REVIEW ARTICLE

A C G publications

Org. Commun. XX:X (20XX) X-XX

organic communications

Synthesis of heterocyclic compounds from camphor

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(Received March 25, 2023; Revised April 25, 2023; Accepted May 10, 2023)

Abstract: In this review, we demonstrated the synthesis of isatin derivative **3** according to the Mannich reaction. Moreover, the synthesis of substituted enamines **6a-b** using urea catalysts were studied. Additionally, the synthesis of azepanes, piperidines, pyrrolidines, pyrazole, pyridine and pyrimidine derivatives were reported. Furthermore, the synthesis of triazolium salts (**34**), enamines derivatives **39** and **40**, tetrapyrazinoporphyrazine magnesium complex (**43**), ligands **49** and **50**, optically active *α*-amino acids **62a,** lactam derivative **67**, and its isomer *α*-camphidone (**68**), camphor dimethyl DL-tartrate (Ct diester) (**70**), and thiazole derivatives from camphor monoterpenes were realized. The biological activities of many compounds were studied toward human cancer cell lines, influenza virus, *Streptococcus pneumoniae, Klebsiella pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa, Methicillin-Resistant Staphylococcus aureus (MRSA), Escherichia coli, Bacillus cereus, Bacillus subtilis* and vaccinia virus, showing interesting results.

Keywords: Camphor; pyrazole; camphor dimethyl DL-tartrate; thiazole; biological activity.

1. Introduction

Cinnamon oil and some aromatic plants, such as basil, sage and rosemary, contain a camphor monoterpene and its derivatives, which are used in traditional medicine. Mono-terpenoids were reported as anti-mutagenic agent against different types of cancer cell lines such as leukemia, breast cancer, liver tumor, gastric cancer and colon cancer.[1] Chemotherapeutic agents, used to treat tumors, are harmful as they kill healthy cells of the body along with the cancer cells during the treatment. Thus, the syntheses of new and less harmful chemotherapy agents to human body starting from mono-terpenes, which are bioactive natural products, are considered to be an important aim.[1] Numerous studies have been conducted on the applications of camphor in environmental, industrial and pharmaceutical fields. For many years, camphor has been used traditionally as anti-irritation and anti-inflammatory medicine.[2] Since camphor has important anti-inflammation, antioxidant, and antitumor activities, recent studies have been focused on the importance and role of camphor in treating deadly diseases, to be used either alone or in combination with other medicines.[1-3]

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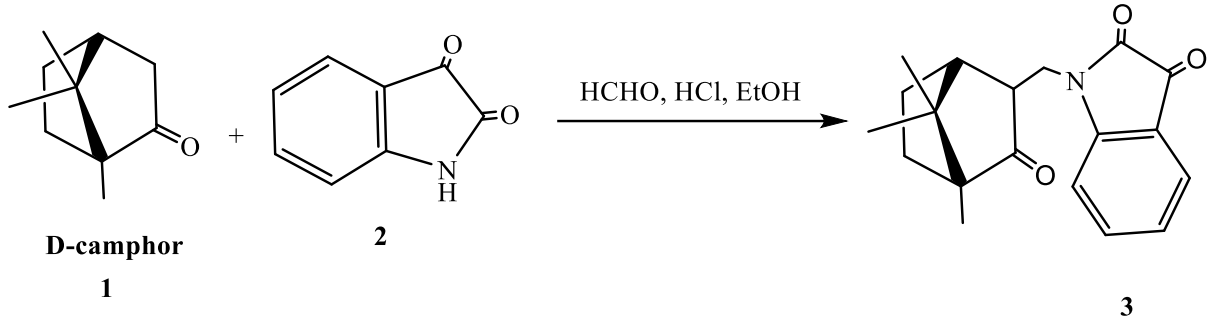
The article was published by ACG Publications
http://www.acgpubs.org/journal/organic-communications © Month-Month 2023 EISSN:1307-6175
DOI: http://doi.org/10.25135/acg.oc.150.2303.2741
Available online: May 22, 2023

Synthesis of biologically active heterocyclic compounds from camphor

Studies on the synthesis of N, O and S-heterocyclic compounds from camphor mono-terpenes are reported in this review. Most of the reported compounds were found to have good biological activities against human cancer cell lines, influenza virus, Gram-positive and Gram-negative bacteria.

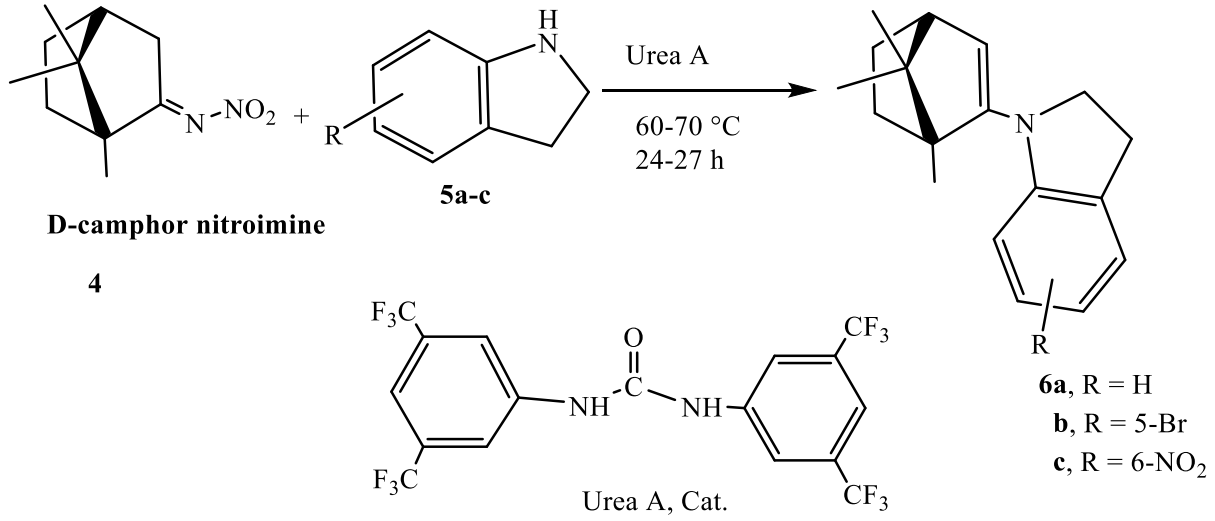
1. Synthesis of N and O-Heterocyclic Compounds from Camphor

Chaudhary et al. demonstrated the synthesis of isatin derivative **3** through the reaction of camphor (**1**) with isatin (**2**) according to the Mannich reaction in ethanol in the presence of formaldehyde and hydrochloric acid, which showed important activity toward human cancer cell lines with GI_{50} values between 1.53 and 26.9 μM (Scheme 1).[4]



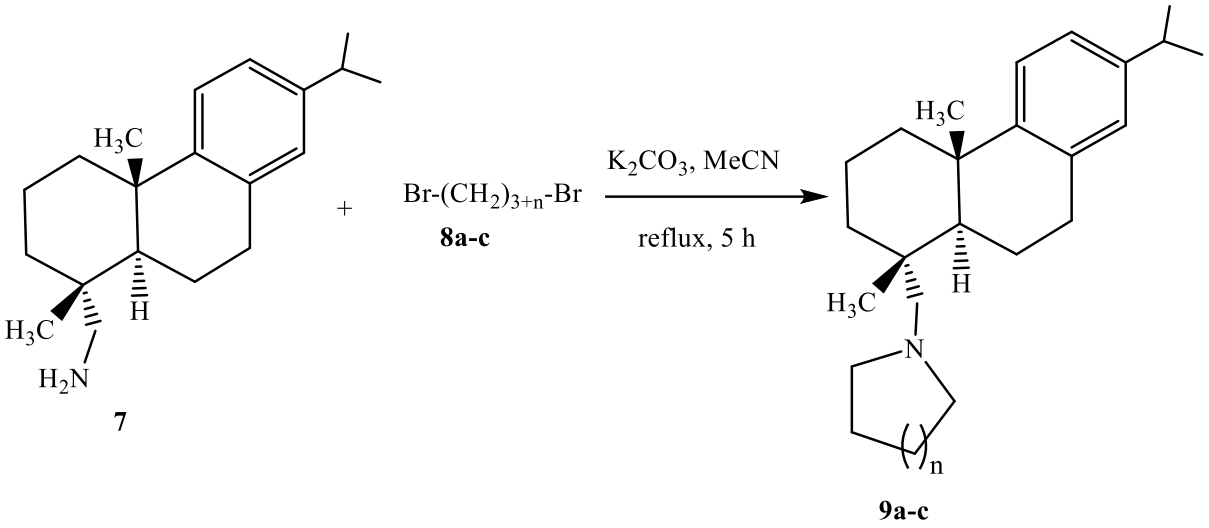
Scheme 1. Synthesis of isatin derivative **3**

Nitroimines and various amines were activated with urea catalysts, reported by Nickerson et al.,[5] to give highly substituted enamines **6a-b** (Scheme 2), which exhibited significant biological activities.[6,7]

