HETEROCYCLES, Vol. 94, No. 10, 2017, pp. 1819 - 1846. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 26th June, 2017, Accepted, 18th July, 2017, Published online, 27th July, 2017
DOI: 10.3987/REV-17-867

5-AMINOTETRAZOLE AS A BUILDING BLOCK FOR MULTICOMPONENT REACTIONS (REVIEW)

Anton V. Dolzhenko[a,b]*

[a] School of Pharmacy, Monash University Malaysia, Jalan Lagoon Selatan, Bandar Sunway, Selangor Darul Ehsan 47500, Malaysia, anton.dolzhenko@monash.edu

[b] School of Pharmacy, Curtin Health Innovation Research Institute, Faculty of Health Sciences, Curtin University, GPO Box U1987 Perth, Western Australia 6845, Australia, anton.dolzhenko@curtin.edu.au

Abstract – 5-Aminotetrazole is a useful building block in organic synthesis, including various multicomponent reactions (MCRs). In MCRs, 5-aminotetrazole usually plays a role of 1,3-binucleophilic reagent, but in some reactions, the only reactive centre is an exocyclic amino group of 5-aminotetrazole. This review systematises MCRs involving 5-aminotetrazole forming a background for further investigations in this area.

CONTENTS

1. INTRODUCTION
2. REACTIONS UTILISING 5-AMINOTETRAZOLE AS 1,3-BINUCLEOPHILE
   2.1. Mannich reaction of 5-aminotetrazole
   2.2. Biginelli reactions of 5-aminotetrazole, aldehydes, and β-ketoesters
   2.3. Biginelli reactions of 5-aminotetrazole, aldehydes, and amides of β-ketoacids
   2.4. Biginelli reactions of 5-aminotetrazole, aldehydes, and 1,3-diketones
   2.5. Biginelli reactions of 5-aminotetrazole, aldehydes, and acylpyruvates
   2.6. Three-component reactions of 5-aminotetrazole, aldehydes, and other enolizable ketones
   2.7. Three-component reactions involving 5-aminotetrazole and ketones
   2.8. Three-component reactions involving 5-aminotetrazole, DMF or its acetal, and enolizable ketones
   2.9. Four-component reactions of 5-aminotetrazole
3. REACTIONS INVOLVING ONLY EXOCYCLIC AMINO GROUP OF 5-AMINOTETRAZOLE

4. CONCLUSION

1. INTRODUCTION

Multicomponent reactions (MCRs) combine three or more building blocks in a single chemical operation to afford a product incorporating substantial parts of the starting materials involved. Some distinct advantages of MCRs include atom-economy, step-efficiency and, as a result, cost-effectiveness.[1] These characteristics together with the associated reduction of waste make MCRs a greener alternative to multistep syntheses.[2] The synthetic methods utilising MCRs are often selective and allow to generate complex organic molecules and achieve high diversity of products in one synthetic step.

Aminoazoles have been recognised as excellent building blocks for MCRs due to the presence of several nucleophilic centres of different reactivity.[3] Particularly, 5-aminopyrazoles and 5-aminotriazoles have been extensively explored as substrates for various MCRs. However, interest towards MCRs of their more nitrogen-rich counterpart 5-aminotetrazole arose only during the last decade and continues to grow since that time due to unique characteristics of tetrazoles.

The reactivity profile of 5-aminotetrazole in MCRs is quite distinct from that of 5-aminopyrazoles and 5-aminotriazoles. For example, unlike synthesis of pyrazolo- and triazolo-fused aminotriazines *via* MCRs of the corresponding aminoazoles, orthoesters, and cyanamide,[4] all attempts to involve 5-aminotetrazole in this reaction were unsuccessful. Sometimes, well established Biginelli reactions, efficiently performed with other aminoazoles, failed when 5-aminotetrazole was used as a substrate.[5] Different reaction pathways were observed for 5-aminotetrazole and other aminoazoles for some MCRs.[6] Therefore, as the first systematization of MCRs utilizing 5-aminotetrazole as a synthon, this review provides a platform for further studies in this field.

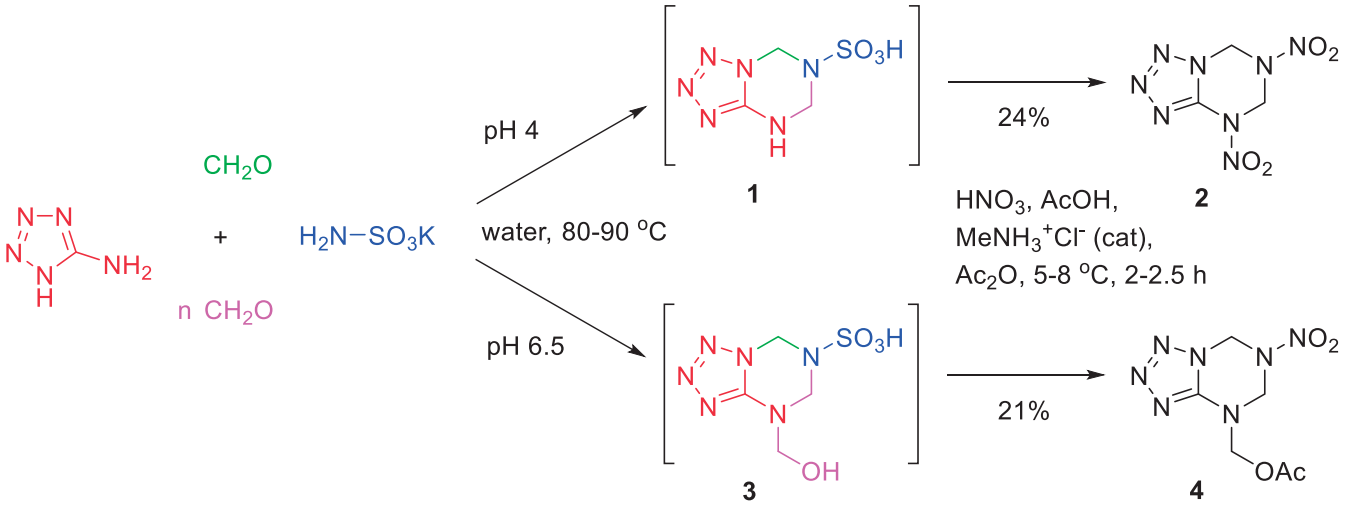
2. REACTIONS UTILISING 5-AMINOTETRAZOLE AS 1,3-BINUCLEOPHILE

Several nucleophilic centres are present in the 5-aminotetrazole molecule *viz*. an exocyclic amino group and tetrazole ring nitrogens. In MCRs, 5-aminotetrazole usually plays a role of 1,3-binucleophile with the exocyclic amino group and the nearby endocyclic nitrogen involved in the reaction. The tetrazole ring of 5-aminotetrazole can be easily deprotonated (pK_a = 5.95)[7] increasing nucleophilicity of the ring. Therefore, reactivity of the nucleophilic centres can be potentially modulated by manipulation of conditions, such as pH, thus providing control of the reaction selectivity.

2.1. Mannich reaction of 5-aminotetrazole

Many variations of Mannich reaction[8] have been developed for more than a century of its presence in the chemists' toolbox. Difficulties in involving 5-aminotetrazole in Mannich reaction have been known for a

long time[9] and it is not surprising that we could not find in the literature many examples of this reaction utilizing 5-aminotetrazole. However, a Mannich reaction variation involving 5-aminotetrazole with potassium sulphamate and formaldehyde was reported.[10] The reaction proceeded in pH dependent manner *via* AB2C or AB3C type of MCR to afford, after nitration of the tetrahydrotetrazolo[1,5-*a*][1,3,5]triazine based intermediates **1** and **3**, corresponding nitramines **2** and **4** (Scheme 1).

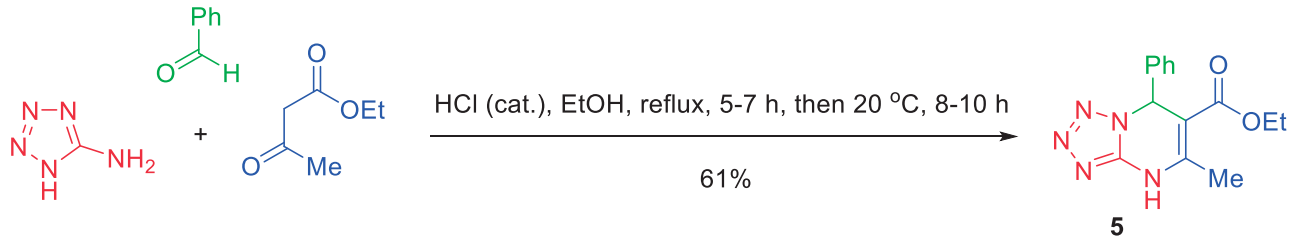


Scheme 1

2.2. Biginelli reactions of 5-aminotetrazole, aldehydes, and β-ketoesters

Biginelli reaction[11] was initially developed in 1891 as MCR of urea, aldehydes and β-ketoesters affording 3,4-dihydropyrimidin-2-ones. To date, a vast number of variations of this reaction have been developed using different equivalents for urea and β-ketoesters.[12] It was found that urea could be effectively substituted in the Biginelli reaction by 5-aminotetrazole. In 2003, Fedorova et al.[13] reported a Biginelli reaction using 5-aminotetrazole instead of classical urea and this reaction afforded ester **5** in 61% yield (Scheme 2). In another study, heating the same reagents at 130-170 °C without solvent for 20-30 min was found to give the product **5** in 71% yield.[14] A library of 40 compounds was prepared applying these conditions for alkyl (Me, Et, *i*-Pr, *i*-Bu, and *t*-Bu) acetoacetates and benzaldehydes in the reaction with 5-aminotetrazole. The yields depended on the substrates and varied from 31% to 80%.

Even higher yield (85%) was achieved when the reaction reported by Fedorova et al.[13] was carried out without solvent at 85 °C for 7 h in the presence of sulfamic acid (10 mol%) as a catalyst.[15] These conditions were successfully applied to perform MCRs of 5-aminotetrazole with methyl or ethyl acetoacetate and a variety of benzaldehydes. The yields in 23 reported examples were in the range of 77-89%.



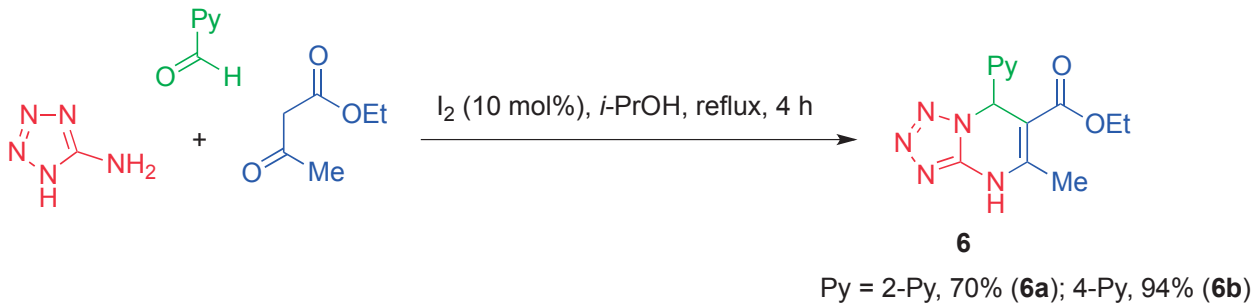
Scheme 2

Trifluoroacetic acid salts were also reported as efficient catalysts for this reaction under solventless conditions. Thus, heating 5-aminotetrazole, methyl or ethyl acetoacetate and aromatic aldehydes under microwave irradiation at 90 °C for 15-40 min in the presence of 50 mol% of pyridinium or diisopropylethylammonium salts of trifluoroacetic acid afforded 4,7-dihydrotetrazolo[1,5-*a*]pyrimidines in 68-98% (9 examples)[16] and 60-98% (12 examples)[17] yields, respectively.

