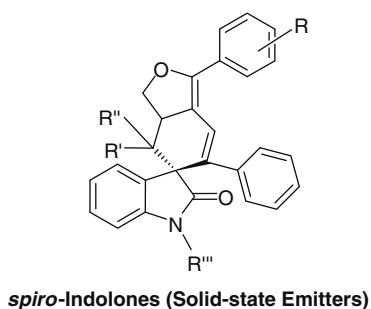
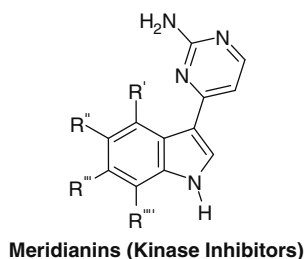
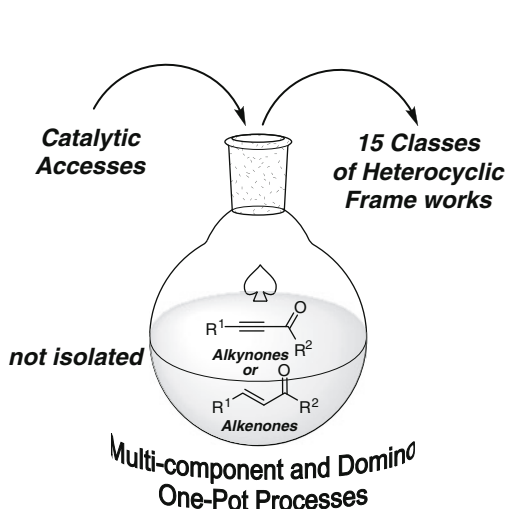


Session 2
Multi-Component Reactions
in Heterocyclic Chemistry

Multi-component Synthesis of Heterocycles by Palladium-catalyzed Generation of Alkynones, Alkenones and Allenes

Thomas J.J. Müller

Multi-component and domino reactions are efficient and effective methods in the sustainable and diversity-oriented synthesis of heterocycles. In particular, transition metal-catalyzed multi-component sequences have recently gained considerable interest. Based upon the Sonogashira entry to alkynones, alkenones, and intermediate allenenes, we have opened new avenues to the one-pot synthesis of numerous classes of heterocyclic frameworks in an MCR fashion. This methodological approach has now found various applications in one-pot syntheses of functional chromophores, pharmaceutically active compounds, and marine alkaloids and derivatives.



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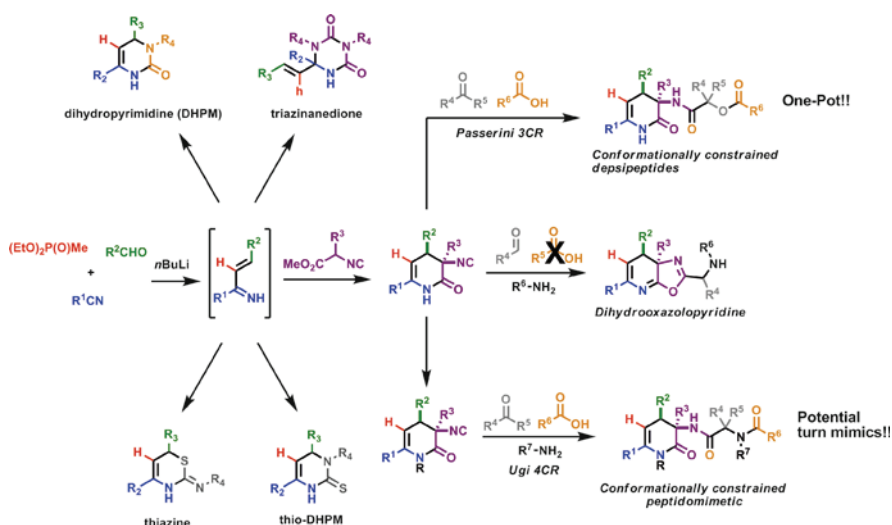
References

- D'Souza DM, Müller TJJ. (2007) Multi-component syntheses of heterocycles by transition-metal catalysis. *Chem Soc Rev* 36:1095–1120.
- Willy B, Müller TJJ. (2008) Consecutive multi-component syntheses of heterocycles via palladium–copper catalyzed generation of alkynones. *ARKIVOC Part I*:195–212.
- Schramm OG, Oeser T, Kaiser M, Brun R, Müller TJJ. (2008) Rapid one-pot synthesis of anti-parasitic quinolines based upon the microwave-assisted coupling-isomerization reaction (MACIR). *Synlett* 2008:359–362.

Multi-component Reactions as Useful Platforms to Explore the Chemical Space

Romano V. A. Orru

The rapid generation of diverse sets of complex molecules can be achieved by employing diversity-oriented synthetic strategies in combination with so-called complexity-generating reactions. Multi-component reactions (MCRs), which combine in one pot at least three simple building blocks, provide a most powerful platform to access diversity as well as complexity in a limited number of reaction steps. Here we describe novel modular reaction sequences based on our previously reported MCR chemistry in combination with other common organic reactions or even with a second MCR. The combination of our MCRs with, e.g., cycloadditions, transition-metal mediated cross-coupling reactions, or more traditional MCRs, such



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as the Biginelli-3CR, the Ugi-4CR, and the Passerini-3CR, will be shown. Examples in which the synthetic methodology was applied for the easy generation of focused libraries for the synthesis of medicinally relevant ligands will be discussed.

References

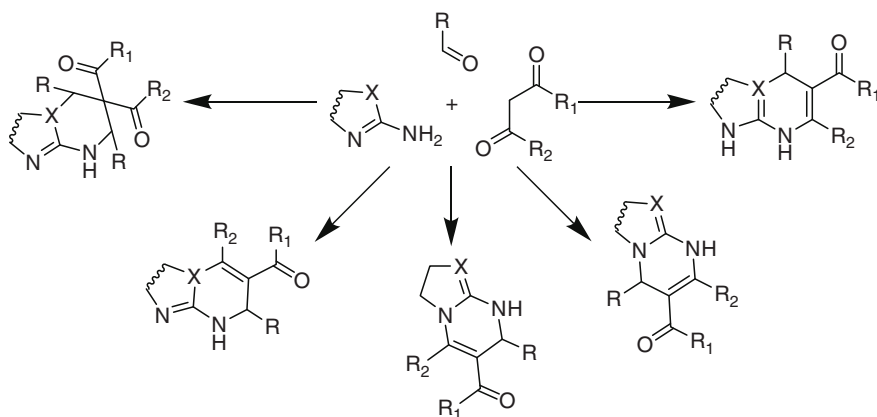
- Bon RS, Vliet van B, Sprenkels NE, Schmitz RF, Kanter de FJJ, Stevens CV, Swart M, Bickelhaupt FM, Groen MB, Orru RVA. (2005) Multicomponent synthesis of 2-imidazolines. *J Org Chem* 70:3542–3546.
- Orru RVA, de Greef M. (2003) Recent advances in solution-phase multicomponent methodology for the synthesis of heterocyclic compounds. *Synthesis* 10:1471–1499.
- Paravidino M, Bon RS, Scheffelaar R, Vugts DJ, Znabet A, Kanter de FJJ, Lutz M, Spek AL, Groen MB, Orru RVA. (2006) Diastereoselective multicomponent synthesis of dihydropyridones with an isocyanide functionality. *Org Lett* 8:5369–5372.
- Elders N, Schmitz RF, de Kanter FJJ, Ruijter E, Groen MB, Orru RVA. (2007) A resource-efficient and highly flexible procedure for a three-component synthesis of 2-imidazolines. *J Org Chem* 72:6135–6142.
- Groenendaal B, Vugts DJ, Schmitz RF, de Kanter FJJ, Ruijter E, Groen MB, Orru RVA. (2008) A multicomponent synthesis of triazinane diones. *J Org Chem* 73:719–725.
- Groenendaal B, Ruijter E, Orru RVA. (2008) 1-Azadienes in cycloaddition and multicomponent reactions towards N-heterocycles. *Chem Commun* (43):5474–5476.

Multi-component Heterocyclizations: Control of Chemo- and Regioselectivity

Valentin A. Chebanov, Yana I. Sakhno, Vyacheslav E. Saraev,
Elena A. Muravyova, Anastasia Yu. Andrushchenko, and Sergey M. Desenko

The control of selectivity, for example chemo- and regioselectivity, is among the most important objectives in organic chemistry. For multi-component reactions involving the simultaneous molecular interaction of three or more components, the issue of selectivity is of particular significance due to the high probability of several potential parallel reaction pathways leading to different product classes. Many different process parameters such as temperature, pressure, solvent, catalyst type, microwave and ultrasonic irradiations, and other factors can be utilized to modulate the selectivity of synthetic transformations.

