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Efficient Synthesis of Heterocyclic Molecules Via Palladium-Mediated and Ultrasound-Assisted Methods

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KEYWORDS

Palladium Catalysis, Ultrasound, Heterocyclic Compounds, Green Chemistry, Multicomponent Reactions.

ABSTRACT:

Heterocyclic Molecules Are Ubiquitous In Bioactive Substances, Medicines, Agrochemicals, And Functional Materials, Making Their Production An Essential Part Of Contemporary Medical And Organic Chemistry. The Synthesis Of A New Benzazocine Derivative Involved A Palladium-Mediated Carbonylative Coupling Of O-Iodoacetanilide With A Phenylnorbornylpalladium Chloride Dimer In A Nitrogen And Carbon Monoxide Regulated Environment. Standard Analytical Procedures Such As Tlc, Glc, Nmr, Ir, Ms, And Elemental Analysis Were Used To Monitor The Reaction, Which Was Carried Out In Dry Dmf Utilizing Schlenk Techniques Using K_2Co_3 As The Base. Following A 6-Hour Nitrogen Incubation, The Cyclic Amide Was Produced In A 94% Yield When Exposed To Ambient Co. The Crystals Were Of Good Quality And Appropriate For X-Ray Diffraction After They Were Purified Using Flash Chromatography And Recrystallization. An Eight-Membered Ring In A Boat Shape Was Revealed By Structural Elucidation, And The Bond Lengths And Angles Were In Agreement With Known Aromatic And Norbornyl Structures. In Addition, The Lattice-Stabilizing Van Der Waals Interactions And Distinctive Dihedral Orientations Were Shown By The Crystal Structure. According To The Mechanistic Study, The Formation Of The Heterocycle Is The Result Of An Intramolecular Assault By The Amide Nitrogen After A Brief Palladacycle And An Acylpalladium Intermediate Have Been Involved.

Introduction

The Extensive Use Of Heterocyclic Compounds In Medicines, Agrochemicals, Dyes, And Innovative Materials Has Made Their Effective Synthesis A Key Area Of Study In Contemporary Organic Chemistry. There Are Many Different Approaches To Building Structurally Varied Heterocycles, But Two That Have Received A Lot Of Attention For Their Potential To Speed Up Reactions, Increase Yields, And Make Processes More Eco-Friendly Include Palladium-Mediated Catalysis And Ultrasound-Assisted Techniques. Synergistic Benefits Between The Two Methods Make It Feasible To Accomplish Alterations That Would Be Challenging, Sluggish, Or Wasteful Under More Traditional Circumstances. Academic And Corporate Researchers Are Finding More And More Uses For These Approaches To Address The Rising Need For Fast, Clean, And Scalable Synthetic Pathways. The Creation Of Carbon-Carbon And Carbon-Heteroatom Bonds, Which Are Essential Building Blocks Of Heterocycles, May Be Accomplished Effectively By Palladium-Mediated Processes. The Palladium Complexes' Extraordinary Selectivity In Activating Bonds And Promoting Cross-

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Coupling Allows Them To Play A Pivotal Role In Reactions Such The Suzuki, Heck, Sonogashira, Stille, And Buchwald-Hartwig Couplings. These Transformations Are Very Useful In Heterocyclic Chemistry For A Number Of Reasons, One Of Which Is That They Facilitate The Efficient Functionalization Of Aromatic And Heteroaromatic Scaffolds And The Predictable Assembly Of Complicated Ring Systems. Because Palladium Catalysts Can Withstand A Broad Variety Of Functional Groups, They Make It Possible To Modify Bioactive Molecules Late In The Process And Speed Up The Process Of Exploring The Structure-Activity Connection. Heterocycles Containing Nitrogen, Oxygen, And Sulfur Are Common Building Blocks Of Medicinal Medicines, And Palladium Catalysis Is An Ideal Method For Synthesising These Compounds Due To Its Benign Reaction Conditions And Well-Established Mechanistic Pathways.

