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Elusive *N*-acyl-1,2,3-triazoles formed by direct acylation of NH-1,2,3-triazoles were isolated and fully characterized, including X-ray crystallography. A preference for the formation of thermodynamic *N*2 isomers was established. Direct evidence of interconversion between *N*1- and *N*2-acyltriazoles confirmed their value in denitrogenative transformations. Efficient synthesis of enamido triflates from NH-triazoles via the intermediacy of *N*2-acyl-1,2,3-triazoles was developed.

1,2,3-Triazoles are important heterocyclic compounds with various biological activities and high synthetic value.¹ There are two general synthetic routes to *N*-substituted 1,2,3-triazoles – cycloaddition reactions of azides with alkynes,² activated ketones,³ or nitroalkenes,⁴ and nitrogen functionalization of NH-1,2,3-triazoles with electrophiles.⁵ Whereas the cycloaddition reaction is widely investigated and established as an efficient and robust method, functionalization of NH-1,2,3-triazoles containing three nucleophilic nitrogen atoms is considered problematic because of unpredictable regioselectivity.^{1a,5} However, NH-1,2,3-triazoles are available starting materials that can be efficiently prepared from inexpensive NaN_3 ⁶ or TMNS_3 ⁷ and alkynes, or NaN_3 , aldehydes and nitroalkanes *via* tandem Henry reaction/[3+2] cycloaddition.⁸ Recently, a number of regioselective protocols for the synthesis of either *N*2⁹ or *N*1-substituted¹⁰ isomers of 1,2,3-triazoles have been developed. Thus, alkylation, arylation, vinylation and Michael addition with NH-1,2,3-triazoles as nucleophiles have been described and extensively studied.^{5,9,10} Sulfenylation of NH-1,2,3-triazoles, which would be a tempting route to synthetically useful *N*1-sulfonyl-1,2,3-triazoles, is not regioselective (Scheme 1B),¹¹ and only regioselective *N*2-sulfonylation *via* radical reaction is known.¹²

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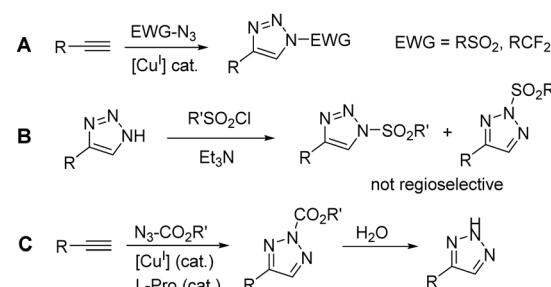
† Electronic supplementary information (ESI) available: Experimental procedures, compound characterization and copies of NMR spectra. CCDC 2244996 and 2244997. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3cc00987d>

***N*-Acyl-1,2,3-triazoles – key intermediates in denitrogenative transformations†**

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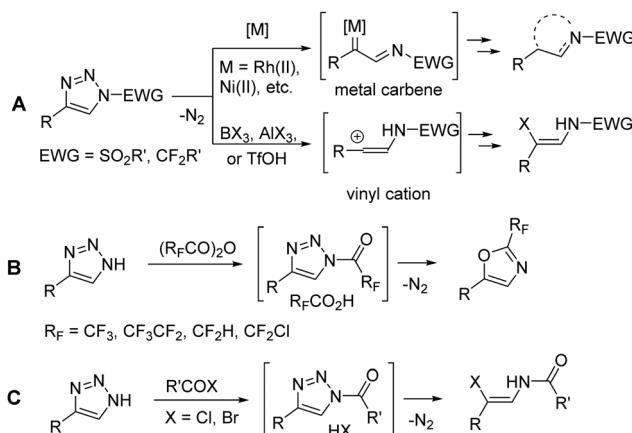
In contrast to a broad variety of known *N*-alkyl-, *N*-fluoroalkyl, *N*-aryl- and *N*-sulfonyl-1,2,3-triazoles (Scheme 1A), *N*-acyl-1,2,3-triazoles are almost unexplored, and only rare and scattered examples have been reported.¹³ Indeed, a click reaction with acyl azide is not a viable route because of the low stability of acyl azides in the presence of a Cu(i) catalyst, resulting in nitrene formation.¹⁴ *N*-Carbamoylation of NH-1,2,3-triazoles was studied giving a mixture of *N*1- and *N*2-isomers.¹⁵ These compounds possess significant application potential in biological studies. For example, 2-carbamoyl-4-aryl-1,2,3-triazole derivatives were used for site-selective incorporation into proteins,^{15a} as selective chemical probes of endocannabinoid biosynthesis enzymes.^{15b,c} Very recently, the formation of *N*2-alkoxycarbonyl-1,2,3-triazoles was observed in click reaction of carbamoyl azides with alkynes due to spontaneous carbamoyl group migration to *N*2-position.¹⁶ The resulting *N*2-carbamoyl triazoles were highly sensitive to hydrolysis to NH-triazoles (Scheme 1C).

