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FULL PAPER

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Unexpected ring opening during the imination of camphor-type bicyclic ketones

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Abstract: A new ring opening reaction was found while attempting to isolate the imines from *ortho*-heteroatom substituted anilines and camphor-like bicyclic ketones. The benzoazoles containing a cyclopentanemethyl group at position 2 of the heterocycle were isolated instead of the expected imines. The detailed study of the transformation, including EPR experiments, revealed the most probable radical mechanism. The proposed reaction pathways were confirmed by quantum chemical calculations. The dichotomy of 1-2 and 2-3 bonds cleavage is discussed together with the evaluation of the stereochemical outcome of the reactions. The benzoazoles obtained via the new reaction are of particular interest for the medicinal chemistry.

Introduction

A promising approach to the development of drugs with a wide range of actions is the synthesis of biologically active compounds containing several different pharmacophore groups in their structure. One of these groups of interest for medicinal chemistry is a benzimidazole core. Monoterpenoids are also biologically active compounds with a wide range of activities. A combination of two biologically active structures in one molecule can increase the efficiency of the pharmacological action of the constituents or give new properties to the resulting hybrid drug.[1]

Benzimidazoles, benzoxazoles, and benzothiazoles are important bioactive heterocyclic scaffolds and exhibit a broad spectrum of biological and pharmacological properties[2–7] including anti-bacterial,[8–11] antiviral,[12–16] anti-fungal,[17–19] anti-inflammatory,[20–22] anti-cancer.[23–25] There is considerable interest in the synthesis and biological evaluation of novel benzimidazole derivatives, including chiral ones, due to their wide range of biological activities.[26–28] There are two classical methods for the synthesis of 2-substituted benzimidazoles, benzoxazoles, and benzothiazoles: the Phillips-Ladenburg reaction based on the reaction of substituted anilines with carboxylic acids and the Weidenhagen reaction based on the reaction of substituted anilines with aldehydes.[29] The first approach is the coupling of *o*-phenylenediamines and carboxylic acids or their derivatives, which commonly require strong acidic conditions.[30] The second approach is a two-step procedure involving the condensation of *o*-phenylenediamine and aldehyde to form a Schiff's base and its consequent oxidative cyclodehydrogenation. The use of aldehydes in the Weidenhagen reaction to produce benzimidazoles requires the subsequent oxidation of the intermediate products.[31] There are examples of the oxidation of dihydrobenzimidazoles using $NaHSO_3$,[32] $Fe(NO_3)_3$,[33] $Yb(OTf)_3$,[34] I_2,[35] as oxidising agents.[29] Some of the earlier methods described above have reasonable drawbacks, such as the use of expensive catalysts, long reaction time, the formation of a large number of

by-products, and harsh reaction conditions. Currently, the synthesis of benzimidazoles from aldehydes and *o*-phenylenediamine has been thoroughly studied. There are many works devoted to the synthesis of this class of heterocyclic compounds using available catalysts and mild reaction conditions, which result in high yields of the target compounds.[36–39]

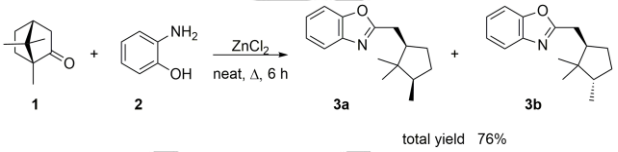
The reaction of ketones with *o*-phenylenediamine using oxidising agents or copper-containing catalysts is worth noting.[40–42] A highly efficient copper-catalysed method for the conjugation of *o*-aromatic diamines with ketones leading to 2,2-disubstituted 2*H*-benzo[*d*]imidazole derivatives has been developed by Juyou Lu *et al.*[42] Inexpensive $Cu(OAc)_2$ as the catalyst, mild reaction conditions, high reaction yields, high selectivity, and easy workup procedure are the main advantages of this method. However, as a result of the described reaction, only 2,2-disubstituted 2*H*-benzo[*d*]imidazole derivatives are formed, including spirocyclic compounds. In 2016, Yanjun Xie *et al.* reported an efficient procedure for the preparation of pyrido[1,2-*a*]benzimidazole from 2-aminopyridines and cyclohexanones under metal-free conditions.[43] Therefore, it is worth noting another work done by Joanna Nowicka-Scheibe.[44] In this work, an unexpected formation of *cis*-1,2,2-trimethyl-3-(benzoxazol-2-yl)cyclopentanecarboxyl ic acid was observed as the result of an oxidative C-C bond cleavage of the camphor ring in the intermediate imine during the condensation reaction between camphoroquinone and *o*-aminophenols conducted under open-air conditions. It should be noted that, firstly, this is the only example of the synthesis of 2-cyclopentyl substituted benzoxazoles which also contain a free carboxyl group. Secondly, this is the only example of the synthesis of this class of compounds using derivatives of monoterpenoids.

We previously showed that (+)-camphor-based imino derivatives had pronounced antiviral properties against the influenza virus.[45] In the course of earlier works, an effective method for the synthesis of imino derivatives of (+)-camphor was developed, which consisted of heating a mixture of ketones and amines with a reflux condenser without solvent in the presence of 5 mol% of anhydrous $ZnCl_2$.[46]

The goal of this work was to study the reaction between o-substituted anilines and monoterpenoids ((+)-camphor and (-)-fenchone). The unexpected outcome of this research was the new ring scission reaction that occurred during the attempted synthesis of imines from camphor-type ketones, including camphor itself, fenchone, and norcamphor. The list of *ortho*-heteroatom substituted anilines included *o*-aminophenol, *o*-aminothiophenol, and *o*-phenylenediamine. The resulted 2-substituted benzoazoles are of particular importance for medicinal chemistry.

Results and Discussion

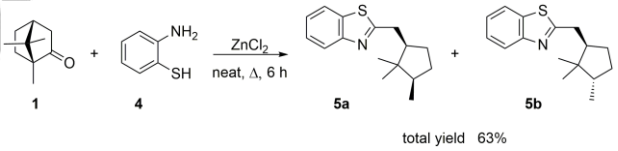
As mentioned earlier, we developed an effective camphor-based imines synthesis method, which consisted of heating a mixture of monoterpenoid with an amine in the presence of 5 mol % of anhydrous $ZnCl_2$ with a reflux condenser. The developed conditions were used in the reaction between (+)-camphor and 2-aminophenol. However, under the indicated conditions, the reaction of (+)-camphor (**1**) and 2-aminophenol (**2**) resulted in the formation of a mixture of two diastereoisomeric 2-substituted benzoxazoles (**3a** and **3b**) instead of the expected imine. The product was isolated as a yellow oil by vacuum distillation with a total yield of 76% and a ratio of 13:7, according to GC-MS and NMR ^1H, ^{13}C (Scheme 1).



Scheme 1. The reaction of (+)-camphor and 2-aminophenol.

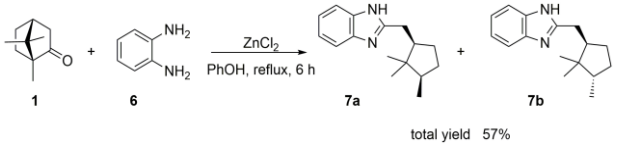
Surprised by this highly unexpected result, we decided to test the effect of other Lewis acids on the final composition of the reaction mixture. First, an increase in the amount of anhydrous $ZnCl_2$ (up to 20 mol %) did not affect the total yield of the target benzoxazoles. Secondly, the replacement of anhydrous $ZnCl_2$ with other Lewis acids ($AlCl_3$, $CoCl_2$, SbF_3, $GdCl_3{\cdot}6H_2O$, $CuCl_2$, $SnCl_2$, and $FeCl_3{\cdot}6H_2O$) either significantly reduced the yield of the target products or decreased the conversion of camphor.

Thus, the optimal conditions for the synthesis of target benzoxazoles were solvent-free heating of reagents with 5 mol % anhydrous $ZnCl_2$ with a reflux condenser. Using these conditions, the reaction of **1** with 2-aminothiophenol (**4**) was carried out and, as a result, a mixture of diastereoisomeric 2-substituted benzothiazoles (**5a**, **b**) was isolated as a yellow oil by vacuum distillation in a ratio of 3:2 according to GC-MS and NMR ^1H, ^{13}C (Scheme 2).



Scheme 2. The reaction of (+)-camphor and 2-aminothiophenol.

The reaction of **1** with *o*-phenylenediamine (**6**) under these conditions was accompanied by the sublimation of **1** and a strong charring of the reactants. To find the optimal solvent for this reaction (Scheme 3), we conducted a series of experiments to study the effect of the solvents used (DMSO, *p*-cresol, *o*-xylene, and phenol) on the final composition of the reaction mixture.

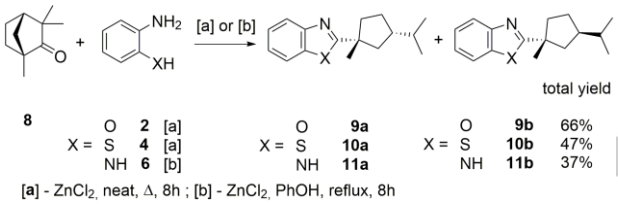


Scheme 3. The reaction of (+)-camphor and *o*-phenylenediamine.

