Review

One-Pot Reactions of Triethyl Orthoformate with Amines

Elina Marinho ![ORCID]

Centre for Textile Science and Technology, University of Minho, Campus de Azurém, 4800-058 Guimarães, Portugal; elinamarinho@2c2t.uminho.pt

Abstract: One-pot reactions offer advantages like easy automation, higher product yields, minimal waste generation, operational simplicity, and thus reduced cost, time and energy. This review presents a comprehensive overview of one-pot reactions including triethyl orthoformate and amines as valuable and efficient reagents for carrying out two-, three- or four-component organic reactions.

1. Introduction

In organic chemistry, the one-pot reaction is a relevant and common topic due to its immense advantages as a simple operation, with high mass efficiency, low cost, a lesser amount of waste disposal, short reaction time, and simplification of practical aspects. The reaction is also clean; it is possible to combine several catalytic procedures in the same reaction vessel and provides high regioselectivity, atom efficiency and does not involve workup and isolation of many intermediates [1]. One-pot multi-component synthesis has great importance in organic synthesis and has increased in prevalence in recent years, particularly in heterocyclic chemistry, which involves the simultaneous construction of multiple new C−C and C−heteroatom bonds [2]. There are several terminologies to describe one-pot synthesis, including "cascade or tandem or domino reaction", "multicomponent reaction" or "one-pot step-by-step synthesis" [3]. The definition of one-pot reactions, Figure 1, based on a single-operation reaction involving one reagent (intramolecular) or two reagents (intermolecular) with sequential chemical transformations should be called a cascade reaction instead of a multi-step reaction; a one-operation reaction with three or more reagents should be called a multicomponent reaction (MCR) instead of a one-pot reaction, although they belong to this category. These are reactions that converge to form a product containing substantial elements from all or most of the atoms of the reagents; a one-pot reaction with multiple steps, with three or more reagents of operation, should be called one-pot stepwise synthesis (OPSS) rather than a cascade reaction because this OPSS is carried out step by step using different reaction conditions for different steps [4–6].

In the last decade, several one-pot syntheses have been reported to construct various molecular scaffolds of biological interest. Synthetic methods are very valuable because they avoid various reaction steps as well as purification of intermediate products [7]. Orthoesters have occupied a significant place in the synthesis of heterocycles since the beginning of the 20th century. Orthoformates are a very valuable group of reagents that are storage-stable and very reactive. As alkylating agents, they transfer the associated alkyl group; on the other hand, as formylation reagents, they are reactive in acidic as well as basic conditions [8]. The reaction of amines with orthoesters is a suitable and commonly used synthetic approach to obtain imidates, amidines, triazachrysenes, and quinazolines [9,10]. Triethyl orthoformate (TEOF), an organic compound with the formula $CH(OEt)_3$, also called diethoxymethoxyethane, ethyl orthoformate and triethoxymethane, is a colorless volatile liquid, orthoester of formic acid and is commercially available ($C_7H_{16}O_3$, MW = 148.23 g/mol, bp = 146 °C, mp = −76 °C and d = 0.891 g/mL), which also being soluble in many organic solvents (water, alcohol, ether, etc.).
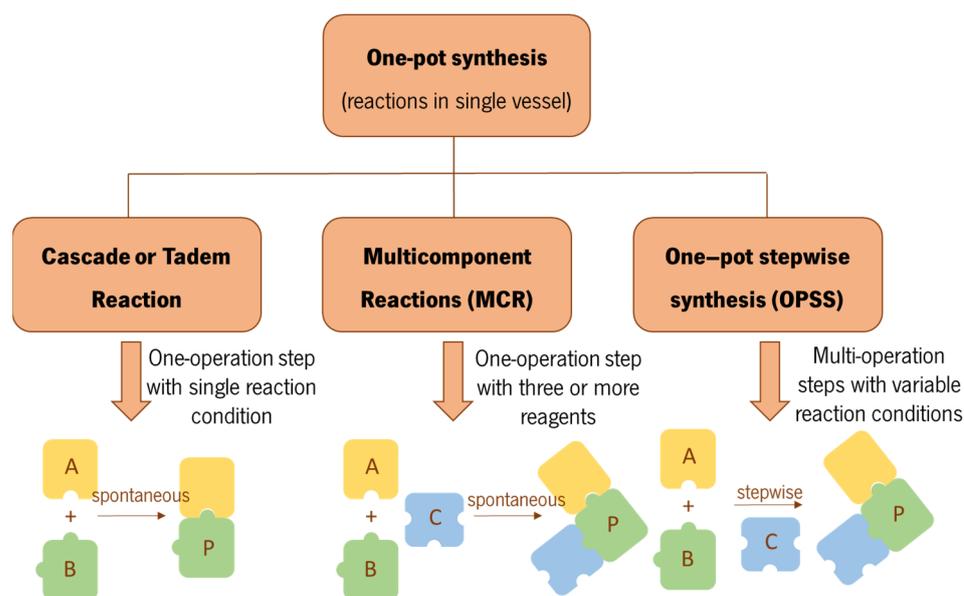
Figure 1. Examples of the three one-pot reactions.

This review summarizes some procedures of triethyl orthoformate reactions in the one-pot synthesis of heterocyclic compounds.

2. Synthesis by Two-Component Reaction

Benzimidazole, benzoxazole, benzothiazole and their derivatives are essential classes of heterocyclic compounds in medicinal chemistry, presenting considerable biological activities [11]. In the past, various synthetic methods have been described in the literature via the condensation reactions of triethyl orthoformate (TEOF) **1** with substituted amino aromatics **2** (Scheme 1), such as *o*-phenylenediamine, *o*-aminophenol, and *o*-aminobenzenethiol, by the presence or absence of catalytic amounts under solvent-free conditions [8,12–14].
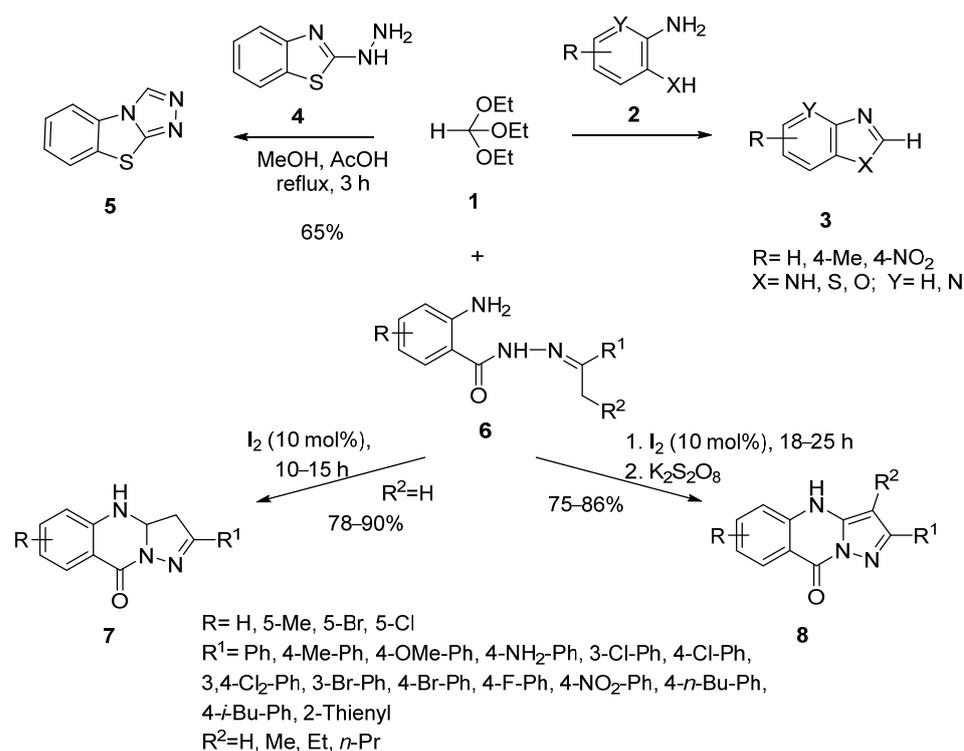

Scheme 1. Reaction of TEOF **1** with aromatics amines or hydrazino reagent.

Numerous other methods for using TEOF with hydrazino reagents have also been documented in the literature [8]. Al-Majidi, in 2014, obtained 1,2,4-triazolo[3,4-*b*]benzothiazole **5** (65%) via treatment of TEOF **1** with 2-hydrazinobenzothiazole **4**, under the reflux of methanol and in the presence of acetic acid (a few drops) for 3 h (Scheme 1) [15].

Wang et al. [16] combined TEOF **1** and 2-amino-*N*-(1-arylethylidene)benzohydrazide **6** catalyzed by 10 mol % iodine (I$_2$) in ionic liquid gave pyrazolo[5,1-*b*]quinazoline moiety **7** (Scheme 1). In the presence of K$_2$S$_2$O$_8$, it can be oxidized and produce aromatized products **8** with excellent yields (75–86%).

Proença et al. [9] described the formation of triazachrysenes **10** through the dimerization of 2-aminobenzonitrile **9** by a cascade reaction (Scheme 2). The sequence involved the reaction of TEOF **1** with 2-aminobenzonitrile **9** using a protic acid as catalyst (H$_2$SO$_4$/HNO$_3$/CH$_3$COOH) ranging from 41 to 83% under different optimization conditions. When water was used as a solvent, one of the dimerization conditions, a new product (**11**),was obtained, with only a yield of 26–33%. The proposed mechanism involves the attack of 2-aminobenzonitrile **9** on the imidate formed by another molecule **9** with TEOF. The nucleophilic attack of the amine on the cyanide group followed by hydrolysis gave rise to the formation of compound **11**, while the additional attack of the imine formed in the earlier step to the nitrile functionality gives the formation of the triazachyrsenes **10**, always isolated like a salt.
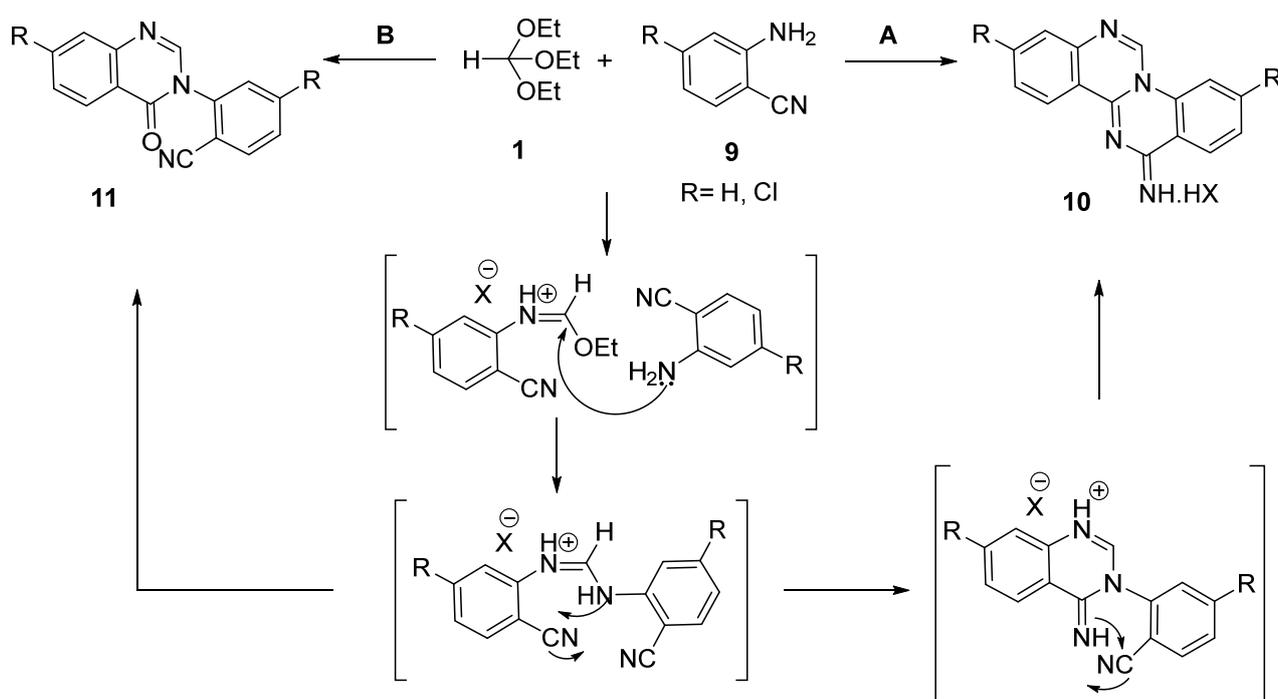
Conditions: A-EtOH or CH$_3$CN, HNO$_3$ or H$_2$SO$_4$, r.t or 40ºC, 3 h–3 days, 41–83%
B- H$_2$O, HNO$_3$ or H$_2$SO$_4$, r.t 19 h–1.5 days, 26–33%

Scheme 2. Formation of triazachrysenes **10** by a cascade reaction.

