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Review Article

Triazolinediones applications and recent advances in click chemistry

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ABSTRACT

Triazolinediones (TADs) are unique reagents in organic synthesis that have also found wide applications in different research disciplines. This work focuses on the recently emerging applications of the triazolinediones chemistry. TAD groups can be reliably clicked onto a range of olefinic reaction partners (Enes and dienes). Recent advances in TAD chemistry includes its roles in bioconjugation of peptides and proteins, derivitization of low-abundant lipid metabolites in biological sample, modular chemical library synthesis, clicking and unclicking protecting groups in organic synthesis, functionalization, and cross-linking of natural plant oils and polymer science.

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Graphical Abstract

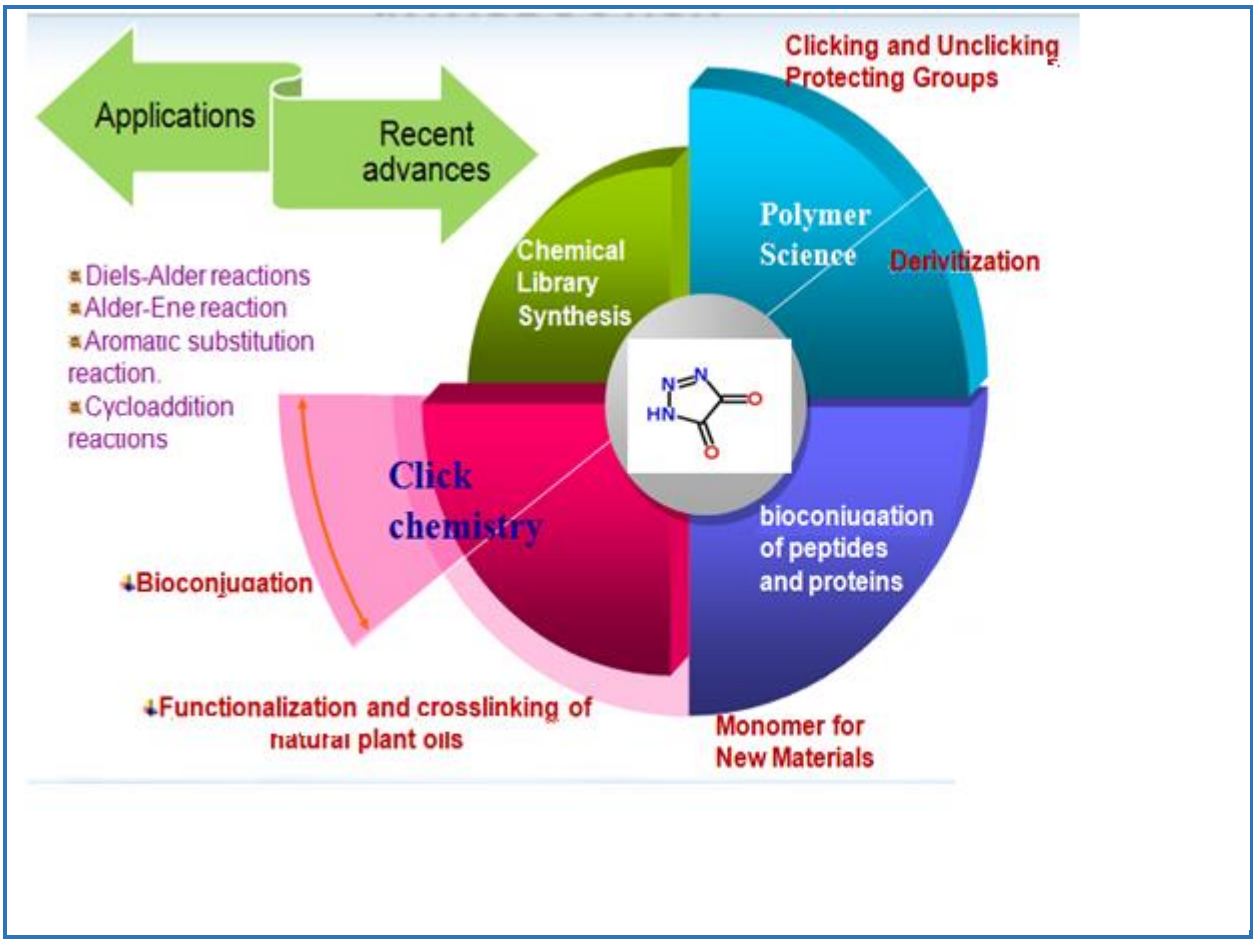

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Table of Contents

Introduction

Click chemistry has recently emerged to become one of the most powerful tools in drug discovery, chemical biology, and proteomic applications. In recent years, the design and synthesis of the pharmacologically relevant heterocyclic molecules by combination techniques have proven to be a promising strategy in the search studies conducted on pharmaceutical lead structures. Click chemistry is one of the powerful reactions for making the carbon-heteroatom-carbon bonds in aqueous environment with a wide variety of chemical and biological applications in various fields.

The term "click chemistry" is generally used to describe the reactions that are quick, highly selective, versatile, and high yielding when connecting two molecular components [1]. Since the initial recognition of the copper catalysed azide-alkyne cycloaddition as a click chemistry, a number of reactions have now been so classified, and the concept was further extended by designating certain chemistries as bioclick or bioorthogonal. The latter terms have been reserved for those reactions that can occur in the presence of the living biological systems (e.g., cells) or fragile biomacromolecules (e.g. proteins) and that do not interfere with their native processes or functions. The bioclick reactions that have grown substantially over the past decade include Michael additions, strain-promoted azide-alkyne cycloadditions (SPAACs), photoinitiated thiol-ene reactions, and inverse electron demand Diels-Alder cycloadditions (IEDDACs). These chemical reactions provide powerful and versatile tools for polymer scientists when modifying or synthesizing polymers for a diverse array of applications, ranging from matrices for regenerative medicine to improved drug delivery systems.

Triazolinediones (TADs) are unique reagents in organic synthesis that have also found wide applications in different research disciplines, in spite of their somewhat "exotic" reputation. Figure 1 represents the chemical structure of triazolinediones.

The remarkable bond forming reactivity of azodicarbonyl derivatives toward normally "unreactive" unsaturated hydrocarbon substrates was first recognized in the pioneering 1920s work by *Diels*et al. [2]. This seminal finding would lead to developing the famous and transformative Diels-Alder reaction, as reagents such as diethyl azodicarboxylate (DEAD) were found to spontaneously form a quantitative 1:1 adduct with cyclopentadiene at room temperature without the need for additives or catalysts. Once isolated, most triazolinediones are generally easy to handle and are stable for prolonged periods when stored in a cold environment (i.e., -18 °C) in the absence of light and moisture [3].