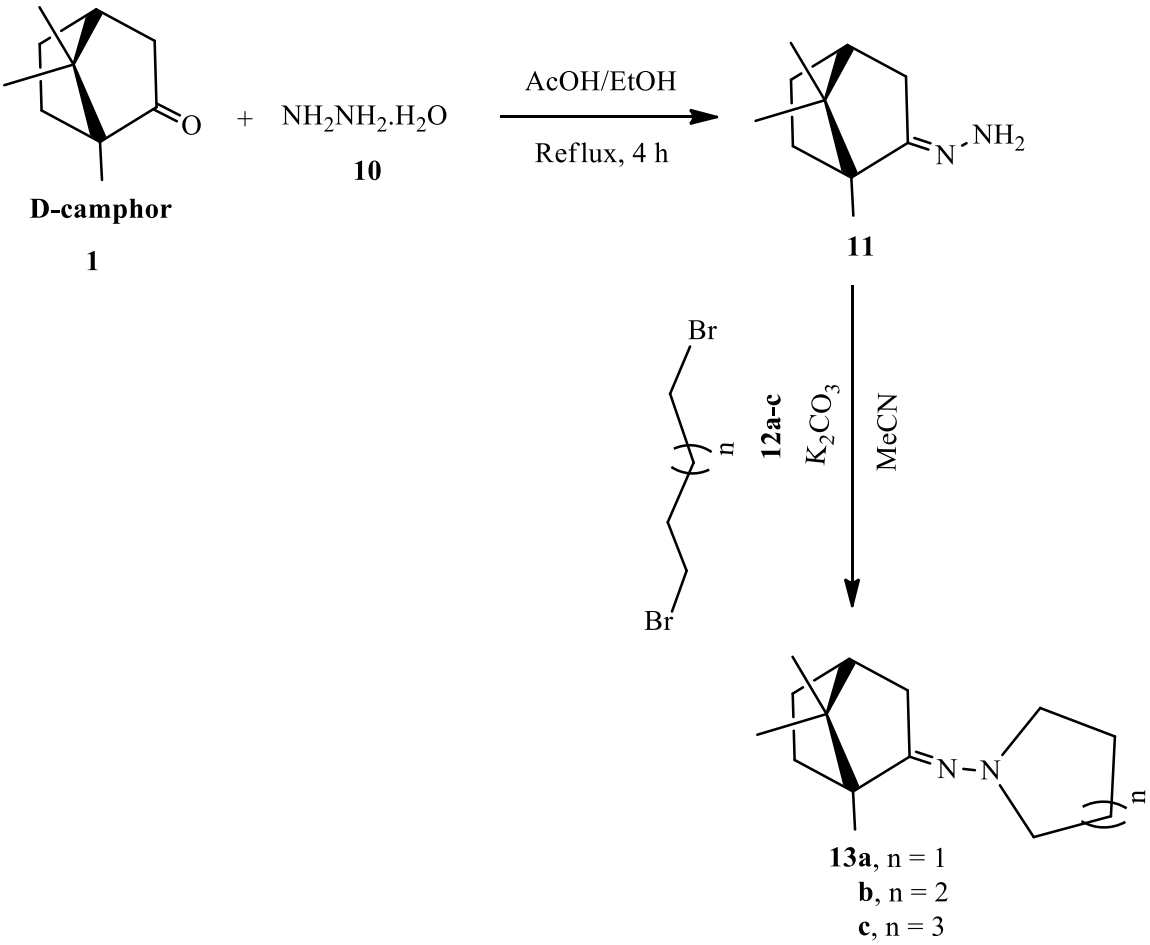


Scheme 2. Synthesis of substituted enamines **6a-c**

Kovaleva et al. reported the synthesis of azepanes, piperidines and pyrrolidines from the cyclo-condensation reaction between the primary amines and dihaloalkanes (Scheme 3).[8]



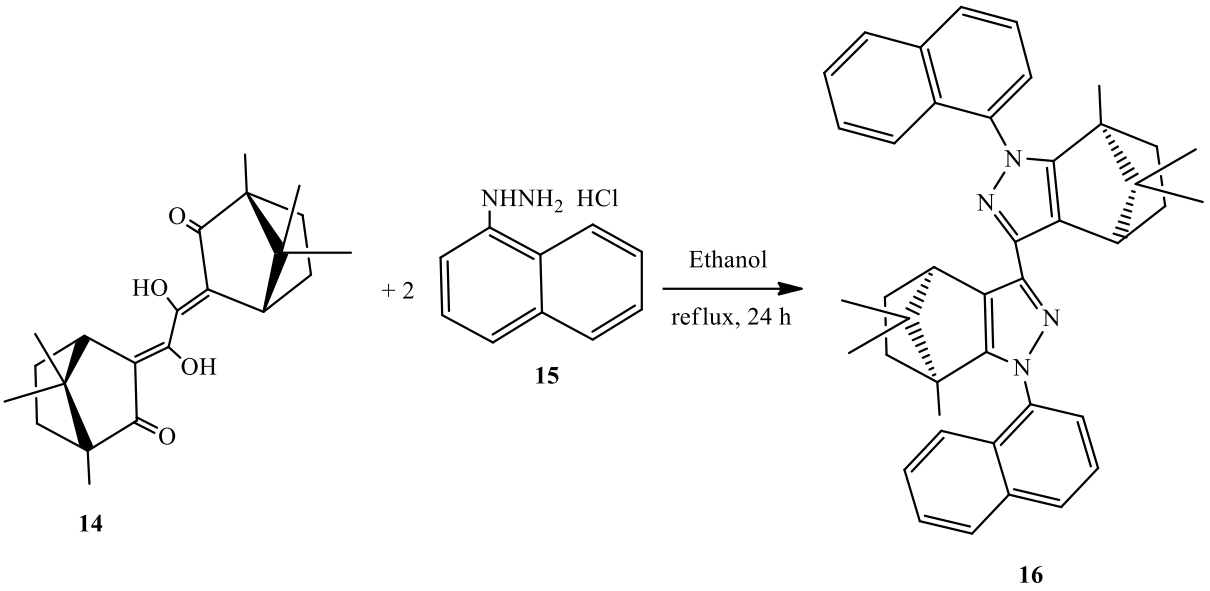
Scheme 3. Synthesis of N-heterocyclic compounds **9a-c**



Scheme 4. Synthesis of N-heterocyclic compounds **13a-c**

Kovaleva et al. described the synthesis of N-heterocyclic compounds **13a-c** from the reaction between camphor (**1**) as a terpenoids compound and hydrazine hydrate (**10**) to produce camphor hydrazone (**11)**, which, in turn, interacted with aliphatic dihalides (**12a-c**) to obtain compounds **13a-c** (Scheme 4). This method is simple and inexpensive. In this study, the synthesized compounds **13a-c** were tested toward pseudoviruses having HIV-1 glycoproteins on their surface, employing the Tzm-bl cell line. They were also tested toward influenza A (H1N1), using MDCK cells. Compound **13a**, containing pyrrolidine, showed the best activity among the three compounds toward the influenza virus, the three N-heterocyclic compounds **13a-c** had no activity toward the pseudoviruses, having HIV-1 glycoproteins on their surface.[9]

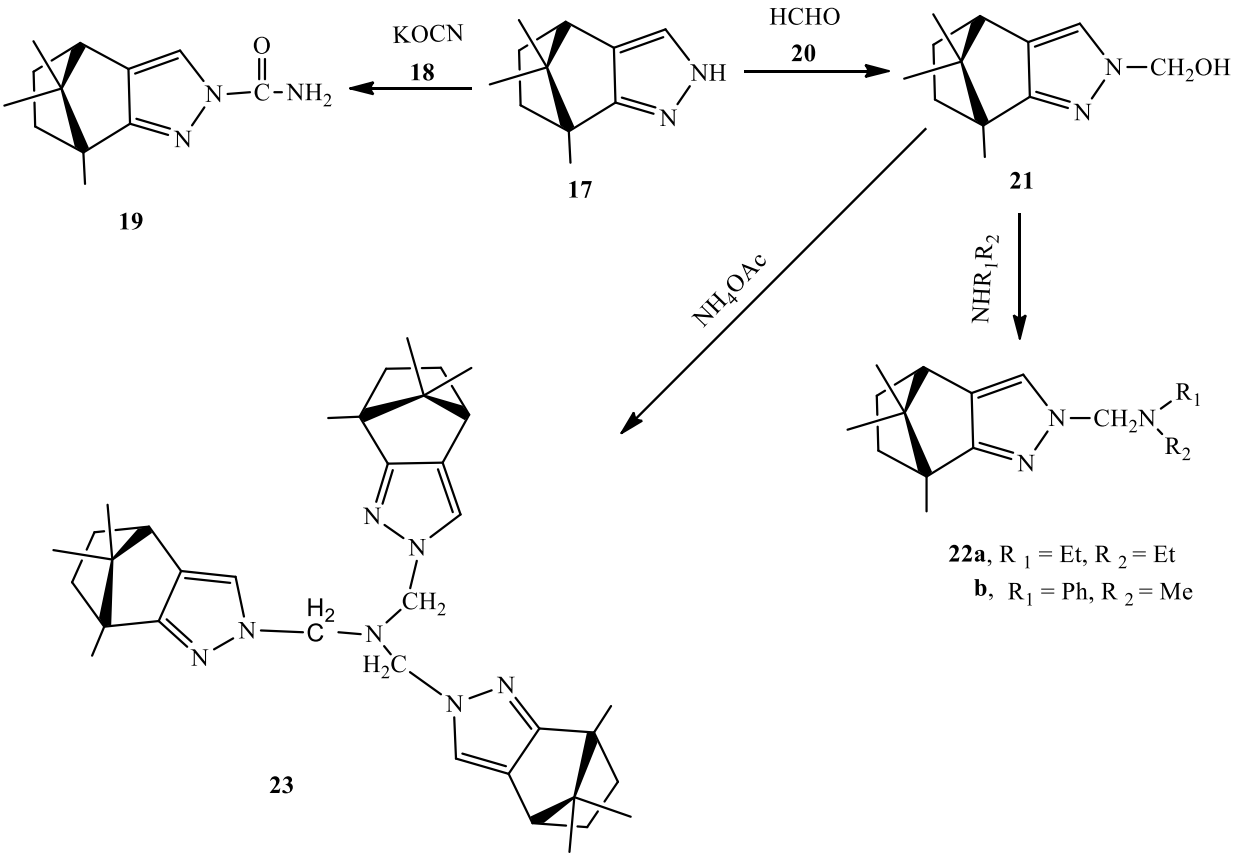
Jannis Barrera et al. reported the synthesis of 3,3'-bi(1,1'-dinaphthylcamphopyrazole) **16** performing a condensation reaction between bis-1,3-diketone (**14**) and α-naphthylhydrazine hydrochloride (**15**) (Scheme **5**).[10]