In the present report some of our results in the tuning of chemo- and regioselectivity of multi-component reactions involving active methylene compounds, carbonyls, and aminoazoles, containing several nonequivalent nucleophilic reaction centers, are observed. The general principles of the direction control for this type of interaction are reported, and synthetic methodology allowing high selectivity in obtaining certain types of heterocycles is presented.



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References

- Chebanov VA, Sakhno YI, Desenko SM, Shishkina SV, Musatov VI, Shishkin OV, Knyazeva IV. (2005) Three-component procedure for the synthesis of 5-aryl-5,8-dihydroazolo[1,5-*a*]pyrimidine-7-carboxylic acids. *Synthesis* (15):2597.
- Chebanov VA, Muravyova EA, Desenko SM, Musatov VI, Knyazeva IV, Shishkina SV, Shishkin OV, Kappe CO. (2006) Microwave-assisted three-component synthesis of 7-aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides and their selective reduction. *J Comb Chem* 8:427.
- Chebanov VA, Saraev VE, Desenko SM, Chernenko VN, Knyazeva IV, Groth U, Glasnov T, Kappe CO. (2008) Tuning of chemo- and regioselectivities in multicomponent condensations of 5-aminopyrazoles, dimedone, and aldehydes. *J Org Chem* 73:5110.
- Sakhno YI, Desenko SM, Shishkina SV, Shishkin OV, Sysoyev DO, Groth U, Kappe CO, Chebanov VA. (2008) Multicomponent cyclocondensation reactions of aminoazoles, arylpyruvic acids and aldehydes with controlled chemoselectivity. *Tetrahedron* 64:11041.

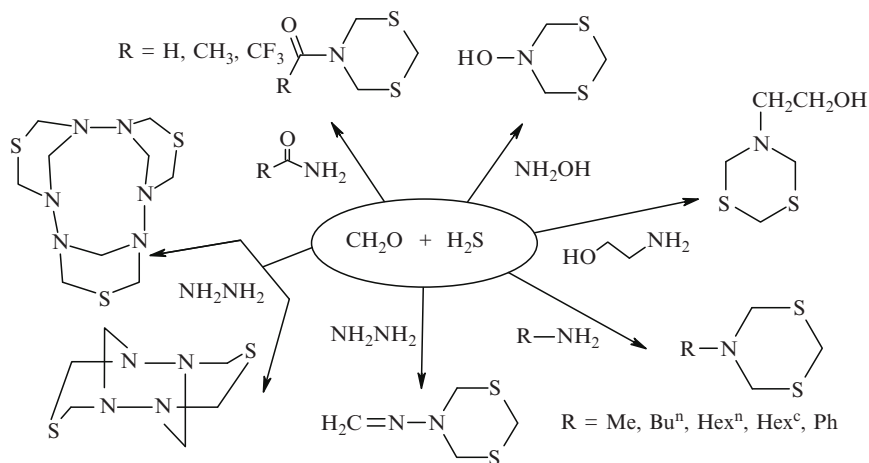
Multi-component Reactions of H_2S with Aldehydes and Amines as an Efficient Route to Heterocycles and Thioaza-Crown Compounds

V. R. Akhmetova, G. R. Khabibullina, E. B. Rakhimova, R. A. Vagapov, R.R. Khairullina, Z.T. Niatshina, and N.N. Murzakova

The approaches to the synthesis of sulfur- and nitrogen-containing mono- and poly-heterocycles obtained by condensation of amines and hydrazines with thiomethylating reagent " $\text{CH}_2\text{O}-\text{H}_2\text{S}$ ".

Nowadays our attention focuses on the investigation of synthetic possibilities of multi-component reactions of H_2S with different carbonyl compounds, amines, and hydrazines to produce new types of heterocyclic compounds, such as substituted thiadiazinanes (**1**), dithiadiazacyclooctanes (**2**), and thiadiazaz- (**3**) and dithiadiazabicyclanes (**4**).

In this report the results of investigations devoted to the *one-pot* design of thioaza-crown compounds are considered. The rules which define intermolecular cyclocondensation of binucleophilic starting compounds with the " $\text{CH}_2\text{O}-\text{H}_2\text{S}$ " reagent will be discussed.

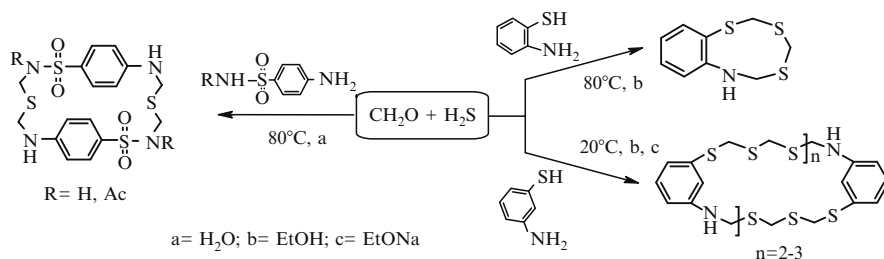


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Sulfur- and nitrogen-containing heterocycles are of special interest as potential antibacterial and antivirus preparations and also as selective sorbents and flotation agents for metals and complexones in supramolecular chemistry.

References

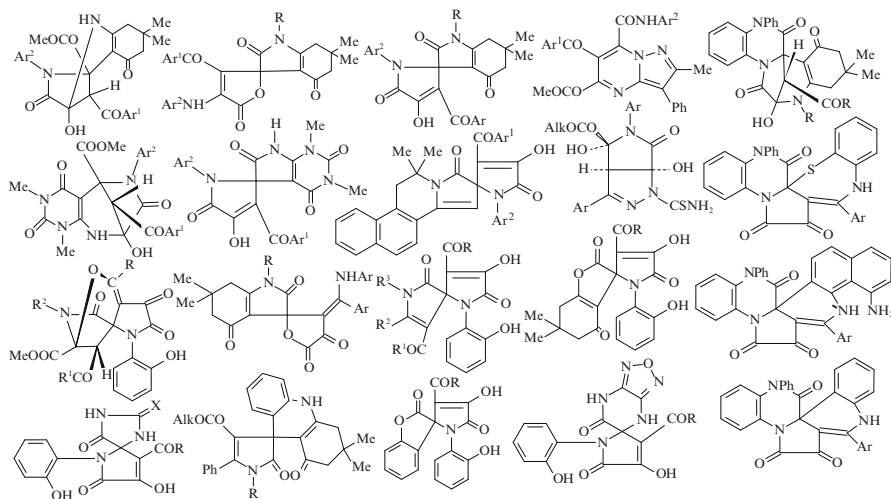
- Akhmetova VR, et al. (2004) Multicomponent heterocyclization of hydrazine, hydrogen sulfide, and formaldehyde. *Russ Chem Bull Int Ed* 8:1717.
- Akhmetova VR, et al. (2004) Multicomponent condensation of aliphatic amines with formaldehyde and hydrogen sulfide. *Russ Chem Bull Int Ed* 2:432.
- Akhmetova VR, et al. (2007) Thiomethylation of amino alcohols using formaldehyde and hydrogen sulfide. *Russ J Org Chem* 6:919.

Cascade Recyclizations of 1*H*-Pyrrole-2,3-diones: A Method of Unusual Heterocyclic Systems Construction

Andrey N. Maslivets

Monocyclic 1*H*-pyrrole-2,3-diones and 1*H*-pyrrole-2,3-diones, in which one pyrrolidone cycle is annexed to an azaheterocyclic fragment, under the action of NH, OH, SH, CH *bi*-nucleophilic reagents undergo cascade recyclizations with unusual condensed, bridged, and spiro-*bis*-azaheterocyclic systems formation. Some examples of the formed compounds that have resulted appear below.

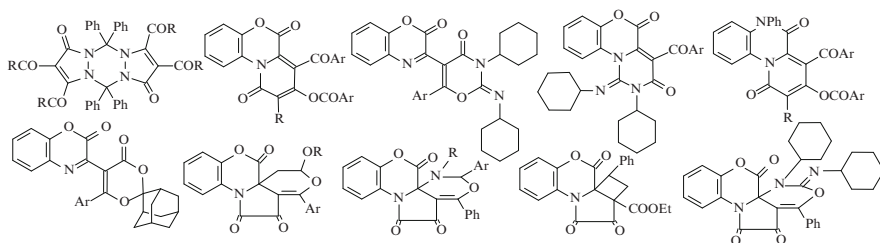
Cycloaddition reactions of 1*H*-pyrrole-2,3-diones and heterocumulenes, generated on their basis, represent a convenient way of unusual condensed azaheterocyclic systems and ensembles of heterocyclic systems formation. Below are some examples of the formed compounds that have resulted.