Click chemistry: an overview

The click reaction must be modular, wide in scope, give very high yields, generate only inoffensive by-products that can be removed by non-chromatographic methods, and be stereospecific (But not necessarily enantioselective)[4]. The required process characteristics include simple reaction conditions (Ideally, the process should be insensitive to oxygen and water), readily available starting materials and reagents, the use of no solvent or a solvent that is benign (Such as water) or easily removed, and simple product isolation. Purification, if required, must be by no chromatographic methods, such as crystallization or distillation, and the product must be stable under physiological conditions. The traditional process of drug discovery based on natural secondary metabolites has often been slow, costly, and labour intensive. Even with the advent of combinatorial chemistry and high-throughput screening in the past two decades, the generation of leads is dependent on the reliability of the individual reactions to construct the new molecular framework. In fact, in several instances, water is the ideal reaction solvent, providing the best yields of the product with the highest rates. For reaction workup and purification, eco-friendly solvents are used that avoid purification techniques likechromatography. Click reactions share the following attributes:*I*) Many click components are derived from alkenes and alkynes, and thus ultimately from the cracking of petroleum. Carbon-carbon multiple bonds provide both energy and mechanistic pathways to be elaborated into reactive structures for click connections.*II*) Most click reactions involve the formation of carbon-heteroatom (Mostly N, O, and S) bonds. This stands in contrast to the march of modern synthetic organic chemistry, which has emphasized the formation of carbon-carbon bonds.*III*)Click reactions are strongly exothermic, by virtue of either highly energetic reactants or strongly stabilized products.*IIII*) Click reactions are usually fusion processes (Leaving no by-products) or condensation processes (Producing water as a by-product).*V*) Many click reactions are highly tolerant of, and often accelerated by, the presence of water.

The copper(I)-catalyzed 1,2,3-triazole formation from azidesand terminal acetylenes is a powerful tool for the generation of privileged medicinal scaffolds, due to its high degree of dependability, complete specificity, and the biocompatibility of the reactants [5]. The triazole scaffolds are found in a number of biologically active compounds exhibiting anti-HIV, antibiotics, antiviral, and antibacterial activities [6]. Click chemistry is one of the powerful tools for the generation of drug candidates. Many researchers used click chemistry as a synthetic tool for the generation of pharmalogically valuable drugs.

Triazolinediones

Triazolinedione is a versatile and reliable synthetic tools, namely, in the field of synthetic chemistry, polymer science as well as in more recently emerging field of click chemistry. Table 1 summerizes the properties of triazolinediones.

Figure 1. Structural representations of triazolinedione

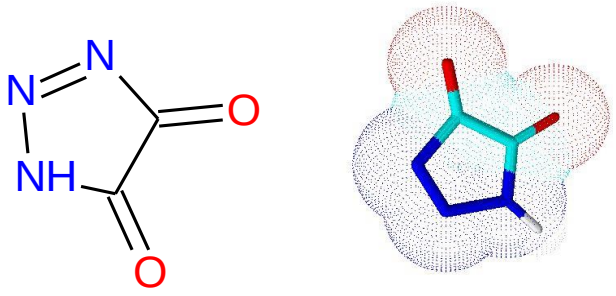


Table 1. Properties of triazolinediones

Properties	Values
Molecular Formula	$C_2HN_3O_2$
Formula Weight	99.04824
Composition	C (24.25%) H (1.02%) N (42.42%) O (32.31%)
Molar Refractivity	20.07 ± 0.5 cm^3
Molar Volume	44.4 ± 7.0 cm^3
Parachor	147.3 ± 8.0 cm^3
Index of Refraction	1.863 ± 0.05
Surface Tension	121.0 ± 7.0 dyne/cm
Density	2.22 ± 0.1 g/cm^3
Polarizability	7.95 ± 0.5 $10^{-24}cm^3$

Synthesis of triazolinediones

The synthesis of triazolinediones can be discussed under two headings.*I*) Synthesis of functionalized urazole precursors. *II*) Oxidation of urazoles to their corresponding 1,2,4-triazoline-3,5-diones

Synthesis of functionalized urazole precursors

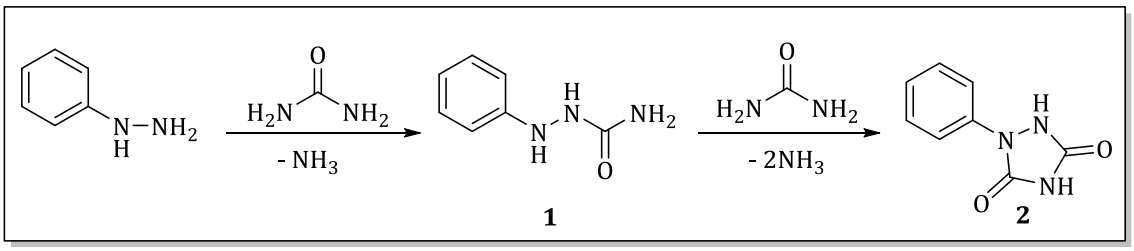
The synthesis of a 1,2,4-triazolidine-3,5-dione (Urazole) dates back to 1887, when pinner noted a peculiar reaction between phenyl hydrazine and urea, the outcome of which depends on the ratio of the reactants. Reaction of urea with phenylhydrazine, as reported by *Pinner* [7]. This reaction is illustrated in Scheme 1. If only 1 equivalent of urea is used,1-phenylsemicarbazide **1** is obtained, while an excess of urea leads to a cyclic compound **2**. Since pinner envisioned that other analogues of 1-phenyl-1,2,4-triazolidine-3,5-dione can be synthesized as well, he introduced the name "urazole" for this class of five-member heterocyclic compounds. This reactions are illustrated in Scheme 2.

Synthesis of a urazole by *pinner* in 1887, i.e., 1-phenyl-1,2,4-triazolidine-3,5-dione **2**, it took until 1894 before the somewhat elusive "parent" heterocycle, unsubstituted urazole, was prepared and isolated, in independent studies by *Thiele* and *Stange* [8] and *Pellizzari* and *Cuneo* [9]. Both approaches acquired urazole **3** by heating hydrazodicarboxamide **4** (Biurea) to 200 °C in the absence of solvent hydrochloride to the original reaction mixture gave 4-phenylurazole **5**, a positional isomer of the previously reported 1-phenylurazole. The mechanism of formation of 4-phenylurazole is of interest to the current report (Vide infra) and is believed to proceed *via* the formation of a 1-arylbiurea, which expels ammonia, followed by cyclization and release of another equivalent of ammonia. While Thiele was the first to report on synthesis of the 4-substituted urazoles.This procedure mostly gives poor isolated yields due to the competitive formation of the diphenylurea **6** and the difficult separation of the products from unreacted or excess starting materials [10]. Synthesis of 1,2,4-triazolidine-3,5- dione (Urazole) and 4-phenylurazole are illustared in Scheme 3.

