



Review Heterocycles by Consecutive Multicomponent Syntheses via Catalytically Generated Alkynoyl Intermediates

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Abstract: Multicomponent processes are beneficial tools for the synthesis of heterocycles. As densely substituted bifunctional electrophiles, ynones are essential intermediates by applying cyclocondensations or cycloadditions in numerous heterocycle syntheses. The respective alkynoyl intermediates are generally accessible by palladium-, copper- and palladium/copper-catalyzed alkynylation. In turn, the mild reaction conditions allow for a fast and versatile entry to functional heterocycles in the sense of consecutive multicomponent processes. This review collates and presents recent advances in accessing thirteen heterocycle classes and their applications by virtue of catalytic alkynoyl generation in diversity-oriented multicomponent syntheses in a one-pot fashion.

Keywords: alkynylation; catalysis; copper; cross-coupling; heterocycles; multicomponent reactions; one-pot reactions; palladium



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1. Introduction

Multicomponent reactions (MCRs) represent a potent and multipurpose synthetic concept, where high efficiency and abundant diversity are elegantly combined for rapidly accessing compound libraries. By definition, in MCRs at least three substrates forming two or more new bonds generate a single product in the sense of a one-pot operation, whereupon the majority of the deployed atoms of the starting materials end up in the products [1,2]. Therefore, MCRs rely on the repeated generation and consumption of reactive functionality in each step, strictly adhering to a one-pot process [3]. MCRs have certain advantages over classical multistep processes, because they combine efficiency and efficacy, simultaneously addressing chemo-, regio- and stereoselectivity. As a consequence, these processes rapidly lead to high levels of structural and functional diversity. As MCRs are efficient and diversityoriented syntheses they have inevitably become a superior synthetic tool. Three different classes of MCRs represent the categories to date [3]. In the domino-type reaction, all reagents are present at the outset of the process and all individual steps proceed without the possibility of isolating intermediary products. Contrary, in sequential MCR all components are added in a defined order and the reaction conditions are maintained constant. This allows for possibly isolating intermediary products. Closely related are consecutive onepot processes where reagents are subsequently likewise added, however, the ancillary possibility to alter conditions for each single step is included. A common feature of all three types is the urge to commence with highly diverse and readily accessible substrates to access a broad scope of physical and structural characteristics, warranting synthetic convergence and explorative space. Particularly in heterocycle syntheses, the versatility of carbon–carbon triple bond functionalization has turned out to be very fruitful [4]. Thus, the catalytic access to alkynes as functional groups with modulating relative reactivities is a key to MCRs, which has been increasingly developed over the past two decades [5].

Heterocyclic systems are ubiquitous both in natural products and applied chemistry and thus their MCR synthesis makes them predestined targets. Alongside their use in life sciences [6–8], heterocycles are increasingly applied in molecular electronics [9] and

photonics [10–12], e.g., as organic field effect transistors (OFETs) [13], in organic lightemitting diodes (OLEDs) [14,15] and in dye-sensitized solar cells (DSSCs) [16]. Particularly, MCR accesses to fluorophores [17] by virtue of transition metal catalysis [18] or via the intermediacy of alkynoyl derivatives [19] aroused growing attention over the past years. Thus, the transition metal catalyzed multicomponent approach [20] furnishes reactive electrophilic building blocks, such as alkynones 1 [21–23], propiolic acid esters 2, and alkyne-1,2-diones 3, set the stage for numerous follow-up transformations (Scheme 1). Hence, this review flashlights recent progresses in the years 2016 to 2021 and updates our previous overview [24] on the synthesis of heterocycles by virtue of the catalytic generation alkynoyl intermediates.



Scheme 1. Alkynones, alkyl propiolates, and alkyne-1,2-diones as pivotal alkynoyl derivatives accessible by catalytic transformations.

After a concise introduction to our catalytic alkynylation-based concept for the generation alkynoyl specimen and recently developed accesses by others (Section 2) the review is rather structured by one-pot syntheses of nitrogen (Section 3) and oxygen containing heterocycles (Section 4) and thiophenes (Section 5) in a multicomponent fashion than by the mode of catalytic ynoyl generation.