As a result of heating with a reflux condenser for six hours, almost 100% (+)-camphor conversion was achieved using phenol as a solvent. Benzimidazoles (**7a**, **b**) were obtained without any by-products in a ratio of 5:2 after recrystallisation from acetonitrile according to GC-MS. The reaction in the other solvents was accompanied by a low

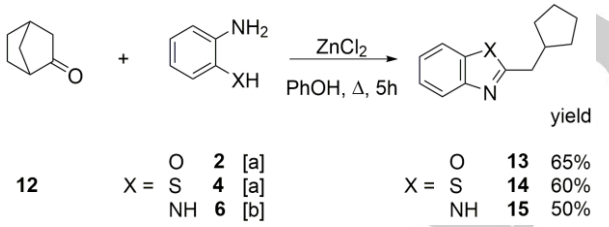
(+)-camphor conversion, the formation of numerous unidentifiable by-products, and the absence of the target benzimidazoles in the reaction mixture. It is worth noting that the purification of the reaction mixture from phenol was carried out by treating the reaction mixture with an aqueous solution of sodium hydroxide.

To search for other ketones capable of reacting with *o*-substituted anilines, we carried out similar transformations with the bicyclic natural monoterpenoid, (-)-fenchone (**8**), and a commercially available norcamphor (**12**). Thus, new diastereoisomeric mixtures of heterocyclic compounds (**9a**, **b**; **10a**, **b**; **11a**, **b**) were synthesised (Scheme 4). Diastereoisomeric 2-substituted benzoxazoles (**9a**, **b**) and benzothiazoles (**10a**, **b**) were isolated as a yellow oil by vacuum distillation with 66% and 47% total yields in a ratio of 7:3 and 3:2 according to GC-MS, respectively. Benzimidazoles (**11a**, **b**) were isolated with a 37% total yield in a ratio of 3:2 after recrystallisation, according to GC-MS. It is worth noting that the reaction time of **8** with *o*-substituted anilines was longer than similar conversions with **1**, apparently due to steric hindrances created by the methyl groups adjacent to the carbonyl function.



Scheme 4. The reaction of (-)-fenchone with *o*-substituted anilines.

The reaction of **12** with *o*-substituted anilines was accompanied by the formation of corresponding heterocyclic compounds (**13**-**15**) in good yields as the only reaction product (Scheme 5).



Scheme 5. The reaction of norcamphor with *o*-substituted anilines.

Attempts to involve monocyclic ketones, cyclohexanone, menthone, and carvone, in a similar transformation were unsuccessful. This means that the existence of the strained bicycle [2.2.1] core was necessary for this reaction.

The structure and stereochemistry of the minor products of the reaction of monoterpenoids with *o*-substituted anilines were not clear before the isolation of the mixtures of two target products. From the ^{13}C NMR spectra, a double set of signals of primary, secondary, tertiary, and quaternary carbon atoms was observed, which clearly showed the ratio of the heterocyclic compounds **a**-**b**. Based on this, we concluded that all synthesised mixtures of heterocyclic compounds contained two diastereoisomers. We also checked the enantiomeric purity of the studied heterocyclic mixtures. It was possible to determine the presence of only two products in mixtures of heterocyclic compounds obtained from camphor and fenchone with different mass spectra of the peaks. Based on the above, it was concluded that the products formed during the reaction of camphor and fenchone with *o*-substituted anilines cannot be enantiomers, but can be diastereoisomers (for experimental details see Supporting Information).

An important point in determining the structure of the synthesised compounds was the determination of the position and stereochemistry of substituents in the cyclopentane fragment of the main isomers. This opened a way to determine the stereochemistry of the minor product as well.

Crystals of **7a** suitable for X-ray diffractometry analysis were obtained by slow recrystallisation from an acetonitrile solution of **7a**. The structure of the molecule of **7a** in the crystal is shown in Figure 1.

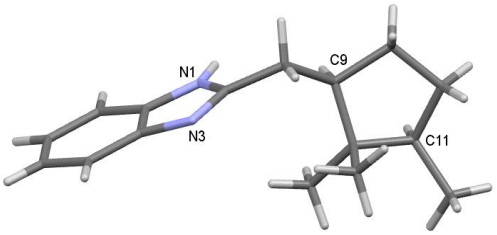


Figure 1. The molecular structure of **7a**. For experimental details, see Supporting Information.

For the separation of isomers in laboratory practice, column chromatography on silica gel impregnated with silver nitrate is frequently used. We performed column chromatography using a mixture of silica gel with silver nitrate as the stationary phase to separate a mixture of benzoxazoles (**3a**, **b**). However, instead of the expected separation of benzoxazoles, we were able to obtain a crystalline product of light purple colour and perform its X-ray diffraction analysis. We determined that during column chromatography, when there was a high concentration of benzoxazoles at the column exit, a complex compound of benzoxazole **3a** with $AgNO_3$ (in a 1:1 molar ratio) was eluted (Figure 2). The separation of mixtures of benzoxazoles, benzothiazoles, and benzimidazoles obtained from fenchone by column chromatography using silica gel with silver nitrate as the stationary phase did not lead to the desired separation of isomers, and the formation of complexes was also not observed.

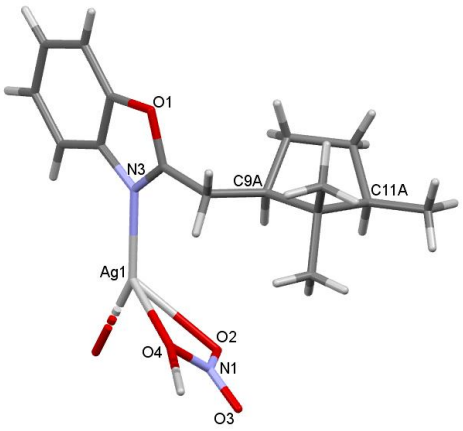


Figure 2. The molecular structure (asymmetric unit) of the complex of compound **3a** with $AgNO_3$. For experimental details, see Supporting Information.

We were able to obtain a complex of benzimidazole **11a** with copper(I) chloride by boiling a mixture of benzimidazoles (**11a**, **b**) with copper chloride in a mixture of CH_3CN and H_2O. After cooling and evaporation of the solvent, it became possible to obtain green crystals. X-ray diffraction analysis confirmed the formation of a (1*S*, 3*R*) 2-substituted benzimidazole as the main product of the reaction between **6** and **8** (Figure 3).

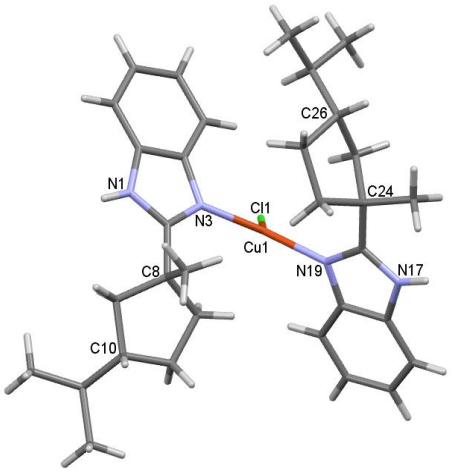


Figure 3. The molecular structure of a complex of compound **11a** with·CuCl. For experimental details, see Supporting Information.

Since we discovered a transformation that was not previously described in the literature, we became interested in how it proceeds. The synthesis of benzimidazoles from aldehydes and *o*-phenylenediamine has been thoroughly studied. However, there has only been a small number of works devoted to the synthesis of benzimidazoles from ketones, and only one work has been devoted to the synthesis of 2-substituted benzoxazole from (1*R*, 4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptane-2,3-dione with a bicyclic framework.[44] Thus, we studied the mechanism of the new transformations at the level at which this seemed possible.

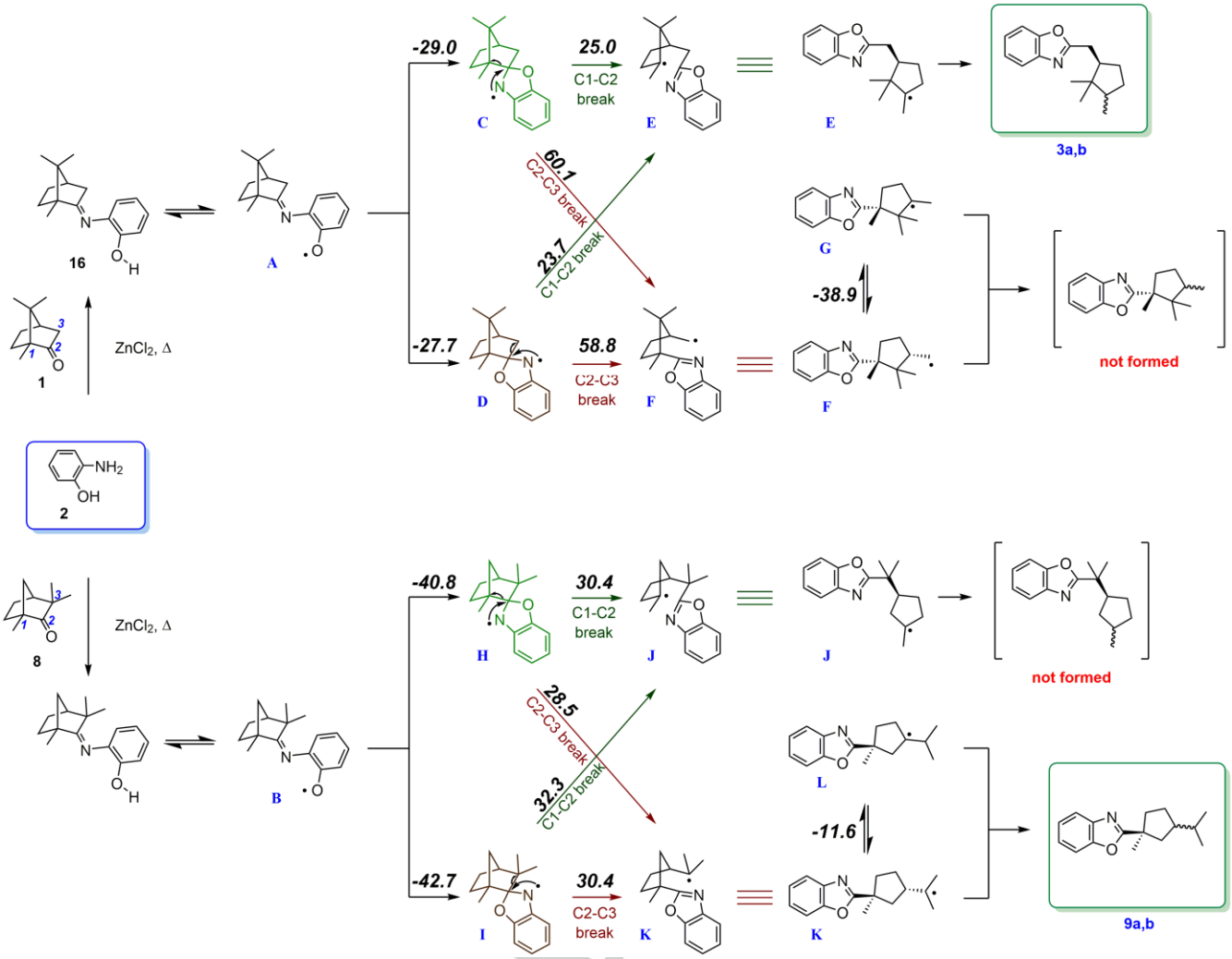
We assumed that at the first stage, the formation of imines from *o*-aminophenol and bicyclic ketones occurred (Schemes 6 and 7; radical and biradical species are indicated by letter ID). The values of the energy differences between stable radical species (**C** - **A**, **I** - **B**, *etc*.) are presented in Schemes 6.