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In the report, schemes of the mentioned transformations will be presented.

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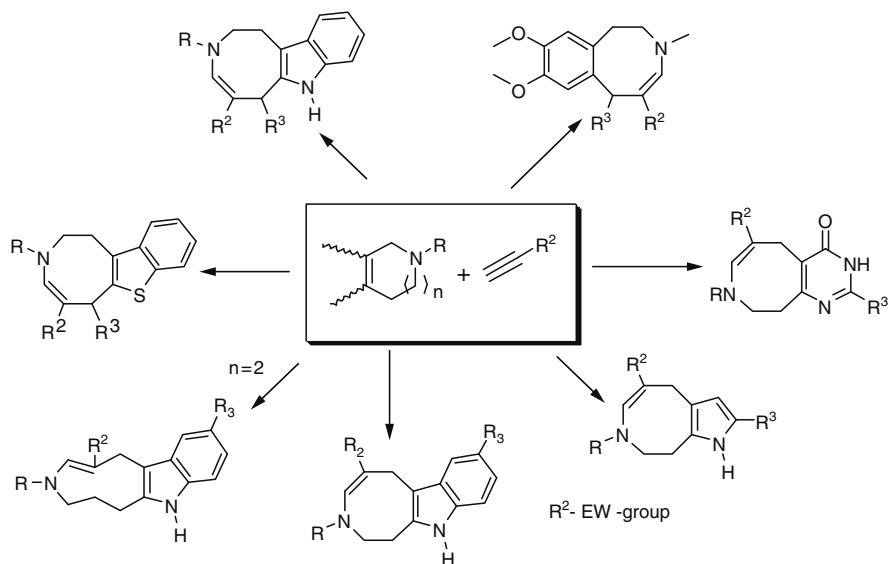
References

- Silaichev PS, Dmitriev MV, Aliev ZG, Maslivets AN. (2010) Five-membered 2,3-dioxoheterocycles: LXVII. Pyrroledione-pyrroledion recyclization of isopropyl 2-(1-aryl-4,5-dioxo-2-phenyl-4,5-dihydro-1*H*-pyrrol-3-yl)-2-oxoacetates under the action of arylamines. Crystal and molecular structure of (z)-isopropyl 2-hydroxy-4,5-dioxo-1-phenyl-3-[phenyl(phenylamino)-methylene]pyrrolidine-2-carboxylate. *Russ J Org Chem* 46(2):255–259.
- Denislamova ES, Maslivets AN. (2010) Five-membered 2,3-dioxoheterocycles: LXVIII. Three pathways in the reaction of methyl 3-aroyl-1-aryl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates with 3-amino-5,5-dimethylcyclohex-2-en-1-one. *Russ J Org Chem* 46(3):389–393.
- Khalturina VV, Shklyayev YS, Aliev ZG, Maslivets AN. (2010) Five-membered 2,3-dioxoheterocycles: LXIX. Direct heterocyclization of [3,4-dihydroisoquinolin-1(2*H*)-ylidene]-acetamides with 5-arylfuran-2,3-diones. Crystalline and molecular structure of (3*E*,5*Z*)-3-[3,3-dimethyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene]-5-(2-oxo-2-phenylethylidene)pyrrolidine-2,4-dione. *Russ J Org Chem* 46(4):539–542.

Alkyne-Induced Tandem Transformations of (Hetero)Annulated Five-, Six-, or Seven-Membered *N*-Heterocycles and a New MCR on This Motif

Leonid G. Voskressensky

Medium-sized N-containing heterocycles, in particular eight- and nine-membered rings, are key structures of various structurally remarkable natural products. As the direct formation of these ring sizes from acyclic precursors is entropically and enthalpically disfavored, the efficient construction of medium-sized cycles is a challenge and has therefore attracted considerable attention in recent years. We have recently reported tetrahydropyridine (THPy) and tetrahydroazepine ring expansion in tetrahydropyrrolopyridines under the action of activated alkynes. Applying this methodology to other THP and tetrahydroazepine-containing substrates showed that this reaction is general for a number of heterocyclic systems (Scheme 1).

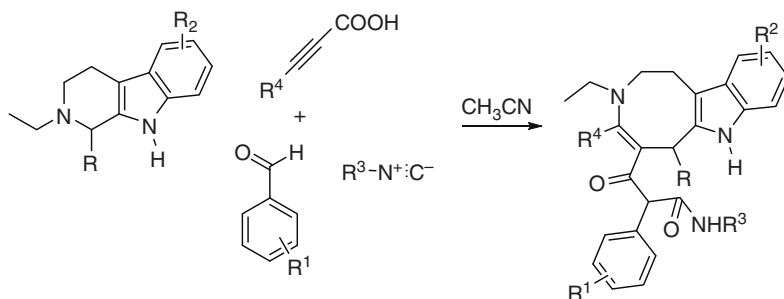


Scheme 1 Synthesis of medium-size heterocycles

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We have elaborated a new isocyanide-based MCR representing the combination of the Passerini reaction with the above-described tetrahydropyridine ring enlargement process (Scheme 2). The scope and limitations of this MCR will be discussed.



Scheme 2 Tandem of the Passerini reaction and tetrahydropyridine ring enlargement

References

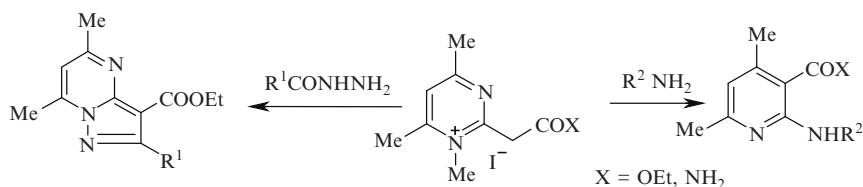
- Voskressensky LG, Borisova TN, Kulikova LN, Varlamov AV, Catto M, Altomare C, Carotti A. (2004) Tandem cleavage of hydrogenated β - and γ -carboline – new practical synthesis of tetrahydroazocino[4,5-*b*]indoles and tetrahydroazocino[5,4-*b*]indoles showing acetylcholinesterase inhibitory activity. *Eur J Org Chem* 2004(14):3128–3135.
- Voskressensky LG, Kulikova LN, Borisova TN, Varlamov AV. (2008) Synthesis of heteroannulated azocine derivatives. *Adv Heterocycl Chem* 96:81–122.

N-C and C-C Recyclizations of Pyrimidinium Salts

Gevorg G. Danagulyan, Armen D. Murtchyan, and Araksya K. Tumanyan

The urgency of the study of pyrimidine systems' nucleophilic rearrangements is doubtless. They attract researchers' attention by the fact that they are not always *a priori* evident and frequently unpredictable. Accompanied with the complex reconstruction of a molecule skeleton resulting in a cardinal change of configuration, they are nevertheless one-stage processes from the preparative point of view that just predetermines the interest toward the study of similar transformations. Recent publications have shown that these reactions have turned into an important method of organic synthesis and have been applied for the transformation of various biologically active and medicinal compounds – nucleosides and drugs.

We have studied in detail rearrangements of recyclizational transformations of pyrimidines into pyridine derivatives (the so-called Kost–Sagitullin rearrangements). In these reactions the nitrogen atom of a pyrimidine ring is substituted by the exocyclic carbon atom being in the second position (*N*-C substitution or *N*-C recyclizations) (Scheme 1); another type of nucleophilic recyclization of pyrimidines,

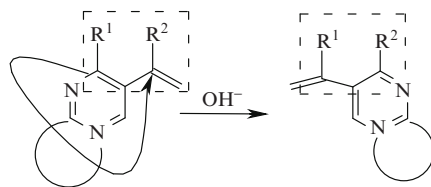


Scheme 1 Kost-Sagitullin rearrangement

G.G. Danagulyan (✉)

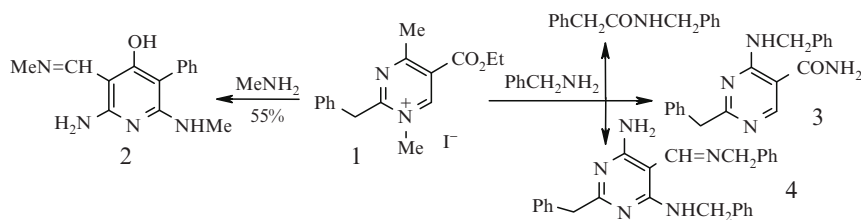
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**Scheme 2** C–C recyclization

which occurs with a heterocycle substitution of the carbon atom by the exocyclic carbon atom, is the C–C recyclization (Scheme 2).