In 2015, Szczepankiewicz and Kuznik [17] reported a one-step reaction for the synthesis of 3-arylquinazolin-4(3*H*)imines **13** by heating TEOF **1** with 2-amino-*N'*-arylbenzamidines **12**, without solvent (Scheme 3).
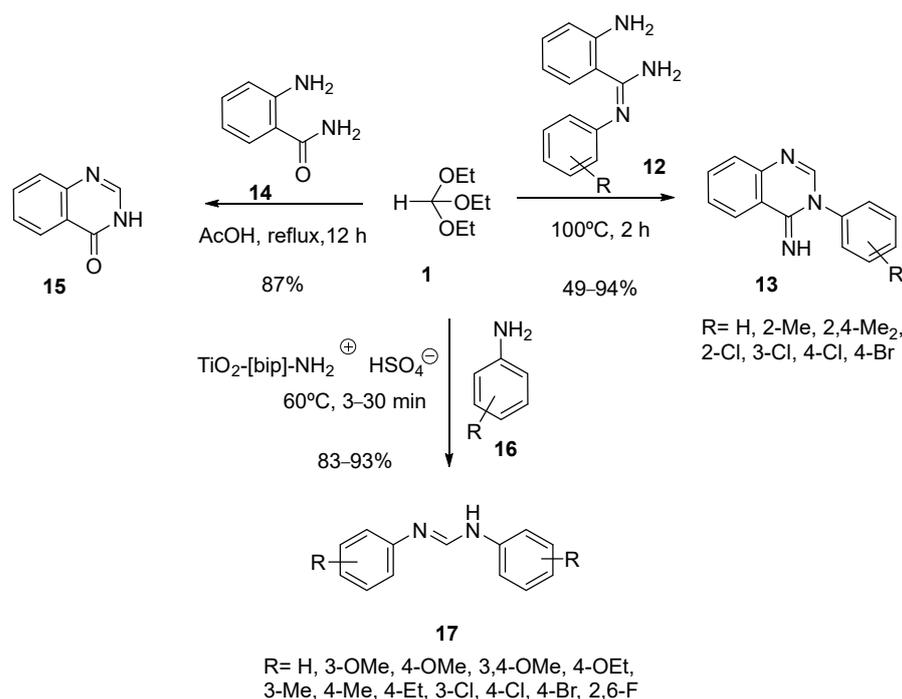
Scheme 3. Synthesis of quinazoline **13**, quinazolinones **15** and *N,N′*-diarylformamidines **17**.

Bunce et al. [18], published the path for the synthesis of quinazolin-4(3*H*)-ones **15** (Scheme 3), from TEOF **1** with 2-aminobenzamide **14**, promoted by acetic acid, in one step.

Formamidines are one of the vital intermediates for the synthesis of heterocyclic and functional group changes. Generally, this synthesis includes the reaction between TEOF and amine derivatives, and can occur in the presence or absence of an acidic catalyst.

F. Shirini et al. [14], described a green and efficient procedure for the synthesis of *N,N′*-diarylformamidines **17**, using nanoporous TiO$_2$ containing an ionic liquid bridge (Scheme 3). The methods provided products with very good yields, short reaction times under solvent-free conditions and catalyst reuse.
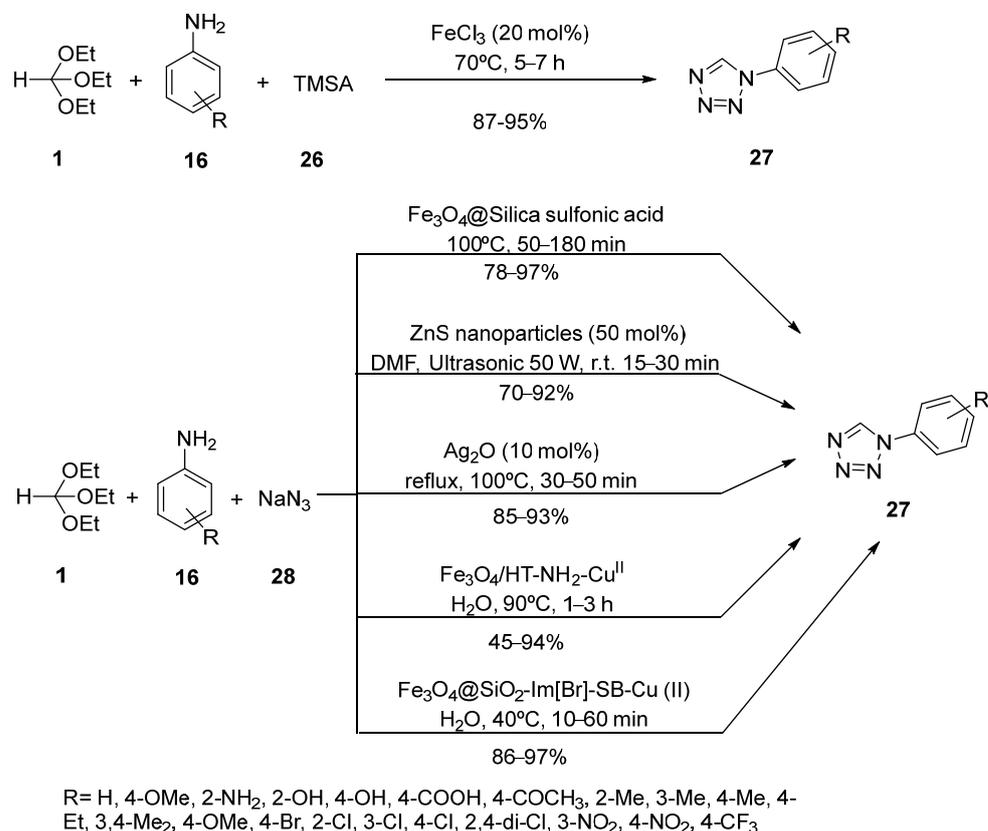
3. Synthesis by Three-Component Reaction

The three-component reaction between TEOF **1**, amines **18** and diethyl phosphite **19** is the most used method for the synthesis of *N*-substituted aminomethylenebisphosphonic acids **20**, Scheme 4. Some of these review approaches were reported in 2016 by Haji [19].

Between 2017 and 2020, Chmielewska et al. studied in some detail the three-component reaction with benzylamines [20], 3-amino-1,2,4-triazole [21], and diamines (like benzenes, cyclohexanes, cyclohexenes and piperazines) [22], which usually mainly resulted in the introduction of mono-substituted products or the formation of bisphosphonates **20**, aminophosphonates **21** or mixtures of the two compounds in the molecule in addition to aminomethylenebisphosphonic acid **22**. In the cases of 1,2-diaminobenzene, 1,2-diaminocyclohexanes and 1,2-diaminocyclohexenes, only one amino group reacted. This reaction often results in product mixtures that are difficult to separate. Cirandur et al. [23] developed the formation of aminomethylene bisphosphonates **23** via the one-pot reaction of various aryl/heteroaryl amines under microwave irradiation and solvent-free conditions, using CuO nanoparticles as catalyst.

Scheme 4. Three-component reaction of TEOF **1**, amines **18** and diethyl phosphite **19**.

Amira et al. [24] describe a simplified eco-friendly method for the synthesis of sulfamide-containing bisphosphonate derivatives **25** (Scheme 5) involving one-pot three-component reactions of TEOF **1**, substituted aromatic sulfamides **24** and diethyl phosphite **19** under microwave irradiation (500 W, 150 °C).

Scheme 5. Three-component reaction of TEOF **1**, aromatic sulfamides **24** and diethyl phosphite **19**.

Tetrazoles are a class of nitrogen-containing heterocyclic compounds, which do not exist in nature but are of certain importance. They have received a lot of attention in recent years due to their wide spectrum of applications in the field of biology and medicine, such as anti-allergic, antibiotic, anticancer, anticonvulsants, anti-HIV, antihypertensive and antiviral applications. Tetrazole is a pharmacophore fragment, which is metabolically more

stable, and acts as a bioisosteric analogue for several functional groups like carboxylic acids, clamidine and furan ring [1,25,26].

   Darvish and Khazraee [27] developed an efficient and facile one-pot multi-component approach for the synthesis of 1-aryl 1*H*-tetrazole derivatives **27** from TEOF **1**, aromatic amine **16** and trimethylsilyl azide (TMSA) **26** with FeCl$_3$ as an environmentally benign catalyst (Scheme 6).

R= H, 4-OMe, 2-NH$_2$, 2-OH, 4-OH, 4-COOH, 4-COCH$_3$, 2-Me, 3-Me, 4-Me, 4-Et, 3,4-Me$_2$, 4-OMe, 4-Br, 2-Cl, 3-Cl, 4-Cl, 2,4-di-Cl, 3-NO$_2$, 4-NO$_2$, 4-CF$_3$
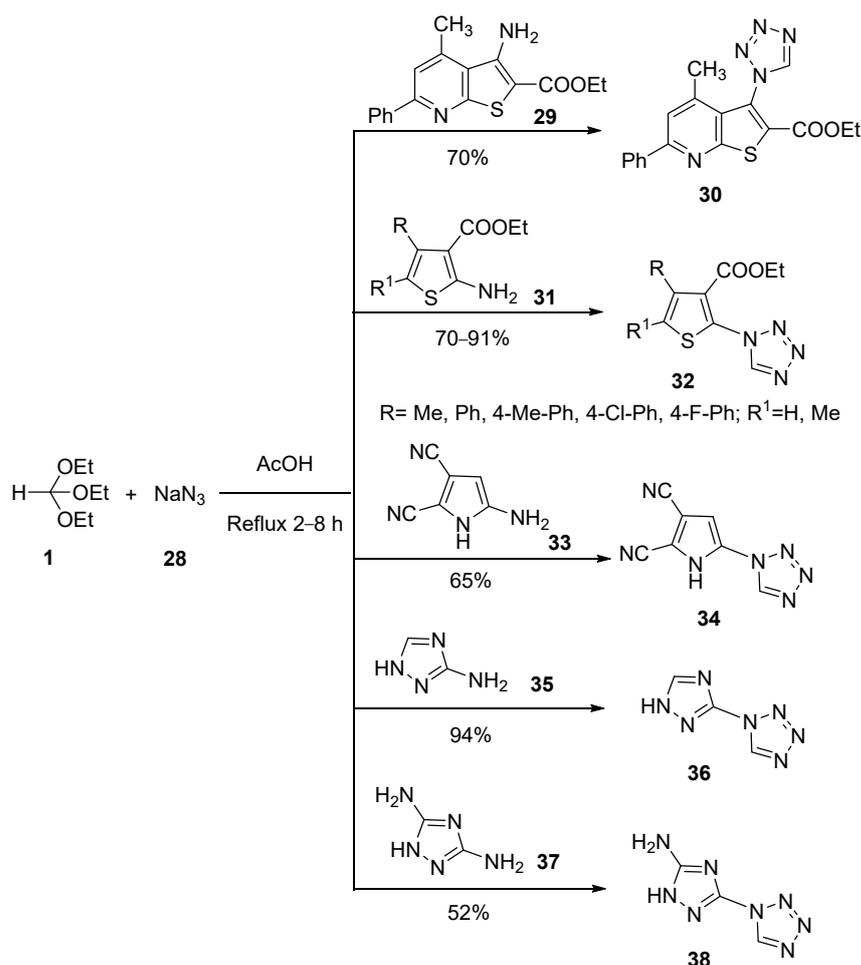
Scheme 6. The synthesis of 1-aryl-1*H*-tetrazoles derivatives **27**.

   Tetrazole compound **27** has also been reported to be produced from sodium azide **28** instead of TMSA. In 2014, Naeimi and Mohamadabadi [28] reported that Fe$_3$O$_4$@silica sulfonic acid can be an efficient and reusable catalyst for the one-pot synthesis of 1-substituted 1*H*-tetrazoles **27**. A wide diversity of aromatic amines containing electron-donating and electron-withdrawing groups, like acetyl, methyl, bromine and chlorine, have undergone condensation in shorter reaction times with very good yields. The catalyst can be effortlessly recovered from the reaction by a magnet and reused six times without weakening the catalytic activity. In 2015, Naeimi and Kiani [29] synthesized 1-substituted-1*H*-tetrazole derivatives **27** using zinc sulphide nanoparticles as a new heterogeneous catalyst at room temperature under ultrasonic irradiation (50 W), in DMF as a solvent. The same research group [30] described, in 2018, the synthesis of **27** by microwave irradiation (600 W, 60 °C), with excellent yields (73–88%) and shorter reaction time (20 min). This method has advantages over other techniques, such as the more environmentally friendly process, the recyclable solid catalyst and solvent-free conditions. These authors also found that the catalyst can be recovered and used seven times with minimal loss of its action.

