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NH-1,2,3-triazoles as versatile building blocks in denitrogenative transformations

Vladimir Motornov * and Petr Beier *

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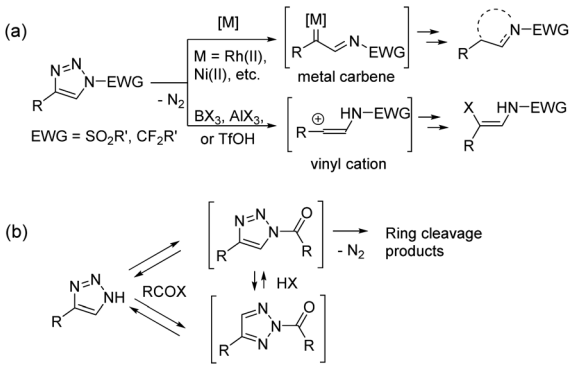
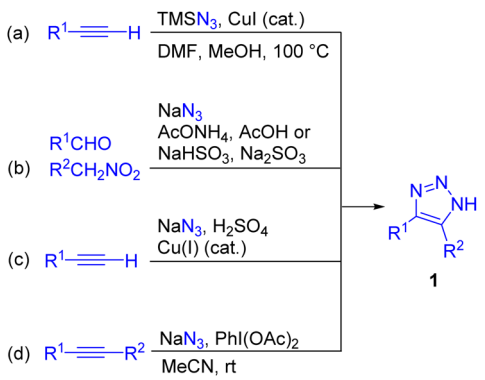
The utilization of NH-1,2,3-triazoles as easily accessible building blocks in denitrogenative ring cleavage transformations with electrophiles to provide multifunctionalized nitrogen heterocycles and *N*-alkenyl compounds is reviewed. Leveraging the ready availability of NH-1,2,3-triazoles, these processes provide a convenient route to a range of pharmaceutically relevant heterocyclic cores and *N*-alkenyl compounds. The synthetic usefulness of *in situ* acylated NH-1,2,3-triazoles as viable alternatives to widely explored *N*-sulfonyl-1,2,3-triazoles in ring cleavage processes is highlighted.

1,2,3-Triazoles are nitrogen heterocycles with versatile reactivity[1] and great medicinal importance.[2] Since the discovery of azide–alkyne click chemistry in 2002,[3] triazole derivatives have gained enormous attention in organic, medicinal, biomolecular, and material sciences. Among them, 1,2,3-triazoles bearing an electron-withdrawing group at position N1 are of special importance because of their propensity to undergo N1–N2 bond cleavage in denitrogenative triazole ring opening transformations (Scheme 1a).[1] *N*-sulfonyl-1,2,3-triazoles[4] and *N*-fluoroalkyl-1,2,3-triazoles[5] are the most explored building blocks, which undergo ring cleavage under metal catalysis or by the action of Lewis or Brønsted acids. Very recently, a new strategy based on the use of NH-1,2,3-triazoles involving the installation of an electron-withdrawing group with *in situ* ring cleavage was described and used with success (Scheme 1b). The present review features the use of free NH-1,2,3-triazoles **1** in denitrogenative transformations, proceeding *via* *N*-acyl-1,2,3-triazoles or their analogues as key intermediates.

N-unsubstituted NH-1,2,3-triazoles **1**, considered in the present review, are the simplest and most readily available triazoles.[6] They can be prepared by azide–alkyne cycloaddition[6] or alternative methods such as cycloaddition/elimination with activated ketones[7] or nitroalkenes.[7] In the last five years, there has been a notable surge of innovative methods for the synthesis of NH-1,2,3-triazoles and several one-pot protocols from inexpensive and commercially available reagents have been developed.[6] To underline the most efficient and practical routes, NH-1,2,3-triazoles were synthesized from $TMSN_3$ and alkynes *via* CuI-catalysed cycloaddition (Scheme 2a),[8] or sodium azide, aldehydes and nitroalkanes *via* a tandem Henry reaction/[3 + 2] cycloaddition (Scheme 2b),[9a–c] including recently developed green chemistry approaches.[9d–h] In 2022, NH-1,2,3-triazoles became available from NaN_3/H_2SO_4 and alkynes, which is so far the simplest and the most straightforward route, although the generation of HN_3 raises safety concerns (Scheme



Scheme 1 Schematic representation of the utilization of (a) *N*–sulfonyl- or *N*-fluoroalkyl-substituted 1,2,3-triazoles and (b) NH-1,2,3-triazoles in ring cleavage denitrogenative transformations.