According to the work by Samanta *et al*[47], stable phenoxyl radicals of type **A** may form from imine **16** in the presence of $ZnCl_2$ (Scheme 6). Highly likely, it is these radicals that we observed in the EPR experiments described below. If radical addition to the carbon atom of the imine double bond occurs, radical **A** can be transformed into the isomeric radical species **C** and **D**. The formation of spirocyclic radicals is a probable process from the point of view of thermodynamics according to theoretical calculations. The energy gain during the formation of radicals **C** and **D** is more than 27 kJ/mol. Further cleavage of the C-C bond requires some energy costs since spirocyclic structures are rather stable compounds. Breaking the C1-C2 bond requires more than 23 kJ/mol of energy, while the opening of the C2-C3 bond requires more than 58 kJ/mol for a camphor-based structure. The radical **E**, which can further lead to the formation of a mixture of products **3a**, **b** observed in the experiment, is formed in the first case. In the second case, the formation of radical particles **F** and **G** most likely does not occur, since such a process requires significant energy consumption (for details, see Computation Details in Supporting Information). This is probably the reason why no alternative products are observed in investigated reactions.

The same processes in the case of fenchone-based radical **B** would lead to the isomeric particles **H** and **I**. The energy gain during the formation of isomeric radicals **I** and **H** is more than 40 kJ/mol. However, upon the cleavage of the C-C bonds in the spirocyclic radicals **I** and **H** of the fenchone-based structure, the result is opposite to that of the camphor-based structure. Breaking the C1-C2 bond requires slightly more energy than breaking the C2-C3 bond. Of course, the transition from **H** to **J** and the transition from **I** to **K** seem to be equally probable in terms of energy, but the following two points must be considered. First, all the processes under consideration are reversible, and, second, the formation of a particle **K** requires the least energy consumption from both particles **H** and **I**. In addition, only a mixture of products **9a**, **b** is observed as a result of the experiment. Most likely, the formation of the particle **J** does not occur according to quantum-chemical calculations and experiment. However, obtaining a mixture of diastereoisomers **9a**, **b** is possible only through the formation of an intermediate radical particle **L**, the formation of which from particle **K** is favourable (for details, see Computation Details in Supporting Information, Figure S80).

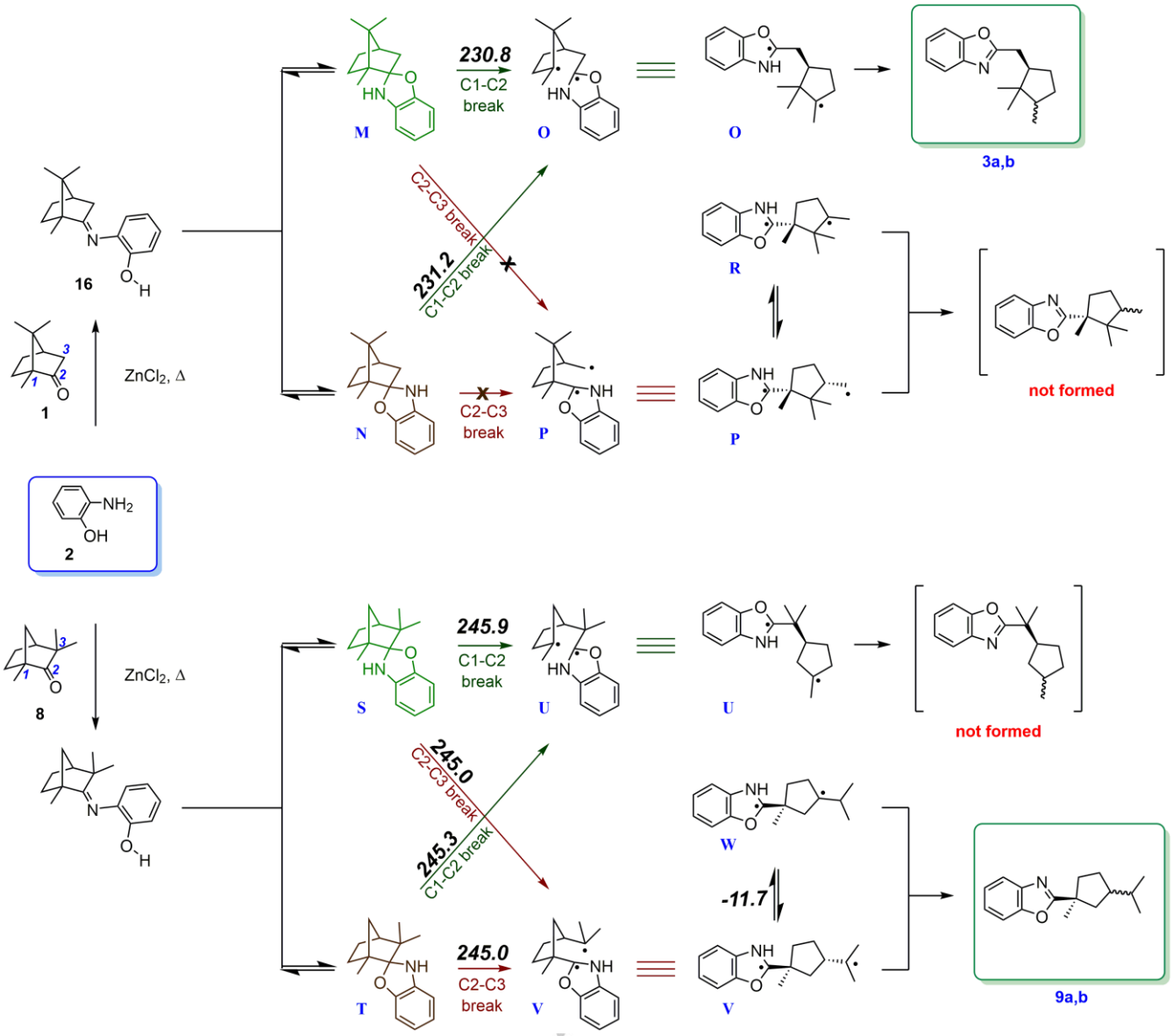
Our calculations confirm that all transformations of (+)-camphor and norcamphor with *o*-substituted anilines proceed through the C1-C2 bond break (the formation of radical particles with a structure similar to **E**), while all reactions of (-)-fenchone go through the C2-C3 bond break (the formation of radical particles with a structure similar to **K** and **L**). This is quite logical, since in these transformations only those bonds are broken, which lead to more substituted radical centers (for Computation details,

see Supporting Information). However, the reason for preferences for formation of **K** rather than **J** is not clear.



Scheme 6. Proposed monoradical reaction mechanisms for the reaction of **2** with **1** and **8**: formation of (+)-camphor and (-)-fenchone imines with subsequent formation of a phenoxyl radicals **A** and **B**; the formation of spirocyclic radicals **C**, **D**, **H**, **I** and the subsequent formation of radicals **E**-**G**, **J**-**L** due to the breaking of the C-C bond of the bicyclic framework. The values of energy differences ($\Delta E_{CA} = E_C - E_A$, $\Delta E_{IB} = E_I - E_B$, *etc*.) were calculated for stable radicals in the gas phase approximation (for details, see Computation Details in Supporting Information). The ΔE values were shown in the figure as the difference in the energies of stable radicals, according to the second corollary of Hess's law (for example, $\Delta E_{A\rightarrow C} = E(C)-E(A)$). QC were carry out in the gas phase approximation (see Computation Details in Supporting Information). All energies are presented in kJ/mol.

