Review
Recent Developments on Five-Component Reactions

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Abstract: Multicomponent reactions (MCRs) have inherent advantages in pot, atom, and step economy (PASE). This important green synthetic approach has gained increasing attention due to high efficiency, minimal waste, saving resources, and straightforward procedures. Presented in this review article are the recent development on 5-component reactions (5CRs) of the following six types: (I) five different molecules A + B + C + D + E; pseudo-5CRs including (II) 2A + B + C + D, (III) 2A + 2B + C, (IV) 3A + B + C, (V) 3A + 2B, and (VI) 4A + B. 5CRs with more than five-reaction centers are also included.

Keywords: multicomponent reaction; five-component; pseudo; one-pot; cascade; consecutive; green synthesis; heterocycle; pot; atom; step economy

1. Introduction

Reactions with a single operational step involving three or more components are called multicomponent reactions (MCRs) [1–4]. They have inherent advantages of pot, atom, and step economy (PASE) in the formation of multiple bonds of complex molecules [5,6]. MCRs integrate most of reactants to the product structures for mass efficiency, bypass the step of intermediate purification to reduce the amount of waste, and perform one-step reaction to simplify procedures and save resources. MCRs and associated one-pot synthesis and cascade reactions are active topics in the development of new methodologies in organic synthesis and catalysis [7,8].

There are couple dozen MCRs named after people, such as the well-known Ugi, Biginelli, Petasis, Hantzsch, Passerini, Huisgen, and Groebke-Blackburn-Bienaymé (GBB) reactions [1–4]. All these reactions are three- or four-component transformations. MCRs involving five or more components are called high-order MCRs, which are more efficient than regular MCRs in assembling complex structures [9]. However, the number of high-order MCRs is limited, because the increased number of competitive reactions for side-products make it harder to incorporate all the components in an orderly manner to form desirable products. Shown in Figure 1 is the distribution of MCRs from three up to nine components [10]. It shows a deep drop in paper numbers with the increase of reaction components.

There are numerous monographs and review articles on 3CRs and 4CRs [1–4], but only two reviews related to 5CRs in 2013 and 2020 [9,11]. Covered in this article are 5CRs mainly published after 2013. The 5CRs are classified into the following six types: (I) 5CR of five different components A + B + C + D + E; pseudo-5CRs of (II) 2A + B + C + D, (III) 2A + 2B + C, (IV) 3A + B + C, (V) 3A + 2B, and (VI) 4A + B. The number of these six kinds of 5CRs are quite different. Figure 2 shows the most popular 5CR is Type-III, followed by Type-II, and then Type-I. The number of the remaining types of MCRs is very limited.
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If a component in the 5CRs has two reaction centers, then, the reaction is a 6-center 5-component reaction (6C5CR). It is important to note that MCRs only have a single operational step to charge all the components to the reaction vessel. If components are introduced in a stepwise manner at different stages of the reaction process, they should be called one-pot reactions instead of MCRs [7].

2. Type-I, 5CRs of A + B + C + D + E

A schematic of a Type-I 5CRs involving five different molecules A + B + C + D + E is shown in Scheme 1. Because of complicated reaction mechanisms, the reported numbers of such reactions are limited. Since all components are different, the product structures could be unique and complex. A large number of analogs can be readily made by using different sets of starting materials.

Figure 1. Publications of different MCRs.

Figure 2. Papers of different 5MCRs covered in this work. Type I—A + B + C + D + E; Type II—2A + B + C + D; Type III—2A + 2B + C; Type IV—3A + B + C; Type V—3A + 2B; Type VI—4A + B.
Khurana and co-workers reported the synthesis of 1,2,3-triazole-linked 1,4-dihydropyridines 1 under ultrasonic or microwave irradiation using PEG-400 as a solvent (Scheme 2) [12]. The produced compounds were evaluated for antibacterial, antifungal, antioxidant activities, and also for photophysical properties. In the proposed reaction mechanism, the first step is a 1,3-dipolar cycloaddition of aryl azides and propargylated benzaldehydes to form 1,2,3-triazoles 2. The next step (path I) is the Knoevenagel reaction of 1,2,3-triazoles 2 with 1,3-cyclohexanediones, followed by the Michael reaction of the enamine from ethyl acetoacetate and ammonium acetate to afford the products 1. Another pathway (path II) is the Knoevenagel reaction of 1,2,3-triazoles 2 and ethyl acetoacetate, followed by Michael reaction of the enamine to afford products 1. It is a 6C5CR, since propargylated benzaldehydes have 2-reaction centers.

Scheme 1. 5CRs of A + B + C + D + E.

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Scheme 2. 6C5CR for triazole-linked pentasubstituted 1,4-dihydropyridines.
Desai and co-workers introduced a reaction of benzyl halides, N-propargyl isatins, sodium azide, malononitrile, and 5,5-dimethyl-1,3-cyclohexanedione (3a), 6-methyl-2H-pyran-2,4(3H)-dione (3b) or 4-hydroxycarbazole (3c) for the synthesis of 1,2,3-triazole-tethered spirochromenocarbazoles 4, 5 or 6 using cellulose-supported CuI nanoparticles (Cell-Cul NPs) as a reusable catalyst (Scheme 3) [13,14]. The first step is the condensation of N-propargyl isatins, malononitrile and 3a, followed by cyclization to form spirochromenes 7. The Huisgen 1,3-dipolar cycloaddition of 7 with benzylic azides affords 1,2,3-triazaoles 4. The Cell-Cul NPs catalyst can be recovered for reuse. It is a 6C5CR since N-propargyl isatins have 2-reaction centers. All the synthesized products have been screened against Mycobacterium tuberculosis H37Ra (ATCC 25177), Mycobacterium bovis BCG (ATCC 35743), as well as panel of cancer cell lines. Some products exhibited antimycobacterial, antitubercular, antibacterial, and anti-proliferative activities.

Scheme 3. 6C5CR for spirochromenocarbazole-tethered 1,2,3-triazoles.

Wu and co-workers reported a photocatalytic reaction of aryldiazonium tetrafluoroborates, styrenes, sulfur dioxide, water, and nitriles for the synthesis of β-sulfonyl amides 8 at room temperature (Scheme 4) [15]. The vicinal aminosulfonylation of styrenes with the insertion of sulfur dioxide proceeded smoothly to give β-sulfonyl amides 8. The aryl radical generated from the reaction of aryldiazonium tetrafluoroborate and DABCO-(SO$_2$)$_2$...
is captured by SO$_2$ to form arylsulfonyl radical which then attacks the terminal position of the styrenes to provide intermediate radicals 9. The excited Ir-photocatalyst oxidizes the radicals to cations 10 through a single electron transfer (SET) mechanism. The nitriles as nucleophiles react with cations 10 to form 11 and then 12 in the presence of Lewis acid and H$_2$O to afford products 8 after isomerization.

Scheme 4. 5CR for β-sulfonyl amides.

Pasha and co-workers developed a reaction of substituted phenylacetonitriles, aryl aldehydes, hydrazine, ammonium acetate, and ethyl acetoacetate for the synthesis of 4,7-dihydro-1H-pyrazolo[3,4-b]pyridin-6-amines 13 under the catalysis of meglumine (Scheme 5) [16]. Meglumine has ammonium and alkoxy groups which can activate ethyl acetoacetate and phenylacetonitriles through hydrogen bonding and also donate electrons from the oxygen atom. As shown in the proposed mechanism, the protonated ethyl acetoacetate reacts with hydrazine to yield 14. The aryl acetonitriles undergo a Knoevenagel condensation with aryl aldehydes to form α,β-unsaturated nitriles 15. The Michael addition of 14 and 15 followed by the nucleophilic attack of NH$_3$ and cyclization afford products 13. It is a 6C5CR, since hydrazine is a 2-centered reactant.

Khurana and co-workers reported a reaction of acetylacetone, aryl azides, aryl aldehydes, isatin, and L-proline for the synthesis of novel heterocyclic triazolyl spirooxindoles 16 (Scheme 6) using DBU as a catalyst and PEG-400 as a solvent [17]. In the reaction process, the triazoles generated from a [3+2] cycloaddition of acetylacetone and azides undergo aldol condensation with aryl aldehydes to form α,β-unsaturated nitriles 15. The Michael addition of 14 and 15 followed by the nucleophilic attack of NH$_3$ and cyclization afford products 13. It is a 6C5CR, since hydrazine is a 2-centered reactant.
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Rahmati and co-workers introduced a reaction of o-benzenediamine, ethyl malonyl chloride, aromatic aldehydes, isocyanides, and water for the synthesis of benzodiazepines 19 using MgCl2 as a catalyst and CH2Cl2 as the solvent (Scheme 7) [18]. The formation of the amide through reaction of o-benzenediamine and ethyl malonyl chloride is followed...
by cyclization to afford seven-membered ring 20 under the catalysis by MgCl₂. Then, Knoevenagel condensation of seven-membered ring and aldehyde leads to α,β-unsaturated molecules 21, which undergo Michael-type addition with isocyanides to form 21 followed by hydrolysis which leads to compounds 22. The final isomerization of compounds 22 gives diazepine amides 19.

\[
\begin{align*}
\text{Ar} = & \text{Ph, 4-FC₆H₄, 4-ClC₆H₄, 4-MeC₆H₄, 2-ClC₆H₃, 2-HOC₆H₄,} \\
& \text{3-NO₂C₆H₄, 2,4-(MeO₂)C₆H₄, 4-HeOC₆H₄, 3-BrC₆H₄} \\
R = & \text{Cy, 2,6-Me₂C₆H₄, 4-MeC₆H₅,SOP₂C₆H₅}
\end{align*}
\]

19, 83–95%

Scheme 7. 5CR for benzodiazepine derivatives.

3. Type-II, Pseudo-5CRs of 2A + B + C + D

A schematic of a Type-II pseudo-5CRs involving 2A + B + C + D is shown in Scheme 8. Two molecules of component A are involved in the reaction process and are incorporated into the product.

Scheme 8. 5CRs of 2A + B + C + D.

Nikoofar and co-workers embedded aspartic acid-guanine ionic liquid on the hydroxylated nano silica face for making a novel bio-based core-shell organic–inorganic nano catalyst (Asp-Gua) IL@PEG-SiO₂, and employed it for the synthesis of tricarboxamide derivatives 23 using two equiv of aromatic amines and one equiv each of aromatic aldehydes, t-butyl isocyanide, and Meldrum’s acid (Scheme 9) [19]. The reaction starts with the Knoevenagel condensation of Meldrum’s acid and aldehydes to form α,β-unsaturated compounds 24. Michael-type addition of isocyanides to 24 followed by intermolecular nucleophilic attack lead to compounds 25. Amidation of 25 with aromatic amines and sequential isomerization produce tricarboxamides 23.