   Similarly, Khan et al. [31] explore a series of 1-aryl 1*H*-tetrazole derivatives **27**, as antibacterial agents, using silver oxide as a reusable catalyst. The synthesized compounds were obtained with high yields between 85 and 93% in a short time of 30–50 min. Another approach for the synthesis of 1-aryl 1*H*-tetrazole derivatives **27** using Fe$_3$O$_4$/HT-NH$_2$-Cu^{II} as a new heterogeneous catalyst was reported by Salimi and Zamanpour [32]. The corresponding products were isolated in good yields in water as solvent. The catalytic activity of

Fe$_3$O$_4$@SiO$_2$-Im[Br]-SB-Cu (II) was investigated, by Mashhoori and Sandaroos [33], in the synthesis of 1-aryl 1*H*-tetrazole derivatives **27**. As proposed by the authors, the mechanism proceeds with TEOF **1** activated by the N$_3$-coordinated Cu(II)Nano-catalyst followed by the attack of amine **16** on TEOF, which results in the formation of an amide acetal intermediate. Nucleophilic attack of the azide anion on the acetal amide followed by cyclization leads to tetrazole **27**.

A similar approach was described by Sarg et al. [34], using the combination of TEOF **1** with 3-amino-thiophene-2-carboxylates **29** in the presence of sodium azide **28** afforded the 3-tetrazolylthienopyridine-2-carboxylate derivative **30** (Scheme 7). Also, treatment with 2-amino-thiophene-3-carboxylates **31** in acetic acid afforded 2-(1*H*-tetrazol-1-yl)thiophenes derivatives **32**, in good yields (Scheme 7) [35].

Scheme 7. Synthesis of tetrazoles **30**, **32**, **34**, **36**, and **38**.

Muralidharan et al. [36], also synthesized tetrazole derivatives such as 2-(1*H*-tetrazol-1-yl)-1*H*-imidazole-4,5-dicarbonitrile **34**, 1-(1*H*-1,2,4-triazol-3-yl)-1*H*-tetrazole **36**, and 5-(1H-tetrazol-1-yl)-1H-1,2,4-triazol-3-amine **3** via the reaction of TEOF **1** and NaN$_3$ **28** with imidazole **33**, and triazole **35** and **37**, respectively (Scheme 7).

The reaction between substituted thiazolylamine or oxazolylamine in DMSO and tributylmethylammonium chloride (TBMAC) as catalyst gives 1-substituted 1*H*-1,2,3,4-tetrazole, isolated in excellent yields (Scheme 8) [37].
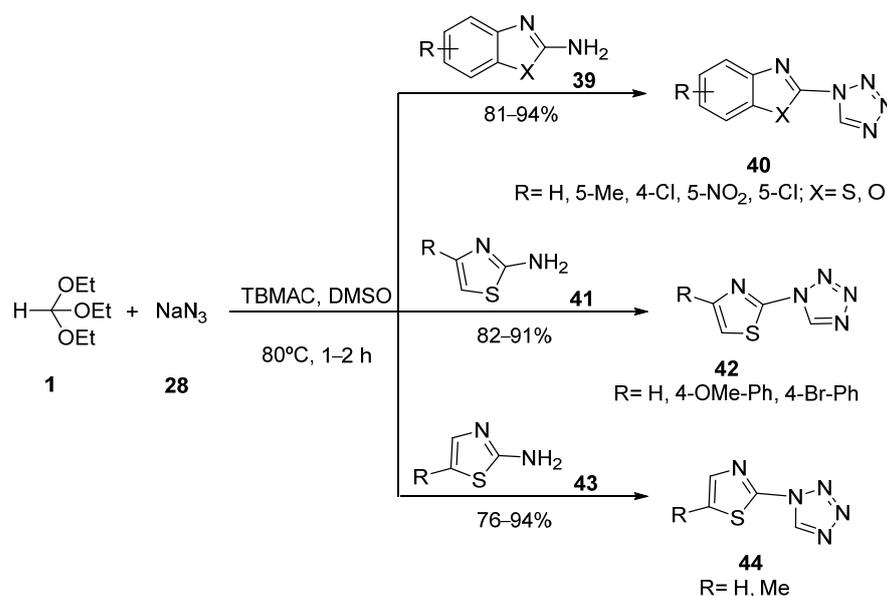
Scheme 8. Synthesis of tetrazoles **40**, **42**, and **44**.

Substituted quinazolines or quinazolinone analogs, bicyclic heterocyclic compounds obtained from the combination of two six-membered aromatic rings of benzene and pyrimidine, are a class of nitrogen-containing heterocyclic compounds which have attracted widespread attention in medicinal chemistry for the design and development of new drugs due to their numerous biological properties that depend on the position and nature of the substituent in their skeleton and include, among others, antibacterial, anticancer, anti-inflammatory, antifungal, antihypertensive, antimicrobial and antiviral properties. Conventional heating methods are generally applied, as well as other strategies that include the use of efficient and more environmentally friendly catalysts, or microwave irradiation. The synthesis of quinazoline derivatives has also attracted great attention in recent years, and numerous synthetic procedures for their formation have been developed [38–43]. It is currently in numerous accepted drugs and biologically active compounds, like erlotinib, gefitinib, prazosin, rutaecarpine and many others, as well as in clinical candidates and biologically active molecules [44–46]. Pyrimidines and their derivatives are an important class of heteroaromatic systems found in natural products, used as key intermediates in medicinal chemistry to generate new chemical structures with a diverse range of pharmacological activities, and are gaining attention due to their structural similarity to the purines [47].

Compounds **46** were prepared in yields of 79–85%, via the one-pot reaction between TEOF **1**, with the 2-amino-thiophene-3-carboxylates **45** and the appropriate amine **18** (Scheme 9) [48].

R= CH$_2$Ph, CH$_2$CH$_2$CH$_3$, -CH$_2$CH$_2$OH, cyclohexyl, pyridyl
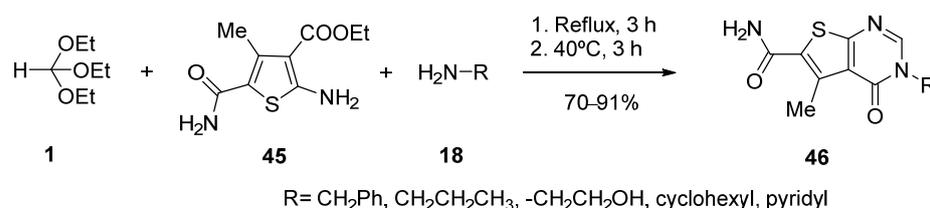
Scheme 9. Synthesis of compound **46**.

An efficient procedure for the synthesis of 4(3*H*)-quinazolinones **48**, (Scheme 10) by one-pot reaction of TEOF **1**, amines **18** and anthranilic acid **47** was also reported in the literature, using Zn(ClO$_4$)$_2$ [49], silica-supported boron trifluoride (BF$_3$–SiO$_2$) [50], CoCl$_2$ [51], thiamine hydrochloride (vitamin B$_1$) [52], and I$_2$ [53] as the organocatalyst. The

different quinazolinone **48** were obtained in yields of 67–98% within 15 min to 8 h, at reflux or room temperature.
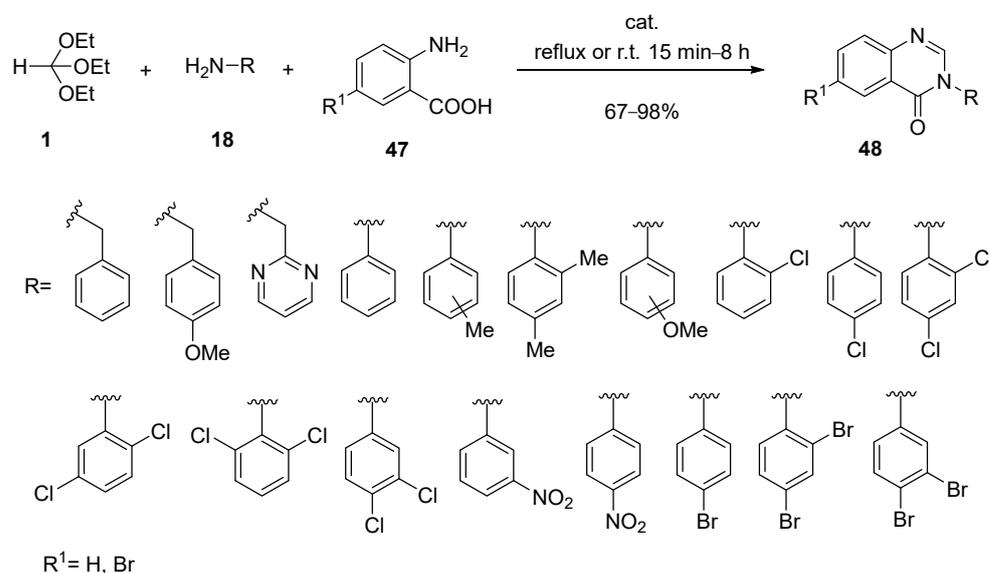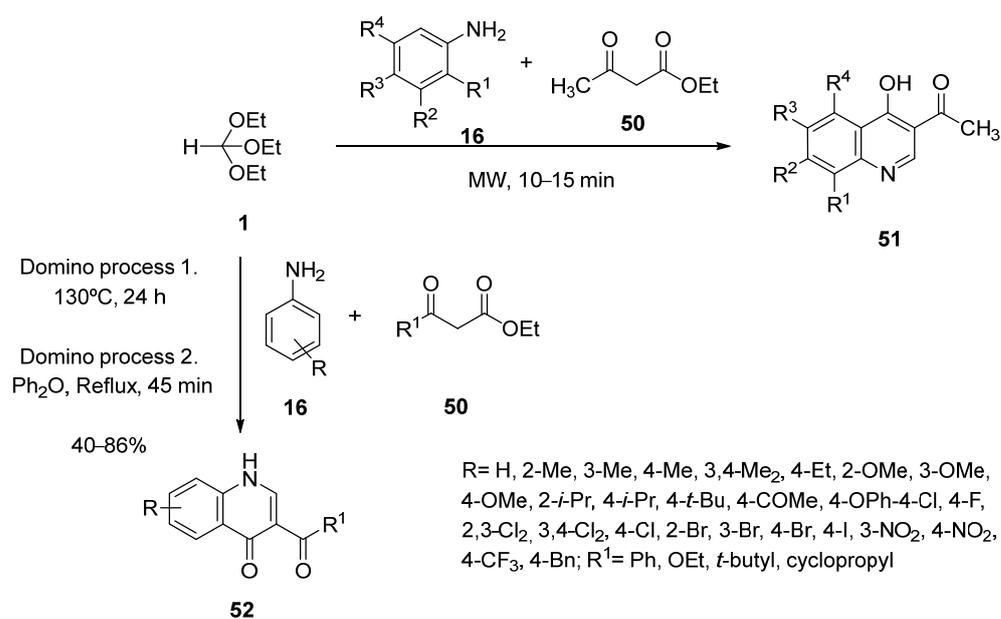

Scheme 10. One-pot synthesis of 4(3*H*)-quinazolinones **48**.

Venkateswarlu et al. [54] describe a facile, three-component, one-pot synthesis of 8*H*-quinazolino[4,3-*b*]quinazolin-8-ones **49** from TEOF **1**, 2-aminobenzonitriles **9** and anthranilic acid derivatives **47**, with good yields, Scheme 11.


R= H, OMe; R¹= H, OMe; R²= H, Me, Br, Cl; R³= H, Me, Et
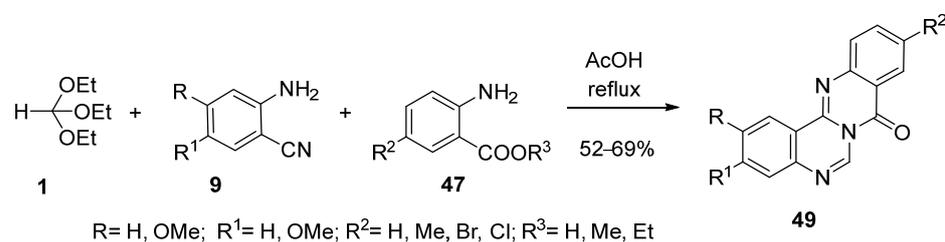
Scheme 11. One-pot synthesis of 8*H*-quinazolino[4,3-*b*]quinazolin-8-ones **49**.