Recently we showed the possibility of isolating spirocyclic compounds from the reaction of (-)-fenchone and anthranilamide.[48] Therefore, in this paper we take into account another possible way for the investigated transformations, i.e. the formation of non-radical neutral spirocyclic intermediates **M**, **N** and **S**, **T** from imines of camphor and fenchone, respectively (Scheme 7). These molecules represent the products of intramolecular nucleophilic cyclizations. In these intermediates upon heating and/or the action of the Lewis acids, the C-C bond of the framework ketone can break along the C1-C2 or C2-C3 pathways homolytically with subsequent formation of biradical particles **O**, **P** and **U**, **V**.. The values of the energy differences between neutral intermediates (**O** - **M**, **V** - **T**, *etc*.) are presented in Scheme 7.



Scheme 7. Alternative reaction mechanisms for the reaction of *o*-aminophenol with ketones **1** and **8**: formation of camphor-based spirocyclic intermediates **M**, **N** and fenchone-based spirocyclic intermediates **S**, **T** with subsequent C-C bonds breaking to obtain biradical particles **O**, **P**, and **U**, **V** (for details, see Computation Details in Supporting Information). The values of energy differences ($\Delta E_{OM} = E_O - E_M$, $\Delta E_{VT} = E_V - E_T$, *etc*.) were calculated for stable intermediates in the gas phase approximation (for details, see Computation Details in Supporting Information). The ΔE values were shown in the figure as the difference in the energies of stable radicals, according to the second corollary of Hess's law (for example, $\Delta E_{M\rightarrow O}$ = E(O)-E(M)). QC were carried out in the gas phase approximation (see Computation Details in Supporting Information). All energies are presented in kJ/mol.

The biradical mechanism of formation of products **3a**, **b**, and **9a**, **b** was also considered from the point of view of thermodynamics. Theoretically, intermediate spirocyclic compounds **M**, **N** and **S**, **T** (Scheme 7) can be in two stereoisomeric states. For the compounds considered based on camphor, and fenchone the energy difference between the stereoisomers does not exceed 1 kJ/mol (for details, see Supporting Information, Figure S81). Biradical particles (**O**-**R** and **U**-**W**) formed as a result of breaking the C1-C2 and C2-C3 bonds in isomers **M**, **N** and **S**, **T** were optimised with the subsequent decision of the vibrational problem.

In the case of a camphor-based structure (Scheme 7), the scission of bond C2-C3 in isomeric intermediates **M**, **N** leads to the formation of an unstable biradical particle **P**, in which the optimisation of both singlet and triplet states failed since the structure tends to "return" to its initial state. Most likely, for the camphor-based structure, the rupture of the spirocyclic compound always occurs along the C1-C2 bond with the subsequent formation of intermediate **O**. Intermediate biradicals of structure **P** or **R** (Scheme 7) are not formed (for details, see Supporting Information, Figure S83).

Theoretically, the scission of the bonds C1-C2 and C2-C3 in the isomeric spirocyclic intermediates **S**, **T** can lead to the formation of biradicals **U** and **V**, both being in the singlet or triplet states (Scheme 7). From the point of view of thermodynamics, the formation of such intermediate compounds is equally probable. Biradical **V** can transform into **W** as a result of an H-shift. In this case, the height of

the activation barrier is 154 kJ/mol. Biradical **W** is more stable than **V** by more than 10 kJ/mol, both in a singlet and a triplet (for details, see Supporting Information, Figure S88). It is probably this fact that allows us to explain the formation of a mixture of products **9a**, **b**.

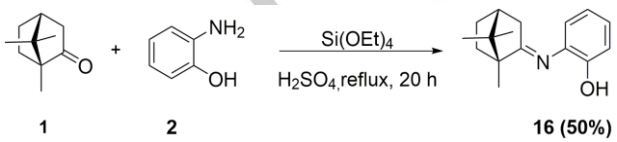
The profile of the potential energy surface during the cleavage of C1-C2 and C2-C3 bonds for alternative mechanisms was estimated for camphor-based structures: the transformation of spirocyclic radicals **C**, **D** into radicals **E**, **F** (Scheme 6), and the opening of spirocyclic intermediates **M**, **N** to form biradicals **O**, **P** (Scheme 7). In both cases, the ring opening of spirocyclic particles requires energy consumption, however, for the opening of particles **C** and **D**, about 89 kJ/mol (the maximum point on the PES profile, Figure S78) is required, and for the opening of intermediates **M** and **N** - about 300 kJ/mol (for details, see Computation Details in Supporting Information, Figure S82).

The breaking of C1-C2 bond in spirocyclic radicals **C** and **D** and intermediates **M** and **N** is more likely than the breaking of the C2-C3 bond. It was found that the difference in the energies of the **E** and **F** radicals is 35.07 kJ/mol in favor of **E** when optimizing their geometric parameters (see Supporting Information, p. 69). At the same time, the optimization of the geometric parameters of the biradical **P**, obtained as a result of the relaxed scanning of the PES, failed (for details, see Supporting Information, Figure S83). In turn, the camphor-based biradical **O** is relatively stable and can exist in both the singlet and triplet states. Thus, the formation of a mixture of products **3a**, **b** is more preferable from the point of view of thermodynamic parameters, regardless the considered reaction mechanism.

The PES profiles of the ring opening of spirocyclic intermediates **S** and **T** have also been investigated and presented in Supporting Information (Figures S85-S87).

Thus, we have shown using quantum chemical calculations that the investigated transformations most likely proceeds through the formation of monoradical species **A** and **B**. However, it should be noted that both proposed mechanisms presented in Schemes 6 and 7 are in good agreement with the observed experimental data.

Additionally, we carried out a series of experiments to confirm the mechanism we proposed in Scheme 6. First, we synthesised one of the possible imines and checked the possibility of obtaining the target heterocyclic compounds directly from the corresponding imine. As the studied transformation, we chose the reaction of **1** and **2**, since a mixture of benzoxazoles **3a**-**b** was formed faster and cleaner than others. Imine **16** was synthesised by a known method[49] and isolated by column chromatography with a 50% yield (Scheme 8).



1 **2** **16 (50%)**

Scheme 8. Synthesis of 2-(((1R,4R,E)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)amino)phenol.

Next, using imine **16**, two experiments were conducted. The first experiment consisted of heating this substance at 180°C in an NMR ampoule under argon atmosphere for 6 hours. Immediately after, the reaction mixture was characterised by NMR and GC-MS. The following substances were found in the final reaction mixture (GC-MS data): 22% **1**, 36% **3a**, 8% **3b**, 19% **16**, and 15% unidentified by-products. Based on these results, it was determined that the formation of target heterocycles probably proceeded through the formation of the corresponding imines.

The second experiment was heating imine **16** in a closed ampoule in a sand bath. The purpose of this experiment was to determine whether benzoxazoles **3a**, **b** would form from imine **16** at lower temperatures. The temperature increased in increments of 20°C, starting at 100°C (the temperature was measured in a sand bath). The mixture was held at each step for one hour, and GC-MS analysis of the reaction mixture was performed after cooling. The formation of the target products was observed at a temperature of 120°C. We then heated **16** at this temperature for 4 hours, and GC-MS analysis of the reaction mixture was performed each hour. As a result, after 5 hours of heating at 120°C, the composition of the mixture was as follows: 38% **3a**, 10% **3b**, 4% **16**, and 48% of unidentified products. Camphor was not found in the mixture.

Based on these two experiments, it was concluded that the formation of the target heterocyclic compounds probably occurred through the formation of the corresponding intermediate imines in the presence of $ZnCl_2$ in the initial mixture. Further, the ring opening of the starting monoterpenoids occurred without the action of the Lewis acid and proceeded at a lower temperature. However, in this case, the formation of numerous by-products was detected. Thus, it is much more profitable to synthesise target benzoazoles by a one-step synthesis from monoterpenoid and *o*-substituted aniline in the presence of the appropriate Lewis acid.

The Electron Paramagnetic Resonance (EPR) method, including *in situ* experiments, was used to detect and identify radicals that could be formed during the reaction of **1** and **2** in the presence of $ZnCl_2$ (*Sample A*), as well as during the heating of imine **16** (*Sample B*). In addition, the radicals formed in reactions of **1** and *p*-aminophenol (*Sample C*) and of **1** and **6** (*Sample D*) in the presence of $ZnCl_2$ (for experimental details, see Supporting Information) were detected by *in situ* EPR.

In *Sample A*, the formation of radicals at a concentration of about 10 μM was detected after 1 min of heating at 130°C (Figure 4). In *Sample B*, the concentration of radicals reached a value of 1 μM only after 1 hour when it was heated at the same temperature (Figure 5). The EPR spectra of *Samples A* and *B* recorded at a temperature of -130°C had absorption lines with g = 2.003 ± 0.001 and a width of ~ 1.5 and 0.8 mT, respectively. The poorly resolved structure of the *hfc* (hyperfine coupling interactions) appeared for *Sample A*.

The concentration of radicals in *Samples A* and *B* reached 500 and 20 μM respectively, after heating the samples at 130°C for 4 hours (Figures 4, 5). The concentration of radicals in *Sample C* reached 20 μM after heating the sample at 140°C for 30 min (Figure 6). The EPR spectra of the *Samples A* and *B* at low temperatures were poorly resolved. Obviously, this is a consequence of

the anisotropy of g and *hfc* tensors, since, the reaction mixtures are in a solid-state at low temperatures. An *hfc* structure consisting of seven equidistant lines with a characteristic splitting of ~ 12 MHz (0.4 mT) appeared in the EPR spectra of the *Samples A*, *B*, and *C* at high temperatures (Figures 4-6).