Rahmati and coworkers developed a method for the synthesis of malonamides 26 with two equiv of amine and one equiv each of Meldrum’s acid, aryldiene malononitrile, and isocyanide in CH₂Cl₂ at ambient temperature (Scheme 10) [20]. The synthesis involves the nucleophilic attack of isocyanides to aryldiene malononitriles followed by the nucleophilic attack of malonamides 23 and sequential isomerization produce tricarboxamides 26.
attack of malonamides 27 produced from reaction between a Meldrum’s acid and two molecules of amine to give the final products after tautomerization.

\[
2 \text{NH}_2 + \text{CHO} + \text{NC} + \text{OOC} \xrightarrow{\text{nano[(Asp-Gua)IL@PEG-SiO}_2]} \text{rt. 1-2 h} \rightarrow \text{solventfree}
\]

\[\text{Ar}^1 = \text{4-BrC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 3-\text{HOCC}_6\text{H}_4, 2-\text{NO}_2\text{C}_6\text{H}_4, 3-\text{NH}_25-\text{Me-Pyrazolyl} \]
\[\text{Ar}^2 = \text{2-ClC}_6\text{H}_4, 2-\text{HO-3-MeC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 2-\text{naphthyl, 2-pyrolyl, 3-indoyl} \]

\[23, 90-95\%
\]

Scheme 9. Pseudo-5CR for tricarboxamide derivatives.

\[2 \text{R}^1\text{NH}_2 + \text{OOC} + \text{R}^2\text{CN} + \text{NC} \xrightarrow{\text{CH}_2\text{Cl}_2} \text{rt. 0.5-2 h} \rightarrow \text{26, 48-83\%}
\]

\[\text{R}^1 = \text{Br, 4-MeC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 2-\text{HOCC}_6\text{H}_4 \]
\[\text{R}^2 = \text{H, Cl, R}^3 = \text{H, Me, MeO, Cl} \]
\[\text{R}^2 = \text{Cy, t-Bu} \]

Scheme 10. Pseudo-5CR for malonamides.
Rahmati and co-workers reported the synthesis of malonamides pseudopeptidic compounds 28 via the reaction of two equiv of amino esters, one equiv each of aromatic aldehydes, isocyanide, and Meldrum’s acid (Scheme 11) [21]. Unsubstituted and electron-deficient aryl aldehydes produce a mixture of two diastereomers such as 28a and 28b, while the electron-rich aryl aldehydes produce only one isomer 28c or 28d. The results could be explained by the order of reactants participation in the reaction. In the reaction of unsubstituted and electron-poor aryl aldehydes, isocyanide reacts with the arylidene Meldrum’s acid 29 and then, with amino esters to give 28b as a mixture of two diastereomers. In the reaction of electron-rich aryl aldehydes, amino esters react with arylidene Meldrum’s acid 29 before the isocyanide to give 28d as a single diastereomer due to the chirality effect of the amino esters.

Scheme 11. Pseudo-5CR for malonamide pseudopeptidic compounds.

Rahmati and Googol reported a synthesis of dialkyl 2-(1-(alkylamino)-1,3-dioxo-3-phenylpropan-2-yl)malonates 30 using two equiv of alcohols, one equiv each of aryl glyoxals, isocyanides and Meldrum’s acid (Scheme 12) [22]. The synthesis involves Knoevenagel condensation of 2-oxo-2-phenyl acetaldehydes and Meldrum’s acid to give 31, followed by Michael-type addition of isocyanides and cyclization to form aminofurans 32. Further
reaction of 32 with two equiv of alcohols then afforded products 30 after tautomerization. The products could be used as low molecular weight supramolecular organogelators.

Scheme 12. Pseudo-5CR for malonates.

Balalaie and co-workers developed a reaction of two equiv of cyclic ketones and one equiv each of hydrazine hydrate, trimethylsilyl azide, and isocyanides α-hydrazino tetrazoles for the synthesis of 33 (Scheme 13) [23]. The reaction process starts with the condensation of two molecules of the cyclic ketones with hydrazine hydrate to form dicycloalkyldimines 34. Nucleophilic additions of isocyanides and then trimethylsilyl azide to 34 give intermediates 35 which undergo dipolar cyclization to provide products 33.

Ghahremanzadeh and co-workers reported a reaction of two equiv of 1H-indene-1,3(2H)-dione and one equiv each of o-benzenediamines, 1H-indene-1,2,3-trione and anilines under the catalysis of p-TSA to give 5-phenyldihydrospiro-(diindenopyridine-indenoquinoxaline) diones 36 (Scheme 14) [24]. The reaction starts with the iminization-aromatization reaction of 1H-indene-1,2,3-trione with o-benzenediamine to afford 37, followed by Knoevenagel condensation with 1H-indene-1,3(2H)-dione to form 38, and then Michael-type addition with a second 1H-indene-1,3(2H)-dione to produce intermediates 39. Finally, the reaction of 39 with anilines followed by cyclization and tautomerization afford products 36.

Wang and co-workers developed a reaction for the synthesis of highly functionalized piperidines 40 using two equiv of aromatic aldehydes, and one equiv each of Meldrum’s acid, substituted β-nitrostyrenes and ammonium acetate under basic conditions (Scheme 15) [25]. First, the Michael addition of Meldrum’s acid to substituted nitrostyrenes followed by nitro-Mannich nucleophilic addition on intermediate arylimine gives amines 41. Second aromatic aldehydes react with amines 41 followed by intramolecular nitro-Mannich nucleophilic addition to give cyclic amines 40.
Balalaie and co-workers developed a reaction of two equiv of cyclic ketones and one equiv each of hydrazine hydrate, trimethylsilyl azide, and isocyanides for the synthesis of \( \alpha \)-hydrazino tetrazoles for the synthesis of 33 (Scheme 13) [23]. The reaction process starts with the condensation of two molecules of the cyclic ketones with hydrazine hydrate to form dicycloalkyldiimines 34. Nucleophilic additions of isocyanides and then trimethylsilyl azide to 34 give intermediates 35 which undergo dipolar cyclization to provide products 33.

Scheme 13. Pseudo-5CR for the synthesis of \( \alpha \)-hydrazino tetrazoles.

Ghahremanzadeh and co-workers reported a reaction of two equiv of 1H-indene-1,3(2H)-dione and one equiv each of \( o \)-benzenediamines, 1H-indene-1,2,3-trione and anilines under the catalysis of \( p \)-TSA to give 5-phenyldihydrospiro(diindenopyridine-indenoquinoxaline) diones 36 (Scheme 14) [24]. The reaction starts with the iminization-aromatization reaction of 1H-indene-1,2,3-trione with \( o \)-benzenediamine to afford 37, followed by Knoevenagel condensation with 1H-indene-1,3(2H)-dione to form 38, and then Michael-type addition with a second 1H-indene-1,3(2H)-dione to produce intermediates 39. Finally, the reaction of 39 with anilines followed by cyclization and tautomerization afford products 36.

Scheme 14. Pseudo-5CR for 5-phenyldihydrospiro(diindenopyridine-indenoquinoxaline) diones.

Wang and co-workers developed a reaction for the synthesis of highly functionalized piperidines 40 using two equiv of aromatic aldehydes, and one equiv each of Meldrum’s acid, substituted \( \beta \)-nitrostyrenes and ammonium acetate under basic conditions (Scheme 15) [25]. First, the Michael addition of Meldrum’s acid to substituted nitrostyrenes followed by nitro-Mannich nucleophilic addition on intermediate arylimine gives amines 41. Second aromatic aldehydes react with amines 41 followed by intramolecular nitro-Mannich nucleophilic addition to give cyclic amines 40.

Scheme 15. Pseudo-5CR for the synthesis of highly functionalized piperidines.

Ramírez and co-workers developed a reaction using two equiv of formaldehyde and one equiv each of primary amine, water and isocyanide for the synthesis of \( N,N \)’-substituted 4-imidazolidinones 42 (Scheme 16) [26]. Trifluoroethanol (TFE) was used as both a solvent and a reagent. Imines generated in situ from formaldehyde and amines react with

Scheme 16. Pseudo-5CR for the synthesis of \( N,N \)’-substituted 4-imidazolidinones.
Scheme 14. Pseudo-5CR for 5-phenyldihydrospiro(diindenopyridine-indenoquinoxaline) diones.

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Scheme 15. Pseudo-5CR for the synthesis of highly functionalized piperidines.

Ramírez and co-workers developed a reaction using two equiv of formaldehyde and one equiv each of primary amine, water and isocyanide for the synthesis of N,N'-substituted 4-imidazolidinones 42 (Scheme 16) [26]. Trifluoroethanol (TFE) was used as both a solvent and a reagent. Imines generated in situ from formaldehyde and amines react with isocyanides and TFE to give amines which then react with second formaldehyde followed by an intramolecular nucleophilic attack and addition of water to form hemiorthoamides 44. Releasing of TFE from 44 gives 4-imidazolidinone 42.