2. Alkynone, Alkyl Propiolate, and Alkyne-1,2-Dione Formation by Catalytic Processes

Over twenty years, we have disclosed a broad collection of complementary syntheses of alkynones based upon Sonogashira alkynylation, which also have been employed by others for one-pot syntheses of heterocycles. The immense explorative potential of these versatile three-carbon building blocks is particularly illustrated in the preparation of nitrogen, oxygen, and sulfur containing five- to seven-membered heterocycles [25]. Here, six complementary methods provide powerful routes to alkynones **1**, which form the starting point of diversity-oriented syntheses (Scheme 2).

Improving the reaction conditions of alkynes and acid chlorides in Pd–Cu-catalyzed alkynylations [26–28] is achieved by restricting the auxiliary base to one stoichiometrically necessary equivalent at the stage of the modified Sonogashira cross-coupling I [29,30]. Omitting copper as a cocatalyst circumvented the inherent alkyne dimerization effectively upon employing an electron-rich palladium complex in variant II [31]. Furthermore, this method allows concatenating single reaction steps to one-pot sequences since the solvent can be readily varied. Toluene, 1,4-dioxane, acetonitrile and dichloromethane work equally well as solvents, and in particular, acetonitrile and dichloromethane are very favorable for subsequent Michael additions. Another possibility to significantly broaden the substrate scope was established by employing oxalyl chloride for en route activation of carboxylic acids III [32], tolerating *N*-heterocyclic substituents and electron-rich π -nucleophiles IV [33].

While the previous approaches are directly founded on the coupling of monosubstituted alkynes a more direct pathway represents the coupling of aryl halides and ethynylmagnesium bromide and then acid chlorides as presented in Kumada–Sonogashira sequence V [34]. Thereby, the unsymmetrically substituted alkynones are easily accessible with a broadened substrate scope. Aryl iodides are preferentially utilized as substrates in the carbonylative cross-coupling Sonogashira reaction VI [35–37]. However, the intro-



duced aryl moiety is regiospecifically ligated to the alkynone's carbonyl group in this complementary synthetic route to alkynones.

Scheme 2. Six Sonogashira alkynylation accesses to alkynone building blocks 1.

Zeng and coauthors dispensed a different approach utilizing Sonogashira coupling of *N*-acylsaccharins **4** and alkynes **5** followed by a selective triethylamine mediated C–N bond cleavage. This palladium-catalyzed sequence retains from high catalyst loadings and from copper complexes enabling a broad substituent pattern for 29 examples embedding electron-rich and electron-poor (hetero)aryls, allyl and alkyl groups in good to excellent yields (Scheme 3) [38].



Scheme 3. Palladium-catalyzed ynone synthesis via N-acylsaccharin substrates 4.

The straightforward Sonogashira coupling of aryl iodides **6** with ethyl propiolate (7) provides 12 examples of aryl propiolates **2** with multi-faceted substituents in up to 97% yield (Scheme 4). By applicating a syringe pump, this access compensated the inherent propensity of ethyl propiolate to undergo oligomerization under basic conditions as well as the reduced alkyne reactivity [39].

Palladium nanoparticle-catalyzed alkynylation of acyl chlorides are vivaciously developing and offer copper-free and aerobic conditions [40] as well as mild conditions without heating likewise [41,42]. The efficiency of the nanoparticle-based catalysts is additionally underlined by four to six recycling cycles with mostly excellent yields.



Scheme 4. 3-Aryl propiolates 2 by Sonogashira coupling of aryl iodides 6 and ethyl propiolate (7).

Guo reported the synthesis of structurally related ynediones **3** under an oxygen atmosphere. Starting from terminal alkynes **5** and α -carbonyl aldehydes **8**, this coppercatalyzed synthesis furnished 22 examples in 42 to 94% yield (Scheme 5) [43].



Scheme 5. Copper-catalyzed oxidative coupling of α -carbonyl aldehydes 8 and alkynes 5 to ynediones 3 under aerobic conditions.

3. Nitrogen Containing Heterocycles by Multicomponent Syntheses

This chapter summarizes recent multicomponent syntheses of pyrazolines, pyrazoles, triazoles, indolones, pyridines, pyrimidines, isoquinolines, and quinoxalines based upon the catalytic entry to alkynoyl intermediates.

