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Ring-opening of pyridines and imidazoles with electron-deficient acetylenes: en route to metal-free organic synthesis

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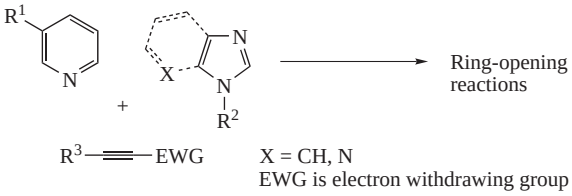
The article is focused on the recently developed methodology for the efficient synthesis of diverse highly unsaturated previously unknown highly functionalized enamines, which comprises the mild transition-metal free hydrative ring-opening of pyridines and imidazoles proceeding *via* zwitterionic adducts of these heterocycles with electron-deficient acetylenes. The synthesized compounds are of high synthetic and pharmaceutical value being promising intermediates for drug design.



Introduction

Controlling the heterocyclic molecular complexity, diversity and reactivity is an acute ever-growing challenge of modern human friendly organic synthesis.[1] In this line, the preference of acetylenes over other reactants in terms of their chemical tunability, atom- and energy-economy is now becoming evident and indisputable.[2–7] Recently, the marriage of fundamental heterocycles with acetylenes especially on transition metal-free playground has demonstrated acknowledged advances.[8–11] This covers the transition metal-free Sonogashira alternative[12–15] and synthesis of key naturally occurring metabolites[16–18] as well as multimolecular self-organization of insect pheromones and mammal hormones-related structures[19,20] triggered by C–H-functionalization processes,[21–26] in strict compliance with modern pot, atom and step economy (PASE) approach.[27,28]

Over the last decades, much attention has been given to the reactions of pyridines[29–38] and imidazoles[39–48] with electron-deficient acetylenes proceeding *via* zwitterionic intermediates

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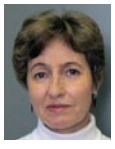

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(1,3-dipoles) under metal-free conditions. These reactions open original and facile routes to new functionalized heterocyclic systems and building blocks for organic synthesis. Generally, the ring-opening of pyridines and imidazoles is a promising methodology leading to 5-amino-2,4-pentadienals, diaminoethylenes and -arenes. Now this approach is rapidly unfolding, despite the known fundamental limitation related to the aromatic nature of these rings.

This obstacle was circumvented, in a few cases, by using pyridinium and imidazolium salts, which were opened with amines (pyridinium salts[49–54]) or water (imidazolium salts[55–58]) to give correspondingly 5-amino-2,4-pentadienals or diaminoethylenes. Aminopentadienals (Zincke aldehydes[49]) as versatile donor–acceptor dienes are getting ever-extending use in the synthesis of heterocycles and alkaloids (*e.g.*, manzamine alkaloids,[59–63] the complex alkaloid gelsemine[64]) and in cascade reactions to generate sophisticated polycyclic structures.[65] As applied to imidazoles, these reactions were successfully employed in investigations of important biological processes, such as genetic effects of oxidative DNA damages.[66] The sequences, such as imidazolium salt ring-opening followed by appropriate treatment of the intermediates and further cyclization, were used for the metal-free synthesis of functionalized heterocyclic derivatives, *e.g.*, 2-substituted imidazoles,[67] imidazol-2-ones,[68] imidazole-2-thiones,[69] and diazepines.[70]

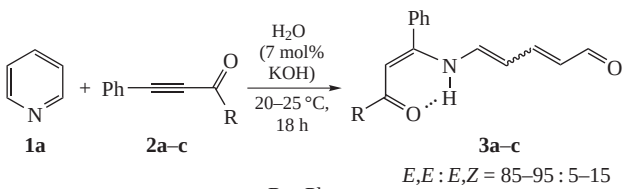
Recently, while exploring the zwitterions generated by the nucleophilic attack of pyridines or imidazoles at the triple bond of electron-deficient acetylenes, a new approach to the unknown family of 5-amino-2,4-pentadienals and diaminoethylenes was discovered, which substantially extends the structural diversity and accessibility of these key synthetic building blocks. In the present survey, we shortly analyze this new type of ring-opening reactions of pyridines and imidazoles with electron-deficient acetylenes involving zwitterionic species.

Stereoselective ring-opening of pyridines with electron-deficient acetylenes

Pyridine **1a**, as it was firstly reported,[71] appeared to be capable of ring-opening under the action of (benzoyl)(phenyl)acetylene **2a**/H_2O system to afford 5-aminopentadienal **3a** in 7% yield (not optimized). The reaction was carried out in the boiling pyridine (115 °C) for 100 h (the molar ratio **2a**:H_2O of 1:1). Further optimization of the reaction conditions (room temperature, the molar ratio **1a**:**2a**:H_2O of 1:1:4, 7 mol% KOH, 18 h) allowed the yield of 5-aminopentadienal **3a** to be raised up to 91%.[72] The synthesis proved to be equally efficient also for other substituted acylacetylenes **2b**,**c** (R = 2-furyl, 2-thienyl, respectively), securing almost quantitative yields of corresponding 5-aminopentadienals **3b**,**c** (Scheme 1).

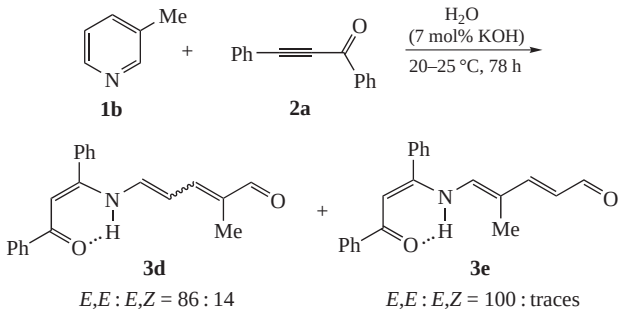
The pyridine ring-opening proceeds stereoselectively: only the *Z*-configuration for ethenyl substituents at the nitrogen atom and preferentially (85–95%) the *E*,*E*-configuration for the 2,4-pentadienal moiety (the second configuration being *E*,*Z*) were detected.