It is unlikely that the spectra we observed are due to intermediate biradical particle similar to the structure **O**. For these biradical particles, the distance between the electrons did not exceed 0.5 nm, and, therefore, for the triplet state, the zero-field splitting parameter D should be of the order of 200 MHz (50 mT).[50] Accordingly, for a frozen sample, a spectrum with splitting between lines of the same order should be observed. However, this is not observed for the spectra recorded at -130°C; the total characteristic width is approximately the same as for liquid samples at high temperature, i.e. of the order of ~ 1 mT.

The best-resolved EPR spectra of the samples can be explained by the formation of stable mono-radicals in which the unpaired electron interacts with the nitrogen and hydrogen nuclei. Indeed, the spectra of *Samples A*, *B*, and *C* in which the second component contains one nitrogen atom can be simulated with good accuracy under the assumption of the *hfc* of an unpaired electron with a nitrogen nucleus and four equivalent protons (*Sample A*: g = 2.0035, $A_N^{iso} = A_{H,1}^{iso} = A_{H,2}^{iso} = A_{H,3}^{iso} = A_{H,4}^{iso}$ = 12 MHz, $\Delta H_{pp}^{Gaussian}$ = 0.43 mT (Figure 4); *Sample B*: g = 2.0035, $A_N^{iso} = A_{H,1}^{iso} = A_{H,2}^{iso} = A_{H,3}^{iso} = A_{H,4}^{iso}$ = 12.5 MHz, $\Delta H_{pp}^{Gaussian}$ = 0.39 mT (Figure 5); *Sample C*: g = 2.0042, $A_N^{iso} = A_{H,1}^{iso} = A_{H,2}^{iso} = A_{H,3}^{iso} = A_{H,4}^{iso}$ = 10.5 MHz, $\Delta H_{pp}^{Gaussian}$ = 0.36 mT (Figure 6)). The hyperfine coupling constants obtained in the simulation have values comparable to those in structurally similar radicals:[47] A_N^{iso} ~= 10 – 25 MHz and A_H^{iso} ~= 5 – 25 MHz. The not quite perfect coincidence of the experimental and simulated spectra (this is especially noticeable for the spectra of *Sample C*) can be explained, firstly, by the fact that the nuclei in radicals may not be entirely equivalent, secondly, by incomplete averaging of anisotropic g and A tensors due to the high the viscosity of the samples, thirdly, the possible formation of various types of radicals, some of which can give by-products.

The EPR spectrum of *Sample C* (Figure 6) probably belongs to a long-lived 4-(((1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)amino)phenoxyl radical. Thus, the EPR spectra observed upon heating of the *Samples A*, *B* most likely correspond to long-lived radical **A** (Scheme 6), but not to **C** or **D**, based on the similarity of EPR spectra of *Sample A, B, and C*.

In summary, the monoradical mechanism presented in Scheme 6 is confirmed by the results of EPR spectroscopy and the data of quantum chemical calculations.

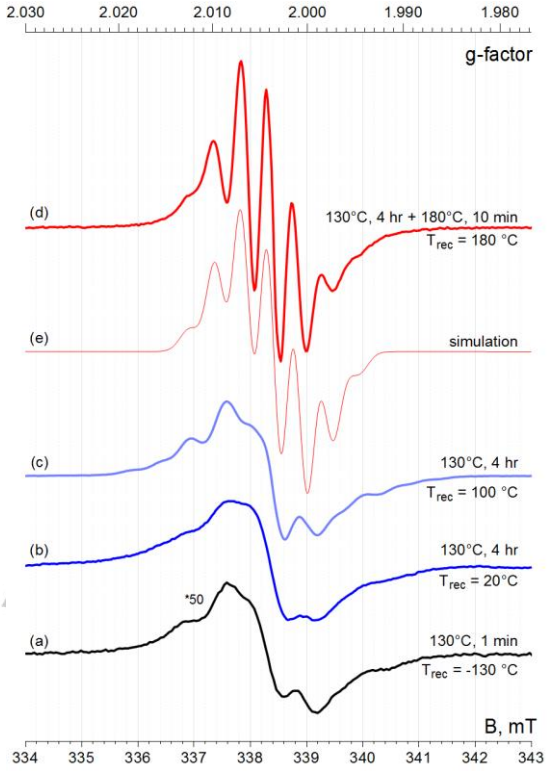


Figure 4. The EPR spectra of *Sample A* recorded after heating at 130°C for 1 min (a), then at 130°C for 4 h (b, c) followed by heating at 180°C for 10 min (d). Spectra recording temperatures (T_{rec}) are shown in the figure. The spectra were multiplied by T to compensate for the Curie–Weiss effect. (e) – the simulated spectrum (see text for simulation parameters). Microwave frequency 9.490 MHz.

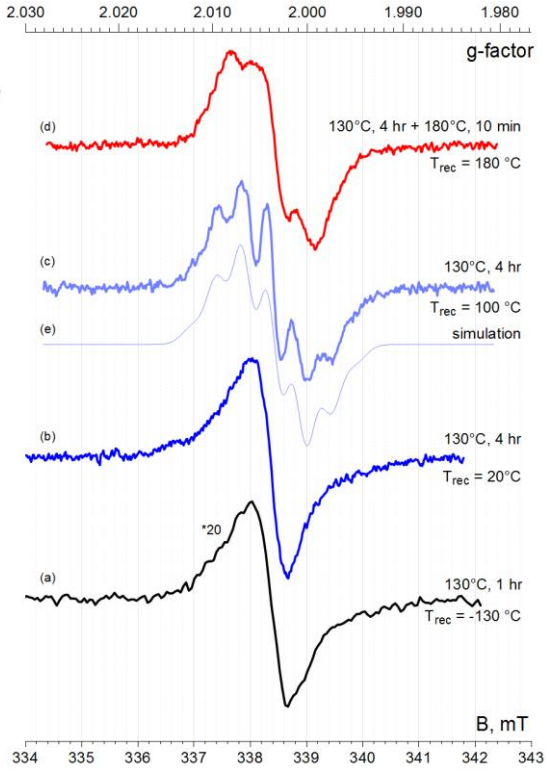


Figure 5. The EPR spectra of *Sample B* recorded after heating at 130°C for 1 h (a), then at 130°C for 4 h (b, c) followed by heating at 180°C for 10 min (d). Spectra recording temperatures (T_{rec}) are shown in the figure. The spectra were multiplied by T to compensate for the Curie–Weiss effect. (e) – the simulated spectrum (see text for simulation parameters). Microwave frequency 9.490 MHz.

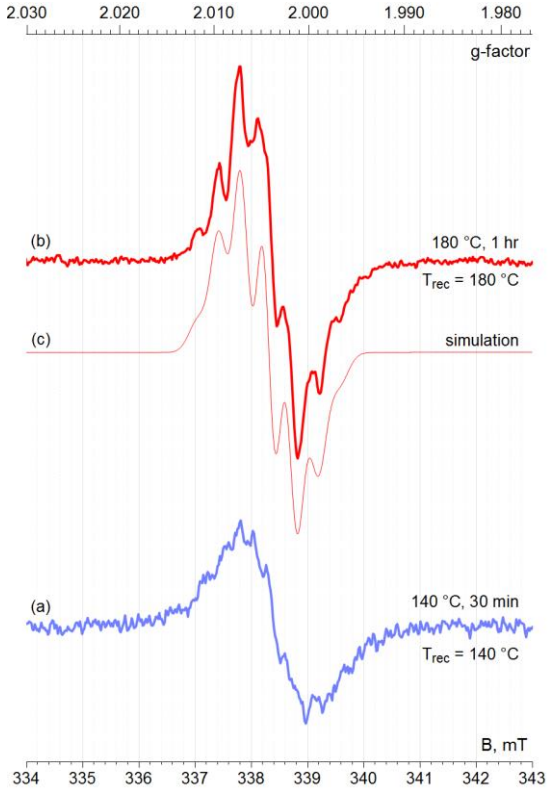


Figure 6. The EPR spectra of *Sample C* recorded after heating at 140°C for 30 min (a), then at 180°C for 1 h (b). Spectra recording temperatures (T_{rec}) are shown in the figure. The spectra were multiplied by T to compensate for the Curie−Weiss effect. (c) – the simulated spectrum (see text for simulation parameters). Microwave frequency 9.490 MHz.

Conclusion

In this paper, we described the unusual results of the reaction of camphor-like ketones with *o*-heteroatom-substituted anilines in the presence of Lewis acids. Instead of the formation of expected imines, new products of ring opening reactions were isolated. The proposed mechanisms included the formation of intermediate imines followed by the breaking of C1-C2 or C2-C3 bonds via the radical pathway. The intermediate radicals were stabilised by the formation of benzoazoles containing cyclopentanemethyl group at position 2. Mechanistic considerations were confirmed by EPR studies and quantum chemical calculations. Such transformations opened a new way to the family of heterocyclic compounds possessing stereochemically determined substituents at position 2, which are of great value for organic and medicinal chemistry.