3.1. Pyrazolines

Pyrazoles and pyrazolines are five-membered heterocycles containing two nitrogen atoms in the ring. These systems, accessible via alkynones, are among the most prominent ring systems and particularly versatile and powerful targets for applications in the life and materials sciences [44–46]. Employing oxalyl chloride in copper-catalyzed alkynylations alkynediones become accessible for subsequent multicomponent reactions. Consequently, 1,5-diacyl-5-hydroxypyrazolines **11** are generated employing a consecutive sequence of activation of glyoxylic acids **9**, alkynylation and cyclization with acylhydrazines **10**. Görgen et al. isolated 17 examples with 3 different points of variation in mostly good yields bearing different (hetero)aryl and alkyl substituents (Scheme 6) [47].

3.2. Pyrazoles

In two complementary routes functional pyrazoles **13** and pyrimidines **15** were accessed by four-component reactions in 35–79% yield. Therefore, the authors established a sequentially Pd-catalyzed alkynone generation followed by cyclocondensation with either hydrazines **12** or benzamidinium chlorides **14** to obtain the heterocycles (Scheme 7) [48]. The resulting scaffolds, in particular, 3,5-diarylpyrazoles with donor-acceptor substitution pattern, are photophysically interesting due to huge emission solvatochromicity. In addition, the methodology was extended to a symmetrical dipyrazole, employing 1,4-diidobenzene in a pseudo-seven-component synthesis. In contrast to the microwave-assisted cyclocondensation of pyrazoles, six examples of pyrimidines were synthesized under conductive heating in 42–51%.



Scheme 6. Consecutive three-component activation–alkynylation–cyclocondensation synthesis of 1,5-diacyl-5-hydroxypyrazolines **11**.

Another approach to pyrazoles starts with the coupling of aryliodides and ethyl propiolates [49]. Whilst the general cross-coupling of aryl halides **6** and terminal alkynes is well established, the direct alkynylation with ethyl propiolate (7) as a substrate requires slow addition (syringe pump) due to its volatility and inherent base sensitivity leading to oligomerization of this versatile building block. The concluding cyclocondensation step with hydrazines **12** gives access to 17 3-hydroxy pyrazoles **16** in 48–95% of the yield in a three-component one-pot fashion (Scheme 8) [50]. Usually, these scaffolds are synthesized by cyclocondensation of hydrazines and β -keto esters. However, due to their higher electrophilicity 3-aryl propiolates **2** are favorable synthetic equivalents of 1,3-diketones suspending the carbonyl group activation. These advantages result in a broad substrate scope of aryl groups bearing electron-poor to electron-rich (hetero)aryls and underline in combination with methyl, alkyl, and benzyl substituted hydrazines the versatility of this method.

The alternative building block (triisopropylsilyl)butadiyne **18** on the pathway to synthesize pyrazoles is presented by Niesobski and coauthors. Starting from acid chlorides **17** and this four-carbon building block 15, examples of 4-pyrazolyl-1,2,3-triazoles **20** with versatile substituents were obtained in a consecutive four-component one-pot fashion and 35–60% yields [51]. This methodology also combines Sonogashira coupling and Medal–Sharpless copper-click reaction in a sequentially Pd–Cu-catalyzed process with a single catalyst source (Scheme 9).



Scheme 7. Consecutive four-component coupling–cyclocondensation syntheses of pyrazoles and pyrimidines.

As previously mentioned, palladium catalysts furnish alkynones for entering ynone-based multicomponent reactions. A promising approach utilizing 3-(2-aminoethylamino)propyl-functionalized MCM-41-immobilized palladium(II) complex [MCM-41-2N-Pd(OAc)₂] has been followed by Cai and coworkers. In addition to the palladium catalyst, CuI catalyzes the alkynalation of acid chlorides **17** with terminal alkynes **5** to give ynones. In a subsequent cyclocondensation of hydrazines 27 pyrazoles **21** with a broad substituent scope were synthesized in moderate-to-good yields in this one-pot process (Scheme 10) [52].

The authors found a higher catalytic activity of the immobilized palladium catalyst compared to $PdCl_2(PPh_3)_2$. Furthermore, the catalyst was recovered and reused for at least ten times without significant depression of activity.



Scheme 8. One-pot alkynylation-cyclocondensation access to 3-hydroxy pyrazoles 16.



Scheme 9. Consecutive four-component formation of 4-pyrazolyl-1,2,3-triazoles 20.



Scheme 10. Consecutive one-pot alkynylation-cyclocondensation formation of pyrazoles 21.