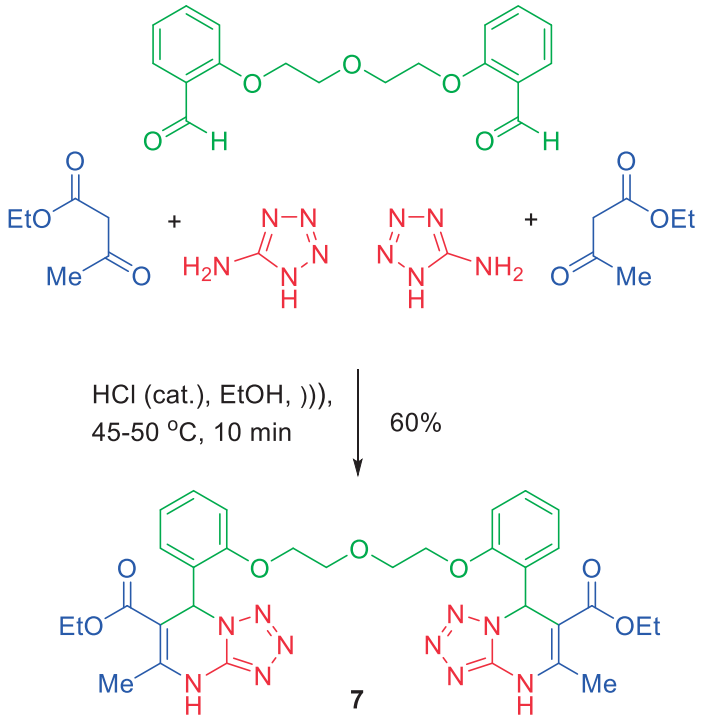
Another magnetically recyclable bionanocomposite catalytic system comprising of cellulose-based nanoparticles loaded with Fe_2O_3 and Ag was recently effectively applied to this reaction by Maleki et al.[18] Using this catalyst, they obtained ester **5** in 90% yield after 1 h heating in ethanol. Under identical conditions, this reaction was successfully performed using 5-aminotetrazole, methyl and ethyl esters of acetoacetic acid and various benzaldehydes to afford corresponding 7-aryl-5-methyl-4,7-dihydro-tetrazolo[1,5-*a*]pyrimidine-6-carboxylates in 85-92% yields (19 examples).

The synthesis of 4,7-dihydrotetrazolo[1,5-*a*]pyrimidines **6** with 2- and 4-pyridyl moieties at position 7 was effectively performed using catalysis by molecular iodine (Scheme 3).[19] The X-ray data of products **6** were reported and their nickel(II), copper(II), and zinc(II) complexes were also prepared and characterised. The copper(II) complexes of **6a** and **6b** demonstrated good anticancer activity, primarily against colon cancer HCT-15 cell line. It was found that these complexes could bind to DNA and induce apoptosis in cancer cells without significant toxicity in the same concentrations against non-cancerous cells.

The synthesis of podand **7**, possessing two 4,7-dihydrotetrazolo[1,5-*a*]pyrimidine rings at both sides, was performed using MCR of 5-aminotetrazole, ethyl acetoacetate and a corresponding podand with two terminal benzaldehyde moieties (Scheme 4).[20] The efficiency of the process was greatly improved by applying ultrasound irradiation. The yield increase to 60% and the reaction time was reduced to 10 min under ultrasound irradiation compared to 42% yield obtained in the same reaction under conventional heating for 32 h.



Scheme 3

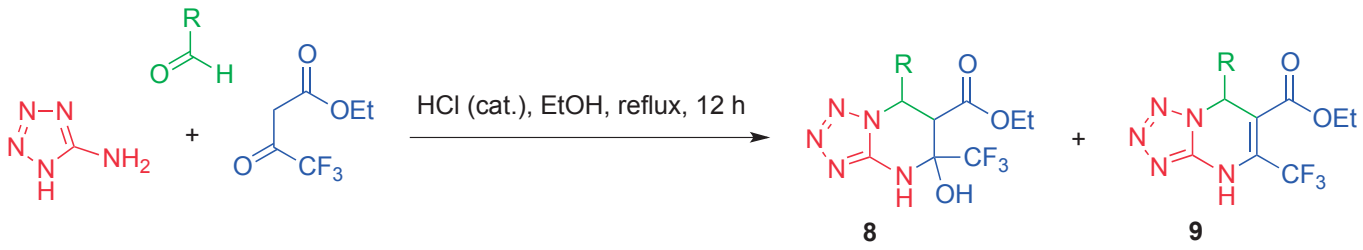


Scheme 4

It was reported[21] that tetrahydrotetrazolo[1,5-*a*]triazine **8a**, bearing a hydroxyl group in the geminal position to the fluorinated substituent, was isolated as a sole product from the Biginelli-like MCR of 5-aminotetrazole with acetaldehyde and ethyl 4,4,4-trifluoroacetoacetate (Scheme 5). The same reaction using benzaldehydes resulted in the formation of dihydrotetrazolo[1,5-*a*]triazines **9** together with their tetrahydro analogues **8**. Unfortunately, separation of these products was not discussed in details. However, dehydration of tetrahydro derivative **8b** by heating in the presence of tosylic acid in benzene for 8 h was reported[21] to afford **9b** in 97% yield.

Interestingly, another research group[22] isolated only ethyl 7-aryl-5-(trifluoromethyl)-4,7-dihydro-tetrazolo[1,5-*a*]triazine-6-carboxylates from the MCR of 5-aminotetrazole, substituted benzaldehydes and ethyl 4,4,4-trifluoroacetoacetate without any catalyst in common organic solvents. However, higher yields

were achieved using ionic liquids as a media for this reaction. Particularly good results were obtained in 3-butyl-1-methyl-1*H*-imidazol-3-ium tetrafluoroborate at 110 °C as illustrated by 11 examples (79-89% yield).

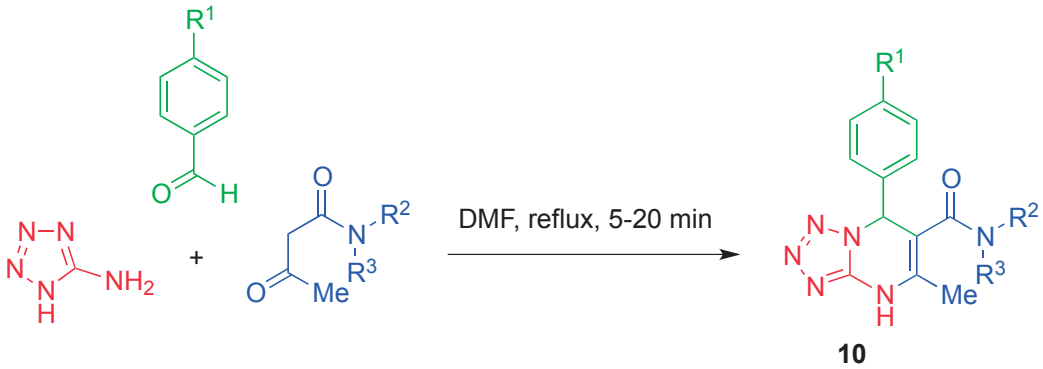


R = Me, 43% (**8a**);
Ph, 47% (**8b**) + 50% (**9b**);
4-MeOC$_6$H$_4$, 53% (**8c**) + 40% (**9c**)

Scheme 5

2.3. Biginelli reactions of 5-aminotetrazole, aldehydes, amides of β-ketoacids

The preparation of 7-aryl-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamides (**10**) using Biginelli reaction was reported by Gladkov et al. in 2007.[23] Thus, heating of a mixture of 5-aminotetrazole, acetoacetamides and benzaldehyde or *p*-anisaldehyde in DMF was found to successfully afford **10** (Scheme 6).



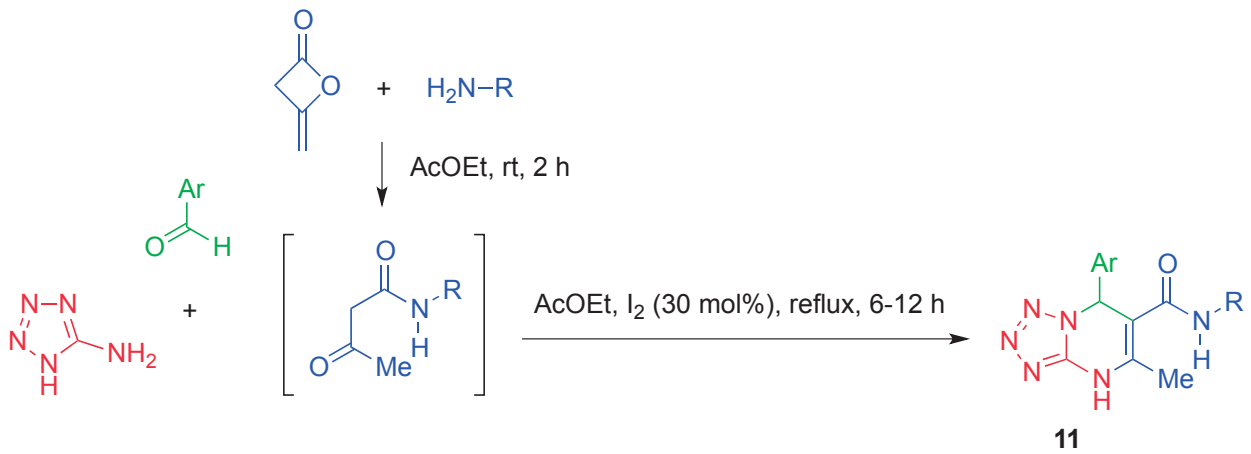
R^1 = H, R^2R^3 = -$(CH_2)_5$-, 35% (**10a**); R^2R^3 = -$(CH_2)_2$-O-$(CH_2)_2$-, 40% (**10b**);
R^2 = H, R^3 = Ph, 55% (**10c**); R^3 = 4-ClC$_6$H$_4$, 78% (**10d**);
R^1 = MeO, R^2 = H, R^3 = Ph, 50% (**10e**); R^3 = 4-ClC$_6$H$_4$, 70% (**10f**)

Scheme 6

Extended libraries of amides were prepared after that by Gein's group[24,25] applying solventless heating of 5-aminotetrazole with amides of acetoacetic acid and various benzaldehydes or nicotinic aldehyde at 120-150 °C. When alkylamides of acetoacetic acid (R^2 = H, R^3 = Me; R^2 = R^3 = Me; R^2 = R^3 = Et) were

used in the reaction, the yields were generally lower (21 examples, 21-72%)[24] than in the case of arylamides (21 examples, 34-83%).[25]

A similar one-pot reaction with *in situ* formation of amides of acetoacetic acid from diketene and aliphatic amines was successfully applied for the synthesis of 4,7-dihydrotetrazolo[1,5-*a*]pyrimidines **11** (Scheme 7) under milder conditions.[26] The process was efficiently catalysed by molecular iodine increasing the yield in the model reaction from 16% to 63%. However, some limitations for the substrate choice were reported for both amines and aldehydes. Thus, no desired product was isolated in an attempt to involve aniline is this reaction. Attempts to carry out this MCR using aliphatic aldehydes were also unsuccessful.



R= Bn, Ar = Ph, 54% (**11a**); 2-ClC_6H_4, 46% (**11b**); 4-ClC_6H_4, 63% (**11c**); 4-$NO_2C_6H_4$, 73% (**11d**); 4-$MeOC_6H_4$, 31% (**11e**)

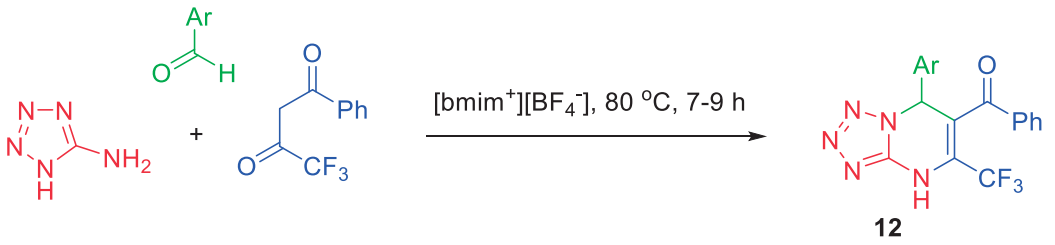
Ar = 4-ClC_6H_4, R = Bu, 61% (**11f**); 2-$FC_6H_4CH_2$, 49% (**11g**); 4-$FC_6H_4CH_2$, 54% (**11h**); 4-$MeOC_6H_4CH_2$, 61% (**11i**)

Scheme 7

2.4. Biginelli reactions of 5-aminotetrazole, aldehydes, and 1,3-diketones

Derivatives of β-ketoacids in Biginelli reaction can be replaced by 1,3-diketones. However, selectivity of the reaction for unsymmetrical ketones is often difficult to control. Therefore, symmetrical cyclic 1,3-diketones have been preferred substrates for this variation of Biginelli reaction, including MCRs of 5-aminotetrazole, aldehydes, and 1,3-diketones.