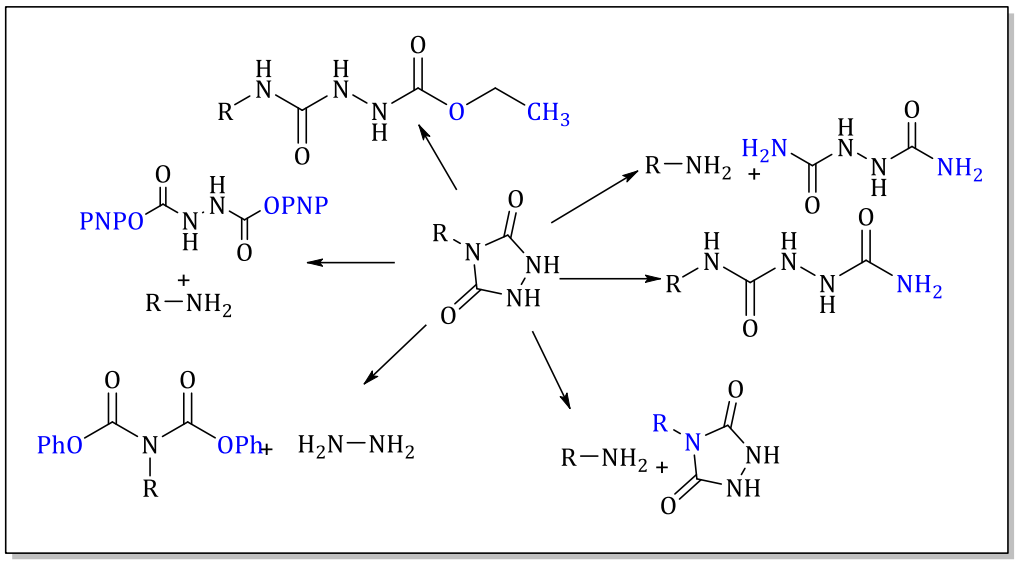
Urazoles via semicarbazides

In the context of urazole synthesis, these more reactive urazole precursors are often simply referred to as "semicarbazides", as will also be done in this review. Significantly, semicarbazides can be generated by plainly mixing an isocyanate with ethyl carbazate (In itself a readily available condensation product of cheap hydrazine and diethyl carbonate) and is thus a very convenient approach. Reactions are depicted in Scheme 4.

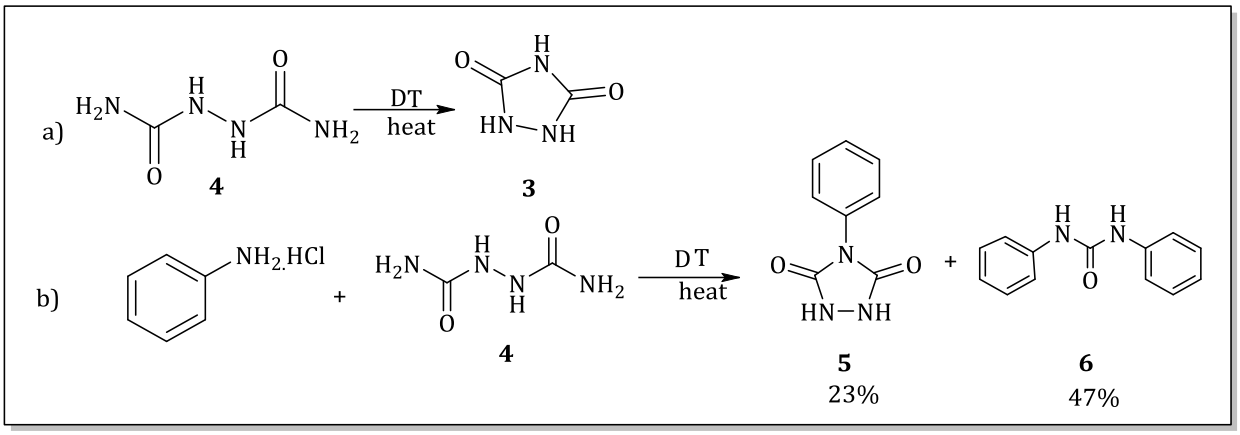
Semicarbazides from isocyanates



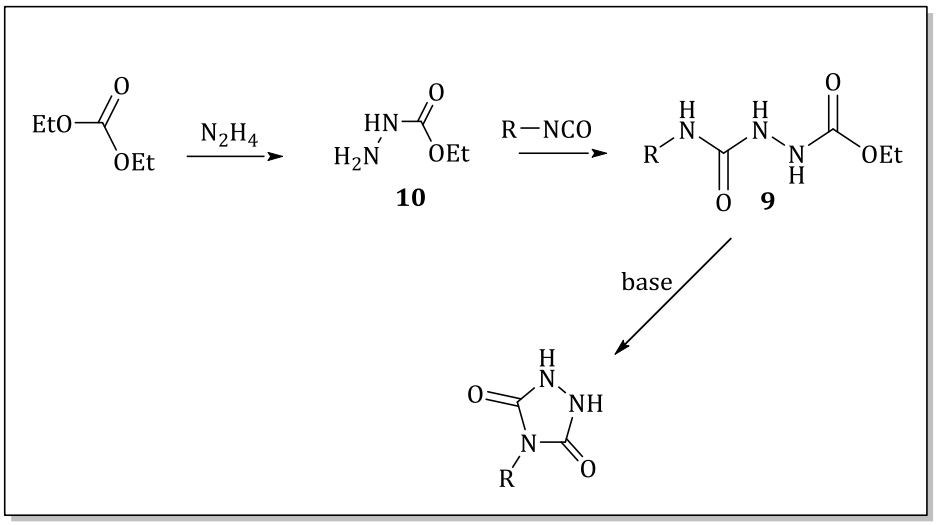
Scheme 1. Synthesis of a 1,2,4-triazolidine-3,5-dione from phenyl hydrazine



Scheme 2. Brief overview of the possible synthetic strategies to obtain 4-substituted 1,2,4-triazolidine-3,5-diones (PNP = para nitrophenyl) from Hydrazodicarboxamide derivatives



Scheme 3. Original Synthesis of a) 1,2,4-triazolidine-3,5- dione (Urazole) and b) 4-phenylurazole



Scheme 4. Cookson/Zinner–Deuckersynthesis of urazoles

Isocyanates are generally highly reactive synthetic moieties. These react readily with ethyl carbazate **10** at room temperature and gives the corresponding semicarbazide adducts in excellent yield (Up to 100%). If the reaction mixture is heated, complete conversions can be achieved in a matter of hours. The role of the solvent is not critical, howeveras the semicarbazide products tend to precipitate from the hydrophobic solvents such as toluene.The use of such solvents vastly simplifies the workup to the point that after collecting and drying the solids, there is generally no need for a further purification step.