In the case of unsymmetric 3-methylpyridine **1b** and ynone **2a**, two regioisomers, namely, the corresponding 2-methyl- and



a R = Ph
b R = 2-furyl
c R = 2-thienyl

Scheme 1

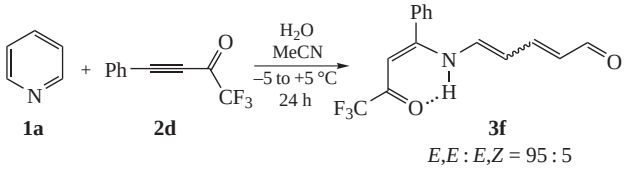


Scheme 2

4-methylaminopentadienals **3d**,**e**, were obtained (7:3 ratio) in 84% total yield (Scheme 2).[72]

It is of interest that 2-methyl- and 4-methylpyridines with (benzoyl)(phenyl)acetylene **2a** gave the expected 5-amino-2,4-pentadienals only in negligible yields (~2%). After full consumption of the acetylene, the major reaction products were cooligomers of the starting compounds.[72]

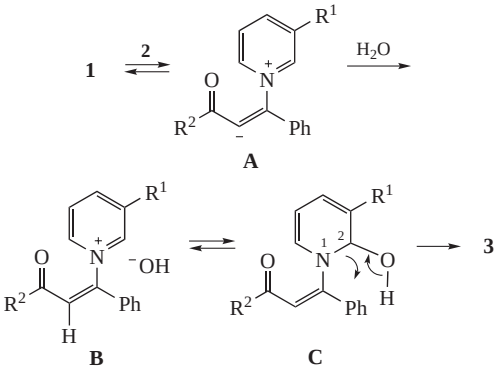
The scope of this reaction was extended over another representative of electron-deficient acetylenes such as (trifluoroacetyl)-(phenyl)acetylene **2d**.[73] In this case the opening of the pyridine ring also took place, expectedly under milder conditions (the **1**:**2d**:H_2O ratio of 1:1:1, reaction temperature –5 to +5 °C, 24 h, in MeCN). Notably, unlike the best above examples the experimental procedure did not require KOH usage. The reaction product, trifluoroacylated aminopentadienal **3f**, was isolated in 26% non-optimized yield. The pyridine ring-cleavage here was also stereoselective: *Z*-stereoselectivity relative to (trifluoroacetyl)(phenyl)ethenyl substituent was close to 100%, and the ratio *E*,*E*:*E*,*Z* of the pentadienal moiety was 95:5 (Scheme 3).



Scheme 3

The mechanism of the pyridine ring-opening is suggested to involve the zwitterions **A**, the adducts of pyridines **1** with ynones **2**. The proton transfer from water molecule to carbanionic center of the intermediates **A** leads to pyridinium hydroxides **B**. The rearrangement of their covalent form **C** accompanied by the cleavage of the N–C(2) bond gives the final products **3** (Scheme 4).

The *Z*-configuration of the acylethenyl substituents was predetermined by the initial nucleophilic attack of pyridine nitrogen at the triple bond, which is known[74,75] to proceed in a *trans*-mode.



Scheme 4

The strong intramolecular hydrogen bonds in the acetylethenyl substituents of **3a**–**f** additionally secure their *Z*-configuration.

The easy deprotonation of methyl substituents of 2- and 4-picolines[76] was considered[72] as a cause of the observed stability of their pyridine rings.

Despite from time to time appearing examples,[77–79] the potential of these classical aminopentadienals (Zincke aldehydes) as useful building blocks for natural product synthesis is admitted[53] largely unexploited. A wider application of these synthetic intermediates was assumed to be hindered by their insufficient structural diversity.[53] In this light it is worthy of note that the above considered new type ring opening of pyridines essentially differs from the classic Zincke–König reaction both by the reactants (pyridine, acylacetylene and water for the former and pyridinium salts and excess secondary amines for the latter) and by structure and properties (advantageous to the classic Zincke–König aldehydes) of the pentadienals obtained. Unlike the common Zincke aldehydes, whose instability represents an issue for their synthetic application,[53] the synthesized 5-{*N*-[(*Z*)-acylethenyl]}-amino-2,4-pentadienals **3** are stable.[72] The synthesized compounds, hitherto unknown family of Zincke aldehydes, are suitable for handling. Due to their higher reactivity [that comes from the (*Z*)-acylethenyl substituent] they represent valuable starting materials corresponding to the current interest in design of drug-oriented natural products.

Fluorine-containing aminopentadienals of the type **3a**–**e** are of special interest. Indeed, fluorine atom in organic molecules usually includes essential changes in their physical-chemical features, imparting them new properties important for the diverse applications.[80] The augmented lipophilicity and metabolic stability together with conformational variations often lead to such a biological activity, that is specially required in drug design.

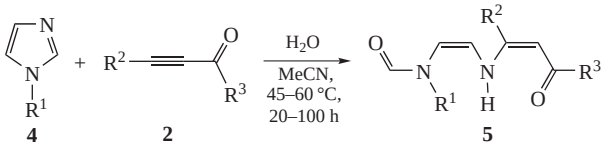
It should be expected that in a near future the stereoselective ring-opening of pyridines under the action of electron-deficient acetylenes will get a further extension and find wide application in organic synthesis to involve diversely substituted pyridines, at least 3- or 5-substituted derivatives, and alkynes with a larger scope of electron-withdrawing substituents, in particular the fluorine-containing ones. The research in this area will be inspired by the structural privileges, which the synthesized compounds would provide: they are individual *Z*-isomers, relative to the aminoethenyl moieties, and often relative to aminopentadienal part of the molecules, and also extra functionalized being actually aminoenones. The exceptionally mild, biomimetic conditions of the reaction (room temperature, water, non-transition metals, small concentration of KOH if any, no solvent) are additional prerequisites for a wider study of this chemistry.

Stereoselective ring-opening of imidazoles with electron-deficient acetylenes

Diazadienes and -trienes, particularly cyclic ones (pyridazines, pyrimidines, pyrazines and their dihydro derivatives), find enormous application in organic, bioorganic, and medicinal chemistry.[81] Their syntheses and modifications are well established and keep being developed.[82] Less studied (and, accordingly, their syntheses much less elaborated) are their open-chained congeners. Meanwhile, they also attract great interest, especially isomerically pure and functionalized ones, as important ligands and synthetic building blocks.[83–85]

Most of the known diazadienes contain the C=N bonds and, hence, are actually the Schiff base type compounds. Diazadienes with both C=C bonds have been unknown until recently, although their N-adjacent double bonds and N functionalities warrant rich reactivity.