Heterocycle Synthesis Is Already Quite Efficient When Using Palladium Catalysis, But Adding Ultrasonic Irradiation Makes It Much More So. The Formation, Growth, And Eventual Collapse Of Small Bubbles In The Reaction Media Is Known As Acoustic Cavitation, And It Is The Basis Of Ultrasound-Assisted Organic Synthesis. Mass Transfer, Reaction Speeds, And Reagent Mixing Are All Improved As A Result Of The Localized Hot Spots Created By This Collapse, Which Are Very Hot And Pressurized For Relatively Brief Periods Of Time. So, Unlike Conventional Thermal Circumstances, Ultrasound May Speed Up Processes That Would Otherwise Take Too Long, While Simultaneously Reducing The Amount Of Heat Required And The Amount Of Potentially Harmful Solvents Used. Ultrasound Irradiation Is A Powerful Instrument In Green Chemistry Since It Increases Product Selectivity And Yields In Many Instances. When Synthesizing Heterocycles, The Combination Of Palladium Catalysts And Ultrasound-Assisted Techniques Has Shown To Be The Most Successful. Inefficient Mixing, Delayed Reactant Diffusion In Solution, And Catalyst Deactivation Are Common Problems With Palladium-Catalyzed Cross-Coupling Processes. By Reducing Metal Particle Agglomeration, Increasing Catalyst Turnover, And Dispersing Palladium Species More Effectively, Ultrasound Irradiation Reduces The Severity Of These Problems.

Cleaner Product Profiles, Quicker Reactions, And Less Catalyst Loading Are The Results Of This. For Example, Even When Performed In Solvent-Free Or Low-Solvent Environments, The Ultrasound-Assisted Suzuki Coupling May Yield Heteroaryl Derivatives Much More Quickly Than Traditional Heating. Intramolecular Heck Cyclizations Have Also Been Successfully Conducted Using Ultrasound, Leading To The Creation Of Fused Heterocyclic Rings That Exhibit Enhanced Regioselectivity And Greater Conversion Rates. The Synthesis Of Nitrogen-Containing Heterocycles Like Indoles, Quinolines, Benzoxazoles, And Pyrroles Is Another Significant Area Where These Coupled Approaches Shine. Without The Requirement For Pre-Functionalized Substrates, Such Frameworks May Be Easily Constructed Using Palladium-Mediated C-H Activation Techniques Augmented By Ultrasonic Irradiation. Because Ultrasound Provides Improved Reaction Kinetics, It Is Possible To Use Softer Settings, Which Makes It More Compatible With Functional Groups That Are Sensitive. Ultrasound Also Has The Ability To Drastically Cut Response Times, Sometimes From Hours To Minutes, Which Is Great For Large-Scale Manufacturing And High-Throughput Synthesis.

One Of The Main Reasons Palladium-Mediated And Ultrasound-Assisted Techniques Are Becoming More Popular Is Their Potential To Reduce Environmental Impact. The Traditional Method Of Synthesizing Heterocycles Produces A Lot Of Waste Due To The Use Of Strong Chemicals, Lengthy Reaction Durations, And Substantial Amounts Of Organic Solvents. Ultrasound Irradiation, On The Other Hand, Contributes To Greener Operations Since It Requires Less Solvent, Less Energy, And A Shorter Reaction Time. Despite Their Hefty Price Tag, Palladium Catalysts Are Incredibly Efficient Because They Need So Little Of The Metal And Have Such A High Turnover Number. One More Way To Lessen The Impact On The Environment Is By Switching To Aqueous Or Solvent-Free Conditions For Many Palladium-Catalyzed Processes That Use Ultrasonic. Because Of Their Reliance On Dependable Synthetic Access To Libraries Of Compounds Rich In Heterocycles, Industries Involved In Drug Research And Development Stand To Gain Substantially From These Developments. Ultrasound And Palladium Catalysis, With Their Improved Efficiency And Repeatability, Allow For The

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Precise And Optimization-Free Generation Of Complex Molecular Structures. The Production Of Novel Chemical Entities With Varied Biological Activities Is Facilitated, And Processes In Medicinal Chemistry Are Expedited.