Experimental Section

Materials and Instruments: Reagents and solvents were purchased from commercial suppliers and used as received. Dry solvents were obtained according to the standard procedures. Imine **16** was prepared as published previously and ^{1}H, ^{13}C NMR spectral data were in good agreement with those of the literature.[49] GC-MS analysis was performed on an Agilent 7820A gas chromatograph combined with an Agilent 5975C mass detector (Agilent Technologies, USA); flame-ionization detector; HP-5 capillary column, helium as carrier gas (flow rate 2 mL/min, flow division 99:1). General conditions for the GC determining the presence of enantiomers of the target mixture of diastereoisomeric heterocyclic compounds by MS were as follows, using an Agilent 6890N gas chromatography-mass spectrometer with an Agilent 5973N mass analyser under the following conditions: carrier gas (helium) flow rate 1 ml/min, 0.2-2.0 µl sample volume, Cyclosil-B as chromatographic column (30 m, 250 mkm, 0.25 mkm), injector temperature 240°C, heating conditions – 2 min. at 50°C, then heating at a rate of 4°C/min to 220°C, then holding at a temperature of 220°C for 10 minutes. The specific optical rotation were determined using a polAAr 3005 spectrometer and expressed as (deg ml) (g dm)$^{-1}$; concentration is expressed as (g) (100 ml)$^{-1}$. ^{1}H and ^{13}C NMR spectra were recorded with Bruker spectrometer Avance III 500 (at 500.03 MHz (^{1}H) and 125.74 MHz (^{13}C)). Chemical shifts δ are reported in parts per million (ppm) relative to residual $CHCl_3$ [δ($C\underline{H}Cl_3$) 7.25, δ($\underline{C}DCl_3$) 77.16 ppm] and the coupling constants *J* are reported in units of Herts [Hz]. The structure of the products was determined by analysing ^{1}H and ^{13}C NMR spectra; assignments on a routine basis by a combination of 1D and 2D experiments (COSY, HSCQ, HMBC). High resolution mass spectra (HRMS, ESI^{+}) were recorded with a DFS Thermo Scientific spectrometer in a full scan mode (15–500 m/z, 70eV electron impact ionisation, direct sample administration). The infrared (IR) spectra were recorded on a Bruker Vector 22 FT-IR spectrometer with KBr pellets. Melting points were determined on a Kofler bench. Column chromatography was performed on silica gel (60-200 l, Macherey-Nagel). Thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F254 precoated plates. Spectral and analytical studies were carried out at the Collective Chemical Service Center of the Siberian Branch of the Russian Academy of Sciences.

X-Ray Single Crystal Diffractometry: The X-ray diffraction data were collected with a Bruker KAPPA APEX II CCD diffractometer with graphite monochromated Mo-Kα radiation (0.71073 Å) at the Collective Chemical Service Center of Siberian Branch of the Russian Academy of Sciences. Absorption corrections were applied with Siemens Area Detector Absorption Correction Software (SADABS). The structure was solved by the direct method. The positions and temperature factors for the non-hydrogen atoms were refined anisotropically by the full-matrix least-squares technique. All computations were done with the SHELX-2018/3 program suite. The crystallographic data, in CIF format, were deposited with the Cambridge Crystallographic Data Centre under number CCDC 2019527 (for **7a**), CCDC 2019526 (for **3a·AgNO$_3$**), and CCDC 2019528 (for **2(11a)·CuCl**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Electron Paramagnetic Resonance: The study was performed using an X-band EPR spectrometer (Bruker ELEXSYS 500) equipped with a standard cell ER 4102ST and digital temperature control unit ER 4131VT. Samples in an amount of ~ 50 mg were placed in a quartz ampoule with an inner diameter of 2 mm and heated at various temperatures for various times. EPR spectra were recorded at various temperatures in the range from -130 to 180°C. The concentration of radicals was estimated by comparing the integrated intensity of the absorption spectra of the samples and a TEMPO solution of the same volume with a known concentration of 100 µM. The accuracy of determining the concentration of radicals was at least 50%. The ESR spectra were simulated using EasySpin software.[51]

Computation Details: All theoretical calculations were performed using the GAUSSIAN 09 program. Hybrid functional (HSEH1PBE)[52] combined with Dunning's correlation consistent basis sets cc-pVTZ[53] were used for geometrical optimisation of biradical structures, intermediates and reaction products (Scheme 6), and frequency calculations. The type of stationary points of the potential energy surface (PES) was characterised by the Hessian matrix. If the Hessian matrix was definitively positive for the total energy, then the stationary point attained a local minimum of the PES. If the Hessian had the only negative eigenvalue (imaginary frequency), then the stationary point corresponded to a saddle point

(transition state, TS). A relaxed PES scan (with geometry optimisation at each point) was performed by the UHSEH1PBE/SVP/auto method.[54,55] All calculations were carried out in the gas phase approximation at 298.15 K.

General Procedure A: Preparation of benzoxazoles **3a**-**b**, **9a**-**b** and benzothiazoles **5a**-**b**, **10a**-**b**: Monoterpenoid (20 g, 131.6 mmol, 1.0 equiv.) and *o*-aminophenol (14.3 g, 131.6 mmol, 1.0 equiv.) or *o*-aminothiophenol (16.4 g, 131.6 mmol, 1.0 equiv.) were mixed in a round bottom flask. Anhydrous zinc chloride (900 mg, 6.6 mmol, 0.05 equiv.) was added, and the mixture was heated with a reflux condenser until a homogeneous yellow mixture formed. This mixture was heated until the monoterpenoid was used up (6-8 hours, as follows from TLC). The residue was taken up in $CHCl_3$, the organic layer was washed with 20% sodium hydroxide solution, and the aqueous layer was back-extracted with $CHCl_3$. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness using rotary evaporation. The crude mixtures were purified by vacuum distillation to obtain mixtures of benzoxazoles **3a**, **b** (24.3 g, total yield 76%, ratio a:b = 13:7), **9a**, **b** (21.1 g, total yield 66%, ratio a:b = 7:3), benzothiazoles **5a**, **b** (21.5 g, total yield 63%, ratio a:b = 3:2), and **10a**, **b** (16.0 g, total yield 47%, ratio a:b = 3:2) as yellow oils. The ratio of isomers in the mixtures was determined according to GC-MS and NMR ^1H, ^{13}C. Mixtures of benzoxazoles and benzothiazoles were purified by silica gel column chromatography using hexane as the eluent. Purification did not help isolate benzoxazoles and benzothiazoles individually; however, it was possible to obtain fractions with the predominant content of the main diastereoisomer. The ratio of isomers **3a**:**3b**, **5a**:**5b**, **9a**:**9b, 10a**:**10b** in the colourless mixtures after silica gel column chromatography was 3:1; 3:1; 4:1; 3:1, respectively, according to NMR ^1H, ^{13}C.

General Procedure B: Preparation of benzimidazoles **7a**--**b**, **11a**-**b**: Monoterpenoid (10 g, 65.8 mmol, 1.0 equiv.) and *o*-phenylenediamine (7.1 g, 65.8 mmol, 1.0 equiv.) were mixed in a round bottom flask. Anhydrous zinc chloride (450 mg, 3.3 mmol, 0.05 equiv.) and excess phenol were added, and the mixture was heated with a reflux condenser until a homogeneous yellow mixture formed. This mixture was heated until the monoterpenoid was used up (6-8 hours, as follows from TLC). The residue was taken up in $CHCl_3$, the organic layer was washed with 20% sodium hydroxide solution, and the aqueous layer was back-extracted with $CHCl_3$. The combined organic layers were dried over anhydrous Na_2SO_4 and then evaporated to dryness using rotary evaporation. The residue was dissolved in a minimal volume of chloroform, then an excess of hexane was added and left in the freezer for 24 hours. As a result, the desired benzimidazoles precipitated as a white powder and was collected by filtration, washed with hexane, and recrystallised from acetonitrile. The total yield of benzimidazoles **7a**, **b** was 9.1 g (57%, ratio a:b = 5:2), and the total yield of benzimidazoles **11a**, **b** was 5.9 g (37%, ratio a:b = 3:2). The ratio of isomers in the mixtures was determined by GC-MS and NMR ^1H, ^{13}C. We tried to separate the mixtures of benzimidazoles by column chromatography (eluent 30% $CHCl_3$/hexane) with external heating (to avoid crystallisation of the substance in the column), but fractions of the main diastereoisomer were predominantly obtained. The ratio of isomers **7a**, **b** and **11a**, **b** after silica gel column chromatography was 17:3 and 19:1, respectively, according to NMR ^1H, ^{13}C.

General Procedure C: Preparation of 13-15: Norcamphor (300 mg, 2.73 mmol, 1.0 equiv.) and *o*-substituted aniline (2.73 mmol, 1.0 equiv.) were mixed in a round bottom flask. Anhydrous zinc chloride (19 mg, 0.14 mmol, 0.05 equiv.) and excess phenol were added, and the mixture heated with a reflux condenser until a homogeneous yellow mixture formed. This mixture was heated until monoterpenoid was used up (5 hours, as follows from TLC). The residue was taken up in $CHCl_3$, the organic layer was washed with 20% sodium hydroxide solution, and the aqueous layer was back-extracted with $CHCl_3$. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness using rotary evaporation. The residues were purified by column chromatography (eluent 5% $CHCl_3$/hexane), isolating **13** (356 mg, 65% yield) and **14** (355 mg, 60% yield) as colourless oils, and **15** (273 mg, 50% yield) as a white powder.