Different types of 3-acetyl-4-hydroxiquinoline derivatives **51** (Scheme 12) were synthesized by a highly efficient multi-component microwave irradiation (MW) with reduced reaction times and good yields using TEOF **1**, and aromatic amines **16** with ethyl acetoacetate **50** [55]. Huang et al. [56] reported two effective, sustainable and clear approaches for the formation of quinolone derivatives based on a branched/linear domino procedure under ecological conditions. The position of the substituent significantly affected the reaction yield. Groups like halogen, methyl, methoxy, nitro, and trifluoromethyl at the *para* position of anilines reacted easily with TEOF **1** and dicarbonyl compound **50** provided the corresponding products **52** with good yields (Scheme 12). If the methyl or methoxy group is situated in the *meta* or *ortho* position, this may result in moderate yields. The reactions of dicarbonyl compounds substituted by phenyl, *t*-butyl and cyclopropyl were carried out under ideal reaction conditions and produced products with moderate to excellent yields. When diethyl malonate was used in the reaction, the product yield was reduced.

Scheme 12. Reaction of TEOF **1** and amines **16** with dicarbonyl compound **50**.

Rad-Moghadam et al. [57] reported a microwave-promoted one-pot method for the synthesis of 4-aminoquinazoline **54** (Scheme 13). The possible mechanism of the reaction mainly includes the formation of the amidine intermediate from the reaction of TEOF **1** with 2-aminobenzonitrile **9** and NH$_4$OAc **53**. This is followed by the nucleophilic attack of the amino group on the carbon atom of the nitrile group which gives the formation of the 4(3*H*)-iminoquinazoline intermediate, tautomerizes and results in product **54**.
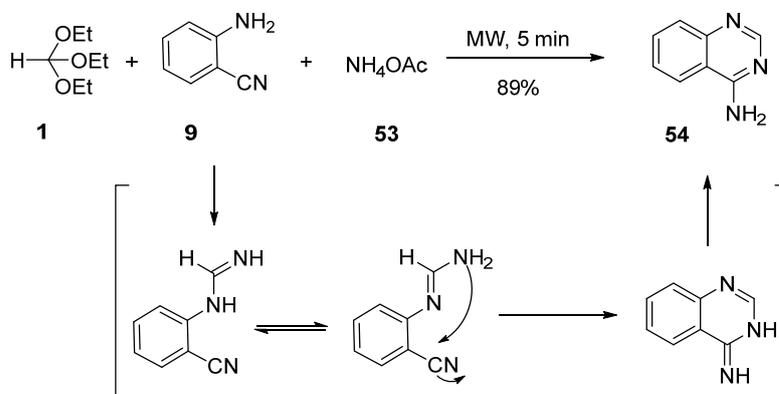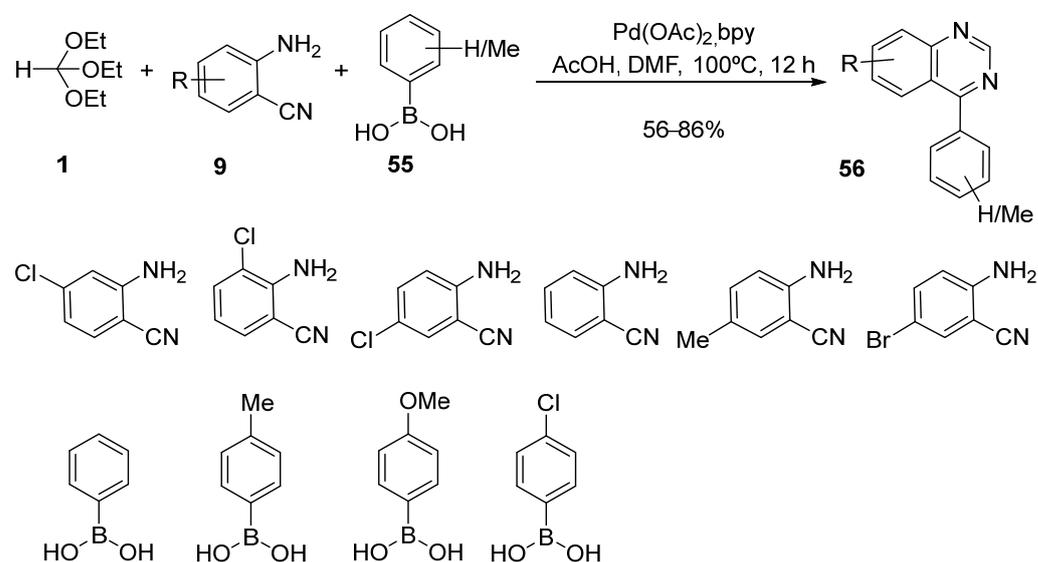
Scheme 13. Synthesis of 4-aminoquinazoline **54**.

The formation of quinazolin-4(3*H*)-imines from TEOF **1**, 2-aminobenzonitrile **9** and variously substituted aniline **18** using ammonium chloride as promoter, assisted by microwave irradiation, has also been reported (Scheme 14) [58]. Using substituted aniline, the reaction gave an excellent yield of the resulting products, regardless of the electron-donating or electron-withdrawing substituent positioned on the aniline ring.
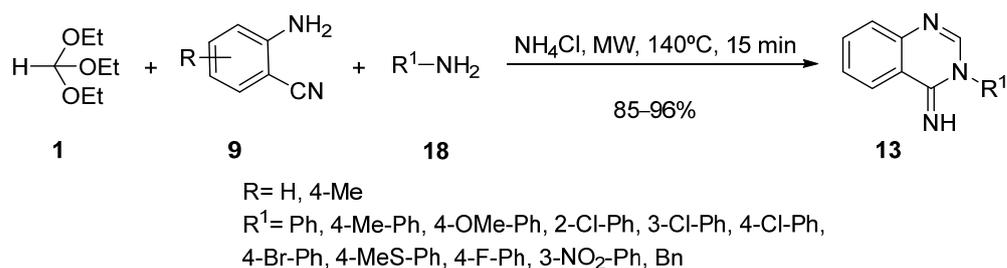
Scheme 14. Synthesis of quinazolin-4(3*H*)-imines **13**.

Zhang et al. [59] described a palladium(II)-catalyzed cascade reaction of TEOF **1** with 2-aminobenzonitriles **9** and boronic acids **55** that produces 4-arylquinazolines **56**, in good yields (Scheme 15). The pathway involves the coupling of the sp-sp2 carbon bond followed by the formation of the intramolecular carbon-nitrogen bond.
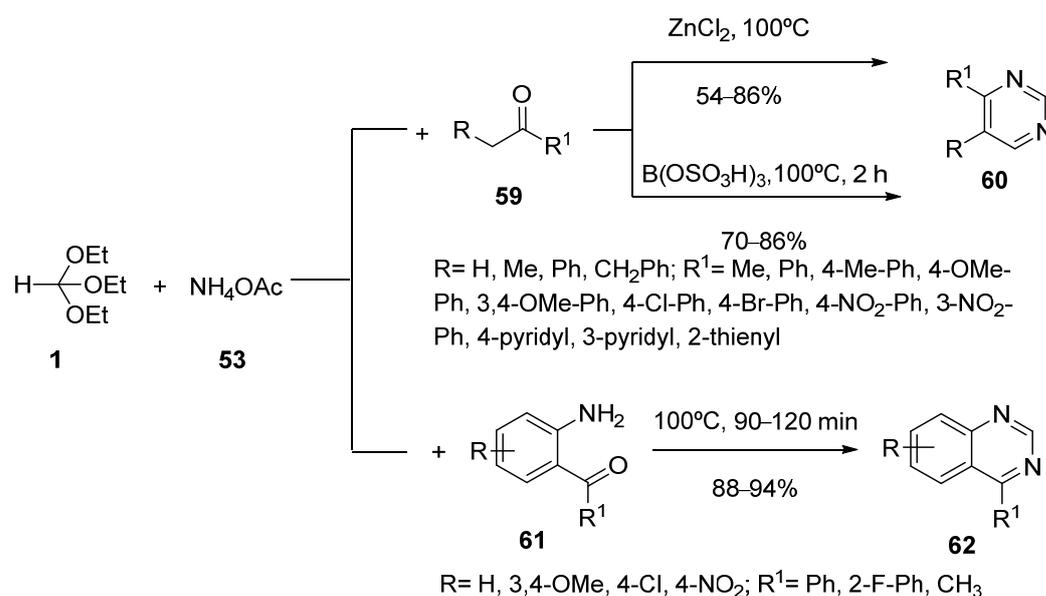

Scheme 15. Synthesis of 4-arylquinazolines **56**.

Rao et al. [60] described the cyclocondensation of TEOF **1** with ethyl 5-amino-4-cyano-3-methylthiophene-2-carboxylate **57**, which, in the presence of a few drops of acetic acid as a catalyst and substituted aniline **16**, gave ethyl (halo substituted phenylamino)-5-methylthieno[2,3-*d*]pyrimidine-6-carboxylate derivatives **58** in good yield (Scheme 16).


R= 4-Cl, 4-F, 3-Cl-4-F, 2,4-di-F
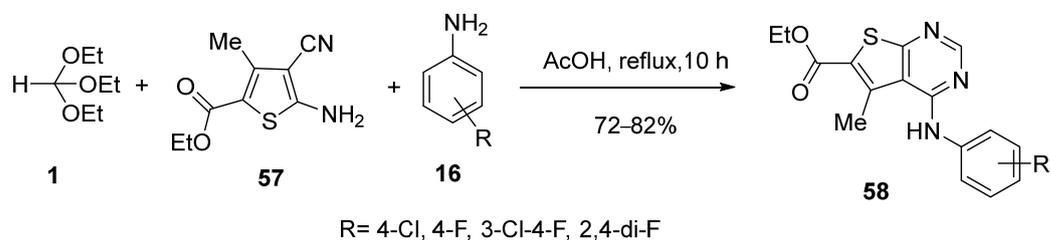
Scheme 16. Synthesis of thieno[2,3-*d*]pyrimidine derivatives **58**.

A simple, one-pot synthesis by a three-component coupling reaction of TEOF **1**, ammonium acetate **53** and ketones **59** or **61** is also reported, as shown in Scheme 17. Konakahara et al. [61] use the multicomponent coupling reaction catalyzed by zinc chloride (ZnCl₂) for the synthesis of the 4,5-disubstituted pyrimidine derivative using ketone **59**, in a single step. Soheilizad et al. [62] report the synthesis of pyrimidine derivatives **60** in the presence of boron sulfuric acid as a recyclable and effective catalyst under solvent-free conditions. This procedure has some advantages, such as catalyst reuse, shorter reaction time (2 h) and good yields (70–86%). Trivedi et al. [63], presented an efficient and ecofriendly method for the synthesis of 4-disubstituted quinazolines **62**, under solvent and catalyst-free conditions at 100 °C, from 2-aminoaryl ketones **61**. This method provides high yields (88–94%) in a moderate reaction time (90–120 min).


Scheme 17. Synthesis of substituted pyrimidines **60** and 2,4-disubstituted quinazolines **62**.