3.3. Triazoles

1,4-Disubstituted 1,2,3-triazoles by Cu-catalyzed alkyne-azide cycloaddition (CuAAC) [53] have found widespread application ranging from drug discovery [54] to lead finding [55] in medicinal chemistry [56], in bioorganic [57,58] as well as in materials chemistry [59–64].

Hayeebueraheng and coauthors described the multicomponent synthesis of 2-(1,2,3-triazolyl)benzamides **23** starting from 2-iodobenzamides **22**, sodium azide, and terminal alkynes **5** leading to 20 examples in 60–96% yield (Scheme 11) [65]. This copper(I)-catalyzed one-step cycloaddition only proceeds in the absence of a base and proceeds quite rapidly.



Scheme 11. Consecutive azidation-alkyne-azide cycloaddition formation of 2-(1,2,3-triazolyl) benzamides **23**.

An alternative three-carbon building block was established by Schreiner and coauthors, implementing propargyl bromide (24) in different one-pot fashion syntheses. In a four-component synthesis, 15 examples of 1,2,3-triazolylmethylarylpropiolates were obtained in moderate to good yields resulting from a sequentially Cu-catalyzed alkyne carboxylation-propargylation and terminating CuAAC. Utilizing the internal triple bond by concatenating a concluding Michael addition, a consecutive five-component synthesis of 1,2,3-triazolylmethyl 3-amino 3-arylacrylates **25** was conceived (Scheme 12). The process benefits from mild reaction conditions enabling two sequentially Cu-catalyzed steps with a single catalyst source, resulting in four new formed bonds in a moderate yield [66].



Scheme 12. 1,2,3-Triazolylmethyl 3-amino 3-arylacrylates **25** by consecutive five-component carboxylation–propargylation–CuAAC–Michael addition sequences.

3.4. Indolones

Spirocyclic oxindoles and indolones have received considerable interest due to their biological properties [67–69]. A promising entrance to rigid, emissive spiro-indolones has been described by Schönhaber and coauthors. Starting with terminal alkynes **5** and *N*-halophenylalkynylamides **26** heterocyclic propynylidene indolones **27** can be obtained in a one-pot fashion with an insertion-alkynylation sequence. Having three different points of variation for the formation of 24 solid-state luminescent propynylidene indolones **27** in moderate-to-excellent yields, the domino synthesis proved to be a straightforward and universal methodology (Scheme 13) [70].

The concept of the domino synthesis of propynylidene indolones led to several consecutive follow-up syntheses. In a 3-component synthesis, 12 examples of 3-piperazinyl propenylidene indolones **28** were obtained in poor-to-excellent yields with a reasonably broad substitution pattern and in vastly short reaction times. Therefore, the solvent system was improved to dichloromethane and acetonitrile at elevated temperatures for the combined sequence and allowing the introduction of electronically diverse substituents on the alkynyl aryl moieties (Scheme 14) [71].



Scheme 13. One-pot insertion-alkynylation synthesis of spiro-indolones 27.

Based on the same principle, an expansion of 3-piperazinyl propenylidene indolone merocyanines was pursued by superseding boc protected piperazine with distinct substituted analogues to obtain merocyanine-triarylamine bichromophores **30**. The one-pot three-component synthesis started from *ortho*-bromo anilidines **29** forming the indolone scaffold and phenylacetylene as alkyne component, before the piperazine analogue was added. Four propenylidene indolone bichromophores **30** examples in poor-to-good yields were furnished by the consecutive insertion-alkynylation-Michael addition sequence (Scheme 15) [72].



Scheme 14. 3-Piperazinyl propenylidene indolone merocyanines **28** by consecutive three-component insertion–alkynylation–Michael addition sequence.

A further expanded sequence takes advantage of 1-(4-bromobenzyl)piperazine (**31**) in a modular strategy, enabling a Suzuki coupling as terminal step. Utilizing different aryl (pinacolato)boronates **32** four 3-piperazinyl propenylidene indolone bichromophores **33** were accessed in a consecutive four-component reaction in moderate-to-good yields (Scheme 16). Whilst an excess of carbonate and boronate was necessary for the Suzuki coupling, no further catalyst had to be added after the catalytic insertion-coupling step.



Upon aggregation, the indolone bichromophores act as white light emissive systems which caused the dual emission of both chromophore units as a result of a partial energy transfer.