Lately, it was found,[86] that 1-substituted imidazoles **4** underwent exceptionally facile stereoselective ring-opening under the action of electron-deficient acetylenes **2** and water (the molar ratio **4**:**2**:H_2O of 1:1:1) in MeCN at 45–60 °C without any catalysts to afford functionalized (*Z*,*Z*)-1,4-diaza-2,5-dienes, (*Z*,*Z*)-propenylaminoethenylformamides **5**, in up to 80% yields (Scheme 5).



4 **2** **5**

R^1 = Me, Bu^i, *n*-hexyl, allyl, Bn
R^2 = Ph, 1-benzyl-4,5,6,7-tetrahydroindol-2-yl
R^3 = Ph, 2-furyl, 2-thienyl

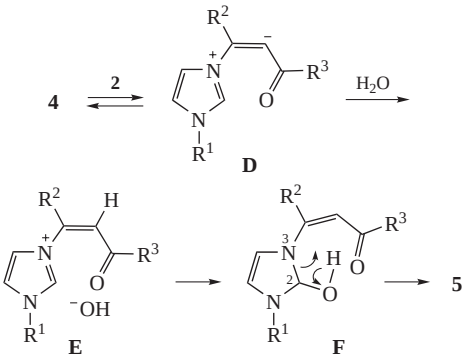
Scheme 5

This three-component reaction was strictly stereoselective providing both alkenyl moieties of *Z*-configuration. In no case the corresponding *E*-isomers were detected in the crude product even in trace amounts (^{1}H NMR). The *Z*-configuration of the acylethenyl moiety was in keeping with the *trans*-mode of the classic nucleophilic addition to acetylenes[74,75] leading to the adduct of the *Z*-configuration. The second alkenyl moiety possessed a *Z*-configuration due to its origination from the imidazole ring-cleavage at the C(2)–N(3) bond.

The yields of 1,4-diaza-2,5-dienes **5** generally ranged 60–80%, sharply dropping (15%) when 1-benzoyl-2-(1-benzyl-4,5,6,7-tetrahydroindol-2-yl)acetylene was employed, obviously due to its steric encumbrance and electron donating effect of pyrrole ring, which decreases electrophilicity of the triple bond.

Noteworthy, monosubstituted (terminal) electron-deficient acetylenes almost did not give the 1,4-diaza-2,5-dienes, just as minor products under the same conditions, for instance with benzoylacetylene, only about 5% of the expected 1,4-diaza-2,5-diene had been detected (^{1}H NMR) in the reaction mixture.

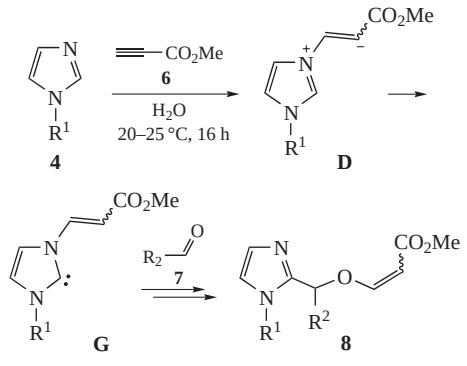
It is assumed that the reaction proceeds as tandem *via* zwitteriones **D** generated by nucleophilic attack of 1-substituted imidazole **4** at the triple bond of acetylene **2** (Scheme 6). The carbanionic center is quenched with the water proton to form *N*-alkenylimidazolium hydroxide **E**. The covalent form of the latter, 2-hydroxy-3-alkenylimidazoline **F**, rearranges to the final product **5** with cleavage of the imidazole ring.



Scheme 6

The obtained previously unknown (*Z*,*Z*)-diazadienes bearing *N*-formyl and *C*-acyl functions represent a promising family of building blocks for organic synthesis.

Interestingly, the usage of high excess water, *i.e.* as solvent, in the reaction between 1-substituted imidazoles **4**, methyl propiolate **6** and aldehydes **7** (the molar ratio **4**:**6**:**7** of 2:3:1, 5 ml of H_2O, 20–25 °C, 16 h) did not cause the imidazole ring-cleavage, but resulted in C(2)-functionalization of the hetero-



Scheme 7

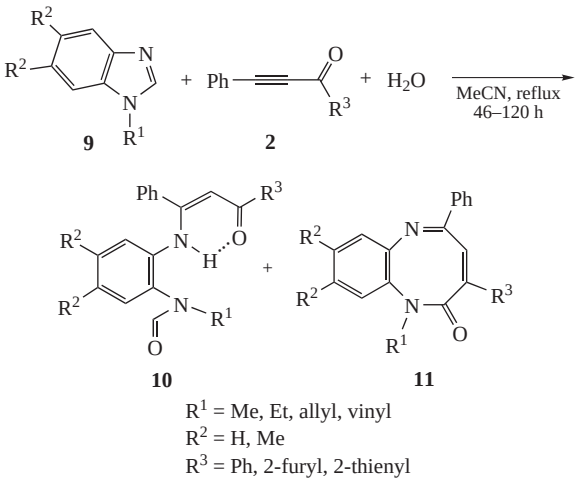
cycle. The yields of C(2)-functionalized imidazoles **8** ranged 28–90% (Scheme 7).[87]

It is assumed that the mechanism of this reaction involves zwitterionic **D** and carbene **G** intermediates. However, it is known that imidazolium carbenes are very sensitive to the trace of moisture and can undergo the ring-opening with formation of diaminoethylene derivatives.[88,89] In addition, the proton transfer from water molecule or from the C(2)-position of imidazole ring to carbanionic center of zwitterion **D** obviously favors the first reaction. The similar functionalization of the imidazole ring but in MeCN or under solvent-free conditions was reported some months before the above work.[90]

The ring-opening of the imidazole moiety in benzimidazoles under the action of acylacetylenes and water opens a simple straightforward route to functionalized 1,2-phenylenediamines, namely β-aminovinyl ketones with the formanilide moiety. Diverse β-aminovinyl ketones possess various biological activities[91] and participate in the synthesis of natural alkaloids.[92] Especially prospective as potential pharmaceuticals or their precursors are β-aminovinyl ketones with heteroaromatic and aromatic substituents. Some representatives of this series show good inhibitory activity of human breast cancer cells.[93]