2-(((1*R*,3*R*)-2,2,3-trimethylcyclopentyl)methyl)benzo[*d*]oxazole (3a): colourless oil (24.3 g, 76% yield). IR: 3059, 2956, 2870, 1659, 1572, 1456, 1242, 1146, 930, 839, 744 cm^{-1}. $[\alpha]_D^{28.5}$= -34 (C_2H_5OH, c = 1.8). ^1H NMR (500.03 MHz, $CDCl_3$, δ): 0.65 (*s*, 3H; 17-CH_3 or 16-CH_3), 0.86 (*d*, *J* = 6.6 Hz, 3H; 18-CH_3), 0.99 (*s*, 3H; 16-CH_3 or 17-CH_3), 1.19–1.27 (*m*, 1H; 14-CH_2), 1.34-1.42 (*m*, 1H; 15-CH_2), 1.55-1.63 (*m*, 1H; 13-CH), 1.77-1.82 (*m*, 1H; 14-CH_2), 1.82-1.86 (*m*, 1H; 15-CH_2), 2.07-2.14 (*m*, 1H; 11-CH), 2.68 (*dd*, *J* = 14.8, 10.9 Hz, 1H; 10-CH_2), 3.00 (*dd*, *J* = 14.8, 4.2 Hz, 1H; 10-CH_2), 7.19-7.22 (*m*, 2H; 7-CH(Ar), 8-CH(Ar)), 7.53-7.56 (*m*, 2H; 6-CH(Ar), 9-CH(Ar)), 10.04 ppm (*br.s*, 1H; 1-NH). $^{13}C\{^1H\}$ NMR (125.74 MHz, $CDCl_3$, δ): 14.0 (18-C), 14.5 (17-C or 16-C), 25.5 (16-C or 17-C), 28.4 (15-C), 29.(97) (10-C or 14-C), 30.(05) (14-C or 10-C), 42.7 (12-C), 45.0 (13-C), 48.9 (11-C), 110.4 (6-C), 119.6 (9-C), 124.2 (8-C), 124.5 (7-C), 141.6 (4-C), 151.0 (5-C), 167.7 (2-C). HRMS (ESI^+): calculated $(C_{16}H_{21}O_1N_1)^{+\cdot}$ 243.1618; found 243.1615.

2-(((1*R*,3*R*)-2,2,3-trimethylcyclopentyl)methyl)benzo[*d*]thiazole (5a): colourless oil (21.5 g, 63% yield). IR: 3063, 2955, 2870, 1595, 1518, 1435, 1367, 1126, 758 cm^{-1}. $[\alpha]_D^{28.0}$= -21.8 (C_2H_5OH, c = 1.2). ^1H NMR (500.03 MHz, $CDCl_3$, δ): 0.68 (*s*, 3H; 17-CH_3 or 16-CH_3), 0.86 (*d*, *J* = 6.8 Hz, 3H; 18-CH_3), 0.99 (*s*, 3H; 16-CH_3 or 17-CH_3), 1.20-1.31 (*m*, 1H; 14-CH_2), 1.37-1.44 (*m*, 1H; 15-CH_2), 1.57-1.65 (*m*, 1H; 13-CH), 1.75-1.83 (*m*, 1H; 14-CH_2), 1.80-1.84 (*m*, 1H; 15-CH_2), 2.02-2.09 (*m*, 1H; 11-CH), 2.88 (*dd*, *J* = 14.3, 11.2 Hz, 1H; 10-CH_2), 3.25 (*dd*, *J* = 14.5, 3.8 Hz, 1H; 10-CH_2), 7.32 (*ddd*, *J* = 8.1, 7.2, 1.1 Hz, 1H; 7-CH(Ar)), 7.43 (*ddd*, *J* = 8.1, 7.2, 1.1 Hz, 1H; 8-CH(Ar)), 7.81 (*d*, *J* = 8.0 Hz, 1H; 9-CH(Ar)), 7.96 (*d*, *J* = 8.0 Hz, 1H; 6-CH(Ar)). $^{13}C\{^1H\}$ NMR (125.74 MHz, $CDCl_3$, δ): 14.0 (18-C), 14.7 (17-C or 16-C), 25.7 (16-C or 17-C), 28.3 (15-C), 30.1 (14-C), 35.8 (10-C), 43.0 (12-C), 45.0 (13-C), 51.3 (11-C), 121.5 (9-C), 122.6 (6-C), 124.7 (7-C), 126.0 (8-C), 135.3 (5-C), 153.3 (4-C), 172.5 (2-C). HRMS (ESI^+): calculated $(C_{16}H_{21}{}^{32}S_1N_1)^{+\cdot}$ 259.1389; found 259.1392.

2-(((1*R*,3*R*)-2,2,3-trimethylcyclopentyl)methyl)-1*H*-benzo[*d*]imidazole (7a): white powder (9.1 g, 57% yield).). $[\alpha]_D^{23.0}$= +20.0 (C_2H_5OH, c = 0.50); m.p. 193.9-200.9°C. IR: 3055, 2955, 2870, 1625, 1540, 1422, 1274, 1015, 750 cm^{-1}. ^1H NMR (500.03 MHz, $CDCl_3$, δ): 0.55 (*s*, 3H; 17-CH_3 or 16-CH_3), 0.79 (*s*, 3H; 16-CH_3 or 17-CH_3), 0.79 (*d*, *J* = 6.7 Hz, 3H; 18-CH_3), 1.11-1.19 (*m*, 1H; 14-CH_2), 1.32-1.40 (*m*, 1H; 15-CH_2), 1.41-1.49 (*m*, 1H; 13-CH), 1.63-1.79 (*m*, 2H; 14-CH_2, 15-CH_2), 2.03-2.10 (*m*, 1H; 11-CH), 2.71 (*dd*, *J* = 14.3, 11.3 Hz, 1H; 10-CH_2), 3.08 (*dd*, *J* = 14.0, 3.9 Hz, 1H; 10-CH_2), 7.19-7.22 (*m*, 2H; 7-CH(Ar), 8-CH(Ar)), 7.53-7.56 (*m*, 2H; 6-CH(Ar), 9-CH(Ar)), 10.04 ppm (*br.s*, 1H; 1-NH). $^{13}C\{^1H\}$ NMR (125.74 MHz, $CDCl_3$, δ): 14.0 (18-C), 14.5 (17-C or 16-C), 25.4 (16-C or 17-C), 28.4 (15-C), 29.9 (14-C), 30.3 (10-C), 42.7 (12-C), 45.0 (13-C), 50.1 (11-C), 114.6 (6-C and 9-C), 122.6 (7-C and 8-C), 137.8 (4-C and 5-C), 155.4 ppm (2-C). HRMS (ESI^+): calculated $(C_{16}H_{22}N_2)^{+\cdot}$ 242.1778; found 242.1779.

2-((1*R*,3*S*)-3-isopropyl-1-methylcyclopentyl)benzo[*d*]oxazole (9a): colourless oil (21.1 g, 66% yield). IR: 3057, 2955, 2870, 1740, 1562, 1456, 1092, 930, 750 cm^{-1}. $[\alpha]_D^{23.0}$= -24 (C_2H_5OH, c = 0.8). ^1H NMR (500.03 MHz, $CDCl_3$, δ): 0.93-0.95 (6H, *d*, H-17, H-18), 1.26-1.30 (1H, *m*, H-13), 1.48-1.52 (1H, *m*, H-16), 1.54 (3H, *s*, H-15), 1.76-1.82 (1H, *m*, H-14), 1.84-1.91 (1H, *m*, H-12), 1.96-2.02 (2H, *m*, H-11,H-13), 2.38-2.43 (1H, *m*, H-14), 7.28-7.30 (2H, *m*, H-7, H-8), 7.48-7.50 (1H, *m*, H-6), 7.69-7.72 ppm (1H, *m*, H-9). $^{13}C\{^1H\}$ NMR (125.74 MHz, $CDCl_3$, δ): 21.6 (C-17, C-18), 26.5 (C-15), 30.3 (C-13), 33.7 (C-16), 38.7 (C-14), 44.0 (C-11), 44.4 (C-10), 46.9 (C-12), 110.4 (C-6), 119.8 (C-9), 124.0 (C-7), 124.4 (C-8), 141.5 (C-5), 151.1 (C-4), 173.9 ppm (C-2). HRMS (ESI^+): calculated $(C_{16}H_{21}O_1N_1)^{+\cdot}$ 243.1618; found 243.1619.

2-((1*R*,3*S*)-3-isopropyl-1-methylcyclopentyl)benzo[*d*]thiazole (10a): colourless oil (16.0 g, 47% yield). IR: 2955, 2868, 1510, 1439, 1009, 758,

729 cm^{-1}. $[\alpha]_D^{23.0}$= -23.0 (C_2H_5OH, c = 2.3). ^1H NMR (500.03 MHz, $CDCl_3$, δ): 0.9(18) (*d*, *J* = 6.6 Hz, 3H; 17-CH_3 or 18-CH_3), 0.9(21) (*d*, *J* = 6.6 Hz, 3H; 18-CH_3 or 17-CH_3), 1.45-1.49 (*m*, 1H; 16-CH), 1.49-1.55 (*m*, 1H; 13-CH_2), 1.53 (*s*, 3H; 15-CH_3), 1.83-1.92 (*m*, 2H; 12-CH, 14-CH_2), 1.93-2.01 (*m*, 2H; 11-CH_2, 13-CH_2), 2.06 (*dd*, *J* = 12.1, 6.9 Hz, 1H; 11-CH_2), 2.33 (*ddd*, *J* = 12.8, 9.4, 5.0 Hz, 1H; 14-CH_2), 7.31 (*ddd*, *J* = 8.1, 7.1, 1.2 Hz, 1H; 7-CH(Ar)), 7.42 (*ddd*, *J* = 8.1, 7.1, 1.2 Hz, 1H; 8-CH(Ar)), 7.83 (*ddd*, *J* = 8.1, 1.1, 0.6 Hz, 1H; 6-CH(Ar)), 7.98 ppm (*ddd*, *J* = 8.1, 1.1, 0.6 Hz, 1H; 9-CH(Ar)). $^{13}C\{^1H\}$ NMR (125.74 MHz, $CDCl_3$, δ): 21.(58) (C-17 or C-18), 21.(61) (C-18 or C-17), 29.0 (C-15), 30.0 (C-13), 33.8 (C-16), 40.7 (C-14), 46.2 (C-11), 46.8 (C-12), 49.2 (C-10), 121.5 (C-6), 122.8 (C-9), 124.5 (C-7), 125.8 (C-8), 135.2 (C-5), 153.4 (C-4), 182.3 ppm (C-2). HRMS (ESI^+): calculated $(C_{16}H_{21}{}^{32}S_1N_1)^{+\cdot}$ 259.1389; found 259.1391.