Scheme 16. Pseudo-5CR for 4-imidazolidinones.
Wang and co-workers reported a method for the diastereoselective synthesis of poly-substituted 2-piperidinones 45 using two equiv of aromatic aldehydes and one equiv each of dialkyl malonates, nitromethane and ammonium acetate (Scheme 17) [27]. The reaction involves Michael addition of the nitromethane to the arylidene malonates 46, followed by nucleophilic addition to arylimines generated from the reaction of aromatic aldehydes and ammonium acetate to form intermediates 47 which undergo lactamization to give trans isomer cyclic piperidinones 45 (racemic) after eliminating the alcohol.

\[
\begin{align*}
\text{CHO} & \quad \text{R}^1\quad \text{R}^2 \quad \text{O} - \quad \text{CH}_3\quad \text{NO}_2 \quad \text{NH}_4\text{OAc} \\
\text{Piperidine} & \quad \text{MeOH or EtOH} \\
& \quad 85^\circ\text{C, 32h} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 &= \text{Ph}, 4-\text{MeC}_{6}\text{H}_4, 4-\text{FC}_{6}\text{H}_4, 4-\text{BrC}_{6}\text{H}_4, 4-[(\text{CH}_3)_2\text{N}]\text{C}_{6}\text{H}_4, \\
&\quad 3-\text{PhOC}_{6}\text{H}_4, 3-\text{C}_{6}\text{H}_5\text{O}-4-\text{FC}_{6}\text{H}_4, 3-\text{Thienyl}, 4-\text{Pyridinyl}, 3-\text{ClC}_{6}\text{H}_4, \\
&\quad 3-\text{MeOC}_{6}\text{H}_4, 3,4-\text{(MeO)}_2\text{C}_{6}\text{H}_4, 4-(\text{Pr})\text{C}_{6}\text{H}_4, 3-\text{EtO}-4-\text{MeO}_{2}\text{C}_{6}\text{H}_4, \\
&\quad 4-\text{MeOC}_{6}\text{H}_4, 4-\text{ClC}_{6}\text{H}_4, 1-\text{Naphthalenyl}, 2-\text{ClC}_{6}\text{H}_4, 2-\text{MeC}_{6}\text{H}_4
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \quad \text{R}^1 \quad \text{R}^2 \quad \text{O} - \quad \text{H}_2\text{C}-\text{NO}_2 \\
\text{H}^- & \quad \text{B}^- \\
\text{R}^2 &= \text{Me, Et}
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2\text{OAc} & \quad \text{NH} \\
\text{R}^1 & \quad \text{R}^2 \quad \text{O} - \quad \text{NH}_2 \\
\text{R}^2 & \quad \text{R}^1 \\
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \quad \text{R}^1\quad \text{R}^2 \quad \text{O} - \quad \text{O} - \quad \text{NH} \\
\text{R}^2 & \quad \text{R}^1
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \quad \text{R}^1\quad \text{R}^2 \quad \text{O} - \quad \text{O} - \quad \text{NH} \\
\text{R}^2 & \quad \text{R}^1
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \quad \text{R}^1\quad \text{R}^2 \quad \text{O} - \quad \text{O} - \quad \text{NH} \\
\text{R}^2 & \quad \text{R}^1
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \quad \text{R}^1\quad \text{R}^2 \quad \text{O} - \quad \text{O} - \quad \text{NH} \\
\text{R}^2 & \quad \text{R}^1
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \quad \text{R}^1\quad \text{R}^2 \quad \text{O} - \quad \text{O} - \quad \text{NH} \\
\text{R}^2 & \quad \text{R}^1
\end{align*}
\]

**Scheme 17.** Pseudo-5CR for polysubstituted 2-piperidinones.

Bodaghifard and co-workers reported a method for the synthesis of substituted 4H-thiopyrans 48 involving two equiv of malononitrile and one equiv each of aldehydes, carbon disulfide and primary amines under the catalysis of Et$_3$N (Scheme 18) [28]. The reaction involves the Knoevenagel reaction of aldehydes and malononitrile followed by Michael addition to form 49. Nucleophilic attack on 49 by amidodithioic acids generated from the reaction of amines and carbon disulfide followed by H-transfer and carbon–sulfur bond cleavage gives isothiocyanates 50. H-shift of 50 and cyclization followed by another H-shift give substituted 4H-thiopyrans 48. This reaction involves five components, but no fragment from the primary amines remains in the products, so primary amines are used as a reagent, not a reactant.

Vereshchagin and co-workers developed a reaction using two equiv of aryl aldehydes and one equiv each of dialkylmalonates, malononitrile or alkyl cyanoacetate, and ammonium acetate or ammonia for the synthesis of 2-piperidinone derivatives 51 or 52 (Scheme 19) [29]. The reaction involves Knoevenagel condensation of aryl aldehydes with malononitrile or alkyl cyanoacetate followed by Michael addition of dialkylmalonates to afford intermediates 53. Then, Mannich-type condensation of 53, aryl aldehydes and ammonium acetate followed by lactamization afford the corresponding 2-piperidinone derivatives 51 or 52.
intermediates followed by lactamization afford the corresponding 2-piperidinone derivatives. The reaction involves Knoevenagel condensation of aryl aldehydes with bromides, malononitrile and isocyanides at ambient temperature in absolute ethanol using two equiv of dialkyl acetylenedicarboxylates and one equiv each of phenacyl bromides, which are generated in situ from the reaction of the isocyanides and the dialkyl acetylenedicarboxylates. The resulting adducts undergo cyclization followed by conjugate addition to afford the products.

The Adib lab developed a method for the synthesis of 3-oxacyclobuta[cd]pentalenes 54 using two equiv of dialkyl acetylenedicarboxylates and one equiv each of phenacyl bromides, malononitrile and isocyanides at ambient temperature in absolute ethanol (Scheme 20) [30]. The phenacyl bromides undergo nucleophilic substitution with malononitrile in the presence of Et$_3$N to form malononitriles 55 which are generated in situ from the reaction of the isocyanides and the dialkyl acetylenedicarboxylates. The resulting adducts 57 undergo cyclization followed by conjugate addition to afford the products 54.

Mohammadpoor-Baltork and co-workers reported a method for the synthesis of biquinoline 58 employing two equiv of methyl propiolate and one equiv each of terephthalaldehydes, naphthalen-1-amine, and $p$-toluidine using reusable Fe$_2$O$_4$-TDSN-Bi(III) catalyst (Bi(III) immobilized on triazine dendrimer-stabilized magnetic nanoparticles) under microwave heating and solvent-free conditions (Scheme 21) [31]. The synthesis may involve the condensation of terephthalaldehydes and $p$-toluidine followed by Diels–Alder reaction and aromatization to form 59. The reaction of 59 and naphthalen-1-amine followed by another Diels–Alder reaction affords biquinoline 58 after aromatization. It is a 6CSCR, since terephthalaldehydes is a 2-centered reactant.
Mohammadpoor-Baltork and co-workers reported a method for the synthesis of biquinoline employing two equiv of methyl propiolate and one equiv each of terephthaldialdehyde, naphthalen-1-amine, and p-toluidine using reusable Fe$_3$O$_4$-TDSN-Bi(III) catalyst (Bi(III) immobilized on triazine dendrimer-stabilized magnetic nanoparticles) under microwave heating and solvent-free conditions (Scheme 21) [31]. The synthesis may involve the condensation of terephthaldialdehyde and p-toluidine followed by Diels–Alder reaction and aromatization to form 59. The reaction of 59 and naphthalen-1-amine followed by another Diels–Alder reaction affords biquinoline 58 after aromatization. It is a 6C5CR, since terephthaldialdehyde is a 2-centered reactant.

Mohammadpoor-Baltork and co-workers developed a method for the synthesis of aminonaphthoquinones 60 by reacting two equiv of 2-hydroxynaphthalene-1,4-dione with one equiv each of terephthaldialdehyde, alkylamines and arylamines using Fe$_3$O$_4$-TDSN-Bi(III) as a reusable catalyst (Scheme 22) [32]. The reaction process involves activation of terephthaldialdehydes with Fe$_3$O$_4$-DSN-Bi(III) followed by condensation with amines and addition of 2-hydroxynaphthalene-1,4-dione to give products 61 after tautomerization and releasing of catalyst Fe$_3$O$_4$-DSN-Bi(III). It is a 6C5CR, since terephthaldialdehyde is a 2-centered reactant.
reaction classify as a 6C5CR. As shown in Figure 2, Type-III reactions are the most popular 5CRs. Product structures could be symmetrical, especially from the 6C5CRs.

Two molecules each of components A and B are involved in the reaction with one equiv of 2,5-dihydroxy-1,4-benzoquinone (Scheme 24) [33]. The amide bands in PEtOx catalyze the Knoevenagel condensation of 1,3-cyclohexanediones and benzaldehydes to afford intermediates 63 which then undergo double Michael additions followed by cyclization and dehydration to give products 62. The magnetic nanocatalyst could be easily separated by an external magnet and reused for five runs without significant loss of activity.

Scheme 22. 6C5CR for bisaminonaphthoquinones.

4. Type-III, Pseudo-5CRs of 2A + 2B + C

A schematic of a Type-III pseudo-5CRs involving 2A + 2B + C is shown in Scheme 23. Two molecules each of components A and B are involved in the reaction with one equiv of compound C. In many cases, component C is a two-centered reactant which makes the reaction classify as a 6C5CR. As shown in Figure 2, Type-III reactions are the most popular 5CRs. Product structures could be symmetrical, especially from the 6C5CRs.

The Moradi group employed immobilized poly(2-ethyl-2-oxazoline) (PEtOx) nanoparticles (Fe₃O₄@SiO₂/PEtOx) for the synthesis of tetrahydrochromeno[2,3-b] xanthene tetraones 62 using two equiv each of arylaldehydes and 1,3-cyclohexanones and one equiv of 2,5-dihydroxy-1,4-benzoquinone (Scheme 24) [33]. The amide bands in PEtOx catalyze the Knoevenagel condensation of 1,3-cyclohexanones and benzaldehydes to afford intermediates 63 which then undergo double Michael additions followed by cyclization and dehydration to give products 62. The magnetic nanocatal-
lyst could be easily separated by an external magnet and reused for five runs without significant loss of activity.

![Diagram](image_url)

Scheme 24. Pseudo-5CR for tetrahydrochromeno[2,3-b]xanthene tetraones.

Pyrazoles, such as bis(1H-pyrazol-5-ols), are important fragments in drug molecules. A common method for the synthesis of 4,4′-(arylmethylene)bis(1H-pyrazol-5-ol) derivatives is to conduct a pseudo-5CR of two equiv each of phenylhydrazines and ethyl acetoacetate with one equiv of aromatic aldehydes through a cycloaddition-Knoevenagel-Michael reaction sequence. In recent years, the synthesis of bis(1H-pyrazol-5-ols) has been accomplished using different catalysts, such as nanocatalyst Pd(0)-guanidine@MCM-41 [34], guanidine hydrochloride [35], α-Casein [36], ZnAl₂O₄ nanoparticle [37], La(OTf)₂-grafted-GO (graphene oxide) [38], amino acid-based ionic liquids (AAILs) [39], and CuCr₂O₄ nanoparticle [40]. Catalyst-free conditions have also been reported [41].

Shown in Scheme 25 is an example for the synthesis of 4,4′-(arylmethylene)-bis(1H-pyrazol-5-ols) 64 through a pseudo-5CR. The reaction reported by the Filian group employed two equiv each of phenylhydrazines and ethyl acetoacetate and one equiv of aromatic aldehydes in the presence of Pd(0)-guanidine@MCM-41 as a nanocatalyst [34]. The carbonyl groups of ethyl acetoacetate are activated by the Pd-nanocatalyst for the reaction with phenyl hydrazine to afford pyrazolone 65 which then undergoes Knoevenagel-type reaction to give intermediate 66 for Michael addition with pyrazolone tautomer to afford bis(1H-pyrazol-5-ols) 64.
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Scheme 25. Pseudo-5CR for 4,4′-(arylmethylene)bis(1H-pyrazol-5-ol) derivatives.