I. Review Of Literature

Michailidis, Fedor. (2021) A Palladium-Assisted Synthesis Of Heterocycles Is The Name Of The Book. Extensive Coverage Of Literature From The Past 20 Years Of Study On Palladium-Catalyzed Synthetic Techniques For Obtaining Heterocycles Of Different Types And Sizes Is Included In This Book. An Assistant Professor In The Department Of Chemistry At Banasthali University, India, Navjeet Kaur Authored The Book. His Research Primarily Involves The Synthesis Of Heterocyclic Compounds Based On 1,4-Benzodiazepines, Which Are Extensively Used In Organic Synthetic And Medicinal Chemistry.

Ramakanth Pagadala (2021) In Order To Create Bioactive Chemicals, Ultrasound-Assisted Multicomponent Reactions In Water Is Excellent Tools To Use. There Has Been A Lot Of Focus On The Methods For Synthesizing Heterocyclic Compounds. In Addition To Using A Lot Of Energy, Several Of These Methods Also Involve The Use Of Potentially Harmful Chemicals, Solvents, And Costly Work-Ups. Superfluous Organic Waste Is Produced By Methods With Low Yields And Several Steps. Therefore, In Order To Build Heterocyclic Analogs And Medicinal Compounds, Researchers Focused On Methods That Were Safe And Environmentally Favorable. Compared To Other Methods, Ultrasound-Assisted Synthesis Of The Desired Organic Moieties Often Results In Greater Product Yields. A Variety Of Heterocyclic Compounds Including Nitrogen, Oxygen, And Sulfur May Be Synthesized Utilizing Water As A Solvent Using Ultrasound-Aided Multicomponent Processes, Which Are The Subject Of This Article. Concerning Yields And Reaction Conditions, The Benefits And Drawbacks Are Addressed. This Review Included All Reports In The Literature From 2014 Forward.

Prasanna, Gutta Et Al., (2017) The Indole Derivatives Mediated By Pd May Now Be Synthesized With Fair To Acceptable Yields Using An Ultrasound-Assisted Technique. The Procedure Included Using Ultrasonic Irradiation In A Solution Of Licl And Nahco3 In Dmf To Catalyze The Coupling-Cyclization Of 2-Iodosulfanilide With Alkynes. The Relevant Indoles Were Produced Via A C-C Followed By C-N Bond Formation Process Involving A Variety Of Internal / Terminal Alkynes. The Current Ultrasound-Based Technique Seems To Be A Practical And Less Expensive Substitute For The Current Procedures, Being Both Quicker And Gentler.

Azua, Arturo Et Al., (2013) We Successfully Isolated And Studied New Palladium N-Heterocyclic Carbbene (Nhc) Complexes Containing 3,4,5-Trimethoxybenzyl, Alkyl, And Sulfonate N-Substituents. Under Pulsed-Ultrasound (P-Us) Activation, The Novel Complexes Served As Pre-Catalysts For The Suzuki-Miyaura Coupling Of Several Aryl Halides/Boron Sources In Glycerol. Mild Reaction Conditions Allowed For High Yields Without The Production Of Undesirable By-Products. Without Column Chromatography, It Was Easy To Recover The Pure Final Cross-Coupling Products, And The Catalytic/Solvent System Could Be Recycled. The Nanoparticles Were Characterized And The Catalysts' Destiny Investigated Using Xps (X-Ray Photoelectron Spectroscopy) And Tem (Transmission Electron Microscopy).

Balme, Geneviève Et Al., (2003) The Use Of Palladium-Mediated Methods In The Design Of Multicomponent One-Pot Syntheses Of Heterocyclic Compounds Has Lately Achieved Some Impressive Successes, Which Are Highlighted In This Study. In This Review, Palladium-Catalyzed Cascade Reactions Are Covered, Along With Procedures That Rely On The Sequential, One-Pot Execution Of Specific Transformations, With Palladium Capping At Least One Of Them.