Scheme 2 Overview of efficient routes for the synthesis of NH-1,2,3-triazoles (a–d).

Institute of Orgranic Chemistry and Biochemistry, Academy of Sciences, Flemingovo nám. 2, 160 00 Prague 6, Czech Republic. E-mail: cuprate51@gmail.com; beier@uochb.cas.cz

2c).[10] Finally, the approach utilizing azidyl radical–alkyne cycloaddition with the use of the NaN_3/$PhI(OAc)_2$ system in mild conditions is highly efficient for complex disubstituted triazoles such as 4,5-diaryltriazoles (Scheme 2d),[11a] and it was also possible to efficiently synthesize these compounds without an oxidant, albeit only under harsh conditions (MW heating at 200 °C).[11b] More examples of novel synthetic methods to access NH-1,2,3-triazoles appeared in recent reviews.[6]

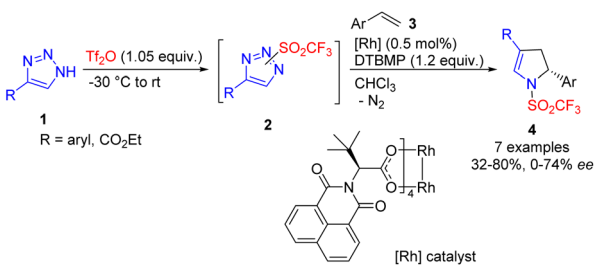
Due to better atom economy, the utilization of readily available NH-triazoles is advantageous compared to the use of *N*-sulfonyl- or *N*-fluoroalkyl-triazoles. Additionally, access to NH-1,2,3-triazoles was possible using "alkyne-free" methods. Both, primary nitro compounds and aromatic aldehydes are easily accessible industrial scale products.[12]

One of the first denitrogenative transformations of 1,2,3-NH-triazoles **1** was reported in 2014. In this process, *in situ* sulfonylation with triflic anhydride and 2,6-di(*tert*-butyl)-4-methylpyridine (DTBMP) as a base was used to generate reactive *N*-triflyl triazoles **2**.[13] Their ring cleavage by a chiral Rh(II) catalyst in the presence of an excess of alkene **3** afforded 2,3-dihydropyrroles **4** with low to good enantiocontrol (Scheme 3).

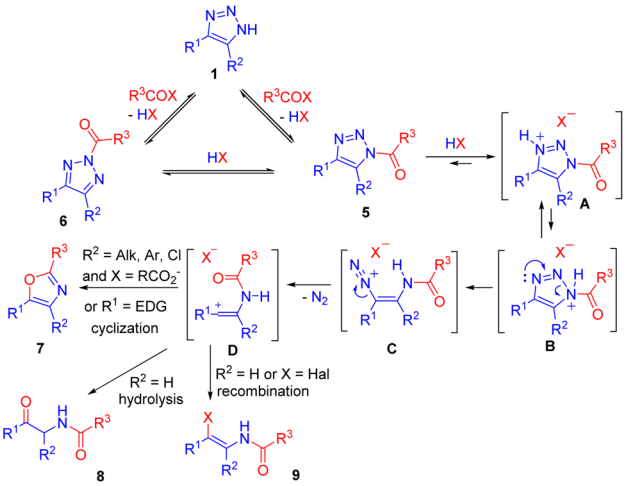
However, besides triflation, there are no other examples of *in situ* sulfonylation of NH-1,2,3-triazoles followed by denitrogenative transformations. Therefore, this reaction is limited to the extremely electron-accepting triflyl group and analogous ring cleavage did not proceed with other *N*-sulfonyl triazoles.

In contrast to sulfonylation, acylation of NH-1,2,3-triazoles is more versatile and has developed into a highly active area of research in recent years.[14] Tandem acylation followed by ring cleavage without isolation of *N*-acyltriazoles was performed using acyl halides or acid anhydrides. The mechanism of this transformation, recently confirmed by us,[14] involved the formation of N1 (**5**) and N2-acylated (**6**) triazoles in equilibrium, followed by acid-mediated cleavage of the former. Denitrogenation and formation of a vinyl cation in an irreversible step was the driving force of N2–N1-acyltriazole interconversion, which ensured the complete transformation of triazoles into ring cleavage products **7–9** (Scheme 4).