In developing our investigations of nucleophilic recyclizations, we studied transformations of pyrimidines on the models that are potentially able to competitively undergo various types of recyclizations – both Dimroth rearrangements and/or Kost–Sagitullin rearrangements, and C–C recyclizations. As a result of the reaction of pyrimidinium salt **1** with alcoholic methylamine, we managed to isolate from the reaction mixture a compound in 55% yield methylimine of 2-amino-4-hydroxy-6-methylamino-5-phenylpyridine-3-aldehyde (**2**). The same salt **1**, when heated in benzylamine, transformed into a mixture of three compounds: the product of destructive aminolysis (33%) and two products of C–C recyclization, pyrimidines **3** and **4** (Scheme 3).

**Scheme 3** Various types of recyclizations

References

- Danagulyan GG, Sahakyan LG, Katritzky AR, Denisenko SN. (2000) Exchange aminations in conversions of pyrimidinium iodides to 2-alkylaminonicotinic acids. *Heterocycles* 53:419.
- Danagulyan GG. (2005) Kost–sagitullin rearrangement and other isomerization recyclizations of pyrimidines. (Review). *Chem Heterocycl Comp* 41:1205.

Synthetic Approach to Highly Functionalized Mesocyclic Heterocycles by Coupling an Ugi or Passerini Reaction (PADAM Strategy) with a Pd-Mediated Cyclocarbonylation

Luca Banfi, Andrea Basso, Fabio De Moliner, Giuseppe Guanti, Elena Petricci, Renata Riva, and Maurizio Taddei

Multi-component reactions are useful tools for the synthesis of innovative and very complex scaffolds according to a convergent approach, providing a molecule that contains fragments derived from all the building blocks employed in the MCR condensation in a single synthetic step. As they can be followed by postcondensation transformations exploiting additional functional groups present in the building blocks and inert during the MCR step, they are particularly suitable for diversity-oriented synthesis.

In this context, we explored the possibility of submitting MCR-derived precursors, endowed with a bromine on an aryl moiety, to an intramolecular cyclocarbonylation reaction, in order to develop a fast new entry to highly functionalized and unusual N-heterocycles.

For this purpose we synthesized a series of compounds, equipped with a free alcoholic hydroxy group or a free secondary amino group. This task was accomplished by exploiting either the PADAM (Passerini-amine deprotection-acyl migration) strategy or an Ugi reaction followed by an unusual rearrangement that leaves the amine-derived nitrogen free to undergo the following process. In both cases we also placed the required bromine atom either on the isocyanide or on the amine moiety.

The acyclic precursors were then submitted to the cyclocarbonylation reaction promoted by a Pd catalyst under carbon monoxide atmosphere and microwave irradiation. The results of these preliminary tests will be discussed.

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References

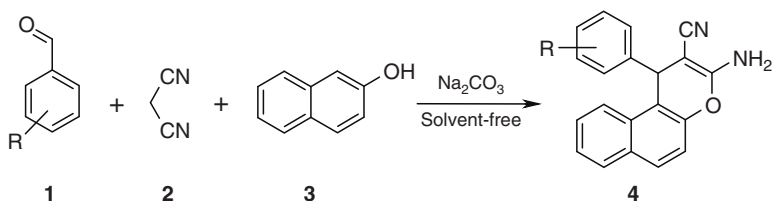
- Burke MD, Schreiber SL. (2004) A planning strategy for diversity-oriented synthesis. *Angew Chem Int Ed* 43:46–58.
- Banfi L, Basso A, Guanti G, Riva R. (2003) Passerini reaction – amine deprotection – acyl migration (PADAM): a convenient strategy for the solid-phase preparation of peptidomimetic compounds. *Mol Div* 6:227–235 and articles quoted within.
- Zhu J, Bienaymé H. (2005) Multicomponent reactions. Weinheim: Wiley.

Solvent-Free Three-Component Condensation of Aldehydes and Malononitrile with Naphthols Affording 2-Amino-4*H*-chromenes

M. Reza Naimi-Jamal, Sara Mashkouri, and Ali Sharifi

Solvent-free and one-pot multi-component condensations represent very powerful green chemical technology procedures from both economical and synthetic points of view and represent a possible instrument to perform a near-ideal synthesis.

2-Amino-4*H*-chromenes represent an important class of compounds; they are the main components of many naturally occurring products and are generally prepared by refluxing malononitrile, an aldehyde, and an activated phenol in the presence of hazardous organic bases such as piperidine in organic solvents such as ethanol and acetonitrile for several hours.



Herein we wish to report the three-component condensation of aldehydes and malononitrile with α - and β -naphthols with excellent yields.

General Procedure for 2-Amino-4*H*-Chromenes

In a typical experiment, a stoichiometric mixture of an aldehyde (**1**), malononitrile (**2**), and β -naphthol (**3**) (1.0 mmol each) and sodium carbonate (0.1 mmol) were mixed using a mortar and pestle. The resulting mixture was heated in a drying oven at

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125°C. After cooling, the mixture was washed with hot water and purified by recrystallization from hot ethanol, if necessary.

Different 2-amino-4*H*-chromenes were prepared with a similar method. The procedure is very simple, efficient, and environmentally friendly, as it does not use any solvent and toxic catalyst.

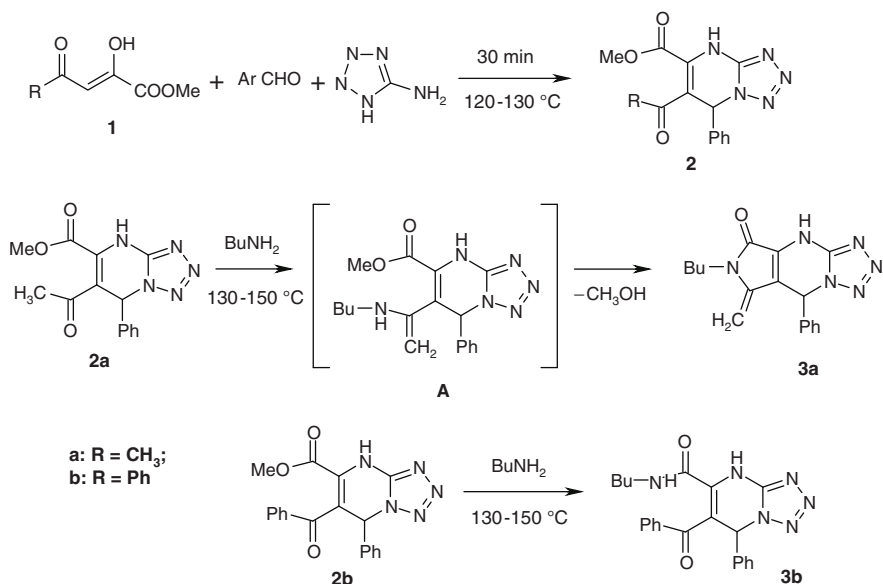
References

- Kaupp G. (2005) Organic solid-state reactions with 100% yield. *Top Curr Chem* 254:95–183.
- Kemnitz W, Kasibhatla S, Jiang S, Zhang H, Zhao J, Jia S, Xu L, Crogan-Grundy C, Denis R, Barriault N, Vaillancourt L, Charron S, Dodd J, Attardo G, Labrecque D, Lamothe S, Gourdeau H, Tseng B, Drewe J, Cai SX. (2005) Discovery of 4-aryl-4*H*-chromenes as a new series of apoptosis inducers using a cell- and caspase-based high-throughput screening assay. 2. Structure–activity relationships of the 7- and 5-, 6-, 8-positions. *Bioorg Med Chem Lett* 15:4745–4751.
- Anderson DR, Hegde S, Reinhard E, Gomez L, Vernier WF, Lee L, Liu S, Sambandam A, Snider PA, Masih L. (2005) Aminocyanopyridine inhibitors of mitogen activated protein kinase-activated protein kinase 2 (MK-2). *Bioorg Med Chem Lett* 15:1587–1590.