Semicarbazides from carboxylic acids

Despite the ease and versatility of the Cookson method, typically accompaniedby a high yield of the overall synthesis, the method is limited by the structural variety in commercially available isocyanates. Therefore, many research studies have been performed to obtain the semicarbazides from the alternative starting materials. Most of the alternative procedures are based on Cookson method. In this method isocyanate is prepared in situ and this avoids the isolation or purification of hazardous intermediates.Thus, the Cookson method has been extended to the preparation of semicarbazides from simple carboxylic acids.

Oxidation of urazolestotheir corresponding 1,2,4-triazoline-3,5-diones

An important remark in the context of TAD synthesis is that, although oxidation of urazoles is a very straightforward reaction, it can sometimes be a true bottleneck of triazolinedione synthesis. Although urazoles are in fact readily oxidized by most oxidants, these reactions are hard to perform

because of two interrelated issues, i.e., the chemoselectivity of the oxidant and the reactivity of the resulting TAD compounds. Especially isolation of TAD reagents from reaction mixtures can be challenging. Ideal oxidation methods should thus be highly chemoselective, give one single triazolinedione reaction product, and generate no waste products or only waste products that are readily removed. Neither the oxidant nor its reduced forms should react with the TAD compound.

Nitrogen-(IV) and nitrogen-(V),oxide-based oxidations

Nitric acid oxidation (HNO_3)

The first nitrogen-(IV)-mediated oxidation was serendipitously observed by Thiele as in scheme 5, when he sought to dissolve a silver salt of an unsubstituted 4*H*-urazole in the concentrated nitric acid, a common solvent for heavy metals and their salt derivatives [10].

Halogen mediated oxidations

Besides N-(IV) and N-(V) oxide-based reagents, a second major chemical class of oxidants used to convert urazoles into triazolinediones comprises halogens and their derivatives. Development of these types of oxidation procedures can again be traced back to the work of Thiele, who was able to generate a red solution of unsubstituted 4H-TAD with hypochlorous acid and aqueous bromine (Scheme 6).

Chlorine and bromine

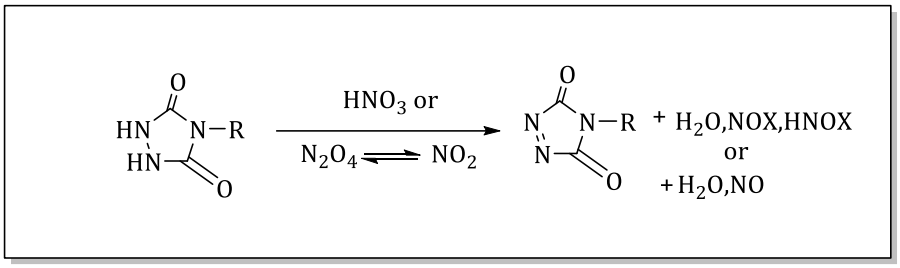
The oxidation of urazoles by the action of chlorine (Scheme 7) was reported to be fast and high yielding [11]. Interestingly, even treatment with sub molar amounts of chlorine gas have also been found to complete the resole oxidation, implicating the involvement of molecular oxygen in a radical chain oxidation process [11]. Chlorine can either be applied as a gas stream bubbled through the resole suspension or as a solution in tetra chloromethane. The use of gaseous chlorine gives slightly higher yields and faster reaction times, but these differences remain very limited. Also bromine is a useful reagent for triazolinedione generation.

Reactivity of triazolinediones

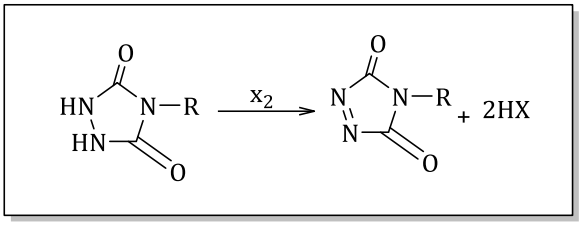
Triazolinediones are used in various reactions such as, Diels-Alder reactions, Alder-Ene reaction, aromatic substitution reaction, and cycloaddition reactions. These reactions are illuststrated in Scheme 8. TAD reagents have an overall resemblance in chemical structure with the more widely known maleimidewhich are a well-established class of important synthetic tools for a wide range of applications, including click chemistry [12]. Also, their modes of reactivity shows some important

similarities. Nevertheless, TAD compounds react much faster than the maleimides and participate in a larger variety of pericyclic reactions with a much wider range of substrates and with simple olefins. In particular, reagents also have a higher intrinsic thermodynamic driving force than the maleimides. Thus, whereas many maleimide-based conjugation reactions are reversible processes, most of the TAD-based reactions are completely irreversible. An important difference is the relative lack of (Controlled) reactivity, which TAD reagents show toward typical nucleophiles including, amines and thiols. Triazolinedione reagents and related compounds such as malemides, azolinediones, singlet oxygen, and andnitosocarbonyls are presented in Scheme 9.

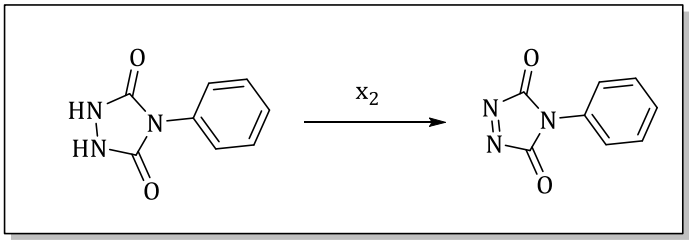
Scheme 5. Nitric acid oxidation



Scheme 6. Halogen-mediated urazole oxidation



Scheme 7. oxidation of urazoles by the action of chlorine



Applications and recent advances of triazolinedionesinclick chemistry

Triazolinediones in click chemistry application

The click chemistry is often just focused on repurposing the long known reactions for new applications. The simple but visionary act to define a set of characteristics that a synthetic bond-forming reaction should ideally meet [Be modular, wide in scope, high yielding, chemoselective, give no offensive by-products (or be atom-economic), and have an intrinsic driving force to follow a single reaction] offers a highly subjective but at the same time quite useful conceptual framework to