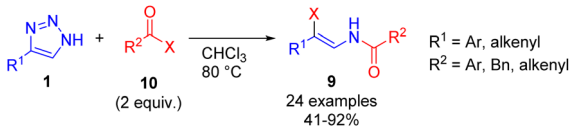
Cleavage of NH-1,2,3-triazoles **1** with an excess of acyl halides **10** (X = Cl, Br) under elevated temperature led to the formation of β-enamido halides **9** in moderate to good yields (Scheme 5).[15] β-Enamido halides are difficult to access by other synthetic routes and are present in natural products, which underlines the synthetic value of the method.



Scheme 3 Synthesis of 2,3-dihydropyrroles by cleavage of NH-triazole in the presence of triflic anhydride. DTBMP – 2,6-di(*tert*-butyl)-4-methylpyridine.



Scheme 4 Mechanism of NH-triazole cleavage with electrophiles.

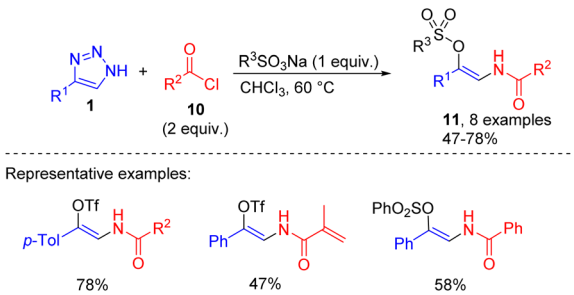


Scheme 5 Cleavage of NH-1,2,3-triazoles with acyl halides.

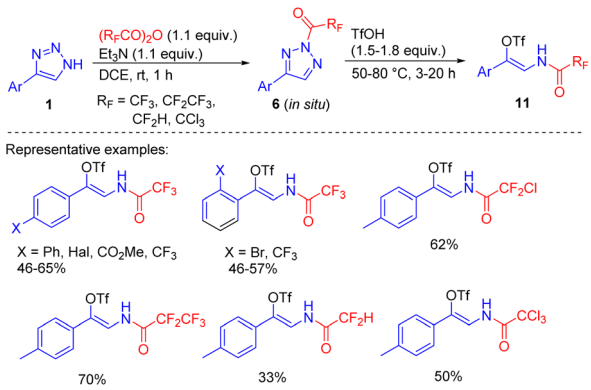
This transformation in the presence of sodium sulfonates was employed in the synthesis of enamido triflates or sulfonates **11**. Mainly compounds with the phenacyl group at the nitrogen were accessed by the mentioned route (Scheme 6).[15]

An alternative method, applicable to the synthesis of β-fluoroacylenamido triflates is based on the formation of N2-acyltriazoles **6** *via* the *in situ* acylation of NH-1,2,3-triazoles with fluorinated acid anhydrides followed by their treatment with triflic acid, which proceeds through N2–N1 acyltriazole interconversion and ring cleavage (Scheme 7).[14]

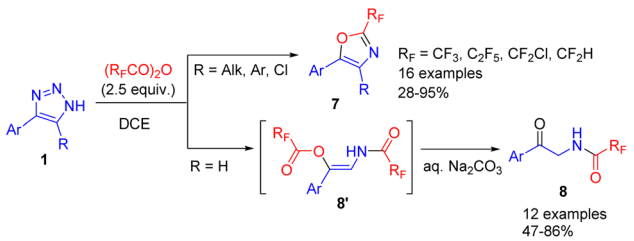
The products are useful building blocks, that can get involved in Pd-catalysed cross-coupling substitution reactions of the triflate group to access multifunctionalized enamide derivatives – attractive drug candidates and synthetic intermediates.[16] None of the methods mentioned was applicable with the less reactive alkyl-substituted acylating agents (Ac_2O, AcCl),



Scheme 6 Synthesis of β-enamido triflates and sulfonates from NH-1,2,3-triazoles, acyl halides, and sodium sulfonates.



Scheme 7 One-pot two step synthesis of β-fluoroacylenamido triflates. DCE = 1,2-dichloroethane.

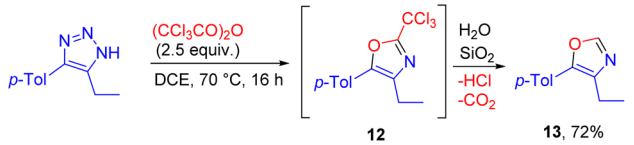


Scheme 8 Synthesis of fluoroalkylated oxazoles and 2-acylaminoketones from NH-1,2,3-triazoles with fluoroalkylated acid anhydrides.