As recently shown, 1-substituted benzimidazoles **9** reacted with acylacetylenes **2** and water (82 °C, MeCN, 46–120 h) to stereoselectively give functionalized arylaminovinyl ketones **10**, products of the imidazole ring-opening, in up to 75% yield and benzodiazocinones **11**, products of the imidazole ring-expansion, in up to 28% yield (Scheme 8).[94,95]

The lower reactivity of substituted benzimidazoles in comparison with that of their uncondensed analogues was likely

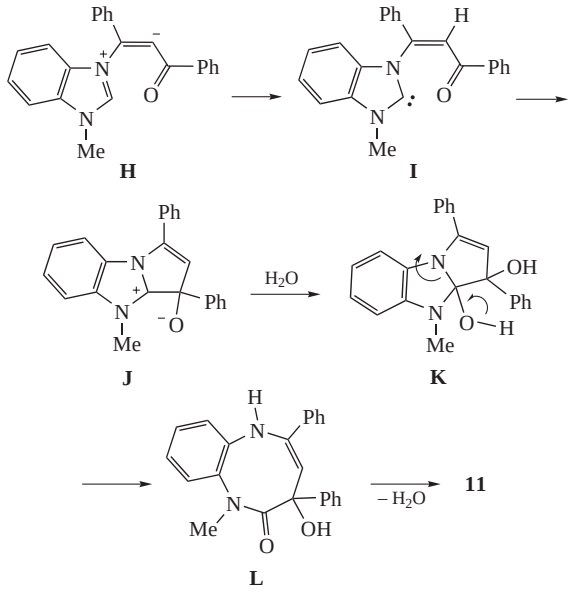


Scheme 8

due to a weaker basicity of benzimidazoles (pK_a ~5.5 for benzimidazole *vs*. ~7.2 for imidazole).[96]

The mechanism of formation of ring-opening products **10** is similar to that of imidazole ring-cleavage (see Scheme 6).[86] The nucleophilic attack of N-3 atom at the triple bond as usually leads to adduct of *Z*-configuration, which is additionally stabilized by strong intramolecular bond between NH and C=O moieties.

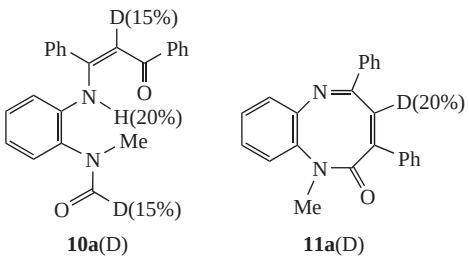
The benzodiazocinones **11** result from another transformation of primary zwitterion **H**. Indeed, if its carbanionic site would be quenched not by the water but by proton transfer from the 2-position of the imidazole ring, then carbene intermediate **I** could attack the carbonyl group thus forming the zwitterionic intermediate **J**. The latter gives imidazolium hydroxide **K**, which rearranges *via* C(2)–N(3) bond cleavage and proton transfer to the nitrogen atom to eight-membered intermediate **L**. Elimination of water molecule from this intermediate, accompanied by the prototropic shift, finally affords benzodiazocinones **11** (Scheme 9).



Scheme 9

Surprisingly, carrying out the reaction of 1-methylbenzimidazole **9a** with (benzoyl)(phenyl)acetylene **2a** in D_2O (**9a**:**2a**:D_2O of 1:1:2.5) and additionally dried reactants and MeCN raised the yield of benzodiazocinone **11a**(D) by a factor of almost 3 (28% instead of 10% yields with H_2O).[94] The yield of the corresponding arylaminovinyl ketone **10a**(D) dropped to 16%. Even more surprising was that in the products **10a**(D) and **11a**(D), the content of protium was much higher than that of deuterium (in the positions to be subjected to deuterium exchange with participation of D_2O). This implied that the protons were supplied from the 2-position of the imidazole ring.

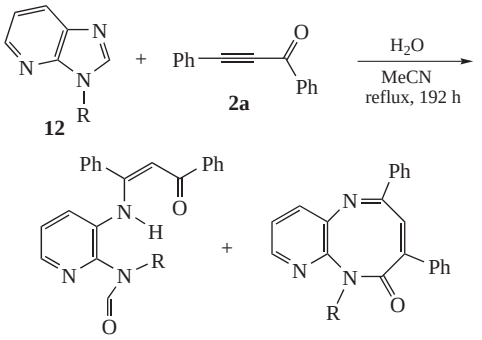
The isotopic effect of deuterium supported the mechanism of benzodiazocinone formation (Scheme 9). Actually, the deuteron transfer is commonly known to be slower than that of proton.



This makes the competition between the deuteron and proton transfer to the carbanionic site of the initial zwitterion to be more favorable for the proton transfer from the 2-position of the imidazole ring. This increases concentration of the carbene intermediate **I** and, hence, the yield of benzodiazocinone **11a**(D).

Recently discovered reaction[97] between substituted imidazopyridines **12** and (benzoyl)(phenyl)acetylene **2a** in the presence of water is of both fundamental and evident synthetic interest. From the facts of generating zwitterions from imidazole and pyridine systems with electron-deficient acetylenes one might expect that either the pyridine or imidazole (or both) counterpart of imidazo[4,5-*b*]pyridine would be involved in the reaction to furnish novel ring-opening products. Therefore, a fundamental issue here is the competition between the imidazole and pyridine nitrogen atoms as nucleophiles towards the electron-deficient acetylenic bond.

Unlike benzimidazoles **9**,[94,95] in imidazopyridines **12** the proton in C(2)-position should be more acidic due to a stronger electron-withdrawing effect of the fused pyridine moiety as compared with the benzene ring. The experiment, carried out with 3-methylimidazopyridine **12a** (R = Me) and (benzoyl)(phenyl)-acetylene **2a** in the presence of water (molar ratio **12a**:**2a**:H_2O of 1:1:1, 82 °C, MeCN), confirmed these expectations. The yield of the ring-expansion product **14a** was 61%, while the yield of ring-opening product, β-aminovinyl ketone **13a**, was 3% (^{1}H NMR) (Scheme 10).