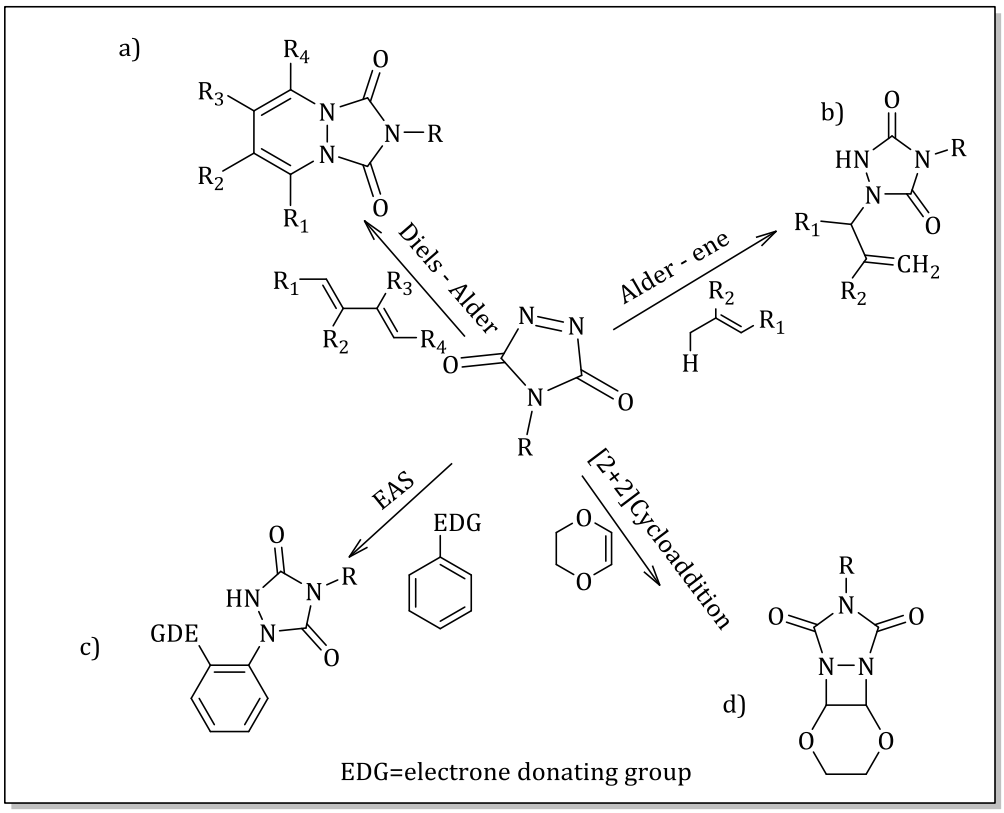
consider chemical reactivity in terms of the possible applications. The initial introduction of the click chemistry concept was tailored for developing the new medicines. For biology oriented applications, compatibility with water and the physiological stability of adducts have been identified as addition. For other areas of research that were quick to adopt click chemistry principles, such as polymer science.Although Hetero-Diels–Alder reactions have been called "beautiful representatives of click chemistry ideals" by *Sharpless* and *Finn* [13], TAD-based chemistry. TAD compounds also have a reputation of being "exotic" reagents and have been generally regarded as highly unstable species. The synthesis of TAD reagents can be straightforward and mostly involves the steps that are high-yielding and do not require a purification step. Triazolinediones brings some unprecedented features to click chemistry, such as dynamic and highly controlled bond formation.

Triazolinediones in click bioconjugation of peptides and proteins

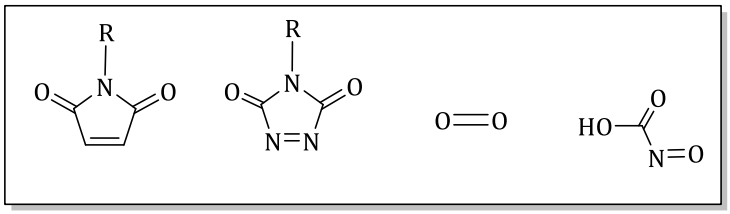
TAD reagents as useful tools for click chemistry, on a "click-like" conjugation strategy for natural peptide and protein substrate. Barbs and co-workers showed the true potential of this tyrosine bio conjugation with a range of additional experiments and a systematic study of TAD orthogonality toward different amino acid side chains. To expand this tyrosine-selective click modification even further, Barbas' group also implemented it for site-selective and orthogonal protein multifunctionalizations. In this case, orthogonal trifunctionalization at tyrosine, cysteine, and lysine residues of bovine serum albumin (BSA) and human serum albumin (HSA) was achieved. Cysteine and lysine were modified with a fluoresceinmaleimide and 11-(dansylamino)undecanoic acid, respectively, while the tyrosine units were successfully reacted with TAD derivatives. Reactions of the tyrosine bioconjugation are illustrated in Scheme 10.

In another biomedical application, *Barbas* and co-workers used the TAD tyrosine click conjugation to couple the anti-HIV drug aplaviroc with a monoclonal antibody. The targeted delivery of drugs through antibody–drug conjugates can be of use for many therapeutic applications. As a model monoclonal antibody, the well-characterized trastuzumab was used. An alkyne-containing derivative of aplaviroc was coupled to an azidourazole by using a CuAAC reaction. This precursor was oxidized to yield the TAD derivative, which was immediately used for labelling of trastuzumab. Again, the obtained protein mostly showed the incorporation of a single drug molecule. This drug–antibody conjugate was further shown to retain both its antiviral as well as its antigen binding activity.

