7.57 (s, 1H), 4.66 (s, 2H), 4.35-4.30 (m, 3H), 3.41-3.31 (m, 1H), 1.74-1.72 (m, 5H), 1.31-1.21 (m, 12H), 0.88-0.85 (m, 3H) ppm; ^{13}C NMR ($CDCl_3 + CCl_4$ (1:1), 100 MHz) δ 146.3, 122.1, 61.7, 50.4, 48.6, 32.3, 31.4, 30.3, 26.4, 25.8, 25.7, 24.2, 23.9, 22.5, 14.0 ppm; HRMS m/z (ESI-MS): calcd. for $C_{15}H_{27}N_3ONa$ (M + Na) 288.2052, found 288.2050.

Synthesis of 4-(1-(benzyloxy)cyclohexyl)-1-phenyl-1*H*-1,2,3-triazole 3w:

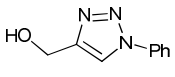


3w

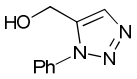
Yield 89% (133 mg), white solid, mp. 93 ºC; IR (KBr): 3029, 2933, 2862, 1493, 1450, 719 cm^{-1}; ^1H NMR ($CDCl_3 + CCl_4$ (1:1), 400 MHz) δ 7.91 (s, 1H), 7.70 (d, 2H, 1.2 Hz), 7.67-7.42

(m, 2H), 7.40-7.33 (m, 2H), 7.31-7.7.27 (m, 3H), 7.24-7.16 (m, 1H), 4.32 (s, 2H), 2.24-2.06 (m, 2H), 1.80-1.76 (m, 5H), 1.59-1.52 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$ + CCl_4 (1:1), 100 MHz) δ 152.7, 139.2, 137, 129.5, 128.3, 128.0, 127.0, 126.9, 120.2, 119.0, 73.9, 35.1, 25.5, 21.9 ppm. HRMS m/z (ESI-MS): calcd. For $C_{21}H_{23}N_3O$ Na (M + Na) 356.1733, found 356.1735.

Synthesis of (1-phenyl-1*H*-1,2,3-triazol-4-yl)methanol and (1-phenyl-1*H*-1,2,3-triazol-5-yl)methanol 3y, 3z:



3y 1,4-isomer (64%)



3z 1,5-isomer (36%)

Yield 93% (135 mg); The NiAAC reaction of phenyl azide and propargyl alcohol provided 1,4- **3y** and 1,5- **3z** regioisomers in 64:36 ratio. The AAC reaction without any catalyst provided 1,4- **3y** and 1,5- **3z** regioisomers in the same ratio but the reaction required heating in a monomode microwave oven to 140 ^{o}C for 2 min in polyethylene glycol 200 (PEG 200) medium. Authentic 1,4-disubstituted triazole (DT) was prepared by heating a mixture of phenyl azide and propargyl alcohol under microwave irradiation at 140 oC for 2 min in PEG-200 medium. The NMR spectral assignments for 1,4- **3y** and 1,5- **3z** DTs were based on the ^{13}C NMR spectral analysis as described by Dondoni and coworkers.[30] Signals belonging to the 1,4-regioisomer (major product) and the 1,5-regioisomer[31] elicited from the ^{1}H and ^{13}C NMR spectra of mixture and presented here.[1] 1,4-Regioisomer **3y**: ^{1}H NMR ($CDCl_3$ + CCl_4 (1:1), 400 MHz) δ 7.99 (s, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.47-7.43 (m, 2H), 7.42-7.38 (m, 1H), 4.80 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$ + CCl_4 (1:1), 100 MHz) δ 148.8, 137.1, 129.9, 128.9, 120.6, 120.3. 56.2 ppm. 1,5-Regioisomer **3z**: ^{1}H NMR ($CDCl_3$ + CCl_4 (1:1), 400 MHz) δ 7.69 (s, 1H), 7.60 (d, J = 7.7 Hz, 2H), 7.47-7.43 (m, 3H), 4.68 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$ + CCl_4 (1:1), 100 MHz) δ 137.5, 136.3, 129.63, 129.60, 124.7, 120.3, 53.1 ppm.

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according to the procedure described in *Vogel's Textbook of Practical Organic Chemistry* Eds. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. 5th ed. Longman Scientific & Technical, NY, 1989, pp 450-451. WARNING: When exposed to air Raney Ni is pyrophoric.

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Raney Ni Catalyzed Azide-Alkyne Cycloaddition Reaction

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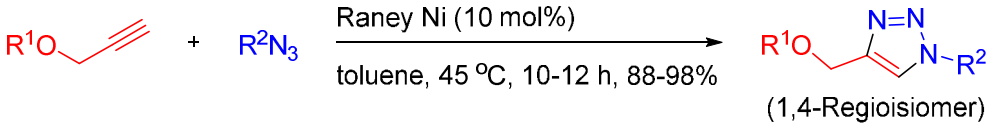

(1,4-Regioisiomer)

* No need for an additonal reducing agent.

* Exclusive 1,4-regioisomer when R^1 = Ph, 4-*t*-Bu-C_6H_4, $C_6H_5CH_2$, *n*-C_6H_{13}, $C_2H_5CCCH_2$, cyclohexyl, thymyl, eugenyl, menthyl, cholesteryl; R^2 = Ph, $C_6H_5CH_2$, *n*-C_6H_{13}.

Major 1,4-regioisomer when R^1 and R^2 = $C_6H_5CH_2$ or cyclohexyl.

* Terminal acetylene selectivity with retention of H of the terminal CH.