1,2,3-Triazoles bearing an electron-withdrawing group at position *N*1 are useful starting materials in denitrogenative ring opening transformations.^{1,17} Among them, *N*-sulfonyl-1,2,3-triazoles are the most widely explored in denitrogenative transformations, which are possible under metal catalysis¹⁷ or by the action of Lewis or Brønsted acids (Scheme 2A).¹⁸ The transannulation process was recently extended by us to *N*-fluoroalkylated triazoles.¹⁹ Moreover, there was one report about denitrogenative cleavage of *N*-(1,2,4-triazolyl)-1,2,3-triazoles.²⁰ However, it is



Scheme 1 Synthetic approaches to *N*-EWG-substituted 1,2,3-triazoles.





Scheme 2 Transformations of N-EWG-substituted 1,2,3-triazoles and denitrogenative reactions of NH-1,2,3-triazoles with acylating reagents.

remarkable that *N*-acyltriazoles have never been used as substrates in denitrogenative transformations. This can be attributed to the low stability and propensity to deacylation.¹⁶ Also, reactions of *N*-acylbenzotriazoles with nucleophiles (amines, alcohols) result in acyl group transfer as well.²¹ Only recently, the first reports of efficient monocyclic 1,2,3-triazole ring cleavage starting from NH-triazoles *via in situ* acylation were published by us (Scheme 2B)²² and Li's group (Scheme 2C).²³ The formation of unstable *N*-acyltriazoles as intermediates in these processes has been proposed. Indeed, the utilization of readily available NH-triazoles is more atom-economical compared to *N*-sulfonyl- and *N*-fluoroalkyl-triazoles. However, the formation, stability and reactivity of *N*-acyl-1,2,3-triazoles remains unexplored. A high efficiency of NH-triazole ring cleavage transformations could support the hypothesis of regioselective *N*1-acylation,²³ while it is well-established that in reactions of NH-triazoles with electrophiles the formation of *N*2-substituted isomers is preferred.^{9*h-j*} We hypothesized that a rapid interconversion between *N*1 and *N*2-acyltriazoles in the presence of an excess of acylation agent might enable the conversion of *N*-acyltriazole into ring cleavage products. Herein we report on our systematic study on *N*-acylation of 1,2,3-NH-triazoles and their regioselectivity, as well as on our study of ring cleavage reactions of *N*-acyltriazoles with Brønsted and Lewis acids.

We initiated our study of the acylation of the model 1,2,3-triazole **1a** with different acylating agents in the presence of stoichiometric amount of base (Et_3N). Acylation of **1a** proceeded quickly at ambient temperature, with nearly quantitative yields (Table 1). In the case of benzoyl chloride or benzoic anhydride, mostly *N*2-acylated triazole **3a** formed (entries 1 and 2). The more electron-deficient 4-nitrobenzoyl chloride led to the exclusive formation of *N*2-substituted acyl triazole **3b** (entry 3), while 4-methoxybenzoylchloride, by contrast, showed a preference for *N*1-isomer **2c** (entry 4). The presence of halogen atoms in *ortho*-positions, exerting steric hindrance, also favoured the formation of *N*1-isomers (entries 5 and 6). Acetic anhydride and fluorinated acid anhydrides afforded almost exclusively *N*2-isomers (entries 7–9). However, ethyl chloroformate gave a nearly 1:1 mixture of isomers (entry 10). Thus, the general