Dolzhenko et al. explored a one-pot reaction using TEOF **1**, and cyanamide **63** with different amines under microwave irradiation (MW), at 150 °C (Scheme 18). This three-component reaction produced a variety of amino substituents, making it perfect for generating compound libraries for drug discovery processes. In general, this multicomponent reaction does not require any catalyst, resulting in the formation of product with high purity and similar yields. These authors confirm that the method is reproducible in diverse microwave reactors and under microwave-like heating. The synthesis of substituted 5-aza-adenines **65** [64,65] or 5-aza-7-deaza-adenines **67** [66] or 5-aza-9-deaza-adenines **69** [67,68] from 5-amino-1,2,4-triazoles **64** or 2-amino-4-phenylimidazole **66** or 5-aminopyrazoles **68** was performed using methanol or ethyl acetate as solvent. In these cases, higher yields were obtained with very short reaction times. Together with the previous components, TEOF **1** and cyanamide **63**, 3-amino-substituted 5-aminopyrazole-4-carbonitriles **70** were used to carry out the synthesis of the new 7-aminosubstituted pyrazolo[1,5-*a*][1,3,5]triazine-8-carbonitriles **71** without catalysis [69] or in the presence of DIPEA [70], both in methanol.
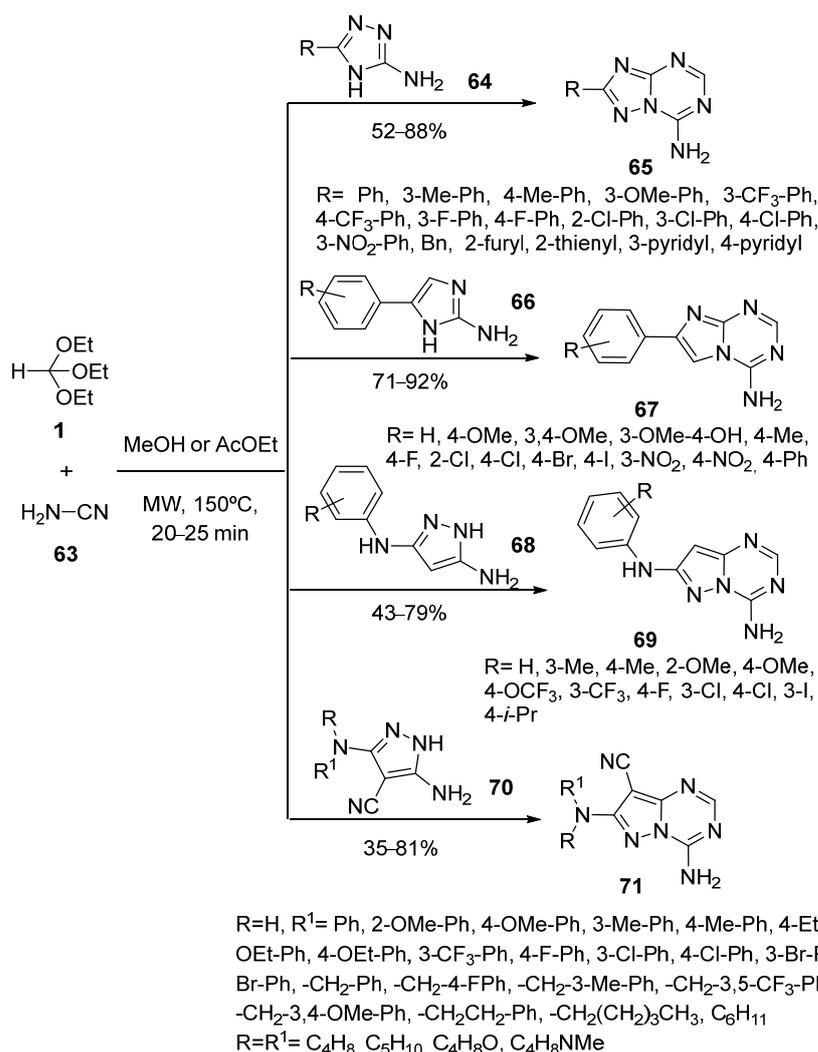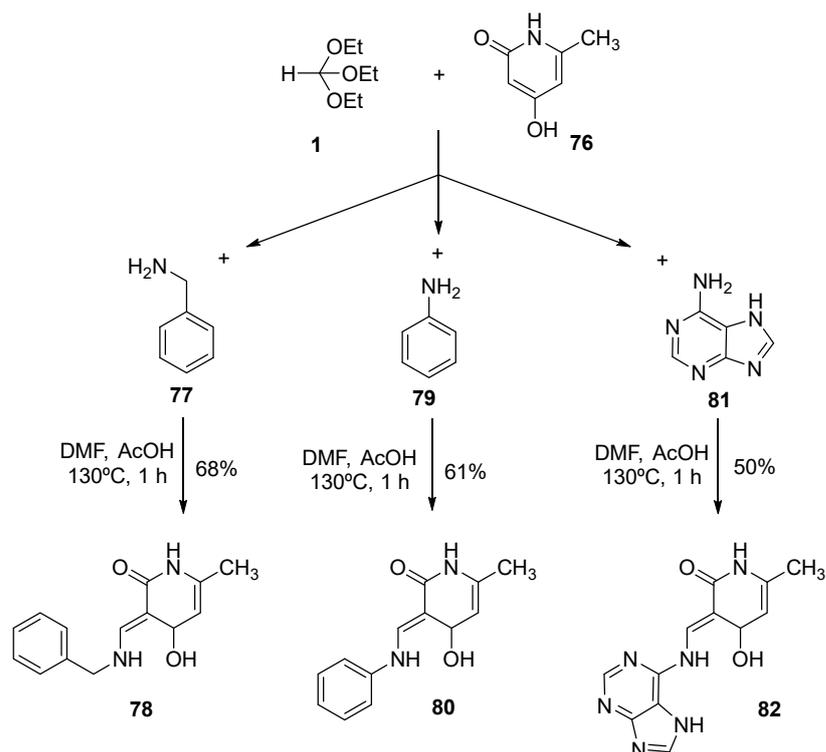
Scheme 18. Synthesis of one-pot three-component reaction between TEOF **1** and cyanamide **63**.

A three-component, microwave-assisted reaction of TEOF **1** with a series of cyclic secondary amines **72** and 5-aminopyrazoles **70**, was also developed by Dolzhenko et al. [71] for the synthesis of the new *N*-pyrazolylformamidines **73** (Scheme 19).
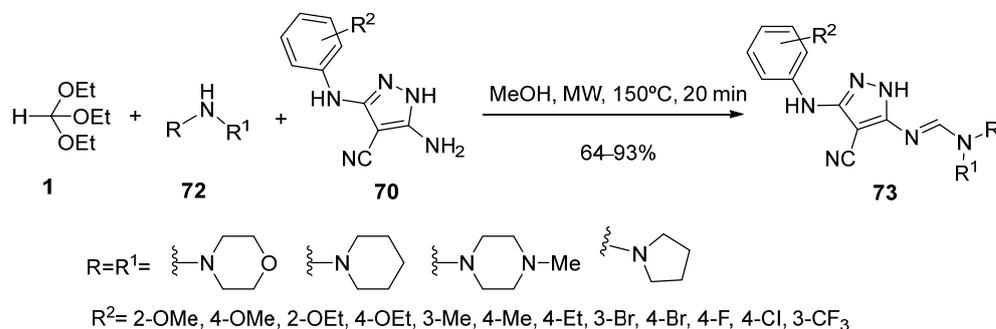
Scheme 19. Synthesis of *N*-pyrazolylformamidines **73**.

The efficient three-component reaction of TEOF **1** with cyanoamide **63** and primary aromatic amines **16** at reflux in toluene provides *N′*-aryl-*N*-cyanoformamidines **74** in high yields (Scheme 20). It is reported that the reaction occurred in toluene as the selected solvent as it forms an azeotrope with the ethanol that can be eliminated from the system by distillation, permitting a fast and broad exchange of reagents [72].

Scheme 20. Synthetic route for aromatic cyanoformamidines **74**.

In 2023, Kalinin et al. [73], reported the synthesis of formamidines **75**, Scheme 21, by a three-component, one-pot method, as key intermediates for the further synthesis of 5-azapurines derivatives.

Scheme 21. Synthesis of formamidines **75**.

Hua et al. [74] described the one-pot synthesis of TEOF **1** and primary amines like benzylamine **77**, aniline **79** and adenine **81** with pyridinone **76** under similar reaction conditions (DMF and AcOH). Monocyclic pyridinones **78–82**, were formed in yields of 68%, 61% and 50%, respectively (Scheme 22).

Scheme 22. One pot reactions with TEOF **1**, pyridinone **76** and primary amines.

The synthesis of a novel class of enaminone derivatives **84** with TEOF **1**, aryl/heteroaryl amines **18** and lawsone **83**, in guanidinium chloride as organocatalyst under solvent-free condition at 90 °C was reported by Olyaei et al. in excellent yields (75–87%) (Scheme 23) [75].
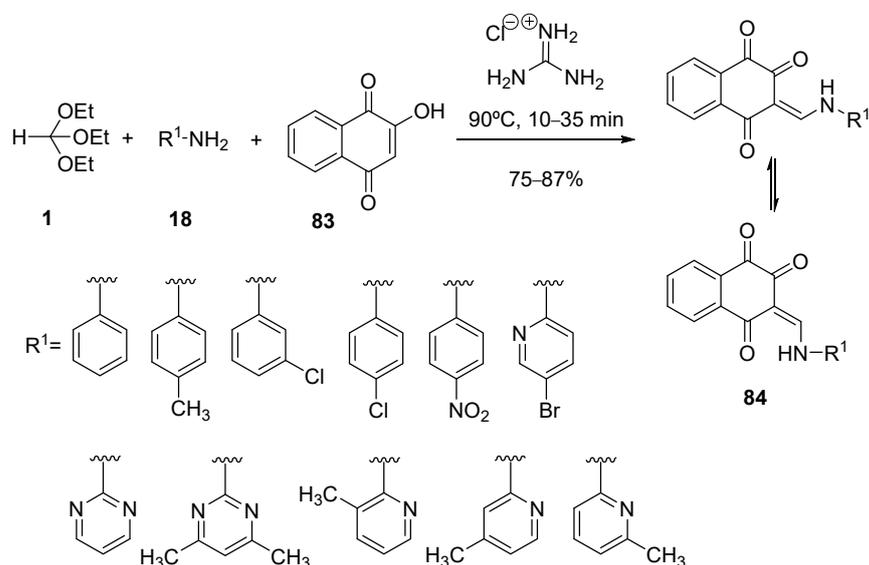
Scheme 23. Synthesis of enaminone derivatives **84**.

In 2015, Sadek et al. [76] reported a one-pot reaction for the synthesis of pyrazolo[1,5-*a*]pyrimdines-7(4*H*)-ones **87** through the reaction of TEOF **1**, 5-aminopyrazoles **18** and Meldrum's acid **85**, under dioxane reflux (Scheme 24). A series of five 5-arylidene Meldrum's acid derivatives **86** were synthesized in 13–68% yield via Knoevenagel condensation from aryl amine **18**, by Pungot et al. [77]. More recently, other derivatives of 5-aminomethylene Meldrum's acid **86** have also been successfully synthesized by Al-Messri [78] with different aromatic amines **18**, TEOF **1** and Meldrum's acid **85**. The reaction proceeded through a

Knoevenagel condensation of TEOF **1** with Meldrum's acid **85** to produce an intermediate such as Michael's acceptor, followed by the regioselective addition of Michael's with the exocyclic amino moiety of the amino compound **18** to obtain the corresponding acyclic adducts **86**. After intramolecular cyclization, elimination of acetone and CO_2, it yielded **87**.
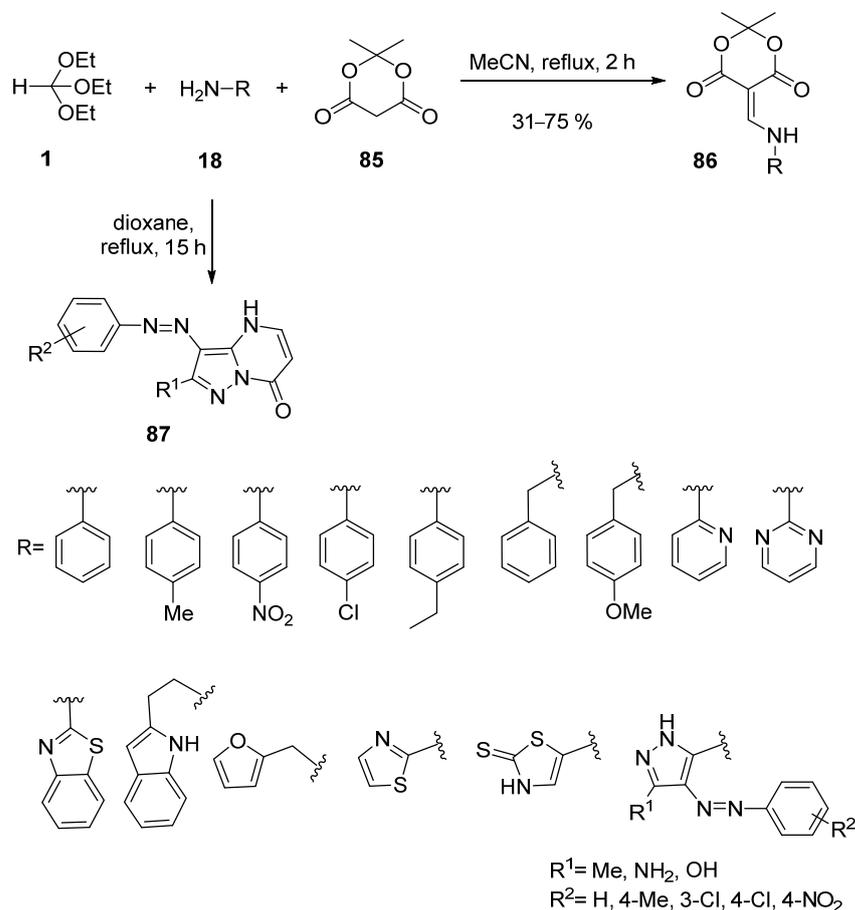

Scheme 24. Synthesis of 5-aminomethylene Meldrum's acid derivatives **86** and pyrazolo[1,5-*a*]pyrimdines-7(4*H*)-ones **87**.

Vandyshev et al. [79,80] explored the cascade heterocyclization reactions of TEOF **1**, 1,2-diamino-4*H*-phenylimidazole **88** with cyclohexanedione **89** or ethyl acetoacetate **50** (Scheme 25). High yields of imidazo[1,5-*b*]pyridazines **90** and **91** were obtained when a mixture of dimethylformamide (DMF), isopropyl alcohol (*i*-PrOH) and acetic acid, in catalytic amounts, were used as solvents.