The formation of 6-benzoyl substituted 4,7-dihydrotetrazolo[1,5-*a*]pyrimidines **12** was suggested for the MCR of 5-aminotetrazole, substituted benzaldehydes and 4,4,4-trifluoro-1-phenylbutane-1,3-dione in the ionic liquid (Scheme 8).[22]

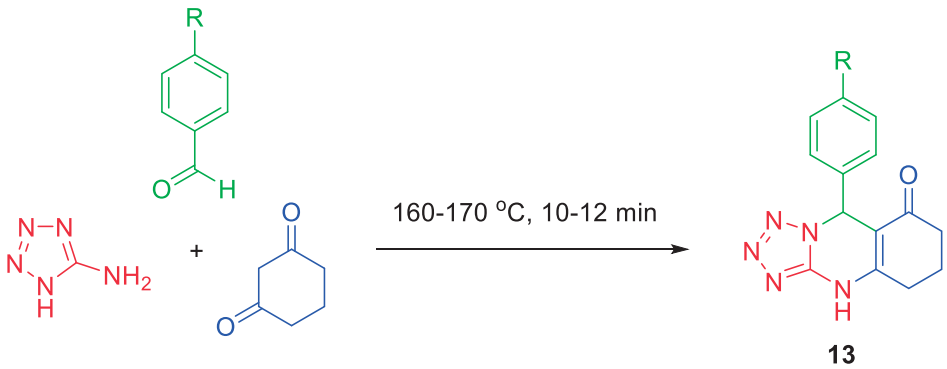


Ar = 2-FC_6H_4, 80% (**12a**); 3-FC_6H_4, 83% (**12b**); 2-ClC_6H_4, 81% (**12c**); 4-BrC_6H_4, 86% (**12d**); 3-$NO_2C_6H_4$, 81% (**12e**); 4-$NO_2C_6H_4$, 85% (**12f**); 3,4-$(OCH_2O)C_6H_3$, 82% (**12g**); 3,4,5-$(MeO)_3C_6H_2$, 78% (**12h**)

Scheme 8

Several reports described MCRs of 5-aminotetrazole, aromatic aldehydes and cyclohexane-1,3-diones using various catalysts and reaction conditions. The first time this reaction was mentioned by Drizin et al. in 2002,[27] but no experimental details were provided.

Gein's research group reported[28] a solventless MCR of 5-aminotetrazole, benzaldehydes and cyclohexane-1,3-dione affording 9-aryl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-ones (**13**) (Scheme 9). These conditions were also successfully applied for the same substrates using dimedone as an active methylene dicarbonyl compound. Several catalytic systems were found to be efficient for this reaction as illustrated by the synthesis of **14** (Scheme 10). Good results were obtained when tosylic acid,[29] molecular iodine,[30] or salts of trifluoroacetic acid[16,17] were used as catalysts.

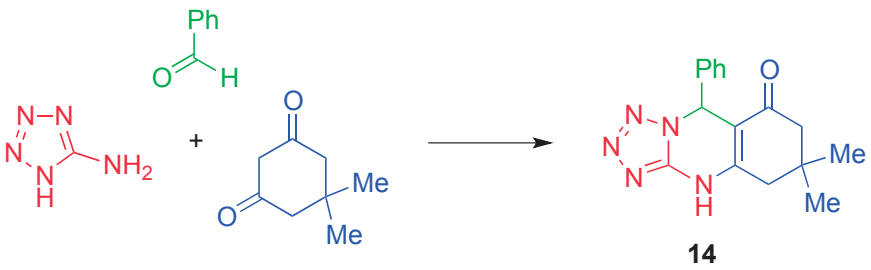


R = H, 62% (**13a**); Cl, 68% (**13b**); MeO, 64% (**13c**); NO_2, 73% (**13d**)

Scheme 9

Hassankhani and Mosaddegh[29] demonstrated that the yield could be significantly improved if the solventless MCR of 5-aminotetrazole, benzaldehydes and dimedone was carried out in the presence of tosylic acid. At the same time, a significant reduction of the reaction temperature and duration was found to be achievable in this case. Moreover, it was proved that the catalyst can be recycled several times

without any lost in yield. The scope of this method was illustrated with preparation of ten 5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-ones using various benzaldehydes.



Conditions	Yield	Reference
160-170 °C, 10-12 min	68%	28
p-TsOH (20 mol%), 80 °C, 5 min	81%	29
I_2 (10 mol%), *i*-PrOH, reflux, 20 min	92%	30
Py•TFA (50 mol%), μW, 90 °C, 25 min	93%	16

Scheme 10

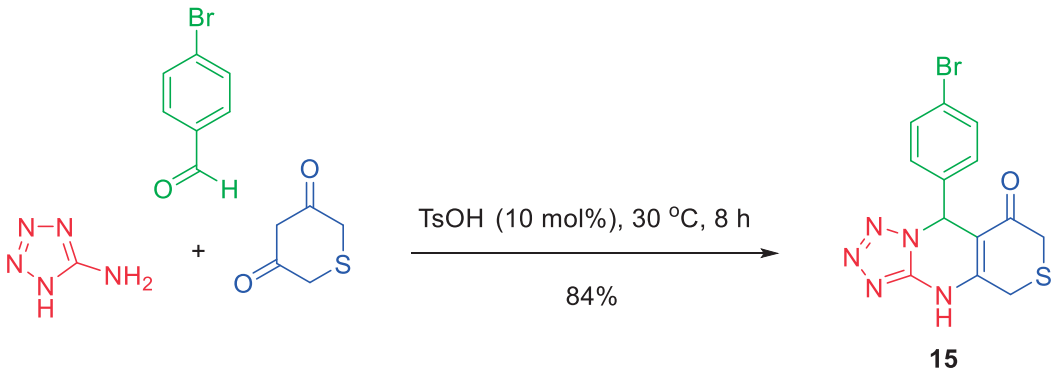
Zeng and Cai[30] reported an iodine catalysed (10 mol%) reaction of 5-aminotetrazole, benzaldehydes and dimedone. The reaction scope was demonstrated by nine examples of analogues of **14** prepared using various benzaldehydes in 63-92% yields by heating the reaction mixture under reflux in isopropanol for 10-70 min.

A library of twelve thiopyrano-fused tetrazolo[1,5-*a*]pyrimidines was successfully prepared using the same approach and utilizing 2*H*-thiopyran-3,5(4*H*,6*H*)-dione as an active methylene dicarbonyl compound.[31] In the model MCR using 5-aminotetrazole, 4-bromobenzaldehyde and 2*H*-thiopyran-3,5(4*H*,6*H*)-dione as substrates, best results were obtained under the solventless conditions and in the presence of tosylic acid (Scheme 11). The experiments on the reaction temperature revealed that even minor deviations from the optimal temperature of 30 °C significantly decreased the yield of **15**. Under similar conditions, eleven analogues of **15** were obtained in 65-80% yields using other substituted benzaldehydes.

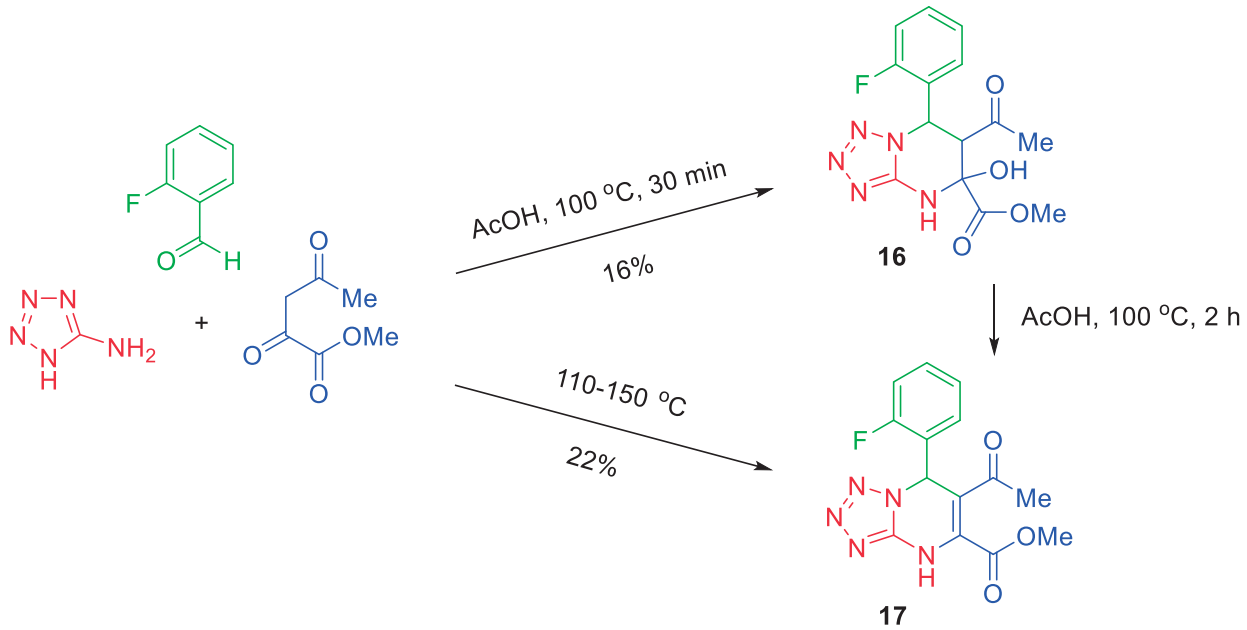
2.5. Biginelli reactions of 5-aminotetrazole, aldehydes, and acylpyruvates

Gein's group[32-37] extensively explored MCRs of 5-aminotetrazole, aromatic aldehydes and acylpyruvic acids and their esters. It was found that heating 5-aminotetrazole, benzaldehydes and methyl acetopyruvate without solvent afforded methyl 6-acetyl-7-aryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-5-carboxylates, *e.g.* **17** (Scheme 12).[32,33] The library of ten compounds was prepared (yields 21-89%)

using various benzaldehydes. It was proposed that the reaction proceeded *via* the formation of tetrahydrotetrazolo[1,5-*a*]pyrimidine intermediates possessing a hydroxyl in the geminal position to the carboxylic group. The isolation of **16** from the reaction of 5-aminotetrazole, 2-fluorobenzaldehyde and methyl acetopyruvate carried out in acetic acid supported this suggestion, which was further confirmed by the preparation of **17** by extension of the reaction to 2 h.[33] Several libraries of compound **17** analogues were prepared using solventless heating of 5-aminotetrazole, aromatic aldehydes and esters of aroyl- (35 examples, 25-91% yield),[32-34] furoyl- (15 examples, 47-89%),[35] thienoyl- (12 examples, 45-70%),[36] or cinnamoyl- (9 examples, 31-65%)[37] pyruvic acids.

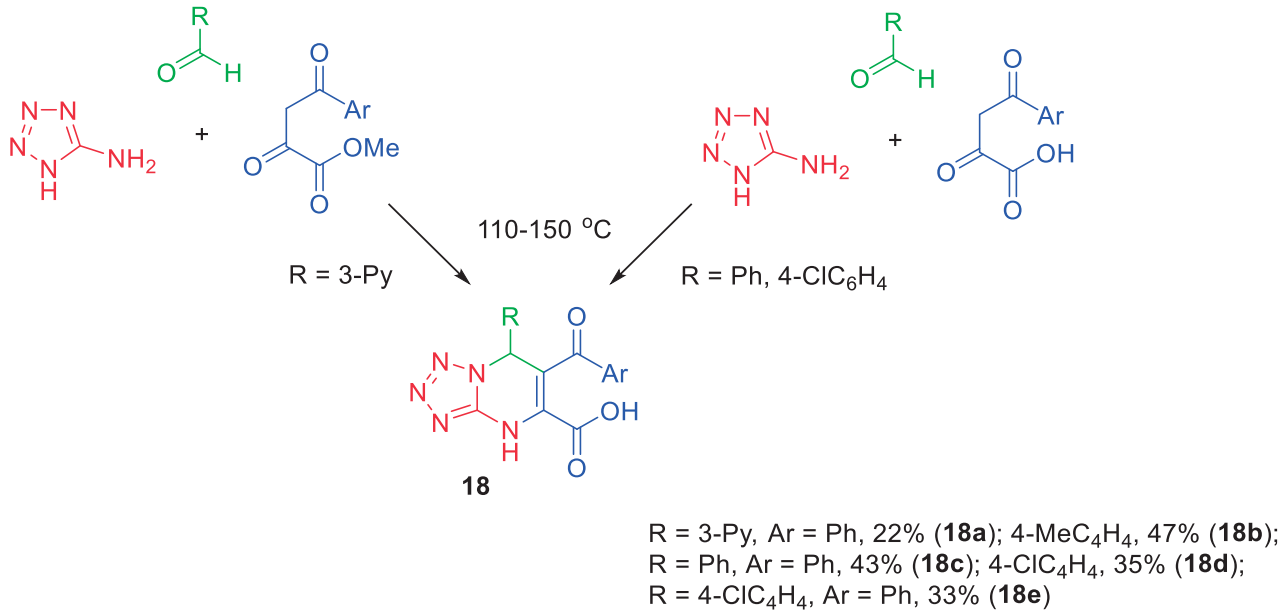


Scheme 11



Scheme 12

Interestingly, when nicotinaldehyde was used in the MCR with 5-aminotetrazole and methyl aroylpyruvates under similar conditions, acids **18a,b** were formed instead of their methyl esters (Scheme 13).[33] Dihydrotetrazolo[1,5-*a*]pyrimidine-5-carboxylic acids **18c-e** were also obtained *via* a three-component condensation of 5-aminotetrazole with corresponding benzaldehydes and aroylpyruvic acids.