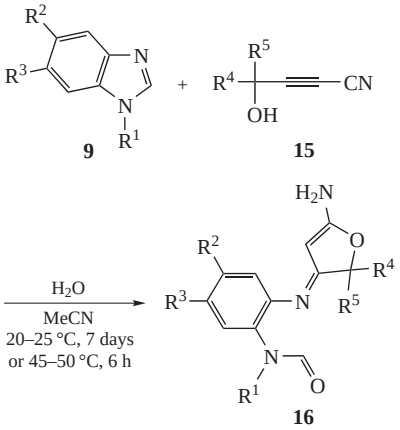
Scheme 10

When 3-methyl group was replaced by benzyl substituent, ring opening/expansion products ratio became 69:31, thus being inverted in favor of the ring-cleavage process. This inversion may result from the expected steric shielding of the 2-position by the *ortho*-hydrogen of benzyl substituent that interfered the formation of carbene **I** and its further intramolecular addition to the carbonyl group.

Noteworthy, the reaction was strictly regioselective: while both nitrogen atoms N-1 and N-4 could form zwitterionic species, in this case, only imidazole nitrogen N-1 triggered the cascade transformations *via* zwitterionic intermediate (see Schemes 6 and 9). Thus, competition between the imidazole and pyridine systems for generation of zwitterions with electron-deficient acetylene is in favor of the imidazole moiety.

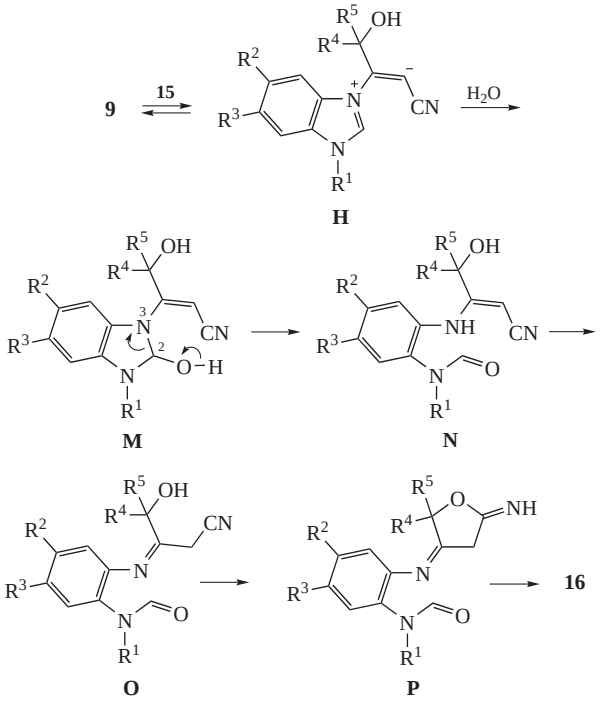
The reaction of substituted benzimidazoles **9** with cyanopropargylic alcohols **15** and water leads to the functionalized 5-amino-3-dihydrofurans **16** in 84–99% yields (Scheme 11).[98]

The reaction is assumed to proceed *via* the primary zwitterion **H**, which further is attacked by a molecule of water so that hydroxide ion would add to the C(2)-position, which had a cationic character, and the proton would quench the carbanionic center to give the intermediate hemiaminal **M** (Scheme 12).



Scheme 11

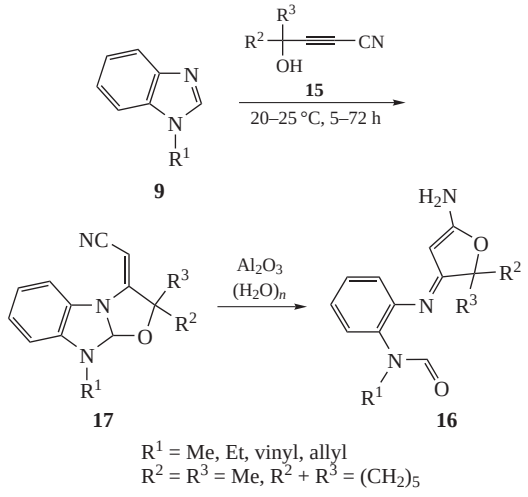
This triggers a cascade sequence that includes cleavage of the C(2)–N(3) bond and rearrangement of the benzimidazole ring to the 2-aminophenylformamide moiety. The resulting intermediate **N** undergoes a double-bond shift from the acrylonitrile moiety to the N-3 atom to give the intermediate **O**, which is capable of undergoing closure of the iminodihydrofuran ring. The intermediate **P** prototropically rearranges to deliver the final product **16**.



Scheme 12

The analogically functionalized aminodihydrofurans **16** were obtained by passing 1,3-oxazolobenzimidazoles **17** through the column with neutral Al_2O_3 or by their treatment with aqueous ethanol (yields 35–85%, Scheme 13).[99]

The dihydrofuran ring is a key structural subunit of many natural products that have promising applications, for example, as pharmaceuticals or flavor and fragrance compounds.[100] Highly substituted furans are of interest because they are useful and versatile intermediates for syntheses of heterocyclic or acyclic compounds.[101] Some substituted furanones are cytotoxic agents.[102]



R^1 = Me, Et, vinyl, allyl
$R^2 = R^3$ = Me, $R^2 + R^3 = (CH_2)_5$

Scheme 13

Conclusion

In this article, the new original transition metal-free methodology based on the employment of the zwitterions, the adducts of pyridines or imidazoles with electron-deficient acetylenes, in the presence of water to afford yet recently unknown, synthetically and pharmaceutically promising families of 5-aminopentadienals, 1,4-diaza-2,5-dienes and arylaminovinyl ketones has been briefly discussed.