A novel series of hetarylaminomethylidene derivatives **93** was reported by Tikhomolova et al. [81], and this author used furan-2(3*H*)-ones **92** by a three-component reaction (Scheme 26). As proposed by the authors, the mechanism can proceed in two ways (Scheme 27). In pathway A, the reaction continues through the formation of intermediate imine **94** in situ by the nucleophilic addition of amine **18** to TEOF **1**, which loses two ethanol molecules. Then, furan-2(3*H*)-one **93** reacts with imine **94** to form intermediate **95**, yielding **93**, after which another ethanol molecule is eliminated. On the other hand, in pathway B, the initial reaction is that of furan-2(3*H*)-one molecule **92** with **1** to form ethoxymethylene derivatives **96**, which are converted into intermediate compounds **95**, by reaction with amine **18**. Product **93** is obtained after eliminating another ethanol molecule.
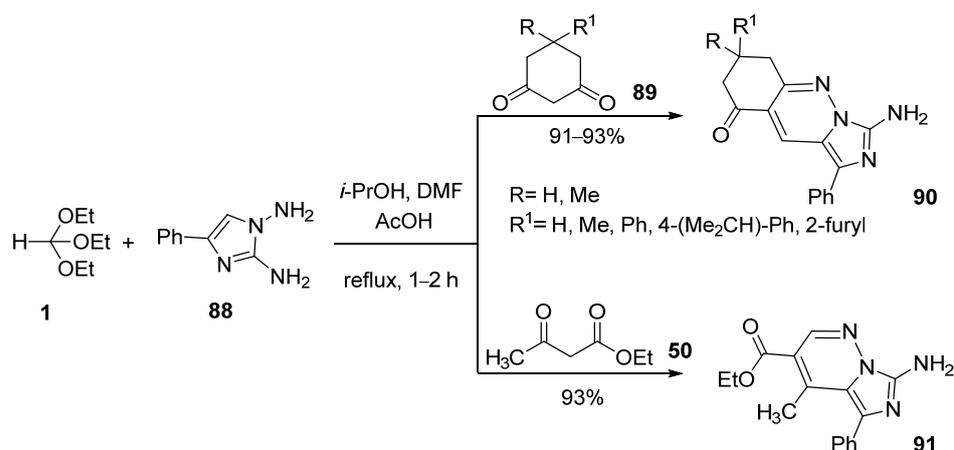
Scheme 25. Cascade reactions of TEOF **1** with 1,2-diaminoimidazole **88** with cyclohexane-1,3-diones **89** or ethyl acetoacetate **50**.
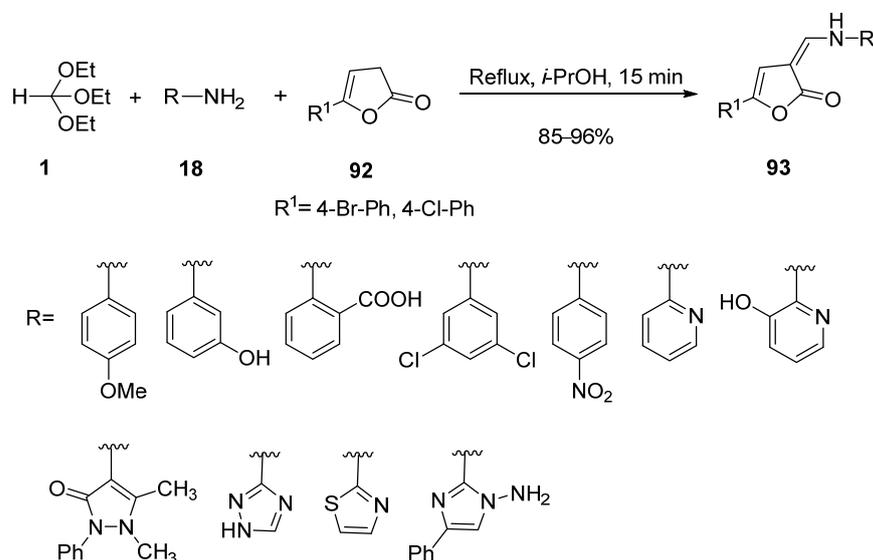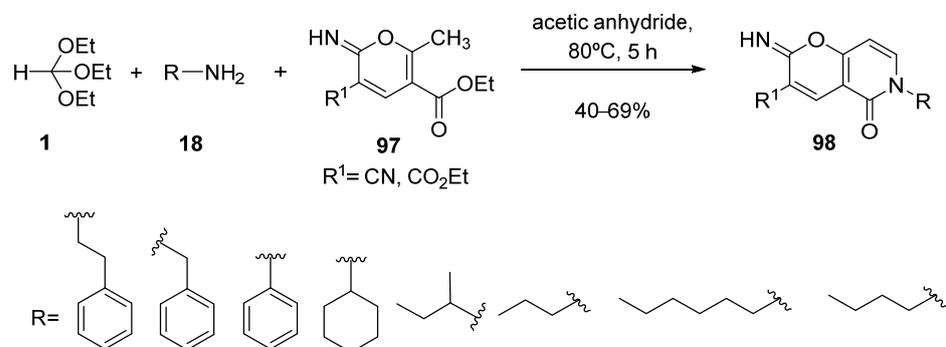

Scheme 26. Three-component synthesis of 3-hetarylaminomethylidenefuran-2(3*H*)-ones **93**.
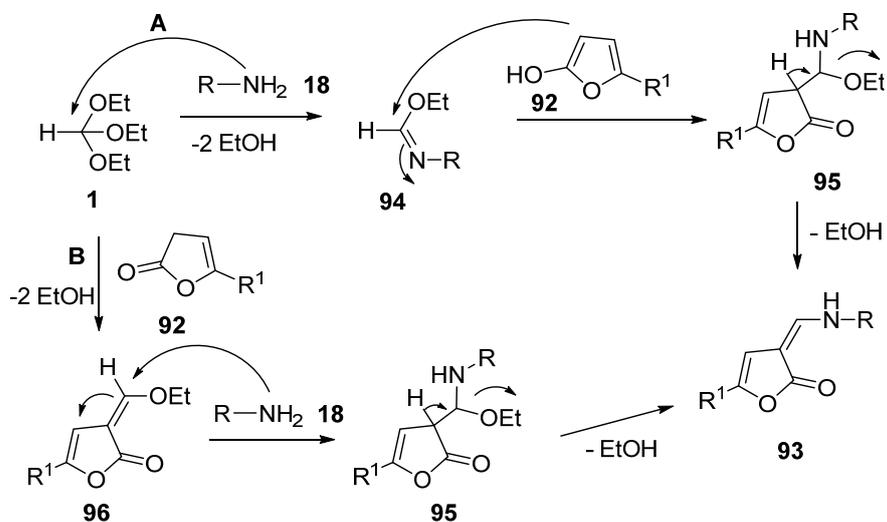
Scheme 27. Probable mechanism for the formation of 3-hetarylaminomethylidenefuran-2(3*H*)-ones **93**.

More recently, Berrichi et al. [82] synthesized the 2-imino-2*H*-pyrano[3,2-*c*]pyridin-5(6*H*)-ones derivatives **98** (Scheme 28) between TEOF **1**, primary amines **18** and 2*H*-iminopyranes **97**. The reaction takes place at 80 °C for 5 h, in the presence of acetic anhydride. Various primary amines such as aromatic, cyclic and aliphatic were used to explore the versatility of this approach in synthesizing new compounds.

Scheme 28. Three-component synthesis of 2-imino-2*H*-pyrano[3,2-*c*]pyridine-5(6*H*)-ones **98**.
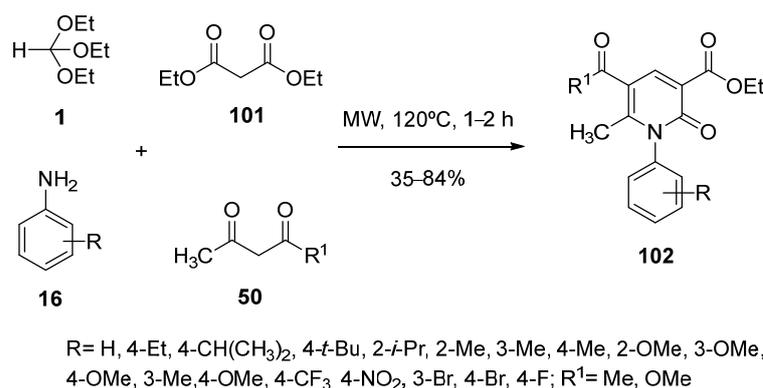
4. Synthesis by Four-Component Reaction

Wu et al. [83] reported a palladium-catalyzed four-component carbonylative coupling system for the formation of 3-aryl-4(3*H*)-quinazolinones **48** in a one-pot approach. A combined mixture of TEOF **1**, 2-bromoanilines **99**, amine **16** and carbon monoxide (CO) **100** with a palladium acetate/di(1-adamantyl)-*n*-butylphosphine [Pd(OAc)$_2$/(BuPAd$_2$)] complex at 100 °C gives 3-aryl-4(3*H*)-quinazolinones **48** with good yields (Scheme 29).
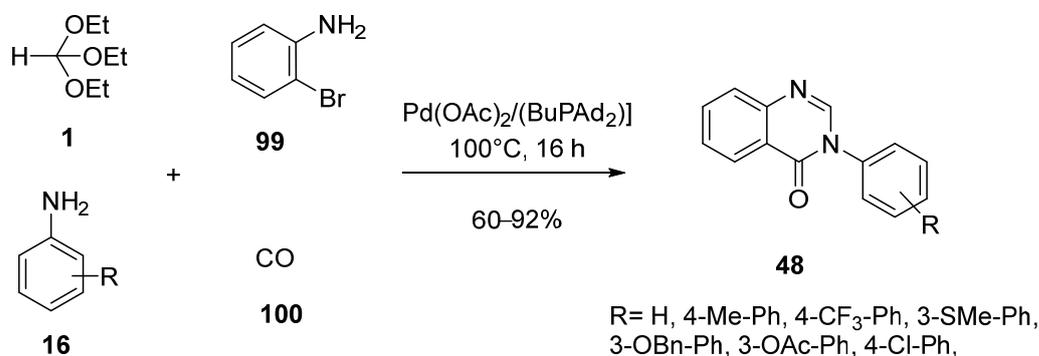
Scheme 29. Synthesis of 4(3*H*)-quinazolinones **48**.

Heterocycles containing a pyridone core have a diversity of biological properties, such as anticancer, antiulcer, ACE-inhibiting, anti-inflammatory, antifungal, anti-HIV, antiviral and cardiotonic activities [84].

Huang et al. [2] described, for the first time, a new four-component synthesis of a substituted 2-piridone derivative **102** (Scheme 30) by branched domino reaction between TEOF **1** as a building block C1, aromatic amines **16** and two categories of dicarbonyl compounds, such as 1,3-acyclic diketones **50** and diethyl malonate **101**, under microwave irradiation (120 °C). The same research group also evaluated the scope and limitations of the reaction with various alkylamines or other amines, and products were obtained in yields of 50 to 78%.

R= H, 4-Et, 4-CH(CH$_3$)$_2$, 4-*t*-Bu, 2-*i*-Pr, 2-Me, 3-Me, 4-Me, 2-OMe, 3-OMe, 4-OMe, 3-Me,4-OMe, 4-CF$_3$, 4-NO$_2$, 3-Br, 4-Br, 4-F; R^1= Me, OMe

Scheme 30. Formation of 2-Pyridones derivatives **102** via four-component reaction.

5. Conclusions

One-pot reactions allow many reactions to be combined so that synthetic efficacy can be initiated to match that of nature, but important tasks remain before this promising method will be able to meet the demands of pharmaceutical chemistry and materials. In summary, we have reviewed recent developments in the one-pot reactions of triethyl orthoformate with different amines and numerous new reaction sequences have been developed in the last decade. The reaction method allows combining several catalytic procedures in the same reaction vessel and provides high regioselectivity, atomic efficiency and does not involve workup and isolation of many intermediates.

Data Availability Statement: Data sharing not applicable.

Conflicts of Interest: The author declares no conflict of interest.