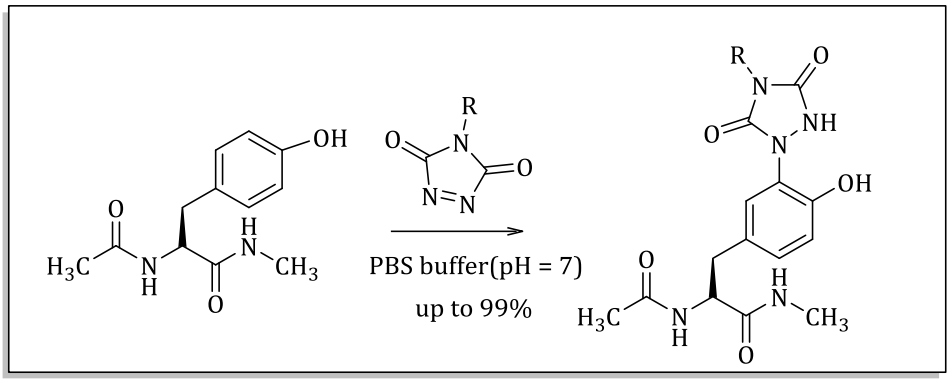
By making use of hetero bifunctional cross linkers, TAD click reactions are used to prepare DNA-protein conjugates. These bifunctional cross-linkers incorporate a TAD moiety to ensure the fast and selective reaction with tyrosines and functionality to couple a DNA strand. For this last coupling, various "click" reactions was tested including, maleimidethiol Michael addition, CuAAC reaction, and



Scheme 8. Reactivity of triazolinediones



Scheme 9. Triazolinedione reagents and related compounds: malemides, azolinediones, singlet oxygen, and andnitosocarbonyls



Scheme 10. Reaction of the tyrosine bioconjugation (R=Ph or Me)

strain-promoted copper-free AAC reaction. All three orthogonal click strategies gave conjugates that outperformed pharmaceutical interest. CRM_{197} is a nontoxic mutant diphtheria toxin that has been extensively used as the protein carrier in many licensed vaccines and has well-proven safety and efficacy.

Triazolinediones in click derivitization of low-abundant lipid metabolites in biological samples

Yamada and co-workers reported in 1990 that triazolinediones are ideal reagents to derivatize conjugated dienes in natural lipids, even in complex and dilute biological samples. *Yamada* and co-workers [14] synthesized the now commercially available fluorescent DMEQ–TAD reagent and used it to assay and quantify various hormonally active and important vitamin D metabolites. The TAD–diene Hetero-Diels–Alder click reaction is so fast and orthogonal that vitamin D metabolites, at a concentration as low as 10–8 M, could be reliably labelled and then quantified *via* HPLC with a fluorescence detector.

Triazolinediones as tools in modular chemical library synthesis

For the parallel synthesis of structurally diverse libraries of chemical compounds, it is important that each reaction step proceeds with the maximum efficiency and that reaction workup and purification can be standardized to a point that allows for automated synthesis and purification steps. Although most Diels–Alder reactions have a high intrinsic driving force, obtained yields and conversions are often limited because of kinetic reasons, as they require considerable thermal activation. The most common and reliable way to achieve good yields in reasonable time frames for Diels–Alder reactions is the use of an excess of one of the reaction partners. However, this straightforward strategy typically requires a chromatographic separation of the desired cycloadduct from the excess of diene or dienophile as an “offensive by-product”. This chromatographic separation can be avoided if the excess diene or dienophile can be selectively derivatized with asecondary Diels–Alder reaction that does meet click chemistry ideals, if this gives nonoffensivecycloadducts that can be easily removed from reaction mixtures.

Triazolinediones in natural plant oils as a versatile feedstock monomer for new materials

Synthesis of the organic polymer materials is a chemical process that requires precise control of reaction conditions, dedicated reaction vessels, and the raw materials (Monomers) having ahigh chemical purity. As the use of TAD based click chemistry was expanding,DuPrez and co-workers showed interest in natural plant oils as complementary partners for TAD reagents. Although most plant oils contain a large number of olefinic bonds, only very limited chemical transformations can

be effected on these natural synthetic handles, often requiring catalysts and/or harsh reactions conditions.

Triazolinediones in clicking and unclicking protecting groups in organic synthesis

TAD reagents can be used as protecting groups for dienes, but the deprotection requires a hydrolysis in strongly alkaline medium at elevated temperatures. Thus, as is often the case in implementing protecting groups in organic synthesis, this strategy adds a lot of practical difficulties to the synthesis process, making it a less efficient process. In ideal synthetic routes, the use of protecting groups should be completely avoided. However, protecting groups than can be installed and removed in a straightforward way, with regard to the click chemistry criteria, could be considered as "ideal" protecting groups.

Triazolinediones in ultrafast macromolecular click derivatization and conjugation

Du Prez and *Winne* were the first ones who investigated the click-like behaviour of TAD chemistry with a range of simple olefin-type substrates. The positive outcome of this study led to the introduction of a general click chemistry platform, based on Hetero-Diels–Alder reactions of TAD reagents. These TAD-click reactions do not require additives or a catalyst and proceed readily at or even below room temperature. It was shown that the involved reactions were upscalable, quantitative (High yielding) under equimolar conditions, ultrafast (Showing rate constants that go up to 160000 L/mo s79), and resulted in a single reaction product. A high degree of orthogonality was demonstrated by performing a TAD–diene reaction in the presence of a wide range of stoichiometric additives including various functional groups. In this study,excellent chemoselectivity molecular weight TAD compound (4-BuTAD) or polymer bound TAD reagent, respectively.

From plant oils to plant foils: straightforward functionalization and cross-linking of natural plant oils with triazolinediones

A first application of TAD chemistry for plant oil derived materials was very recently reported by Biswas et al., in which soybean oil was modified with readily available4-phenyl-1,2,4-triazoline-3,5-dione and shown to be applicable as lubricants and/or thickeners.

Model study with fatty acid derivatives

To assess the reactivity of TAD reagents with natural triglycerides of polyunsaturated fatty acids, a model study was first conducted on isolated mono and polyunsaturated fatty acids (or derivatives thereof), which would reveal the relative reactivity and reaction rates of the various olefins found in

fatty acids under normal reaction conditions (At ambienttemperature, no inert atmosphere). Hence, oleyl alcohol (1), elaidyl alcohol (5), methyl ricinoleate (7), 10-undecenoic acid (9), methyl linoleate (10) and methyl linolenate(12), (Scheme 11) were mixed with phenyl-TAD (2) in equimolar amount for chemical structures of fatty acids. Reaction of oleyl alcohol with phenyl TAD is illustrated in Scheme 12.

Direct cross-linking of plant oils

The reactivity of TAD reagents with most fatty acids, the direct cross-linking of a range of commercially available plant oils with the aromatic TAD cross-linker **4** (bis-TAD) was tested at ambient conditions. The oils tested are olive, sunflower, colza, corn, groundnut, pumpkinseed, soybean, and castor oils. None of the oils tested in this study were subjected to any pretreatment and reactions have been performed under air.

Thermal characterization

The thermal properties, the networks prepared were subjected to differential scanning calorimetry (DSC) as well as to thermogravimetric analysis (TGA). When the midpoint Tg's are compared, it can be seen that a range from 60 up to 124 °C was obtained for the different plant oils. These relatively high glass transition temperatures reflect the rigid structure of the added aromatic bis-TAD cross-linker. The figure helps to select the plant oil composition as a function of the desired Tg for the corresponding cross-linked material, we anticipated that more Tg variations could also be obtained by starting from aliphatic cross-linkers or by varying the amount of cross-linker.