II. Material And Methods

General Procedures

The First Components Were Already-Purified Commercial Items. 4 Å Molecular Sieves Were Used To Dry The Dmf, And It Was Then Kept Under Nitrogen. The Reactions Were Conducted Using Schlenk Methods Under Nitrogen. We Used Silica Gel Plates From Merck For Analytical Tlc. A 30-Meter-Long Capillary Column (With Se-30 As The Stationary Phase) Was Used To Execute Glc Studies On A Carlo Erba Hrgc 5300 Equipment. The Eluent Used For Flash

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Chromatography Was Hexane-Ethyl Acetate, While The Stationary Phase Was Silica Gel 60 (Icn Silica 32-63). The Electrothermal Equipment Was Used To Determine The Melting Points, And These Points Have Not Been Altered. Bruker Ac-300 Spectrometers Were Used To Obtain ^{1}h- And ^{13}c-Nmr In $Cdcl_3$ At 20 °C With The Solvent As Reference At 300.1 And 75.4 Mhz, Respectively. The Ft-Ir Spectrophotometer Used Was A Perkin-Elmer 298. Using An Ionization Energy Of 70 Ev, A Finnigan Mat Ssq 710 Instrument Was Used To Conduct Mass Spectra (M/Z, Relative Intensity %). An Ea 1108-Elemental Analyzer By Carlo Erba Was Used For The Elemental Analysis.

5,-Acetyl-10b,11,12,13,14,14a-Hexahydro-11,14-Methanotribenz[B,D,F]Azocin-6-One (3)

A 16-Milliliter (Ml) Dmf Solution Of Phenylnorbornylpalladium Chloride Dimer 1 (31 Mg, 0.05 Mmol) Was Added To A Schlenk-Type Flask Containing Solid K2co3 (14 Mg, 0.1 Mmol) Under Nitrogen. After A Few Minutes Of Stirring, The Mixture's Hue Changed To A Pale Purple. Stirring Was Maintained For 6 Hours At Room Temperature After Adding A 1 Ml Solution Of O-Iodoacetanilide In Dmf (26 Mg, 0.1 Mmol). After 24 Hours Of Stirring At Ambient Temperature, Carbon Monoxide Was Added To The Reaction In Lieu Of Nitrogen At Atmospheric Pressure. The Solution Was Thinned With 20 Ml Of Water And Then Extracted With 3x10 Ml Of Diethyl Ether. Anhydrous Na2so4 Was Used To Dry The Mixed Organic Phase, And The Solvent Was Extracted At Decreased Pressure. A 7:3 Combination Of Hexane And Ethyl Acetate Was Used As The Eluent For Flash Chromatography On Silica Gel, Which Was Used To Purify The Resultant Crude. Bright Needles Were Obtained By Recrystallizing Compound 3, A White Solid With An Isolated Concentration Of 31 Mg (94%).

X-Ray Analysis

When We Reduced The Data, We Also Adjusted For The Lorentz And Polarization Effects. The Structure Was Improved Using Anisotropic Full-Matrix Least-Squares With Shelx93 After Being Solved Using Direct Techniques With Sir97. A ΔF Map Was Used To Find And Refine All Hydrogen Atoms Isotropically. Å And ° Are The Bond Lengths And Angles That Were Reported In Table 1.

Table 1: Values Between Nodes

Bond Lengths	Angles	(Uncertainty)
C1 - C6	1.589	9
C1 - C25	1.505	8
C6 - C8	1.518	7
C8 - C13	1.401	10
C13 - C14	1.507	12
C14 - N16	1.407	9
N16 - C20	1.452	8
C20 - C25	1.390	10
C6 - C1 - C25	113.7	5
C1 - C6 - C8	115.6	5
C6 - C8 - C13	121.3	6
C13 - C14 - N16	114.2	5
C14 - N16 - C20	117.8	5

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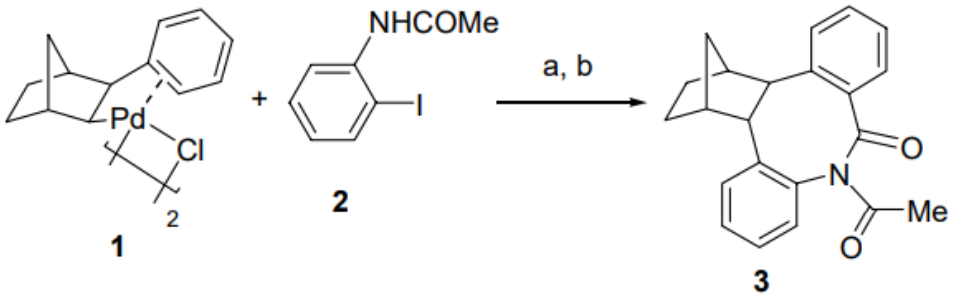
N16 - C20 - C25	120.3	5
C1 - C25 - C20	118.6	5