2-((1*R*,3*S*)-3-isopropyl-1-methylcyclopentyl)-1*H*-benzo[*d*]imidazole (11a): white powder (5.9 g, 37% yield).). $[\alpha]_D^{23.0}$= +9.0 (C_2H_5OH, c = 0.80); m.p. 198.8-199.7°C. IR: 3051, 2956, 1622, 1531, 1411, 1276, 992, 751 cm^{-1}. ^1H NMR (500.03 MHz, $CDCl_3$+CD_3OD, δ): 0.83 (*d*, *J* = 6.9 Hz, 3H; 17-CH_3 or 18-CH_3), 0.84 (*d*, *J* = 6.9 Hz, 3H; 18-CH_3 or 17-CH_3), 1.35-1.38 (*m*, 1H; 12-CH), 1.40-1.43 (*m*, 1H; 13-CH_2), 1.43 (*s*, 3H; 15-CH_3), 1.78-1.86 (*m*, 3H; 11-CH_2, 14-CH_2, 16-CH), 1.89-1.96 (*m*, 1H; 13-CH_2), 1.97-2.03 (1H, *m*; 11-CH_2), 2.27 (*ddd*, *J* = 15.4, 9.8, 5.5 Hz, 1H; 14-CH_2), 3.66 (*br.s*, 1H; 1-NH), 7.14-7.16 (*m*, 2H; 7-CH(Ar), 8-CH(Ar)), 7.51-7.53 ppm (*m*, 2H; 6-CH(Ar), 9-CH(Ar)). $^{13}C\{^1H\}$ NMR (125.74 MHz, $CDCl_3$, δ): 21.4 (17-C or 18-C), 21.5 (18-C or 17-C), 27.5 (15-C), 29.6 (13-C), 33.8 (12-C), 38.7 (14-C), 44.2 (10-C), 44.5 (11-C), 46.3 (16-C), 114.6 (6-C, 9-C), 122.4 (7-C, 8-C), 137.6 (4-C, 5-C), 162.6 ppm (2-C). HRMS (ESI^+): calculated $(C_{16}H_{22}N_2)^{+\cdot}$ 242.1778; found 242.1775.

2-(cyclopentylmethyl)benzo[*d*]oxazole (13): colourless oil (356 mg, 65% yield). IR: 3057, 2953, 1570, 1456, 1242, 1169, 837, 746 cm^{-1}. $[\alpha]_D^{28.5}$= +30.4 ($CHCl_3$, c = 1.17). ^1H NMR (500.13 MHz, $CDCl_3$, δ): 1.27-1.34 (*m*, 2H; 12-CH_2, 15-CH_2), 1.53-1.61 (*m*, 2H; 13-CH_2, 14-CH_2), 1.63-1.71 (*m*, 2H; 13-CH_2, 14-CH_2), 1.83-1.89 (*m*, 2H; 12-CH_2, 15-CH_2), 2.47 (*hept*, *J* = 7.7 Hz, 1H; 11-CH), 2.93 (*d*, *J* = 7.5 Hz, 2H; H-10), 7.26-7.29 (*m*, 2H; H-7, H-8), 7.44-7.48 (*m*, 1H; H-6), 7.64-7.67 ppm (*m*, 1H; H-9). $^{13}C\{^1H\}$ NMR (125.74 MHz, $CDCl_3$, δ): 25.1 (C-13, C-14), 32.6 (C-12, C-15), 34.6 (C-10), 38.3 (C-11), 110.4 (C-6), 119.7 (C-9), 124.1 (C-8), 124.5 (C-7), 141.6 (C-4), 150.9 (C-5), 167.1 ppm (C-2). HRMS (ESI^+): calculated $(C_{13}H_{15}O_1N_1)^{+\cdot}$ 201.1148; found 201.1149.

2-(cyclopentylmethyl)benzo[*d*]thiazole (14): colourless oil (355 mg, 60% yield). IR: 3063, 2951, 1518, 1437, 1311, 1244, 1105, 758 cm^{-1}. $[\alpha]_D^{27.7}$= +27.6 ($CHCl_3$, c = 1.04). ^1H NMR (500.03 MHz, $CDCl_3$, δ): 1.28-1.35 (*m*, 2H; H-12, H-15), 1.53-1.61 (*m*, 2H; H-13, H-14), 1.64-1.70 (*m*, 2H; H-13, H-14), 1.82-1.88 (*m*, 2H; H-12, H-15), 2.39 (*hept*, *J* = 7.6 Hz, 1H; H-11), 3.10 (*d*, *J* = 7.5 Hz, 2H; H-10), 7.33 (*ddd*, *J* = 8.4, 7.1, 1.2 Hz, 1H; H-7), 7.43 (*ddd*, *J* = 8.4, 7.1, 1.2 Hz, 1H; H-8), 7.82 (*ddd*, *J* = 8.1, 1.1, 0.6 Hz, 1H; H-6), 7.96 ppm (*ddd*, *J* = 8.1, 1.1, 0.6 Hz, 1H; H-6). $^{13}C\{^1H\}$ NMR (125.74 MHz, $CDCl_3$, δ): 25.2 (C-13, C-14), 32.7 (C-12, C-15), 40.5 (C-10), 40.7 (C-11), 121.6 (C-6), 122.7 (C-9), 124.7 (C-7), 125.9 (C-8), 135.4 (C-5), 153.4 (C-4), 171.9 ppm (C-2). HRMS (ESI^+): calculated $(C_{13}H_{15}{}^{32}S_1N_1)^{+\cdot}$ 217.0920; found 217.0923.

2-(cyclopentylmethyl)-1*H*-benzo[*d*]imidazole (15): white powder (273 mg, 50% yield). $[\alpha]_D^{28.0}$= +24.6 ($CHCl_3$, c = 1.30); m.p. 213.3-214.4°C. IR: 3084, 2945, 2864, 2683, 1624, 1541, 1435, 1275, 1030, 743 cm^{-1}. ^1H NMR (500.03 MHz, $CDCl_3$, δ): 1.22–1.30 (*m*, 2H; H-12, H-15), 1.47-1.54 (*m*, 2H; H-13, H-14), 1.56-1.63 (*m*, 2H; H-13, H-14), 1.75-1.81 (*m*, 2H; H-12, H-15), 2.43 (*hept*, *J* = 7.8 Hz, 1H; H-11), 2.95 (*d*, *J* = 7.6 Hz, 2H; H-10), 7.19-7.22 (*m*, 2H; H-7, H-8), 7.52-7.56 (*m*, 2H; H-6, H-9), 11.55 ppm (*br.s.*, 1H; H-1). $^{13}C\{^1H\}$ NMR (125.74 MHz, $CDCl_3$, δ): 25.1 (C-13, C-14), 32.8 (C-12, C-15), 35.5 (C-10), 39.5 (C-11), 114.8 (C-6, C-9), 122.2 (C-7, C-8), 138.7 (C-4, C-5), 155.1 ppm (C-2). HRMS (ESI^+): calculated $(C_{13}H_{16}N_2)^{+\cdot}$ 200.1308; found 200.1310.

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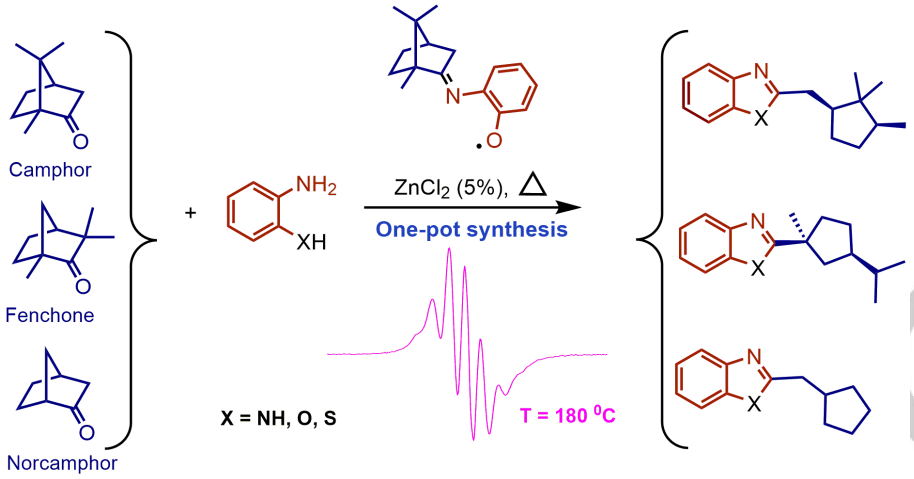
Graphical Abstract.



New condensation reaction of camphor-like ketones with *o*-substituted anilines leading to formation of 2-substituted benzoazoles is reported. A new reaction proceeds via ring opening of the bicyclic core. Quantum chemical calculations and EPR spectroscopy study suggest that imine radicals are key-intermediates responsible for this unusual process.