Triazolinediones enable ultrafast and reversible click chemistry for the design of dynamic polymer systems

TAD molecules are heterocyclic compounds with an azomoiety connected to two carbonyl functionalities [15]. This electronic conjugation stabilizes the azo function but the electron-withdrawing carbonyls and the symmetry of the electronic system also give it a very particular orbital-controlled electrophilic reactivity, similar to that of carbenes or singlet oxygen, which are highly reactive but unstable reagents with very short lifetimes [16]. Indeed, TAD molecules have a very similar reactivity profile to that of singlet oxygen, and favour ultrafast Diels–Alder and ene-type reactions. These reaction types are known for their inherent orthogonality and reversibility, although most systems (Such as the well-known Diels–Alder reaction of furans and maleimides) do not meet all click-chemistry requirements [17].

Conversely, TAD compounds offer a range of selective and predictable covalent linking reactions that are high yielding under equimolar conditions at low temperature (<20 °C), without the need for a catalyst [18]. Although TADs can undergo a very wide range of reactions with many different functional groups, these reactions are usually not observed in the presence of suitable Diels–Alder or ene reaction partners and, moreover, TAD compounds show high kinetic preferences for electron-rich π systems, which allows for good selectivity between alternatively substituted (di) enes. An additional benefit of these reactions is the intense colour of TAD compounds, which provides a visual feedback system, as most of the corresponding urazoles are colourless [19]. The reactivity of TADs in Diels–Alder and ene reactions has been studied extensively using the commercially available 4-phenyl-1,2,4-triazoline-3,5-dione with components of low molecular weight in organic synthesis in pharmaceutical applications and in orthogonal peptide labelling. In some of these cases, an efficient reaction has even been performed at room temperature in water. TADs have also been used in polymer science, mostly in stepwise Diels-Alder and ene-type polymerizations [20].

A wide range of TAD reagents can be prepared easily in a large scale from the corresponding, readily available isocyanates in three high-yielding steps (Overall yield up to 95%) that do not require purification. Thus,4-butyl-1,2,4-triazoline-3,5-dione (BuTAD) was prepared and reacted at room temperature with 2,4-hexadien-1-ol (HDEO), an abundant diene building block. This resulted in an almost instantaneous and completely chemo and stereoselective conversion into the expected Diels–Alder adduct, accompanied by a sudden colour change from deep red to transparent Similarly, BuTAD was found to give very efficient and selective click-type reactions witha range of alternative dienes and enes, such as 2,3-dimethyl-2-butene (DMB). To check the reversible or dynamic nature of this efficient linking reaction, the resulting urazole products were mixed with a competitive reactant for TAD moieties (2,4-hexadiene-1,6-diol (HDD)) and heated in dimethylsulfoxide (DMSO) in a pressurized vessel up to 250 °C for a prolonged period (More than one hour). The TAD–HDEO adduct proved to be thermally stable as it was fully recovered from these reactions and no trace of the possibly transclicked TAD–HDD cycloadducts was observed. These experiments were repeated with a number simple diene and ene reaction partners for BuTAD, which gave very similar results. Thus, the expected reversed reaction does not occur within a useful temperature range for most organic materials, and these TAD-based click reactions can be considered as completely irreversible for most applications although the retro reaction of TAD Diels–Alder adducts has found quite a few applications in organic synthesis, such as a protecting group for dienes, most of these require pyrolysis conditions (>300 °C) and/or an irreversible hydrolysis of the TAD moiety [21]. During our investigations of the relevant literature, we were thus intrigued by a report from Baran et al., wherein indole compounds were regenerated from their ene-type adducts with 4-methyl-1,2,4-triazoline-3,5-

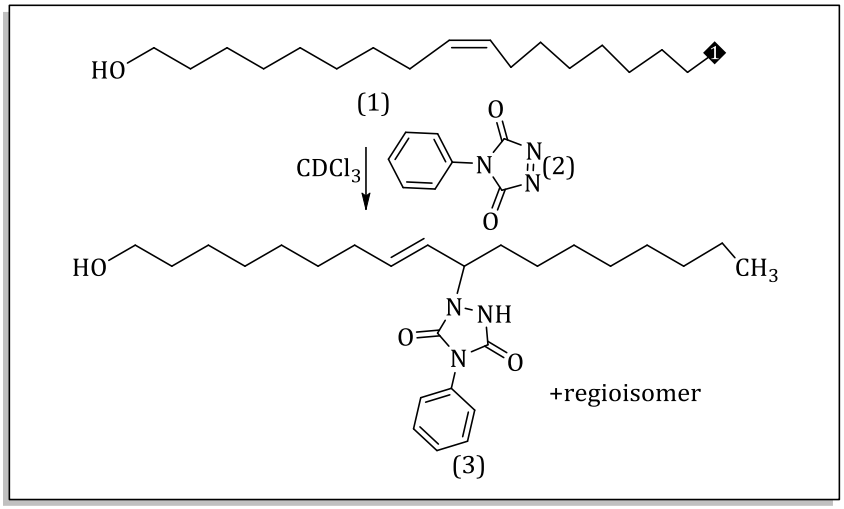
dione (MeTAD) by simply heating the neat compounds in vacuo at 100–150 °C, which removes the volatile MeTAD. This reported reversible TAD-based chemistry, which was described as a protecting group strategy for indoles, made us consider indoles as reaction partners for the reversible formation of TAD adduct.