III. Results And Discussion

Chemical Synthesis Involving A Phenylnorbornylpalladium Chloride Dimer, O-Iodoacetanilide, Carbon Monoxide, K2co3 As A Base, And Dmf As A Solvent Resulted In The Almost Quantitative Yield Of Compound 3. Running The Reaction Under Nitrogen For 6 Hours At Ambient Temperature Was The Initial Step, Followed By Running It Under Atmospheric Pressure Of Carbon Monoxide. Using Flash Chromatography, Compound 3 Was Successfully Extracted As A White Solid With A Yield Of 94%. The Hexane-Methylene Chloride Solution Was Recrystallized To Produce Colorless Crystals That Were Acceptable For X-Ray Examination. Spectroscopic Approaches Were Inadequate To Verify The Existence Of An Eight-Membered Ring, Hence Crystal Structure Determination Was Needed To Conclusively Describe Compound 3.



Scheme 1: Synthesis Of Compound 3 From 1 And 2 Under N_2 And Co Conditions

(A) 6 H. (B) Under Co, 24 H K2co3, Dmf, Under N2, Room Temperature

Find The Crystal Structure In Figure 1. The Aromatic Ring And Norbornyl Moiety Both Have Normal Geometries And Bond Lengths And Angles Do Not Considerably Differ From What Is Predicted. They Are Planar Within 0.011(6) Å. A Dihedral Angle Of 118.7(2)° Is Formed By The Mean Planes Of The Two Aromatic Rings C8-C13 And C20-C25, Which Are Situated On The Same Side With Respect To The Basal Plane. The Eight-Membered Ring Is Arranged In A Boat Conformation, With Four Atoms (C1, C6, C14, N16) Lying Almost In A Basal Plane And The Other Four Forming The Bow (C8, C13) And The Stern (C20, C25). The Molecules In The Crystal Are Bound Together By Standard Van Der Waals Interactions, With The Shortest Contact Being H10...O18i = 2.44(8) Å, Where I Is An Integer Between X, Y-1, And Z.

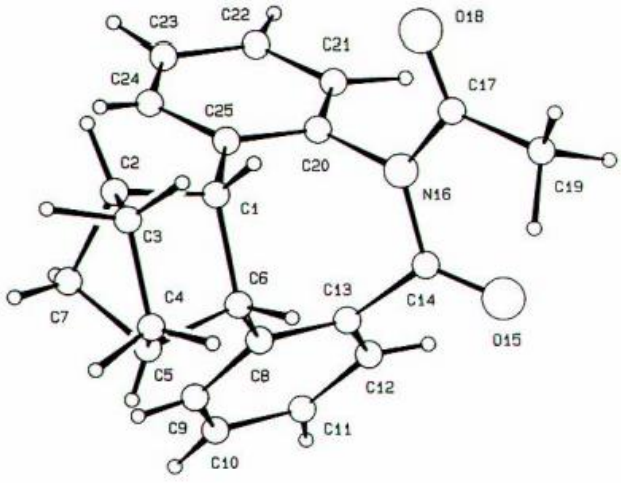


Figure 1: Projection Of Compound 3 With Arbitrary Numbering Scheme.

The Proposed Pathway For The Formation Of The Cyclic Amide Is Described In Scheme 2.