New Pyrido[3,2-*c*]pyridones and Pyrido[3,2-*c*]pyrazoles Accessible by a One-Step Multi-component Synthesis

Nikolai M. Przhevalski, Elena N. Rozhkova, Gennadii P. Tokmakov,
and Igor V. Magedov

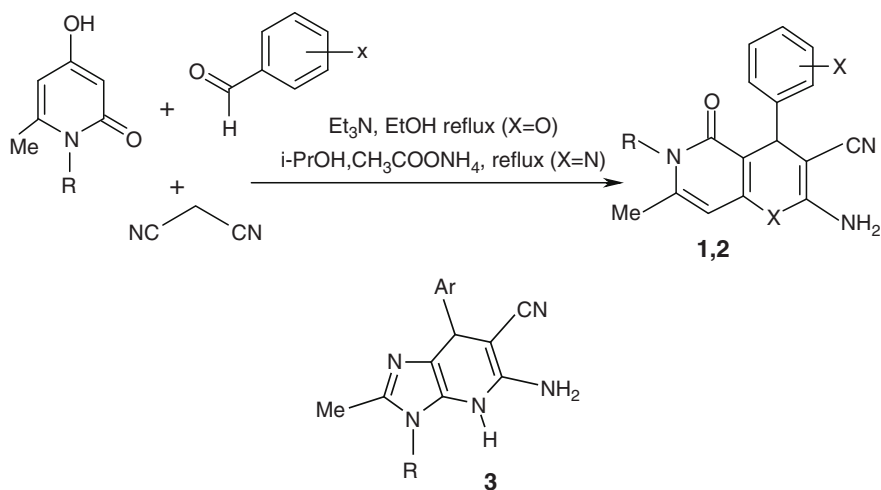
We have recently initiated a research program aimed at the structural simplification of natural products, specifically by utilizing multi-component synthetic processes. We showed that the stereochemically complex structure of an important anticancer lead podofillotoxin can be efficiently simplified to a dihydropyridopyrazole scaffold, which is accessible via a one-step multi-component synthetic reaction. The resulting library of compounds retains a significant portion of podofillotoxin's



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cytotoxic potency and apoptosis-inducing potential. In these efforts, we have been investigating a compound library based on pyrano[3,2-*c*]pyridine (**1**, X=O) and pyrano[3,2-*c*]quinolone scaffolds. A three-component reaction of pyridon (or quinolone) with malononitril and various aromatic aldehydes in a 1:1:1 ratio proceeds smoothly in refluxing ethanol containing a small quantity of Et₃N.

To develop compound libraries, we considered a reaction of 4-hydroxypyridones (as well as pyrazolones) with aldehydes, malononitril, and ammonium acetate. Indeed, we found that the desired compounds, pyrido[3,2-*c*]pyridones (**2**) and pyridopyrazoles (**3**), can be synthesized via a four-component reaction.



References

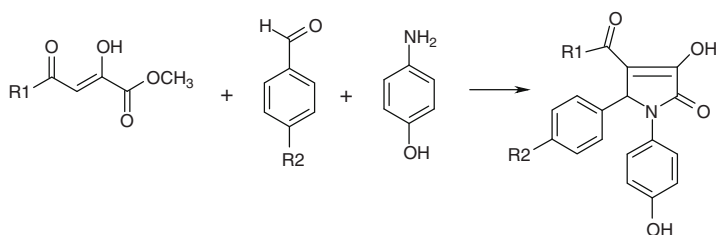
- Magedov IV, Manpadi M, Rozhkova EN, Przheval'skii NM, Rogelj S, Shors ST, Steelant WFA, Van Slambrouck S, Kornienko A. (2007) Structural simplification of bioactive natural products with multicomponent synthesis: dihydropyridopyrazole analogues of podophyllotoxin. *Bioorg Med Chem Lett* 17:1381.
- Magedov I, et al. (2008) Structural simplification of bioactive natural products with multicomponent synthesis. 2. Antiproliferative and antitubulin activities of pyrano[3,2-*c*]pyridones and pyrano[3,2-*c*]quinolones. *J Med Chem* 51:2561.
- Magedov IV, Manpadi M, Van Slambrouck S, Steelant WFA, Rozhkova E, Przheval'skii NM, Rogelj S, Kornienko A. (2007) Discovery and investigation of antiproliferative and apoptosis-inducing properties of new heterocyclic podophyllotoxin analogues accessible by a one-step multicomponent synthesis. *J Med Chem* 50:5183.

Synthesis of 1-Hydroxyaryl-4-Acyl-5-Aryl-3-Hydroxy-3-Pyrrolin-2-Ones

M. N. Armisheva, N. A. Rassudihina, M. I. Vahrin, and V. L. Gein

Multi-component reactions have attracted enormous interest. Among the multi-component reactions, the three-component processes have been developed into useful organic procedures. The 3-hydroxy-3-pyrrolin-2-one derivatives are important due to their therapeutic and pharmacological properties.

Our investigations have shown that equivalent amounts of methylic esters of acylpyruvic acids, 4-aminophenoles, and aromatic aldehyde in glacial acid, with good yields, lead to 1-hydroxyaryl-4-acyl-5-aryl-3-hydroxy-3-pyrrolin-2-ones (**I–XXX**).



I–XXX

- I** ($R^1 = \text{Ph}$, $R^2 = \text{H}$), **II** ($R^1 = \text{H}$, $R^2 = \text{H}$), **III** ($R^1 = \text{H}$, $R^2 = 4\text{-Cl}$), **IV** ($R^1 = \text{Ph}$, $R^2 = 4\text{-Cl}$),
V ($R^1 = \text{H}$, $R^2 = 2\text{-NO}_2$), **VI** ($R^1 = \text{H}$, $R^2 = 2\text{-OCH}_3$), **VII** ($R^1 = \text{H}$, $R^2 = 4\text{-CH}_3$),
VIII ($R^1 = \text{H}$, $R^2 = 2\text{-NO}_2$), **IX** ($R^1 = \text{H}$, $R^2 = 2\text{-Cl}$), **X** ($R^1 = \text{H}$, $R^2 = 2,5(\text{OCH}_3)_2$),
XI ($R^1 = \text{H}$, $R^2 = 2\text{-F}$), **XII** ($R^1 = \text{H}$, $R^2 = 4\text{-C}_3\text{H}_7$), **XIII** ($R^1 = \text{H}$, $R^2 = 4\text{-NO}_2$),
XIV ($R^1 = \text{H}$, $R^2 = 3\text{-OCH}_3$), **XV** ($R^1 = \text{H}$, $R^2 = \text{Ph}$), **XVI** ($R^1 = \text{H}$, $R^2 = 4\text{-F}$),
XVII ($R^1 = \text{H}$, $R^2 = 3\text{-OCH}_3\text{-4-OH}$), **XVIII** ($R^1 = \text{H}$, $R^2 = 3\text{-F}$), **XIX** ($R^1 = \text{Ph}$, $R^2 = 3,4\text{-(OCH}_3)_2$),
XX ($R^1 = \text{Ph}$, $R^2 = 2\text{-NO}_2$), **XXI** ($R^1 = \text{Ph}$, $R^2 = 3\text{-NO}_2$), **XXII** ($R^1 = 4\text{-CH}_3$, $R^2 = 4\text{-CH}_3$),
XXIII ($R^1 = 4\text{-CH}_3$, $R^2 = \text{Ph}$), **XXIV** ($R^1 = 4\text{-CH}_3$, $R^2 = 3\text{-F}$), **XXV** ($R^1 = 4\text{-CH}_3$, $R^2 = 2\text{-Cl}$),
XXVI ($R^1 = 4\text{-CH}_3$, $R^2 = 4\text{-NO}_2$), **XXVII** ($R^1 = \text{Ph}$, $R^2 = \text{Ph}$), **XXVIII** ($R^1 = 4\text{-CH}_3$, $R^2 = 4\text{-F}$),
XXIX ($R^1 = 4\text{-CH}_3$, $R^2 = 4\text{-Br}$), **XXX** ($R^1 = 4\text{-CH}_3$, $R^2 = 4\text{-OCH}_3$).

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The proposed structures of the synthesized compounds were confirmed by IR and ^1H NMR spectroscopy.

Reference

Gein VL. (2004) Tetrahydropyrrol- and tetrahydrofuran-2,3-diones. Perm, Russia: PSPA.