14 **15** **16**

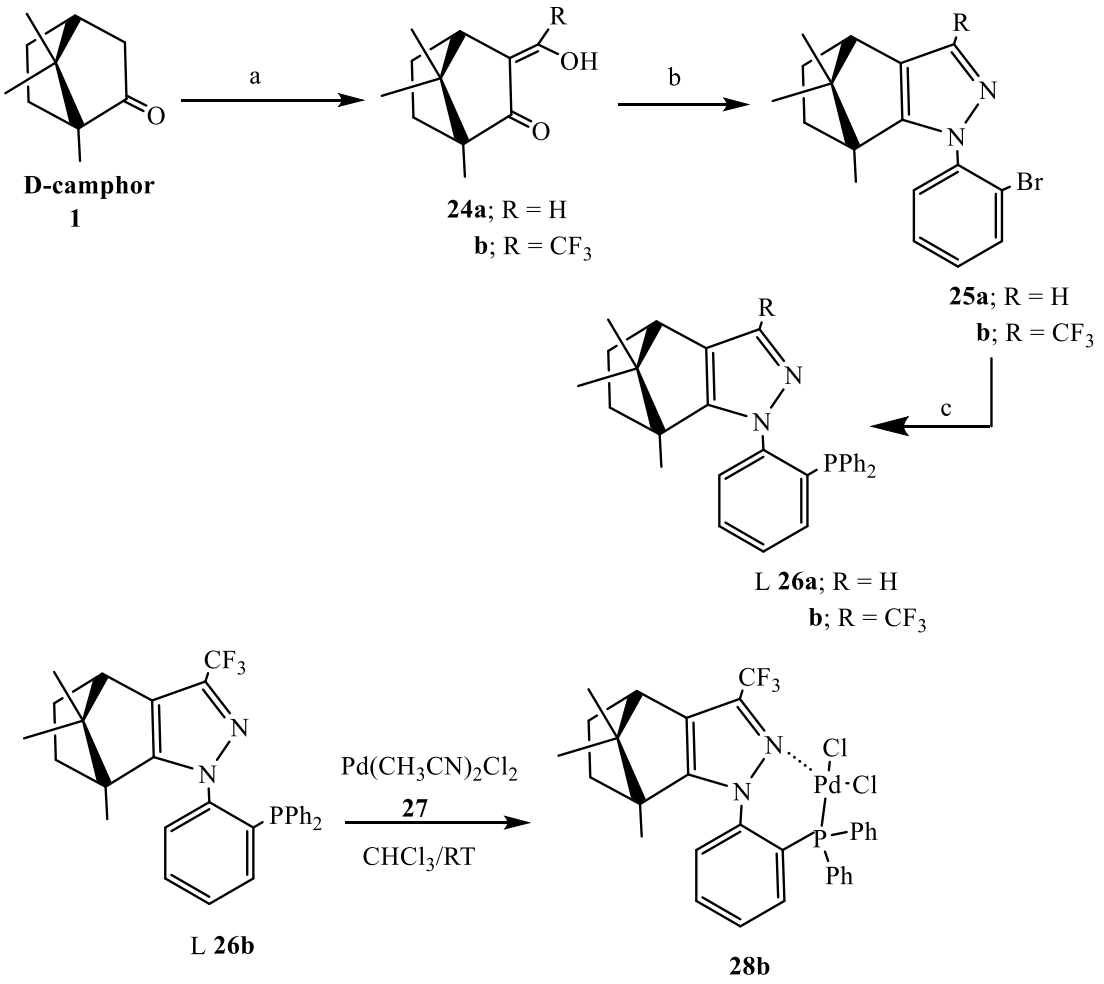
Scheme 5. Synthesis of 3,3/-bi(1,1/-dinaphthyl-camphopyrazole) **16**

The carbamoyl derivative **19** was produced from the reaction between the chiral pyrazole (**17**) and an excess of potassium cyanate (**18**). A chiral analog of the compound **19** played an important role in removing heavy metals due to its chelating properties and controlling the pH.[11-13] Driessen et al. reported the synthesis of many multidentate pyrazole-containing ligands from N-(hydroxymethyl)pyrazoles, and their metal complexes were studied.[11-15] Andrew A. Watson et al. used this approach to synthesize the ligands **22a** and **22b**. Thus, the reaction between the chiral pyrazole (**17**) and formaldehyde (**20**) afforded the hydroxymethyl of the chiral pyrazole (**21**), which reacted with diethylamine and N-methylaniline to produce excellent yields of the bidentate ligands **22a** and **22b**, respectively. Moreover, the chiral tripodal ligand (**23**) was prepared from the reaction between the three moles of hydroxymethyl derivative **21** and ammonium acetate (Scheme 6). The coordination chemistry and chirality of the ligand (**23**) were also studied.[16,17]



Scheme 6. Synthesis of chelating ligands **22a,b** and **23** derived from camphor

The acyl derivatives **26a**[18] and **26b** were synthesized from D-camphor (**1**) under the conditions mentioned in Scheme **7**. The condensation reaction between either of the compounds **24a** or **24b** and 2-bromophenyl hydrazine hydrochloride afforded the pyrazole derivatives **25a** and **25b**, which were reacted with *n*-butyllithium. It was followed by treatment with PPh_2Cl to give the optically active ligands **26a** and **26b**. The reaction between ligand **26b** with $Pd(CH_3CN)_2Cl_2$ in $CHCl_3$ in the presence of silver hexafluoroantimonate ($AgSbF_6$) gave a palladium complex (**28**).[19] For many years, pyrazolate-bridged polynuclear and binuclear transition metal complexes have garnered a lot of attention.[19-21] In addition, the preparation of coordination complexes is considered to be very important part due to their activities in biological processes. For example, guanfacine (GUAF), clonidine (CLN), tolbutamide (TBA), captopril (CPL), theophylline (TEO), nicotinic acid (NIC), nicotinamide (NAM) and pyrazinamide (PZA) are pharmaceutical substances, which were reacted with transition metals to produce improved pharmaco-technical and pharmacological properties.[22]

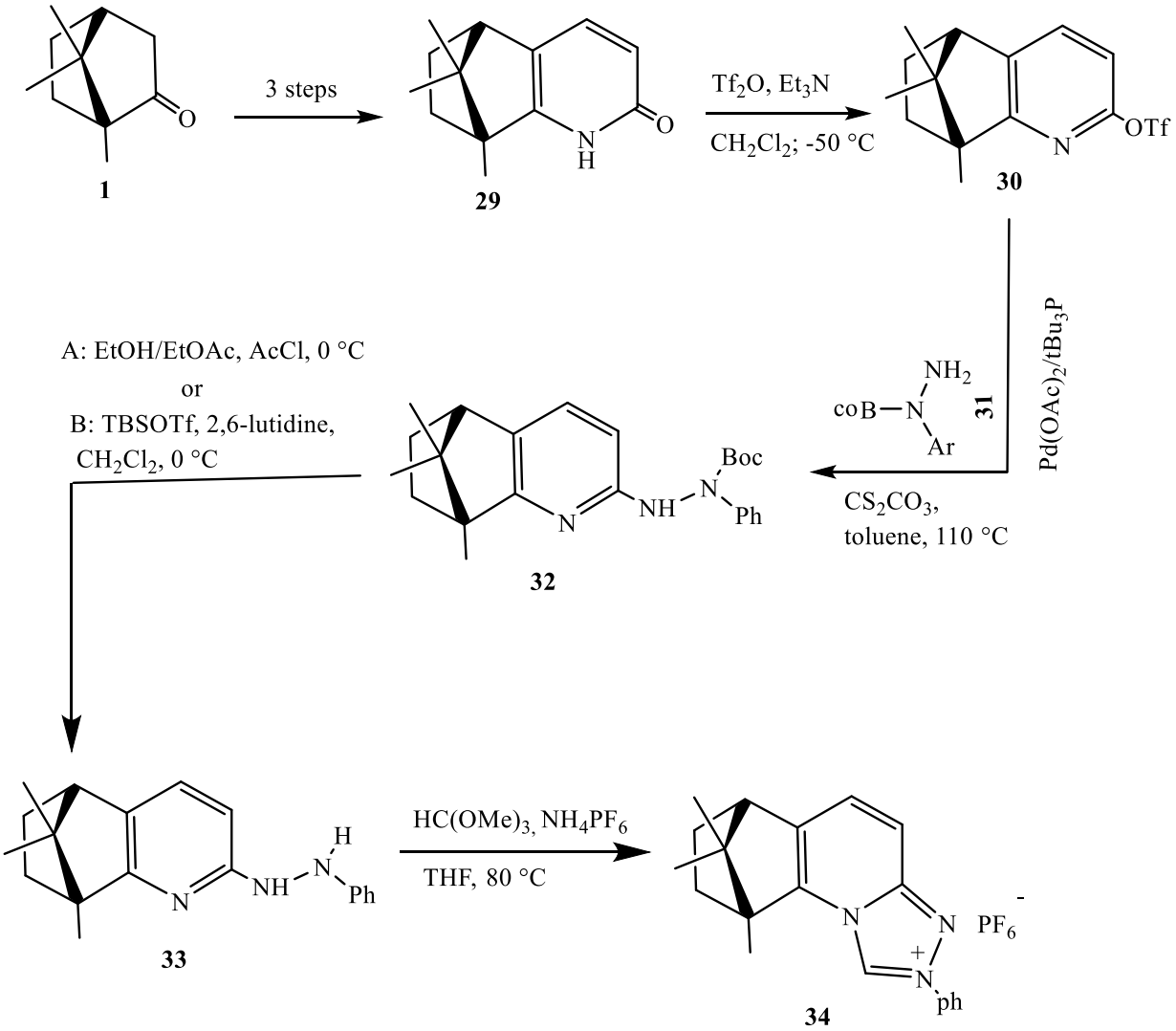


(a) KH, HCO_2Et, THF (when R = H), 92%, NaH, DME, CF_3CO_2Et (when R = CF_3), 60%; (b) 2-bromophenylhydrazine hydrochloride, MeOH, reflux. 90%, (when R = H), 75% (when R = CF_3); (c) *n*-BuLi, THF. -78 °C, PPh_2Cl, -78 °C, 85% (when R = H), 83% (when R= CF_3).