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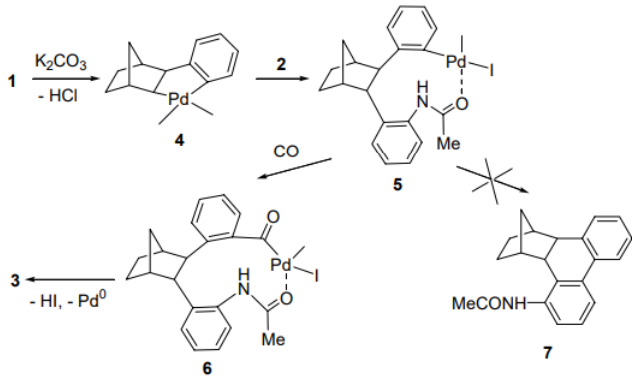

Scheme 2: Proposed Mechanism For The Formation Of Compound 3

Using A Suitable Base, Such K2co3 In Dmf As A Solvent, Compound 1 May Easily Be Converted Into The Five-Membered Alkylaromatic Palladacycle 4. Metallacycle 4's Potential As An Intermediary Has Been Advanced Before. Complex 5 Is Able To Introduce Carbon Monoxide, Resulting In Species 6, After Reacting With O-Iodoacetanilide. The Acylpalladium Complex 6 Is Attacked By The Nh Group, Resulting In The Cyclic Amide 3. Complex 4 Reacts With O-Iodoacetanilide By Oxidative Addition To The Palladacycle, Forming A Palladium(Iv) Metallacycle. This Cycle Then Undergoes Reductive Elimination To Yield 5. In The Past, We Have Reported Palladium(Iv) Complexes That Were Formed By Oxidatively Adding Alkyl Halides To Alkylaromatic Palladacycles.

Through A Newly Discovered Mechanism Incorporating Palladacycle Production, The Whole Process Provides A Novel Approach To Accessing A Rare Class Of Heterocyclic Eight-Membered Rings In High Yield. The Current Findings Are Surprising Given What Is Known About The Behavior Of Alkylaromatic Palladacycles From The Authors' Lab. For Example, Compound 7 Shows That Complex 5 Can Form A Six-Membered Ring By Coupling The Two Aryl Groups, But Complex 5 Admits Carbon Monoxide, Resulting In The Acylpalladium Complex 6. Thus, In Order To Explain Complex 5's Behavior, We Postulate Amido Group Coordination. Whether An Aromatic Ring Has A Meta Or Para Substituent, The Reaction Will Proceed Normally.

Even When Working Under Circumstances Of High Basicity And With Chelating Ligands Have Not Been Able To Achieve A Seven-Membered Ring, Which Would Be The Result Of The Nh Group Attacking The Arylpalladium Bond Directly. Since The Eight-Membered Ring Was Easily Produced, Steric Hindrance In The Crowded Transition State Is Probably To Blame For This Ring's Inability To Close.

Finally, By Capitalizing On The Peculiarities Of Species 5, Which Arise From The Alkylaromatic Palladacycle–O-Iodoacetanilide Reaction, We Have Synthesized A Novel Benzazocine Derivative. Additional Research On This Idea Is Now Underway.

IV. Conclusion

An Efficient And Environmentally Friendly Method For Synthesizing Heterocyclic Compounds May Be Achieved By Combining Palladium-Mediated Catalysis With Ultrasound-Assisted Approaches, As Shown In The Conclusion. By Combining The Accuracy And Adaptability Of Palladium Catalysts With The Increased Reaction Rates And Better Mass Transfer Provided By Ultrasonic Irradiation, These Two Approaches Work Well Together. Combined, They Overcome Several Drawbacks Of Conventional Synthetic Methods, Including Lengthy Reaction Times, Difficult Conditions, And Excessive Solvent Use. These Methods Are Especially Useful For Building Complex Heterocyclic Frameworks, Which Are Essential For Medicines, Agrochemicals, And Advanced Functional Materials; They Offer Cleaner Transformations, Greater Yields, And Wider Substrate Compatibility, Thanks To The Synergy They Establish. The Remarkable Decrease In Energy Consumption And Reaction Waste Is In Line With Green Chemistry Principles, Further Demonstrating The Approaches' Positive Impact On The Environment. It Is Anticipated That The Scope Of These Integrated Approaches Will Grow Further As Research Continues To Improve Catalyst Design, Optimize Sonication Settings, And Investigate New Reaction Pathways. When It Comes To The Future Of Efficient, Scalable, And Environmentally Friendly Heterocycle Synthesis, Palladium-Mediated And Ultrasound-Assisted Approaches Show A Lot Of Promise In Both The Academic And Industrial Spheres.

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