Synthesis of Highly Stable, Unusual Charge-Separated Pyridinium-, Isoquinolinium-, Quinolinium-, and N-Methylimidazolium-Tetronic Acid Zwitterions

Ahmad Shaabani, Ali Hossein Rezayan, Afshin Sarvary, Marjan Heidary, and Seik Weng Ng

In connection of our current studies on multi-component reactions involving zwitterionic species, and of our interest in the chemistry of tetronic acid, herein we would like to present a unique strategy for the synthesis of the highly stable, unusual charge-separated pyridinium-, isoquinolinium-, quinolinium-, and *N*-methylimidazolium-tetronic acid zwitterions from the three-component reaction of pyridine, isoquinoline, quinoline, and *N*-methylimidazole with dialkyl acetylenedicarboxylates and 3-chlorotetronic acid in EtOH at room temperature.

References

- Shaabani A, Maleki A, Moghimi-Rad J. (2007) A novel isocyanide-based three-component reaction: synthesis of highly substituted 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives. *J Org Chem* 72:6309–6317.
- Shaabani A, Maleki A, Mofakham H, Moghimi-Rad J. (2008) A novel one-pot pseudo-five-component synthesis of 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives. *J Org Chem* 73:3925–3931.
- Shaabani A, Maleki A, Mofakham H. (2008) Novel multicomponent one-pot synthesis of tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide derivatives. *J Comb Chem* 10:595–604.
- Shaabani A, Soleimani E, Maleki A. (2007) One-pot three-component synthesis of 3-aminoimidazo[1,2-*a*]pyridines and -pyrazines in the presence of silica sulfuric acid. *Monatsh Chem* 138:73–76.
- Shaabani A, Farhangi E, Rahmati A. (2006) Synthesis of tetrahydrobenzimidazo[1,2-*b*]quinazolin-1(2*H*)-one and tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-8(4*H*)-one ring systems under solvent-free conditions. *Comb Chem High Throughput Screen* 9:771–776.
- Shaabani A, Maleki A. (2007) Ionic liquid promoted one-pot three-component reaction: synthesis of annulated imidazo[1,2-*a*]azines using trimethylsilylcyanide. *Monatsh Chem* 138:51–56.

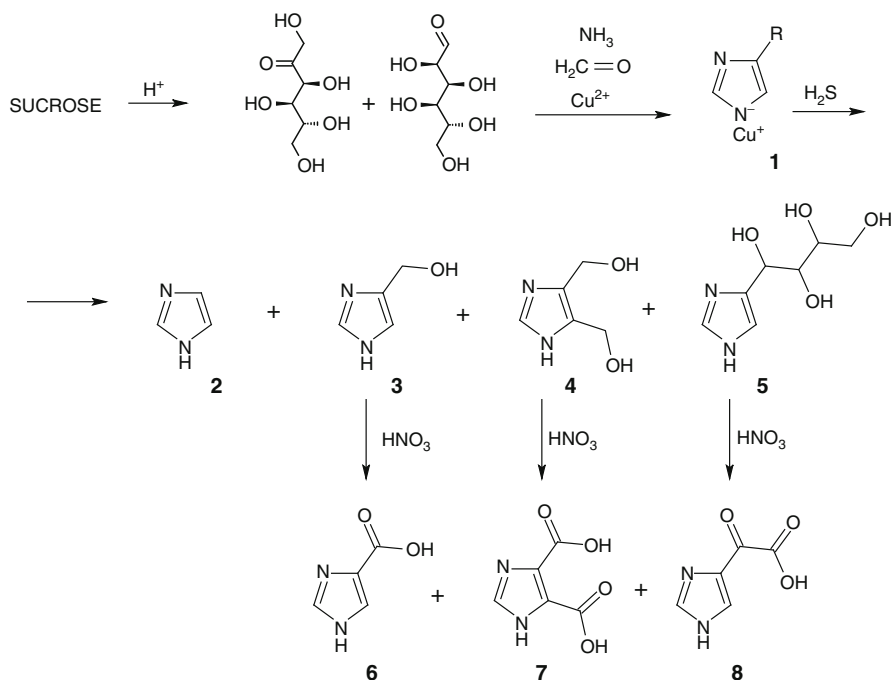
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Synthesis of 4(5)-Imidazolecarboxylic Acid Derivatives

Nikolai A. Beliaev, Vladimir S. Mokrushin, and Igor V. Paramonov

Products of the well-known multi-component imidazole ring formation reaction (the Weidenhagen method) were studied. Earlier it was known that, depending on the reaction conditions, 1*H*-imidazol-4-ylmethanol (3) [1,2,3,4] or 1-(1*H*-imidazol-4-yl)butane-1,2,3,4-tetrol (5) [4] forms. We have found that regardless of reaction conditions, copper salt 1 always contains imidazoles 2–5 in the following amounts: 2, 2–3%; 3, 16–19%; 4, 5–7%; 5, 6–8%. The decomposition of salt 1 in acid media,



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the removal of copper by H_2S , and the oxidation of the resulting mixture with diluted nitric acid at a high temperature gave acids 6–8, which were separated based on their different solubility and acidity. These results made it possible to elaborate the preparative synthesis method. After modification, the method was successfully used for the production of acids 6–8 (important intermediates) in kilogram amounts.

References

- Weidenhagen R, Herrmann R, Wegner H. (1937) Über neue Abkömmlinge des Imidazols (IV. Mitteil. über Imidazole). *Chem Ber* 70:575.
- Totter JR, Darby WJ. (1944) 4(5)-hydroxymethylimidazole hydrochloride. *Organic Synth* 24:64.
- Darby WJ, Lewis HB, Totter JR. (1942) The preparation of 4(5)-hydroxymethylimidazole. *J Am Chem Soc* 64:463.
- Parrod J. (1932) *Bull Soc Chim Fr* 51(4):1424–1426.
- Parrod J. (1933) *Ann Chim (Cachan, Fr)* 19(10):205, 232, 233, 238, 245.

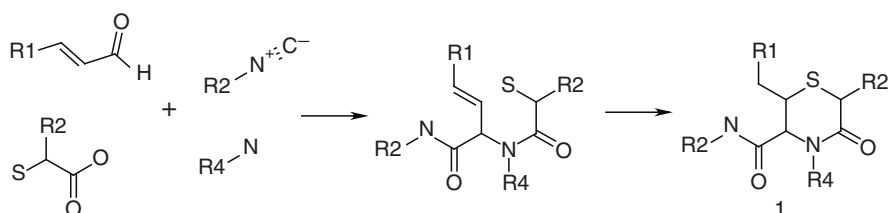
Short Communications: Synthesis Reactions

Polyfunctional U-MCR Reagents: Convenient Pathway to Novel Heterocyclic Systems

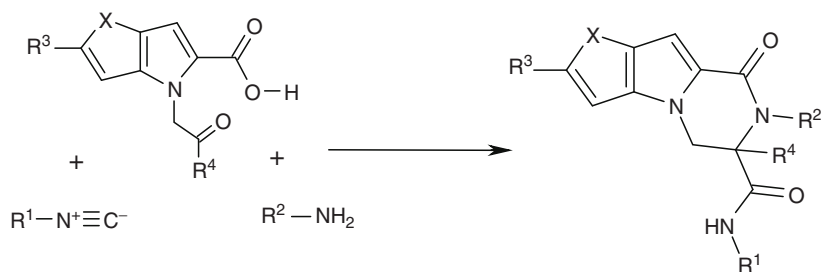
Alexey Ilyin

U-4MCR is a well-known synthetic method for the synthesis of different polyfunctional organic molecules. The use of bi- or tri-functional reagents usually leads to ring systems, some of which cannot be synthesized by other methods.