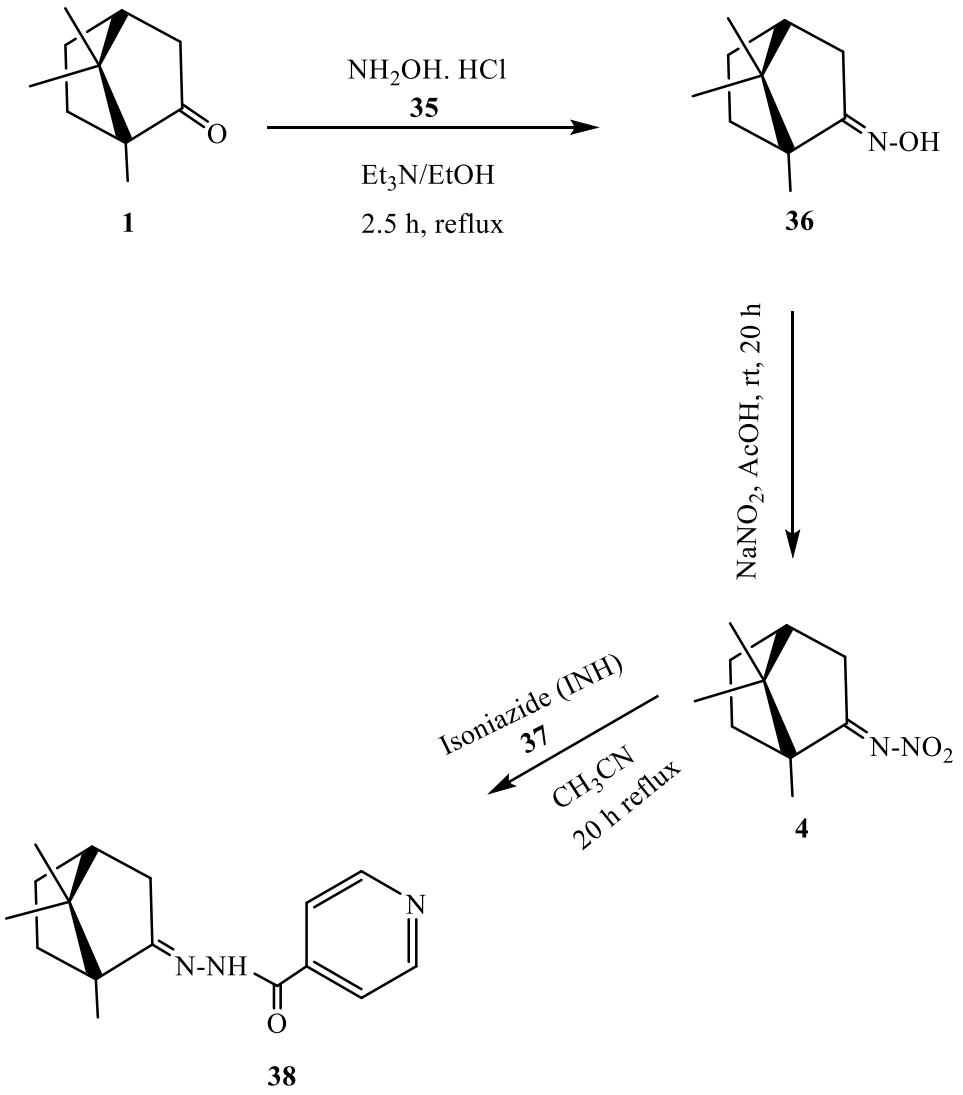
Scheme 7. Synthesis of ligands **26a, b** and Pd complex **28b**

LeCloux et al. reported the synthesis of pyridone (**29**) from D-camphor (**1**) in three steps.[18] The reaction between pyridone (**29**) and triflic anhydride in the presence of catalytic amount of triethylamine produced compound **30**, which was followed by its coupling reaction with N-Boc phenylhydrazine (**31**) in the presence of $Pd(OAc)_2/tBu_3P$ to afford diaryl hydrazide (**32**). N,N'-diaryl hydrazines (**33**) was furnished by deprotection of (**32**). The reaction between compound **33** and trialkyl orthoformate gave the triazolium salts (**34**) (Scheme 8).[23]

Adriele et al. reported the synthesis of the oxime derivative **36** from the reaction between camphor (**1**) and hydroxylamine hydrochloride (**35**). Nitroimine **4**, synthesized applying the reaction between oxime derivative **36** with sodium nitrite, was reacted with isoniazide (INH) (**37**) in acetonitrile under reflux for 20 h to afford the pyridine derivative **38** (Scheme 9). The pyridine derivative **38** was tested against the three cancer cell lines of HCT-116 (colon), SF-295 (glioblastoma) and OVCAR-8 (ovary), the result of which showed that compound **38** had no biological activities against the three cancer cell lines.[24]

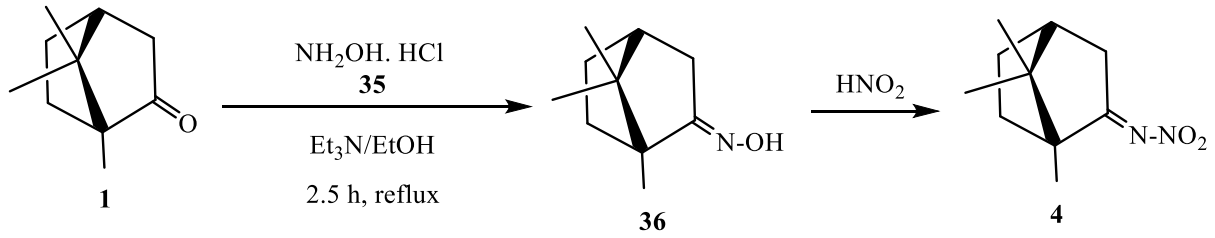


Scheme 8. Deprotection of N-Boc diaryl hydrazines **32** and synthesis of triazolium salts **34**



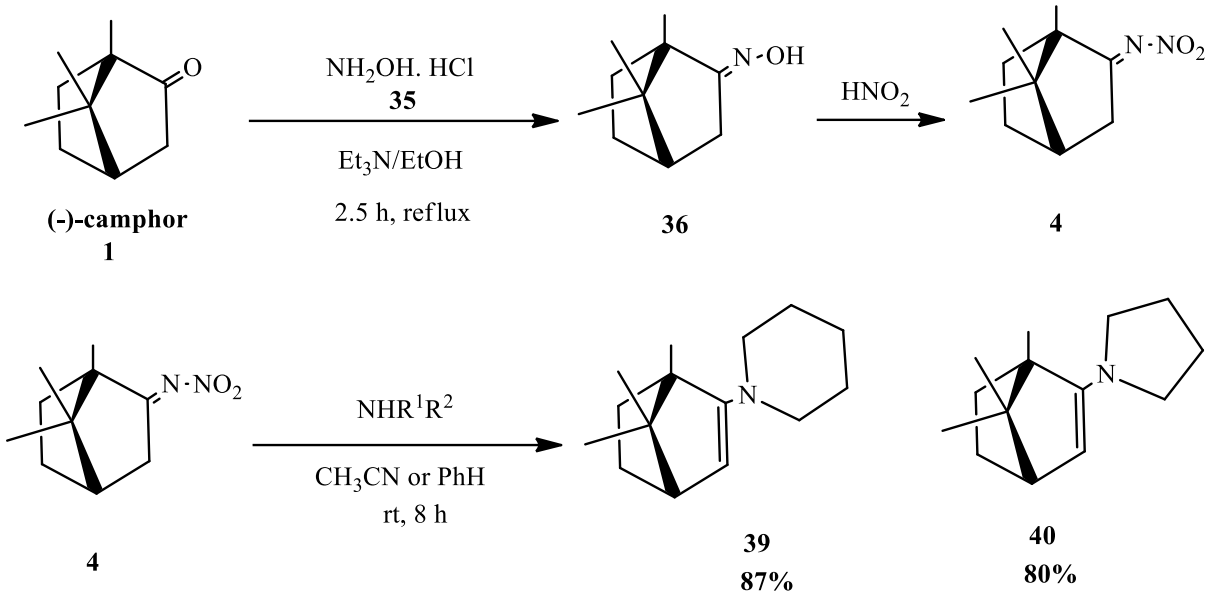
Scheme 9. Synthesis of pyridine derivative **38**

In 1895, Angeli et al. described the synthesis of a nitroimine of camphor (**4**) from the reaction of camphor oxime **36** with nitrous acid (Scheme 10). [6,25]



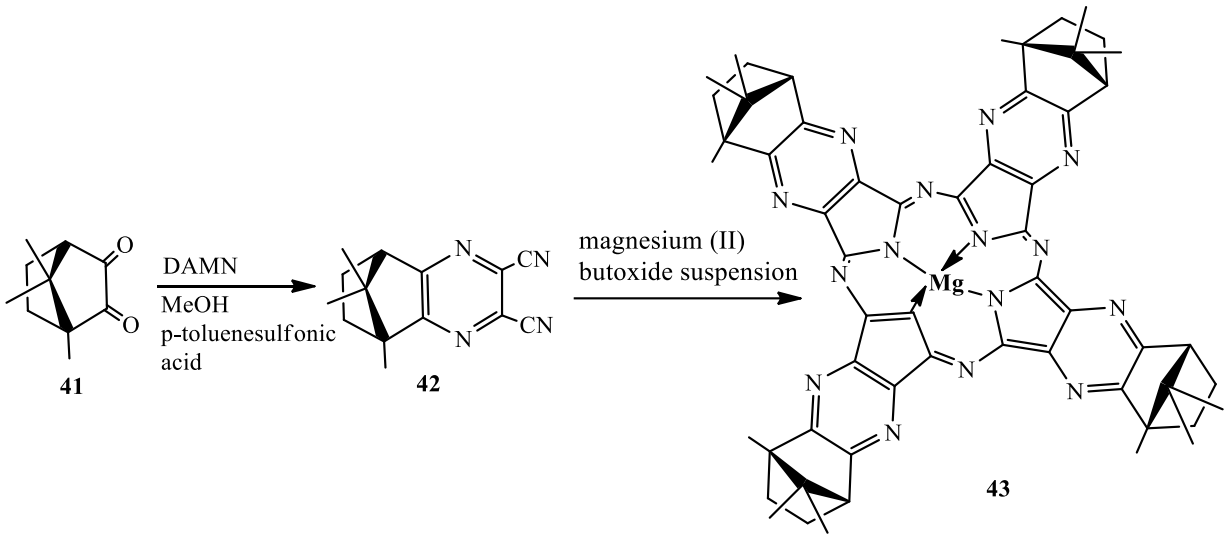
Scheme 10. Synthesis of compound **36** and **4**

Bondavalli et al. synthesized terpenoid enamines reacting camphor nitroimine with secondary amines. Enamine derivatives **39** and **40** were synthesized applying the reaction of piperidine or pyrrolidine with camphor nitroimine **4** in acetonitrile or benzene at room temperature (Scheme 11).[26]



Scheme 11. Synthesis of camphor piperidine **39** and camphor pyrrolidine **40**

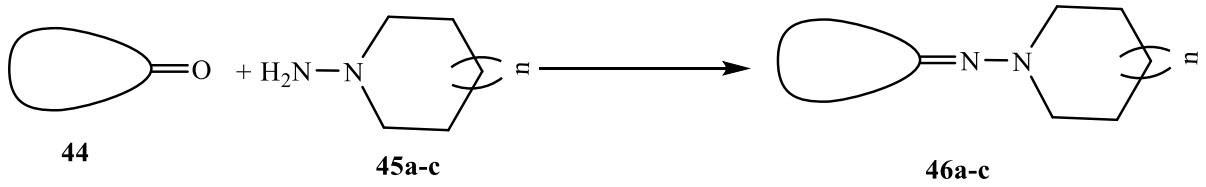
The reaction between the racemic mixture of (±)-camphorquinone (**41**) and diaminomaleonitrile using a catalytic amount of *p*-toluenesulfonic acid gave the 2,3-dicyanopyrazine derivative (**42**), which was followed by its reaction with magnesium (II) butoxide suspension, synthesized from magnesium turning with iodine crystal as a catalyst in *n*-butanol under reflux to afford tetrapyrazinoporphyrazine magnesium complex (**43**) (Scheme 12).[27]