References

1. Damera, T.; Pagadala, R.; Rana, S.; Jonnalagadda, S.B. A Concise Review of Multicomponent Reactions Using Novel Heterogeneous Catalysts under Microwave Irradiation. *Catalysts* **2023**, *13*, 1034. [CrossRef]
2. Bai, H.; Sun, R.; Liu, S.; Yang, L.; Chen, X.; Huang, C. Construction of Fully Substituted 2-Pyridone Derivatives via Four-Component Branched Domino Reaction Utilizing Microwave Irradiation. *J. Org. Chem.* **2018**, *83*, 12535–12548. [CrossRef]
3. Hayashi, Y. Pot economy and one-pot synthesis. *Chem. Sci.* **2016**, *7*, 866–880. [CrossRef]
4. Biesen, L.; Müller, T.J.J. Multicomponent and One-pot Syntheses of Quinoxalines. *Adv. Synth. Catal.* **2021**, *363*, 980–1006. [CrossRef]
5. Shivam Tiwari, G.; Kumar, M.; Chauhan, A.N.S.; Erande, R.D. Recent advances in cascade reactions and their mechanistic insights: A concise strategy to synthesize complex natural products and organic scaffolds. *Org. Biomol. Chem.* **2022**, *20*, 3653–3674. [CrossRef]
6. Brusa, A.; Iapadre, D.; Casacchia, M.E.; Carioscia, A.; Giorgianni, G.; Magagnano, G.; Pesciaioli, F.; Carlone, A. Acetaldehyde in the Enders triple cascade reaction via acetaldehyde dimethyl acetal. *Beilstein J. Org. Chem.* **2023**, *19*, 1243–1250. [CrossRef] [PubMed]
7. Ciulla, M.G.; Zimmermann, S.; Kumar, K. Cascade reaction based synthetic strategies targeting biologically intriguing indole polycycles. *Org. Biomol. Chem.* **2019**, *17*, 413–431. [CrossRef]
8. Bunce, R.A. Orthoesters in heterocycle synthesis. *Arkivoc* **2020**, *i*, 400–436. [CrossRef]
9. Marinho, E.; Araújo, R.; Proença, F. The reaction of anthranilonitrile and triethylorthoformate revisited: Formation of dimeric and trimeric species. *Tetrahedron* **2010**, *66*, 8681–8689. [CrossRef]
10. Hamed, M.M.; Abou El Ella, D.A.; Keeton, A.B.; Piazza, G.A.; Engel, M.; Hartmann, R.W.; Abadi, A.H. Quinazoline and tetrahydropyridothieno[2,3-*d*]pyrimidine derivatives as irreversible EGFR tyrosine kinase inhibitors: Influence of the position 4 substituent. *Med.Chem.Commun.* **2013**, *4*, 1202–1207. [CrossRef]
11. Nguyen, T.T.; Nguyen, X.-T.T.; Nguyen, T.-L.H.; Tran, P.H. Synthesis of Benzoxazoles, Benzimidazoles, and Benzothiazoles Using a Brønsted Acidic Ionic Liquid Gel as an Efficient Heterogeneous Catalyst under a Solvent-Free Condition. *ACS Omega* **2019**, *4*, 368–373. [CrossRef] [PubMed]
12. Bastug, G.; Eviolitte, C.; Markó, I.E. Functionalized orthoesters as powerful building blocks for the efficient preparation of heteroaromatic bicycles. *Org. Lett.* **2012**, *14*, 3502–3505. [CrossRef] [PubMed]

13. Grieco, G.; Blacque, O.; Berke, H. A facile synthetic route to benzimidazolium salts bearing bulky aromatic *N*-substituents. *Beilstein J. Org. Chem.* **2015**, *11*, 1656–1666. [CrossRef] [PubMed]

14. Mazloumi, M.; Shirini, F.; Goli-Jolodar, O.; Seddighi, M. Nanoporous TiO$_2$ containing an ionic liquid bridge as an efficient and reusable catalyst for the synthesis of *N,N'*-diarylformamidines, benzoxazoles, benzothiazoles and benzimidazoles. *New J. Chem.* **2018**, *42*, 5742–5752. [CrossRef]

15. Al-Majidi, S.M.H. Synthesis of some new 4-oxo-thiazolidines, tetrazole and triazole derived from 2-SH-benzothiazole and antimicrobial screening of some Synthesized. *J. Saudi Chem. Soc.* **2014**, *18*, 893–901. [CrossRef]

16. Zhou, Y.-J.; Zhang, M.-M.; Li, Y.-L.; Liu, Y.; Wang, X.-S. Iodine-catalyzed synthesis of 2-arylpyrazolo[5,1-*b*]quinazolin-9(3*H*)-one derivatives in ionic liquids via domino reaction. *Tetrahedron* **2014**, *70*, 3440–3446. [CrossRef]

17. Szczepankiewicz, W.; Kuźnik, N. Synthesis of 3-arylquinazolin-4(3H)-imines from 2-amino-*N'*-arylbenzamidines and triethyl orthoformate. *Tetrahedron Lett.* **2015**, *56*, 1198–1199. [CrossRef]

18. Gavin, J.T.; Annor-Gyamfi, J.K.; Bunce, R.A. Quinazolin-4(3H)-ones and 5,6-Dihydropyrimidin-4(3H)-ones from β-Aminoamides and Orthoesters. *Molecules* **2018**, *23*, 2925. [CrossRef]

19. Haji, M. Multicomponent reactions: A simple and efficient route to heterocyclic phosphonates. *Beilstein J. Org. Chem.* **2016**, *12*, 1269–1301. [CrossRef]

20. Miszczyk, P.; Turowska-Tyrk, I.; Kafarski, P.; Chmielewska, E. Three-Component Reaction of Benzylamines, Diethyl Phosphite and Triethyl Orthoformate: Dependence of the reaction Course on the Structural Features of the Substrates and Reaction Conditions. *Molecules* **2017**, *22*, 450. [CrossRef]

21. Miszczyk, P.; Wieczorek, D.; Gałęzowska, J.; Dziuk, B.; Wietrzyk, J.; Chmielewska, E. Reaction of 3-Amino-1,2,4-Triazole with Diethyl Phosphite and Triethyl Orthoformate: Acid-Base Properties and Antiosteoporotic Activities of the Products. *Molecules* **2017**, *22*, 254. [CrossRef] [PubMed]

22. Petruczynik, P.; Kafarski, P.; Psurski, M.; Wietrzyk, J.; Kiełbowicz, Z.; Kuryszko, J.; Chmielewska, E. Three-Component Reaction of Diamines with Triethyl Orthoformate and Diethyl Phosphite and Anti-Proliferative and Antiosteoporotic Activities of the Products. *Molecules* **2020**, *25*, 1424. [CrossRef]

23. Tellamekala, S.; Gundluru, M.; Sudileti, M.; Sarva, S.; Putta, C.R.K.; Cirandur, S.R. Green one-pot synthesis of *N*-bisphosphonates as antimicrobial and antioxidant agents. *Monatshefte Chem. Chem. Mon.* **2020**, *151*, 251–260. [CrossRef]

24. Amira, A.; K'tir, H.; Aouf, Z.; Khaldi, T.; Bentoumi, H.; Khattabi, L.; Zerrouki, R.; Ibrahim-Ouali, M.; Aouf, N.-E. One-Pot Microwave-Assisted Synthesis, in Vitro Antiinflammatory Evaluation and Computer-Aided Molecular Design of Novel Sulfamide-Containing Bisphosphonates Derivatives. *ChemistrySelect* **2022**, *7*, e202201889. [CrossRef]

25. Neochoritis, C.G.; Zhao, T.; Dömling, A. Tetrazoles via Multicomponent Reactions. *Chem. Rev.* **2019**, *119*, 1970–2042. [CrossRef]

26. Dhiman, N.; Kaur, K.; Jaitak, V. Tetrazoles as anticancer agents: A review on synthetic strategies, mechanism of action and SAR studies. *Bioorganic Med. Chem.* **2020**, *28*, 115599. [CrossRef] [PubMed]

27. Darvish, F.; Khazraee, S. FeCl$_3$ Catalyzed One Pot Synthesis of 1-Substituted 1*H*-1,2,3,4-Tetrazoles under Solvent-Free Conditions. *Int. J. Org. Chem.* **2015**, *5*, 75–80. [CrossRef]

28. Naeimi, H.; Mohamadabadi, S. Sulfonic acid-functionalized silica-coated magnetic nanoparticles as an efficient reusable catalyst for the synthesis of 1-substituted 1H-tetrazoles under solvent-free conditions. *Dalton Trans.* **2014**, *43*, 12967–12973. [CrossRef]

29. Naeimi, H.; Kiani, F. Ultrasound-promoted one-pot three component synthesis of tetrazoles catalyzed by zinc sulfide nanoparticles as a recyclable heterogeneous catalyst. *Ultrason. Sonochemistry* **2015**, *27*, 408–415. [CrossRef]

30. Naeimi, H.; Kiani, F.; Moradian, M. Rapid microwave promoted heterocyclization of primary amines with triethyl orthoformate and sodium azide using zinc sulfide nanoparticles as recyclable catalyst. *Green Chem. Lett. Rev.* **2018**, *11*, 361–369. [CrossRef]

31. Khan, F.A.K.; Zaheer, Z.; Sangshetti, J.N.; Ahmed, R.Z. Facile one-pot synthesis, antibacterial activity and in silico ADME prediction of 1-substituted-1*H*-1,2,3,4-tetrazoles. *Chem. Data Collect.* **2018**, *15–16*, 107–114. [CrossRef]

32. Salimi, M.; Zamanpour, A. Green synthesis of the 1-substituted 1*H*-1,2,3,4-tetrazoles over bifunctional catalyst based on copper intercalated into Mg/Al hydrotalcite modified magnetite nanoparticles. *Appl. Organomet. Chem.* **2020**, *34*, e5682. [CrossRef]

33. Mashhoori, M.-S.; Sandaroos, R. New ecofriendly heterogeneous nano-catalyst for the synthesis of 1-substituted and 5-substituted 1*H*-tetrazole derivatives. *Sci. Rep.* **2022**, *12*, 15364. [CrossRef] [PubMed]

34. Hassan, A.Y.; Sarg, M.T.; Said, M.M.; El-Sebaey, S.A. Utility of thieno[2,3-*b*] pyridine derivatives in the synthesis of some condensed heterocyclic compounds with expected biological activity. *Univers. Org. Chem.* **2013**, *1*, 2. [CrossRef]

35. Pokhodylo, N.T.; Matiychuk, V.S.; Obushak, M.D. New convenient synthesis of 2,3-diaminothieno[2,3-*d*] pyrimidin-4(3*H*)-one derivatives from substituted alkyl 2-(1*H*-tetrazol-1-yl)thiophene-3-carboxylates. *Tetrahedron* **2008**, *64*, 1430–1434. [CrossRef]

36. Srinivas, D.; Ghule, V.D.; Muralidharan, K. Synthesis of nitrogen-rich imidazole, 1,2,4-triazole and tetrazole-based compounds. *RSC Adv.* **2014**, *4*, 7041–7051. [CrossRef]

37. Nagaraju, K.; Lalitha, G.; Singh, P.; Rao, C.V. One-pot synthesis of 1-substituted 1*H*-1,2,3,4-tetrazoles from 2-aminothiazoles using tributylmethylammonium chloride as a catalyst. *Heterocycl. Commun.* **2017**, *23*, 365–368. [CrossRef]

38. Marinho, E.; Proença, M.F. The Reaction of 2-(Acylamino)Benzonitriles with Primary Aromatic Amines: A Convenient Synthesis of 2-Substituted 4-(Arylamino)Quinazolines. *Synthesis* **2015**, *47*, 1623–1632. [CrossRef]

39. Khan, I.; Zaib, S.; Batool, S.; Abbas, N.; Ashraf, Z.; Iqbal, J.; Saeed, A. Quinazolines and quinazolinones as ubiquitous structural fragments in medicinal chemistry: An update on the development of synthetic methods and pharmacological diversification. *Bioorg. Med. Chem.* **2016**, *24*, 2361–2381. [CrossRef]

...

40. Ismail, R.S.M.; Ismail, N.S.M.; Abuserii, S.; El Ella, D.A.A. Recent advances in 4-aminoquinazoline based scaffold derivatives targeting EGFR kinases as anticancer agents. *Future J. Pharm. Sci.* **2016**, *2*, 9–19. [CrossRef]

41. Marinho, E.; Proença, M.F. Reactivity and regioselectivity in the acylation of 2,4-diaminoquinazolines. *Tetrahedron* **2016**, *72*, 4383–4389. [CrossRef]

42. Khabnadideh, S.; Sadeghian, S. A Review on Current Synthetic Methods of 4-Aminoquinazoline Derivatives. *J. Chem.* **2022**, *2022*, 8424838. [CrossRef]

43. Zayed, M.F. Medicinal Chemistry of Quinazolines as Anticancer Agents Targeting Tyrosine Kinases. *Sci. Pharm.* **2023**, *91*, 18. [CrossRef]

44. Devi, P.; Srivastava, A.; Srivastava, K.; Bishnoi, A. Green approaches towards the synthesis of substituted quinazolines. *Curr. Green Chem.* **2017**, *4*, 25–37. [CrossRef]

45. Das, D.; Hong, J. Recent advancements of 4-aminoquinazoline derivatives as kinase inhibitors and their applications in medicinal chemistry. *Eur. J. Med. Chem.* **2019**, *170*, 55–72. [CrossRef] [PubMed]

46. Tamatam, R.; Kim, S.-H.; Shin, D. Transition-metal-catalyzed synthesis of quinazolines: A review. *Front. Chem.* **2023**, *11*, 1140562. [CrossRef] [PubMed]

47. Gore, R.P.; Rajput, A.P. A review on recent progress in multicomponent reactions of pyrimidine synthesis. *Drug Invent. Today* **2013**, *5*, 148–152. [CrossRef]

48. Habib, N.S.; Soliman, R.; El-Tombary, A.A.; El-Hawash, S.A.; Shaaban, O.G. Synthesis and biological evaluation of novel series of thieno[2,3-*d*]pyrimidine derivatives as anticancer and antimicrobial agents. *Med. Chem. Res.* **2013**, *22*, 3289–3308. [CrossRef]

49. Jing, X.-B.; Li, Z.; Pan, X.; Shi, Y.-C. A Novel Method for the Synthesis of 4(3*H*)-Quinazolinones. *J. Chin. Chem. Soc.* **2008**, *55*, 1145–1149. [CrossRef]

50. Wu, L.; Ma, W.; Yang, L.; Yan, F. Silica-Supported Boron Trifluoride (BF₃-SiO₂): An Efficient, Environment Frendly and Recyclable Catalyst for The One-Pot Synthesis of 4(3*H*)-quinazolinones. *Asian J. Chem.* **2010**, *22*, 6053–6058.