Scheme 15. Consecutive three-component insertion–alkynylation–Michael addition synthesis of 3-piperazinyl propenylidene indolone bichromophores **30**.



Scheme 16. Consecutive four-component insertion–alkynylation-Michael addition–Suzuki formation of 3-piperazinyl propenylidene indolone bichromophores **33**.

Pursuing a similar concept, Elsner and coauthors synthesized indolone-3-aminopropenylidene merocyanine dimers by employing bifunctional symmetric 1,4-phenylenedimethanamines **34** as amino components. When introducing different alkynes and secondary amino moieties, four unimolecular indolone dimers **35** were obtained in a pseudo-five-component synthesis in moderate yield (Scheme 17) [73]. Contrary to the previously described 3piperazinyl propenylidene indolone bichromophores, aggregation-induced emission is not prevalent for the symmetric structures. The authors gave a variable temperature NMR supported estimation of the rotational barriers of the terminal amino moieties.



Scheme 17. Domino synthesis of indolone-3-minopropenylidene merocyanine dimers 35.

3.5. Pyridines

Pyridines and their fused derivatives are amongst evergreens in all fields of applications [74]. In the past few years, especially one-pot syntheses of six-membered heterocycles aroused increasing attention due to multifold properties [75,76]. Dohe and coauthors established a coupling–Bagley–Bohlmann–Rahtz synthesis of 15 tri- and tetrasubstituted pyridines **37** in poor-to-good yields, with an efficient yield per bond forming step of up to 82% (Scheme 18) [77]. The catalytically formed ynone was subsequently reacted in the same reaction vessel with ethyl 3-aminocrotonate (**36**) in a consecutive three- and fourcomponent sequence under relatively harsh conditions with an excess of acetic acid at high temperature for 24 h furnishing the heterocyclic 3-ethoxycarbonyl 2-methylpyridines **37**.

Another multicomponent approach to tri- and tetrasubstituted pyridines via ethyl acetoacetate and ammonium acetate as third and fourth components furnishes pyridines in moderate yields, while yields per bond-forming step account for up to 83% and for the formation of four new bonds.

Bakulina and coauthors presented a one-pot-sequence starting with the catalytic ynone generation and subsequent transformation to pyridinium salts. Therefore, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (**38**) and aluminium chloride were added to the formed alkynones furnishing tricyclic 2-aminopyridinium salts **39**. The isolation of 15 examples in 10–96% yield was possible with a broad variation of substituents for the acid chloride as well as for the alkyne components (Scheme 19). In addition, the obtained structures were corroborated by X-ray structure analyses [78].



Scheme 18. Consecutive coupling-cyclocondensation formation of tri- and tetrasubstituted pyridines 37.



Scheme 19. Consecutive MCR synthesis of tricyclic 2-aminopyridinium salts 39.

Apart from DBU, different other bicyclic amidines, such as hexahydro-2*H*-pyrido[1,2a]pyrimidine, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), as well as tetrahydro-3*H*-pyrrolo[1,2a]imidazole, were employed in the sequence. All but one example ($R^1 = p$ -BrC₆H₄, $R^2 =$ biphenyl) of the tricyclic 2-aminopyridinium salts are potent luminophores and appliable under physiological conditions. Additionally, in solution all the products' luminesce was intensely blue to turquoise. They are hygroscopic and highly soluble in both water and organic solvents.

3.6. Pyrimidines

Among the three diazines pyrimidines are particularly prominent with respect to application [79]. A quite unusual substrate for a multicomponent reaction was chosen by Cheremnykh and coauthors (Scheme 20). With 5'-ethynyllappaconitine (40) as a terminal alkyne the alkynone formation and subsequent cyclocondensation with acetamidine hydrochloride or guanidine carbonate furnished diterpene alkaloid-pyrimidine hybrid structures 41. Two examples were synthesized in good yield under consecutive one-pot conditions in a two-step fashion. Therefore, it was necessary to evaporate the solvent under reduced pressure and to replace it by acetonitrile for the terminal step [80]. According to a two-step protocol and the isolation of the ynone intermediate and severed cyclization enabled the synthesis of seven additional examples.

Scheme 20. Diterpene alkaloid functionalized pyrimidines **41** by a two-step coupling-cyclocondensation synthesis.