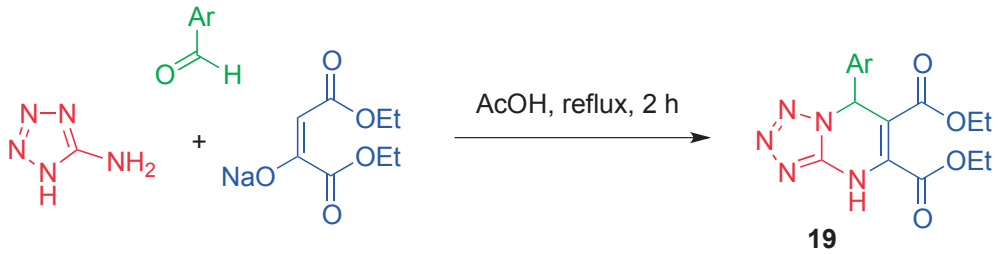


Scheme 13

2.6. Three-component reactions of 5-aminotetrazole, aldehydes, and other enolizable ketones

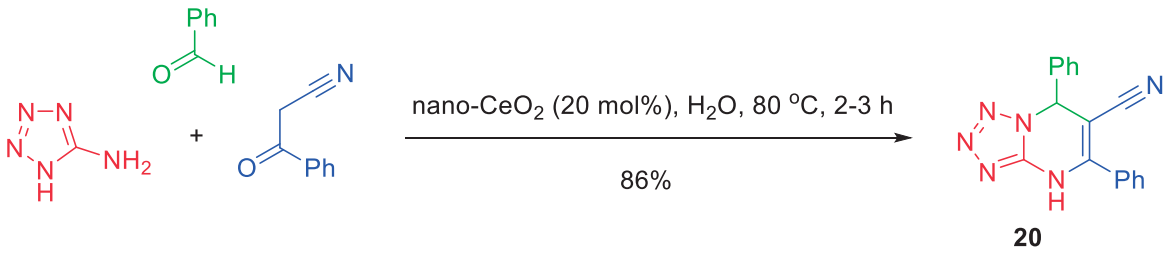
A variety of ketones was effectively involved in Biginelli reaction of 5-aminotetrazole instated of β-ketoesters. It was found that reaction of 5-aminotetrazole, benzaldehydes and diethyl oxosuccinate (introduced into the reaction in form of sodium salt of its enolic tautomer) in acetic acid proceeded in a manner similar to the Biginelli reactions of acylpyruvic acid derivatives mentioned above and afforded diethyl 7-aryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-5,6-dicarboxylates (**19**) (Scheme 14).[38] X-Ray crystallographic analysis of **19g** confirmed the structure assignments.

The one-pot, three-component condensation of 5-aminotetrazole with benzaldehyde and benzoylacetonitrile was found to proceed chemo- and regioselectively in water under catalysis with cerium oxide nanoparticles affording 4,7-dihydrotetrazolo[1,5-*a*]pyrimidines **20** (Scheme 15).[39] The scope of this MCR was demonstrated by the preparation of fifteen examples of compound **20** analogues using various aromatic aldehydes (82-90% yields).



Ar = Ph, 68% (**19a**); 4-FC_6H_4, 71% (**19b**); 4-ClC_6H_4, 74% (**19c**); 2-$NO_2C_6H_4$, 69% (**19d**); 3-$NO_2C_6H_4$, 72% (**19e**); 3-$MeOC_6H_4$, 67% (**19f**); 2,4-$(MeO)_2C_6H_3$, 65% (**19g**); 2,5-$(MeO)_2C_6H_3$, 62% (**19h**)

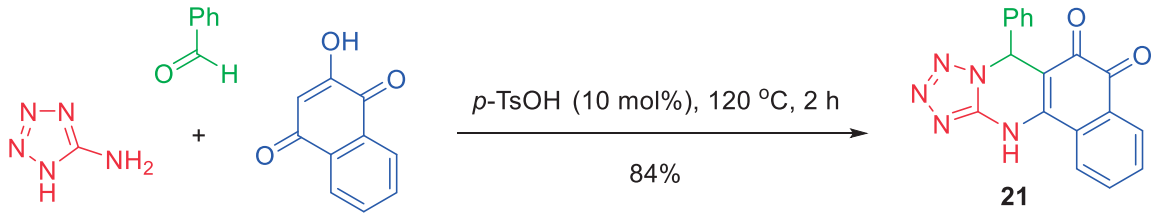
Scheme 14



Scheme 15

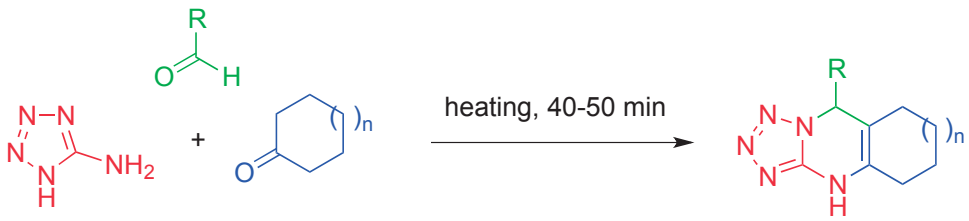
In the search for anticancer agents, Wu[40] developed an MCR of 5-aminotetrazole, aldehydes and 2-hydroxy-1,4-naphthoquinone. In the model reaction with benzaldehyde under solventless conditions, the screening of catalysts identified that the highest yield of tetracyclic compound **21** was achieved in the presence of tosylic acid (Scheme 16). Using substituted benzaldehyde, a library of eighteen compounds was prepared according to this method in generally good yields (68-91%). Moreover, when polyformaldehyde was used instead of benzaldehyde, 7,12-dihydrobenzo[*h*]tetrazolo[5,1-*b*]-quinazoline-5,6-dione was obtained in 65% yield. The prepared compounds were tested against three cancer cell lines *in vitro* and demonstrated good bioactivity. The most potent analogue of **21** possessed 3,5-dimethoxypenyl moiety on position 7 and was found to be 20 times more potent than taxol against human colon cancer HCT116 and human hepatoma HepG2 cells (IC_{50} = 0.22 and 1.18 μM, respectively). This compound also demonstrated good selectivity towards cancer cells, affecting non-cancerous human liver cells L02 only at higher concentrations (IC_{50} = 1.96 μM).

The synthesis of **21** was also effectively performed at room temperature in deep eutectic solvent composed of choline chloride and urea (1:2) using the magnetic polymeric nanocomposite functionalized with sulphonic acid as a stable and recyclable catalyst.[41] The MCR under these conditions afforded **21** in the 93% yield. A series of seventeen different aldehydes was used in this reaction to demonstrate the scope of the method and the products were obtained in good yields (84-95%).



Scheme 16

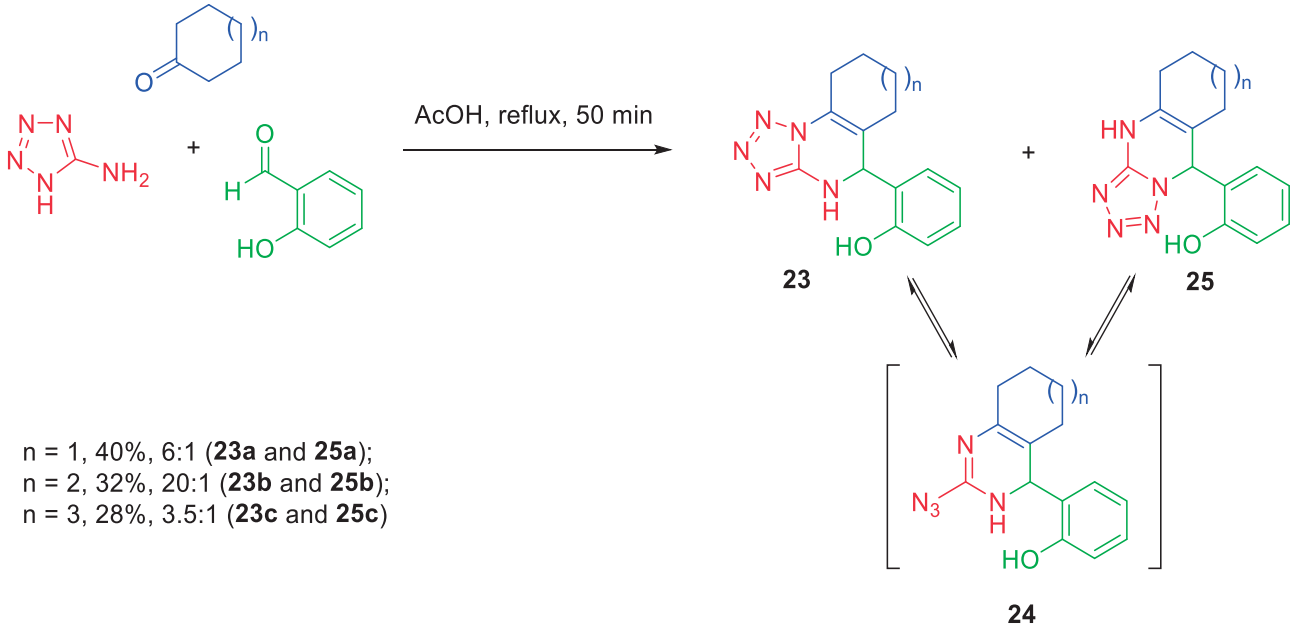
Several cyclic ketones were successfully involved in three-component reactions with 5-amoinotetrazole and aldehydes. Heating 5-aminotetrazole and cyclic ketones with benzaldehyde or furfural was reported[42] to afford tricyclic compounds **22** (Scheme 17). The reaction was found to proceed selectively with the formation of linearly fused structures, which were confirmed by X-ray analysis of **22d**.[43] A similar tricyclic product was also obtained in 35% yield using an MCR of 5-aminotetrazole, 5-nitrothiophene-2-carbaldehyde and cyclohexanone, when they were heated in acetic acid for 5 h.[44]



R = Ph, n = 1, 40% (**22a**); n = 2, 53% (**22b**); n = 3, 67% (**22c**);
R = 2-Furyl, n = 1, 40% (**22d**); n = 2, 39% (**22e**); n = 3, 68% (**22f**)

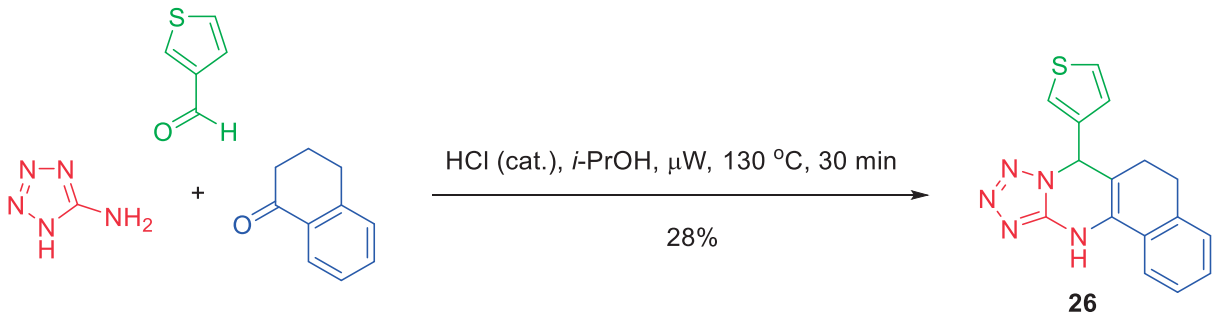
Scheme 17

However, in the MCR of 5-aminotetrazole with cyclic ketones and salicylaldehyde, mixtures of isomeric compounds **23** and **25** were obtained and the isomers **23** were major products (Scheme 18).[45] These observations shed some light on the general mechanism of MCRs involving 5-aminotetrazole. The reactions of 5-aminotetrazole, cyclic ketones and aldehydes typically led to the formation of thermodynamically more stable linearly fused cycloalka[*d*]tetrazolo[1,5-*a*]pyrimidines. These compounds were suggested to be the products of the rearrangement of initially formed cycloalka[*e*]tetrazolo[1,5-*a*]pyrimidines. In case of salicylaldehyde participating in this MCR, angular isomers **23** were stabilised by intramolecular hydrogen bonding between the *ortho*-hydroxy group and the NH on the adjacent ring. Therefore, in the azide-tetrazole equilibrium, azides **24** were preferentially transformed to tricyclic compounds **23**.