Table 1 Acylation of NH-triazole **1a**^a

Entry	RCOX	Products	Yield ^b (%)	Acylation
			2 + 3	ratio ^c 2/3
1	PhCOCl	2a + 3a	>98	14:86
2	(PhCO) ₂ O	2a + 3a	>98	8:92
3	4-O ₂ N-C ₆ H ₄ COCl	3b	quant. ^d	<1:99
4	4-MeO-C ₆ H ₄ COCl	2c + 3c	>98	73:27
5	2-Cl-C ₆ H ₄ COCl	2d + 3d	94	80:20
6	2-Br-C ₆ H ₄ COCl	2e + 3e	96	79:21
7	Ac ₂ O	2f + 3f	98	5:95
8	(HCF ₂ CO) ₂ O	3g	quant. ^d	<1:99
9	(CF ₃ CO) ₂ O	3h	quant. ^d	<1:99
10	ClCO ₂ Et	2i + 3i	97	45:55

^a Reaction conditions: **1a** (0.10 mmol) and RCOX (0.10–0.11 mmol) mmol), Et_3N (0.10–0.11 mmol), DCE (0.5 ml), rt, 1 h. ^b Isolated yield.

^c Determined by ¹H NMR. ^d Yield of crude products, not purified from triethylammonium salt.

observation is that *N*2-acylation is favoured and that only soft, weak and bulky acylating reagents favour *N*1-acylation. Solvent effects and effects of substituents at position 4 affect only slightly the reaction outcome, compared to the remarkable effect of acylating agents (see the ESI† for full details).

X-ray diffraction analysis of *N*1-isomer **2c** and *N*2-isomer **3f** confirmed their structure (Fig. 1). Surprisingly, acylated triazoles **2** and **3** are stable enough to be isolated by solvent extraction using aqueous workup and to be fully characterized spectroscopically. Products **3b**, **3g** and **3h** were found to be hydrolytically very unstable and aqueous workup could not be used. All acylated triazoles underwent partial or full decomposition during silica gel column chromatography.

The structures of the obtained *N*1- and *N*2-acyltriazoles were additionally confirmed by ¹H-¹⁵N HMBC NMR data. ¹H-¹⁵N HMBC data values, namely $\delta^{(15)\text{N}}$ and J_{HN} were compared with calculated values for 4-phenyl-*N*-difluoroacetyl-1,2,3-triazoles, which confirmed the presence of a difluoroacetyl group at the *N*2 position (see ESI†). Importantly, ¹H-¹⁵N HMBC NMR of **2c** confirmed the presence of an acyl group at position *N*1; this result is corroborated by single crystal X-ray analysis data (Fig. 1). Regarding ¹H NMR of *N*-acyltriazole mixtures, the isomers could be identified by their chemical shifts of H5, which was shifted by 0.2–0.4 ppm downfield for *N*1-acyltriazoles ($\delta_{\text{H}5} = 8.4$ –8.7 ppm) compared to *N*2-acyltriazoles ($\delta_{\text{H}5} = 8.1$ –8.3 ppm). This tendency

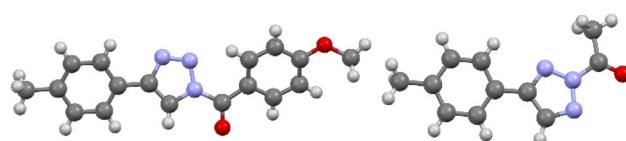
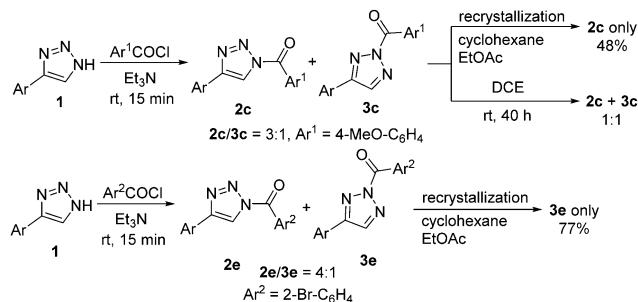


Fig. 1 X-ray crystal structures of **2c** (left, CCDC 2244997) and **3f** (right, CCDC 2244996). Ellipsoids are set at a 50% probability level.