Some unsaturated carbonyl compounds in combination with oxy-, amino-, or mercaptoacids are suitable in U-4MCR with spontaneous postcondensation cyclization:



Also, the usage of aldehydo- or ketoacids in U-3MCR is convenient for the synthesis of different heterocyclic systems:

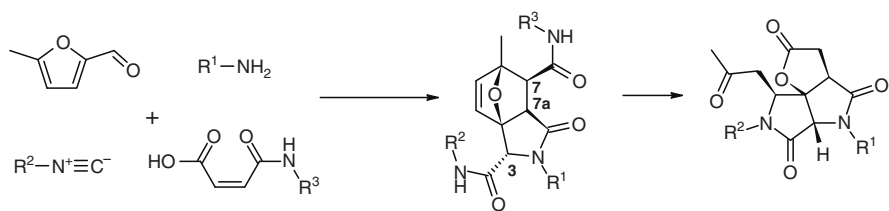


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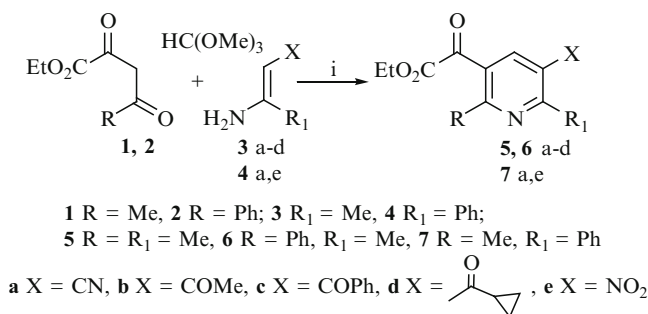
Also, interesting postcondensation skeleton rearrangements of tandem U-4MCR products lead to natural-like tricyclic products:



One-Pot Synthesis of Pyridines by Cyclocondensation of Acetyl- and Benzoylpyruvates, Trimethyl Orthoformate, and Enamines

Anna K. Garkushenko, Maria A. Dushek, Galina P. Sagitullina,
and Reva S. Sagitullin

The one-pot synthesis of nonsymmetrical pyridines by cyclocondensation of acetyl- (benzoyl)pyruvic acid esters, trimethyl orthoformate, and various enamines has been developed (Scheme 1).

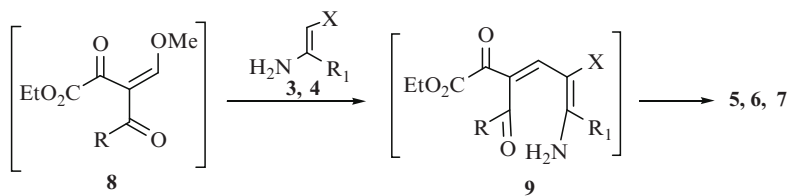


Scheme 1 One-pot synthesis of pyridines

The synthesis scheme to prepare pyridines **5–7** comprised of diketoesters' **1, 2** reaction with trimethyl orthoformate results in acetyl-(benzoyl)pyruvate methoxymethylene derivatives. The subsequent conjugated addition of enamines **3, 4** to the activated double bond of structure **8** (Michael reaction) followed by the two-step elimination of ethanol leads to intermediate **9**. The latter undergoes an intramolecular heterocyclization by the interaction of amino- and acetyl groups to form substituted pyridines **5–7** (Scheme 2).

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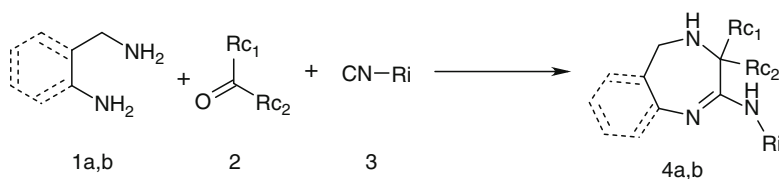
Scheme 2 Mechanism of the reaction

Acknowledgment Financial support of this work by the Russian Foundation for Basic Research (grant no. 07-03-00783-a) is gratefully acknowledged.

Unprecedented Multi-component Approach to 1,4-Diazepine- and 1,4-Benzodiazepine Ring Formation

Volodymyr Kysil, Alexander Khvat, Sergey Tsirulnikov, Sergey Tkachenko, and Alexandre Ivachtchenko

The isocyanide-based multi-component reaction of primary 1,3-diamines **1** with carbonyl compounds **2** has been developed as a novel approach to the 1,4-diazepine ring formation. The reaction of 1,3-diaminopropane **1a** and 2-aminobenzylamine **1b** affords hitherto unknown 2-aminoderivatives of 1,4-diazepine **4a** and 1,4-benzodiazepine **4b**, respectively, including those based on their *spiro*-heterocyclic compounds.



Importantly, the reaction of nonsymmetrical diamine **1b** proved to be highly regioselective, providing only one isomer, **4b**.

Detailed experimental features, mechanisms, and further applications of the developed reaction as well as its scope regarding each component will be discussed.

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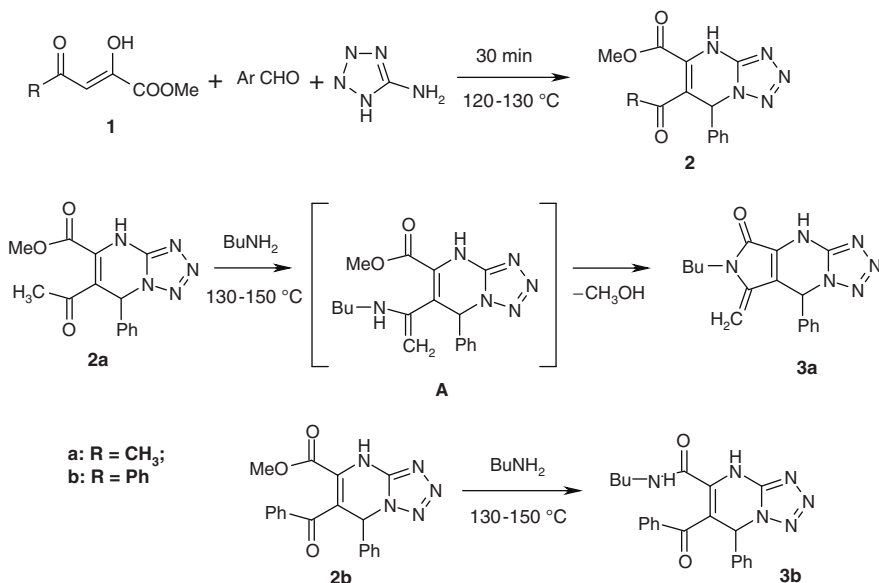
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Synthesis and Interaction with Butylamine of Methyl 6-Acyl-7-Phenyl-4,7-Dihydrotetrazolo[1,5-*a*]Pyrimidine-5-Carboxylates

Vladimir L. Gein and Olga S. Panova

Multi-component reactions have attracted an enormous interest due to their efficacy for the creation of heterocyclic compounds in a single synthetic step. Among the multi-component reactions, the three-component processes have been developed into useful organic procedures. The 1-*H*-1,2,4-tetrazole derivatives are important due to their therapeutic and pharmacological properties.



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Reaction of methyl esters acylpyruvic acids, 5-aminotetrazole, and benzaldehyde leads to the formation of corresponding methyl 6-acyl-7-phenyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-5-carboxylates (**2a, b**) under solvent-free conditions. As the next step, to investigate chemical properties, we studied the interaction of heterocyclic compounds **2a, b** with butylamine.

It has been observed that the product derived from the reaction of methyl 6-acyl-7-phenyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-5-carboxylates (**2a, b**) with butylamine depends on the substitute in the sixth position of the heterocyclic compound. In the case of the acetyl group, in the sixth position, the 6-butyl-7-methylen-8-phenyl-6,7-dihydro-4-pyrrolo[3,4-*d*]tetrazolo[1,5-*a*]pyrimidin-5(8)-one (**3a**), whose structure was confirmed by X-ray crystallography, is formed. If the sixth position is occupied by a benzoyl radical, the *N*-butyl-6-benzoyl-7-phenyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidin-5-carboxamide (**3b**) is obtained.

We propose the following mechanism of formation of 6-butyl-7-methylen-8-phenyl-6,7-dihydro-4-pyrrolo[3,4-*d*]tetrazolo[1,5-*a*]pyrimidin-5(8)-one (**3a**). At the first stage, the intermediate amine derivative A is formed. Then its enamine form is cyclized into compound **3a**.

Structures of **2a, b** and **3a, b** were established by elemental analysis, IR and ¹H NMR spectroscopic data.

One-Pot Synthesis of 5-Oxo-1,3,4,5-Tetrahydro-Pyrrolo[4,3,2-*de*]Isoquinoline-3-Carboxamides

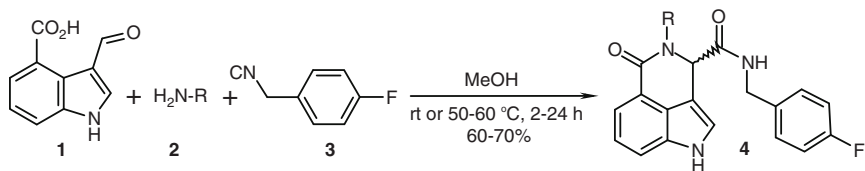
Alexey P. Ilyn, Dmitri V. Kravchenko, Victor V. Potapov,
and Alexandre V. Ivachtchenko

Fused tricyclic systems containing heteroaromatic moiety with different substituents' profiles are in the top list of privileged heterocyclic scaffolds with pronounced pharmacological worth. However, due to a nontrivial structural composition, such compounds have still not found a robust and convenient synthetic decision for the preparation of the focused combinatorial libraries of high diversity. Therefore, the development of effective synthetic strategies to this type of heterocyclic compounds is one of the key objectives in modern combinatorial chemistry.