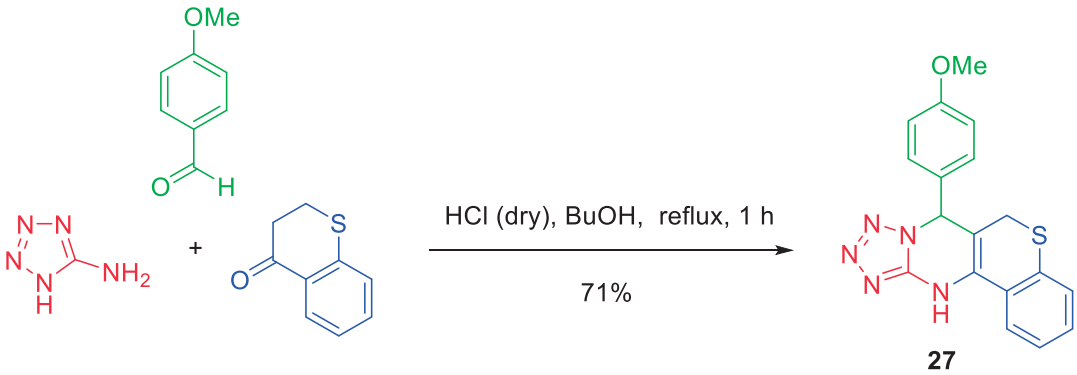
Scheme 18

Recently, Kantin and Krasavin[46] reported a microwave-assisted protocol for the synthesis of benzo-fused analogues of **22** using α-tetralone as an active methylene reagent. Thus, an MCR of 5-aminotetrazole, α-tetralone and 3-thiophenecarboxaldehyde under acidic catalysis resulted in the formation of compound **26** in 28% yield (Scheme 19). The reaction was performed successfully using a selection of eleven aromatic aldehydes affording analogues of **26** in moderate yields (20-52%). However, a steric hindrance in case of 2,6-dichlorobenzaldehyde adversely affected this reaction resulting in the decrease of yield to 5%.



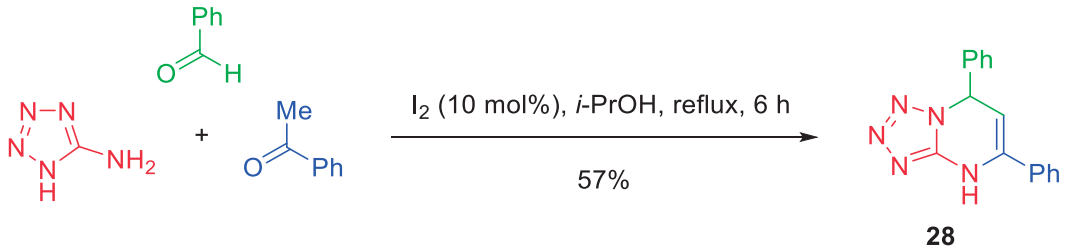
Scheme 19

In a similar reaction, tetralone was successfully replaced by thiochroman-4-one, which in the MCR with 5-aminotetrazole and *p*-anisaldehyde was found to give compound **27** (Scheme 20).[47]



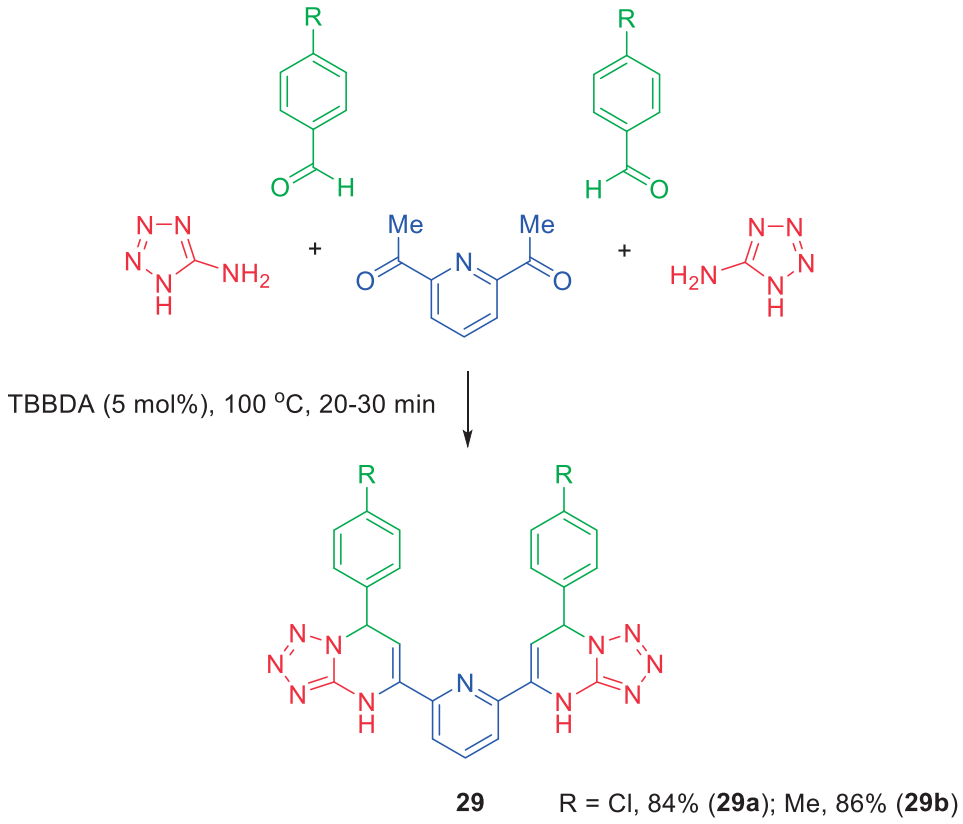
Scheme 20

The molecular iodine catalyzed reaction of 5-aminotetrazole with benzaldahyde and acetophenone was reported to afford 5,7-diphenyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine (**28**) (Scheme 21).[30] This reaction was found to be more efficient under the *N,N,N′,N′*-tetrabromobenzene-1,3-disulfonylamide (TBBDA) catalysis and solventless conditions.[48] Thus, **28** was obtained in 90% yield after heating of 5-aminotetrazole, benzaldahyde and acetophenone at 100 °C for 20 min in the presence of TBBDA (5 mol%). Similarly, preparation of eleven analogues was reported using aromatic aldehydes and several acetophenones. The reaction time varied from 10 to 80 min depending on the structure of substrates. The yield of the products was in the range of 82-98%. The catalyst was demonstrated to be reusable in a few cycles without any substantial loss of the activity.



Scheme 21

This method was further extended to two MCRs, which cannot be formally classified as three-component, but they are discussed here due to similarity of chemical transformations involved. For example, interesting bis-4,7-dihydrotetrazolo[1,5-*a*]pyrimidines **29** with a pyridine ring linkage were obtained in a similar MCR when acetophenone was replaced by 2,6-diacetylpyridine (Scheme 22).[48]

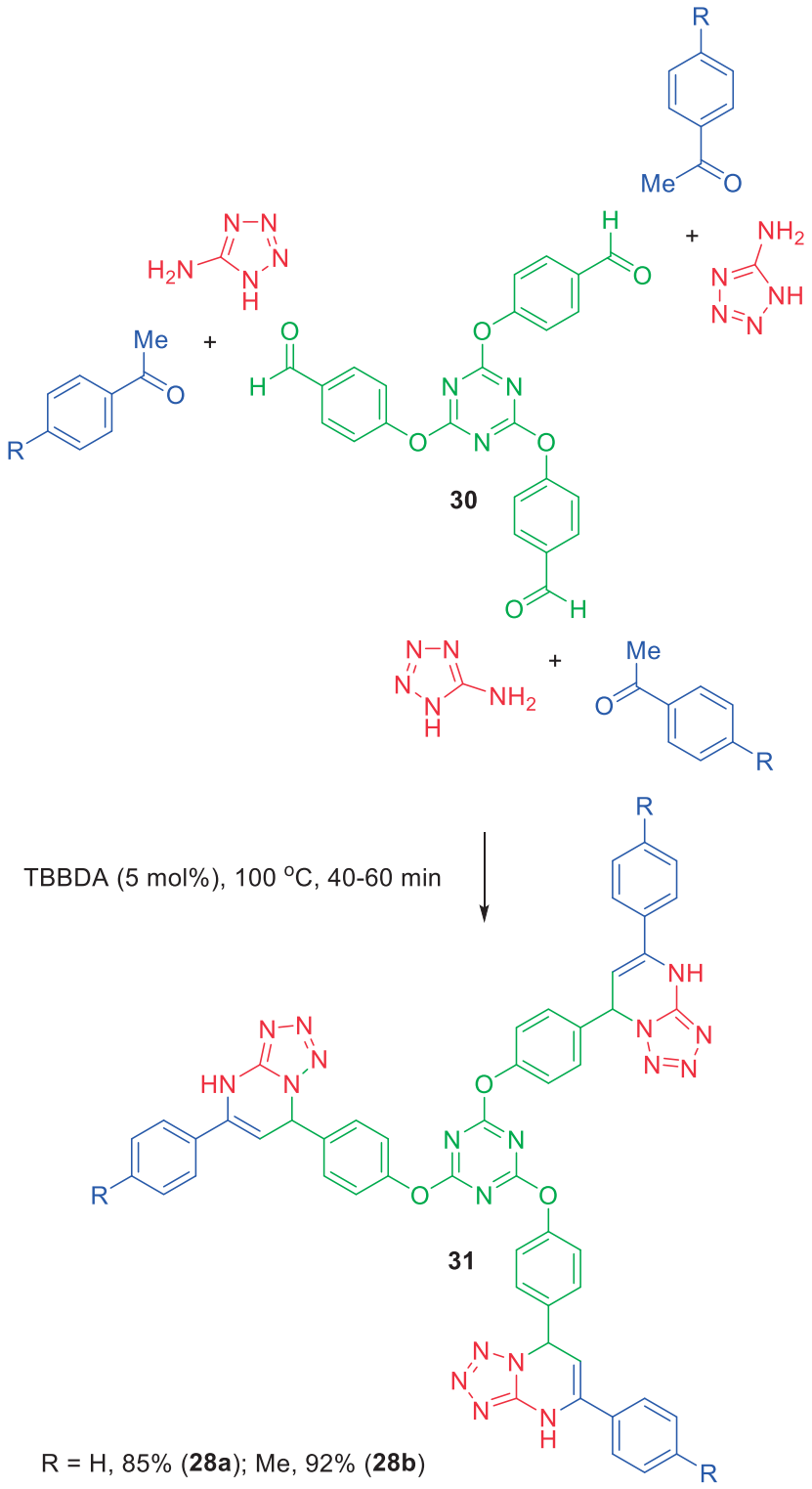


Scheme 22

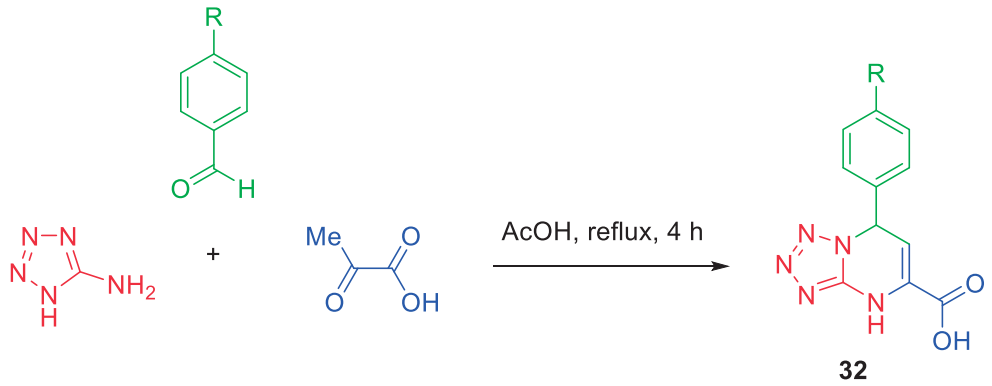
The same research group also reported[48] a synthesis of dendrimeric compounds **31** with three 4,7-dihydrotetrazolo[1,5-*a*]pyrimidine rings build around the 1,3,5-triazine core upon treatment of tris-benzaldehyde **30** with 5-aminotetrazole and acetophenones in one-pot fashion under TBBDA catalysis (Scheme 23).