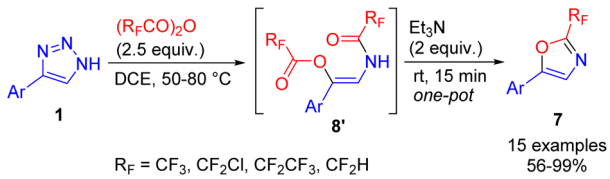
because the resulting acyltriazoles were resistant to ring cleavage even at elevated temperatures.[14]

The cleavage of NH-1,2,3-triazoles with an excess of fluoroalkylated acid anhydrides led to highly pharmaceutically relevant 2-fluoroalkyl oxazoles **7** (in the cases of 4,5-disubstituted triazoles) or 2-acylaminoketones (for 4-substituted triazoles, R = H) (Scheme 8).[17] In the first case intramolecular cyclization took place, whereas in the second, unstable β-acyloxyenamide **8′** formed, which underwent ester hydrolysis to 2-acylaminoketone **8** upon treatment with an aqueous base. The difference in chemoselectivity was attributed to the increased vinyl cation stability of disubstituted examples, which made them more prone to intramolecular cyclization.

4,5-disubstituted NH-1,2,3-triazole reacted with trichloroacetic anhydride to give 2-unsubstituted oxazole **13**, due to the low stability of the trichloromethyl-substituted product **12** during silica gel column chromatography. The whole transformation is a rare and unique case of a reaction involving trichloroacetic anhydride as a one-carbon building block (Scheme 9).[17]



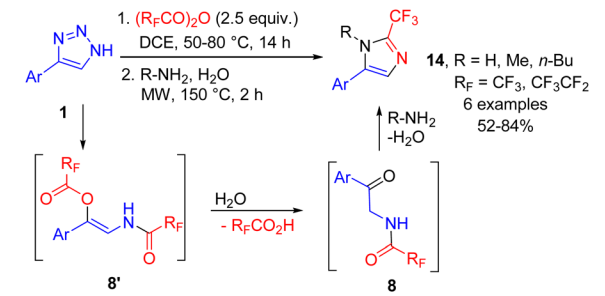
Scheme 9 Formation of 2-unsubstituted oxazole from NH-1,2,3-triazole and trichloroacetic anhydride.



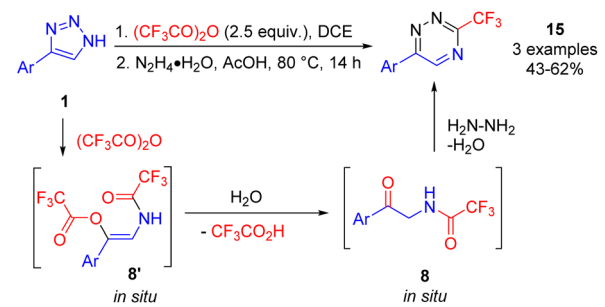
Scheme 10 One-pot synthesis of fluoroalkylated oxazoles from NH-1,2,3-triazoles, acid anhydrides and Et_3N.

The limitation of oxazole synthesis to only disubstituted triazoles was overcome by the cyclization of *in situ* formed β-acyloxyenamide **8′** to oxazoles **7** using Et_3N and proceeded quickly and nearly quantitatively under ambient conditions.[18] This one-pot triazole cleavage procedure provided an efficient access to 2-fluoroalkylated oxazoles from monosubstituted triazoles in good to excellent yields (Scheme 10).

The easy access to fluorinated 2-acylaminoketones **8** was utilized in a number of one-pot syntheses of fluoroalkylated heterocycles directly from NH-1,2,3-triazoles **1**. First, 2-fluoroalkyl imidazoles **14** were prepared by cleavage with trifluoroacetic or perfluoropropanoic anhydrides, followed by the treatment of the ketamide intermediate with an aqueous solution of the primary amine (or ammonium acetate for R = H) under microwave conditions. The acid formed after hydrolysis of the enamide to yield 2-acylaminoketone promoted the Robinson–Gabriel cyclization of the latter. This procedure afforded imidazoles **14** in moderate to good yields in a one-pot manner starting from triazoles (Scheme 11).[17]



Scheme 11 One-pot synthesis of 2-fluoroalkyl-imidazoles from NH-1,2,3-triazoles.