Scheme 12. Synthesis of tetrapyrazinoporphyrazine magnesium complex **43**

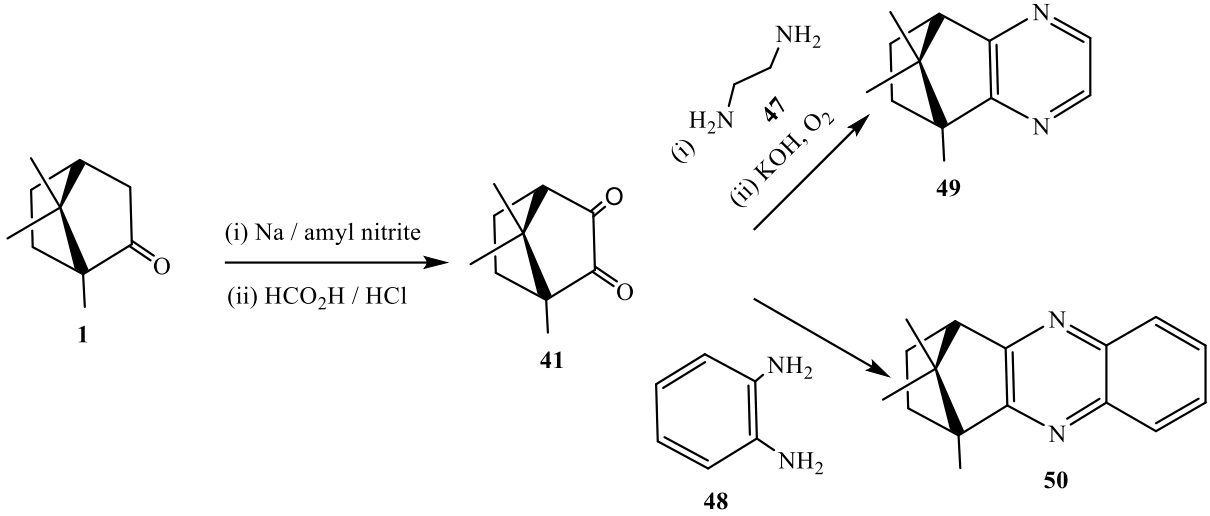
Synthesis of biologically active heterocyclic compounds from camphor

Ghiglieri-Bertez et al. reported the synthesis of N-heterocyclic compounds reacting aldehyde or ketone with 1-aminoazepane, 1-aminopiperidine and 1-aminopyrrolidine (Scheme 13).[28,29]



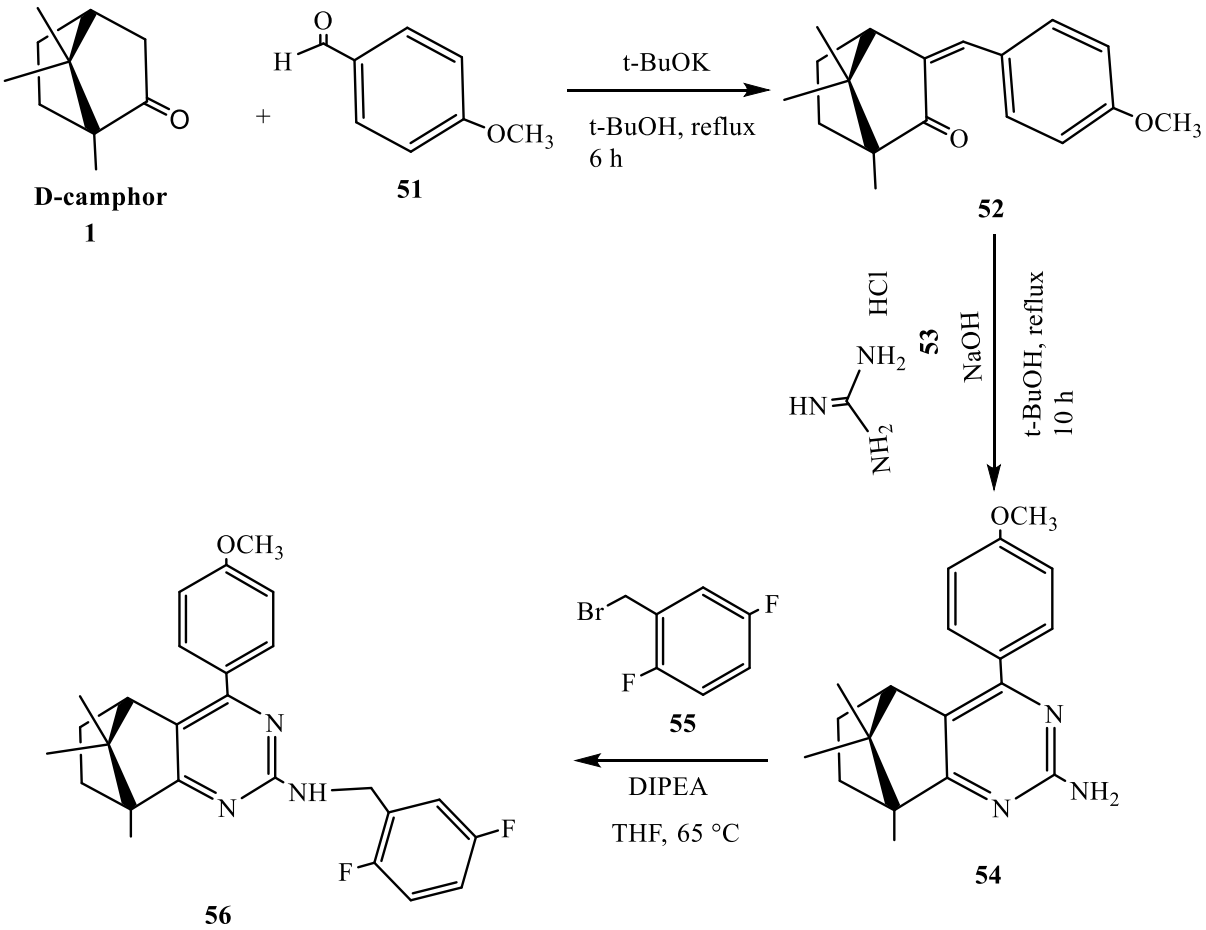
Scheme 13. Synthesis of N-heterocyclic compounds **46a-c**

Christopher et al. investigated the synthesis of ligands **49** and **50** through the reaction of camphor-D with Na/amyl nitrite in the presence of formic acid/HCl to produce the intermediate quinone-monoxime, which was followed by hydrolysis[30] to obtain camphorquinone (**41**). The latter was reacted with ethylenediamine **47** to give a dihydropyrazine,[31] followed by oxidation to ligand (**49**) or o-phenylenediamine **48** to furnish ligand **50** (Scheme **14**).[32]



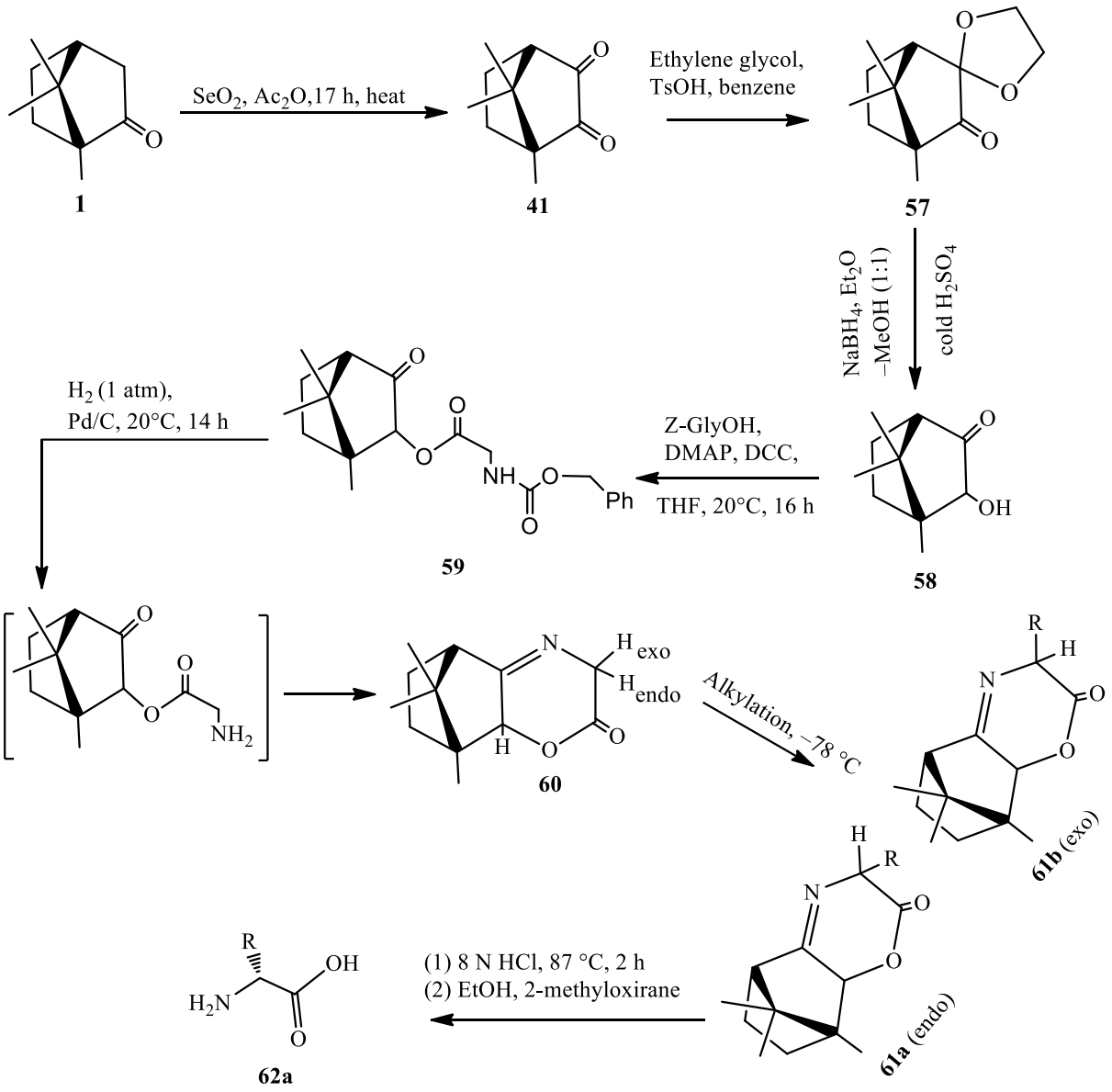
Scheme 14. Synthesis of ligands **49** and **50**