The MCR of 5-aminotetrazole with pyruvic acid and benzaldehydes was reported by Chebanov et al.[49] The best results were obtained when acetic acid was used as a solvent for this reaction (Scheme 24). Only Schiff bases of 5-aminotetrazole and aldehydes were formed when this reaction was performed under reflux in methanol, ethanol or isopropanol. The product **32** was isolated in the mixture with the Schiff bases when the reaction was carried out in *n*-butanol. The formation of carboxylic acid **32** was also observed when the reaction was performed in DMF, but yields were lower than in acetic acid.

However, this reaction was also found to afford 4,7-dihydrotetrazolo[1,5-*a*]pyrimidine **32c** in ethanol (as well as in a range of other solvents) in the presence of molecular iodine as a catalyst.[50] The best results were obtained in ethyl acetate and 15 mol% of iodine, which was proposed to play role of a mild Lewis acid, activating carbonyl groups in the reaction. This method tolerated different benzaldehydes as was demonstrated with ten examples of compounds **32** prepared in yield of 63-77%.



Scheme 23

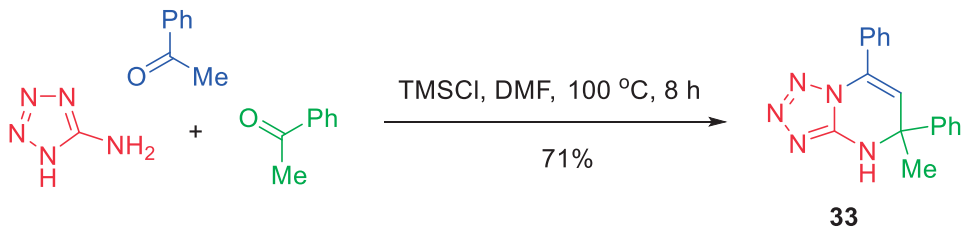


R = H, 55% (**32a**); F, 54% (**32b**); Br, 65% (**32c**); OMe, 60% (**32d**); CO_2Me, 59% (**32e**)

Scheme 24

2.7. Three-component reactions involving 5-aminotetrazole and ketones

Several MCRs of 5-aminotetrazole involving two molecules of identical or different ketones have been reported in the literature. The chlorotrimethylsilane (TMSCl), effectively used in many Biginelli reactions of 5-aminotetrazole as a catalyst,[51] was also found to be effective in the MCR of 5-aminotetrazole with acetophenone affording 4,5-dihydrotetrazolo[1,5-*a*]pyrimidine **33** as a product of three-component condensation of the ABB' type (Scheme 25).[52]

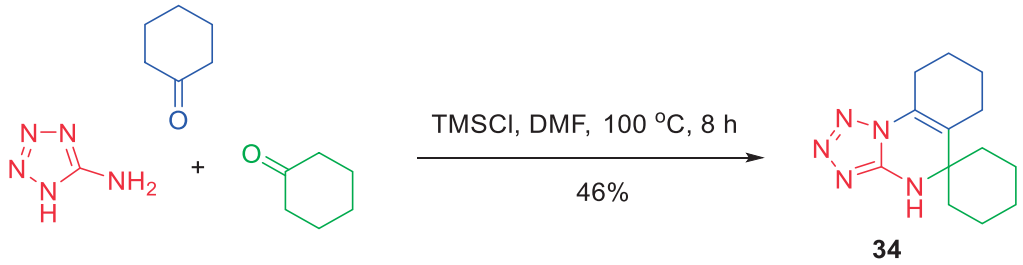


Scheme 25

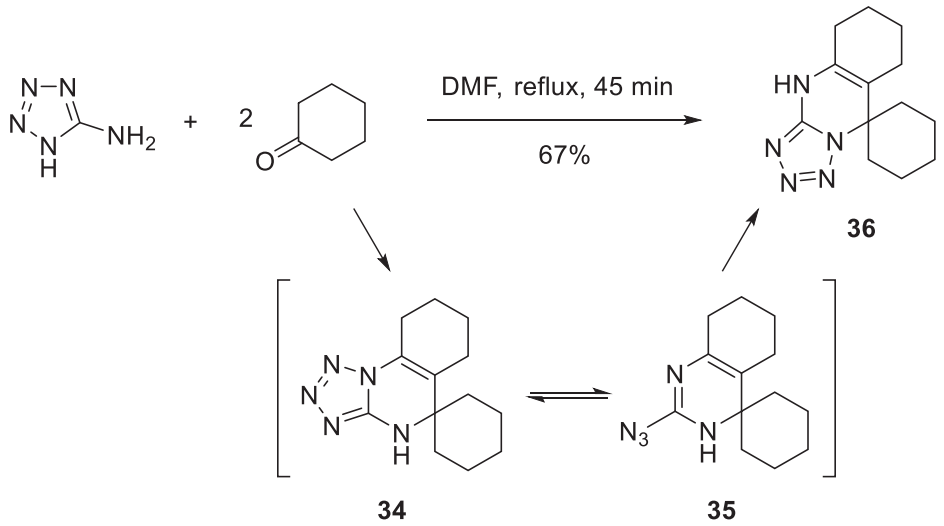
The reaction of 5-aminotetrazole with two molecules of cyclohexanone in the presence of TMSCl was reported[52] to produce spiro-compound **34** (Scheme 26). However, a similar MCR without any catalyst was suggested to result in the formation of the regioisomeric product **36**, which structure was confirmed by X-ray crystallographic data.[53] It was proposed that this reaction proceeded *via* initial formation of intermediate **34** followed by tetrazolo-azide rearrangement to **35** and then recyclization to **36**. (Scheme 27).

The tosylic acid catalysed reaction of 5-aminotetrazole with dimedone and isatin in aqueous polyethylene glycol (PEG) was reported[54] to afford spiro-fused compound **37** (Scheme 28). It was demonstrated that using aqueous PEG (1:1) improved the yield compare to conventional organic solvents employed as a

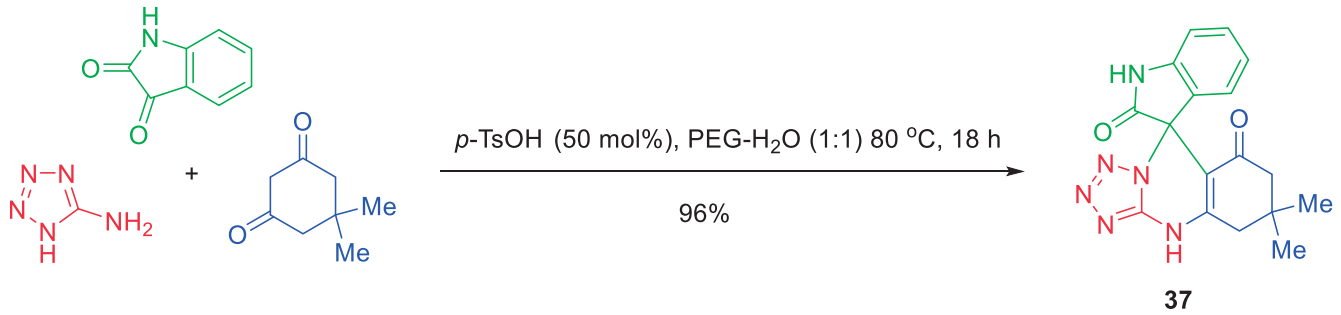
media to this reaction, but unfortunately the type of PEG was not specified. Using substituted isatins in this reaction did not significantly affect the reaction outcome as was demonstrated by the preparation of ten examples of substituted **37** (75-90% yields).



Scheme 26



Scheme 27



Scheme 28

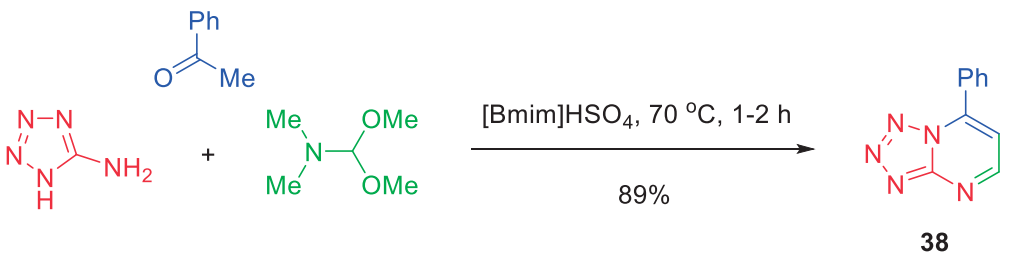
The same reaction was also efficiently performed in aqueous ethanol using the mixture of acetic acid and perchloric acid (1:1, 10 mol%) as a catalyst.[55] The scope of the reaction was explored using ten different

isatins and spiro-compounds of general structure **37** were obtained in 80-92% yields. It was claimed that a superacid formed *via* the protonation of acetic acid by perchloric acid catalysed the reaction. However, validity of such claims for aqueous media is questionable. Discussing the reaction mechanism, these two papers[54,55] suggested different sequences of transformations, but no evidences supporting any of these pathway were provided.

2.8. Three-component reactions involving 5-aminotetrazole, DMF or its acetal, and ketones

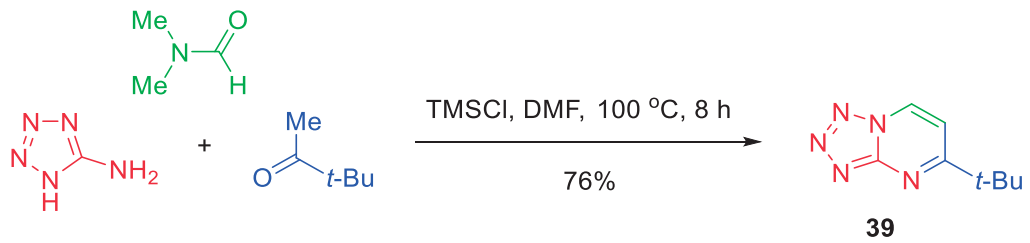
DMF or more often its dimethyl acetal (DMF-DMA) found their application in heterocyclic chemistry as a one-carbon building block. They have also been utilized in this capacity in many MCRs, including those, which involve 5-aminotetrazole. The one-pot reaction of 5-aminotetrazole with DMF-DMA and acetophenone was reported[56] to afford 7-phenyltetrazolo[1,5-*a*]pyrimidine (**38**) (Scheme 29). When the reaction was carried out in water and conventional solvents, yields of **38** were rather low, but significant improvements (higher yields and shorter reaction time) were achieved when ionic liquids were used as media. Particularly effective ionic liquid was 1-butyl-3-methylimidazolium hydrogen sulphate ([Bmim]HSO_4), which was proposed to catalyse the process. Moreover, this ionic liquid was found to be reusable in several runs without significant yield changes. The reaction scope was demonstrated by twelve examples of tetrazolo[1,5-*a*]pyrimidines similar to **38** prepared in good yields (86-92%) using various acetophenones or their heteroaromatic analogues.[56] These compounds were tested *in vitro* against α-glucosidase as potential antidiabetic agents. The greatest inhibitory activity in the series was observed for 7-(4-methylphenyl)tetrazolo[1,5-*a*]pyrimidine, which possessed IC_{50} value of 49.8 μM.

It was suggested that the reaction involved the initial formation of enaminoketones in the condensation of acetophenones with DMF-DMA. It should be noted that reported reaction and the proposed pathway do not exclude formation of isomeric structures with substituents in the position 5 instead of 7. This is also possible due to potential rearrangement of products *via* azide intermediates. Moreover, the coexistence of **38** in the equilibrium with its regioisomer and the ring-opened azide tautomer was earlier reported[57] in solutions. The nature of solvents dictated the isomer preferences in the equilibrium.



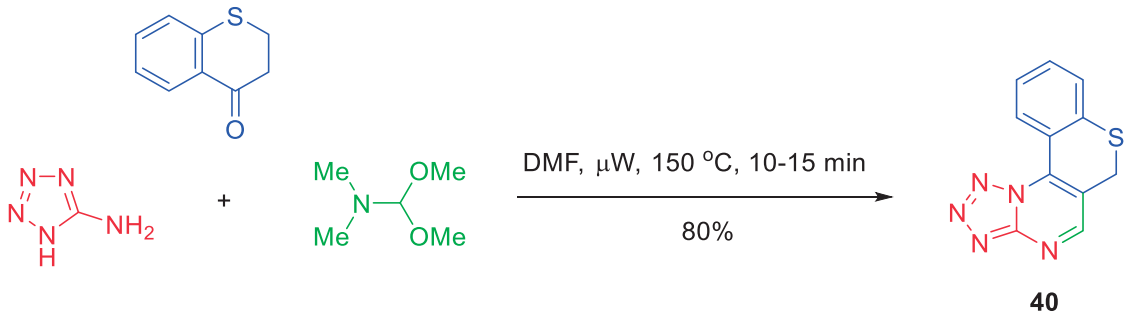
Scheme 29

When 5-aminotetrazole was heated with *tert*-butyl methyl ketone in the presence of TMSCl using DMF as a solvent, DMF also participated in the reaction resulting in the formation of 5-*tert*-butyltetrazolo[1,5-*a*]pyrimidine (**39**) (Scheme 30).[52] The pyrimidine ring closure was found to be regioselective and the product structure **39** was suggested on the basis of comparison with spectral data of structurally related molecules.