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References

1 V. P. Ananikov, K. I. Galkin, M. P. Egorov, A. M. Sakharov, S. G. Zlotin, E. A. Redina, V. I. Isaeva, L. M. Kustov, M. L. Gening and N. E. Nifantiev, *Mendeleev Commun.*, 2016, **26**, 365.
2 B. A. Trofimov and N. K. Gusarova, *Russ. Chem. Rev.*, 2007, **76**, 507 (*Usp. Khim.*, 2007, **76**, 550).
3 H. Schobert, *Chem. Rev.*, 2014, **114**, 1743.
4 I.-T. Trotuş, T. Zimmermann and F. Schüth, *Chem. Rev.*, 2014, **114**, 1761.
5 B. A. Trofimov and E. Yu. Schmidt, *Russ. Chem. Rev.*, 2014, **83**, 600.
6 K. I. Galkin and V. P. Ananikov, *Russ. Chem. Rev.*, 2016, **85**, 226.
7 N. K. Gusarova, A. I. Mikhaleva, E. Yu. Schmidt and A. G. Mal'kina, *Khimiya atsetilena. Novye glavy (The Chemistry of Acetylene. New Chapters)*, Nauka, Novosibirsk, 2013 (in Russian).
8 E. Yu. Schmidt, E. V. Ivanova, N. V. Semenova, I. V. Tatarinova, I. A. Ushakov and B. A. Trofimov, *Mendeleev Commun.*, 2015, **25**, 131.
9 B. A. Trofimov, E. Yu. Schmidt, I. A. Bidusenko and N. A. Cherimichkina, *Mendeleev Commun.*, 2015, **25**, 17.
10 B. A. Trofimov, A. I. Mikhaleva, E. Yu. Schmidt and L. N. Sobenina, *Chemistry of Pyrroles*, CRC Press, Boca Raton, 2015.
11 B. A. Trofimov, O. A. Shemyakina, A. G. Mal'kina, A. V. Stepanov, O. G. Volostnykh, I. A. Ushakov and A. V. Vashchenko, *Eur. J. Org. Chem.*, 2016, 5465.
12 B. A. Trofimov and L. N. Sobenina, in *Targets in Heterocyclic Systems – Chemistry and Properties*, eds. O. A. Attanasi and D. Spinelli, Italian Society of Chemistry, Rome, 2009, vol. 13, pp. 92–119.
13 L. N. Sobenina, D. N. Tomilin and B. A. Trofimov, *Russ. Chem. Rev.*, 2014, **83**, 475.
14 D. N. Tomilin, B. Pigulski, N. Gulia, A. Arendt, L. N. Sobenina, A. I. Mikhaleva, S. Szafert and B. A. Trofimov, *RSC Adv.*, 2015, 73241.
15 B. Pigulski, A. Arendt, D. N. Tomilin, L. N. Sobenina, B. A. Trofimov and S. Szafert, *J. Org. Chem.*, 2016, **81**, 9188.
16 B. A. Trofimov, O. A. Shemyakina, A. G. Mal'kina, I. A. Ushakov, O. N. Kazheva, G. G. Alexandrov and O. A. Dyachenko, *Org. Lett.*, 2010, **12**, 3200.
17 B. A. Trofimov, A. G. Mal'kina, V. V. Nosyreva, O. A. Shemyakina, A. P. Borisova, L. I. Larina, O. N. Kazheva, G. G. Alexandrov and O. A. Dyachenko, *Tetrahedron*, 2010, **66**, 1699.
18 A. G. Mal'kina, V. V. Nosyreva, O. A. Shemyakina, A. I. Albanov and B. A. Trofimov, *Mendeleev Commun.*, 2017, **27**, 14.
19 B. A. Trofimov, E. Yu. Schmidt, I. A. Ushakov, A. I. Mikhaleva, N. V. Zorina, N. I. Protsuk, E. Yu. Senotrusova, E. V. Skital'tseva, O. N. Kazheva, G. G. Alexandrov and O. A. Dyachenko, *Eur. J. Org. Chem.*, 2009, 5142.
20 E. Yu. Schmidt, I. A. Bidusenko, N. A. Cherimichkina, I. A. Ushakov and B. A. Trofimov, *Tetrahedron*, 2016, **72**, 4510.
21 B. A. Trofimov, E. Yu. Schmidt, I. V. Tatarinova, E. V. Ivanova, N. V. Zorina, I. A. Ushakov and B. A. Trofimov, *Org. Lett.*, 2013, **15**, 104.
22 T. E. Glotova, D. A. Shabalin, M. Yu. Dvorko, I. A. Ushakov, E. Yu. Schmidt, A. V. Kuzmin and A. I. Mikhaleva, *Adv. Synth. Catal.*, 2013, **355**, 1535.
23 E. Yu. Schmidt, I. A. Bidusenko, N. I. Protsuk, I. A. Ushakov and B. A. Trofimov, *Eur. J. Org. Chem.*, 2013, 2453.
24 E. Yu. Schmidt, E. V. Ivanova, I. V. Tatarinova, I. A. Ushakov, N. V. Semenova, A. V. Vashchenko and B. A. Trofimov, *Org. Lett.*, 2016, **18**, 2158.