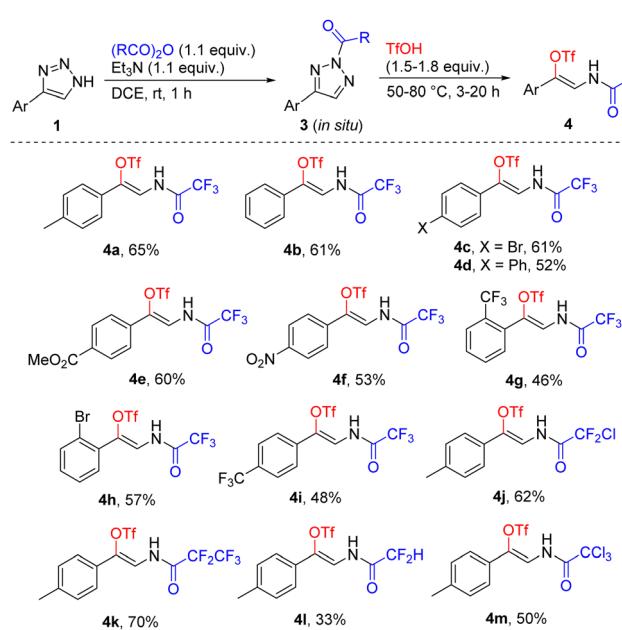


Scheme 3 Evidence of *N*1- to *N*2-acyltriazole interconversion process (Ar = *p*-tolyl).

corresponds to literature δ_{H5} shifts observed for *N*1- and *N*2-tosyl-4-phenyl-1,2,3-triazoles.^{12,24}

*N*1- and *N*2-isomers of acylated triazoles convert to one another. The *N*1- to *N*2-acyltriazole interconversion (Scheme 3) can be driven by thermodynamics, as in the case of the slow conversion of 2c to 3c at room temperature, or by the formation of a crystal lattice during crystallization of sterically hindered *N*2-isomer 3e (Scheme 3). By contrast, we succeeded in isolating pure *N*1-isomer 2c by recrystallization of a 2c/3c mixture. The process of *N*1- to *N*2-interconversion depends on solvent, the concentration and even the reaction scale, which complicated its detailed study.

Nevertheless, denitrogenative triazole ring cleavage can only take place from *N*1 isomers. We demonstrated that the reverse process of *N*2- to *N*1-acyltriazole interconversion is crucial for the success of *N*-acyltriazole cleavage with the involvement of *N*2-isomers in denitrogenative transformations. *In situ* formed *N*2-acylated triazoles 3 react efficiently with triflic acid to produce enamido triflates 4 (Scheme 4). Previously, trifluoroacetylated



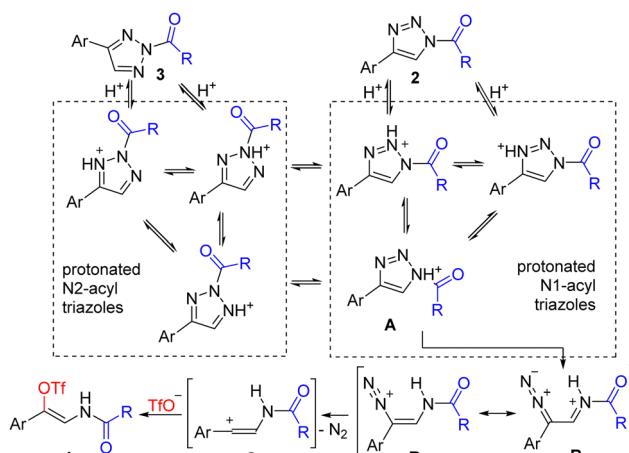
Scheme 4 Formation of enamido triflates 4 from NH-triazoles 1. Reaction conditions: 1 (0.3 mmol), (RCO)₂O (0.33 mmol), Et₃N (0.33 mmol) in DCE (1 ml) stirred for 1 h, then TfOH (0.45–0.54 mmol), 50–80 °C, 3–20 h.