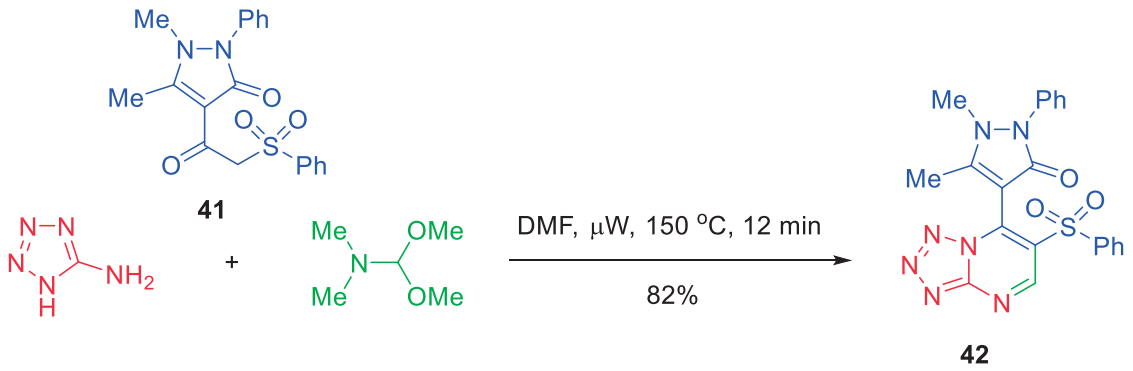
Scheme 30

The microwave-assisted synthesis of tetrazolo-fused tetracyclic system **40** was achieved using a three-component reaction of 5-aminotetrazole, 1-benzothiopyran-4-one and DMF-DMA (Scheme 31).[58] The same product **40** was also prepared sequentially with isolation of an enaminoketone formed in the reaction of 1-benzothiopyran-4-one with DMF-DMA in the first step, followed by the reaction with 5-aminotetrazole in the second step.



Scheme 31

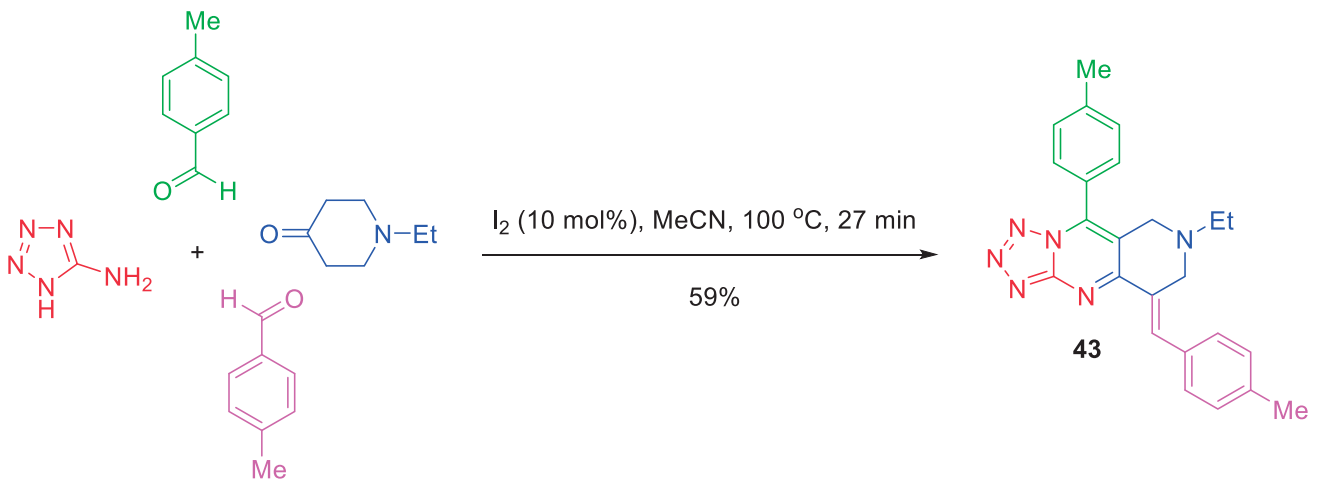
Another microwave-assisted MCR using 5-aminotetrazole, β-ketosulphone **41** and DMF-DMA was reported[59] to proceed similarly resulting in the formation of tetrazolo[1,5-*a*]pyrimidine **42** (Scheme 32). This compound (**42**) was found to inhibit enzyme dipeptidyl peptidase-IV with IC_{50} value of 14 nM and also demonstrated a significant oral hypoglycaemic activity in the alloxan model of diabetes in mice.



Scheme 32

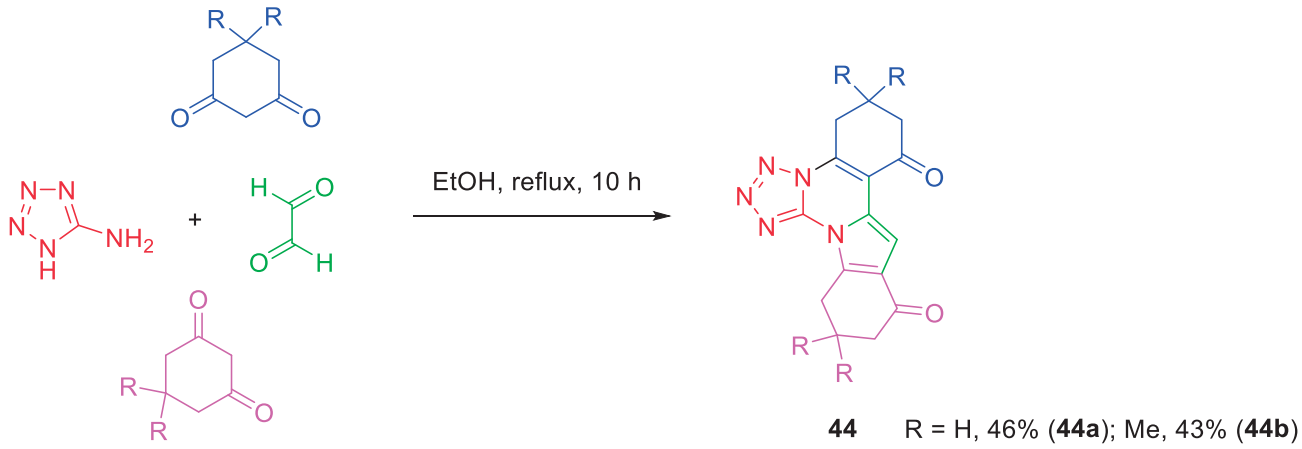
2.9. Four-component reactions of 5-aminotetrazole

Four-component reactions of 5-aminotetrazole are less common and only two reactions of that type (excluding Mannich condensation described in 2.1 of this review) have been reported. In the reaction of 5-aminotetrazole with *N*-ethylpiperidin-4-one and two molar equivalents of *p*-tolualdehyde under the molecular iodine catalysis, a spontaneous oxidation of the dihydropyrimidine ring, constructed in a typical Biginelli process, was observed. Moreover, a condensation with the second molecule of the aldehyde also took place giving a product of ABB'C type of MCR, compound **43** (Scheme 33).[60]



Scheme 33

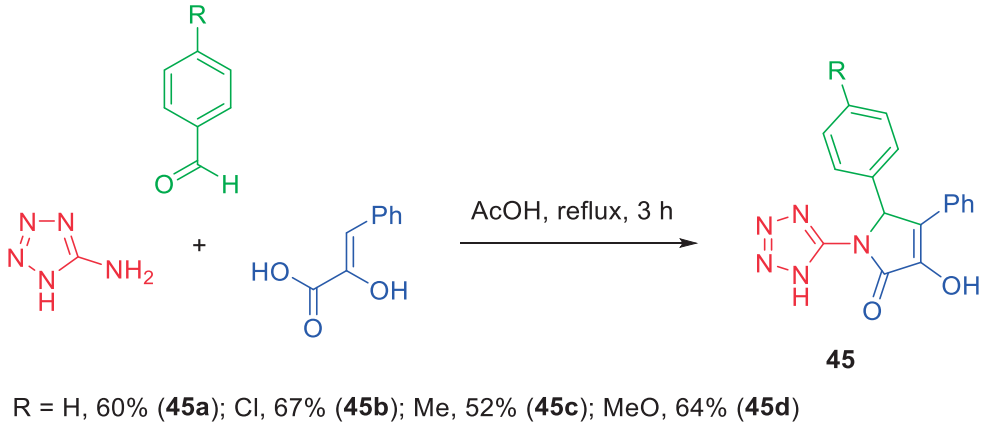
Interesting pentacyclic indolo[1,2-*c*]tetrazolo[1,5-*a*]quinazoline-8,10-diones **44** were constructed *via* a four-component reaction, which involved condensation of 5-aminotetrazole, glyoxal and two molecules of cyclohexane-1,3-diones (Scheme 34).[61]



Scheme 34

3. REACTIONS INVOLVING ONLY EXOCYCLIC AMINO GROUP OF 5-AMINOTETRAZOLE

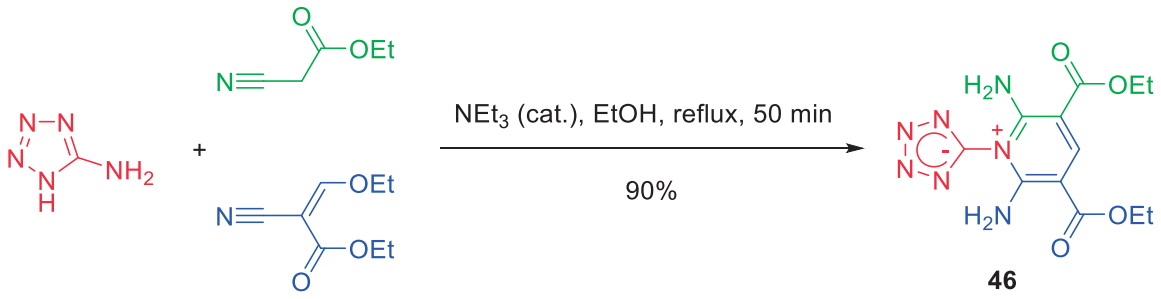
Overall, MCRs of 5-aminotetrazole without participation of the ring nitrogen atoms are rather limited. Two reactions with formation of a heterocylic ring around the primary amino group of 5-aminotetrazole have been reported in the literature. Interesting results were obtained when 5-aminotetrazole was involved in the three-component reaction with phenylpyruvic acid and benzaldehydes.[6] Instead of typical for aminoazoles formation of a dihydropyrimidine ring fused to the tetrazole, a pyrrole ring was built around the amino group of 5-aminotetrazole to form compounds **45** (Scheme 35).



Scheme 35

In the study on reactions of ethyl 2-ethoxymethylidenecyanoacetate with 5-aminotetrazole, a zwitterionic pyridine derivative **46** was isolated when the reaction was performed under catalysis with a base.[62] It was proposed that this reaction involved formation of ethyl cyanoacetate as an intermediate, which further

participated in the construction of the pyridinium ring. An attempt to carry out the reaction in a multicomponent fashion using ethyl 2-ethoxymethylidenecyanoacetate, ethyl cyanoaetate and 5-aminotetrazole afforded **46** in good yield (Scheme 36). The structure of **46** was confirmed by X-ray crystallographic data.



Scheme 36

4. CONCLUSION

5-Aminotetrazole has been recognized as a useful building block in MCRs. Many efficient methods for the synthesis of diverse heterocyclic compounds have been developed using this approach. However, very often assignments of structures for the products of the 5-aminotetrazole involving MCRs are based on the analogy with behaviour of other similar aminoazoles. Due to unique properties of tetrazolo-fused heterocycles, particularly their potential for the rearrangement *via* azide intermediates, these assumptions may become a source for inaccurate structure attributions of the reaction products. The interest towards MCRs of 5-aminotetrazole has been growing over the last decade and this growth is expected to continue. Therefore, particular attention should be devoted to the structural characterization of MCR products.

ACKNOWLEDGEMENTS

This work is supported by the Ministry of Higher Education, Malaysia under Fundamental Research Grant Scheme (FRGS).