Safaei-Ghomi and coworkers developed a method for the synthesis of bis(pyrazol-5-ol) derivatives 67 using two equiv each of arylhydrazine, acetylenedicarboxylates and one equiv of aromatic aldehydes under the catalysis of CeO$_2$ nanoparticles (Scheme 26) [42]. Nucleophilic reaction of arylhydrazine with acetylenedicarboxylates followed by cyclization form pyrazolone intermediate 68. Knoevenagel condensation of 68 and aromatic aldehydes followed by Michael addition with 68 afford bis(pyrazol-5-ol) derivatives 67. The Xu group conducted a similar reaction using Dabco-base ionic liquid as a catalyst [43].

Mohammadpoor-Baltork and co-workers extended the 2A + B + C + D type pseudo-5CR shown in Scheme 21 to a 2A + 2B + C type by using diamines (Scheme 27A) or dialdehydes (Scheme 27B) as two-centered reactants in the synthesis of symmetric bisquinolines 69 and 70 [31]. It only took 15–20 min for accomplishing the reaction under microwave irradiation condition.

Heravi and coworkers developed a method for the synthesis of 5,5′-(arylmethylene)bis(4-hydroxythiazole-2(3H)-one) derivatives 71 by reacting one equiv of aryl aldehydes and two equiv each of monochloroacetic acid and ammonium thiocyanate in TFE/water (1:1) under ultrasound irradiation at room temperature (Scheme 28) [44]. In this reaction, the condensation between monochloroacetic acid and ammonium thiocyanate followed by hydrolysis and cyclization affords thiazolone 72. Knoevenagel condensation of 72 with aromatic aldehydes followed by Michael addition and tautomerization then affords final products 71.

The Hamidinasab group employed magnetic nanocatalyst NiFe$_2$O$_4$@TiO$_2$-DEA-OSO$_3$H in the synthesis of bis-1H-indazolo[1,2-b]phthalazinetriones 73a and 73b through a reaction of two equiv each of dimedone and phthalhydrazide and one equiv of diarylaldheydes (Scheme 29) [45]. The reaction process involves acidic nanocatalyst-promoted Knoevenagel condensation of dialdehydes and dimedones followed by Michael-type addition with phthalhydrazide to give intermediates 74. Cyclization of 74 and tautomeration gives products 73.
Scheme 25. Pseudo-5CR for 4,4′-(arylmethylene)bis(1H-pyrazol-5-ol) derivatives. Safaei-Ghomi and coworkers developed a method for the synthesis of bis(pyrazol-5-ol) derivatives using two equiv each of arylhydrazine, acetylenedicarboxylates and one equiv of aromatic aldehydes under the catalysis of CeO$_2$ nanoparticles (Scheme 26) [42]. Nucleophilic reaction of arylhydrazine with acetylenedicarboxylates followed by cyclization form pyrazolone intermediate 68. Knoevenagel condensation of 68 and aromatic aldehydes followed by Michael addition with 68 afford bis(pyrazol-5-ol) derivatives 67. The Xu group conducted a similar reaction using Dabco-base ionic liquid as a catalyst [43].

Scheme 26. Pseudo-5CR for the synthesis of bis(pyrazol-5-ol) derivatives.

Mohammadpoor-Baltork and co-workers extended the 2A + B + C + D type pseudo-5CR shown in Scheme 21 to a 2A + 2B + C type by using diamines (Scheme 27A) or dialdehydes (Scheme 27B) as two-centered reactants in the synthesis of symmetric bisquinolines 69 and 70 [31]. It only took 15–20 min for accomplishing the reaction under microwave irradiation condition.

Scheme 27. 6C5CR for symmetric bisquinolines. (A) Diamines involved reaction. (B) Dialdehydes involved reaction.

Heravi and coworkers developed a method for the synthesis of 5,5′-(arylmethylene)bis(4-hydroxythiazole-2(3H)-one) derivatives 71 by reacting one equiv of aryl aldehydes and two equiv each of monochloroacetic acid and ammonium thiocyanate in TFE/water (1:1) under ultrasound irradiation at room temperature (Scheme 28) [44]. In this reaction, the condensation between monochloroacetic acid and ammonium thiocyanate followed by hydrolysis and cyclization affords thiazolone 72. Knoevenagel condensation of 72 with aromatic aldehydes followed by Michael addition and tautomerization then affords final products 71.

Scheme 28. Pseudo-5CR for 5,5′-(arylmethylene)bis(4-hydroxythiazole-2(3H)-one) derivatives.

The Hamidinasab group employed magnetic nanocatalyst NiFe$_2$O$_4$@TiO$_2$-DEA-OSO$_3$H in the synthesis of bis-1H-indazolo[1,2-b]phthalazinetriones 73a and 73b through a reaction of two equiv each of dimedone and phthalhydrazide and one equiv of diarylaldehydes (Scheme 29) [45]. The reaction process involves acidic nanocatalyst-promoted Knoevenagel condensation of dialdehydes and dimedones followed by Michael-type addition with phthalhydrazide to give intermediates 74. Cyclization of 74 and tautomerization gives products 73.

Scheme 29. Pseudo-5CR for symmetric bisquinolines. (A) Diamines involved reaction. (B) Dialdehydes involved reaction.
Scheme 27. 6C5CR for symmetric bisquinolines. (A) Diamines involved reaction. (B) Dialdehydes involved reaction.

Heravi and coworkers developed a method for the synthesis of \(5,5'-(\text{arylmethylene})-\text{bis}(4\text{-hydroxythiazole-2(3H)}-)\) derivatives \(71\) by reacting one equiv of aryl aldehydes and two equiv each of monochloroacetic acid and ammonium thiocyanate in TFE/water (1:1) under ultrasound irradiation at room temperature (Scheme 28) [44]. In this reaction, the condensation between monochloroacetic acid and ammonium thiocyanate followed by hydrolysis and cyclization affords thiazolone \(72\). Knoevenagel condensation of \(72\) with aromatic aldehydes followed by Michael addition and tautomerization then affords final products \(71\).

Scheme 28. Pseudo-5CR for \(5,5'-(\text{arylmethylene})\)-bis(4-hydroxythiazole-2(3H)-one) derivatives.

The Mukhopadhyay group reported a method for the synthesis of highly-functionalized spiro[indole-3,2'-pyrrole] compounds \(75a\) using two equiv each of arylamines and isatins and one equiv of \(\beta\)-keto esters in the presence of wet picric acid (Scheme 30) [46]. The condensation of \(\beta\)-keto esters with isatins followed by condensation with arylamines give intermediates \(76\). The nucleophilic addition of \(76\) and intermediates \(77\) generated from condensation of arylamines and isatins affords syn products \(75\) via Si-facial attack in a wet picric acid-stabilized charge transfer complex transition state.

Scheme 29. Pseudo-5CR for bis-1H-indazolo[1,2-b]phthalazine-triones.
Scheme 29. Pseudo-5CR for bis-1H-indazolo[1,2-b]phthalazine-triones.

The Mukhopadhyay group reported a method for the synthesis of highly-functionalized spiro[indole-3,2′-pyrrole] compounds 75a using two equiv each of arylamines and isatins and one equiv of β-keto esters in the presence of wet picric acid (Scheme 30) [46].

The condensation of β-keto esters with isatins followed by condensation with arylamines give intermediates 76. The nucleophilic addition of 76 and intermediates 77 generated from condensation of arylamines and isatins affords syn-products 75 via Si-facial attack in a wet picric acid-stabilized charge transfer complex transition state.

Scheme 30. Pseudo-5CR for spiro[indole-3,2′-pyrrole] compounds.

The Lalitha group reported a method for the synthesis of novel bis(2-phenyl-2,3-dihydroquinazolin-4(1H)-one) derivatives 78 using two equiv each of isatoic anhydride and aromatic aldehydes and one equiv of p-phenylenediamine in glacial acetic acid under reflux conditions (Scheme 31) [47]. The synthesized products have been evaluated for antioxidant property and anticancer activity. The reaction process involves a nucleophilic attack of p-phenylenediamine on the carbonyl group of protonated isatoic anhydride followed by decarboxylation to afford intermediate 79. Double condensations of 79 with two aldehydes give imines for cyclization to afford products 78. It is a 6C5CR, since p-phenylenediamine is a 2-centered reactant. The same group modified the reaction by using terephthalaldehyde to replace p-phenylenediamine as a 2-centered reactant in the synthesis of 2,2′-(1,4-phenylene)bis(3-phenyl-2,3-dihydroquinazolin-4(1H)-one) derivatives 80 (Scheme 32) [47]. The Nikoofar group recently employed multi-layered nano [(Asp-Gua)IL@PEG-SiO2] catalyst for the synthesis of bis(2-phenyl-2,3-dihydroquinazolin-4(1H)-one) derivatives using p-phenylenediamine as a 2-centered reactant [19].
The Lalitha group reported a method for the synthesis of novel bis(2-phenyl-2,3-dihydroquinazolin-4(1H)-ones) 82 after dehydration. Two intramolecular nucleophilic additions of 82 lead to the formation of products 81. The same group applied this method for the synthesis of bis[spiro(quinazoline-oxindole)] derivatives 81 using two equiv each of isatoic anhydride and isatins and one equiv of diamines under the catalysis of alum (KAl(SO₄)₂·12H₂O) (Scheme 33) [48]. The condensation of two isatoic anhydride with ethylenediamine followed by second condensation with isatins give iminoisatins 82 after dehydration. Two intramolecular nucleophilic additions of 82 lead to the formation of products 81.

The Mohammadi group developed a 6C5CR for the synthesis of novel bis[spiro (quinazoline-oxindole)] derivatives 81 using two equiv each of isatoic anhydride and isatins and one equiv of diamines under the catalysis of alum (KAl(SO₄)₂·12H₂O) (Scheme 33) [48]. The condensation of two isatoic anhydride with ethylenediamine followed by second condensation with isatins give iminoisatins 82 after dehydration. Two intramolecular nucleophilic additions of 82 lead to the formation of products 81. The same group applied this method for the synthesis of bis(quinazolinon-4(1H)-one) derivatives 83 by replacing isatins with orthoesters (Scheme 34) [49].
Mohammadpoor-Baltork and co-workers extended the 2A + B + C + D pseudo-5CR shown in Scheme 22 to a 2A + 2B + C pseudo-5CR by using diamines (Scheme 35A) or dialdehydes (Scheme 35B) as 2-centered reactants in the synthesis of symmetric bisaminonaphthoquinones 84 and 85 [32].