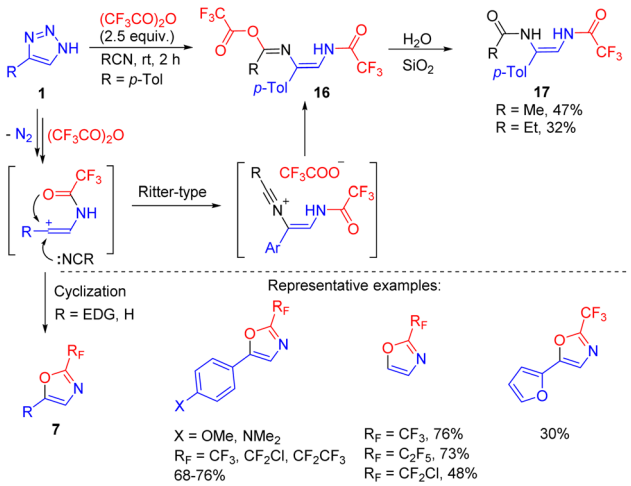
Scheme 12 Synthesis of 3-fluoroalkyl-1,2,4-triazines from NH-1,2,3-triazoles.

Alternatively, condensation of the formed acyloxyenamide **8′** with hydrazine hydrate after switching the solvent to acetic acid provided fluoroalkylated 1,2,4-triazines **15** (Scheme 12).[17]

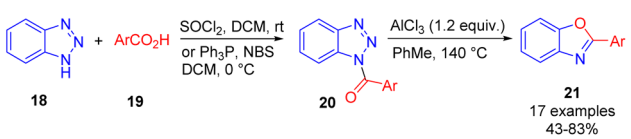
The formation of the vinyl cation intermediate in *N*-acyltriazole cleavage was confirmed by changing the solvent from a chlorinated one to acetonitrile or propionitrile.[18] In one special case (Scheme 13, R = *p*-Tol) adducts **16** of the Ritter reaction were formed and hydrolysed to bis(enamides) **17**. However, this reaction was not general and in the cases of electron-richer triazoles, cyclization of the vinyl cation to oxazoles **7** took place (Scheme 13, R = H, EDG). This route is an alternative to one mentioned above (Scheme 10), and is applicable to electron-rich substrates. The straightforward formation of oxazoles **7** rather than enamides **8′** in polar MeCN was explained by the decreased stability of the vinyl cation–trifluoroacetate anion contact ion pair, which prevented recombination and favoured cyclization.[18]

Several efficient NH-1,2,3-triazole ring cleavage protocols were also developed for NH-benzotriazole **18**, which can be easily and regioselectively acylated on N1. The treatment of the formed *N*-acylbenzotriazole **20** with $AlCl_3$ as a Lewis acid promotor facilitated ring cleavage leading to benzoxazoles under relatively harsh conditions (Scheme 14).[19]

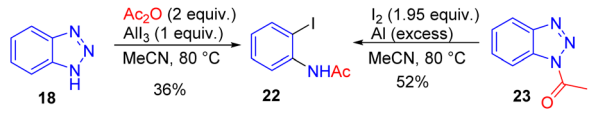
Rare examples of *ortho*-iodoacetanilide **22** formation in moderate yields from NH- and related *N*-acylbenzotriazole were reported in which the All_3/Ac_2O system or aluminium and iodine in acetonitrile were used.[20] These are the only cases of *N*-acetylbenzotriazole **23** ring cleavage known. Importantly, the reaction of *N*-acetylbenzotriazole **23** with $AlCl_3$ was not efficient



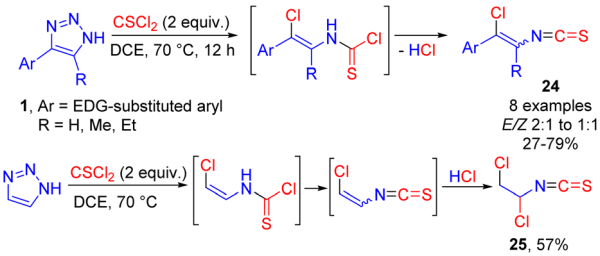
Scheme 13 Formation of bis(enamides) **17** and oxazoles **7** by the cleavage of NH-1,2,3-triazoles with trifluoroacetic anhydride in nitrile solvent.



Scheme 14 Synthesis of benzoxazoles from NH-benzotriazoles.



Scheme 15 Formation of *o*-iodoacetanilide by All_3-mediated cleavage of N1-acetylbenzotriazole.