Condensation of camphor-D (**1**) with *p*-methoxybenzaldehyde (**51**) in tert-butanol in the presence of a catalytic amount of potassium tert-butoxide gave the intermediate product **52**, followed by the cyclization reaction with guanidine hydrochloride (**53**) to give (5R,8S)-4-(4-methoxyphenyl)-8,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methanoquinazolin-2-amine (**54**) which, in turn, was reacted with 2-(bromomethyl)-1,4-difluorobenzene (**55**) in tetrahydrofuran to produce camphoryl pyrimidine amine derivative **56** (Scheme **15**). It was of a great value to mention that compound **56** showed an excellent antimicrobial activity against *Streptococcus pneumoniae, Klebsiella pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa, Methicillin-Resistant Staphylococcus aureus (MRSA), Escherichia coli, Bacillus cereus*. Moreover, it showed anti-inflammatory potency against mouse mononuclear macrophages leukemia cells (RAW) with (IC_{50} = 1.87μM, which was more potent than the control drug aspirin (IC_{50} = 1.91 μM).[33]



Scheme 15. Synthesis of camphoryl pyrimidine amine derivative **56**

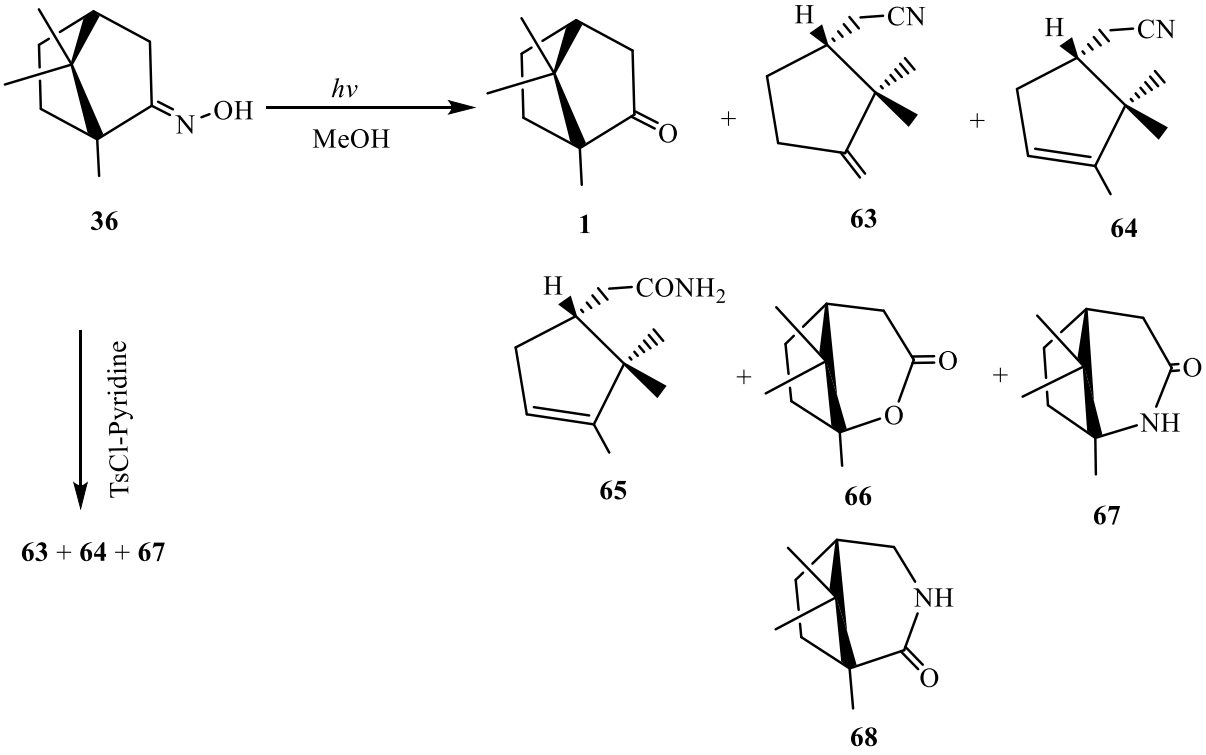
Shokova et al. described the synthesis of optically active *α*-amino acids **62a**[34] using camphor derivative as chiral auxiliaries in asymmetric synthesis. For this objective, oxazin-2-one derivative **(**iminolactone **60**) was synthesized using the hydroxy group of camphor (**58**). The synthesis of hydroxy of camphor (**58**) was reported.[35-38] Treatment of hydroxy moiety of the ketone **58** with N-(benzyloxycarbonyl)glycine, N,N′-dicyclohexylcarbodiimide and 4-dimethylaminopyridine in the presence of anhydrous THF led to the formation of the ester of camphor **59**. The chiral template **60** was afforded from hydrogenation of ester **59** over Pd catalyst in ethanol and cyclization after the benzyloxycarbonyl (Cbz) protection group was removed. Alkylation of iminolactone **60** at –78 °C under different reaction conditions lead to the production of monosubstituted **61a** and **61b** with an excellent yield and diastereoselectivity. Hydrolysis of **61a** with 8 N HCl at 87 °C gave the corresponding (S)-*α*-amino acids **62a** (Scheme 16).[39]



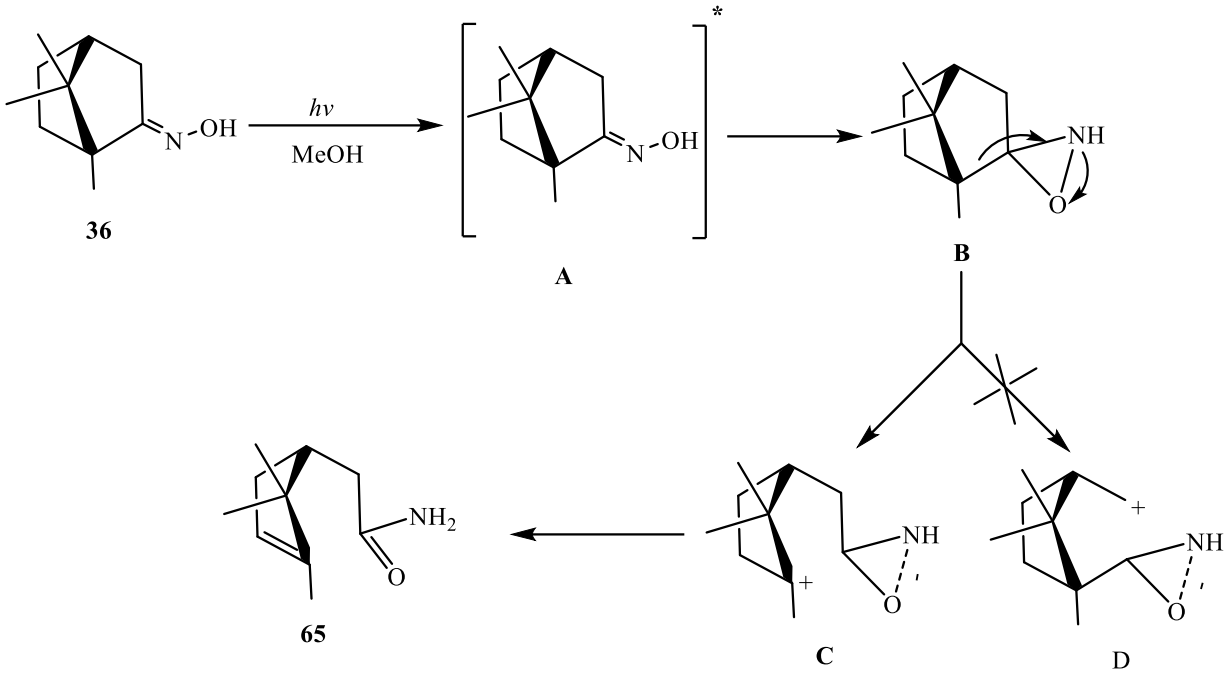
Scheme 16. Synthesis of oxazin-2-one derivatives **61a** and **61b**

D-camphor oxime (**36**) was subjected to photochemical reaction using a Rayonet photochemical reactor. Irradiation of the oxime was generated under nitrogen with a low-pressure Hg in methanol at 20-30 °C for 15 h. An oily mixture of the products was afforded in 85% conversion, which was separated applying an extensive PLC according to the order of polarity. The result of separation gave D-camphor (**1**), a mixture of isomeric nitriles (**63**) and (**64**), amide (**65**), 1,8,8-trimethyl-2-oxabicyclo[3.2.l]octan-3-one (**66**), lactam derivative **67** and its isomer *α*-camphidone (**68**) (Scheme 17). The authors reported that the photochemical formation of the compounds **63** and **64** was from *α*-fission of camphor oxime (**36**), whereas, the lactone (**66**) was a secondary photoproduct produced from the reaction between an intermediate formed from the excited camphor oxime and a trace of oxygen contaminated in solvent methanol. Moreover, camphor oxime (**36**), excited to camphor oxime (**A**), was in-turn transformed into oxaziridine (**B**). The amide (**65**), formed through the ionic thermal rearrangement of oxaziridine intermediate (**B**), was subjected to a regiospecific ionic cleavage of the oxaziridine ring to produce a tertiary carbocation (**C**), which was found to be more stable than the primary carbocation (**D**). It was then lost a proton to give the amide (**65**) (Scheme 18). Finally, the lactams (**67**) and (**68**) were obtained from the excited alicyclic ketone oximes with the rearrangement of excited oxaziridine intermediates in a controlled manner.[40] Previously, the authors carried out a

Beckmann rearrangement reaction of camphor oxime to produce the lactam (**67**) in low yield (0.17 %). On the other hand, Schmidt's reaction of camphor oxime (**36**) with azide-sulphuric acid-chloroform produced *α*-camphidone (**68**) in a very low yield of < 1%.[41] Furthermore, Szczepanski and Krow reported the synthesis of *α*-camphidone (**68**) from the reaction between camphor and hydroxylamine-0-sulphonic acid in the presence of formic acid in a yield of 46%.[42] In addition, the compounds **63**, **64**, and **67** were obtained from the treatment of D-camphor oxime (**36**) with toluene-*p*-sulphonyl chloride-pyridine under the same reaction condition of the Beckmann rearrangement (Scheme 17).[40]