The Safaei-Ghomi group employed a nanocrystalline nano-CdZr_{4}(PO_{4})_{6} ceramic as a retrievable catalyst in the synthesis of bisthiazolidinone derivatives 86 through a reaction of two equiv each of aldehydes and thioglycolic acid with one equiv of 2-centered reactant ethylenediamine in toluene under reflux conditions (Scheme 36) [50]. The condensation of two aldehyde molecules with ethylenediamine followed by attacking of two thioglycolic acids gives 87. The final step of double cyclization of 87 affords bisthiazolidinone products 86.
The Safaei-Ghomi group employed a nanocrystalline nano-CdZr$_4$(PO$_4$)$_6$ ceramic as a catalyst for the synthesis of bis(quinazolinon-4(1H)-ones). Intermediates 89a and 89b could also be converted to products 89b through decarboxylation of the α-carboxylic esters.

\[
\text{CHO} + 2 \text{CHO} + 2 \text{H}_2\text{N}-\text{X}-\text{NH}_2 \xrightarrow{\text{Fe}_3\text{O}_4-\text{TDSN-Bi(III)}} \text{OH}_\text{R} \xrightarrow{\mu\text{w}, 85^\circ\text{C}, 15-25\text{ min}} \text{R, 84, 90-98\%}
\]

\[
\text{CHO} \xrightarrow{\mu\text{w}, 85^\circ\text{C}, 15-45\text{ min}} \text{OH}_\text{R} \xrightarrow{\mu\text{w}, 85^\circ\text{C}, 15-45\text{ min}} \text{R, 85, 85-98\%}
\]

**Scheme 35.** 6C5CR for symmetric bis-aminonaphthoquinones. (A) Diamines involved reaction. (B) Dialdehydes involved reaction.

**Scheme 36.** Pseudo 5-CR for the synthesis of bis-thiazolidinone derivatives.

The Olyaei group reported a solvent-free 6C5CR for the synthesis of bisBetti bases (bis(1-aminomethyl-2-hydroxy)naphthalenes) 88 using two equiv each of aryl aldehydes and heteroaryl amines and one equiv of 2,3-dihydroxynaphthalene under the catalysis of formic acid at 80 °C (Scheme 37) [51].

The Wang group developed an Et$_3$N-promoted reaction using two equiv each of aryl aldehydes and substituted cyanoacetates and one equiv of nitromethane to give densely functionalized cyclohexene β-aminoesters 89a and 89b (Scheme 38) [52]. The Knoevenagel condensation of aromatic aldehydes and nitromethane followed by the Michael addition of cyanoacetate anions affords intermediates 90. Next, Knoevenagel condensation of aromatic aldehydes and cyanoacetate followed by the Michael addition of 90 and intramolecular nucleophilic addition affords intermediates 91 and then, products 89a after tautomerization.
Intermediates 91 could also be converted to products 89b through decarboxylation of the α-carboxylic esters.

Scheme 37. 6C5CR for bis(1-aminomethyl-2-hydroxy)naphthalenes.

Prajapati and co-workers reported a microwave reaction using two equiv each of 1,3-indanediones and aromatic aldehydes and one equiv of ammonium acetate for the synthesis of novel spiroindenotetrahydropyridine derivatives 92 under catalyst- and solvent-free conditions involving cascade Knoevenagel/aza-Diels-Alder reactions (Scheme 39) [53]. The Knoevenagel condensation of indanedione and aldehydes gives dienophiles 93. Condensation of 93 with ammonium acetate followed by aza–Diels–Alder cycloaddition of dienophiles 93 affords products 92.

Scheme 38. Pseudo-5CR for functionalized cyclohexene β-aminoesters.
Scheme 38. Pseudo-5CR for functionalized cyclohexene β-aminoesters.

Prajapati and co-workers reported a microwave reaction using two equiv each of 1,3-indanediones and aromatic aldehydes and one equiv of ammonium acetate for the synthesis of novel spiroindenotetrahydropyridine derivatives 92 under catalyst- and solvent-free conditions involving cascade Knoevenagel/aza-Diels-Alder reactions (Scheme 39) [53]. The Knoevenagel condensation of indanedione and aldehydes gives dienophiles 93. Condensation of 93 with ammonium acetate followed by aza–Diels–Alder cycloaddition of dienophiles 93 affords products 92.

Scheme 39. Pseudo-5CR for spiroindenotetrahydropyridine derivatives.

Ghahremanzadeh and co-workers reported a reaction for diastereoselective synthesis of dispiro[furan-2,1′-naphthalene-4′,2″-furan]tetracarboxylates 94 using two equiv each of isocyanides and dialkyl acetylenedicarboxylates and one equiv of 2,3-dichloronaphthalene-1,4-dione in acetonitrile at room temperature (Scheme 40) [54]. The isocyanides react with dialkyl acetylenedicarboxylates to form 1:1 zwitterionic intermediates 95 for nucleophilic attack at both carbonyls of 2,3-dichloronaphthalene-1,4-dione to form the species for dipolar cyclization to give products 94.

Scheme 40. Pseudo-5CR for dispiro[furan-2,1′-naphthalene-4′,2″-furan]tetracarboxylates.

The Zhang group reported the first example of a double 1,3-dipolar cycloaddition of two nonstabilized azomethine ylides for the diastereoselective synthesis of polycyclic pyrrolidines 96 using two equiv each of aromatic aldehydes and N-substituted maleimides and one equiv of amino acids (Scheme 41) [55]. The first decarboxylative [3+2] cycloaddition affords pyrrolidine diastereomers 97 and 97′, which then react with aromatic aldehydes to generate a second 1,3-dipolar species for another [3+2] cycloaddition with maleimides to form pyrrolidine-containing tetracyclic compounds 96. The same group has previously reported another double 1,3-dipolar cycloaddition using amino esters instead of amino acids.

Scheme 41. Pseudo-5CR for polycyclic pyrrolidine compounds.

The Quiroga group also reported a reaction of amino esters in the synthesis of polycyclic pyrrolidines 98 (Scheme 42) [57].

Scheme 42. Pseudo-5CR for polycyclic pyrrolidine compounds.
acids [56]. The Quiroga group also reported a reaction of amino esters in the synthesis of polycyclic pyrrolidines 98 (Scheme 42) [57].

Scheme 41. Pseudo-5CR for polycyclic pyrrolidine compounds.

The Wu group developed an iodine-promoted reaction using two equiv each of phenylhydrazines and acetoacetate esters and one equiv of aryl methyl ketones for the synthesis of pyrazolone-oxepine-pyrazoles 99 (Scheme 43) [58]. Aryl methyl ketones are converted to 100 via iodination and Kornblum oxidation, while phenylhydrazines react with acetoacetate esters through dehydration condensation/aminolysis sequence to form intermediates 101. The condensation of 100 and 101 followed by Michael addition with another molecule of 101 forms 102. Iodination of 102 generates 103a or 103b followed by iodine-based oxidative coupling which affords products 99.

Scheme 42. Pseudo-5CR for the synthesis of pyrazolylpyrrolizine derivatives.
Scheme 42. Pseudo-5CR for the synthesis of pyrazolylpyrrolizine derivatives.

The Wu group developed an iodine-promoted reaction using two equiv each of phenylhydrazines and acetoacetate esters and one equiv of aryl methyl ketones for the synthesis of pyrazolone-oxepine-pyrazoles (Scheme 43) [58]. Aryl methyl ketones are converted to intermediates via iodination and Kornblum oxidation, while phenylhydrazines react with acetoacetate esters through dehydration condensation/aminolysis sequence to form intermediates. The condensation of and followed by Michael addition with another molecule of generates products 99.

Scheme 43. Pseudo-5CR for pyrazolone-oxepine-pyrazoles.

Piperidine is a privileged N-heterocyclic ring and its derivatives possess diverse pharmacological activities such as anticancer, antimicrobial, antioxidant, anti-inflammatory, and acetylcholinesterase inhibitory activities [59]. There are several papers on the synthesis of piperidine derivatives through the reaction of aromatic aldehydes, anilines, and β-keto esters under different conditions. Catalysts used for the reactions include acetic acid [60], ethylenediammonium diformate (EDDF) [61], nanostructured PbCr$_x$Fe$_{12-x}$O$_{19}$ [62], Fe$_3$O$_4$@TDSN-Bi(III) [63], anionic surfactants sodium dioctyl sulfosuccinate (SDOSS), and sodium dodecyl sulfate (SDS) [64].
The Abbas lab reported a silica sulfuric acid (SSA)-catalyzed reaction for the synthesis of highly functionalized piperidine compounds 104 using two equiv each of aldehydes and amines and one equiv of β-ketoesters (Scheme 44) [65]. The amines reacted with β-ketoesters and aldehydes to afford β-enaminoenes 105 and imines 106, respectively. Intermolecular Mannich reaction of 105 and 106 followed by condensation with another aldehyde affords intermediates 107. The tautomers 108 undergo intramolecular Mannich-type reaction followed by tautomerization to generate the corresponding intramolecular Mannich-type reaction, affording desired products 104.

Scheme 44. Pseudo-5CR for functionalized piperidines.

The Amrollahi lab reported a catalyst-free 6C5CR for the synthesis of symmetric carboxamide compounds 109 using two equiv each of alkyl isocyanides and Meldrum’s acids and one equiv of 2-centered reactant 4,4′-methylene- or 4,4′-oxydianiline (Scheme 45) [66]. Cycloaddition of isocyanides and alkylidene-substituted Meldrum’s acids followed by conjugate addition with dianilines gives intermediates 110. The elimination of acetone via electrocyclic ring opening of Meldrum’s acid moiety of 110 followed by double cyclization delivers desired products 109.
Van der Eycken’s group reported an aldehyde–alkyne–amine (A3)-coupling reaction for the synthesis of tertiary propargylic amines 111 by integrating two molecules each of aldehydes and alkynes and one molecule of amino esters under the catalysis of CuBr in toluene at 100 °C (Scheme 46) [67].

![Scheme 45. 6C5CR for the synthesis of carboxamide compounds.](image)

The Asghari lab reported an unexpected 6C5CR of two equiv each of acetylenic esters and alkyl isocyanides and one equiv of N,N'-diphenylthioparabanic acid amide to form γ-dispiroiminolactones 112 (Scheme 47) [68]. The reaction mechanism could involve the Michael-type reaction of isocyanides with dialkyl acetylenedicarboxylates to form reactive zwitterionic intermediates 113 which react with a carbonyl group of N,N'-diphenylthioparabanic acid amide to afford intermediates 114 for sequential cyclization to form γ-spiroiminolactones 115. Another carbonyl group of 115 reacts with zwitterionic intermediates 113 followed by a second cyclization to give γ-dispiroiminolactone products 112.