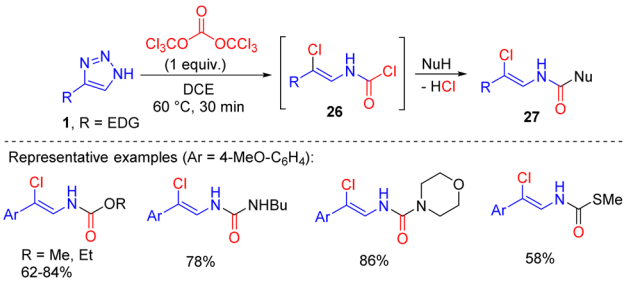
Scheme 16 Cleavage of NH-1,2,3-triazoles with thiophosgene.

and led only to deacylation, and not to the desired ring cleavage product (Scheme 15).[19]

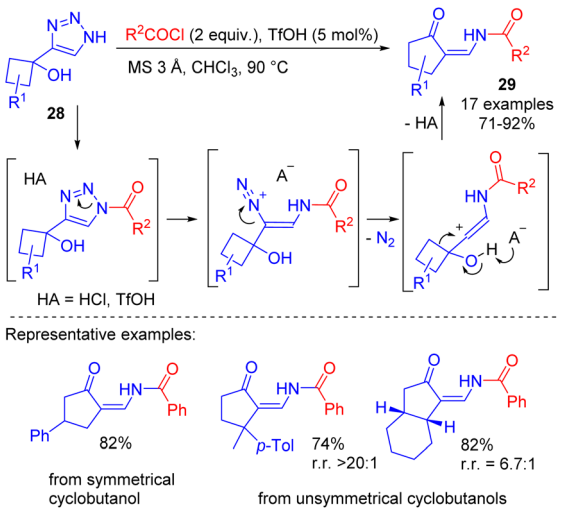
Cleavage of electron-rich 4-aryl-NH-1,2,3-triazoles **1** was successfully achieved with thiophosgene leading to the formation of vinyl isothiocyanates **24** by HCl elimination from the vinyl chloride intermediate (Scheme 16).[21] The vinyl isothiocyanate moiety is present in natural products with antifungal and antibacterial activity and is difficult to access by traditional methods. Switching from electron-rich aromatic NH-triazoles to unsubstituted NH-1,2,3-triazole afforded product **25** of HCl addition across the double bond in moderate yield.

A similar transformation with triazoles **1** bearing an electron-rich aryl or alkenyl substituent in position 4 proceeded with triphosgene.[21] The *in situ* formed carbamoyl chlorides **26** were treated with nucleophiles to gain access to multifunctional compounds **27**, such as *N*-alkenyl carbamates, ureas and thiocarbamates (Scheme 17).

The denitrogenative transformation of NH-1,2,3-triazoles was studied also on more complex substrates such as 4-(1-hydroxycyclobutyl)-1,2,3-triazoles **28**. Their cleavage with acyl chlorides **10** catalysed by triflic acid provided efficient access to cyclic enaminones **29** (Scheme 18).[22] The reaction proceeded *via* the cleavage of *N*-acyltriazole and semipinacol rearrangement



Scheme 17 Synthesis of multifunctional *N*-alkenyl compounds by the cleavage of NH-1,2,3-triazoles with triphosgene.



Scheme 18 Synthesis of cyclic enaminones by TfOH-catalyzed cleavage of 4-(1-hydroxycyclobutyl)-1,2,3-triazoles with acyl chlorides.

cascade. The procedure was found to be easily scalable to give multifunctional substrates in good yields.

Conclusions

In conclusion, NH-1,2,3-triazoles are commercially available or easily synthesized starting materials that exhibit a remarkable versatility in transformations to diverse nitrogen-containing heterocycles and functionalized *N*-alkenyl compounds *via* denitrogenative cleavage. *In situ* prepared *N*-acylated 1,2,3-triazoles are key intermediates in these transformations. Acid-mediated triazole ring opening of *N*-acylated 1,2,3-triazoles, followed by nitrogen elimination affords vinyl cation intermediates, which undergo a variety of reactions such as cyclization or heteroatom capture. Further development of denitrogenation of NH-1,2,3-triazoles accompanied by C–C bond forming reactions, C–H insertion or rearrangement of the vinyl cation can be expected, providing access to a structural diversity of products with potential applications in drug development. Moreover, due to easy availability of NH-1,2,3-triazoles they are excellent starting materials for the development of new industrial synthetic processes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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