3.7. Isoquinolines

As fused carbocyclic pyridine derivatives, isoquinolines receive an ongoing interest [74]. The Ugi four-component reaction (Ugi-4CR) was first reported in 1959 and is, to date, one of the most prominent domino multicomponent reactions inciting numerous fields of research [81]. Inspired by the Ugi-4CR, the groups of Riva and Müller disclosed a one-pot synthesis of 3-hydroxyisoquinolines focusing on a diversity-oriented approach with four different starting molecules. Eight examples of the highly functionalized isoquinolinones **42** were obtained in 45–97% yields (Scheme 21). A subsequent aromatization to 3-hydroxyisoquinoline **43** was also demonstrated in a one-step process; however, the yields for the final step was largely affected by the nature of starting materials, even under the same optimized conditions. The authors concluded that the conditions of the aromatization need dedicated fine-tuning, while the other three steps (Ugi/Heck/DMB removal) proceeded well for all substituents, often leading to a two-step protocol [82]. The eight isoquinolinole examples **43** showed intensively blue luminescence upon excitation and could be isolated in moderate-to-good yields.

Inspired by this sequence, starting as well with an Ugi-4CR of aryl aldehyde, propiolic acid, isonitrile, and 2,4-dimethoxybenzylamine furoisoquinolines **44** were synthesized in mostly good yields (Scheme 22). The conceived five-component process led to 15 examples in a rather unusual formation via a subsequent insertion–alkynylation reaction, debenzylation, and base-catalyzed terminating 5-*exo-dig* cycloisomerization [83].

Scheme 21. Two-step synthesis of 3-hydroxyisoquinolines **43** by sequential Ugi four-component reaction/reductive Heck cyclization.

Scheme 22. Furoisoquinolines 44 by consecutive five-component Ugi–insertion–alkynylation–deprotection–cycloisomerization sequence.

3.8. Quinoxalines

Quinoxalines are benzofused derivatives of pyrazines with a considerable application potential [84]. Two complementary synthetic protocols to obtain 3-ethynylquinoxaline derivatives starting from either electron-rich heteroarenes or glyoxylic acid arenes were described by Gers and coauthors [85]. These diversity-oriented approaches both proceed via en route formed glyoxylic acid chlorides and are followed by Cu-catalyzed alkynylation. The thus formed ynediones react in a one-pot-fashion by concluding Hinsberg cyclization with 1,2-diaminoarenes and the triple bond is even addressable by a terminating fourth or fifth step in a one-pot sequence. Ten examples of 3-(2-aminovinyl)quinoxalines **45** could be isolated after concluding the Michael reaction of secondary amines in moderate-to-good yields (Scheme 23) [86].

Scheme 23. Two complementary synthetic one-pot syntheses of 3-(2-aminovinyl)quinoxalines 45.

The photophysical properties of the synthesized quinoxalines show solvatochromicity as well as protochromicity and underline the charge transfer character of absorption and emission bands of the title compounds. In addition, fluorescence quenching is induced by hydrogen bonding and protonation.

A quite similar approach takes advantage of the direct activation of glyoxylic acids following the more general consecutive activation–alkynylation–cyclocondensation synthesis of 3-ethynylquinoxalines **46**. The three-component synthesis furnished 24 chromophore examples in moderate to excellent yields (Scheme 24). Due to a broad substrate scope, emission solvatochromicity in a range from blue–green to deep–orange are found [87].

Starting with 2-(5-bromothiophen-2-yl)-2-oxoacetic acid (**47**) 5-bromothienyl 3-ethynylquinoxalines derivatives **48** are accessible in good-to-excellent yields in the sense of a three-component process (Scheme 25). While the introduced 1,2-diaminoarene moiety allows diversification of obtained products, a level 2 functionalization to extended π systems **49**, **50**, and **51** is facilitated by both Buchwald–Hartwig and Suzuki coupling via the 5-bromothienyl building block **48** [88].

Scheme 24. Three-component activation–alkynylation–cyclocondensation synthesis of 3-ethynylquin-oxalines 46.

An expansion of the established one-pot syntheses of quinoxalines can be carried out with a concluding Cu-catalyzed alkyne-azide cycloaddition (CuAAC) for transforming the in situ formed triple bond into conjugated heterocycles. Desilylation is readily received upon addition of potassium fluoride in the presence of azides, thus, resulting in 18 examples of 3-triazolylquinoxalines **52** in moderate-to-excellent yields (Scheme 26). Not only the diversity rich synthesis protocol, but also average yields per bond-forming step of 90% clearly support the superiority of the one-pot concept over stepwise reaction protocols [89].