25 E. Yu. Schmidt, B. A. Trofimov, I. A. Bidusenko, N. A. Cherimichkina, I. A. Ushakov, N. I. Protzuk and Y. V. Gatilov, *Org. Lett.*, 2014, **16**, 4040.
26 E. Yu. Schmidt, I. A. Bidusenko, N. A. Cherimichkina, I. A. Ushakov, T. N. Borodina, V. I. Smirnov and B. A. Trofimov, *Chem. Eur. J.*, 2015, **21**, 15944.
27 P. A. Clarke, S. Santos and W. H. C. Martin, *Green Chem.*, 2007, **9**, 438.
28 A. N. Vereshchagin, M. N. Elinson, Yu. E. Anisina, F. V. Ryzhkov, A. S. Goloveshkin, I. S. Bushmarinov, S. G. Zlotin and M. P. Egorov, *Mendeleev Commun.*, 2015, **25**, 424.
29 B. A. Trofimov, L. V. Andriyankova, S. A. Zhivet'ev, A. G. Mal'kina and V. K. Voronov, *Tetrahedron Lett.*, 2002, **43**, 1093.
30 B. A. Trofimov, L. V. Andriyankova, S. I. Shaikhudinova, T. I. Kazantseva, A. G. Mal'kina and A. V. Afonin, *Synthesis*, 2002, 853.
31 L. V. Andriyankova, A. G. Mal'kina, A. V. Afonin and B. A. Trofimov, *Mendeleev Commun.*, 2003, **13**, 186.
32 L. V. Andriyankova, A. G. Mal'kina, L. P. Nikitina, K. V. Belyaeva, I. A. Ushakov, A. V. Afonin, M. V. Nikitin and B. A. Trofimov, *Tetrahedron*, 2005, **61**, 8031.
33 B. A. Trofimov, L. V. Andriyankova, R. T. Tlegenov, A. G. Mal'kina, A. V. Afonin, L. N. Il'icheva and L. P. Nikitina, *Mendeleev Commun.*, 2005, **15**, 33.
34 I. Yavari and S. Nasiri-Gheidari, *Helv. Chim. Acta*, 2011, **94**, 811.
35 K. V. Belyaeva, A. V. Afonin, L. V. Andriyankova, O. G. Volostnykh, L. P. Nikitina, A. G. Mal'kina, I. A. Ushakov, V. I. Smirnov, L. V. Klyba and B. A. Trofimov, *Mendeleev Commun.*, 2014, **24**, 156 and references cited therein.
36 C. G. Neochoritis, T. Zarganes-Tzitzikas and J. Stephanidou-Stephanatou, *Synthesis*, 2014, **46**, 537 and references cited therein.
37 N. K. Gusarova, P. A. Volkov, N. I. Ivanova, S. N. Arbuzova, K. O. Khrapova, A. I. Albanov, V. I. Smirnov, T. N. Borodina and B. A. Trofimov, *Tetrahedron Lett.*, 2015, **56**, 4804.
38 S. Kalantari, M. Piltan and S. A. Zarei, *J. Iran. Chem. Soc.*, 2016, **13**, 743.
39 I. Yavari, M. Sabbaghan and Z. Hossaini, *Synlett*, 2006, 2501.
40 B. A. Trofimov, L. V. Andriyankova, A. G. Mal'kina, K. V. Belyaeva, L. P. Nikitina, O. A. Dyachenko, O. N. Kazheva, A. N. Chekhlov, G. V. Shilov, A. V. Afonin, I. A. Ushakov and L. V. Baikalova, *Eur. J. Org. Chem.*, 2007, 1018.
41 A. Shaabani, A. H. Rezayan, A. Sarvary, M. Heidary and S. W. Ng, *Tetrahedron*, 2009, **65**, 6063.
42 L. V. Andriyankova, K. V. Belyaeva, L. P. Nikitina, A. G. Mal'kina, A. V. Afonin and B. A. Trofimov, *Synthesis*, 2010, 2828.
43 Y. Shen, S. Cai, C. He, X. Lin, P. Lu and Y. Wang, *Tetrahedron*, 2011, **67**, 8338.
44 B. A. Trofimov, L. V. Andriyankova and K. V. Belyaeva, *Chem. Heterocycl. Compd.*, 2012, **48**, 147 (*Khim. Geterotsikl. Soedin.*, 2012, 153) and references cited therein.
45 B. A. Trofimov, L. V. Andriyankova, L. P. Nikitina, K. V. Belyaeva, A. G. Mal'kina, O. A. Dyachenko, O. N. Kazheva, A. N. Chekhlov and A. V. Afonin, *Arkivoc*, 2012, **vi**, 229.
46 B. A. Trofimov and L. V. Andriyankova, *Vestnik SPbGU, Ser. 4*, 2014, **1** (**59**), 547 (in Russian).
47 L. V. Andriyankova, L. P. Nikitina, K. V. Belyaeva, A. G. Mal'kina, A. V. Afonin, A. V. Vashchenko, V. I. Smirnov and B. A. Trofimov, *Chem. Heterocycl. Compd.*, 2014, **50**, 807 (*Khim. Geterotsikl. Soedin.*, 2014, 876).