In the present work we have focused specifically on broadening the scope and synthetic potential of the modified Ugi MCR that we have recently developed and comprehensively evaluated. This synthetic strategy is based fundamentally on the use of bifunctional reagents in Ugi-type condensation. Thus, the combinatorial library of rare 5-oxo-1,3,4,5-tetrahydro-pyrrolo[4,3,2-*de*]isoquinoline-3-carboxamides was obtained using a modified Ugi four-center, three-component reaction (U-4C-3CR). During the initial stage of our synthetic strategy, we obtained a bifunctional aldehydo-acid **1** based on the reaction of methyl 1*H*-indole-4-carboxylate with POCl₃ in DMF followed by alkali hydrolysis of the intermediate ester. We have further found that the reaction of 3-formyl-1*H*-indole-4-carboxylic acid **1** with primary amines **2** and isonitrile **3** in methanol at room temperature or 50–60°C for 12–24 h directly led to novel carboxamide derivatives of 5-oxo-1,3,4,5-tetrahydro-pyrrolo[4,3,2-*de*]isoquinolines **4**. The process presumably follows the same initial course as the classical Ugi condensation with an intermediate Schiff base being attacked by the isonitrile to give a nitrilium intermediate, which then undergoes intramolecular cyclization. As proof of the mechanism suggested, we have not observed the formation of both the classical Passerini and branched Ugi-type products. Based on sufficient analytical data (¹H NMR, LC–MS, as well as HR–MS analysis), we have unhesitatingly concluded that tricyclic product **4** was properly formed under the applied conditions. Therefore, the developed MCR may

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provide a valuable practical tool for the synthesis of novel physiologically active agents containing the title core fragment.

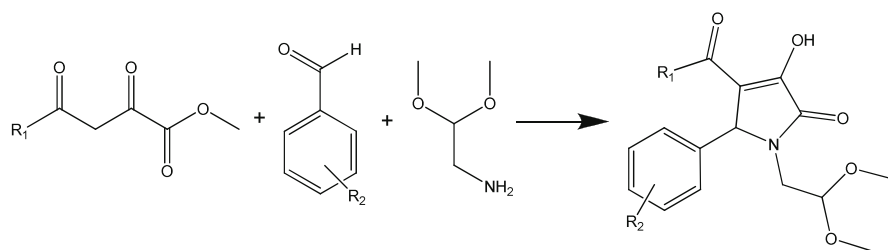


Synthesis of 4-Acyl-5-Aryl-1-(2,2-dimethoxyethyl)-3-Hydroxy-3-Pyrrolin-2-Ones

V. N. Vichegjanina, E. B. Levandovskaya, V. L. Gein, and M. I. Vahrin

It is known that derivatives of tetrahydropyrrol-2,3-diones have expressed antimicrobial activity. With the purpose of synthesizing new tetrahydropyrrol-2,3-diones and studying the influence of their structure on antimicrobial action, it was of interest to enter the 2,2-dimethoxyethyl group into position 1 of the heterocycle.

With this purpose in mind, we investigated the interaction of methyl ether-substituted pyruvic acids with a mix of aromatic aldehyde and 2,2-dimethoxyethanamine. As previous research has shown, the reaction proceeds in dioxane at room temperature with the formation of 4-acyl-5-aryl-1-(2,2-dimethoxyethyl)-3-hydroxy-3-pyrrolin-2-ones (**I–III**).



Ia-c, IIa-c, IIIa-h

- | | |
|--|---|
| R ¹ = CH ₃ (I); | R ² = H (Ia), 4-NO ₂ (Ib); 3-OH (Ic); |
| R ¹ = C ₆ H ₅ (II); | R ² = H (IIa), 4-NO ₂ (IIb); 3-OH (IIc); |
| R ¹ = C ₆ H ₅ (III); | R ² = H (IIIa), 4-NO ₂ (IIIb); 3-OH (IIIc), 2-Cl (IIId),
4-OC ₂ H ₅ (IIIe), 4-OH (IIIf), 3-NO ₂ (IIIg), 4-Cl (IIIh) |

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The received compounds (**I–III**) are colorless crystal substances that are soluble in ethanol, acetone, and dimethyl sulfoxide and insoluble in water.

The structure of all the received compounds is established on the basis of data ^1H NMR spectroscopy. In ^1H NMR spectra of compounds, the group of signals of aromatic protons as a multiplet at 7.2–7.8, a singlet of a proton C5H at 5.18–5.45, signals of protons 1-dimethoxyethyl substituent: a singlet of six protons of two methoxy groups at 3.11–3.22, a multiplet of a proton C1H at 4.35–4.44, a multiplet of a proton C1HaHb at 2.47–2.53, a multiplet of a proton C1HaHb at 3.65–3.72 are present.

All the received compounds (**I–III**) form with an alcoholic solution of FeCl_3 ; their intense cherry color testifies to their existence in enolic form.

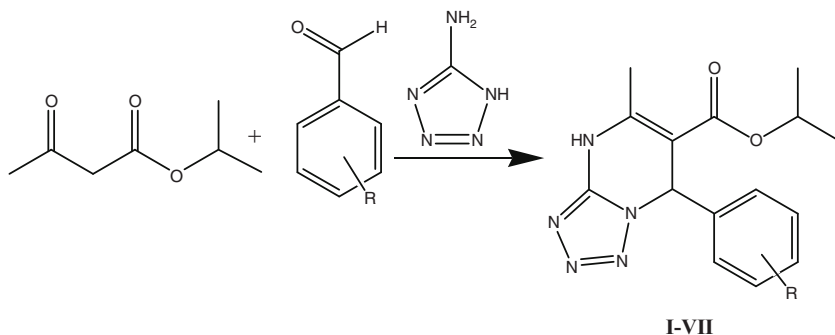
Synthesis and Structure of Isopropyl 5-Methyl-7-aryl-4,7-Dihydrotetrazolo[1,5-a]Pyrimidine-6-Carboxylates

I. N. Vladimirov, A. A. Zorina, N. V. Nosova, V. L. Gein, O. V. Fedorova, and M. I. Vahrin

It was previously established that the interaction of ethers of ketoacids with a mix of aromatic aldehyde and 5-aminotetrazole or 3-amino-1,2,4-triazole leads to condensed heterocyclic systems. With the purpose of receiving new alkyl 1,5-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylates, we have been investigating the interaction of isopropyl ethers of acetoacetic acids with a mix of 5-aminotetrazole and aromatic aldehyde.

Our research has shown that heating equimolar quantities of initial reagents at 130–170°C for 20–30 min leads to formed 5-methyl-7-aryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylic acid isopropyl esters (**I–VII**).

The received substances (**I–VII**) are colorless or painted crystal substances, soluble in dimethylsulfoxide and dimethylformamide, and insoluble in ethanol and water.



R=H(**I**); 3-F (**II**); 4-F (**III**); 4-OH (**IV**); 4-CH₃O (**V**); 3,4-(CH₃O)₂ (**VI**); 4-OH-3-OC₂H₅ (**VII**)

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The structure of all the received compounds (**I–VII**) is established on the basis of data ^1H NMR and infrared spectroscopy. In a nuclear magnetic resonance ^1H spectra of compounds (**I–VII**), except for signals of alkoxygroups, there is the group of signals of aromatic protons as a multiplet at 6.50–6.90, a signal of the proton C5H as a singlet in the field of 6.50–6.70, a signal of the NH-proton at 11.3–11.4, and signals of the CH_3 group as a singlet in the field of 2.25–2.45. In IR spectra the shifts caused by valent fluctuations of the NH-group in the field of 3,200–3,450 cm^{-1} , ether groups in the field of 1,650–1,750 cm^{-1} , and also a shift of valent fluctuations of compounds $\text{C}=\text{C}$ in the field of 1,660–1,700 cm^{-1} .

The establishment of the structure of the crystal of 5-methyl-7-phenyl-4,7-dihydro-tetrazolo[1,5-*a*] pyrimidine-6-carboxylic acid isopropyl ester (**I**) has been received by slow crystallization from ethanol. We have carried out its rentgeno-structure research. The received results testify to the full conformity of the offered structure of the compound.

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