Use of triazolinedionesinpolymer science

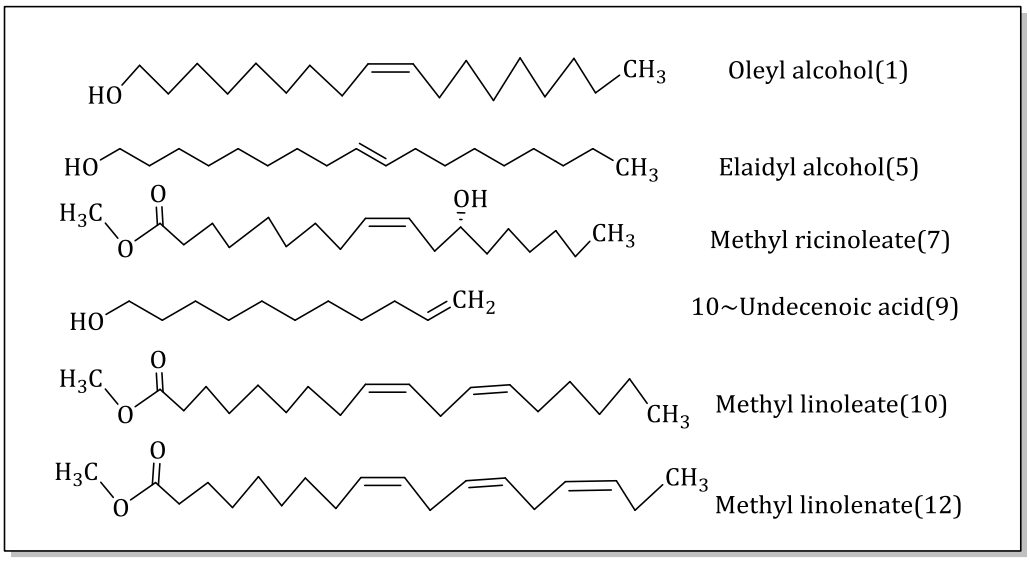
Following the introduction of TAD compounds as versatile reagents in organic synthesis in the 1960s, the polymer community also developed an interest for the unique reactivity of TADs.Important side reactions involving TAD: a) Dimerization of TAD under UV irradiation or when heated above 160 °C, b) Hydrolysis of TAD, c) Oxidation of Thiols, and d) Oxidation of alcohols to aldehydes or ketones.

Homopolymerization of TAD-based monomers

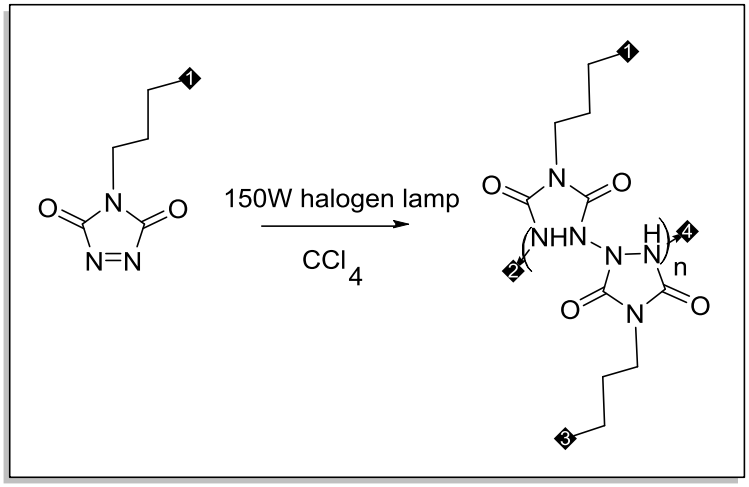
In 1970, *Pirkle* and *Stickler* investigated a direct polymerization reaction of TAD-based molecules, to obtain polymers with an exotic all nitrogen backbone (Scheme 13) [22].In this report, a 0.3 M carbon tetrachloride solution of 4-butyl-1,2,4-triazoline-3,5-dione (BuTAD) was irradiated with a halogen lamp for 8 min, giving a colorless polymer with an average molecular weight of 4200 g/mol (Around 20 monomer units). However, the obtained polymer had a very limited lifetime in the original CCl_4 solution, such as depolymerization slowly occurs within a time frame of 30 min to a few days. Moreover, the polymer is fully degraded within minutes in the presence of trace amounts of pyridine. The same experiments did not give polymers when aromatic TAD components were used.



Scheme 11. reaction of oleyl alcohol with phenyl TAD



Scheme 12. fatty acid derivatives



Scheme 13. Direct polymerization reaction of TAD-based molecules

Copolymerization of monofunctional TAD monomers

TAD molecules possess a very intriguing reactivity toward a wide range of relatively simple reaction partners, supplying different mechanisms as possible tools for a copolymerization. An interesting feature of the TAD is its powerful electron acceptor activity. On the basis of this, shortly following the work of *Pirkle*, *Stickler*, and *Butler*et al. showed that 4-phenyl-1,2,4-triazoline-3,5-dione (PhTAD) could react with a variety of electron-donating alkenes to yield alternating copolymers [22].

Copolymerization of bifunctional TAD monomers

Most research on TAD compounds focuses on their ability to be used as very reactive dienophiles and/or enophiles. The obtained polymers contained a rather rigid mainchain structure with Mn up to 18000 g/mol. A Diels–Alder reaction under nonstoichiometric conditions offered the opportunity to prepare rigid rod telechelics with TAD end groups. In a later stage, these telechelics have been used as cross-linkers for polydienes.

Conclusion

Triazolinediones are very reactive species that can participate in a whole range of reactions with specific classes of olefin-type substrates. Despite their high reactivity, many TAD reagents can be isolated in pure form and are bench-stable compounds. However, more functionalized and/or sensitive TAD compounds can be easily generated in situ or used as a freshly prepared solution. This remarkable combination of stability and high reactivity can be appreciated by the vast body of literature on these reagents in the field of polymer synthesis and modification, which emphasizes its robustness, scalability, and relative safety when used under solvent-free conditions (50–100 g scale). Furthermore, 4-phenyl-TAD is a reagent that is commercially available in multigramscale. TAD reactions are characterized by a very pronounced kinetic selectivity toward electron-rich π-systems, predominantly resulting in very fast Hetero-Diels-Alder and Hetero-Alder-ene type reactions. Importantly, many TAD-based reactions match all of the typical click chemistry requirements. The scope and modularity of such reactions have been demonstrated in this review by highlighting applications ranging from organic synthesis, polymer chemistry, and surface modification to site-selective labelling of natural proteins and peptides. Moreover, the extraordinary kinetics of TAD-based reactions have also resulted in the development of unprecedented “dynamic” click reactions, including our introduction of the concept of “transclick” reactions as a means to program or direct successive and selective covalent exchange reactions. This resulted in the development of TAD based polymer chemistry.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Abbreviations

TAD	*Triazolinedione*
SPAAC	*Strain-promoted azide-alkyne cycloaddition*
IEDDAC	*Inverse electron demand Diels-Alder cycloaddition*
DEAD	*Diethyl azodicarboxylate*
HNO_3	*Nitric acid*
N	*Nitrogen*
BSA	*Bovine serum albumin*
HSA	*Human serum albumin*
CuAAC	*Copper Azide-alkyne Huisgen cycloaddition*
AAC	*Azide-alkyne Huisgen cycloaddition*
CRM_{197}	*Cross-Reactive-Material*-197
HPLC	*High-performance liquid chromatography*
DSC	*Differential scanning calorimetry*
TGA	*Thermo-gravimetric analysis*
HDEO	*Heady duty engine oil*
DMB	*3-dimethyl-2-butene*
HDD	*2,4-hexadiene-1,6-diol*
DMSO	*Dimethyl sulfoxide*

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