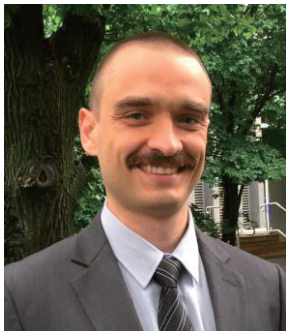
REFERENCES

1. T. Zarganes-Tzitzikas, A. L. Chandgude, and A. Dömling, *Chem. Rec.*, 2015, **15**, 981; P. K. Maji, R. Ul Islam, and S. K. Bera, *Heterocycles*, 2014, **89**, 869; A. Dömling, W. Wang, and K. Wang, *Chem. Rev.*, 2012, **112**, 3083.
2. R. C. Cioc, E. Ruijter, and R. V. A. Orru, *Green Chem.*, 2014, **16**, 2958.
3. V. A. Chebanov, K. A. Gura, and S. M. Desenko, *Top. Heterocycl. Chem.*, 2010, **23**, 41.

4. F. P. L. Lim, G. Luna, and A. V. Dolzhenko, *Tetrahedron Lett*., 2015, **56**, 7016; F. P. L. Lim, G. Luna, and A. V. Dolzhenko, *Tetrahedron Lett*., 2015, **56**, 521; F. P. L. Lim, G. Luna, and A. V. Dolzhenko, *Tetrahedron Lett*., 2014, **55**, 5159; S. A. Kalinina, D. V. Kalinin, and A. V. Dolzhenko, *Tetrahedron Lett.*, 2013, **54**, 5537; A. V. Dolzhenko, S. A. Kalinina, and D. V. Kalinin, *RSC Adv.*, 2013, **3**, 15850.
5. E. S. Gladkov, V. A. Chebanov, S. M. Desenko, O. V. Shishkin, S. V. Shishkina, D. Dallinger, and C. O. Kappe, *Heterocycles*, 2007, **73**, 469.
6. Y. I. Sakhno, S. M. Desenko, S. V. Shishkina, O. V. Shishkin, D. O. Sysoyev, U. Groth, C. O. Kappe, and V. A. Chebanov, *Tetrahedron*, 2008, **64**, 11041.
7. A. A. A. Borai, *J. Chem. Eng. Data*, 2001, **46**, 939.
8. C. Mannich and W. Krösche, *Arch. Pharm. Pharm. Med. Chem*., 1912, **250**, 647.
9. S. S. Novikov, Z. Ya. Lapshina, V. A. Rudenko, and L. S. Semenenok, *Russ. Chem. Bull*., 1960, **9**, 1211.
10. A. S. Ermakov, S. A. Serkov, V. A. Tartakovskii, T. S. Novikova, and L. I. Khmel'nitskii, *Chem. Heterocycl. Compd*., 1994, **30**, 976.
11. P. Biginelli, *Ber. Dtsch. Chem. Ges.*, 1891, **24**, 1317.
12. H. Nagarajaiah, A. Mukhopadhyay, and J. N. Moorthy, *Tetrahedron Lett.*, 2016, **57**, 5135.
13. O. V. Fedorova, M. S. Zhidovinova, G. L. Rusinov, and I. G. Ovchinnikova, *Russ. Chem. Bull.*, 2003, **52**, 1768.
14. V. L. Gein, I. N. Vladimirov, O. V. Fedorova, A. A. Kurbatova, N. V. Nosova, I. V. Krylova, and M. I. Vakhrin, *Russ. J. Org. Chem.*, 2010, **46**, 699.
15. C. Yao, S. Lei, C. Wang, C. Yu, and S. Tu, *J. Heterocycl. Chem.*, 2008, **45**, 1609.
16. C. Raju, M. Kalaipriya, R. Uma, R. Sridhar, and S. Ramakrishna, *Curr. Chem. Lett.,* 2012, **1**, 27.
17. C. Raju, K. Madhaiyan, R. Uma, R. Sridhar, and S. Ramakrishna, *RSC Adv.*, 2012, **2**, 11657.
18. A. Maleki, P. Ravaghi, M. Aghaei, and H. Movahed, *Res. Chem. Intermed.*, 2017, doi:10.1007/s11164-017-2941-4.
19. A. Haleel, P. Arthi, N. Dastagiri Reddy, V. Veena, N. Sakthivel, Y. Arun, P. T. Perumald, and A. Kalilur Rahiman, *RSC Adv*., 2014, **4**, 60816.
20. M. S. Zhidovinova, O. V. Fedorova, G. L. Rusinov, and I. G. Ovchinnikova, *Mol. Divers.*, 2003, **6**, 323.
21. M. V. Pryadeina, Y. V. Burgart, V. I. Saloutin, M. I. Kodess, E. N. Ulomskii, and V. L. Rusinov, *Russ. J. Org. Chem.*, 2004, **40**, 902.
22. T.-J. Li, C.-S. Yao, C.-X. Yu, X.-S. Wang, and S.-J. Tu, *Synth. Commun*., 2012, **42**, 2728.
23. E. Gladkov, S. Sirko, B. Khanetskii, E. Lukinova, and S. Desenko, *Chem. Pap.*, 2007, **61**, 146.

24. V. L. Gein, T. M. Zamaraeva, A. A. Zorina, E. B. Levandovskaya, N. V. Nosova, and M. I. Vakhrin, *Russ. J. Org. Chem.*, 2009, **45**, 942; V. L. Gein, T. M. Zamaraeva, N. V. Nosova, M. I. Vakhrin, and P. A. Slepukhin, *Russ. J. Org. Chem.*, 2012, **48**, 419.
25. V. L. Gein, T. M. Zamaraeva, A. A. Kurbatova, E. V. Voronina, and M. I. Vakhrin, *Pharm. Chem. J.*, 2010, **44**, 366.
26. L.-Y. Zeng, F. Ji, and C. Cai, *J. Heterocycl. Chem.*, 2012, **49**, 237.
27. I. Drizin, M. W. Holladay, L. Yi, H. Q. Zhang, S. Gopalakrishnan, M. Gopalakrishnan, K. L. Whiteaker, S. A. Buckner, J. P. Sullivan, and W. A. Carroll, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1481.
28. V. L. Gein, M. I. Kazantseva, T. M. Zamaraeva, L. F. Gein, and P. A. Slepukhin, *Russ. J. Gen. Chem.*, 2015, **85**, 1984.
29. A. Hassankhani and E. Mosaddegh, *Sci. Iran. C*, 2015, **22**, 942; M. Mohamadi, A. Hassankhani, S. Y. Ebrahimipour, and M. Torkzadeh-Mahani, *Int. J. Biol. Macromol.*, 2017, **94**, 85.
30. L.-Y. Zeng and C. Cai, *J. Comb. Chem.*, 2010, **12**, 35.
31. S. Shen, H. Zhang, C. Yu, C. Yao, T. Li, B. Qin, J. Lu, and D. Wang, *Res. Chem. Intermed.*, 2013, **39**, 1799.
32. V. L. Gein, L. F. Gein, E. P. Tsyplyakova, and E. A. Rozova, *Russ. J. Org. Chem.*, 2003, **39**, 753.
33. V. L. Gein, L. F. Gein, E. P. Tsyplyakova, and O. S. Panova, *Russ. J. Org. Chem.*, 2007, **43**, 1382.
34. V. L. Gein, T. M. Zamaraeva, O. S. Panova, and V. D. Belonogova, *Russ. J. Gen. Chem.*, 2015, **85**, 2299.
35. V. L. Gein, T. M. Zamaraeva, V. V. Mishunin, and V. P. Kotegov, *Russ. J. Gen. Chem.*, 2016, **86**, 286.
36. V. L. Gein, V. V. Mishunin, E. P. Tsyplyakova, M. I. Vakhrin, and P. A. Slepukhin, *Russ. J. Org. Chem.*, 2011, **47**, 1077.
37. V. L. Gein and T. M. Zamaraeva, *Russ. J. Gen. Chem.*, 2016, **86**, 196.
38. V. L. Gein, T. M. Zamaraeva, and M. V. Dmitriev, *Russ. J. Org. Chem.*, 2016, **52**, 558.
39. L. Suresh, P. S. V. Kumar, T. Vinodkumar, and G. V. P. Chandramouli, *RSC Adv.*, 2016, **6**, 68788.
40. L. Wu, *RSC Adv.*, 2015, **5**, 24960.
41. A. Maleki, M. Aghaei, and T. Kari, *Polycycl. Aromat. Compd.*, 2017, doi:10.1080/10406638.2017.1325746.
42. A. A. Matveeva, N. V. Poplevina, N. O. Borisova, and A. P. Kriven'ko, *Chem. Heterocycl. Compd.*, 2013, **48**, 1877.
43. A. A. Matveeva, P. V. Reshetov, and A. P. Kriven'ko, *J. Struct. Chem.*, 2013, **54**, 642.
44. N. O. Vasil'kova, A. A. Anis'kov, and A. P. Kriven'ko, *Russ. J. Org. Chem.*, 2015, **51**, 1766.

45. N. O. Vasil'kova, V. N. Filimonova, and A. P. Kriven'ko, *Russ. J. Org. Chem*., 2017, **53**, 639.
46. G. P. Kantin and M. Krasavin, *Chem. Heterocycl. Compd.*, 2016, **52**, 918.
47. M. A. Metwally and M. Abdel-Mogib, *Heterocycl. Commun.*, 1999, **5**, 423.
48. R. Ghorbani-Vaghei, Z. Toghraei-Semiromi, M. Amiri, and R. Karimi-Nami, *Mol. Divers.*, 2013, **17**, 307.
49. V. A. Chebanov, Y. I. Sakhno, S. M. Desenko, S. V. Shishkina, V. I. Musatov, O. V. Shishkin, and I. V. Knyazeva, *Synthesis*, 2005, 2597.
50. L.-Y. Zeng, Y.-M. Ren, and C. Cai, *Synth. Commun.*, 2011, **41**, 3635.
51. S. V. Ryabukhin, A. S. Plaskon, S. Y. Boron, D. M. Volochnyuk, and A. A. Tolmachev, *Mol. Divers.*, 2011, **15**, 189.
52. S. V. Ryabukhin, V. S. Naumchik, O. O. Grygorenko, and A. A. Tolmachev, *J. Heterocycl. Chem.*, 2012, **49**, 1147.
53. S. M. Desenko, E. S. Gladkov, S. A. Komykhov, O. V. Shishkin, and V. D. Orlov, *Chem. Heterocycl. Compd.*, 2001, **37**, 747.
54. M. Shen, J. Wang, S. Shang, and Z. Song, *Chem. Lett.*, 2014, **43**, 1239.
55. Y. Dai, G. Qi, and X. Qian, *J. Chem. Res.*, 2013, **37**, 705.
56. L. Suresh, P. Onkara, P. S. V. Kumar, Y. Pydisetty, and G. V. P. Chandramouli, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 4007.
57. V. P. Krivopalov, V. I. Mamatyuk, and E. B. Nikolaenkova, *Russ. Chem. Bull*., 1995, **44**, 1435.
58. E. M. H. Abbas, S. M. Gomha, and T. A. Farghaly, *Arab. J. Chem.*, 2014, **7**, 623.
59. S. M. Gomha, T. M. A. Eldebss, M. G. Badrey, M. M. Abdulla, and A. S. Mayhoub, *Chem. Biol. Drug Des.*, 2015, **86**, 1292.
60. T. A. Farghaly, A. S. Shawali, E. M. H. Abbas, and N. A. Abdel-hafez, *Curr. Org. Synth.*, 2015, **12**, 95.
61. O. N. Petrova, L. L. Zamigajlo, S. V. Shishkina, O. V. Shishkin, V. I. Musatov, A. V. Borisov, and V. V. Lipson, *Tetrahedron*, 2013, **69**, 11185.
62. M. V. Goryaeva, Ya. V. Burgart, M. A. Ezhikova, M. I. Kodess, and V. I. Saloutin, *Beilstein J. Org. Chem.*, 2015, **11**, 385.



Anton V. Dolzhenko received his degree (with Distinction) in Pharmacy in 2000 and then a PhD degree in Medicinal Chemistry in 2004, both from the Perm State Pharmaceutical Academy (Russia). After that he joined National University of Singapore and worked there for 6 years before he moved to the School of Pharmacy, Curtin University (Australia) in 2010 and continued his academic career as a Senior Lecturer. In 2013, he joined Monash University Malaysia, where he has been working as an Associate Professor and the Deputy Head (Research) of School of Pharmacy. He also acts as the Director of the NMR Campus Infrastructure Platform, which he established in the campus. His current research interests include synthetic and structural aspects of chemistry of nitrogen heterocycles. He has been actively working on the development of new synthetic methods for the preparation of potentially bioactive heterocyclic compounds. He is particularly interested in green chemistry approaches for drug discovery.