![Scheme 46. Pseudo 5-CR for tertiary propargylic amines.](image)
Van der Eycken’s group reported an aldehyde–alkyne–amine (A3)-coupling reaction for the synthesis of tertiary propargylic amines by integrating two molecules each of aldehydes and alkynes and one molecule of amino esters under the catalysis of CuBr in toluene at 100 °C (Scheme 46) [67].

Scheme 46. Pseudo 5-CR for tertiary propargylic amines.

The Asghari lab reported an unexpected 6C5CR of two equiv each of acetylenic esters and alkyl isocyanides and one equiv of \(N,N’\)-diphenyl thioparabanic acid amide to form \(\gamma\)-dispiroiminolactones (Scheme 47) [68]. The reaction mechanism could involve the Michael-type reaction of isocyanides with di alkyl acetylenedicarboxylates to form reactive zwitterionic intermediates which react with a carbonyl group of \(N,N’\)-diphenyl thioparabanic acid amide to afford intermediates for sequential cyclization to form \(\gamma\)-spiroiminolactones. Another carbonyl group of \(\gamma\)-dispiroiminolactones reacts with zwitterionic intermediates followed by a second cyclization to give \(\gamma\)-dispiroiminolactone products.

Scheme 47. 6C5CR for \(\gamma\)-dispiroiminolactones.

Mukhopadhyay and coworkers reported a catalyst-free reaction involving Knoevenagel/Michael-type addition/ring closure/cyclization/aromatization sequence for the synthesis of functionalized 1,6-naphthyridines using two equiv each of methyl ketones and malononitrile and one equiv of amines (Scheme 48) [69]. Knoevenagel condensation of aromatic ketones with malononitrile followed by Michael-type reaction and subsequent elimination of malononitrile afford intermediate 117. Malononitrile attacks 117 triggering the ring closure to form intermediates which then react with an amine to produce final products after aromatization. A similar process reported by the Thirumalai group using same components, but different molar ratio, gave similar products [70]. The biological evaluation results indicated that all the synthesized products possess in-vitro anti-inflammatory and antioxidant activities.
A schematic of a Type-IV pseudo-5CRs involving 3A + B + C is shown in Scheme 49. Reactions of three molecules of component A with one molecule each of B and C is very rare. The Ravikumar group reported a Rh-catalyzed reaction for the synthesis of aza-polycyclic aromatic hydrocarbons (N-PAHs) involving three molecules of component A with one molecule each of B and C is very rare. The Ravikumar group reported a Rh-catalyzed reaction for the synthesis of aza-polycyclic aromatic hydrocarbons (N-PAHs) through cascade triple C − H bond activations and multiple bond formations. The beginning of the reaction is the activation of [Cp*RhCl₂]₂ with AgOAc to form a rhodium catalyst which undergoes cyclometallation with E-((1-phenylethylidene)amino)oxy)sulfonic acid (HOSA) (Scheme 50) [71]. In this reaction, the aminating reagent HOSA acts as an in situ redox-neutral directing group for the construction of N-PAHs and Cp*Rh(I) is oxidized by Cu(II) to regenerate the catalyst.

Scheme 48. Pseudo-5CR for functionalized 1,6-naphthyridines.

Scheme 49. 5CRs of 3A + B + C.

Scheme 50. Pseudo-5CR for the synthesis of N-PAHs.
6. Type-V, Pseudo-5CRs of 3A + 2B

A schematic of a Type-V pseudo-5CRs involving 3A + 2B is shown in Scheme 51. Reactions of three molecules of A with two molecules of B is a very special MCR process. Rong and co-workers developed a reaction involving three equiv of isatins and two equiv of 3-oxo-N-arylbutanamides for the synthesis of pyrrolo[3,4-c]quinoline derivatives 126 (Scheme 52) [72]. In the reaction process, isatins first react with two molecules of acetacetanilides followed by the Knoevenagel condensation reaction with two molecules of isatins to form intermediates 127. Intramolecular annulation of 127 and hemiaminal ring opening followed by losing two molecules of water gives products 126.

Scheme 50. Pseudo-5CR for the synthesis of N-PAHs.

Scheme 51. 5CRs of 3A + 2B.
6. Type-V, Pseudo-5CRs of 3A + 2B

A schematic of a Type-V pseudo-5CRs involving 3A + 2B is shown in Scheme 51. Reactions of three molecules of A with two molecules of B is a very special MCR process. Rong and co-workers developed a reaction involving three equiv of isatins and two equiv of 3-oxo-N-arylbutanamide for the synthesis of pyrrolo[3,4-c]quinoline derivatives (Scheme 52) [72]. In the reaction process, isatins first react with two molecules of acetoacetanilides followed by the Knoevenagel condensation reaction with two molecules of isatins to form intermediates. Intramolecular annulation of and hemiaminal ring opening followed by losing two molecules of water gives products.

Scheme 51. 5CRs of 3A + 2B.

7. Type-VI, Pseudo-5CRs of 4A + B

A schematic of a Type-VI pseudo-5CRs involving 4A + B is shown in Scheme 53. MCRs of four molecules of A with one molecule of B is a very special reaction. We only found one example from the literature. Yan, Sun, and co-workers reported a method for the synthesis of unique polycyclic bicyclo[2.2.2]octane derivatives (Scheme 54) [73]. The reaction process involves a base-catalyzed cyclotrimerization of 1,3-indanedione to form active cyclic diene followed by the endo-selective Diels–Alder reaction with in situ generated 2-arylidene-1,3-indanediones to give bicyclo[2.2.2]octane derivatives as pure diastereomers.

Scheme 52. Pseudo-5CR for pyrroloquinoline derivatives.

Scheme 53. 5CRs of 4A + B.

8. Conclusions

Multicomponent reactions and associated one-pot and cascade reactions are increasing their popularity in the synthesis of complex molecules due to their inherent advantages on mass efficiency, simple operation, resource saving, and less waste disposal. Five-component reactions play a special role in MCRs. Compared to popular 3CRs and 4CRs, the number of reported 5CRs is much less and it is hard to develop new 5CRs due to competitive side reactions. However, 5CRs are more efficient in the construction of complex structures which have a large space for structural complexity and substitution diversity using commercially available starting materials such as amines/hydrazines, alcohols, azides, aldehydes/ketones, isonitriles, and carboxylic acids/esters.

Presented in this paper are six different kinds of 5CRs including five pseudo-5CRs which demonstrate the feasibility of 5CRs for the construction of complex molecules, especially polycyclic and heterocyclic molecules. The power of 5CRs could be enhanced by the following modifications: (1) performing step-wise reactions instead of addition of all components together to improve conversion and product selectivity; (2) conducting post-condensation reactions including consecutive MCRs, cyclization and cycloaddition reactions to access new structures with high diversity and complexity [7,8]; and (3) integrating 5CRs with other reactions, such as radical cascade reactions, photoredox-, transition metal- and organocatalysis, and electrochemical reactions. We have no doubt that 5CRs and other high-order MCRs will be unique tools in making complex molecules with potential biological and functional material applications.
Scheme 53. 5CRs of 4A + B.

Scheme 54. Pseudo-5CR for bicyclo[2.2.2]octane derivatives.

8. Conclusions

Multicomponent reactions and associated one-pot and cascade reactions are increasing their popularity in the synthesis of complex molecules due to their inherent advantages on mass efficiency, simple operation, resource saving, and less waste disposal. Five-component reactions play a special role in MCRs. Compared to popular 3CRs and 4CRs, the number of reported 5CRs is much less and it is hard to develop new 5CRs due to competitive side reactions. However, 5CRs are more efficient in the construction of complex structures which have a large space for structural complexity and substitution diversity using commercially available starting materials such as amines/hydrazines, alcohols, azides, aldehydes/ketones, isonitriles, and carboxylic acids/esters.

Presented in this paper are six different kinds of 5CRs including five pseudo-5CRs which demonstrate the feasibility of 5CRs for the construction of complex molecules, especially polycyclic and heterocyclic molecules. The power of 5CRs could be enhanced by the following modifications: (1) performing step-wise reactions instead of addition of all components together to improve conversion and product selectivity; (2) conducting post-condensation reactions including consecutive MCRs [74], cyclization and cycloaddition reactions to access new structures with high diversity and complexity [7,8]; and (3) integrating 5CRs with other reactions, such as radical cascade reactions, photoredox-, transition metal- and organocatalysis, and electrochemical reactions. We have no doubt that 5CRs and other high-order MCRs will be unique tools in making complex molecules with potential biological and functional material applications.
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References

1. Zhu, J.; Bienaymé, H. (Eds.) Multicomponent Reactions; Wiley-VCH: Weinheim, Germany, 2005.
2. Zhu, J.; Wang, Q.; Wang, M.-X. (Eds.) Multicomponent Reactions in Organic Synthesis; Wiley-VCH: Weinheim, Germany, 2015.
3. Herrera, R.P.; Marques-Lopez, E. (Eds.) Multicomponent Reactions—Concepts and Applications for Design and Synthesis; Wiley: Hoboken, NJ, USA, 2015.
4. Ameta, K.L.; Dandia, A. Multicomponent Reactions—Synthesis of Bioactive Heterocycles; CRC Press: London, UK, 2017.
5. Clarke, P.A.; Santos, S.; Martin, W.H.C. Combining pot, atom and step economy (PASE) in organic synthesis. Synthesis of tetrahydropyran-4-ones. Green Chem. 2007, 9, 438–440. [CrossRef]
6. Hayashi, Y. Pot economy and one-pot synthesis. Chem. Sci. 2016, 7, 866–880. [CrossRef]
7. Zhang, W.; Yi, W.-B. One-pot Organic Reactions. In Green Synthetic Processes and Procedures; Ballini, R., Ed.; RSC: Cambridge, UK, 2019; pp. 20–28.
8. Brauch, S.; van Berkel, S.S.; Westermann, B. Higher-order multicomponent reactions: Beyond four reactants. Chem. Soc. Rec. 2013, 42, 4948–4962. [CrossRef]
9. Nikbakht, A.; Ramezanpour, S.; Balalaie, S.; Rominger, F. Efficient and stereoselective synthesis of α-hydrazino tetrazoles through a pseudo five-component domino reaction. Tetrahedron 2015, 71, 6790–6795. [CrossRef]
10. Web of Science Search on “x-Component Reaction”. Available online: https://clarivate.libguides.com/webofscienceplatform/alldb (accessed on 6 February 2021).