51. Nasreen, A.; Borik, R.M. Cobalt(II) Chloride Catalyzed one Pot Synthesis of 2-substituted and 3-substituted-4(3*H*)-Quinazolinones. *Orient. J. Chem.* **2014**, *30*, 761–768. [CrossRef]

52. Kawade, D.S.; Chaudhari, M.A.; Gujar, J.B.; Shingare, M.S. Thiamine hydrochloride (vitamin B1) as an efficient catalyst for the synthesis of 4-(3*H*)-Quinazolinone derivatives using grinding method. *Iran. J. Catal.* **2016**, *6*, 313–318.

53. Fan, Y.; Luo, F.; Su, M.; Li, Q.; Zhong, T.; Xiong, L.; Li, M.; Yuan, M.; Wang, D. Structure optimization, synthesis, and biological evaluation of 6-(2-amino-1*H*-benzo[*d*]imidazole-6-yl)-quinazolin-4(3*H*)-one derivatives as potential multi-targeted anticancer agents via Aurora A/PI3K/BRD4 inhibition. *Bioorganic Chem.* **2023**, *132*, 106352. [CrossRef] [PubMed]

54. Venkateswarlu, S.; Satyanarayana, M.; Ravikiran, P.; Siddaiah, V. Reaction of Imidoformates with Anthranilates: Facile, One-Pot, Three-Component Synthesis of 8*H*-Quinazolino[4,3-*b*]quinazolin-8-ones. *J. Heterocycl. Chem.* **2013**, *50*, 1089–1093. [CrossRef]

55. Zaman, A.U.; Khan, M.A.; Munawar, M.A.; Athar, M.M.; Pervaiz, M.; Pervaiz, A.; Mahmood, A. Microwave Assisted Gould-Jacobs Reaction for Synthesis of 3-Acetyl-4-hydroxyquinoline Derivatives. *Asian J. Chem.* **2015**, *27*, 2823–2826. [CrossRef]

56. Bai, H.; Liu, F.; Wang, X.; Wang, P.; Huang, C. Three-Component One-Pot Approach to Highly Efficient and Sustainable Synthesis of the Functionalized Quinolones via Linear/Branched Domino Protocols, Key Synthetic Methods for the Floxacin of Quinolone Drugs. *ACS Omega* **2018**, *3*, 11233–11251. [CrossRef] [PubMed]

57. Rad-Moghadam, K.; Samavi, L. One-pot Three-component Synthesis of 2-Substituted 4-Aminoquinazolines. *J. Heterocycl. Chem.* **2006**, *43*, 913–916. [CrossRef]

58. Hussen, A.S.; Bagchi, S.; Sharma, A. Ammonium Chloride Assisted Microwave Mediated Domino Multicomponent Reaction: An Efficient and Sustainable Synthesis of Quinazolin-4(3*H*)-imines under Solvent Free Condition. *ChemistrySelect* **2019**, *4*, 10169–10173. [CrossRef]

59. Wang, Z.; Chen, W.; He, C.; Zhang, G.; Yu, Y. Palladium(II)-Catalyzed Three-Component Tandem Cyclization Reaction for the One-Pot Assembly of 4-Arylquinazolines. *Synthesis* **2021**, *53*, 1356–1364. [CrossRef]

60. Kotaiah, Y.; Harikrishna, N.; Nagaraju, K.; Rao, C.V. Synthesis and antioxidant activity of 1,3,4-oxadiazole tagged thieno[2,3-*d*]pyrimidine derivatives. *Eur. J. Med. Chem.* **2012**, *58*, 340–345. [CrossRef] [PubMed]

61. Sasada, T.; Kobayashi, F.; Sakai, N.; Konakahara, T. An Unprecedented Approach to 4,5-Disubstituted Pyrimidine Derivatives by a ZnCl₂-Catalyzed Three-Component Coupling Reaction. *Org. Lett.* **2009**, *11*, 2161–2164. [CrossRef] [PubMed]

62. Soheilizad, M.; Adib, M.; Sajjadifar, S. One-pot and three-component synthesis of substituted pyrimidines catalysed by boron sulfuric acid under solvent-free conditions. *J. Chem. Res.* **2014**, *38*, 524–527. [CrossRef]

63. Bhat, S.I.; Das, U.K.; Trivedi, D.R. An Efficient Three-component, One-pot Synthesis of Quinazolines under Solvent-free and Catalyst-free Condition. *J. Heterocycl. Chem.* **2015**, *52*, 1253–1259. [CrossRef]

64. Kalinina, S.A.; Kalinin, D.V.; Dolzhenko, A.V. A one-pot, three-component, microwave-promoted synthesis of 2-amino-substituted 7-amino-1,2,4-triazolo[1,5-*a*]-[1,3,5]triazines. *Tetrahedron Lett.* **2013**, *54*, 5537–5540. [CrossRef]

65. Dolzhenko, A.V.; Kalinina, S.A.; Kalinin, D.V. A novel multicomponent microwave-assisted synthesis of 5-aza-adenines. *RSC Adv.* **2013**, *3*, 15850–15855. [CrossRef]

66. Lim, F.P.L.; Low, S.T.; Ho, E.L.K.; Halcovitch, N.R.; Tiekink, E.R.T.; Dolzhenko, A.V. A multicomponent reaction of 2-aminoimidazoles: Microwave-assisted synthesis of novel 5-aza-7-deaza-adenines. *RSC Adv.* **2017**, *7*, 51062–51068. [CrossRef]

67. Lim, F.P.L.; Luna, G.; Dolzhenko, A.V. A new, one-pot, multicomponent synthesis of 5-aza-9-deaza-adenines under microwave irradiation. *Tetrahedron Lett.* **2014**, *55*, 5159–5163. [CrossRef]

68. Lim, F.P.L.; Luna, G.; Tan, K.C.; Tiekink, E.R.T.; Dolzhenko, A.V. A synthesis of new 7-amino-substituted 4-aminopyrazolo[1,5-*a*][1,3,5]triazines via a selective three-component triazine ring annulation. *Tetrahedron* **2019**, *75*, 2322–2329. [CrossRef]

69. Lim, F.P.L.; Luna, G.; Dolzhenko, A.V. A one-pot, three-component, microwave-assisted synthesis of novel 7-amino-substituted 4-aminopyrazolo[1,5-*a*][1,3,5]triazine-8-carbonitriles. *Tetrahedron Lett.* **2015**, *56*, 7016–7019. [CrossRef]

70. Lim, F.P.L.; Luna, G.; Dolzhenko, A.V. A one-pot, three-component aminotriazine annulation onto 5-aminopyrazole-4-carbonitriles under microwave irradiation. *Tetrahedron Lett.* **2015**, *56*, 521–524. [CrossRef]

71. Lim, F.P.L.; Luna, G.; Dolzhenko, A.V. A New, One-Pot, Multicomponent Synthesis of Bioactive *N*-Pyrazolylformamidines under Microwave Irradiation. *Synthesis* **2015**, *48*, 2423–2428. [CrossRef]

72. De Nino, A.; Maiuolo, L.; Nardi, M.; Pasceri, R.; Procopio, A.; Russo, B. Development of one-pot three component reaction for the synthesis of *N'*-aryl-*N*-cyanoformamidines, essential precursors of formamidine pesticides family. *Arab. J. Chem.* **2016**, *9*, 32–37. [CrossRef]

73. Siutkina, A.I.; Kalinina, S.; Liu, R.; Heitman, L.H.; Junker, A.; Daniliuc, C.G.; Kalinin, D.V. Microwave-Assisted Synthesis, Structure, and Preliminary Biological Evaluation of Novel 6-Methoxy-5,6-dihydro-5-azapurines. *ACS Omega* **2023**, *8*, 14097–14112. [CrossRef] [PubMed]

74. Prior, A.M.; Gunaratna, M.J.; Kikuchi, D.; Desper, J.; Kim, Y.; Chang, K.-O.; Maezawa, I.; Jin, L.-W.; Hua, D.H. Syntheses of 3-[(Alkylamino)methylene]-6-methyl-1*H*-pyridine-2,4-diones, Fluorescence Probes 3-Substituted 7-Methyl-6*H*-pyrano[3,2-*c*]pyridine-2,5-diones, and Tetrahydro-6*H*-2,10-dioxa-9-azaanthracen-1-ones. *Synthesis* **2014**, *46*, 2179–2190. [CrossRef] [PubMed]

75. Olyaei, A.; Mohamadi, A.; Rahmani, N. Green synthesis of new lawsone enaminones and their Z/E(C=C)-isomerization induced by organic solvente. *RSC Adv.* **2021**, *11*, 12990–12994. [CrossRef]

76. Hameed, A.M.A.; Nour-Eldin, A.M.; Ibrahim, M.M.; Sadek, K.U. Regioselectivity in the Multicomponent Reaction of 5-aminopyrazoles, Meldrum's Acid and Triethyl Orthoformate. *Am. Chem. Sci. J.* **2015**, *8*, 1–5. [CrossRef]

77. Adnan, A.I.; Pungot, N.H.; Ash'ari, N.A.N. Convenient Synthesis of 5-arylidene Meldrum's Acid Derivatives via Knoevenagel Condensation. *J. Acad.* **2021**, *9*, 80–84.

78. Hussien, H.A.K.; Al-Messri, Z.A.K. Synthesis, Characterization and Evaluation of Some Meldrum's Acid Derivatives as Lubricant Additives. *Iraqi J. Sci.* **2023**, *64*, 1041–1048. [CrossRef]

79. Vandyshev, D.Y.; Shikhaliev, K.S.; Potapov, A.Y.; Krysin, M.Y. Cascade two- and three-component cyclization reactions using 1,2-diamino-4-phenylimidazole and cyclohexane-1,3-diones. *Chem. Heterocycl. Compd.* **2014**, *50*, 1428–1433. [CrossRef]

80. Kruzhilin, A.A.; Kosheleva, E.A.; Shikhaliev, K.S.; Denisov, G.L.; Vandyshev, D.Y. Regioselective Synthesis of Imidazo[1,5-*b*]pyridazines by Cascade Cyclizations of 1,2-Diamino-4H-phenylimidazole with 1,3-Diketones, Acetoacetic Ester and Their Derivatives. *ChemistrySelect* **2021**, *6*, 5801–5806. [CrossRef]

81. Tikhomolova, A.S.; Grinev, V.S.; Yegorova, A.Y. One-Pot Synthesis, *E*-/*Z*-Equilibrium in Solution of 3-Hetarylaminomethylidenefuran-2(3*H*)-ones and the Way to Selective Synthesis of the *E*-Enamines. *Molecules* **2023**, *28*, 963. [CrossRef] [PubMed]

82. Mehiaoui, N.; Hassaine, R.; Berrichi, A.; Kibou, Z.; Choukchou-Braham, N. Synthesis of Highly Heterocyclic Fluorescent Molecules: 2-imino-2*H*-pyrano[3,2-*c*] Pyridin-5(6*H*)-ones Derivatives. *J. Fluoresc.* **2023**, *33*, 1995–2001. [CrossRef] [PubMed]

83. He, L.; Li, H.; Neumann, H.; Beller, M.; Wu, X.-F. Highly efficient four-component synthesis of 4(3*H*)-Quinazolinones: Palladium-catalyzed carbonylative coupling reactions. *Angew. Chem. Int. Ed.* **2014**, *53*, 1420–1424. [CrossRef] [PubMed]

84. Sangwan, S.; Yadav, N.; Kumar, R.; Chauhan, S.; Dhanda, V.; Walia, P.; Duhan, A. A score years' update in the synthesis and biological evaluation of medicinally important 2-pyridones. *Eur. J. Med. Chem.* **2022**, *232*, 114199. [CrossRef]