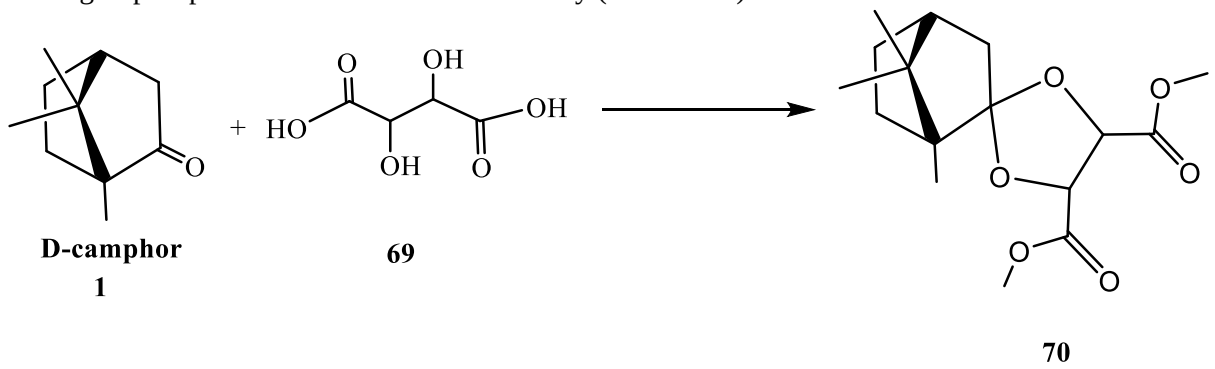


Scheme 17. Synthesis of compounds **1**; **63-68**



Scheme 18. Synthesis of unsaturated amides **65** generated from oxaziridine intermediates

Thermoplastics pose environmental hazards due to their low degradation, despite their stable and excellent properties, and to solve this problem, the authors designed camphor dimethyl DL-tartrate (Ct diester) (**70**) as a monomer, containing a bridged bicyclic structure and a rigid spiro-ring containing a ketal group responsible for their thermal stability (Scheme 19).



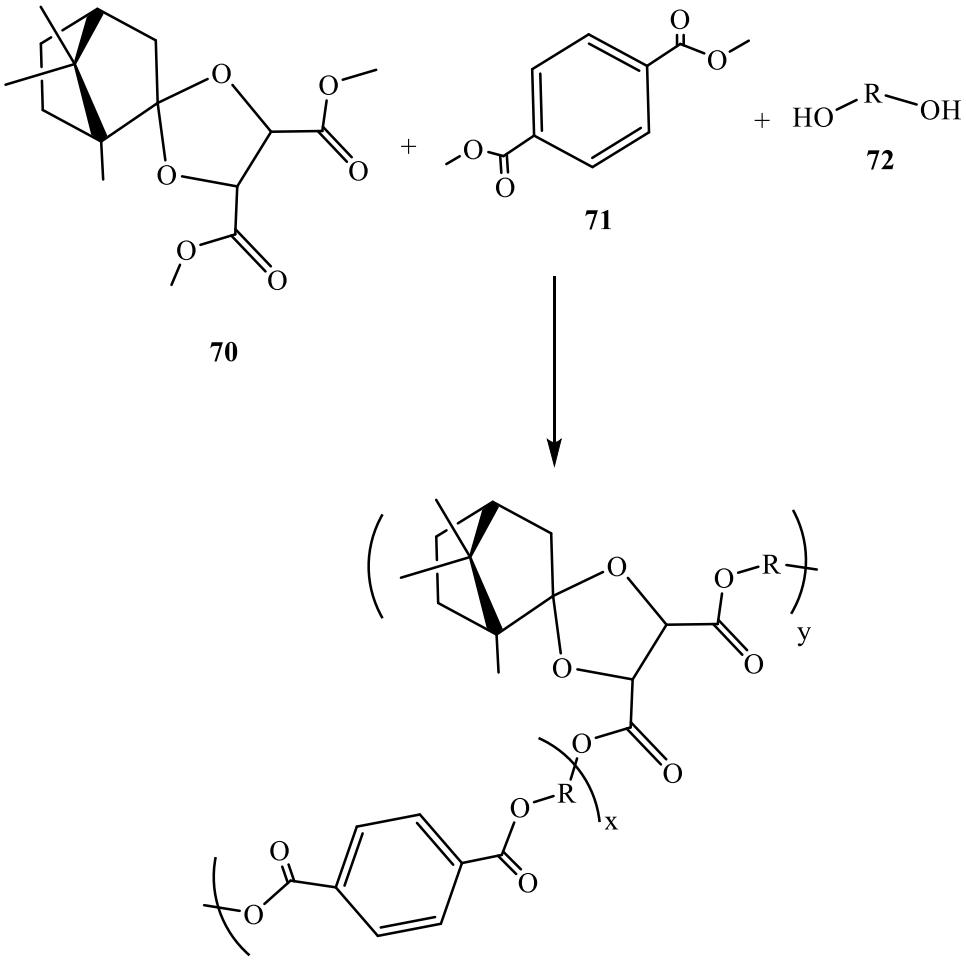
D-camphor
1

69

70

Scheme 19. Synthesis of 1,3-dioxolane-4',5'-dicarboxylate derivative **70**

The Ct diester (**70**) reacted with dimethyl terephthalate (**71**) and diols (**72**) to produce a series of polyester (**73**), showing a high glass transition temperature and appropriate thermal stability up to 414 °C (Scheme 20). Amorphous regions were found to be important for this thermal behavior, which was proportional to the increase in the content of the Ct diester. It decomposed in both aqueous and acidic media.[43]

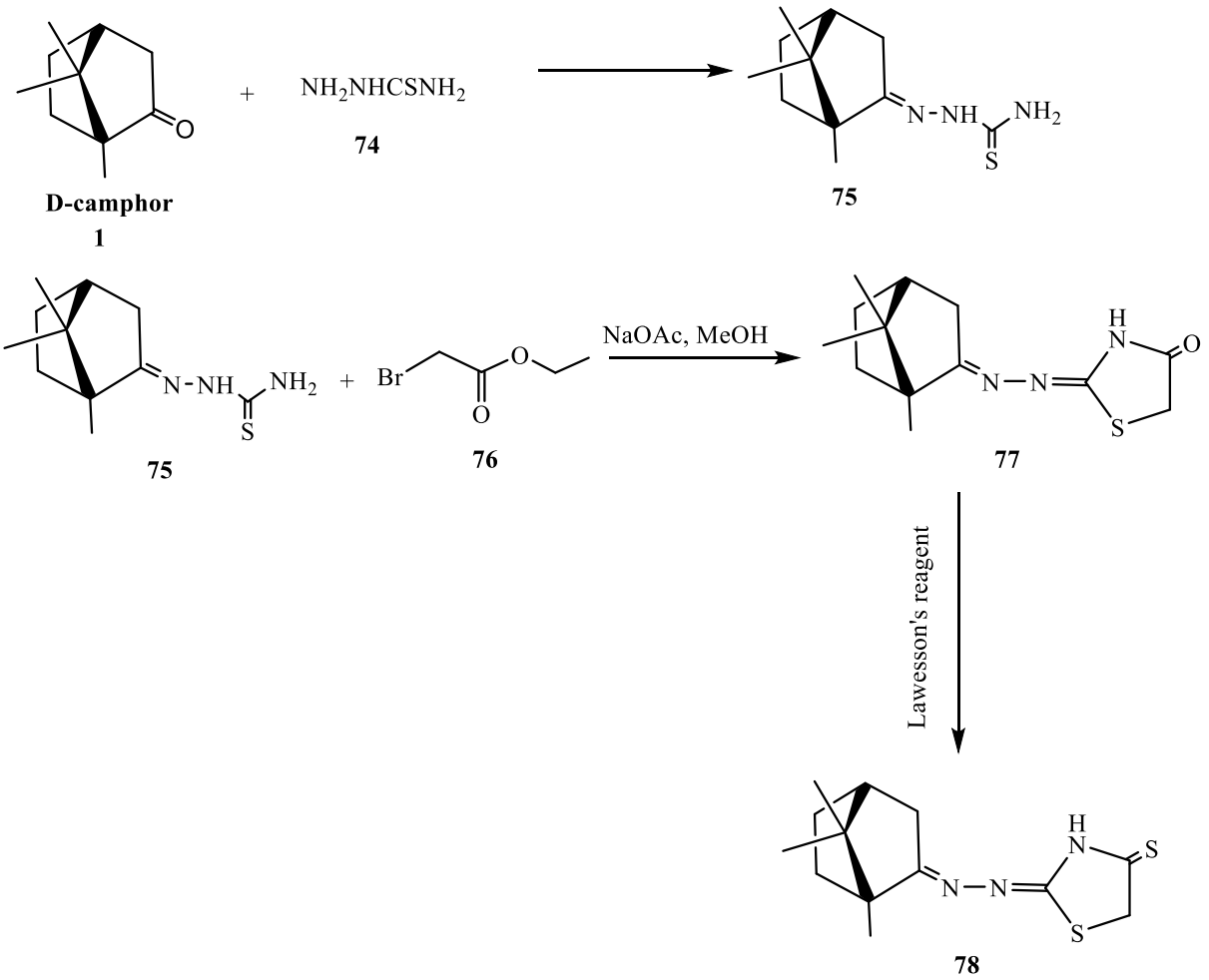


70 **71** **72** **73**

Scheme 20. Melt polymerization of PET100 homo-polyester and PETxCty (PBTCt and PHTCt) co-polyester (R= –(CH2)2–, –(CH2)4–, –(CH2)6–, x = 90, 70, 60, 50 and y =10, 30, 40, 50, x and y: feed ratio of DMT to Ct diester

2. Synthesis of Thiazole Derivatives from Camphor

Thiazolidin-4-one derivative **77** was obtained from the reaction between thiosemicarbazone (**75**) and ethyl-2-bromoacetate (**76**). This reaction was carried out in three steps, the first one was alkylation at the nitrogen atom followed by substitution of the carbonyl group for thiocarbonyl and a condensation reaction. 4-Thiazolidinethione derivative **78** was afforded from the reaction between thiazolidin-4-one derivative **77** with Lawesson's reagent, which is responsible for converting oxygen functionalities into their thio analogs (Scheme 21).[44] Compound **78** was investigated for antiviral activity and cytotoxicity using an adapted method.[45] The result exhibited that 4-thiazolidinethione derivative **78** showed important antiviral activity with IC_{50} = 3.3 μM; TC_{50} = 17.5 μM.