Scheme 25. Consecutive three-component access to 5-bromothienyl 3-ethynylquinoxalines and level 2 transformation to π -conjugation expanded 5-(hetero)aryl-thien-2-yl substituted 3-ethynyl quinoxalines **49**, **50**, and **51**.

Scheme 26. Consecutive five-component glyoxylation–alkynylation–cyclocondensation–CuAAC synthesis of 3-triazolylquinoxalines **52**.

4. Oxygen Containing Heterocycles by Multicomponent Syntheses

This chapter summarizes recent multicomponent syntheses of isoxazoles, pyranones, coumarins, and oxazaborinines based upon the catalytic entry to alkynoyl intermediates.

4.1. Isoxazoles

Isoxazoles are constitutional isomers of oxazoles with broad application [90]. Görgen and coworkers described a facile synthesis isoxazoles under copper-free palladium catalysis. Isoxazoles were formed in a consecutive three-component sequence of alkynylation of aroyl chloride and alkyne followed by cyclization withsodium azide and acetic acid at room temperature. The procedure waives high catalyst loading for the alkynylation step as well as high temperature for the utilization of an azide. In addition, remarkably, the oxygen of the aroyl chloride is embedded in the final product. The authors assume Cu(I)N₃ complex formation from Cu(I) and azide anions. After the loss of nitrogen copper nitride is generated that might transform alkynones to enaminones. Therefore, copper-free conditions for the alkynylation have to be considered, and finally, nine examples of 3,5-di(hetero)aryl-substituted isoxazoles **53** are obtained in poor-to-good yields (Scheme 27) [91].

Scheme 27. Disubstituted isoxazoles **53** by consecutive three-component alkynylation-cyclocondensation sequence.

Another alluring approach to isoxazoles was described by Thirukovela and coworkers employing hydroxylammonium chloride and sodium acetate in a regioselective one-pot synthesis. Therefore, in a Cu-free alkynylation of aroyl chlorides and aryl acetylenes alkynone moieties are generated in aqueous PEG-400 solution in the presence of Pd-nanoparticles (PdNPs). Depending on the reaction conditions a beneficial effect of the homogeneously dispersed PdNPs is their recycling after the reaction. Without losing significant catalytic efficiency the PdNPs were reused in five successive cycles. In this process, 14 examples of isoxazoles **54** were obtained in good-to-excellent yields (Scheme 28) [92]. In addition, 19 examples of 1,3,5-substituted pyrazoles were obtained in 75–92% yield by adding (phenyl)hydrazine to the in situ generated ynones underlining the versatility of the one-pot sequence. Similarly, Deden and coauthors showed that this cyclocondensation route was readily elaborated to a sequentially Pd-catalyzed four-component synthesis of intensively fluorescent biaryl-substituted isoxazoles with donor-acceptor decoration in moderate-to-good yields [93].

4.2. Pyranones

Pyranone derivatives find broad application in various fields [94]. Commencing with the in situ generation of alkynones from (hetero)aroyl chlorides and terminal alkynes, Breuer and coauthors described a promising one-pot access α -pyrones 55. Therefore, only low catalyst loading PdCl₂(PPh₃)₂ (0.25 mol%) and CuI (0.50 mol%) is needed to give reactive intermediates for the reaction with malonates furnishing unsaturated lactones 55 bearing electron-donating and electron-withdrawing aryl substituents as well as heterocyclic groups. From this three-component reaction arose 14 pyranones in moderate-to-good yields (Scheme 29) [95].

Scheme 28. Isoxazole synthesis **54** by consecutive three-component alkynylation–cyclocondensation sequence.

Scheme 29. α-Pyridones 55 by consecutive three-component coupling–cyclocondensation sequence.

Moreover, a consecutive four-component alkynylation–Michael addition–cyclocondensation–ammonolysis sequence has been conceived by adding an excess of ammonia in the final step. After reaction at 90 °C for 4 h a mixture of α -pyridones with and without ester functionality were obtained in moderate yields, while the ester separated α -pyridones were in the majority because of the concomitant acyl cleavage [96].