48 B. A. Trofimov, L. V. Andriyankova, L. P. Nikitina, K. V. Belyaeva, A. G. Mal'kina, I. Yu. Bagryanskaya, A. V. Afonin and I. A. Ushakov, *Eur. J. Org. Chem.*, 2016, 1199.
49 T. Zincke, *Justus Liebigs Ann. Chem*., 1903, **330**, 361.
50 W. König, *J. Prakt. Chem.*, 1904, **69**, 105.
51 M. Arvand and M. Eskandarnejad, *Anal. Lett*., 2008, **41**, 2877.
52 N. O. Mahmoodi, M. Mamaghani, A. Ghanadzadeh, M. Arvand and M. Fesanghari, *J. Phys. Org. Chem*., 2010, **23**, 266.
53 T. M. Nguyen, S. Peixoto, C. Ouairy, T. D. Nguyen, M. Bénéchie, C. Marazano and P. Michel, *Synthesis*, 2010, 103.
54 B. Delpech, in *Advances in Heterocyclic Chemistry*, ed. A. R. Katritzky, Elsevier, 2014, vol. 111, pp. 1–41.
55 M. J. Loosemore and R. F. Pratt, *FEBS Lett.*, 1976, **72**, 155.
56 S. S. Ramos, S. S. Almeida, P. M. Leite, R. E. F. Boto, S. Silvestre and P. Almeida, *Tetrahedron*, 2014, **70**, 8930.
57 H. Kimoto, K. L. Kirk and L. A. Cohen, *J. Org. Chem*., 1978, **43**, 3403.
58 W. Zuo and P. Braunstein, *Dalton Trans.*, 2012, **41**, 636.
59 A. Kaiser, X. Billot, A. Gateau-Olesker, C. Marazano and B. C. Das, *J. Am. Chem. Soc.*, 1998, **120**, 8026.
60 K. Jakubowicz, K. B. Abdeljelil, M. Herdemann, M.-T. Martin, A. Gateau-Olesker, A. A. Mourabit, C. Marazano and B. C. Das, *J. Org. Chem.*, 1999, **64**, 7381.
61 J.-C. Wypych, T. M. Nguyen, P. Nuhant, M. Bénéchie and C. Marazano, *Angew. Chem. Int. Ed*., 2008, **47**, 5418.
62 L.-H. Yan, P. Nuhant, I. Sinigaglia, Y. Fromentin, C. Marazano, B. Delpech and E. Poupon, *Eur. J. Org. Chem*., 2012, 1147.
63 L.-H. Yan, A. Skiredj, Y. Dory, B. Delpech and E. Poupon, *Eur. J. Org. Chem.*, 2014, 4973.
64 J. K. Lam, S. B. Joseph and C. D. Vanderwal, *Tetrahedron Lett*., 2015, **56**, 3165.
65 C. D. Vanderwal, *J. Org. Chem.*, 2011, **76**, 9555.
66 M. A. Kalam, K. Haraguchi, S. Chandani, E. L. Loechler, M. Moriya, M. M. Greenberg and A. K. Basu, *Nucl. Acids Res.*, 2006, **34**, 2305.
67 H. Kimoto, K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, 1978, **43**, 3403.
68 T. Itaya, T. Kanai, M. Iwata and M. Azuma, *Chem. Pharm. Bull*., 1997, **45**, 75.
69 J. Xu and J. C. Yadan, *J. Org. Chem.*, 1995, **60**, 6296.
70 Kh. Ya. Lopatinskaya, N. A. Klyuev and A. K. Sheinkman, *Chem. Heterocycl. Compd*., 1985, **21**, 1279 (*Khim. Geterotsikl. Soedin*., 1985, 1551).
71 B. A. Trofimov, L. V. Andriyankova, L. P. Nikitina, K. V. Belyaeva, A. G. Mal'kina and A. V. Afonin, *Russ. J. Org. Chem*., 2015, **51**, 1038 (*Zh. Org. Khim*., 2015, **51**, 1055).
72 B. A. Trofimov, L. V. Andriyankova, K. V. Belyaeva, L. P. Nikitina, A. V. Afonin and A. G. Mal'kina, *Eur. J. Org. Chem.*, 2015, 7876.
73 L. V. Andriyankova, L. P. Nikitina, K. V. Belyaeva, A. G. Mal'kina, A. V. Afonin, V. M. Muzalevskii, V. G. Nenajdenko and B. A. Trofimov, *Zh. Org. Khim*., 2016, **52**, 1863 (in Russian).
74 S. I. Miller and R. Tanaka, in *Selective Organic Transformations*, ed. B. S. Thyagarajan, Wiley-Interscience, New York, 1970, vol. 1, p. 143.
75 J. I. Dickstein and S. I. Miller, in *The Chemistry of the Carbon–Carbon Triple Bond*, ed. S. Patai, Wiley, New York, 1978, vol. 2, p. 814.
76 D. M. Smith, in *Comprehensive Organic Chemistry*, eds. D. Barton, W. D. Ollis and P. G. Sammes, Pergamon Press, Oxford, 1979, vol. 4, pp. 57–59.
77 J. Becher, *Synthesis*, 1980, 589.
78 A. M. Kearney and C. D. Vanderwal, *Angew. Chem. Int. Ed*., 2006, **45**, 7803.
79 D. B. C. Martin and C. D. Vanderwal, *J. Am. Chem. Soc*., 2009, **131**, 3472.
80 P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, 2013.
81 *Progress in Heterocyclic Chemistry*, eds. G. W. Gribble and J. A. Joule, Elsevier, 2015, vol. 27.
82 A. A. Aly and A. A. Hassan, in *Advances in Heterocyclic Chemistry*, ed. A. R. Katritzky, Elsevier, 2014, vol. 112, pp. 145–181.
83 A. A. Trifonov, I. A. Borovkov, E. A. Fedorova, G. K. Fukin, J. Larionova, N. O. Druzhkov and V. K. Cherkasov, *Chem. Eur. J*., 2007, **13**, 4981.
84 T. V. Makhrova, G. K. Fukin, A. V. Cherkasov and A. A. Trifonov, *Russ. Chem. Bull., Int. Ed*., 2008, **57**, 2285 (*Izv. Akad. Nauk, Ser. Khim*., 2008, 2242).
85 L. Hintermann, *Beilstein J. Org. Chem*., 2007, **3**, 22.
86 B. A. Trofimov, L. V. Andriyankova, L. P. Nikitina, K. V. Belyaeva, A. G. Mal'kina, L. N. Sobenina, A. V. Afonin and I. A. Ushakov, *Org. Lett.*, 2013, **15**, 2322.
87 F. Cruz-Acosta, P. De Armas and F. Garcia-Tellado, *Synlett*, 2010, 2421.
88 O. Hollóczki, P. Terleczky, D. Szieberth, G. Mourgas, D. Gudat and L. Nyulászi, *J. Am. Chem. Soc*., 2011, **133**, 780.
89 A. P. Marchenko, H. N. Koidan, A. N. Hurieva, I. I. Pervak, S. V. Shishkina, O. V. Shishkin and A. N. Kostyuk, *Eur. J. Org. Chem*., 2012, 4018.
90 B. A. Trofimov, L. V. Andriyankova, K. V. Belyaeva, A. G. Malkina, L. P. Nikitina, A. V. Afonin and I. A. Ushakov, *Eur. J. Org. Chem*., 2010, 1772.
91 I. O. Edafiogho, K. V. V. Ananthalakshmi and S. B. Kombian, *Bioorg. Med. Chem*., 2006, **14**, 5266.
92 J. D. White and D. C. Ihle, *Org. Lett*., 2006, **8**, 1081.
93 A. S. Shawali, S. M. Sherif, M. M. El-Merzabani and M. A. A. Darwish, *J. Heterocycl. Chem*., 2009, **46**, 548.
94 K. V. Belyaeva, L. V. Andriyankova, L. P. Nikitina, I. Yu. Bagryanskaya, A. V. Afonin, I. A. Ushakov, A. G. Mal'kina and B. A. Trofimov, *Tetrahedron*, 2015, **71**, 2891.
95 K. V. Belyaeva, L. V. Andriyankova, L. P. Nikitina, A. V. Afonin, I. A. Ushakov, A. G. Mal'kina and B. A. Trofimov, *Mendeleev Commun*., 2015, **25**, 254.
96 T. C. Bruice and G. L. Schmir, *J. Am. Chem. Soc.*, 1958, **80**, 148.
97 B. A. Trofimov, L. P. Nikitina, K. V. Belyaeva, L. V. Andriyankova, A. G. Mal'kina, I. Yu. Bagryanskaya, A. V. Afonin and I. A. Ushakov, *Mendeleev Commun*., 2016, **26**, 16.
98 B. A. Trofimov, L. V. Andriyankova, L. P. Nikitina, K. V. Belyaeva, A. G. Mal'kina and A. V. Afonin, *Synthesis*, 2010, 1536.
99 B. A. Trofimov, L. V. Andriyankova, A. G. Mal'kina, K. V. Belyaeva, L. P. Nikitina, O. A. Dyachenko, O. N. Kazheva, A. N. Chekhlov, G. V. Shilov, A. V. Afonin, I. A. Ushakov and L. V. Baikalova, *Eur. J. Org. Chem*., 2007, 1018.
100 S. Okombi, D. Rival, S. Bonnet, A.-M. Mariotte, E. Perrier and A. Boumendjel, *J. Med. Chem*., 2006, **49**, 329.
101 T. G. Kilroy, T. P. O'Sullivan and P. J. Guiry, *Eur. J. Org. Chem*., 2005, 4929 and references cited therein.
102 K. M. Marks, E. S. Park, A. Arefolov, K. Russo, K. Ishihara, J. E. Ring, J. Clardy, A. S. Clarke and H. E. Pelish, *J. Nat. Prod.*, 2011, **74**, 567.

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