Scheme 21. Synthesis of thiazole derivatives **77** and **78**

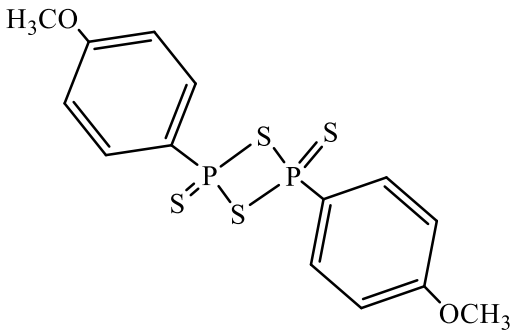
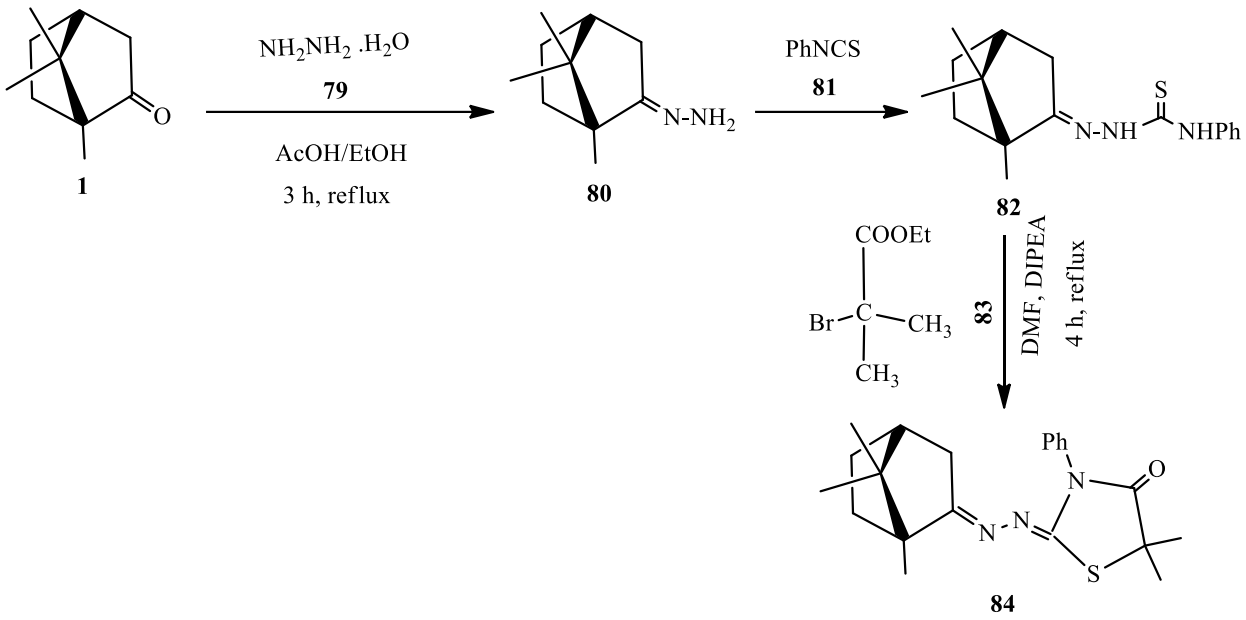


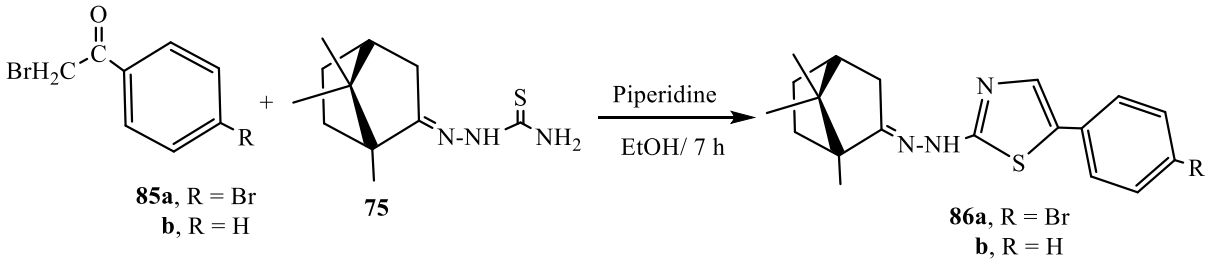
Figure 1. Lawesson's reagent

Vladislav et al. reported the synthesis of camphor hydrazone (**80**) from the reaction of camphor (**1**) with hydrazine hydrate (**79**). The reaction was carried out according to the described method,[46] followed by its reaction with phenylisothiocyanate (**81**) to give N-phenyl thiosemicarbazone derivative **82**. It was reacted with ethyl 2-bromoisobutyrate (**83**) under reflux for 4 h in the presence of dimethylformamide and N,N-diisopropylethylamine to furnish the 5,5-dimethyl-2-iminothiazolidinone derivative **84**. The target product was isolated and purified using column chromatography (Scheme **22**). The antiviral activity of 5,5-dimethyl-2-iminothiazolidinone (**84**) containing a methyl substituent at the nitrogen atom of the heterocyclic fragment was studied and the compound exhibited low toxicity against the vaccinia virus.[47]



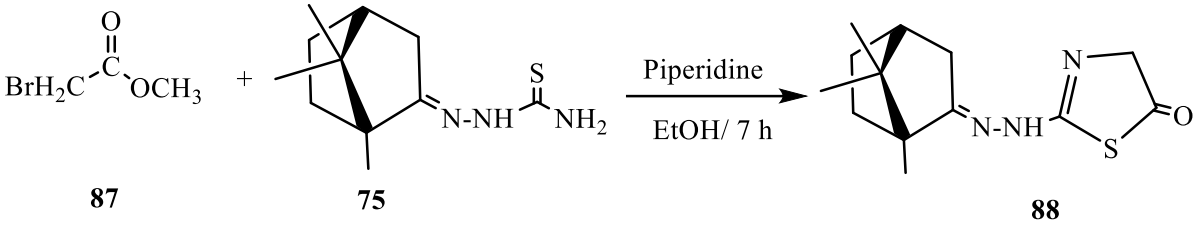
Scheme 22. Synthesis of thiazolidin-4-one derivative **84**

The reaction between 4'-bromophenacyl bromide (**85a**) or phenacyl bromide (**85b**) with camphor-D thiosemicarbazone (**75**) in ethanol containing a catalytic amount of piperidine gave the 5-(4-bromophenyl)-2-(2-((1S,4R,E)-1,7,7-trimethylbicyclo[2.2.1]heptane-2-yli-dene)hydrazinyl)thiazol (**86a**) and 5-phenyl-2-(2-((1S,4R,E)-1,7,7-trimethylbicyclo[2.2.1] heptane-2-ylidene)hydrazi-nyl)thiazol (**86b**) (Scheme **23**).



Scheme 23. Synthesis of 1,7,7-trimethylbicyclo[2.2.1]heptane-2-yli-dene) hydrazinyl)thiazol derivatives **86a,b**

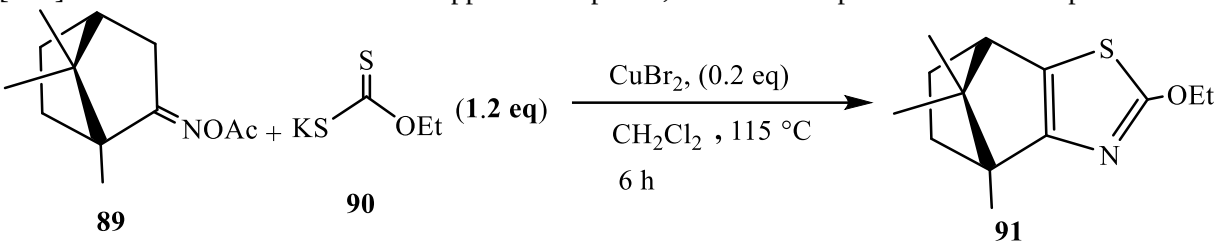
Similarly, the reaction between methyl ester of *α*-bromoacetic acid (**87**) and camphor thiosemicarbazone (**75**) in ethanol containing a catalytic amount of piperidine afforded 2-(2-((1S,4R,E)-1,7,7-trimethylbicyclo[2.2.1]heptane-2-ylidene)hydrazinyl)thiazol-5(4H)-one (**88**) (Scheme **24**). Compounds **86a,b** and **88** were screened against *Staphylococcus aureus, Bacillus subtilis* as Gram-positive and *Pseudomonas aeruginosa, Escherichia coli* as Gram-negative bacteria. The compounds showed low inhibition activities against the bacterial strains.[48]



87 **75** **88**

Scheme 24. Synthesis of 1,7,7-trimethylbicyclo[2.2.1]heptane-2-ylidene)hydrazinyl)thiazol-5(4H)-one (**88**)

Zhongzhi Zhu et al. reported the synthesis of thiazole derivative **91** from the reaction between camphor oxime acetate (**89**) and potassium O-ethyl carbonodithioate (**90**) in the presence of a novel copper-catalyst[49] (Scheme **25**). The authors explained that this transformation occurred through the [3+2] annulation reaction and can be applied to aliphatic, aromatic compounds and natural products.[49,50]



89 **90** **91**

Scheme 25. Synthesis of thiazole derivative **91** from camphor oxime acetate

3. Conclusion

In this review, N, O, and S-heterocyclic compounds were synthesized from camphor mono-terpenes. Such as isatin, substituted enamines, azepanes, piperidines, pyrrolidines pyrazole, pyridine, pyrimidine derivatives, triazolium salts, tetrapyrazinoporphyrazine magnesium complex, optically active *α*-amino acids**,** lactam derivative and its isomer *α*-camphidone, camphor dimethyl DL-tartrate (Ct diester) were overviewed. The biological activities of some compounds were studied toward human cancer cell lines, influenza virus, *Streptococcus pneumoniae, Klebsiella pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa, Methicillin-Resistant Staphylococcus aureus (MRSA), Escherichia coli, Bacillus cereus, Bacillus subtilis,* and vaccinia virus. They showed pronounced activities, which raises our interest to synthesize more organic heterocyclic compounds derived from camphor.

Acknowledgements

The authors would like to thank the Faculty of Pharmaceutical Sciences & Pharmaceutical Industries, Future University in Egypt, and the Faculty of Science, Cairo University, for affording facilities to complete this work.

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