enamido triflates were prepared by the reaction of *N*-perfluoroalkyl-1,2,3-triazoles with triflic acid,^{19e} but the present methodology benefits from the use of readily available NH-triazoles and trifluoroacetic anhydride. The reaction was found to be applicable for the synthesis of products 4, bearing neutral aryl substituents (4a, 4b, 4d) or a bromine atom (4c), in good yields. Electron-withdrawing and bulky substituents on the aryl ring were also tolerated (4e–4h). Importantly, the method broadens the scope of enamido triflates to compounds with other fluoroalkyl groups than trifluoromethyl (CF₂Cl, CF₂CF₃, CF₂H; 4j–4l), as well as the trichloroacetyl group (4m). 4-Alkyltriazoles giving unstabilized vinyl cation afforded complex mixtures.

For the above-mentioned transformations, the following mechanism of acyltriazole cleavage to form enamido triflates is proposed: Protonation of acyltriazoles 2 or 3 can theoretically lead to six protonated species, which are in equilibrium due to acyl group and proton shifts. By analogy to our earlier investigations and DFT calculations^{19f} only species A undergoes *N*1–*N*2 cleavage to give the diazo/diazonium intermediate B. Diazonium B undergoes denitrogenation to vinyl cation C, and recombination with the triflate anion gives enamido triflate 4 (Scheme 5).

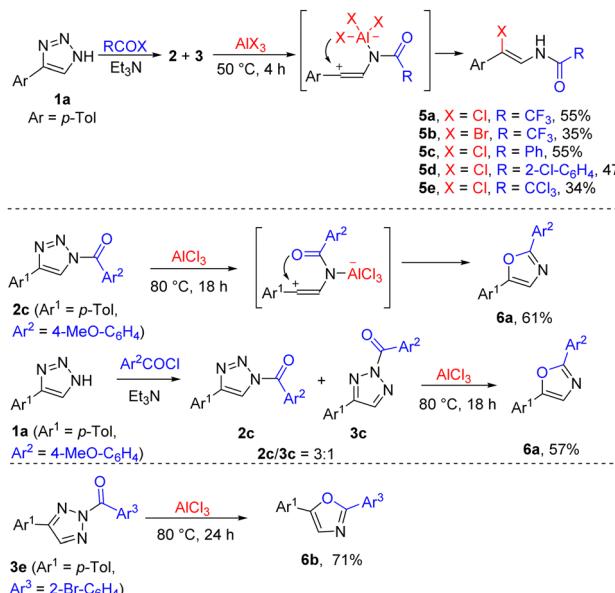
Acylated triazoles can be also cleaved with Lewis acids. *In situ*-formed acylated triazoles 2 and 3 reacted with an equimolar amount of AlX₃ to produce β -haloenamides 5, presumably *via* cleavage of forming *N*1-acyltriazole to a vinyl cation (Scheme 6). The less electron-deficient *N*1- or *N*2-acylated triazoles 2c, 3c, or 3e cyclized to give oxazoles 6, showing that both isomers can be converted to the same ring-cleavage and cyclization products.

In conclusion, *N*-acylation of 1,2,3-NH-triazoles was investigated and *N*2-acyltriazoles were found to be the main products; however, electron-rich and bulky acylating reagents induced the formation of a mixture of *N*1- and *N*2-acylated triazoles. Interconversion between regioisomers of *N*-acyltriazoles under thermodynamic conditions, during crystal formation, or in the presence of Brønsted or Lewis acids was observed. Triazole denitrogenative ring cleavage starting from *N*2-acyltriazoles is reported for the first time. Efficient synthetic access to valuable vinyl triflates from NH-triazoles was developed.



Scheme 5 Mechanism of β -enamido triflate formation.





Scheme 6 Ring cleavage of acylated triazoles using Lewis acids.

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Conflicts of interest

There are no conflicts to declare.

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