11. Nenajdenko, V.G. Access to molecular complexity. Multicomponent reactions involving five or more components. Russ. Chem. Rev. 2020, 89, 1274–1336. [CrossRef]
12. Singh, H.; Sindhu, J.; Khurana, J.M.; Sharma, C.; Aneja, K.R. A facile eco-friendly one-pot five-component synthesis of novel 1,2,3-triazole-linked pentasubstituted 1,4-dihydropyridines and their biological and photophysical studies. Aust. J. Chem. 2013, 66, 1088–1096. [CrossRef]
13. Chavan, P.V.; Pandit, K.S.; Desai, U.V.; Wadgaonkar, P.P.; Nawale, L.; Bhangali, S.; Sarkar, D. Click-chemistry-based multicomponent condensation approach for design and synthesis of spirochromene-tethered 1,2,3-triazoles as potential antitubercular agents. Res. Chem. Intermed. 2017, 43, 5675–5690. [CrossRef]
14. Chavan, P.V.; Desai, U.V.; Wadgaonkar, P.P.; Tapase, S.R.; Kodam, K.M.; Choudhari, A.; Sarkar, D. Click chemistry based multicomponent approach in the synthesis of spirochromenocarbazole tethered 1,2,3-triazoles as potential anticancer agents. Bioorg. Chem. 2019, 85, 475–486. [CrossRef]
15. Zong, Y.; Lang, Y.; Yang, M.; Li, X.; Fan, X.; Wu, J. Synthesis of β-sulfonyl amides through a multicomponent reaction with the insertion of sulfur dioxide under visible light irradiation. Org. Lett. 2019, 21, 1935–1938. [CrossRef] [PubMed]
16. Govindaraju, S.; Tabassum, S.; Khan, R.R.; Pasha, M.A. Meglumine catalyzed one-pot green synthesis of novel 4,7-dihydro-1H-pyrazolo[3,4-b]pyridin-6-amines. Chin. Chem. Lett. 2017, 28, 437–441. [CrossRef]
17. Kumari, S.; Singh, H.; Khurana, J.M. An efficient green approach for the synthesis of novel triazolyl spirocyclic oxindole derivatives via one-pot five component protocol using DBU as catalyst in PEG-400. Tetrahedron Lett. 2016, 57, 3081–3085. [CrossRef]
18. Fan, S.M.; Rahmati, A.; Mirkhanii, V. One-pot isocyanide-based five-component reaction: Synthesis of highly functionalized N-cyclohexyl-2-(2,4-dioxo-2,3,4,5 tetrahydro-1H-benzo[b][1,5]diazepin-3-yl)-2-phenylacetamides. Synth. Commun. 2017, 47, 557–565. [CrossRef]
19. Nikooofar, K.; Shahriyari, F. Novel bio-based core-shell organic-inorganic nanohybrid from embedding aspartic acid-guanine ionic liquid on the hydroxylated nano silica surface (nano [Asp-Gua] IL@PEG-SiO2): A versatile nanoshell for the synthesis of bis(2,3-dihydroquinazolin-4(1H)-one) derivatives and tricarboxamides under green media. Polyhedron 2020, 179, 114361. [CrossRef]
20. Rahmati, A.; Kenarkoohi, T.; Ahmadizadeh, M. Synthesis of novel series of malonamides derivatives via a five-component reaction. Mol. Divers. 2013, 17, 619–625. [CrossRef] [PubMed]
21. Kenarkoohi, T.; Rahmati, A. Synthesis of malonamides pseudopeptidic compounds using a pseudo five-component reaction and evaluation of their gelation properties. J. Mol. Liq. 2019, 276, 714–720. [CrossRef]
22. Googol, F.; Rahmati, A. Synthesis of a new series of multifunctional dialkyl 2-(1-alkylamino)-1,3-dioxo-3-phenylpropan-2-yl)malonates as low molecular weight supramolecular organogelators using five-component reaction. Tetrahedron 2018, 74, 240–252. [CrossRef]
23. Nikbakht, A.; Ramezanpour, S.; Balalaie, S.; Rominger, F. Efficient and stereoselective synthesis of α-hydrazino tetrazoles through a pseudo five-component domino reaction. Tetrahedron 2015, 71, 6790–6795. [CrossRef]
24. Amanpour, T.; Bazgir, A.; Ardekanii, A.M.; Ghahremanzadeh, R. Pseudo five-component synthesis of 5-phenyldihydrospiro[4H-indeno[1,2,3-c]pyridine-7,8-dihydropyran-3,4,5-indenoquinoxaline-4,5-dione derivatives via a one-pot condensation reaction. Monatsh. Chem. 2014, 145, 627–632. [CrossRef]
25. Li, Y.; Xue, Z.; Ye, W.; Liu, J.; Yao, J.; Wang, C. One-pot multicomponent synthesis of highly functionalized piperidines from substituted β-nitrostyrenes, Meldrum’s acid, aromatic aldehydes, and ammonium acetate. ACS Comb. Sci. 2014, 16, 113–119. [CrossRef]

26. Attorresi, C.I.; Bonifazi, E.L.; Ramirez, J.A.; Gola, G.F. One-step synthesis of N,N’-substituted 4-imidazolidinones by an isocyanide-based pseudo-five-multicomponent reaction. Org. Biomol. Chem. 2018, 16, 8944–8949. [CrossRef]

27. Liu, H.; Sun, Q.; Zhou, Z.; Liu, J.; Yang, J.; Wang, C. One-pot synthesis of polysubstituted 2-piperidinones from aromatic aldehydes, nitromethane, ammonium acetate, and dialkyl malonates. Monatsh. Chem. 2013, 144, 1031–1041. [CrossRef]

28. Mobinikhaledi, A.; Bodaghifard, M.A.; Asadbegi, S. A novel four- and pseudo-five-component reaction: Unexpected efficient one-pot synthesis of 4H-thiopyran derivatives. Mol. Divers. 2016, 20, 461–468. [CrossRef]

29. Vereshchagin, A.N.; Karpenko, K.A.; Elinson, M.N.; Minaeva, A.P.; Goloveshkin, A.S.; Hansford, K.A.; Egorov, M.P. One-pot five-component high diastereoselective synthesis of polysubstituted 2-piperidinones from aromatic aldehydes, nitriles, dialkyl malonates and ammonium acetate. Tetrahedron Lett. 2014, 55, 4983–4986. [CrossRef]

30. Asadi, B.; Landarani-Isfahani, A.; Mohammadpoor-Baltork, I.; Tangestaninejad, S.; Moghadam, M.; Mirkhani, V.; Rudbari, H.A. Microwave-assisted, regioselective one-pot synthesis of quinolines and bis-quinolines catalyzed by Bi(III) immobilized on triazine dendrimer stabilized magnetic nanoparticles. Tetrahedron Lett. 2017, 58, 71–74. [CrossRef]

31. Asadi, B.; Mohammadpoor-Baltork, I.; Tangestaninejad, S.; Moghadam, M.; Mirkhani, V.; Landarani-Isfahani, A. Synthesis and characterization of Bi(III) immobilized on triazine dendrimer-stabilized magnetic nanoparticles: A reusable catalyst for the synthesis of aminonaphthoquinones and bis-aminonaphthoquinones. New J. Chem. 2016, 40, 6171–6184. [CrossRef]

32. Rahnamafar, R.; Moradi, L.; Khoobi, M. Synthesis of benzol[β]thiophene-triones and tetrahydrochromone[2,3-b]thiophene tetaenones via three- or pseudo-five-component reactions using Fe3O4@SiO2/PEtOx as a novel, magnetically recyclable, and eco-friendly nanocatalyst. J. Heterocycl. Chem. 2020, 57, 1825–1837. [CrossRef]

33. Filan, H.; Kohzadian, A.; Mohammadi, M.; Ghorbani-Choghamarani, A.; Karami, A. Pd(0)-guanidine@MCM-41: A very effective catalyst for rapid production of bis (pyrazoloyl)methanes. Appl. Organometal. Chem. 2020, 34, e5579. [CrossRef]

34. Noruzian, F.; Olyaei, A.; Hajinasiri, R.; Sadeghpour, M. Guanidine hydrochloride catalyzed efficient one-pot pseudo five-component synthesis of 4,4′-(arylmethylene)bis{1H-pyrazol-5-ols} in water. Synth. Commun. 2019, 49, 2717–2724. [CrossRef]

35. Filan, H.; Kohzadian, A.; Mohammadpoor-Baltork, I.; Tangestaninejad, S.; Moghadam, M.; Mirkhani, V.; Landarani-Isfahani, A. Synthesis and characterization of Bi(III) immobilized on triazine dendrimer-stabilized magnetic nanoparticles: A reusable catalyst for the synthesis of aminonaphthoquinones and bis-aminonaphthoquinones. New J. Chem. 2016, 40, 6171–6184. [CrossRef]

36. Asadi, B.; Mohammadpoor-Baltork, I.; Tangestaninejad, S.; Moghadam, M.; Mirkhani, V.; Landarani-Isfahani, A. Synthesis and characterization of Bi(III) immobilized on triazine dendrimer-stabilized magnetic nanoparticles: A reusable catalyst for the synthesis of aminonaphthoquinones and bis-aminonaphthoquinones. New J. Chem. 2016, 40, 6171–6184. [CrossRef]

37. Safaie-Ghomi, J.; Khojastehbakhht-Kooppaei, B.; Shahbazi-Alavi, H. Pseudo five-component process for the synthesis of 4,4′-(arylmethylene)bis{3-methyl-1H-pyrazol-5-ol} derivatives using ZnAl2O4 nanoparticles in aqueous media. RSC Adv. 2014, 4, 46106–46113. [CrossRef]

38. Soubani, S.; Zariﬁ, F.; Skibsted, J. Immobilized lanthanum(III) trflate on graphene oxide as a new multifunctional heterogeneous catalyst for the one-pot five-component synthesis of bis(pyrazoloyl)methanes. ACS Sustain. Chem. Eng. 2017, 5, 4598–4606. [CrossRef]

39. Khaled, N.G.; Mihankhah, T.; Gorjian, H.; Johan, M.R. Greener and facile synthesis of 4,4′-(arylmethylene)bis{3-methyl-1-phenyl-1H-pyrazol-5-ols} through a conventional heating procedure. Synth. Commun. 2020, 50, 3276–3286. [CrossRef]