4.3. Coumarins

Coumarins constitute natural products and cover a broad spectrum of biological properties [94]. Papadopoulos and coauthors described a consecutive three-component coupling–addition sequence of diverse substituted coumarin derivatives. Starting from triflyl coumarins, terminal alkynes and amino components the synthesis takes advantage of the vinyloguous Michael system for an addition of the secondary amines. Upon applying a strictly equimolar ratio of all three reactants and the auxiliary base, 23 examples of *E*-configured merocyanines **56** in moderate-to-excellent yields are obtained (Scheme 30). The substrate scope ranges from neutral to electron-rich coumarins, alkyl, silyl and aryl acetylenes as well as acyclic and ali(hetero)cyclic secondary amines [97].

Scheme 30. Coumarin-based merocyanines **56** by consecutive three-component alkynylation-addition sequence.

4.4. Oxazaborinines

Difluoro oxazaborinines are highly polar π -systems with interesting electronic ground and excited state properties [98]. (Hetero)aroyl chlorides, alkynes, anilines, and boron trifluoride react according to Dohe and coauthors a consecutive four-component one-pot sequence to give difluoro oxazaborinines. Therefore, catalytically generated alkynones are directly transformed with added amines and boron trifluoride as the activating Lewis acid to furnish 29 examples of difluoro oxazaborinines **57** in poor-to-excellent yields (Scheme 31). While electron-rich amines hampered a domino process, a stepwise addition of the amine to the formed alkynone and subsequent boron trifluoride circumvented this issue. The obtained oxazaborinines show solid state emission upon UV excitation, whereas no example displayed emission in solution [99].

Scheme 31. Difluoro oxazaborinines **57** by consecutive four-component coupling-addition-borylation sequence.

5. Thiophenes by Multicomponent Syntheses

Apart from oxygen and nitrogen, sulfur is a valuable heteroatom in the composition of heterocycles. Five membered thiophenes are decisive building blocks not only for natural products and pharmaceutical active compounds [100], but also for materials in electronic and opto-electronic devices [101]. The rising demand for efficient synthetic strategies of sulfur containing heterocycles has been reviewed mainly focused on ring-forming multicomponent reactions [102]. Teiber and coauthors described a one-pot protocol of diethyl terthiophene-5,5"-dicarboxylates starting with 2,5-bis(trimethylsilyl-ethynyl) thiophene [103]. This compound is a stable storage analogue of the sensitive 2,5-diethynyl thiophene. After in situ desilylation and extractive workup subsequent Sonogashira coupling with acid chlorides terminated by a Fiesselmann reaction with ethyl 2-mercaptoacetate

furnishes the title compounds. In the sense of a pseudo five-component syntheses these terthiophene diesters **58** were obtained in moderate-to good-yields (Scheme 32).

Scheme 32. Diethyl terthiophene-5,5"-dicarboxylates **58** by consecutive pseudo five-component coupling–cyclocondensation sequence.

The diethyl dicarboxylates **58** acted as intermediates, which were transformed in a second step into 11 examples of corresponding 5,5^{''}-diamide substituted terthiophenes in good-to-excellent yields [104]. Apart from the two-step protocol a chosen example was reacted in an extended pseudo-seven component reaction in a one-pot fashion. Therefore, the reaction conditions of the terminating amidation step had to be adjusted by increasing the catalyst loading, added amine and reaction time leading to an overall yield of 54% of the illustrated example. The 5,5^{''}-diacceptor substituted terthiophene products luminesce intensively blue in solution and they possess reversible oxidation potentials between 300 and 1550 mV. Therefore, the dyes can be considered as redox-switchable systems.

6. Conclusions and Outlook

As outlined in this review, MCRs via transition metal catalyzed generation of alkynoyl intermediates display a variegated entry to myriads of diversity-oriented syntheses of heterocycles. Moreover, the alkynone are formed under mild reaction conditions and their generation is compatible with a plethora of polar functionalities. Consequently, novel consecutive multicomponent entries to chromophores are thereby enabled. Methodolog-ically, one-pot processes are clearly advantageous over classical approaches, especially upon underlining the perfect compatibility of consecutive one-pot protocols in the sense of programmed reactivity. Evidently, catalytic formation of alkynoyl functionalities has set the stage for modular syntheses of heterocycles in numerous applications.

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