40. Sufan, H.; Asgari-Keidarabi, M.; Khojastehbakhht-Kooppaei, B.; Shahbazi-Alavi, H. Multicomponent synthesis of C-tethered bispyrazol-5-ols using CeO2 nanoparticles as an efficient and green catalyst. Res. Chem. Intermed. 2016, 42, 827–837. [CrossRef]

41. Yang, C.; Liu, P.; Xu, D. A green and efficient one-pot pseudo-five-component reaction for synthesis of bis(pyrazol-5-ol) derivatives via tandem cyclocondensation-Knoevenagel-Michael reaction. ChemistrySelect 2017, 2, 1232–1236. [CrossRef]

42. Heravi, M.R.P.; Naghliou, M. Effective preparation of 5,5′-(arylmethylene)bis{4-hydroxystilbene-2(3H)-one} in an aqueous fluoroalcohol solvent system under ultrasound irradiation at room temperature. Chin. Chem. Lett. 2017, 28, 1039–1043. [CrossRef]

43. Hamidinasab, M.; Bodaghiard, M.A.; Mobinikhaledi, A. Synthesis of new, vital and pharmacologically important bis phthalazine-triones using an efficient magnetic nanocatalyst and their HF and NBO investigation. J. Mol. Struct. 2020, 1200, 127091. [CrossRef]

44. Sengupta, A.; Maity, S.; Mondal, A.; Rudra, S.; Mukhopadhyay, C. Pseudo five component reaction towards densely functionalized spiro[indole-3,2′-pyrrole] by picric acid, an efficient syn-diastereoselective catalyst: Insight into the diastereoselection on C(sp3)3-C(sp3)2 axial conformation. Org. Biomol. Chem. 2019, 17, 1254–1265. [CrossRef]

45. Sivaguru, P.; Parameswaran, K.; Lalitha, A. Antioxidant, anticancer and electrochemical redox properties of new bis(2,3-dihydroquinoxalin-4(1H)-one) derivatives. Mol. Divers. 2017, 21, 611–620. [CrossRef]
48. Mohammadi, A.A.; Taheri, S.; Askari, S.; Ahdenov, R. KAl(SO\textsubscript{4})\textsubscript{2}•12H\textsubscript{2}O (Alum): An efficient catalyst for the synthesis of novel bis[spiro(quinazoline-oxindole)] derivatives via one-pot pseudo five-component reactions. J. Heterocycl. Chem. 2015, 52, 1871–1875. [CrossRef]
49. Mohammadi, A.A.; Taheri, S.; Askari, S. One-pot pseudo five-component synthesis of some new bis(quinazolinon-4(1H)-one) derivatives. J. Heterocycl. Chem. 2017, 54, 484–488. [CrossRef]
50. Safaei-Ghomi, J.; Nazemzadeh, S.H.; Shahbazi-Alavi, H. Nano-CdZr\textsubscript{4}(PO\textsubscript{4})\textsubscript{6} as a reusable and robust catalyst for the synthesis of bis-thiazolidinones by a multicomponent reaction of aldehydes, ethylenediamine and thioglycolic acid. J. Sulfur Chem. 2017, 38, 195–205. [CrossRef]
51. Olyaei, A.; Abforushha, E.S.; Khoeiniha, R. Simple and efficient synthesis of novel bis-Betti bases via a one-pot pseudo-five-component reaction. Lett. Org. Chem. 2017, 14, 103–108. [CrossRef]
52. Yao, J.; Zhou, L.; Tan, C.; Wang, C. One-pot synthesis of densely functionalized cyclic β-aminoesters containing four stereocenters, based on a Et\textsubscript{3}N N-promoted pseudo five-component reaction. Mol. Divers. 2015, 19, 43–53. [CrossRef]
53. Bhuyan, D.; Sarmah, M.M.; Dommaraju, Y.; Prajapati, D. Microwave-promoted efficient synthesis of spiroindenotetrahydropyridine derivatives via a catalyst- and solvent-free pseudo one-pot five-component tandem Knoevenagel/aza-Diels–Alder reaction. Tetrahedron Lett. 2014, 55, 5133–5136. [CrossRef]
54. Sadabad, H.R.; Bazgir, A.; Eskandari, M.; Ghahremanzadeh, R. Pseudo five-component reaction of isocyanides, dialkyl acetylenedicarboxylates, and 2,3-dichloronaphthalene-1,4-dione: A highly diastereoselective synthesis of novel dispiro[furan-2,1'-naphthalene-4',2'-furanyl] functionalized monomers. Monatsh. Chem. 2014, 145, 1851–1855. [CrossRef]
55. Zhang, X.; Qiu, W.; Evans, J.; Kaur, M.; Jasinski, J.P.; Zhang, W. Double 1,3-dipolar cycloadditions of two nonstabilized azomethine ylides for polycyclic pyrrolidines. Org. Lett. 2019, 21, 2176–2179. [CrossRef] [PubMed]
56. Lu, Q.; Song, G.; Jasinski, J.P.; Keeley, A.C.; Zhang, W. One-pot double [3+2] cycloaddition for diastereoselective synthesis of tetracyclic pyrrolidine compounds. Green Chem. 2012, 14, 3010–3012. [CrossRef]
57. Quiroga, J.; Galvez, J.; Abonia, R.; Insuasty, B.; Ortiz, A.; Cobo, J.; Nogueras, M. Highly efficient and diastereoselective synthesis of new pyrazolylpyrrolizine and pyrazolylpyrrolidine derivatives by a three-component domino process. Molecules 2014, 19, 4284–4300. [CrossRef]
58. Zhao, P.; Wu, X.; Geng, X.; Wang, C.; Wu, Y-D.; Wu, A.-X. Iodine-promoted five-component reaction using fragment assembly strategy to construct dihydroxepines. Tetrahedron Lett. 2018, 59, 4323–4330. [CrossRef]
59. Kaur, G.; Devi, M.; Kumari, A.; Devi, R.; Banerjee, B. One-pot pseudo five component synthesis of biologically relevant 1,2,6-triaryl-4-arylamino-piperidine-3-ene-3-carboxylates: A decade update. ChemistrySelect 2018, 3, 9892–9910. [CrossRef]
60. Lashkari, M.; Maghsoudlou, M.T.; Hazeri, N.; Habibi-Khorassani, S.M.; Sadajikhah, S.S.; Doostmohamadi, R. Synthesis of highly functionalized piperidines via one-pot, five-component reactions in the presence of acetic acid solvent. Synth. Commun. 2013, 43, 635–644. [CrossRef]
61. Zarei, M.; Sadajikhah, S.S. Green and facile synthesis of dihydroprro2-ones and highly substituted piperidines using ethylenediammonium diformate (EDDF) as a reusable catalyst. Res. Chem. Intermed. 2016, 42, 7005–7016. [CrossRef]
62. Sobhani-Nasab, A.; Ziarati, A.; Rahimi-Nasrabadi, M.; Ganjali, M.R.; Badiei, A. Five-component domino synthesis of tetrahydropyridines using hexagonal PbCr\textsubscript{12}Fe\textsubscript{12}O\textsubscript{19} as efficient magnetic nanocatalyst. Res. Chem. Intermed. 2017, 43, 6155–6165. [CrossRef]
63. Asadi, B.; Landaran-Isfahani, A.; Mohammadpoor-Baltork, I.; Tantestaniejad, S.; Moghadam, M.; Mirkhai, V.; Rudbari, H.A. Diastereoselective synthesis of symmetrical and unsymmetrical tetrahydropyridines catalyzed by Bi(III) immobilized on triazine dendrimer stabilized magnetic nanoparticles. ACS Comb. Sci. 2017, 19, 356–364. [CrossRef] [PubMed]
64. Parikh, N.; Roy, S.R.; Seth, K.; Kumar, A.; Chakraborti, A.K. ‘On-Water’ multicomponent reaction for the diastereoselective synthesis of functionalized tetrahydropyridines and mechanistic insight. Synthesis 2016, 8, 547–556. [CrossRef]
65. Basyouni, W.M.; El-Bayouki, K.A.M.; Tohamy, W.M.; Abbas, S.Y. Silica sulfuric acid: An efficient, reusable, heterogeneous catalyst for the one-pot pseudo five-component reaction. J. Heterocycl. Chem. 2015, 52, 1871–1875. [CrossRef]
66. Asghari, S.; Qandalee, M.; Sarmadi, A.A. One-pot synthesis of γ-spiroimino lactones and γ-dispiroimino lactones using N,N'-disubstituted parabanic acid and thioparabanic acid derivatives. Mol. Divers. 2017, 21, 69–79. [CrossRef] [PubMed]
67. Mukhopadhyay, C.; Das, P.; Butler, R.J. An expeditious and efficient synthesis of highly functionalized [1,6]-naphthyridines under catalyst-free conditions in aqueous medium. Org. Lett. 2011, 13, 4664–4667. [CrossRef] [PubMed]
68. Lavanya, M.; Thirumalai, D.; Asharani, I.V.; Aravindan, P.G. Domino synthesis of functionalized 1,6-naphthyridines and their in vitro anti-inflammatory and anti-oxidant efficacies. RSC Adv. 2015, 5, 86330–86336. [CrossRef]
69. Biswal, P.; Banjare, S.K.; Pati, B.V.; Mohanty, S.R.; Ravikumar, P.C. Rhodium-catalyzed one-pot access to N-polycyclic aromatic hydrocarbons from aryl ketones through triple C-H bond activations. J. Org. Chem. 2021, 86, 1108–1117. [CrossRef]
72. Mao, K.; Dai, L.; Liu, Y.; Rong, L. An efficient five-component reaction for the synthesis of 4,4′-((2-oxoindoline-3,3-diy1)bis(methylene))bis(2-aryl-1H-pyrrolo[3,4-c]quinoline-1,3(2H)-dione) derivatives. *J. Heterocycl. Chem.* 2019, 56, 2111–2120. [CrossRef]

73. Cao, J.; Shi, R.-G.; Sun, J.; Liu, D.; Liu, R.; Xia, X.; Wang, Y.; Yan, C.-G. Domino reaction of aromatic aldehydes and 1,3-indanediones for construction of bicyclo[2.2.2]octanes and dibenzo[b,g]indenol[1′,2′:3,4]fluoreno[1,2-d]oxonines. *J. Org. Chem.* 2020, 85, 2168–2179. [CrossRef]

74. Zhi, S.; Ma, X.; Zhang, W. Consecutive multicomponent reactions for the synthesis of complex molecules. *Org. Biomol. Chem.* 2019, 17, 7632–7650. [CrossRef] [PubMed]